Nonlinear Modeling of Tumor Growth I: Basic Models

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P. Macklin, M.S. 2003, Ph.D. 2007 (expected);
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Motivation

- Provide biophysically justified *in silico* virtual system to study
- Help experimental investigations; design new experiments
- Therapy protocols

Outline

- Introduction to tumor growth

    Multiscale complex soft matter problem

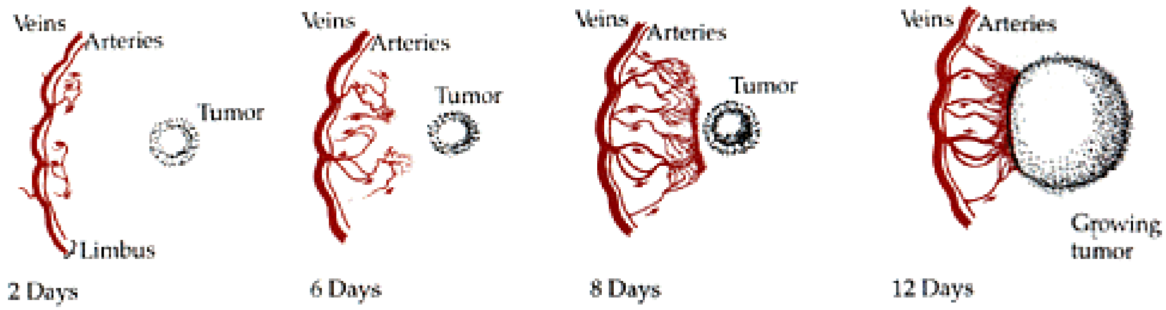
- Mathematical Models, Simplifications and Analysis (limited biophysics)

- Numerical Methods

- Results

Example of solid tumor growth

genetic mutations



Avascular growth
Diffusion dominated

Angiogenesis

Vascular growth
invasive
metastasis
malignancy

•Goal: Model all Phases of growth

In this talk, I will simplify the biophysics.
More complex biophysics will be considered in subsequent talks.

Cancer/Solid Tumor

•complex micro-structured soft matter

Micro scale
•Cell: ~10 micron
•Sub cell (genes, large proteins): nanometer

Macro scale
Carcinoma:
billion to 1000 billion cells
or
1—10 centimeter

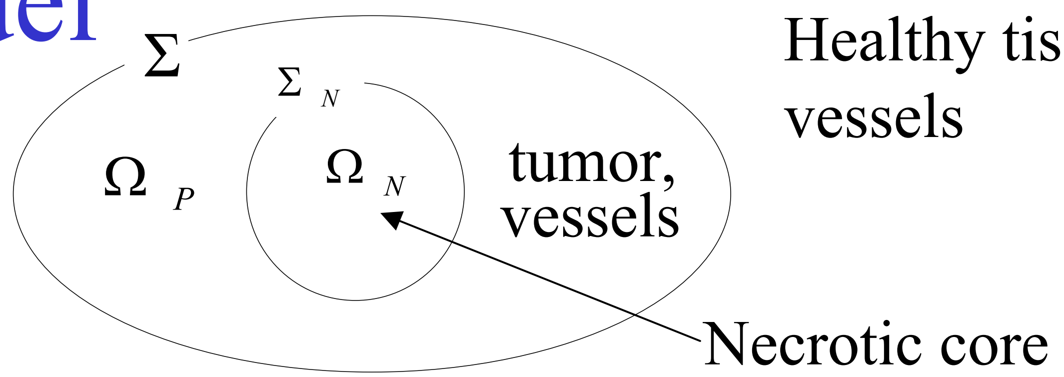
Processes at cell scale

Tumor cell aggregation,
Tumor growth and spread

Signals at sub-cell scale

Recent Reviews: Adam, Chaplain, Bellomo-Preziosi, Araujo-McElwain, Komarova,…

Present model



- Continuum approximation: super-cell macro scale

- Role of cell adhesion and motility on tissue invasion and metastasis
  Idealized mechanical response of tissues

- Coupling between growth and angiogenesis (neo-vascularization): necessary for maintaining uncontrolled cell proliferation

- Genetic mutations: random changes in microphysical parameters cell apoptosis and adhesion

- Limitations: poor feedback from macro scale to micro scale
  (Greenspan, Byrne & Chaplain, Anderson & Chaplain,Levine…)

Cell proliferation and tissue invasion

Greenspan, Chaplain, Byrne, …

Assume constant tumor cell density: cell velocity

Assume 1 diffusing nutrient of concentration σ

Cell proliferation: in the tumor is a balance of mitosis and apoptosis (mitosis is responsible for reproduction of mutated genes) and is one of the two main factors responsible for tissue invasion

Cell-to-cell adhesion

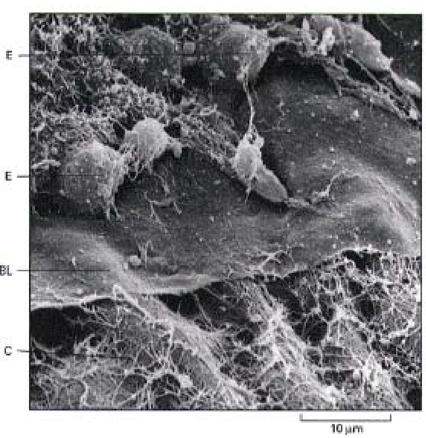
$$\nabla \bullet \mathbf{u} = \begin{cases} \lambda_M(\sigma) - \lambda_A \quad \text{in } \Omega_P \\ -\lambda_N \quad \text{in } \Omega_N = \{\mathbf{x} \mid \sigma(\mathbf{x},t) \le \sigma_N\} \end{cases}$$

$$P = \tau\kappa \quad \text{on } \Sigma$$

Darcy's law $\quad \mathbf{u} = -\mu \nabla P$

Viability concentration

Rate of enzymatic breakdown of necrotic cells (death due to lack of nutrient)



Cell mobility: reflect strength of cell adhesion to other cells and to the Extra-Cellular Matrix (ECM), the other main factor leading to tissue invasion

Spatial distribution of the oncotic pressure

Cell death responsible for release of angiogenic factors: INPUT TO ANGIOGENESIS

Evolution of nutrient: Oxygen/Glucose

Greenspan, Chaplain, Byrne, …

=0 (quasi-steady assumption). Tumor growth time scale (~1 day) large compared to typical diffusion time (~1 min)

Diffusion

nutrient concentration in blood

Oncotic pressure: affects blood flow and delivery of nutrients (and chemotherapy drugs)

$$\frac{\partial \sigma}{\partial t} = \nabla \bullet (D \nabla \sigma) - \lambda_C \cdot \sigma + \lambda_B(\sigma_B - \sigma, \mathrm{P}_B - P, \mathbf{x}, t)$$

Nutrient consumption by the cells

Blood-to-tissue nutrient transfer rate function. Spatial distribution of capillaries: OUTPUT FROM ANGIOGENESIS

Limited Biophysics

- Simplified cell-cycling model $\lambda_M(\sigma) = b\sigma$

- Simplified Blood-tissue transfer $\lambda_B(\sigma_B - \sigma, P_B - P, \mathbf{x}, t) = \lambda_B \cdot (\sigma_B - \sigma)$

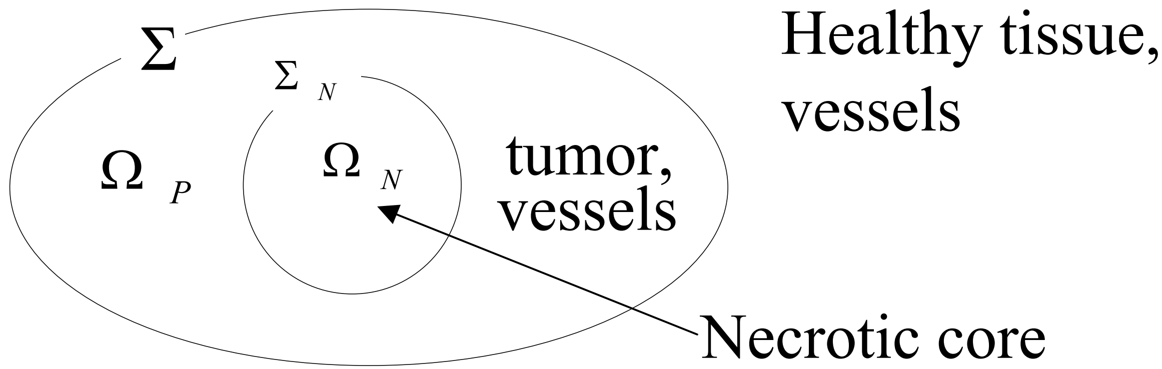
- Avascular or fully vascularized growth (i.e. no angiogenesis)

