PDE Tumor models

Bei Hu

Department of Applied and Computational Mathematics and Statistics
University of Notre Dame, Notre Dame, IN 46556

July 2012

Coauthors: Avner Friedman, Ohio State,
Andrew Sommese, Weirui Hao, Yongtao Zhang, Yuan Liu, Notre Dame
Jon Hauenstein, Texas A&M
Greenspan, 1972 and 1976, McElwin-Morris, 1978, models for growth of solid tumor by diffusion, ...

Adam-Maggelakis 1990, Britton-Chaplain 1993, models of tumor in fixed domains,

1990’s –>((...)), Byrne, Chaplain, Bellomo, Britton, Frank, King, Cui, Eschler, Friedman, ..., solid tumor, at tissue level, with diffusion, cell-to-cell adhesiveness, ...
PDE Tumor models

- Greenspan, 1972 and 1976, McElwin-Morris, 1978, models for growth of solid tumor by diffusion, ...
- Adam-Maggelakis 1990, Britton-Chaplain 1993, models of tumor in fixed domains,
- 1990’s →(...)), Byrne, Chaplain, Bellomo, Britton, Frank, King, Cui, Eschler, Friedman, ..., solid tumor, at tissue level, with diffusion, cell-to-cell adhesiveness, ...
Greenspan, 1972 and 1976, McElwin-Morris, 1978, models for growth of solid tumor by diffusion, ...

Adam-Maggelakis 1990, Britton-Chaplain 1993, models of tumor in fixed domains,

1990’s –>((...)), Byrne, Chaplain, Bellomo, Britton, Frank, King, Cui, Eschler, Friedman, ..., solid tumor, at tissue level, with diffusion, cell-to-cell adhesiveness, ...
- Chaplain, Britton, Byrnes 1990 → (...).
Chaplain, Britton, Byrnes 1990 \textnormal{\textendash} ((...)).


(Simulation of the tumor growth, Simulation of linear stability, etc)
Chaplain, Britton, Byrnes 1990 → (...).


Chaplain, Britton, Byrnes 1990 -> ((...)).
Adam, 1996, General aspect of modeling tumor growth and immune response.


Adam, 1996, General aspect of modeling tumor growth and immune response.


Adam, 1996, General aspect of modeling tumor growth and immune response.


Adam, 1996, General aspect of modeling tumor growth and immune response.


Adam, 1996, General aspect of modeling tumor growth and immune response.


Outline

1. Tumor model with Darcy’s law
   - Problem setup
   - The results

2. Tumor model with Stokes equation
   - The governing equations
   - Our results
   - Comparison: Darcy’s law and Stokes equation
Outline

1. Tumor model with Darcy’s law
   - Problem setup
   - The results

2. Tumor model with Stokes equation
   - The governing equations
   - Our results
   - Comparison: Darcy’s law and Stokes equation
Problem setup

Governing equations:

- **Diffusion of the nutrients:**
  \[
  \varepsilon \sigma_t - \Delta \sigma + \sigma = 0 \quad \text{in } \Omega(t).
  \]

- **Conservation of mass:** \( \text{div} \vec{V} = S \), \( S = \) proliferation rate. Here we assume linear dependence on \( \sigma \): \( S = \mu (\sigma - \tilde{\sigma}) \), (here \( \tilde{\sigma} > 0 \) comes from apoptosis)

- **Porous medium in tumor region:** Darcy's law: \( \vec{V} = -\nabla p \). Thus
  \[
  \Delta p = -\mu (\sigma - \tilde{\sigma}) \quad \text{in } \Omega(t).
  \]

- **Continuity:** \( V_n = -\frac{\partial p}{\partial n} \) on \( \partial \Omega(t) \)
  where \( V_n = \) velocity in the normal \( n \) direction.
Problem setup

Governing equations:

- Diffusion of the nutrients:
  \[ \varepsilon \sigma_t - \Delta \sigma + \sigma = 0 \quad \text{in } \Omega(t). \]

- Conservation of mass: \( \text{div} \vec{V} = S \), \( S = \) proliferation rate. Here we assume linear dependence on \( \sigma \):
  \[ S = \mu (\sigma - \tilde{\sigma}), \] (here \( \tilde{\sigma} > 0 \) comes from apoptosis)

- Porous medium in tumor region: Darcy’s law: \( \vec{V} = -\nabla p \). Thus
  \[ \Delta p = -\mu (\sigma - \tilde{\sigma}) \quad \text{in } \Omega(t). \]

- Continuity: \( V_n = -\frac{\partial p}{\partial n} \) on \( \partial \Omega(t) \)
  where \( V_n = \) velocity in the normal \( n \) direction.
Problem setup

Governing equations:

- **Diffusion of the nutrients:**
  \[ \varepsilon \sigma_t - \Delta \sigma + \sigma = 0 \quad \text{in} \quad \Omega(t). \]

- **Conservation of mass:** \( \text{div} \vec{V} = S \), \( S = \) proliferation rate. Here we assume linear dependence on \( \sigma \):
  \[ S = \mu(\sigma - \tilde{\sigma}), \quad \text{(here} \quad \tilde{\sigma} > 0 \text{ comes from apoptosis)} \]

- **Porous medium in tumor region:** Darcy’s law: \( \vec{V} = -\nabla p \). Thus
  \[ \Delta p = -\mu(\sigma - \tilde{\sigma}) \quad \text{in} \quad \Omega(t). \]

- **Continuity:** \( V_n = -\frac{\partial p}{\partial n} \) on \( \partial \Omega(t) \)
  where \( V_n = \) velocity in the normal \( n \) direction.
Problem setup

Governing equations:

- **Diffusion of the nutrients:**
  \[ \varepsilon \sigma_t - \Delta \sigma + \sigma = 0 \quad \text{in } \Omega(t). \]

- **Conservation of mass:** \( \text{div} \vec{V} = S \), \( S = \) proliferation rate. Here we assume linear dependence on \( \sigma \):
  \[ S = \mu(\sigma - \tilde{\sigma}), \quad (\text{here } \tilde{\sigma} > 0 \text{ comes from apoptosis}) \]

- **Porous medium in tumor region:** Darcy’s law: \( \vec{V} = -\nabla p \). Thus
  \[ \Delta p = -\mu(\sigma - \tilde{\sigma}) \quad \text{in } \Omega(t). \]

- **Continuity:** \( V_n = -\frac{\partial p}{\partial n} \) on \( \partial \Omega(t) \)
  where \( V_n \) = velocity in the normal \( n \) direction.
The simple Tumor growth model

Equations:

\[ \varepsilon \sigma_t - \Delta \sigma + \sigma = 0 \quad \text{in } \Omega(t), \]
\[ \Delta p = -\mu (\sigma - \bar{\sigma}) \quad \text{in } \Omega(t). \]

Free boundary conditions:

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

Boundary conditions:

\[ \sigma = 1 \quad \text{on } \partial \Omega(t), \]
\[ p = \kappa \quad \text{on } \partial \Omega(t). \]
Hele Shaw model

- If $\mu \equiv 0, \cdots$

\[ \Delta p = 0 \quad \text{in } \Omega(t), \]

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

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

- Stationary solutions are radially symmetric.

