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Bifurcation Analysis for a Free Boundary Problem Modeling Growth of Solid Tumor with Inhibitors

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Abstract: This paper is concerned with the bifurcation analysis for a free boundary problem modeling the growth of solid tumor with inhibitors. In this problem, surface tension coefficient plays the role of bifurcation parameter, it is proved that there exists a sequence of the nonradially stationary solutions bifurcate from the radially symmetric stationary solutions. Our results indicate that the tumor grown in vivo may have various shapes. In particular, a tumor with an inhibitor is associated with the growth of protrusions.

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1 Introduction

During the past forty years, a number of mathematical models have been studied and developed, see review papers [1]–[5] and the references therein. Among those, the growth of solid tumor models, described by partial differential equations with a free boundary, have been given considerable attention, see [6]–[21]. Solid tumor growth can be regarded as a result of various interactions within the micro environment, such as nutrient (e.g. oxygen, glucose), or inhibitors (e.g. inhibitory material developed from the immune system of healthy cells, anti-cancer drugs and radiation administered by medical treatment), etc.

In this paper, we consider a mathematical model describing the stationary state of an

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avascular solid tumor with inhibitor:

$$\Delta\sigma = f(\sigma) \qquad \text{in } \Omega, \tag{1.1}$$

$$\Delta\beta = g(\beta) \qquad \text{in } \Omega, \tag{1.2}$$

$$-\Delta p = h(\sigma,\beta) \qquad \text{in } \Omega, \tag{1.3}$$

$$\sigma = \bar{\sigma} \qquad \text{on } \partial\Omega, \tag{1.4}$$

$$\beta = \bar{\beta} \qquad \text{on } \partial\Omega, \tag{1.5}$$

$$\frac{\partial p}{\partial \nu} = 0 \qquad \text{on } \partial\Omega, \tag{1.6}$$

$$p = \gamma\kappa \qquad \text{on } \partial\Omega. \tag{1.7}$$

In this model, $\Omega \subseteq \mathbf{R}^3$ is the domain occupied by the tumor. σ, β denote the concentration of nutrient and inhibitor within the tumor, respectively. The pressure p within the tumor comes from the proliferation of the tumor cells. $f(\sigma)$, $g(\sigma)$, $h(\sigma,\beta)$ are the nutrient consumption rate, inhibitor consumption rate and tumor-cell proliferation rate function, respectively. $\bar{\sigma}$ and $\bar{\beta}$ are positive constants, $\sigma = \bar{\sigma}$ and $\beta = \bar{\beta}$ mean that the tumor receives constant nutrient and inhibitor supply from the exterior surface, respectively. ν is the outward normal of the free boundary $\partial\Omega$, γ is the surface tension coefficient, and κ is the mean curvature of the free boundary $\partial\Omega$.

According to the medicine and biology, as well as the need of the mathematics, we assume that f, g, h are functions satisfying the following conditions:

(A_1) $f \in C^\infty[0,\infty)$, $\quad g \in C^\infty[0,\infty)$, $\quad h \in C^\infty([0,\infty)\times[0,\infty))$;

(A_2) $f'(\sigma) > 0$ for $\sigma \geq 0$ and $f(0) = 0$;

(A_3) $g'(\beta) > 0$ for $\beta \geq 0$ and $g(0) = 0$;

(A_4) $\dfrac{\partial h(\sigma,\beta)}{\partial\sigma} > 0$, $\dfrac{\partial h(\sigma,\beta)}{\partial\beta} < 0$ for $\sigma > 0$, $\beta > 0$ and $h(0,0) < 0$.

$f(\sigma)$ is strictly monotone increasing about σ means the concentration of nutrient is much larger, the tumor cells consume more nutrient in the unit time. $f(0) = 0$ means the nutrient consumption is zero when there is no nutrient, we can make similar explanation for $g(\beta)$. $h(\sigma,\beta)$ is strictly monotone increasing about σ and decreasing about β means increasing the concentration of the nutrient and inhibitor will enlarge and lower the proliferation rate of the tumor cells, respectively. $h(0,0) < 0$ means that the number of tumor cells decreases when the concentration of nutrient and inhibitor are all zero. Obviously, these assumptions satisfy the medicine and biology principle.

For the system (1.1)–(1.7) without inhibitors, i.e., $\beta = 0$, the authors of [13], [15] and [16] studied the linear case: $f(\sigma) = \sigma$, $h(\sigma) = \mu(\sigma - \widetilde{\sigma})$, and proved the existence of a unique radially symmetric solution and a sequence of nonradially stationary solutions for this system in two-dimensional case and three-dimensional case respectively. In [11], the above results were extended to general case with $f(\sigma)$, $h(\sigma)$ are smooth functions. For the case $\beta \neq 0$, the existence of radially symmetric stationary solutions and nonradially stationary solutions were analysed for the linear case of (1.1)–(1.7) by Cui *et al.* in [10], [12], [20] and [21]. For general case of (1.1)–(1.7), the existence of the radially symmetric solutions was studied by

Wei and Cui in [19]. In this paper, we study the existence of nonradially solutions of the problem (1.1)–(1.7). We shall regard (1.1)–(1.7) as a bifurcation problem with γ being the bifurcation parameter, and reduce this problem into the following bifurcation equation with the form:

$$\mathcal{F}(\rho, \gamma) = 0, \tag{1.8}$$

where $\mathcal{F}$ is nonlinear operator. By studying the linearized problem, we compute all eigenvalues of its Fréchet derivative $D_\rho \mathcal{F}(0, \gamma)$, then applying Crandall-Rabinowitz bifurcation theorem (cf. Theorem 1.7 in [14]), we obtain that there exists a null sequence of numbers $\{\gamma_k\}$, and an integer $k^* \geq 2$ such that in a neighborhood of each γ_k with $k \geq k^*$, the problem (1.1)–(1.7) has a branch of nonradially symmetric solutions bifurcating from the radially symmetric solutions.

The rest of this paper is organized as follows. In Section 2, we study the linearization of (1.1)–(1.7) at radially symmetric solution. In Section 3, we reduce problem (1.1)–(1.7) into the abstract form (1.8) and study the properties of the operators $\mathcal{F}(\,\cdot\,, \gamma)$. In Section 4, we study bifurcation solutions and prove our main result. Some conclusions are also given in the last section.

