Nonlinear Tumor Modeling II: Tissue inhomogeneities and necrosis

John Lowengrub

Dept Math, UCI

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

Motivation

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

Outline

- Review of basic model and results

- Extension to a (simple) model of tissue inhomogeneity

- Numerical methods

- Results

Mathematical 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

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

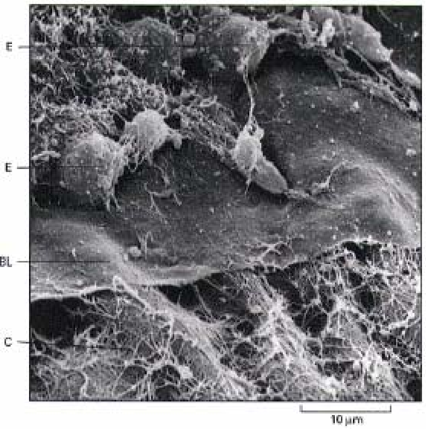
Viability concentration

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

Darcy's law

$$\mathbf{u} = -\mu\,\nabla P$$

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

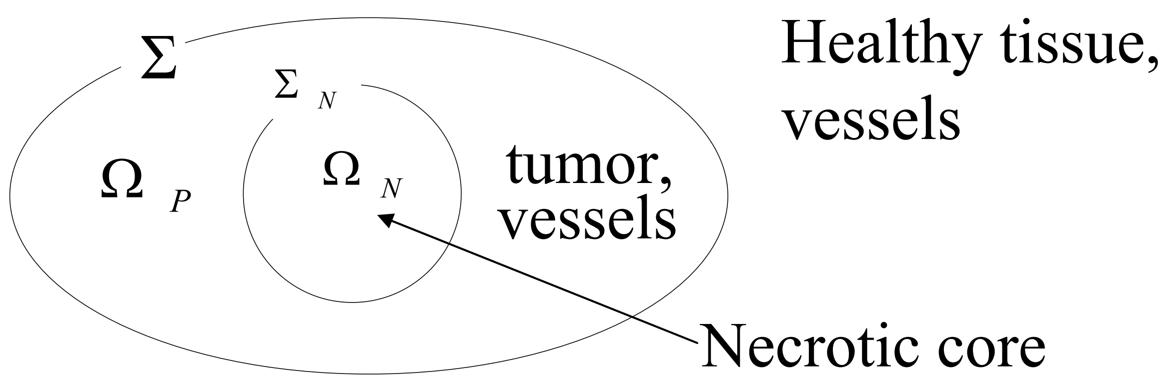
- Simplified cell-cycling model $\lambda_M(\sigma) = b\sigma$
- Simplified Blood-tissue transfer $\lambda_B(\sigma_B - \sigma, P_B - P, \mathbf{x}, t) = \lambda_B \cdot (\sigma_B - \sigma)$
- Avascular or fully vascularized growth (i.e. no angiogenesis)

$\longrightarrow$

- Insight to biophysical system
- Benchmark for more complicated systems

Previous (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

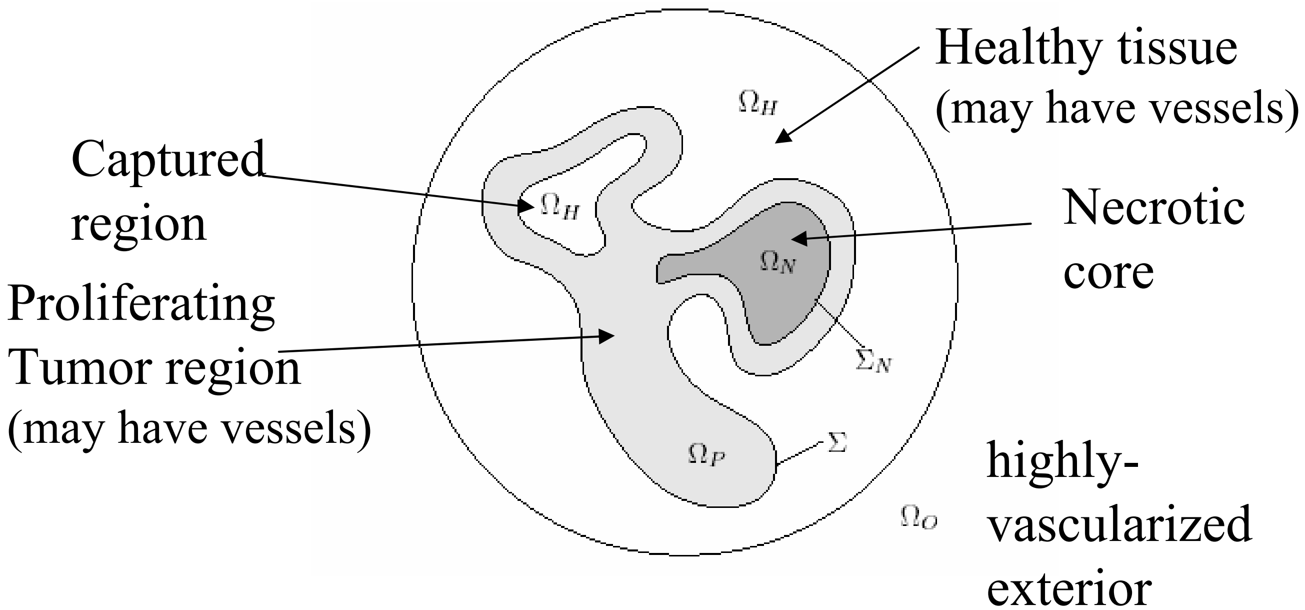
$$\mathbf{u} = -\mu\nabla P, \quad \nabla \bullet u = \begin{cases} \lambda_P & \text{in } \Omega_P \\ -\lambda_N & \text{in } \Omega_N \end{cases}$$

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

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

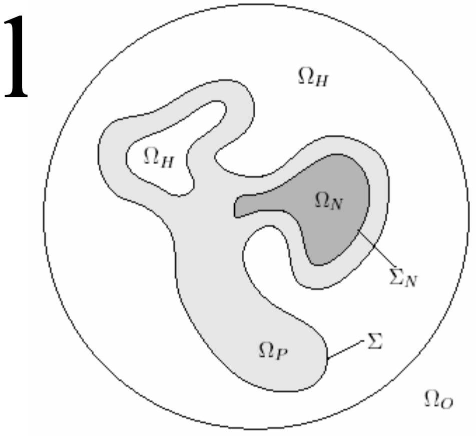
normal velocity

Extended model



Extended Model

Macklin, Lowengrub, In preparation.



Nutrient

$$0 = \nabla \bullet \left(D \nabla \sigma \right) + \Gamma$$

$$\Gamma = \begin{cases} -\lambda_B \left(\sigma - \sigma_B \right) - \lambda \sigma & \text{in} \quad \Omega_\mathrm{P} \\ -\lambda_{B,H} \left(\sigma - \sigma_B \right) - \lambda_H \sigma & \text{in} \quad \Omega_\mathrm{H} \\ 0 & \text{in} \quad \Omega_\mathrm{N} \end{cases}$$

$$[\![\sigma]\!]_\Sigma = [\![D \nabla \sigma \bullet \mathbf{n}]\!]_\Sigma = 0$$

$$[\![\sigma]\!]_{\Sigma_N} = [\![D \nabla \sigma \bullet \mathbf{n}]\!]_{\Sigma_N} = 0$$

$$\left(\sigma \right)_{\partial \Omega_0} = \sigma_\infty$$

Pressure

$$\mathbf{u} = -\mu \nabla P,$$

$$\nabla \bullet \mathbf{u} = \begin{cases} \lambda_P & \text{in } \Omega_P \\ 0 & \text{in } \Omega_H \\ -\lambda_N & \text{in } \Omega_N \end{cases}$$

$$[\![P]\!]_\Sigma = \gamma \kappa, \quad [\![\mu \nabla P \bullet \mathbf{n}]\!]_\Sigma = 0$$

$$[\![P]\!]_{\Sigma_N} = [\![\mu \nabla P \bullet \mathbf{n}]\!]_{\Sigma_N} = 0$$

$$\left(p \right)_{\partial \Omega_0} = p_\infty$$

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

normal velocity

- Let D and μ vary in Ω_p and Ω_H

Interpretation

In Ω_H,

- D is an indirect measure of perfusion

  i.e., D large $\longrightarrow$ nutrient rich

- μ is a measure of mechanical properties of extra-tumoral tissue

  i.e., μ small $\longrightarrow$ tissue hard to penetrate (less mobile)

- Although a very simplified model of these effects, this does provide insight on how inhomogeneity influences tumor growth.

Nondimensionalization

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

Intrinsic length scale: $L_D = D_P^{1/2}\left(\lambda_B + \lambda\right)^{-1/2}$ Adhesion time scale: λ_R^{-1},

$\lambda_R = \gamma \mu_P / L_D^3$

Previous nondimensional parameters:

- Vascularization: $B = \frac{\sigma_B}{\sigma^\infty}\frac{\lambda_B}{\lambda_B + \lambda}$
- Apoptosis vs. mitosis $A = \frac{\lambda_A/\lambda_M - B}{1 - B}$
- Mitosis vs. adhesion $G = \frac{\lambda_M}{\lambda_R}\,(1 - B)$
- Necrosis vs. mitosis $G_N = \lambda_N / \lambda_M$ $\lambda_M = b\sigma^\infty$
- Viability $N = \frac{\sigma_N}{\sigma_\infty} - B$

New nondimensional parameters:

- Diffusion ratio: $\chi_D = D_H / D_P$
- Mobility (adhesion) ratio: $\chi_\mu = \mu_H / \mu_P$
- Transfer ratio: $\chi_B = \lambda_{B,H} / \lambda_B$
- Uptake ratio: $\chi_\lambda = \lambda_H / \lambda$

- Reduces to basic model when: $\chi_D, \chi_\mu \to \infty$, χ_λ, χ_B bounded

Nondimensional System

Nutrient: $c = (\sigma / \sigma_\infty - B)/(1 - B)$ Pressure: $p = (P - P_\infty)/(\gamma / L_D)$

→ Generic Poisson-type problems for c and p:

$(w = c \text{ or } p)$

$$\nabla \bullet \left(\chi \nabla w\right) = f(x, w), \text{ in } \Omega = \Omega_N \bigcup \Omega_P \bigcup \Omega_H$$

$$[\![w]\!]_\Sigma = g, \quad [\![\chi \nabla w \bullet \mathbf{n}]\!]_\Sigma = 0$$

$$[\![w]\!]_{\Sigma_N} = [\![\chi \nabla w \bullet \mathbf{n}]\!]_{\Sigma_N} = 0$$

$$(w)_{\partial \Omega_0} = w_\infty$$

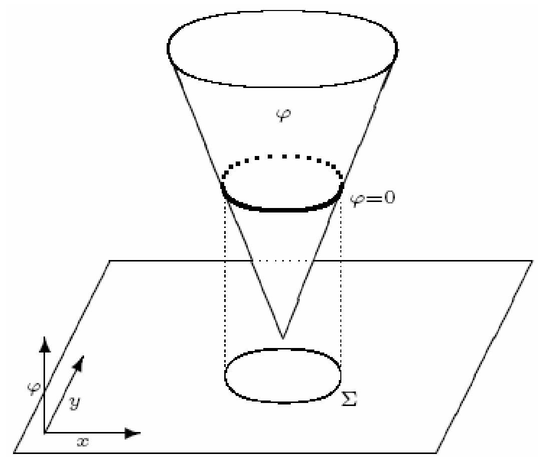
$$\mathbf{n} \cdot \frac{d\mathbf{x}_\Sigma}{dt} = V = -\nabla p \cdot \mathbf{n}$$

More Complex Biophysics

- Non-uniform parameters
- Necrosis
- Complex morphology
- angiogenesis

→ Level-set method

- Continuum description



$$\phi_t + V\,|\nabla \phi| = 0$$

$$V = \mathbf{u} \bullet \mathbf{n}$$

Difficulties:

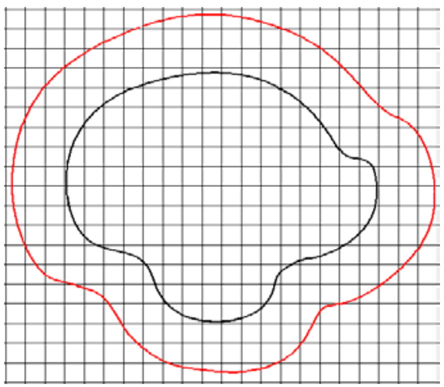
- Stability– sensitive to geometry $V \sim H(\kappa_s)$
- Accurate extension/interpolation
- Stable discretizations of $\mathbf{n}$ and κ

2^{nd} Order Accurate Ghost Fluid/Level-Set Method

Fedkiw, Gibou, Osher,..