- Local in time problem is well posed. The regularity: the surface $x_n = f(x_1, \cdots, x_{n-1}, t)$ representing $\partial \Omega(t)$ locally stays in the class $f, D_x f \in C^{3+\alpha, 1+\alpha/3}$.

- Inhomogeneous Hele-Shaw? (replacing with $\Delta p = g$) Same result if $g$ is smooth. (Chen-Hong-Yi [1996])
Hele Shaw model

- If $\mu \equiv 0, \ldots$

\[
\Delta p = 0 \quad \text{in } \Omega(t),
\]
\[
p = \kappa \quad \text{on } \partial \Omega(t),
\]
\[
V_n = -\frac{\partial p}{\partial n} \quad \text{on } \partial \Omega(t).
\]

- Stationary solutions are radially symmetric.

- Local in time problem is well posed. The regularity: the surface $x_n = f(x_1, \cdots, x_{n-1}, t)$ representing $\partial \Omega(t)$ locally stays in the class $f, D_x f \in C^{3+\alpha, 1+\alpha/3}$.

- Inhomogeneous Hele-Shaw? (replacing with $\Delta p = g$) Same result if $g$ is smooth. (Chen-Hong-Yi [1996])
Hele Shaw model

- If $\mu \equiv 0, \cdots$

\[
\Delta p = 0 \quad \text{in } \Omega(t),
\]
\[
p = \kappa \quad \text{on } \partial \Omega(t),
\]
\[
V_n = -\frac{\partial p}{\partial n} \quad \text{on } \partial \Omega(t).
\]

- Stationary solutions are radially symmetric.

- Local in time problem is well posed. The regularity: the surface \( x_n = f(x_1, \cdots, x_{n-1}, t) \) representing \( \partial \Omega(t) \) locally stays in the class \( f, D_x f \in C^{3+\alpha,1+\alpha/3} \).

- Inhomogeneous Hele-Shaw? (replacing with \( \Delta p = g \)) Same result if \( g \) is smooth. (Chen-Hong-Yi [1996])
Hele Shaw model

- If $\mu \equiv 0, \cdots$

  \[ \Delta p = 0 \quad \text{in} \quad \Omega(t), \]
  \[ p = \kappa \quad \text{on} \quad \partial \Omega(t), \]
  \[ V_n = -\frac{\partial p}{\partial n} \quad \text{on} \quad \partial \Omega(t). \]

- Stationary solutions are radially symmetric.
- Local in time problem is well posed. The regularity: the surface $x_n = f(x_1, \cdots, x_{n-1}, t)$ representing $\partial \Omega(t)$ locally stays in the class $f, D_x f \in C^{3+\alpha,1+\alpha/3}$.
- Inhomogeneous Hele-Shaw? (replacing with $\Delta p = g$) Same result if $g$ is smooth. (Chen-Hong-Yi [1996])
Many numerical and analytic results are mentioned earlier.

Bifurcation and Stability results:

- [Friedman-Reitich, 99, J. Math. Bio.] Stationary radial solution exists if $\tilde{\sigma} < 1$. For small $\mu$, it is asymptotically stable with respect to perturbations of radial functions; radial time dependent solution is global.

- [Friedman-Reitich, 00, Tran. Amer. Math.] Non-radial stationary solution exists (2d), bifurcating from certain $\mu_l$. (Done through an *analytical expansion*).

- [Bazaliy-Friedman, 03, Indiana U. Math.] For small $\mu$, the stationary radial solution (2d) is stable, subject to a translation of the origin.
Many numerical and analytic results are mentioned earlier.

Bifurcation and Stability results:

- [Friedman-Reitich, 99, J. Math. Bio.] Stationary radial solution exists if $\tilde{\sigma} < 1$. For small $\mu$, it is asymptotically stable with respect to perturbations of radial functions; radial time dependent solution is global.

- [Friedman-Reitich, 00, Tran. Amer. Math.] Non-radial stationary solution exists (2d), bifurcating from certain $\mu_l$. (Done through an analytical expansion).

- [Bazaliy-Friedman, 03, Indiana U. Math.] For small $\mu$, the stationary radial solution (2d) is stable, subject to a translation of the origin.
The simple tumor model: the results

Many numerical and analytic results are mentioned earlier.

Bifurcation and Stability results:

- [Friedman-Reitich, 99, J. Math. Bio.] Stationary radial solution exists if $\tilde{\sigma} < 1$. For small $\mu$, it is asymptotically stable with respect to perturbations of radial functions; radial time dependent solution is global.

- [Friedman-Reitich, 00, Tran. Amer. Math.] Non-radial stationary solution exists (2d), bifurcating from certain $\mu_l$. (Done through an analytical expansion).

- [Bazaliy-Friedman, 03, Indiana U. Math.] For small $\mu$, the stationary radial solution (2d) is stable, subject to a translation of the origin.
The simple tumor model: the results

Many numerical and analytic results are mentioned earlier.

Bifurcation and Stability results:

- [Friedman-Reitich, 99, J. Math. Bio.] Stationary radial solution exists if $\tilde{\sigma} < 1$. For small $\mu$, it is asymptotically stable with respect to perturbations of radial functions; radial time dependent solution is global.

- [Friedman-Reitich, 00, Tran. Amer. Math.] Non-radial stationary solution exists (2d), bifurcating from certain $\mu_l$. (Done through an analytical expansion).

- [Bazaliy-Friedman, 03, Indiana U. Math.] For small $\mu$, the stationary radial solution (2d) is stable, subject to a translation of the origin.
Extensions

- Cui, Escher, etc, Replacing the right-hand sides by more general functions, or replacing the spherical solution by an infinite strip.
- Cui, Friedman, Include necrotic core.
- ... inhibitors, ...
Extensions

- Cui, Escher, etc, Replacing the right-hand sides by more general functions, or replacing the spherical solution by an infinite strip.
- Cui, Friedman, Include necrotic core.
- ... inhibitors, ...
Extensions

- Cui, Escher, etc, Replacing the right-hand sides by more general functions, or replacing the spherical solution by an infinite strip.
- Cui, Friedman, Include necrotic core.
- ... inhibitors, ...
Simple Tumor model

Stationary solutions can be obtained explicitly by solving ODEs:

\[
\sigma_S(r) = \frac{R_S}{\sinh R_S} \frac{\sinh r}{r}
\]

\[
p_S(r) = \frac{1}{R_S} + \mu - \mu \tilde{\sigma} \frac{R_S^2}{6}
\]

where \( R_S \) is uniquely determined by

\[
\frac{1}{R_S^2} (R_S \coth R_S - 1) = \frac{1}{3} \tilde{\sigma}
\]

In vitro, tumor grows as a spheroid, but in vivo, it is not.

