Bifurcation for a free boundary problem modeling the growth of a tumor with a necrotic core

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Abstract

We consider a free boundary problem for a system of partial differential equations, which arises in a model of tumor growth with a necrotic core. For any positive numbers $\rho < R$, there exists a radially symmetric stationary solution with tumor boundary $r = R$ and necrotic core boundary $r = \rho$. The system depends on a positive parameter μ, which describes the tumor aggressiveness. There also exists a sequence of values $\mu_2 < \mu_3 < \cdots$ for which branches of symmetry-breaking stationary solutions bifurcate from the radially symmetric solution branch.

Keywords: Bifurcation, free boundary problem, tumor model, necrotic core

Introduction

Tumor growth models are challenging both theoretically and numerically. They are free boundary problems where the changing shape of the tumor is of prime importance. Spherical solutions are often straightforward to compute, but values of the controlling parameter, called the tumor-aggressiveness factor, where bifurcations occur are nontrivial to compute. Moreover, analytically finding nonspherical solutions on a branch far from a spherical solution is intractable. Another difficult and important question is to determine the linear stability of the solution branches.

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In this article, we analyze a highly nontrivial tumor growth model. The paper is organized into five sections. In §1, we discuss tumor models and explicitly set up the system of differential equations controlling tumor growth for the necrotic core model. In §2, we derive an analytical formula for the radially symmetric stationary solutions. In §3, we establish the existence of bifurcation branches from radially symmetric stationary, explicitly provide the formula describing where the bifurcation branches occur, and study the bifurcation diagram. In §4, we derive the linearized system and determine linear stability in a small neighborhood of the bifurcation at μ_2.

1. The model

Mathematical models of solid tumor growth, which consider the tumor tissue as a density of proliferating cells, have been developed and studied in many papers; see [1; 2; 3; 4; 5; 7; 9; 10; 11; 13; 14; 16; 17; 18; 19; 20] and the references provided therein. The case of radially symmetric tumors have been discussed extensively.

Tumors grown in vitro have a nearly spherical shape, but tumors grown in vivo may develop different kinds of protrusions. It is therefore interesting to explore the existence of non-spherical solutions of tumor models.

If dead cells are not removed in an efficient manner from the tumor, they accumulate inside to form a necrotic core [7] and [9]. A necrotic tumor growth model consists of a core of necrotic cells and shell adjacent to this necrotic core of proliferating cells. In particular, let $\Omega(t)$ denote the tumor domain at time t, and $D(t) \subset \Omega(t)$ be the necrotic core within the tumor domain.

Let p be the pressure within the tumor resulting from proliferation of the tumor cells. The density of the cells, c, depends on the concentration of nutrients, σ, and, assuming that this dependence is linear, we simply identify c with σ. We also assume the proliferation rate, S, depends linearly upon σ in the living tumor region. That is,

$$S = \mu(\sigma - \widetilde{\sigma}) \quad \text{in } \Omega(t) \setminus D(t),$$

where $\widetilde{\sigma} > 0$ is a threshold concentration and μ is a positive parameter measuring the aggressiveness of the tumor. This equation represents the balance of the growth of the tumor by cell division and the contraction of the tumor by necrosis. The linear approximation $\mu(\sigma - \widetilde{\sigma})$ used here is the result of first order Taylor expansion for the fully nonlinear model.

We assume that there is no proliferation in the necrotic core, i.e, $S = 0$ in $D(t)$. Combining these two equations, we have

$$S = \mu(\sigma - \widetilde{\sigma})\chi_{\{\Omega(t)\setminus D(t)\}}(x) \quad \text{in } \Omega(t), \tag{1}$$

where $\chi_{\{\Omega(t)\setminus D(t)\}}(x)$ is the indicator function of $\Omega(t) \setminus D(t)$.

If we assume that necrotic cells do not consume nutrients and the consumption rate of nutrients by the living tumor cells is proportional to the concentration of the nutrients, then after normalization, σ satisfies

$$\sigma_t - \Delta\sigma = -\sigma\chi_{\{\Omega(t)\setminus D(t)\}}(x) \quad \text{in } \Omega(t) \text{ and } \sigma = 1 \quad \text{on } \partial\Omega(t). \tag{2}$$

Additionally, if we assume that the density of cells in the necrotic core remains constant, we have $\sigma = \underline{\sigma}$ in $D(t)$.

Most tumor models assume that the tissue has the structure of a porous medium so that Darcy's law holds. In particular, $\vec{v} = -\nabla p$ where $\vec{v}$ is the velocity of the cells and p is the pressure. By conservation of mass, div $\vec{v} = S = \mu(\sigma - \widetilde{\sigma})\chi_{\{\Omega(t)\setminus D(t)\}}(x)$ and thus $\Delta p = -\mu(\sigma - \widetilde{\sigma})\chi_{\{\Omega(t)\setminus D(t)\}}(x)$ in $\Omega(t)$ As in [6], the cell-to-cell adhesiveness condition at the tumor boundary is represented by $p = \kappa$ on $\partial\Omega(t)$. To simplify notation, let $\chi(x,t) = \chi_{\{\Omega(t)\setminus D(t)\}}(x)$. The necrotic core system is

$$\begin{cases} \sigma_t - \Delta\sigma = -\sigma\chi(x,t) \text{ and } -\Delta p = \mu(\sigma - \widetilde{\sigma})\chi(x,t) & \text{in } \Omega(t), \\ \sigma = \underline{\sigma} & \text{in } D(t), \\ \sigma = 1; \ \ p = \kappa; \ \text{ and } \ \frac{\partial p}{\partial n} = -V_n & \text{on } \partial\Omega(t), \end{cases} \tag{3}$$

where n denotes the exterior normal vector. Additionally, it is reasonable to assume $\underline{\sigma} < \widetilde{\sigma} < 1$.

An important question is the existence and stability of steady-state solutions. Biologically, a stable steady-state solution means that the tumor can remain inside a patient for a long time without causing much trouble. An unstable tumor is a tumor that is very likely to spread beyond the region it occupies. The steady-state necrotic core tumor model is

$$\Delta\sigma = \sigma\chi(x) \quad \text{in } \Omega, \tag{4}$$
$$-\Delta p = \mu(\sigma - \widetilde{\sigma})\chi(x) \quad \text{in } \Omega, \tag{5}$$
$$\sigma = \underline{\sigma} \quad \text{in } D, \tag{6}$$
$$\sigma = 1 \quad \text{on } \partial\Omega, \tag{7}$$
$$p = \kappa \quad \text{on } \partial\Omega, \tag{8}$$
$$\frac{\partial p}{\partial n} = 0 \quad \text{on } \partial\Omega. \tag{9}$$

2. Radially symmetric stationary solutions

We recall some basic formulas for the modified bessel functions $K_n(x)$ and $I_n(x)$. These functions form a fundamental solution set of $x^2y'' + xy' - (x^2 + n^2)y = 0$. In particular,

$$I_{n+1}(x) = I_{n-1}(x) - \frac{2n}{x}I_n(x), \ K_{n+1} = K_{n-1}(x) + \frac{2n}{x}K_n(x), \ n \geq 1, \tag{1}$$
$$I_n'(x) = \frac{1}{2}[I_{n-1}(x) + I_{n+1}(x)], \ K_n'(x) = -\frac{1}{2}[K_{n-1}(x) + K_{n+1}(x)], \ n \geq 1, \tag{2}$$
$$I_n'(x) = I_{n-1}(x) - \frac{n}{x}I_n(x), \qquad K_n'(x) = -K_{n-1}(x) - \frac{n}{x}K_n(x), \ n \geq 1, \tag{3}$$
$$I_n'(x) = \frac{n}{x}I_n(x) + I_{n+1}(x), \qquad K_n'(x) = \frac{n}{x}K_n(x) - K_{n+1}(x), \ n \geq 0. \tag{4}$$

Additionally,

$$I_n'(x) > 0 \quad \text{and} \quad K_n'(x) < 0. \tag{5}$$

In this paper, we will only consider the case of two space dimensions. The 3-dimensional case can be considered in a similar manner, except that the formula are more complicated.

Solving (4) with the boundary conditions (6) and (7), we obtain

$$\sigma_s(r) = \frac{(-\underline{\sigma}K_0(R) + K_0(\rho))I_0(r) - (I_0(\rho) - \underline{\sigma}I_0(R))K_0(r)}{-I_0(\rho)K_0(R) + I_0(R)K_0(\rho)} \qquad \rho < r < R; \tag{6}$$

Solving (5), we obtain

$$p_s(r) = \frac{1}{4}\mu\widetilde{\sigma}r^2 + c_1(R,\rho)\ln r + c_2(R,\rho) - \mu\sigma_s(r) \qquad \rho < r < R; \tag{7}$$

where $c_1(R,\rho)$ and $c_2(R,\rho)$ are constants to be determined. The boundary conditions (8) and (9) imply that

$$p_s(R) = \frac{1}{R}, \qquad \frac{\partial p_s}{\partial r}(R) = 0, \tag{8}$$

and (5) implies that p_s is a constant with the necrotic core. Since the first order derivative of p_s and σ_s are continuous across the boundary of necrotic core,

$$\frac{\partial p_s}{\partial r}(\rho) = 0 \quad \text{and} \quad \frac{\partial \sigma_s}{\partial r}(\rho) = 0. \tag{9}$$

Substituting (7) into (8) and (9), we have

$$\frac{1}{4}\mu\widetilde{\sigma}R^2 + c_1(R,\rho)\ln R + c_2(R,\rho) - \mu = \frac{1}{R}, \tag{10}$$

$$\frac{1}{2}\mu\widetilde{\sigma}R + c_1(R,\rho)\frac{1}{R} - \mu\frac{\partial \sigma_s}{\partial r}(R) = 0, \tag{11}$$

$$\frac{1}{2}\mu\widetilde{\sigma}\rho + c_1(R,\rho)\frac{1}{\rho} - \mu\frac{\partial \sigma_s}{\partial r}(\rho) = 0. \tag{12}$$

From (12) and (9), $c_1(R,\rho) = -\frac{1}{2}\mu\widetilde{\sigma}\rho^2$.