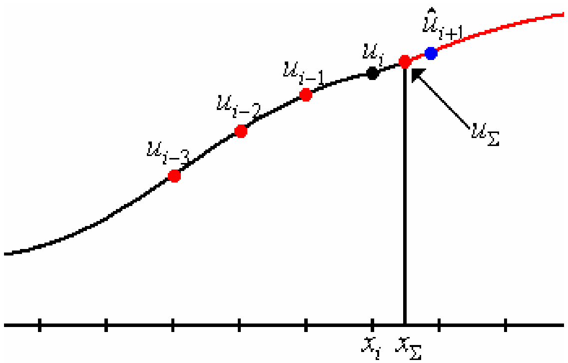
Macklin, Lowengrub, J. Comp. Phys. **203** (2005).
Macklin, Lowengrub, J. Comp. Phys. (2005) in press.

- Embed in Rectangular domain



- Incorporate sub-cell resolution And physical boundary conditions

$$u_{xx} = \frac{u_{i-1} - 2u_i + \hat{u}_{i+1}}{\Delta x^2} + O\left(\Delta x^2\right)$$



- Solve equations on full Cartesian mesh

Difficulties:

- Stability– sensitive to geometry $V \sim H(\kappa_s)$
- Accurate extension/interpolation
- Stable discretizations of $\mathbf{n}$ and κ

2^{nd} Order Accurate Method

Extension

Cubic extrapolation

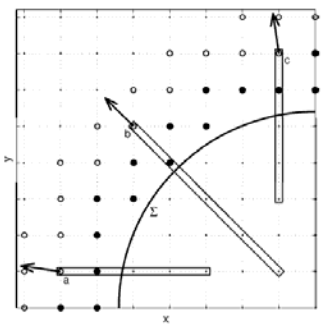


Fig. A.3. Gradient Extension: We extend a scalar function beyond $\Omega \cup \Sigma$ by one-dimensional, grid-aligned extrapolation. The points used in the extrapolation are chosen according to the direction of the normal vector. We preserve outward information flow by choosing the next point for extension according to the value of the level set function at the remaining points (open circles).

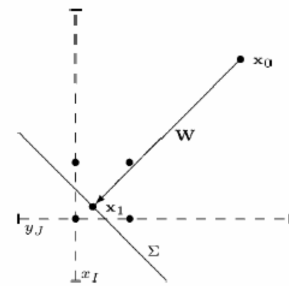


Fig. A.4. Finding the closest point on the interface. $\mathbf{W} = -\varphi(\mathbf{x_0})\mathbf{n}(\mathbf{x_0})$.

Bilinear interpolation

Normal Vector/ Curvature

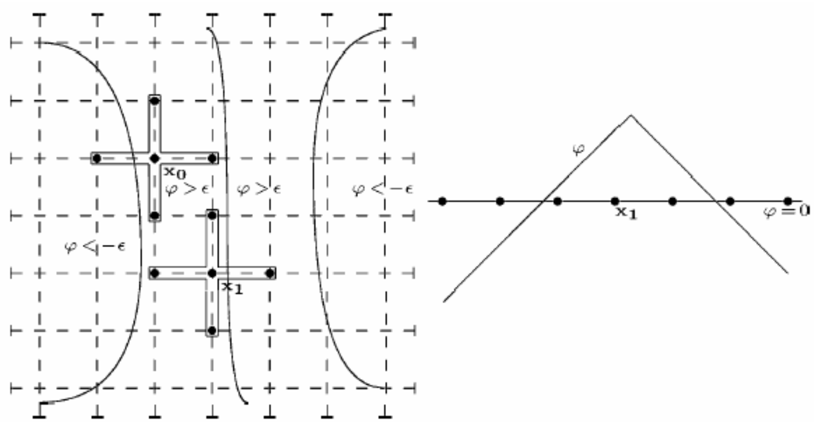


Fig. A.5. Effect of Level Set Irregularity on κ and $\mathbf{n}$: In the left figure, two interfaces are close together. The middle curve shows the points equidistant from both interfaces, and the level set function is irregular along this curve. The standard techniques for calculating κ and $\mathbf{n}$ work well at $\mathbf{x_0}$ (where φ_x and φ_y are continuous), whereas they break down numerically at $\mathbf{x_1}$. The right figure shows a cross-section through $\mathbf{x_1}$ of the level set function; the "peak" in the middle is equidistant from the two interfaces and a point of irregularity in φ.

1-sided method

Gaussian smoothing

$$\hat{f}_I = \frac{1}{A}\frac{1}{N\sqrt{2\pi}}\sum_{i=-3N}^{3N} f_{I-i}\exp\left(-\frac{1}{2}\left(\frac{i}{N}\right)^2\right),$$

N=3

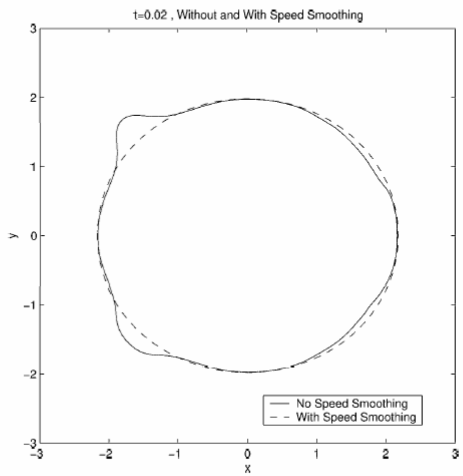


Fig. A.8. Effect of Smoothing on Overall Stability and Accuracy: Initially small perturbations have grown to grossly distort the shape of the interface by $t = 0.01$. The dashed curve shows the solution at the same time with speed smoothing.

Curvature/Normal Vector

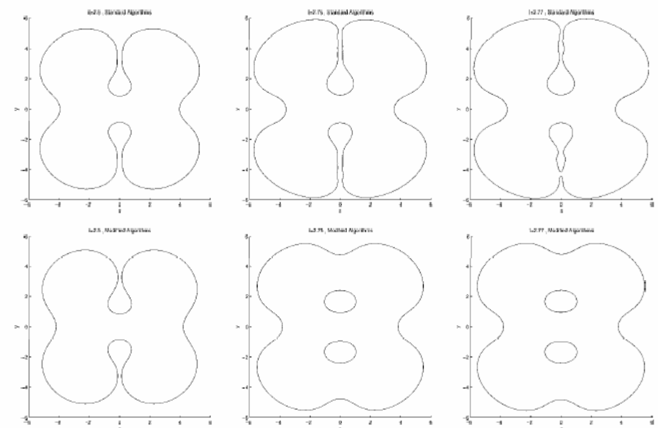


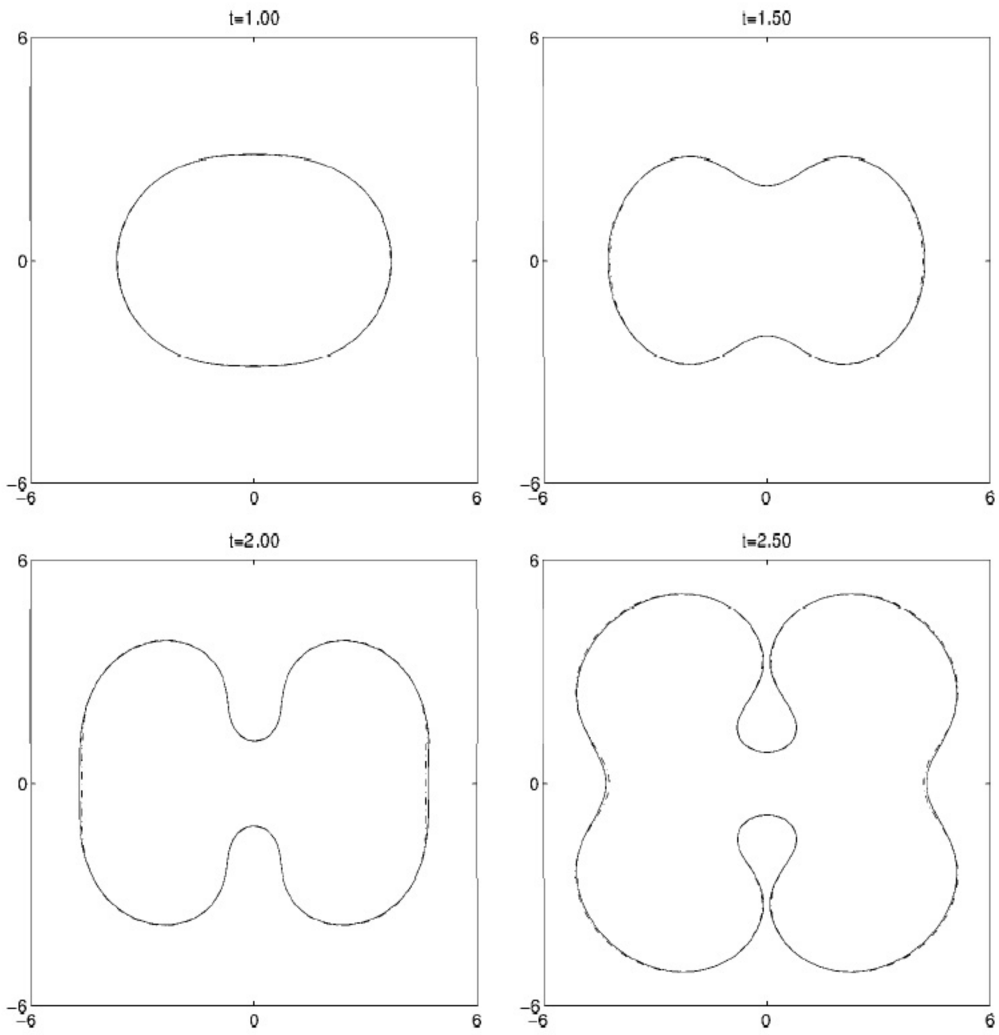
Fig. A.10. Effect of the Curvature and Normal Vector Modifications on a Tumor Growth Simulation: The plots show the solution to the problem in Section 5.3 at $t = 2.5$, $t = 2.75$, and $t = 2.77$. The top row shows the calculation using standard centered differences for κ and $\mathbf{n}$; the bottom row shows the same calculation with our modified algorithms.