What about non-radially symmetric solutions?
Stationary solutions can be obtained explicitly by solving ODEs:

\[
\sigma_S(r) = \frac{R_S}{\sinh R_S} \frac{\sinh r}{r}
\]

\[
p_S(r) = \frac{1}{R_S} + \mu - \mu \tilde{\sigma} \frac{R_S^2}{6}
\]

where \( R_S \) is uniquely determined by

\[
\frac{1}{R_S^2}(R_S \coth R_S - 1) = \frac{1}{3} \tilde{\sigma}
\]

In vitro, tumor grows as a spheroid, but in vivo, it is not. What about non-radially symmetric solutions?
**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

1. $F(0, \mu) = 0$ for all $\mu$ in a neighborhood of $\mu_0$,
2. $\text{Ker } F_x(0, \mu_0)$ is one dimensional space, spanned by $x_0$,
3. $\text{Im } F_x(0, \mu_0) = Y_1$ has codimension 1,
4. $F_{\mu x}(0, \mu_0)x_0 \notin Y_1$.

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 $\Gamma_1$ 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:

$$\Gamma_2 : (x(\epsilon), \mu(\epsilon)), \ |\epsilon| \text{ small },$$

$$(x(0), \mu(0)) = (0, \mu_0), \ x'(0) = x_0.$$
Existence of non-radial stationary solution. Consider a family of domains with boundaries \( \partial \Omega_\varepsilon : r = R_S + \tilde{R}(\theta, \phi) \) where \( \tilde{R}(\theta, \phi) = \varepsilon S(\theta, \phi) \). Let \((\sigma, p)\) form the solution of

\[
-\Delta \sigma + \sigma = 0 \quad \text{in } \Omega_\varepsilon,
-\Delta p = \mu (\sigma - \tilde{\sigma}) \quad \text{in } \Omega_\varepsilon \quad (\tilde{\sigma} < 1),
\sigma = 1 \quad \text{on } \partial \Omega_\varepsilon,
p = \kappa \quad \text{on } \partial \Omega_\varepsilon.
\]

We define \( F \) by

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

Then \((\sigma, p, R_S + \tilde{R})\) is a stationary solution of if and only if \( F(\tilde{R}, \mu) = 0 \).
[Fontelos-Friedman, 03, Asymptotic Anal.] Non-radial stationary solution exists (3d), bifurcating from certain $\mu_n$. Hanzawa transformation used. Proof shorter.

**Theorem (Fontelos-Friedman, 03)**

There are Symmetric breaking stationary solutions emanating from $\mu_n$ \((n \geq 2)\), with free boundary \(r = R + \varepsilon Y_{n,0} + o(\varepsilon)\).

\[
\mu_n = \frac{n[n(n + 1) - 2]l_{1/2}(R)}{2R^3 l_{3/2}(R) \left[ \frac{l_{5/2}(R)}{l_{3/2}(R)} - \frac{l_{n+3/2}(R)}{l_{n+1/2}(R)} \right]}, \quad \mu_n(R) < \mu_{n+1}(R), \forall R.
\]
The simple tumor model: the results (continued)

- [Fontelos-Friedman, 03, Asymptotic Anal.] Non-radial stationary solution exists (3d), bifurcating from certain $\mu_n$. Hanzawa transformation used. Proof shorter.

**Theorem (Fontelos-Friedman, 03)**

*There are Symmetric breaking stationary solutions emanating from $\mu_n$ ($n \geq 2$), with free boundary $r = R + \varepsilon Y_{n,0} + o(\varepsilon)$.*

\[
\begin{align*}
\varepsilon & \quad \mu_2 \quad \mu_3 \quad \mu_4 \quad \mu_5 \\
\mu_n & = \frac{n[n(n + 1) - 2] I_{1/2}(R)}{2 R^3 I_{3/2}(R) \left[ \frac{I_{5/2}(R)}{I_{3/2}(R)} - \frac{I_{n+3/2}(R)}{I_{n+1/2}(R)} \right]}, \quad \mu_n(R) < \mu_{n+1}(R), \forall R.
\end{align*}
\]
Theorem

There exists a function \( \mu^* = \mu^*(R_S) \) such that the stationary solution is linearly stable if \( \mu < \mu^*(R_S) \), and linearly unstable if \( \mu > \mu^*(R_S) \).

One might expect that \( \mu^*(R_S) \) to coincide with the first bifurcation point \( \mu_2(R_S) \). But this is not the case.

Theorem

There exists a positive number \( \overline{R} \) such that \( \mu^*(R_S) < \mu_2(R_S) \) if \( R_S < \overline{R} \) and \( \mu^*(R_S) = \mu_2(R_S) \) if \( R_S > \overline{R} \); \( \overline{R} \) is approximately 0.62207.

What happens here is that, if \( R_S > \overline{R} \), then at the bifurcation point \( \mu^*(R_S) = \mu_2(R_S) \) one “eigenvalue” which determines the stability of the free boundary problem crosses the imaginary axis at the origin, whereas if \( R_S < \overline{R} \), a pair of “eigenvalues” cross the imaginary axis at \( \mu^*(R_S) \).
The simple tumor model: the nonlinear results (continued)


**Theorem**

There exists a function $\mu_*=\mu_*(R_S)$ such that the stationary solution is asymptotically stable if $\mu < \mu_*(R_S)$.

Need to find the necessary PDE estimates to estimate the nonlinear error terms.
In particular, since the problem is translation invariant, we need to find the *correct* origin. This origin depends on the perturbation.
Linearization about a radial solution

Set
\[ \sigma(r, \theta, \phi, t) = \sigma_S(r) + \varepsilon w(r, \theta, \phi, t), \quad p(r, \theta, \phi, t) = p_S(r) + \varepsilon q(r, \theta, \phi, t), \]
\[ \partial \Omega(t) : r = R_S + \varepsilon \rho(\theta, \phi, t) \quad (R_S \equiv R), \]

Then
\[ V_n = \varepsilon \rho_t + O(\varepsilon^2), \quad \kappa = \frac{1}{R} - \frac{\varepsilon}{R^2} \left( \rho + \frac{1}{2} \Delta \omega \rho \right) + O(\varepsilon^2), \]
\[ \text{here } \Delta \omega \rho = \frac{1}{\sin \theta} \frac{\partial}{\partial \theta} \left( \sin \theta \frac{\partial \rho}{\partial \theta} \right) + \frac{1}{\sin^2 \theta} \frac{\partial^2 \rho}{\partial \phi^2}. \]

