ARTICLE IN PRESS YJDEQ:9249

Available online at www.sciencedirect.com

ScienceDirect

J. Differential Equations ●●● (●●●●) ●●●–●●●

Journal of Differential Equations

www.elsevier.com/locate/jde

Analysis of a free boundary problem modeling the growth of multicell spheroids with angiogenesis ☆

Yuehong Zhuang, Shangbin Cui *

School of Mathematics, Sun Yat-Sen University, Guangzhou 510275, PR China

Received 23 December 2017

Abstract

In this paper we study a free boundary problem modeling the growth of vascularized tumors. The model is a modification to the Byrne–Chaplain tumor model that has been intensively studied during the past two decades. The modification is made by replacing the Dirichlet boundary value condition with the Robin condition, which causes some new difficulties in making rigorous analysis of the model, particularly on existence and uniqueness of a radial stationary solution. In this paper we successfully solve this problem. We prove that this free boundary problem has a unique radial stationary solution which is asymptotically stable for large surface tension coefficient, whereas unstable for small surface tension coefficient. Tools used in this analysis are the geometric theory of abstract parabolic differential equations in Banach spaces and spectral analysis of the linearized operator.

MSC: 35R35; 35B35; 35B40

Keywords: Free boundary problem; Tumor growth; Well-posedness; Stationary solution; Asymptotic stability

1. Introduction

It has been recognized for over eighty years that under a constant circumstance, an evolutionary tumor (or a multicell spheroid in a different phrase) will finally evolve into a stationary or

☆ This work is supported by China National Natural Science Foundation under the grant number 11571381.
* Corresponding author.
E-mail address: cuishb@mail.sysu.edu.cn (S. Cui).

https://doi.org/10.1016/j.jde.2018.03.005
0022-0396/© 2018 Published by Elsevier Inc.

Please cite this article in press as: Y. Zhuang, S. Cui, Analysis of a free boundary problem modeling the growth of multicell spheroids with angiogenesis, J. Differential Equations (2018), https://doi.org/10.1016/j.jde.2018.03.005

dormant state [1]. During 1970's, Greenspan proposed the first mathematical model in the form of free boundary problem of reaction diffusion equations to explain this phenomenon [22,23]. His model was very well improved by Byrne and Chaplain during 1990's [3,4]. Since then many different tumor models have been established by different groups of researchers, cf. the reviewing articles [2,16] and references cited therein. Rigorous mathematical analysis of those tumor models has attracted much attention over the past two decades, and many interesting results have been obtained, cf. [5–13,17,18,20,21,25–30] and references cited therein.

In this paper we study the following free boundary problem modeling the growth of vascularized tumors:

$$\begin{cases} \Delta\sigma = f(\sigma), & x \in \Omega(t),\ t > 0, \\ -\Delta p = g(\sigma), & x \in \Omega(t),\ t > 0, \\ \partial_{\mathbf{n}}\sigma = \beta(\bar{\sigma} - \sigma), & x \in \partial\Omega(t),\ t > 0, \\ p = \gamma\kappa, & x \in \partial\Omega(t),\ t > 0, \\ V_{\mathbf{n}} = -\partial_{\mathbf{n}} p, & x \in \partial\Omega(t),\ t > 0, \\ \Omega(0) = \Omega_0. \end{cases} \tag{1.1}$$

Here $\Omega(t)$ is the domain in $\mathbb{R}^n$ occupied by the tumor at time t, $\sigma = \sigma(x,t)$ and $p = p(x,t)$ are the nutrient concentration in the tumor region and the pressure between tumor cells, respectively, $\partial_{\mathbf{n}}$ represents the derivative in the direction of the outward normal $\mathbf{n}$ of the tumor surface $\partial\Omega(t)$, $\bar{\sigma}$ is a positive constant reflecting the constant concentration of nutrient in the host tissue of the tumor, κ is the mean curvature of the tumor surface $\partial\Omega(t)$ whose sign is designated by the convention that for the sphere it is positive, V_{n} is the normal velocity of the tumor surface movement, β is a positive constant reflecting the ability that the tumor attracts blood vessel from its host tissue, γ is another positive constant reflecting the surface tension of the tumor surface and is usually referred to as *surface tension coefficient*, f and g are given functions with $f(\sigma)$ being the (normalized) consumption rate of nutrient by tumor cells when its concentration is at level σ and $g(\sigma)$ the (normalized) proliferation rate of tumor cells when the nutrient concentration is at level σ, and Ω_0 is the domain that the tumor initially occupies. Naturally, from physical viewpoint we have $n = 3$; but for mathematical interest we consider the general case $n \geqslant 2$.

The above model, in the case that f and g are linear functions

$$f(\sigma) = \lambda\sigma \quad \text{and} \quad g(\sigma) = \mu(\sigma - \tilde{\sigma}), \tag{1.2}$$

was proposed by Friedman and Lam in [19] as an essential modification to the corresponding model of Byrne and Chaplain mentioned above. The modification is made by considering nutrient supply mechanism of the tumor in a different viewpoint from that of Byrne and Chaplain. Indeed, in the model of Byrne and Chaplain [3,4], tumor surface is obstacle-free to nutrient diffusion, so that instead of the Robin boundary condition in the third line of (1.1) (referred to as $(1.1)_3$ in what follows), in their model the Dirichlet boundary condition

$$\sigma = \bar{\sigma}, \quad x \in \partial\Omega(t),\ t > 0 \tag{1.3}$$

is imposed, which means that nutrient in the host tissue diffuses into the tumor from its surface without any obstruction, and the effect of vascularization of the tumor is reflected in the structure of the function f: Roughly speaking, the denser the capillary vessel of the tumor is, the larger the

Please cite this article in press as: Y. Zhuang, S. Cui, Analysis of a free boundary problem modeling the growth of multicell spheroids with angiogenesis, J. Differential Equations (2018), https://doi.org/10.1016/j.jde.2018.03.005

coefficient λ in the function f in (1.2) will be. In the above model (1.1), however, tumor surface is a barrier to nutrient diffusion, and nutrient enters the tumor only from blood vessels penetrated into the tumor from the host tissue. The positive constant β reflects strength of the blood vessel system of the tumor: the smaller β is, the weaker the blood vessel system of the tumor will be, and $\beta = 0$ corresponds to the case that the tumor does not have its own capillary vessel system so that nutrient is isolated on both sides of the surface of the tumor.

We can understand the boundary condition $(1.1)_3$ in a different viewpoint: Even if the tumor does not have its own capillary vessel system, the nutrient is still able to diffuse through its surface into its inner part with reduction caused by the barrier effect of the surface, and $1/\beta$ reflects reduction rate of nutrient by the tumor surface as a barrier: $1/\beta = 0$ means that tumor surface is obstacle-free to nutrient diffusion, whereas $1/\beta = \infty$ means that tumor surface is a complete barrier to nutrient, i.e., nutrients in the tumor and in host tissues are completely isolated. In this viewpoint, the Robin boundary condition $(1.1)_3$ is more realistic than the Dirichlet boundary condition (1.3).

When the Robin boundary condition $(1.1)_3$ is replaced by the Dirichlet boundary condition (1.3), the corresponding free boundary problem has been intensively studied by many authors during the past two decades, cf. [5–10,13,17,18,20,21], for instance. It is natural to ask whether the results obtained in those literatures can be extended to the problem (1.1). Evidently, to tackle the Robin boundary condition problem some new difficulties different from those encountered in the Dirichlet boundary condition problem must be overcome. In the above-mentioned work of Friedman and Lam [19], the authors studied the radial version of the problem (1.1) in the special case that f and g are linear functions given by (1.2) (but with a more general boundary condition for σ: β is not a constant but a given positive function of t). Recently, the first author of this paper considered the special case that f is a linear function and the space dimension $n = 3$ [31]. In the present paper we aim at studying the problem (1.1) for a general nonlinear f.

As in [6,7,9,10], in this paper we assume that f and g are general functions defined in $[0, \infty)$ satisfying the following group of conditions:

(A1) $f \in C^\infty[0, \infty)$, $g \in C^\infty[0, \infty)$;
(A2) $f'(\sigma) > 0$ for all $\sigma \in [0, \infty)$, and $f(0) = 0$;
(A3) $g'(\sigma) > 0$ for all $\sigma \in [0, \infty)$, and there exists $\widetilde{\sigma} > 0$ such that $g(\widetilde{\sigma}) = 0$;
(A4) $\bar{\sigma} > \widetilde{\sigma}$.

Note that the condition (A4) is imposed only for the purpose to ensure that a nontrivial dynamics of the problem (1.1) exists: if this condition is not satisfied then the tumor will finally vanish. Indeed, by the maximum principle we have $0 \leqslant \sigma(x,t) < \bar{\sigma}$ for all $x \in \Omega(t)$ and $t > 0$. Hence, by the transport formula and the Green's formula, we have the following deduction:

$$\frac{\mathrm{d}}{\mathrm{d}t}\Big(\int\limits_{\Omega(t)} \mathrm{d}x\Big) = \int\limits_{\partial\Omega(t)} V_{\mathbf{n}}(x,t)\mathrm{d}S_x = -\int\limits_{\partial\Omega(t)} \partial_{\mathbf{n}} p(x,t)\mathrm{d}S_x$$
$$= -\int\limits_{\Omega(t)} \Delta p(x,t)\mathrm{d}x = \int\limits_{\Omega(t)} g(\sigma(x,t))\mathrm{d}x < g(\bar{\sigma})\Big(\int\limits_{\Omega(t)} \mathrm{d}x\Big).$$

Since the condition $\bar{\sigma} \leqslant \widetilde{\sigma}$ and the assumption (A3) imply that $g(\bar{\sigma}) \leqslant 0$, we get

$$\lim_{t\to\infty} \mathrm{Vol}(\Omega(t)) = 0.$$

From biological viewpoint, this can be explained as follows: $\widetilde{\sigma}$ is the threshold value of nutrient concentration to sustain tumor cells alive and proliferating. Hence, if $\bar{\sigma} \leqslant \widetilde{\sigma}$ then in the tumor region nutrient is not sufficient to sustain tumor cells alive, yielding the result that the tumor diminishes in time and finally disappears. For more discussions on the assumptions (A1)–(A4), we refer the reader to see [6,10].

In this paper we study the problem (1.1) from the following four aspects: (1) Existence and uniqueness of a radial stationary solution. (2) Asymptotic stability of the radial stationary solution under radial perturbations. (3) Local well-posedness of the problem (1.1). (4) Asymptotic stability of the radial stationary solution under non-radial perturbations. In what follows we give precise statements of the main results obtained in this paper.

