Multiscale Models of Solid Tumor Growth and Angiogenesis: The effect of the microenvironment

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P. Macklin, Ph.D. 2007 (expected);
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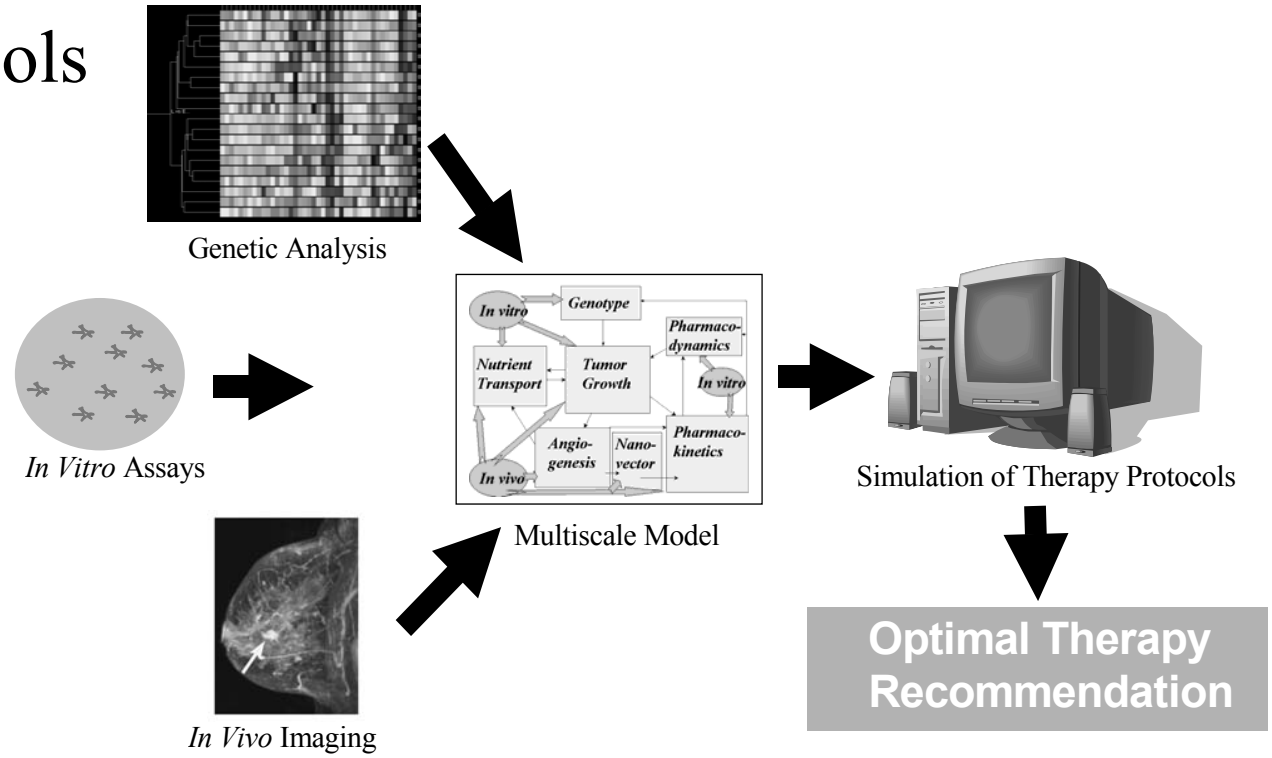
X. Zheng (U. Mich.)

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

- Models and analysis of invasion

- Numerical methods and results

- Models of angiogenesis

- Nonlinear coupling of angiogenesis and invasion

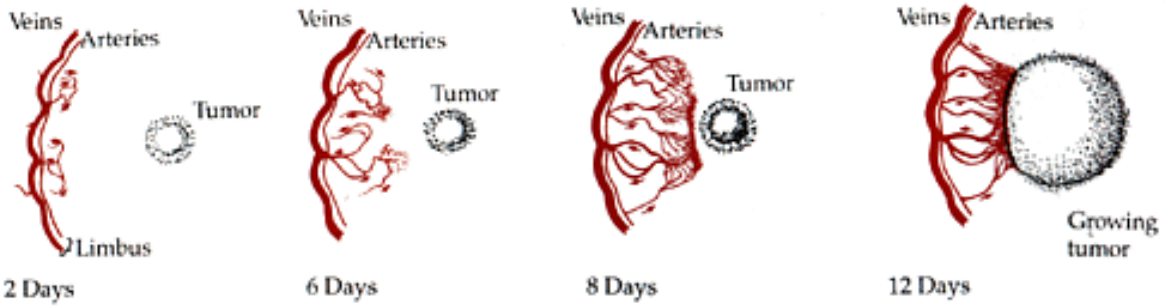
The Six Basic Capabilities of Cancer

(Hanahan and Weinberg, 2000)

- Genetic-Level (Nanoscopic)
  - Self-sufficiency in Growth Signals
  - Insensitivity to Growth-inhibitory Signals
  - Evasion of Programmed Cell Death
  - Limitless Replicative Potential
- Tissue-Level (Microscopic)
  - Tissue Invasion and Metastasis
  - Sustained Angiogenesis

Cartoon of solid tumor growth

genetic mutations



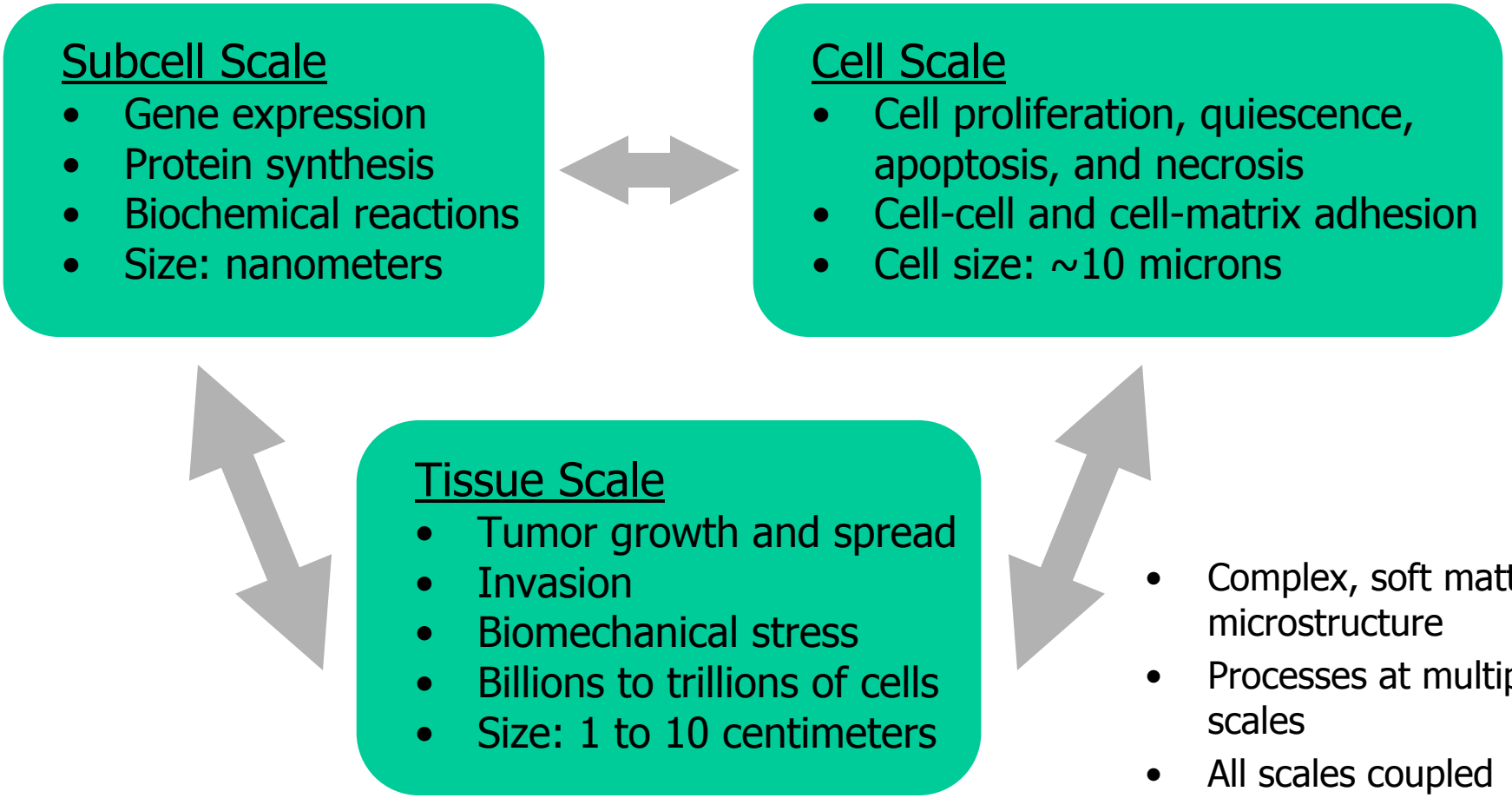
Avascular growth
Diffusion dominated

Angiogenesis

Vascular growth
invasive
metastasis
malignancy

•Goal: Model all Phases of growth

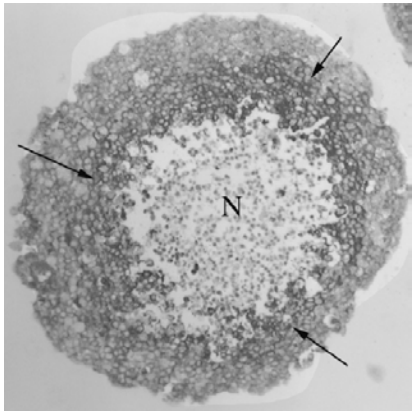
Cancer: Multiscale Problem

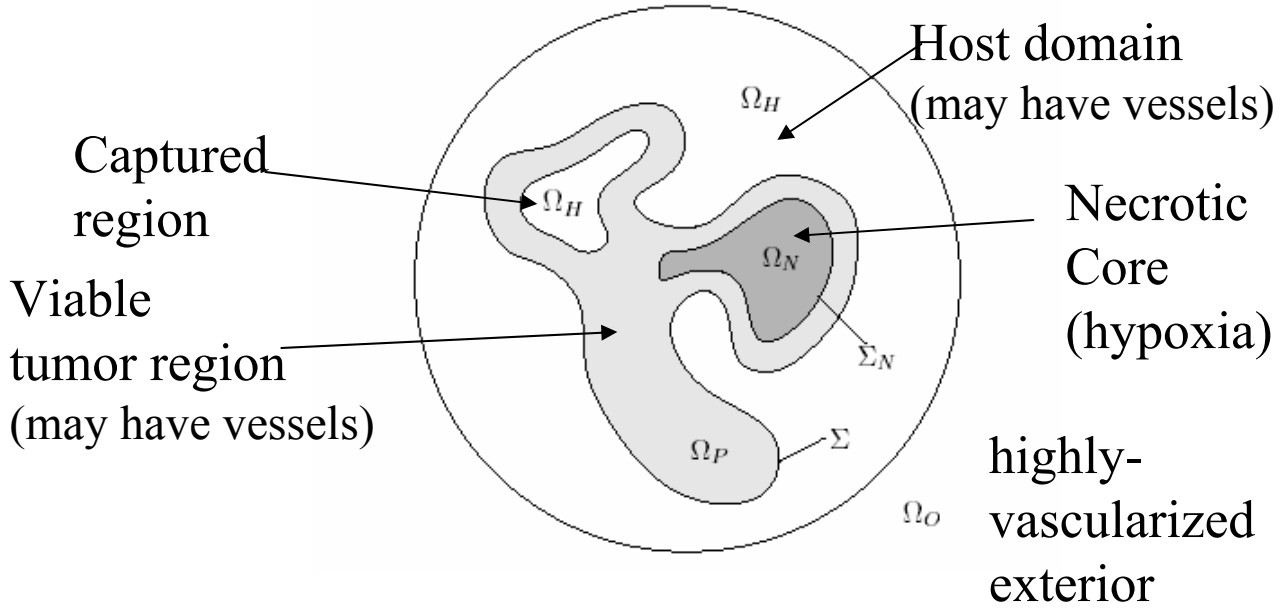


Recent Reviews: Bellomo-Preziosi (2003), Araujo-McElwain (2004), Byrne et al (2006)

Nonlinear (continuum) simulations: Cristini et al (2003), Zheng et al. (2005), Macklin-L. (2005,2006), Hogea et al (2005,2006), Wise et al. (in review)

Modeling





- Continuum approximation: super-cell macro scale
  (Collective motion)

- 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

Key variables

Minimal set.

- the mass fraction of the viable tumor cells ρ_{V},
- the mass fraction of the dead (e.g. necrotic) tumor cells ρ_{D},
- the mass fraction of both viable and dead tumor cells ρ_{T},
- the mass fraction of the host (healthy) cells ρ_{H},
- the mass fraction of the water ρ_{W},
- the cellular, necrotic, host and water velocities $\mathbf{u}_{\mathrm{V}}$, $\mathbf{u}_{\mathrm{D}}$, $\mathbf{u}_{H}$ and $\mathbf{u}_{\mathrm{W}}$.

Tumor fraction: $\rho_{\mathrm{T}} = \rho_{\mathrm{V}} + \rho_{\mathrm{D}}.$

Will discuss refinements later.

Equations governing tumor growth and tissue invasion

Wise, Lowengrub, Frieboes, Cristini, Bull. Math. Biol., in review.

$$\frac{\partial \rho_{\mathrm{V}}}{\partial t} + \nabla \cdot (\mathbf{u}_{\mathrm{V}} \rho_{\mathrm{V}}) = -\nabla \cdot \mathbf{J}_V + S_V$$

$$\frac{\partial \rho_{\mathrm{D}}}{\partial t} + \nabla \cdot (\mathbf{u}_{\mathrm{D}} \rho_{\mathrm{D}}) = -\nabla \cdot \mathbf{J}_D + S_D,$$

$$\frac{\partial \rho_{\mathrm{H}}}{\partial t} + \nabla \cdot (\mathbf{u}_{\mathrm{H}} \rho_{\mathrm{H}}) = -\nabla \cdot \mathbf{J}_H + S_H,$$

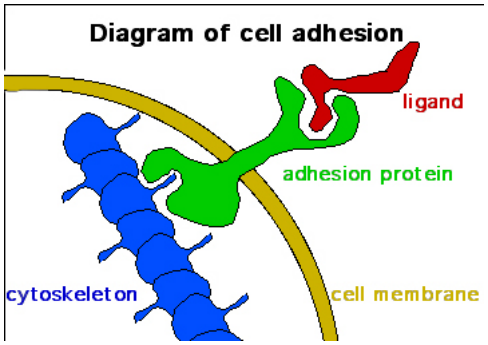
$$\frac{\partial \rho_{\mathrm{W}}}{\partial t} + \nabla \cdot (\mathbf{u}_{\mathrm{W}} \rho_{\mathrm{W}}) = S_W,$$

$\mathbf{J}$ -- Adhesion fluxes

S – Net sources/sinks of mass

Mixture models: Ambrosi-Preziosi (2002), Byrne-Preziosi (2003)– ill-posed.