Poisson 2: Quadratic extrapolation of ghost-value
linear approximation of ghost-point

WENO5: Reinitialization/Advection

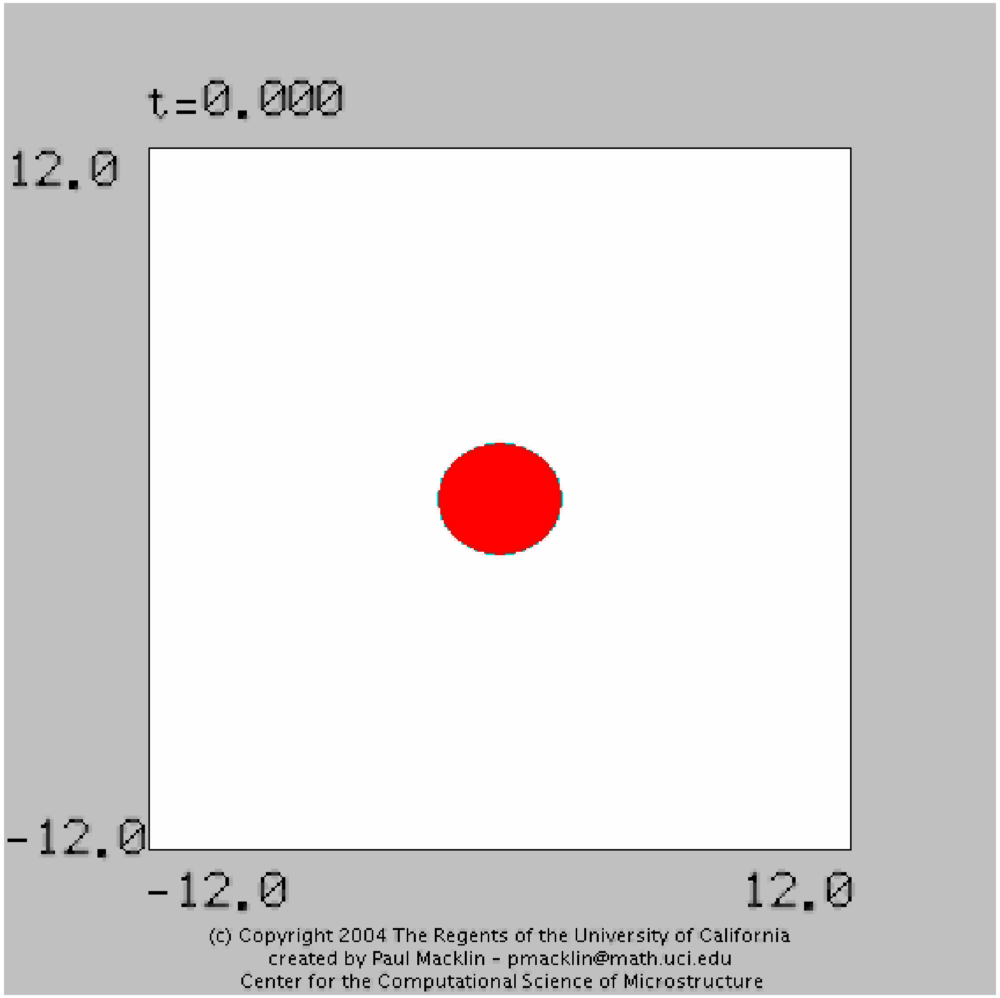
Validation with benchmark boundary integral result

Solid: BI
Dashed: GF



- Excellent agreement

Post-transition dynamics



- Repeated capture of healthy tissue

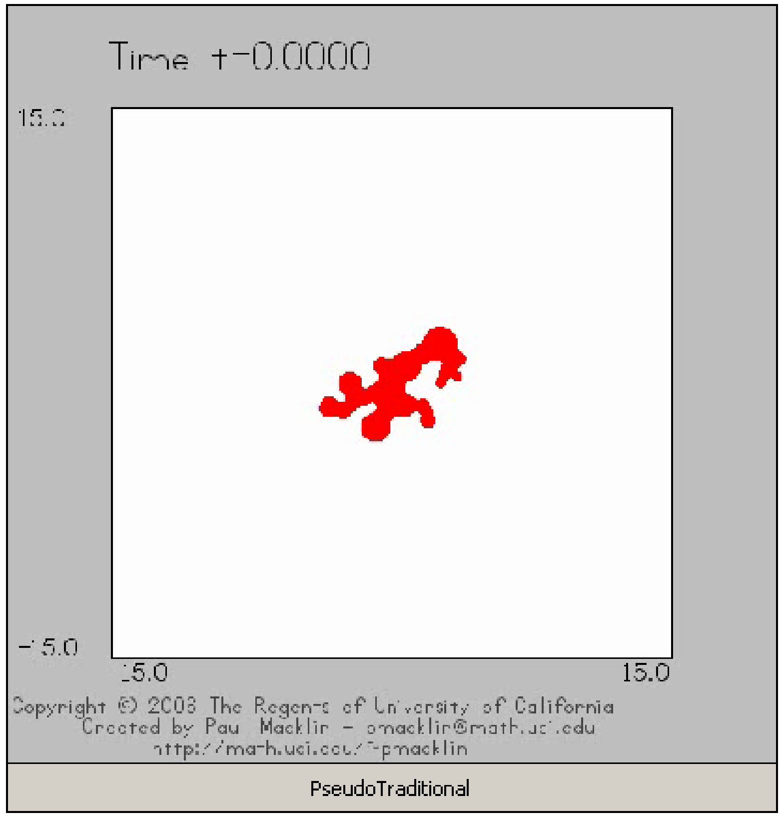
  Observed in tumors
  In vivo

- Captured tissue acts like blood vessels (nutrient supply from 3D)

  Mimics tumor growing into uniformly vascularized tissue

Growth with necrosis and without 3D nutrient supply

- Captured regions do not act as nutrient source



- Many topology transitions of tissue and necrotic core
- Quite different morphology

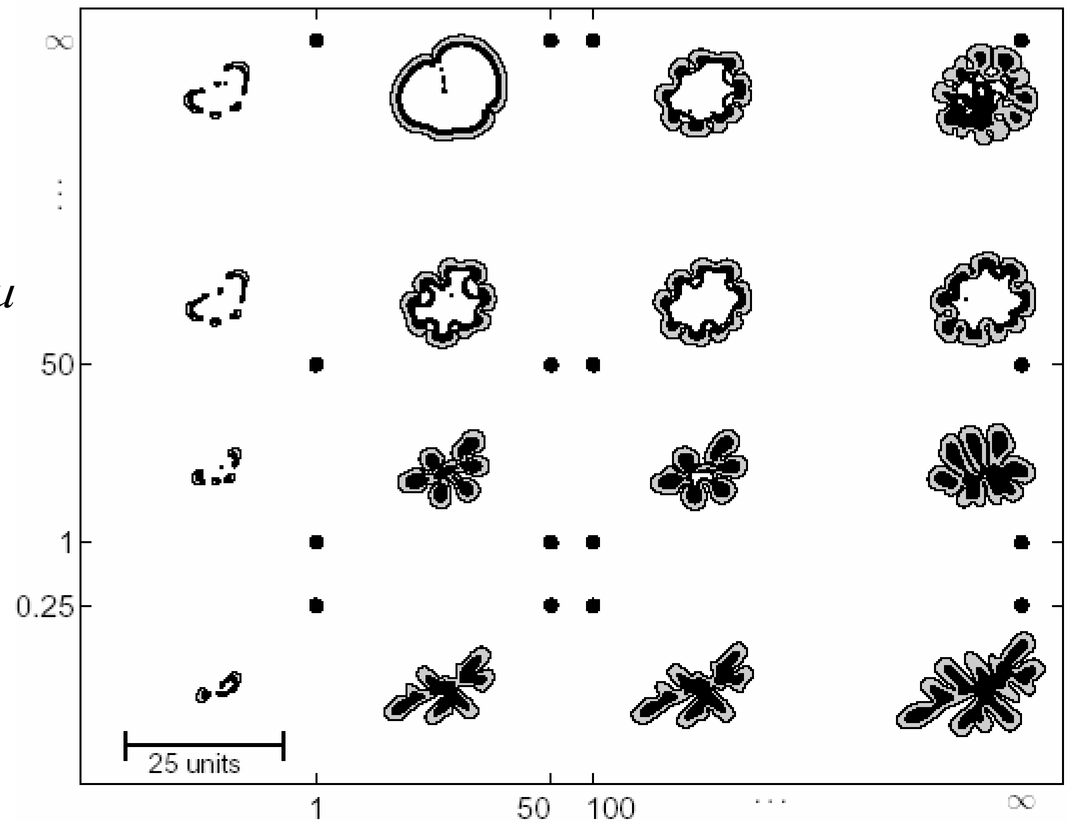
Morphology diagram

$A=0,\ G=20, G_N=1$
$N=0.35$

Effect of extra-tumoral tissue

χ_μ

Increased tissue resistance (decreased mobility)



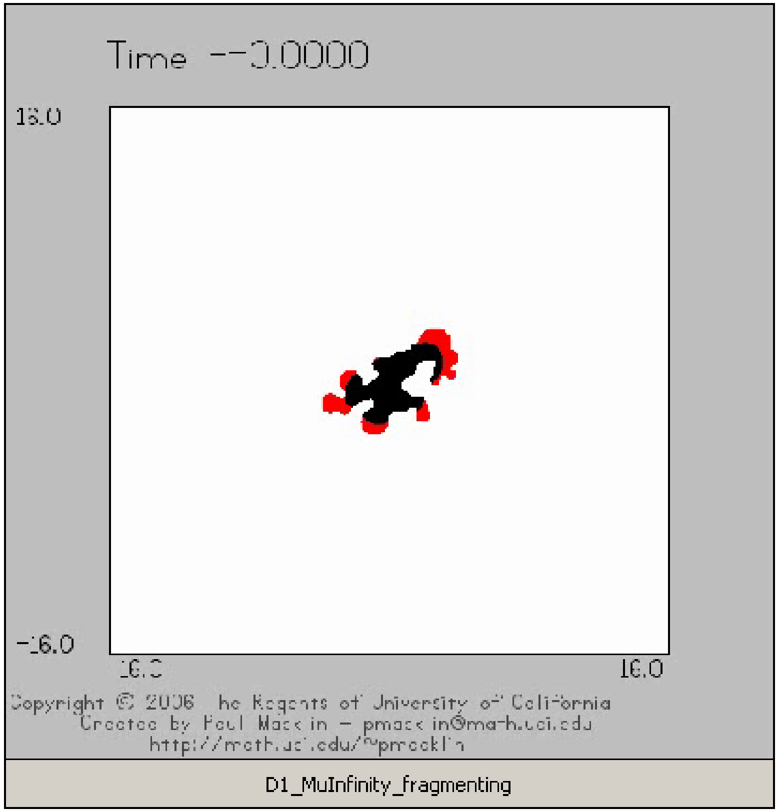
χ_D

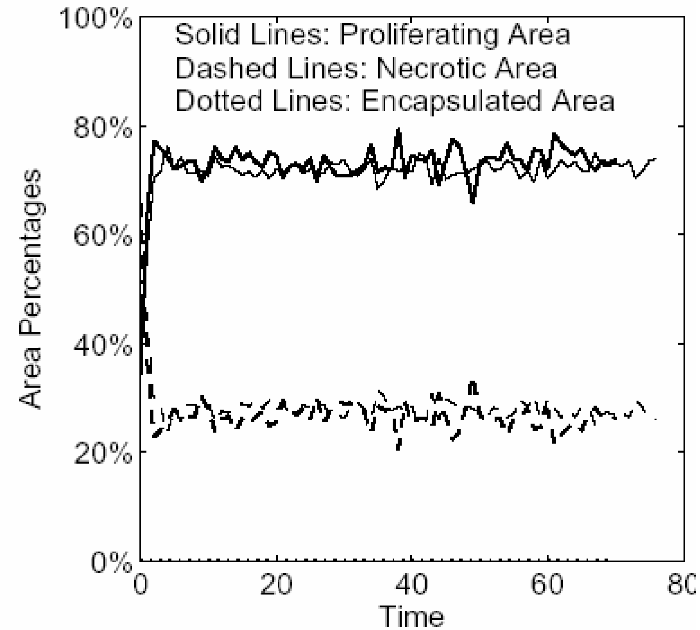
Higher degree of vascularization

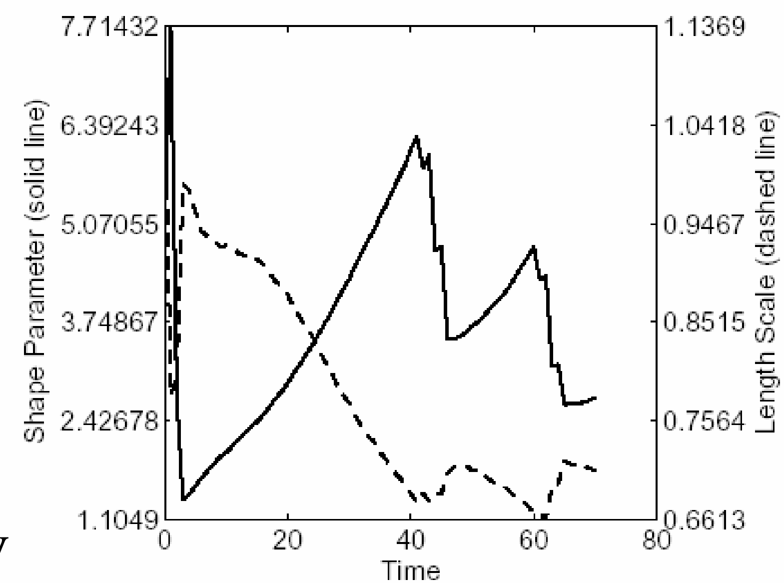
- 3 distinct regimes:
  - Fragmented (nutrient-poor)
  - Fingered (high tissue resistance)
  - Hollowed (low tissue resistance, nutrient-rich)