By a *radial stationary solution* of the problem (1.1) we mean a triple $(\sigma_s(r), p_s(r), \Omega_s)$ with $\Omega_s = B(0, R_s) = \{0 \leqslant r < R_s\}$ (r represents the radial coordinate in $\mathbb{R}^n$) and $\sigma_s(r)$, $p_s(r)$ being functions defined for $0 \leqslant r \leqslant R_s$, such that the following equations are satisfied:

$$\begin{cases} \sigma_s''(r) + \frac{n-1}{r}\sigma_s'(r) = f(\sigma_s(r)), \quad 0 < r < R_s, \\ p_s''(r) + \frac{n-1}{r}p_s'(r) = -g(\sigma_s(r)), \quad 0 < r < R_s, \\ \sigma_s'(0) = 0, \quad \sigma_s'(R_s) = \beta(\bar{\sigma} - \sigma_s(R_s)), \\ p_s'(0) = 0, \quad p_s(R_s) = \gamma/R_s, \\ p_s'(R_s) = 0. \end{cases} \tag{1.4}$$

These equations are obtained from (1.1) by assuming that $\sigma(x,t)$, $p(x,t)$, $\Omega(t)$ are independent of t, $\Omega(t) = \Omega_s = B(0, R_s)$ and σ, p are radial functions in x. We introduce a function $F(R)$ defined for $R \geqslant 0$ as follows:

$$F(R) = \int_0^1 g(U(\rho R, R))\rho^{n-1}d\rho, \tag{1.5}$$

where $U = U(r, R)$ is a function defined for all $R \geqslant 0$ and $0 \leqslant r \leqslant R$ as follows: $U(r, 0) \equiv \bar{\sigma}$, and for any $R > 0$, $U(r, R)$ $(0 \leqslant r \leqslant R)$ is the unique solution of the following boundary value problem:

$$\begin{cases} U''(r,R) + \dfrac{n-1}{r}U'(r,R) = f(U(r,R)), \quad 0 < r < R, \\ U'(0,R) = 0, \quad U'(R,R) = \beta(\bar{\sigma} - U(R,R)), \end{cases} \tag{1.6}$$

where $U'(r,R) = \frac{\partial U}{\partial r}(r,R)$ and $U''(r,R) = \frac{\partial^2 U}{\partial r^2}(r,R)$. Note that since f is a smooth monotone increasing function and $\beta > 0$, by standard theory for elliptic boundary value problems we easily see that the above problem has a unique solution which is smooth for $R > 0$ and $0 \leqslant r \leqslant R$ (see §2 for details).

The first main result of this paper is the following

Please cite this article in press as: Y. Zhuang, S. Cui, Analysis of a free boundary problem modeling the growth of multicell spheroids with angiogenesis, J. Differential Equations (2018), https://doi.org/10.1016/j.jde.2018.03.005

Theorem 1.1. *Let the assumptions* (A1)–(A4) *be satisfied. Then the function* F *has a unique positive root which we denote as* R_s*, and the problem* (1.4) *has a unique solution* $(\sigma_s(r), p_s(r), R_s)$ *given as follows:* $\sigma_s(r) = U(r, R_s)$*, and*

$$p_s(r) = \frac{\gamma}{R_s} + \int_r^{R_s} \int_0^{\eta} g(U(\xi, R_s))\Big(\frac{\xi}{\eta}\Big)^{n-1} \mathrm{d}\xi \mathrm{d}\eta \quad \text{for } 0 \leqslant r \leqslant R. \tag{1.7}$$

To study asymptotic stability of the radial stationary solution $(\sigma_s(r), p_s(r), \Omega_s)$ under radial perturbations, we need to consider radial transient solutions of the problem (1.1). A *radial transient solution* of the problem (1.1) is a triple $(\sigma(r,t), p(r,t), \Omega(t))$ with $\Omega(t) = B(0, R(t))$ $(t \geqslant 0)$ and $\sigma(r,t)$, $p(r,t)$ being functions defined for $t \geqslant 0$ and $0 \leqslant r \leqslant R(t)$, satisfying the following system of equations:

$$\begin{cases} \dfrac{\partial^2\sigma}{\partial r^2}(r,t) + \dfrac{n-1}{r}\dfrac{\partial\sigma}{\partial r}(r,t) = f(\sigma(r,t)), \quad 0 < r < R(t), \ t > 0, \\ \dfrac{\partial^2 p}{\partial r^2}(r,t) + \dfrac{n-1}{r}\dfrac{\partial p}{\partial r}(r,t) = -g(\sigma(r,t)), \quad 0 < r < R(t), \ t > 0, \\ \dfrac{\partial\sigma}{\partial r}(0,t) = 0, \quad \dfrac{\partial\sigma}{\partial r}(R(t),t) = \beta(\bar\sigma - \sigma(R(t),t)), \quad t > 0, \\ \dfrac{\partial p}{\partial r}(0,t) = 0, \quad p(R(t),t) = \dfrac{\gamma}{R(t)}, \quad t > 0, \\ R'(t) = \dfrac{1}{(R(t))^{n-1}} \displaystyle\int_0^{R(t)} g(\sigma(r,t)) r^{n-1} dr, \quad t > 0, \\ R(0) = R_0, \end{cases} \tag{1.8}$$

where $R_0 > 0$ is a given initial data of $R(t)$. These equations are obtained from (1.1) by assuming that $\Omega(t) = B(0, R(t))$ and $\sigma(x,t)$, $p(x,t)$ are radial functions in x for any $t \geqslant 0$.

Theorem 1.2. *Let the assumptions* $(A1)$–$(A4)$ *be satisfied. Then for any* $R_0 > 0$*, the problem* (1.8) *has a unique solution* $(\sigma(r,t), p(r,t), R(t))$ $(0 \leqslant r \leqslant R(t))$ *for all* $t \geqslant 0$ *with the following properties:*

(i) $R \in C^1[0,\infty)$*, and* $R(t) > 0$ *for all* $t \geqslant 0$*;*
(ii) $\sigma(rR(t),t) \in C^{2,1}([0,1] \times [0,\infty))$*, and*

$$0 \leqslant \sigma(r,t) \leqslant \bar\sigma \quad \text{for } 0 \leqslant r \leqslant R(t), \ t \geqslant 0; \tag{1.9}$$

(iii) *The following relations hold:*

$$\lim_{t\to\infty} R(t) = R_0, \tag{1.10}$$

$$\lim_{t\to\infty} \max_{0\leqslant r\leqslant R(t)} |\sigma(r,t) - \sigma_s(r)| = 0, \tag{1.11}$$

Please cite this article in press as: Y. Zhuang, S. Cui, Analysis of a free boundary problem modeling the growth of multicell spheroids with angiogenesis, J. Differential Equations (2018), https://doi.org/10.1016/j.jde.2018.03.005

$$\lim_{t\to\infty}\max_{0\leqslant r\leqslant R(t)}|p(r,t)-p_s(r)|=0. \tag{1.12}$$

Next we consider non-radial solutions of the problem (1.1). To state the main results on this line we first introduce some notations. For a bounded domain Ω in $\mathbb{R}^n$ with a smooth boundary $\partial\Omega$ and a given number $s>0$, we denote by $c^s(\overline{\Omega})$ the so-called little Hölder space of order s on Ω, which is, by definition, the closure of $C^\infty(\overline{\Omega})$ in the usual Hölder space $C^s(\overline{\Omega})$. A important special case is the space $c^s(\overline{\mathbb{B}^n})$ on the unit ball $\mathbb{B}^n=\{x\in\mathbb{R}^n:|x|<1\}$. Similarly, for a closed smooth hypersurface $\Gamma\subseteq\mathbb{R}^n$ we write $c^s(\Gamma)$ for the closure of $C^\infty(\Gamma)$ in $C^s(\Gamma)$. A important special case is the space $c^s(\mathbb{S}^{n-1})$ on the unit sphere $\mathbb{S}^{n-1}$.

Fix an integer $m\geqslant 3$ and a number $0<\alpha<1$. We shall deal with the problem (1.1) in the $c^{m+\alpha}$ space. Let $\Omega_0\subseteq\mathbb{R}^n$ be the bounded initial domain given in the problem (1.1). We assume that there exists a closed smooth hypersurface Γ in a very small neighborhood of $\partial\Omega_0$ such that $\partial\Omega_0$ is exactly the image of the mapping $\xi\mapsto\xi+\eta_0(\xi)\mathrm{n}_\Gamma(\xi)$, $\forall\xi\in\Gamma$, where n_Γ is the outward normal field of Γ, and η_0 is a function on Γ (uniquely determined by $\partial\Omega_0$). For $\delta>0$ sufficiently small, we denote

$$O_\delta:=\{\eta\in c^{m+\alpha}(\Gamma):\|\eta\|_{c^{m+\alpha}(\Gamma)}<\delta\}. \tag{1.13}$$

We assume that δ is so small that the mapping $X:(\xi,s)\mapsto\xi+s\mathrm{n}_\Gamma(\xi)$ from $\Gamma\times(-\delta,\delta)$ to $\mathbb{R}^n$ is an one-to-one correspondence of $\Gamma\times(-\delta,\delta)$ onto its image (see §3 for details). Given $\eta\in O_\delta$, we use the notation Ω_η to denote the domain in $\mathbb{R}^n$ enclosed by the closed hypersurface $x=\xi+\eta(\xi)\mathrm{n}_\Gamma(\xi)$ $(\xi\in\Gamma)$. Using this notation, we rephrase more precisely the condition on the initial domain Ω_0 as follows: There exists $\eta_0\in O_\delta$ such that $\Omega_0=\Omega_{\eta_0}$.

The third main result of this paper is concerned with local well-posedness of the problem (1.1), which reads as follows:

Theorem 1.3. *Let Ω_0 be given with Γ and $\eta_0\in O_\delta$ as above. There exist a number $T>0$, a function*

$$\eta\in C([0,T],c^{m+\alpha}(\Gamma))\cap C^1((0,T],c^{m-3+\alpha}(\Gamma)),$$

and a pair of functions $(\sigma,p)=(\sigma(x,t),p(x,t))$ defined for $x\in\Omega_{\eta(t)}$ and $0\leqslant t\leqslant T$, such that the triple (σ,p,Ω), where $\Omega(t)=\Omega_{\eta(t)}$ $(0\leqslant t\leqslant T)$, is the unique classical solution of the problem (1.1) on the time interval $[0,T]$.

Remark. Note that in the above result regularity of the pair of functions (σ,p) is not specified. This is because when $\Omega(t)$ is obtained, (σ,p) is the solution of the elliptic boundary value problem $(1.1)_1$–$(1.1)_4$ and, by standard knowledge, regularity of the solution of elliptic boundary value problem whose coefficients and given functions are smooth is completely determined by regularity of its domain.

To state the result on asymptotic behavior of non-radial solution (σ,p,Ω) of the problem (1.1), we need to introduce some further notations. We denote $\Gamma_s=R_s\mathbb{S}^{n-1}=\{x\in\mathbb{R}^n:|x|=R_s\}$ and, with m,α,δ as before, let

$$O_\delta^s:=\{\eta\in c^{m+\alpha}(\Gamma_s):\|\eta\|_{c^{m+\alpha}(\Gamma_s)}<\delta\}. \tag{1.14}$$

Accordingly, given $\eta \in O_\delta^s$, the notation Ω_η denotes the bounded domain enclosed by the hypersurface $x = \xi + \eta(\xi)\mathrm{n}_{\Gamma_s}(\xi)$ $(\xi \in \Gamma_s)$. We note that an important character of the problem (1.1) is that it is invariant under coordinate translations, i.e., if (σ, p, Ω) is the solution of (1.1) with initial data $\Omega(0) = \Omega_0$, then for any $x_0 \in \mathbb{R}^n$, by letting

$$\sigma^{[x_0]}(\cdot, t) = \sigma(\cdot - x_0, t), \quad p^{[x_0]}(\cdot, t) = p(\cdot - x_0, t), \quad \Omega^{[x_0]}(t) = \Omega(t) + x_0,$$

we see that $(\sigma^{[x_0]}, p^{[x_0]}, \Omega^{[x_0]})$ is the solution of (1.1) with initial data $\Omega^{[x_0]}(0) = \Omega_0 + x_0$. It follows that stationary solutions of the problem (1.1) are not isolated in any function spaces. Hence, in order to study asymptotic stability of the radial stationary solution $(\sigma_s, p_s, \Omega_s)$ ensured by Theorem 1.1, we must module the solutions of (1.1) via coordinate translations of $\mathbb{R}^n$. To this end, given $x_0 \in \mathbb{R}^n$, we denote by $(\sigma_s^{[x_0]}, p_s^{[x_0]}, \Omega_s^{[x_0]})$ the translated radial stationary solution defined similarly as above.

