Nonlinear tumor modeling III: Angiogenesis, vascular growth and future directions

John Lowengrub

Dept Math, UCI

X. Zheng Ph.D. 2005
F. Gonzalez M.S. 2005
S. Wise (UCI)

V. Cristini (Dept Biomed Eng, UCI)

Motivation

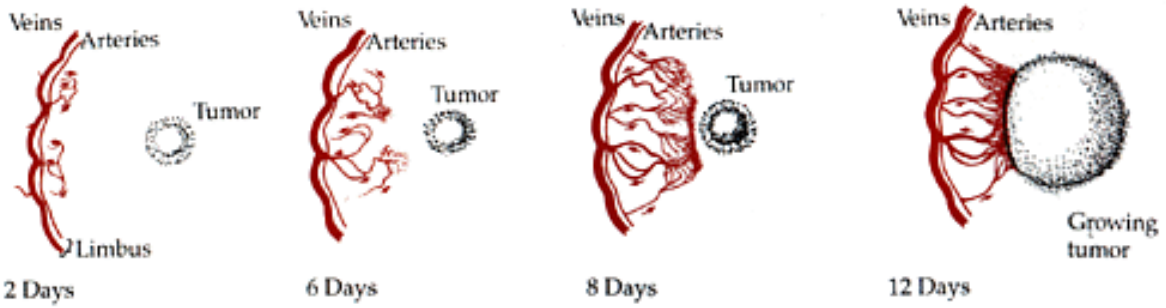
- Provide biophysically justified *in silico* virtual system to study
- Help experimental investigations; design new experiments
- Therapy protocols

Outline

- Review of tumor growth model
- Angiogenesis (experiment)
- Angiogenesis (model)
- Numerical implementation
- Results

Example of solid tumor growth

genetic mutations →



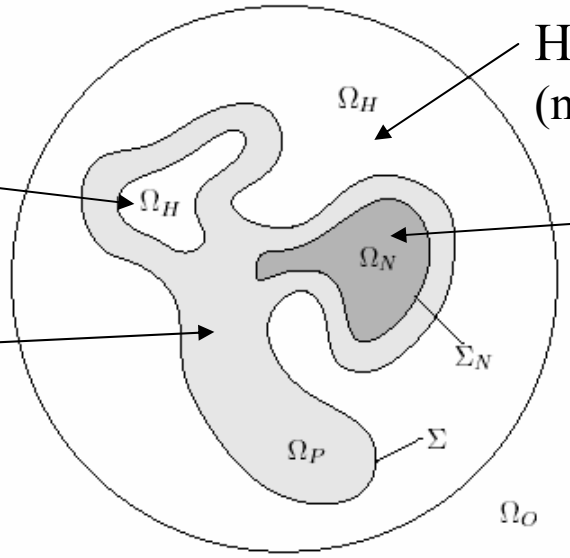
Avascular growth
Diffusion dominated

Angiogenesis

Vascular growth
invasive
metastasis
malignancy

•Goal: Model all Phases of growth

Present model



Healthy tissue
(may have vessels)

Captured
region

Necrotic
core

Proliferating
Tumor region
(may have vessels)

highly-
vascularized
exterior

•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

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

viscosity

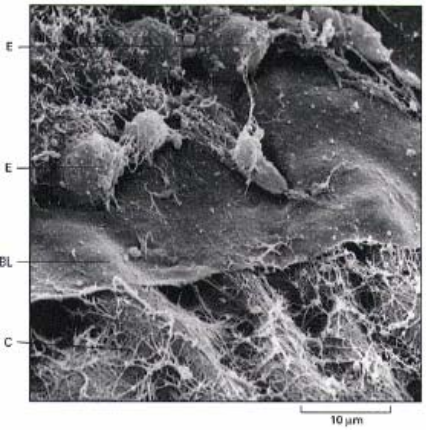
$$[\![P]\!] = \tau\,\kappa \quad \text{on } \Sigma$$

Darcy-Stokes

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

Viability concentration

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



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

Spatial distribution of the oncotic pressure

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

Evolution of nutrient: Oxygen/Glucose

Greenspan, Chaplain, Byrne, …

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

Diffusion

nutrient concentration in blood

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

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

Nutrient consumption by the cells

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

More complex Biophysics

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

- Blood-tissue transfer of nutrient

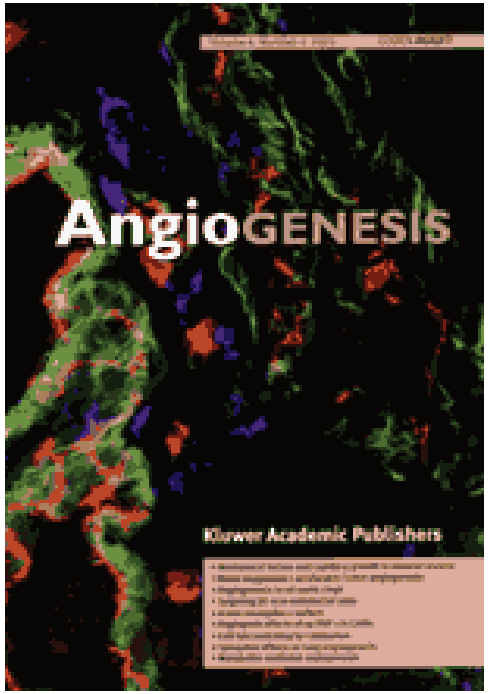
$$\lambda_B(\sigma_B - \sigma, P_B - P, \mathbf{x}, t) = \lambda_B\, h(\sigma_B - \sigma)\cdot(P_B - P)_+$$

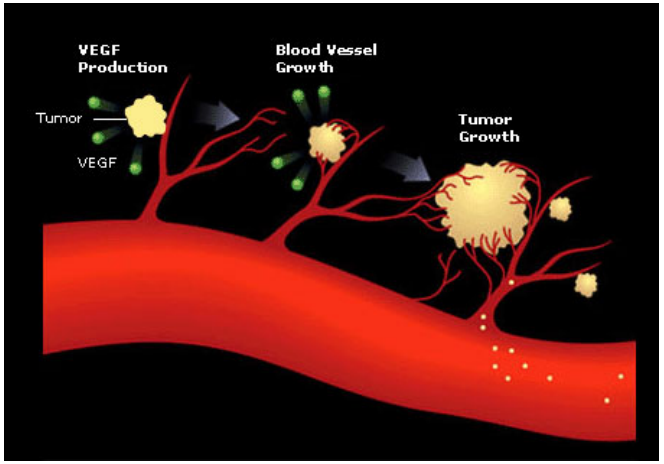
$$h(\sigma_B - \sigma) = (\sigma_B - \sigma)\delta_{Capillary}$$

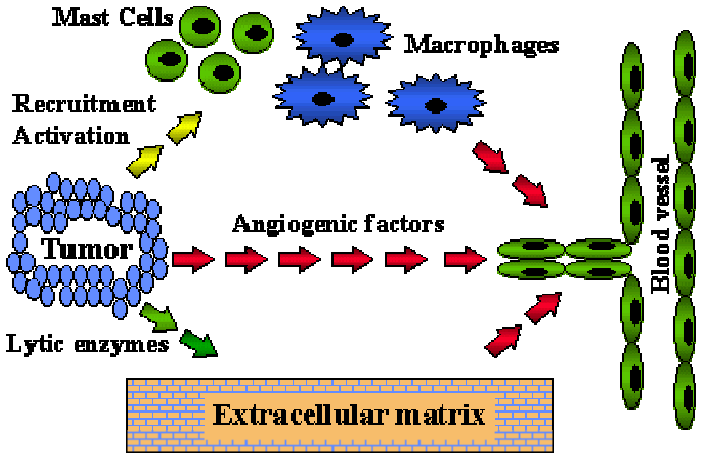
- Avascular, angiogenesis and fully vascularized growth

- Nonlinear interaction between developing vasculature and tumor growth

Angiogenesis







Angiogenic factors:

VEGF (Vascular Endothelial cell Growth Factor)

FGF (Fibroblast Growth Factor)

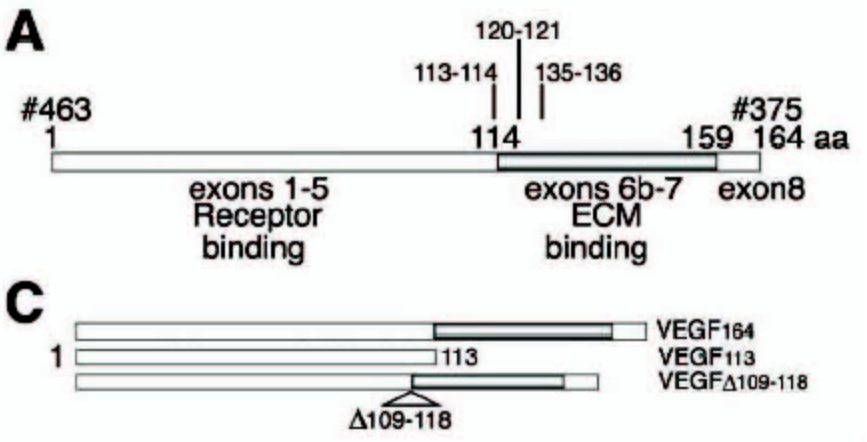
Angiogenin

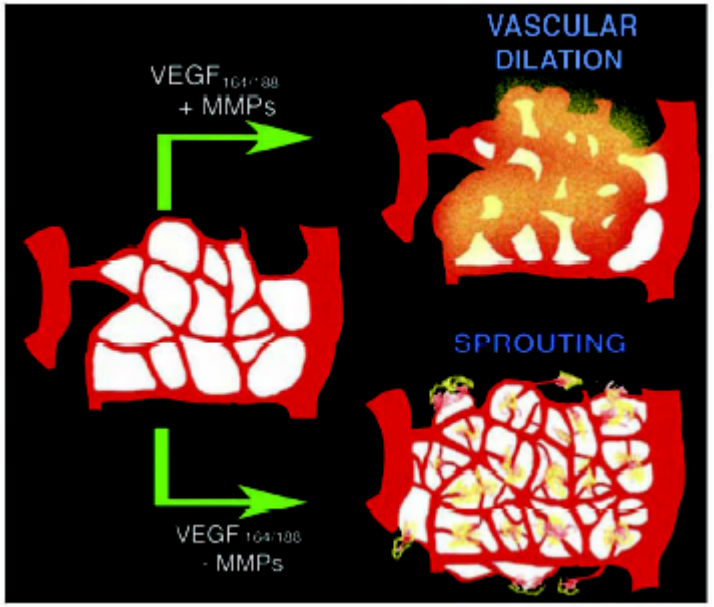
TGF (Transforming Growth Factor),….

ECM/MMP Regulation of VEGF

Lee, Jilani, Nikolova, Carpizo, Iruela-Arispe JCB. 2005.

VEGF-A isoforms





soluble

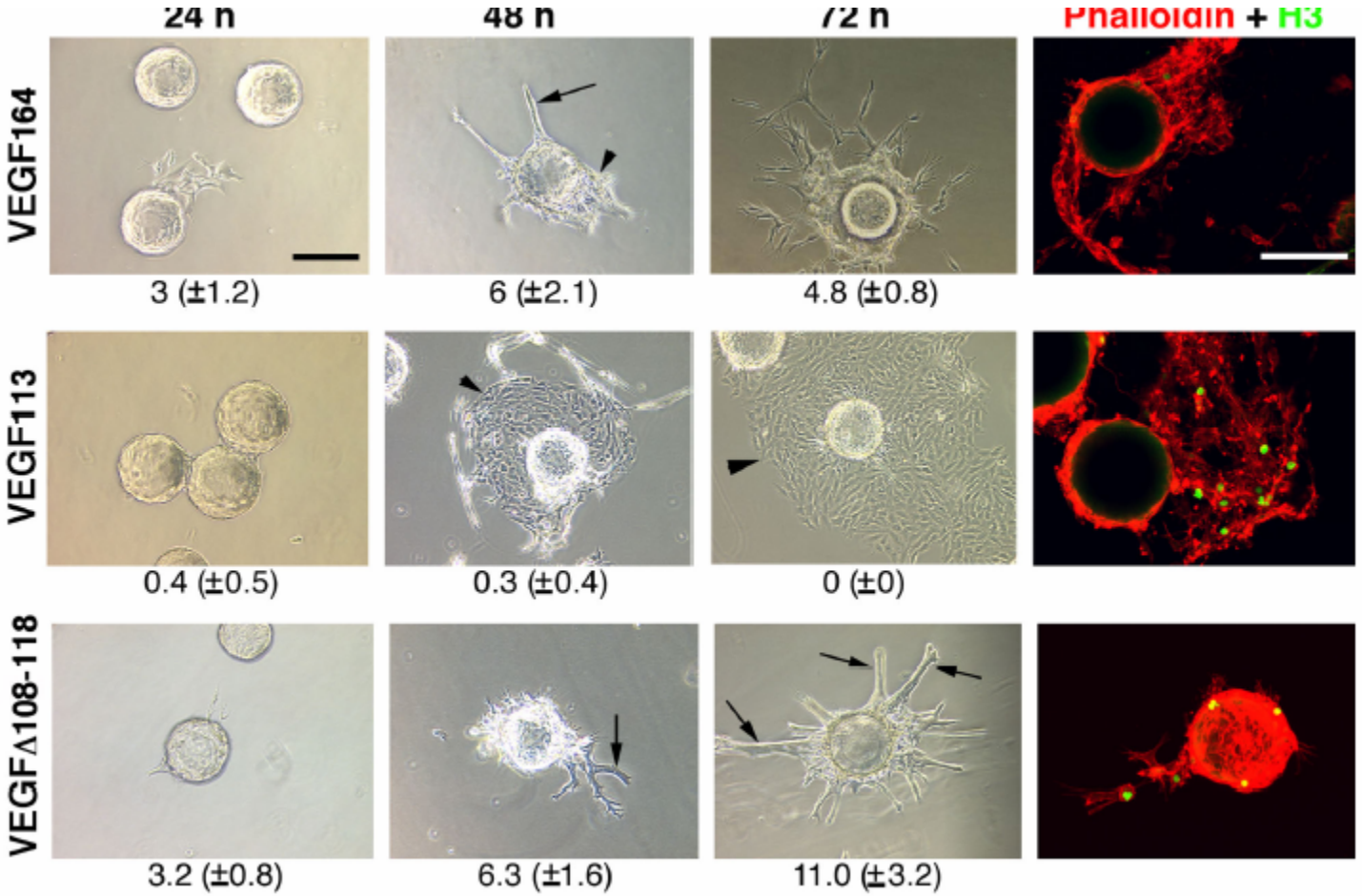
insoluble

- Insoluble VEGF (ECM) + Matrix Metalloproteinases (Endothelial cells) ⟶ Soluble VEGF + MMPs