Fragmented

$$\chi_D = 1, \quad \chi_\mu = \infty$$







- Hypoxia leads to invasion

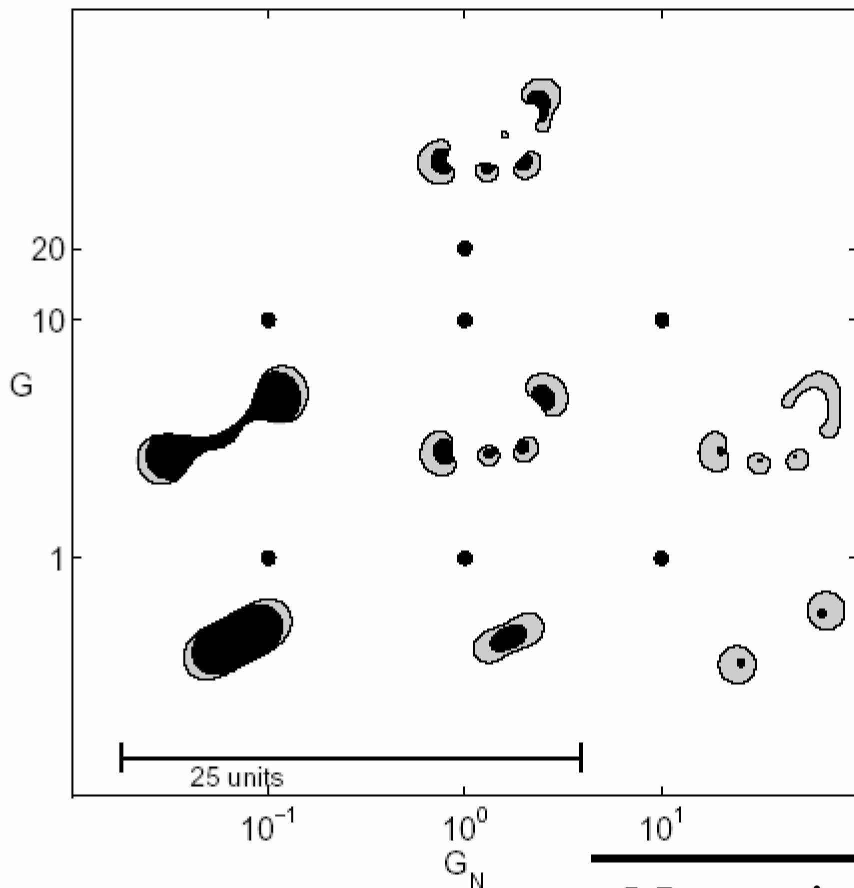
  i.e., inhomogeneous nutrient distribution, imperfect vasculature
- Strong metastatic potential
- Implications for antiangiogenic therapy

  Combine with anti-invasive therapy

Dependence on other parameters

$\chi_D = 1, \quad \chi_\mu = 1$

adhesiveness



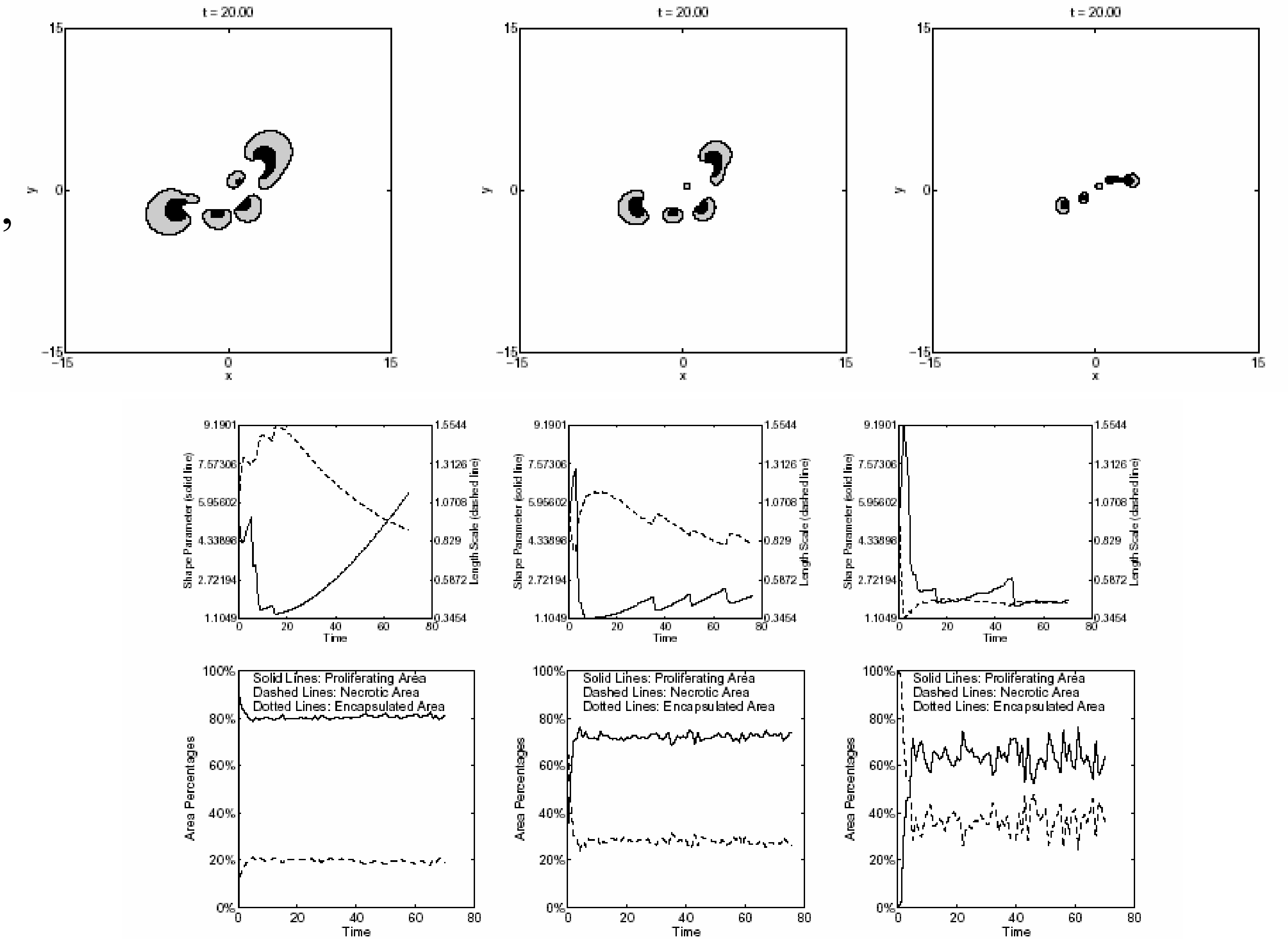
Necrosis (degradation)

- Increasing G or G_N enhances instability
- Increasing G_N decreases necrotic core

Dependence on N

N=0.175 N=0.35 N=0.70

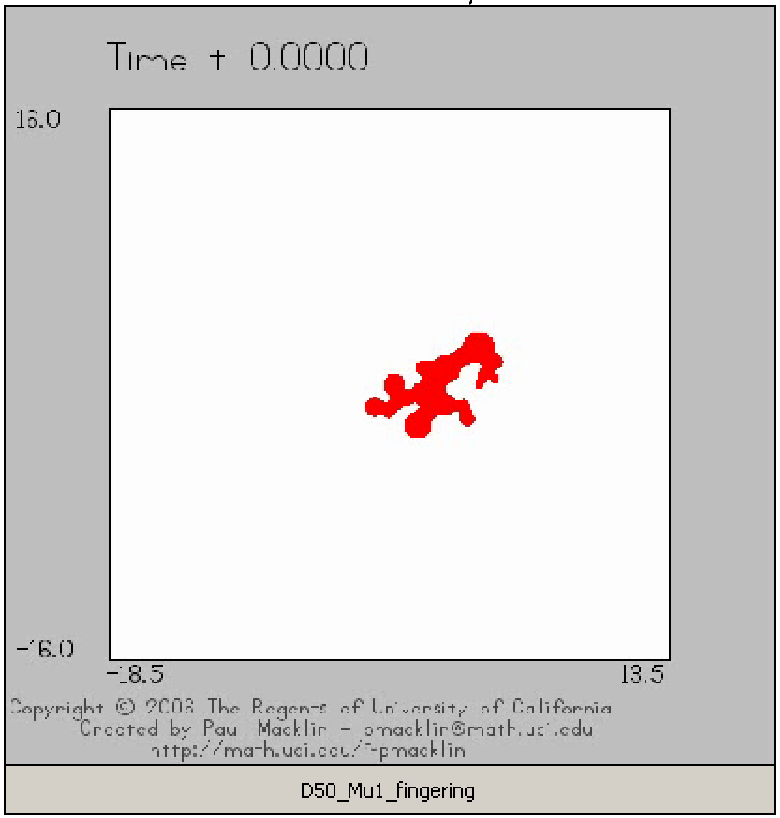
$$\chi_D = 1,\quad \chi_\mu = 1,\quad G = 20,\quad G_N = 1$$