2 Linearization

It was shown in [19] that there exists a unique radially symmetric solution ($\sigma_0(r)$, $\beta_0(r)$, $p_0(r)$, Ω_0) of the problem (1.1)–(1.7) with $\Omega_0 = \{x \in \mathbf{R}^3 : |x| < R_s\}$. In this section, we determine the linearization of the problem (1.1)–(1.7) at the radially symmetric solution. We also provide conditions which imply that the linearized problem has nontrivial solutions.

For $S(\omega) \in \mathbb{S}^2$, denote $\Omega_\varepsilon = \{x \in \mathbf{R}^3 : r < R_s + \varepsilon S(\omega)\}$, we consider the perturbations of the radially symmetric solution ($\sigma_0(r)$, $\beta_0(r)$, $p_0(r)$, Ω_0) of the form

$$\begin{aligned} \sigma(x) &= \sigma_0(r) + \varepsilon\sigma_1(r, \omega) + o(\varepsilon^2), \\ \beta(x) &= \beta_0(r) + \varepsilon\beta_1(r, \omega) + o(\varepsilon^2), \\ p(x) &= p_0(r) + \varepsilon p_1(r, \omega) + o(\varepsilon^2), \end{aligned}$$

where $r = |x|$ and $w = \dfrac{x}{|x|}$. Moreover, ε is a small parameter and σ_1, β_1, p_1 are functions to be determined. Let Δ_w be the Laplace-Beltrami operator on the sphere $\mathbb{S}^2$. Similar to [11], substituting the aforementioned expressions into (1.1)–(1.7) and using the relations

$$\sigma_0''(r) + \frac{2}{r}\sigma_0'(r) = f(\sigma_0(r)), \tag{2.1}$$

$$\beta_0''(r) + \frac{2}{r}\beta_0'(r) = g(\beta_0(r)), \tag{2.2}$$

$$p_0''(r) + \frac{2}{r}p_0'(r) = -h(\sigma_0(r), \beta_0(r)), \tag{2.3}$$

we can get that the linearizations of (1.1)–(1.7) satisfy the following:

$$\frac{\partial^2 \sigma_1}{\partial r^2} + \frac{2}{r}\frac{\partial \sigma_1}{\partial r} + \frac{1}{r^2}\Delta_w \sigma_1 = f'(\sigma_0(r))\sigma_1, \tag{2.4}$$

$$\frac{\partial^2 \beta_1}{\partial r^2} + \frac{2}{r}\frac{\partial \beta_1}{\partial r} + \frac{1}{r^2}\Delta_w \beta_1 = g'(\beta_0(r))\beta_1, \tag{2.5}$$

$$\frac{\partial^2 p_1}{\partial r^2} + \frac{2}{r}\frac{\partial p_1}{\partial r} + \frac{1}{r^2}\Delta_w p_1 = -\frac{\partial h}{\partial \sigma}(\sigma_0(r), \beta_0(r))\sigma_1 - \frac{\partial h}{\partial \beta}(\sigma_0(r), \beta_0(r))\beta_1, \tag{2.6}$$

$$\sigma_1(R_s, \omega) + \sigma_0'(R_s)S(\omega) = 0, \tag{2.7}$$

$$\beta_1(R_s, \omega) + \beta_0'(R_s)S(\omega) = 0, \tag{2.8}$$

$$\frac{\partial p_1}{\partial r}(R_s, \omega) - h(\bar{\sigma}, \bar{\beta})S(\omega) = 0, \tag{2.9}$$

$$p_1(R_s, \omega) + \frac{\gamma}{R_s^2}\Big[S(\omega) + \frac{1}{2}\Delta_\omega S(\omega)\Big] = 0. \tag{2.10}$$

Thus we have the following result.

Lemma 2.1 *The linearization of the problem* (1.1)–(1.7) *at the radially symmetric solutions* $(\sigma_0(r),\ \beta_0(r),\ p_0(r),\ \Omega_0)$ *is given by the problem* (2.4)–(2.10).

We now investigate the question of whether there exists γ such that the problem (2.4)–(2.10) has nontrivial solutions. For this purpose we first note that standard results for second order elliptic partial differential equations imply that all solutions $\sigma_1,\ \beta_1,\ p_1$ are smooth, namely, $\sigma_1, \beta_1, p_1 \in C^\infty(\bar{B}_{R_s}) \subseteq C^\infty([0, R_s],\ C^\infty(\mathbb{S}^2))$, and $S \in C^\infty(\mathbb{S}^2)$. Thus these functions can be expanded in the following way:

$$\sigma_1 = \sum_{k=1}^{\infty}\sum_{l=-k}^{k} u_{kl}(r)Y_{kl}(\omega), \tag{2.11}$$

$$\beta_1 = \sum_{k=1}^{\infty}\sum_{l=-k}^{k} v_{kl}(r)Y_{kl}(\omega), \tag{2.12}$$

$$p_1 = \sum_{k=1}^{\infty}\sum_{l=-k}^{k} \Big(j_{kl}(r)Y_{kl}(\omega) + q_{kl}(r)Y_{kl}(\omega)\Big), \tag{2.13}$$

$$S(\omega) = \sum_{k=1}^{\infty}\sum_{l=-k}^{k} c_{kl}Y_{kl}(\omega), \tag{2.14}$$

where $Y_{kl}(\omega)$ $(k \geq 0,\ -k \leq l \leq k)$ denotes the spherical harmonics of the order $(k,\ l)$. Substituting (2.11)–(2.14) into (2.4)–(2.10), using the relation

$$\Delta_\omega Y_{kl}(\omega) = -k(k+1)Y_{kl}(\omega),$$

we get

$$u_{kl}''(r) + \frac{2}{r}u_{kl}'(r) - \frac{k(k+1)}{r^2}u_{kl}(r) = f'(\sigma_0)u_{kl}(r), \tag{2.15}$$

$$v_{kl}''(r) + \frac{2}{r}v_{kl}'(r) - \frac{k(k+1)}{r^2}v_{kl}(r) = g'(\beta_0)v_{kl}(r), \tag{2.16}$$

