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

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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

- Models and analysis of invasion

- Numerical methods and results

- Models of angiogenesis

- Nonlinear coupling of angiogenesis and invasion

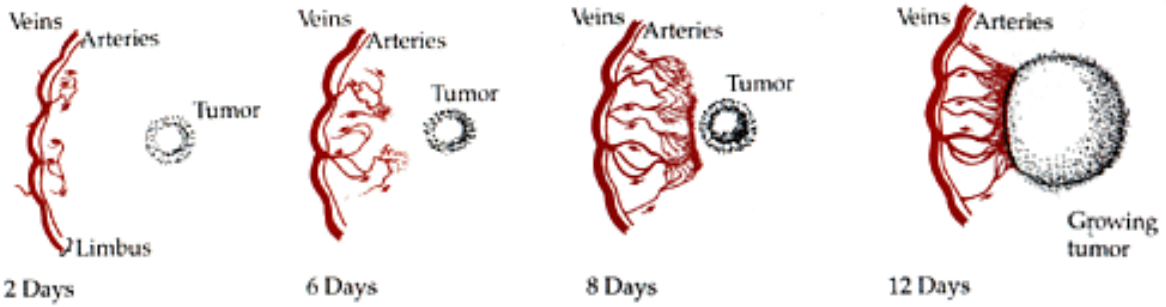
The Six Basic Capabilities of Cancer

(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



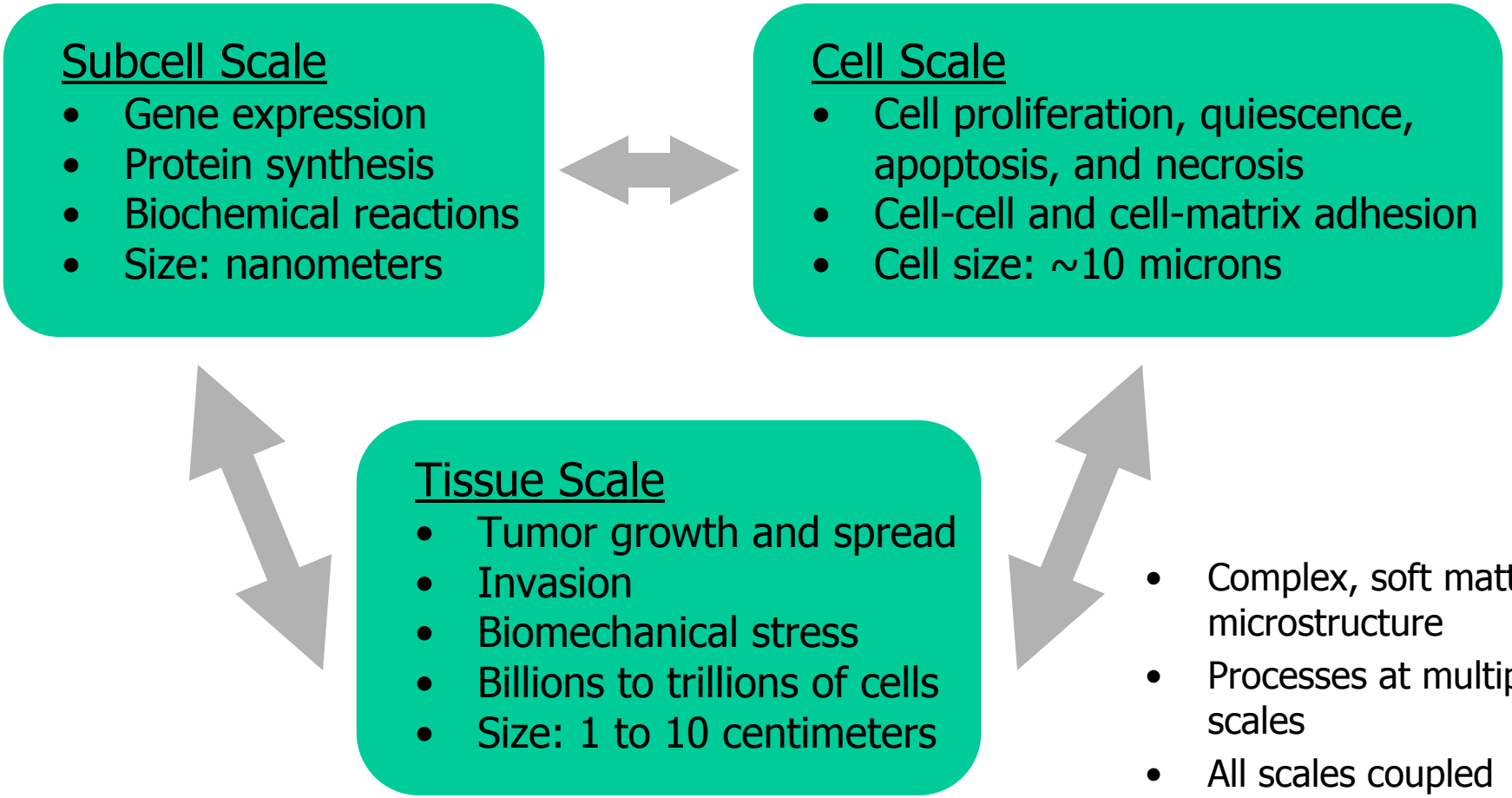
Avascular growth
Diffusion dominated

Angiogenesis

Vascular growth
invasive
metastasis
malignancy

•Goal: Model all Phases of growth

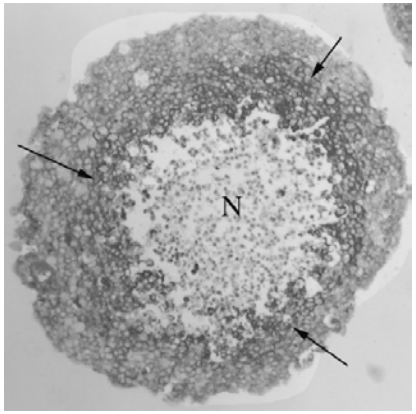
Cancer: Multiscale Problem

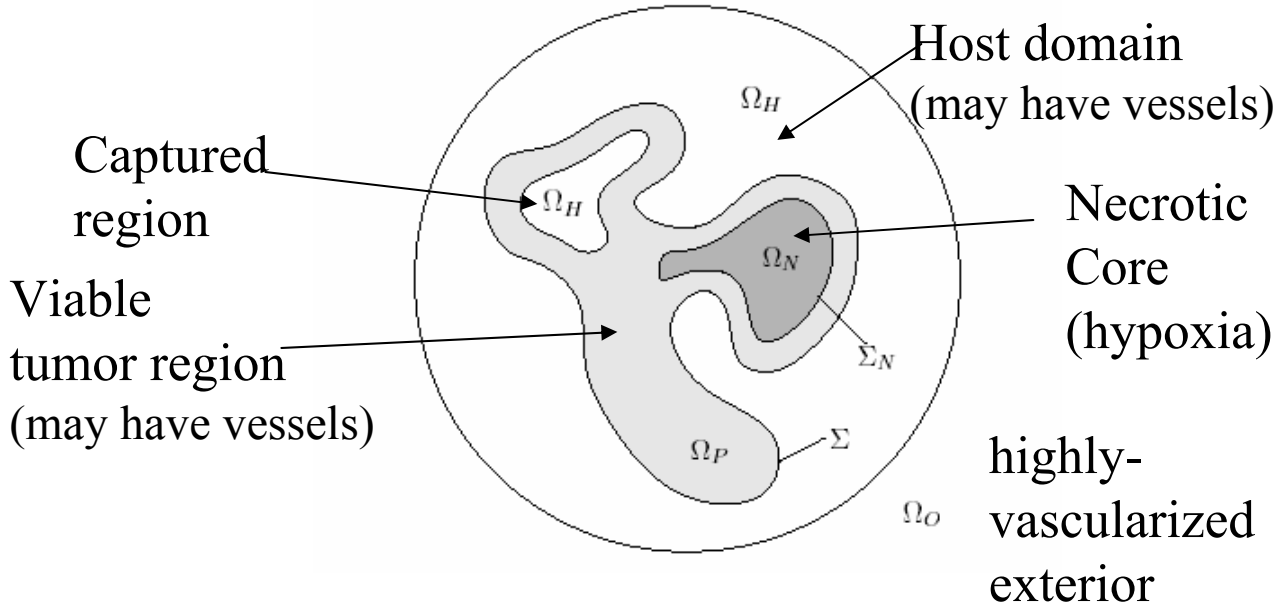


Recent Reviews: Bellomo-Preziosi (2003), Araujo-McElwain (2004), Byrne et al (2006)

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.

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

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

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

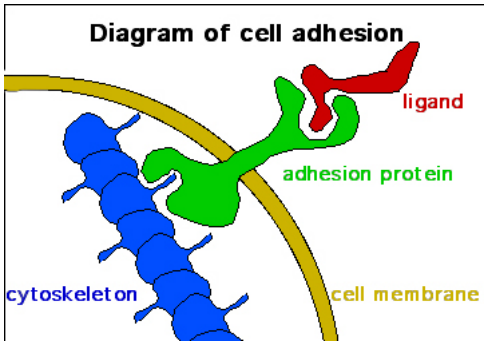
$$\frac{\partial \rho_{\mathrm{W}}}{\partial t} + \nabla \cdot (\mathbf{u}_{\mathrm{W}} \rho_{\mathrm{W}}) = S_W,$$

$\mathbf{J}$ -- Adhesion fluxes

S – Net sources/sinks of mass

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

Adhesion

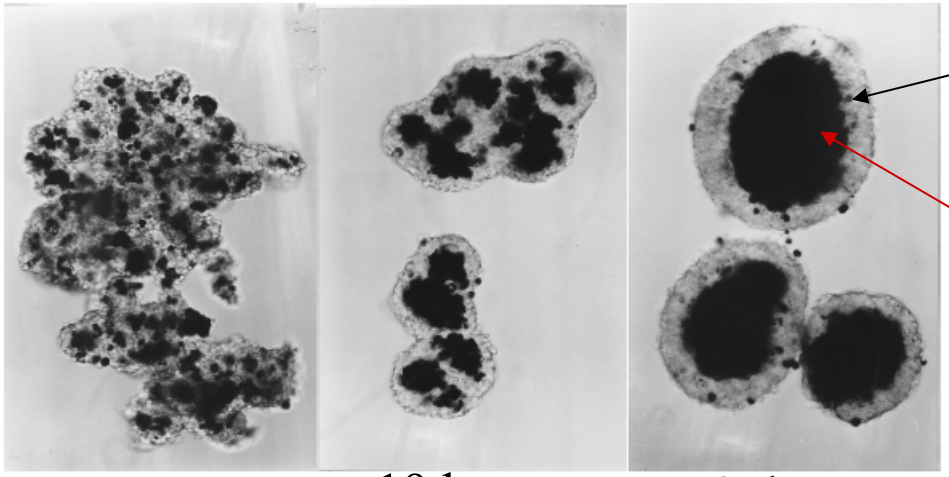


Fundamental biophysical mechanism.

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)

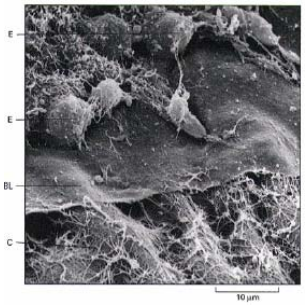
- Water density is constant: $\rho_{\mathrm{W}}(\mathbf{x}, t) = \bar{\rho}_1.$ ⟶ Water decouples
- Close-packing: $\rho_{\mathrm{T}} + \rho_{\mathrm{H}} = \bar{\rho}_0,$
- Cell-velocities are matched using Darcy's law:

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

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:

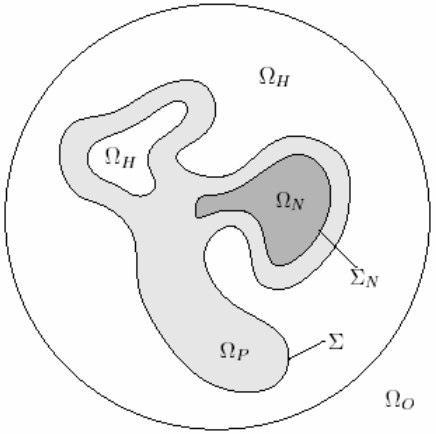
$$0 = \nabla \bullet \left(D\left(\rho_{\mathrm{T}}\right) \nabla n \right) + T_{\mathrm{C}}\left(n_{\mathrm{C}}, n, p, \delta_{C}\right) - \nu_{\mathrm{U}} n \rho_{\mathrm{V}}$$

=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

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

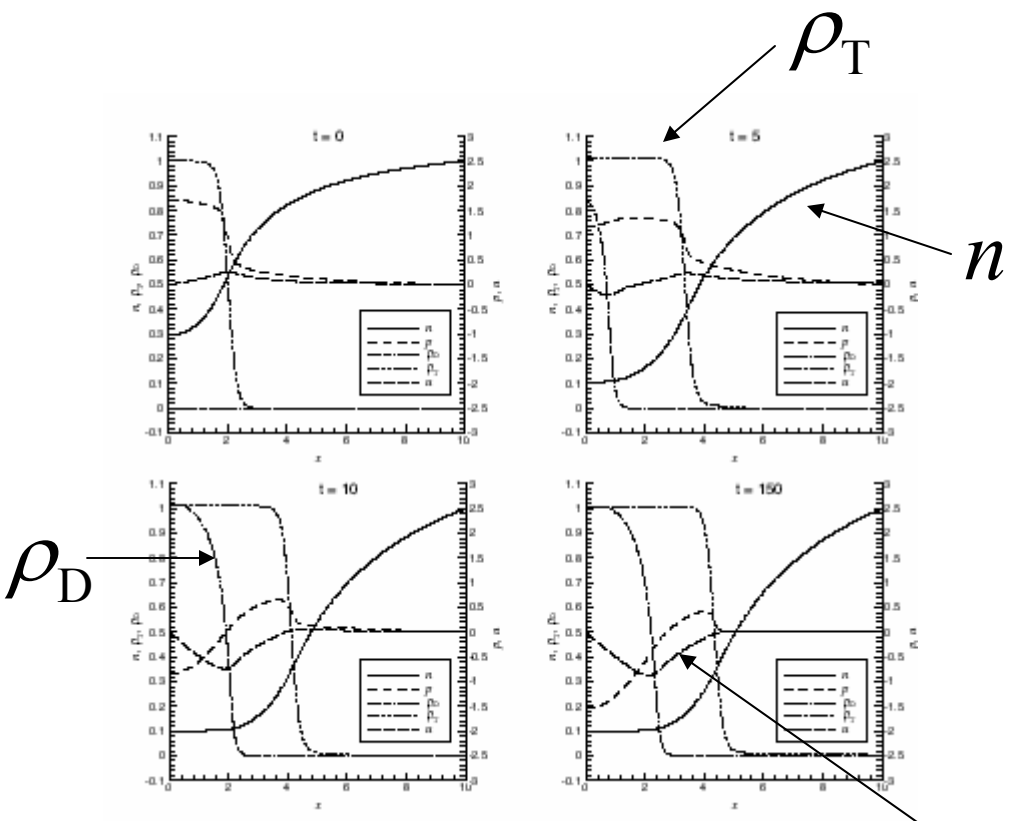
Microenvironmental:

- 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 $N = \frac{n_N}{n_\infty}$