Substituting these quantities into the simple tumor model and collecting only the linear terms in \( \varepsilon \), we obtain the linearized system:
\[ w_t - \Delta w + w = 0 \quad \text{in } B_R \times \{ t > 0 \} \quad (B_R = \{ r < R \}), \]
\[ w(R, \theta, \phi, t) = -\lambda \rho(\theta, \phi, t) \quad \text{for } t > 0 \quad (\lambda = \left. \frac{\partial}{\partial r} \sigma_S(r) \right|_{r=R}), \]
\[ \Delta q = -\mu w \quad \text{in } B_R \times \{ t > 0 \}, \quad q(R, \theta, \phi, t) = -\frac{1}{R^2} \left( \rho + \frac{1}{2} \Delta \omega \rho \right), \]
\[ \frac{d\rho}{dt} = -\frac{\partial^2 p_S}{\partial r^2} \bigg|_{r=R} \rho - \frac{\partial q}{\partial r} \bigg|_{r=R} \quad \text{for } t > 0. \]
Linearization about a radial solution

Set
\[ \sigma(r, \theta, \phi, t) = \sigma_S(r) + \varepsilon w(r, \theta, \phi, t), \quad p(r, \theta, \phi, t) = p_S(r) + \varepsilon q(r, \theta, \phi, t), \]
\[ \partial \Omega(t) : r = R_S + \varepsilon \rho(\theta, \phi, t) \quad (R_S \equiv R), \]

Then
\[ V_n = \varepsilon \rho t + O(\varepsilon^2), \quad \kappa = \frac{1}{R} - \frac{\varepsilon}{R^2} \left( \rho + \frac{1}{2} \Delta \omega \rho \right) + O(\varepsilon^2), \]

here \( \Delta \omega \rho = \frac{1}{\sin \theta} \frac{\partial}{\partial \theta} \left( \sin \theta \frac{\partial \rho}{\partial \theta} \right) + \frac{1}{\sin^2 \theta} \frac{\partial^2 \rho}{\partial \phi^2} \).

Substituting these quantities into the simple tumor model and collecting only the linear terms in \( \varepsilon \), we obtain the linearized system:
\[ w_t - \Delta w + w = 0 \quad \text{in} \ B_R \times \{ t > 0 \} \quad (B_R = \{ r < R \}), \]
\[ w(R, \theta, \phi, t) = -\lambda \rho(\theta, \phi, t) \quad \text{for} \ t > 0 \quad (\lambda = \frac{\partial}{\partial r} \sigma_S(r) \bigg|_{r=R}), \]
\[ \Delta q = -\mu w \quad \text{in} \ B_R \times \{ t > 0 \}, \quad q(R, \theta, \phi, t) = -\frac{1}{R^2} \left( \rho + \frac{1}{2} \Delta \omega \rho \right), \]
\[ \frac{d \rho}{dt} = -\frac{\partial^2 p_S}{\partial r^2} \bigg|_{r=R} \rho - \frac{\partial q}{\partial r} \bigg|_{r=R} \quad \text{for} \ t > 0. \]
Linearized problem

Abstract version: \[ \frac{d(w(r, \theta, \phi, t), \rho(\theta, \phi, t))}{dt} = A(w(r, \theta, \phi, t), \rho(\theta, \phi, t)), \quad t > 0. \]

The linear stability depends on the resolvent of \( A \).

The linear operator \( A \) is nonlocal. It depends on two parameters: \( R \) (or \( \tilde{\sigma} \)) and \( \mu \).

The rest of the proof consists of using PDE estimates and a simple lemma in complex variable to estimate the roots:

Lemma: If \( M_1(s) \) and \( M_2(s) \) are holomorphic functions (except poles) on the simply connected domain \( D \), and

\[ |M_1(s) - M_2(s)| < |M_1(s)| \quad \text{on} \quad \partial D, \]

then

\[ (\text{number of poles} - \text{number of roots}) \text{ of } M_2(s) \]
\[ = (\text{number of poles} - \text{number of roots}) \text{ of } M_1(s) \]
The detailed estimates of these roots. $M_2(s)$ is given by the system, build $M_1(s)$

- simple enough
- the roots can easily be computed and with the same sign of the imaginary parts
Asymptotic stability: Full nonlinear problem

Full nonlinear problem – what do we do?

- **This is a free boundary problem.** Domain is changing in time.
- Step 1: Fix it - Hanzawa transform.
- Step 2. Linearize around a radial stationary solution, but keep all error. Consider it as a inhomogeneous Hele-Shaw and want to apply Hele-Shaw estimates $C^{3+\alpha, 1+\alpha/3}$.
- Step 3. Translate the center to kill the zero from the mode 1 terms. However, we can only do so for the fixed inhomogeneous terms by using a fixed point theorem.
- Step 4. Prove that the small error is really small and that the errors decays exponentially fast, is of the correct order, and use another fixed point theorem.
Asymptotic stability: Full nonlinear problem

Full nonlinear problem – what do we do?

- **This is a free boundary problem.** Domain is changing in time.
- **Step 1:** Fix it - Hanzawa transform.
- **Step 2:** Linearize around a radial stationary solution, but keep all error. Consider it as an inhomogeneous Hele-Shaw and want to apply Hele-Shaw estimates $C^{3+\alpha,1+\alpha/3}$.
- **Step 3:** Translate the center to kill the zero from the mode 1 terms. However, we can only do so for the fixed inhomogeneous terms by using a fixed point theorem.
- **Step 4:** Prove that the small error is really small and that the errors decays exponentially fast, is of the correct order, and use another fixed point theorem.
Asymptotic stability: Full nonlinear problem

Full nonlinear problem – what do we do?

- This is a free boundary problem. Domain is changing in time.
- Step 1: Fix it - Hanzawa transform.
- Step 2. Linearize around a radial stationary solution, but keep all error. Consider it as a inhomogeneous Hele-Shaw and want to apply Hele-Shaw estimates $C^{3+\alpha,1+\alpha/3}$.
- Step 3. Translate the center to kill the zero from the mode 1 terms. However, we can only do so for the fixed inhomogeneous terms by using a fixed point theorem.
- Step 4. Prove that the small error is really small and that the errors decays exponentially fast, is of the correct order, and use another fixed point theorem.
Asymptotic stability: Full nonlinear problem

Full nonlinear problem – what do we do?

- **This is a free boundary problem.** Domain is changing in time.
- **Step 1:** Fix it - Hanzawa transform.
- **Step 2.** Linearize around a radial stationary solution, but keep all error. Consider it as an inhomogeneous Hele-Shaw and want to apply Hele-Shaw estimates $C^{3+\alpha, 1+\alpha/3}$.
- **Step 3.** Translate the center to kill the zero from the mode 1 terms. However, we can only do so for the fixed inhomogeneous terms by using a fixed point theorem.
- **Step 4.** Prove that the small error is really small and that the errors decays exponentially fast, is of the correct order, and use another fixed point theorem.
Asymptotic stability: Full nonlinear problem

Full nonlinear problem – what do we do?

