STATIONARY SOLUTIONS OF A FREE BOUNDARY PROBLEM
MODELING GROWTH OF ANGIGENESIS TUMOR
WITH INHIBITOR

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Abstract. We consider a free boundary problem modeling the growth of angiogenesis tumor with inhibitor, in which the tumor aggressiveness is modeled by a parameter $\mu$. The existences of radially symmetric stationary solution and symmetry-breaking stationary solution are established. In addition, it is proved that there exist a positive integer $m^{**}$ and a sequence of $\mu_m$, such that for each $\mu_m (m > m^{**})$, the symmetry-breaking stationary solution is a bifurcation branch of the radially symmetric stationary solution.

1. Introduction. This paper is concerned with a free boundary problem modeling the tumor growth with angiogenesis and inhibitor. Angiogenesis is an essential process in wound healing and new birth. Tumor-induced angiogenesis is a process that tumor cells secrete cytokines that stimulate the vascular system to grow toward the tumor. As a result of angiogenesis, the tumor possesses its own vasculature, then the nutrient may be supplied to tumor via the capillary network. In mathematical model of tumor-induced angiogenesis, the distribution of nutrient in the tumor satisfies the following reaction-diffusion equation [2, 4, 19, 22]:

$$\frac{\partial \sigma}{\partial t} = D_1 \Delta \sigma + \hat{\Gamma}_1 (\sigma_B - \sigma) - \lambda_1 \sigma \quad \text{in } \Omega(t), \quad (1)$$

where $\Omega(t)$ is the tumor domain at time $t$ with a moving boundary $\partial \Omega(t)$, $\sigma$ denotes the concentration of a nutrient which diffuses throughout the tumor, with diffusion coefficient $D_1$, the term $\hat{\Gamma}_1 (\sigma_B - \sigma)$ accounts for the transfer of nutrient by means of the vasculature stemming from tumor-induced angiogenesis, $\hat{\Gamma}_1$ is the transfer rate of nutrient-in-blood-tissue, and $\sigma_B$ is the concentration of nutrient in the vasculature. The last term on the right side describes the nutrient consumption by tumor cells at the rate of $\lambda_1$.

Tumor inhibitors come from some blood-borne anti-cancer drugs or immune system of the body. Let $\beta$ denote the concentration of inhibitor. Assume that the similar effect governs the evolution of tumor inhibitor. Then it follows that [2, 5, 8]:

$$\frac{\partial \beta}{\partial t} = D_2 \Delta \beta + \hat{\Gamma}_2 (\beta_B - \beta) - \lambda_2 \beta \quad \text{in } \Omega(t), \quad (2)$$

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where \( D_2, \Gamma_2, \beta_B \) and \( \lambda_2 \) are similarly defined as those for the nutrient concentration \( \sigma \). And \( \Gamma_2 = 0 \) if the inhibitor is secreted by neighbouring healthy cells, in response to the “foreign” body, delivered by diffusion across the tumor boundary.

Using non-dimensional scales \([2, 4, 5]\), we rewrite the equations (1) and (2):

\[
\delta_1 \frac{\partial \sigma}{\partial t} = \Delta \sigma - \sigma \quad \text{in } \Omega(t),
\]

\[
\delta_2 \frac{\partial \beta}{\partial t} = \Delta \beta - \lambda \beta \quad \text{in } \Omega(t),
\]

where \( \delta_1, \delta_2 \) are small parameters.

The pressure \( p \) stems from the transport of cells which proliferate or die. Formulated by the conservation of mass \( \text{div } u = \mu(\sigma - \tilde{\sigma} - \tau \beta) \) with Darcy’s law \( u = -\nabla p \), we have

\[-\Delta p = \mu(\sigma - \tilde{\sigma} - \tau \beta) \quad \text{in } \Omega(t),\]

where \( u \) is the velocity of tumor cells, the term \( \mu(\sigma - \tilde{\sigma}) \) on the right side is the proliferation rate, \( \mu \) is a parameter expressing the “intensity” of the expansion by mitosis, \( \tilde{\sigma} \) is a threshold concentration and the term \( \mu \tau \beta \) is the death rate of tumor cells caused by the inhibitor.

Since the nutrient enters tumor by the vascular system and diffusion across the boundary, using homogenization \([18, 32]\), it is assumed that \( \sigma \) satisfies the boundary condition:

\[\frac{\partial \sigma}{\partial n} + \alpha(t)(\sigma - \bar{\sigma}) = 0 \quad \text{on } \partial \Omega(t),\]

where \( n \) is the outward normal, \( \bar{\sigma} \) is the nutrient concentration outside the tumor, \( \alpha(t) \) is the rate of nutrient supply to the tumor, which may vary in time, and angiogenesis results in an increase in it; conversely, if the tumor is treated with anti-angiogenic drugs, it will decrease and the starved tumor will shrink. In this paper, we assume that \( \alpha(t) \equiv \alpha \) is a positive constant.

As for the inhibitor, it is assumed to be secreted by neighbouring healthy cells, in response to the “foreign” body, delivered by diffusion across the tumor boundary, then

\[\beta = \bar{\beta} \quad \text{on } \partial \Omega(t),\]

where \( \bar{\beta} \) is the inhibitor concentration outside the tumor.

Due to cell-to-cell adhesiveness and the continuity of the velocity field through the boundary \([2]\), we derive the boundary conditions of \( p \):

\[p = \kappa \quad \text{on } \partial \Omega(t),\]

\[\frac{\partial p}{\partial n} = -V_n \quad \text{on } \partial \Omega(t),\]

where \( \kappa \) is the mean curvature, and \( V_n \) is the velocity of the free boundary in the direction \( n \).