- Different signaling outcomes through VEGFR2

Effect on EC growth

Beads containing cells embedded in fibrin/fibronectin gels

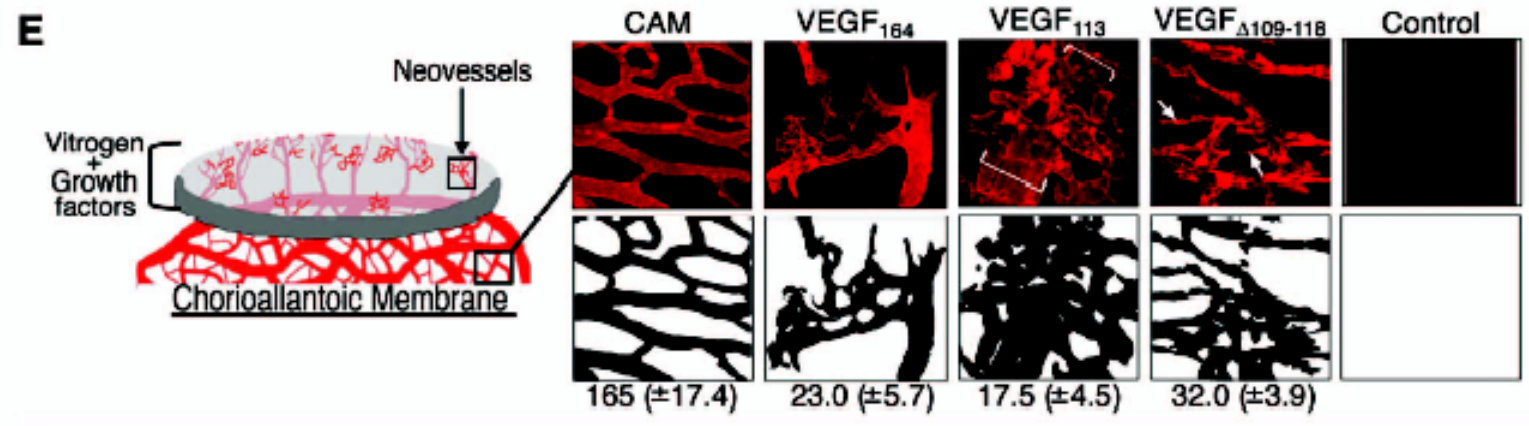


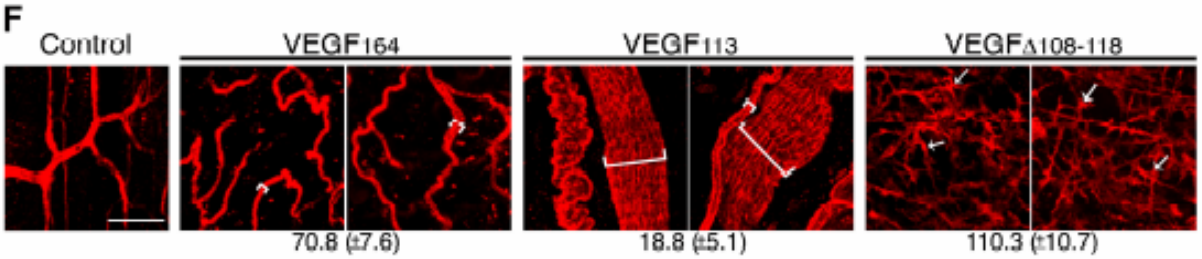
(stain to measure proliferation)

- VEGF 113: Sheets
  VEGFD108-118: Chords
  VEGF 164: Both

Effect on Vessel Morphology

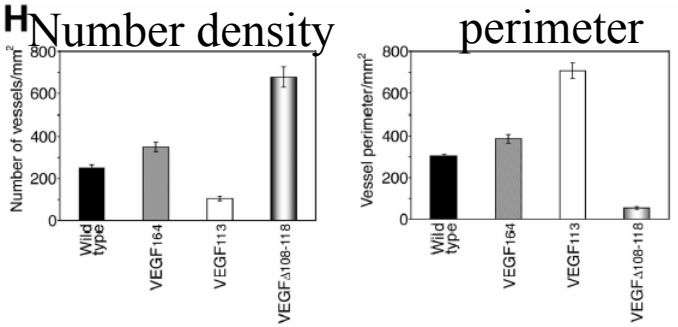
Wild Soluble Insoluble





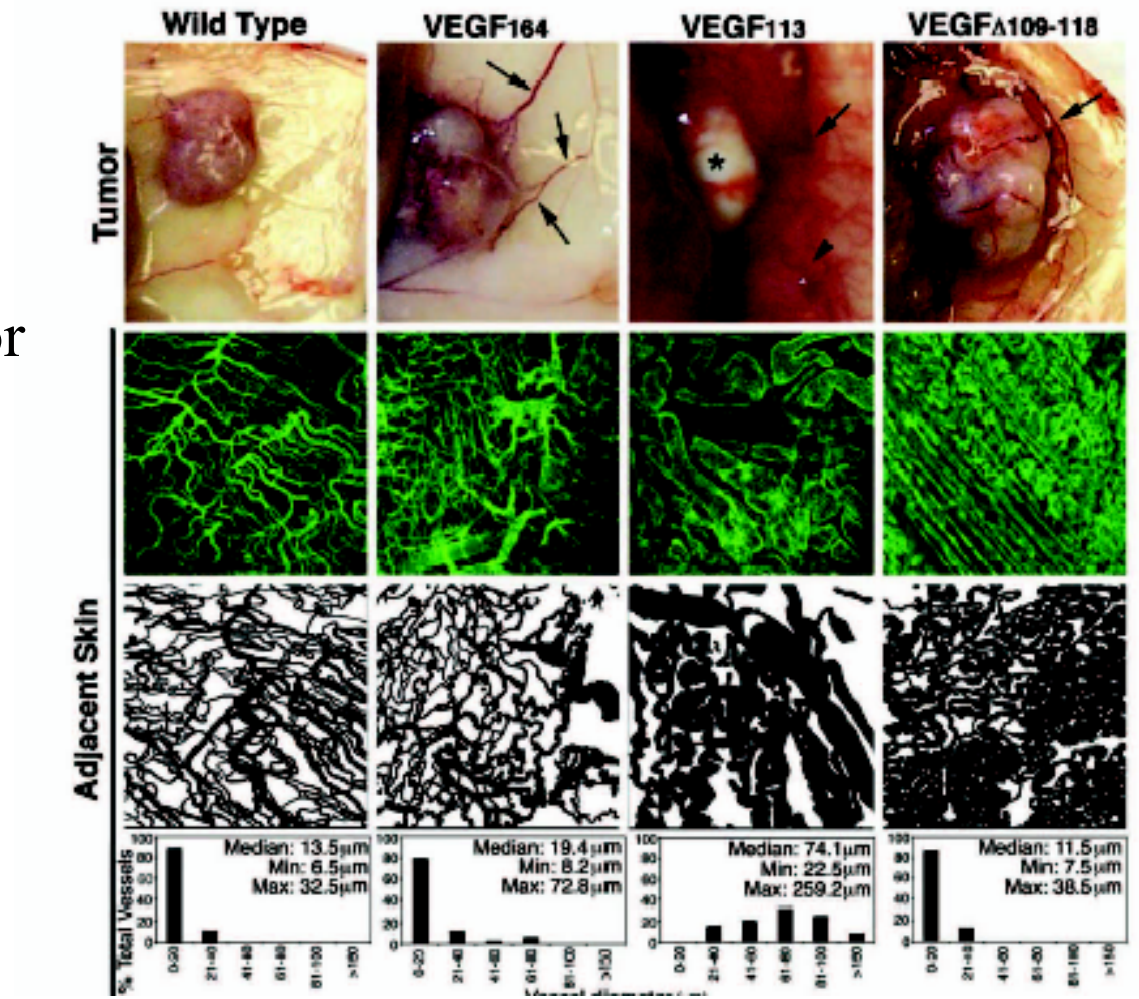
(diameters) 15μm 109μm 16μm

- Morphology strongly depends on type



Effect on tumor growth

- Soluble VEGF poor prognosticator of tumor progression
- Matrix-bound VEGF yields more efficient angiogenic response



Mathematical model

Anderson, Chaplain, Macdougall, Levine, Sleeman, Zheng,Wise,Cristini BMB 2005,...

Endothelial cell concentration *e*:
form the lining of the capillary

Chemotaxis Haptotaxis

$$\frac{\partial e}{\partial t} = \bar{D}_e \nabla^2 e - \nabla \cdot \left(\left(\frac{\bar{\chi}_c}{1 + \alpha c/\bar{c}_0} \nabla c + \bar{\chi}_f \nabla f + \chi_{\mathbf{u}} \mathbf{u} \right) e \right)$$

$$+ \bar{\rho}_{\mathrm{P}} \frac{e(\bar{e}_0 - e)}{\bar{e}_0} \mathcal{H}(c - \bar{c}^{\star}) \frac{c - \bar{c}^{\star}}{\bar{c}_0}$$

Proliferation

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

Decay

Uptake by the endothelial cells

$$0 = \bar{D}_c \nabla^2 c - \bar{\beta}_{\mathrm{D}} c - \bar{\beta}_{\mathrm{U}} c e/\bar{e}_0,$$

$$c = 1 \text{ on } \Sigma_{\mathrm{N}}$$

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

$$\frac{\partial f}{\partial t} = \eta_{\mathrm{P}} e - \eta_{\mathrm{U}} f e - \eta_{\mathrm{N}} \chi_{\Omega_{\mathrm{N}}} f,$$

production degradation

•Recast in a biased random-walk model to follow the evolution of the capillaries (Anderson, Chaplain)

Numerical method

- Level-set/Finite-element formulation (Mixed methods, LDG, EPC)

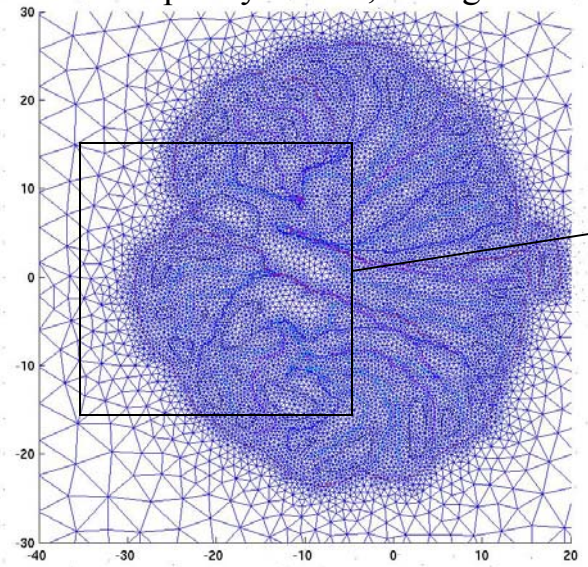
  Zheng, Wise, Cristini,. Bull. Math. Biol. 2005

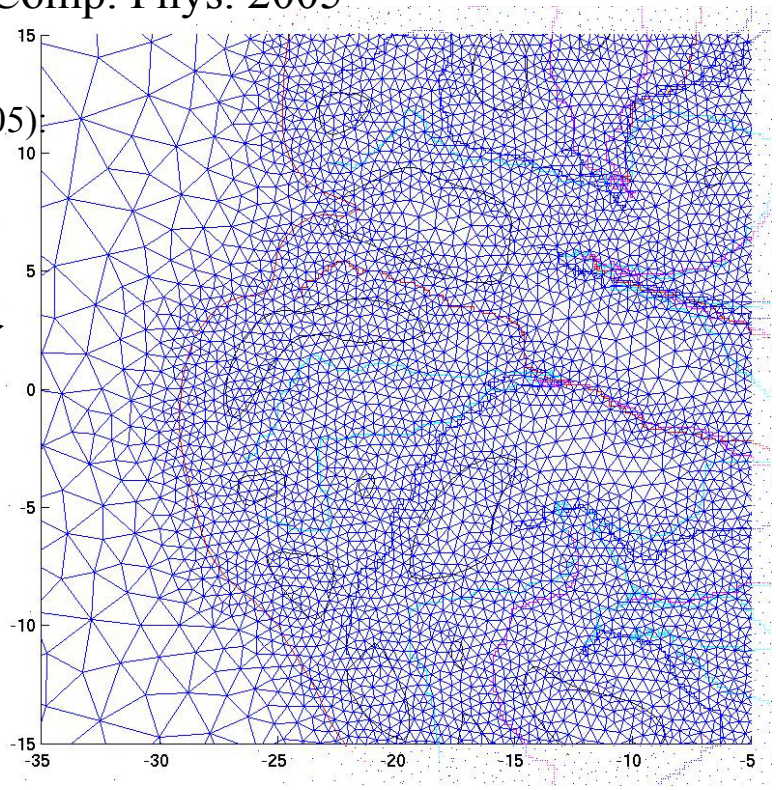
  Zheng, Anderson, Cristini, J. Comp. Phys. 2005

  Zheng, Lowengrub, Anderson, Cristini, J. Comp. Phys. 2005

- Adaptive computational mesh

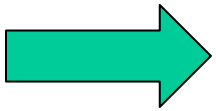
Cristini *et al.* J. Comp. Phys. 2001, Zheng et al. J. Comp. Phys (2005):





Mesh: System of springs (energy)

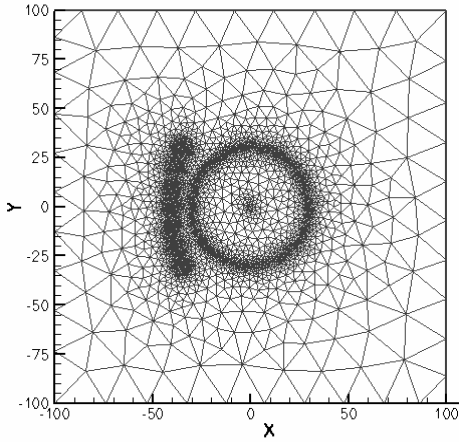
Local Operations ⟶ Minimum energy ⟶ Optimal mesh

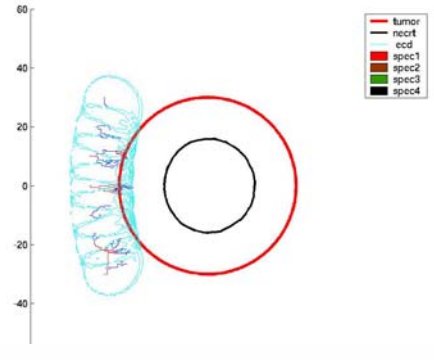


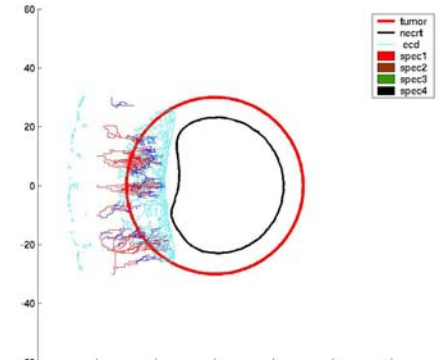
Resolution of physical scales $l_{eq} = \min(l_1, l_2, \ldots)$

•Vary D_c and β_D to mimic Soluble/Insoluble VEGF-A Parameters from literature.

