Free Boundary Problems Arising in Mathematical Biology

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Introduction

- Recent years have seen a dramatic increase in the number and variety of new mathematical models of biological processes that are formulated by systems of PDEs.

- I will describe such models, with free boundary, state mathematical results, and suggest open problems.

Tumor in porous-like tissue

Consider species $p_i (1 \le i \le m)$ with velocities $\vec{v}_i$ interacting with rates k_{ij}

Conservation Law:

$$\frac{\partial p_i}{\partial t} + div(\vec{v}_i p) = \Sigma k_{ij} p_j$$

$p_1 =$ density of proliferating cells (cancer cells)

$p_2 =$ density of quiescent cells

$p_3 =$ density of dead cells

$k_{ij} = k_{ij}(c)$

$$\frac{\partial c}{\partial t} = \Delta c - \Sigma \lambda_i p_i c$$

Assume

$\Sigma p_i(x,t) \equiv const. = 1$

$\vec{v}_i = \vec{v} = -\nabla \pi$ Darcy's Law (π = pressure)

$$\Delta\pi = -\Sigma k_{ij}(c)\, p_j \text{ in } \Omega(t)$$

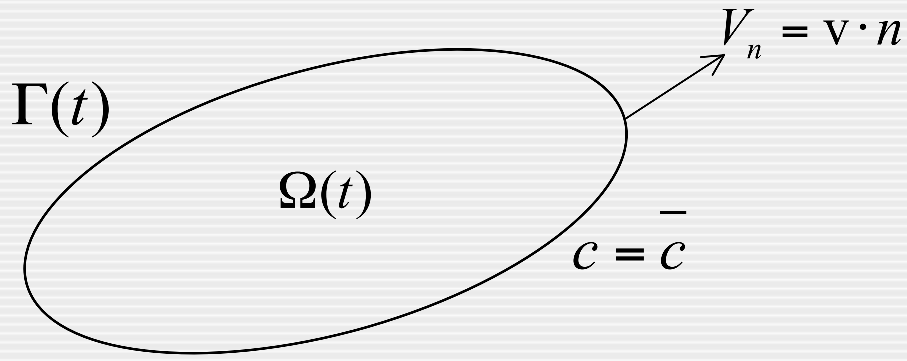
$$\pi = \gamma k \text{ on } \Gamma(t)$$

$$\mathrm{V}_n = \vec{v}\cdot\vec{n} = -\frac{\partial\pi}{\partial n} \text{ on } \Gamma(t)$$

$$c = \overline{c} \text{ on } \Gamma(t)$$

$$c(x,0) = c_o(x) \text{ on } \Omega(0)$$

$$p_i(x,0) = p_{io} \text{ on } \Omega(0)$$



<u>Theorem 1.</u> (X. Chen, Friedman) For smooth $k_{ij}(c), \Gamma(0)$ and $c_o(x), p_{io}(x)$, there exists a unique smooth solution for small time interval.

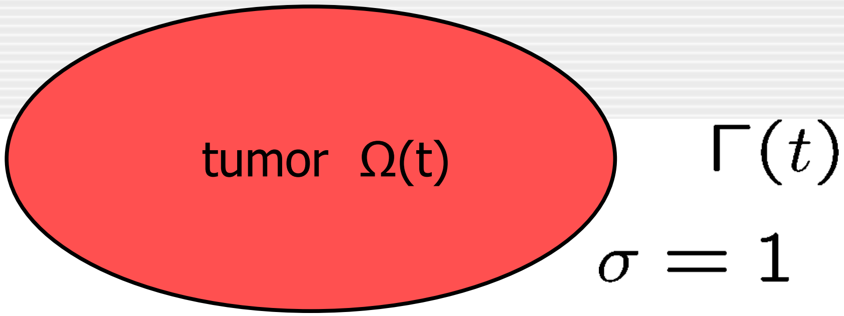
<u>Theorem 2.</u> For radially symmetric data there exists a unique radially symmetric solution with smooth free boundary r = R(t) for all t>o.

Questions

1.Does there exist a unique stationary radially symmetric solution? Is it asymptotically stable?

2.Are there non-radially symmetric stationary solutions?

Nearly complete answers are known only in the special where $p_1 \equiv 1, p_2 \equiv p_3 \equiv 0.$



σ = nutrient concentration

Tumor cells density is uniform.

Proliferation of tumor cells: $\mu(\sigma - \tilde{\sigma})$, $0 < \tilde{\sigma} < 1$.

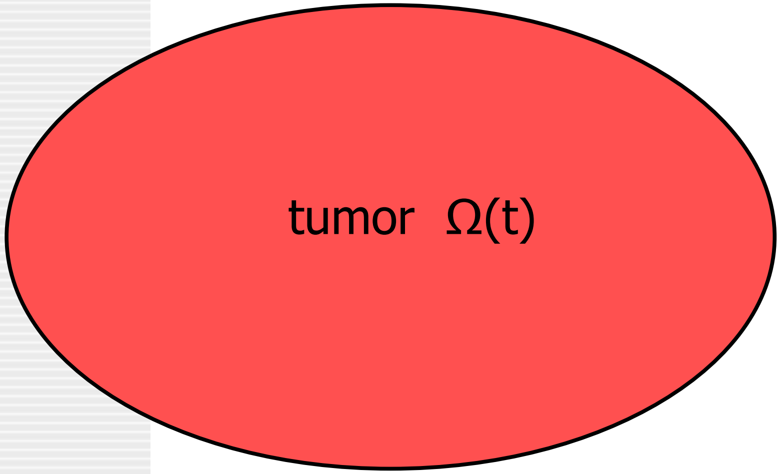
Tumor cells move with velocity $\vec{v}$.