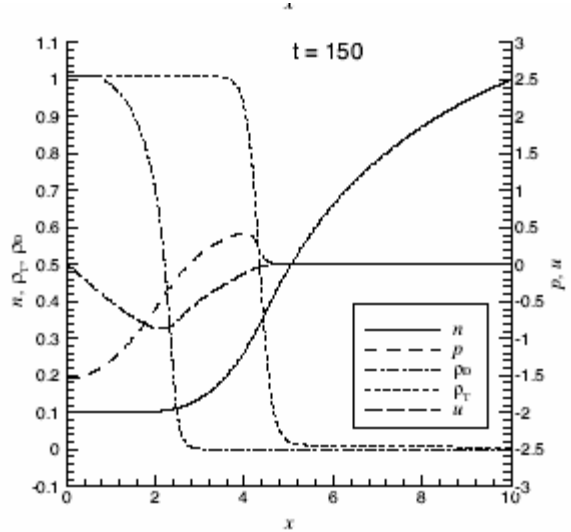
Spherical Solutions



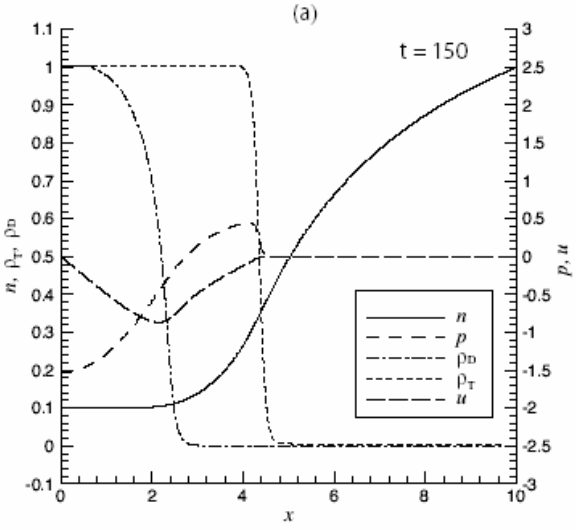
Growth to a steady spheroid

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

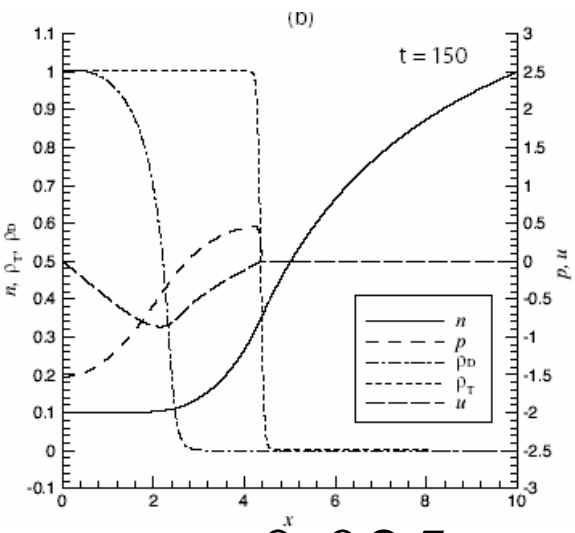
Convergence to sharp interface



$\varepsilon = 0.10$



$\varepsilon = 0.05$



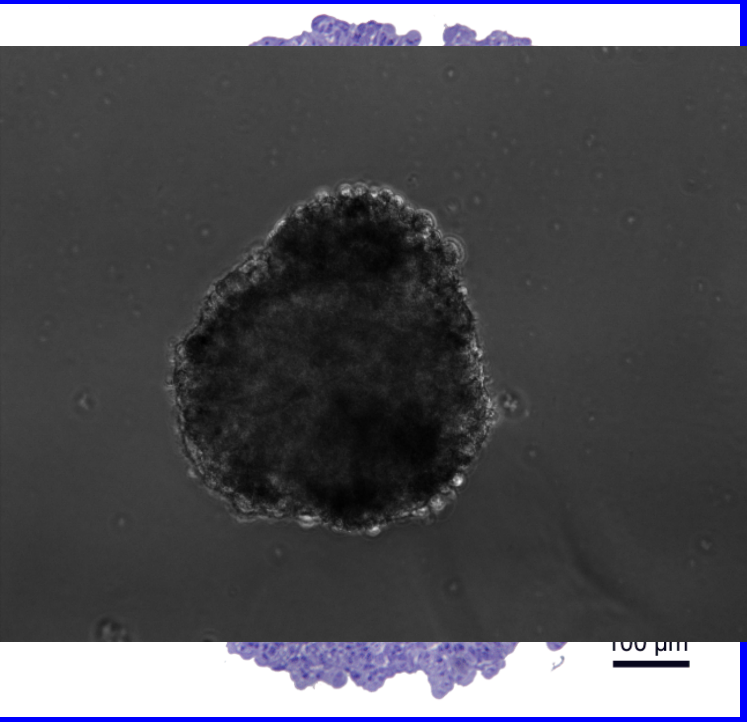
$\varepsilon = 0.025$

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

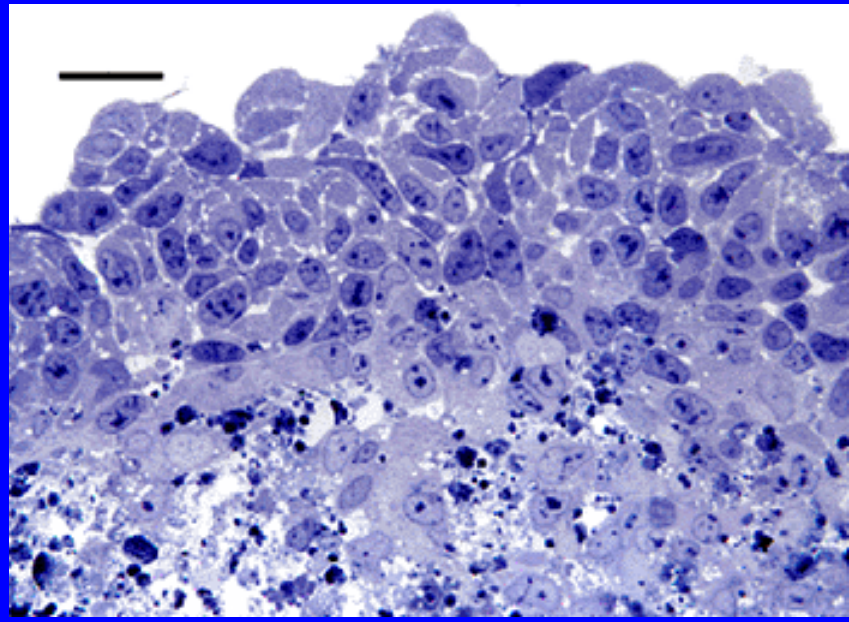
Tumor Spheroids: Validation *in vitro*

In vitro growth: No vascularization (diffusion-dominated)

Dormant (steady) states



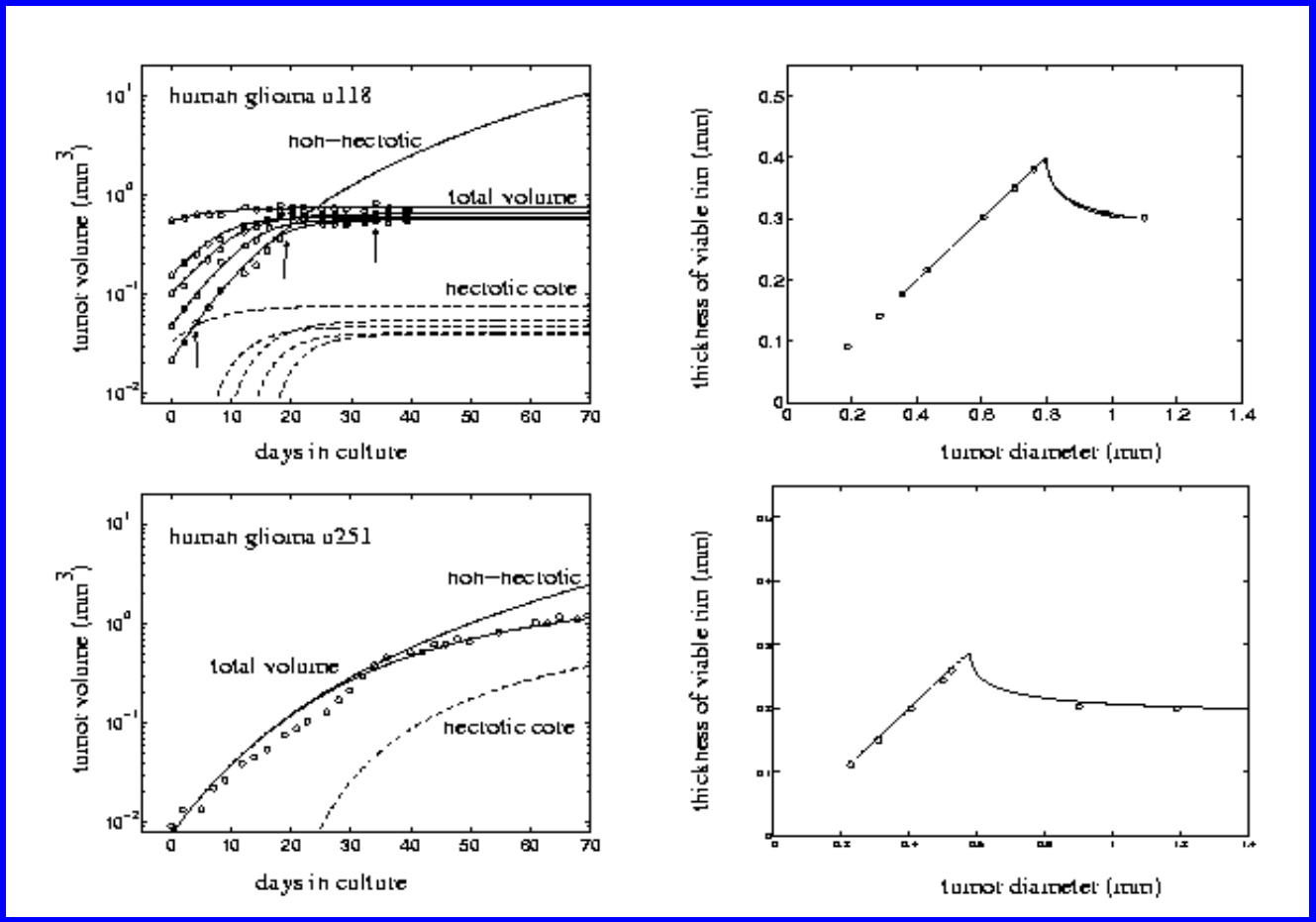
One micron section of tumor spheroid showing outer living shell of growing cells and inner core of necrosis.



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

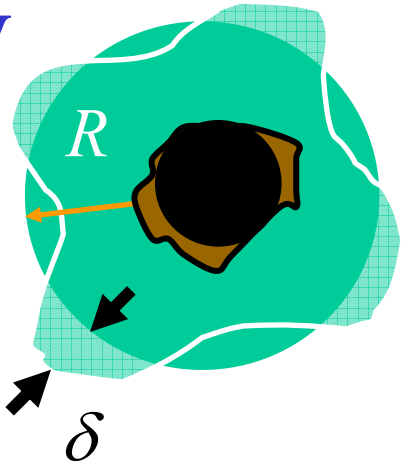
$\lambda_M \approx 0.3\ \text{day}^{-1}$ $D \approx 3\times10^{-3}\ \text{mm}^2/s$

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

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

Diffusional Instability--Avascular

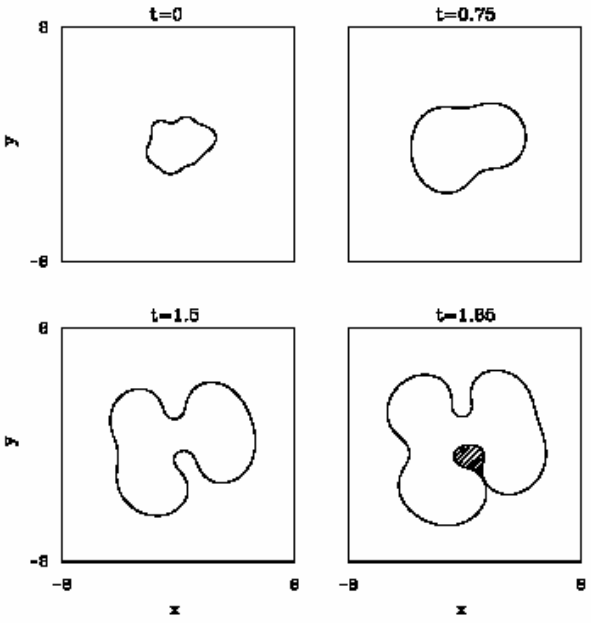
2D: Cristini, Lowengrub and Nie, J. Math. Biol. 46, 191-224, 2003

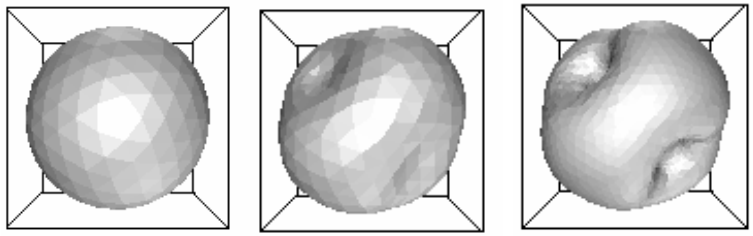
3D:, Li, Cristini, Nie and Lowengrub, DCDS-B, In review

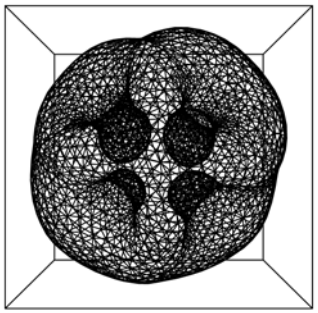
2D **Avascular** (tumor spheroid) 3D

(low cell-to-cell adhesion)

$G > G_{critical}$



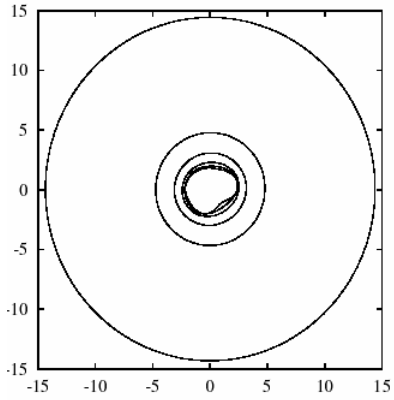




•Growth-by-bumps
ejection of cells from bulk

• topology change

Highly vascularized



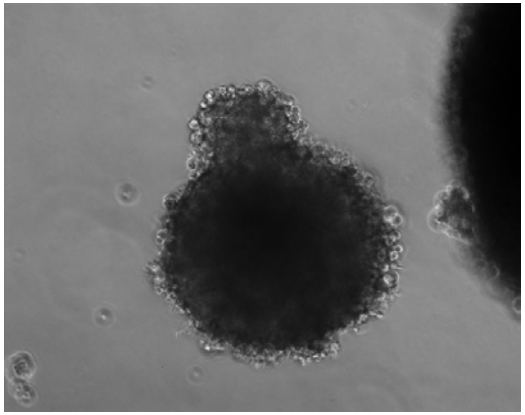
•Stable evolution

(isotropic vasculature)

Boundary integral method

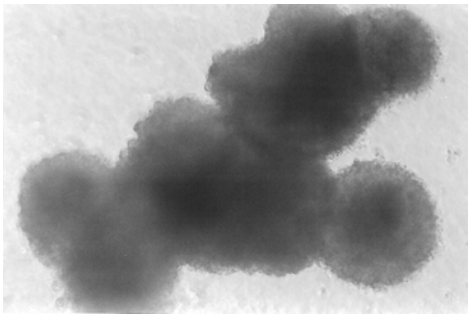
Diffusional Instability

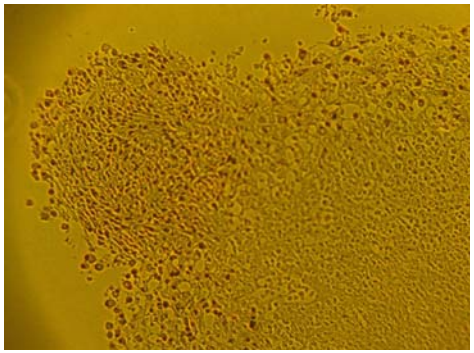
•Perturbed tumor spheroids/Complex Morphology



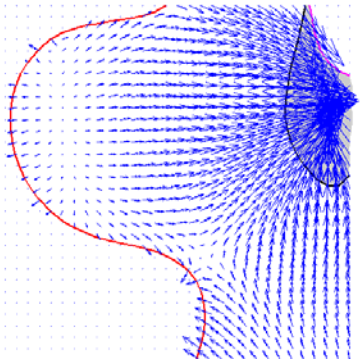
Frieboes, *et al.*

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.

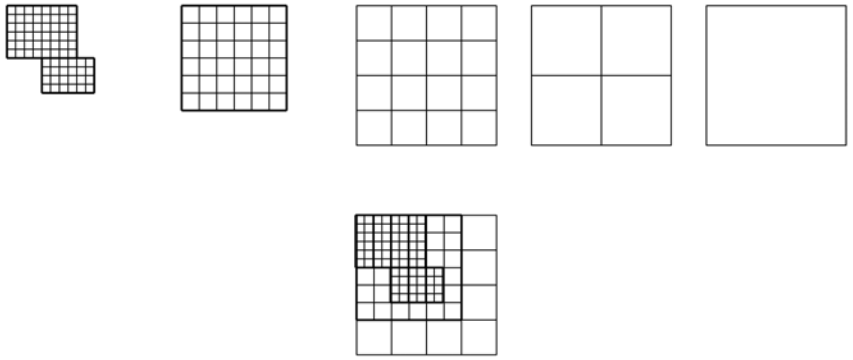
Nonlinear Simulations

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

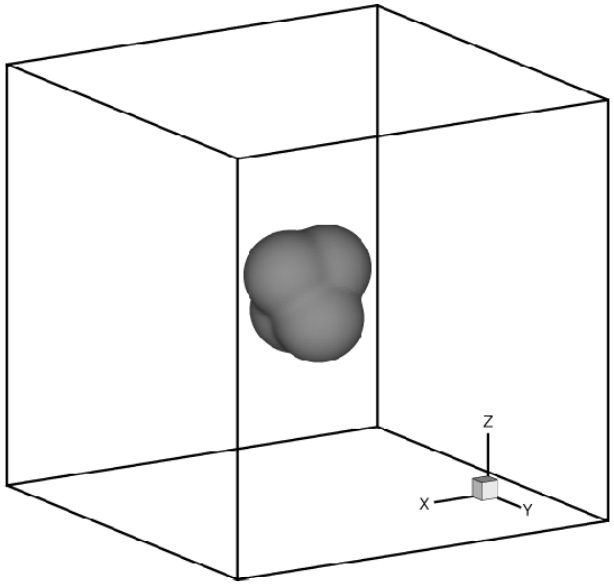
- Hard to analyze: quantify smoothing properties of the nonlinear relaxation scheme