$\longrightarrow$

- Insight to biophysical system
- Benchmark for more complicated systems

Basic model

Greenspan, Chaplain, Byrne, Friedman-Reitich, Cristini-Lowengrub-Nie,…



Nutrient

$$0 = D\nabla^2\sigma + \Gamma,$$

$$\Gamma = -\lambda_B\ (\sigma - \sigma_B) - \lambda\, \sigma.$$

$$(\sigma)_\Sigma = \sigma^\infty$$

Pressure

$$\mathbf{u} = -\mu\nabla P, \quad \nabla\bullet u = \begin{cases} \lambda_P & \text{in } \Omega_P \\ -\lambda_N & \text{in } \Omega_N \end{cases}$$

$$(P)_\Sigma = \gamma\kappa \qquad \lambda_P = b\sigma - \lambda_A,$$

$$V = -\mu\, \mathbf{n}\cdot(\nabla P)_\Sigma\,.$$

normal velocity

Nondimensionalization

(Cristini, Lowengrub and Nie, J. Math. Biol. 46, 191-224, 2003)

Intrinsic length scale: $L_D = D^{\frac{1}{2}} (\lambda_B + \lambda)^{-\frac{1}{2}}$

Adhesion time scale: $\lambda_R^{-1}, \quad \lambda_R = \gamma\mu / L_D^3$

Nondimensional Parameters:

- Vascularization: $B = \dfrac{\sigma_B}{\sigma^\infty} \dfrac{\lambda_B}{\lambda_B + \lambda}$
- Apoptosis vs. mitosis $A = \dfrac{\lambda_A/\lambda_M - B}{1 - B}$ — healthy tissue: $A \approx 1$; genetic mutation: $A < 1$
- Mitosis vs. adhesion $G = \dfrac{\lambda_M}{\lambda_R} (1 - B)$ — $\lambda_M = b\sigma^\infty$ Mitosis rate
- Necrosis vs. mitosis $G_N = \lambda_N / \lambda_M$
- Viability $N = \dfrac{\sigma_N}{\sigma_\infty} - B$

Nondimensional basic system

nutrient

$$c = (\sigma / \sigma_\infty - B)/(1 - B)$$

pressure

$$p = P/(\gamma / L_D)$$

Free Boundary Problem:

$$\Delta c = c \quad \text{in } \Omega_P \qquad \Delta p = G \cdot \begin{cases} (A - c) & \text{in } \Omega_P \\ G_N & \text{in } \Omega_N \end{cases}$$

where $\Omega_N(t) = \{\mathbf{x} \mid c(\mathbf{x}, t) \le N\}$

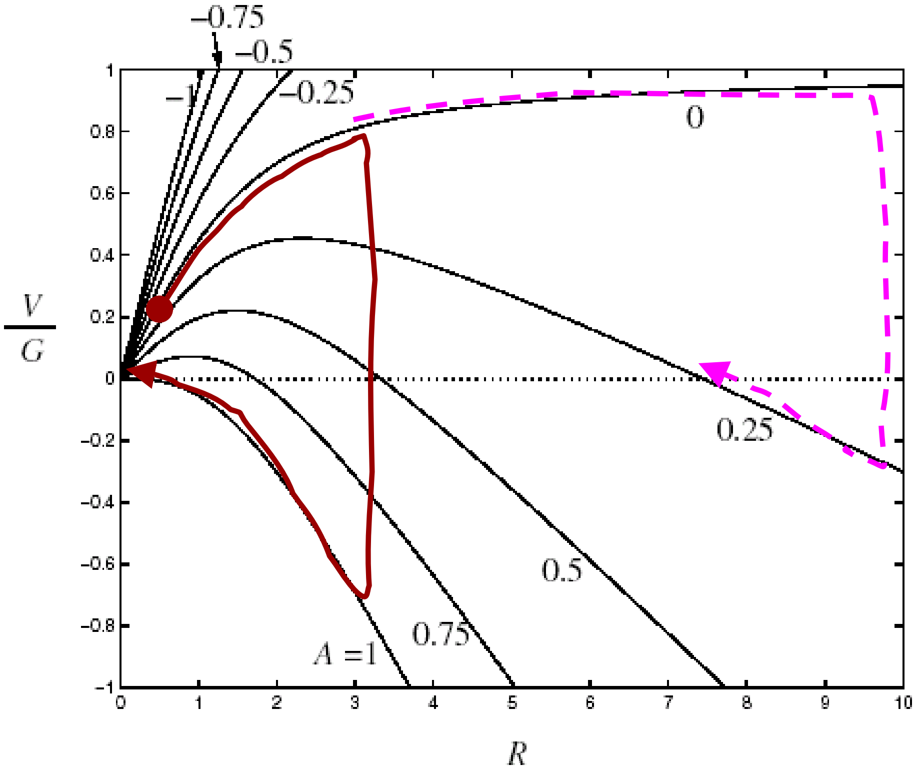
On Σ :

$$p = \kappa$$

$$c = 1$$

$$\mathbf{n} \cdot \frac{d\mathbf{x}_\Sigma}{dt} = V = -\nabla p \cdot \mathbf{n}$$

Evolution of a spherical tumor:



1. Low vascularization:

$$A > 0 \quad and \quad G > 0$$

Dormant state, Shrinkage to zero

2. Moderate vascularization: $A < 0 \quad and \quad G > 0$

Mimic angiogenesis, unbounded growth

3. High vascularization: $G < 0$

Unbounded growth, shrinkage to zero

Treatment

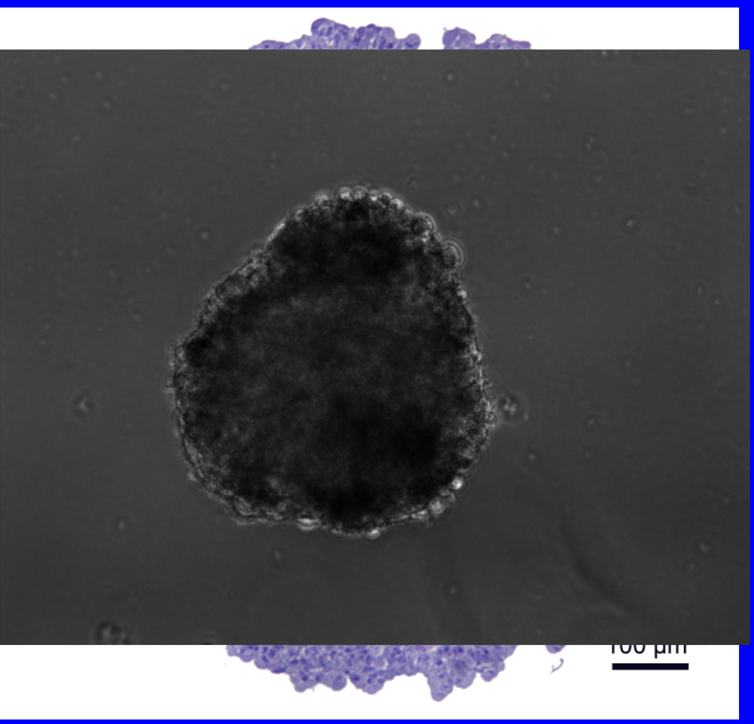
Transition between phases

→ Agreement w/ observed growth

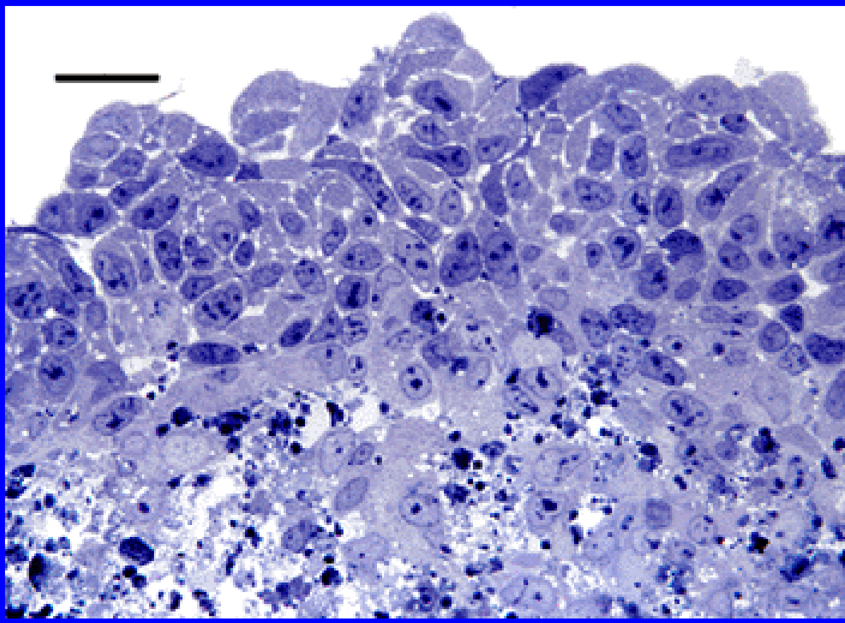
Tumor Spheroids: *In vitro* study

In vitro growth: No vascularization (diffusion-dominated)