$$j_{kl}''(r) + \frac{2}{r}j_{kl}'(r) - \frac{k(k+1)}{r^2}j_{kl}(r) = -\frac{\partial h}{\partial \sigma}(\sigma_0, \beta_0)u_{kl}(r), \tag{2.17}$$

$$q_{kl}''(r) + \frac{2}{r}q_{kl}'(r) - \frac{k(k+1)}{r^2}q_{kl}(r) = -\frac{\partial h}{\partial \beta}(\sigma_0, \beta_0)v_{kl}(r), \tag{2.18}$$

$$u_{kl}(R_s) + \sigma_0'(R_s)c_{kl} = 0, \tag{2.19}$$

$$v_{kl}(R_s) + \beta_0'(R_s)c_{kl} = 0, \tag{2.20}$$

$$(j_{kl} + q_{kl})'(R_s) - h(\bar{\sigma}, \bar{\beta})c_{kl} = 0, \tag{2.21}$$

$$(j_{kl} + q_{kl})(R_s) + \frac{\gamma}{R_s^2}\left(1 - \frac{k(k+1)}{2}\right)c_{kl} = 0. \tag{2.22}$$

Let $\bar{u}_k(r)$, $\bar{v}_k(r)$ are the solutions of the following problems, respectively,

$$\bar{u}_k''(r) + \frac{2k+2}{r}\bar{u}_k'(r) = f'(\sigma_0(r))\bar{u}_k(r), \tag{2.23}$$

$$\bar{u}_k(0) = 1, \qquad \bar{u}_k'(0) = 0 \tag{2.24}$$

and

$$\bar{v}_k''(r) + \frac{2k+2}{r}\bar{v}_k'(r) = g'(\beta_0(r))\bar{v}_k(r), \tag{2.25}$$

$$\bar{v}_k(0) = 1, \qquad \bar{v}_k'(0) = 0. \tag{2.26}$$

Denote

$$u_{kl}(r) = a_{kl}r^k\bar{u}_k(r), \tag{2.27}$$

$$v_{kl}(r) = b_{kl}r^k\bar{v}_k(r), \tag{2.28}$$

then $u_{kl}(r)$, $v_{kl}(r)$ satisfy the equations (2.15) and (2.16), where a_{kl}, b_{kl} are arbitrary constants.

Similarly, the solutions of (2.17)-(2.18) are given by:

$$j_{kl}(r) = a_{kl}r^k\bar{j}_k(r) + d_{kl}r^k, \tag{2.29}$$

$$q_{kl}(r) = b_{kl}r^k\bar{q}_k(r) + e_{kl}r^k, \tag{2.30}$$

where a_{kl} is as before, d_{kl}, e_{kl} are arbitrary constants proportional to a_{kl} and b_{kl} for an arbitrary constant c, respectively, and $j_{kl}(r)$ is the following boundary value problem

$$\bar{j}_k''(r) + \frac{2k+2}{r}\bar{j}_k'(r) = -\frac{\partial h}{\partial \sigma}(\sigma_0(r),\ \beta_0(r))\bar{u}_k(r), \tag{2.31}$$

$$\bar{j}_k(0) = 0, \qquad \bar{j}_k'(0) = 0 \tag{2.32}$$

and $q_{kl}(r)$ is the solution of the following problem

$$\bar{q}_k''(r) + \frac{2k+2}{r}\bar{q}_k'(r) = -\frac{\partial h}{\partial \beta}(\sigma_0(r),\ \beta_0(r))\bar{v}_k(r), \tag{2.33}$$

$$\bar{q}_k(0) = 0, \qquad \bar{q}_k'(0) = 0. \tag{2.34}$$

Substituting (2.27)-(2.28), (2.29)-(2.30) into (2.19)–(2.22), after simplification, we get the following equation for a_{kl}, b_{kl}, c_{kl}, $d_{kl} + e_{kl}$ satisfying:

$$a_{kl}R_s^k\bar{u}_k(R_s) + \sigma_0'(R_s)c_{kl} = 0, \tag{2.35}$$

$$b_{kl}R_s^k\bar{v}_k(R_s) + \beta_0'(R_s)c_{kl} = 0, \tag{2.36}$$

$$\begin{aligned} a_{kl}(kR_s^{k-1}\bar{j}_k(R_s) + R_s^k\bar{j}_k'(R_s)) + b_{kl}(kR_s^{k-1}\bar{q}_k(R_s) + R_s^k\bar{q}_k'(R_s)) \\ + (d_{kl} + e_{kl})kR_s^{k-1} - h(\bar{\sigma}, \bar{\beta})c_{kl} = 0, \end{aligned} \tag{2.37}$$

$$a_{kl}R_s^k\bar{j}_k(R_s) + b_{kl}R_s^k\bar{q}_k(R_s) + (d_{kl} + e_{kl})R_s^k + \frac{\gamma}{R_s^2}\left(1 - \frac{k(k+1)}{2}\right)c_{kl} = 0. \tag{2.38}$$

Hence, (2.4)–(2.10) has a nontrivial solution if and only if there exists $k \geq 2$ such that (2.35)–(2.38) has a nontrivial solution. In the following, we provide conditions on γ which guarantee that (2.35)–(2.38) has a nontrivial solution.