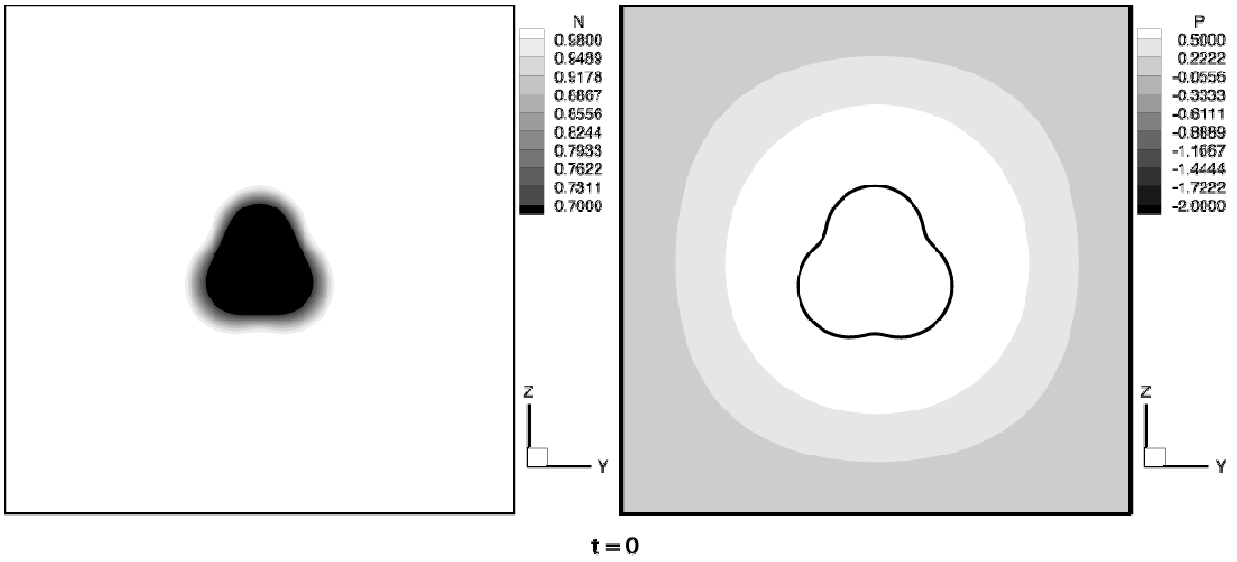
Well-perfused host domain

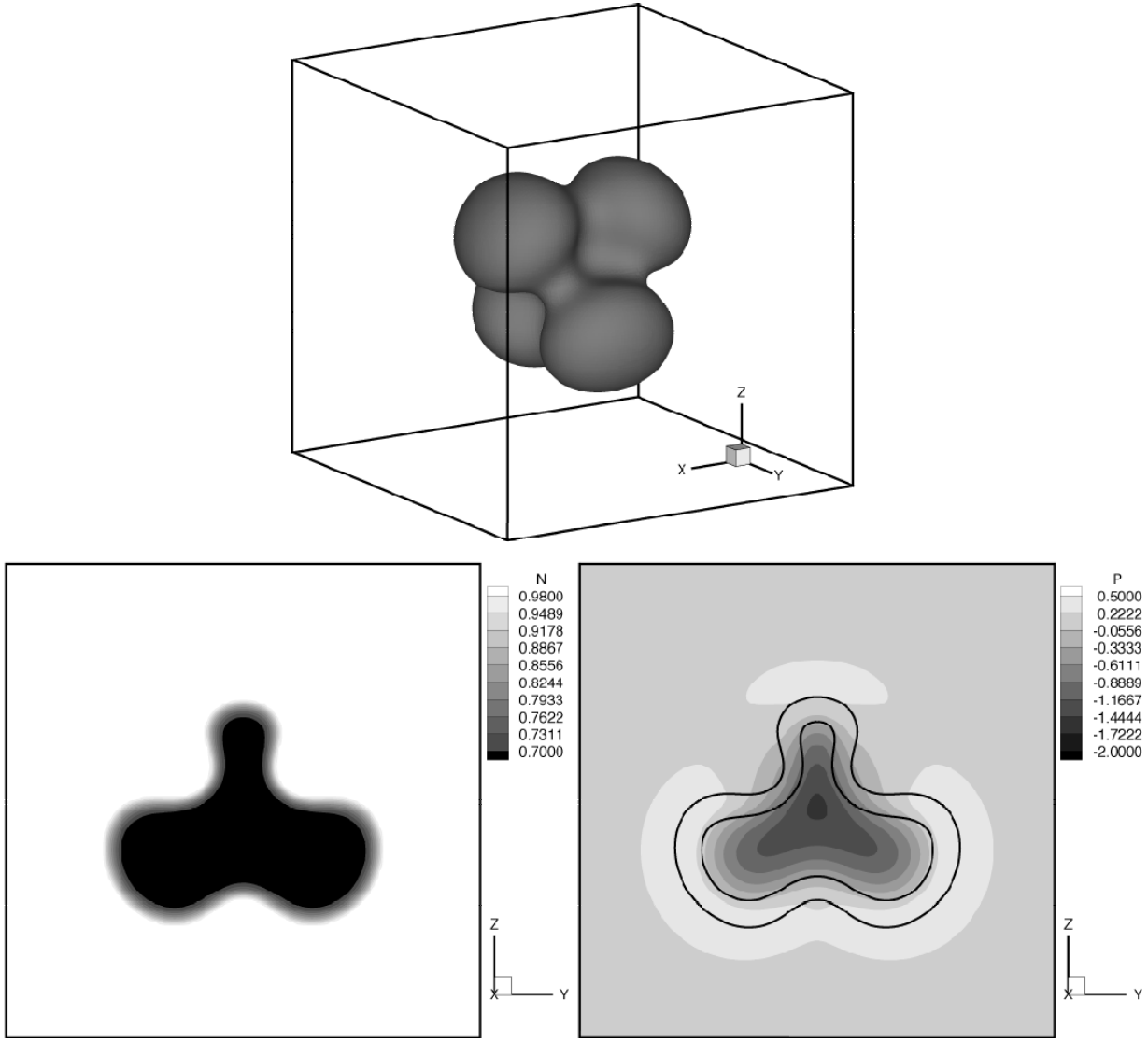
χ_D large

$\chi_\mu = 1$

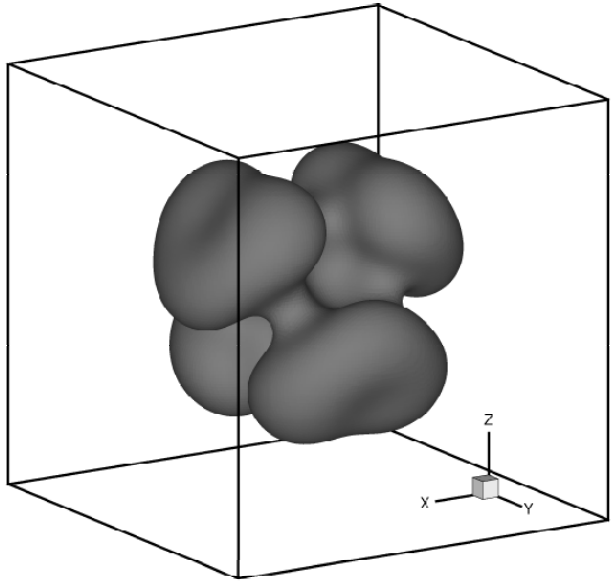
- Small nutrient gradients in host






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 = 12.5


Z
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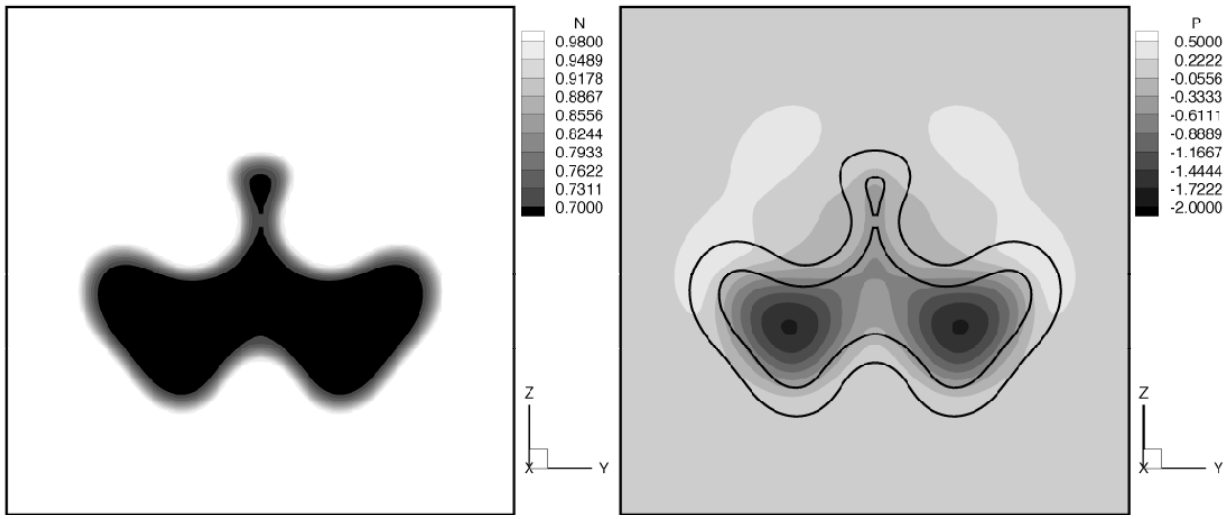
N
0.9800
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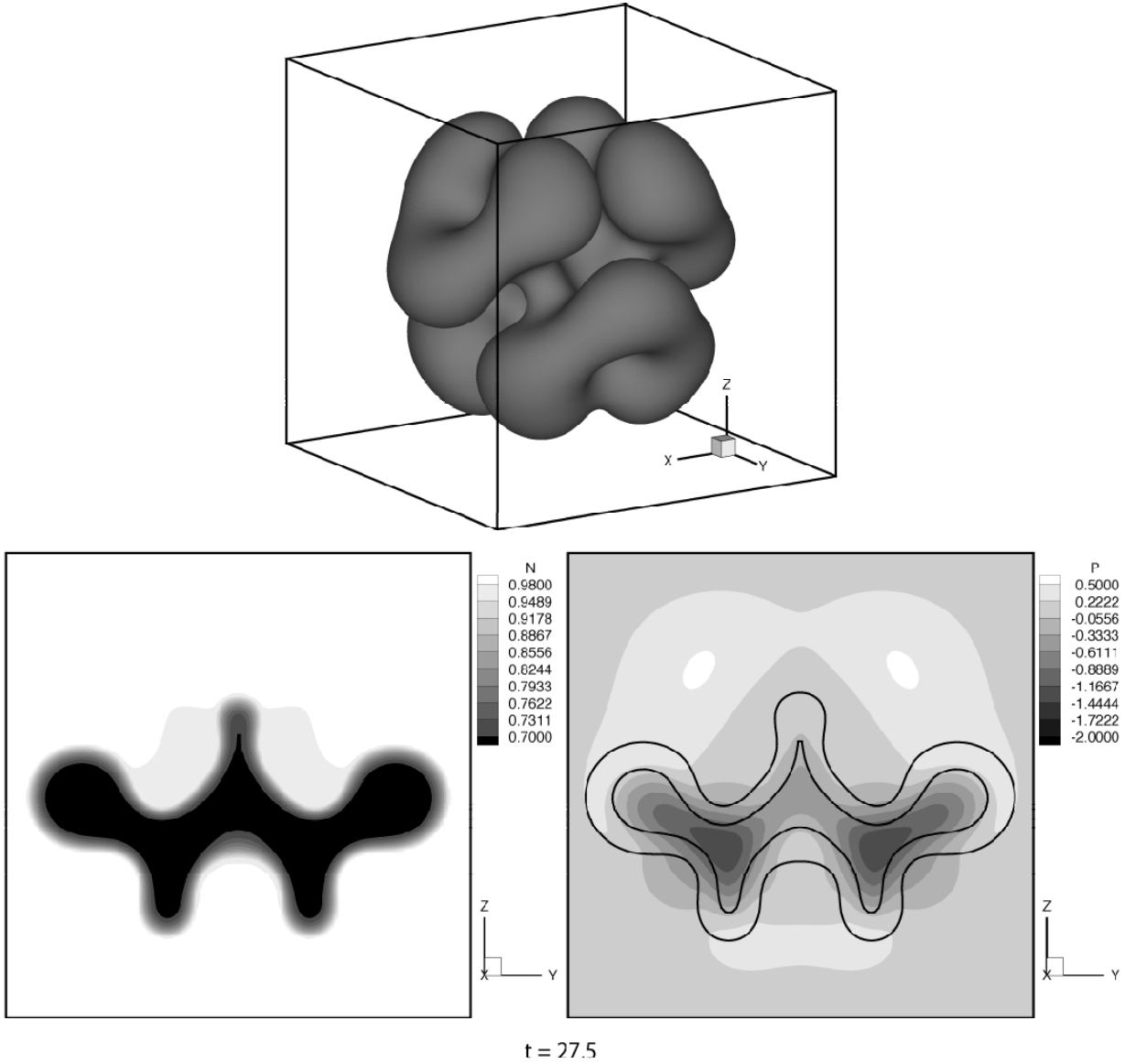
0.7622
0.7311
0.7000
Z
X
Y
P
0.5000
0.2222
-0.0556
-0.3333
-0.6111
-0.8889
-1.1667
-1.4444
-1.7222
-2.0000
Z
X
Y

t = 20

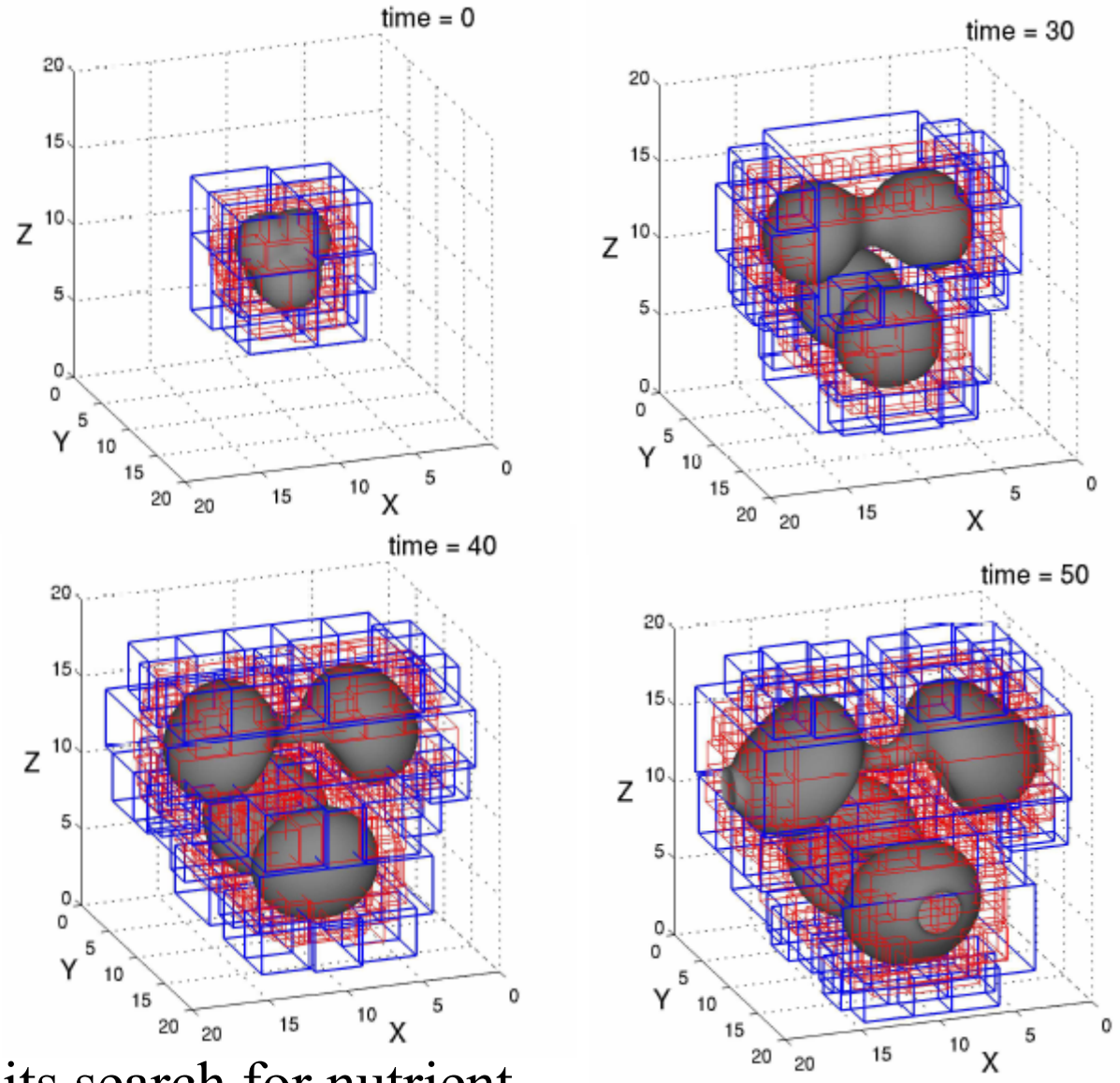


- Tumor develops folds to increase access to nutrient

Large nutrient gradients

$\chi_D = \chi_\mu = 1$

- Large nutrient gradients in host



- Tumor breaks up in its search for nutrient

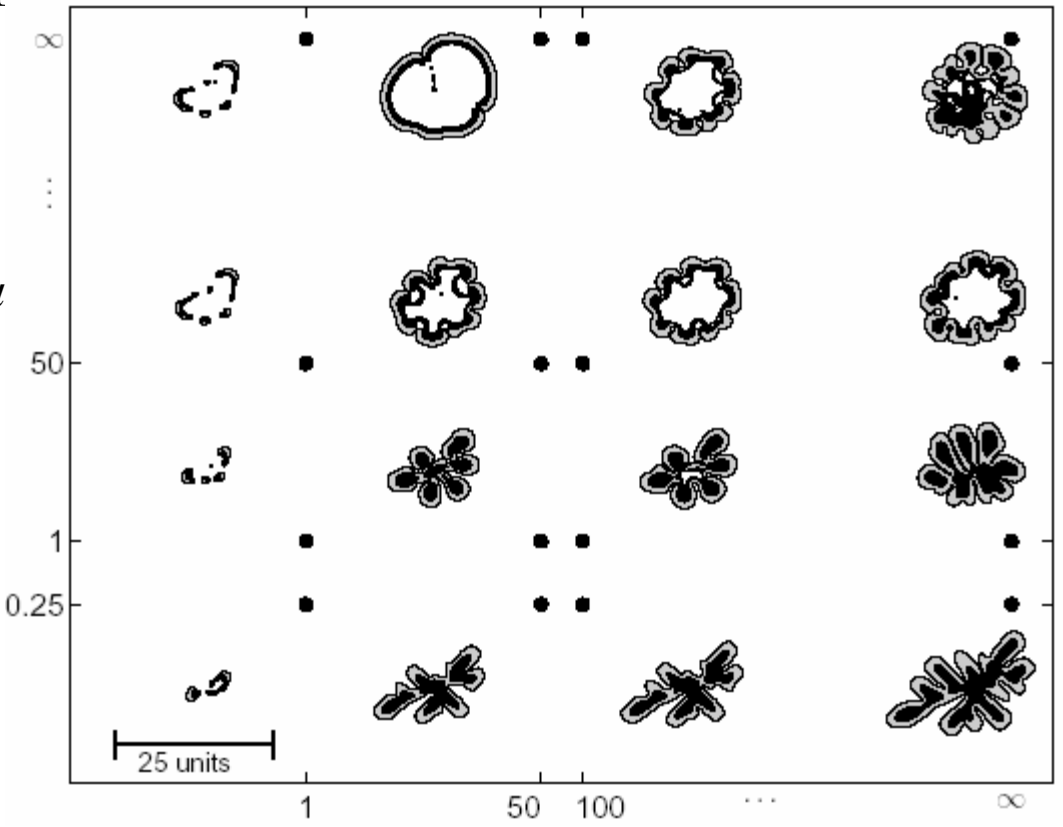
Morphology diagram

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)

