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

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Motivation

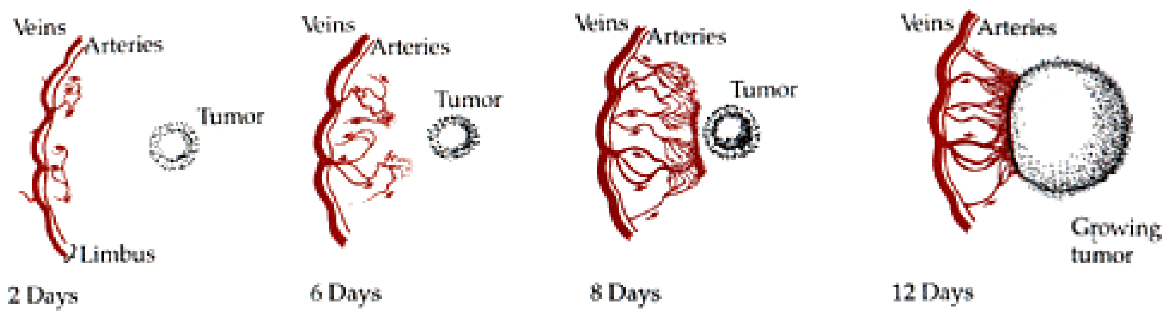
- Provide biophysically justified *in silico* virtual system to study
- Help experimental investigations; design new experiments
- Therapy protocols

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

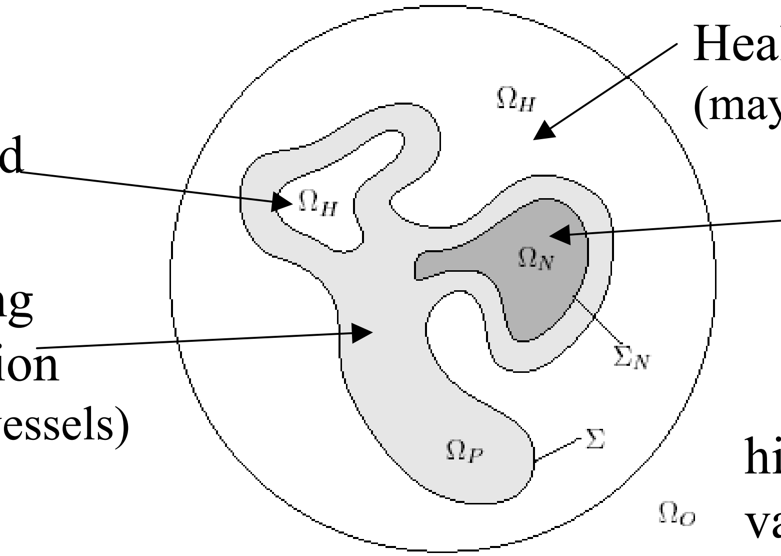
invasive

metastasis

malignancy

•Goal: Model all Phases of growth

Present model



- Continuum approximation: super-cell macro scale

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

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

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

- Limitations: poor feedback from macro scale to micro scale

(Greenspan, Byrne & Chaplain, Anderson & Chaplain, Levine…)

Cell proliferation and tissue invasion

Greenspan, Chaplain, Byrne, …

Assume constant tumor cell density: cell velocity

Assume 1 diffusing nutrient of concentration σ

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

Cell-to-cell adhesion

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

Viability concentration

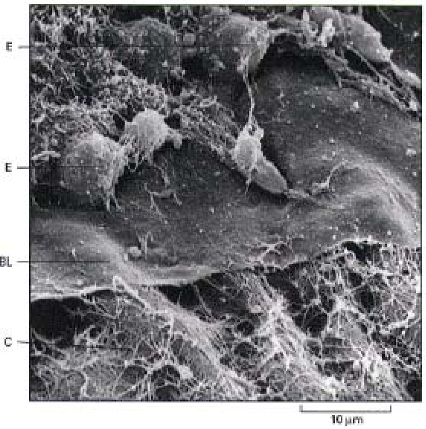
viscosity

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

Darcy-Stokes

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

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



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

Spatial distribution of the oncotic pressure

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

Evolution of nutrient: Oxygen/Glucose

Greenspan, Chaplain, Byrne, …

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

Diffusion

nutrient concentration in blood

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

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

Nutrient consumption by the cells

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

More complex Biophysics

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

- Blood-tissue transfer of nutrient

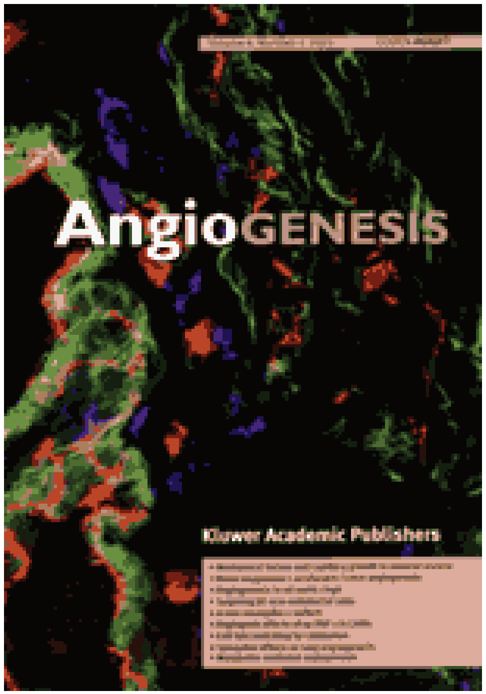
$$\lambda_B(\sigma_B - \sigma, P_B - P, \mathbf{x}, t) = \lambda_B\, h(\sigma_B - \sigma) \cdot (P_B - P)_+$$

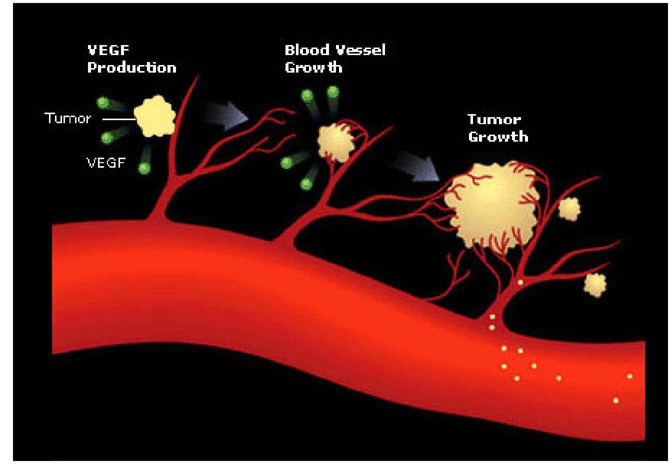
$$h(\sigma_B - \sigma) = (\sigma_B - \sigma)\delta_{Capillary}$$

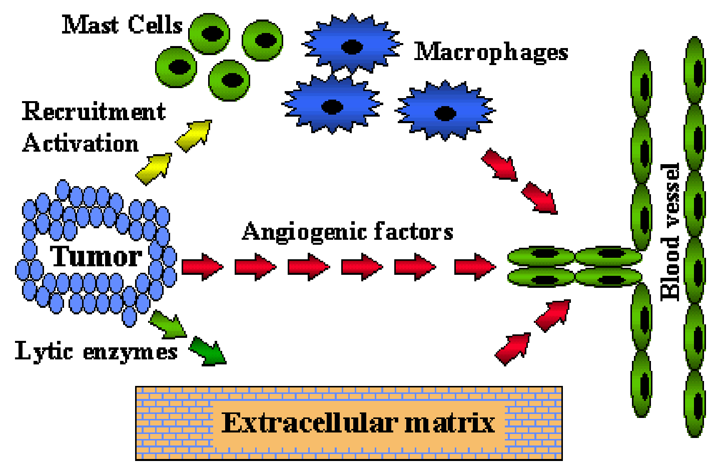
- Avascular, angiogenesis and fully vascularized growth