Lemma 2.2 *The system* (2.35)–(2.38) *has a nontrivial solution if and only if* $\gamma = \gamma_k$, *where*

$$\gamma_k = \frac{2R_s^3}{(k^2+k-2)k}\left(h(\bar{\sigma},\ \bar{\beta}) - \frac{\sigma_0'(R_s)}{\bar{u}_k(R_s)R_s^{2k+2}}\int_0^{R_s}\frac{\partial h}{\partial \sigma}(\sigma_0(\rho),\ \beta_0(\rho))\bar{u}_k(\rho)\rho^{2k+2}\mathrm{d}\rho\right.$$
$$\left. - \frac{\beta_0'(R_s)}{\bar{v}_k(R_s)R_s^{2k+2}}\int_0^{R_s}\frac{\partial h}{\partial \beta}(\sigma_0(\rho),\ \beta_0(\rho))\bar{v}_k(\rho)\rho^{2k+2}\mathrm{d}\rho\right), \qquad k \geq 2. \tag{2.39}$$

In this case, the nontrivial solutions of (2.35)–(2.38) *are unique up to a constant factor. Moreover, there exists a positive integer* k^* *such that*

$$\gamma_{k+1} < \gamma_k, \qquad k \geq k^*. \tag{2.40}$$

Proof. A simple computation shows that the determinant of the coefficient matrix of (2.35)–(2.38) is equal to the product of $R_s^{2k-1}\bar{u}_k(R_s)$ with

$$-h(\bar{\sigma},\ \bar{\beta})R_s - \frac{\beta_0'(R_s)}{\bar{v}_k(R_s)}R_s\bar{q}_k'(R_s) - \frac{R_s\sigma_0'(R_s)}{\bar{u}_k(R_s)}\bar{j}_k'(R_s) - k\left(\frac{\gamma}{R_s^2}\right)\left(1-\frac{k(k+1)}{2}\right) \equiv D_k(\gamma).$$

Hence, (2.35)–(2.38) has a nontrivial solution if and only if $D_k(\gamma)=0$, namely,

$$\gamma = \gamma_k = \frac{2R_s^3}{(k^2+k-2)k}\left(h(\bar{\sigma},\ \bar{\beta}) + \frac{\sigma_0'(R_s)}{\bar{u}_k(R_s)}\bar{j}_k'(R_s) + \frac{\beta_0'(R_s)}{\bar{v}_k(R_s)}\bar{q}_k'(R_s)\right).$$

From (2.31) and (2.33) we further infer that

$$\bar{j}_k'(R_s) = -\frac{1}{R_s^{2k+2}}\int_0^{R_s}\frac{\partial h}{\partial \sigma}(\sigma_0(\rho),\ \beta_0(\rho))\bar{u}_k(\rho)\rho^{2k+2}\,\mathrm{d}\rho,$$
$$\bar{q}_k'(R_s) = -\frac{1}{R_s^{2k+2}}\int_0^{R_s}\frac{\partial h}{\partial \beta}(\sigma_0(\rho),\ \beta_0(\rho))\bar{v}_k(\rho)\rho^{2k+2}\,\mathrm{d}\rho,$$

which implies that γ_k is given by (2.39). If $\gamma=\gamma_k$, then clearly the solutions of (2.35)–(2.38) are unique up to a constant factor.

To verify (2.40), we first observe (2.23) and (2.25), which imply that

$$\bar{u}_k'(r) = \frac{1}{r^{2k+2}}\int_0^r f'(\sigma_0(\rho))\bar{u}_k(\rho)\rho^{2k+2}\mathrm{d}\rho > 0, \qquad 0<r<R,$$
$$\bar{v}_k'(r) = \frac{1}{r^{2k+2}}\int_0^r g'(\beta_0(\rho))\bar{v}_k(\rho)\rho^{2k+2}\,\mathrm{d}\rho > 0, \qquad 0<r<R.$$

Hence $\bar{u}_k'(r)$, $\bar{v}_k'(r)$ are increasing. Let us introduce the notation

$$\delta_{k_1} = \frac{\beta_0'(R_s)}{\bar{v}_k(R_s)R_s^{2k+2}}\int_0^{R_s}\frac{\partial h}{\partial \beta}(\sigma_0(\rho),\ \beta_0(\rho))\bar{v}_k(\rho)\rho^{2k+2}\mathrm{d}\rho,$$
$$\delta_{k_2} = \frac{\sigma_0'(R_s)}{\bar{u}_k(R_s)R_s^{2k+2}}\int_0^{R_s}\frac{\partial h}{\partial \sigma}(\sigma_0(\rho),\ \beta_0(\rho))\bar{u}_k(\rho)\rho^{2k+2}\mathrm{d}\rho.$$

Integration by parts shows that

$$\begin{aligned}\delta_{k_1} &= \frac{\beta_0'(R_s)}{\bar{v}_k(R_s)R_s^{2k+2}}\int_0^{R_s}\frac{\partial h}{\partial \beta}(\sigma_0(\rho),\ \beta_0(\rho))\bar{v}_k(\rho)\mathrm{d}\left(\frac{\rho^{2k+3}}{2k+3}\right)\\ &= \frac{R_s\beta_0'(R_s)}{2k+3}\frac{\partial h}{\partial \beta}(\bar{\sigma},\ \bar{\beta})\\ &\quad - \frac{\beta_0'(R_s)}{(2k+3)\bar{v}_k(R_s)R_s^{2k+2}}\int_0^{R_s}\left[\frac{\partial^2 h}{\partial\beta\partial\sigma}\sigma_0'(\rho) + \frac{\partial^2 h}{\partial\beta^2}\beta_0'(\rho)\right]\bar{v}_k(\rho)\rho^{2k+3}\mathrm{d}\rho\end{aligned}$$

$$
\begin{aligned}
&-\frac{\beta_0'(R_s)}{(2k+3)\bar{v}_k(R_s)R_s^{2k+2}}\int_0^{R_s}\frac{\partial h}{\partial\beta}(\sigma_0(\rho),\ \beta_0(\rho))\bar{v}_k'(\rho)\rho^{2k+3}\,\mathrm{d}\rho \\
&=\frac{R_s\beta_0'(R_s)}{2k+3}\frac{\partial h}{\partial\beta}(\bar\sigma,\ \bar\beta)-\frac{\beta_0'(R_s)}{(2k+3)\bar{v}_k(R_s)R_s^{2k+2}}\left[\frac{\partial^2 h}{\partial\beta\partial\sigma}\sigma_0'(\rho)+\frac{\partial^2 h}{\partial\beta^2}\beta_0'(\rho)\right]\bar{v}_k(\rho)\rho^{2k+3}\mathrm{d}\rho \\
&-\frac{\beta_0'(R_s)}{(2k+3)\bar{v}_k(R_s)R_s^{2k+2}}\int_0^{R_s}\int_0^{\rho}\frac{\partial h}{\partial\beta}(\sigma_0(\rho),\ \beta_0(\rho))\rho g'(\beta_0(\eta))\bar{v}_k(\eta)\eta^{2k+2}\mathrm{d}\eta\mathrm{d}\rho \\
&\equiv\frac{R_s\beta_0'(R_s)}{2k+3}\frac{\partial h}{\partial\beta}(\bar\sigma,\ \bar\beta)-\frac{\beta_0'(R_s)}{2k+3}\varepsilon_{k_1}(R_s),
\end{aligned}
$$