Adhesion

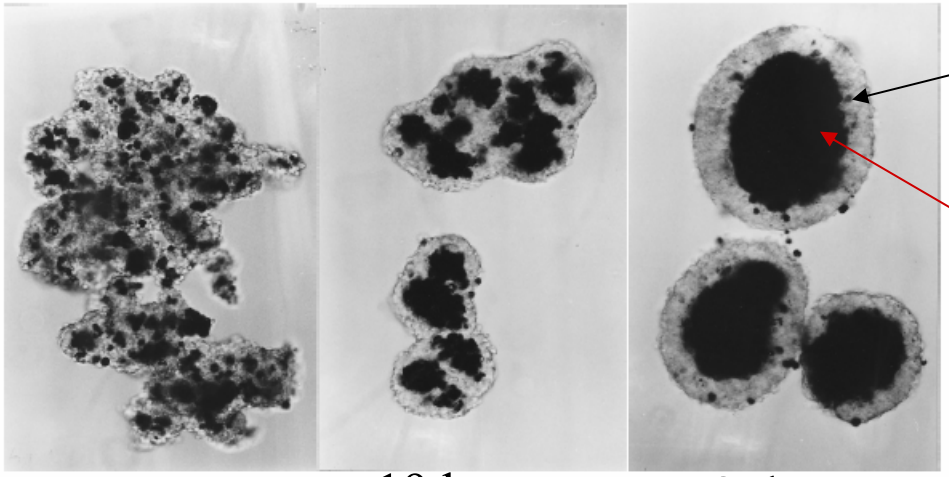


Fundamental biophysical mechanism.

Cell-cell binding through cell-surface proteins (CAMs, cadherins)

•Cell-sorting due to cell-cell adhesion

Chick embryo
Armstrong (1971)



•Cells of like kind prefer to stay together.

Cell-ECM binding through other cell-surface proteins (integrins)

Adhesion Energy

- Assume tumor cells prefer to be together.

  Different phenotypes may have different adhesivity (can extend the model)

$$E = \int_{\Omega} \left(f(\rho_{\mathrm{T}}) + \frac{\varepsilon^2}{2} |\nabla \rho_{\mathrm{T}}|^2 \right) d^3\mathbf{x},$$

Double-well potential

Gradient energy (allows intermixing)

- Thermodynamic consistency:

$$\mathbf{J}_{\mathrm{V}} = -M\rho_{\mathrm{V}} \nabla \frac{\delta E}{\delta \rho_{\mathrm{V}}}, \qquad \mathbf{J}_{\mathrm{D}} = -M\rho_{\mathrm{D}} \nabla \frac{\delta E}{\delta \rho_{\mathrm{D}}}, \qquad \mathbf{J}_H = -(\mathbf{J}_V + \mathbf{J}_D)$$

where $\frac{\delta E}{\delta \rho_{\mathrm{V}}} = \frac{\delta E}{\delta \rho_{\mathrm{D}}} = f'(\rho_{\mathrm{T}}) - \varepsilon^2 \nabla^2 \rho_{\mathrm{T}}.$ ⟶ Generalized Cahn-Hilliard equation

Other approaches: Nonlocal energy (Katsulakis et al.), Armstrong et al. (2006)

Constitutive Assumptions

Simplest assumptions. Can be generalized. (X.Li, L., Cristini, Wise)

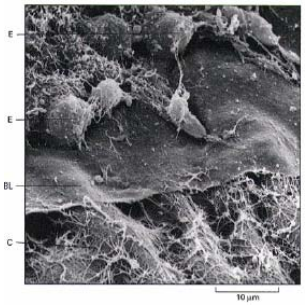
- Water density is constant: $\rho_{\mathrm{W}}(\mathbf{x}, t) = \bar{\rho}_1.$ ⟶ Water decouples
- Close-packing: $\rho_{\mathrm{T}} + \rho_{\mathrm{H}} = \bar{\rho}_0,$
- Cell-velocities are matched using Darcy's law:

$$\mathbf{u}_{\mathrm{V}} = \mathbf{u}_{\mathrm{D}} = \mathbf{u}_{\mathrm{H}} = -\mu\left(\nabla p - \frac{\delta E}{\delta \rho_{\mathrm{T}}}\nabla \rho_{\mathrm{T}}\right)$$

Excess adhesion

Cell mobility: reflects strength of cell-cell and cell-matrix adhesion

Oncotic (hydrostatic) solid pressure



(arises from thermodynamic considerations)

Constitutive Assumptions Contd.

Heaviside function

Cell proliferation: Nutrient (oxygen) Viability level of nutrient

$$S_V = \bar{\lambda}_{\mathrm{M}} n/\bar{n}_\infty \rho_{\mathrm{V}} - \bar{\lambda}_{\mathrm{A}} \rho_{\mathrm{V}} - \bar{\lambda}_{\mathrm{N}} \mathcal{H}(\bar{n}_{\mathrm{N}} - n)\rho_{\mathrm{V}},$$

mitosis apoptosis necrosis

Necrotic cells:

$$S_D = \bar{\lambda}_{\mathrm{A}} \rho_{\mathrm{V}} + \bar{\lambda}_{\mathrm{N}} \mathcal{H}(\bar{n}_{\mathrm{N}} - n)\rho_{\mathrm{V}} - \bar{\lambda}_{\mathrm{L}} \rho_{\mathrm{D}},$$

lysing (enzymatic degradation)

Host domain:

$$S_H = 0,$$

Water:

$$S_W = -(S_V + S_D + S_H) = -\bar{\lambda}_{\mathrm{M}} n/n_\infty \rho_{\mathrm{V}} + \bar{\lambda}_{\mathrm{L}} \rho_{\mathrm{D}}$$

Evolution of nutrient

Oxygen:

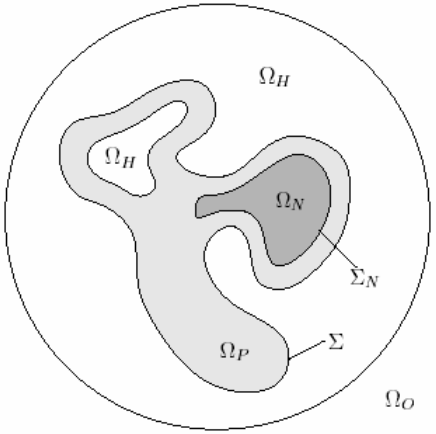
$$0 = \nabla \bullet \left(D\left(\rho_{\mathrm{T}}\right) \nabla n \right) + T_{\mathrm{C}}\left(n_{\mathrm{C}}, n, p, \delta_{C}\right) - \nu_{\mathrm{U}} n \rho_{\mathrm{V}}$$

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

Source due to capillaries (angiogenesis)

uptake by viable cells

Interpretation



In Ω_H,

- *D* is an indirect measure of perfusion

  i.e., D large → nutrient rich

- μ is a measure of mechanical/adhesive properties of extra-tumor tissue

  i.e., μ small → tissue hard to penetrate (less mobile)

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

The equations (nondimensionalized)

$$\mathcal{L} = \left(\bar{D}_{\mathrm{T}}/\bar{\nu}_{\mathrm{U}}\right)^{\frac{1}{2}} \quad \text{and} \quad \mathcal{T} = \bar{\lambda}_{\mathrm{M}}^{-1},$$

length time

$$\frac{\partial \rho_{\mathrm{T}}}{\partial t} = M\nabla\left(\rho_V \nabla\mu\right) + S_{\mathrm{T}} - \nabla\cdot\left(\mathbf{u}\rho_{\mathrm{T}}\right),$$

$$\mu = f'(\rho_{\mathrm{T}}) - \varepsilon^2\nabla^2\rho_{\mathrm{T}},$$

$$\frac{\partial \rho_{\mathrm{D}}}{\partial t} = M\nabla\cdot\left(\rho_{\mathrm{D}}\nabla\mu\right) + S_{\mathrm{D}} - \nabla\cdot\left(\mathbf{u}\rho_{\mathrm{D}}\right),$$

$$\nabla\cdot\mathbf{u} = S_{\mathrm{T}},$$

$$S_{\mathrm{T}} = S_{\mathrm{V}} + S_{\mathrm{D}}$$

- Only one Cahn-Hilliard Equation to be solved for ρ_{T}
- Generalizes to multiple species easily.

Nondimensional parameters

$\lambda_H = \lambda_B = \lambda_A = 0$

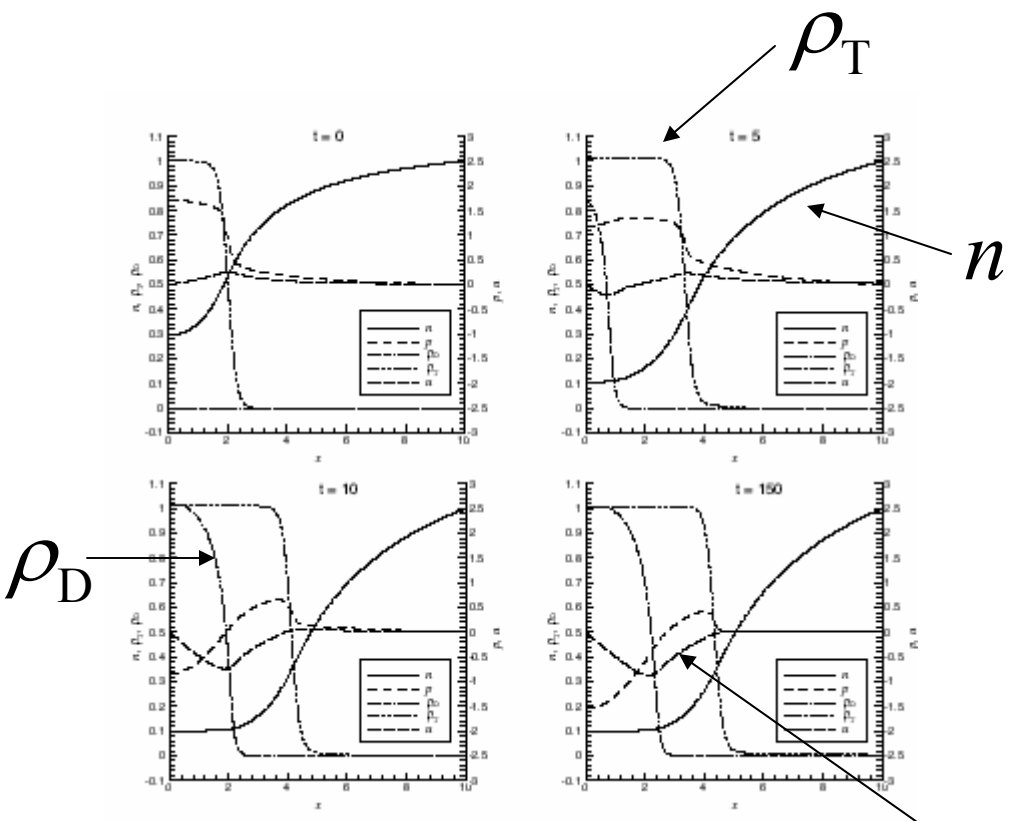
Microenvironmental:

- Diffusion ratio: $\chi_D = D_H / D_V$
- Mobility (adhesion) ratio: $\chi_\mu = \mu_H / \mu_V$

Cell-based:

- Adhesion $G = \frac{\lambda_M}{\lambda_R}$
- Intermixing: ε
- Necrosis $G_N = \lambda_L / \lambda_M$, $\overline{G}_N = \lambda_N / \lambda_M$
- Viability $N = \frac{n_N}{n_\infty}$

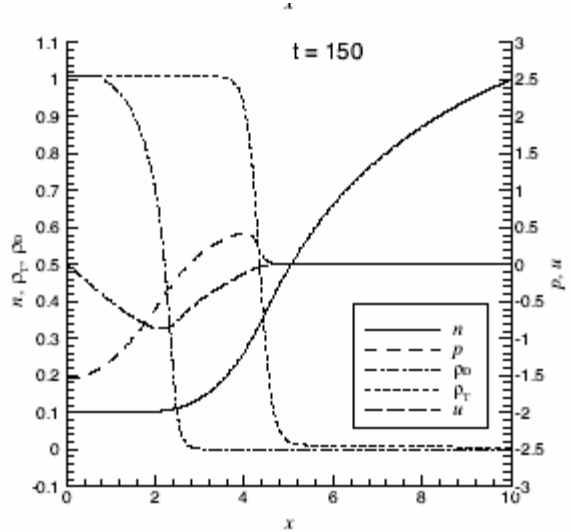
Spherical Solutions



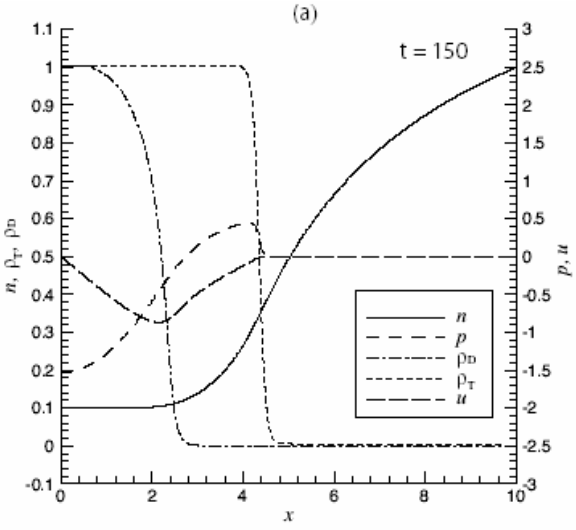
Growth to a steady spheroid

- Balance between proliferation/necrosis/lysing.
- Viable tumor cells move to center. (water moves outward)
- Necrotic boundary is diffuse

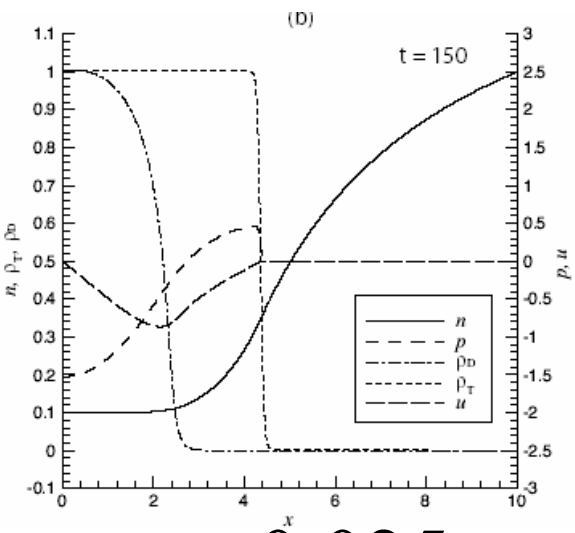
Convergence to sharp interface



$\varepsilon = 0.10$



$\varepsilon = 0.05$



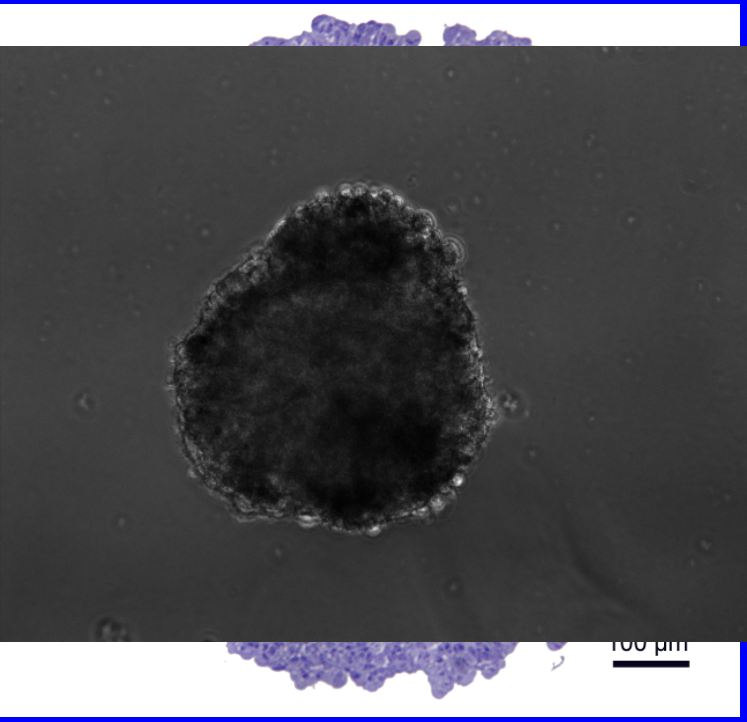
$\varepsilon = 0.025$

- Method of matched asymptotic expansions can be used to suggest convergence to classical sharp interface models as $\varepsilon \to 0$ provided M is bounded