Substituting c_1 into (10), we obtain $c_2(R,\rho) = \frac{1}{R} + \mu - \frac{1}{4}\mu\widetilde{\sigma}R^2 + \frac{1}{2}\mu\widetilde{\sigma}\rho^2\ln R$. Thus

$$p_s(r) = \frac{1}{4}\mu\widetilde{\sigma}(r^2 - R^2) + \frac{1}{R} + \frac{1}{2}\mu\widetilde{\sigma}\rho^2\ln\frac{R}{r} - \mu\big(\sigma_s(r) - 1\big), \quad \rho < r < R; \tag{13}$$

It remains to verify that (9) and (11) hold. We shall use (9) and (11) to determine $\rho, R, \widetilde{\sigma}$. By (4), $I_0'(r) = I_1(r)$ and $K_0'(r) = -K_1(r)$. Using (6), the equation (9) is equivalent to

$$(-\underline{\sigma}K_0(R) + K_0(\rho))I_1(\rho) + (I_0(\rho) - \underline{\sigma}I_0(R))K_1(\rho) = 0, \tag{14}$$

and (11) can be rewritten as

$$\frac{1}{2}\widetilde{\sigma}R - \frac{1}{2}\widetilde{\sigma}\frac{\rho^2}{R} - \frac{\partial \sigma_s}{\partial r}(R) = 0, \tag{15}$$

where, by (6),

$$\frac{\partial \sigma_s}{\partial r}(R) = \frac{(-\underline{\sigma} K_0(R) + K_0(\rho))I_1(R) + (I_0(\rho) - \underline{\sigma} I_0(R))K_1(R)}{-I_0(\rho)K_0(R) + I_0(R)K_0(\rho)}. \tag{16}$$

For this system, we need to compute ρ and R for given $\mu, \underline{\sigma}$ and $\widetilde{\sigma}$. For technical reasons, we will instead solve for $\widetilde{\sigma}$ for a given ρ. It will produce radially symmetric solution for any given ρ.

Lemma 2.1. *For any given $\mu > 0$ and $\rho > 0$, there exists a unique $\widetilde{\sigma}$ such that a stationary solution $(\sigma_s(r), p_s(r), \rho, R)$ is given by (6) and (13) where*

(a) R is uniquely determined by (14), $R > \rho$, and

(b) $\widetilde{\sigma}$ is uniquely determined over the interval $(\underline{\sigma}, 1)$ by (15).

Proof. To establish (a), we denote

$$f(s) = (-\underline{\sigma} K_0(s) + K_0(\rho))I_1(\rho) + (I_0(\rho) - \underline{\sigma} I_0(s))K_1(\rho),$$

then, recalling that $\overline{\sigma} < 1$,

$$f(\rho) = (1 - \underline{\sigma})(K_0(\rho)I_1(\rho) + I_0(\rho)K_1(\rho)) > 0$$

and $f(s) \to -\infty$ as $s \to \infty$. Therefore, $f(s)$ must have at least one root, say $s = R$, in the interval (ρ, ∞).

To show that $f(s)$ is monotone, consider $g(s) = \frac{K_1(s)}{I_1(s)}$. We know

$$\frac{dg}{ds}(s) = -\frac{I_1(s)K_0(s) + K_1(s)I_0(s)}{I_1(s)^2} < 0.$$

Therefore, g is decreasing function. In particular, if $s > \rho$, then $g(s) < g(\rho)$. This implies $K_1(s)I_1(\rho) < K_1(\rho)I_1(s)$ yielding

$$\frac{df}{ds}(s) = -\underline{\sigma}(K_1(s)I_1(\rho) - I_1(s)K_1(\rho)) > 0.$$

This implies that R is the unique solution to (14) on (ρ, ∞).

To establish (b), we note that it is easy to solve for $\widetilde{\sigma}$ using (15). Thus, we only need to establish that $\underline{\sigma} < \widetilde{\sigma} < 1$.

In fact, from equations (14) and (15), we can compute $\underline{\sigma}$ and $\widetilde{\sigma}$:

$$\underline{\sigma} = \frac{K_0(\rho)I_1(\rho) + I_0(\rho)K_1(\rho)}{K_0(R)I_1(\rho) + I_0(R)K_1(\rho)}, \tag{17}$$

$$\widetilde{\sigma} = \frac{2R\frac{\partial \sigma_s}{\partial r}(R)}{R^2 - \rho^2}. \tag{18}$$

We next establish that $\widetilde{\sigma} > \underline{\sigma}$. After simplification using (16), recalling also that the denominator in (16) satisfies (by (5))

$$-I_0(\rho)K_0(R) + I_0(R)K_0(\rho) > K_0(R)\big(-I_0(\rho) + I_0(R)\big) > 0,$$

we find that this inequality is equivalent to

$$\begin{aligned}
&2R(K_0(\rho)I_1(R)+I_0(\rho)K_1(R))(K_0(R)I_1(\rho)+I_0(R)K_1(\rho))\\
&\quad > \quad \{(R^2-\rho^2)[I_0(R)K_0(\rho)-I_0(\rho)K_0(R)]+2R[K_0(R)I_1(R)+I_0(R)K_1(R)]\}\cdot\\
&\qquad (K_0(\rho)I_1(\rho)+I_0(\rho)K_1(\rho)).
\end{aligned}$$

We let $f_1(s)$ be the function consisting of the difference of the left-hand side and the right-hand side of the above inequality after replacing ρ by s, i.e., after simplification,

$$\begin{aligned}
f_1(s) \quad = \quad & I_0(R)I_0(s)I_1(s)\Big(\frac{K_0(s)}{I_0(s)}-\frac{K_0(R)}{I_0(R)}\Big)\cdot\\
& \Big\{2RI_1(R)\Big(\frac{K_1(s)}{I_1(s)}-\frac{K_1(R)}{I_1(R)}\Big)-(R^2-s^2)I_0(s)\Big(\frac{K_0(s)}{I_0(s)}+\frac{K_1(s)}{I_1(s)}\Big)\Big\}. \qquad (19)
\end{aligned}$$

We want to establish $f_1(s)>0$ for $s<R$. Clearly, for $s<R$, we know $I_0(R)I_0(s)I_1(s)\Big(\frac{K_0(s)}{I_0(s)}-\frac{K_0(R)}{I_0(R)}\Big)>0$. Thus, it suffices to verify that, for $s<R$,

$$h_1(s):=2RI_1(R)\Big(\frac{K_1(s)}{I_1(s)}-\frac{K_1(R)}{I_1(R)}\Big)-(R^2-s^2)I_0(s)\Big(\frac{K_0(s)}{I_0(s)}+\frac{K_1(s)}{I_1(s)}\Big)>0. \qquad (20)$$

It is clear that $h_1(R)=0$ and

$$h_1'(s)=\frac{\Big(2\big(sI_1(s)-RI_1(R)\big)+(R^2-s^2)I_0(s)\Big)\Big(I_1(s)K_0(s)+I_0(s)K_1(s)\Big)}{I_1(s)^2}.$$

Let $i_1(s)=2\big(sI_1(s)-RI_1(R)\big)+(R^2-s^2)I_0(s)$, then

$$i_1'(s)=sI_0(s)+(R^2-s^2)I_1(s)>0 \quad \text{and} \quad i_1(R)=0.$$

Thus, $i_1(s)>0$ for any $s\in(0,R)$. Utilizing (20), we find $h_1'(s)<0$ for $s<R$. Combining this with $h_1(R)=0$, we conclude that $h_1(s)>0$ for $s<R$.

Finally, we will prove that $\widetilde{\sigma}<1$, which is equivalent to

$$\begin{aligned}
&2R(K_0(\rho)I_1(R)+I_0(\rho)K_1(R))(K_0(R)I_1(\rho)+I_0(R)K_1(\rho))\\
&\quad < \quad (R^2-\rho^2)\Big(I_0(R)K_0(\rho)-I_0(\rho)K_0(R)\Big)\Big(K_0(R)I_1(\rho)+I_0(R)K_1(\rho)\Big)\\
&\qquad +2R\Big(K_0(R)I_1(R)+I_0(R)K_1(R)\Big)\Big(K_0(\rho)I_1(\rho)+I_0(\rho)K_1(\rho)\Big). \qquad (21)
\end{aligned}$$

Similarly, we let $f_2(s)$ be the function consisting of the difference of the left-hand side and the right-hand side of (22) after replacing ρ by s. After simplification, we find

$$\begin{aligned}
f_2(s) \quad = \quad & I_0(R)I_0(s)I_1(s)\Big(\frac{K_0(s)}{I_0(s)}-\frac{K_0(R)}{I_0(R)}\Big)\\
& \Big\{2RI_1(R)\Big(\frac{K_1(s)}{I_1(s)}-\frac{K_1(R)}{I_1(R)}\Big)-(R^2-s^2)I_0(R)\Big(\frac{K_0(R)}{I_0(R)}+\frac{K_1(s)}{I_1(s)}\Big)\Big\}.
\end{aligned}$$

We want to show that $f_2(s) < 0$, for $s < R$. It suffices to establish

$$h_2(s) := 2RI_1(R)\left(\frac{K_1(s)}{I_1(s)} - \frac{K_1(R)}{I_1(R)}\right) - (R^2 - s^2)I_0(R)\left(\frac{K_0(R)}{I_0(R)} + \frac{K_1(s)}{I_1(s)}\right) < 0. \tag{22}$$

It is clear that $h_2(R) = 0$ and

$$h_2'(s) = \frac{\Big(2\big(sI_1(s)m(s) - RI_1(R)\big) + (R^2 - s^2)I_0(R)\Big)\Big(I_1(s)K_0(s) + I_0(s)K_1(s)\Big)}{I_1(s)^2},$$

where $m(s) = \dfrac{I_1(s)K_0(R) + K_1(s)I_0(R)}{I_1(s)K_0(s) + K_1(s)I_0(s)}$. We will show $m(s) > 1$ for $s < R$, so that

$$h_2'(s) > \frac{i_2(s)\Big(I_1(s)K_0(s) + I_0(s)K_1(s)\Big)}{I_1(s)^2}, \tag{23}$$

where $i_2(s) = 2\big(sI_1(s) - RI_1(R)\big) + (R^2 - s^2)I_0(R)$. Clearly, $i_2'(s) = 2sI_0(s) - 2sI_0(R) < 0$ and $i_2(R) = 0$. Thus, $i_2(s) > 0$ for $s < R$.. Since $h_2(R) = 0$, we have established (22).