$$
\begin{aligned}
\delta_{k_2}=&\frac{R\sigma_0'(R_s)}{2k+3}\frac{\partial h}{\partial\sigma}(\bar\sigma,\ \bar\beta) \\
&-\frac{\sigma_0'(R_s)}{(2k+3)\bar{u}_k(R_s)R_s^{2k+2}}\int_0^{R_s}\left[\frac{\partial^2 h}{\partial\sigma^2}\sigma_0'(\rho)+\frac{\partial^2 h}{\partial\sigma\partial\beta}\beta_0'(\rho)\right]\bar{u}_k(\rho)\rho^{2k+3}\,\mathrm{d}\rho \\
&-\frac{\sigma_0'(R_s)}{(2k+3)\bar{u}_k(R_s)R_s^{2k+2}}\int_0^{R_s}\int_0^{\rho}\frac{\partial h}{\partial\sigma}(\sigma_0(\rho),\beta_0(\rho))\rho f'(\sigma_0(\eta))\bar{u}_k(\eta)\eta^{2k+2}\,\mathrm{d}\eta\,\mathrm{d}\rho \\
\equiv&\frac{R_s\sigma_0'(R_s)}{2k+3}\frac{\partial h}{\partial\sigma}(\bar\sigma,\ \bar\beta)-\frac{\sigma_0'(R_s)}{2k+3}\varepsilon_{k_2}(R_s).
\end{aligned}
$$

Since $\bar{u}_k(r)$, $\bar{v}_k(r)$ are increasing, we have

$$
0\le\frac{\bar{v}_k(\rho)\rho^{2k+2}}{\bar{v}_k(R_s)R_s^{2k+2}}\le\left(\frac{\rho}{R_s}\right)^{2k+2},\quad 0\le\frac{\bar{u}_k(\rho)\rho^{2k+2}}{\bar{u}_k(R_s)R_s^{2k+2}}\le\left(\frac{\rho}{R_s}\right)^{2k+2},\qquad 0\le\rho\le R_s,
$$

which implies that

$$
\lim_{k\to\infty}\frac{\bar{v}_k(\rho)\rho^{2k+2}}{\bar{v}_k(R_s)R_s^{2k+2}}=0,\quad \lim_{k\to\infty}\frac{\bar{u}_k(\rho)\rho^{2k+2}}{\bar{u}_k(R_s)R_s^{2k+2}}=0,\qquad 0\le\rho<R_s.
$$

Hence, by dominated convergence, we see that

$$
\lim_{k\to\infty}\varepsilon_{k_1}(R_s)=0,\qquad \lim_{k\to\infty}\varepsilon_{k_2}(R_s)=0,
$$

or

$$
\delta_{k_1}=\frac{R_s\beta_0'(R_s)}{2k+3}\frac{\partial h}{\partial\beta}(\bar\sigma,\ \bar\beta)(1+o(1)),\quad \delta_{k_2}=\frac{R_s\sigma_0'(R_s)}{2k+3}\frac{\partial h}{\partial\sigma}(\bar\sigma,\ \bar\beta)(1+o(1))\qquad\text{as}\ \ k\to\infty.
$$

Substituting the above expressions into (2.39), we have

$$
\begin{aligned}
\gamma_k=\frac{2R_s^3}{(k^2+k-2)k}\Bigg(h(\bar\sigma,\ \bar\beta)&-\frac{R_s\beta_0'(R_s)}{2k+3}\frac{\partial h}{\partial\beta}(\bar\sigma,\ \bar\beta)(1+o(1)) \\
&-\frac{R_s\sigma_0'(R_s)}{2k+3}\frac{\partial h}{\partial\sigma}(\bar\sigma,\ \bar\beta)(1+o(1))\Bigg),
\end{aligned}
$$

we deduce that

$$
\gamma_{k+1}-\gamma_k=-\frac{6R_s^3}{k^4}h(\bar\sigma,\ \bar\beta)(1+o(1))\qquad\text{as}\ \ k\to\infty,
$$

so that γ_k is strictly decreasing for k sufficiently large. This is to say that there exists a positive integer k^* such that for $k\ge k^*$, $\gamma_{k+1}<\gamma_k$. This completes the proof of (2.40).

We now summarize the main result of this section.

Theorem 2.1 *The system of* (2.4)–(2.10) *has a nontrivial solution if and only if* $\gamma=\gamma_k$ *for some* $k\ge 2$.

3 Reduction of the Problem

In this section, we perform the deduction of reducing problem (1.1)–(1.7) into an abstract equation of the form (1.8), and study properties of the operators $\mathcal{F}(\,\cdot\,,\gamma)$.

Recall $\Omega_0 = \{x \in \mathbf{R}^3\colon |x| < R_s\}$ and $\partial\Omega_0 = \{x \in \mathbf{R}^3\colon |x| = R_s\}$. We first introduce the so-called Hanzawa transformation to convert the free boundary problem (1.1)–(1.7) into a nonlinear problem on the fixed domain Ω_0. For this purpose, we take a function $\chi \in C^\infty[0, \infty)$ such that

$$\chi(t) = 0 \quad \text{for} \quad 0 \le t \le \frac{1}{2}; \quad \chi(t) = 1 \quad \text{for} \quad t \ge 1; \quad 0 \le \chi'(t) \le 3 \quad \text{for} \quad t \ge 0. \tag{3.1}$$

Let $m \ge 3$ and $0 < \alpha < 1$. For a sufficiently small positive $\delta < \dfrac{1}{3}\min\{R_s, 1\}$, we denote

$$\mathcal{O}_\delta^{m+\alpha}(\partial\Omega_0) = \{\rho \in C^{m+\alpha}(\partial\Omega_0) : \parallel \rho \parallel_{C^1(\partial\Omega_0)} < \delta\}.$$