Dormant (steady) states



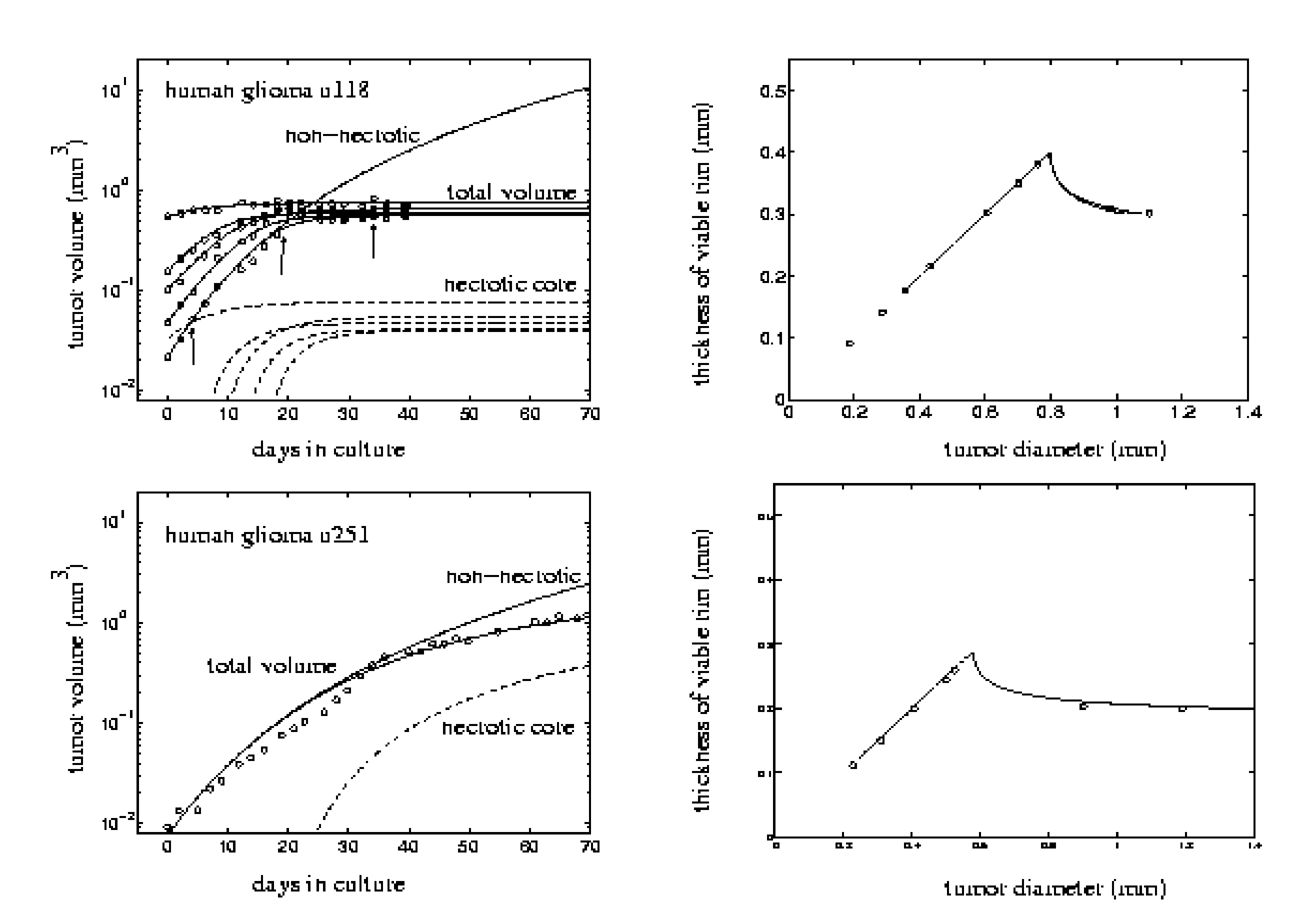
One micron section of tumor spheroid showing outer living shell of growing cells and inner core of necrosis.



3-D video holography through biological tissue
P. Yu, G. Mustata, and D. D. Nolte, Dept. of Physics, Purdue University

Tumor Modeling: The basic model

Model validation:



In vitro data:
Karim & Carlsson
Cancer Res.

- Agreement w/ observed growth
- Determine microphysical parameters

Microphysical parameters

- A=0, $G_N = \begin{cases} 4.0 & u118 \\ 0.31 & u251 \end{cases}$ $N \approx 10^{-2}$

$\lambda_M \approx 0.3 \text{ day}^{-1}$ $D \approx 3\times10^{-3} \text{ mm}^2/s$

$\lambda_C \approx 2\, s^{-1}$ $L \approx 4\times10^{-2} \text{ mm}$

(approximately 7 cells)

G can be estimated indirectly.

Estimation of G

Frieboes, Cristini, et al. Clin. Canc. Res., to appear.

Low vascularization regime. B=0, G>0.

In proliferating region,

$$P \sim L_D^2 \lambda_M / \mu$$

At tumor boundary,

$$P \sim \tau / L_D R$$

R – nondimensional tumor radius

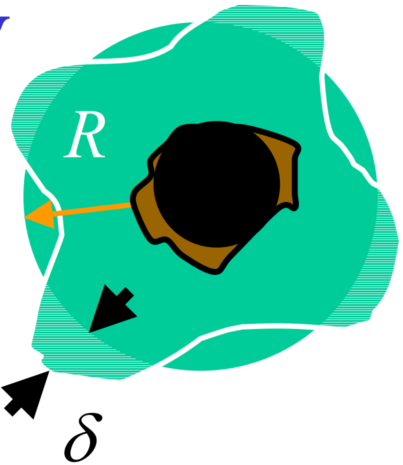
At steady-state,

$$L_D^2 \lambda_M / \mu \sim \tau / L_D R$$ which implies $$G \sim 1/R$$

$$\longrightarrow \quad G \sim 4$$ for u118 and u251

$\left\{\begin{array}{l}\text{Experiments} \\ \text{Linear stability theory}\end{array}\right.$ needed for further refinement.