→ •Nonlinear interaction between developing vasculature and tumor growth

Angiogenesis







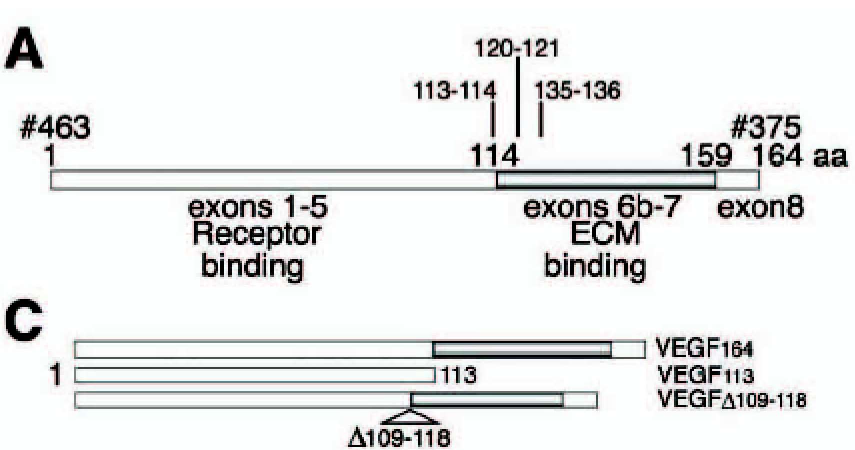
Angiogenic factors:

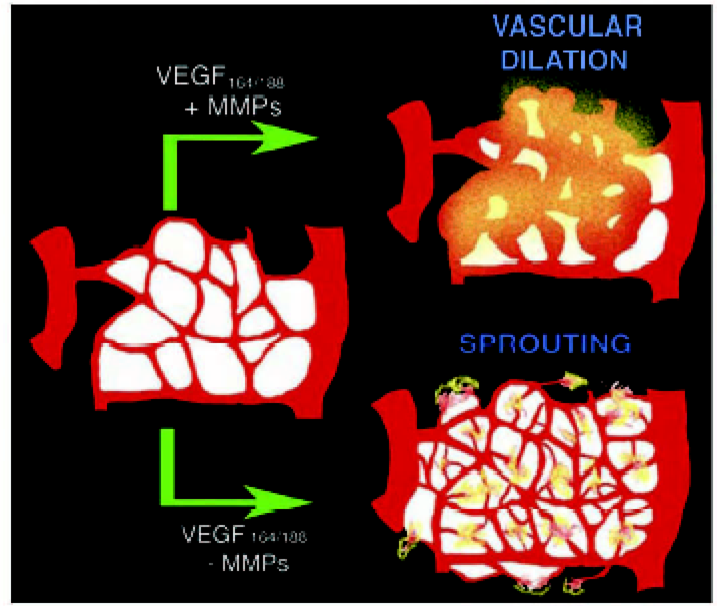
- VEGF (Vascular Endothelial cell Growth Factor)
- FGF (Fibroblast Growth Factor)
- Angiogenin
- TGF (Transforming Growth Factor),….