During the last few decades, many mathematical models in the form of free boundary problems of partial differential equations have been proposed to model the growth of tumors; see survey papers \([1, 11, 12, 13, 25]\) and the references therein, also the recent papers \([9, 18, 29, 30, 31, 34], [23]-[27]\). Among those, some theoretical and numerical results are established for the problem \((3)-(9)\) with different boundary conditions. If the boundary condition \((6)\) is replaced by \( \sigma = \tilde{\sigma} \) (which is formally the case \( \alpha(t) = \infty \)) and the inhibitor is absent \( (\beta = 0) \), it is proved in \([10, 14, 15, 19, 20]\) that under the assumption \( \tilde{\sigma} < \sigma \), there exists a unique radially
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symmetric stationary solution on \( B_{R_s} \), and a branch of symmetry-breaking stationary solutions bifurcates from the above radially symmetric stationary solution for each \( \mu_n(R_s)(n \geq 2) \) with free boundary

\[
r = R_s + \varepsilon Y_{n,0}(\theta) + O(\varepsilon^2),
\]

where \( Y_{n,0} \) is the spherical harmonic of order \((n,0)\). Moreover, Friedman and Hu [14] showed that the bifurcation branches stemming from \( \mu_n(R_s)(n \geq 3) \) are all unstable. The above results have been extended to the tumor model where the nutrient consumption rate and the proliferation rate are general nonlinear functions, tumor growth with a necrotic core, tumor growth in fluid-like tissue, tumor cord, multilayer model and so on; see the papers [6, 7, 9, 16, 23, 33]. Moreover, Zhou and Wu [27, 30, 34], Xu et al. [31] established the asymptotic stability and bifurcation analysis for the case that the boundary condition (6) is nonlinear with Gibbs-Thomson relation. In the presence of inhibitor, the asymptotic stability and bifurcation of radially symmetric stationary solution were studied in [5, 8, 26, 28, 29]. It was shown that there exists a threshold value \( \gamma^* \) for the surface tension coefficient which separates instability from stability for the radially symmetric equilibrium with respect to small enough non-radial perturbations, and a branch of non-radial solutions bifurcates from the radially symmetric solution for each \( \gamma_n \) with \( n > n^** \).

In this paper, we are interested in the tumor model with the boundary condition (6) stemming from angiogenesis. For the problem (3)-(9) in the absence of inhibitor, Lam and Friedman [18] established the existence of the radially symmetric stationary solution and the boundedness of free boundary for the bounded \( \alpha(t) \). Recently, Huang, Zhang and Hu [24] showed that when \( \alpha(t) \equiv \alpha \), there exists a branch of symmetry-breaking stationary solutions bifurcating from the radially symmetric stationary solution for each \( \mu_n(n \geq 2) \). Motivated by the above papers, we study the stationary solution of the problem (3)-(9) and seek the effect of inhibitor on the growth of dormant tumor with angiogenesis. Namely, we consider the following problem:

\[
\begin{align*}
\Delta \sigma &= \sigma, & x \in \Omega, \\
\Delta \beta &= \lambda \beta, & x \in \Omega, \\
-\Delta p &= \mu(\sigma - \bar{\sigma} - \tau \beta), & x \in \Omega, \\
\frac{\partial \sigma}{\partial n} + \alpha(\sigma - \bar{\sigma}) &= 0, & x \in \partial \Omega, \\
\beta &= \bar{\beta}, & x \in \partial \Omega, \\
p &= \kappa, & x \in \partial \Omega, \\
\frac{\partial p}{\partial n} &= 0, & x \in \partial \Omega.
\end{align*}
\]

We firstly obtain the existence of the radially symmetric solution of the problem (10)-(16) for all \( \mu \), then prove that there exist a positive integer \( m^{**} \) and a sequence of \( \mu_m \), such that for each \( \mu_m(m > m^{**}) \), there exists a branch of symmetry-breaking solutions bifurcating from the above radially symmetric solution. We also prove that \( \mu_m \) is increasing with respect to the supply of inhibitor \( \bar{\beta} \).

Noticing that the aggressiveness of tumor growth in this paper is measured by the parameter \( \mu \), the larger the \( \mu \) is the more aggressive the tumor is. It is seen from our results that when \( \mu \) is at \( \mu_m \) for large enough \( m \), the tumor will develop
finger and invasive; in addition, for the same branch protrusion, the more supply of inhibitors would require bigger tumor aggressiveness parameter to form the symmetry-breaking stationary state. Namely, increasing the amount of inhibitor can not only reduce the size of the stable dormant tumor ([23, 24]), but also play a positive role in stabilizing radially symmetric tumors.

The rest of this paper is organized as follows. In Section 2, we establish the existence of radially symmetric solution to the problem (10)-(16); in Section 3, we solve the linearized problem of the problem (10)-(16) at the radially symmetric solution; then we obtain the existence of symmetry-breaking solution by the bifurcation theorem in Section 4.

2. Radially symmetric solutions. In this section, we look for the explicit radially symmetric solution to the problem (10)–(16). Let \( r = |x| \). Then in radial case, the problem (10)–(16) clearly equals to the following system:

\[
\begin{align*}
\sigma''(r) + \frac{2}{r} \sigma'(r) &= \sigma(r) \quad \text{for} \quad 0 < r < R, \\
\beta''(r) + \frac{2}{r} \beta'(r) &= \lambda \beta(r) \quad \text{for} \quad 0 < r < R, \\
p''(r) + \frac{2}{r} p'(r) &= -\mu (\sigma(r) - \bar{\sigma} - \tau \beta(r)) \quad \text{for} \quad 0 < r < R, \\
\sigma'(R) + \alpha (\sigma(R) - \bar{\sigma}) &= 0, \quad \beta(R) = \bar{\beta}, \quad p(R) = \frac{1}{R}, \\
p'(R) &= 0.
\end{align*}
\]

For a fixed \( R_s > 0 \), solving the problem (17)–(20), we obtain

\[
\begin{align*}
\sigma_s(r) &= \frac{\alpha \bar{\sigma}}{\alpha + \coth R_s - \frac{1}{R_s} r \sinh R_s} R_s \sinh r \\
\beta_s(r) &= \frac{\beta R_s \sinh(\sqrt{\lambda}r)}{r \sinh(\sqrt{\lambda}R_s)} \\
p_s(r) &= \frac{1}{6} \mu \bar{\sigma} r^2 - \mu \sigma_s(r) + \frac{\mu \tau}{\lambda} \beta_s(r) + C_p \quad \text{for} \quad 0 < r < R_s,
\end{align*}
\]

where

\[
C_p = \frac{1}{R_s} - \frac{1}{6} \mu \bar{\sigma} R_s^2 + \frac{\mu \alpha \bar{\sigma}}{\alpha + \coth R_s - \frac{1}{R_s} r \sinh R_s} - \frac{\mu \tau \bar{\beta}}{\lambda}.
\]