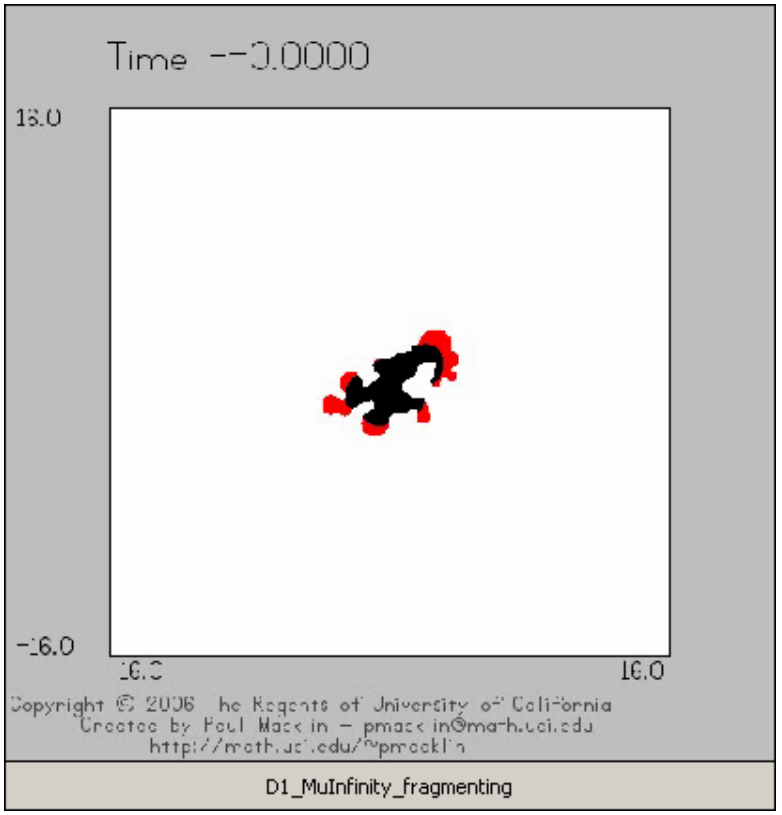
χ_D

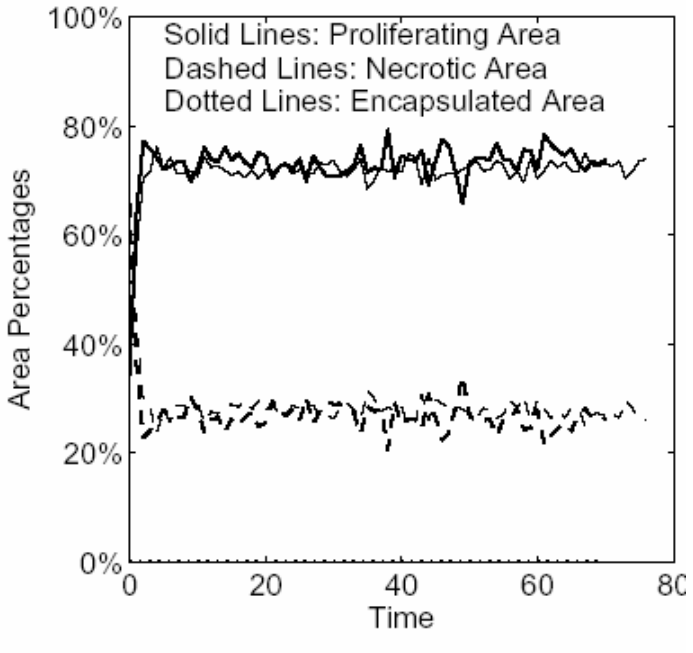
Higher degree of perfusion

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

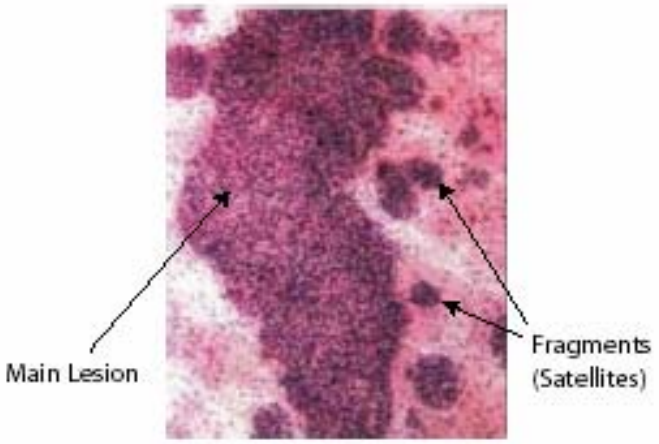
Fragmented

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





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

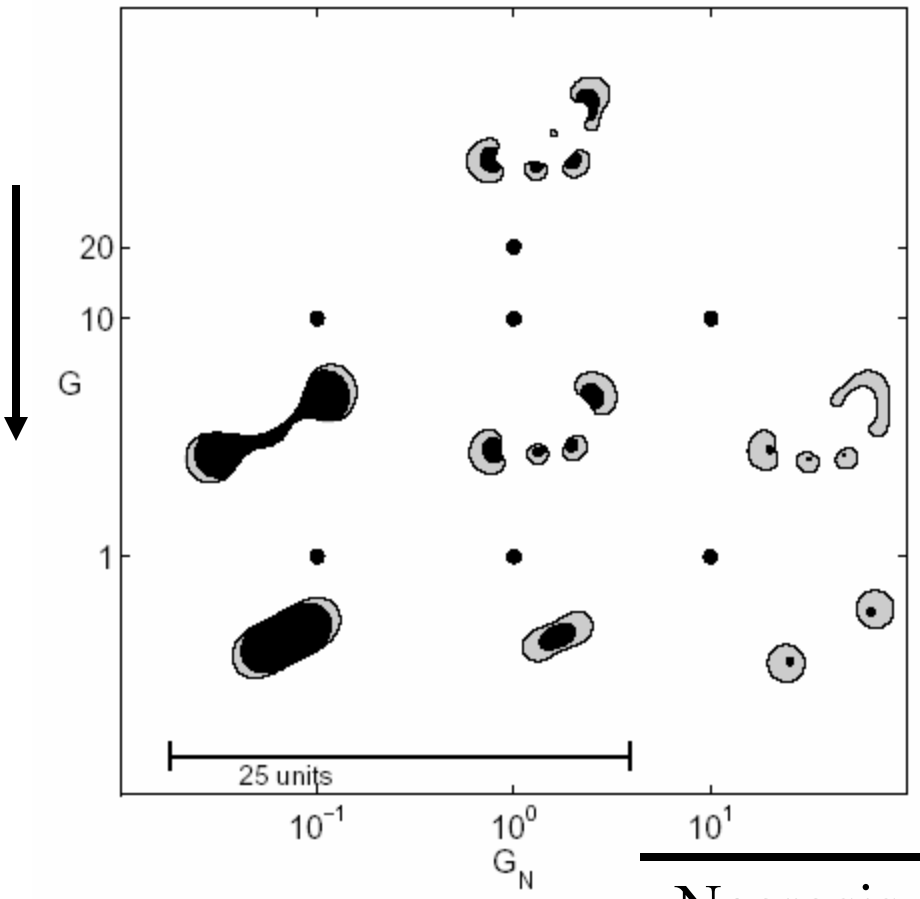


G55 human glioblastoma tumors in vivo becoming invasive after anti-angiogenic therapy
Rubinstein et al. Neoplasia (2000)

Effect of Cell-based Parameters

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

adhesiveness



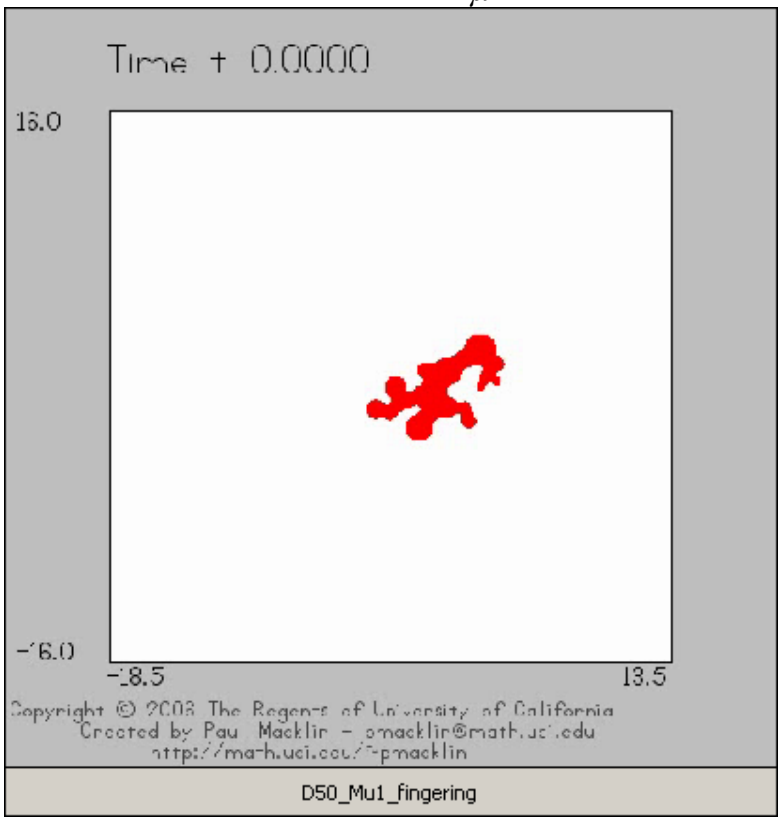
Necrosis (degradation)

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

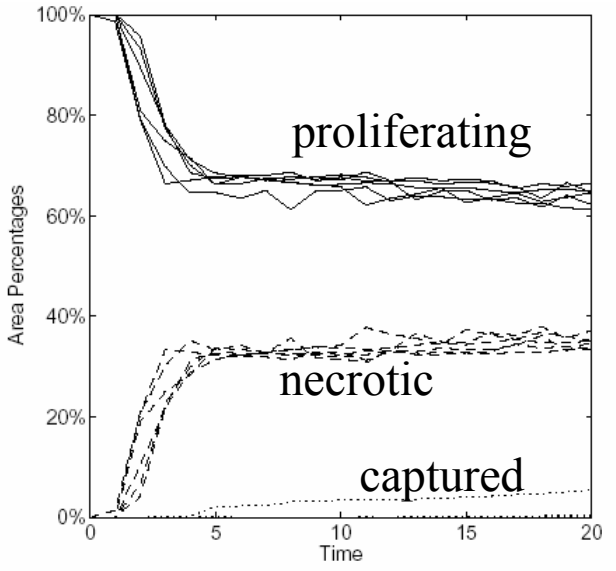
- Behavior qualitatively similar

Invasive fingering

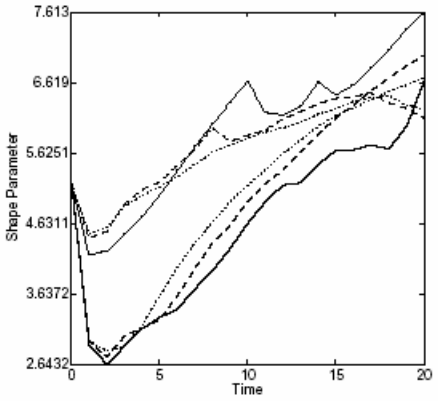
$\chi_D = 50, \quad \chi_\mu = 1$



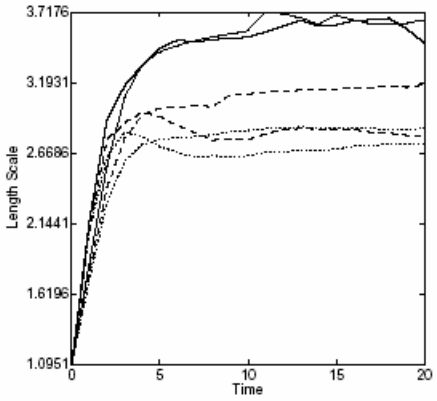
Area ratios



Shape parameter



Length scale



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

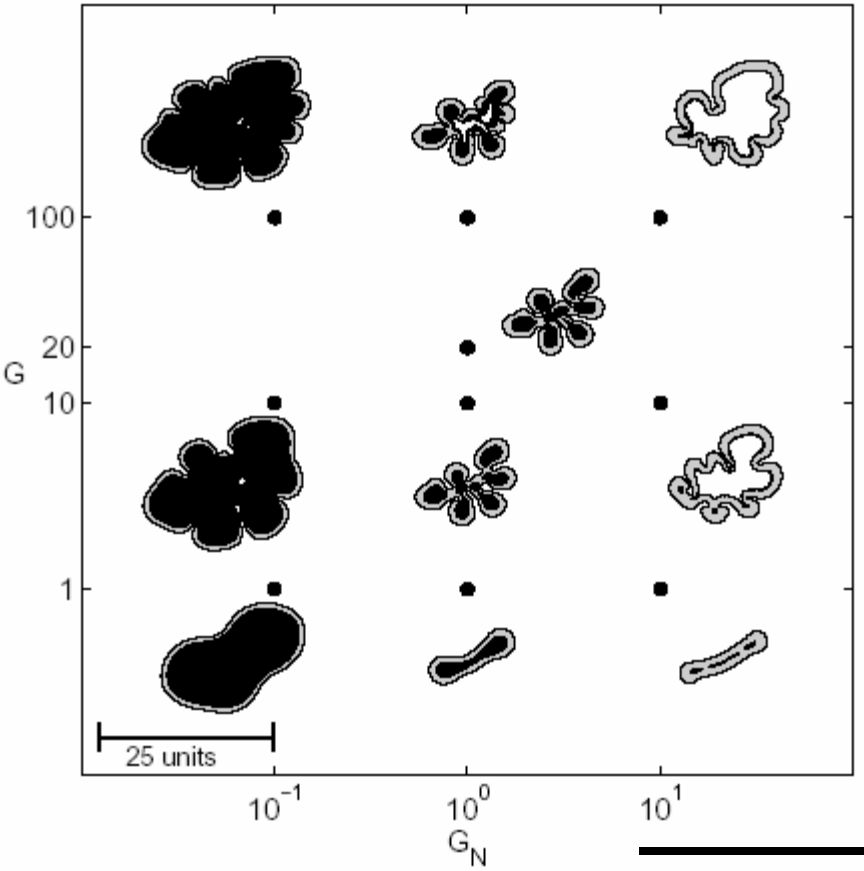
Thick: $\chi_\mu = 1$

Thin: $\chi_\mu = 0.25$

Dependence on cell-based parameters

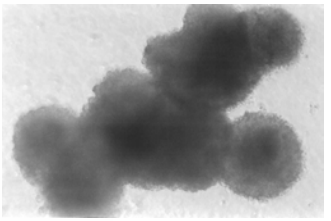
$\chi_D = 50, \quad \chi_\mu = 1$

adhesiveness

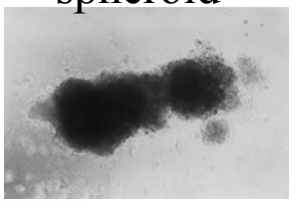


Necrosis (degradation)

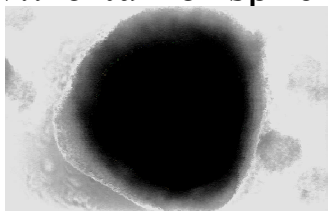
spheroid



spheroid



In vitro tumor spheroid

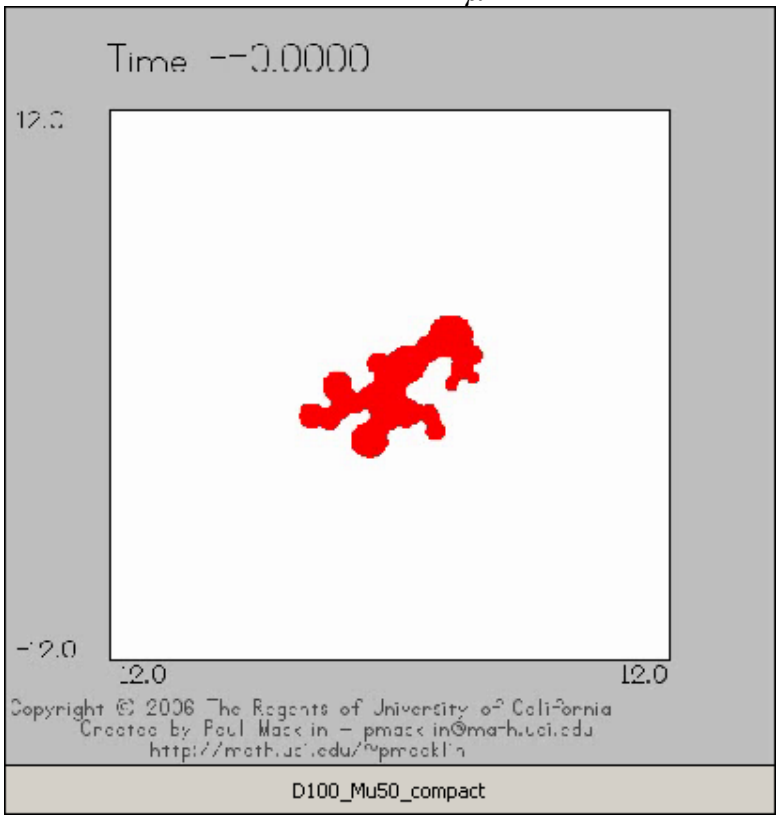


Frieboes et al, Canc. Res. (2006).