ECM/MMP Regulation of VEGF

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

VEGF-A isoforms





soluble

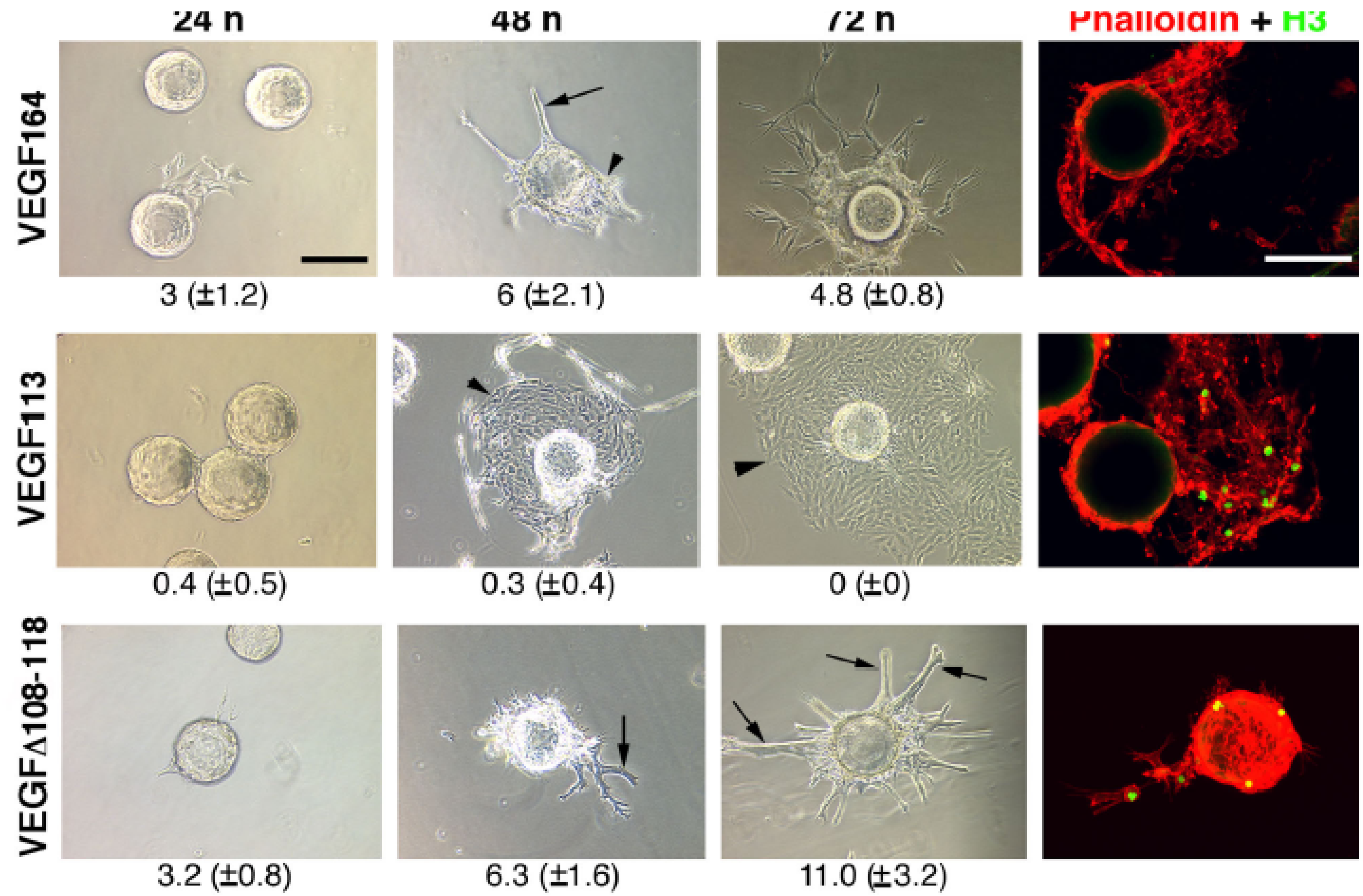
insoluble

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

- Different signaling outcomes through VEGFR2

Effect on EC growth

Beads containing cells embedded in fibrin/fibronectin gels

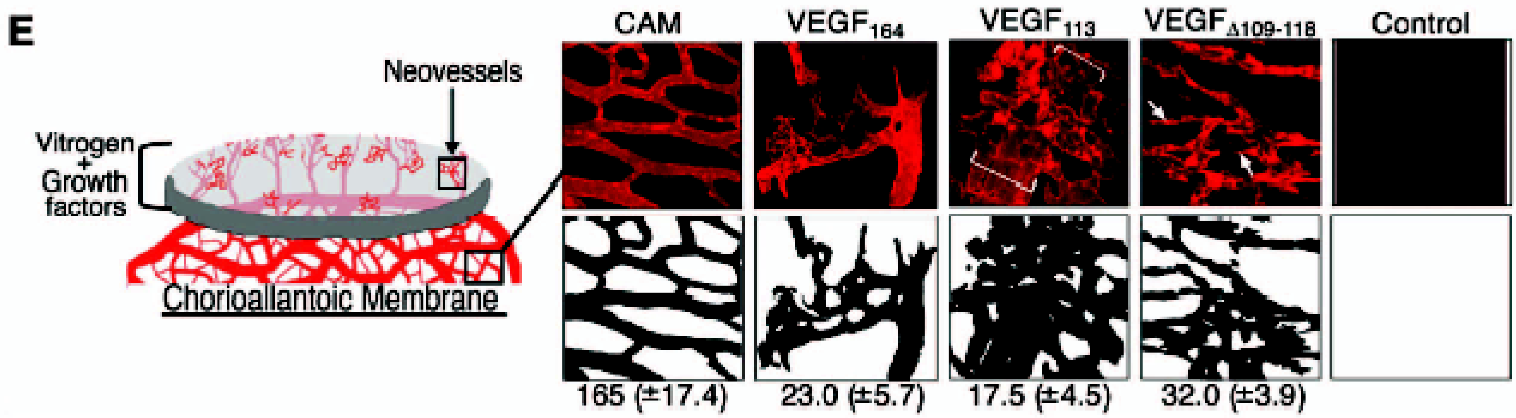


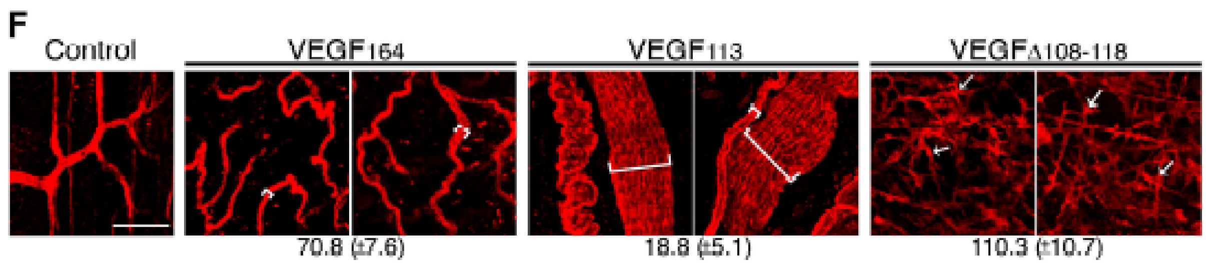
(stain to measure proliferation)