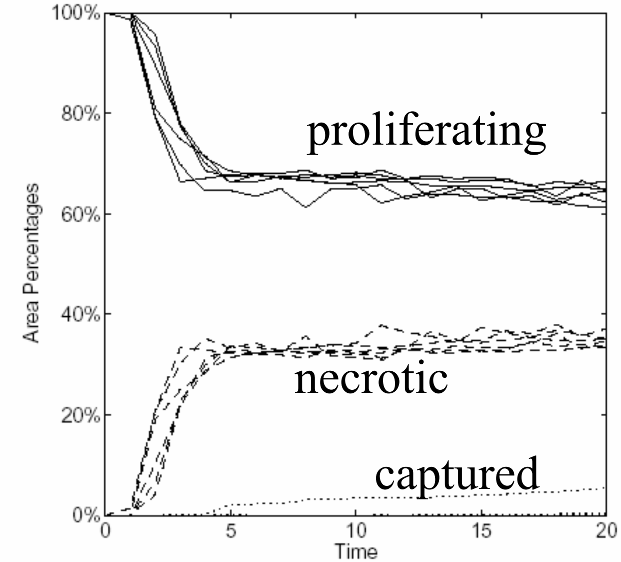
•Strong effect on size

Fingered

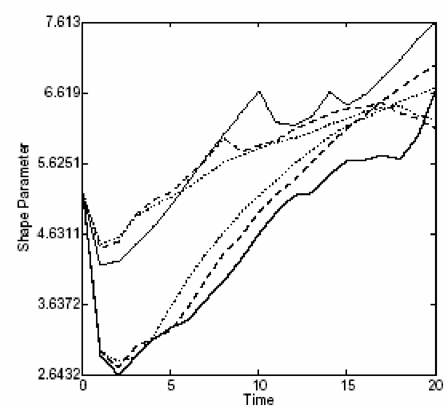
$$\chi_D = 50, \quad \chi_\mu = 1$$



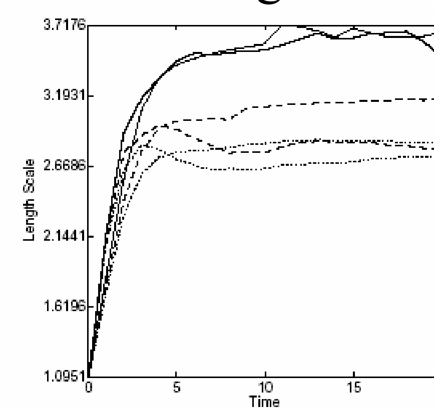
Area ratios



Shape parameter



Length scale

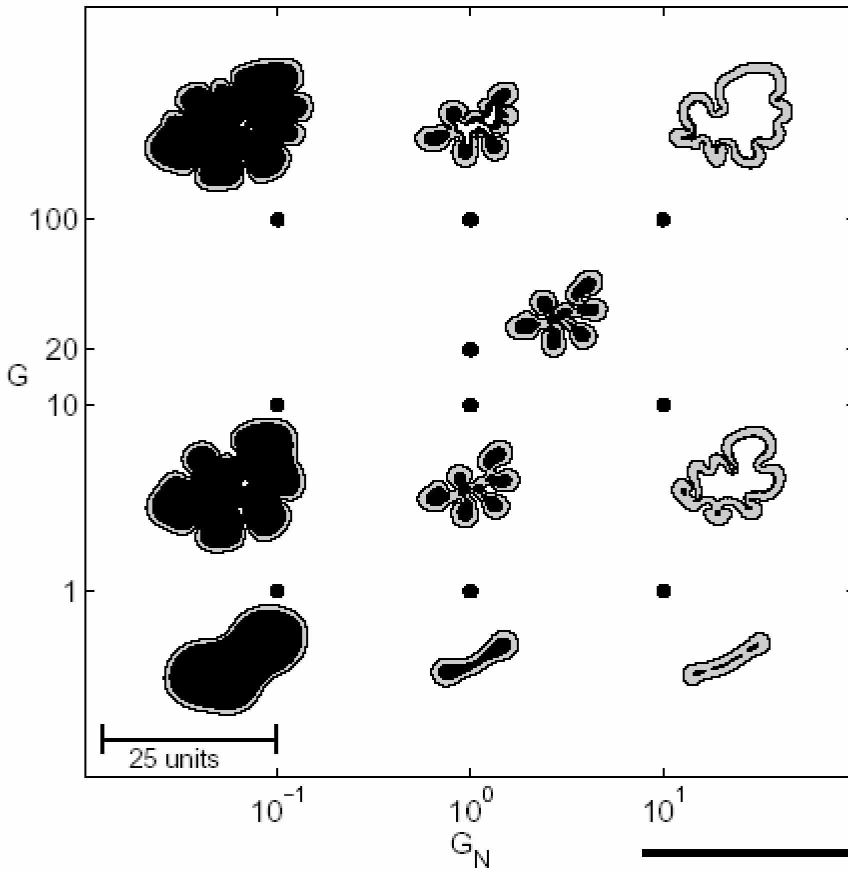


- Growth into lower mobility regions results in larger invasive tumors
- Implication for therapy (decrease adhesion)

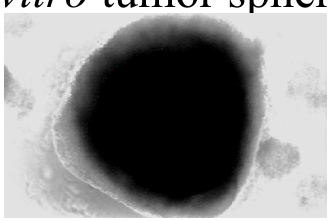
Dependence on other parameters

$\chi_D = 50, \quad \chi_\mu = 1$

adhesiveness

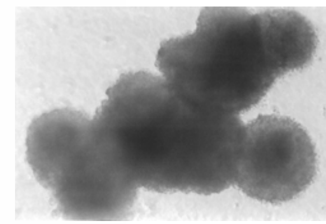


In vitro tumor spheroid

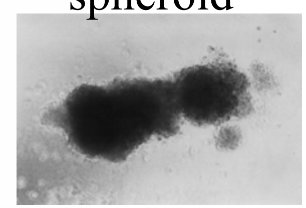


Cristini et al, Cancer Res, in review.

spheroid



spheroid



Necrosis (degradation)

- Increasing G or G_N enhances instability
- Increasing G_N decreases necrotic core
- Strong effect on morphology– compact, 1D-like, hollow