Then \((\sigma_s, \beta_s, p_s)\) given by (22)–(24) is a radially symmetric solution of the system (10)–(16), if \( R_s \) is a positive solution of \( p'_s(R) = 0 \), i.e.,

\[
\frac{1}{3} \bar{\sigma} R_s - \sigma'_s(R_s) + \frac{\tau}{\lambda} \beta'_s(R_s) = 0.
\]

**Theorem 2.1.** For the given positive constants \( \bar{\sigma}, \bar{\beta}, \bar{\sigma}, \mu, \tau, \alpha, \) and \( \bar{\sigma} - \bar{\sigma} - \tau \bar{\beta} > 0 \), there is at least one radially symmetric solution of the system (10)–(16), which is given by (22)–(24).

**Proof.** Obviously, we only need to show the existence of solutions to the problem (17)–(21). It is seen that \((\sigma_s, \beta_s, p_s)\) given by (22)–(24) satisfies the problem (17)–(20). It remains to verify that the boundary condition (21) is satisfied, namely, (25) has at least one positive solution.

Denote

\[
g(r) = \coth r - \frac{1}{r}.
\]
For \( s > 0 \), it follows that \( g'(s) > 0, \) \( (g(s)/s)' < 0 \) and \( g(s) \) satisfies [25]:
\[
\lim_{s \to 0^+} g(s) = 0, \quad \lim_{s \to +\infty} g(s) = 1, \quad \lim_{s \to 0^+} \frac{g(s)}{s} = \frac{1}{3}, \quad \lim_{s \to +\infty} \frac{g(s)}{s} = 0. \tag{26}
\]

Then, \( \sigma_s(r) \) can be rewritten as
\[
\sigma_s(r) = \frac{\alpha \tilde{\sigma}}{\alpha + g(R_s)} \frac{R_s \sinh r}{r \sinh R_s}.
\]

We compute
\[
\sigma'_s(R_s) = -\alpha (\sigma_s(R_s) - \tilde{\sigma}) = -\alpha \left( \frac{\alpha \tilde{\sigma}}{\alpha + g(R_s)} - \tilde{\sigma} \right),
\]
\[
\beta'_s(R_s) = \tilde{\beta} \sqrt{\lambda} \left( \coth(\sqrt{\lambda} R_s) - \frac{1}{\sqrt{\lambda} R_s} \right) = \tilde{\beta} \sqrt{\lambda} g(\sqrt{\lambda} R_s).
\tag{28}
\]

Substituting (27) and (28) into (25), we get
\[
\frac{1}{3} \tilde{\sigma} R_s + \alpha \left( \frac{\alpha \tilde{\sigma}}{\alpha + g(R_s)} - \tilde{\sigma} \right) + \frac{\tau \tilde{\beta}}{\sqrt{\lambda}} g(\sqrt{\lambda} R_s) = 0,
\]
which is equivalent to the following
\[
\alpha \tilde{\sigma} \frac{g(R_s)}{R_s} - \tau \tilde{\beta} \frac{g(\sqrt{\lambda} R_s)}{\sqrt{\lambda} R_s} (\alpha + g(R_s)) - \frac{1}{3} \tilde{\sigma} (\alpha + g(R_s)) = 0.
\]

Let
\[
T(s) = \alpha \tilde{\sigma} \frac{g(s)}{s} - \tau \tilde{\beta} \frac{g(\sqrt{\lambda} s)}{\sqrt{\lambda} s} (\alpha + g(s)) - \frac{1}{3} \tilde{\sigma} (\alpha + g(s)).
\]

Then from (26), we see that
\[
\lim_{s \to 0^+} T(s) = \frac{1}{3} \alpha \tilde{\sigma} - \frac{1}{3} \tilde{\beta} \alpha - \frac{1}{3} \tilde{\sigma} \alpha = \frac{\alpha}{3} (\tilde{\sigma} - \tilde{\sigma} - \tau \tilde{\beta}),
\]
\[
\lim_{s \to +\infty} T(s) = -\frac{1}{3} \tilde{\sigma} (\alpha + 1).
\]

Since \( \tilde{\sigma} - \tilde{\sigma} - \tau \tilde{\beta} > 0, \alpha > 0, \tilde{\sigma} > 0 \), we conclude that \( T(s) = 0 \) has at least one positive root on \((0, \infty)\) by using the continuity of \( T(s) \) and the intermediate value theorem. The proof is complete. \( \square \)

3. **Linearized problem.** In this section, we consider the linearization of the problem (10)–(16) at radially symmetric solution \((\sigma_s, \beta_s, p_s)\) with radius \( R_s \) and solve it by employing spherical harmonics and modified Bessel functions.

Let \((\sigma, \beta, p)\) be the solution of the problem (10)–(16) on the domains with boundaries \( \partial \Omega_s : r = R_s + \bar{R} \); here \( \bar{R} = \varepsilon S(\theta, \varphi) \). For simplicity, we denote \( R = R_s \).