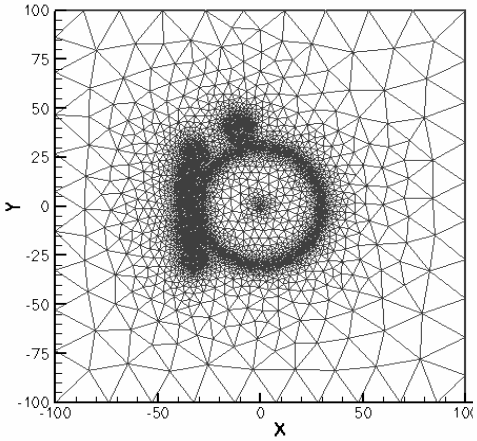
Day 0 | Day 10 | Day 20

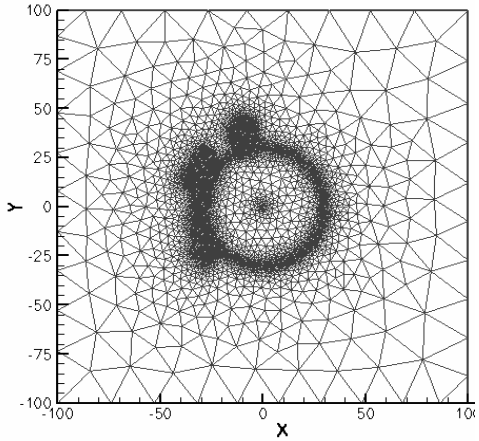






Insoluble

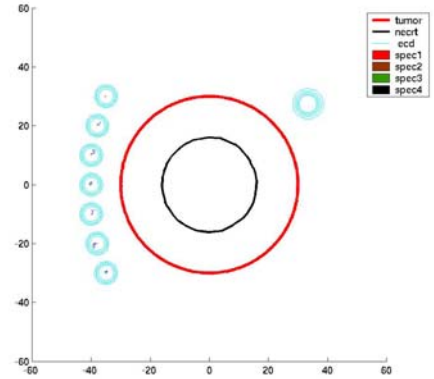


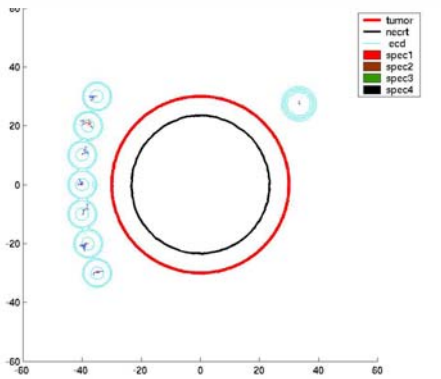


Partly soluble

•Chemotaxis/ Branching enhanced with insoluble VEGF

•Qualitative agreement with experiments



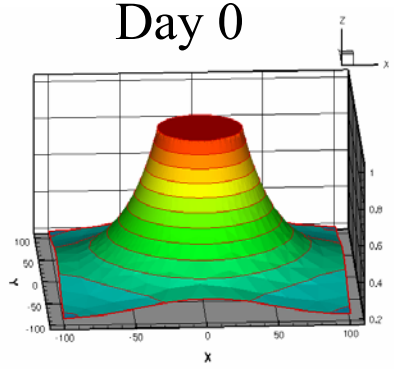
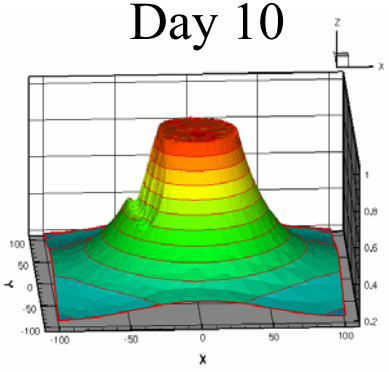
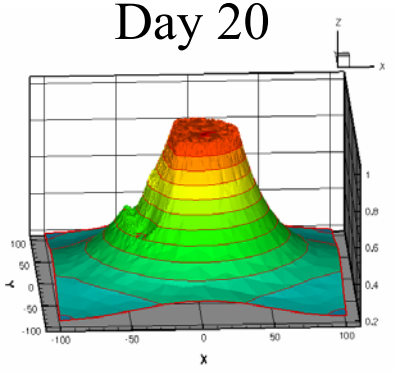


Soluble

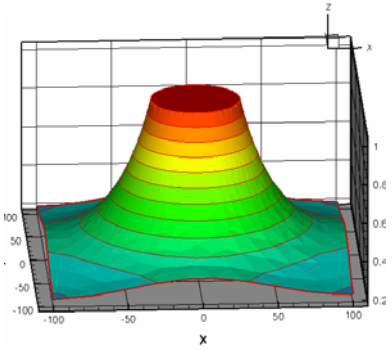
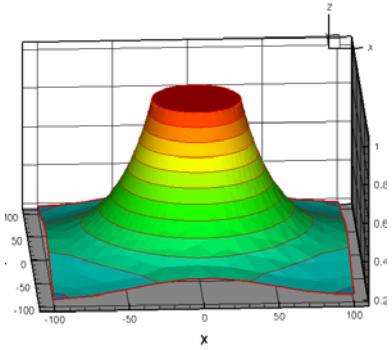
Mechanism

Distribution of VEGF:

Day 0 | Day 10 | Day 20

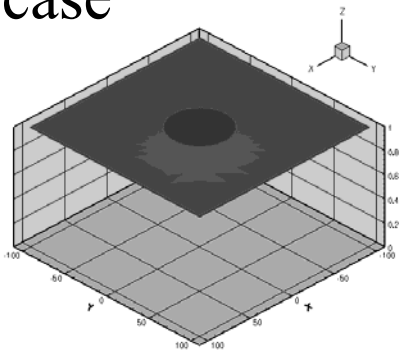
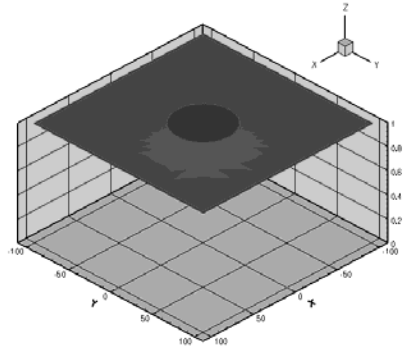




Insoluble

Partly soluble

- Uptake of ECM-bound VEGF-A by EC produces large gradient in insoluble case
- Gradients enhance chemotaxis

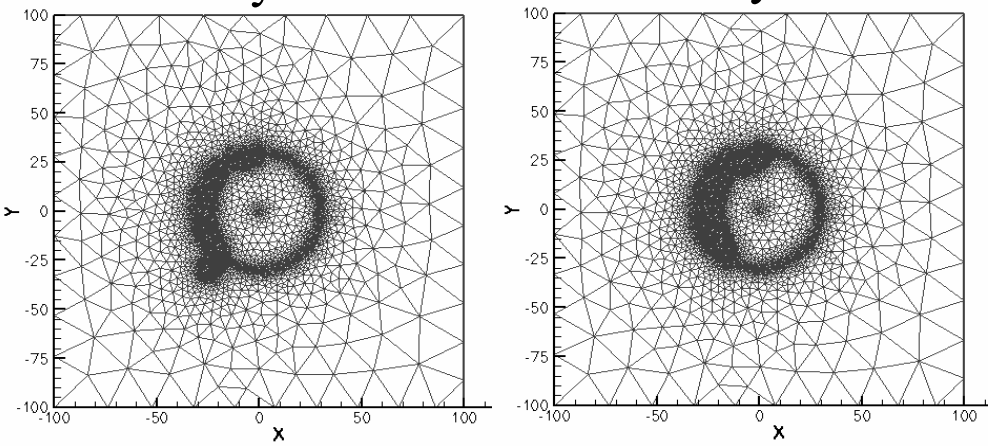



Soluble

Later times

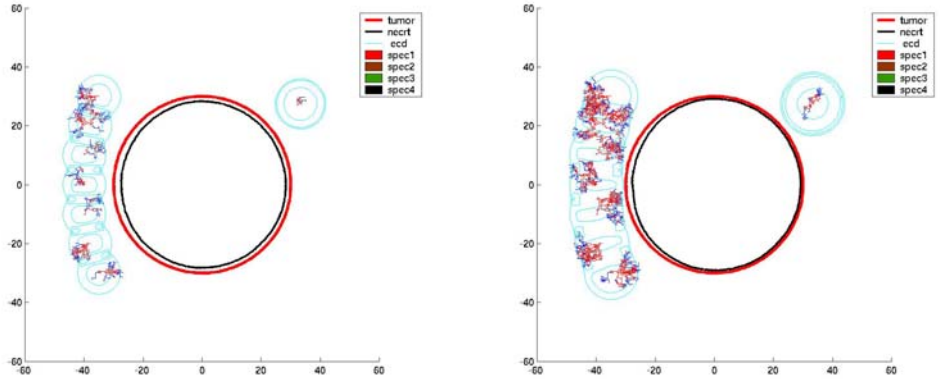
Day 45 | Day 70

Partly Soluble



- Brush-border effect
- penetration

Soluble

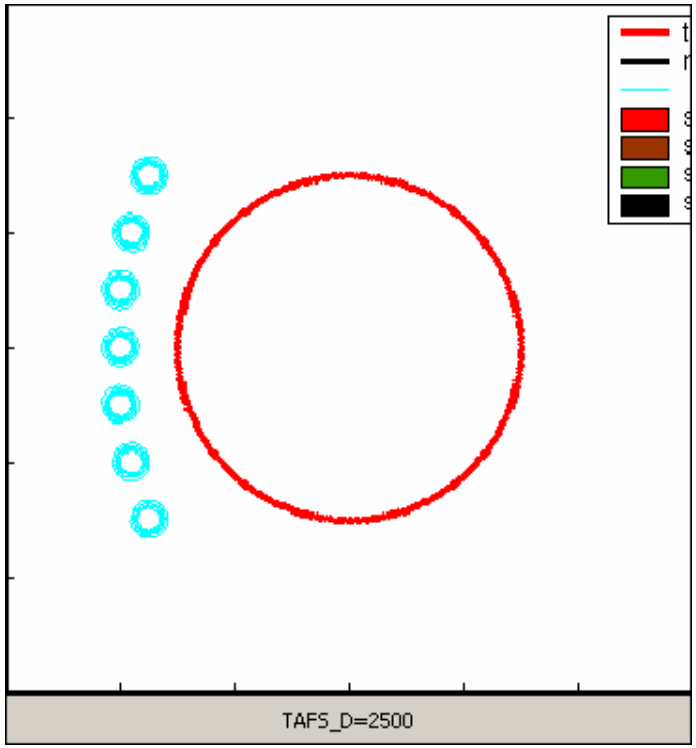


- Irregular vascular development
- No penetration

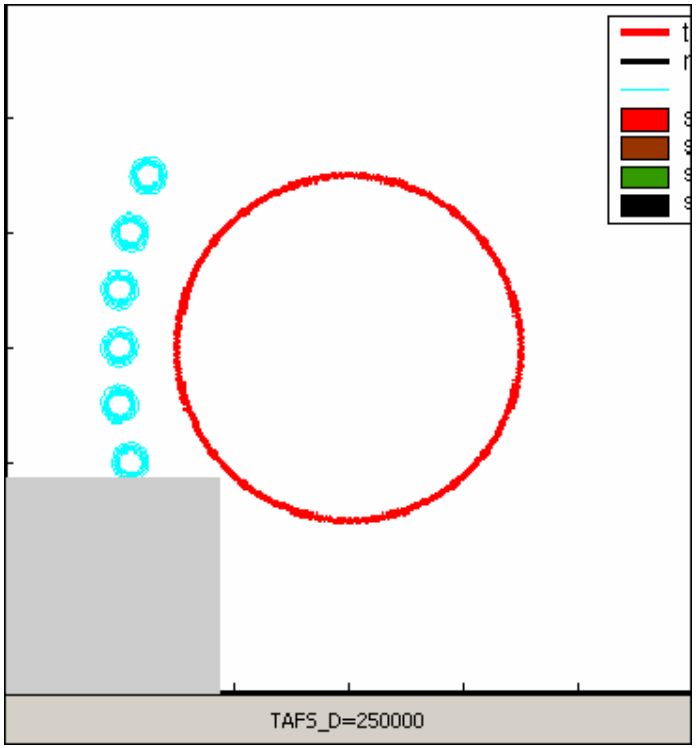
- Qualitative agreement with experiment
- Experimental results consistent with increased D_c and/or decreased β_c

Movies

Insoluble



Soluble



More sophisticated model

Insoluble

$$\frac{\partial C_I}{\partial t} = \nabla \left(D \nabla C_I \right) - \beta_D C_I - \beta_U C_I \frac{e}{e_0} - \beta_{cleave} \frac{e}{e_0} C_I$$

Cleaving

Soluble

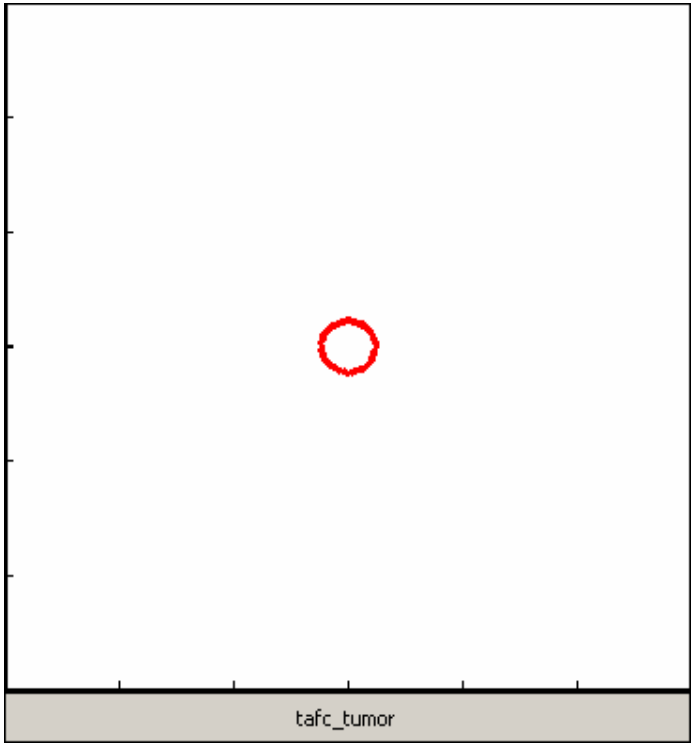
$$0 = D_{sc} \nabla^2 C_S - \beta_{SD} C_S - \beta_{SU} C_S \frac{e}{e_0} + \beta_{cleave} \frac{e}{e_0} C_I$$

- Variable diffusion for insoluble TAF

- Test coupling with full tumor model
  - -tumor and vessel development nonlinearly coupled