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

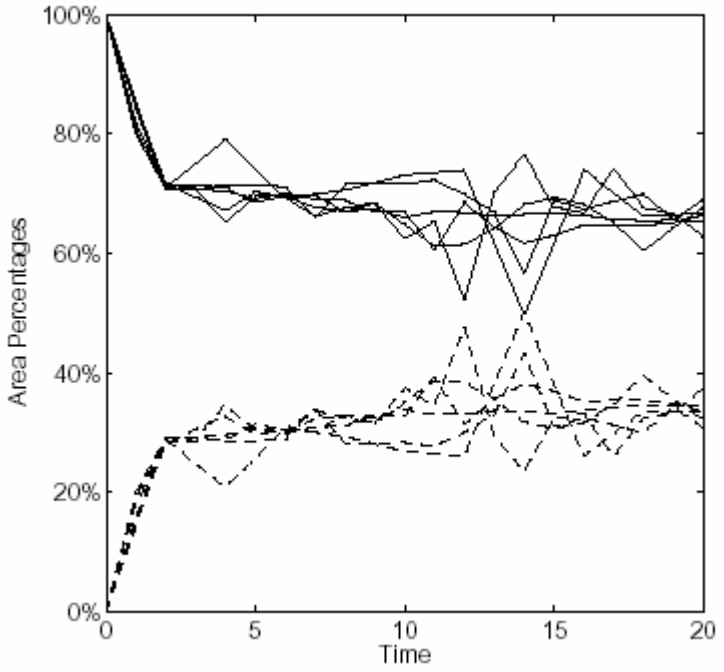
Hollow/Necrotic Growth

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

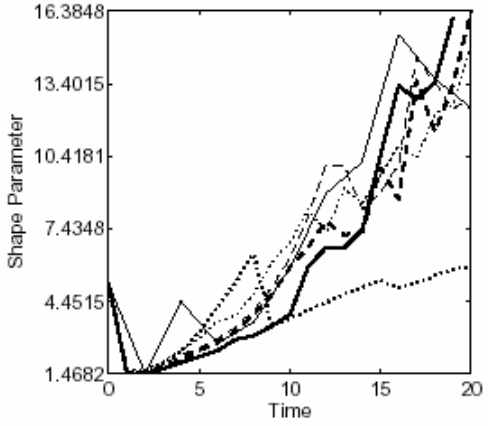


- Repeated capture and coalescence leads to hollow/necrotic structure

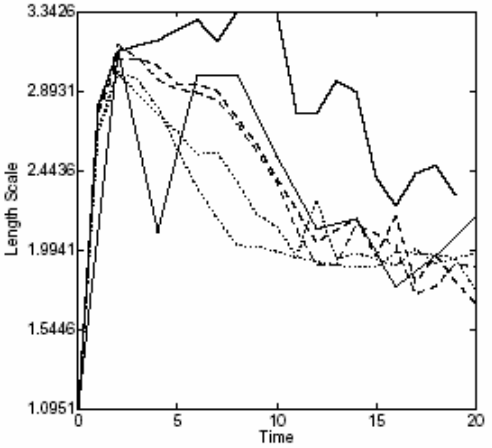
Area ratios



shape parameter



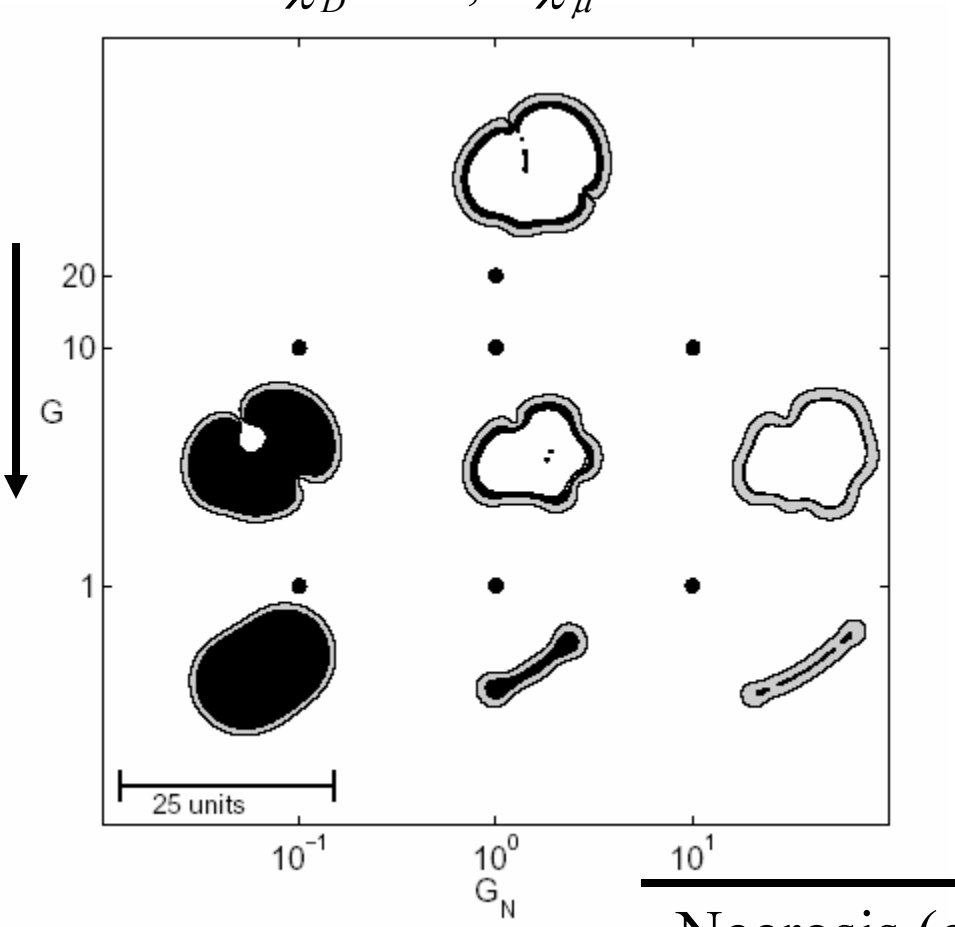
length scale



Dependence on cell-based parameters

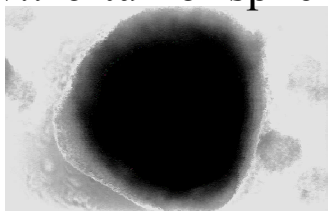
$\chi_D = 50, \quad \chi_\mu = \infty$

adhesiveness



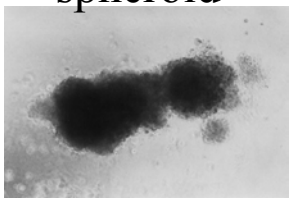
Necrosis (degradation)

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)

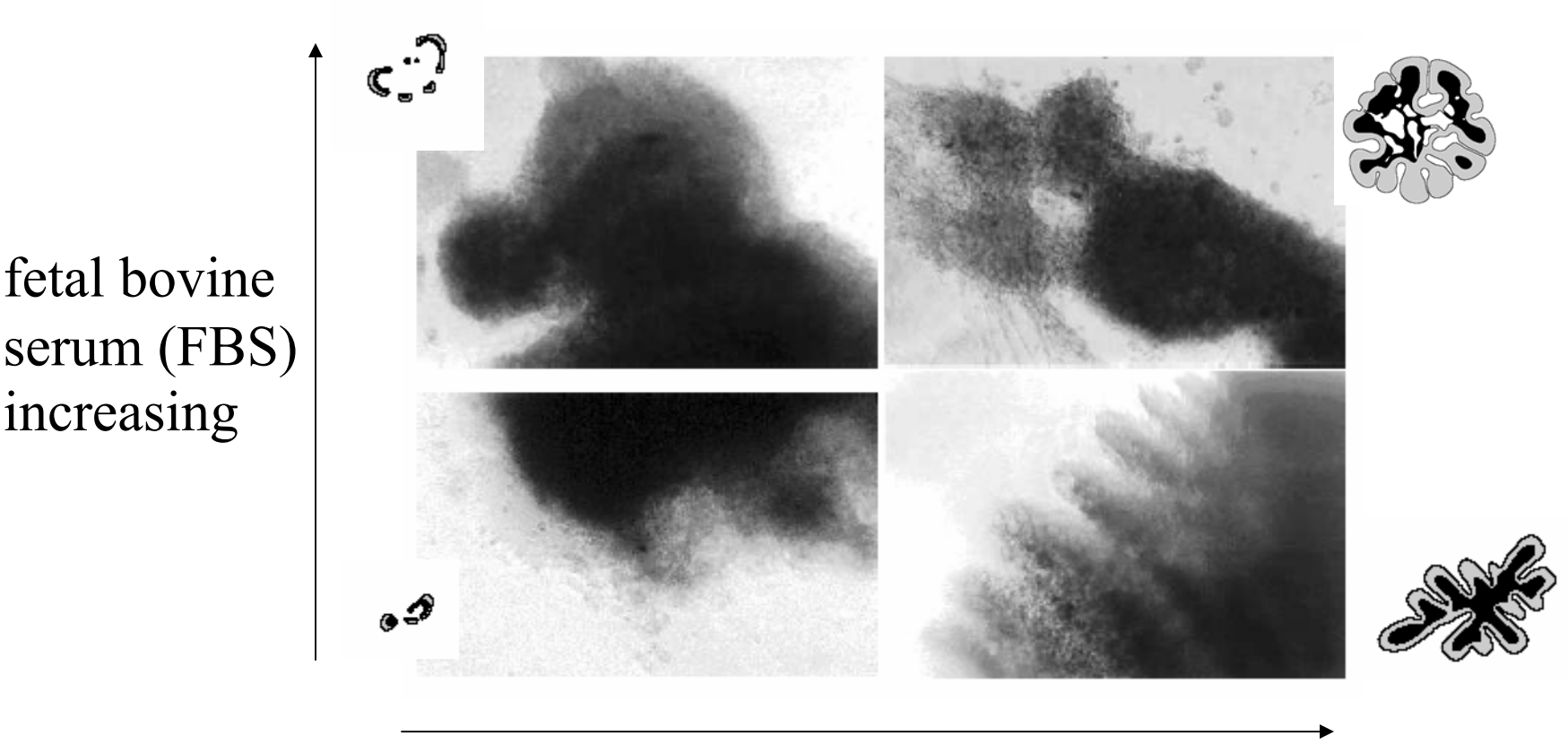
- Internal structure (e.g. size of necrotic, proliferating regions) determined by cell-based parameters

- Implications for therapy

- Experimental evidence for this behavior?

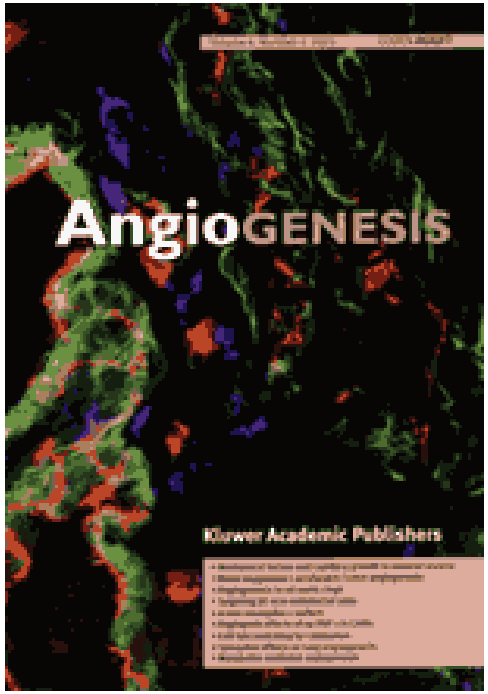
Comparison with experiment

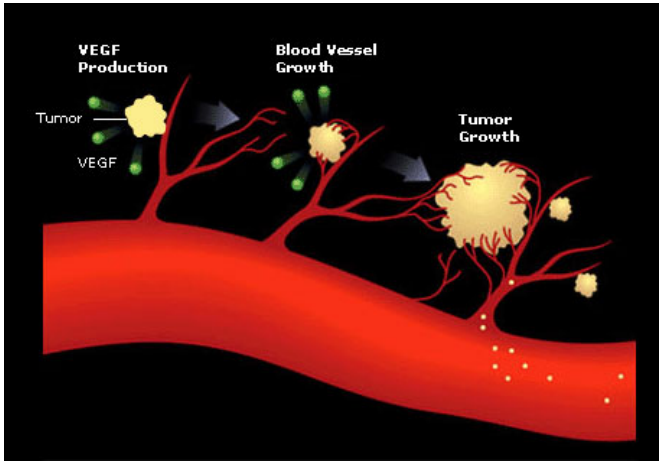
Frieboes et al., Cancer Res. (2006).

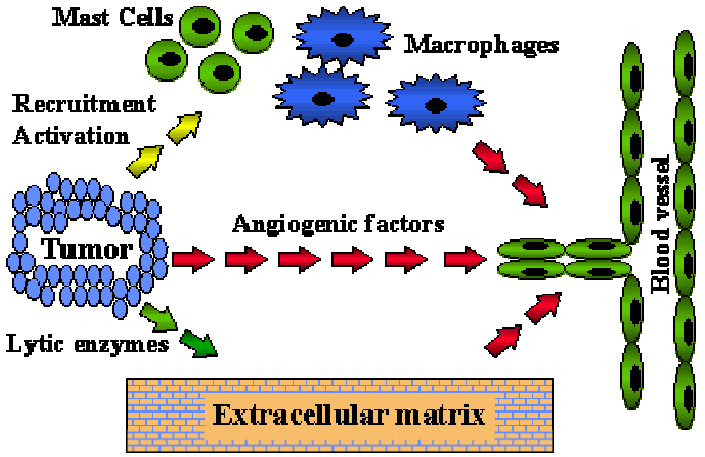


- Model is qualitatively consistent with experimental results

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

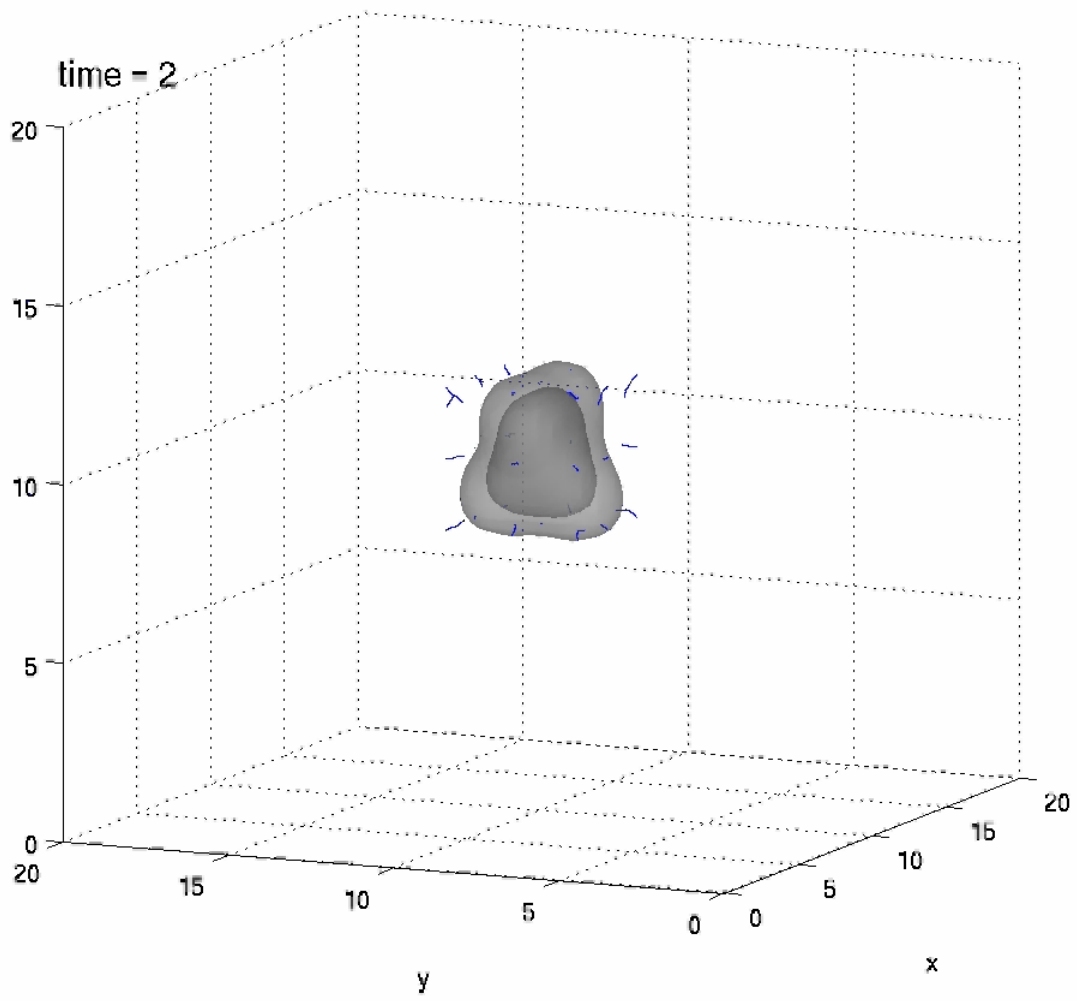
Parameters appropriate for glioblastoma

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

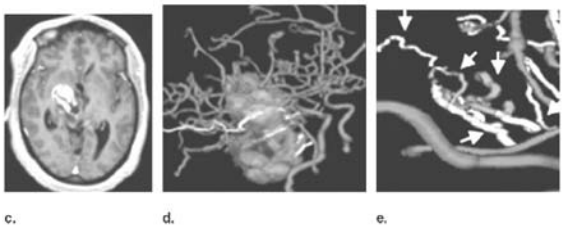
Frieboes, Wise, Zheng, Lowengrub, Cristini, Neuroimage (in prep)