$div \vec{v} = \mu(\sigma - \tilde{\sigma})$ (conservation of mass)

1. $\sigma_t - \Delta\sigma + \sigma = 0$

Darcy's Law $\vec{v} = -\nabla p$

2. $\Delta p = -\mu(\sigma - \tilde{\sigma}),\ 0 < \tilde{\sigma} < 1$



$\sigma = 1$

$p = \gamma\kappa$

$V_n = \vec{v} \cdot \vec{n} = -\frac{\partial p}{\partial n}$

By scaling, $\gamma = 1$.

Stationary Spherical Solution

$$\sigma_S(r) = \frac{R_S}{\sinh R_S}\frac{\sinh r}{r}, \; p_S(r) = C - \mu\sigma_S(r) + \frac{\mu}{6}\tilde{\sigma}r^2,$$

where $C = 1/R_S + \mu - \mu\tilde{\sigma}R_S^2/6$ and R_S is uniquely determined by the

$$\frac{R_s \coth R_s - 1}{R_s^2} = \frac{\tilde{\sigma}}{3}.$$

Let μ be bifurcation parameter.

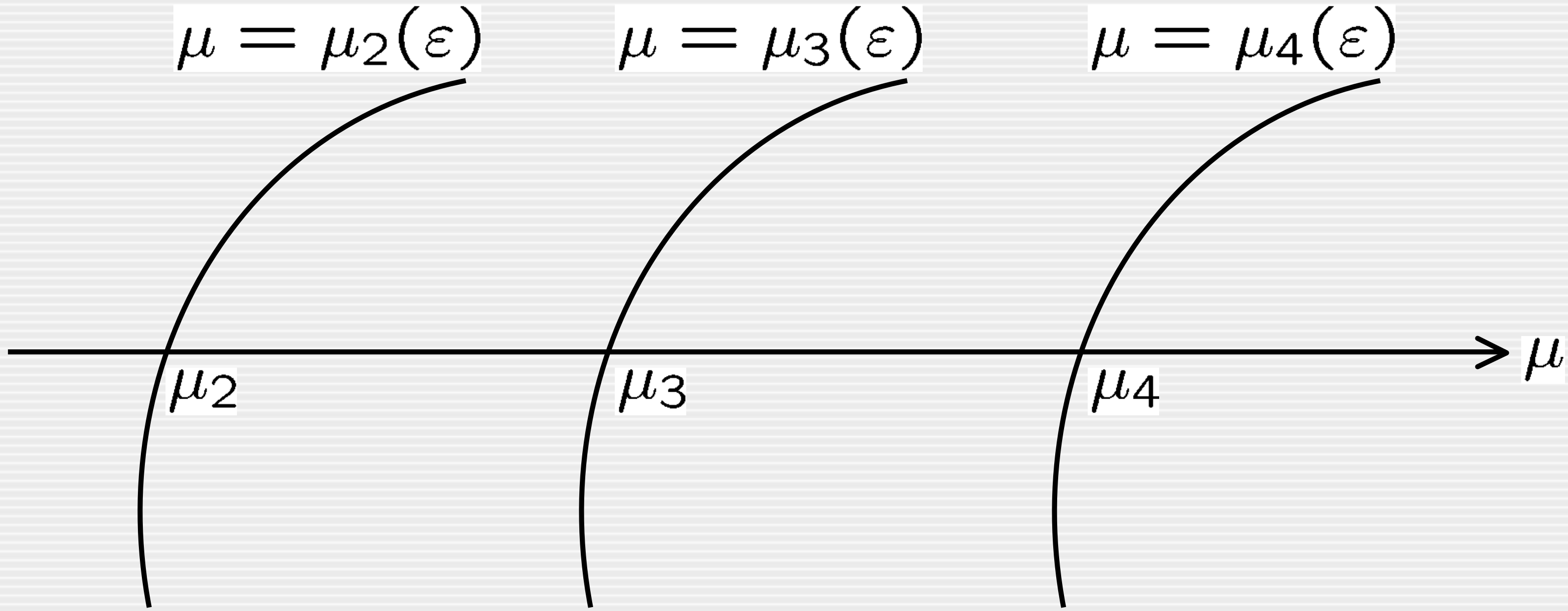
Theorem (Reitich, Fontelos, Friedman) $\exists$ infinite number of symmetry breaking bifurcation branches of solutions:

$$r = R_s + \epsilon Y_{n,0}(\theta) + O(\epsilon^2)$$

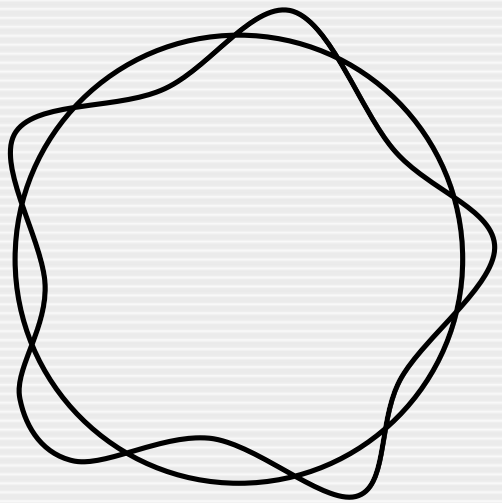
$$\mu = \mu_n + \epsilon\mu_{n1} + O(\epsilon^2)$$