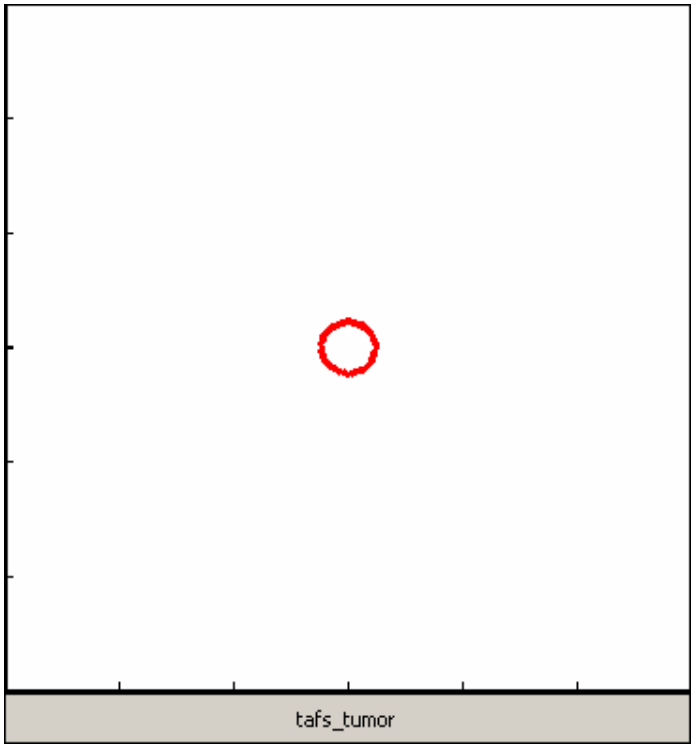
Fully coupled model

Insoluble



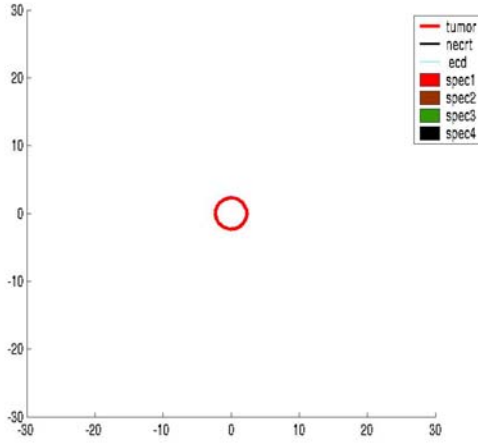
- Brush-border effect
- Penetration
- Growth of tumor

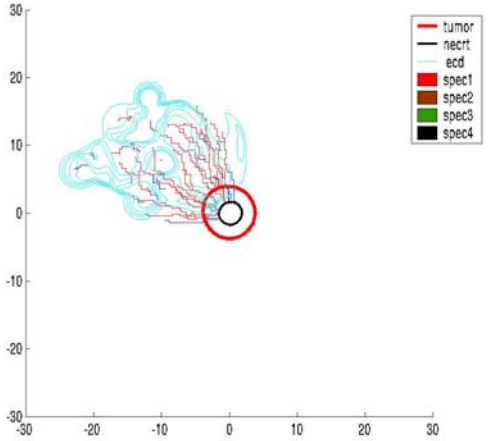
Soluble

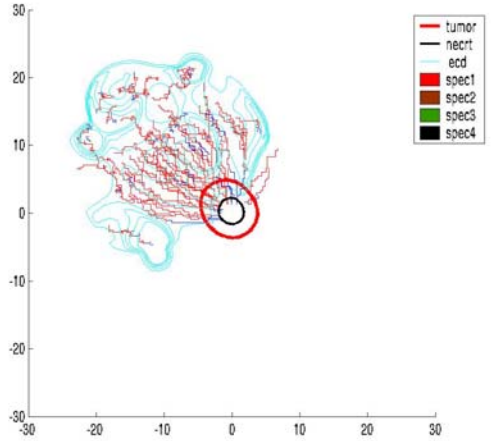


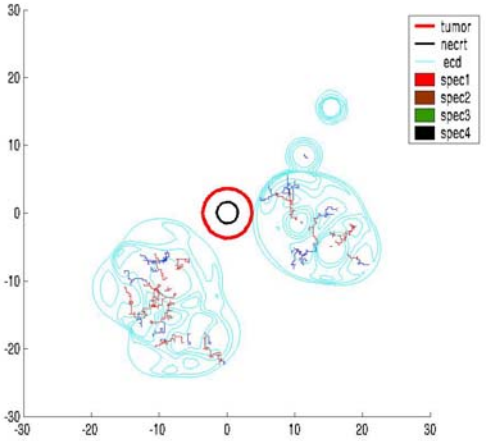
- Irregular vascular development
- little penetration
- Less growth

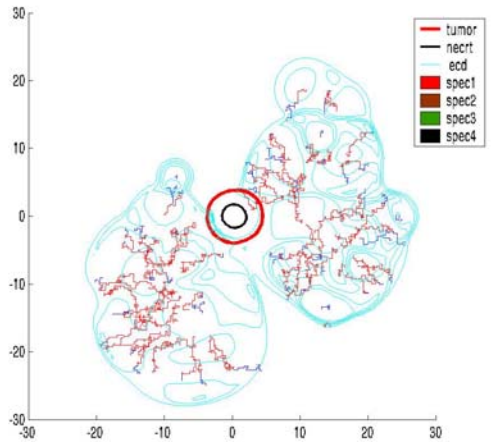
Stills


tumor
necrt
ecd
spec1
spec2
spec3
spec4


tumor
necrt
ecd
spec1
spec2
spec3
spec4

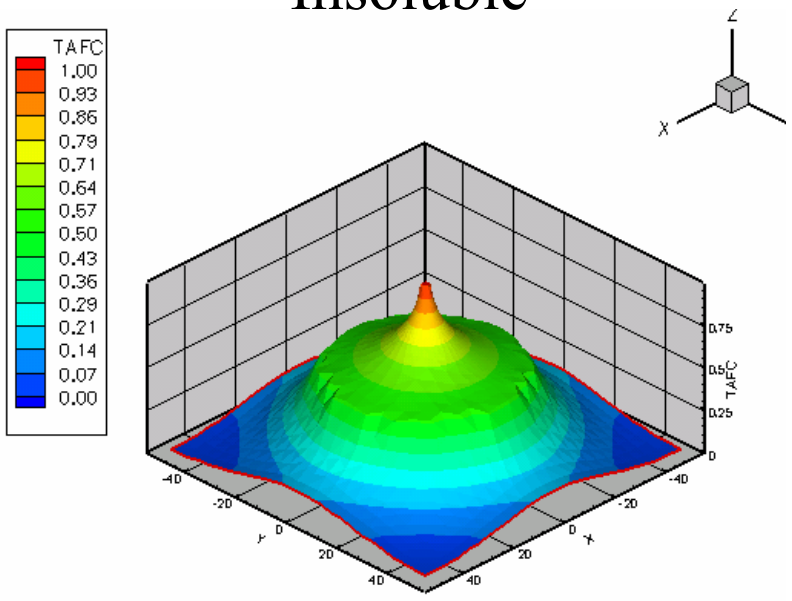

tumor
necrt
ecd
spec1
spec2
spec3
spec4

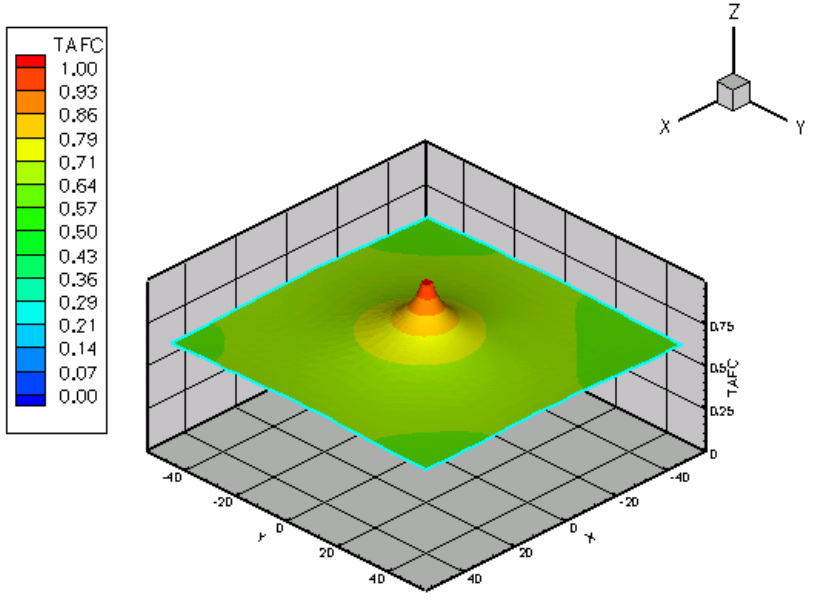

tumor
necrt
ecd
spec1
spec2
spec3
spec4


tumor
necrt
ecd
spec1
spec2
spec3
spec4

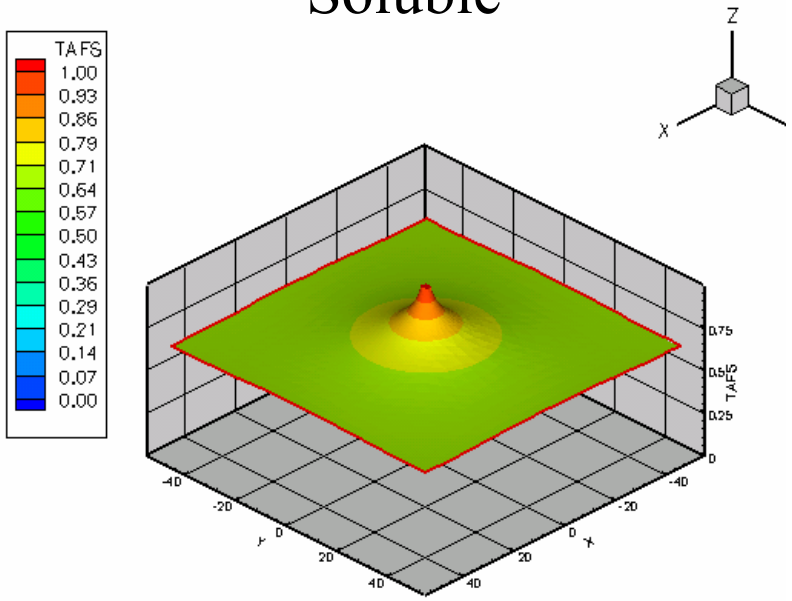
VEGF

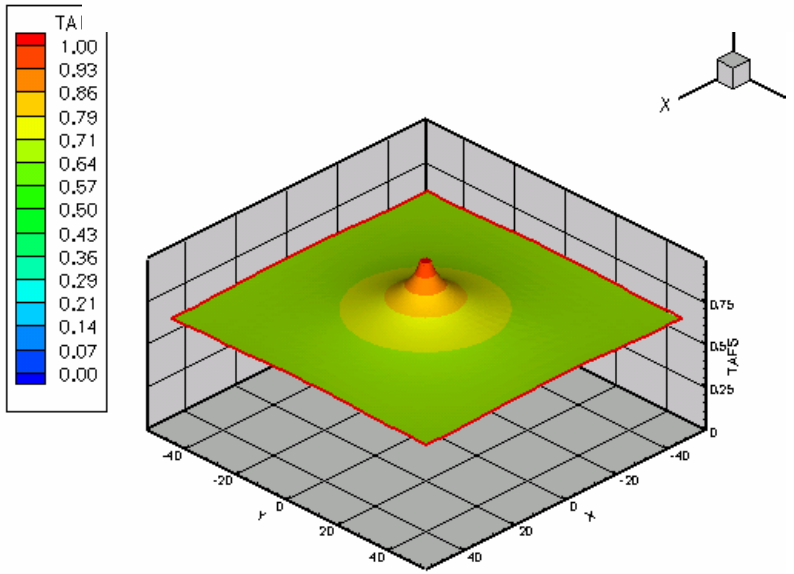
Insoluble





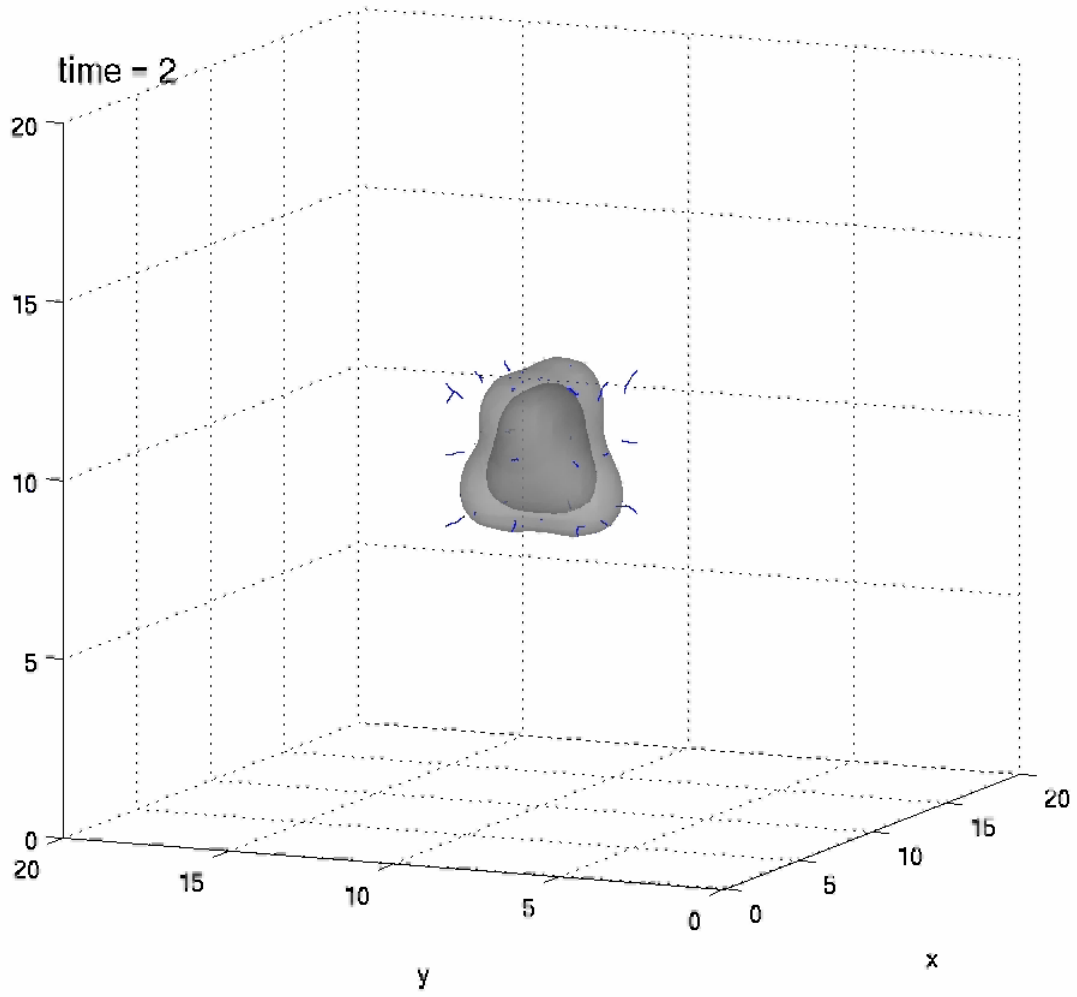
Soluble



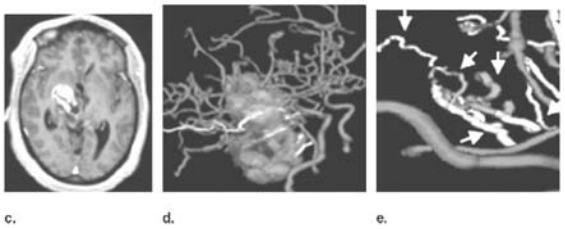


Vascular cooption

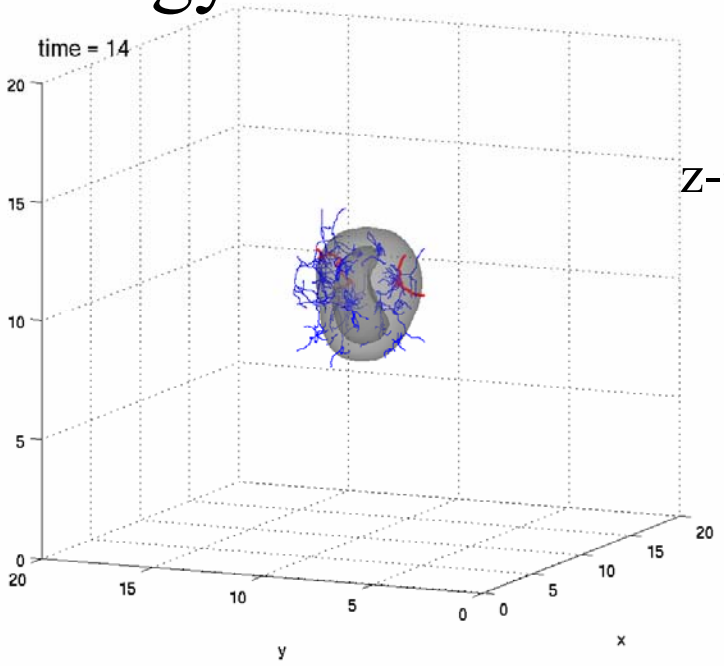
- Initial capillaries present
- Growing tumor surrounds vessels
- Uses up available vasculature
- Secondary angiogenesis
- Observe bursts of growth as the nutrient supply increases (like a fire)