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

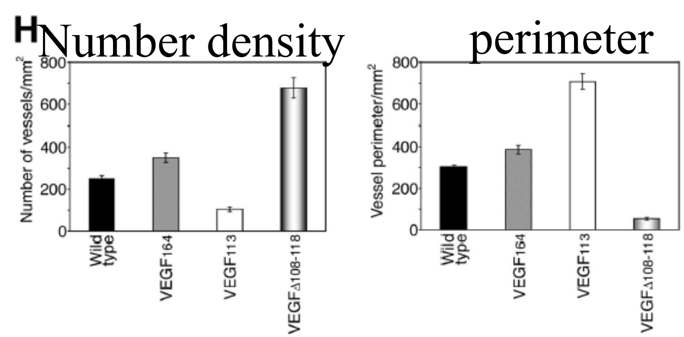
Effect on Vessel Morphology

Wild Soluble Insoluble





(diameters) 15 μm 109 μm 16 μm

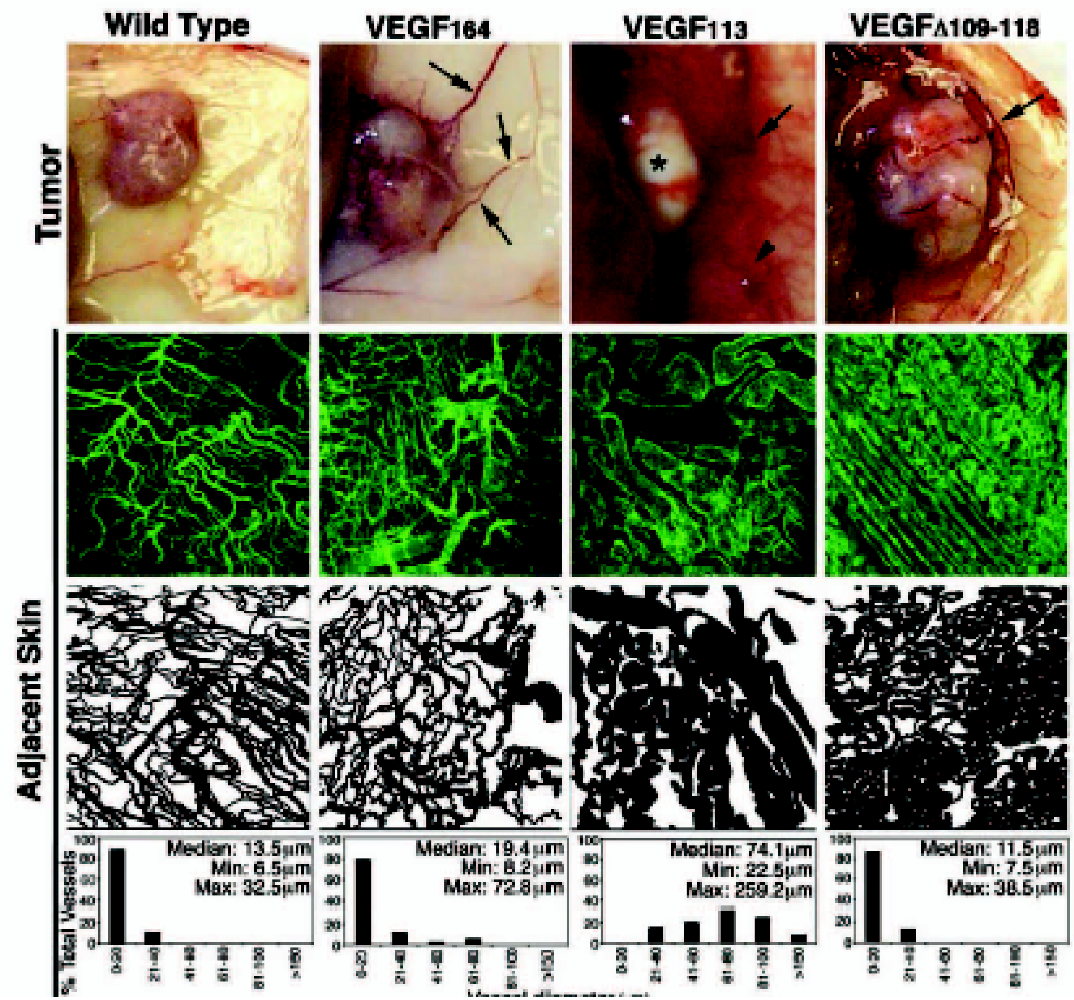


- Morphology strongly depends on type

Effect on tumor growth

- Soluble VEGF poor prognosticator of tumor progression

- Matrix-bound VEGF yields more efficient angiogenic response



Mathematical model

Anderson, Chaplain, 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

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

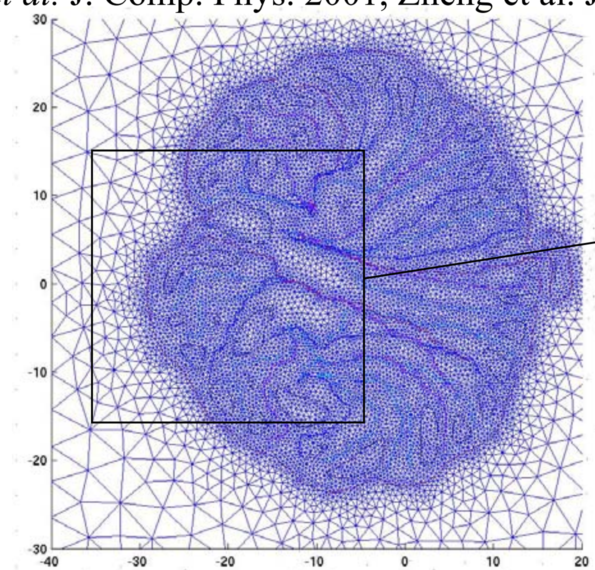
production   degradation

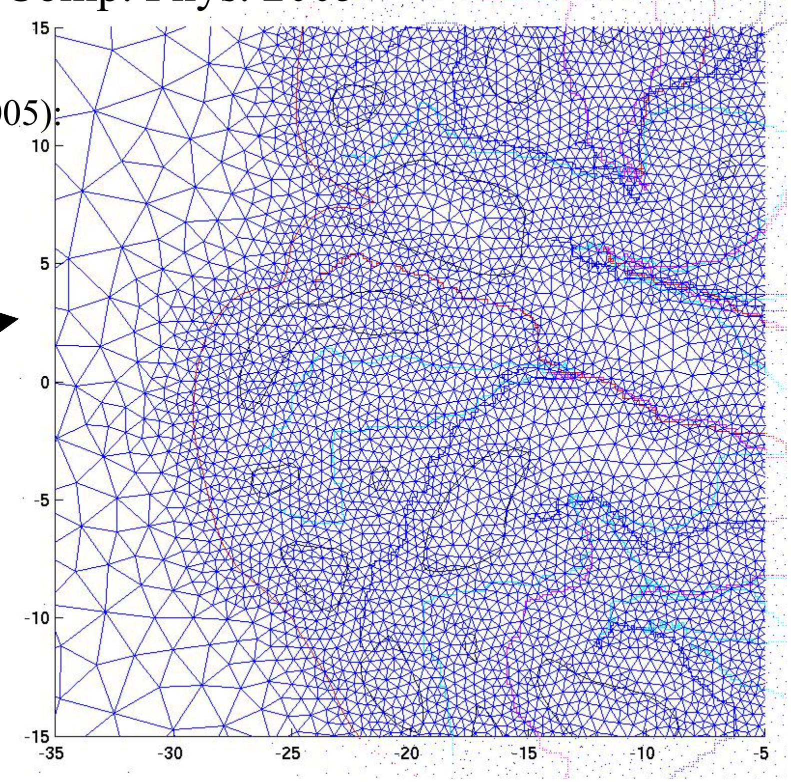
- Recast in a biased random-walk model to follow the evolution of the capillaries (Anderson, Chaplain)

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):





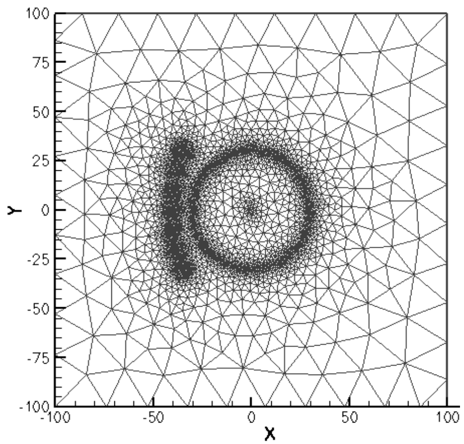
Mesh: System of springs (energy)

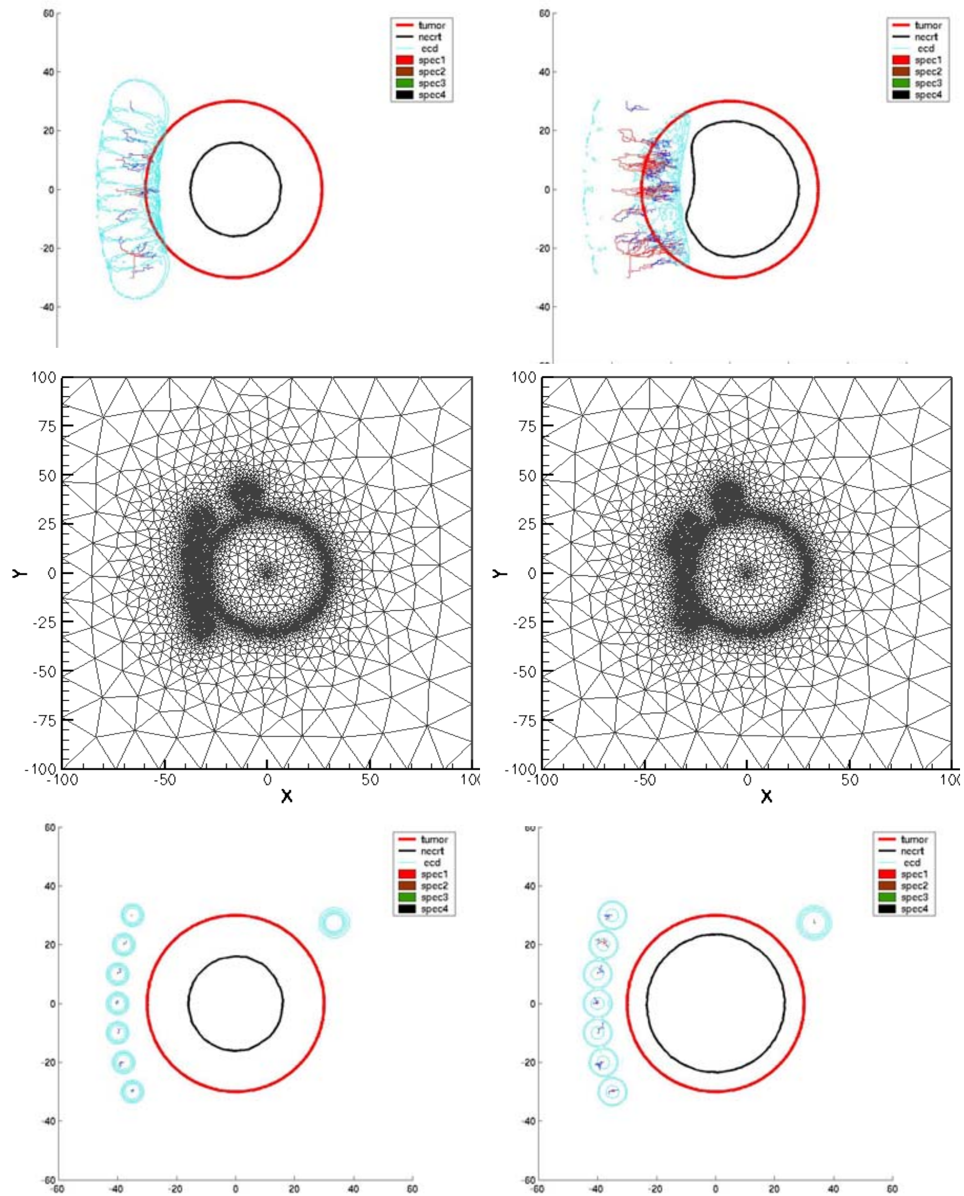
Local Operations → Minimum energy → Optimal mesh