$$\mu_n = \frac{n[n(n+1)-2]I_{1/2}(R_S)}{2R_S^3 I_{3/2}(R_S)[I_{5/2}(R_S)/I_{3/2}(R_S) - I_{n+3/2}(R_S)/I_{n+1/2}(R_S)]},$$

and $\mu_n(R_S) < \mu_{n+1}(R_S)$.



dim 2 :



$$r = R_s + \varepsilon \cos n\theta + 0(\varepsilon^2)$$

$$\mu = \mu_n + \mu_{n'}\varepsilon + 0(\varepsilon^2)$$

In addition to the branch of solutions with $r = R_0 + \varepsilon Y_{n,0}(\theta) + \cdots$ there exist solutions

$$r = R_s + \varepsilon \tilde{Y}_n(\theta, \rho, \varepsilon),$$

$$\tilde{Y}_n(\theta, \rho, \varepsilon) = \sum_{k=0}^{\infty} \varepsilon^k \sum_{m=-n}^{n} \alpha_{knm} Y_{nm}(\theta, \rho)$$

where $\tilde{Y}_n$ is invariant under a group of transformations
as reported in the book by M. Golubitsky, I. Stewart, D.G. Shaeffer:
"Singularities and Groups in Bifurcation Theory, Vol. II)."

$n = 3$	$O(2), O, D_6^d$
n=5	$O(2), D_{2m}^d \quad (2 \leq m \leq 5)$
n=7,11:	$O(2), O, D_{2m}^d \quad (n/3 < m \leq n)$
n=9,13,17,19,23,29:	$O(2), O, O, D_{2m}^d \quad (n/3 < m \leq n)$
all other odd n:	$O(2), O, O, [], D_{2m}^d \quad (n/3 < m \leq n)$
n=2:	$O(2) \oplus Z_2^c$
n=4,8,14:	$O(2) \oplus Z_2^c, O \oplus Z_2^c$
all other even n:	$O(2) \oplus Z_2^c, O \oplus Z_2^c, [] \oplus Z_2^c.$

For $n = 2, \tilde{Y}_n = \tilde{Y}_n(\theta, \varepsilon)$ is the only solution, for $n = 3$ there are two more solutions, etc.

Proof of Bifurcation Branches

$r = R_S + \tilde{R}(\theta, \varphi)$

solve all the PDE system except for the free boundary condition $\vec{v} \cdot \vec{n} = 0$.

Define

$$F(\tilde{R}, \lambda) = \vec{v} \cdot \vec{n} \qquad (\lambda = \mu/\gamma)$$

and try to solve

$$F(\tilde{R}, \lambda) = 0, \quad \tilde{R} \neq 0$$

We need:

$$\frac{\partial F}{\partial \lambda} = 0$$

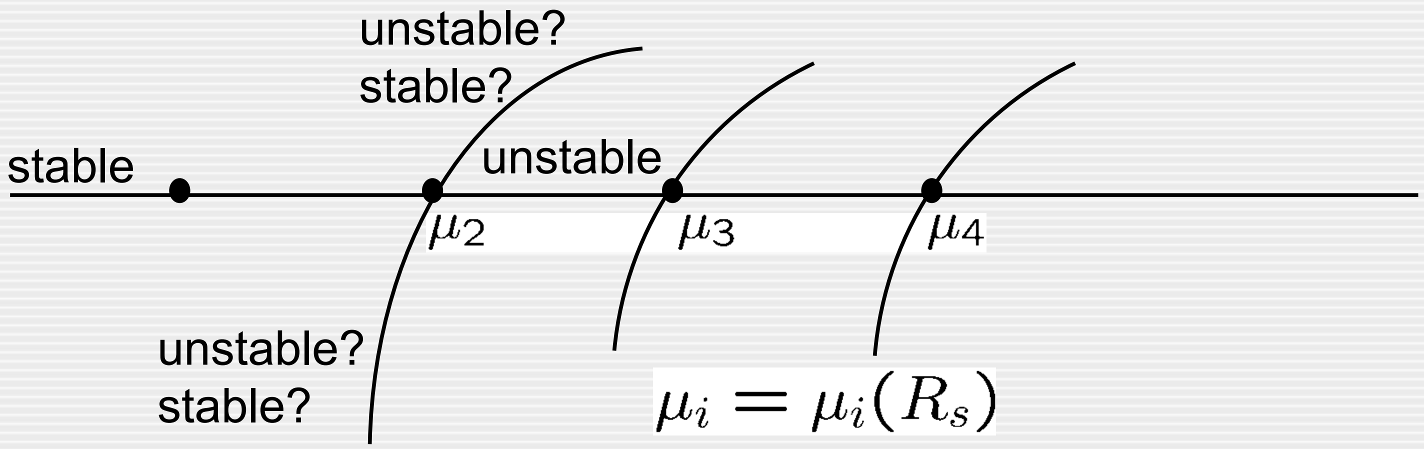
This determines $\lambda = \mu_n$

Tools: Crandall-Rabinowitz Theorem

The spherical solution is unstable for $\mu > \mu_2$.