- **This is a free boundary problem.** Domain is changing in time.
- **Step 1:** Fix it - Hanzawa transform.
- **Step 2:** Linearize around a radial stationary solution, but keep all error. Consider it as a inhomogeneous Hele-Shaw and want to apply Hele-Shaw estimates $C^{3+\alpha,1+\alpha/3}$.
- **Step 3:** Translate the center to kill the zero from the mode 1 terms. However, we can only do so for the fixed inhomogeneous terms by using a fixed point theorem.
- **Step 4:** Prove that the small error is really small and that the errors decays exponentially fast, is of the correct order, and use another fixed point theorem.
Asymptotic stability: the system

\[
\frac{\partial w}{\partial t} - \Delta w + w = \varepsilon \left[ -A_1^1 w + A_\varepsilon w \right] \equiv \varepsilon f^1 \quad \text{in } B_R, \quad t > 0,
\]

\[
\Delta q + \mu w = -\varepsilon A \varepsilon q \equiv \varepsilon f^2 \quad \text{in } B_R, \quad t > 0,
\]

\[
\frac{\partial \rho}{\partial t} - \mu (1 - \tilde{\sigma}) \rho + \frac{\partial q}{\partial r} = \varepsilon B_\varepsilon^1 \quad \text{on } \partial B_R,
\]

\[
w + (\sigma_s) r(R) \cdot \rho = \varepsilon B_\varepsilon^2 \quad \text{on } \partial B_R,
\]

\[
q + \frac{1}{R^2} \left( \rho + \frac{1}{2} \Delta \omega \rho' \right) = \varepsilon B_\varepsilon^3 \quad \text{on } \partial B_R,
\]

where

\[
A_\varepsilon = \frac{2 \chi' \rho - \varepsilon \chi'^2 \rho^2}{(1 - \varepsilon \chi')^2} \frac{\partial^2}{\partial r'^2} - \frac{\chi'' \rho}{(1 - \varepsilon \chi')^3} \frac{\partial}{\partial r'} \epsilon \left( \frac{2}{(r' + \varepsilon \chi \rho)(1 - \varepsilon \chi') - \frac{2}{r'}} \right) \frac{\partial}{\partial r'}
\]

\[
+ \frac{1}{\varepsilon (r' + \varepsilon \chi \rho)^2} \left( \frac{2}{r'^2} - \frac{1}{r^2} \right) \Delta \omega' - \frac{\chi}{(r' + \varepsilon \chi \rho)^2(1 - \varepsilon \chi') \Delta \omega' \rho \frac{\partial}{\partial r'}
\]

\[
+ \frac{1}{(r' + \varepsilon \chi \rho)^2} \left\{ -2 \chi \rho \frac{\partial^2}{\partial r' \partial \theta'} - \left[ \frac{\varepsilon^2 \chi'' \rho^2 \theta'}{(1 - \varepsilon \chi')^3} + \frac{2 \varepsilon \chi' \rho^2}{1 - \varepsilon \chi'} \frac{\partial}{\theta'} \right] \frac{\partial}{\partial r'}
\]

\[
+ \frac{1}{(r' + \varepsilon \chi \rho)^2 \sin^2 \theta'} \left\{ -2 \chi \rho \frac{\partial^2}{\partial r' \partial \phi'} - \left[ \frac{\varepsilon^2 \chi'' \rho^2 \phi'}{(1 - \varepsilon \chi')^3} + \frac{2 \varepsilon \chi' \rho^2}{1 - \varepsilon \chi'} \frac{\partial}{\phi'} \right] \frac{\partial}{\partial r'} \right\},
\]
Asymptotic stability: continued

- Need to show that small terms are small.
- This is done in conjunction with the choice of the center through the fixed point theorems.

Theorem: If the initial data is $\varepsilon$-close to a radial solution centered at 0, then there exists another $a = O(\varepsilon)$

$$\partial \Omega(t) \to \text{sphere}, \ |x - a| = R,$$

the convergence is exponentially fast.
Asymptotic stability: continued

- Need to show that small terms are small.
- This is done in conjunction with the choice of the center through the fixed point theorems.

Theorem: If the initial data is $\varepsilon$-close to a radial solution centered at 0, then there exists another $a = O(\varepsilon)$

$$\partial \Omega(t) \to \text{sphere, } |x - a| = R,$$

the convergence is exponentially fast.
Need to show that small terms are small.

This is done in conjunction with the choice of the center through the fixed point theorems.

Theorem: If the initial data is $\varepsilon$-close to a radial solution centered at 0, then there exists another $a = O(\varepsilon)$

$$\partial \Omega(t) \to \text{sphere, } |x - a| = R,$$

the convergence is exponentially fast.
The simple tumor model: the results for small $R_S$

- [Friedman-Hu, 08, Tran. Amer. Math. Soc.]

**Theorem (Hopf bifurcation)**

For $R_S < \bar{R} \approx 0.62$, and $\mu = \mu_0^*$ (the critical value for stability).

(i) (Existence) there exists a family of periodic solutions of the form:

$$\rho(\theta, \phi, t) = C_1 \sin \beta t + C_2 \cos \beta t + \sum_{m=-1}^{1} D_m Y_{1,m}(\theta, \phi).$$

for the linearized problem, where $\beta > 0$ and $\pm i \beta$ are roots of some function $h_0(s)$.

(ii) (Uniqueness) any period solution to the linearized problem, is of the form (E).

(iii) For any initial data $w_0 \in L^2(B_R)$, $\rho_0 \in L^2(\Sigma)$, the solution of the linearized problem converges exponentially fast to a periodic solution of the form (E).
The bifurcation theory is nice – but

- it is applicable only in a small neighborhood of the bifurcation point
- the verification of the assumptions of Crandall-Rabinowitz is a challenge

The system, after discretization, becomes

\[ F(X) = 0 \]

note that here the discretization mesh itself is part of the unknown since we have a free boundary problem.
The bifurcation theory is nice – but
  - it is applicable only in a small neighborhood of the bifurcation point
  - the verification of the assumptions of Crandall-Rabinowitz is a challenge

The system, after discretization, becomes

\[ F(X) = 0 \]

note that here the discretization mesh itself is part of the unknown since we have a free boundary problem.
Along the radially symmetric branch, the mesh points are known.