⇒ 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

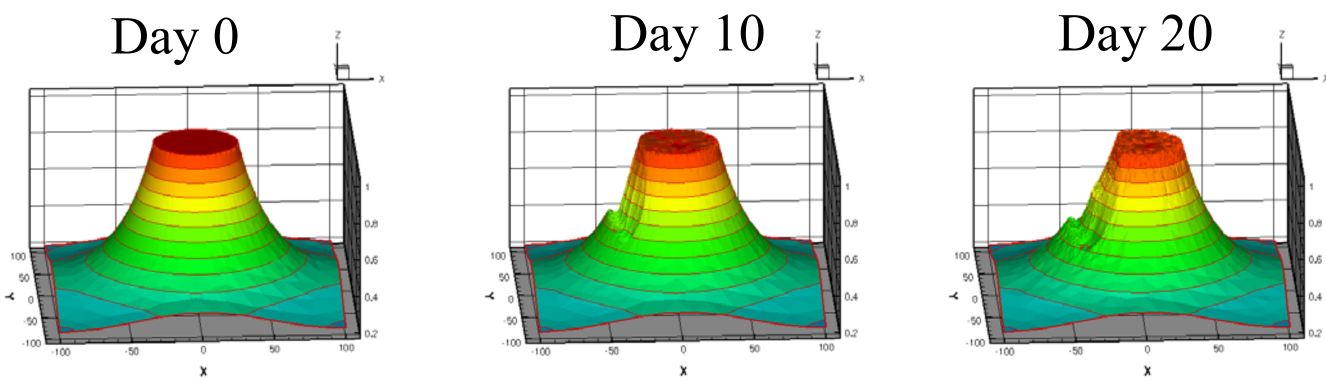
Soluble

•Chemotaxis/ Branching enhanced with insoluble VEGF

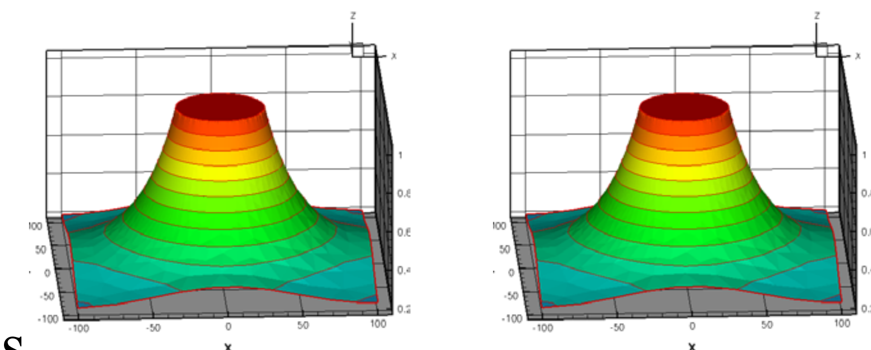
•Qualitative agreement with experiments

Mechanism

Distribution of VEGF:

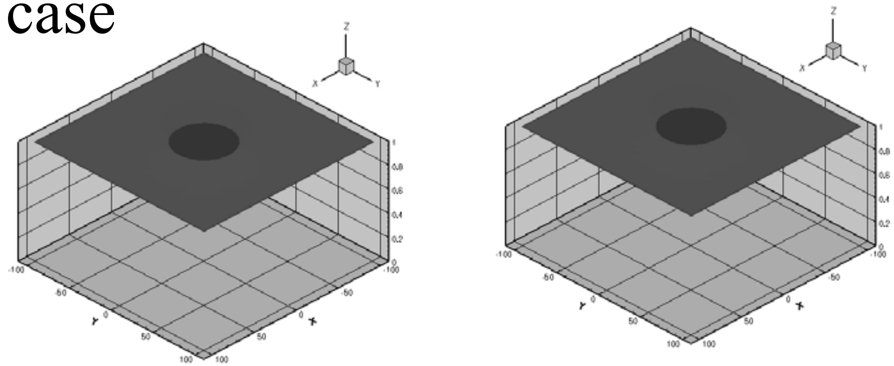


Insoluble



Partly soluble

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



- Gradients enhance chemotaxis

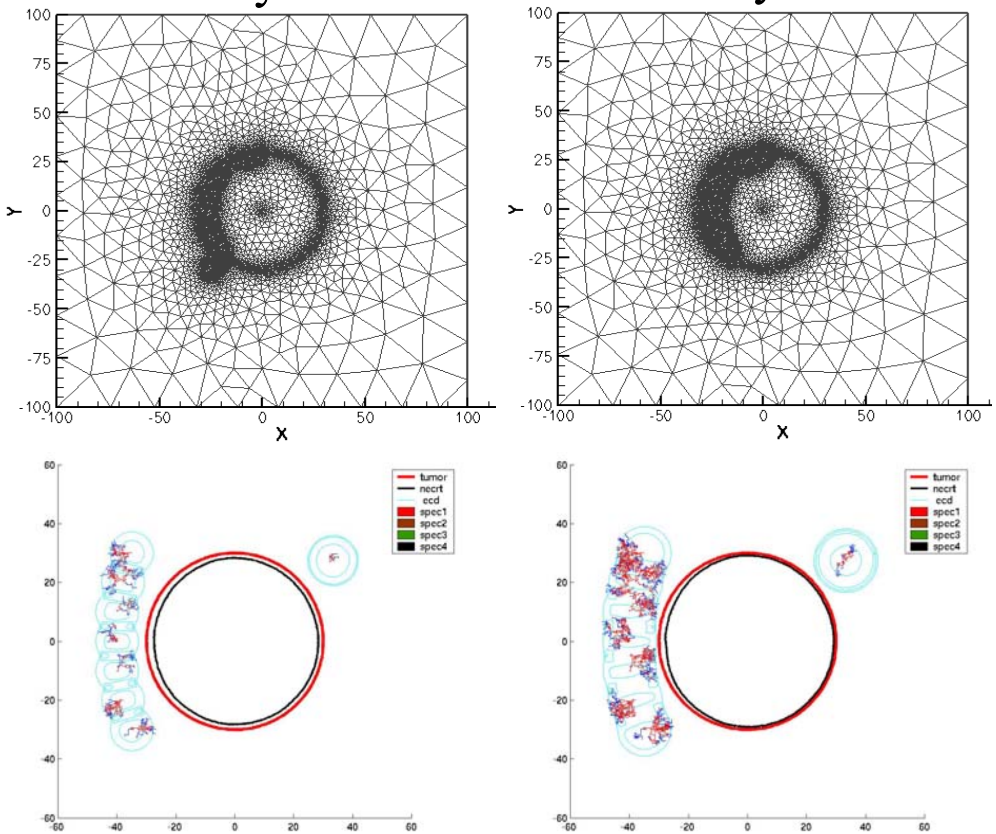
Soluble

Later times

Day 45 | Day 70

Partly Soluble

Soluble



- Brush-border effect
- penetration

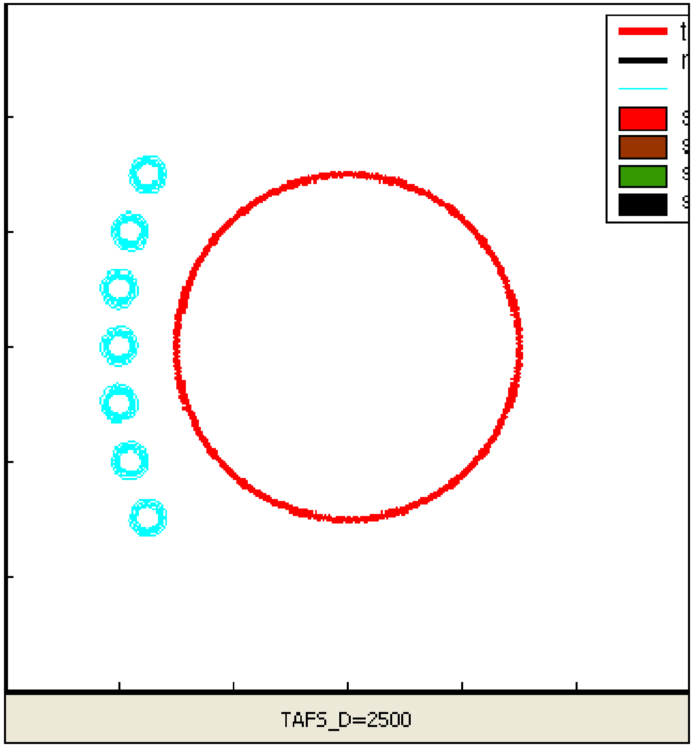
- Irregular vascular development
- No penetration