Given $\rho \in \mathcal{O}_\delta^{m+\alpha}(\partial\Omega_0)$, we denote

$$\Omega_\rho = \{x \in \mathbf{R}^3 : x = r\omega,\ 0 \le r < R_s + \rho(R_s\omega),\ \omega \in \mathbb{S}^2\}. \tag{3.2}$$

Now, the Hanzawa transformation $\Psi_\rho : \mathbf{R}^3 \to \mathbf{R}^3$ can be defined by $\Psi_\rho(0) = 0$ and

$$\Psi_\rho(x) = x - \rho(R_s\omega)\chi\left(\frac{r}{R_s + \rho(R_s\omega)}\right)\omega, \qquad x \in \mathbf{R}^3,$$

where $r = |x|$ and $\omega = \dfrac{x}{|x|}$ for $x \ne 0$. Clearly, $\Psi_\rho(\Omega_\rho) = \Omega_0$. Using (3.1), we can easily verify that the function $r \to r - \rho\chi\left(\dfrac{r}{R_s} + \rho\right)$ is strictly monotone increasing for any fixed $\omega \in \mathbb{S}^2$, hence $\Psi_\rho \in \mathit{Diff}^{m+\alpha}(\mathbf{R}^3,\ \mathbf{R}^3) \cap \mathit{Diff}^{m+\alpha}(\Omega_\rho,\ \Omega_0)$. As usual, we denote by Ψ_ρ^* and $(\Psi_\rho)_*$ the pullback and push-forward operators induced by Ψ_ρ, respectively, that is,

$$\Psi_\rho^* u = u \circ \Psi_\rho \quad \text{for} \quad u \in C(\overline{\Omega}_0) \quad \text{and} \quad (\Psi_\rho)_* v = v \circ \Psi_\rho^{-1} \quad \text{for} \quad v \in C(\overline{\Omega}_\rho).$$

Clearly, if $\rho \in C^{m+\alpha}(\partial\Omega_0)$, then

$$\Psi_\rho^* \in L(C^{m+\alpha}(\overline{\Omega}_0),\ C^{m+\alpha}(\overline{\Omega}_\rho)) \quad \text{and} \quad (\Psi_\rho)_* \in L(C^{m+\alpha}(\overline{\Omega}_\rho),\ C^{m+\alpha}(\overline{\Omega}_0)).$$

Next, given $\rho \in \mathcal{O}_\delta^{m+\alpha}(\partial\Omega_0)$ ($m \ge 3,\ 0 < \alpha < 1$), we define operators $\mathcal{L}(\rho) : C^{m+\alpha}(\overline{\Omega}_0) \to C^{m+\alpha-2}(\overline{\Omega}_0)$ and $\mathcal{N}(\rho) : C^{m+\alpha}(\overline{\Omega}_0) \to C^{m+\alpha-1}(\partial\Omega_0)$, respectively, by

$$\mathcal{L}(\rho) = (\Psi_\rho)_* \circ \Delta \circ \Psi_\rho^* \quad \text{and} \quad \mathcal{N}(\rho) = (\Psi_\rho|_{\partial\Omega_\rho})_* \circ \frac{\partial}{\partial n} \circ \Psi_\rho^*,$$

where $\dfrac{\partial}{\partial n}$ denotes the outward normal derivative operator on $\partial\Omega_\rho$, and $\Psi_\rho|_{\partial\Omega_\rho}$ denotes the restriction of Ψ_ρ on $\partial\Omega_\rho$. Note that $\mathcal{L}(\rho)$ is a second-order elliptic partial differential operator on Ω_0 with variable coefficients, and $\mathcal{N}(\rho)$ is a first-order boundary differential operator. Clearly,

$$\mathcal{L} \in C^\infty(\mathcal{O}_\delta^{m+\alpha}(\partial\Omega_0), L(C^{m+\alpha}(\overline{\Omega}_0), C^{m+\alpha-2}(\overline{\Omega}_0))),$$
$$\mathcal{N} \in C^\infty(\mathcal{O}_\delta^{m+\alpha}(\partial\Omega_0), L(C^{m+\alpha}(\overline{\Omega}_0), C^{m+\alpha-1}(\partial\Omega_0))).$$

Finally, for ρ as mentioned earlier, we define $\kappa : C^{m+\alpha}(\partial\Omega_0) \to C^{m+\alpha-2}(\partial\Omega_0)$ by

$$\kappa(\rho)(R_s\omega)$$
$$=\{\text{the mean curvature of the hypersurface } r = R_s + \rho(R_s\omega) \text{ at the point } \Psi_\rho^{-1}(R_s\omega)\}.$$

Note that for any $\omega \in \mathbb{S}^2$, we have

$$\Psi_\rho^{-1}(R_s\omega) = (R_s + \rho(R_s\omega))\omega.$$

Using these notation, it is not difficult to verify that the Hanzawa transformation (3.2) converts problem (1.1)–(1.7) into the following equivalent system:

$$\mathcal{L}(\rho)u = F(u) \qquad \text{in } \Omega_0, \tag{3.3}$$

$$\mathcal{L}(\rho)v = G(v) \qquad \text{in } \Omega_0, \tag{3.4}$$

$$\mathcal{L}(\rho)w = -H(u,v) \qquad \text{in } \Omega_0, \tag{3.5}$$

$$u = \bar{\sigma} \qquad \text{on } \partial\Omega_0, \tag{3.6}$$

$$v = \bar{\beta} \qquad \text{on } \partial\Omega_0, \tag{3.7}$$

$$w = \gamma\kappa(\rho) \qquad \text{on } \partial\Omega_0, \tag{3.8}$$

$$\mathcal{N}(\rho)w = 0 \qquad \text{on } \partial\Omega_0, \tag{3.9}$$

More precisely, we have

Lemma 3.1 *If (σ,β,p,Ω), where σ, $\beta \in C^{m+\alpha}(\overline{\Omega})$, $p \in C^{m+\alpha-2}(\overline{\Omega})$ and $\Omega = \Omega_\rho$ for some $\rho \in C^{m+\alpha}(\partial\Omega_0)$, is a solution of problem* (1.1)–(1.7), *then by setting $u = (\Psi_\rho)_*\sigma$, $v = (\Psi_\rho)_*\beta$ and $w = (\Psi_\rho)_*w$, we obtain a solution (u,v,w,ρ) of problem* (3.3)–(3.9). *Conversely, if $(u,v,w,\rho) \in C^{m+\alpha}(\overline{\Omega}_0)\times C^{m+\alpha}(\overline{\Omega}_0)\times C^{m+\alpha-2}(\overline{\Omega}_0)\times C^{m+\alpha}(\partial\Omega_0)$ is a solution of problem* (3.3)–(3.9), *then by setting $\sigma = \Psi_\rho^* u$, $\beta = \Psi_\rho^* v$, $w = \Psi_\rho^* w$ and $\Omega = \Omega_\rho$, we obtain a solution of the problem* (1.1)–(1.7).