Morphological stability



Perturbation

$$r_\Sigma = R(t) + \delta(t) \begin{cases} \cos(l\theta) & \text{in } 2D \\ Y_{lm}(\theta,\phi) & \text{in } 3D \end{cases}$$

Underlying Growth
d=2,3

$$G^{-1}\frac{dR}{dt} = -\frac{AR}{d} + \begin{cases} I_1(R)/I_0(R) & \text{in } 2D \\ \coth(R) - 1/R & \text{in } 3D \end{cases} + F(N, G_N, R)$$

$\longrightarrow$ $G_N = G_N^{steady}(R, N, A)$ such that $dR/dt = 0$

(balance between proliferation, necrosis and apoptosis)

If N=0, then reduces to $A = A^{steady}(R)$

Shape evolution

$$\left(\frac{\delta}{R}\right)^{-1}\frac{d}{dt}\left(\frac{\delta}{R}\right) = H_{growth}(l, R, A, G, G_N, N) - H_{decay}(l, R, A, G, G_N, N)$$

$\xrightarrow{\text{Self-similar evolution}}$ $G = G^{crit}(l, R, G_N, N, A)$ such that $d(\delta/R)/dt = 0$

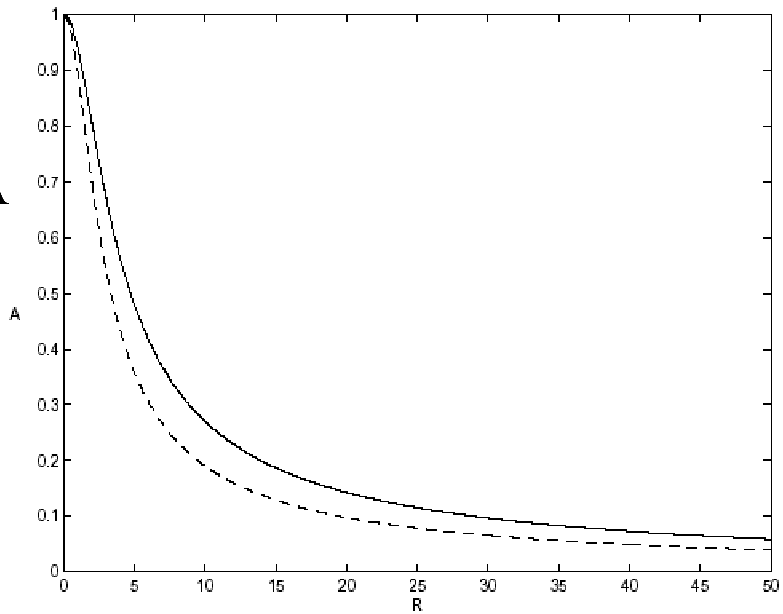
If N=0, then can also get $A = A^{crit}(l, R, G)$

Nontrivial steady states

$\dot{R} = 0$ and $\dot{\delta} = 0$ $\xrightarrow{\text{Non-necrotic.}}$ $A = A^{steady}(R)$

$G = G^{crit}(l, R, A^{steady})$

A

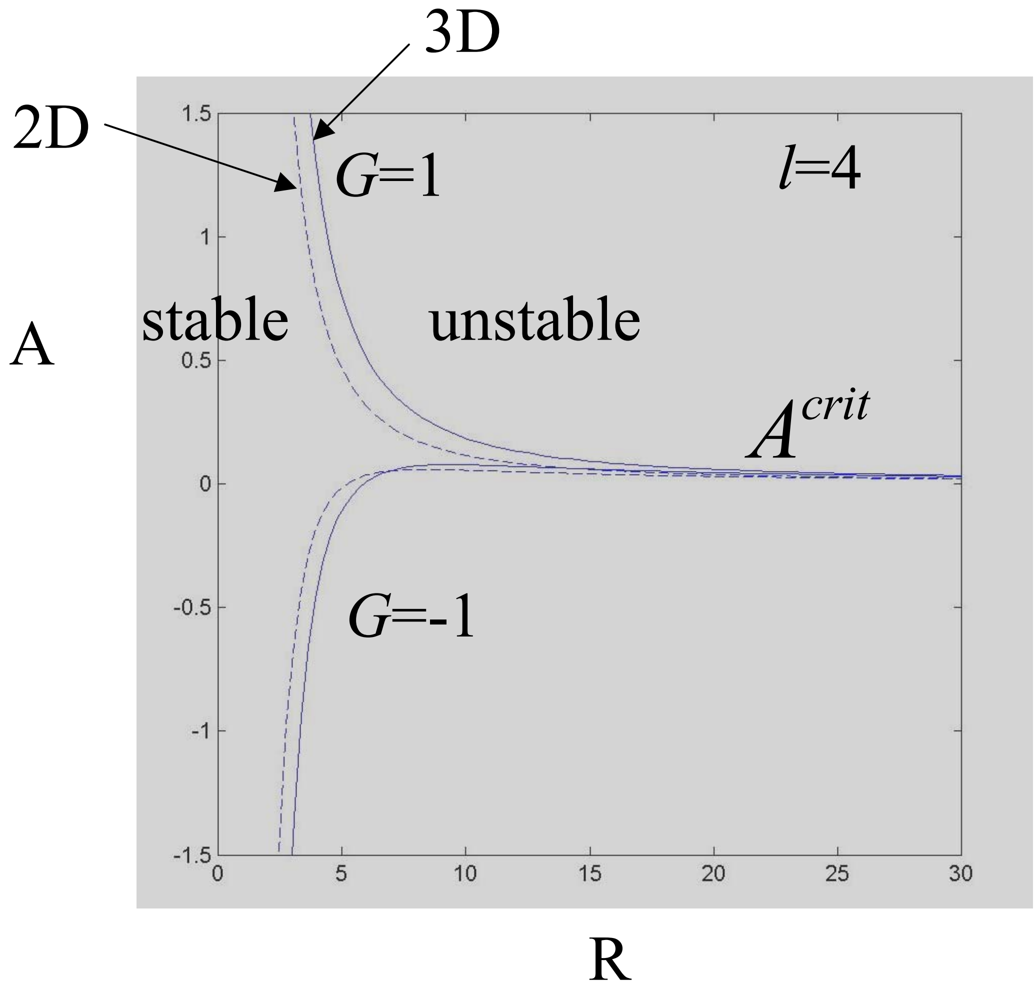


R_∞ (steady radius)

$$G_l = \begin{cases} \dfrac{1}{R_\infty^3} \dfrac{2l(l^2-1)}{2-A\left[2+R_\infty \frac{I_{l+1}(R_\infty)}{I_l(R_\infty)}\right]} & d=2 \\ \dfrac{1}{R_\infty^3} \dfrac{3l(l-1)(l+2)}{3-A\left[3+R_\infty \frac{I_{l+\frac{3}{2}}(R_\infty)}{I_{l+\frac{1}{2}}(R_\infty)}\right]} & d=3 \end{cases}$$

Self-similar evolution

$$\left(\frac{\delta}{R}\right)^{\bullet} = 0 \quad \xrightarrow{\text{Non-necrotic.}} \quad A = A^{crit}(l, R, G)$$

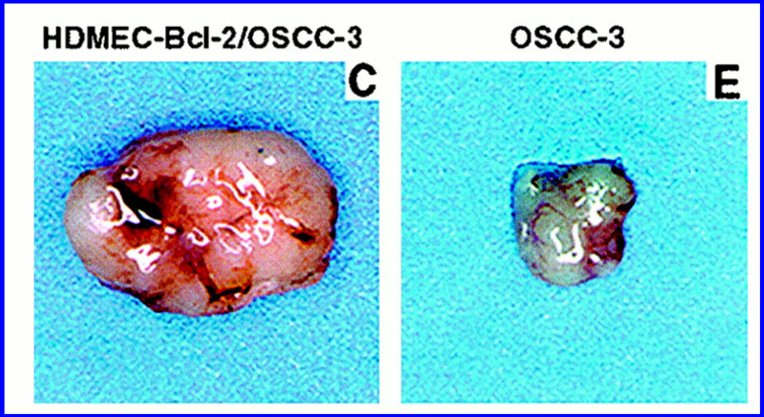


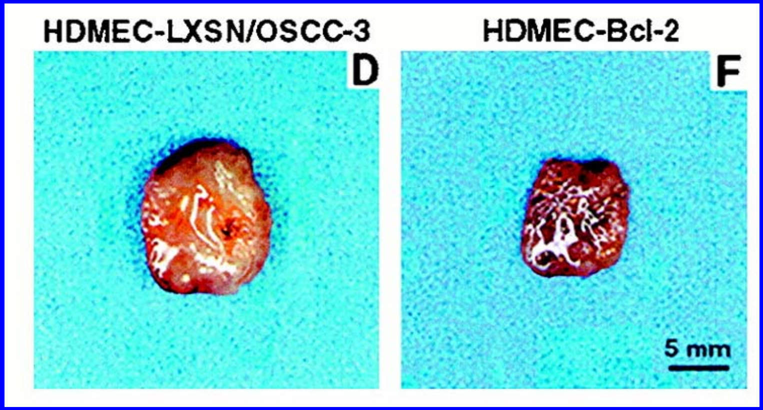
Summary of Linear Stability Results

- Qualitatively similar for 2D/3D
- Necrosis enhances instability

1. Low vascularization (diffusion-dominated): (A,G>0) — Stable/Shape-preserving/Unstable
2. Moderate vascularization: (A<0, G>0) — Stable
3. High vascularization: (G<0) — Stable

Experimental evidence (Polverini et al., Cancer Res. 2001)





Shape instability with high vascularization ⟷ Vascular/mechanical inhomogeneity

Nonlinear Simulations

Non-necrotic.