- Qualitative agreement with experiment

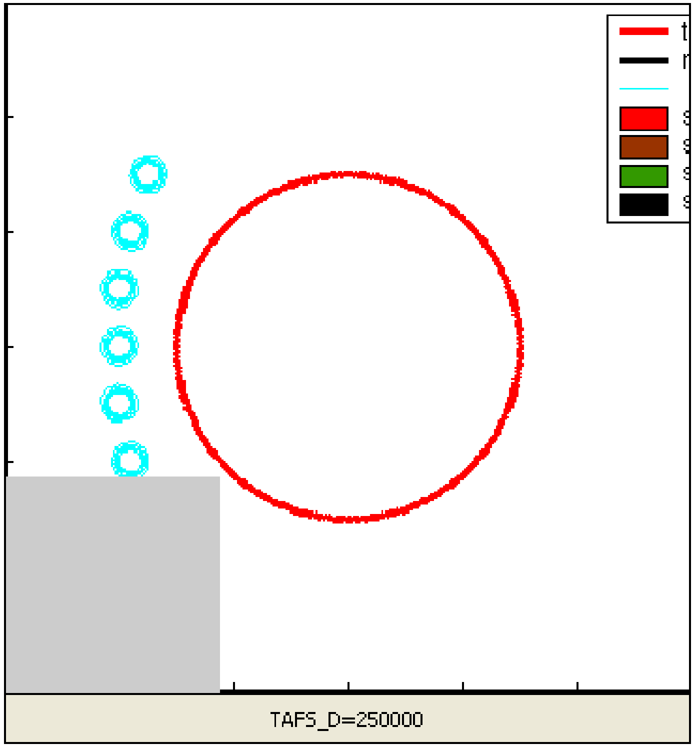
- Experimental results consistent with increased D_c and/or decreased β_c

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

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

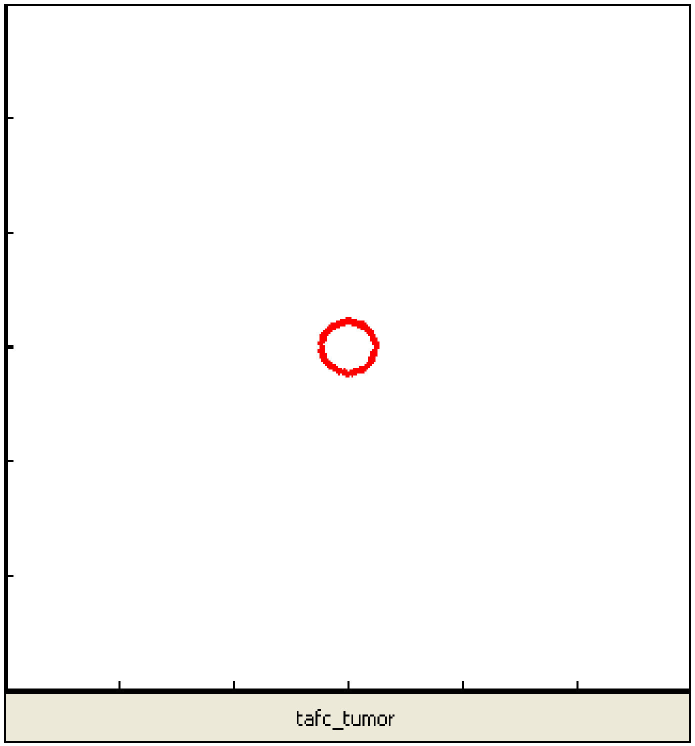
•Variable diffusion for insoluble TAF

•Test coupling with full tumor model

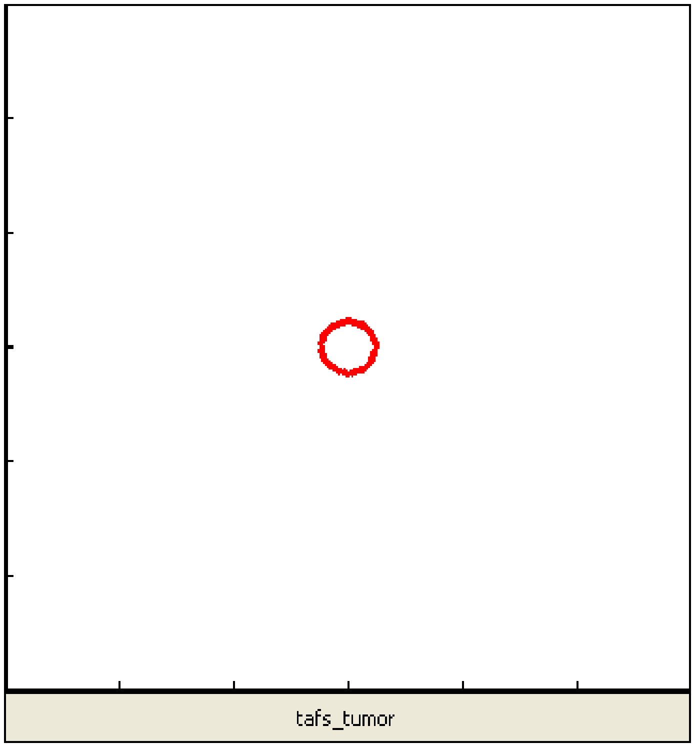
-tumor and vessel development nonlinearly coupled