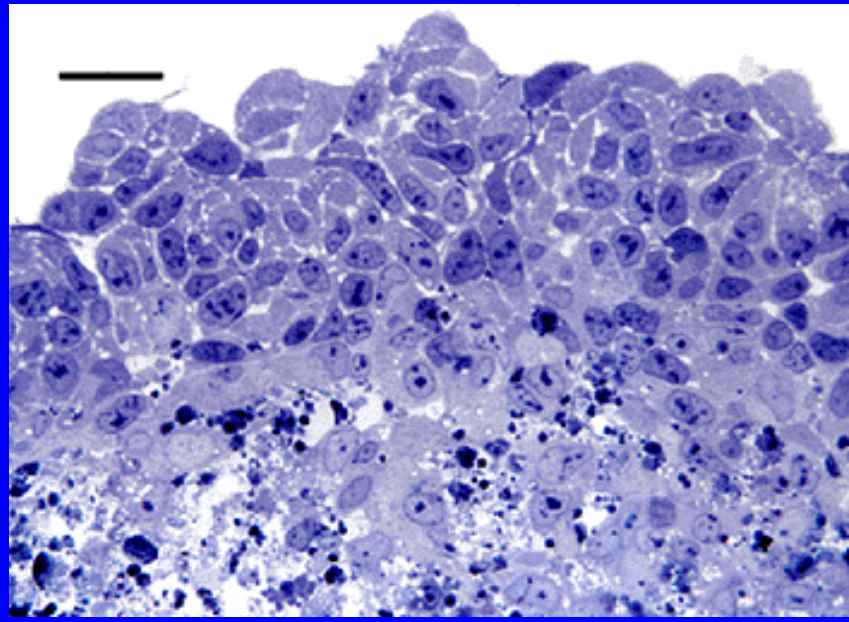
Tumor Spheroids: Validation *in vitro*

In vitro growth: No vascularization (diffusion-dominated)

Dormant (steady) states



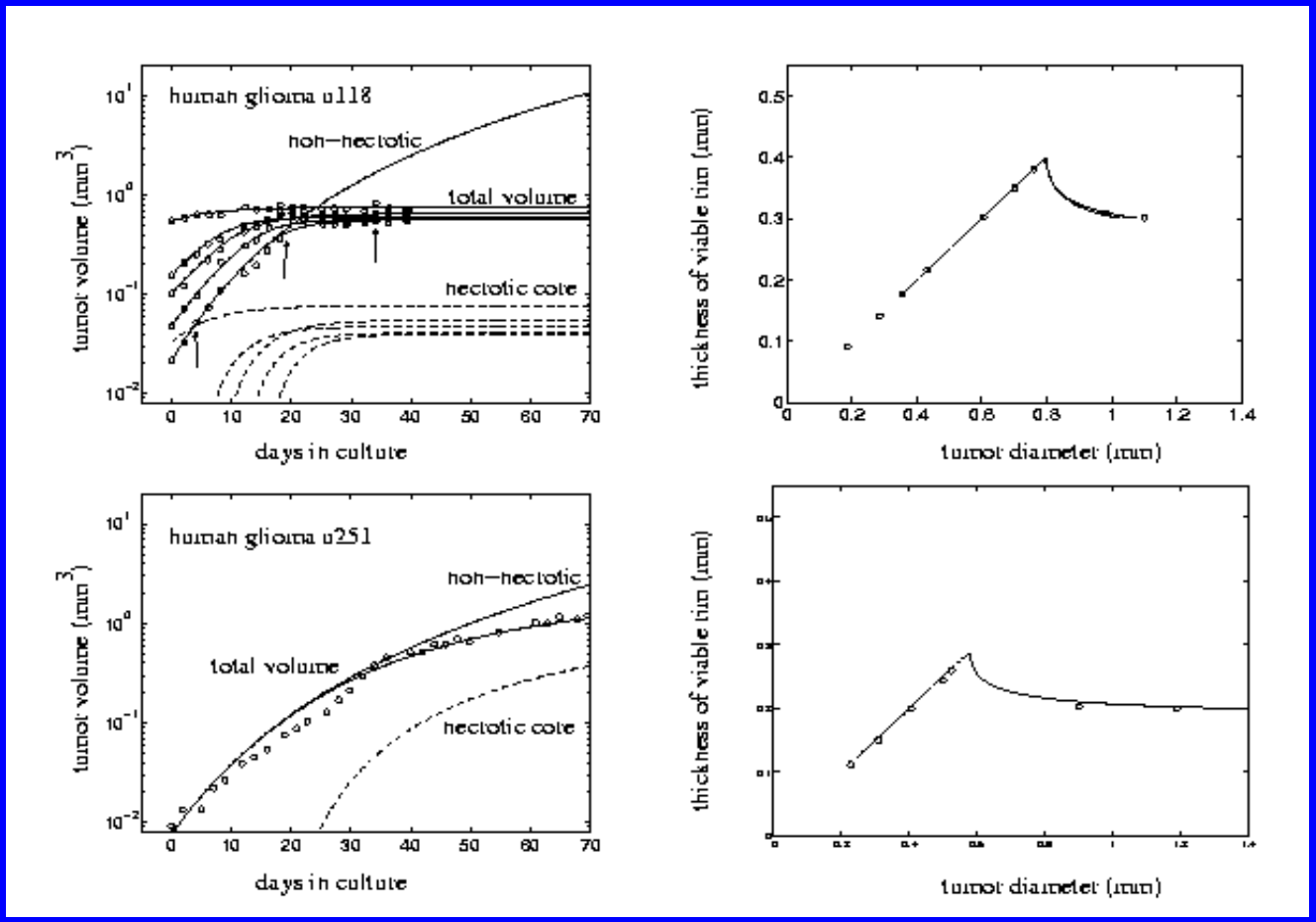
One micron section of tumor spheroid showing outer living shell of growing cells and inner core of necrosis.



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

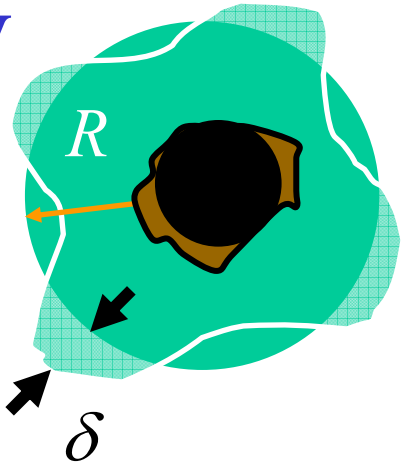
$\lambda_M \approx 0.3\ \text{day}^{-1}$ $D \approx 3\times10^{-3}\ \text{mm}^2/s$

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

(approximately 7 cells)

G is not determined: $\begin{cases} \text{Experiments} \\ \text{Stability analysis} \end{cases}$

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

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

(balance between proliferation, necrosis and apoptosis)

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

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

Self-similar evolution

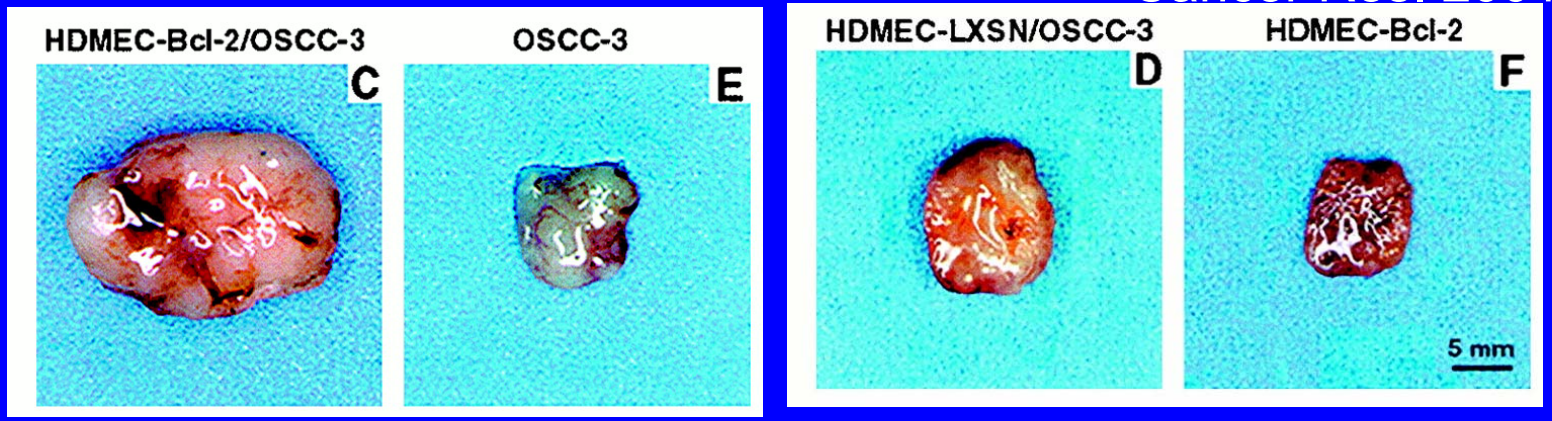
$$\longrightarrow \quad G = G^{crit}(l, R, G_N, N, A) \ \text{ such that } \ d(\delta/R)/dt = 0$$

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

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

1. Low vascularization (A,G>0) (diffusion-dominated): } 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 anisotropy

Diffusional Instability--Avascular

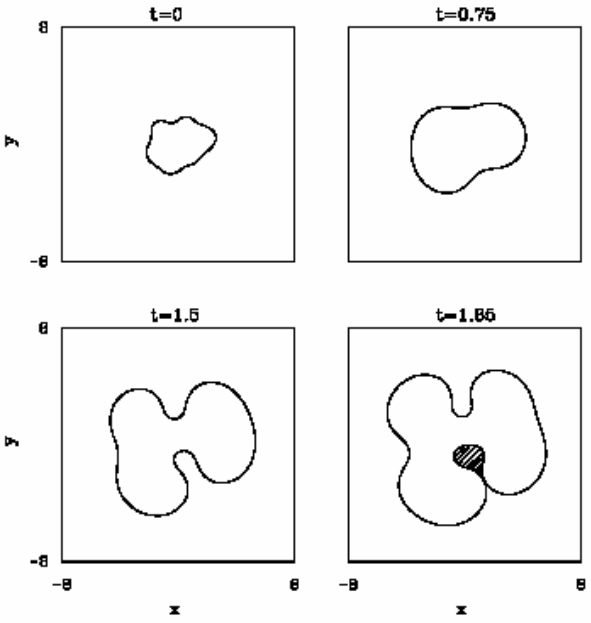
2D: Cristini, Lowengrub and Nie, J. Math. Biol. 46, 191-224, 2003

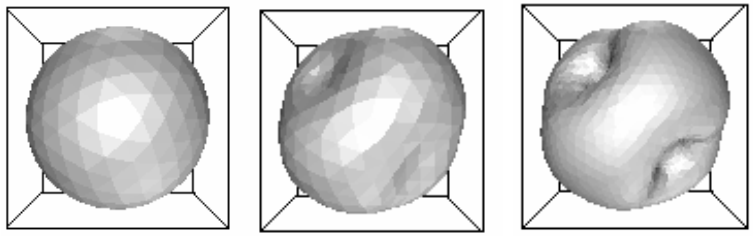
3D:, Li, Cristini, Nie and Lowengrub, DCDS-B, In review

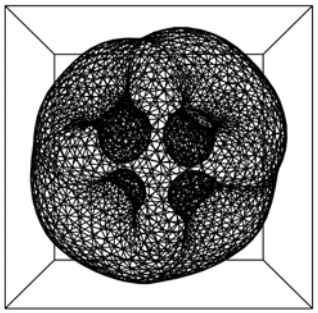
2D **Avascular** (tumor spheroid) 3D

(low cell-to-cell adhesion)

$G > G_{critical}$



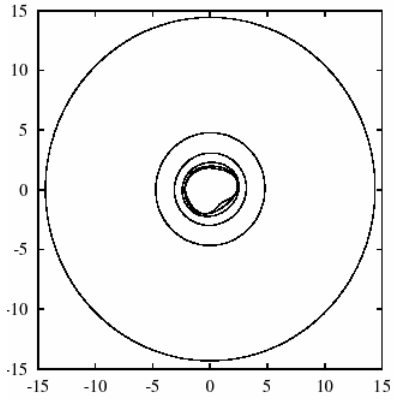




•Growth-by-bumps
ejection of cells from bulk

• topology change

Highly vascularized



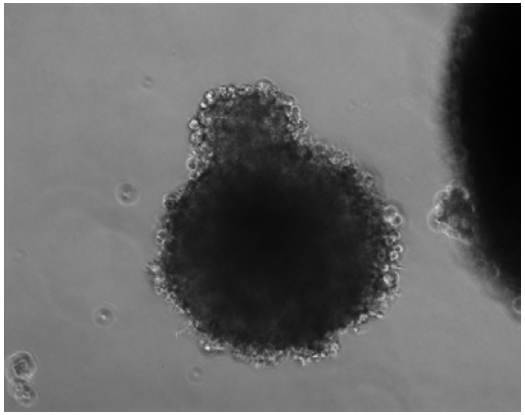
•Stable evolution

(isotropic vasculature)

Boundary integral method

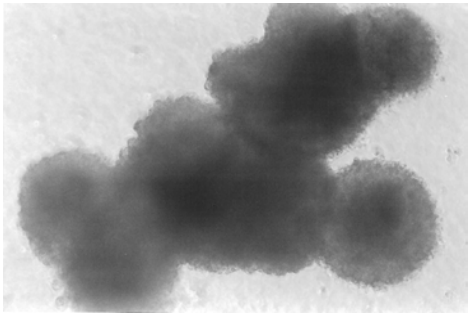
Diffusional Instability

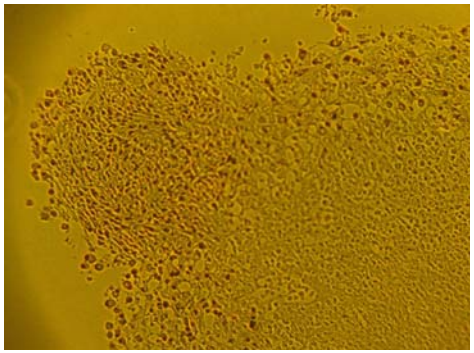
•Perturbed tumor spheroids/Complex Morphology



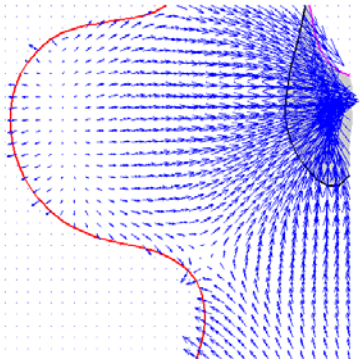
Frieboes, *et al.*

glioblastoma





Swirling ejection from bulk



Velocity field
(simulation)

•Theory:

Possible mechanism for invasion into soft tissue

Cristini, Lowengrub, Nie J. Math. Biol (2003)
Cristini, Gatenby, et. al., Clin. Cancer Res. 11 (2003) 6772.
Macklin, Lowengrub, J. Theor. Biol. (2007, in press)

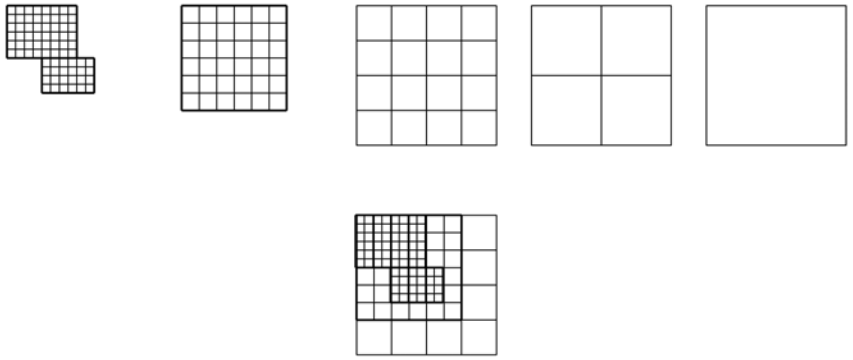
Nonlinear Simulations

Numerical Scheme

- Implicit time discretization (Gradient Stable)
  fully implicit treatment of system

- Second order accurate, centered difference scheme.
  Conservative form. Adaptive spatial discretization.
  Chombo, Mitran

- Nonlinear, Multilevel,
  multigrid method



Kim, Kang, Lowengrub, J. Comp. Phys. (2004)
Wise, Lowengrub, Kim, Thornton, Voorhees, Johnson, Appl. Phys. Lett. (2005)
Wise, Kim, Lowengrub J. Comp. Phys., in review

Advantages of Multigrid

- Complexity is O(N)
  Optimal convergence rate

- Handles large inhomogeneity/ nonlinearity seamlessly (no additional cost)
  - Smoothing is performed by, for example, the nonlinear Gauss-Seidel method.
  - Local linearization. No global linearization, for example via Newton's Method, is needed.