The last main result of this paper is the following:

Theorem 1.4. *There exists a constant $\gamma_* > 0$ such that the following two assertions hold:*

(i) *If $\gamma > \gamma_*$ then the radial stationary solution $(\sigma_s, p_s, \Omega_s)$ is asymptotically stable module translations, i.e., there exists a constant $\delta > 0$ such that for any $\eta_0 \in O_\delta^s$ the problem (1.1) has a unique global in-time classical solution (σ, p, Ω_η) which converges, as time $t \to \infty$, exponentially fast to a translated radial stationary solution $(\sigma_s^{[x_0]}, p_s^{[x_0]}, \Omega_s^{[x_0]})$ for some $x_0 \in \mathbb{R}^n$, or more precisely, there exist constants $C > 0$ and $c > 0$ (independent of the initial data) such that the following estimate holds for all $t \geqslant 0$:*

$$\|\eta(t) - \eta_s^{[x_0]}\|_{C^{m+\alpha}(\Gamma_s)} + \|\sigma(\cdot, t) - \sigma_s^{[x_0]}\|_{C^{m+\alpha}(\overline{\Omega(t)})} + \|p(\cdot, t) - p_s^{[x_0]}\|_{C^{m+\alpha-2}(\overline{\Omega(t)})} \leqslant Ce^{-ct},$$

where $\eta_s^{[x_0]}$ is the unique smooth function on Γ_s such that $\Omega_s^{[x_0]} = \Omega_{\eta_s^{[x_0]}}$.

(ii) *If $0 < \gamma < \gamma_*$ then the radial stationary solution $(\sigma_s, p_s, \Omega_s)$ is unstable.*

Let us make some comments on the above results. As we mentioned earlier, when the Robin boundary condition $(1.1)_3$ is replaced by Dirichlet boundary condition, then the corresponding model has been very well studied during the past twenty years. For the present model with the Robin boundary condition $(1.1)_3$, the proof of local well-posedness of the problem is quite similar to that of the problem with Dirichlet boundary condition. However, proofs of existence and uniqueness of the radial stationary solution as well as its asymptotic stability turn out to be different, and some new difficulties have to be overcome; see the proof of Lemma 2.1 in §2 and the computation of the spectrum of the linearized operator presented in §4. Hence, in the following sections we shall make detailed discussion on these different aspects and only give skeletons of the arguments that are similar to those in existing literatures.

The structure of the rest part is as follows: In Section 2 we give the proofs of Theorems 1.1 and 1.2. In Section 3 we prove Theorem 1.3. The proof of Theorem 1.4 will be given in the last section.

2. Proofs of Theorems 1.1 and 1.2

In this section we give the proofs of Theorems 1.1 and 1.2.

Please cite this article in press as: Y. Zhuang, S. Cui, Analysis of a free boundary problem modeling the growth of multicell spheroids with angiogenesis, J. Differential Equations (2018), https://doi.org/10.1016/j.jde.2018.03.005

Let us first study properties of the solution $U(r, R)$ of the boundary value problem (1.6). As before we use the notations $'$, $''$ and $'''$ to respectively denote the first, the second and the third order derivatives in the variable r. Besides, we use the notation of subscripts R, RR to respectively denote the first and the second order derivatives in the variable R, i.e., $U_R(r, R) = \frac{\partial U}{\partial R}(r, R)$, $U_{RR}(r, R) = \frac{\partial^2 U}{\partial R^2}(r, R)$, $U'_R(r, R) = \frac{\partial^2 U}{\partial R \partial r}(r, R)$, and so on.

The following lemma will play a crucial role in later analysis:

Lemma 2.1. *Let the conditions* (A1) *and* (A2) *be satisfied. We have the following assertions:*

(1) $0 < U(r, R) < \bar{\sigma}$ *for all* $R > 0$ *and* $0 \leqslant r \leqslant R$, $0 < U'(r, R) \leqslant \frac{f(\bar{\sigma})}{n} r$ *for all* $R > 0$ *and* $0 < r \leqslant R$, *and* $0 < U''(r, R) \leqslant f(\bar{\sigma})$ *for all* $R > 0$ *and* $0 \leqslant r \leqslant R$.

(2) *The following relations hold for all* $R > 0$ *and* $0 < r \leqslant R$:

$$-f(\bar{\sigma})\left(\frac{1}{\beta} + \frac{R}{n}\right) \leqslant U_R(r, R) \leqslant 0, \quad U'_R(r, R) \leqslant 0.$$

(3) *For any* $\rho \in (0, 1)$ *fixed, the function* $R \mapsto U(\rho R, R)$ *is strictly monotone decreasing.*

(4) *The following relations hold:*

$$\lim_{R \to 0^+} U(\rho R, R) = \bar{\sigma} \text{ for all } \rho \in (0, 1); \tag{2.1}$$

$$\lim_{R \to \infty} U(\rho R, R) = 0 \text{ for all } \rho \in (0, 1). \tag{2.2}$$

Proof. (1) Since $U \equiv \bar{\sigma}$ and $U \equiv 0$ are a pair of upper and lower solutions of the problem (1.6) and the function f is smooth and monotone increasing, using a standard result for elliptic boundary value problems we see that for any $R > 0$ the problem (1.6) has a unique solution satisfying the following condition:

$$0 \leqslant U(r, R) \leqslant \bar{\sigma} \quad \text{for } 0 \leqslant r \leqslant R. \tag{2.3}$$

From (1.6) we easily get

$$U'(r, R) = \frac{1}{r^{n-1}} \int_0^r f(U(\rho, R))\rho^{n-1} d\rho \quad \text{for } 0 < r \leqslant R, \tag{2.4}$$

which combined with (2.3) yields

$$0 < U'(r, R) \leqslant \frac{f(\bar{\sigma})}{n} r \quad \text{for } 0 < r \leqslant R \text{ and } R > 0. \tag{2.5}$$

From the relation $U'(R, R) > 0$ and the second boundary condition in (1.6) we obtain $U(R, R) < \bar{\sigma}$. The assertion $U(0, R) > 0$ follows from uniqueness of the solution of the initial value problem

$$\begin{cases} U''(r, R) + \dfrac{n-1}{r} U'(r, R) = f(U(r, R)), & r > 0, \\ U(0, R) = a, \quad U'(0, R) = 0. \end{cases}$$

Indeed, by a standard contraction mapping argument, we see that for any $a \geqslant 0$ there exists corresponding $\delta > 0$ such that the above problem has a unique solution defined for $0 \leqslant r \leqslant \delta$. Hence, we must have $U(0, R) > 0$ for otherwise (i.e., if $U(0, R) = 0$ then) a contradiction would follow. We claim that $U''(r, R)$ has the following expression:

$$U''(r, R) = \frac{1}{r^n} \int_0^r f'(U(\rho, R))U'(\rho, R)\rho^n d\rho + \frac{1}{r} U'(r, R), \ \ 0 < r \leqslant R. \tag{2.6}$$

In fact, using integration by parts and the relation (2.4), we have

$$\begin{aligned} &\frac{1}{r^n} \int_0^r f'(U(\rho, R))U'(\rho, R)\rho^n d\rho + \frac{1}{r} U'(r, R) \\ &= \frac{1}{r^n} \Big(f(U(\rho, R))\rho^n \Big|_{\rho=0}^r - n \int_0^r f(U(\rho, R))\rho^{n-1} d\rho \Big) + \frac{1}{r} U'(r, R) \\ &= f(U(r, R)) - \frac{n-1}{r} U'(r, R), \end{aligned}$$

which is exactly $U''(r, R)$, by $(1.6)_1$. Thus (2.6) follows. From (2.5) and (2.6) we see that

$$U''(r, R) > 0, \quad 0 < r \leqslant R, \tag{2.7}$$

and the L'Hospital's rule implies that $U''(0, R) = \frac{1}{n} f(U(0, R)) > 0$. Moreover, from $(1.6)_1$ we further have

$$U''(r, R) \leqslant U''(r, R) + \frac{n-1}{r} U'(r, R) = f(U(r, R)) \leqslant f(\bar{\sigma}). \tag{2.8}$$

This proves the assertion (1).

(2) Differentiating the relation $U'(R, R) + \beta(U(R, R) - \bar{\sigma}) = 0$ in R we get

$$U''(R, R) + U_R'(R, R) + \beta(U'(R, R) + U_R(R, R)) = 0. \tag{2.9}$$

Differentiating the relation $U''(r, R) + \frac{n-1}{r} U'(r, R) = f(U(r, R))$ (for fixed r) in R we obtain

$$U_R''(r, R) + \frac{n-1}{r} U_R'(r, R) - f'(U(r, R))U_R(r, R) = 0, \quad 0 < r < R. \tag{2.10}$$

Observe that

$$U_R'(0, R) = 0, \qquad U_R'(R, R) + \beta U_R(R, R) < 0 \ \ \text{(by (2.5), (2.6), (2.9))}. \tag{2.11}$$

From (2.10), (2.11) and the maximum principle it follows that

$$U_R(r, R) \leqslant 0, \quad 0 \leqslant r < R. \tag{2.12}$$

Moreover, from (2.10) and the first relation in (2.11) we easily see that

$$U_R'(r,R) \leqslant 0, \quad 0 \leqslant r < R, \tag{2.13}$$

which implies

$$U_R(r,R) \geqslant U_R(R,R), \quad 0 \leqslant r < R. \tag{2.14}$$

Using these relations and (2.9) we compute

$$\begin{aligned}\beta U_R(R,R) &= -U_R'(R,R) - U''(R,R) - \beta U'(R,R) \geqslant -U''(R,R) - \beta U'(R,R) \\ &\geqslant -f(\bar\sigma) - \frac{\beta f(\bar\sigma)}{n} R.\end{aligned}$$

Hence the assertion (2) follows.