Fully coupled model

Insoluble



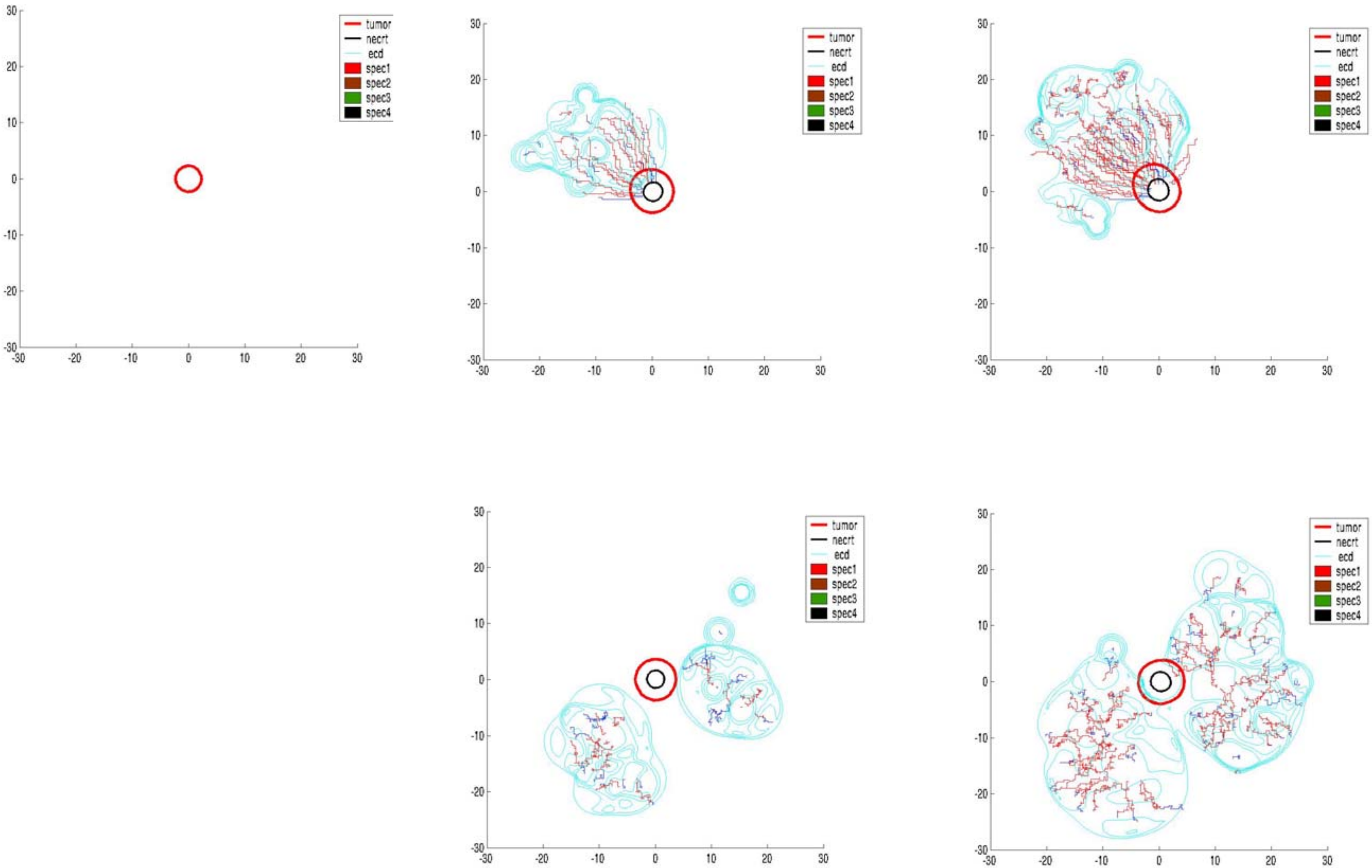
Soluble



- Brush-border effect
- Penetration
- Growth of tumor

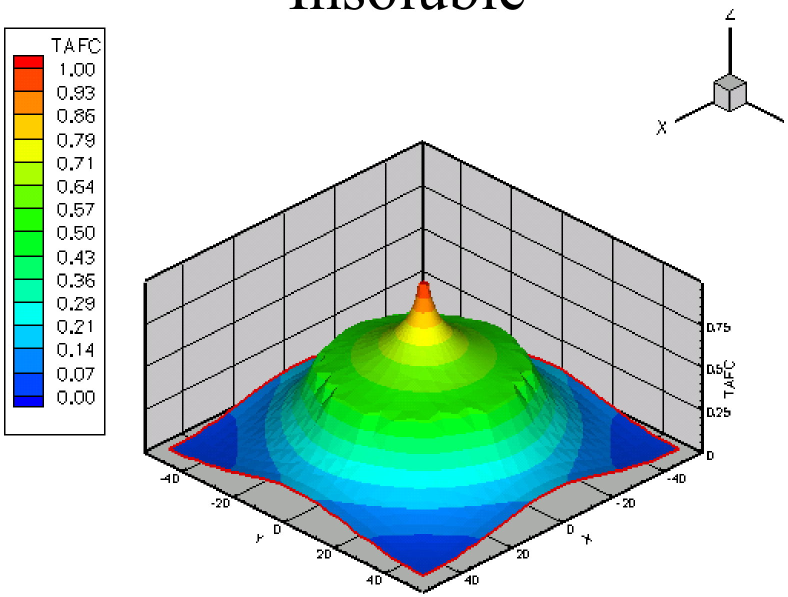
- Irregular vascular development
- little penetration
- Less growth

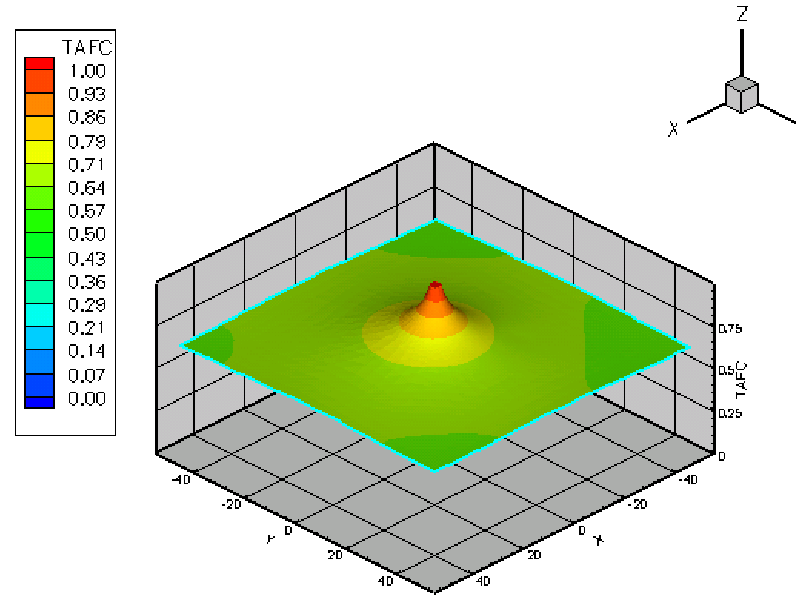
Stills



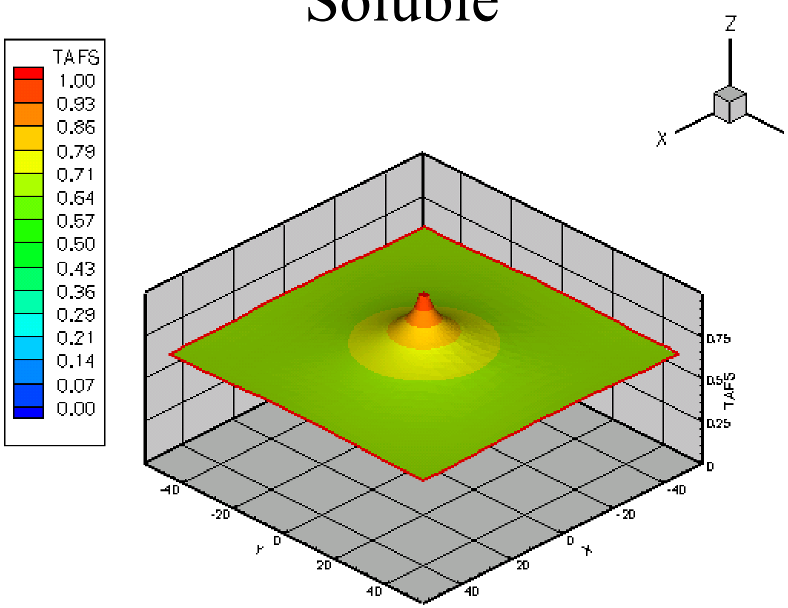
VEGF

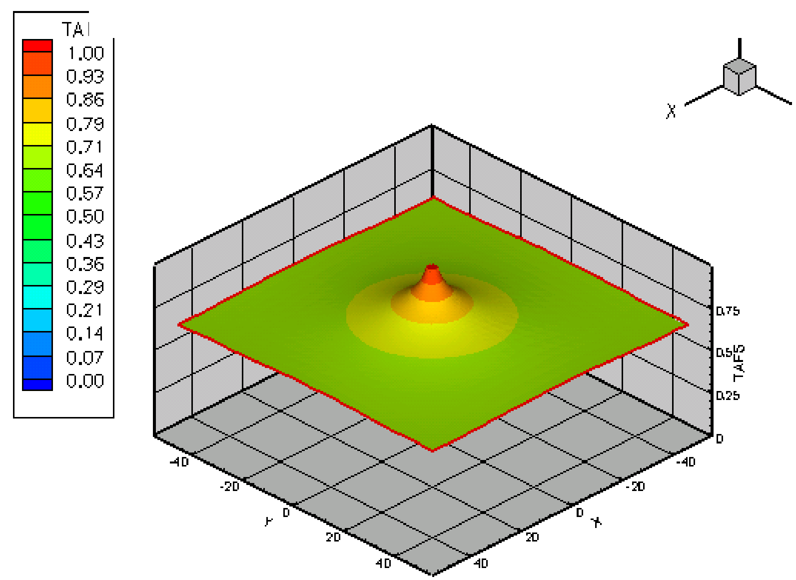
Insoluble





Soluble





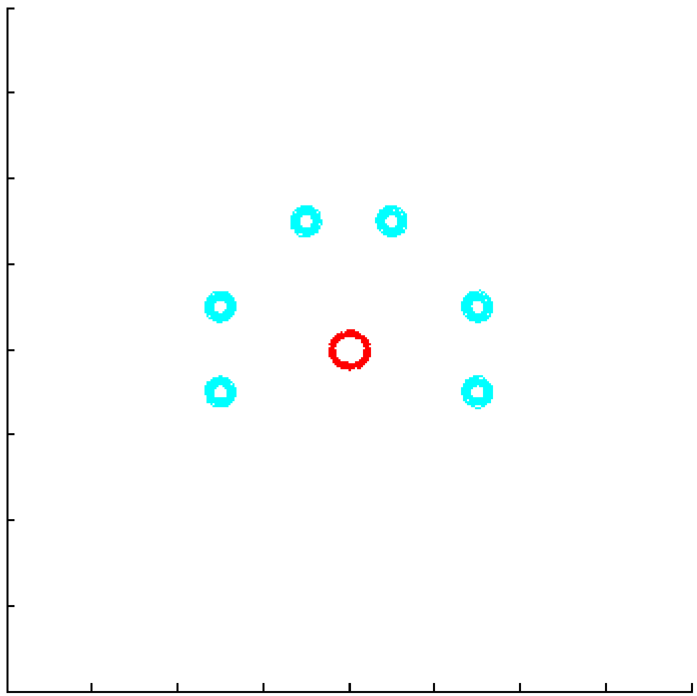
Growth of Glioblastoma Multiforme

(parameters from experiments and clinical data)

Simulated growth time: ca. 8 years

Zheng, Wise, Cristini, BMB 2005.