Bullitt et al (2005). Glioma



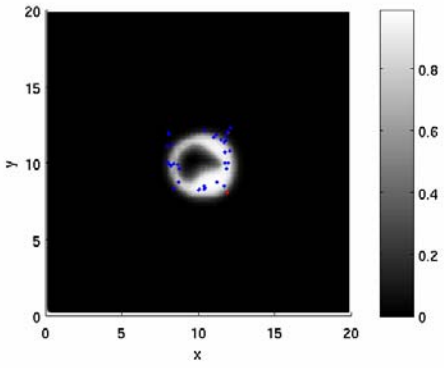
Histology Slices

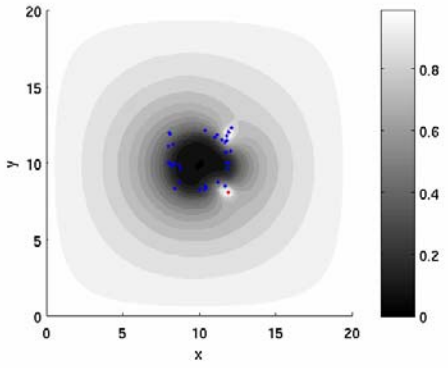


Viable cells

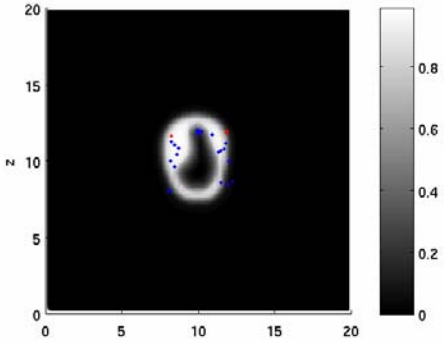
Nutrient

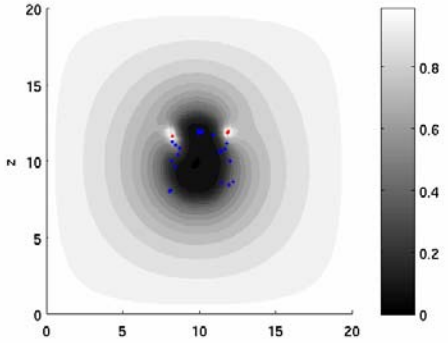
z-slice



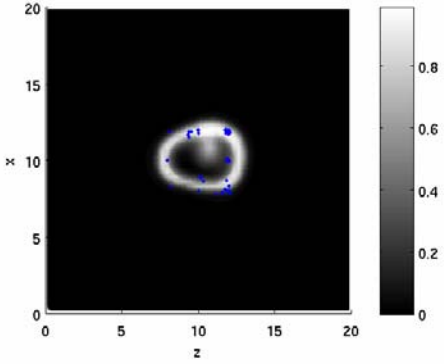


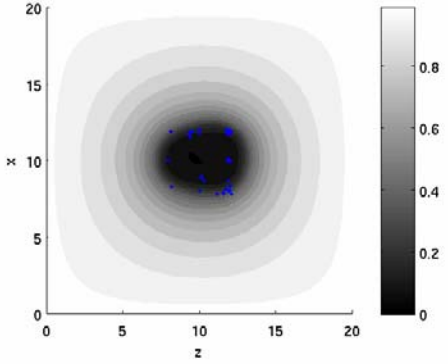
x-slice



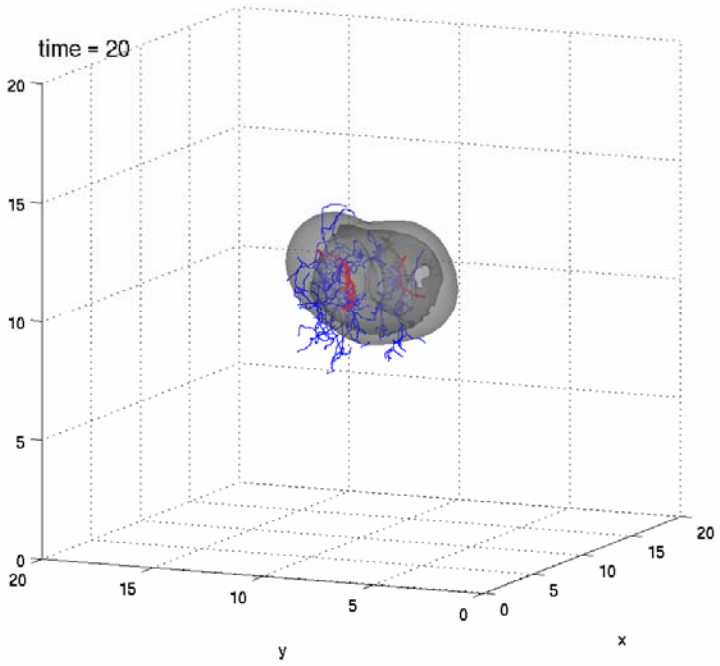


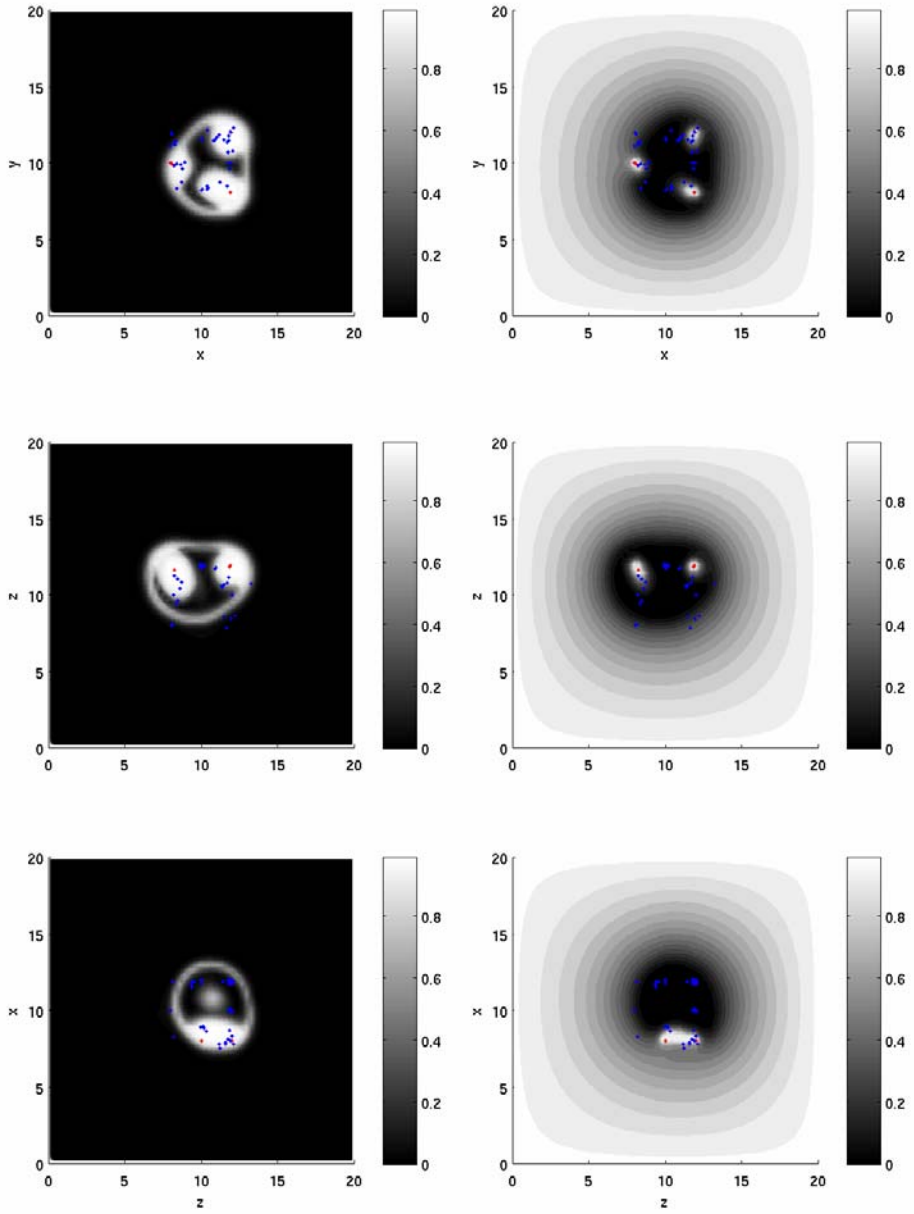
y-slice



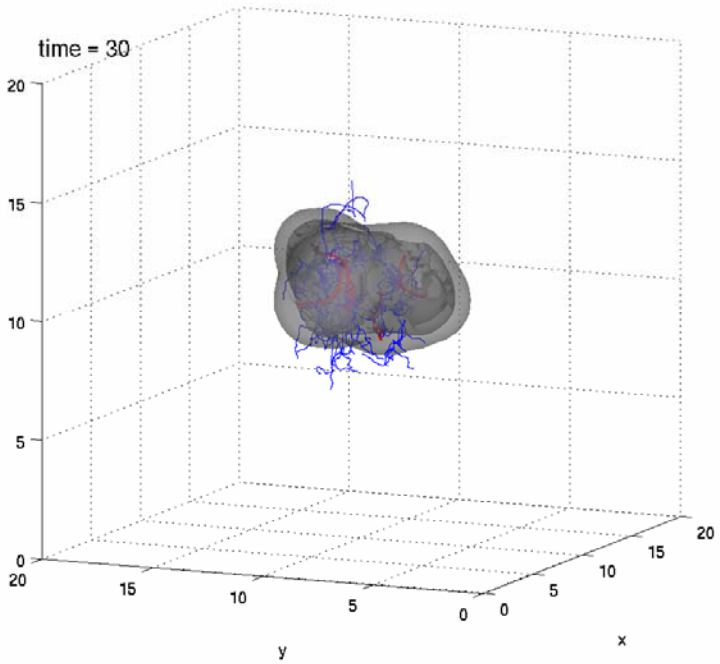


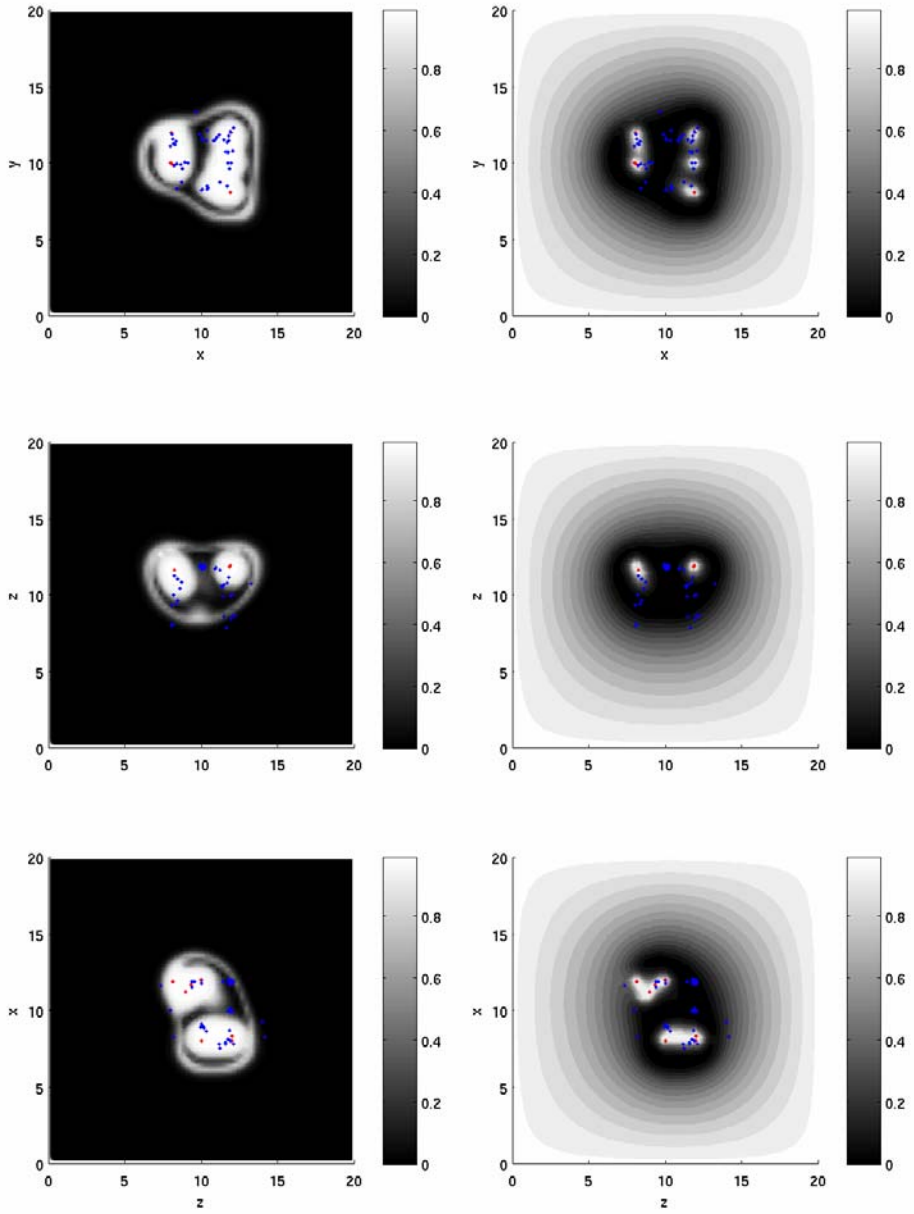
- Note nutrient supply localized near red (nutrient-releasing) vessels
- Observe corresponding (tumor) near vessels cell growth