Assume that \((\sigma, \beta, p)\) has the expansion as follows:
\[
\sigma = \sigma_s + \varepsilon \sigma_1 + O(\varepsilon^2), \tag{29}
\]
\[
\beta = \beta_s + \varepsilon \beta_1 + O(\varepsilon^2), \tag{30}
\]
\[
p = p_s + \varepsilon p_1 + O(\varepsilon^2), \tag{31}
\]
where \( \sigma_1, \beta_1, p_1 \) are the functions to be determined.
Substituting (29)-(31) into (10)-(15), collecting all $\varepsilon$-order terms, we obtain the linearized problem which is satisfied by $\sigma_1, \beta_1, p_1$:

$$\Delta \sigma_1 = \sigma_1 \quad \text{in } B_R, \quad (32)$$

$$\frac{\partial \sigma_1}{\partial r} + \alpha \sigma_1 = - (\sigma_s'' + \alpha \sigma_s') S(\theta, \varphi) \quad \text{on } \partial B_R, \quad (33)$$

$$\Delta \beta_1 = \lambda \beta_1 \quad \text{in } B_R, \quad (34)$$

$$\beta_1 = - \beta_s'(R) S(\theta, \varphi) \quad \text{on } \partial B_R, \quad (35)$$

$$\Delta p_1 = - \mu \sigma_1 + \mu \tau \beta_1 \quad \text{in } B_R, \quad (36)$$

$$p_1 = - \frac{1}{R^2} \left( S(\theta, \varphi) + \frac{1}{2} \Delta_\omega S(\theta, \varphi) \right) \quad \text{on } \partial B_R, \quad (37)$$

where $\Delta_\omega = \frac{1}{\sin \theta} \frac{\partial}{\partial \theta} (\sin \theta \frac{\partial}{\partial \theta}) + \frac{1}{\sin^2 \theta} \frac{\partial^2}{\partial \varphi^2}$ is the Laplace operator on the unit sphere.

Here we used the fact that $(\sigma_s, \beta_s, p_s)$ is a solution of the problem (17)-(21) and on the boundary [21]:

$$\kappa = \frac{1}{R} - \varepsilon \left( S(\theta, \varphi) + \frac{1}{2} \Delta_\omega S(\theta, \varphi) \right) + O(\varepsilon^2).$$

Before solving the problem (32)-(37), we recall some properties of the spherical harmonic functions and the modified Bessel functions.

Let $Y_{m,l}(\theta, \varphi)$ denote the spherical harmonic functions. Then the family \{ $Y_{m,l}$ \} forms a normalized complete orthonormal basis for $L^2(\Sigma)$, where $\Sigma$ is the unit sphere, and

$$\Delta_\omega Y_{m,l} = -m(m + 1) Y_{m,l}. \quad (38)$$

For $m > 0, \xi > 0$, let $I_m(\xi)$ be the modified Bessel function [15, 26]:

$$I_m(\xi) = \left( \frac{\xi}{2} \right)^m \sum_{k=0}^{\infty} \frac{1}{k! \Gamma(m + k + 1)} \left( \frac{\xi}{2} \right)^{2k}. \quad (39)$$

It satisfies the ordinary differential equation:

$$I_m''(\xi) + \frac{1}{\xi} I_m'(\xi) - \left( 1 + \frac{m^2}{\xi^2} \right) I_m(\xi) = 0, \quad (40)$$

and the following

$$I_m'(\xi) + \frac{m}{\xi} I_m(\xi) = I_{m-1}(\xi) \quad \text{for } m \geq 1, \quad (41)$$

$$I_m'(\xi) - \frac{m}{\xi} I_m(\xi) = I_{m+1}(\xi) \quad \text{for } m \geq 0, \quad (42)$$

$$I_m(\xi) = \sqrt{\frac{2m}{\pi \xi}} \left( \frac{e \xi}{2m} \right)^m \left( 1 + O \left( \frac{1}{m} \right) \right) \quad \text{as } m \to \infty. \quad (43)$$

**Computation of $\sigma_1, \beta_1, p_1.$** Set $S(\theta, \varphi) = Y_{m,l}(\theta, \varphi)$ in (32)-(37). Using a separation of variables, we seek a solution of the form:

$$\sigma_1(r, \theta, \varphi) = \hat{\sigma}_1(r) Y_{m,l}(\theta, \varphi),$$

$$\beta_1(r, \theta, \varphi) = \hat{\beta}_1(r) Y_{m,l}(\theta, \varphi),$$

$$p_1(r, \theta, \varphi) = \hat{p}_1(r) Y_{m,l}(\theta, \varphi).$$
It is seen from (32)-(33) and (38) that \( \hat{\sigma}_1(r) \) satisfies:
\[
\hat{\sigma}_1''(r) + \frac{2}{r} \hat{\sigma}_1'(r) - \frac{m(m+1)}{r^2} \hat{\sigma}_1(r) = \hat{\sigma}_1(r) \quad \text{for } 0 < r < R,
\]
\[
\hat{\sigma}_1'(R) + \alpha \hat{\sigma}_1(R) = -\lambda_1,
\]
where
\[
\lambda_1 = \sigma_s''(R) + \alpha \sigma_s'(R) = \frac{\alpha \sigma}{\alpha + g(R)} \left[ 1 + \alpha g(R) - \frac{2}{R} g(R) \right].
\]
From the formulae of modified Bessel functions (39)-(42), we derive
\[
\hat{\sigma}_1(r) = \frac{-\lambda_1 R^2}{R^2 I_{m+\frac{1}{2}}(R) + I_{m+\frac{1}{2}}(R) + \alpha I_{m+\frac{1}{2}}(R)} \frac{I_{m+\frac{1}{2}}(r)}{r^\frac{1}{2}} Y_{m,l}(\theta, \phi).
\]
Hence, the solution of the problem (32)-(33) is given by:
\[
\sigma_1(r, \theta, \phi) = \frac{-\lambda_1 R^2}{R^2 I_{m+\frac{1}{2}}(R) + I_{m+\frac{1}{2}}(R) + \alpha I_{m+\frac{1}{2}}(R)} \frac{I_{m+\frac{1}{2}}(r)}{r^\frac{1}{2}} Y_{m,l}(\theta, \phi).
\]
Similarly, \( \hat{\beta}_1(r) \) satisfies:
\[
\hat{\beta}_1''(r) + \frac{2}{r} \hat{\beta}_1'(r) - \frac{m(m+1)}{r^2} \hat{\beta}_1(r) = \lambda \hat{\beta}_1(r) \quad \text{for } 0 < r < R,
\]
\[
\hat{\beta}_1'(R) + \alpha \hat{\beta}_1(R) = 0.
\]
The solution of the above problem is given explicitly by:
\[
\hat{\beta}_1(r) = -\frac{\beta''(R) R^2 I_{m+\frac{1}{2}}(\sqrt{\lambda} r)}{r^\frac{1}{2} I_{m+\frac{1}{2}}(\sqrt{\lambda} R)} = -\bar{\beta} \sqrt{\lambda} g(\sqrt{\lambda} R) \frac{R^2 I_{m+\frac{1}{2}}(\sqrt{\lambda} r)}{r^\frac{1}{2} I_{m+\frac{1}{2}}(\sqrt{\lambda} R)}.
\]
Furthermore, the solution of the problem (34)-(35) is as follows:
\[
\beta_1(r, \theta, \phi) = -\bar{\beta} \sqrt{\lambda} g(\sqrt{\lambda} R) \frac{R^2 I_{m+\frac{1}{2}}(\sqrt{\lambda} r)}{r^\frac{1}{2} I_{m+\frac{1}{2}}(\sqrt{\lambda} R)} Y_{m,l}(\theta, \phi).
\]
It remains to solve \( p_1 \). On the boundary, from (37), (38), we get
\[
\hat{p}_1(R) = -\frac{1}{R^2} \left( 1 - \frac{m(m+1)}{2} \right).
\]
Let \( \hat{\eta} = \hat{p}_1 + \mu \hat{\sigma}_1 - \frac{\mu T}{\lambda} \hat{\beta}_1 \). Then \( \hat{\eta}(r) \) satisfies the following problem:
\[
\hat{\eta}'' + \frac{2}{r} \hat{\eta}' - \frac{m(m+1)}{r^2} \hat{\eta} = 0 \quad \text{for } 0 < r < R,
\]
\[
\hat{\eta}(R) = \hat{p}_1(R) + \mu \hat{\sigma}_1(R) - \frac{\mu T}{\lambda} \hat{\beta}_1(R).
\]
By the modified Bessel functions and (44), (45), it admits a solution in the form
\[
\hat{\eta}(r) = \hat{C}_1 r^m
\]
with
\[
\hat{C}_1 = \frac{1}{R^m} \left[ \frac{1}{R^2} \left( \frac{m(m+1)}{2} - 1 \right) - \frac{\mu \lambda_1}{h_m(R) + \alpha} + \frac{\mu T}{\sqrt{\lambda}} g(\sqrt{\lambda} R) \right],
\]
where
\[
h_m(R) = \frac{I_{m+\frac{1}{2}}(R)}{I_{m+\frac{1}{2}}(R)}.
\]
Thus, the solution of problem (36) and (37) is given by:

\[ p_1(r,\theta,\varphi) = \left[ \frac{1}{R^2}\left( \frac{m(m+1)}{2} - 1 \right) - \frac{\mu\lambda_1}{h_m(R) + \alpha} + \frac{\mu\tau\beta}{\sqrt{\lambda}} \right] g(\sqrt{\lambda}R) \left( \frac{r}{R} \right)^m Y_{m,l}(\theta,\varphi) \]

\[ - \mu\sigma_1(r,\theta,\varphi) + \frac{\mu\tau}{\lambda} \beta_1(r,\theta,\varphi). \]

**Rigorous justification.** For \( S \in C^{k+\gamma}(\Sigma) \), \( k \geq 3 \), we set \( \Omega_{\varepsilon} = \{ r < R + \varepsilon S \} \). Note that \((\sigma,\beta,p)\) is defined only on \( \Omega_{\varepsilon} \), while \((\sigma_s,\beta_s,p_s)\) is defined on whole \( \mathbb{R}^3 \) and \((\sigma_1,\beta_1,p_1)\) is defined on \( B_R \). We need to transform all these functions to the same domain \( \Omega_{\varepsilon} \) by the Hanzawa transformation, which is a diffeomorphism defined by

\[ (r,\theta,\varphi) = H_\varepsilon(r',\theta',\varphi') = (r' + \chi(R - r')\varepsilon S(\theta',\varphi'),\theta',\varphi'), \]

where

\[ \chi \in C^\infty, \quad \chi(z) = \begin{cases} 0, & \text{if } |z| \geq 3\delta_0/4, \\ 1, & \text{if } |z| < \delta_0/4, \end{cases} \quad \left| \frac{d^k\chi}{dz^k} \right| \leq C_2. \]

Observe that \( H_\varepsilon \) maps \( B_R \) onto \( \Omega_{\varepsilon} \), while keeping the ball \( \{ r < R - (3\delta_0/4) \} \) fixed. The inverse Hanzawa transformation \( H_\varepsilon^{-1} \) maps \( \Omega_{\varepsilon} \) onto \( B_R \). Set

\[ \tilde{\sigma}_1(r,\theta,\varphi) = \sigma_1(H_\varepsilon^{-1}(r,\theta,\varphi)) \quad \text{in } \Omega_{\varepsilon}. \]

Then \( \sigma,\sigma_s,\text{ and } \tilde{\sigma}_1 \) are all defined on the same domain \( \Omega_{\varepsilon} \).

The Schauder estimates yield the following results, see Lemma 3.2 of [17],

\[ \|\sigma - \sigma_s - \varepsilon\tilde{\sigma}_1\|_{C^{3+\gamma}(\Omega_\varepsilon)} \leq C\varepsilon^2\|S\|_{C^{3+\gamma}(\Sigma)}, \]

\[ \|\beta - \beta_s - \varepsilon\tilde{\beta}_1\|_{C^{3+\gamma}(\Omega_\varepsilon)} \leq C\varepsilon^2\|S\|_{C^{3+\gamma}(\Sigma)}, \]

\[ \|p - p_s - \varepsilon\tilde{p}_1\|_{C^{3+\gamma}(\Omega_\varepsilon)} \leq C\varepsilon^2\|S\|_{C^{3+\gamma}(\Sigma)}, \]

where \( C \) is independent of \( \varepsilon \) and \( S \).

This indicates that the expansions in (29)–(31) are rigorous. We shall prove that it also satisfies the stationary boundary condition (16).

4. Symmetry-breaking solutions. In this section, we reduce the problem (10)–(16) to a bifurcation problem by taking the aggressive parameter \( \mu \) as a bifurcation parameter, then obtain the existence of symmetry-breaking solutions by using the following Crandall-Rabinowitz bifurcation theorem [3].