Figure: Solving \( F(X) = 0 \). Condition number \( CN = \| J(x) \| \| J^{-1}(x) \| \) along radially symmetric solution branch as a function of \( \mu \).
The simple tumor model (2d): Discretization

Theoretical value $\mu_2(R) = 3.702687$. In polar coordinate system,

<table>
<thead>
<tr>
<th>$N_\theta$</th>
<th>$N_R$</th>
<th>$\mu_2$</th>
<th>abs. error</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>10</td>
<td>3.725819</td>
<td>0.023132</td>
</tr>
<tr>
<td>48</td>
<td>12</td>
<td>3.720450</td>
<td>0.017763</td>
</tr>
<tr>
<td>52</td>
<td>13</td>
<td>3.718400</td>
<td>0.015713</td>
</tr>
<tr>
<td>60</td>
<td>15</td>
<td>3.715204</td>
<td>0.012517</td>
</tr>
<tr>
<td>80</td>
<td>20</td>
<td>3.710412</td>
<td>0.007725</td>
</tr>
</tbody>
</table>

Table: Comparing (discretized) bifurcation value of $\mu_2$ on a sequence of grids
Bifurcation along a nonradial branch is much more interesting for biology and is a common thing in our tumor study. Homotopy tracking using high precision is a powerful tool to compute bifurcations along a nonradial branch.

Figure: Solution behavior. $\varepsilon(\mu) = \pm (\text{Max} - \text{Min})$ radius
Tracking along bifurcation

Figure: Non-radially symmetric solutions
Other solutions? – domain decomposition

Are there other stationary solutions that are not from tracking diagram?

Ideas of domain decomposition:

- We start with smaller number of grid points, with free boundary as part of the unknowns.
- After obtaining a nonradial solution, we used higher order schemes and finer grids to refine the solutions using Homotopy (Similar to "Newton’s method").
- After the refinement, some “fake” solutions were found and discarded. For example, with $\mu = 3$, we found 24 solutions using this process. For example, it took under 4 hours for $\mu = 0.5$ and roughly 2 days for $\mu = 3$.

Figure: Some solutions for $\mu = 3$
Are there other stationary solutions that are not from tracking diagram?

**Ideas of domain decomposition:**

- We start with a smaller number of grid points, with free boundary as part of the unknowns.
- After obtaining a nonradial solution, we used higher order schemes and finer grids to refine the solutions using Homotopy (Similar to "Newton’s method").
- After the refinement, some “fake” solutions were found and discarded. For example, with $\mu = 3$, we found 24 solutions using this process. For example, it took under 4 hours for $\mu = 0.5$ and roughly 2 days for $\mu = 3$.

![Some solutions for $\mu = 3$](image-url)
Other solutions? – domain decomposition

Are there other stationary solutions that are not from tracking diagram?

Ideas of domain decomposition:

- We start with smaller number of grid points, with free boundary as part of the unknowns.
- After obtaining a nonradial solution, we used higher order schemes and finer grids to refine the solutions using Homotopy (Similar to "Newton’s method").
- After the refinement, some “fake” solutions were found and discarded. For example, with $\mu = 3$, we found 24 solutions using this process. For example, it took under 4 hours for $\mu = 0.5$ and roughly 2 days for $\mu = 3$.

Figure: Some solutions for $\mu = 3$
Other solutions? – domain decomposition

Are there other stationary solutions that are not from tracking diagram?

**Ideas of domain decomposition:**

- We start with smaller number of grid points, with free boundary as part of the unknowns.
- After obtaining a nonradial solution, we used higher order schemes and finer grids to refine the solutions using Homotopy (Similar to "Newton’s method").
- After the refinement, some “fake” solutions were found and discarded. For example, with $\mu = 3$, we found 24 solutions using this process. For example, it took under 4 hours for $\mu = 0.5$ and roughly 2 days for $\mu = 3$.

![Figure: Some solutions for $\mu = 3$](image-url)
Are there other stationary solutions that are not from tracking diagram?

**Ideas of domain decomposition:**

- We start with smaller number of grid points, with free boundary as part of the unknowns.
- After obtaining a nonradial solution, we used higher order schemes and finer grids to refine the solutions using Homotopy (Similar to "Newton’s method").
- After the refinement, some “fake” solutions were found and discarded. For example, with $\mu = 3$, we found 24 solutions using this process. For example, it took under 4 hours for $\mu = 0.5$ and roughly 2 days for $\mu = 3$.

![Some solutions for $\mu = 3$]

**Figure:** Some solutions for $\mu = 3$
Yes: The computation can be reproduced for 3D.

Yes: all results can be reproduced.

Features: Two free boundaries. One dead-core boundary, and the other the outer boundary of the tumor.
Let \( \Omega(t) \) be the tumor region with a dead-core \( D(t) \). Let 
\( \chi(x, t) = \chi(\Omega(t) \setminus D(t))(x) \). The necrotic core system is

\[
\begin{cases}
\sigma_t - \Delta \sigma = -\sigma \chi(x, t) \quad \text{and} \quad -\Delta p = \mu(\sigma - \tilde{\sigma})\chi(x, t) & \text{in } \Omega(t), \\
\sigma = \sigma & \text{in } D(t), \\
\sigma = 1; \quad p = \kappa; \quad \text{and} \quad \frac{\partial p}{\partial n} = -V_n & \text{on } \partial \Omega(t),
\end{cases}
\]

where \( n \) denotes the exterior normal vector. Additionally, it is reasonable to assume \( \sigma < \tilde{\sigma} < 1 \).
Outline

1. Tumor model with Darcy’s law
   - Problem setup
   - The results

2. Tumor model with Stokes equation
   - The governing equations
   - Our results
   - Comparison: Darcy’s law and Stokes equation
The governing equations

- **Diffusion of the nutrients:** \( \sigma_t - \Delta \sigma + \sigma = 0 \) in \( \Omega(t) \).
- **Conservation of mass:** \( \text{div} \vec{V} = S \), \( S = \) proliferation rate. We assume linear dependence on \( \sigma \): \( S = \mu(\sigma - \bar{\sigma}) \), (here \( \bar{\sigma} > 0 \) is the death rate)
- Instead of Darcy’s law, Stoke’s equation is used:
  \[-\nu \Delta \vec{v} + \nabla p - \frac{1}{3} \nu \nabla \text{div} \vec{v} = 0 \] in \( \Omega(t) \).
- Introducing the stress tensor \( Q = \nu (\nabla \vec{v} + (\nabla \vec{v})^T) - (p + \frac{2}{3} \nu \text{div} \vec{v}) I \) with components \( Q_{ij} = \nu \left( \frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i} \right) - \delta_{ij} \left( p + \frac{2}{3} \nu \text{div} \vec{v} \right) \), we then have
  \[ Q \vec{n} = -\gamma \kappa \vec{n} \quad \text{on} \quad \Gamma(t), \quad t > 0, \]
  where the cell-to-cell adhesion equal to a constant \( \gamma \), \( \kappa \) is the mean curvature.
- **Continuity:** \( V_n = \vec{v} \cdot \vec{n} \) on \( \partial \Omega(t) \)
  where \( V_n = \) velocity in the normal \( n \) direction.
- Since \( \vec{v} \) is determined up to \( \vec{b} \times \vec{x} \), some additional constraints are needed.
The governing equations