Vascular cooption

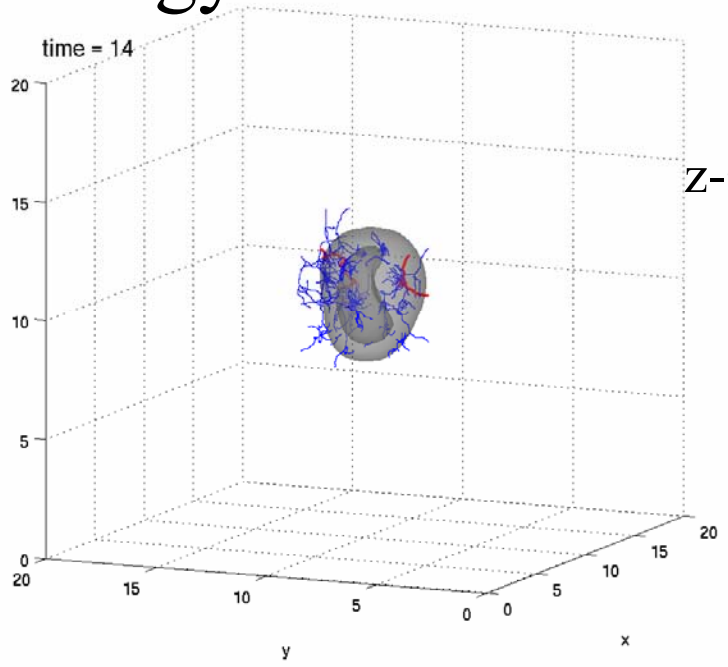
- Initial capillaries present
- Growing tumor surrounds vessels
- Uses up available vasculature
- Secondary angiogenesis
- Observe bursts of growth as the nutrient supply increases (like a fire)



Bullitt et al (2005). Glioma



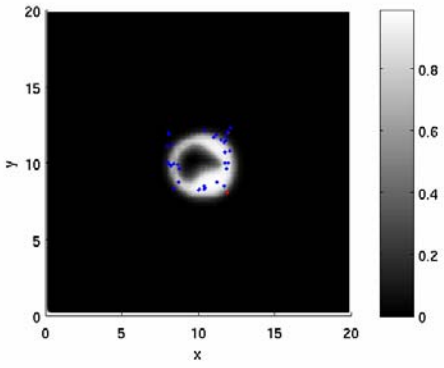
Histology Slices

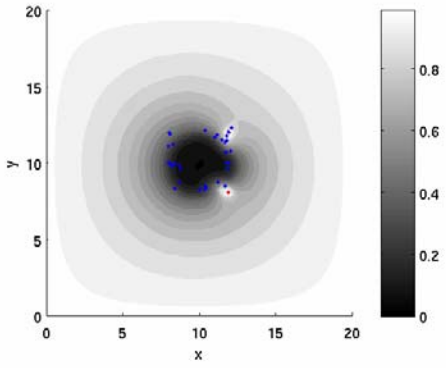


Viable cells

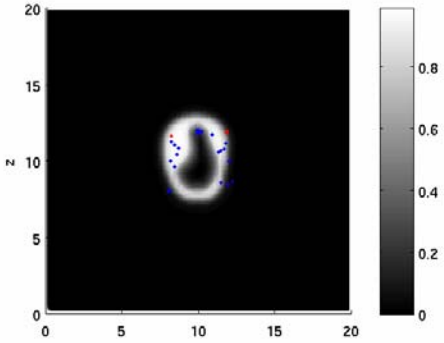
Nutrient

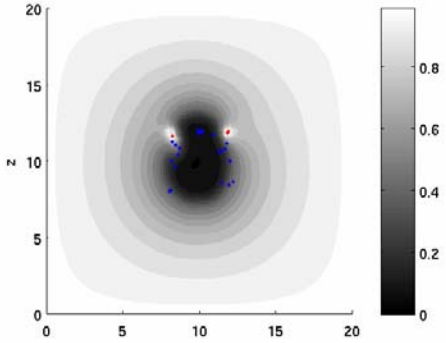
z-slice



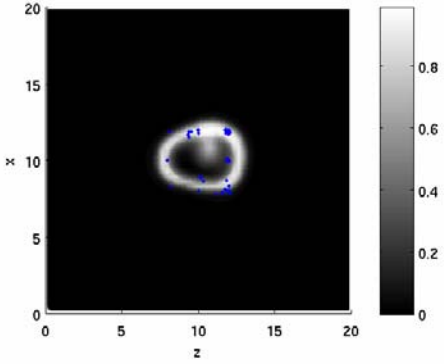


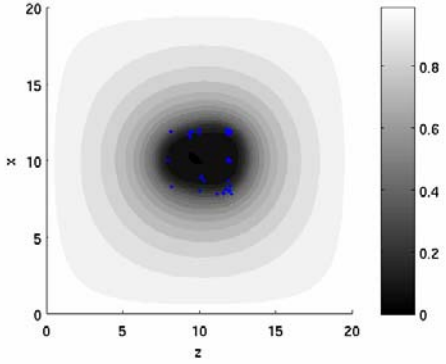
x-slice



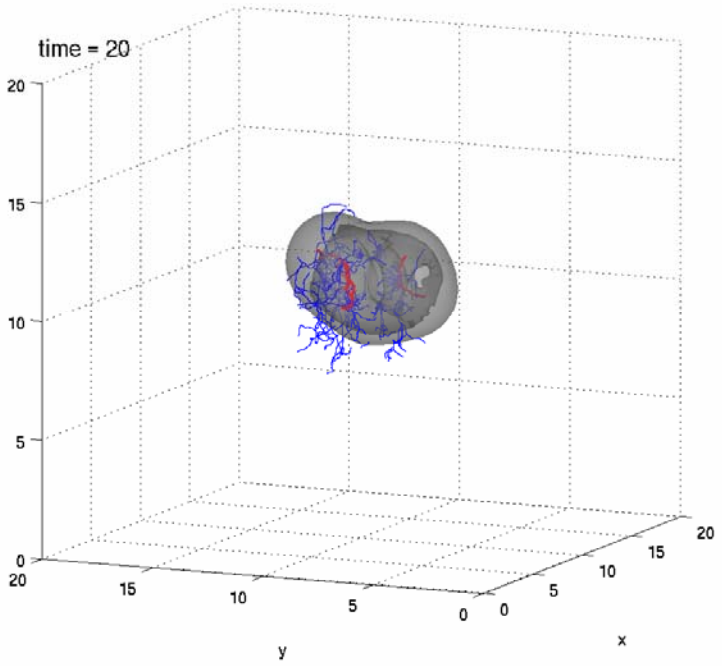


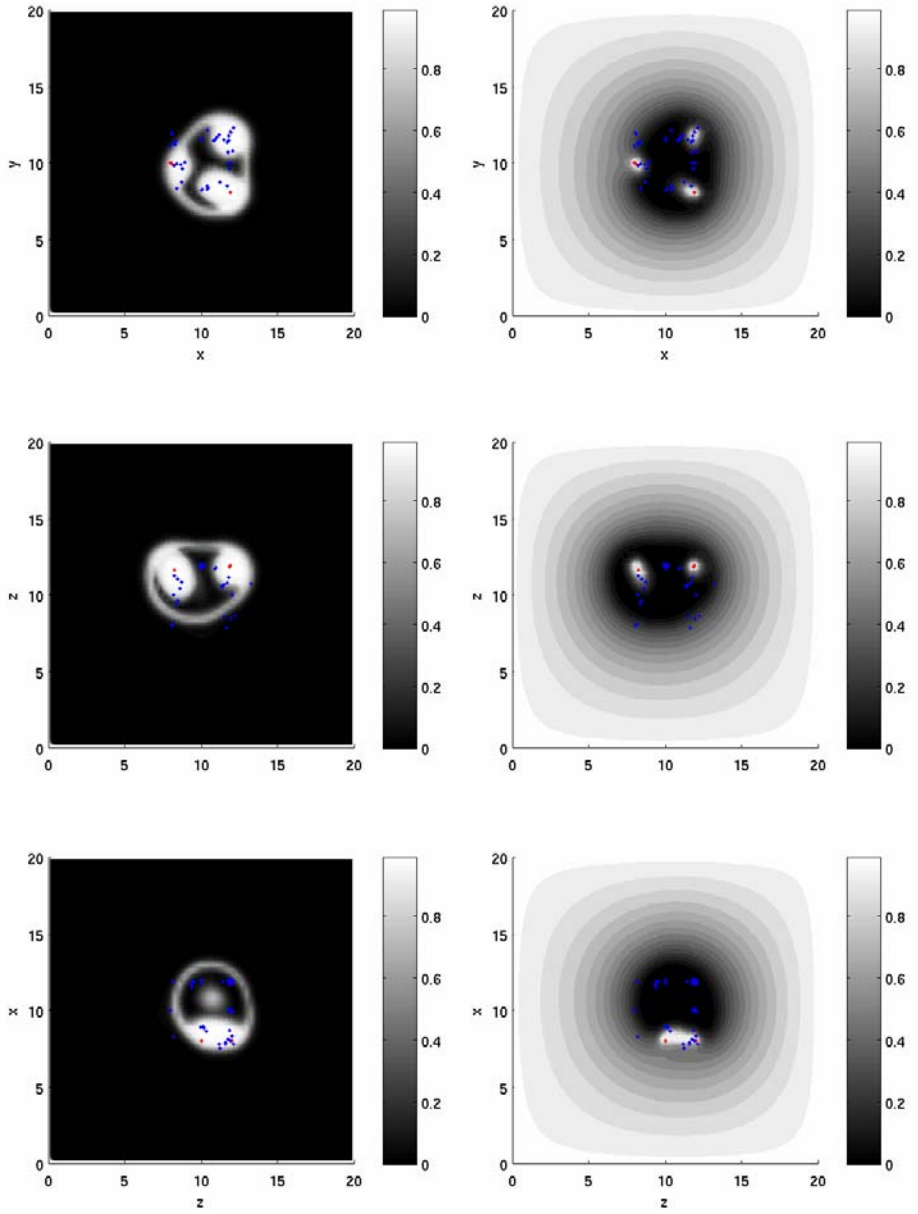
y-slice



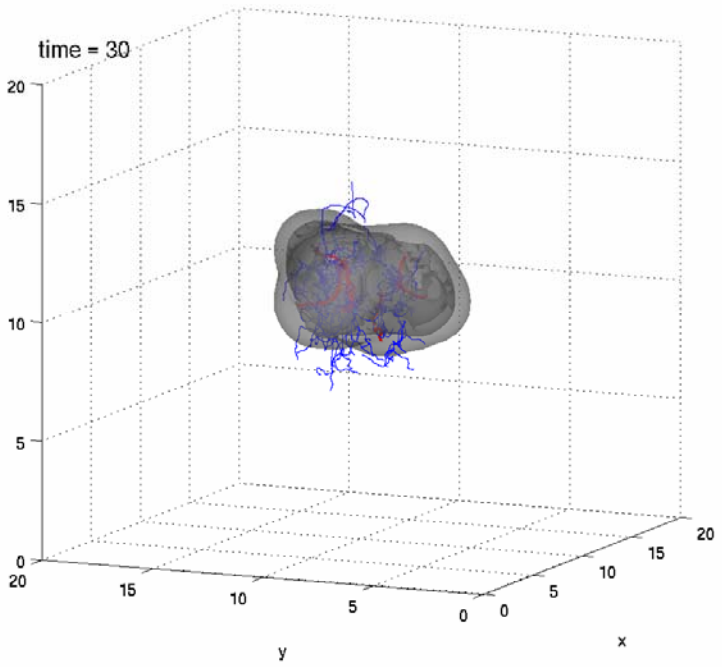


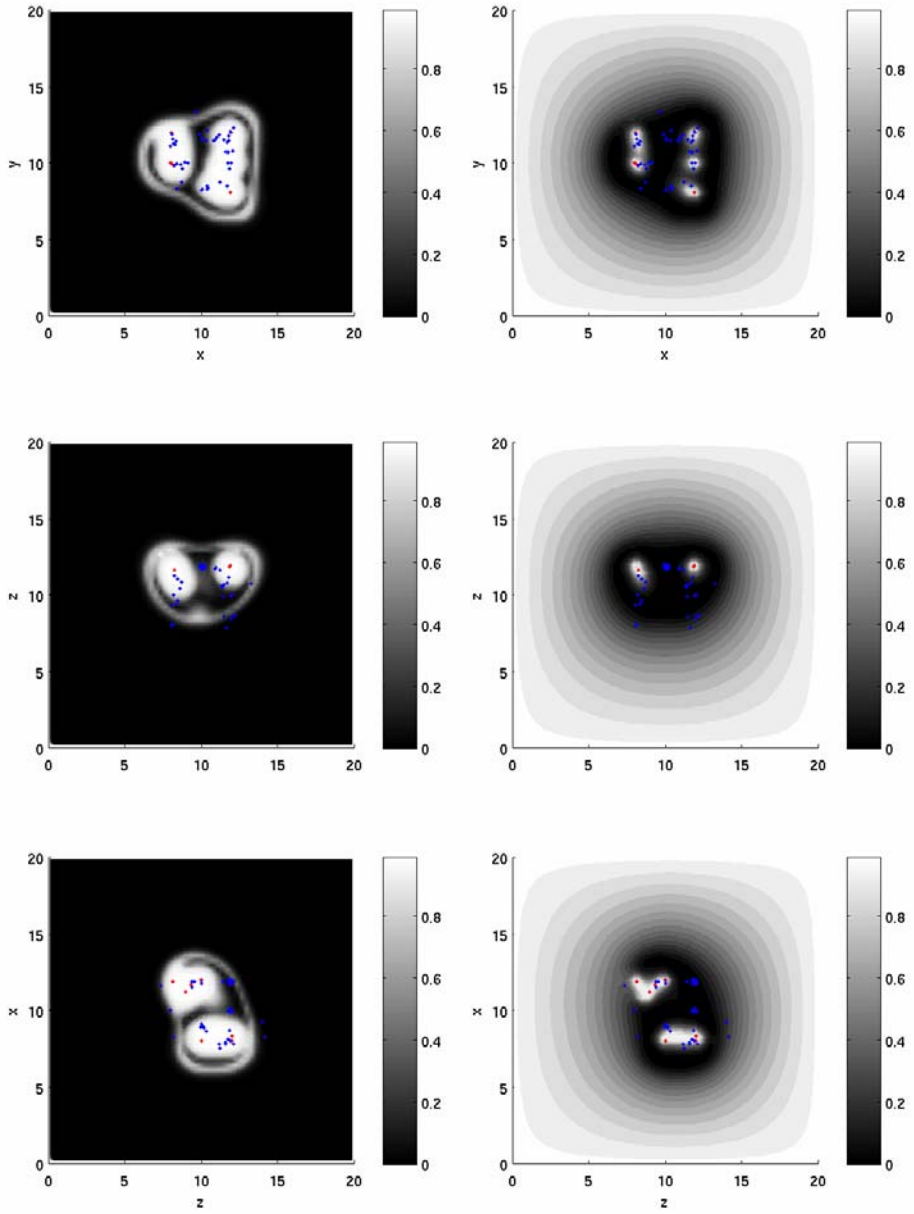
- Note nutrient supply localized near red (nutrient-releasing) vessels
- Observe corresponding (tumor) near vessels cell growth