**Theorem 4.1. (Crandall-Rabinowitz theorem)** 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 \( \mu \) in a neighborhood of \( \mu_0 \);

(ii) \( \text{Ker}[F_x(0,\mu_0)] \) is one-dimensional space, spanned by \( x_0 \);

(iii) \( \text{Im}[F_x(0,\mu_0)] = Y_1 \) has codimension 1;

(iv) \( |F_{x\mu}(0,\mu_0)x_0 - Y_1| \).

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 \( \Gamma_1 \) and \( \Gamma_2 \) which intersect only at the point \((0,\mu_0)\); \( \Gamma_1 \) is the curve \((0,\mu) \) and \( \Gamma_2 \) can be parameterized as follows:

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

For each \( \tilde{R} = \varepsilon S(\theta,\varphi), \mu \), define a function \( F \) by

\[ F(\tilde{R},\mu) = \frac{\partial p}{\partial n}|_{\partial \tilde{\Omega}_\varepsilon}. \]  

(46)
Then \((\sigma, \beta, p)\) given by (29)-(31) is a solution of the problem (10)–(16) if and only if \(F(\hat{R}, \mu) = 0\) for some \(\hat{R}\) and \(\mu\). In order to apply the Crandall-Rabinowitz theorem, we need to compute the Fréchet derivative of \(F(\hat{R}, \mu)\). From the definition of \(F(\hat{R}, \mu)\), we have the Fréchet derivative:

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

Setting \(S(\theta, \varphi) = Y_{m,l}(\theta, \varphi)\) as that in the last section, we compute the two terms on the right side of the above equality:

\[
\frac{\partial^2 p_s(R)}{\partial r^2} = -\mu \left( \frac{\alpha \bar{\sigma}}{\alpha + g(R)} - \bar{\sigma} - \tau \beta \right),
\]

\[
\frac{\partial p_1}{\partial r} (R, \theta, \varphi) = \frac{m}{R} \left[ \left( \frac{m(m+1)}{2} \right) \frac{1}{R^2} - \frac{\mu \lambda}{h_m(R) + \alpha} + \frac{\mu \tau \beta}{\sqrt{\lambda}} g(\sqrt{\lambda}R) \right] Y_{m,l}(\theta, \varphi)
\]

\[\quad - \frac{\partial \sigma_1}{\partial r} (R, \theta, \varphi) + \frac{\mu \tau \beta}{\lambda} \frac{\partial \beta_1}{\partial r} (R, \theta, \varphi),\]

where

\[
\frac{\partial \sigma_1}{\partial r} (R, \theta, \varphi) = -(\alpha \sigma_1(R) + \lambda_1) Y_{m,l}(\theta, \varphi) = -\frac{\lambda_1 h_m(R)}{h_m(R) + \alpha} Y_{m,l}(\theta, \varphi),
\]

\[
\frac{\partial \beta_1}{\partial r} (R, \theta, \varphi) = -\frac{\beta}{\sqrt{\lambda}} g(\sqrt{\lambda}R) \frac{R^2}{I_{m+\frac{3}{2}}(\sqrt{\lambda}R)} \left( \frac{I_{m+\frac{3}{2}}(\sqrt{\lambda}R)}{I_{m+\frac{1}{2}}(\sqrt{\lambda}R)} \frac{r^2}{r^2} \right)'_r Y_{m,l}(\theta, \varphi)
\]

\[\quad = -\frac{\beta}{\sqrt{\lambda}} g(\sqrt{\lambda}R) h_m(\sqrt{\lambda}R) Y_{m,l}(\theta, \varphi).
\]

Therefore, we have

\[
\frac{\partial p_1}{\partial r} (R, \theta, \varphi) = \left[ \left( \frac{m(m+1)}{2} \right) \frac{1}{R^2} - \frac{\mu \lambda}{h_m(R) + \alpha} \frac{I_{m+\frac{3}{2}}(R)}{I_{m+\frac{1}{2}}(R)} \right] Y_{m,l}(\theta, \varphi)
\]

\[\quad - \frac{\partial \sigma_1}{\partial r} (R, \theta, \varphi) + \frac{\mu \tau \beta}{\lambda} \frac{\partial \beta_1}{\partial r} (R, \theta, \varphi).
\]

The equation

\[
\left[ \frac{\partial F}{\partial R} (0, \mu) \right] Y_{m,l}(\theta, \varphi) = 0
\]

is then reduced to \(A_m - \mu B_m = 0\), where

\[
A_m = \frac{m}{R^3} \left( \frac{m(m+1)}{2} - 1 \right) = \frac{m(m-1)(m+2)}{2R^3},
\]

\[
B_m = \frac{\alpha \bar{\sigma}}{\alpha + g(R)} - \bar{\sigma} - \tau \beta - \frac{\lambda_1}{h_m(R) + \alpha} \frac{I_{m+\frac{3}{2}}(R)}{I_{m+\frac{1}{2}}(R)} + \frac{\mu \tau \beta}{\sqrt{\lambda}} g(\sqrt{\lambda}R) \frac{I_{m+\frac{3}{2}}(\sqrt{\lambda}R)}{I_{m+\frac{1}{2}}(\sqrt{\lambda}R)}.
\]

Denote

\[
\mu_m = \frac{A_m}{B_m}.
\]

We now proceed to establish our main lemma.

**Lemma 4.2.** If \(\frac{\alpha \bar{\sigma}}{\alpha + g(R)} - \bar{\sigma} - \tau \beta > 0\), then there exists \(m^* \in \mathbb{N}\), such that \(\mu_m\) is positive for \(m > m^*\) and increases with respect to \(m\) for \(m > m^*\); moreover,

\[
\lim_{m \to \infty} \mu_m = +\infty.
\]
Thus, the lemma follows from (48) and (49).