(3) Differentiating the relation $U''(r,R) + \frac{n-1}{r} U'(r,R) = f(U(r,R))$ (for fixed R) in r, we get

$$U'''(r,R) + \frac{n-1}{r} U''(r,R) - f'(U(r,R))U'(r,R) = \frac{n-1}{r^2} U'(r,R), \quad 0 < r < R.$$

Summing up this relation with (2.10), we get

$$\Sigma''(r,R) + \frac{n-1}{r} \Sigma'(r,R) - f'(U(r,R))\Sigma(r,R) = \frac{n-1}{r^2} U'(r,R) > 0, \quad 0 < r < R, \tag{2.15}$$

where $\Sigma(r,R) = U'(r,R) + U_R(r,R)$. Moreover, observe that

$$\Sigma(0,R) = U'(0,R) + U_R(0,R) = U_R(0,R) \leqslant 0 \text{ (by (2.12))} \tag{2.16}$$

$$\Sigma'(R,R) + \beta\Sigma(R,R) = 0 \text{ (by (2.9))}. \tag{2.17}$$

From (2.15), (2.16), (2.17) and the maximum principle it follows that

$$\Sigma(r,R) < 0, \quad 0 < r < R.$$

Hence, for any $\rho \in (0,1)$ fixed, we have

$$\frac{d}{dR} U(\rho R, R) = \rho U'(\rho R, R) + U_R(\rho R, R) \leqslant \Sigma(\rho R, R) < 0.$$

This proves the assertion (3).

(4) Due to (2.3) and the assertion (3), we define

$$\Lambda(\rho) = \lim_{R\to 0^+} U(\rho R, R) \quad \text{for all } \rho \in (0,1);$$

$$\Theta(\rho) = \lim_{R\to \infty} U(\rho R, R) \quad \text{for all } \rho \in (0,1).$$

We assert that $\Lambda(\rho) = \bar{\sigma}$, $\Theta(\rho) = 0$ for all $\rho \in (0, 1)$. Indeed, by using (2.4), we obtain

$$U'(R, R) = \frac{1}{R^{n-1}} \int_0^R f(U(\rho, R))\rho^{n-1} d\rho = R \int_0^1 f(U(\rho R, R))\rho^{n-1} d\rho. \tag{2.18}$$

It follows that

$$\lim_{R \to 0^+} U'(R, R) = 0. \tag{2.19}$$

This further implies, by $(1.6)_2$, that

$$\lim_{R \to 0^+} U(R, R) = \bar{\sigma}. \tag{2.20}$$

Again from (2.4), we have

$$U'(r, R) = r \int_0^1 f(U(r\eta, R))\eta^{n-1} d\eta \leqslant r \int_0^1 f(U(R\eta, R))\eta^{n-1} d\eta, \quad 0 < r \leqslant R.$$

Integrating the above inequality from ρR to R with respect to r (for fixed $0 < \rho < 1$), we get

$$0 \leqslant U(R, R) - U(\rho R, R) \leqslant \frac{R^2(1-\rho^2)}{2} \int_0^1 f(U(R\eta, R))\eta^{n-1} d\eta \leqslant \frac{R^2 f(\bar{\sigma})(1-\rho^2)}{2n}. \tag{2.21}$$

From (2.20) and (2.21) we immediately obtain (2.1). Next, we observe that $\Theta(\rho)$ is increasing in $\rho \in (0, 1)$. From $(1.6)_2$ and (2.18), we have

$$R \int_0^1 f(U(\rho R, R))\rho^{n-1} d\rho + \beta(U(R, R) - \bar{\sigma}) = 0.$$

Dividing both sides of the above equality by R and letting $R \to \infty$ we get

$$\int_0^1 f(\Theta(\rho))\rho^{n-1} d\rho = 0.$$

This implies $\Theta(\rho) = 0$, a.e. $\rho \in (0, 1)$. By monotonicity of $\Theta(\rho)$ we conclude $\Theta(\rho) \equiv 0$ for all $\rho \in (0, 1)$. This proves the assertion (4) and completes the proof of Lemma 2.1. □

Proof of Theorem 1.1. Clearly, given $R_s > 0$, the function $\sigma_s(r) = U(r, R_s)$ solves the equation in $(1.4)_1$ subject to the boundary conditions in $(1.4)_3$. Substituting this expression of $\sigma_s(r)$ into $(1.4)_2$ and integrating it subject to the first boundary condition in $(1.4)_4$, we obtain

Please cite this article in press as: Y. Zhuang, S. Cui, Analysis of a free boundary problem modeling the growth of multicell spheroids with angiogenesis, J. Differential Equations (2018), https://doi.org/10.1016/j.jde.2018.03.005

$$p_s'(r) = -\frac{1}{r^{n-1}} \int_0^r g(U(\rho, R_s)\rho^{n-1} d\rho, \quad 0 < r \leqslant R_s. \tag{2.22}$$

Integrating this equation subject to the second boundary condition in (1.4)$_4$, we see that (1.7) follows. Next, substituting the expression $\sigma_s(r) = U(r, R_s)$ into (2.22) and recalling the definition (1.5) of the function F, we see that (1.4)$_5$ becomes the following equation:

$$F(R_s) = 0.$$

Since

$$\lim_{R\to 0^+} F(R) = (\text{by } (2.1)) \int_0^1 g(\bar{\sigma})\rho^{n-1} d\rho = \frac{1}{n} g(\bar{\sigma}) > 0,$$

$$\lim_{R\to \infty} F(R) = (\text{by } (2.2)) \int_0^1 g(0)\rho^{n-1} d\rho = \frac{1}{n} g(0) < 0,$$

and

$$F'(R) = \int_0^1 g'(U(\rho R, R)) \cdot \frac{d}{dR} U(\rho R, R) d\rho < 0 \text{ (by Assertion (3) of Lemma 2.1)},$$

we conclude that the function F has a unique positive root R_s, which completes the proof. □

Remark 2.1. The following assertions can be easily verified:

(1) There is no radial stationary solution in case $\widetilde{\sigma} \geqslant \bar{\sigma}$.
(2) $\widetilde{\sigma} < \sigma_s(R_s) < \bar{\sigma}$. □

Proof of Theorem 1.2. Clearly, if $R(t)$ is known, then the function

$$\sigma(r, t) = U(r, R(t)), \quad 0 \leqslant r \leqslant R(t), \ \ t \geqslant 0 \tag{2.23}$$

is a solution of the equation (1.8)$_1$ subject to the boundary conditions in (1.8)$_3$. Next, substituting the above expression into (1.8)$_2$ and integrating it subject to the boundary conditions in (1.8)$_4$, we obtain

$$p(r, t) = \frac{\gamma}{R(t)} + \int_r^{R(t)} \int_0^{\eta} g(U(\rho, R(t))\left(\frac{\rho}{\eta}\right)^{n-1} d\rho d\eta, \quad 0 < r \leqslant R(t), \ \ t > 0. \tag{2.24}$$

Finally, substituting the expression (2.23) into (1.8)$_5$, we see that the problem (1.8) reduces into the following initial value problem of an ordinary differential equation for $R(t)$:

Please cite this article in press as: Y. Zhuang, S. Cui, Analysis of a free boundary problem modeling the growth of multicell spheroids with angiogenesis, J. Differential Equations (2018), https://doi.org/10.1016/j.jde.2018.03.005

$$\begin{cases} R'(t) = R(t)F(R(t)), & t > 0, \\ R(0) = R_0. \end{cases}$$

Since $F(R_s) = 0$ and $F'(R) < 0$ for all $R > 0$, by a standard result in the ODE theory we immediately obtain the relation (1.10). From (1.10) and (2.23), (2.24) it is not hard to check that the relations (1.11) and (1.12) are true. This completes the proof of Theorem 1.2. □

3. Proof of Theorem 1.3

In this section we give the proof of Theorem 1.3. Since the proof is similar to those of the corresponding results in existing literatures on this topic (cf. e.g., [13,14]), we only give an outline of the proof and omit most of its details.

Let us first introduce Hanzawa transformation. Let $m \in \mathbb{Z}$, $m \geq 3$, and $0 < \alpha < 1$ be fixed. Given a bounded domain $\Omega_0 \subseteq \mathbb{R}^n$ with $c^{m+\alpha}$-class boundary, we choose a closed C^∞ hypersurface Γ in a small neighborhood of $\partial\Omega_0$ such that for some $\delta > 0$ sufficiently small, $\partial\Omega_0$ is contained in the 4δ-neighborhood of Γ (see [13]). More precisely, denoting by n_Γ the unit outward normal of Γ, we assume that the mapping

$$X : \Gamma \times (-4\delta, 4\delta) \to \mathbb{R}^n, \qquad X(\xi, s) = \xi + s\mathrm{n}_\Gamma(\xi), \tag{3.1}$$

is a C^∞ diffeomorphism from $\Gamma \times (-4\delta, 4\delta)$ onto its image $\mathrm{Im}(X)$, and there exists a function $\eta_0 \in O_\delta$ (see (1.13) for the notation O_δ), such that $\partial\Omega_0$ is the image of the mapping $\xi \mapsto X(\xi, \eta_0(\xi)) = \xi + \eta_0(\xi)\mathrm{n}_\Gamma(\xi)$, $\xi \in \Gamma$. We decompose the inverse of X as $X^{-1} = (P, \Lambda)$, where

$$P \in C^\infty(\mathrm{Im}(X), \Gamma), \qquad \Lambda \in C^\infty(\mathrm{Im}(X), (-4\delta, 4\delta)). \tag{3.2}$$

Note that the identity $y = P(y) + \Lambda(y)\mathrm{n}_\Gamma(P(y))$ holds for all $y \in \mathrm{Im}(X)$. We use the notation D to denote the domain enclosed by the hypersurface Γ.

Next we choose an even function $\chi \in C^\infty(\mathbb{R})$ such that

$$0 \leqslant \chi \leqslant 1; \qquad \chi(t) = \begin{cases} 1, & |t| \leqslant \delta, \\ 0, & |t| \geqslant 3\delta; \end{cases} \qquad -\frac{1}{\delta} \leqslant \chi'(t) \leqslant 0 \text{ for } t \geqslant 0. \tag{3.3}$$

Then the Hanzawa transformation $\Psi_\eta : \mathbb{R}^n \to \mathbb{R}^n$ is defined as follows (cf. [9,10,13–15] for details):

$$\Psi_\eta(y) := \begin{cases} y + \chi(\Lambda(y))\eta(P(y))\mathrm{n}_\Gamma(P(y)), & y \in \mathrm{Im}(X), \\ y, \ y \notin \mathrm{Im}(X). \end{cases} \tag{3.4}$$

As usual, we denote by Ψ_*^η and Ψ_η^* the push-forward and pull-back operators induced by Ψ_η, respectively, i.e.,

$$\Psi_*^\eta u = u \circ \Psi_\eta^{-1}, \text{ for all } u \in C(\overline{D}), \qquad \Psi_\eta^* v = v \circ \Psi_\eta, \text{ for all } v \in C(\overline{\Omega}_\eta). \tag{3.5}$$

We also define

$$A(\eta) = \Psi_\eta^* \circ \triangle \circ \Psi_*^\eta, \qquad B(\eta) = (\Psi_\eta|_{\partial\Omega_\eta})^* \circ \partial_{\mathrm{n}} \circ \Psi_*^\eta, \tag{3.6}$$

where ∂_{n} is the normal derivative mapping from $c^{m+\alpha}(\overline{\Omega}_\eta)$ to $c^{m-1+\alpha}(\partial\Omega_\eta)$. It is known that the following relations hold (cf. [9,10,13–15]):

$$A \in C^\infty(O_\delta, L(c^{m+\alpha}(\overline{D}), c^{m-2+\alpha}(\overline{D}))), \ B \in C^\infty(O_\delta, L(c^{m-2+\alpha}(\overline{D}), c^{m-3+\alpha}(\Gamma))). \tag{3.7}$$