Boundary integral methods

2D: Cristini, Lowengrub and Nie, J. Math. Biol. 46, 191-224, 2003
3D: Li, Lowengrub, Pham, Cristini, Nie. In preparation

Modified pressure:

$$\tilde{p} = p + G(c-1) - AG\,|\mathbf{x}|^2 / 2d \quad \text{then} \quad \Delta \tilde{p} = 0$$

2D: Double-layer potentials for $\tilde{p}$ and c:

$$c(x) = \frac{1}{2\pi}\int_{\Sigma} \beta(\mathbf{x}')\,\mathbf{n}\cdot\nabla K_0(|\mathbf{x}-\mathbf{x}'|)\,d\Sigma(\mathbf{x}')$$

$$\tilde{p}(\mathbf{x}) = \int_{\Sigma} \mu(\mathbf{x}')\,\mathbf{n}\cdot\nabla G(\mathbf{x}-\mathbf{x}')\,d\Sigma(\mathbf{x}')$$

$K_0(r)$

Modified Bessel function

$$G(\mathbf{x}) = \frac{1}{2\pi}\log|\mathbf{x}|$$

Green's function

2nd kind Fredholm integral equations for β, μ

V (normal velocity) evaluated by the Dirichlet-Neumann Map

Difficulties

•Singular kernels

•Compute singular contribution explicitly to remove singularity.

•Spectrally accurate discretization.

•Stiffness $V \sim H(\kappa_s) \longrightarrow \Delta t \leq \Delta s^3$

Explicit methods.

2D: Equal arclength parametrization.

Special choice of tangential velocity.

Small scale decomposition.

Nonstiff, explicit time integration schemes

Hou, Lowengrub, Shelley, J. Comp. Phys. 1994.

Numerical Results

- Steady-states
- Self-similar evolution
- Stable evolution
- Diffusional Instability

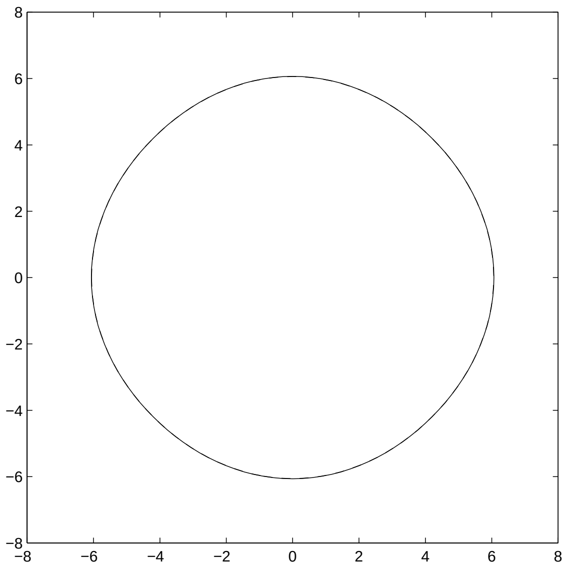
Nonlinear Steady-States

Friedman, Reitich 2001

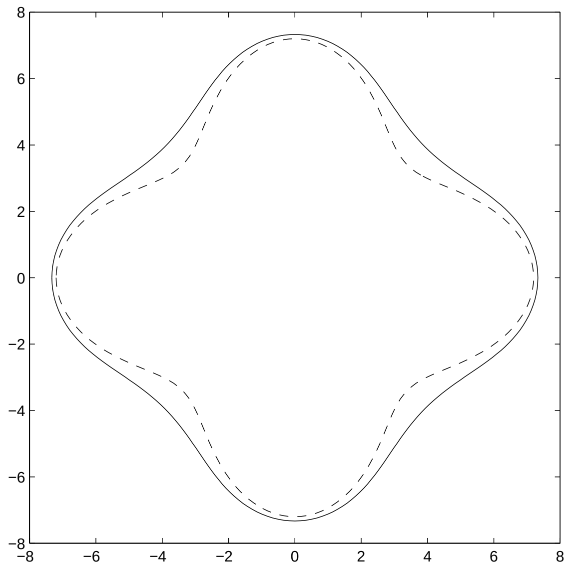
$$\dot{R} = 0 \text{ and } \dot{\delta} = 0 \longrightarrow \begin{array}{l} A = A^{steady}(R) \\ G = G^{crit,Nonlinear}(l, R, A^{steady}) \end{array}$$

l=4, A=0.3

δ/R=0.01

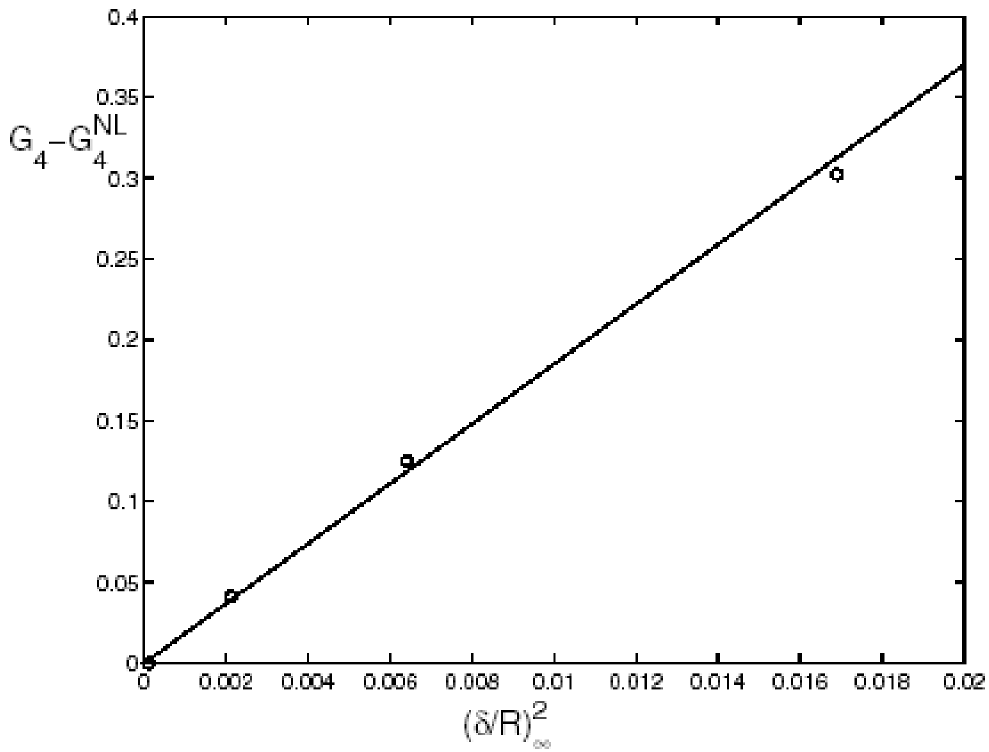


δ/R=0.20



Dashed: linear solution, Solid: Nonlinear solution

Critical G for nontrivial steady state

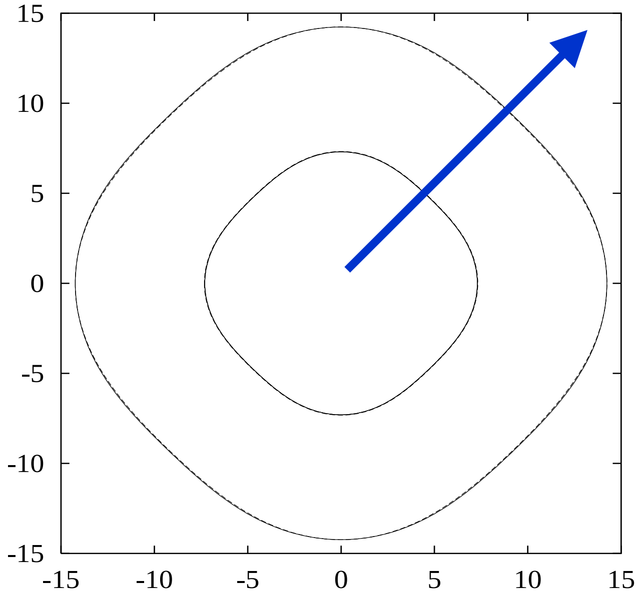


- Convergence to linear theory for small perturbations
- Nonlinearity reduces the critical G