- Flexible implementation of b.c.'s (compare with pseudo-spectral, spectral methods)

- Seamlessly made adaptive

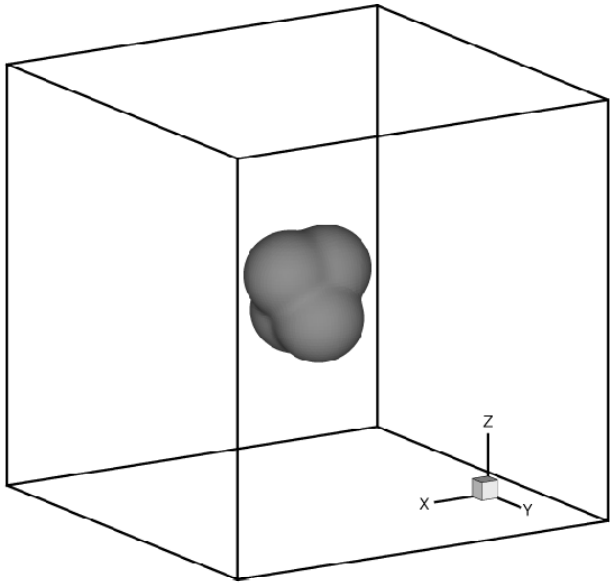
- Hard to analyze: quantify smoothing properties of the nonlinear relaxation scheme

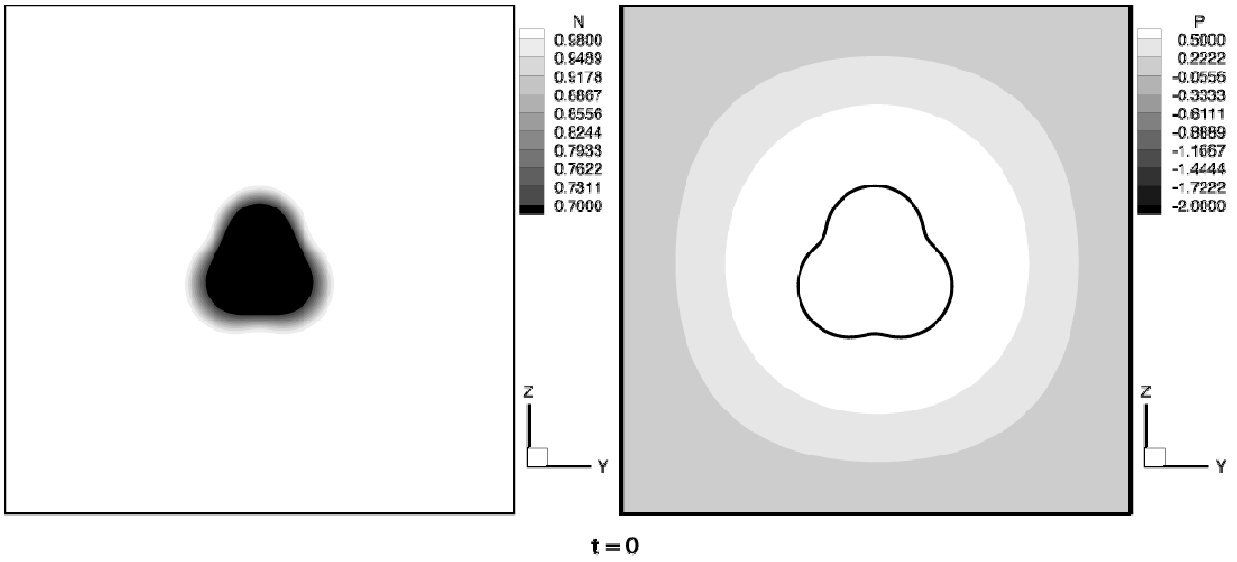
Well-perfused host domain

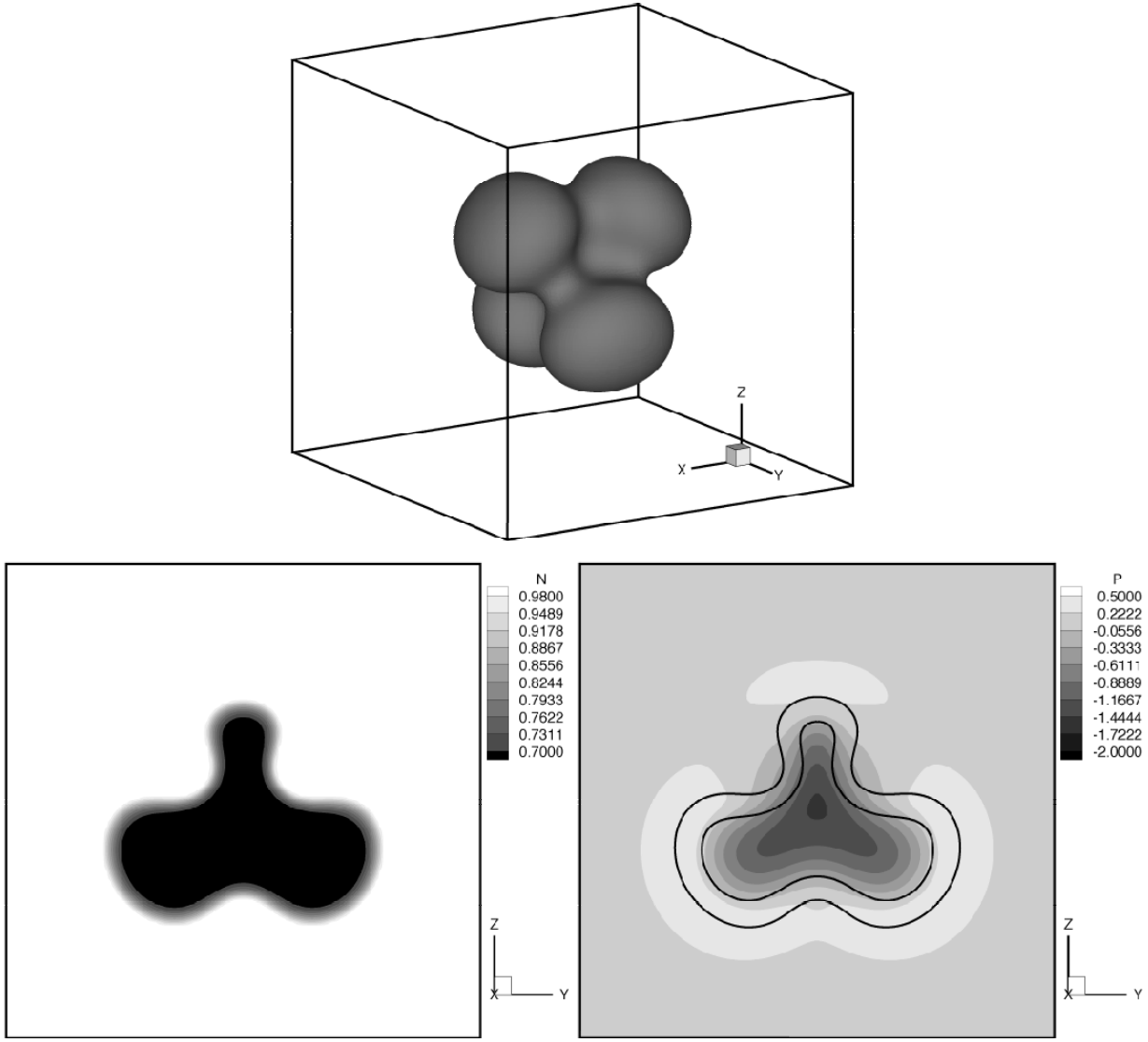
χ_D large

$\chi_\mu = 1$

- Small nutrient gradients in host



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X
Y
N
0.9800
0.9489
0.9178
0.8867
0.8556
0.8244
0.7933
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0.7311
0.7000
Z
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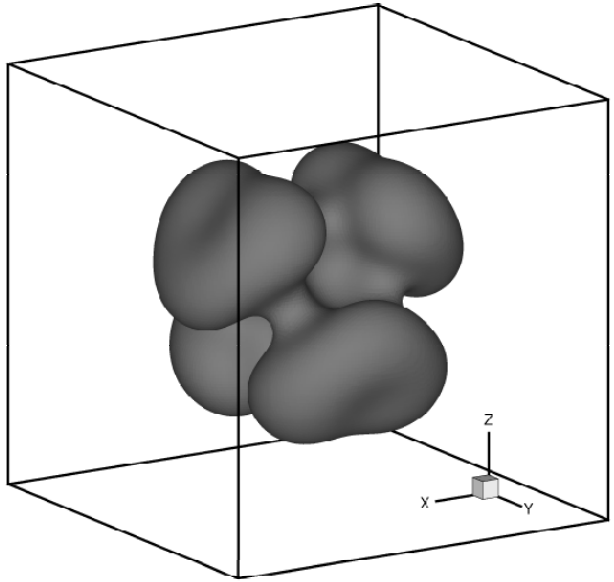
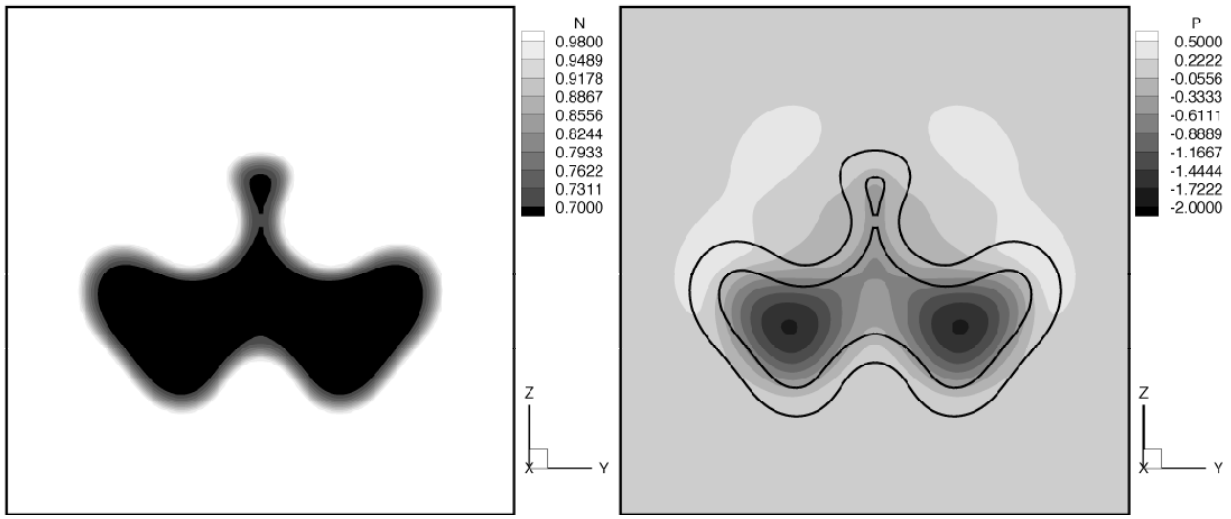
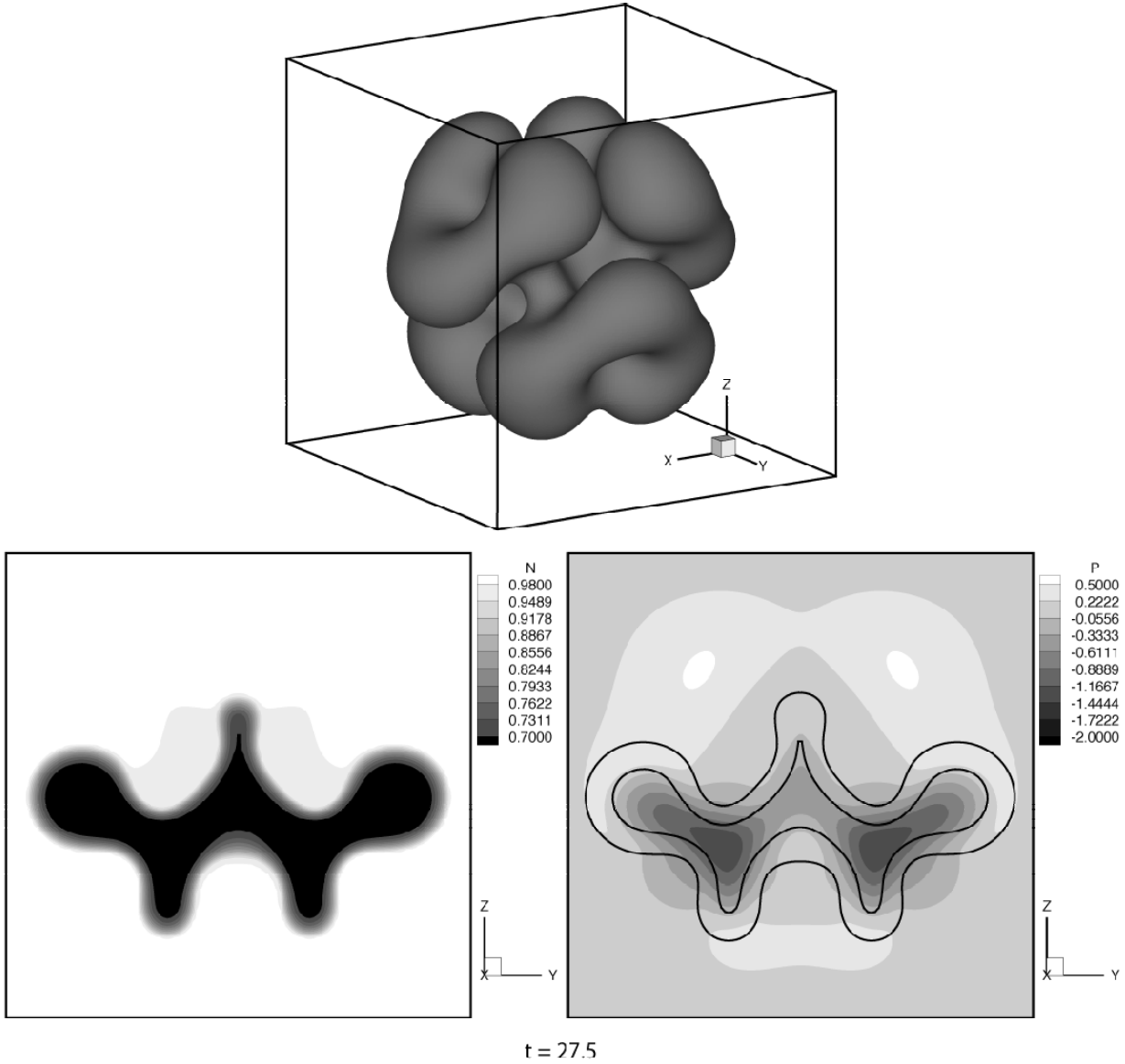
Y
P
0.5000
0.2222
-0.0556
-0.3333
-0.6111
-0.8889
-1.1667
-1.4444
-1.7222
-2.0000
Z
X
Y