Then,

$$F_{\mu m} = \frac{\lambda_1}{h_m(R)} I_{m+\frac{1}{2}}(R) + \alpha \frac{1}{m} I_{m+\frac{1}{2}}(R) + \tau \beta g(\sqrt{\lambda R}) I_{m+\frac{1}{2}}(\sqrt{\lambda R}).$$

Denote

$$q_m(R) = -\frac{\lambda_1}{h_m(R)} I_{m+\frac{1}{2}}(R) + \tau \beta g(\sqrt{\lambda R}) I_{m+\frac{1}{2}}(\sqrt{\lambda R}).$$

Then,

$$q_m(R) \sim \left( -\frac{\lambda_1}{R + \alpha} + \tau \beta g(R) \right) \frac{R}{2m} + O\left( \frac{1}{m^2} \right) \quad \text{as} \quad m \to \infty. \quad (48)$$

From (47), we rewrite $\mu_m$ as

$$\mu_m = \frac{A_m}{B_m} = \frac{m(m-1)(m+2)}{2R^2} \cdot \frac{\alpha \beta}{\alpha g(R)} - \bar{\sigma} - \tau \bar{\beta} + q_m(R). \quad (49)$$

Notice that $\frac{\alpha}{\alpha + 1} \bar{\sigma} - \bar{\beta} > 0$ and $0 < g(R) < 1$ imply that $\frac{\alpha \beta}{\alpha g(R)} - \bar{\sigma} - \tau \bar{\beta} > 0$. Thus, the lemma follows from (48) and (49).

In the following, we show that $(0, \mu_m)$ is the bifurcation point of the equation $F(R, \mu) = 0$ for sufficiently large $m$.

For $m^*$ given in Lemma 4.2, define $m^{**}$ as follows

$$m^{**} = \text{inf}\{ m \in \mathbb{N}^+ : \mu_m \geq \max\{\mu_2, \mu_3, \ldots, \mu_{m^*}\} \}.$$ 

For $m > m^{**}$, we introduce the Banach spaces:

$$X^{m+\gamma} = \{ R \in C^{m+\gamma}(\Sigma), R \text{ is } \pi\text{-periodic in } \theta, 2\pi\text{-periodic in } \varphi \},$$

$$X_2^{m+\gamma} = \text{closure of the linear space spanned by } \{ Y_{j,0}, j = 0, 2, 4, \ldots \} \text{ in } X^{m+\gamma}. \text{ Then } F(R, \mu) \text{ maps } X_2^{m+\gamma} \text{ into } X_2^2. \text{ We choose } X = X_2^{3+\gamma}(\Sigma), Y = X_2^2(\Sigma).$$

Since we have proved in Lemma 4.2 that $\mu_m$ are all distinct, for even integer $m \geq m^{**}$, we have

$$\text{Ker}[F_R(0, \mu_m)] = \text{span}\{ Y_{m,0} \}. \text{ On the other hand, } F_R(0, \mu_m)Y_{k,0} = (A_k - \mu_mB_k)Y_{k,0}, \text{ where } A_k - \mu_mB_k \neq 0 \text{ for } k \neq m. \text{ This implies that } \text{Im}[F_R(0, \mu)] + \text{Ker}[F_R(0, \mu)] = Y.$$ 

Note that

$$[F_{\mu R}(0, \mu_m)]Y_{m,0} = -B_mY_{m,0} \notin \text{Im}[F_R(0, \mu_m)].$$

By Crandall-Rabinowitz theorem and Lemma 4.2, for even integer $m \geq m^{**}$, $(0, \mu_m)$ is a bifurcation point of the equation $F(R, \mu) = 0$. From the definition of $F(R, \mu)$ given in (46), we have shown the existence of the symmetry-breaking solution to the system (10)–(16).

Now, we conclude our main result as follows.

**Theorem 4.3.** If $\frac{\alpha}{\alpha + 1} \bar{\sigma} - \bar{\beta} > 0$, then there is a positive integer $m^{**}$, such that for every even $m > m^{**}$, $(0, \mu_m)$ is a bifurcation point of the equation $F(R, \mu) = 0,$
then $\mu_m$ is a bifurcation point of the problem (10)-(16), and the corresponding branch of solutions has the expressions:

$$\begin{align*}
\sigma_\varepsilon &= \sigma_s + \varepsilon \hat{\sigma}_1 Y_{m,0}(\theta, \varphi) + O(\varepsilon^2), \\
\beta_\varepsilon &= \beta_s + \varepsilon \hat{\beta}_1 Y_{m,0}(\theta, \varphi) + O(\varepsilon^2), \\
p_\varepsilon &= p_s + \varepsilon \hat{p}_1 Y_{m,0}(\theta, \varphi) + O(\varepsilon^2),
\end{align*}$$

with the free boundaries:

$$r = R_s + \varepsilon Y_{m,0}(\theta, \varphi) + O(\varepsilon^2).$$

**Remark 1.** Since $\frac{\alpha}{\alpha + g(R)} - O(\hat{\beta}) > 0$ if $\lambda < 1$, combining with Theorem 2.1, we see that Theorem 4.3 is also valid for $\lambda < 1$.

Furthermore, for the above aggressiveness parameter $\mu_m$, we can show that it is a monotonous function of the inhibitor supply $\hat{\beta}$.

**Lemma 4.4.** $\mu_m$ is an increasing function of $\hat{\beta}$.

**Proof.** In order to prove this lemma, we only need to verify that the following function is decreasing in $\hat{\beta}$:

$$z(\hat{\beta}) = -\tau \hat{\beta} + q_m(R).$$

Combining the definition $q_m(R)$, we get

$$z(\hat{\beta}) = -\tau \hat{\beta} - \frac{\lambda_1}{h_m(R) + \alpha} \frac{I_{m+\frac{1}{2}}(R)}{I_{m+\frac{1}{2}}(\sqrt{\lambda R})} + \tau \hat{\beta} g(\sqrt{\lambda R}) \frac{I_{m+\frac{1}{2}}(\sqrt{\lambda R})}{I_{m+\frac{1}{2}}(\sqrt{\lambda R})}$$

$$= -\tau \hat{\beta} \left( 1 - \frac{I_{\frac{1}{2}}(\sqrt{\lambda R}) I_{m+\frac{1}{2}}(\sqrt{\lambda R})}{I_{\frac{1}{2}}(\sqrt{\lambda R}) I_{m+\frac{1}{2}}(\sqrt{\lambda R})} \right) - \frac{\lambda_1}{h_m(R) + \alpha} \frac{I_{m+\frac{1}{2}}(R)}{I_{m+\frac{1}{2}}(\sqrt{\lambda R})}.$$ 

Recalling that (see (6.2) in [28])

$$1 - \frac{I_{\frac{1}{2}}(\sqrt{\lambda R}) I_{m+\frac{1}{2}}(\sqrt{\lambda R})}{I_{\frac{1}{2}}(\sqrt{\lambda R}) I_{m+\frac{1}{2}}(\sqrt{\lambda R})} > 0,$$

we obtain $z'(\hat{\beta}) < 0$. The proof is complete. \qed

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**REFERENCES**

[1] R. P. Araujo and D. L. S. McElwain, A history of the study of solid tumour growth: The contribution of mathematical modeling, *Bull. Math. Biol.*, 66 (2004), 1039–1091.