Examples of Shape preserving evolution

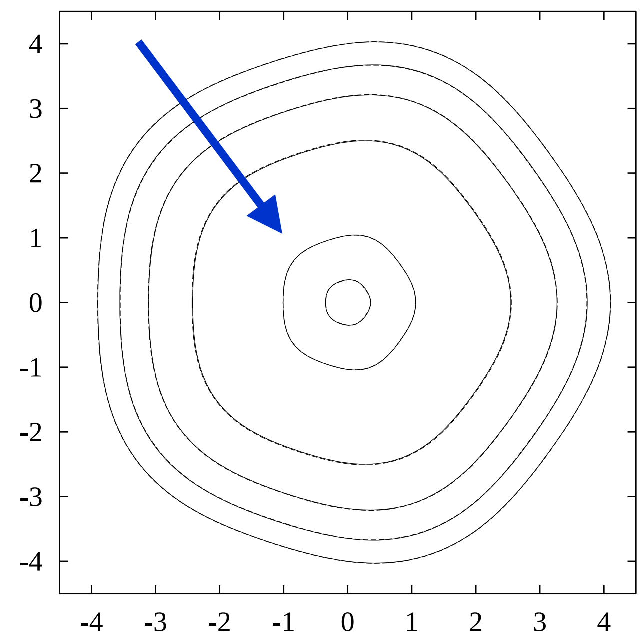
$$A = A^{crit}(l, R, G)$$

Growth



l=4, G=1

Shrinkage



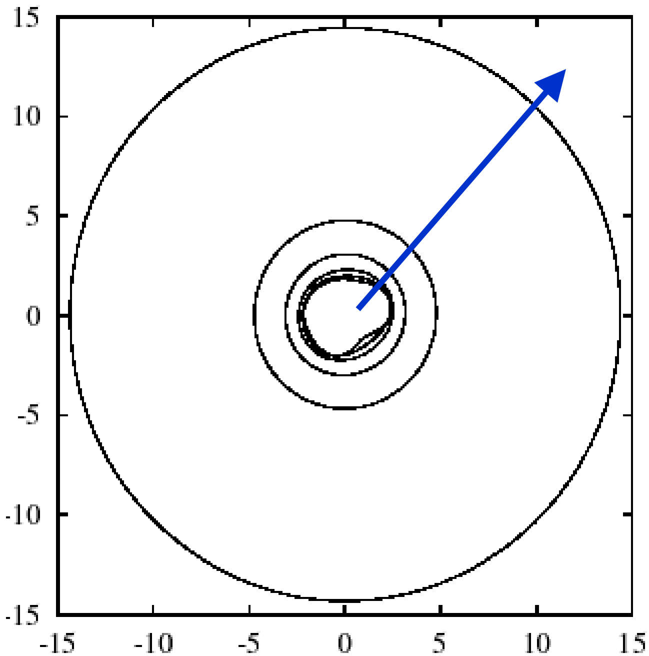
l=5, G=1

•Strongly suggests existence of nonlinear self-similar evolution

Stable evolution

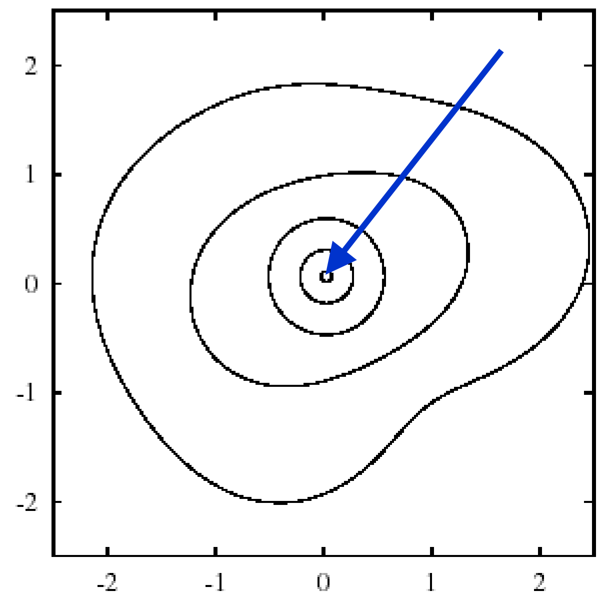
Highly vascularized regime.

Growth



A=0.8, *G*=-5

Shrinkage



A=0.2, *G*=-5

•Nonlinear results consistent with linear theory.

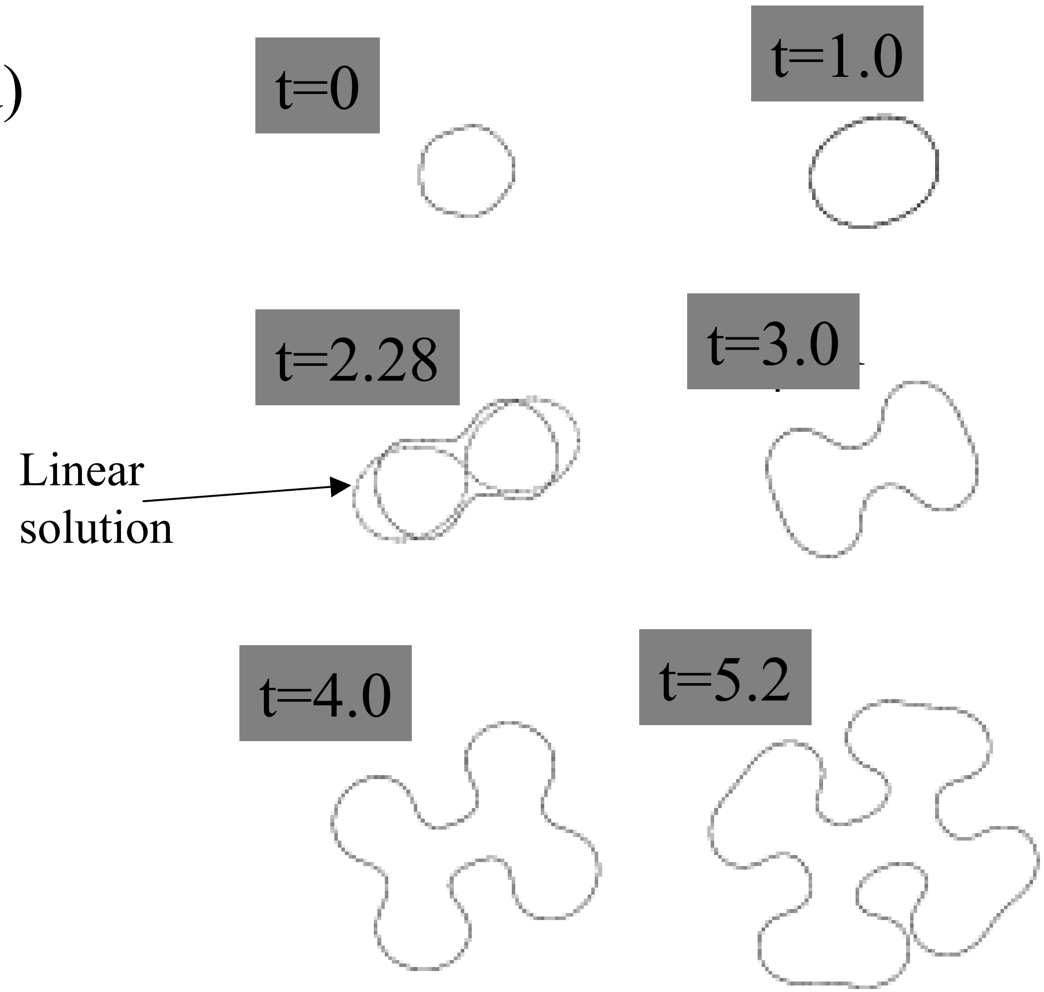
Diffusional Instability

2D: Cristini, Lowengrub and Nie, J. Math. Biol. 46, 191-224, 2003
3D:, Li, Lowengrub, Pham Cristini, and Nie. In preparation

A=0.6, G=20

Avascular (tumor spheroid)
(low cell-to-cell adhesion)