To finish the proof, we need to show $m(s) > 1$ for $s < R$. Clearly,

$$\begin{aligned}\frac{d}{dR} \quad & \Big(\big(I_1(s)K_0(R) + K_1(s)I_0(R)\big) - \big(I_1(s)K_0(s) + K_1(s)I_0(s)\big)\Big) \\ & = I_1(s)I_1(R)\left(-\frac{K_1(R)}{I_1(R)} + \frac{K_1(s)}{I_1(s)}\right) > 0,\end{aligned}$$

Since $\big(I_1(s)K_0(R) + K_1(s)I_0(R)\big)|_{R=s} - \big(I_1(s)K_0(s) + K_1(s)I_0(s)\big)|_{R=s} = 0$, for $R > s$, we know

$$\Big(\big(I_1(s)K_0(R) + K_1(s)I_0(R)\big) - \big(I_1(s)K_0(s) + K_1(s)I_0(s)\big)\Big) > 0.$$

Hence $m(s) > 1$ for $s < R$. □

3. Bifurcation from radially symmetric stationary solution

We now turn our attention to compute nonradially symmetric stationary solutions of the form

$$\sigma = \sigma_s + \epsilon\sigma_1 + O(\epsilon^2), \tag{1}$$
$$p = p_s + \epsilon p_1 + O(\epsilon^2), \tag{2}$$
$$\partial\Omega_\epsilon : \quad r = R + \epsilon S(\theta) + O(\epsilon^2), \tag{3}$$
$$\partial D_\epsilon : \quad r = \rho + \epsilon\rho_1 S(\theta) + O(\epsilon^2), \tag{4}$$

where σ_1, p_1, and ρ_1 are constants to be determined.

3.1. Formal expansion

In order to compute the Frechét derivative in the direction $S(\theta)$, we first formally compute σ_1, ρ_1, and p_1.

Computation of σ_1: Clearly,

$$\epsilon\sigma_1|_{\partial B_R} = \epsilon\sigma_1|_{\partial\Omega_\epsilon} + O(\epsilon^2) = 1 - \sigma_s(R+\epsilon S) + O(\epsilon^2) = -\epsilon\sigma_s'(R)S(\theta) + O(\epsilon^2).$$

Similarly $\epsilon\sigma_1|_{\partial D_\rho} = -\epsilon\sigma_s'(\rho)\rho_1 S(\theta) + O(\epsilon^2) = O(\epsilon^2)$. Thus, after dropping higher terms,

$$\begin{cases} -\Delta\sigma_1 + \sigma_1 &= 0 & \text{in } B_R \setminus D_\rho, \\ \sigma_1 &= -\sigma_s'(R)S & \text{on } \partial B_R, \\ \sigma_1 &= 0 & \text{on } \partial D_\rho. \end{cases}$$

It follows that, for $S(\theta) = \cos(l\theta), l = 2, 3, 4, 5, ...$, by separation of variables

$$\sigma_1(r) = -\sigma_s'(R)\cos(l\theta)Q_l(r;\rho,R), \tag{5}$$

where

$$Q_l(r;\rho,R) = \frac{K_l(\rho)I_l(r) - I_l(\rho)K_l(r)}{K_l(\rho)I_l(R) - K_l(R)I_l(\rho)} \tag{6}$$

satisfies

$$r^2Q_l'' + rQ_l' - (r^2+l^2)Q_l = 0, \quad Q_l(\rho;\rho,R) = 0, \quad Q_l(R;\rho,R) = 1, \tag{7}$$

where Q_l' and Q_l'' are the first and second derivatives of Q_l with respect to r, respectively.

Computation of ρ_1: To compute ρ_1, we note that

$$\frac{\partial(\sigma_s + \epsilon\sigma_1)}{\partial n}\Big|_{\partial D_\epsilon} = O(\epsilon^2), \tag{8}$$

that is, $\epsilon\Big(\frac{\partial^2\sigma_s(\rho)}{\partial r^2}\rho_1 S + \frac{\partial\sigma_1}{\partial r}(\rho)\Big) = O(\epsilon^2)$. After dropping higher terms, we obtain

$$\frac{\partial\sigma_1}{\partial r}(\rho) = -\frac{\partial^2\sigma_s(\rho)}{\partial r^2}\rho_1 S(\theta), \tag{9}$$

which implies that

$$\rho_1 = \rho_1(l;\rho,R) = \frac{\sigma_s'(R)}{\sigma_s''(\rho)} \cdot Q_l'(\rho;\rho,R) = \frac{\sigma_s'(R)}{\sigma_0} \cdot Q_l'(\rho;\rho,R). \tag{10}$$

Computation of p_1: Similarly, for p_1 (see [15])

$$\kappa = \frac{1}{R} - \frac{\epsilon}{R^2}(S + S'') + O(\epsilon^2). \tag{11}$$

After dropping the higher order terms, we have

$$\begin{cases} -\Delta p_1 &= \mu\sigma_1 & \text{in } B_R \setminus D_\rho, \\ -\Delta p_1 &= 0 & \text{in } D_\rho. \end{cases}$$

As for boundary conditions, when $S(\theta) = \cos(l\theta)$,

$$-\frac{1}{R^2}(S + S'') = \left(\frac{1}{R^2} + \frac{l^2}{R^2}\right)\cos(l\theta), \tag{12}$$

so that, after dropping the higher order terms, $p_1 = \left(-\frac{1}{R^2} + \frac{l^2}{R^2}\right)\cos(l\theta)$ on ∂B_R.

We next formally derive two boundary conditions on ∂D_ρ. Clearly,

$$-\Delta p_s - \epsilon\Delta p_1 = \mu(\sigma_s - \widetilde{\sigma})\chi_{\Omega_\epsilon \setminus D_\epsilon} + \epsilon\mu\sigma_1\chi_{\Omega_\epsilon\setminus D_\epsilon} + O(\epsilon^2). \tag{13}$$

Since $-\Delta p_s = \mu(\sigma_s - \widetilde{\sigma})\chi_{B_R\setminus D_\rho}$, the function p_1 satisfies

$$-\Delta p_1 = \mu\sigma_1\chi_{\Omega_\epsilon\setminus D_\epsilon} + \frac{\mu}{\epsilon}(\sigma_s - \widetilde{\sigma})f_\epsilon, \tag{14}$$

where f_ϵ is given by $f_\epsilon = \chi_{\Omega_\epsilon\setminus D\epsilon} - \chi_{B_R\setminus D_\rho}$. Clearly, $\mu\sigma_1\chi_{\Omega_\epsilon\setminus D_\epsilon} \to \mu\sigma_1\chi_{B_R\setminus D_\rho}$ as $\epsilon \to 0$. It is also clear that $\frac{1}{\epsilon}f_\epsilon\rho_1 S(\theta)$ converges to a δ-function on ∂D_ρ, thus p_1 is continuous on ∂D_ρ, $p_1(\rho+) = p_1(\rho-)$, where we use $\rho+$ to denote the limit from the tumor side and $\rho-$ to denote the limit from necrotic core side.

To derive a second condition across the free boundary $\{r = \rho\}$, consider

$$\left\{\begin{array}{rcll} -\Delta q_1^\epsilon & = & \mu\sigma_1\chi_{\Omega_\epsilon\setminus D_\epsilon} & \text{in } \Omega_\epsilon, \\ q_1^\epsilon & = & p_1 & \text{on } \partial\Omega_\epsilon, \end{array}\right.$$

yielding

$$\left\{\begin{array}{rcll} -\Delta(p_1 - q_1^\epsilon) & = & \frac{\mu}{\epsilon}(\sigma_\epsilon - \widetilde{\sigma})f_\epsilon & \text{in } \Omega_\epsilon, \\ q_1^\epsilon - p_1 & = & 0 & \text{on } \partial\Omega_\epsilon. \end{array}\right.$$

For any test function ζ with compact support in B_R, then

$$-\iint_{\Omega_\epsilon}\zeta\Delta(p_1 - q_1^\epsilon) = \iint_{\Omega_\varepsilon}\frac{\mu}{\epsilon}(\sigma_s - \widetilde{\sigma})f_\epsilon\zeta,$$

that is,

$$\iint_{\Omega_\epsilon}\nabla\zeta\nabla(p_1 - q_1^\epsilon) = \int_{\partial D_\epsilon}\mu(\sigma_s - \widetilde{\sigma})\rho_1 S(\theta)\zeta + O(\epsilon).$$

In the limit as $\epsilon \to 0$,

$$\iint_{B_R}\nabla\zeta\nabla(p_1 - q_1) = \int_{\partial D_\rho}\mu(\sigma_s - \widetilde{\sigma})\rho_1 S(\theta)\zeta.$$

Note that in the limit $-\Delta(p_1 - q_1) \equiv 0$ in $D_\rho \cup (B_R \setminus \overline{D_\rho})$ so that integration by parts yields

$$0 = \iint_{B_R}\nabla\zeta\nabla(p_1 - q_1) - \int_{\partial(B_R\setminus D_\rho)}\zeta\frac{\partial(p_1 - q_1)}{\partial n} - \int_{\partial D_\rho}\zeta\frac{\partial(p_1 - q_1)}{\partial n},$$

where $\vec{n}$ on ∂D_ρ points into the tumor region while $\vec{n}$ on $\partial(B_R \setminus D_\rho)$ points into the necrotic core. Thus, in the limit,

$$\int_{\partial(B_R\setminus D_\rho)} \zeta \frac{\partial(p_1-q_1)}{\partial n} + \int_{\partial D_\rho} \zeta \frac{\partial(p_1-q_1)}{\partial n} = \int_{\partial D_\rho} \mu(\sigma_s - \widetilde{\sigma})\rho_1 S(\theta)\zeta. \quad (15)$$

Since ∇q_1 is continuous across the necrotic core,

$$\frac{\partial p_1}{\partial n}(\rho+) + \frac{\partial p_1}{\partial n}(\rho-) = \mu(\underline{\sigma} - \widetilde{\sigma})\rho_1 S(\theta). \quad (16)$$

or, recalling the definition of $\vec{n}$, $-\frac{\partial p_1}{\partial r}(\rho+) + \frac{\partial p_1}{\partial r}(\rho-) = \mu(\underline{\sigma} - \widetilde{\sigma})\rho_1 S(\theta)$.