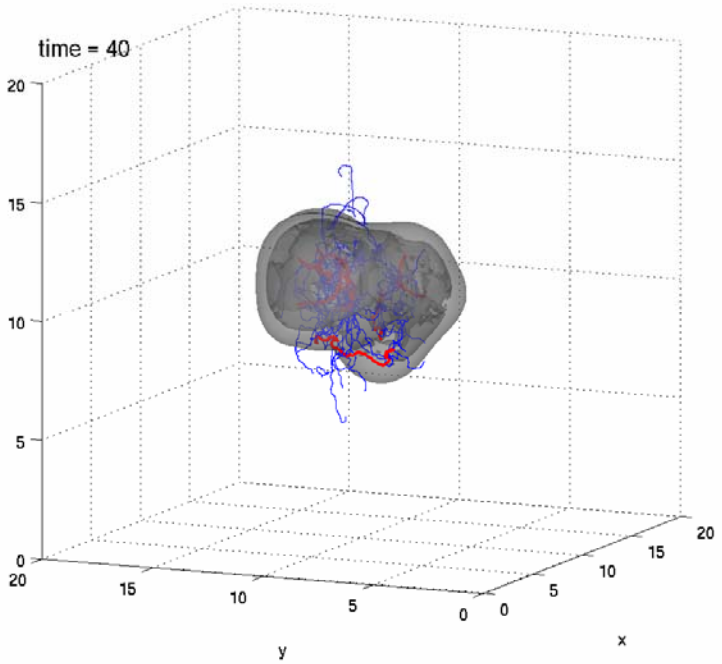


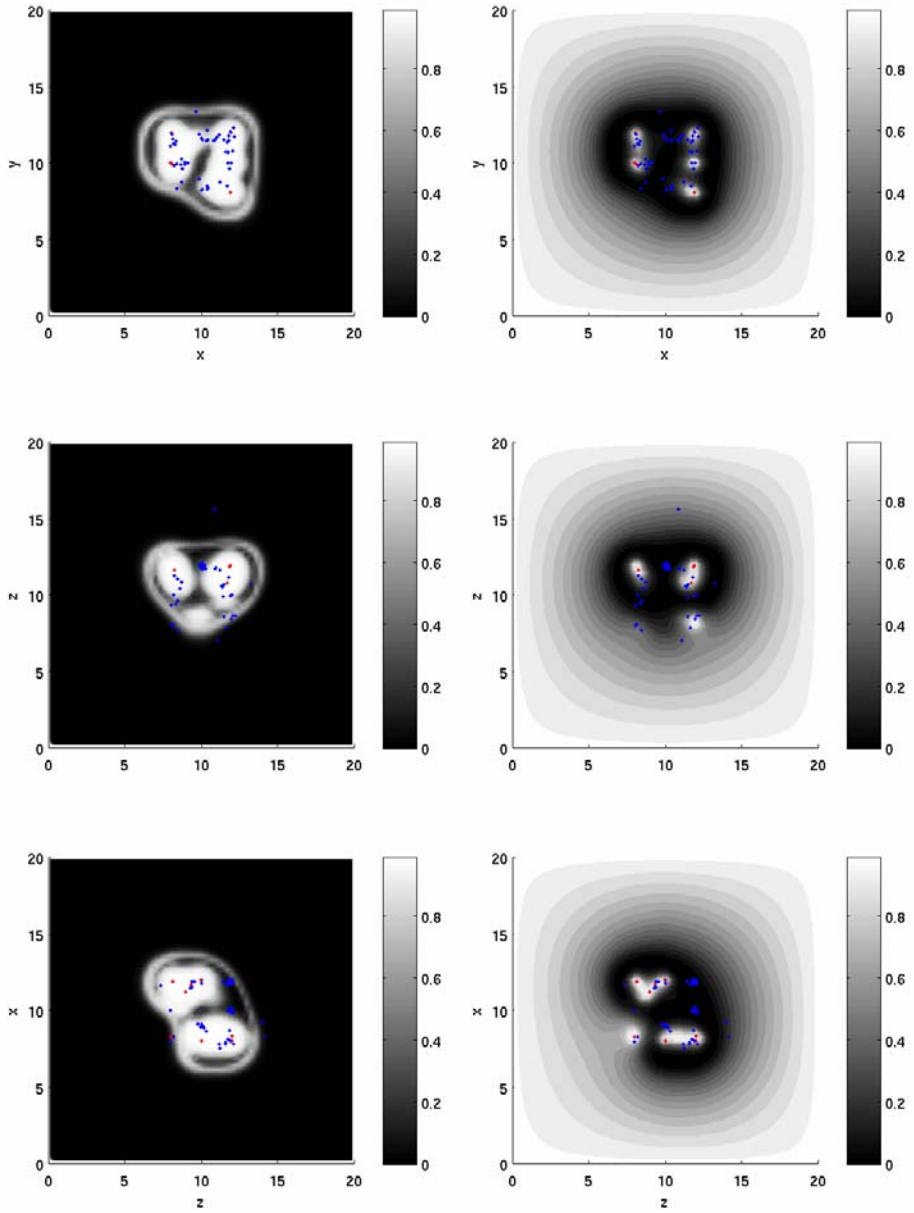


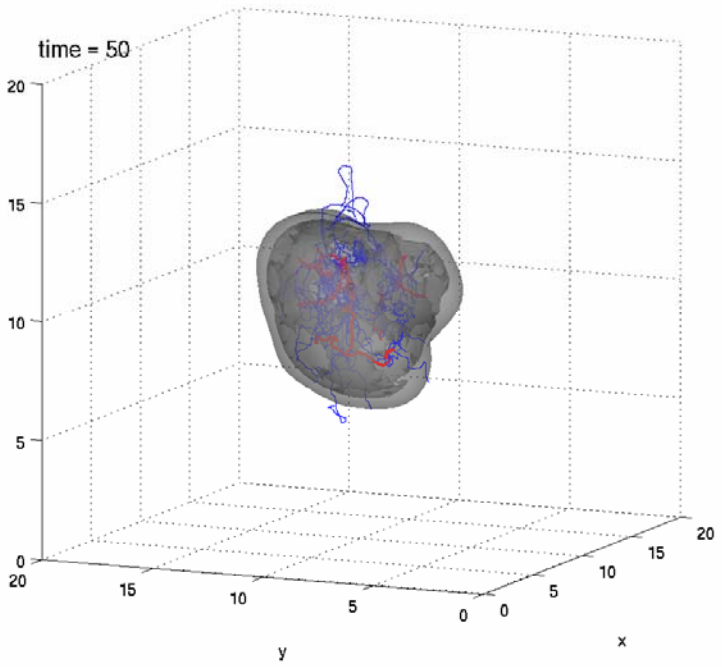
•Regions of hypoxia separate cell clusters


time = 30
20
15
10
5
0
y
x


y
x
z
0.8
0.6
0.4
0.2
0


time = 40
y
x


y
x
z
x
z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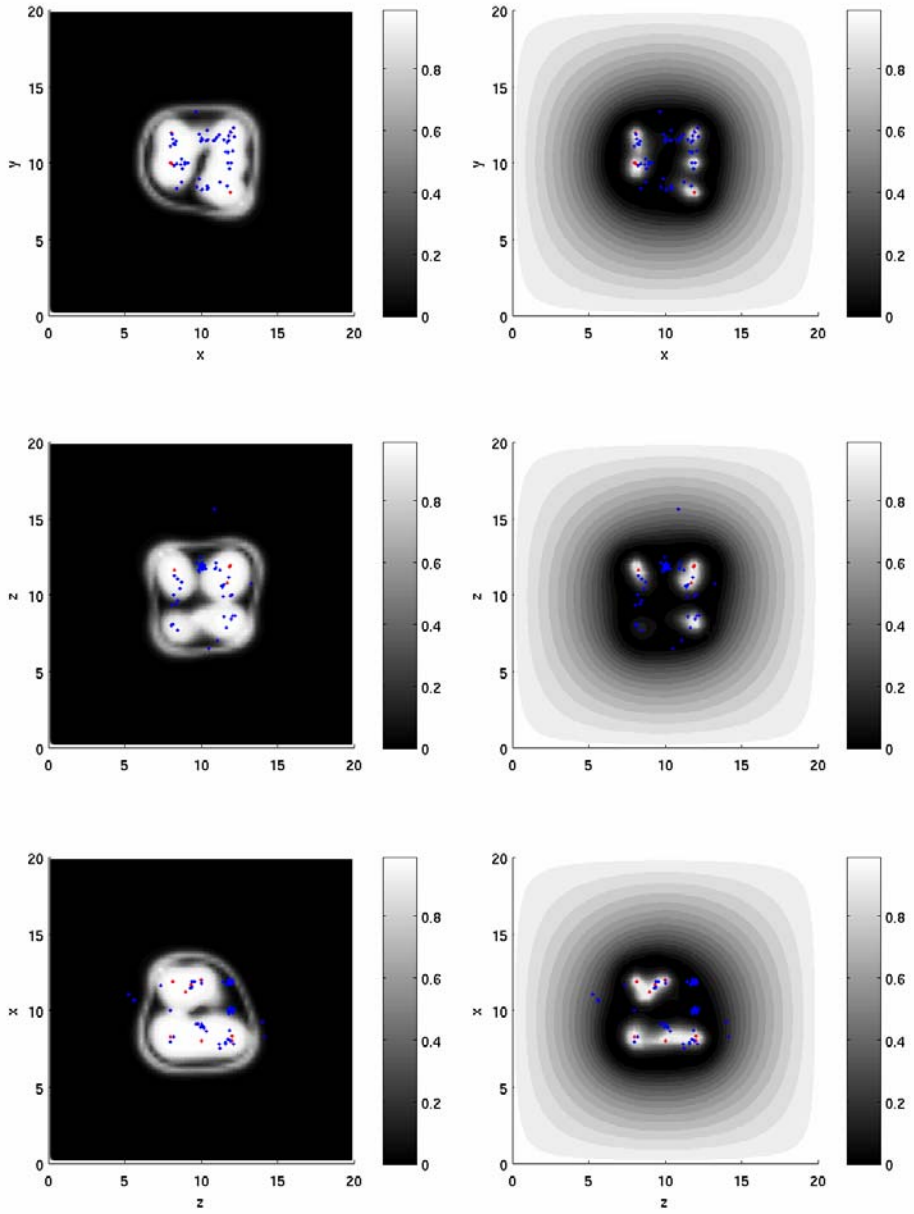
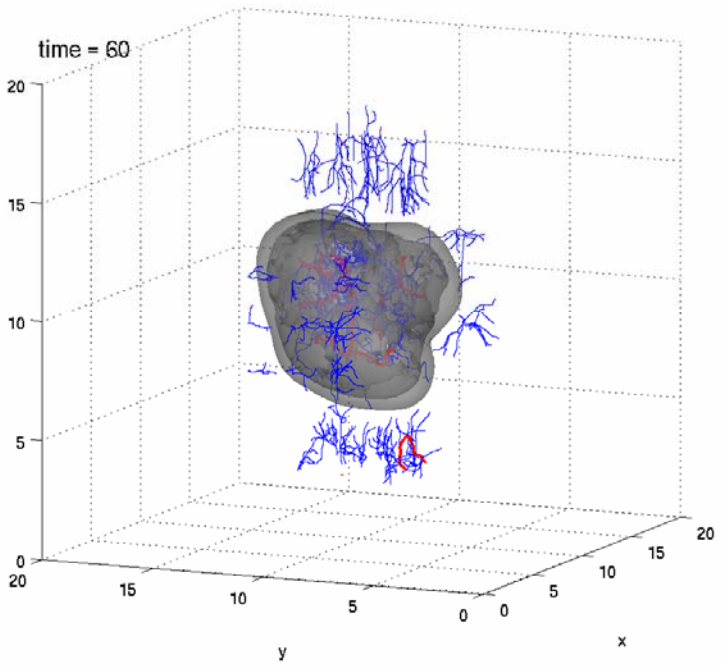
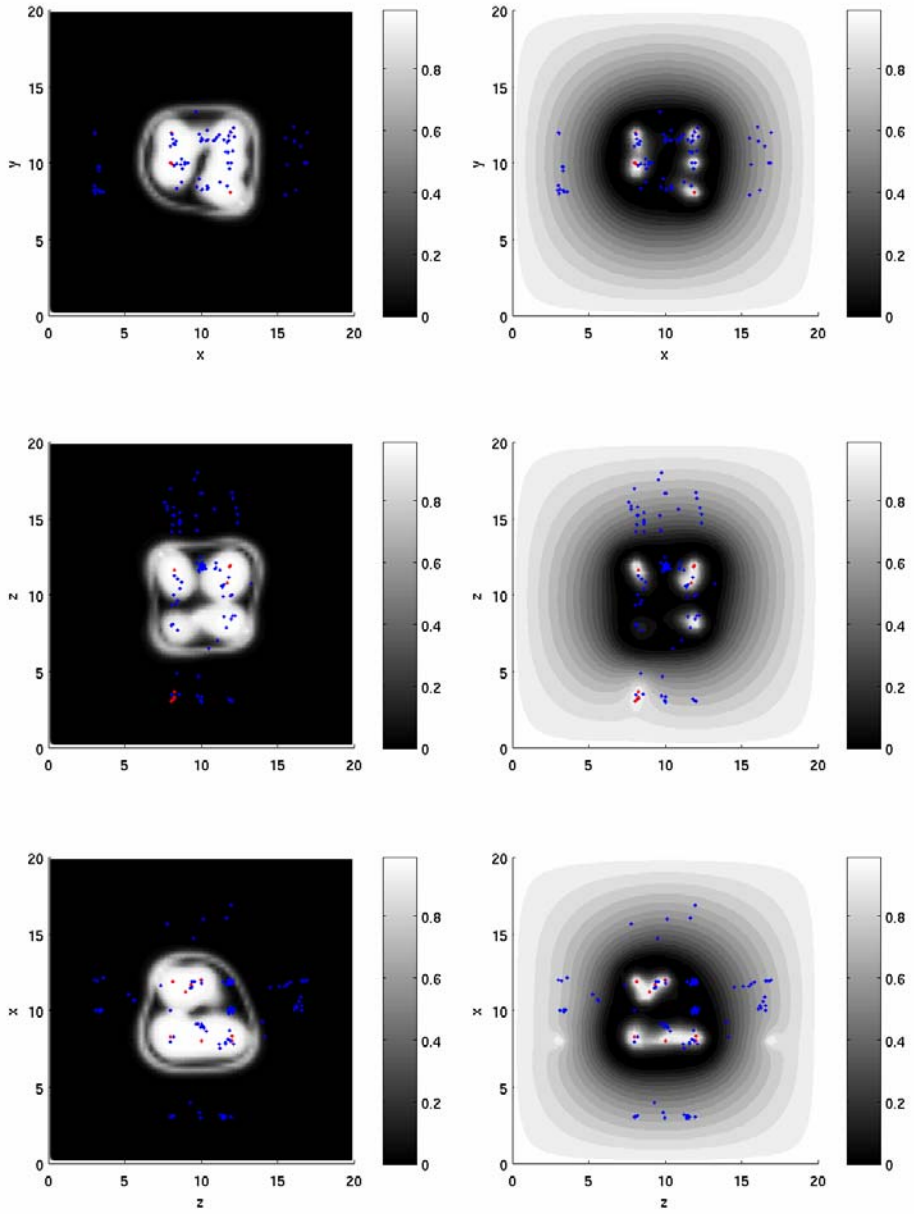
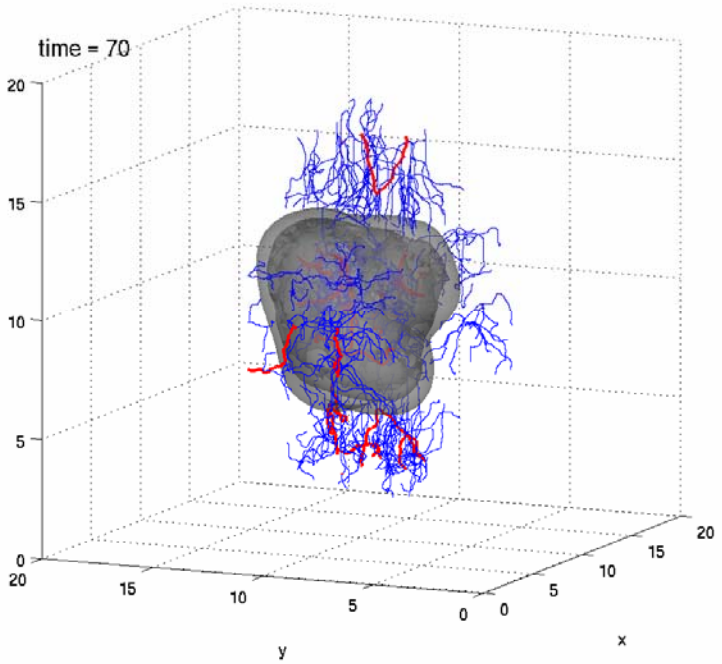
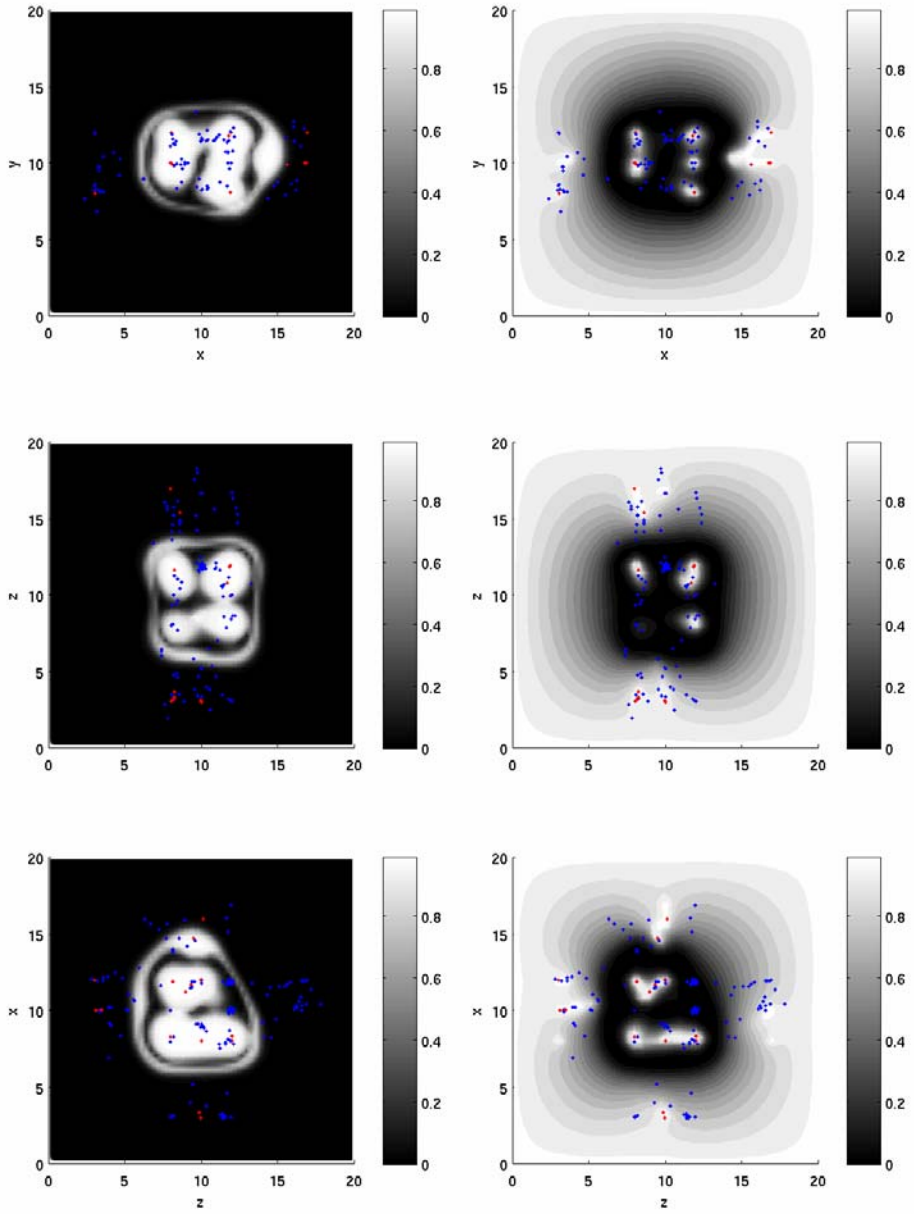
20
15
10
5
0
y
x