But is it asymptotically stable for $\mu < \mu_2$?

Or does it lose stability at some $\mu < \mu_2$.



We begin with linear stability:

Results (joint with Bei Hu)

1. If $R_s > \bar{R}$ the sphere is stable for all $\mu < \mu_2$
2. If $R_s < \bar{R}$ the sphere becomes unstable at $\mu_2^*(R_s)$

   $\mu_2^*(R_s) < \mu_2$.

   $\bar{R} = 0.622207\ldots$

Proof of Linear Stability

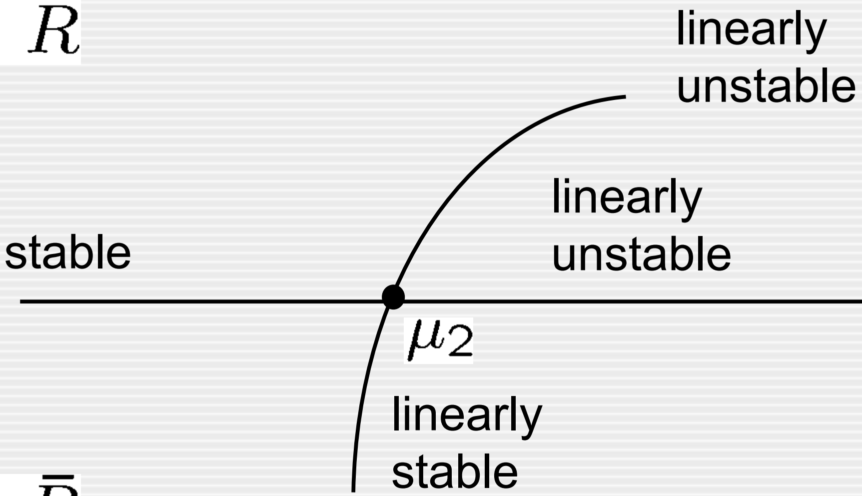
- Linearize the system
- Develop the solution in terms of spherical harmonics
- Take Laplace transform
- Solve for the Laplace transform of the free boundary

$$\rho(s,\theta) = \sum \rho_n(s) Y_{n,0}(\theta) :$$

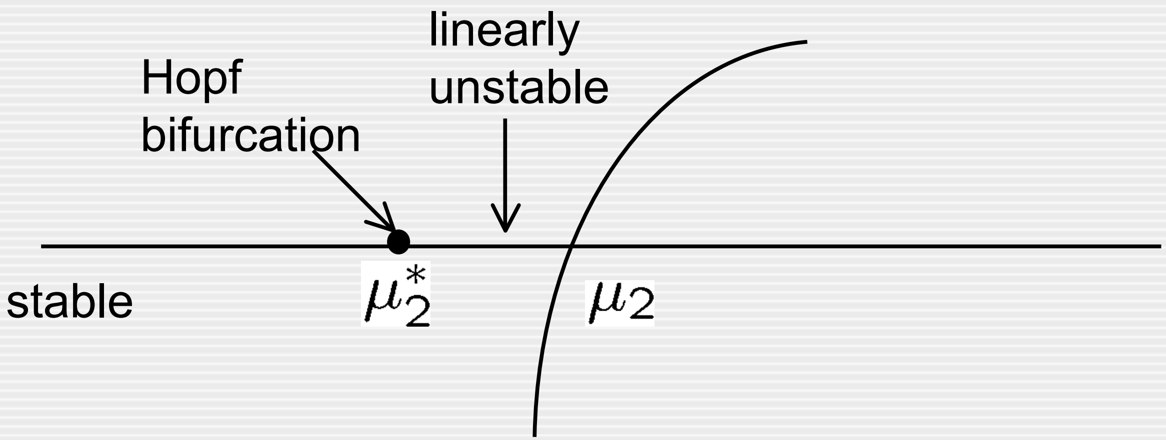
$$\rho_n(s) = \frac{k_n(s)}{h_n(s,\mu)}$$

- Study the location of the zeros of $h_n(s,\mu)$.

$R_s > \bar{R}$



$R_s < \bar{R}$



At $\mu = \mu_2^*$ every solution of the linearized problem is asymptotically convergent to a periodic solution.

Nonlinear stability is hard, because the problem is invariant under translation. We need to use the contraction fixed point theorem, but at each iteration step we need to move the coordinate system using another fixed point theorem:

Theorem. Let $(X, \|\cdot\|)$ be a Banach space and let $\bar{B}_K(a)$ denote the closed ball in X with center a and radius K. Let F be a mapping from $\bar{B}_K(a)$ into X such that

(i) its Frechét derivative $F\prime(x)$ exists,

(ii) the operator $F\prime(a)$ is invertible, and

(iii) there exists a positive constant $\beta < 1$ such that

$$\|F(a)\| \leq \frac{1-\beta}{\|(F\prime(a))^{-1}\|},$$

$$\|F\prime(x) - F\prime(a)\| \leq \frac{\beta}{\|(F\prime(a))^{-1}\|} \quad for \quad x \in \bar{B}_K(a),$$

where $\|A\|$ denotes the norm of a linear operator A from X to X. Then the equation $F(x) = 0$ has a unique solution x in $\bar{B}_K(a)$.