Solving p_1 in the regions $\{r<\rho\}$ and $\{\rho<r<R\}$ respectively, we obtain

$$\begin{cases} p_1 = c_4 r^l \cos(l\theta) & 0<r<\rho, \\ p_1 + \mu\sigma_1 = \left(-\frac{1}{R^2} - \mu\sigma_s'(R) + \frac{l^2}{R^2}\right)\frac{r^l}{R^l}\cos(l\theta) + c_3\left(r^{-l} - \frac{r^l}{R^{2l}}\right)\cos(l\theta) & \rho<r<R, \end{cases}$$

where the constants c_3 and c_4 are determined by matching all the boundary conditions

$$\left(-\frac{1}{R^2} - \mu\sigma_s'(R) + \frac{l^2}{R^2}\right)\frac{\rho^l}{R^l} + c_3\left(\rho^{-l} - \frac{\rho^l}{R^{2l}}\right) = c_4\rho^l, \quad (17)$$

and

$$\left(-\frac{1}{R^2} - \mu\sigma_s'(R) + \frac{l^2}{R^2}\right)\frac{l\rho^{l-1}}{R^l} - c_3\left(l\rho^{-l-1} + \frac{l\rho^{l-1}}{R^{2l}}\right) + \mu\sigma_s''(\rho)\rho_1 = c_4 l\rho^{l-1} - \rho_1\mu(\underline{\sigma} - \widetilde{\sigma}). \quad (18)$$

The combination $l \times (17) - \rho \times (18)$ gives

$$c_3 2l\rho^{-l} - \mu\underline{\sigma}\rho_1\rho = -\rho_1\mu(\underline{\sigma} - \widetilde{\sigma})\rho \quad (19)$$

yielding $c_3 = \frac{\rho_1\rho^{l+1}\mu\widetilde{\sigma}}{2l}$. We can now solve for c_4 using (17).

For each $S(\theta)$ and μ, define

$$F(S,\mu) = \frac{\partial p}{\partial n}\Big|_{\partial\Omega_\epsilon}. \quad (20)$$

Then, S induces an stationary solution if and only if $F(S,\mu)=0$. Clearly

$$\frac{\partial p}{\partial n}\Big|_{r=R+\epsilon S} = \epsilon\left(\frac{\partial^2 p_s(R)}{\partial r^2}S + \frac{\partial p_1}{\partial r}\right) + O(\epsilon^2). \quad (21)$$

Thus, formally, the Frechét derivative in the direction $\cos(l\theta)$ is given by

$$\left[\frac{\partial F}{\partial S}(0,\mu)\right]\cos(l\theta) = \frac{\partial^2 p_s(R)}{\partial r^2}\cos(l\theta) + \frac{\partial p_1}{\partial r}. \quad (22)$$

We claim that the condition for bifurcation is

$$\left[\frac{\partial F}{\partial S}(0,\mu)\right]\cos(l\theta) \equiv 0, \tag{23}$$

and this will determine $\mu = \mu_l$. We now proceed to rigorously derive this. From (13), we have

$$\frac{\partial^2 p_s(R)}{\partial r^2} = \frac{1}{2}\mu\widetilde{\sigma} + \frac{1}{2}\mu\widetilde{\sigma}\frac{\rho^2}{R^2} - \mu\sigma_s''(R). \tag{24}$$

Using the formula for p_1,

$$\frac{\partial p_1}{\partial r}(R) + \mu\frac{\partial \sigma_1}{\partial r}(R) = \left(-\frac{1}{R^2} - \mu\sigma_s'(R) + \frac{l^2}{R^2}\right)\frac{l}{R}\cos(l\theta) - c_3\frac{2l}{R^{l+1}}\cos(l\theta). \tag{25}$$

Using (8), we know $\dfrac{\partial \sigma_1}{\partial r}(R) = -\sigma_s'(R)\cos(l\theta)Q_l'(R;\rho,R)$. Substituting this into (25) and using (22) and (23), we find

$$\frac{1}{2}\mu\widetilde{\sigma}\left(1+\frac{\rho^2}{R^2}\right) - \mu\sigma_s''(R) + \left(-\frac{1}{R^2} - \mu\sigma_s'(R) + \frac{l^2}{R^2}\right)\frac{l}{R} - c_3\frac{2l}{R^{l+1}} + \mu\sigma_s'(R)Q_l'(R;\rho,R) = 0.$$

Substituting c_3 into the above equation, we have

$$\frac{1}{2}\mu\widetilde{\sigma}\left(1+\frac{\rho^2}{R^2}\right) - \mu\sigma_s''(R) + \left(-\frac{1}{R^2} - \mu\sigma_s'(R) + \frac{l^2}{R^2}\right)\frac{l}{R} - \frac{\rho_1\rho^{l+1}}{R^{l+1}}\mu\widetilde{\sigma} + \mu\sigma_s'(R)Q_l'(R;\rho,R) = 0.$$

Thus, $A_l \cdot \mu_l + B_l = 0$ where

$$A_l = \frac{1}{2}\widetilde{\sigma}\left(1+\frac{\rho^2}{R^2}\right) - \sigma_s''(R) - \frac{l}{R}\sigma_s'(R) - \frac{\rho_1\rho^{l+1}}{R^{l+1}}\widetilde{\sigma} + \sigma_s'(R)Q_l'(R;\rho,R), \tag{26}$$

$$B_l = \left(-\frac{1}{R^2} + \frac{l^2}{R^2}\right)\frac{l}{R}. \tag{27}$$

Clearly, if $A_l \neq 0$, then $\mu_l = -\dfrac{B_l}{A_l}$,

3.2. Bifurcation

We shall apply the following Crandall-Rabinowitz theorem.

Theorem 3.1 (see [8, Theorem 1.7]). *Let X, Y be real Banach spaces and $F(x,\mu)$ a C^p map, $p \geq 3$, of a neighborhood $(0,\mu_0)$ in $X \times \mathbb{R}$ into Y. Suppose*

(i). $F(0,\mu) = 0$ for all μ in a neighborhood of μ_0,
(ii). Ker $F_x(0,\mu_0)$ is one dimensional space, spanned by x_0,
(iii). Im $F_x(0,\mu_0) = Y_1$ has codimension 1,
(iv). $F_{\mu x}(0,\mu_0)x_0 \notin Y_1$.

Then $(0,\mu_0)$ *is a bifurcation point of the equation* $F(x,\mu)=0$ *in the following sense: In a neighborhood of* $(0,\mu_0)$ *the set of solutions of* $F(x,\mu)=0$ *consists of two* C^{p-2} *smooth curves* Γ_1 *and* Γ_2 *which intersect only at the point* $(0,\mu_0)$*;* Γ_1 *is the curve* $(0,\mu)$ *and* Γ_2 *can be parameterized as follows:*

$$\Gamma_2 : (x(\varepsilon),\mu(\varepsilon)),\ |\varepsilon| \text{ small}, \qquad (x(0),\mu(0))=(0,\mu_0),\ x'(0)=x_0.$$

As in [12] we introduce the Banach spaces: for $k\geq 2$,

$$X_0^{k+\alpha} = \Big\{ S\in C^{k+\alpha}(-\infty,\infty),\ S \text{ is } 2\pi\text{-periodic}\Big\}, \tag{28}$$

$$X_1^{k+\alpha} = \text{closure of the linear space spanned by } \{\cos(j\theta), j=0,1,2,3,\cdots\} \text{ in } X^{k+\alpha}, \tag{29}$$

$$X_2^{k+\alpha} = \text{closure of the linear space spanned by } \{\cos(j\theta), j=0,2,4,6,\cdots\} \text{ in } X^{k+\alpha}. \tag{30}$$

We shall take $X=X_2^{k+\alpha}$ and $Y=X_2^{k-1+\alpha}$ and define F by (20), for any $S\in X_2^{k+\alpha}$. Then $F: X_2^{k+\alpha}\to X_2^{k-1+\alpha}$. It is also clear that $F: X_j^{k+\alpha}\to X_j^{k-1+\alpha}$, $j=0$ and $j=1$.