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

[3] M. G. Crandall and P. H. Rabinowitz, Bifurcation from simple eigenvalues, *J. Functional Analysis*, 8 (1971), 321–340.

[4] V. Cristini, J. Lowengrub and Q. Nie, Nonlinear simulation of tumor growth, *J. Math. Biol.*, 46 (2003), 191–224.

[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 and J. Escher, Bifurcation analysis of an elliptic free boundary problem modelling the growth of avascular tumors, *SIAM J. Math. Anal.*, 39 (2007), 210–235.

[7] S. Cui and J. Escher, Asymptotic behaviour of solutions of a multidimensional moving boundary problem modeling tumor growth, *Comm. Partial Differential Equations*, 33 (2008), 636–655.

[8] S. Cui and A. Friedman, Analysis of a mathematical model of the effect of inhibitors on the growth of tumors, *Math. Biosci.*, 164 (2000), 103–137.

[9] J. Escher and A. V. Matioc, Bifurcation analysis for a free boundary problem modeling tumor growth, *Arch. Math.*, 97 (2011), 79–90.

[10] M. A. Fontelos and A. Friedman, Symmetry-breaking bifurcations of free boundary problems in three dimensions, *Asymptot. Anal.*, 35 (2003), 187–206.

[11] A. Friedman, A hierarchy of cancer models and their mathematical challenges, *Discrete Contin. Dyn. Syst. Ser. B*, 4 (2004), 147–159.

[12] A. Friedman, Cancer models and their mathematical analysis, in *Lecture Notes in Math.*, Vol. 1872, Springer, (2006), 223–246.

[13] A. Friedman, Mathematical analysis and challenges arising from models of tumor growth, *Math. Models Methods Appl. Sci.*, 17 (2007), 1751–1772.

[14] A. Friedman and B. Hu, Bifurcation from stability to instability for a free boundary problem arising in a tumor model, *Arch. Ration. Mech. Anal.*, 180 (2006), 293–330.

[15] A. Friedman and B. Hu, Asymptotic stability for a free boundary problem arising in a tumor model, *J. Differential Equation*, 227 (2006), 598–639.

[16] A. Friedman and B. Hu, Bifurcation for a free boundary problem modeling tumor growth by Stokes equation, *SIAM J. Math. Anal.*, 39 (2007), 174–194.

[17] A. Friedman and B. Hu, Stability and instability of Liapunov-Schmidt and Hopf bifurcation for a free boundary problem arising in a tumor model, *Trans. Amer. Math. Soc.*, 360 (2008), 5291–5342.

[18] A. Friedman and K. Y. Lam, Analysis of a free-boundary tumor model with angiogenesis, *J. Differential Equations*, 259 (2015), 7636–7661.

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

[20] A. Friedman and F. Reitich, Symmetry-breaking bifurcation of analytic solutions to free boundary problems: an application to a model of tumor growth, *Trans. Amer. Math. Soc.*, 353 (2001), 1587–1634.

[21] A. Friedman and F. Reitich, Nonlinear stability of a quasi-static Stefan problem with surface tension: A continuation approach, *Ann. Scuola Norm. Sup. Pisa Cl. Sci. (4)*, 30 (2001), 341–403.

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

[23] W. Hao, J. D. Hauenstein, B. Hu, Y. Liu, A. J. Sommese and Y. -T. Zhang, Bifurcation for a free boundary problem modeling the growth of a tumor with a necrotic core, *Nonlinear Anal. Real World Appl.*, 13 (2012), 694–709.

[24] Y. Huang, Z. Zhang and B. Hu, Bifurcation for a free-boundary tumor model with angiogenesis, *Nonlinear Anal. Real World Appl.*, 35 (2017), 483–502.

[25] J. S. Lowengrub, H. B. Frieboes, F. Jin, Y. -L. Chuang, X. Li, P. Macklin, S. M. Wise and V. Cristini, Nonlinear modelling of cancer: Bridging the gap between cells and tumours, *Nonlinearity*, 23 (2010), R1–R91.

[26] Z. Wang, Bifurcation for a free boundary problem modeling tumor growth with inhibitors, *Nonlinear Anal. Real World Appl.*, 19 (2014), 45–53.

[27] J. Wu, Stationary solutions of a free boundary problem modeling the growth of tumors with Gibbs-Thomson relation, *J. Differential Equations*, 260 (2016), 5875–5893.

[28] J. Wu and S. Cui, Asymptotic behaviour of solutions of a free boundary problem modelling the growth of tumours in the presence of inhibitors, *Nonlinearity*, 20 (2007), 2389–2408.

[29] J. Wu and S. Cui, Bifurcation analysis of a mathematical model for the growth of solid tumors in the presence of external inhibitors, *Math. Methods Appl. Sci.*, 38 (2015), 1813–1823.

[30] J. Wu and 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.
[31] S. Xu, M. Bai and F. Zhang, Analysis of a free boundary problem for tumor growth with Gibbs-Thomson relation and time delays, *Discrete Contin. Dyn. Syst. Ser. B*, 22 (2017), online.

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

[33] F. Zhou, J. Escher and S. Cui, Bifurcation for a free boundary problem with surface tension modeling the growth of multi-layer tumors, *J. Math. Anal. Appl.*, 337 (2008), 443–457.

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

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