Tumor in fluid-like tissue

The growth of a tumor depends on the tissue constituency in the environment.

For some tumor it is reasonable to replace Darcy's Law $\vec{v} = -\nabla p$ by Stoke's equation

$$-\Delta \vec{v} + \nabla p = \frac{1}{3} \nabla (div \vec{v})$$

Model Equations

$$\sigma_t - \Delta\sigma + \sigma = 0, \quad x \in \Omega(t), \ t > 0$$

$$\sigma = 1, \quad x \in \Gamma(t), t > 0$$

$$-\Delta\vec{v} + \nabla p = \tfrac{\mu}{3}\nabla(\sigma - \tilde{\sigma}), \quad x \in \Omega(t), \ t > 0$$

$$div\vec{v} = \mu(\sigma - \tilde{\sigma}), \quad x \in \Omega(t), \ t > 0 \ \ (\tilde{\sigma} < 1)$$

$$T(\vec{v}, p)\vec{n} = -\gamma k\vec{n}, \quad x \in \Gamma(t), t > 0$$

$$V_n = \vec{v} \cdot \vec{n} \text{ on } \Gamma(t)$$

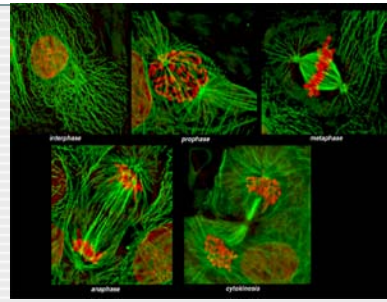
subject to the constraints

$$\int_{\Omega(t)} \vec{v}dx = 0, \qquad \int_{\Omega(t)} \vec{v} \times \vec{x}dx = 0;$$

$$T_0(\vec{v}, p) = (\nabla\vec{v})^T + \nabla\vec{v} - pI$$

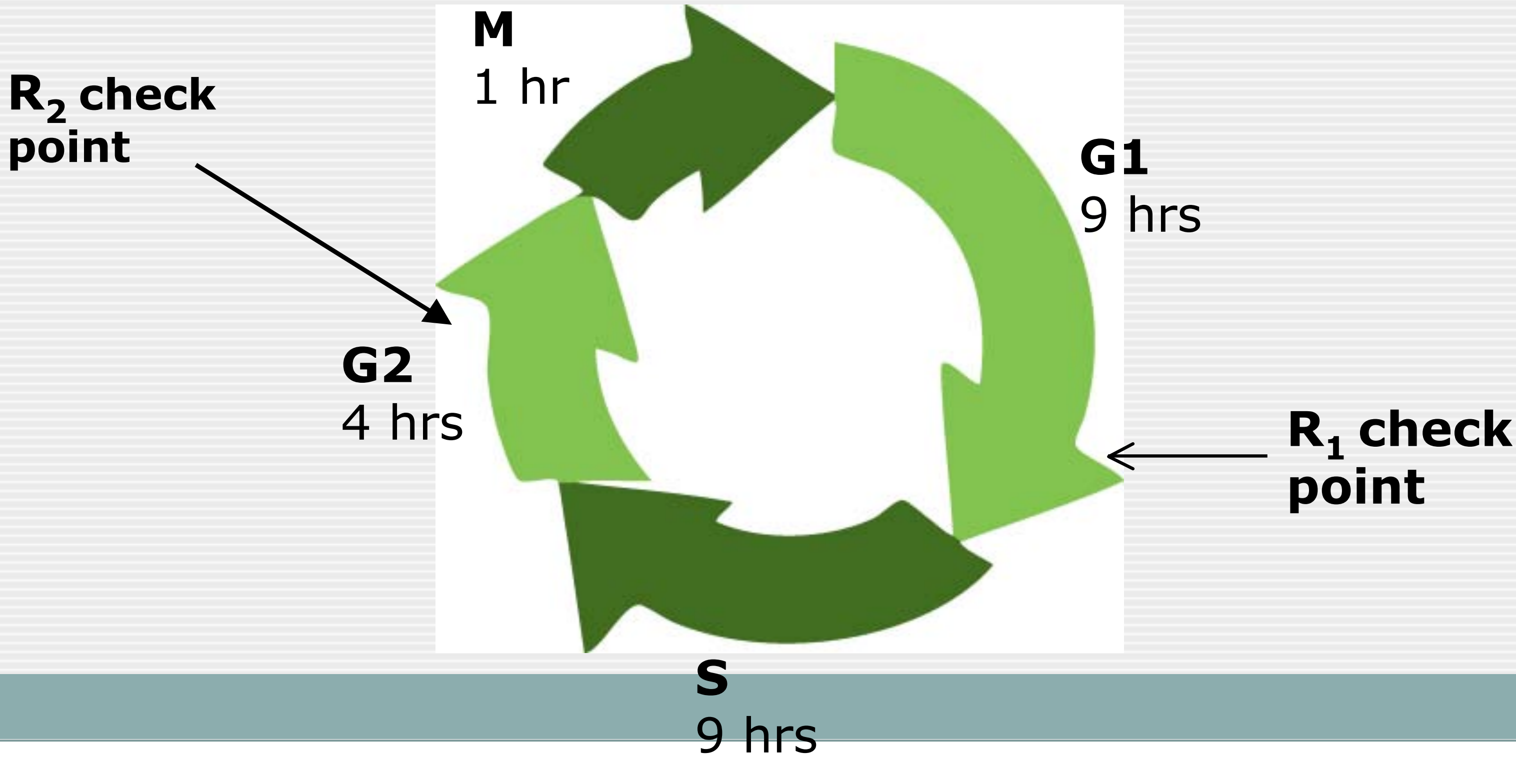
$$T(\vec{v}, p) = T_0(\vec{v}, p) - \tfrac{2}{3}\mu(1 - \tilde{\sigma})$$