Dependence on N

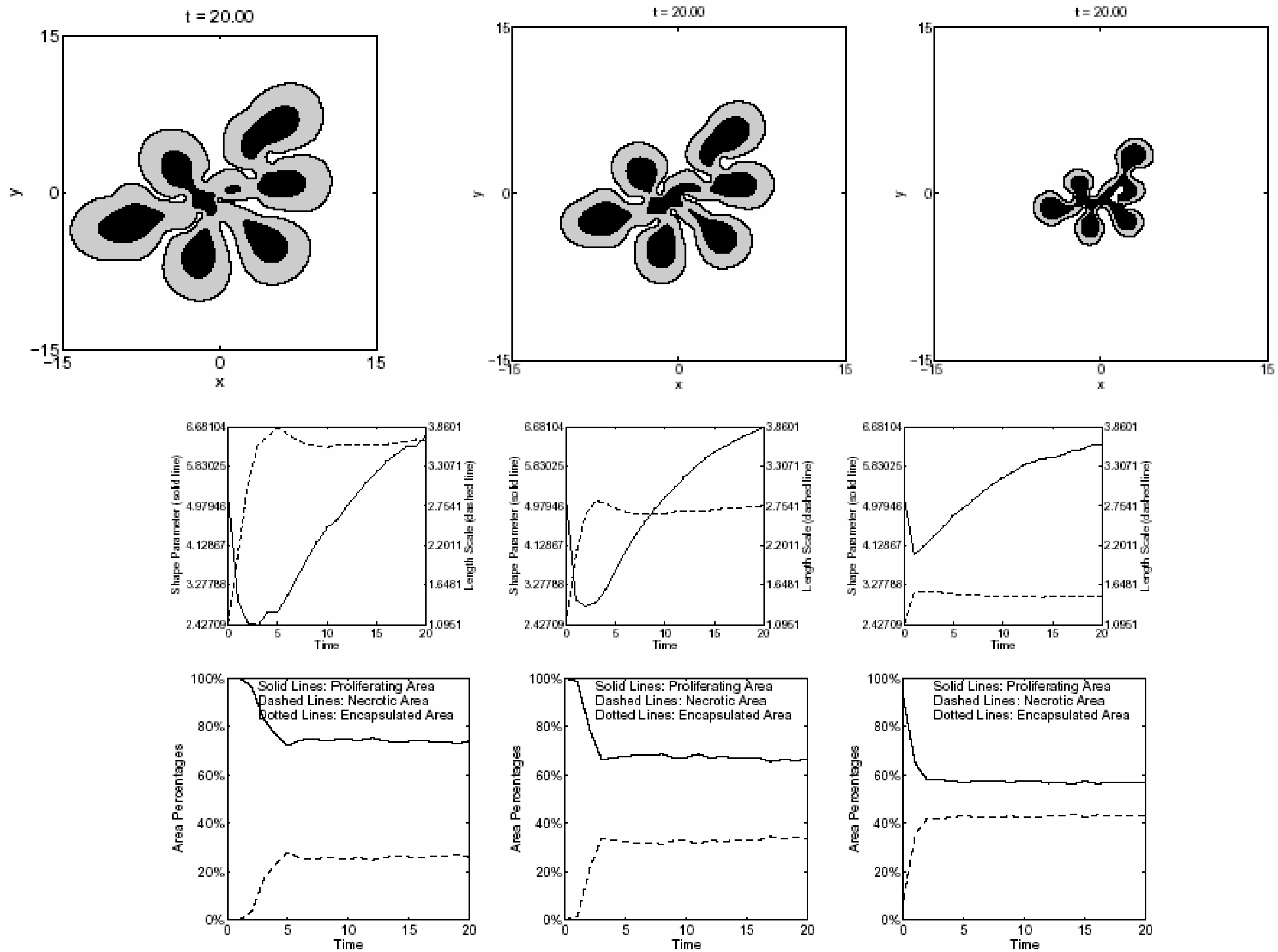
$\chi_D = 50,$

$\chi_\mu = 1,$

$G = 20,$

$G_N = 1$

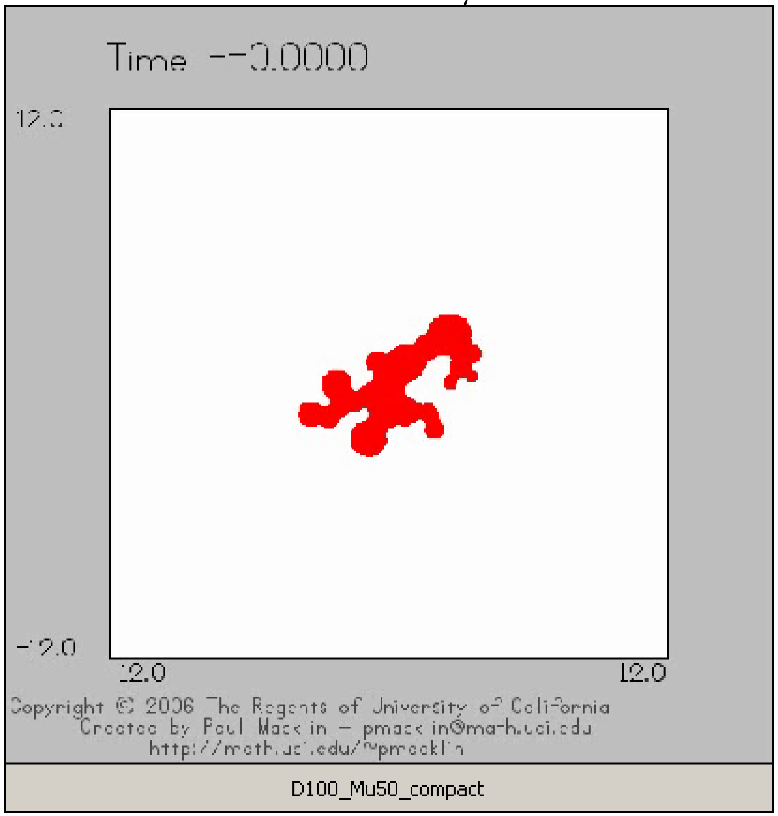
N=0.175 N=0.35 N=0.70



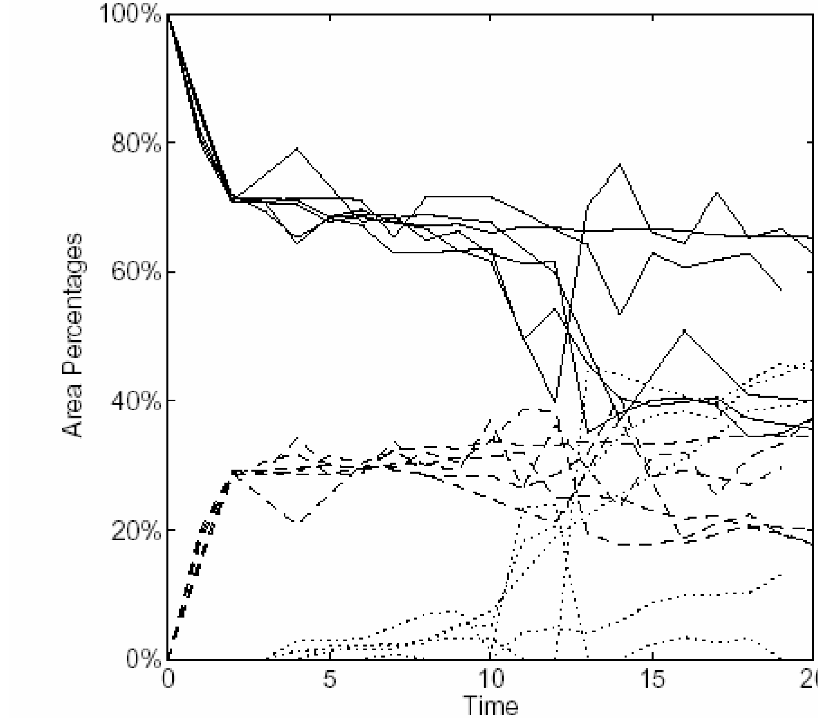
•Strong effect on size

Hollowed

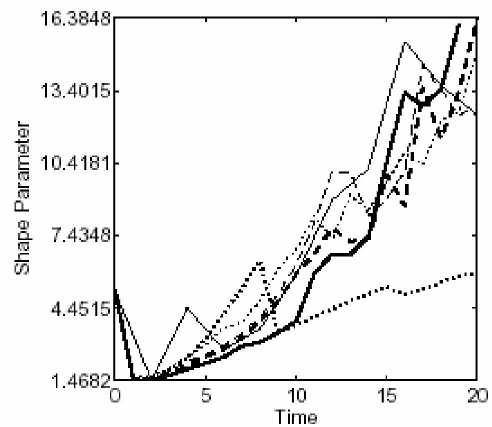
$\chi_D = 100, \quad \chi_\mu = 50$



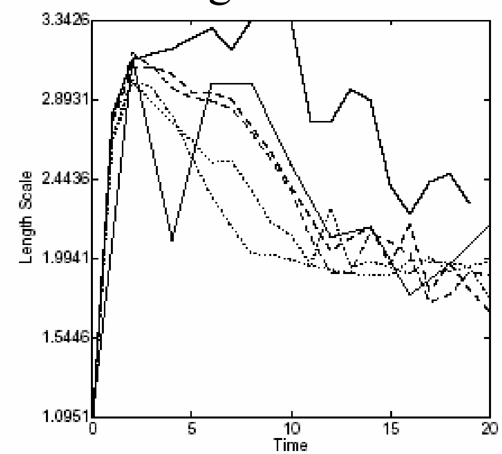
Area ratios



shape parameter



length scale

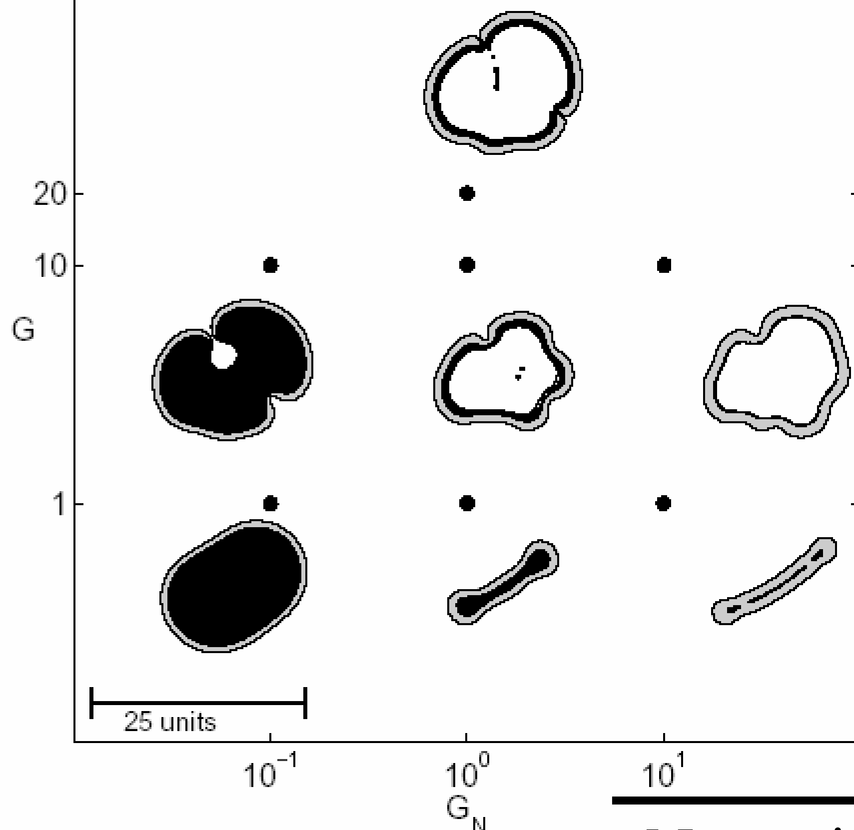


- Repeated capture and coalescence leads to hollow structure

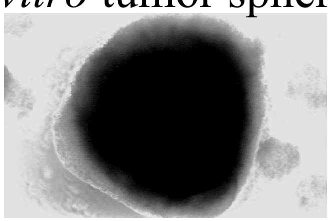
Dependence on other parameters

$$\chi_D = 50, \quad \chi_\mu = \infty$$

adhesiveness

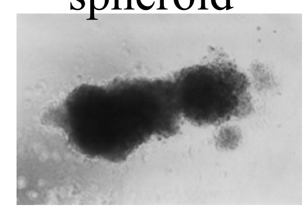


In vitro tumor spheroid



Cristini et al, Cancer Res, in review

spheroid



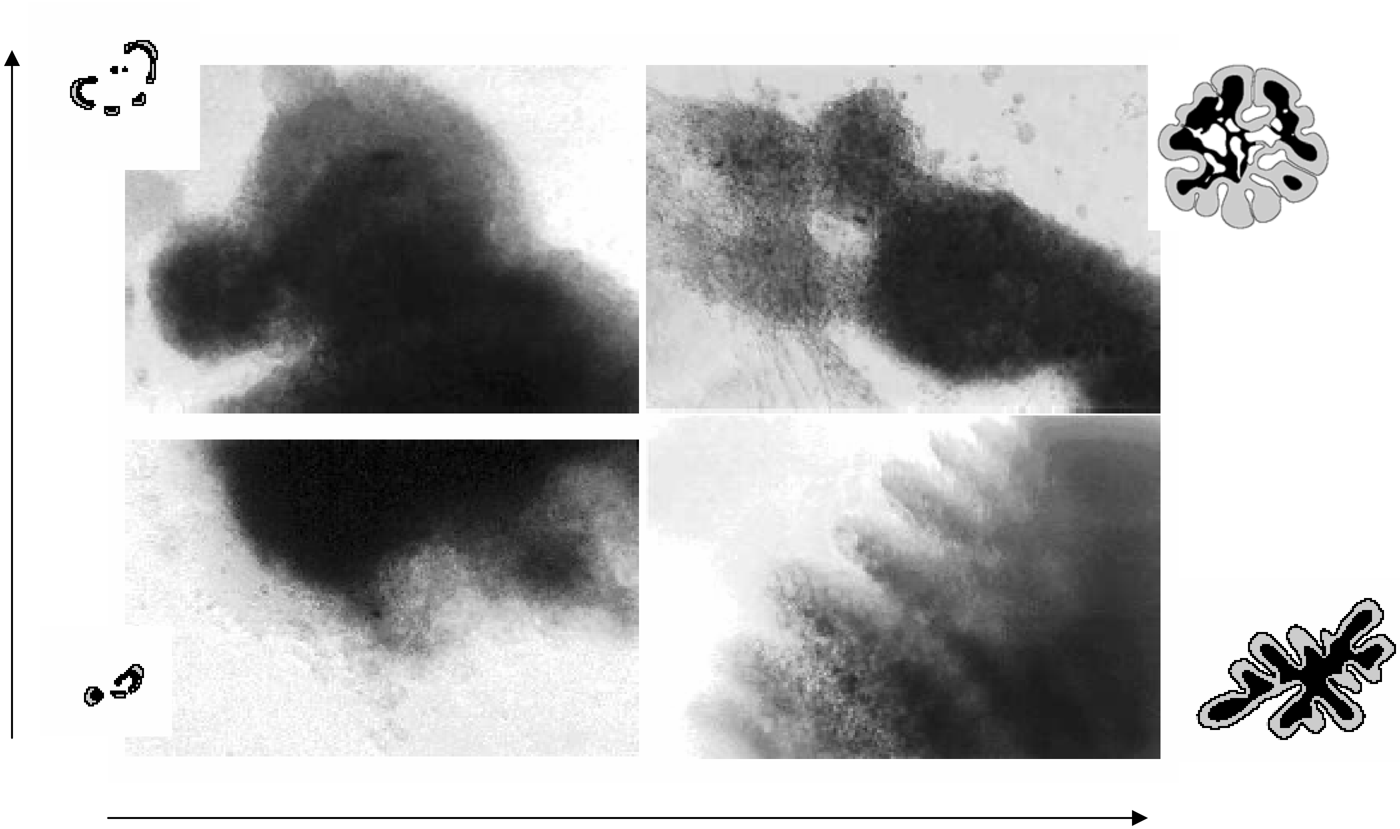
Necrosis (degradation)

- Increasing G or G_N enhances instability
- Increasing G_N decreases necrotic core
- Strong effect on morphology– compact, 1D-like, hollow

Comparison with experiment

Frieboes et al., Cancer Res. (2006).