$G > G_{critical}$



- Growth-by-budding
  ejection of cells from bulk
- Topology change
  Capture of healthy tissue.
- Deviation from linear theory

$R_0 = 2.0, \quad R_\infty = 2.51$

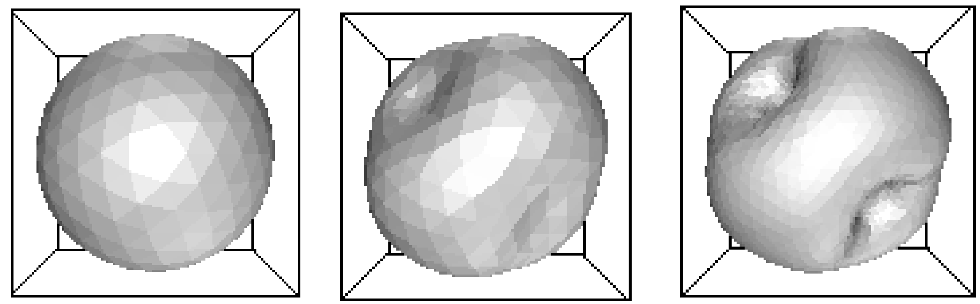
3D Evolution Similar

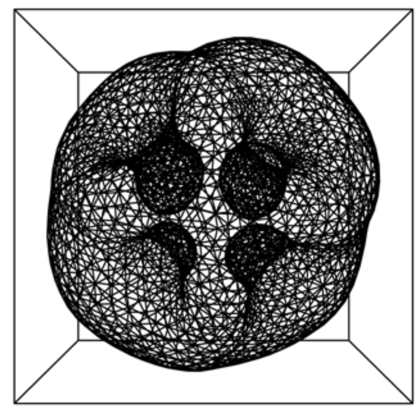
3D:, Li, Lowengrub, Pham Cristini, and Nie. In preparation

Avascular (tumor spheroid)

(low cell-to-cell adhesion)

$$G > G_{critical}$$





Numerical method:

- Single layer representation of c.
- Vector potential representation for $\tilde{p}$

$$p(\mathbf{x}) = \frac{1}{4\pi} \oint_{\Sigma} \nu(\mathbf{x}') \frac{(\mathbf{x}' - \mathbf{x}) \cdot \mathbf{n}(\mathbf{x})}{|\mathbf{x}' - \mathbf{x}|^3} dS(\mathbf{x}')$$

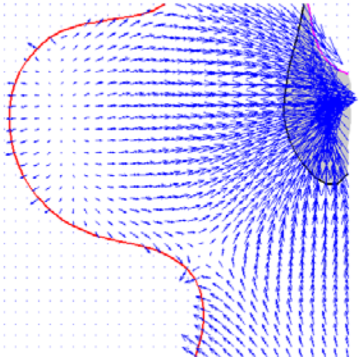
- Adaptive surface mesh

  Cristini et al. J. Comp. Phys, 2001

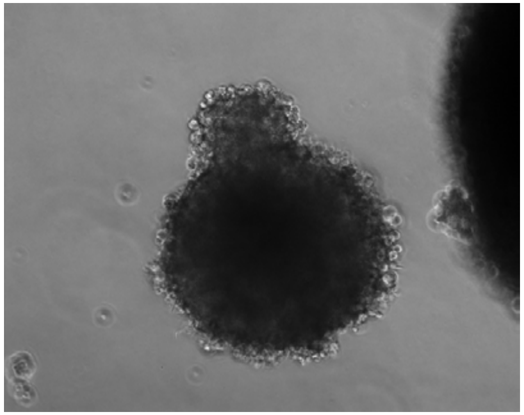
- Rescaled coordinates
- Adaptive quadrature of singular integrals
- Smoothing

Experimental Evidence

•Diffusional Instability. (Tumor spheroids)

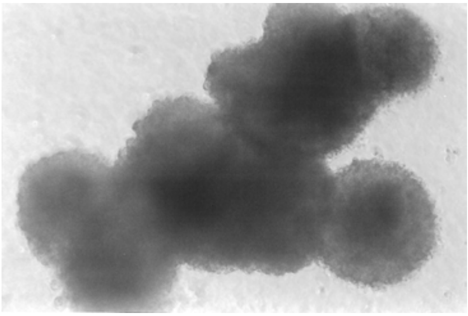


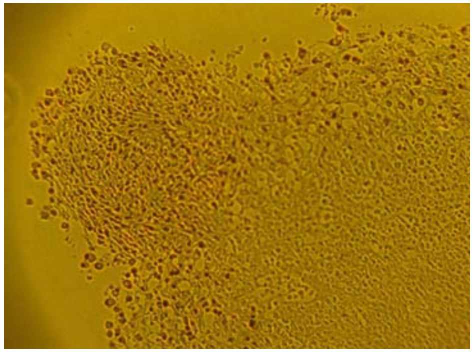
Velocity field (simulation)



Frieboes, *et al.*

glioblastoma





Swirling ejection from bulk

•Theory:

Possible mechanism for invasion into soft tissue

Cristini, Lowengrub, Nie J. Math. Biol (2003)

Cristini, Gatenby, et. al., Clin. Cancer Res. 11 (2005) 6772.

Diffusional Instability during shrinkage

$$A = A^{crit}(l, R, G)$$

•Deviation from linear theory
(dashed)

•Fragmentation

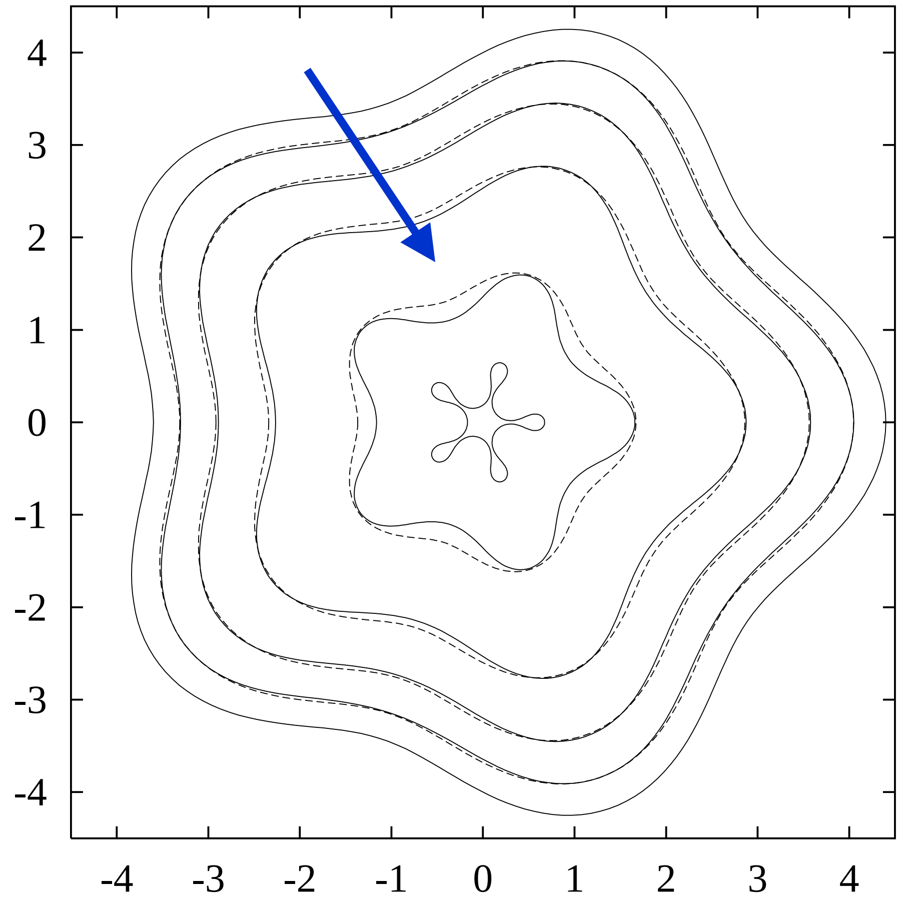
•Metastasis

•Implication for therapy

Cut off blood supply
(antiangiogenic therapy)