Lemma 3.2. *If* $j\in\{0,1\}$ *and* $F: X_j^{k+\alpha}\to X_j^{k-1+\alpha}$*, then*

$$[F_S(0,\mu)]\cos(l\theta)\equiv 0$$

if and only if $l=1$*, or* $l\geq 2$ *and* $\mu=\mu_j$*,* $j\geq 2$*.*

Proof. If $l=1$, clearly $B_1=0$ in (27). To verify $A_1=0$, we evaluate the various terms in (26). By plugging (19) into (16), and after a lengthy simplification, we find that

$$\sigma_s'(R)=\frac{K_1(\rho)I_1(R)-K_1(R)I_1(\rho)}{K_0(R)I_1(\rho)+I_0(R)K_1(\rho)}.$$

Since by (5), $K_l'(r)<0$ and $I_l'(r)>0$, we derive $\sigma_s'(R)>0$. Moreover, using (3), we obtain

$$Q_1'(r;\rho,R) \;=\; \frac{K_1(\rho)I_0(r)+I_1(\rho)K_0(r)}{K_1(\rho)I_1(R)-K_1(R)I_1(\rho)}-\frac{1}{r}\frac{K_1(\rho)I_1(r)-I_1(\rho)K_1(r)}{K_1(\rho)I_1(R)-K_1(R)I_1(\rho)},$$

so that $Q_1'(R;\rho,R)=\frac{K_0(R)I_1(\rho)+I_0(R)K_1(\rho)}{K_1(\rho)I_1(R)-K_1(R)I_1(\rho)}-\frac{1}{R}$ and $Q_1'(\rho;\rho,R)=\frac{K_1(\rho)I_0(\rho)+I_1(\rho)K_0(\rho)}{K_1(\rho)I_1(R)-K_1(R)I_1(\rho)}$. Then, substituting $\sigma_s(R)$,$\underline{\sigma}$ into (10) , we derive $\rho_1(1;\rho,R)=1$. Moreover, by the equation for σ_s and the boundary condition, $\sigma_s''(R)+\frac{1}{R}\sigma_s'(R)=\Delta\sigma_s(R)=\sigma_s(R)=1$. It follows that $A_1=\sigma_s'(R)\left(\frac{1}{R}+Q_1'(R;\rho,R)\right)-1=0$.

The case for $l\geq 2$ is a corollary of Theorem 3.3 and $A_l\neq 0$ for $l\geq 2$. □

We remark that $l=1$ corresponds to the translation of the original radially symmetric solution.

From this lemma it is clear that $\cos\theta \in \ker[F_S(0,\mu)]$ for all μ if we choose our space to be $X_0^{k+\alpha}$ or $X_1^{k+\alpha}$ and Crandall-Rabinowitz theorem cannot be used. For this reason we choose our space to be $X_2^{k+\alpha}$ (so that $\cos(\theta)$ is excluded). The above lemma then implies that, in $X_2^{k+\alpha}$,

$$\ker[F_S(0,\mu)] = \{0\} \quad \text{if } \mu \neq \mu_2, \mu_4, \mu_6, \cdots . \tag{31}$$

It is also clear that, for each fixed μ_l,

$$\ker[F_S(0,\mu_l)] = \text{closure of the linear space spanned by } \{\cos(m\theta); \mu_m = \mu_l\}.$$

Thus, for each fixed $l \geq 2$, the dimension of Ker $F_S(0,\mu_l)$ is 1 if and only if $\mu_l \neq \mu_m$ for all $m \neq l$.

Theorem 3.3. *The points $(0,\mu_n)$ ($n \geq 2$ and even) are bifurcation points for the problem (6)-(9), and the corresponding free boundaries are of the form*

$$\partial\Omega_\epsilon : \qquad r = R + \epsilon S(\theta) + O(\epsilon^2), \partial D_\epsilon : \qquad r = \rho + \epsilon\rho_1 S(\theta) + O(\epsilon^2),$$

where ρ_1 is a constant given by (10).

We note that theorem establishes the bifurcations only for even $n \geq 2$. For odd $n \geq 3$ we may apply the Crandall-Rabinowitz theorem in a more delicate manner.

To use the theorem, we need to show that all μ_l are distinct. Now we consider the property of $Q_l'(r;\rho,R)$.

Lemma 3.4. *(i). $\{Q_l'(\rho;\rho,R)\}$ is a positive decreasing sequence in l;*
(ii). $\{Q_l'(R;\rho,R)\}$ is a positive increasing sequence in l.

Proof. We rewrite (7) as

$$\begin{cases} -\Delta Q_l + (\frac{l^2}{r^2}+1)Q_l &= 0 \quad \text{in } B_R \setminus \bar{D}_\rho, \\ Q_l &= 1 \quad \text{on } \partial B_R, \\ Q_l &= 0 \quad \text{on } \partial D_\rho. \end{cases}$$

By the maximum principle, $0 < Q_l < (r/R)^l$ for $\rho < r < R$, so that by the strong maximum principle

$$Q_l'(\rho;\rho,R) > 0 \ \text{ and } \ Q_l'(R;\rho,R) > \frac{l}{R}. \tag{32}$$

Let $F = \frac{\partial Q_l}{\partial l}$, then

$$\begin{cases} -\Delta F + (\frac{l^2}{r^2}+1)F &= -\frac{2l}{r^2}Q_l \quad \text{in } B_R \setminus \bar{D}_\rho, \\ F &= 0 \quad \text{on } \partial B_R, \\ F &= 0 \quad \text{on } \partial D_\rho. \end{cases}$$

Since $Q_l > 0$ in $B_R \setminus \bar{D}_\rho$, we know $F < 0$ in $B_R \setminus \bar{D}_\rho$. Thus, $\frac{\partial F}{\partial r}|_{r=\rho} < 0$ and $\frac{\partial F}{\partial r}|_{r=R} > 0$, i.e., $Q_l'(\rho;\rho,R) > 0$ is a decreasing sequence in l, and $Q_l'(R;\rho,R)$ is an increasing sequence in l. □

Lemma 3.5. (*i*). *For any* $\rho < r \le R$, $\Big\{ \dfrac{Q_l'(r;\rho,R)}{Q_l(r;\rho,R)} - \dfrac{l}{r} \Big\}$ *is a positive decreasing sequence in* l;

(*ii*). *for* $l \ge 2$, $-\frac{l}{R} + Q_l'(R;\rho,R) < -\frac{l+1}{R} + Q_{l+1}'(R;\rho,R) + \frac{d_l}{l+1}$, *where* $d_l = \max_{\rho\le r\le R} \frac{2r^2}{R}\Big\{ Q_l'(r;\rho,R) - \frac{l}{r} Q_l(r;\rho,R) \Big\}$.

Proof. For any $\rho < s \le R$, it is clear that

$$\psi_1(r) = \frac{r}{s} Q_l(r;\rho,R) - \frac{Q_l(s;\rho,R)}{Q_{l+1}(s;\rho,R)} Q_{l+1}(r;\rho,R)$$

satisfies

$$\begin{cases} -\Delta\psi_1 + \Big(\frac{(l+1)^2}{r^2} + 1\Big)\psi_1 &=& \frac{2}{s}\Big\{ \frac{l}{r} Q_l - Q_l' \Big\} & \text{for } \rho < r < s, \\ \psi_1 &=& 0 & \text{for } r = \rho, \\ \psi_1 &=& 0 & \text{for } r = s. \end{cases}$$

Using (6) and (4), we find that

$$\Big\{ \frac{l}{r} Q_l - Q_l' \Big\} = \frac{-\Big(K_l(\rho) I_{l+1}(r) + I_l(\rho) K_{l+1}(r) \Big)}{K_l(\rho) I_l(R) - K_l(R) I_l(\rho)} < 0. \tag{33}$$

Thus we can use the maximum principle to derive $\psi_1 < 0$ for $\rho < r < s$. In particular, $\frac{d\psi_1}{dr}\Big|_{r=s} > 0$, and this implies that

$$-\frac{l}{s} + \frac{Q_l'(s;\rho,R)}{Q_l(s;\rho,R)} > -\frac{l+1}{s} + \frac{Q_{l+1}'(s;\rho,R)}{Q_{l+1}(s;\rho,R)}. \tag{34}$$

Replacing s by r in the above inequality, we obtain (i).

To establish (ii), we let

$$\psi_2(r) = \frac{r}{R} Q_l(r;\rho,R) - Q_{l+1}(r;\rho,R) + \frac{d_l}{(l+1)^2}\Big(1 - \frac{r^{l+1}}{R^{l+1}} \Big),$$

A direct computation shows

$$\begin{cases} -\Delta\psi_2 + \Big(\frac{(l+1)^2}{r^2} + 1\Big)\psi_2 &=& G & \text{for } \rho < r < R, \\ \psi_2 &=& \frac{d_l}{(l+1)^2}\Big(1 - \frac{\rho^{l+1}}{R^{l+1}} \Big) > 0 & \text{for } r = \rho, \\ \psi_2 &=& 0 & \text{for } r = R, \end{cases}$$

where $G = \frac{2}{R}\Big\{ \frac{l}{r} Q_l - Q_l' \Big\} + \frac{d_l}{(l+1)^2}\Big(1 - \frac{r^{l+1}}{R^{l+1}} \Big) + \frac{d_l}{r^2}$. By the definition of d_l it is clear that $G > 0$. In this case, we can apply the maximum principle to conclude $\psi_2 > 0$ for $\rho < r < R$ and hence $\frac{d\psi_2}{dr}\Big|_{r=s} < 0$. This implies that, for $l \ge 2$,

$$-\frac{l}{R} + Q_l'(R;\rho,R) < -\frac{l+1}{R} + Q_{l+1}'(R;\rho,R) + \frac{d_l}{R(l+1)}. \tag{35}$$

This establishes the lemma. □

The following lemma will be established using computations performed in a reasonable range of R and ρ, namely, $0 < R \leq 10$ and $0 < \rho \leq 10$.

Lemma 3.6. $\mu_2 < \mu_3 < \mu_4 < \cdots$.