fetal bovine serum (FBS) increasing

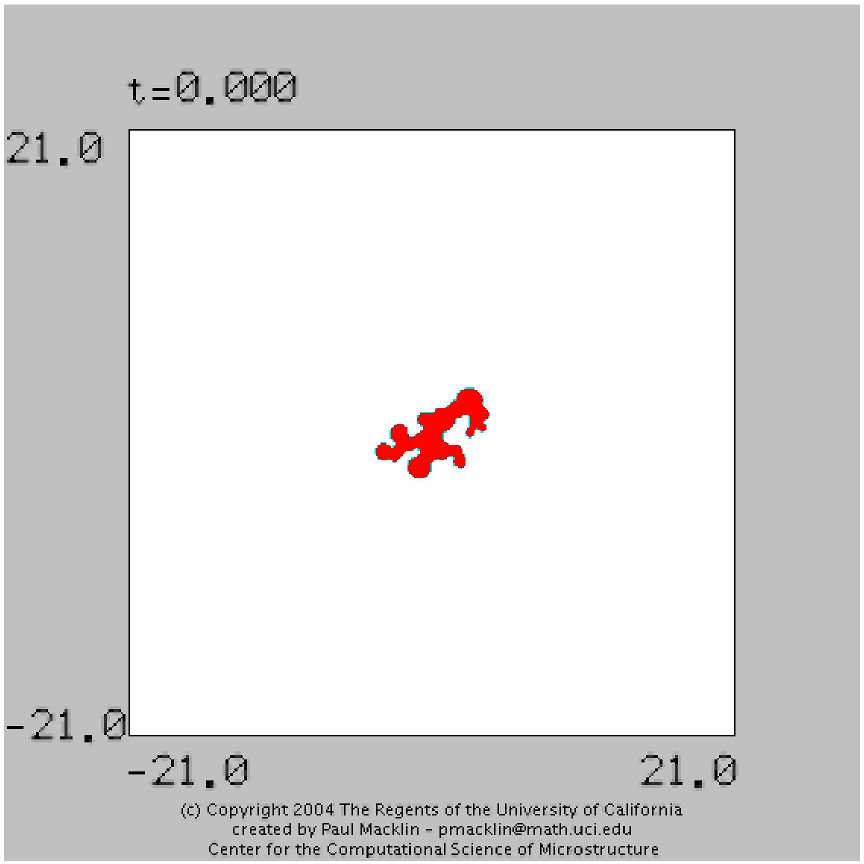


glucose increasing

- Model is qualitatively consistent with experimental results

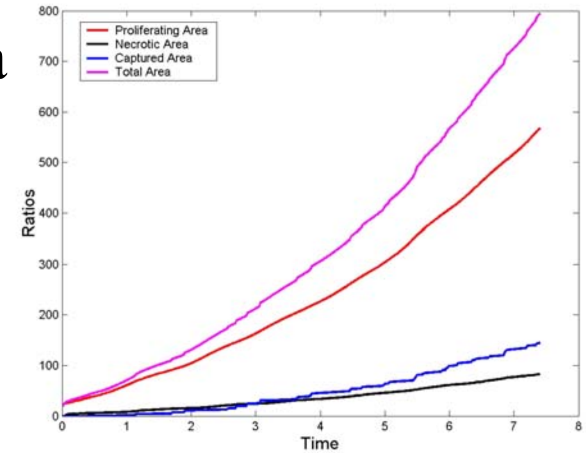
Growth into highly vascularized tissue

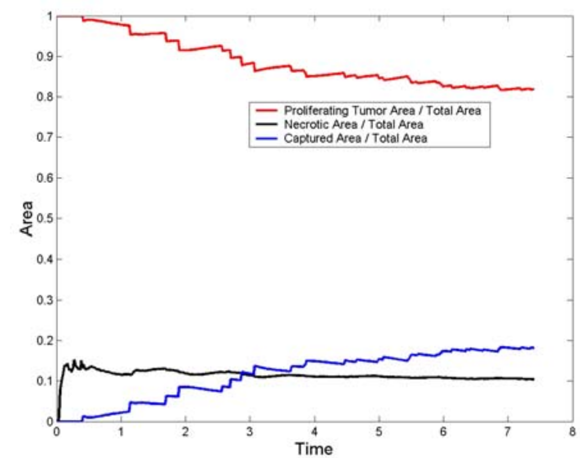
$$G = 20, \quad G_N = 1, \quad \chi_D = \chi_\mu = \infty$$



Macklin, Lowengrub, J. Comp. Phys. **203** (2005).

Area





Relative Area

- Multifocal tumor
- Statistically self-similar

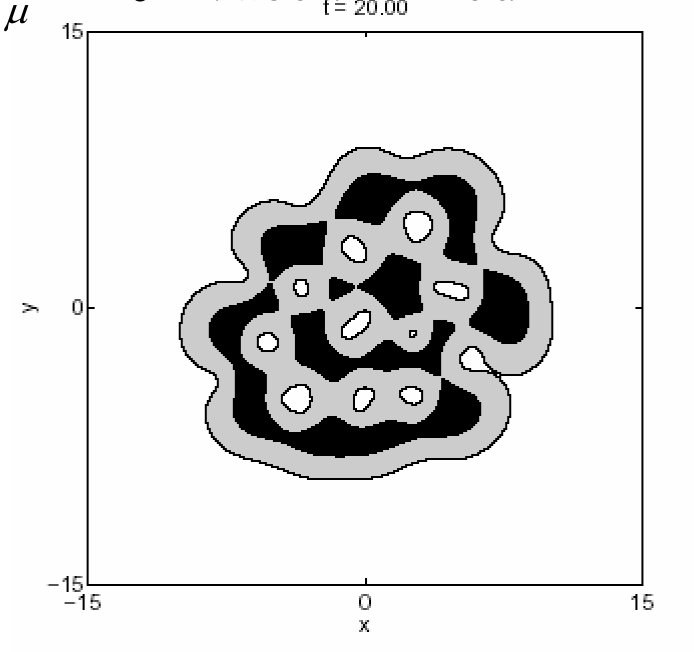
Time

Effect of vascularization in captured regions

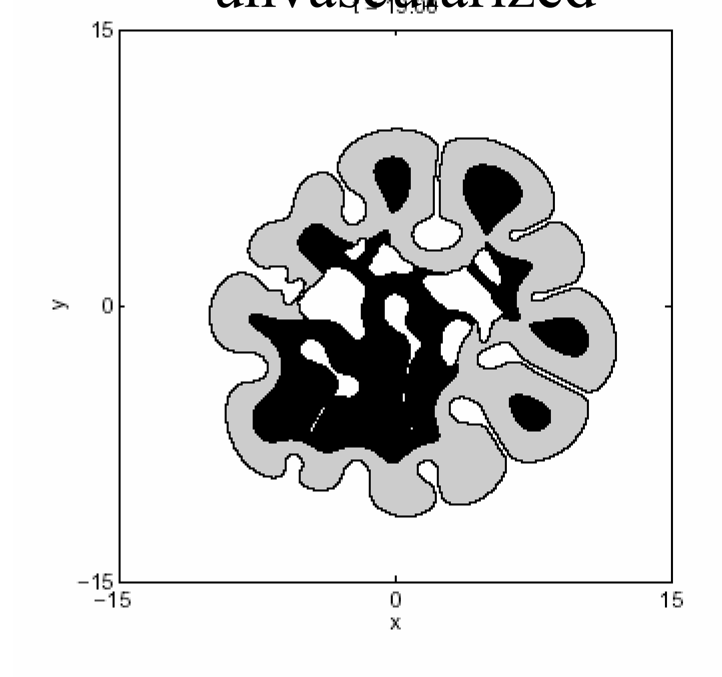
$G = 20, \quad G_N = 1,$

$\chi_D = \chi_\mu = \infty$

vascularized



unvascularized



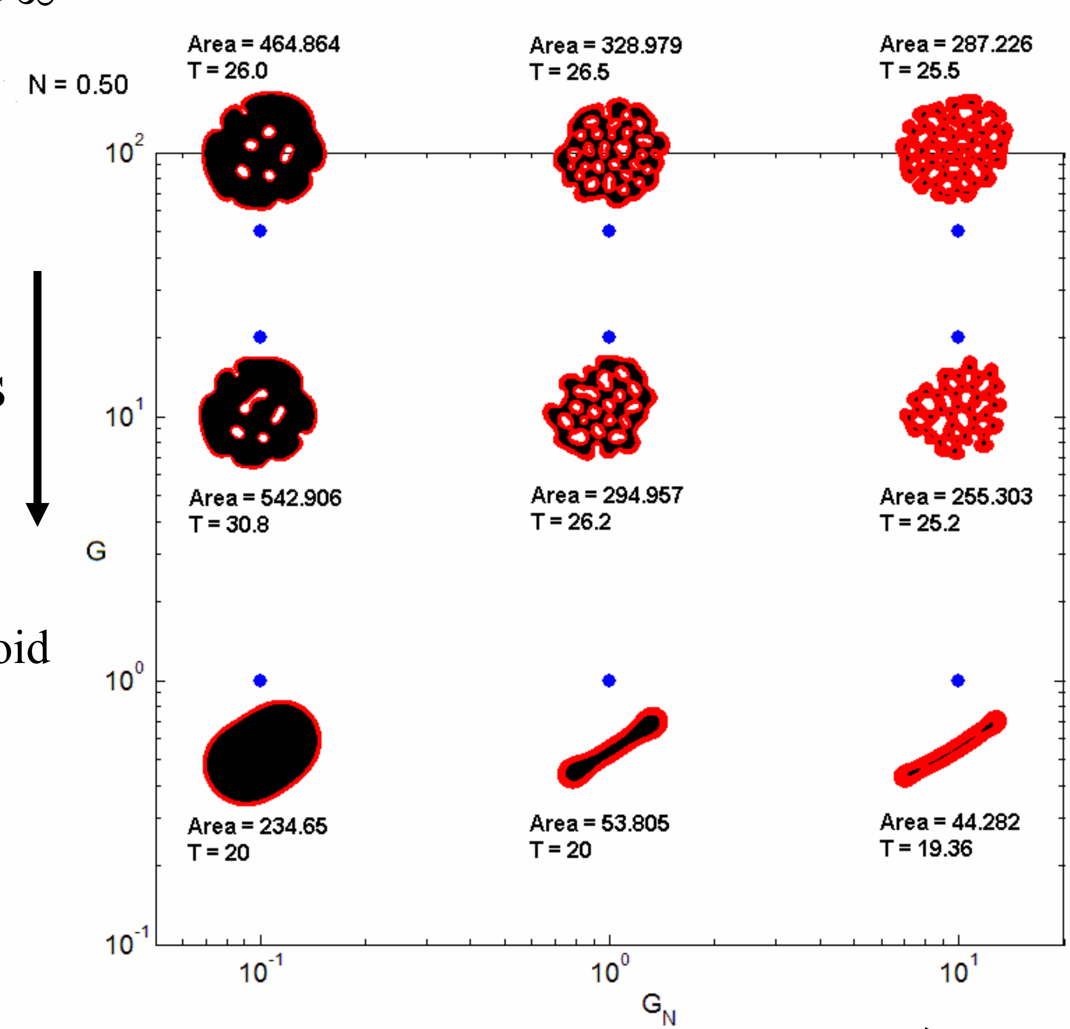
- Vascularized tumor is more compact as predicted by previous theory.

Phase Diagram: Highly vascularized tissue

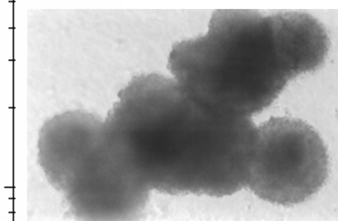
Macklin, Lowengrub, in preparation

$$\chi_D = \infty, \quad \chi_\mu = \infty$$

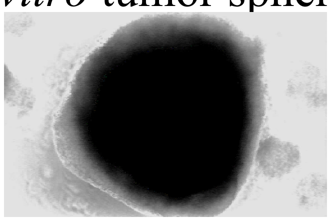
adhesiveness



spheroid

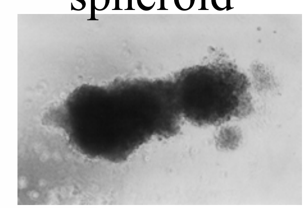


In vitro tumor spheroid



Cristini et al, Cancer Res, in review

spheroid



Necrosis (degradation)

- 3 distinct morphologies
- Evolution becomes independent of *G* for *G*>>1

Conclusions

- Extra-tumoral tissue strongly affects the size and morphology of growing tumors

- Inhomogeneity in nutrient distribution may lead to invasion, fragmentation and metastasis through diffusional instability

- Additional instability introduced by growth into less mobile tissue

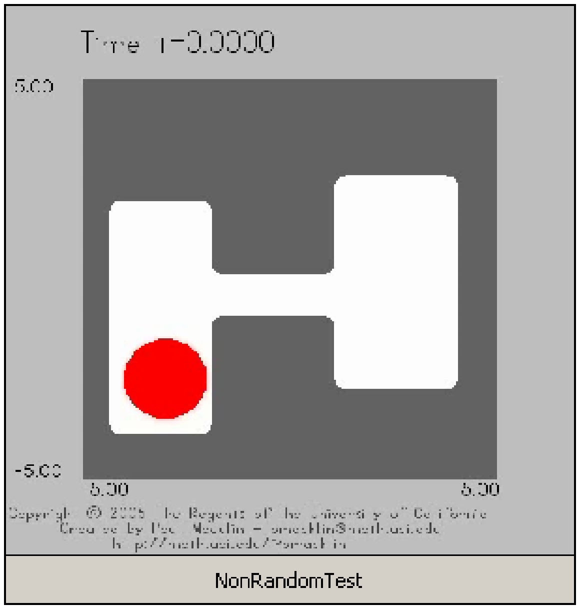
Next Steps

- More complex/realistic biophysics
  - Angiogenesis
  - Multiphase/Multiscale models
  - More realistic mechanical response
  - Finite, complex domains
  - Stochastic models