Multiscale model



Cell cycle is divided into 4 stages

DNA is replicated in *S* phase (*S* for <u>s</u>ynthesis). Chromosomes condense and segregate in *M* phase (*M* for <u>m</u>itosis). Gap phases *G1* and *G2* separate *S* and *M* phases.



$$\frac{\partial p_i}{\partial t}+\frac{\partial p_i}{\partial s_i}+div(p_i\vec{v}) = \lambda_i(w)p_i \quad \textit{for} \quad 0 < s_i < A_i \quad (i = 0, 1, 2, 3),$$

$$\frac{\partial p_4}{\partial t}+div(p_4\vec{v}) = \mu_1 p_1(x,t,A_1)+\mu_2 p_2(x,t,A_2)-\lambda_4 p_4 \quad \textit{for} \quad 0 < s_4 < A_4$$

$$\begin{aligned} p_1(x,t,0) &= p_3(x,t,A_3), \\ p_2(x,t,0) &= p_1(x,t,A_1)[1 - K(w(x,t),Q(x,t)) - \mu_1] + p_0(x,t,A_0), \\ p_3(x,t,0) &= (1-\mu_2)p_2(x,t,A_2), \\ p_0(x,t,0) &= p_1(x,t,A_1)K(w(x,t),Q(x,t)). \end{aligned}$$

$$K(w,Q) + \mu_1 < 1,$$

$$K(w,Q)\uparrow \quad \textit{if} \quad w \downarrow, \quad \textit{or} \quad Q\uparrow .$$

$$Q_i = \int_0^{Ai} P_i(x,t,s_i)ds_i$$

$$Q = \sum_{i=o}^{3} Q_i$$

$$\sum \quad \frac{\partial Q_i}{\partial t} + div(Q_i v) = \sum_{i=o}^{3} \lambda_i(w)Q \; - \lambda_4 Q_4$$

Assume $\sum_{i=o}^{4} Q_i \equiv const. = 1$ and use Darcy's Law

The above system has a local in-time solution, and, in the radially symmetric case, the solution is global in time with free boundary $r = R(t)$

If mutations occur such that

$$K(w,Q) = const. = \delta$$

then $R(t) \to \infty$ as $t \to \infty$ if $\delta > \delta_*$ (cancer)

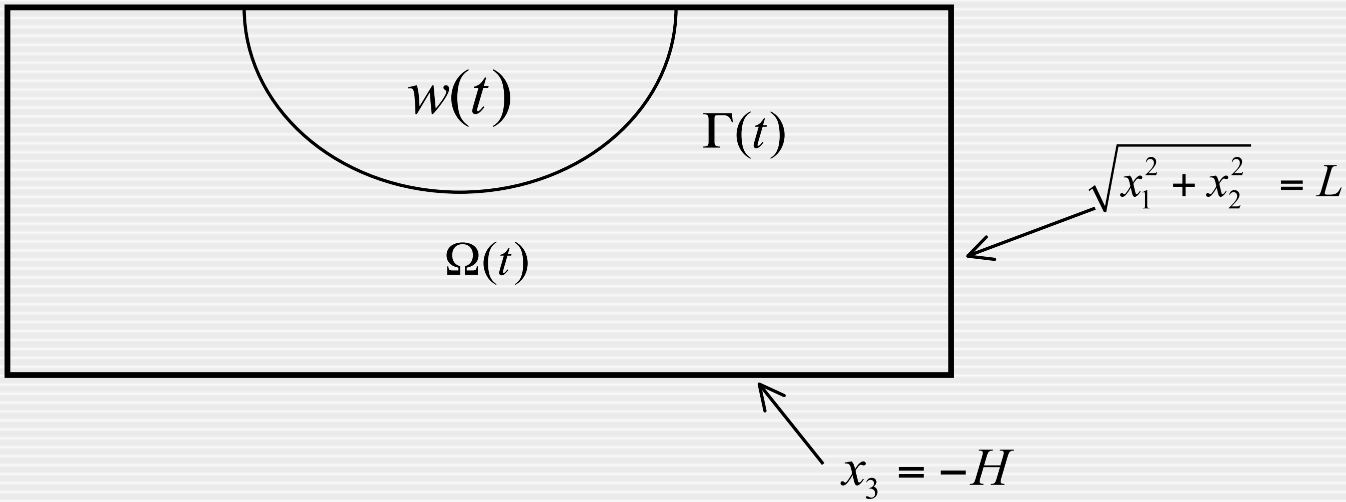
$R(t) \to 0$ as $t \to \infty$ if $\delta > \delta_*$.