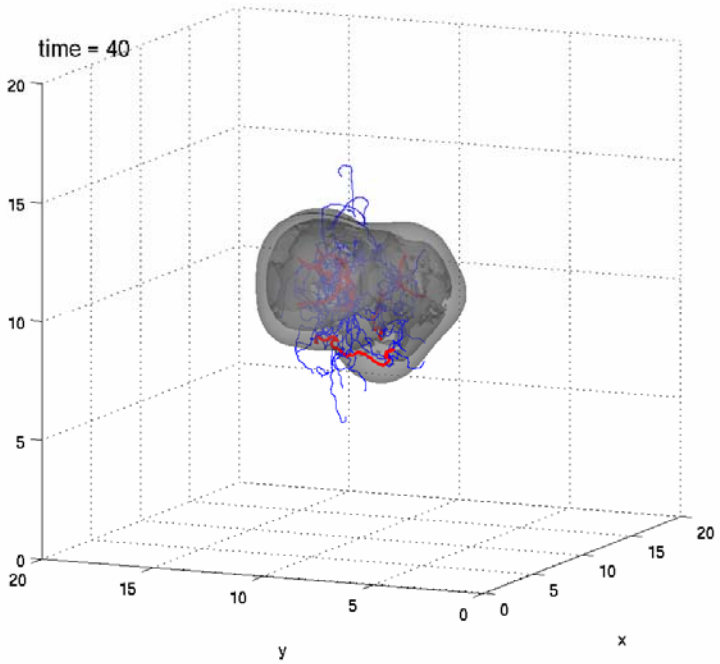


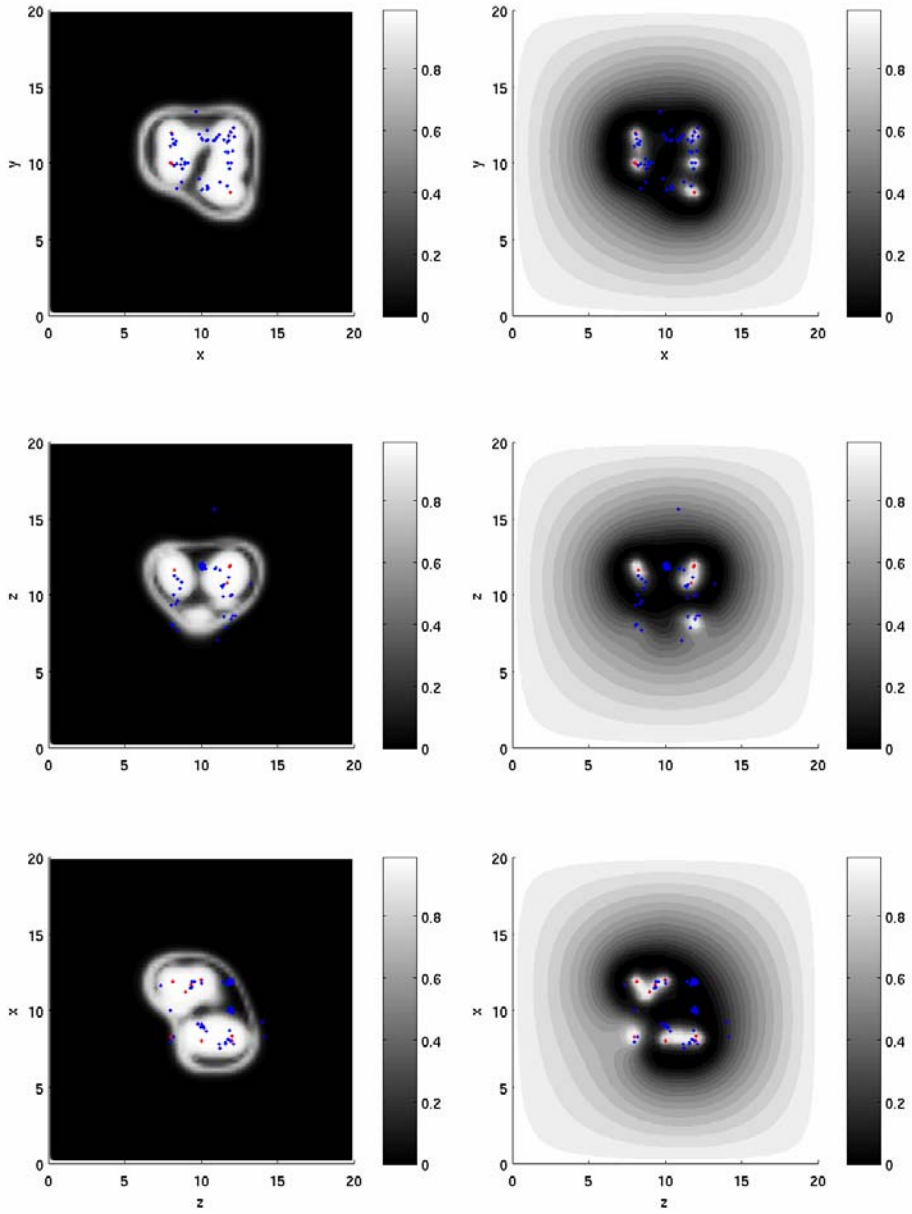


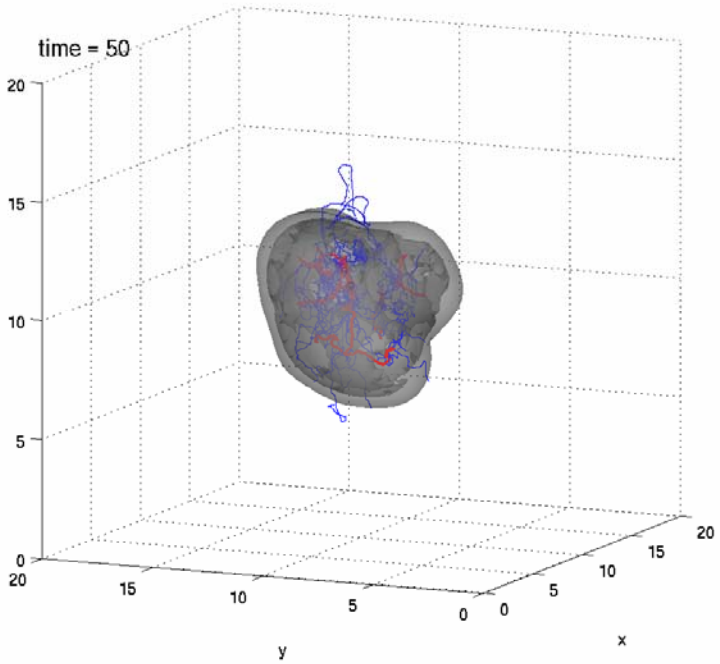
•Regions of hypoxia separate cell clusters