(Note that actually $B \in C^\infty(O_\delta, L(c^{m-k+\alpha}(\overline{D}), c^{m-k-1+\alpha}(\Gamma)))$ for any $0 \leqslant k \leqslant m-1$, but we shall only use the case $k = 2$.) We finally define $K : O_\delta \to c^{m-2+\alpha}(\Gamma)$ as follows:

$$K(\eta)(x) = \text{the mean curvature of the hypersurface } \partial\Omega_\eta \text{ at the point } \Psi_\eta^{-1}(x).$$

It is well-known (cf., e.g., [14,15]) that this is a second-order quasilinear elliptic partial differential operator on the manifold Γ, and it has the following decomposition:

$$K(\eta) = \mathcal{P}(\eta)\eta + \mathcal{Q}(\eta), \tag{3.8}$$

where $\mathcal{P}(\eta)$ is a second-order linear elliptic partial differential operator on Γ (for fixed $\eta \in O_\delta$), $\mathcal{Q}$ is a first-order nonlinear partial differential operator on Γ, and the following relations hold:

$$\mathcal{P} \in C^\infty(O_\delta, L(c^{m+\alpha}(\Gamma), c^{m-2+\alpha}(\Gamma))), \qquad \mathcal{Q} \in C^\infty(O_\delta, c^{m-1+\alpha}(\Gamma)). \tag{3.9}$$

Having introduced the above notations, we can easily deduce that, after performing the Hanzawa transformation, the free boundary problem (1.1) transforms into the following initial boundary value problem on the fixed domain D:

$$\begin{cases} A(\eta)u = f(u) & \text{in } D \times (0,\infty), \\ B(\eta)u + \beta(u - \bar{\sigma}) = 0 & \text{on } \Gamma \times (0,\infty), \\ A(\eta)v = -g(u) & \text{in } D \times (0,\infty), \\ v = \gamma K(\eta) & \text{on } \Gamma \times (0,\infty), \\ \partial_t \eta = -B(\eta)v & \text{on } \Gamma \times (0,\infty), \\ \eta(0) = \eta_0. \end{cases} \tag{3.10}$$

Namely, we have the following preliminary result:

Lemma 3.1. *If (u, v, η) is a solution of the problem (3.10), then by letting*

$$\sigma = \Psi_*^\eta u, \quad p = \Psi_*^\eta v, \quad \Omega(t) = \Omega_{\eta(t)}, \tag{3.11}$$

we obtain a solution (σ, p, Ω) of the problem (1.1), and vice versa. □

Given $\eta \in O_\delta$, we denote by $u = \mathcal{U}(\eta)$ the unique solution of the boundary value problem $(3.10)_1$ and $(3.10)_2$, whose existence and uniqueness can be proved as follows: It is clear that when $\eta \in O_\delta$ is given, the boundary value problem $(3.10)_1$ and $(3.10)_2$ is equivalent to the following boundary value problem:

Please cite this article in press as: Y. Zhuang, S. Cui, Analysis of a free boundary problem modeling the growth of multicell spheroids with angiogenesis, J. Differential Equations (2018), https://doi.org/10.1016/j.jde.2018.03.005

$$\begin{cases} \Delta\sigma = f(\sigma), & x \in \Omega_\eta, \\ \partial_{\mathbf{n}}\sigma = \beta(\bar{\sigma} - \sigma), & x \in \partial\Omega_\eta. \end{cases} \tag{3.12}$$

That is, if u is a solution of the problem $(3.10)_1$ and $(3.10)_2$, then $\sigma = \Psi_*^\eta u$ is a solution of the above problem, and, conversely, if σ is a solution of the above problem then $u = (\Psi_*^\eta)^{-1}\sigma$ is a solution of $(3.10)_1$ and $(3.10)_2$. By a similar argument as in the proof of the assertion (1) of Lemma 2.1, we see that the above problem has a unique solution satisfying the condition $0 \leqslant \sigma \leqslant \bar{\sigma}$. Hence the boundary value problem $(3.10)_1$ and $(3.10)_2$ has a unique solution. Moreover, using some similar argument as in existing literatures (cf., e.g. [10,13,14]), we can prove the following relation:

$$\mathcal{U} \in C^\infty(O_\delta, c^{m+\alpha}(\overline{D})). \tag{3.13}$$

We omit the details here. Next, as in [9], given $\eta \in O_\delta$, we denote by $\mathcal{S}(\eta)$ and $\mathcal{T}(\eta)$ the solution operators of the following problems, respectively:

$$\begin{cases} A(\eta)u = f & \text{in } D, \\ u = 0 & \text{on } \Gamma; \end{cases} \qquad \begin{cases} A(\eta)u = 0 & \text{in } D, \\ u = g & \text{on } \Gamma. \end{cases}$$

Namely, $u = \mathcal{S}(\eta)f$ and $u = \mathcal{T}(\eta)g$ are solutions of the above two problems, respectively. From [9,10,14,15] we know that the following relations hold:

$$\begin{aligned} &\mathcal{S} \in C^\infty(O_\delta, L(c^{m-2+\alpha}(\overline{D}), c^{m+\alpha}(\overline{D}))), \\ &\mathcal{T} \in C^\infty(O_\delta, L(c^{m-k+\alpha}(\Gamma), c^{m-k+\alpha}(\overline{D}))), \quad k = 1, 2. \end{aligned} \tag{3.14}$$

(Note that actually $\mathcal{T} \in C^\infty(O_\delta, L(c^{m-k+\alpha}(\Gamma), c^{m-k+\alpha}(\overline{D})))$ for any $0 \leqslant k \leqslant m-2$ and $\mathcal{T} \in C^\infty(O_\delta, L(c^{j+\alpha}(\Gamma), c^{2+\alpha}(D) \cap c^{j+\alpha}(\overline{D})))$ for $j = 0, 1$, but we shall only use the cases $k = 1, 2$.) It follows that the unique solution of the equation $(3.10)_3$ subject to the boundary value condition $(3.10)_4$ is given by

$$v = -\mathcal{S}(\eta)g(\mathcal{U}(\eta)) + \gamma\mathcal{T}(\eta)K(\eta). \tag{3.15}$$

Now we substitute (3.15) into the equation $(3.10)_5$. It follows that, by letting

$$\mathbb{A}(\eta) = -\gamma B(\eta)\mathcal{T}(\eta)\mathcal{P}(\eta), \quad \mathbb{F}_0(\eta) = B(\eta)\mathcal{S}(\eta)g(\mathcal{U}(\eta)) - \gamma B(\eta)\mathcal{T}(\eta)\mathcal{Q}(\eta),$$

the problem (3.10) reduces into the following initial value problem of an abstract differential equation in the Banach space $c^{m-3+\alpha}(\Gamma)$:

$$\begin{cases} \partial_t\eta = \mathbb{A}(\eta)\eta + \mathbb{F}_0(\eta), & t > 0, \\ \eta(0) = \eta_0. \end{cases} \tag{3.16}$$

We are now ready to give the proof of Theorem 1.3.

Please cite this article in press as: Y. Zhuang, S. Cui, Analysis of a free boundary problem modeling the growth of multicell spheroids with angiogenesis, J. Differential Equations (2018), https://doi.org/10.1016/j.jde.2018.03.005

Proof of Theorem 1.3. From (3.7), (3.9), (3.13), (3.14) and the expressions of $\mathbb{A}(\eta)$ and $\mathbb{F}_0(\eta)$, we see that the following relations hold:

$$\mathbb{A} \in C(O_\delta, L(c^{m+\alpha}(\Gamma), c^{m-3+\alpha}(\Gamma))), \qquad \mathbb{F}_0 \in C^\infty(O_\delta, c^{m-2+\alpha}(\Gamma)).$$

Moreover, from the references [9,10,14,15] we know that for fixed $\eta \in O_\delta$, we have

$$\mathbb{A}(\eta) \in \mathcal{H}(c^{m+\alpha}(\Gamma), c^{m-3+\alpha}(\Gamma)). \tag{3.17}$$

Hence the equation $(3.16)_1$ is a quasilinear parabolic differential equation in the Banach space $c^{m-3+\alpha}(\Gamma)$. It follows by the abstract theory for such equations (cf., e.g., [24]), that for any $\eta_0 \in O_\delta$, there exists corresponding constant $T > 0$ such that the problem (3.16) has a unique solution $\eta \in C([0, T], O_\delta) \cap C^1((0, T], c^{m-3+\alpha}(\Gamma))$. After getting the solution η of the problem (3.16), we let $u = \mathcal{U}(\eta)$ and v be as in (3.15). Then we obtain a solution (u, v, η) of the problem (3.10). By Lemma 3.1, we obtain a unique solution $(\sigma(\cdot, t), p(\cdot, t), \Omega(t))$ defined for $0 \leqslant t \leqslant T$, where σ, p and Ω are given by (3.11). This proves Theorem 1.3. $\square$

4. Proof of Theorem 1.4

In this section we give the proof of Theorem 1.4. As in [10], we use the linearized stability theorem for abstract quasilinear parabolic differential equations in Banach spaces to prove this theorem. To this end, the key step is to compute spectrum of the linearized operator. In what follows we do this job.

It is not hard to check that the linearization of the problem (1.1) at the radial stationary solution $(\sigma_s, p_s, \Omega_s)$ is as follows (see [9,10,31] for similar computation):

$$\begin{cases} \dfrac{\partial^2 \varphi}{\partial r^2} + \dfrac{n-1}{r}\dfrac{\partial \varphi}{\partial r} + \dfrac{1}{r^2}\Delta_\omega \varphi = f'(\sigma_s(r))\varphi, \quad 0 < r < R_s, \ \omega \in \mathbb{S}^{n-1}, \ t > 0, \\ \dfrac{\partial \varphi}{\partial r}\Big|_{r=R_s} + \beta\varphi|_{r=R_s} = -(\beta\sigma_s'(R_s) + \sigma_s''(R_s))\rho, \quad \omega \in \mathbb{S}^{n-1}, \ t > 0, \\ \dfrac{\partial^2 \psi}{\partial r^2} + \dfrac{n-1}{r}\dfrac{\partial \psi}{\partial r} + \dfrac{1}{r^2}\Delta_\omega \psi = -g'(\sigma_s(r))\varphi, \quad 0 < r < R_s, \ \omega \in \mathbb{S}^{n-1}, \ t > 0, \\ \psi|_{r=R_s} + \dfrac{\gamma}{R_s^2}\Big(\rho + \dfrac{1}{n-1}\Delta_\omega \rho\Big) = 0, \quad \omega \in \mathbb{S}^{n-1}, \ t > 0, \\ \partial_t \rho = -\dfrac{\partial \psi}{\partial r}\Big|_{r=R_s} + g(\sigma_s(R_s))\rho, \quad \omega \in \mathbb{S}^{n-1}, \ t > 0, \end{cases} \tag{4.1}$$

where $\varphi = \varphi(r, \omega, t)$, $\psi = \psi(r, \omega, t)$, $\rho = \rho(\omega, t)$.