Proof. We can rewrite (26) as $A_l \triangleq -\alpha - \beta_l - \gamma_l$, where $\alpha = -\frac{1}{2}\widetilde{\sigma}(1 + \frac{\rho^2}{R^2}) + \sigma_s''(R)$ is independent of l, and using (10),

$$\beta_l = \frac{\rho_1 \rho^{l+1}}{R^{l+1}}\widetilde{\sigma} = \sigma_s'(R)\frac{\widetilde{\sigma}}{\underline{\sigma}}\left(\frac{\rho}{R}\right)^{l+1} Q_l'(\rho;\rho,R) \quad \text{and} \quad \gamma_l = -\sigma_s'(R)\left(Q_l'(R;\rho,R) - \frac{l}{R}\right).$$

Since $\sigma_s'(R) > 0$, the preceding lemma implies that

$$\gamma_l - \gamma_{l+1} \geq -\sigma_s'(R)\,\frac{d_l}{R(l+1)} \qquad \text{for } l \geq 2. \tag{36}$$

From Lemmas 3.3 and 3.4, and the fact that $\sigma_s'(R) > 0$, it is clear that β_l is a decreasing sequence and that γ_l is an increasing sequence. The inequality $\mu_l < \mu_{l+1}$ is equivalent to:

$$\frac{l^3 - l}{\alpha + \beta_l + \gamma_l} < \frac{(l+1)^3 - (l+1)}{\alpha + \beta_{l+1} + \gamma_{l+1}}. \tag{37}$$

We next show that $\alpha + \beta_l + \gamma_l > 0$. Clearly,

$$\alpha \;=\; -\frac{1}{2}\widetilde{\sigma}(1 + \frac{\rho^2}{R^2}) + \sigma_s''(R) = 1 - \sigma_s'(R)\left(\frac{2R}{R^2 - \rho^2}\right).$$

By (22), we know $\alpha > 0$. On the other hand, $\alpha + \beta_l + \gamma_l \geq \alpha + \gamma_l$, the right-hand side of the above inequality is an increasing sequence in l. We will show $\alpha + \gamma_2 > 0$, which will then imply $\alpha + \beta_l + \gamma_l > 0$ for all $l \geq 2$.

Clearly, (37) is equivalent to

$$3\alpha + (l+2)\beta_l - (l-1)\beta_{l+1} + (l+2)\gamma_l - (l-1)\gamma_{l+1} > 0. \tag{38}$$

We now proceed to estimate the left-hand side of the above inequality.

$$\begin{aligned} j(l,\rho,R) \;&:=\; 3\alpha + (l+2)\beta_l - (l-1)\beta_{l+1} + (l+2)\gamma_l - (l-1)\gamma_{l+1} \\ &=\; 3(\alpha + \beta_l + \gamma_l) + (l-1)(\beta_l - \beta_{l+1}) + (l-1)(\gamma_l - \gamma_{l+1}) \\ &>\; 3(\alpha + \gamma_l) - (l-1)\sigma_s'(R)\frac{d_l}{R(l+1)}. \end{aligned} \tag{39}$$

By Lemma 3.4 (i), $d_l > d_{l+1}$ for all $l \geq 1$. Thus

$$j(l,\rho,R) \;>\; 3(\alpha + \gamma_4) - \sigma_s'(R)\frac{d_4}{R} \qquad \text{for } l \geq 4, \tag{40}$$

$$j(3,\rho,R) \;>\; 3(\alpha + \gamma_3) - \frac{1}{2}\sigma_s'(R)\frac{d_3}{R}, \tag{41}$$

$$j(2,\rho,R) \;>\; 3(\alpha + \gamma_2) - \frac{1}{3}\sigma_s'(R)\frac{d_2}{R}. \tag{42}$$

The right-hand sides of the above inequalities are functions of ρ and R. We explicitly computed these three functions as functions of ρ and R and found that they are all positive (see Figures 1, 2, and 3). This also implies that $\alpha + \gamma_2 > 0$, which was used in the proof. □

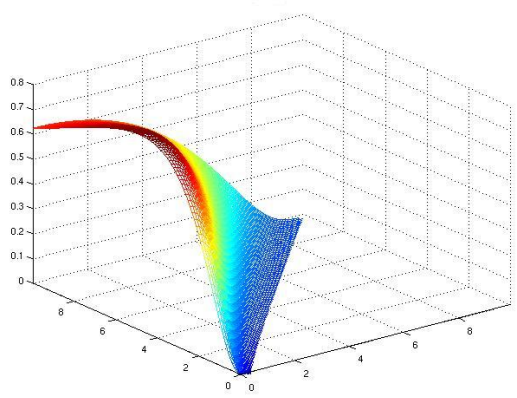


Figure 1: $3(\alpha + \gamma_4) - \sigma_s'(R)\frac{d_4}{R} \geq 0$

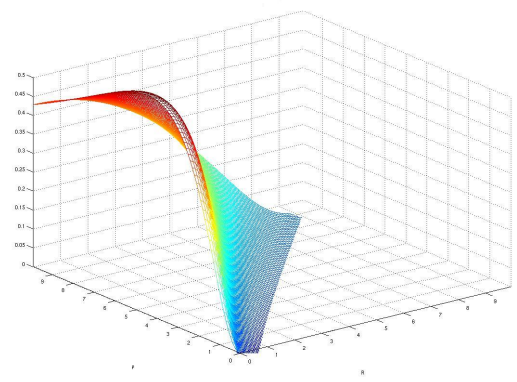


Figure 2: $3(\alpha + \gamma_3) - \frac{1}{2}\sigma_s'(R)\frac{d_3}{R} \geq 0$

Consider

$$Y_1 = \text{closure of the liner space spanned by } \{\cos(m\theta); m \neq l\}.$$

We know

$$\text{Ker } [F_S(0, \mu_l)] = \text{span } \{\cos(l\theta)\}, \tag{43}$$

$$\text{Im } [F_S(0, \mu_l)] = Y_1, \tag{44}$$

$$[F_{S\mu}(0, \mu_l)] \cos(l\theta) \notin Y_1. \tag{45}$$

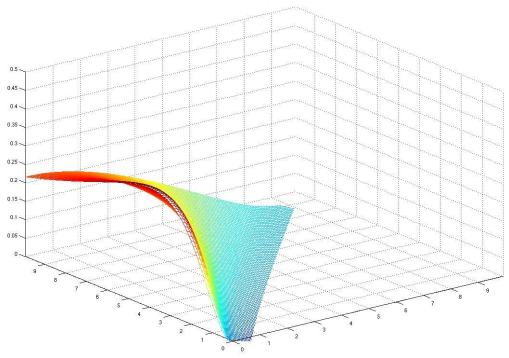


Figure 3: $3(\alpha+\gamma_2)-\frac{1}{3}\sigma_s'(R)\geq 0$

It is clear that Y_1 has codimension 1 since its direct sum with $\{\cos(l\theta)\}$ gives the whole space. Thus we can apply Theorem 3.1 to get bifurcation branches for all $\mu=\mu_l$ ($l\geq 2$ even).

4. Linear stability

Assume

$$\partial\Omega_0: \qquad r=R_0(\theta). \tag{1}$$

Then the linearization of the two boundaries $\partial\Omega(t)$ and $\partial D(t)$ are given by

$$\partial\Omega_\epsilon: \qquad r=R_0(\theta)+\epsilon R_1(\theta,t)+O(\epsilon^2), \tag{2}$$
$$\partial D_\epsilon: \qquad r=\rho_0(\theta)+\epsilon\rho_1(\theta,t)+O(\epsilon^2), \tag{3}$$
$$\sigma=\sigma_0(r,\theta)+\epsilon\sigma_1(r,\theta,t)+O(\epsilon^2), \tag{4}$$
$$p=p_0(r,\theta)+\epsilon p_1(r,\theta,t)+O(\epsilon^2). \tag{5}$$

The mean curvature is given by

$$\kappa=\frac{r^2+2r_\theta^2-rr_{\theta\theta}}{(r^2+r_\theta^2)^{\frac{3}{2}}}. \tag{6}$$

So that the linearization of κ is given by

$$\begin{aligned}\kappa\,|_{\partial\Omega_\epsilon} &= \frac{r^2+2r_\theta^2-rr_{\theta\theta}}{(r^2+r_\theta^2)^{\frac{3}{2}}}\\ &= \frac{(R_0+\epsilon R_1)^2+2(R_{0\theta}+\epsilon R_{1\theta})^2-(R_0+\epsilon R_1)(R_{0\theta\theta}+\epsilon R_{1\theta\theta})}{[(R_0+\epsilon R_1)^2+(R_{0\theta}+\epsilon R_{1\theta})^2]^{\frac{3}{2}}}+O(\epsilon^2)\\ &\doteq \kappa_0+\epsilon\kappa_1+O(\epsilon^2),\end{aligned}$$

where

$$\kappa_0 = \frac{R_0^2 + 2R_{0\theta}^2 - R_0 R_{0\theta\theta}}{(R_0^2 + R_{0\theta}^2)^{\frac{3}{2}}}, \tag{7}$$

and

$$\begin{aligned} \kappa_1 &= \frac{2R_0R_1 + 4R_{0\theta}R_{1\theta} - R_1R_{0\theta\theta} - R_0R_{1\theta\theta}}{(R_0^2 + R_{0\theta}^2)^{\frac{3}{2}}} \\ &\quad -\frac{3}{2}\frac{(R_0^2 + 2R_{0\theta}^2 - R_0R_{0\theta\theta})(2R_0R_1 + 2R_{0\theta}R_{1\theta})}{(R_0^2 + R_{0\theta}^2)^{\frac{5}{2}}}. \end{aligned} \tag{8}$$

Clearly, the linearized equations for σ and p are:

$$\begin{cases} \sigma_{1t} - \Delta\sigma_1 + \sigma_1 = 0 & \text{in } \Omega_0 \\ -\Delta p_1 = \mu\sigma_1 & \text{in } \Omega_0. \end{cases} \tag{9}$$