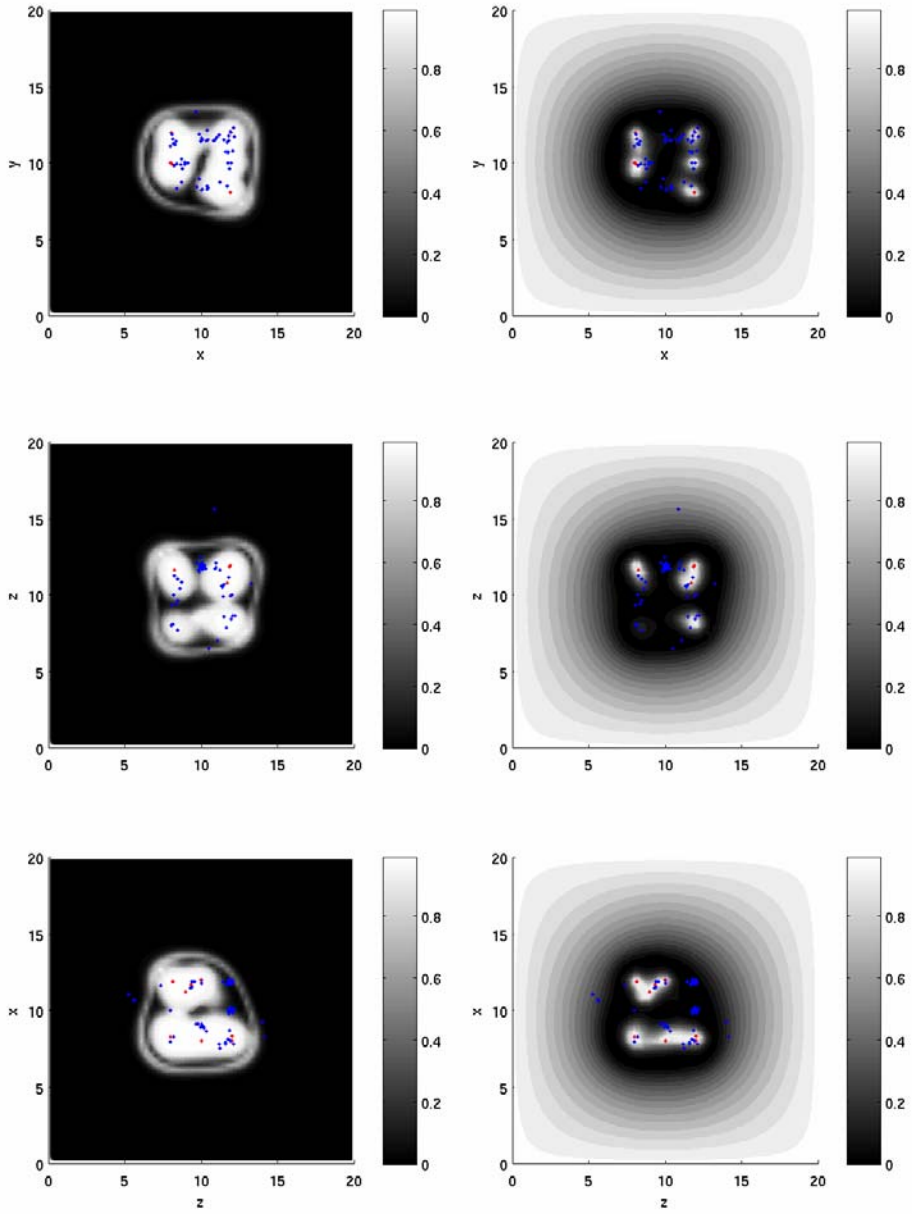

time = 30
20
15
10
5
0
y
x

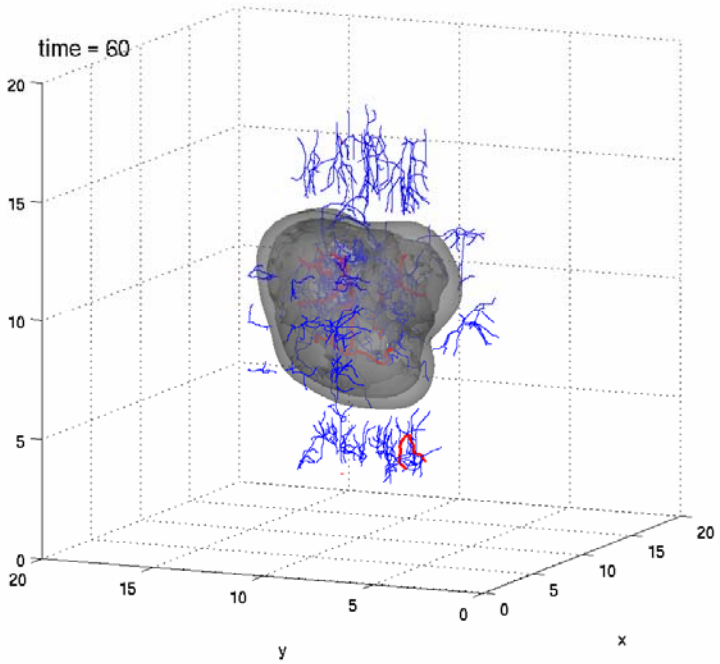

y
x
z
0.8
0.6
0.4
0.2
0
5
10
15
20

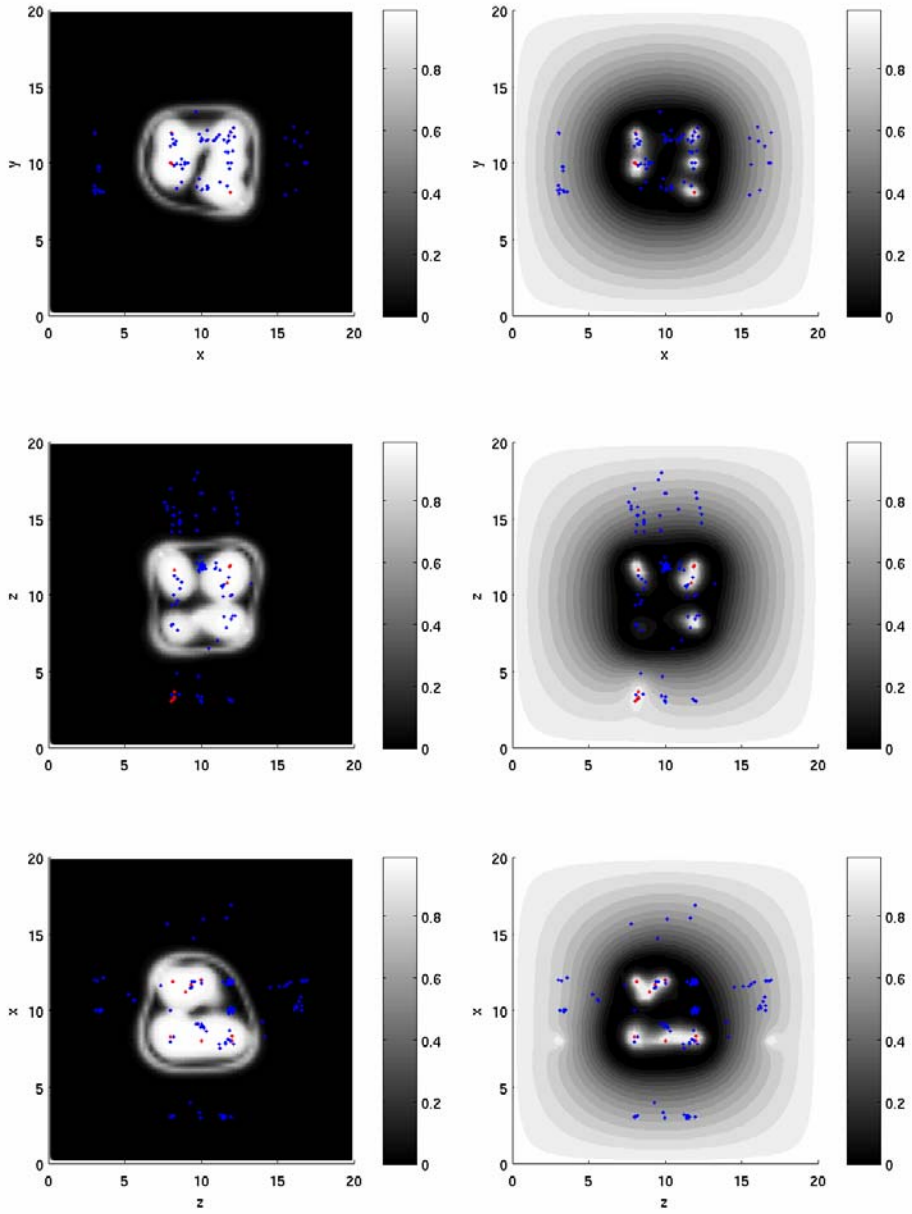

time = 40
20
15
10
5
0
y
x

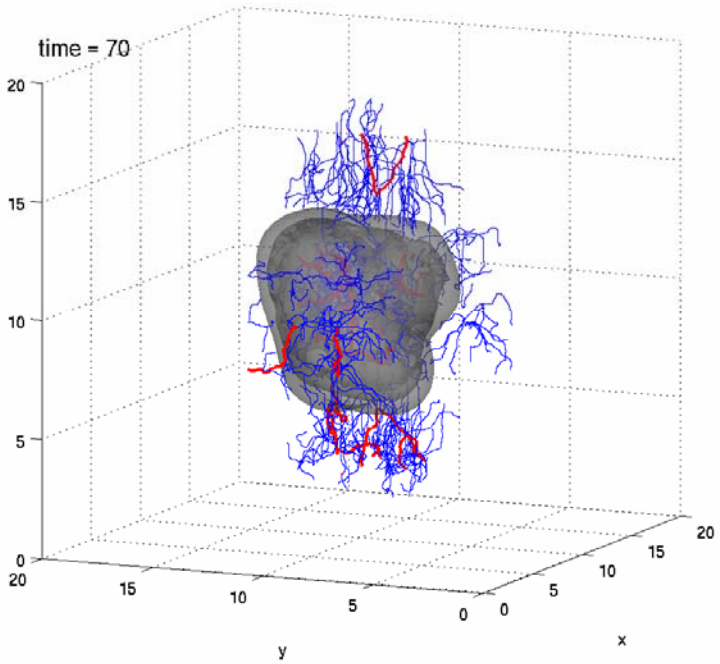

y
x
z
0.8
0.6
0.4
0.2
0
5
10
15
20

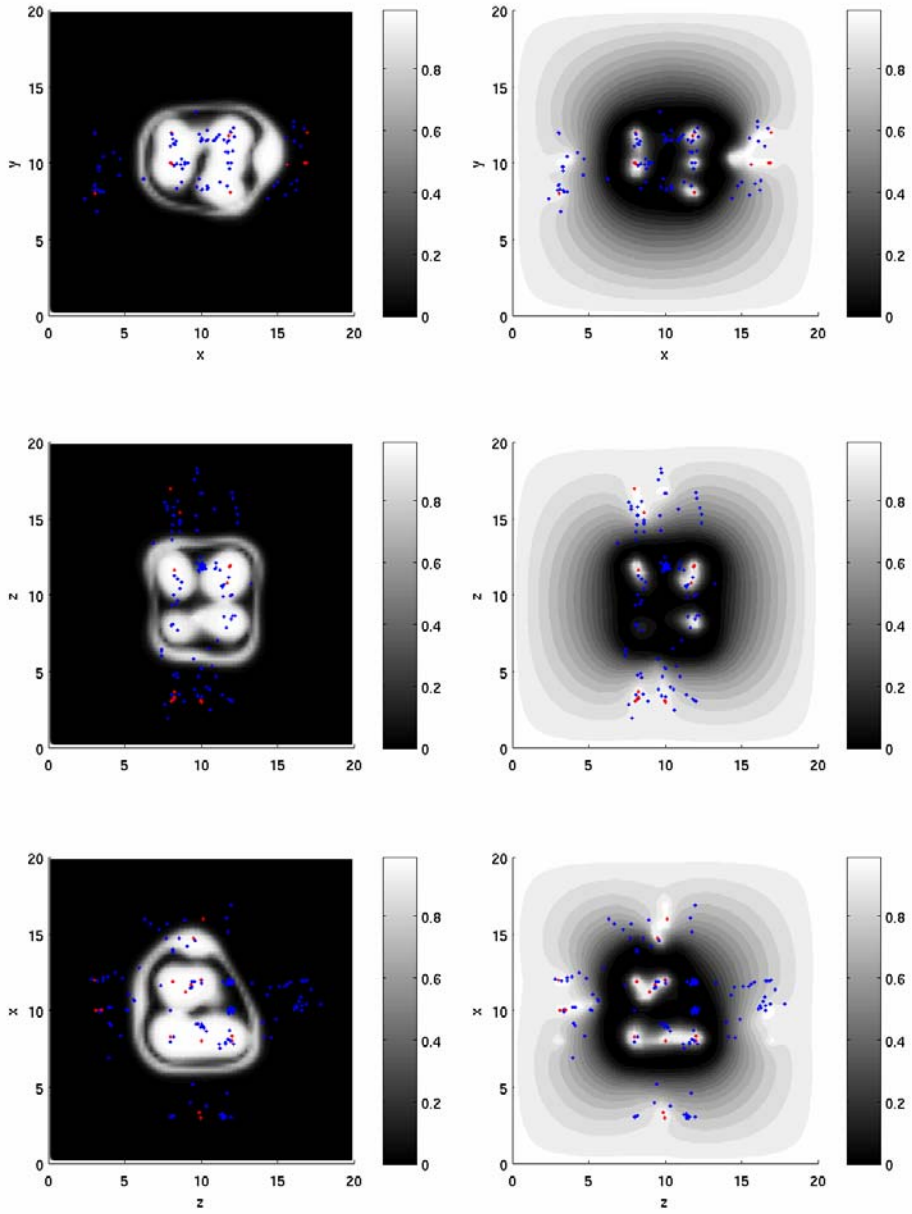

time = 50
20
15
10
5
0
y
x

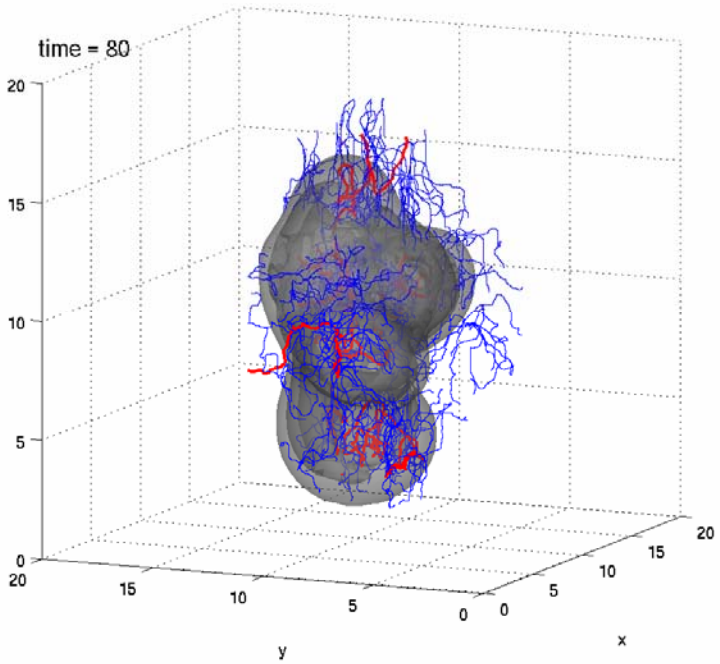

y
x
z
0.8
0.6
0.4
0.2
0
5
10
15
20

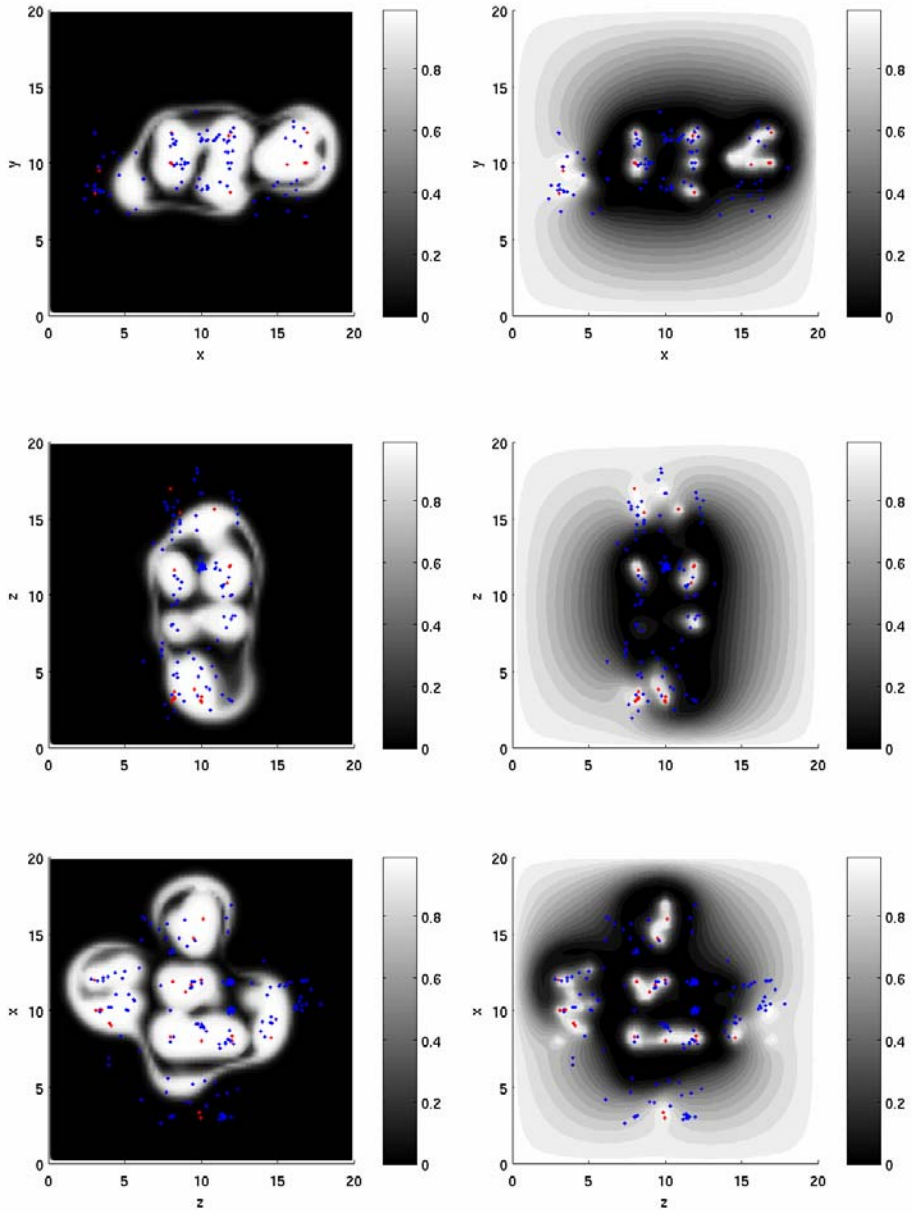

time = 60
20
15
10
5
0
y
x

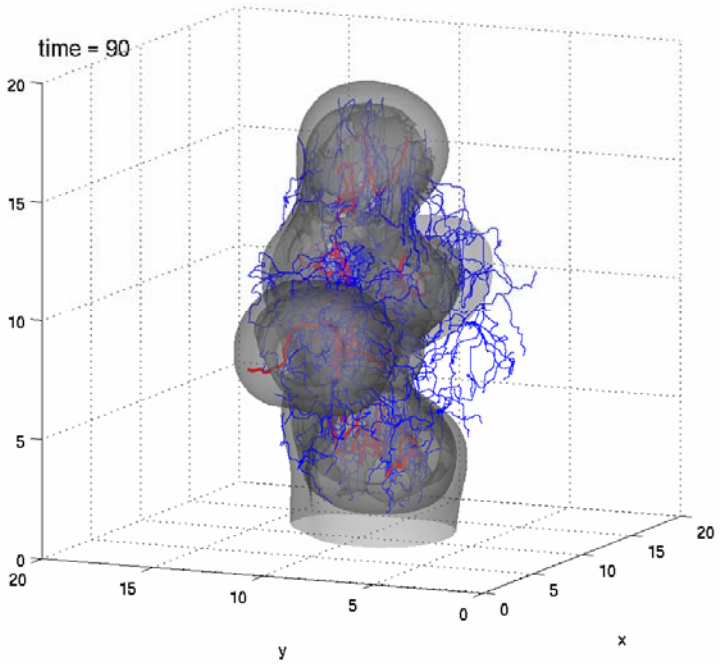

y
x
z
x
z

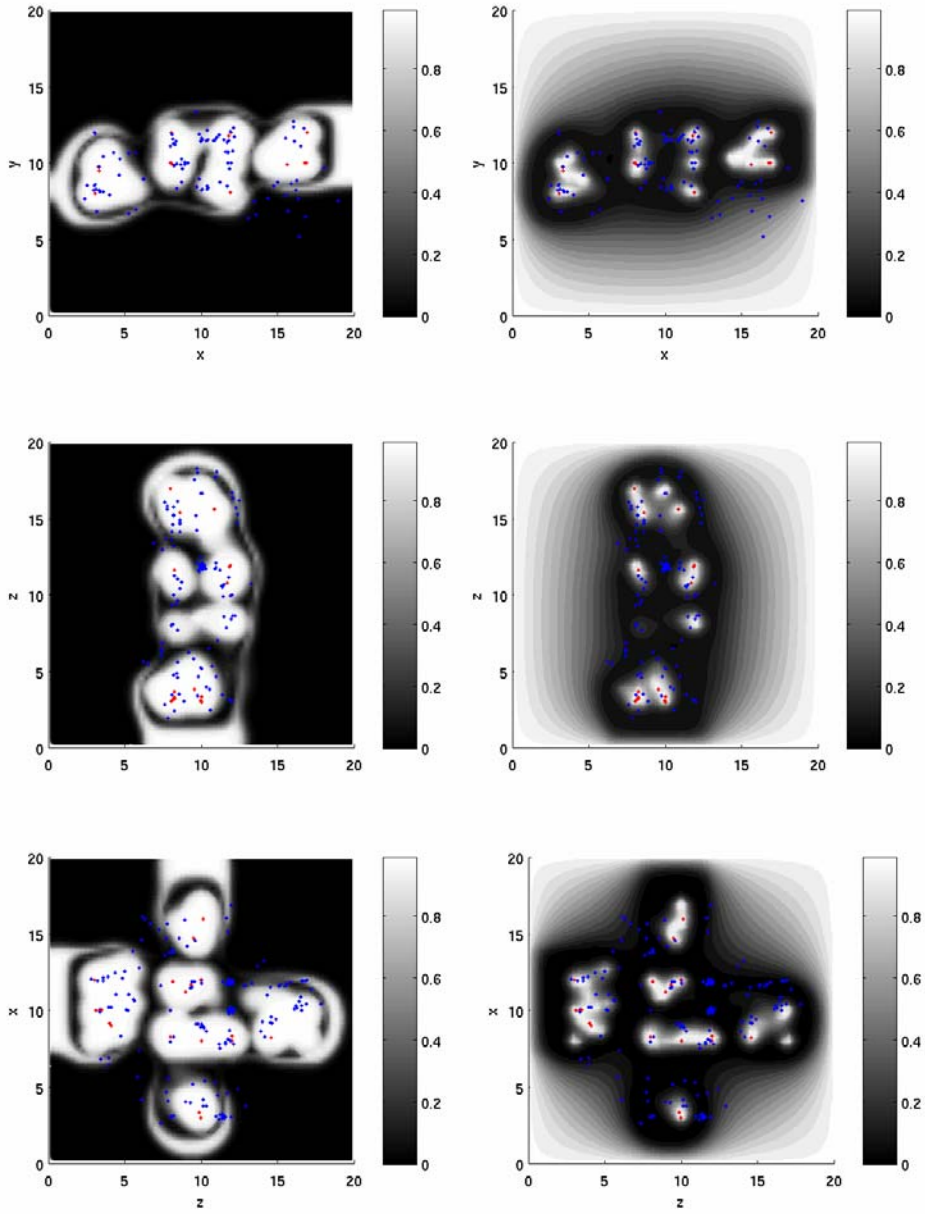

time = 70
20
15
10
5
0
y
x


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

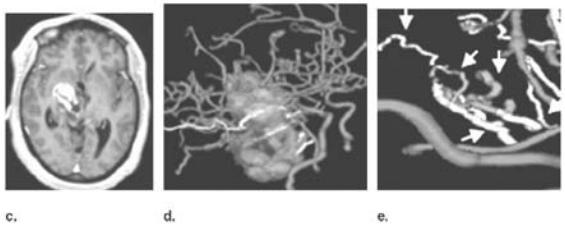

time = 80
20
15
10
5
0
y
x


y
x
z
x
z

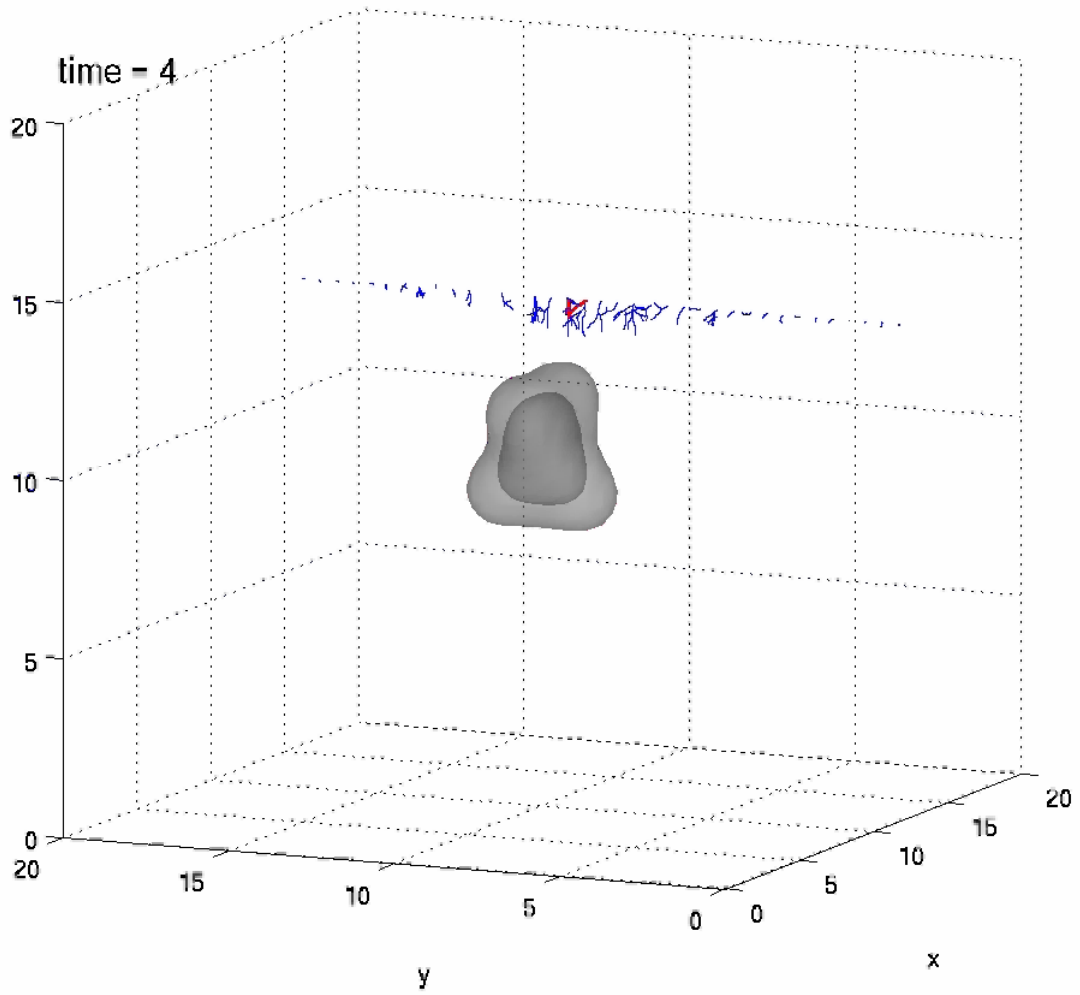




Bullitt et al (2005). Glioma

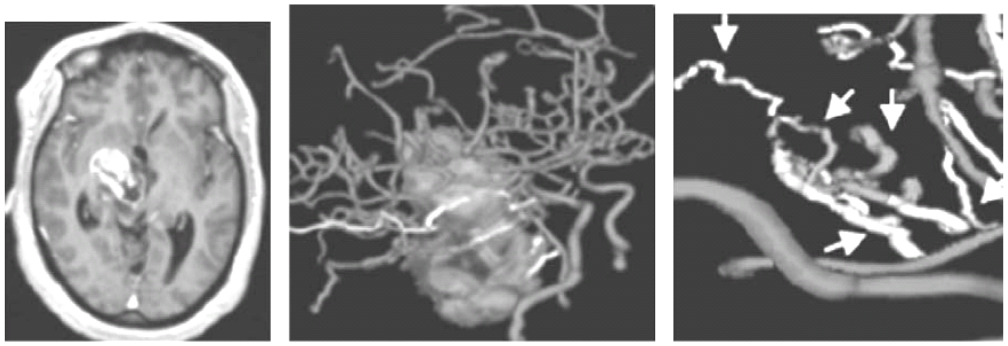


Vascular co-option

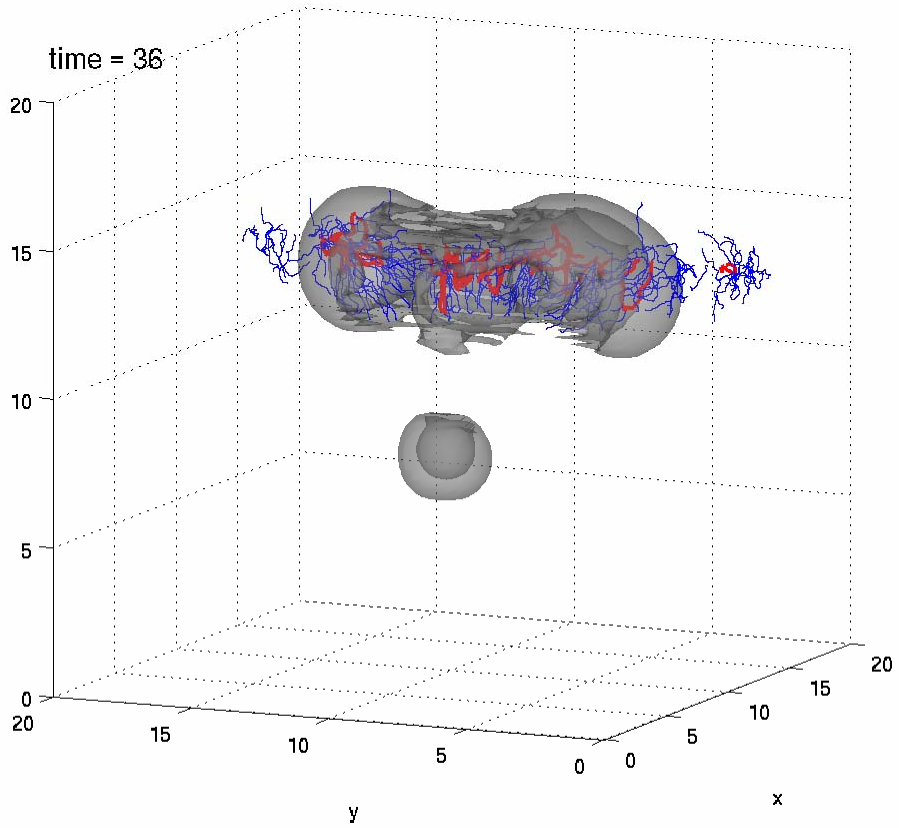


- Initial capillary present
- Growing tumor surrounds vessels
- Continuous angiogenesis.

Bullitt et al (2005). Glioma