As in [9,10,31], we use the notation ω to denote a variable in the sphere $\mathbb{S}^{n-1}$. For each $k \in \mathbb{Z}_+ = \{k \in \mathbb{Z} : k \geqslant 0\}$, choose a normalized orthogonal basis (in $L^2(\mathbb{S}^{n-1})$ inner product) of the space of all spherical harmonics of degree k and denote the basis functions as $Y_{k,l}(\omega)$, $l = 1, 2, ..., d_k$, where d_k is the dimension of this space, i.e.,

$$d_0 = 1, \qquad d_1 = n, \quad d_k = \binom{k+n-1}{k} - \binom{k+n-3}{k-2}, \quad k = 2, 3, \cdots. \tag{4.2}$$

The following relations are well-known:

$$\Delta_\omega Y_{k,l}(\omega) = -\lambda_k Y_{k,l}(\omega), \quad \lambda_k = k^2 + (n-2)k, \quad k = 0, 1, 2, \cdots, \tag{4.3}$$

where Δ_ω denotes the Baltrame–Laplacian on the sphere $\mathbb{S}^{n-1}$, or the spherical part of the usual Laplacian Δ on $\mathbb{R}^n$ (neglecting the coefficient $\frac{1}{r^2}$). We then expand φ, ψ, ρ in the following form:

$$\begin{cases} \varphi(r,\omega,t) = \displaystyle\sum_{k=0}^{\infty}\sum_{l=1}^{d_k} u_{k,l}(r,t)Y_{k,l}(\omega), \\ \psi(r,\omega,t) = \displaystyle\sum_{k=0}^{\infty}\sum_{l=1}^{d_k} v_{k,l}(r,t)Y_{k,l}(\omega), \\ \rho(\omega,t) = \displaystyle\sum_{k=0}^{\infty}\sum_{l=1}^{d_k} c_{k,l}(t)Y_{k,l}(\omega). \end{cases} \tag{4.4}$$

Substituting (4.4) into (4.1), using (4.3), and comparing coefficients of each $Y_{k,l}(\omega)$, we get

$$\begin{cases} \dfrac{\partial^2 u_{k,l}}{\partial r^2} + \dfrac{n-1}{r}\dfrac{\partial u_{k,l}}{\partial r} - \dfrac{\lambda_k}{r^2}u_{k,l} = f'(\sigma_s(r))u_{k,l}, \\ \dfrac{\partial u_{k,l}}{\partial r}(R_s,t) + \beta u_{k,l}(R_s,t) = -(\beta\sigma_s'(R_s) + \sigma_s''(R_s))c_{k,l}(t), \\ \dfrac{\partial^2 v_{k,l}}{\partial r^2} + \dfrac{n-1}{r}\dfrac{\partial v_{k,l}}{\partial r} - \dfrac{\lambda_k}{r^2}v_{k,l} = -g'(\sigma_s(r))u_{k,l}, \\ v_{k,l}(R_s,t) = -\dfrac{\gamma}{R_s^2}(1 - \dfrac{\lambda_k}{n-1})c_{k,l}(t), \\ c_{k,l}'(t) = -\dfrac{\partial v_{k,l}}{\partial r}(R_s,t) + g(\sigma_s(R_s))c_{k,l}(t). \end{cases} \tag{4.5}$$

For each $k \in \mathbb{Z}_+$, let $\bar{u}_k$ be the unique solution of the following boundary value problem:

$$\begin{cases} \bar{u}_k''(r) + \dfrac{2k+n-1}{r}\bar{u}_k'(r) = f'(\sigma_s(r))\bar{u}_k(r), \quad 0 < r < R_s, \\ \bar{u}_k(0) = 1, \quad \bar{u}_k'(0) = 0. \end{cases} \tag{4.6}$$

One can easily verify that the solution of the equation $(4.5)_1$ is as follows:

$$u_{k,l}(r,t) = \alpha_{k,l}(t)r^k\bar{u}_k(r), \tag{4.7}$$

where $\alpha_{k,l}(t)$ is the coefficient to be determined. Substituting (4.7) into $(4.5)_2$ we get

$$\alpha_{k,l}(t) = \frac{-(\beta\sigma_s'(R_s) + \sigma_s''(R_s))c_{k,l}(t)}{\beta R_s^k\bar{u}_k(R_s) + kR_s^{k-1}\bar{u}_k(R_s) + R_s^k\bar{u}_k'(R_s)}. \tag{4.8}$$

For each $k \in \mathbb{Z}_+$, let $\bar{v}_k$ be the unique solution of the following boundary value problem:

$$\begin{cases} \bar{v}_k''(r) + \dfrac{2k+n-1}{r}\bar{v}_k'(r) = -g'(\sigma_s(r))\bar{u}_k(r), \quad 0 < r < R_s, \\ \bar{v}_k(0) = 1, \quad \bar{v}_k'(0) = 0. \end{cases} \tag{4.9}$$

Please cite this article in press as: Y. Zhuang, S. Cui, Analysis of a free boundary problem modeling the growth of multicell spheroids with angiogenesis, J. Differential Equations (2018), https://doi.org/10.1016/j.jde.2018.03.005

It is easy to see that the solution of (4.5)$_3$ is given by

$$v_{k,l}(r,t)=\alpha_{k,l}(t)r^k\bar{v}_k(r)+\beta_{k,l}(t)r^k, \tag{4.10}$$

where $\alpha_{k,l}(t)$ is as before, and $\beta_{k,l}(t)$ is the coefficient to be determined. Substituting (4.10) into (4.5)$_4$, we get

$$\beta_{k,l}(t)=\frac{c_{k,l}(t)}{R_s^k}\left[\frac{(\beta\sigma_s'(R_s)+\sigma_s''(R_s))\bar{v}_k(R_s)}{\beta\bar{u}_k(R_s)+kR_s^{-1}\bar{u}_k(R_s)+\bar{u}_k'(R_s)}-\frac{\gamma}{R_s^2}(1-\frac{\lambda_k}{n-1})\right].$$

Hence we have

$$v_{k,l}(r,t)=\frac{r^k}{R_s^k}\left[\frac{-(\beta\sigma_s'(R_s)+\sigma_s''(R_s))(\bar{v}_k(r)-\bar{v}_k(R_s))}{\beta\bar{u}_k(R_s)+kR_s^{-1}\bar{u}_k(R_s)+\bar{u}_k'(R_s)}-\frac{\gamma}{R_s^2}(1-\frac{\lambda_k}{n-1})\right]c_{k,l}(t). \tag{4.11}$$

Substituting this expression into (4.5)$_5$, we see that the system of equations (4.5) reduces into the following equation:

$$c_{k,l}'(t)=a_k(\gamma)c_{k,l}(t) \tag{4.12}$$

$(l=1,2,\cdots,d_k,\ k=1,2,\cdots)$, where

$$a_k(\gamma)\equiv g(\sigma_s(R_s))+\frac{\gamma k(n-1-\lambda_k)}{(n-1)R_s^3}+\frac{(\beta\sigma_s'(R_s)+\sigma_s''(R_s))\bar{v}_k'(R_s)}{\beta\bar{u}_k(R_s)+kR_s^{-1}\bar{u}_k(R_s)+\bar{u}_k'(R_s)} \tag{4.13}$$

$(k=1,2,\cdots)$. We denote

$$\gamma_k=\frac{(n-1)R_s^3}{k(\lambda_k-(n-1))}\left[g(\sigma_s(R_s))+\frac{(\beta\sigma_s'(R_s)+\sigma_s''(R_s))\bar{v}_k'(R_s)}{\beta\bar{u}_k(R_s)+kR_s^{-1}\bar{u}_k(R_s)+\bar{u}_k'(R_s)}\right],\quad k=2,3,\cdots, \tag{4.14}$$

$$c_k=g(\sigma_s(R_s))+\frac{(\beta\sigma_s'(R_s)+\sigma_s''(R_s))\bar{v}_k'(R_s)}{\beta\bar{u}_k(R_s)+kR_s^{-1}\bar{u}_k(R_s)+\bar{u}_k'(R_s)},\quad k=0,1. \tag{4.15}$$

A simple calculation shows that $a_k(\gamma)$ has the following expression:

$$\begin{cases} a_0(\gamma)=c_0, & \forall\gamma>0,\\ a_1(\gamma)=c_1, & \forall\gamma>0,\\ a_k(\gamma)=\dfrac{k(n-1-\lambda_k)}{(n-1)R_s^3}(\gamma-\gamma_k), & k=2,3,\cdots. \end{cases} \tag{4.16}$$

Lemma 4.1. $c_0<0$, *and* $c_1=0$.

Proof. First we note that $\bar{u}_k(r) > 0$, $\bar{u}_k'(r) > 0$ for all $r > 0$, $k \in \mathbb{Z}_+$, and $\sigma_s(r) > 0$, $\sigma_s'(r) > 0$, $\sigma_s''(r) > 0$ for $0 < r \leqslant R_s$, by a similar argument as in the proof in Lemma 2.1. Next we note that by integration by parts we have

$$g(\sigma_s(R_s)) = \frac{1}{R_s^n} \int_0^{R_s} g'(\sigma_s(r))\sigma_s'(r) r^n \, dr, \tag{4.17}$$

and from (4.9) we have

$$\bar{v}_k'(r) = \frac{-1}{r^{2k+(n-1)}} \int_0^r g'(\sigma_s(\rho))\bar{u}_k(\rho)\rho^{2k+(n-1)} \, d\rho. \tag{4.18}$$

In order to prove $c_0 < 0$, we first prove the following relation:

$$\frac{\sigma_s'(R_s)}{\sigma_s''(R_s)} < \frac{\bar{u}_0(R_s)}{\bar{u}_0'(R_s)}. \tag{4.19}$$

Let $\Psi(r) = \frac{\sigma_s''(r)}{\sigma_s'(r)}$ $(0 < r \leqslant R_s)$ and $\Phi(r) = \frac{\bar{u}_0'(r)}{\bar{u}_0(r)}$ $(0 \leqslant r \leqslant R_s)$. Differentiating $(1.4)_1$, we get

$$\sigma_s'''(r) + \frac{n-1}{r}\sigma_s''(r) - \frac{n-1}{r^2}\sigma_s'(r) = f'(\sigma_s(r))\sigma_s'(r), \quad 0 < r < R_s. \tag{4.20}$$

From this relation we easily get

$$\Psi'(r) + \frac{n-1}{r}\Psi(r) + \Psi^2(r) = f'(\sigma_s(r)) + \frac{n-1}{r^2}, \quad 0 < r < R_s.$$

From $(4.6)_1$ (choosing $k = 0$) we get

$$\Phi'(r) + \frac{n-1}{r}\Phi(r) + \Phi^2(r) = f'(\sigma_s(r)), \quad 0 < r < R_s.$$

Hence we have:

$$[\Psi(r) - \Phi(r)]' + \Big(\frac{n-1}{r} + \Psi(r) - \Phi(r)\Big)[\Psi(r) - \Phi(r)] > 0, \quad 0 < r < R_s.$$

Since $\lim_{r \to 0^+} \Psi(r) = +\infty$ and $\Phi(0) = 0$, from the above inequality we immediately obtain $\Psi(r) > \Phi(r)$ for all $0 < r \leqslant R_s$, by which (4.19) follows. Next we prove the following relation:

$$\frac{\sigma_s'(r)}{\beta\sigma_s'(R_s) + \sigma_s''(R_s)} < \frac{\bar{u}_0(r)}{\beta\bar{u}_0(R_s) + \bar{u}_0'(R_s)}, \quad 0 < r < R_s. \tag{4.21}$$