t = 12.5


Z
X
Y


N
0.9800
0.9489
0.9178
0.8867
0.8556
0.8244
0.7933
0.7622
0.7311
0.7000
Z
X
Y
P
0.5000
0.2222
-0.0556
-0.3333
-0.6111
-0.8889
-1.1667
-1.4444
-1.7222
-2.0000
Z
X
Y

t = 20

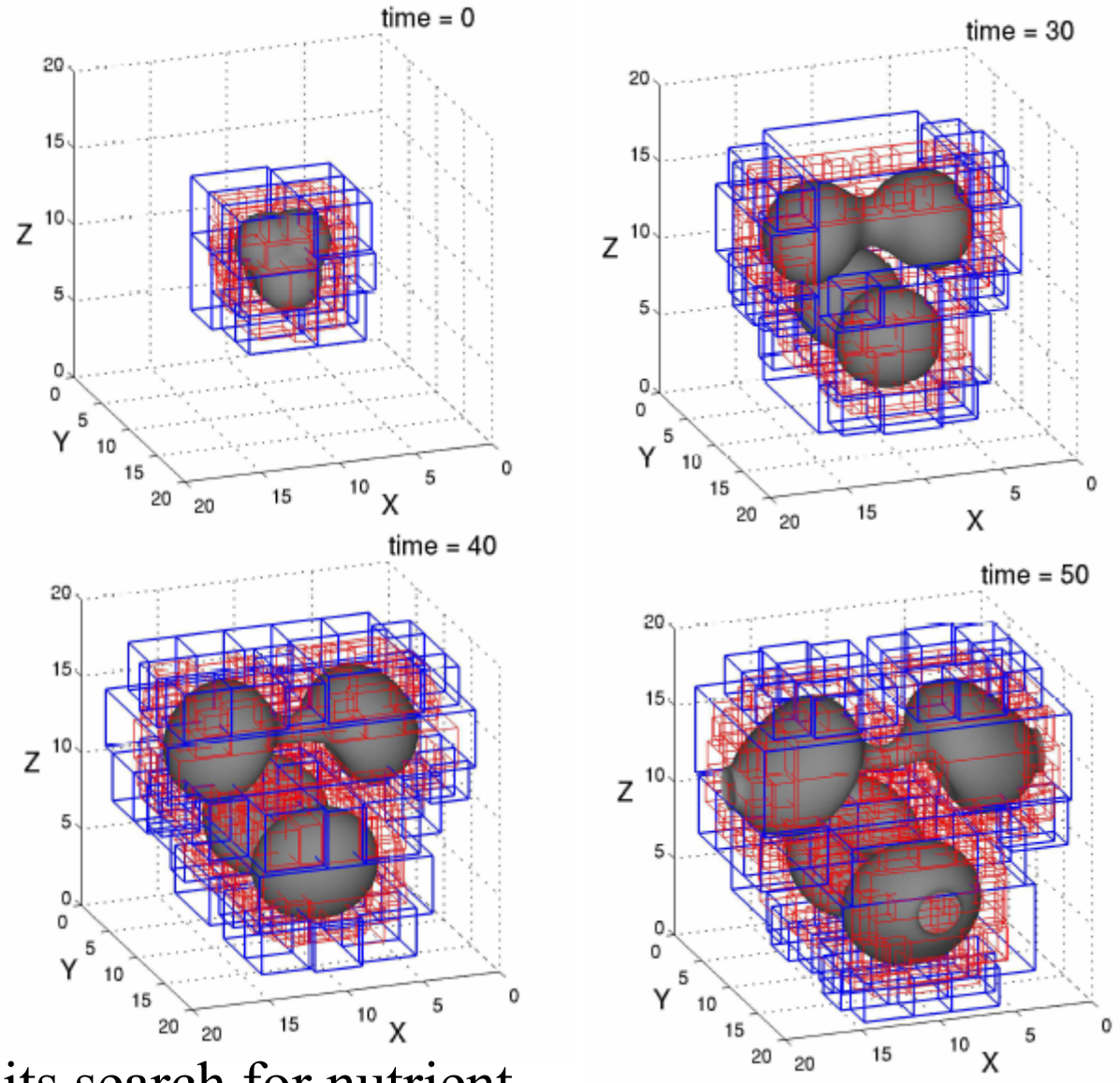


- Tumor develops folds to increase access to nutrient

Large nutrient gradients

$\chi_D = \chi_\mu = 1$

- Large nutrient gradients in host



- Tumor breaks up in its search for nutrient

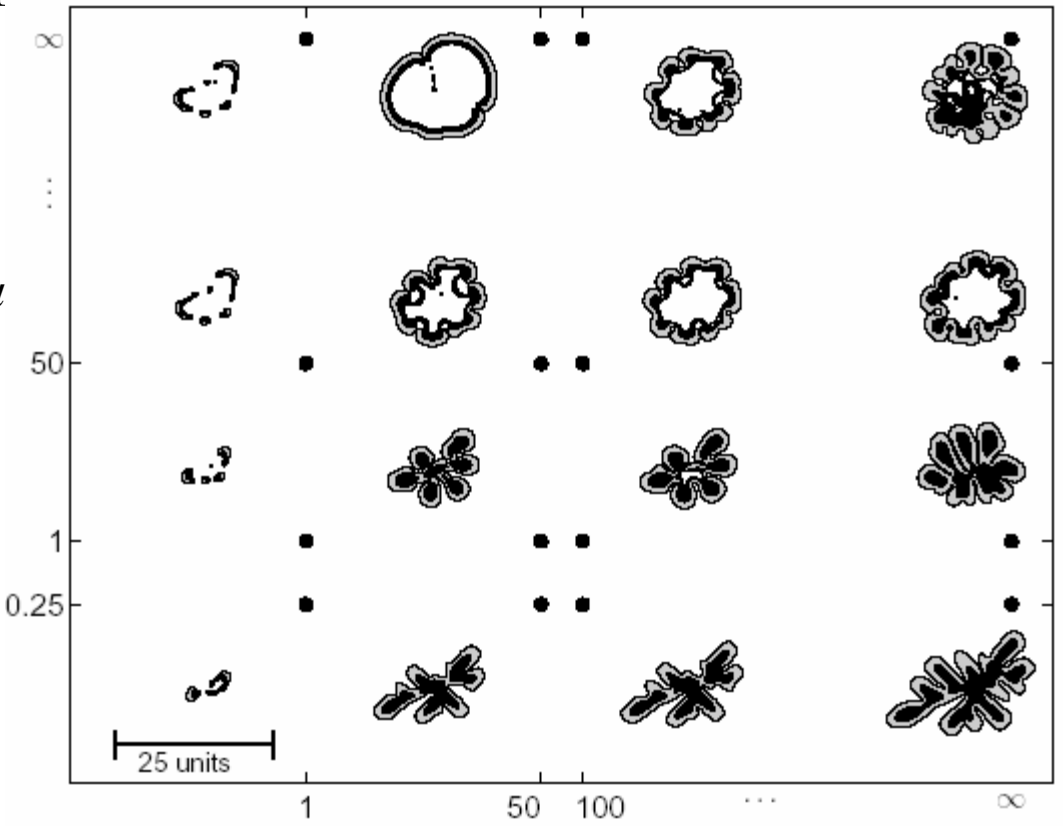
Morphology diagram

Macklin, Lowengrub JTB, in press

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

$N=0.35$

Effect of microenvironment



χ_μ

Increased tissue resistance

(decreased mobility)

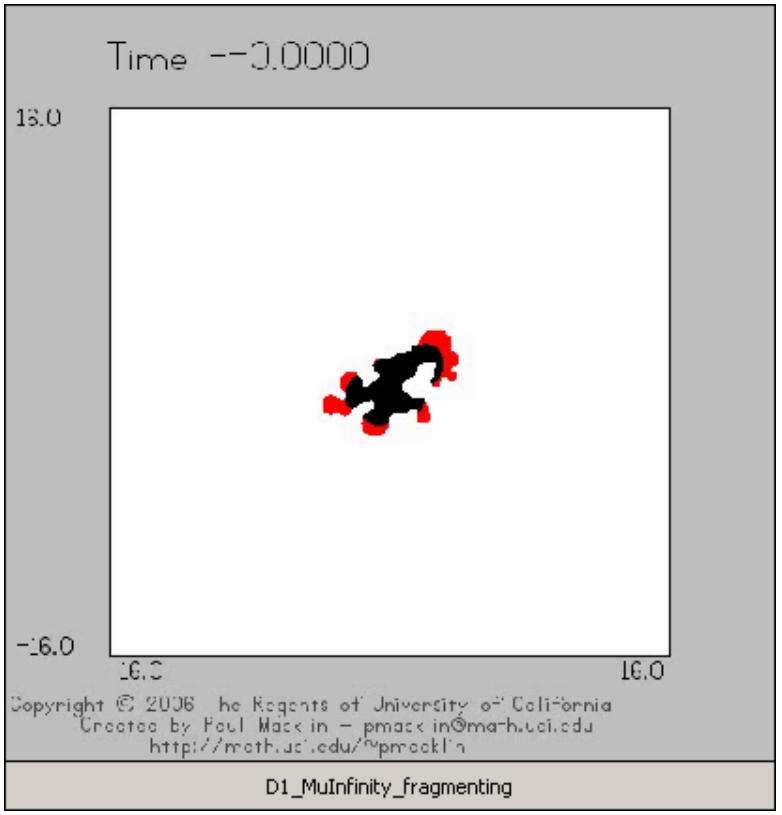
χ_D

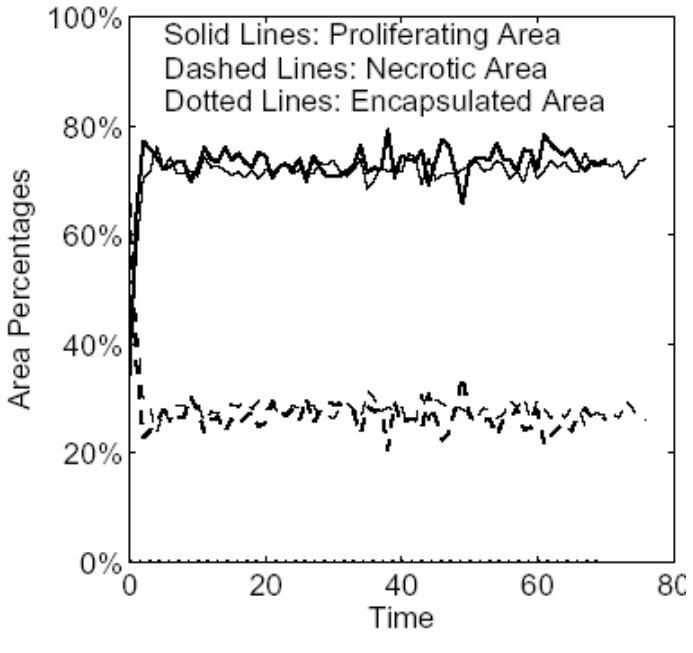
Higher degree of perfusion

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

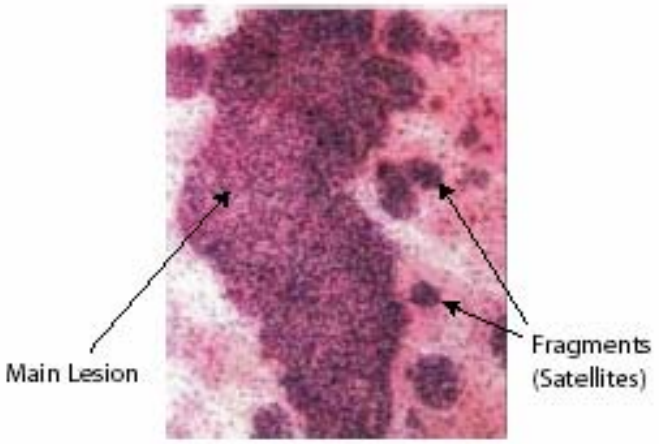
Fragmented

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





- Hypoxia leads to cluster invasion
  i.e., inhomogeneous nutrient distribution, imperfect vasculature
- Strong metastatic potential
- Implications for antiangiogenic therapy
  Combine with anti-invasive therapy

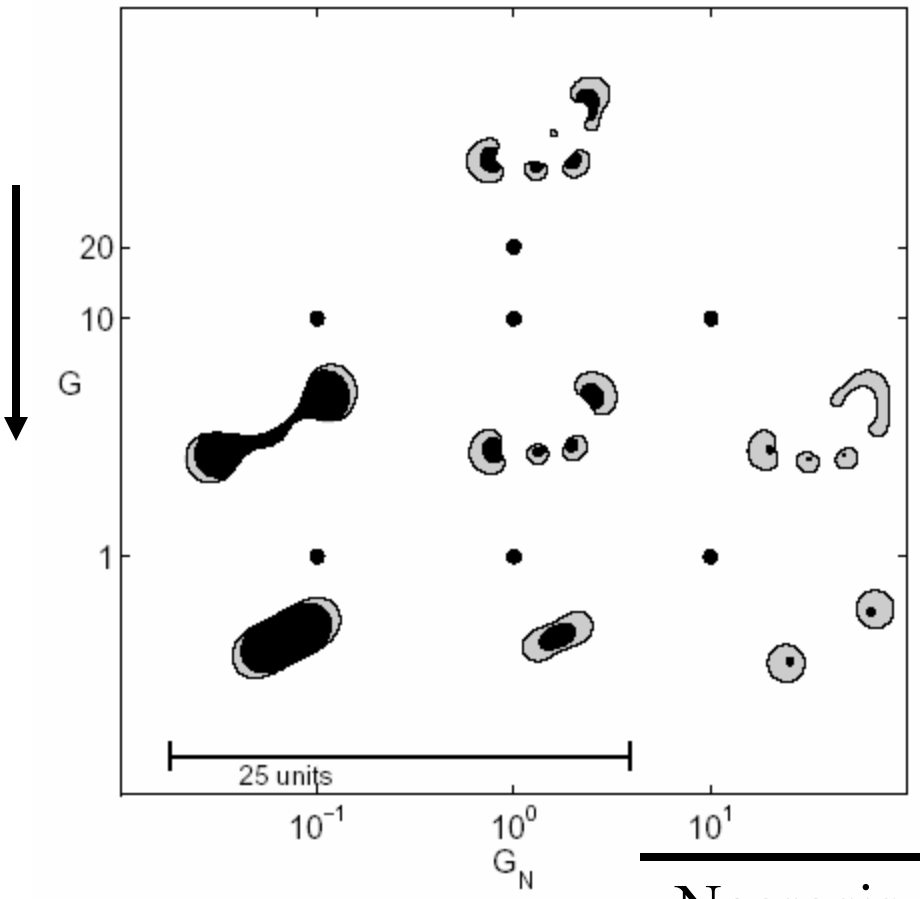


G55 human glioblastoma tumors in vivo becoming invasive after anti-angiogenic therapy
Rubinstein et al. Neoplasia (2000)