The boundary conditions are

$$\begin{aligned} 1 &= \sigma\mid_{r=R_0+\epsilon R_1+O(\epsilon^2)} \\ &= \sigma_0\mid_{r=R_0} + \epsilon R_1\sigma_{0r}\mid_{r=R_0} + \epsilon\sigma_1\mid_{r=R_0} + O(\epsilon^2) \\ &= 1 + \epsilon R_1\sigma_{0r}\mid_{r=R_0} + \epsilon\sigma_1\mid_{r=R_0} + O(\epsilon^2). \end{aligned}$$

It follows that the boundary condition for σ_1 is

$$\sigma_1\mid_{r=R_0} = -R_1 \cdot \sigma_{0r}\mid_{r=R_0}. \tag{10}$$

Similarly,

$$\begin{aligned} (\kappa_0 + \epsilon\kappa_1)\mid_{\partial\Omega_\epsilon} &= \kappa\mid_{r=R_0+\epsilon R_1+O(\epsilon^2)} \\ &= (p_0 + \epsilon p_1)\mid_{r=R_0+\epsilon R_1} + O(\epsilon^2) \\ &= p_0\mid_{r=R_0} + p_{0r}\mid_{r=R_0} \cdot \epsilon R_1 + \epsilon p_1\mid_{r=R_0} + O(\epsilon^2) \\ &= \kappa_0 + p_{0r}\mid_{r=R_0} \cdot \epsilon R_1 + \epsilon p_1\mid_{r=R_0} + O(\epsilon^2) \end{aligned}$$

that is,

$$p_1\mid_{r=R_0} = \kappa_1 - R_1 \cdot p_{0r}\mid_{r=R_0}. \tag{11}$$

To derive the equation for R_1, we note that in the polar coordinate system

$$\begin{cases} \vec{e_r} = \cos\theta\ \vec{e_1} + \sin\theta\ \vec{e_2}; \\ \vec{e_\theta} = -\sin\theta\ \vec{e_1} + \cos\theta\ \vec{e_2}. \end{cases} \tag{12}$$

If we write in vector form

$$\vec{e_r} = (\cos\theta, \sin\theta)^T, \quad \vec{e_\theta} = (-\sin\theta, \cos\theta)^T \tag{13}$$

we then have

$$\nabla_{(x,y)} = \vec{e_r}\partial_r + \vec{e_\theta} \cdot \frac{1}{r}\partial_\theta, \tag{14}$$

that is

$$\begin{pmatrix} \partial_x \\ \partial_y \end{pmatrix} = \begin{pmatrix} \cos\theta \\ \sin\theta \end{pmatrix} \partial_r + \frac{1}{r} \begin{pmatrix} -\sin\theta \\ \cos\theta \end{pmatrix} \partial_\theta.$$

For the surface $F(x,y)=0$, the normal is given by $\vec{n} = \dfrac{\pm\nabla F}{|\nabla F|}$, thus, we have

$$\vec{n}\mid_{r=R_0+\epsilon R_1} = \frac{\vec{e_r} - \frac{1}{r}(R_{0\theta}+\epsilon R_{1\theta})\vec{e_\theta}}{\sqrt{1+\frac{1}{r^2}(R_{0\theta}+\epsilon R_{1\theta})^2}}. \tag{15}$$

In particular,

$$\begin{aligned} \vec{n}\mid_{r=R_0+\epsilon R_1} &= \frac{r\vec{e_r} - (R_{0\theta}+\epsilon R_{1\theta})\vec{e_\theta}}{\sqrt{r^2+(R_{0\theta}+\epsilon R_{1\theta})^2}} \\ &= \frac{(R_0+\varepsilon R_1)\vec{e_r} - (R_{0\theta}+\varepsilon R_{1\theta})\vec{e_\theta}}{\left((R_0+\varepsilon R_1)^2+(R_{0\theta}+\varepsilon R_{1\theta})^2\right)^{\frac{1}{2}}} \\ &\doteq \vec{n}_0 + \epsilon\vec{n}_1 + O(\epsilon^2), \end{aligned}$$

where

$$\vec{n}_0 = \frac{R_0\vec{e_r} - R_{0\theta}\vec{e_\theta}}{(R_0^2+R_{0\theta}^2)^{\frac{1}{2}}},$$

$$\begin{aligned} \vec{n}_1 &= \frac{R_1\vec{e_r} - R_{1\theta}\vec{e_\theta}}{(R_0^2+R_{0\theta}^2)^{\frac{1}{2}}} - \frac{(R_0R_1+R_{0\theta}R_{1\theta})(R_0\vec{e_r} - R_{0\theta}\vec{e_\theta})}{(R_0^2+R_{0\theta}^2)^{\frac{3}{2}}} \\ &= \frac{R_1R_{0\theta}^2 - R_0R_{0\theta}R_{1\theta}}{(R_0^2+R_{0\theta}^2)^{\frac{3}{2}}}\vec{e_r} + \frac{R_0R_1R_{0\theta} - R_0^2R_{1\theta}}{(R_0^2+R_{0\theta}^2)^{\frac{3}{2}}}\vec{e_\theta}. \end{aligned}$$

Since

$$\begin{cases} p_{0r}\mid_{r=R_0+\epsilon R_1} = p_{0r}\mid_{r=R_0} + p_{0rr}\mid_{r=R_0}\cdot\epsilon R_1 + O(\epsilon^2); \\ p_{0\theta}\mid_{r=R_0+\epsilon R_1} = p_{0\theta}\mid_{r=R_0} + p_{0\theta r}\mid_{r=R_0}\cdot\epsilon R_1 + O(\epsilon^2), \end{cases} \tag{16}$$

we have

$$\begin{aligned} \frac{\partial p}{\partial n}\Big|_{r=R_0+\epsilon R_1} &= \left\{\vec{e_r}(p_{0r}+\epsilon p_{1r}) + \frac{\vec{e_\theta}}{r}(p_{0\theta}+\epsilon p_{1\theta})\right\}\Big|_{r=R_0+\epsilon R_1}\cdot(\vec{n}_0+\varepsilon\vec{n}_1) \\ &= \left\{\vec{e_r}(p_{0r}+\epsilon R_1 p_{0rr}+\varepsilon p_{1r}) + \frac{\vec{e_\theta}(p_{0\theta}+\varepsilon R_1 p_{0\theta r}+\epsilon p_{1\theta})}{R_0+\varepsilon R_1}\right\}\cdot(\vec{n}_0+\varepsilon\vec{n}_1) \\ &= \left\{(\vec{e_r}p_{0r} + \vec{e_\theta}\frac{p_{0\theta}}{R_0}) + \varepsilon\big[(R_1p_{0rr}+p_{1r})\vec{e_r} + \frac{R_0R_1p_{0\theta r}+R_0p_{1\theta}-R_1p_{0\theta}}{R_0^2}\vec{e_\theta}\big]\right\} \\ &\quad\cdot(\vec{n}_0+\varepsilon\vec{n}_1). \end{aligned}$$

Notice that p_0 is a stationary solution with

$$0 = \frac{\partial p_0}{\partial n_0}|_{r=R_0} = \frac{p_{0r}}{(1+\frac{1}{r^2}R_{0\theta}^2)^{\frac{1}{2}}} - \frac{\frac{1}{r^2}p_{0\theta}R_{0\theta}}{(1+\frac{1}{r^2}R_{0\theta}^2)^{\frac{1}{2}}}. \tag{17}$$

The $O(\epsilon)$ term is

$$
\begin{aligned}
&(\vec{e_r}p_{0r} + \vec{e_\theta}\frac{p_{0\theta}}{R_0}) \cdot \vec{n}_1 + \left[(R_1 p_{0rr} + p_{1r})\vec{e_r} + \frac{R_0 R_1 p_{0\theta r} + R_0 p_{1\theta} - R_1 p_{0\theta}}{R_0^2}\vec{e_\theta}\right] \cdot \vec{n}_0 \\
= \quad & \frac{p_{0r}(R_1 R_{0\theta}^2 - R_0 R_{0\theta} R_{1\theta})}{(R_0^2 + R_{0\theta}^2)^{\frac{3}{2}}} + \frac{p_{0\theta}(R_0 R_1 R_{0\theta} - R_0^2 R_{1\theta})}{R_0(R_0^2 + R_{0\theta}^2)^{\frac{3}{2}}} + \frac{R_0(R_1 p_{0rr} + p_{1r})}{(R_0^2 + R_{0\theta}^2)^{\frac{1}{2}}} \\
& - \frac{R_{0\theta}(R_0 R_1 p_{0\theta r} + R_0 p_{1\theta} - R_1 p_{0\theta})}{R_0^2(R_0^2 + R_{0\theta}^2)^{\frac{1}{2}}}.
\end{aligned}
$$

On the other hand, the velocity of the free boundary $\partial\Omega_\epsilon$ in the direction $\vec{n}$ would be

$$
\begin{aligned}
v_n &= \frac{(R_0 + \epsilon R_1)_t}{\sqrt{1 + \frac{1}{(R_0+\epsilon R_1)^2}(R_{0\theta} + \epsilon R_{1\theta})^2}} \\
&= \frac{\epsilon R_{1t}}{\sqrt{1 + \frac{1}{(R_0+\epsilon R_1)^2}(R_{0\theta}^2 + 2\epsilon R_{0\theta} R_{1\theta} + \epsilon^2 R_{1\theta}^2)}} \\
&= \epsilon \frac{R_{1t}}{\sqrt{1 + \frac{1}{R_0^2} R_{0\theta}^2}} + O(\epsilon^2)
\end{aligned}
$$

that is, $-v_n = -\epsilon \dfrac{R_{1t} R_0}{(R_0^2 + R_{0\theta}^2)^{\frac{1}{2}}} + O(\epsilon^2)$.