Fix $m \in \mathbf{N}$ with $m \geq 3$, $0 < \alpha < 1$ and $0 < \delta < \dfrac{1}{3}\min\{R_s,\, 1\}$. Given $\rho \in \mathcal{O}_\delta^{m+\alpha}(\partial\Omega_0)$, we use the standard Schauder theory for elliptic boundary value problems to solve (3.3)–(3.8). Then we obtain a unique solution

$$(u,v,w) = (\mathcal{U}(\rho),\mathcal{V}(\rho),\mathcal{W}_\gamma(\rho)) \in C^{m+\alpha}(\overline{\Omega}_0) \times C^{m+\alpha}(\overline{\Omega}_0) \times C^{m+\alpha-2}(\overline{\Omega}_0) \times C^{m+\alpha}(\partial\Omega_0).$$

Substituting $w = \mathcal{W}_\gamma(\rho)$ into (3.9) and denoting $\mathcal{F}(\rho,\ \gamma) = \mathcal{N}(\rho)\mathcal{W}_\gamma(\rho)$, we obtain the following equation:

$$\mathcal{F}(\rho,\ \gamma) = 0. \tag{3.10}$$

By the reduction and standard theory of elliptic equations, we can verify that

$$\mathcal{F}(\,\cdot\,,\gamma) \in C^\infty\Big(\mathcal{O}_\delta^{m+\alpha}(\partial\Omega_0),\ C^{m+\alpha-3}(\partial\Omega_0)\Big). \tag{3.11}$$

The following result will play an important role in later discussion:

Lemma 3.2 *The Fréchet derivative of $\mathcal{F}(\rho,\gamma)$ at $\rho = 0$ is a Fourier multiplication operator and has the following expression: For any $\rho \in C^\infty(\partial\Omega_0)$ with expansion $\rho = \sum\limits_{k=1}^{\infty}\sum\limits_{l=-k}^{k} c_{kl}Y_{kl}(\omega)$, we have*

$$D_\rho\mathcal{F}(0,\gamma)\rho = \sum_{k=1}^{\infty}\sum_{l=-k}^{k} \eta_k(\gamma)c_{kl}Y_{kl}(\omega), \tag{3.12}$$

where

$$\eta_0(\gamma) \equiv \eta_0 = -f'(u) \neq 0, \qquad \eta_0(\gamma) = 0, \tag{3.13}$$

and

$$\eta_k(\gamma) = \frac{k(k^2+k-2)}{2R_s^3}(\gamma-\gamma_k), \qquad (k \geq 2). \tag{3.14}$$

Proof. Because the equation (3.10) is equivalent to the problem (1.1)–(1.7), the linearization of (3.10) at $\rho = 0$, that is, the equation $D_\rho\mathcal{F}(0,\gamma)\rho = 0$, is correspondingly equivalent to the system of equations (2.15)–(2.22). Hence, from the deduction in Section 2, we see that $D_\rho\mathcal{F}(0,\gamma)\rho$ has an expression of the form (3.12). Furthermore, this argument also shows that the coefficient of $Y_{kl}(\omega)$ in the expression of $D_\rho\mathcal{F}(0,\gamma)\rho$, that is, $\eta_k(\gamma)c_{kl}$ equals the left-hand side of (2.21), by a direct calculation, we obtain (3.13) and (3.14).

4 Bifurcation

In this section, we study bifurcation solutions for the problem (1.1)–(1.7). The main result of this paper is as follows:

Theorem 4.1 *Let* $(\sigma_0, \beta_0, p_0, \Omega_0)$ *be a radial solution of problem* (1.1)–(1.7) *satisfying* $p_0'(R_s) \neq 0$. *If* $h(\sigma, \beta) > 0$, *then there exists a null sequence of positive numbers* $\gamma_k\{k \geq k^*\}$, *where* k^* *is an integer,* $k^* \geq 2$, *such that for each* $k \geq k^*$ *even, in an neighborhood of* $(\sigma_0, \beta_0, p_0, \Omega_0, \gamma_k)$, *there exists a bifurcation branch of solutions* $(\sigma_\varepsilon, \beta_\varepsilon, p_\varepsilon, \Omega_\varepsilon, \gamma_\varepsilon)$ *of problem* (1.1)–(1.7) *with the following form*:

$$\begin{aligned}
&\sigma_\varepsilon(r,\omega) = \sigma_0(r) + u_k(r)Y_{k0}(\omega)\varepsilon + o(\varepsilon),\\
&\beta_\varepsilon(r,\omega) = \beta_0(r) + v_k(r)Y_{k0}(\omega)\varepsilon + o(\varepsilon),\\
&p_\varepsilon(r,\omega) = p_0(r) + w_k(r)Y_{k0}(\omega)\varepsilon + o(\varepsilon),\\
&\Omega_\varepsilon = r = R_s + \varepsilon Y_{k0}(\omega)\varepsilon + o(\varepsilon),\\
&\gamma_\varepsilon = \gamma_k + (2k+2)\varepsilon + o(\varepsilon),
\end{aligned}$$

where $r = |x|$, $\omega = \dfrac{x}{|x|}$, ε *is a real parameter varying in the interval* $(-\xi_k, \xi_k)$ *for some small* $\xi_k > 0$, $u_k(\cdot), v_k(\cdot)$ *and* $w_k(\cdot)$ *are certain smooth functions,* $Y_{k0}(\omega)$ *is the spherical harmonic of order* $(k, 0)$.