Partly soluble Tumor Angiogenesis Factor (e.g. VEGF)



- Tumor and blood vessel morphology develop together
- Significant growth of both

Conclusions

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

- Nonlinear coupling of neovascular development and tissue/tumor growth

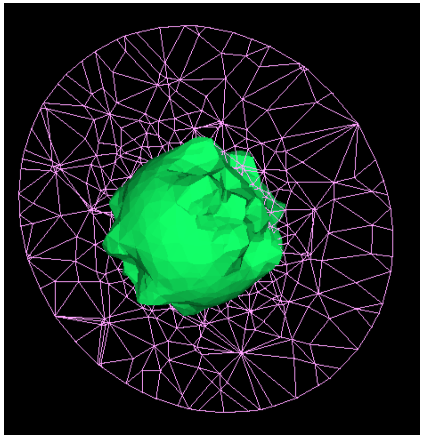
- Qualitative agreement with experiments by Iruela-Arispe for neovascular morphology

  morphology controlled by diffusion/degradation of VEGF-A

- Needs further work: MMPs, identification of biophysical mechanisms

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

Multiscale Mixture Models

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

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

solid and water components

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

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

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

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

σ_k stress tensor

π_k interaction forces

u_k internal energy

- ϵ_k interaction energies

Thermodynamics

$\psi_k = u_k - \theta \eta_k$ → Constitutive Relations

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

Li, Lowengrub, Cristini in preparation

Biphasic Tumor Model

ϕ : tumor (solid matter),

$1-\phi$: water

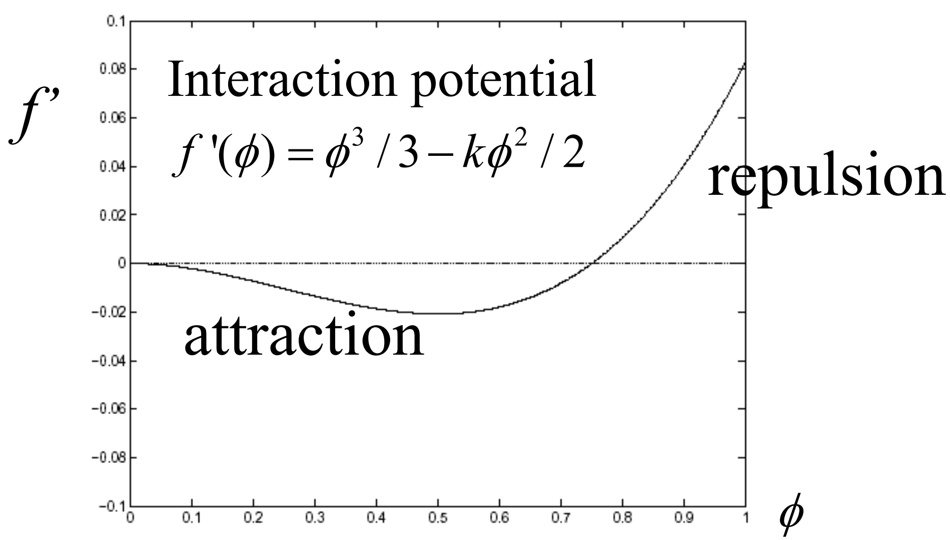
Simplest thermodynamically consistent model. (no necrosis)

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

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

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

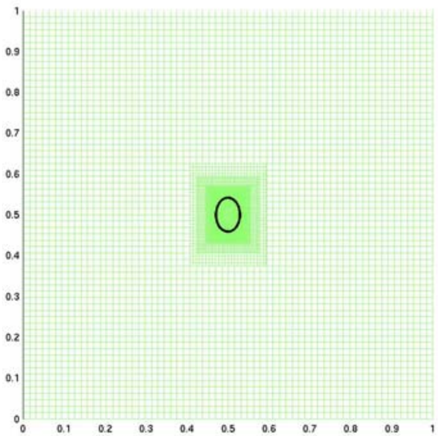
$$\nabla \bullet (D \nabla c) = c\phi$$ Nutrient diffusion/consumption



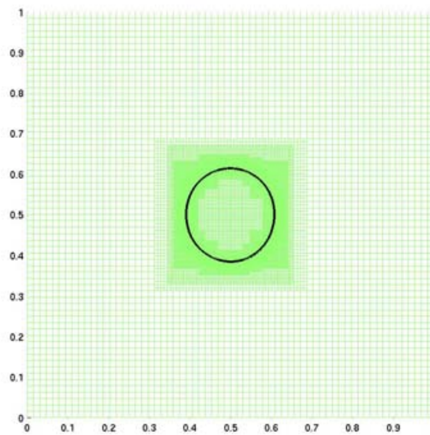
Mixture Model

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

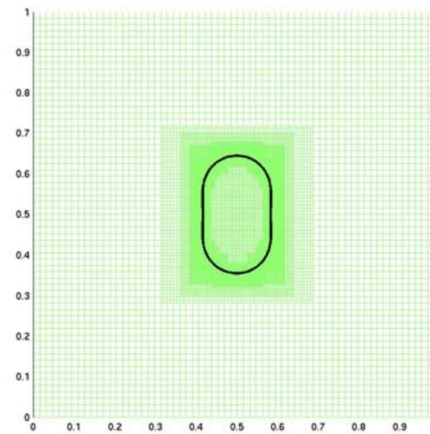
T=1



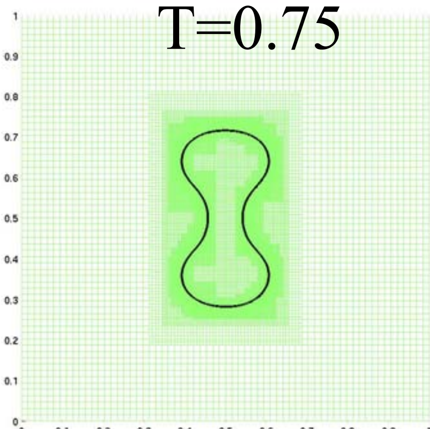
T=0.25



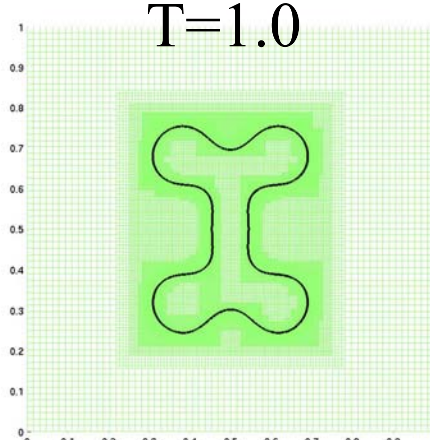
T=0.5



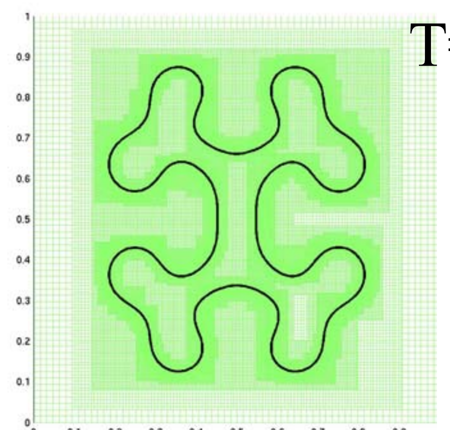
T=0.75



T=1.0



T=1.38



Volume fraction