Effect of Cell-based Parameters

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

adhesiveness



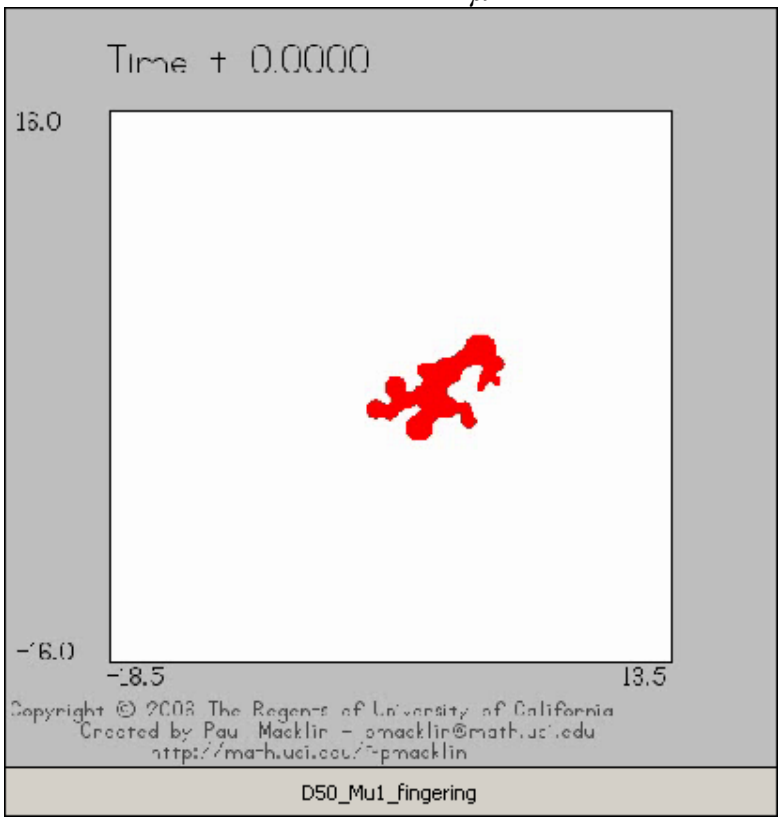
Necrosis (degradation)

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

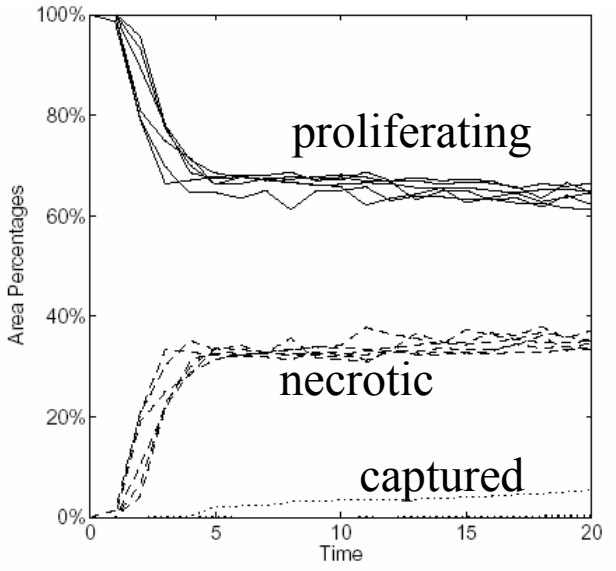
- Behavior qualitatively similar

Invasive fingering

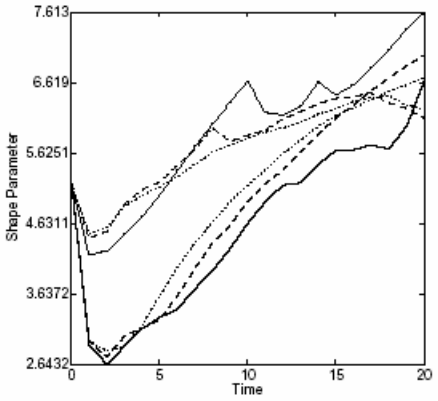
$\chi_D = 50, \quad \chi_\mu = 1$



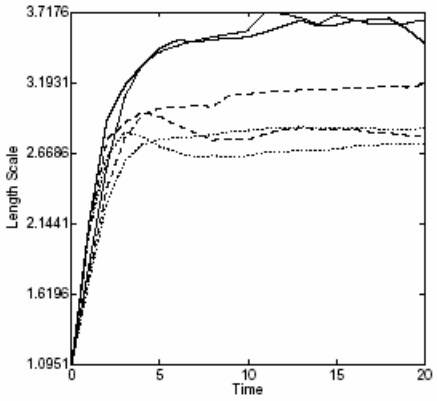
Area ratios



Shape parameter



Length scale

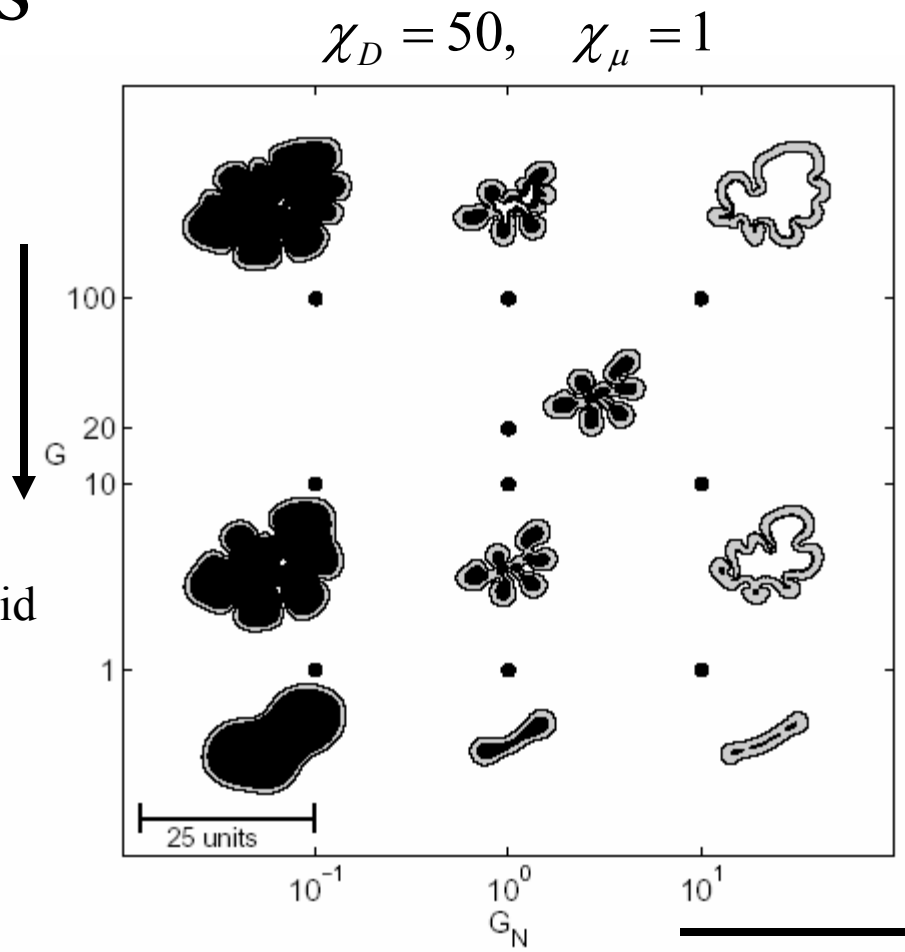


- Growth into lower mobility regions results in larger invasive tumors
- Implication for therapy (decrease adhesion)

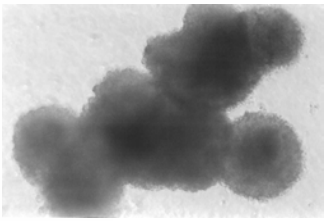
Thick: $\chi_\mu = 1$

Thin: $\chi_\mu = 0.25$

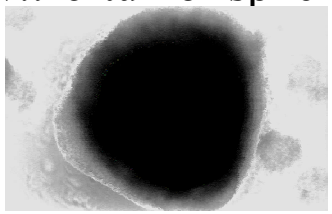
Dependence on cell-based parameters



spheroid

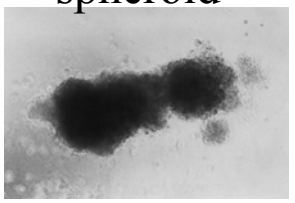


In vitro tumor spheroid



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

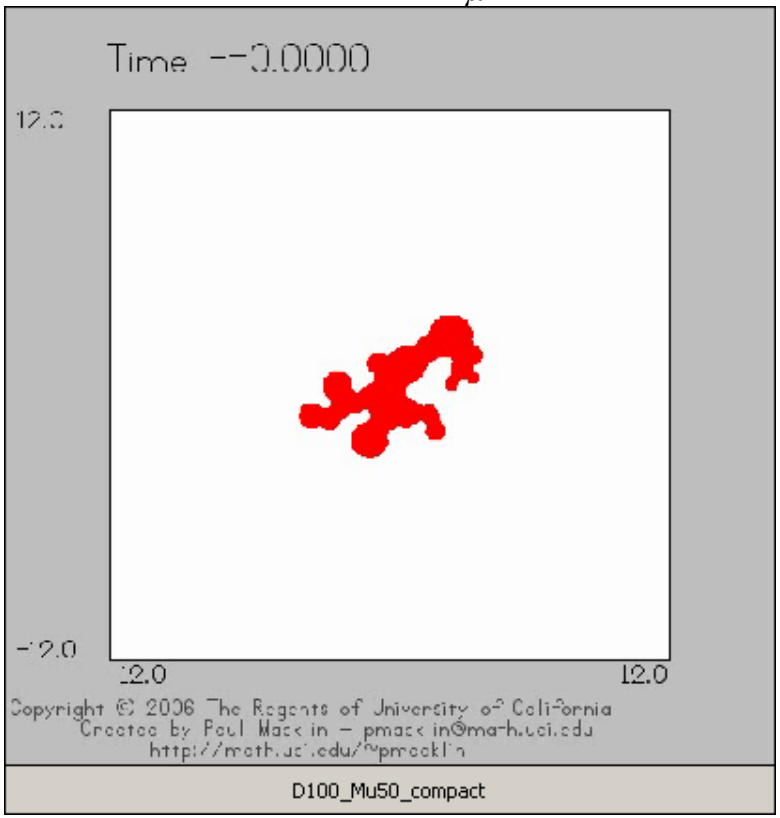
spheroid



- Increasing G or G_N enhances instability
- Increasing G_N decreases necrotic core
- May cause transition from fingering to compact, hollow (1D-like)

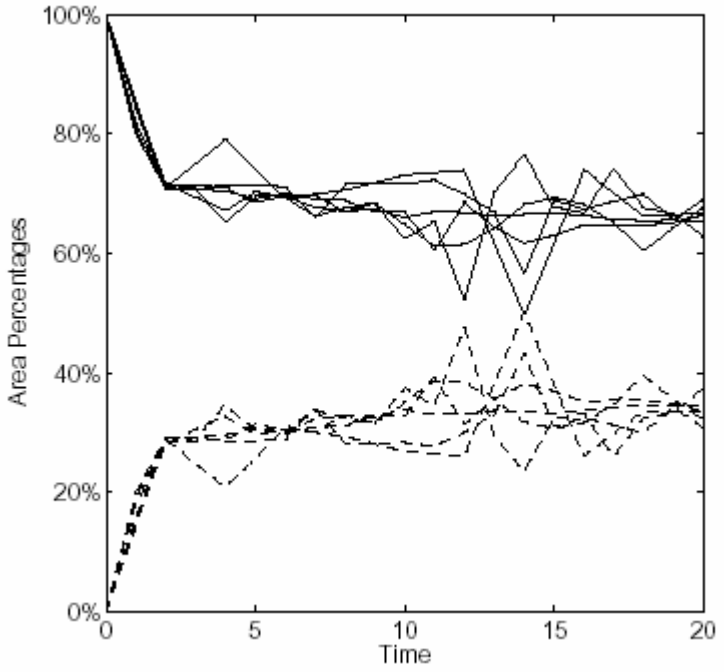
Hollow/Necrotic Growth

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

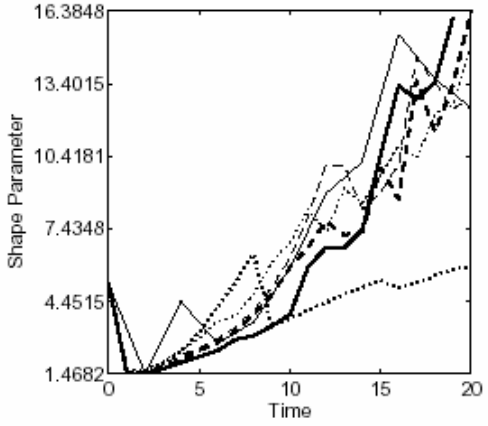


- Repeated capture and coalescence leads to hollow/necrotic structure

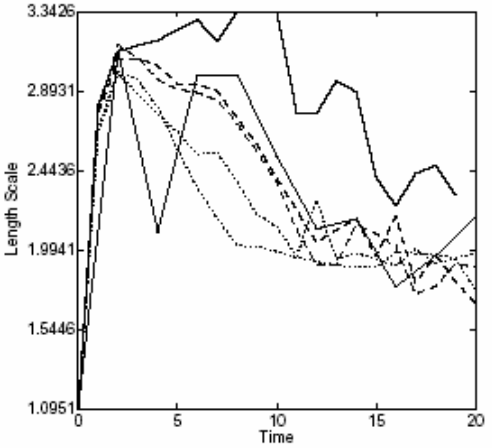
Area ratios



shape parameter



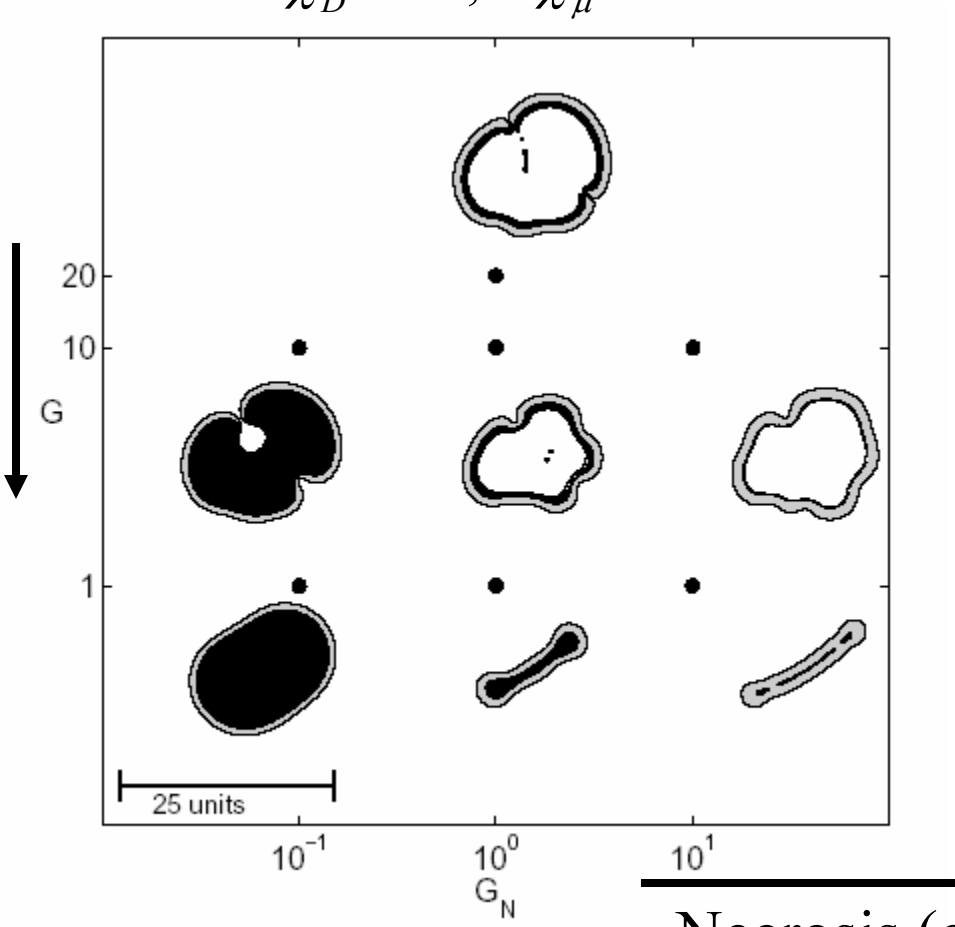
length scale



Dependence on cell-based parameters

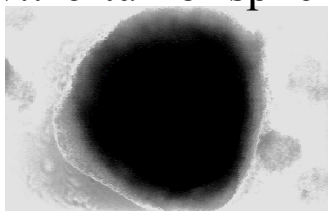
$\chi_D = 50, \quad \chi_\mu = \infty$

adhesiveness



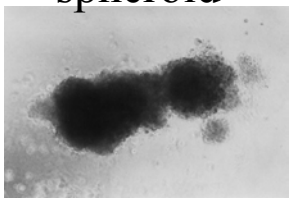
Necrosis (degradation)