It should be pointed out that the bifurcation equation (3.10) is not of the classical type. By Lemma 3.2, we see that Fréchet derivative $D_\rho\mathcal{F}(0,\gamma)$ has a kernel of dimension 3, implying that $D_\rho\mathcal{F}(0,\gamma)$ is always degenerate. Indeed, because any translation of a solution of (1.1)–(1.7) is still a solution, thus all solutions of (3.10) obtained from translating radial solutions make up a 3-dimension manifold, so it is natural.

For any $m \geq 3$ and $0 < \alpha < 1$, we introduce

$X =$ the closure of the span $\{Y_{k0}(\omega), k = 0, 2, 4, \cdots\}$ in $C^{m+\alpha}(\partial\Omega_0)$,

$Y =$ the closure of the span $\{Y_{k0}(\omega), k = 0, 2, 4, \cdots\}$ in $C^{m-3+\alpha}(\partial\Omega_0)$.

Note that in the spherical coordinates (θ, ϕ), $0 \leq \theta \leq \pi$, $0 \leq \phi \leq 2\pi$, the spherical harmonics

$$Y_{kl}(\theta,\phi) = (-1)^l\sqrt{\frac{(2k+1)(k-l)!}{2(k+l)!}}P_k^l(\cos\theta)\frac{\mathrm{e}^{il\phi}}{\sqrt{2\pi}},$$

where

$$P_k^l(z) = \frac{1}{2^k k!}(1-z^2)^{\frac{1}{2}}\frac{d^{k+l}}{dz^{k+l}}(z^2-1)^k.$$

It is easy to verify that for $k \geq 0$ even, $Y_{k0}(\theta,\ \phi)$ is independent of ϕ and satisfies $Y_{k0}(\theta) = Y_{k0}(\pi - \theta)$. Hence, for any function $\rho \in X$, ρ is independent of ϕ and $\rho(\theta) = \rho(\pi - \theta)$. Using this fact and (3.11), we can verify that

$$\mathcal{F}(\,\cdot\,, \gamma) \in C^\infty(\mathcal{O}_\delta^{m+\alpha}(\partial\Omega_0) \cap X,\ Y). \tag{4.1}$$

Later we say γ_k is distinct if $j \neq k$ then $\gamma_j \neq \gamma_k$. The following result holds:

Theorem 4.2 *For distinct* γ_k ($k \geq k^*$ even), $(0,\ \gamma_k)$ *is a bifurcation point of the equation* $\mathcal{F}(\rho,\ \gamma) = 0$. *More precisely, there exists a constant* $\xi_k > 0$ *and a smooth mapping* $\varepsilon \to (\rho_\varepsilon,\ \gamma_\varepsilon)$ *from* $(-\xi_k,\ \xi_k)$ *to* $X \times \mathbf{R}^+$ *of the form*:

$$\rho_\varepsilon = \varepsilon Y_{k0}(\omega) + o(\varepsilon); \quad \gamma_\varepsilon = \gamma_k + (2k+2)\varepsilon + o(\varepsilon) \quad \text{for} \quad \varepsilon \in (-\xi_{\rm k}, \xi_{\rm k}), \tag{4.2}$$

such that $\mathcal{F}(\rho_\varepsilon, \gamma_\varepsilon) = 0$.

Proof. By the reduction in Section 3 and the definition of operator $\mathcal{F}(\,\cdot\,, \gamma)$, it is clear that

$$\mathcal{F}(0,\ \gamma) = 0. \tag{4.3}$$

From Lemma 3.2, we see that

$$D_\rho \mathcal{F}(0,\ \gamma) Y_{00}(\omega) = \alpha_0 Y_{00}(\omega) \neq 0,$$

and

$$D_\rho \mathcal{F}(0, \gamma) Y_{k0}(\omega) = \frac{k(k^2+k-2)}{2R_s^3}(\gamma - \gamma_k) Y_{k0}(\omega) \qquad \text{for } k \geq k^* \text{ even.}$$

Hence, for distinct $\gamma_k (k \geq k^*$ even), we have

$$\ker D_\rho \mathcal{F}(0, \gamma_k) = \operatorname{span}\{Y_{k0}(\omega)\}, \tag{4.4}$$

$$\operatorname{Im} D_\rho \mathcal{F}(0, \gamma_k) \text{ has codimension 1.} \tag{4.5}$$

and

$$D_{\gamma\rho} \mathcal{F}(0, \gamma_k) Y_{k0}(\omega) = -\frac{k(k^2+k-2)}{2}\gamma_k Y_{k0}(\omega) \notin \operatorname{Im} D_\rho \mathcal{F}(0, \gamma_k). \tag{4.6}$$

By (4.3)–(4.6), we see all suppositions of the well-known Crandall-Rabinowitz bifurcation theorem (Theorem 1.7 in [22]) are satisfied, thus $(0,\ \gamma_k)$ is a bifurcation point of the equation $\mathcal{F}(\rho,\ \gamma) = 0$, and the proof is completed.

Proof of Theorem 4.1 Assume $h(\sigma,\ \beta) > 0$ and let $k \geq k^*$ even. By Lemma 2.2, we see that γ_k is distinct, so that $(0,\ \gamma_k)$ is a bifurcation point of the equation $\mathcal{F}(\rho,\ \gamma) = 0$. Then by the reductions in Sections 2 and 3, the assertion of Theorem 4.1 follows.

5 Conclusion

Although the tumor model with inhibitor we studied is quite simple, we may nevertheless draw some interesting biological conclusions from the mathematical result. Tumors grown in culture are typically sphere. However, tumor grown in vivo may have various shapes. In particular, a tumor with an inhibitor is associated with the growth of protrusions. In our model, these protrusions are expressed by the shape $r = R_s + \varepsilon Y_{m,0}(\theta, \varphi) + o(\varepsilon^2)$ of the free boundary. We show that in case $h(\sigma, \beta) > 0$, there exist infinite many nonradial branches of solutions bifurcating at each γ_k ($k \geq k^*$ even).

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