- Diffusion of the nutrients: \( \sigma_t - \Delta \sigma + \sigma = 0 \) in \( \Omega(t) \).
- Conservation of mass: \( \text{div} \vec{V} = S \), \( S = \) proliferation rate.
  We assume linear dependence on \( \sigma \): \( S = \mu(\sigma - \bar{\sigma}) \), (here \( \bar{\sigma} > 0 \) is the death rate)
- Instead of Darcy’s law, Stoke’s equation is used:
  \[-\nu \Delta \vec{v} + \nabla p - \frac{1}{3} \nu \nabla \text{div} \vec{v} = 0 \] in \( \Omega(t) \).
- Introducing the stress tensor \( Q = \nu(\nabla \vec{v} + (\nabla \vec{v})^T) - (p + \frac{2}{3} \nu \text{div} \vec{v})I \)
  with components \( Q_{ij} = \nu \left( \frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i} \right) - \delta_{ij} \left( p + \frac{2}{3} \nu \text{div} \vec{v} \right) \), we then have
  \[ Q \vec{n} = -\gamma \kappa \vec{n} \] on \( \Gamma(t), \ t > 0 \),
  here the cell-to-cell adhesion equal to a constant \( \gamma \), \( \kappa \) is the mean curvature.
- Continuity: \( V_n = \vec{v} \cdot \vec{n} \) on \( \partial \Omega(t) \)
  where \( V_n \) = velocity in the normal \( n \) direction.
- Since \( \vec{v} \) is determined up to \( \vec{b} \times \vec{x} \), some additional constraints are needed.
The governing equations

- Diffusion of the nutrients: \( \sigma_t - \Delta \sigma + \sigma = 0 \) in \( \Omega(t) \).
- Conservation of mass: \( \text{div} \vec{V} = S \), \( S = \) proliferation rate.
  
  We assume linear dependence on \( \sigma \): \( S = \mu(\sigma - \bar{\sigma}) \), (here \( \bar{\sigma} > 0 \) is the death rate)
- Instead of Darcy's law, Stoke's equation is used:
  
  \[-\nu \Delta \vec{v} + \nabla p - \frac{1}{3} \nu \nabla \text{div} \vec{v} = 0 \quad \text{in} \ \Omega(t).\]
- Introducing the stress tensor \( Q = \nu(\nabla \vec{v} + (\nabla \vec{v})^T) - (p + \frac{2}{3} \nu \text{div} \vec{v})I \)
  
  with components \( Q_{ij} = \nu \left( \frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i} \right) - \delta_{ij} \left( p + \frac{2 \nu}{3} \text{div} \vec{v} \right) \), we then have
  
  \[ Q \vec{n} = -\gamma \kappa \vec{n} \quad \text{on} \ \Gamma(t), \quad t > 0, \]
  
  here the cell-to-cell adhesion equal to a constant \( \gamma \), \( \kappa \) is the mean curvature.
- Continuity: \( V_n = \vec{v} \cdot \vec{n} \) on \( \partial \Omega(t) \)
  
  where \( V_n \) = velocity in the normal direction.
- Since \( \vec{v} \) is determined up to \( \vec{b} \times \vec{x} \), some additional constraints are needed.
The governing equations

- **Diffusion of the nutrients**: \( \sigma_t - \Delta \sigma + \sigma = 0 \) in \( \Omega(t) \).

- **Conservation of mass**: \( \text{div} \vec{V} = S \), \( S = \) proliferation rate. We assume linear dependence on \( \sigma \): \( S = \mu (\sigma - \bar{\sigma}) \), (here \( \bar{\sigma} > 0 \) is the death rate)

- Instead of Darcy’s law, Stoke’s equation is used:
  \[-\nu \Delta \vec{V} + \nabla p - \frac{1}{3} \nu \nabla \text{div} \vec{V} = 0 \] in \( \Omega(t) \).

- Introducing the stress tensor \( Q = \nu (\nabla \vec{V} + (\nabla \vec{V})^T) - (p + \frac{2}{3} \nu \text{div} \vec{V}) I \) with components \( Q_{ij} = \nu \left( \frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i} \right) - \delta_{ij} \left( p + \frac{2}{3} \nu \text{div} \vec{V} \right) \), we then have
  \[ Q \vec{n} = -\gamma \kappa \vec{n} \] on \( \Gamma(t), \ t > 0 \),
  here the cell-to-cell adhesion equal to a constant \( \gamma \), \( \kappa \) is the mean curvature.

- **Continuity**: \( V_n = \vec{v} \cdot \vec{n} \) on \( \partial \Omega(t) \)
  where \( V_n = \) velocity in the normal \( n \) direction.

- Since \( \vec{V} \) is determined up to \( \vec{b} \times \vec{x} \), some additional constraints are needed.
The governing equations

- Diffusion of the nutrients: \( \sigma_t - \nabla \sigma + \sigma = 0 \) in \( \Omega(t) \).

- Conservation of mass: \( \text{div} \vec{V} = S \), \( S \) = proliferation rate.

We assume linear dependence on \( \sigma \): \( S = \mu (\sigma - \bar{\sigma}) \), (here \( \bar{\sigma} > 0 \) is the death rate)

- Instead of Darcy’s law, Stoke’s equation is used:

  \[ -\nu \Delta \vec{v} + \nabla p - \frac{1}{3} \nu \nabla \text{div} \vec{v} = 0 \text{ in } \Omega(t). \]

- Introducing the stress tensor \( Q = \nu (\nabla \vec{v} + (\nabla \vec{v})^T) - (p + \frac{2}{3} \nu \text{div} \vec{v}) I \)

  with components \( Q_{ij} = \nu \left( \frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i} \right) - \delta_{ij} \left( p + \frac{2\nu}{3} \text{div} \vec{v} \right) \), we then have

  \[ Q \vec{n} = -\gamma \kappa \vec{n} \text{ on } \Gamma(t), \ t > 0, \]

  here the cell-to-cell adhesion equal to a constant \( \gamma \), \( \kappa \) is the mean curvature.

- Continuity: \( V_n = \vec{v} \cdot \vec{n} \) on \( \partial \Omega(t) \)

  where \( V_n = \) velocity in the normal \( n \) direction.