Let $W(r) = \frac{\sigma_s'(r)}{\beta\sigma_s'(R_s)+\sigma_s''(R_s)}$, $V(r) = \frac{\bar{u}_0(r)}{\beta\bar{u}_0(R_s)+\bar{u}_0'(R_s)}$, $0 \leqslant r \leqslant R_s$. It is clear that $W(0) < V(0)$, and, by (4.19), we also have $W(R_s) < V(R_s)$. From (4.20) and $(4.6)_1$ for $k = 0$ we infer that $LW(r) < LV(r)$ for $0 < r < R_s$, where L is the following second-order differential operator:

Please cite this article in press as: Y. Zhuang, S. Cui, Analysis of a free boundary problem modeling the growth of multicell spheroids with angiogenesis, J. Differential Equations (2018), https://doi.org/10.1016/j.jde.2018.03.005

$$Lu(r) = -u''(r) - \frac{n-1}{r}u'(r) + f'(\sigma_s(r))u(r), \quad 0 < r < R_s.$$

Hence, by the maximum principle it follows that $W(r) < V(r)$, $0 \leqslant r \leqslant R_s$. This proves (4.21). Now the assertion $c_0 < 0$ follows from (4.17), (4.18), (4.21) and a simple computation as follows:

$$\begin{aligned}
c_0 &= g(\sigma_s(R_s)) + \frac{(\beta\sigma_s'(R_s) + \sigma_s''(R_s))\bar{v}_0'(R_s)}{\beta\bar{u}_0(R_s) + \bar{u}_0'(R_s)} \\
&= \frac{1}{R_s^n}\int_0^{R_s} g'(\sigma_s(r))\sigma_s'(r)r^n dr - \frac{\beta\sigma_s'(R_s) + \sigma_s''(R_s)}{\beta\bar{u}_0(R_s) + \bar{u}_0'(R_s)}\frac{1}{R_s^{n-1}}\int_0^{R_s} g'(\sigma_s(r))\bar{u}_0(r)r^{n-1}dr \\
&= \frac{\beta\sigma_s'(R_s) + \sigma_s''(R_s)}{R_s^{n-1}}\int_0^{R_s} g'(\sigma_s(r))\Big[\frac{r}{R_s}\frac{\sigma_s'(r)}{\beta\sigma_s'(R_s) + \sigma_s''(R_s)} - \frac{\bar{u}_0(r)}{\beta\bar{u}_0(R_s) + \bar{u}_0'(R_s)}\Big]r^{n-1}dr \\
&< 0.
\end{aligned}$$

In order to prove $c_1 = 0$, we first note that a simple computation shows that the following relation holds:

$$\sigma_s'(r) = \frac{1}{n}f(\sigma_s(0))r\bar{u}_1(r), \quad 0 \leqslant r \leqslant R_s. \tag{4.22}$$

Using this relation we have

$$\beta\sigma_s'(R_s) + \sigma_s''(R_s) = \frac{1}{n}f(\sigma_s(0))R_s\Big[\beta\bar{u}_1(R_s) + R_s^{-1}\bar{u}_1(R_s) + \bar{u}_1'(R_s)\Big]. \tag{4.23}$$

Moreover, from (4.17), (4.18) and (4.22) we have

$$\bar{v}_1'(R_s) = -\frac{1}{R_s^{n+1}}\int_0^{R_s} g'(\sigma_s(r))\bar{u}_1(r)r^{n+1}dr = -\frac{ng(\sigma_s(R_s))}{f(\sigma_s(0))R_s}. \tag{4.24}$$

Recalling the definition (4.15) (taking $k = 1$) of c_1, we see that $c_1 = 0$ by (4.23) and (4.24). This completes the proof of Lemma 4.1. □

Lemma 4.2. *$\gamma_k > 0$ for sufficiently large k, and*

$$\gamma_k \sim Mk^{-3} \quad as\ k \to \infty, \tag{4.25}$$

where $M = (n-1)R_s^3 g(\sigma_s(R_s)) > 0$, so that $\lim_{k\to\infty}\gamma_k = 0$.

Proof. Since $\sigma_s(R_s) > \widetilde{\sigma}$, we have $g(\sigma_s(R_s)) > 0$. By (4.18) and the fact that $\bar{u}_k(r) < \bar{u}_k(R_s)$ (for $0 \leqslant r < R_s$), we have

$$\left|\bar{v}_k'(R_s)\right| \leqslant \bar{u}_k(R_s)\int_0^{R_s} g'(\sigma_s(r))dr \equiv C\bar{u}_k(R_s), \quad k=2,3,\cdots.$$

Thus

$$\begin{aligned}\left|\frac{\bar{v}_k'(R_s)}{\beta\bar{u}_k(R_s)+kR_s^{-1}\bar{u}_k(R_s)+\bar{u}_k'(R_s)}\right| &\leqslant \frac{C\bar{u}_k(R_s)}{\beta\bar{u}_k(R_s)+kR_s^{-1}\bar{u}_k(R_s)} \\ &= \frac{C}{\beta+kR_s^{-1}} \to 0 \ (\text{as } k\to\infty).\end{aligned}$$

Using this fact and recalling the definition of γ_k and the relation $\lambda_k = k^2 + (n-1)k$, $k = 0, 1, 2, \cdots$, we can easily obtain (4.25). This proves the lemma. □

We now define

$$\gamma_* = \max_{k\geqslant 2}\gamma_k.$$

It is clear that $\gamma_* > 0$. Recalling the definition of $a_k(\gamma)$ (see (4.16)), we immediately have the following corollary:

Corollary 4.3. *For any $\gamma > 0$ we have the following relation:*

$$a_k(\gamma) = -\frac{\gamma k^3}{(n-1)R_s^3}\left[1+O\left(\frac{1}{k}\right)\right] \ \text{as } k\to\infty.$$

Moreover, the following assertions hold:

(1) *If $\gamma > \gamma_*$ then $a_k(\gamma) < 0$, $k = 2, 3, \cdots$;*
(2) *If $0 < \gamma < \gamma_*$ then there exists an integer $k_0 \geqslant 2$ such that $a_{k_0}(\gamma) > 0$.* □

We introduce an operator $\mathscr{L} : c^{m+\alpha}(\mathbb{S}^{n-1}) \to c^{m-3+\alpha}(\mathbb{S}^{n-1})$ as follows: Given $\rho \in c^{m+\alpha}(\mathbb{S}^{n-1})$, we substitute it into the equations in the first four lines of (4.1) (so that the variable t does not appear here). Solving the equation $(4.1)_1$ subject to the boundary condition $(4.1)_2$, we get a function $\varphi \in c^{m+\alpha}(\overline{\Omega}_s)$. Substituting this function into the equation $(4.1)_3$ and solving it subject to the boundary condition $(4.1)_4$, we obtain a function $\psi \in C^{m-2+\alpha}(\overline{\Omega}_s)$. We now define $\mathscr{L}\rho$ to be the function in the right-hand side of $(4.1)_5$, i.e.,

$$\mathscr{L}\rho(\omega) = -\frac{\partial\psi}{\partial r}(R_s,\omega) + g(\sigma_s(R_s))\rho(\omega), \quad \omega\in\mathbb{S}^{n-1}.$$

It is easy to see that $\mathscr{L} \in L(c^{m+\alpha}(\mathbb{S}^{n-1}), c^{m-3+\alpha}(\mathbb{S}^{n-1}))$, and the problem (4.1) reduces into the following equation:

$$\partial_t\rho = \mathscr{L}\rho. \tag{4.26}$$

Please cite this article in press as: Y. Zhuang, S. Cui, Analysis of a free boundary problem modeling the growth of multicell spheroids with angiogenesis, J. Differential Equations (2018), https://doi.org/10.1016/j.jde.2018.03.005

From the above definition of the operator $\mathscr{L}$ and the computation performed before (see (4.12)), we immediately have the following preliminary result:

Lemma 4.4. *The operator $\mathscr{L}$ is a Fourier multiplier in the sense that it has the following expression: For $\rho \in C^\infty(\mathbb{S}^{n-1})$, if $\rho(\omega) = \sum_{k=0}^{\infty}\sum_{l=1}^{d_k} c_{k,l}Y_{k,l}(\omega)$ then*

$$\mathscr{L}\rho(\omega) = \sum_{k=0}^{\infty}\sum_{l=1}^{d_k} a_k(\gamma)c_{k,l}Y_{k,l}(\omega).$$

Consequently, we have

$$\sigma(\mathscr{L}) = \sigma_p(\mathscr{L}) = \{a_k(\gamma) : k = 2, 3, ...\} \cup \{0, c_0\}. \quad \square$$

Remark. By using Corollary 4.3 and Lemma 4.4, we can easily prove that the operator $\mathscr{L}$ generates a strongly continuous analytic semigroup $e^{t\mathscr{L}}$ $(t \geqslant 0)$ in the Sobolev space $H^s(\mathbb{S}^{n-1})$ for any $s \geqslant 0$ (regarding $\mathscr{L}$ as a densely defined closed linear operator in this space with domain $H^{s+3}(\mathbb{S}^{n-1})$). It follows that for any $\rho_0 \in H^s(\mathbb{S}^{n-1})$, the linear differential equation (4.26) has a unique mild solution $\rho(t) = e^{t\mathscr{L}}\rho_0$ $(t \geqslant 0)$ satisfying the initial condition $\rho(0) = \rho_0$. It is easy to see that for fixed $t \geqslant 0$, the operator $e^{t\mathscr{L}}$ is also a Fourier multiplier, having the following expression: For $\rho_0 \in H^s(\mathbb{S}^{n-1})$, if $\rho_0(\omega) = \sum_{k=0}^{\infty}\sum_{l=1}^{d_k} c_{k,l}Y_{k,l}(\omega)$ then

$$e^{t\mathscr{L}}\rho_0(\omega) = \sum_{k=0}^{\infty}\sum_{l=1}^{d_k} e^{ta_k(\gamma)}c_{k,l}Y_{k,l}(\omega).$$

From this expression, by using Lemma 4.1 and Corollary 4.3 we see that if $\gamma > \gamma_*$ then

$$\lim_{t\to\infty} e^{t\mathscr{L}}\rho_0(\omega) = \sum_{l=1}^{n} c_{1,l}Y_{1,l}(\omega) \text{ in } H^s(\mathbb{S}^{n-1}),$$

which means that the trivial solution is asymptotically stable module the n-dimensional subspace span$\{Y_{1,l}, Y_{1,2}, \cdots, Y_{1,n}\}$, whereas if $\gamma < \gamma_*$ then there exists nonzero $\rho_0 \in C^\infty(\mathbb{S}^{n-1})$ such that $e^{t\mathscr{L}}\rho_0 = e^{ta(\gamma)}\rho_0$ for some positive constant $a(\gamma)$, which goes to ∞ as $t \to \infty$, so that the trivial solution is unstable. In the following, however, we shall not use this result.

We are now ready to give the proof of Theorem 1.4.