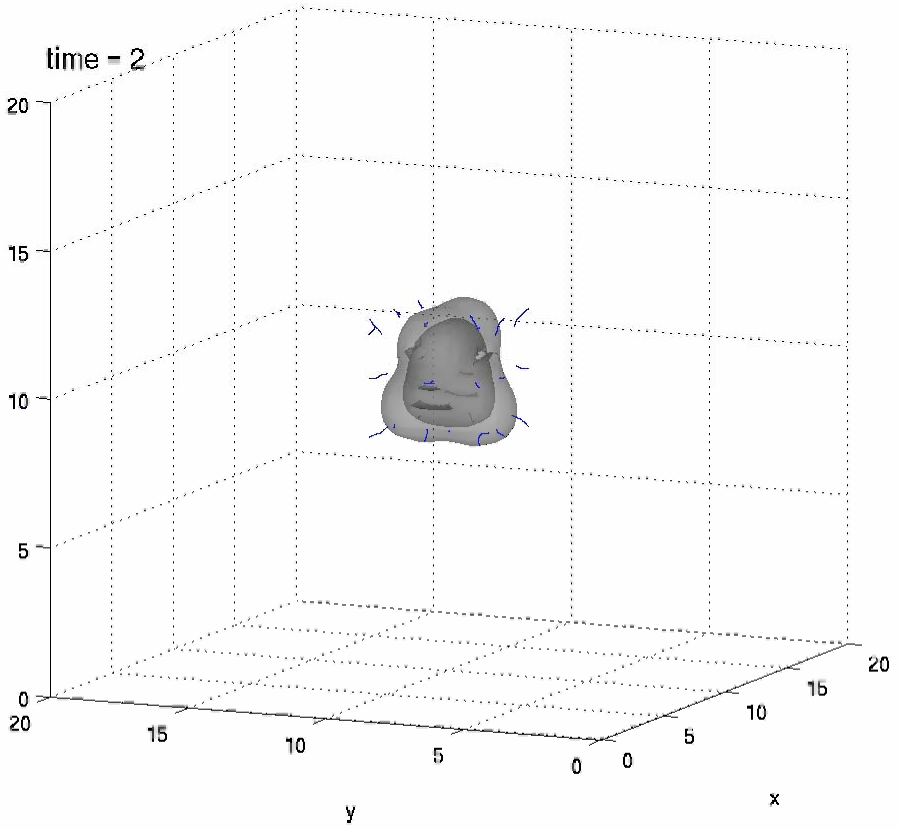


c. d. e.

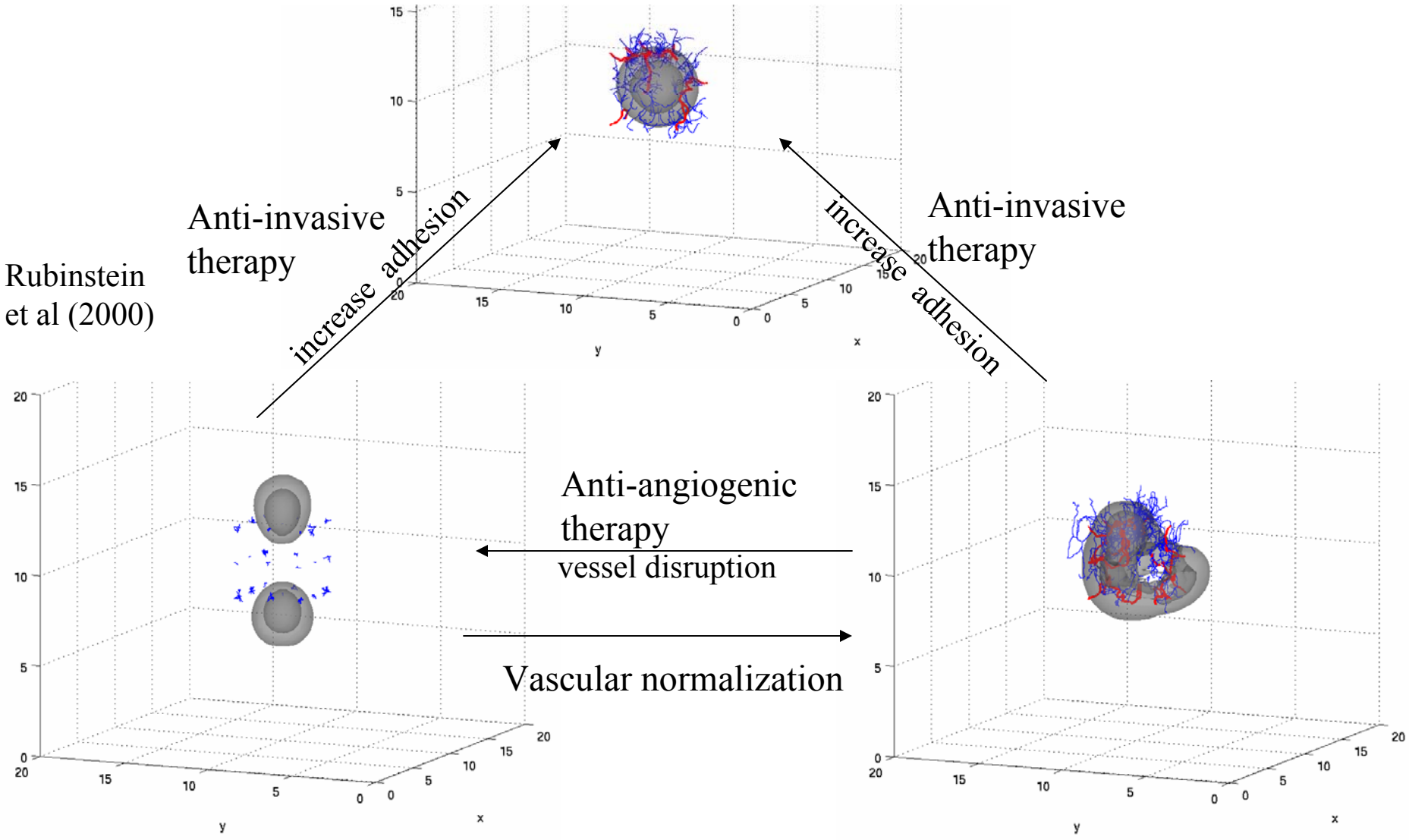


Effect of vessel aging

- As vessels age, the perfusion is reduced.
- Typically angiogenesis occurs very close to the tumor
- Observe bursts of growth as the nutrient supply increases and decreases (like a fire)



Implications for therapy



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

Conclusions

- Developed a framework to model tumors through all phases of growth

•Nonlinear coupling of neovascular development and tissue/tumor growth

- Qualitative agreement with experiments by Iruela-Arispe for neovascular morphology

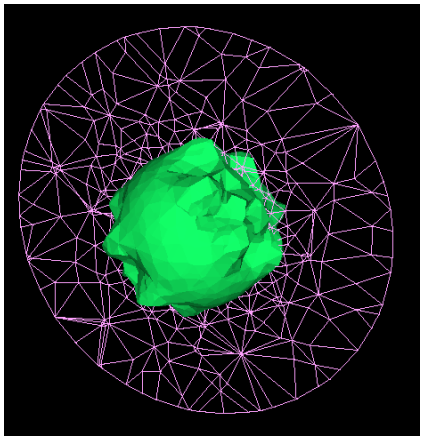
morphology controlled by diffusion/degradation of VEGF-A

•Needs further work: MMPs, identification of biophysical mechanisms

•Vascular remodeling/flow, etc.

Ongoing and Future work

- 3D



- Direct modeling of VEGF-A/ECM/MMP interaction on Neovascular morphology.

- Realistic mechanical/diffusional description of tissue

- Cell-signaling– macro/micro nonlinear coupling