In vitro tumor spheroid



Frieboes et al, Cancer Res (2006).

spheroid



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

Invasion Summary

- Microenvironment is a primary determinant for tumor growth and morphology

  (fragmented, invasive fingering, hollow/necrotic)

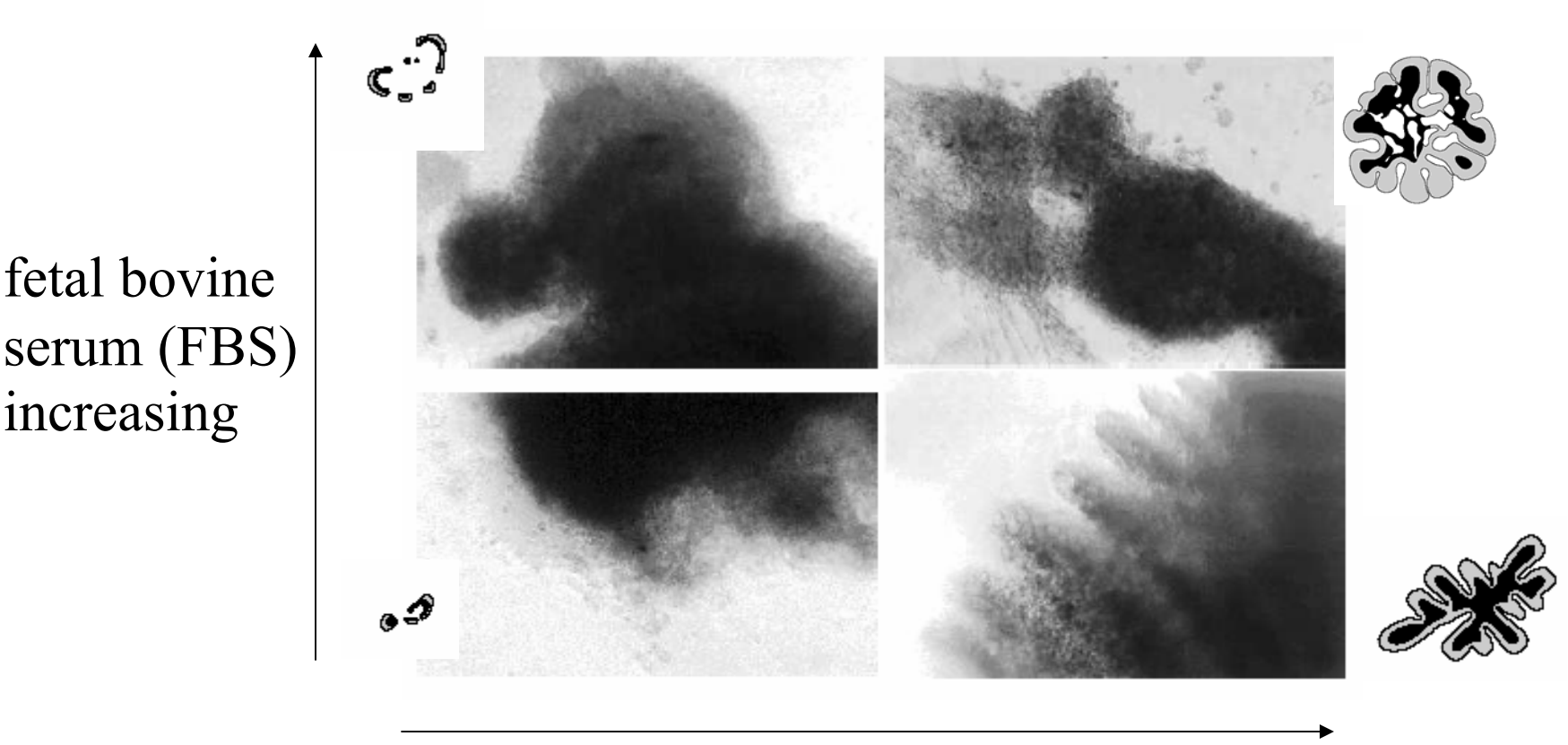
- Internal structure (e.g. size of necrotic, proliferating regions) determined by cell-based parameters

- Implications for therapy

- Experimental evidence for this behavior?

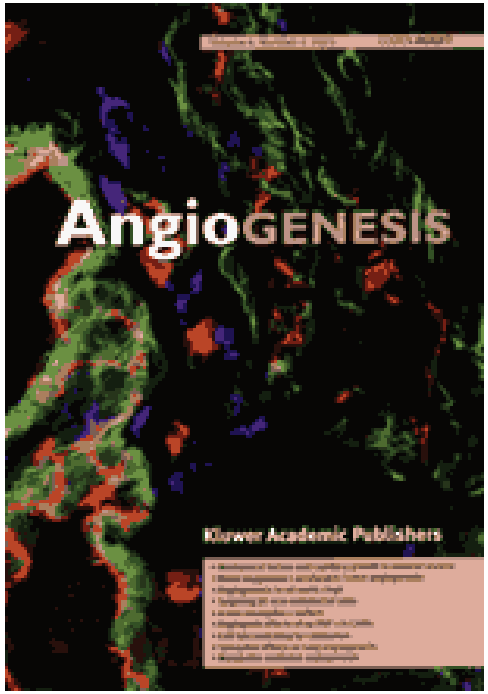
Comparison with experiment

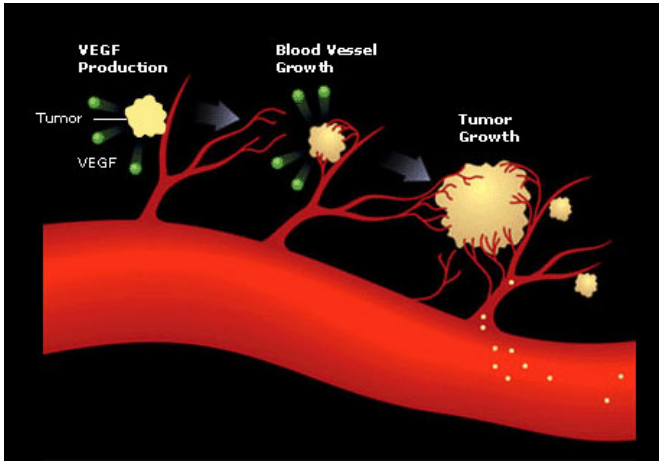
Frieboes et al., Cancer Res. (2006).

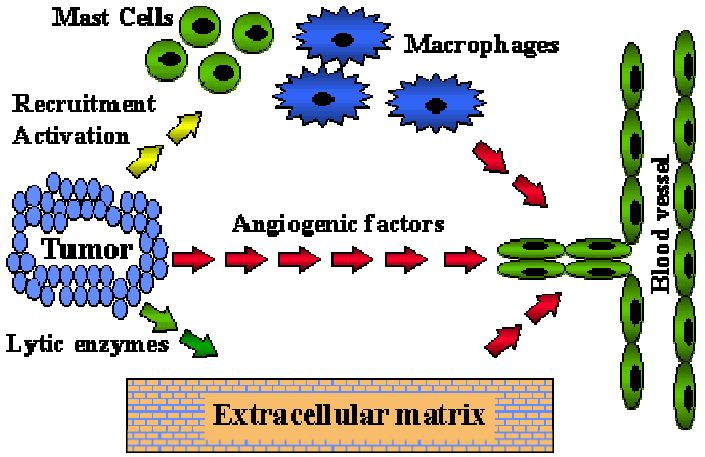


- Model is qualitatively consistent with experimental results

Angiogenesis







Angiogenic factors:

VEGF (Vascular Endothelial cell Growth Factor)

FGF (Fibroblast Growth Factor)

Angiogenin

TGF (Transforming Growth Factor),….

Mathematical model

Anderson, Chaplain, McDougall, Levine, Sleeman, Zheng,Wise,Cristini,

Tumor Angiogenic Factor: c

Tumor angiogenic factor (e.g., VEGF-A): potent mitogen, drives motion

Decay

Uptake by the endothelial cells

$$0 = D_C \nabla^2 c - \beta_D c - \beta_U c e + S_c(\rho_T, \rho_D) c$$

Endothelial Cell (localized) density

production

Cell receptor ligand f (e.g., Fibronectin) in the ECM. Regulates cell adhesion and motion

Matrix degradation by vascular endothelial cells

$$\frac{\partial f}{\partial t} = \eta_P e - \eta_U f e - \eta_N \chi_{\Omega_N} f,$$

production degradation

Gradient-based, biased circular random walk

Othmer, Stevens; Planck-Sleeman

Idea: track the capillary tip. Use the trace to describe the vessel. Not lattice-based.

- Endothelial cell travels with speed *s* with direction given by the polar and azimuthal angles
- Endothelial cells tend to move up the gradients of c and *f* (chemotaxis, haptotaxis)
- Reinforced random walk for angles. Master equation:

$$p(\theta, t+\Delta t) - p(\theta, t) = \hat{\tau}^+(\theta-\delta, t)\cdot p(\theta-\delta, t) + \hat{\tau}^-(\theta+\delta, t)\cdot p(\theta+\delta, t) - (\hat{\tau}^+(\theta, t) + \hat{\tau}^-(\theta, t))\cdot p(\theta, t). \quad ($$

Prob. Density function

Transition rate (gradient approach from Othmer-Stevens)

Model contd.

•Branching: Tip is allowed to split with a certain probability. (always takes 60 degree angle, from Exps).

•Anastomosis: If vessels are close, they may merge with a certain probability. If merged vessels are from different roots (i.e. pressure drop across) then may release nutrient (simple model of blood flow)

Nonlinear coupling with tumor:

- •Release of TAF by tumor cells affects EC motion
- •Source of nutrient from neovasculature affects tumor evolution via mitosis

(in reality is much more complicated but this is a start)

Simulation of Tumor-Induced Angiogenesis

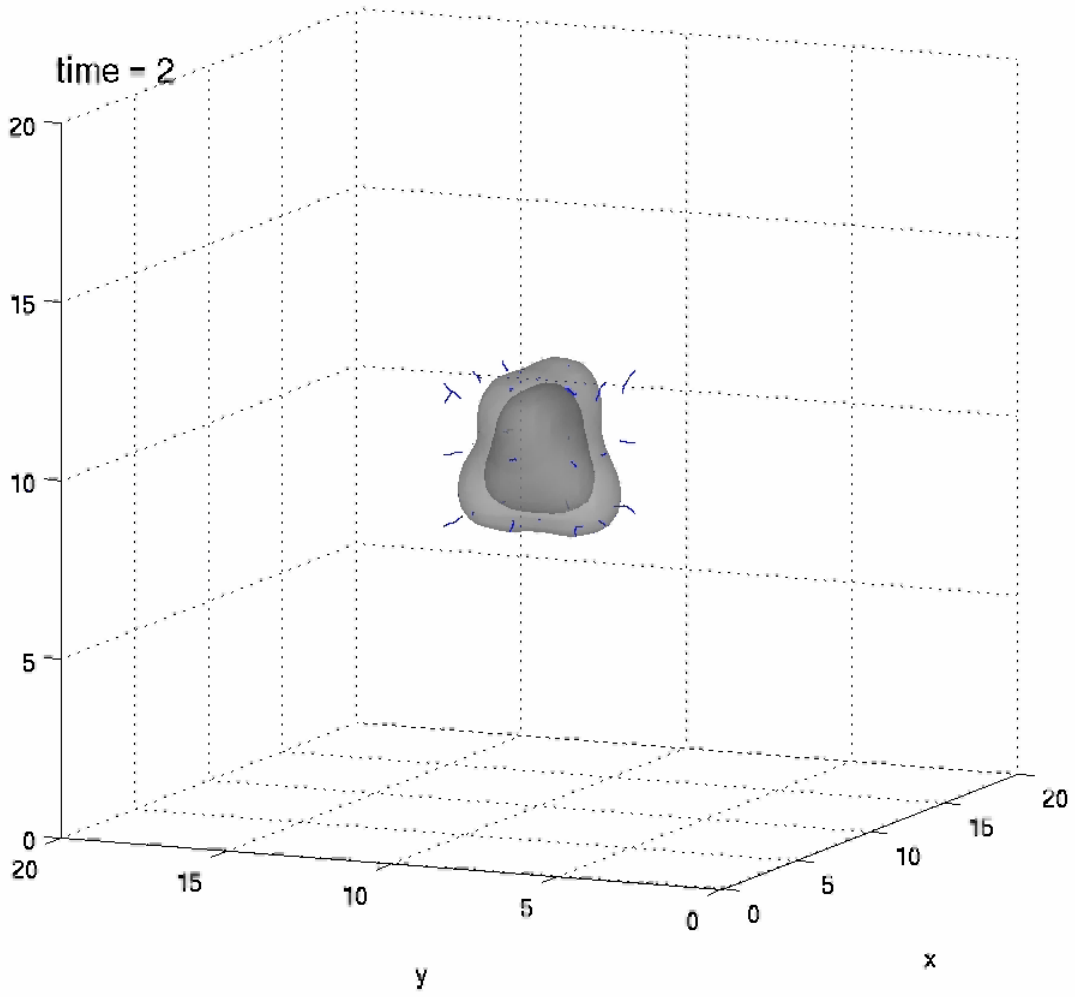
Parameters appropriate for glioblastoma

Wise, Lowengrub, Frieboes, Zheng, Cristini, Bull. Math. Biol, in review

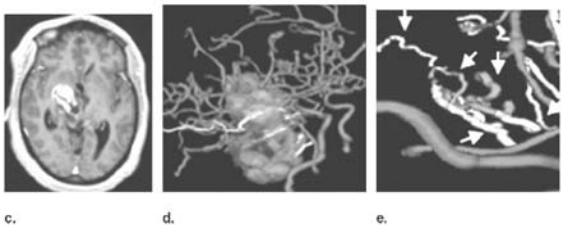
Frieboes, Lowengrub, Wise, Zheng, , Cristini, Neuroimage (in press)