Proof of Theorem 1.4. The proof follows a similar procedure as that used in the proof of Theorem 1.2 of [10], but with modification in the center manifold argument: Unlike [10] where some arguments of [15] are followed, here we directly use Theorem 2.1 of [7] (see also Theorem 3.4 of [8]). We divide the proof into four steps.

Step 1: For Ω_0 sufficiently closed to Ω_s, we perform the Hanzawa transformation to transform the free boundary problem (1.1) into an initial boundary value problem in the fixed domain Ω_s.

This follows from a similar argument as that in §3, but replacing the hypersurface Γ used in §3 with the sphere Γ_s and, accordingly, replacing the set O_δ appearing in §3 with the set O_δ^s given by (1.14). The transformed problem has a similar form as (3.10), but with D and Γ replaced with Ω_s and Γ_s, respectively.

Step 2: Next, as in the paragraph following Lemma 3.1, for given $\eta \in O_\delta^s$ we solve the elliptic boundary value problem $(3.10)_1$–$(3.10)_4$ (with D and Γ replaced by Ω_s and Γ_s, respectively), and get v in the form of (3.15) (operators appearing there should be accordingly modified). Substituting this v into $(3.10)_5$ we finally reduce the problem $(3.10)_1$–$(3.10)_4$ (with D and Γ replaced by Ω_s and Γ_s, respectively) into an initial value problem in the Banach space $c^{m+\alpha}(\Gamma_s)$ which has a similar form as (3.16). To save spaces we do not write this reduced problem here, and in what follows we use (3.16) to pretend it.

Step 3: We denote by π^* and π_* the pull-back and push-forward operators induced by natural projection π from Γ_s onto $\mathbb{S}^{n-1}$, respectively, i.e., for $u \in C(\mathbb{S}^{n-1})$ and $v \in C(\Gamma_s)$,

$$
\begin{aligned}
(\pi^* u)(\xi) &= u(\pi(\xi)) = u(\xi/|\xi|), \quad \xi \in \Gamma_s,\\
(\pi_* v)(\omega) &= v(\pi^{-1}(\omega)) = v(R_s\omega)), \quad \omega \in \mathbb{S}^{n-1},
\end{aligned}
$$

and define an operator $\mathcal{A} : \pi_*(O_\delta^s) \to c^{m-3+\alpha}(\mathbb{S}^{n-1})$ as follows:

$$\mathcal{A}(\rho) = \pi_*[\mathbb{A}(\eta)\eta + \mathbb{F}_0(\eta)], \quad \forall \rho \in \pi_*(O_\delta^s),$$

where $\eta = \pi_*^{-1}(\rho)$. For η and η_0 appearing in (3.16), let $\rho = \pi_*\eta$, $\rho_0 = \pi_*\eta_0$. It follows that the problem (3.16) can be rewritten into the following equivalent initial value problem in the Banach space $c^{m-3+\alpha}(\mathbb{S}^{n-1})$:

$$
\begin{cases}
\partial_t \rho = \mathcal{A}(\rho), & \text{on } \mathbb{S}^{n-1} \times (0, \infty)\\
\rho(0) = \rho_0.
\end{cases}
\tag{4.27}
$$

Step 4: Since the linearization of the problem (1.1) at the stationary solution $(\sigma_s, p_s, \Omega_s)$ is the problem (4.1), it follows that the linearization of the equation $(4.27)_1$ at the stationary solution $\rho = 0$ is the equation (4.26). This means that the following relation holds:

$$\mathcal{A}'(0) = \mathscr{L}. \tag{4.28}$$

Now we first assume that $\gamma > \gamma_*$. From the above relation and Lemma 4.4 we see that

$$\omega_- := -\sup\{\mathrm{Re}\lambda : \lambda \in \sigma(\mathcal{A}'(0))\backslash\{0\}\} > 0.$$

Moreover, it is clear that $\dim\mathrm{Ker}\mathcal{A}'(0) = n$. Besides, by a similar argument as that in [7], we see that the equation (4.27) is quasi-invariant under the Lie group action $(\mathbb{G}, p)$ as introduced in [7], and the assumptions $(B1)$-$(B4)$ of Theorem 2.1 in [7] are all satisfied. Hence, by using Theorem 2.1 of [7], we conclude that there exist constant $C > 0$ and $c > 0$ such that for any $\rho_0 \in \pi_*(O_\delta^s)$ with $\|\rho_0\|_{C^{m+\alpha}(\mathbb{S}^{n-1})}$ sufficiently small, the solution $\rho = \rho(t)$ of the problem (4.27) is global, and there exists corresponding $x_0 \in \mathbb{R}^n$ such that the following relation holds:

$$\|\rho(t) - \rho_s^{[x_0]}\|_{C^{m+\alpha}(\mathbb{S}^{n-1})} \leqslant Ce^{-ct} \quad \text{for } t \geqslant 0,$$

where $\rho_s^{[x_0]} = \pi_* \eta_s^{[x_0]}$ (see the statement of Theorem 1.4 for the notation $\eta_s^{[x_0]}$). From this result, one sees easily that the assertion (1) of Theorem 1.4 holds. Next we assume that $0 < \gamma < \gamma_*$. In this case, from the assertion (2) of Corollary 4.3, Lemma 4.4 and the relation (4.28) we see that

$$\sigma(\mathcal{A}'(0)) \cap \{z \in \mathbb{C} : \operatorname{Re} z > 0\} \neq \emptyset.$$

Hence, by using a standard result in the theory of parabolic differential equations in Banach spaces (cf. Theorem 9.1.3 of [24]) we infer that the trivial solution of (4.27) is unstable. Returning to the problem (1.1) we conclude that the radial stationary solution of it is unstable. The proof is complete. □

References

[1] J. Adam, N. Bellomo, A Survey of Models for Tumor-Immune System Dynamics, Birkhäuser, Boston, 1997.
[2] R.P. Araujo, D.L. McElwain, A history of the study of solid tumor growth: the contribution of mathematical modeling, Bull. Math. Biol. 66 (2004) 1039–1091.
[3] H.M. Byrne, M.A.J. Chaplain, Growth of nonnecrotic tumors in the presence and absence of inhibitors, Math. Biosci. 130 (1995) 151–181.
[4] H.M. Byrne, M.A.J. Chaplain, Growth of necrotic tumors in the presence and absence of inhibitors, Math. Biosci. 135 (1996) 187–216.
[5] S. Cui, Analysis of a mathematical model for the growth of tumors under the action of external inhibitors, J. Math. Biol. 44 (2002) 395–426.
[6] S. Cui, Analysis of a free boundary problem modelling tumor growth, Acta Math. Sin. Engl. Ser. 21 (2005) 1071–1083.
[7] S. Cui, Lie group action and stability analysis of stationary solutions for a free boundary problem modelling tumor growth, J. Differential Equations 246 (2009) 1845–1882.
[8] S. Cui, Linearized stability theorem for invariant and quasi-invariant parabolic differential equations in Banach manifolds with applications to free boundary problems, preprint, arXiv:1606.09393.
[9] S. Cui, J. Escher, Bifurcation analysis of an elliptic free boundary problem modelling the growth of avascular tumors, SIAM J. Math. Anal. 39 (2007) 210–235.
[10] S. Cui, J. Escher, Asymptotic behavior of solutions of multidimensional moving boundary problem modeling tumor growth, Comm. Partial Differential Equations 33 (2008) 636–655.
[11] S. Cui, A. Friedman, A free boundary problem for a singular system of differential equations: an application to a model of tumor growth, Trans. Amer. Math. Soc. 355 (9) (2003) 3537–3590.
[12] S. Cui, S. Xu, Analysis of mathematical models for the growth of tumors with time delays in cell proliferation, J. Math. Anal. Appl. 336 (2007) 523–541.
[13] J. Escher, Classical solutions to a moving boundary problem for an elliptic-parabolic system, Interfaces Free Bound. 6 (2004) 175–193.
[14] J. Escher, G. Simonett, Classical solutions of multidimensional Hele-Shaw models, SIAM J. Math. Anal. 28 (1997) 1028–1047.
[15] J. Escher, G. Simonett, A centre manifold analysis for the Mullins-Sekerka model, J. Differential Equations 143 (1998) 267–292.
[16] A. Friedman, Mathematical analysis and challenges arising from models of tumor growth, Math. Models Methods Appl. Sci. 17 (Suppl.) (2007) 1751–1772.
[17] A. Friedman, B. Hu, Asymptotic stability for a free boundary problem arising in a tumor model, J. Differential Equations 227 (2006) 598–639.
[18] A. Friedman, B. Hu, Bifurcation for a free boundary problem modeling tumor growth by Stokes equation, SIAM J. Math. Anal. 39 (2007) 174–194.
[19] A. Friedman, K.Y. Lam, Analysis of a free-boundary tumor model with angiogenesis, J. Differential Equations 259 (2015) 7636–7661.
[20] A. Friedman, F. Reitich, Analysis of a mathematical model for the growth of tumors, J. Math. Biol. 38 (1999) 262–284.
[21] A. Friedman, F. Reitich, Symmetry-breaking bifurcation of analytic solutions to free boundary problems, Trans. Amer. Math. Soc. 353 (2000) 1587–1634.

Please cite this article in press as: Y. Zhuang, S. Cui, Analysis of a free boundary problem modeling the growth of multicell spheroids with angiogenesis, J. Differential Equations (2018), https://doi.org/10.1016/j.jde.2018.03.005

[22] H.P. Greenspan, Models for the growth of solid tumor by diffusion, Stud. Appl. Math. 51 (1972) 317–340.

[23] H.P. Greenspan, On the growth and stability of cell cultures and solid tumors, J. Theoret. Biol. 56 (1976) 229–242.

[24] A. Lunardi, Analytic Semigroups and Optimal Regularity in Parabolic Problems, Birkhäuser, Basel, 1995.

[25] J. Wu, Analysis of a mathematical model for tumor growth with Gibbs–Thomson relation, J. Math. Anal. Appl. 450 (2017) 532–543.

[26] J. Wu, S. Cui, Asymptotic stability of stationary solutions of a free boundary problem modelling the growth of tumours with fluid tissues, SIAM J. Math. Anal. 41 (2009) 391–414.

[27] J. Wu, F. Zhou, Asymptotic behavior of solutions of a free boundary problem modeling the growth of tumors with fluid-like tissue under the action of inhibitors, Trans. Amer. Math. Soc. 365 (2013) 4181–4207.

[28] J. Wu, F. Zhou, Asymptotic behavior of solutions of a free boundary problem modeling tumor spheroid with Gibbs–Thomson relation, J. Differential Equations 262 (2017) 4907–4930.

[29] S. Xu, Analysis of a free boundary problem for avascular tumor growth with a periodic supply of nutrients, Discrete Contin. Dyn. Syst. Ser. B 21 (2016) 997–1008.

[30] F. Zhou, J. Wu, Stability and bifurcation analysis of a free boundary problem modeling multi-layer tumors with Gibbs–Thomson relation, European J. Appl. Math. 26 (2015) 401–425.

[31] Y. Zhuang, Asymptotic behavior of solutions of a free-boundary tumor model with angiogenesis, submitted for publication.

Please cite this article in press as: Y. Zhuang, S. Cui, Analysis of a free boundary problem modeling the growth of multicell spheroids with angiogenesis, J. Differential Equations (2018), https://doi.org/10.1016/j.jde.2018.03.005