If however $K = K(Q)$ can control Q ,

then $R(t)$ remains bounded, and $R(t)$ $R(0)$. [A. Friedman, B. Hu, C.Y. Kao]

Wound Healing

P
isotropic
pressure
in $\Omega(t)$



$$\sum_{i=1}^{3} \eta \frac{\partial}{\partial x_i}\left(\frac{\partial v_i}{\partial x_i} + \frac{\partial v_j}{\partial x_i}\right) = \frac{\partial P}{\partial x_j} \text{ in } \Omega(t)$$

$$\sum_{i=1}^{3} \eta \left(\frac{\partial v_i}{\partial x_i} + \frac{\partial v_j}{\partial x_i}\right)\eta_i = P v_j \text{ on } \Gamma(t)$$

$$v_1 = v_2 = v_3 = 0 \text{ on } \sqrt{x_1^2 + x_2^2} = L \text{ and on } x_3 = -H$$

$$\frac{\partial v_1}{\partial v_3} = \frac{\partial v_2}{\partial x_3} = u_1 \quad v_3 = 0 \text{ on } \mathrm{x}_3 = 0 \text{ outside the wound}$$

$$P = P(\rho) = const.\, F\left(\frac{\rho}{\rho_0} - 1\right)$$

$$\frac{\partial \rho}{\partial t} + div(\vec{v}\rho) = \frac{kw}{w+k} f\left(1 - \frac{\rho}{\rho_{\max}}\right) - \lambda\rho$$

The free boundary $ø(t, x) = 0$ satisfies

$$ø_t + n \cdot \nabla ø = 0 \text{ or } \Gamma(t)$$

<u>Theorem</u> (A. Friedman, B. Hu, C. Xue, 2011)
There exists a unique solution for small time interval.

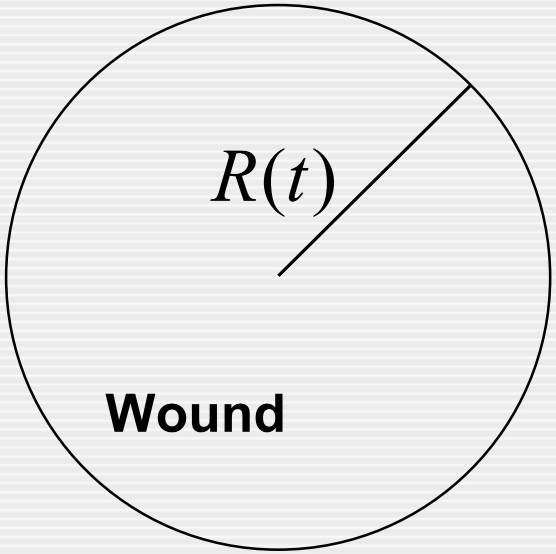
<u>Step 1</u>. Given f, w, prove existence and estimates for the coupled conservation law for ρ, and the elliptic free boundary system.

<u>Step 2</u>. Include f, w and several other variables (satisfying PDEs) and use a fixed point theorem.

Open problems:

Global existence
Properties of the wound's boundary

Recent results in the radially symmetric 2-d case (Friedman, B. Hu, C. Xue 2011),



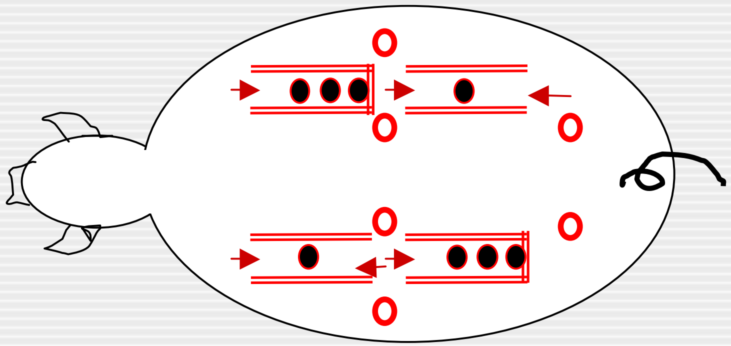
$$(1-\alpha)(w-w_0)+\alpha\frac{\partial w}{\partial n}=0$$

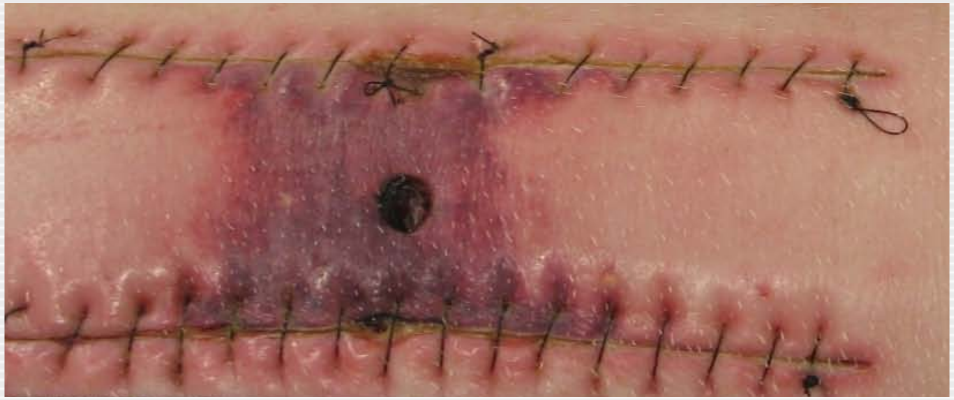
- The free boundary is $r = R(t)$ is decreasing in t