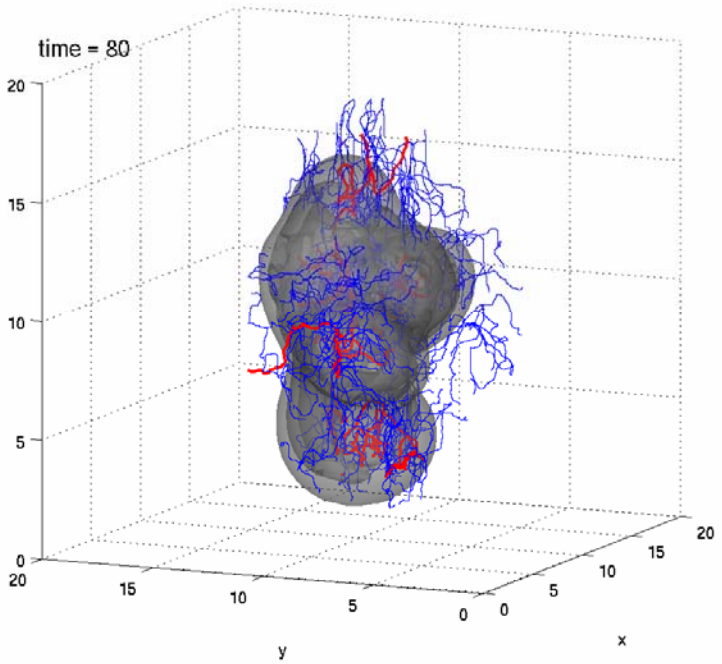

y
x
z
0.8
0.6
0.4
0.2
0
5
10
15
20


time = 60
20
15
10
5
0
y
x


y
x
z
x
z
0
5
10
15
20
0.2
0.4
0.6
0.8


time = 70
y
x


y
x
z
x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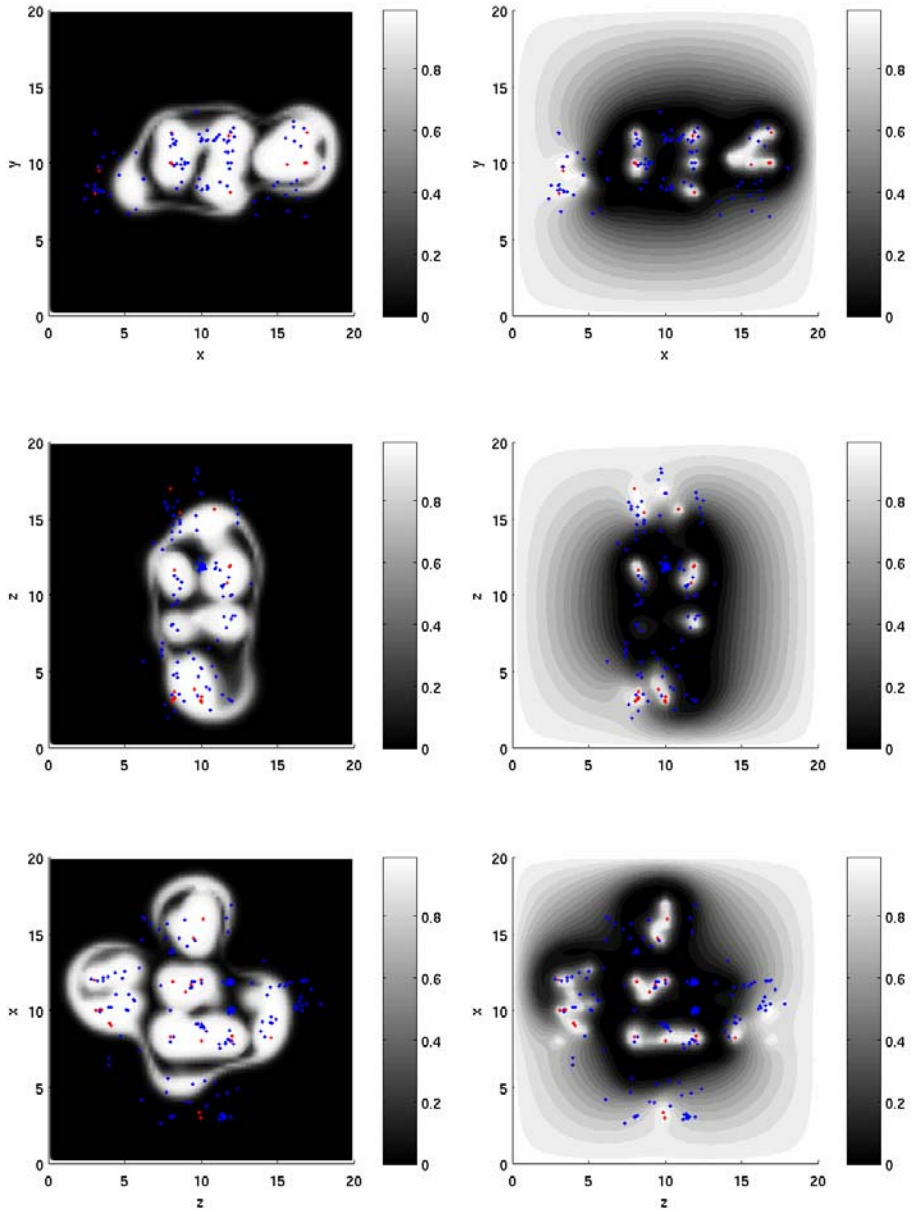
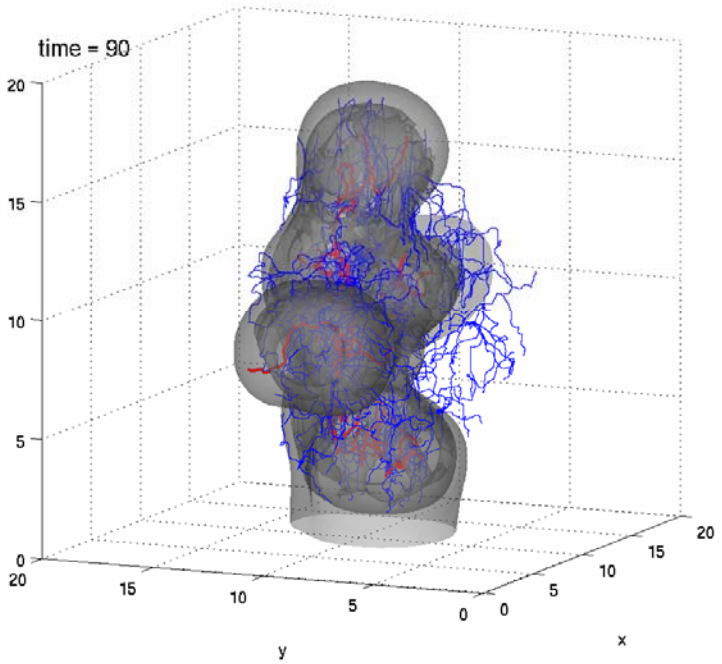
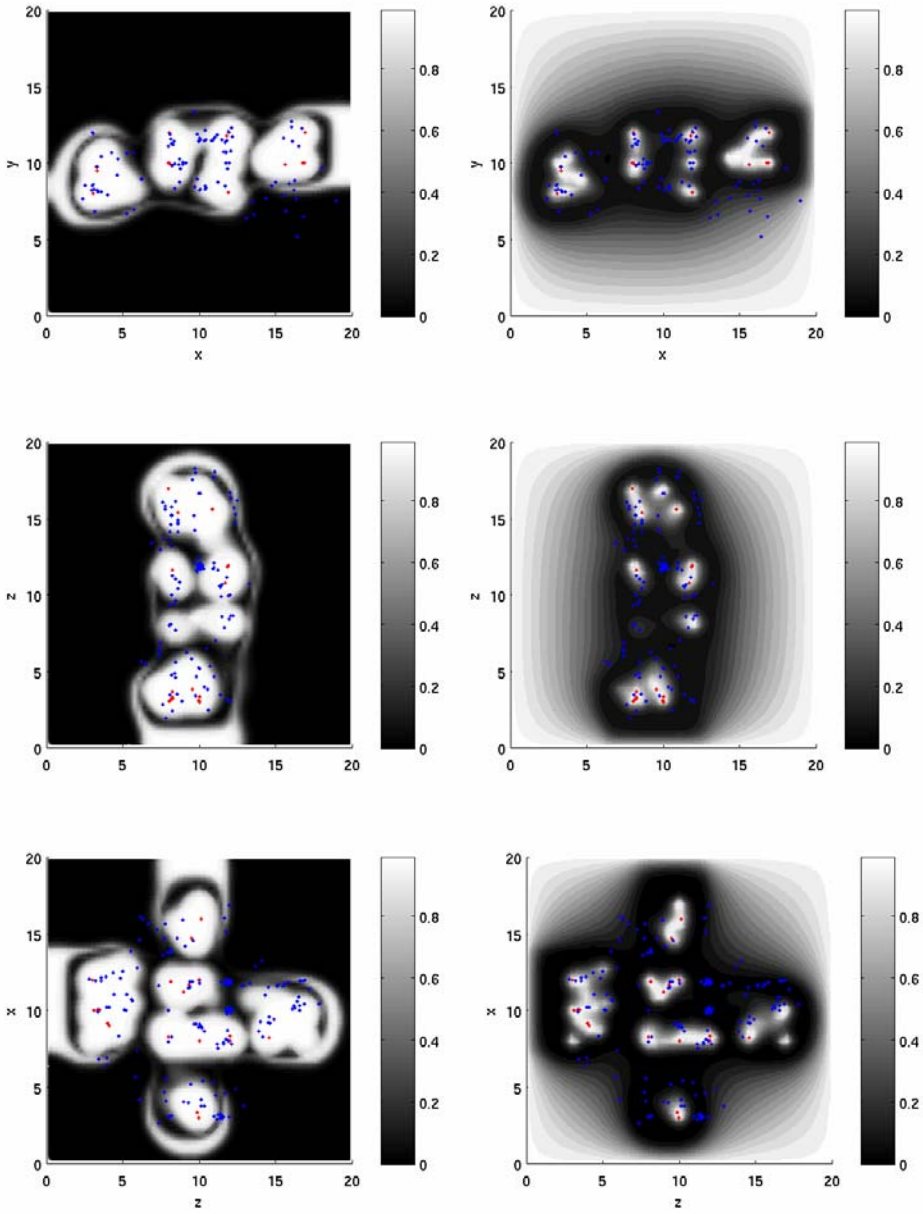
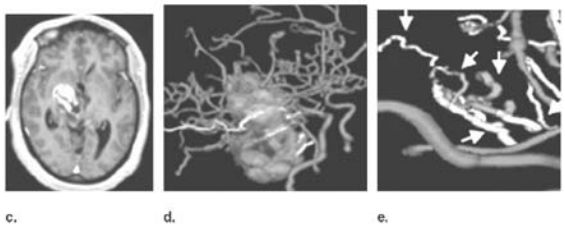
y
x


x
y
z

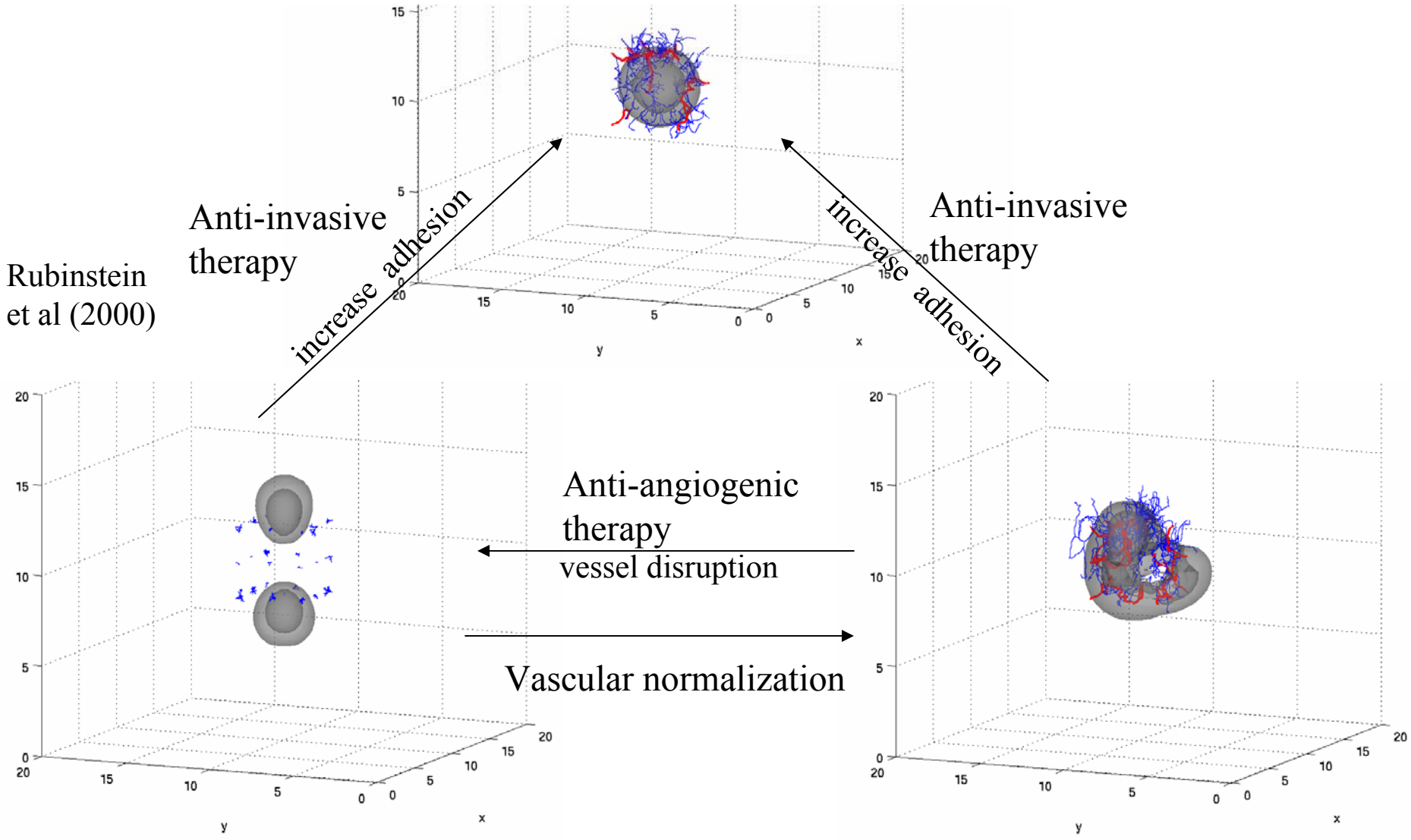




Bullitt et al (2005). Glioma



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