- Since \( \vec{v} \) is determined up to \( \vec{b} \times \vec{x} \), some additional constraints are needed.
The governing equations

- Diffusion of the nutrients: \( \sigma_t - \Delta \sigma + \sigma = 0 \) in \( \Omega(t) \).
- Conservation of mass: \( \text{div} \vec{V} = S \), \( S = \) proliferation rate. We assume linear dependence on \( \sigma \): \( S = \mu (\sigma - \tilde{\sigma}) \), (here \( \tilde{\sigma} > 0 \) is the death rate)
- Instead of Darcy’s law, Stoke’s equation is used:
  \( -\nu \Delta \vec{v} + \nabla p - \frac{1}{3} \nu \nabla \text{div} \vec{v} = 0 \) in \( \Omega(t) \).
- Introducing the stress tensor \( Q = \nu (\nabla \vec{v} + (\nabla \vec{v})^T) - (p + \frac{2}{3} \nu \text{div} \vec{v}) I \)
  with components \( Q_{ij} = \nu \left( \frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i} \right) - \delta_{ij} \left( p + \frac{2\nu}{3} \text{div} \vec{v} \right) \), we then have
  \[ Q \vec{n} = -\gamma \kappa \vec{n} \quad \text{on } \Gamma(t), \quad t > 0, \]
  here the cell-to-cell adhesion equal to a constant \( \gamma \), \( \kappa \) is the mean curvature.
- Continuity: \( V_n = \vec{v} \cdot \vec{n} \quad \text{on } \partial \Omega(t) \)
  where \( V_n= \) velocity in the normal \( n \) direction.
- Since \( \vec{v} \) is determined up to \( \vec{b} \times \vec{x} \), some additional constraints are needed.
The Governing equations

\[ \sigma_t - \Delta \sigma + \sigma = 0, \quad x \in \Omega(t), \quad t > 0, \]
\[ \sigma = 1, \quad x \in \Omega(t), \quad t > 0, \]
\[ -\Delta \vec{v} + \nabla p = \frac{\mu}{3} \nabla (\sigma - \bar{\sigma}), \quad x \in \Omega(t), \quad t > 0, \]
\[ \text{div} \vec{v} = \mu (\sigma - \bar{\sigma}), \quad x \in \Omega(t), \quad t > 0 \quad (\bar{\sigma} < 1), \]
\[ T(\vec{v}, p) \vec{n} = \left( -\gamma \kappa + \frac{2}{3} \mu (1 - \bar{\sigma}) \right) \vec{n}, \quad x \in \Gamma(t), \quad t > 0, \]
\[ T(\vec{v}, p) = (\nabla \vec{v})^T + \nabla \vec{v} - \rho \ I, \quad I = (\delta_{ij})_{i,j=1}^3, \]
\[ V_n = \vec{v} \cdot \vec{n} \quad \text{on} \ \Gamma(t), \]

subject to the constraints

\[ \int_{\Omega(t)} \vec{v} \ dx = 0, \quad \int_{\Omega(t)} \vec{v} \times \vec{x} \ dx = 0. \]
The Radially symmetric solution


1.) Radially symmetric solution can be found explicitly:

$$\sigma_S(r) = \frac{R}{\sinh R} \frac{\sinh r}{r} = \frac{R^{1/2}}{l_{1/2}(R)} \frac{l_{1/2}(r)}{r^{1/2}},$$

$$\vec{v}_S = \mu G(r) \vec{x} = \mu G(r) r \vec{e}_r, \quad \rho_S(r) = \frac{\gamma}{R} + \frac{4\mu}{3} [\sigma_S(r) - \tilde{\sigma}],$$

where

$$G(r) = \frac{R^{1/2}}{l_{1/2}(R)} \frac{l_{3/2}(r)}{r^{3/2}} - P_0(R),$$

and $R = R_S$ is solved by $P_0(R_S) \equiv \frac{1}{R_S^2} (R_S \coth R_S - 1) = \frac{\tilde{\sigma}}{3}$.

2). The problem is well posed.
The Bifurcation theorem


**Theorem**

For even \( n \geq 2 \), if \( R = R_S \) is such that \( M_n(R) \) are all distinct, then the point \((0, M_n)\) is a bifurcation point for the problem and the corresponding branch of solutions have free boundaries of the form

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

where \( \frac{\mu}{\gamma} = M_n(R_S) + O(\varepsilon) \),

\[
M_n(R) = \frac{(n-1)n(n+2)}{2} \frac{1}{R^5 P_0(R) [P_1(R) - P_n(R)]},
\]

\[
P_n(R) = I_{n+3/2}(R)/[R I_{n+1/2}(R)].
\]
The Bifurcation theorem


**Theorem**

The \( \{M_n(R)\} \) is not monotonically increasing. In fact, it is monotone increasing beginning only from some \( n = \bar{n}(R) \); furthermore, if \( M_{n^*}(R)(R) = \min\{M_n(R); \ n = 2, 3, 4, \cdots \} \), then

\[
n^*(R) \to \infty \quad \text{if} \ R \to \infty,
\]

and

for \( R \) small, \( n^*(R) = 3 \), and \( M_3(R) < M_2(R) < M_4(R) \).
The Bifurcation theorem

Clearly the spherical tumor cannot remain stable when

\[ \frac{\mu}{\gamma} \text{ increases to the number } M_{n^*}(R_S)(R_S). \]


**Theorem**

The spherical stationary solution is linearly stably if \( \frac{\mu}{\gamma} < N^*(R_S, \gamma) \) and linearly unstable if \( \frac{\mu}{\gamma} > N^*(R_S, \gamma) \), where \( N^*(R_S, \gamma) < M_{n^*}(R_S)(R_S) \); furthermore

\[ N^*(R_S, \gamma) < M_{n^*}(R_S)(R_S) \]

if \( \gamma \) is small and if \( \gamma \) is large, which means that stability breaks down before we reach the first bifurcation point. Numerical calculations show that it holds for all \( \gamma \) if \( R_S < 310 \).
In the case of Stokes equation, \( n_*(R_S) \to \infty \) if \( R_S \to \infty \). In the case of Darcy’s law, the minimum of the \( \mu_n(R) \) is always reached when \( n = 2 \). The parameter \( \mu \) is the proliferation rate; the larger the \( \mu \) the more aggressive the tumor is. The parameter \( \gamma \) is the cell-to-cell adhesiveness; it plays an important role in keeping the tumor cohesive. A smaller value of \( \gamma \) enables the tumor to develop fingers more easily and thus be more prone to invasion. In our model the two parameters appear as a quotient \( \mu/\gamma \). Thus we expect that as this parameter will increase, the tumor will lose its spherical shape, develop fingers, and become invasive.
The ability of a tumor to invade into the surrounding tissue depends also on the material properties of its surrounding. If the tissue is a porous medium, then the smallest value of $\mu/\gamma$ which generates protrusions is $M_2(R_S)$, at which time the tumor will have just three protrusions, no matter how large the radius $R_S$ is. In contrast, in fluid-like tissue as in the present paper, the smallest value of $\mu/\gamma$ which generates protrusions is $M_{n^*}(R_S)$, where $n^* \to \infty$ as $R_S \to \infty$. Thus, when a large spherical tumor develops protrusions, it does so right away with a large number of protrusions, namely with a number proportional to $n^*(R_S)$. This makes the tumor invasion more hazardous, since it increases the probability that one or several of the many invasive protrusions will reach a blood vessels and lead to metastasis.
The discretization for this problem is much more expensive than the one with Darcy’s law!
Thank you!