Vascular cooption

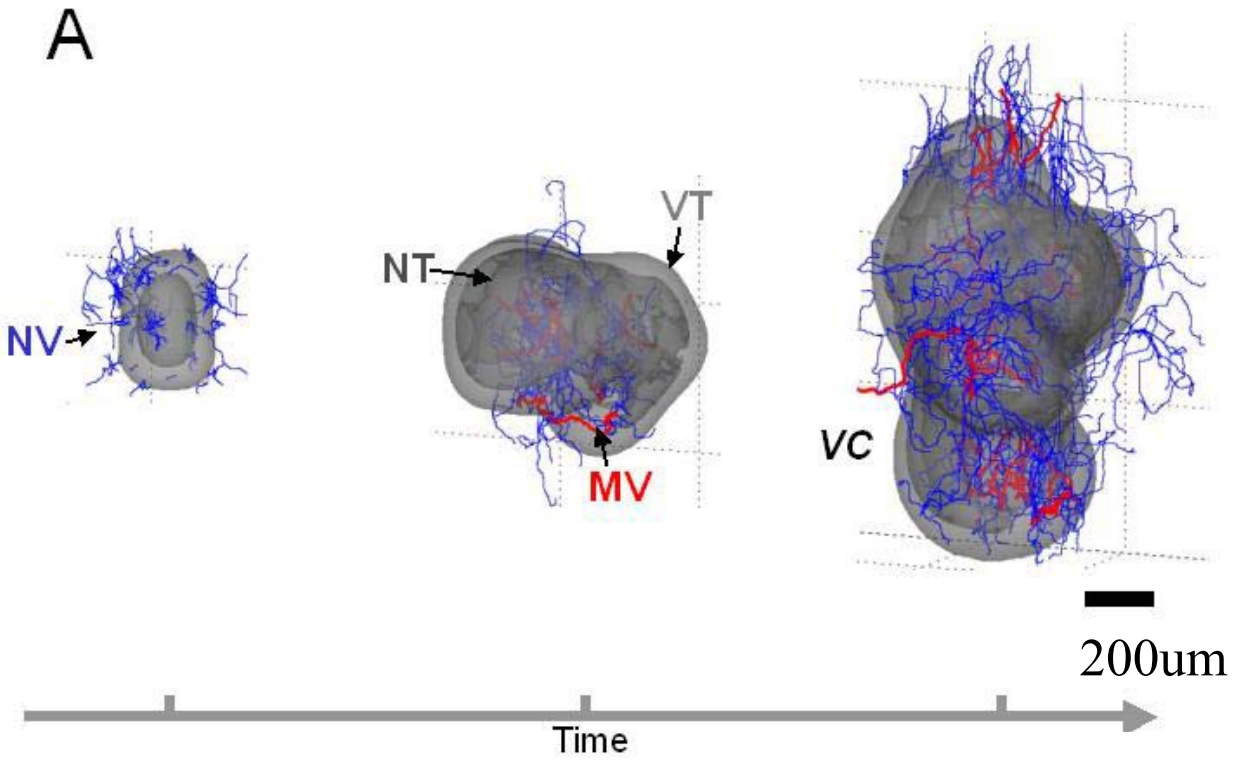
- Initial capillaries present
- Growing tumor surrounds vessels
- Uses up available vasculature
- Secondary angiogenesis
- Observe bursts of growth as the nutrient supply increases (cyclical bouts of angiogenesis)

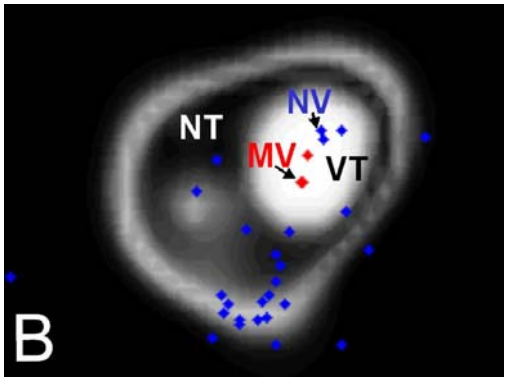


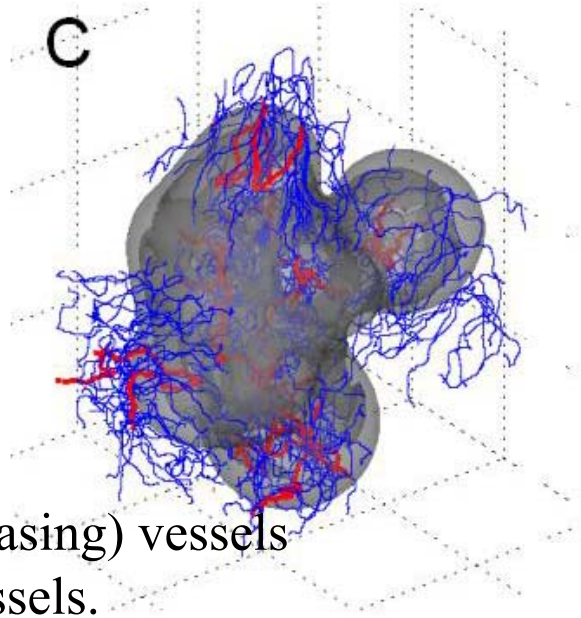
Bullitt et al (2005). Glioma



Progression

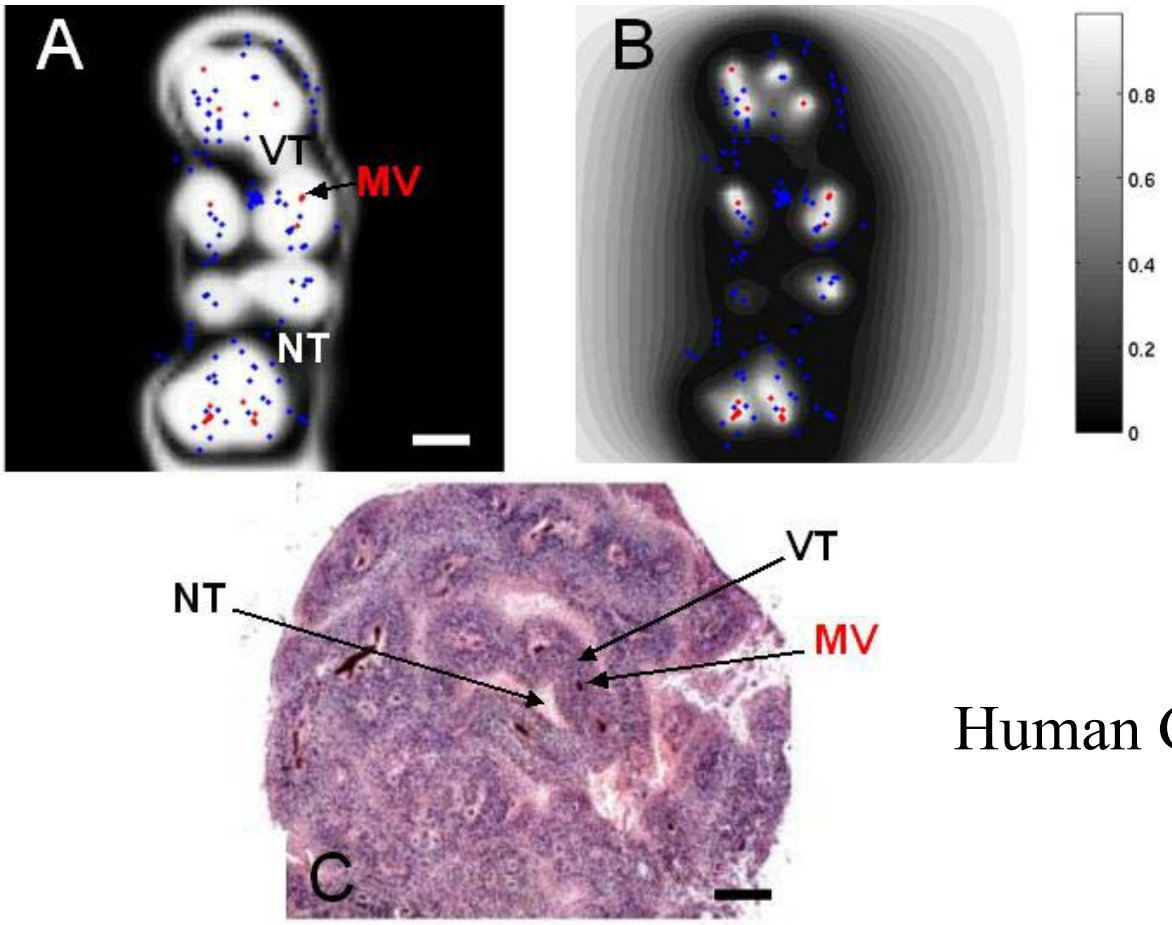






- Note nutrient supply localized near red (nutrient-releasing) vessels
- Observe corresponding viable tumor cells around vessels.

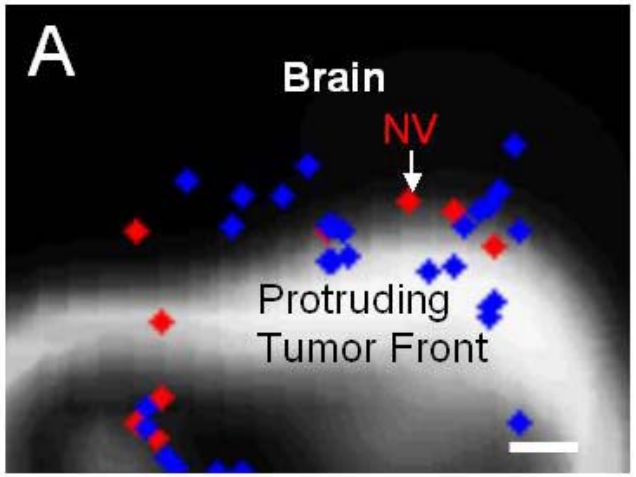
Simulation

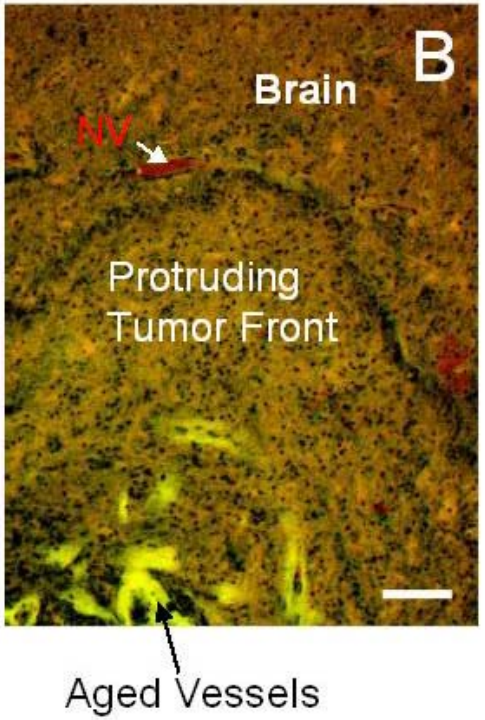


Human Glioma

- Tumor architecture is *determined* by cellular metabolism and intra-tumoral diffusion nutrient gradients of required nutrients provided by the vasculature,
- Confirms the presence of substrate gradients and the parameter estimates for diffusion length used in the simulations Bar, 200 um.

simulation

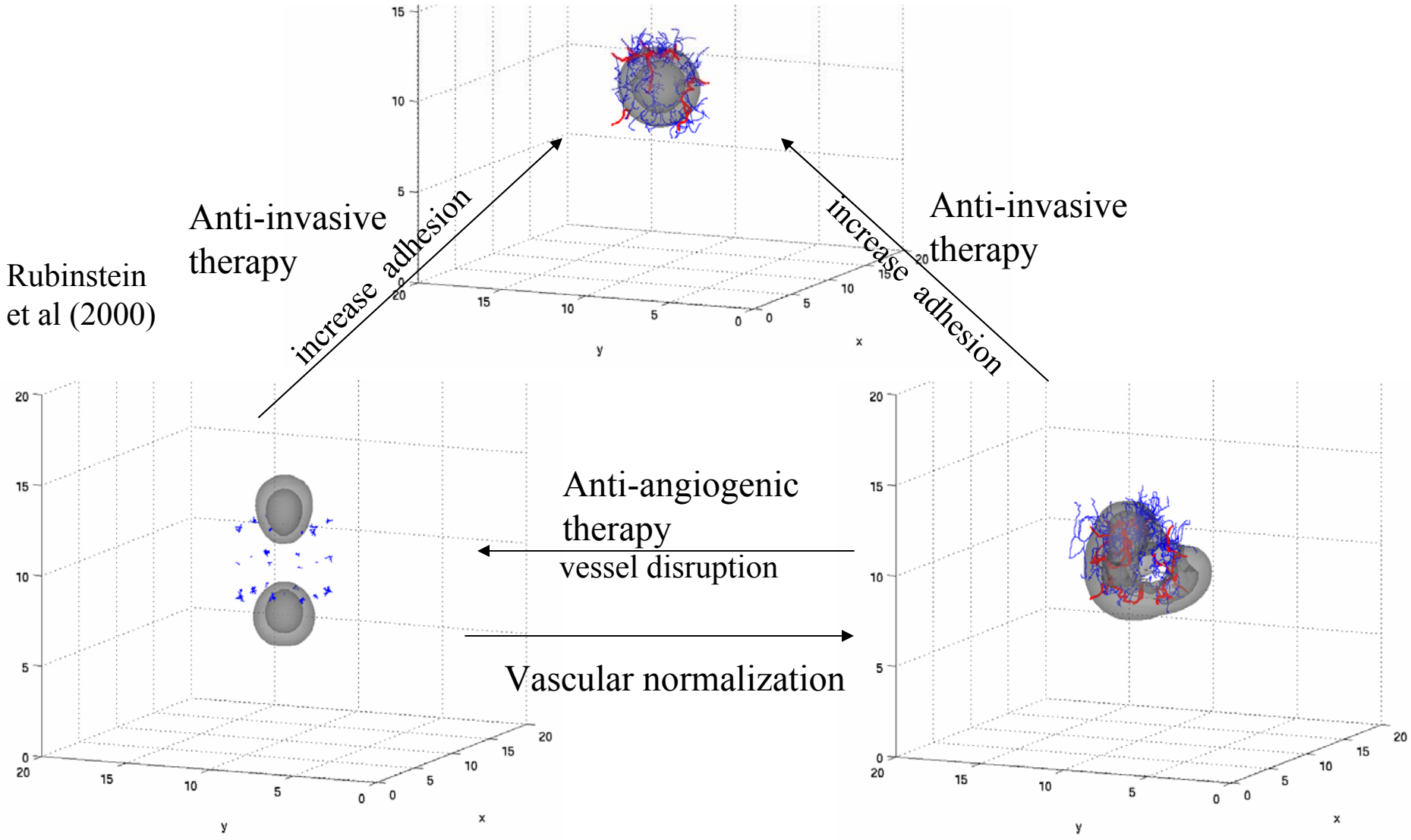




Human glioma

•Multiscale model predicts that tumor tissue invasion is driven by diffusion gradients. Bar: 100um

Implications for therapy



2D: Cristini, et al., Cancer Res. (2006)

Next Steps

- More complex/realistic biophysics
  - Improved invasion models
  - Improved Angiogenesis models
  - Integrative models– match parameters with experiments. Collaboration with Bullitt (Angiogenesis) Gatenby (Invasion and Morphologic instability)
  - Hybrid continuous/discrete models
  - Finite, complex domains
  - More realistic mechanical response
- Even biophysically simplified modeling can provide insight though