Since $\dfrac{\partial p}{\partial n} = -v_n$ on $\partial\Omega_t$,

$$
\begin{aligned}
-R_{1t} R_0 &= \frac{p_{0r}(R_1 R_{0\theta}^2 - R_0 R_{0\theta} R_{1\theta})}{R_0^2 + R_{0\theta}^2} + \frac{p_{0\theta}(R_0 R_1 R_{0\theta} - R_0^2 R_{1\theta})}{R_0(R_0^2 + R_{0\theta}^2)} \\
&\quad + R_0(R_1 p_{0rr} + p_{1r}) - \frac{R_{0\theta}(R_0 R_1 p_{0\theta r} + R_0 p_{1\theta} - R_1 p_{0\theta})}{R_0^2}.
\end{aligned}
$$

We derive

$$
\begin{aligned}
-R_{1t} &= \frac{p_{0r} R_1 \rho_{0\theta}^2 - p_{0r}\rho_0\rho_{0\theta}\rho_{1\theta} + p_{0\theta}\rho_1\rho_{0\theta} - p_{0\theta}\rho_{1\theta}\rho_0}{\rho_0(\rho_0^2 + \rho_{0\theta}^2)} + \rho_1 p_{0rr} + p_{1r} \\
&\quad - \rho_{0\theta}\frac{\rho_1 p_{0\theta r} + p_{1\theta}}{\rho_0^2} + \frac{\rho_{0\theta}\rho_1 p_{0\theta}}{\rho_0^3} \\
&= \left[\frac{p_{0r}\rho_{0\theta}^2}{\rho_0(\rho_0^2 + \rho_{0\theta}^2)} + \frac{p_{0\theta}\rho_{0\theta}}{\rho_0(\rho_0^2 + \rho_{0\theta}^2)} + p_{0rr} - \frac{\rho_{0\theta} p_{0\theta r}}{\rho_0^2} + \frac{\rho_{0\theta} p_{0\theta}}{\rho_0^3}\right]\rho_1 \\
&\quad - \left[\frac{p_{0r}\rho_{0\theta}}{\rho_0^2 + \rho_{0\theta}^2} + \frac{p_{0\theta}}{\rho_0^2 + \rho_{0\theta}^2}\right]\rho_{1\theta} + \left[p_{1r} - \frac{\rho_{0\theta} p_{1\theta}}{\rho_0^2}\right].
\end{aligned}
$$

Thus

$$\begin{aligned} R_{1t} &= \left[-\frac{p_{0r}\rho_{0\theta}^2}{\rho_0(\rho_0^2+\rho_{0\theta}^2)}-\frac{p_{0\theta}\rho_{0\theta}}{\rho_0(\rho_0^2+\rho_{0\theta}^2)}-p_{0rr}+\frac{\rho_{0\theta}p_{0\theta r}}{\rho_0^2}-\frac{\rho_{0\theta}p_{0\theta}}{\rho_0^3}\right]\rho_1 \\ &+\left[\frac{p_{0r}\rho_{0\theta}}{\rho_0^2+\rho_{0\theta}^2}+\frac{p_{0\theta}}{\rho_0^2+\rho_{0\theta}^2}\right]\rho_{1\theta}+\left[\frac{\rho_{0\theta}p_{1\theta}}{\rho_0^2}-p_{1r}\right]. \end{aligned}$$

From (13) and (20), we can get the linear equations on the boundary ∂D_0:

$$\begin{aligned} \sigma_{1r}|_{r=\rho_0} &= -\rho_1\frac{\partial^2\sigma_0}{\partial n^2}|_{r=\rho_0} \\ \frac{\partial p_1}{\partial n}|_+ - \frac{\partial p_1}{\partial n}|_- &= \mu(\sigma-\widetilde{\sigma})\rho_1, \end{aligned}$$

where

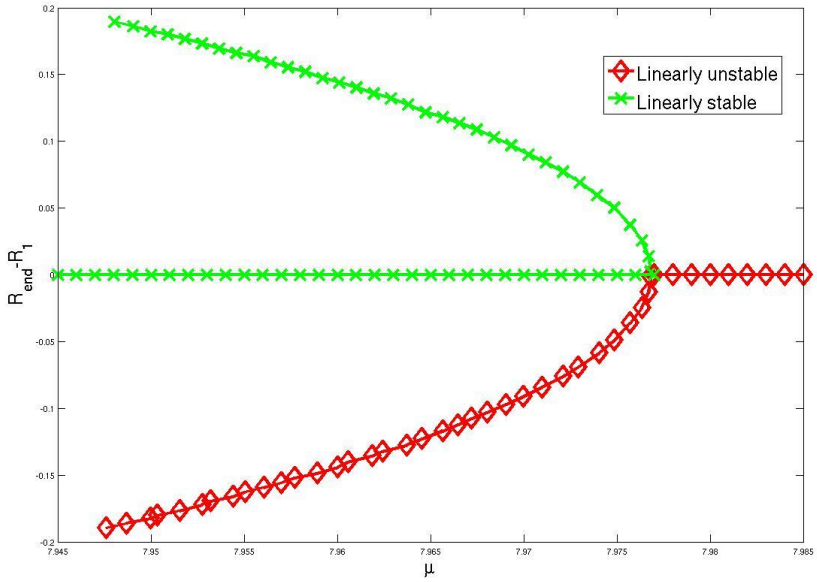
$$\begin{aligned} \frac{\partial}{\partial n}|_{r=\rho} &= \frac{\rho^2\partial_r-\rho_\theta\partial_\theta}{\rho\sqrt{\rho^2+\rho_\theta^2}}, \\ \frac{\partial^2}{\partial n^2}|_{r=\rho} &= \frac{\rho_\theta^2(\rho+\rho_{\theta\theta})\partial_r+\rho^2(\rho^2+\rho_\theta^2)\partial_{rr}-2\rho_\theta(\rho^2+\rho_\theta^2)\partial_{\theta r}}{(\rho^2+\rho_\theta^2)^2} \\ &+ \frac{\rho\rho_\theta(2\rho^2+\rho_\theta^2+\rho\rho_{\theta\theta})\partial_\theta+\rho_\theta^2(\rho^2+\rho_\theta^2)\partial_{\theta\theta}}{\rho^2(\rho^2+\rho_\theta^2)^2}. \end{aligned}$$

Combing all the above computation, the linearized system is

$$\begin{aligned} \sigma_{1t} &= \Delta\sigma_1-\sigma_1 \text{ in } \Omega_0, \\ \Delta p_1 &= -\mu\sigma_1 \text{ in } \Omega_0, \\ \sigma_{1r} &= -\rho_1\frac{\partial^2\sigma_0}{\partial n^2} \text{ on } \partial D_0 \\ \mu(\sigma-\widetilde{\sigma})\rho_1 &= \frac{\partial p_1}{\partial n}|_+-\frac{\partial p_1}{\partial n}|_- \text{ on } \partial D_0, \\ \sigma_1 &= -R_1\sigma_{0r} \text{ on } \partial\Omega_0, \\ \frac{\partial p}{\partial n} &= 0 \text{ on } \partial\Omega_0, \\ p_1 &= \frac{2R_0R_1+4R_{0\theta}R_{1\theta}-R_1R_{0\theta\theta}-R_0R_{1\theta\theta}}{(R_0^2+R_{0\theta}^2)^{\frac{3}{2}}}-R_1p_{0r} \\ &-\frac{3}{2}\frac{(R_0^2+2R_{0\theta}^2-R_0R_{0\theta\theta})(2R_0R_1+2R_{0\theta}R_{1\theta})}{(R_0^2+R_{0\theta}^2)^{\frac{5}{2}}} \text{ on } \partial\Omega_0, \\ R_{1t} &= \Big(-\frac{p_{0r}R_{0\theta}^2}{R_0(R_0^2+R_{0\theta}^2)}-p_{0rr}+\frac{p_{0\theta r}R_{0\theta}}{R_0^2}-\frac{p_{0\theta}R_{0\theta}}{R_0^3} \\ &-\frac{p_{0\theta}R_{0\theta}}{R_0(R_0^2+R_{0\theta}^2)}\Big)R_1+\Big(\frac{p_{0r}R_{0\theta}}{R_0^2+R_{0\theta}^2}+\frac{p_{0\theta}}{R_0^2+R_{0\theta}^2}\Big)R_{1\theta} \\ &+\Big(\frac{p_{1\theta}R_{0\theta}}{R_0^2}-p_{1r}\Big) \qquad \text{on } \partial\Omega_0. \end{aligned} \tag{18}$$

We tested numerically for linear stability. For radial symmetric solutions, we use (6) and (7) to obtain the solutions. For non-radial symmetric solutions, we use (1)-(4) and drop the higher term to get approximations of solutions in a small neighborhood of μ_2: we take ϵ to be a small value such as $10^{-2}, 10^{-3}$. Once the solution is computed, we can recover the parameter μ from the linearized equation (18) and test linear stability by checking the spectrum of the linearized system. Doing this, the linear stability in a small neighborhood of μ_2 has been numerically verified and is shown in Figure 4.

Figure 4: Linear stability of the solution branches



5. Conclusion

Although the tumor model with a necrotic core analyzed in this paper is quite simple, we may nevertheless draw some interesting biological conclusions from the mathematical results. Tumors grown in culture are typically sphere. However, tumor grown in vivo may have a variety of shapes. In particular, a tumor with a necrotic core is associated with the growth of protrusions. In our model, these protrusions are expressed by the shape

$$r = R + \epsilon \cos(n\theta) + O(\epsilon^2), r = \rho + \epsilon\rho_1 \cos(n\theta) + O(\epsilon^2)$$

of the free boundaries; the number of protrusions depend on n. The aggressiveness of a tumor is measured by the parameter μ. the larger the μ is the more aggressive the tumor is. As this parameter increases, the tumor will lose its spherical shape, develop fingers, and become invasive. The linear stability asserts that radial instability occurs when μ reaches the first bifurcation point μ_2. Moreover, there is non-radial stability for part of a neighborhood of μ_2 on a non-radial branch. The numerical algorithms we use to carry out these computations will be presented in another paper, which in particular show that the non-radial solutions have non-spherical shapes.

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