Radiotherapy/chemotherapy may lead to instability

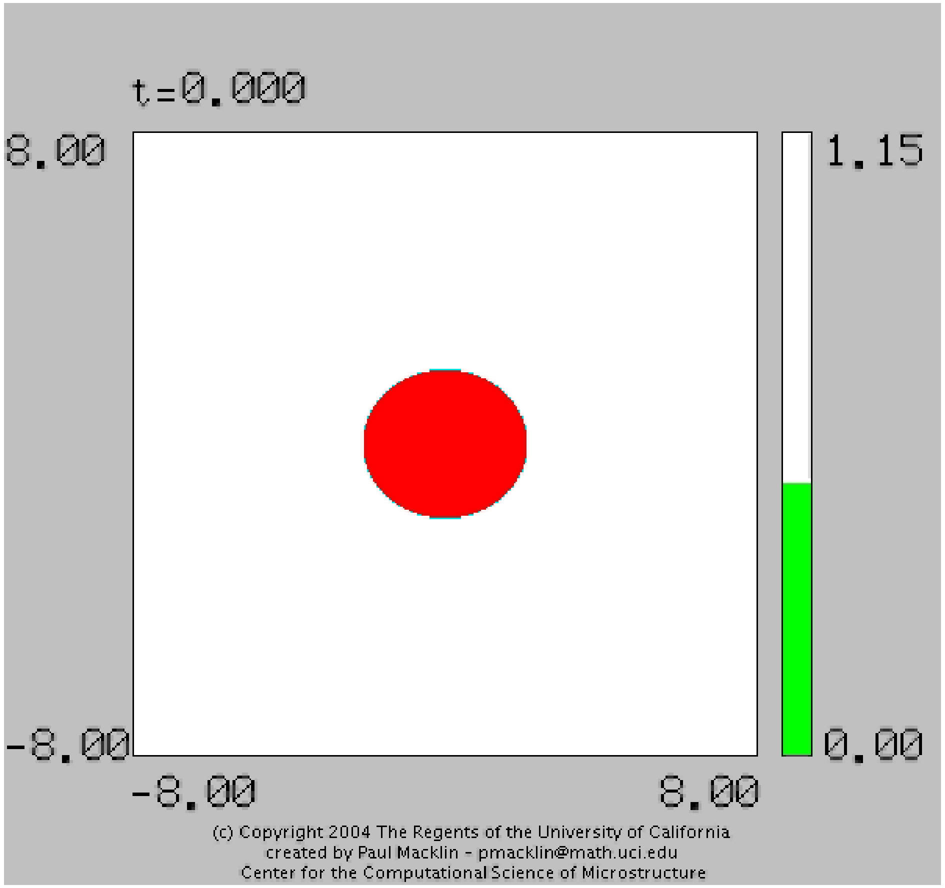
l=5, G=1



$R_0 = 4, \quad \delta_0 = 0.4$

Therapy

Vary A (Radiotherapy)



A

•Can lead to tumor fission. Metastases.

Diffusional instability implications

- Fundamental instability
- Increased surface area to volume ratio
- Overcome diffusion-limitations on growth
- Mechanism for invasion of soft tissue
- Topology changes may lead to metastasis
- Therapy may lead to fragmentation and metastasis

Key features:

- Nonuniform cell-proliferation
- Competition between mitosis, apoptosis and adhesion

Conclusions

- Basic model is able to capture basic qualitative/quantitative features of tumor growth

- Instability in high vascularization regime requires vascular or mechanical inhomogeneity

- Diffusional instability provides a mechanism to overcome diffusional limitations on growth and can lead to invasive growth and metastasis

Next Steps

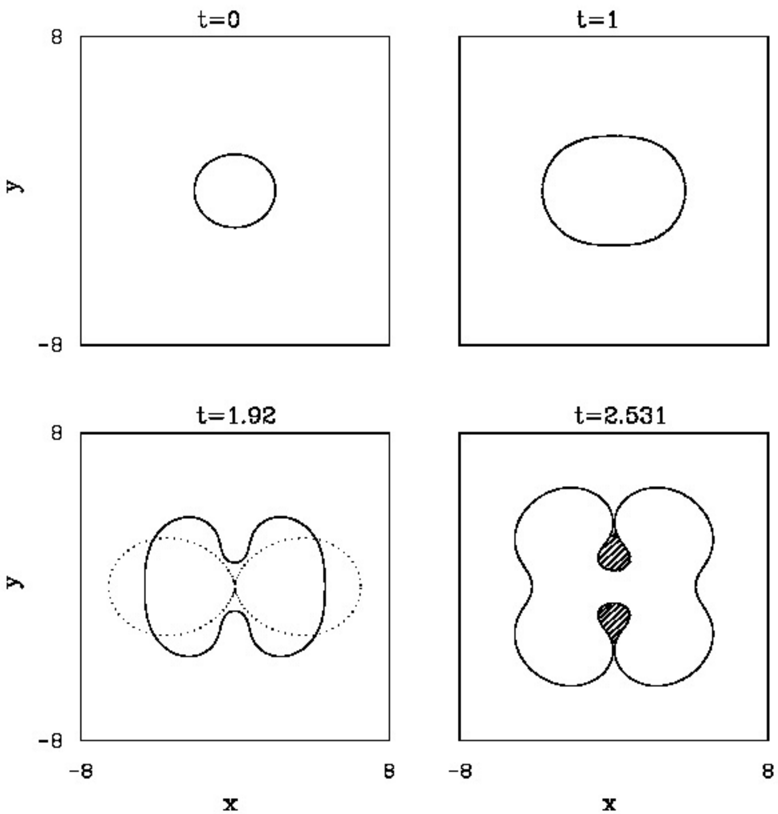
- More complex/realistic biophysics
  - Going beyond fragmentation/tissue capture
  - Effect of tissue inhomogeneities
  - Angiogenesis
  - Multiphase/Multiscale models
  - More realistic mechanical response
- Requires new, robust numerical methods

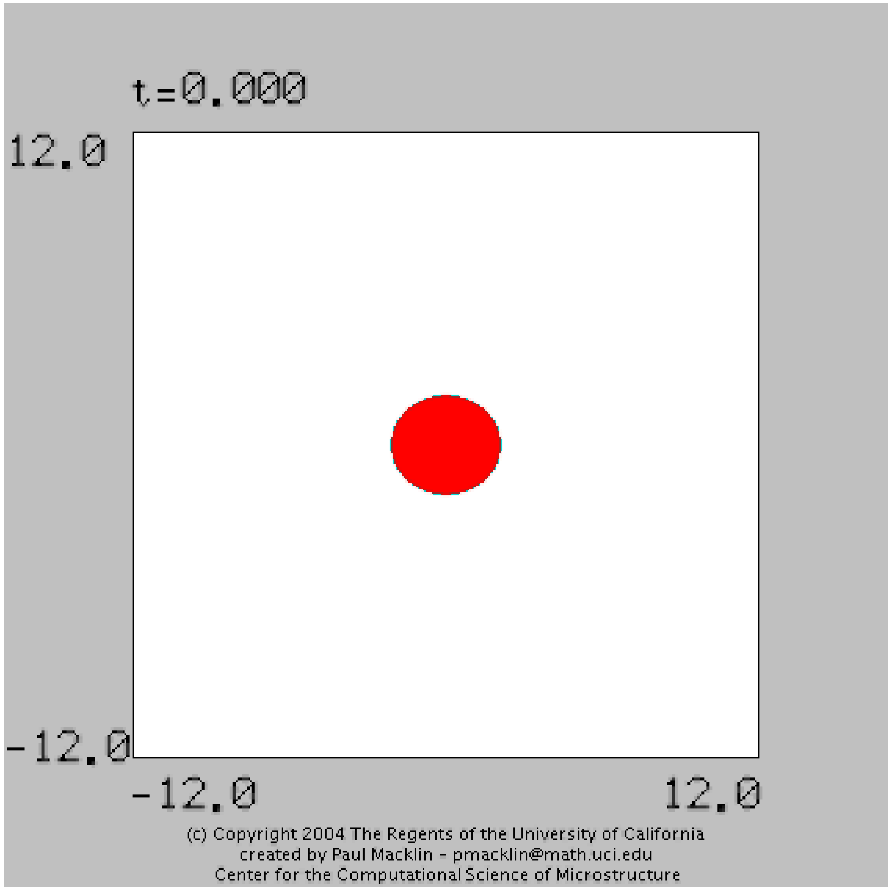
Going beyond capture

A=0.5, *G*=20

Ghost-fluid/level-set method.

Boundary integral





Macklin, Lowengrub J. Comp. Phys. 2005