- If α is near 1 (not much oxygen inflow) then $R(t) = const. > 0$ for all t large ($t > t_0$)

“Ischemic wounds do not heal”

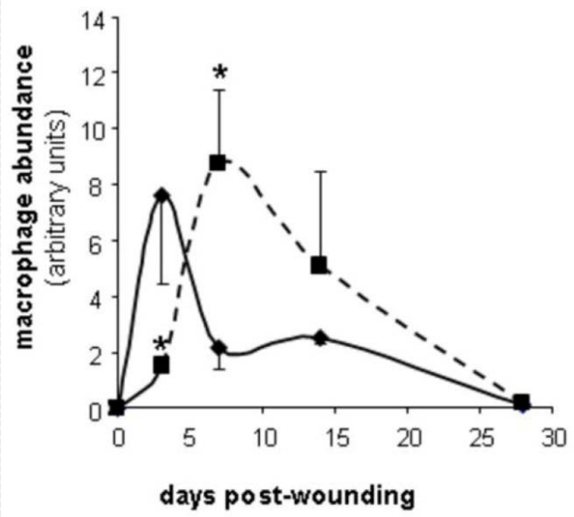
Experiments Conducted in the Comprehensive Wound Center at OSU

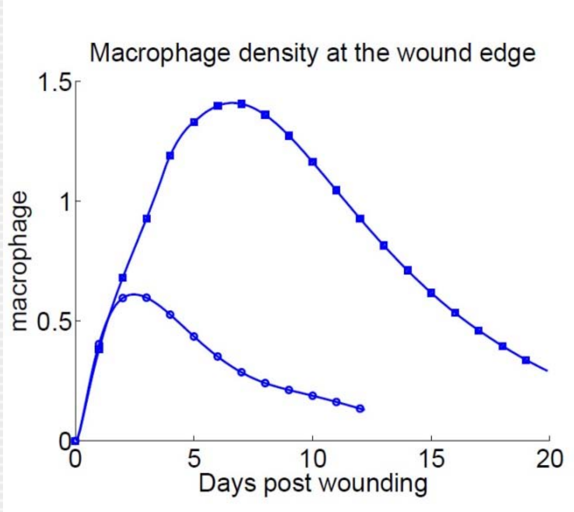


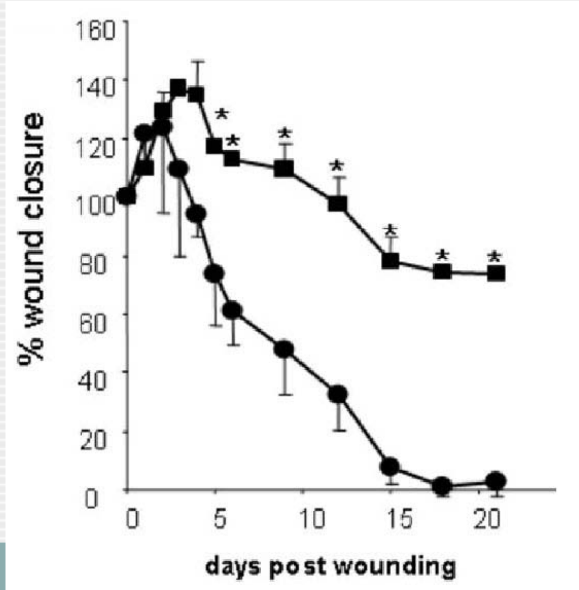


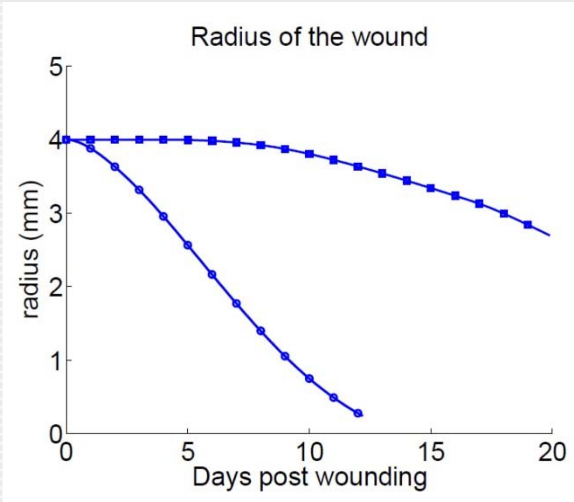
Model Simulations and Experimental Results

C. Xue, A. Friedman, C. Sen (PNAS, 2010)









Back to the 3-d wound.

Problem.

Give conditions on P and Γ(0) so that the wound will begin to close.

For example, in the axially symmetric case, if

$$\tilde{A}(t) = \left\{ x_3 = z(t,r) \right\}, \; r = (x_1^2 + x_2^2)^{\frac{1}{2}},$$

for which $P(x,0)$ and $\tilde{A}(0)$

$$z_t \big|_{t=o} > 0 \;\; ?$$

i.e. $\bar{v}_1 z_r - v_3 < 0 \qquad \bar{v}_1 = (v_2^1 + v_2^2)^{\frac{1}{2}}$

This is an elliptic problem in a fixed domain!