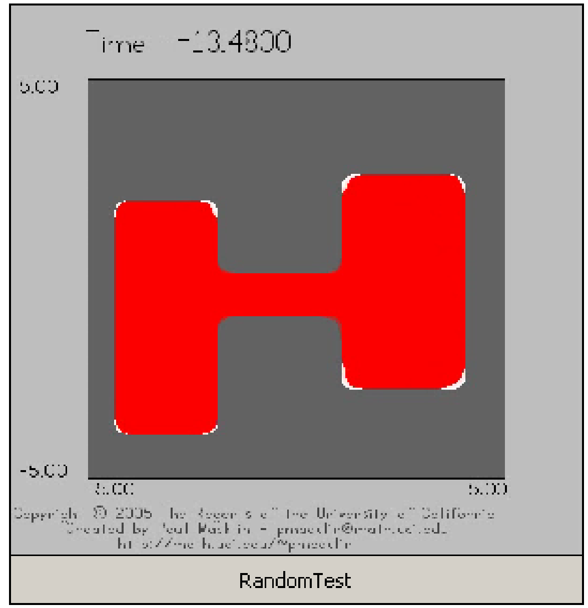
Future work

•Genetic mutations, cell-differentiation and spatial structure

Non-random



Random



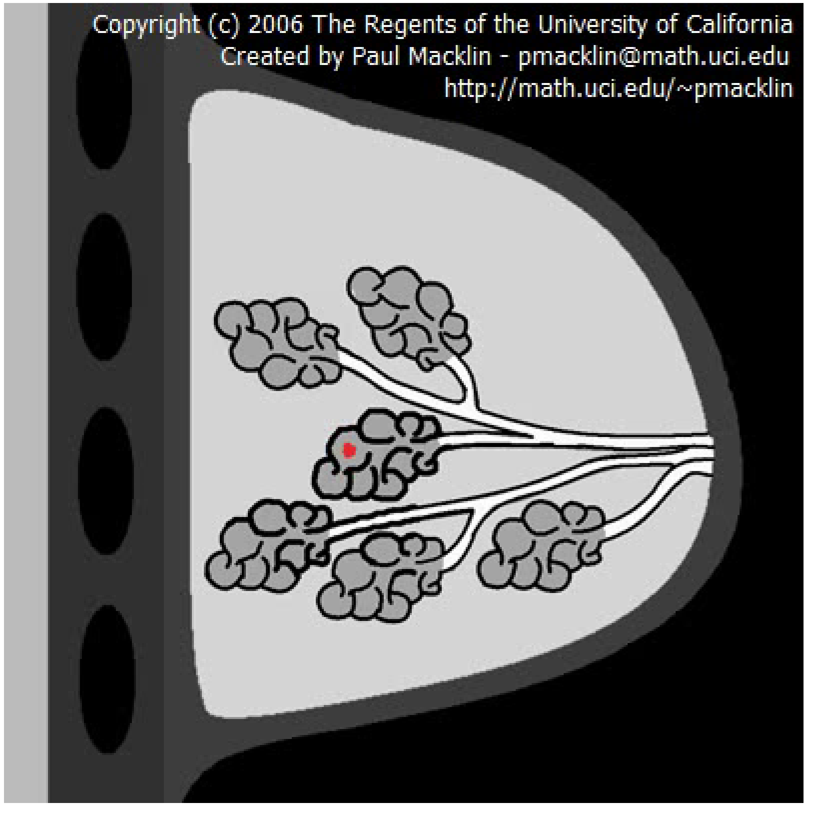
Komarova, Macklin, L.

Highly simplified model: $dX_{\Sigma} = dt + dW$

•Strong interaction among length scales with geometry of domain leads to delayed invasion

Modeling growth in real organs

Breast cancer model



Multiscale Mixture Models

Please, Byrne, Preziosi and co-workers (tumors), many others for biomechanics

volume fractions ϕ_k for $k = 1, \ldots, N$ $\quad \sum_{k=1}^{N} \phi_k(\mathbf{x}, t) = 1.$

solid and water components

- Mass, momentum and energy balance equations posed for each component

$$\partial_t \phi_k + \nabla \cdot (\phi_k \mathbf{v}_k) = \Gamma_k / \rho_k,$$

$$\nabla \cdot \sigma_k = \pi_k,$$

$$\rho_k \phi_k \frac{D^k u_k}{Dt} = \sigma_k : \nabla \mathbf{v}_k + \rho_k \phi_k r_k + \nabla \cdot \left(\sum_{j=1}^{N} \mathbf{t}_{kj} \frac{D^k \phi_j}{Dt} \right) + \sum_{l=1}^{L} z_{kl} \frac{D^k c_l}{Dt} + \epsilon_k$$

$$\left.\begin{array}{ll} \sigma_k & \text{stress tensor} \\ \pi_k & \text{interaction forces} \\ u_k & \text{internal energy} \\ -\epsilon_k & \text{interaction energies} \end{array}\right\}$$

Thermodynamics $\longrightarrow$ Constitutive Relations

$$\psi_k = u_k - \theta \eta_k$$

$$\psi_k(\phi_1, \ldots, \phi_N, \nabla \phi_1, \ldots, \nabla \phi_N, c_1 \phi_k, \ldots, c_L \phi_k),$$

Li, Lowengrub, Cristini in preparation

Biphasic Tumor Model

ϕ : tumor (solid matter),

$1-\phi$: water

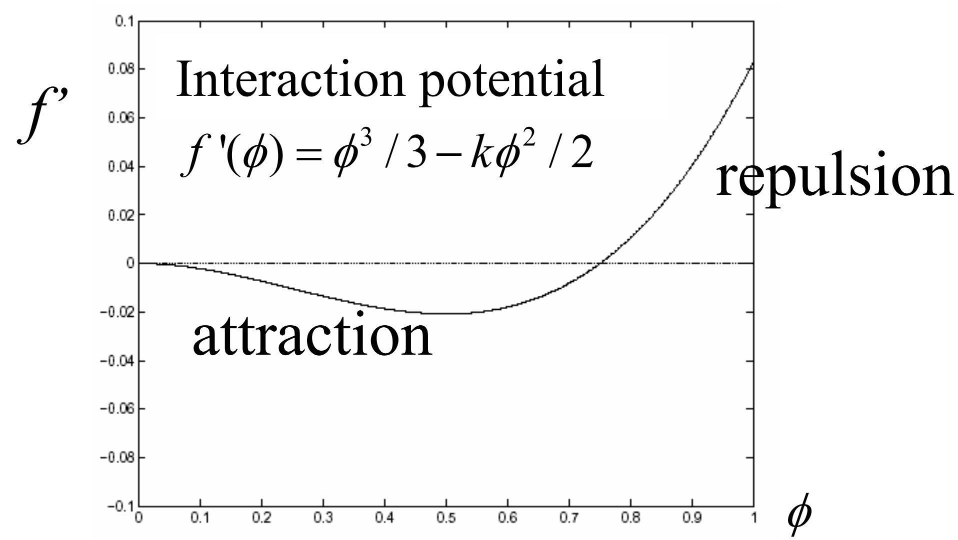
Simplest thermodynamically consistent model. (no necrosis)

$$\phi_t + \nabla \bullet (\phi \mathbf{u}) = c\phi - A\phi$$ mass

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

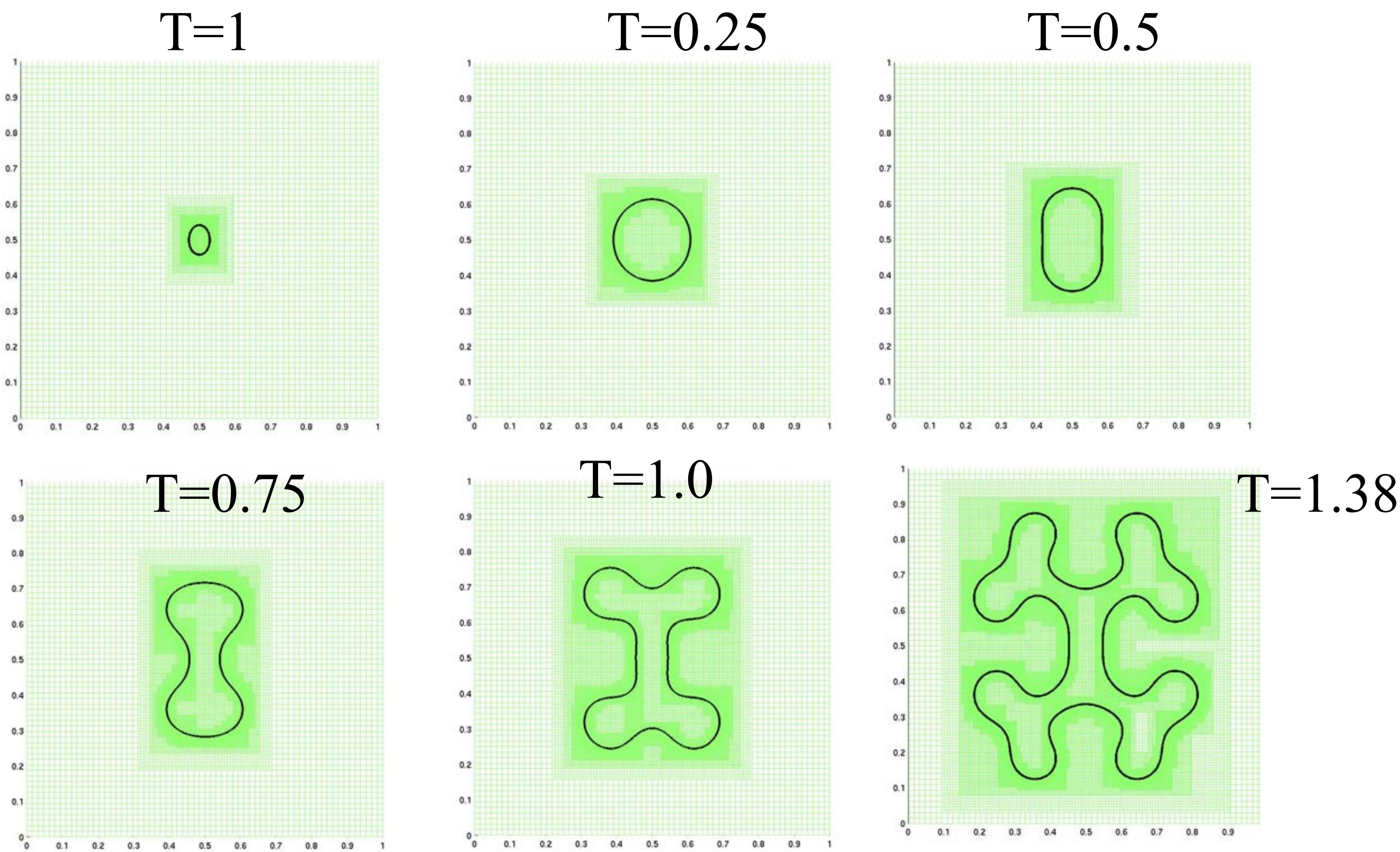
$$\mu = \frac{\delta \psi(\phi, \nabla \phi)}{\delta \phi} = f'(\phi) - \varepsilon^2 \Delta \phi$$ Constitutive Reln

$$\nabla \bullet (D \nabla c) = c\phi$$ Nutrient diffusion/consumption



Mixture Model

$$\lambda = 1, A = 0.5, M = 80, Dt = 1, De = 100, \Delta t = 0.01, \varepsilon = 0.05$$



Volume fraction