Continuum Methods III

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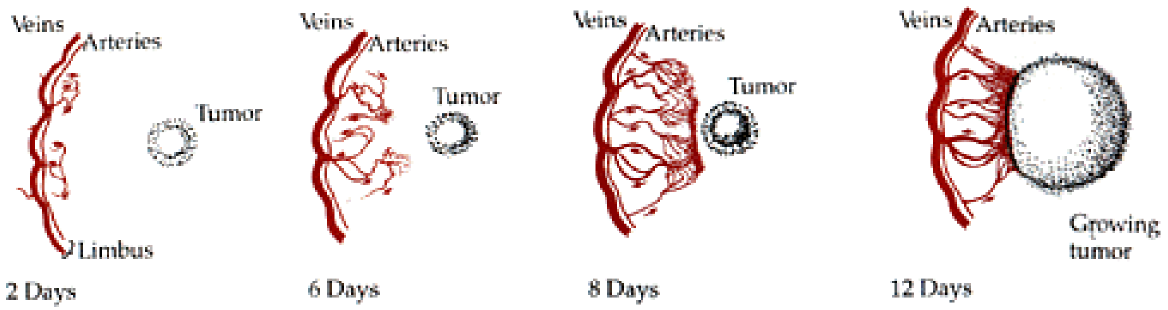
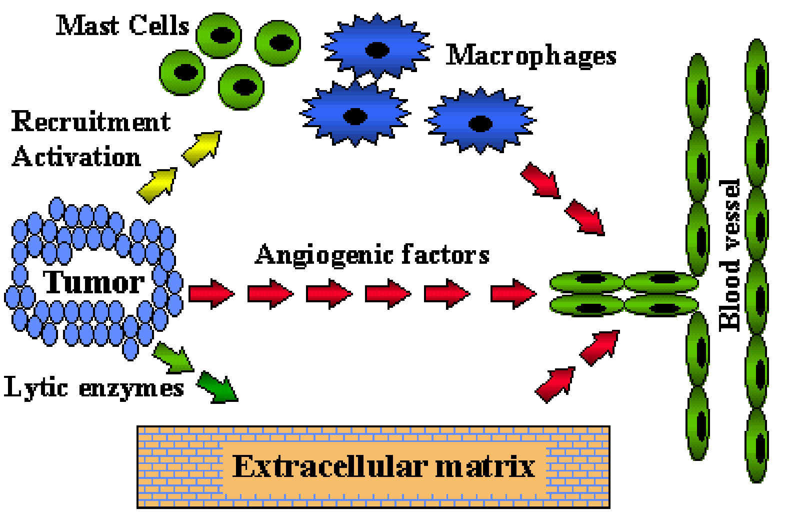
Outline

- Angiogenesis, neovascularization in context of solid tumor growth

- Systems Biology: PDE models of cell signaling.

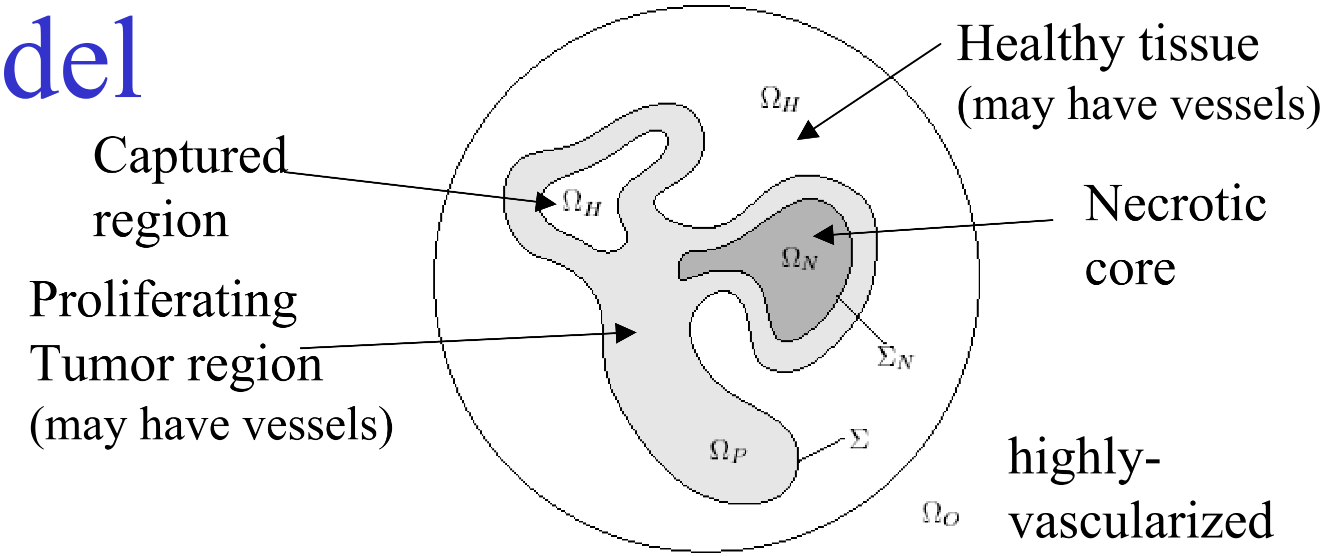
Mechanism of tumor neo-vascularization





- •Tumor cells prefer glucose as a nutrient.
- •Angiogenic phenotype is the result of a net balance of endogenous stimulators and inhibitors of angiogenesis.
- •The expression of angiogenic growth factors is increased in the tumor regions neighboring its necrotic area.
- •Both hypoxia and hypoglycaemia may increase the expression of angiogenic factors.

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

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

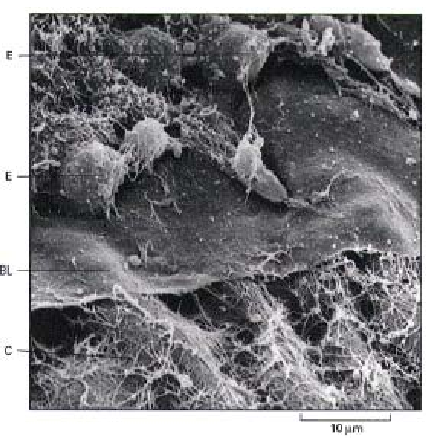
Viability concentration

viscosity

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

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

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

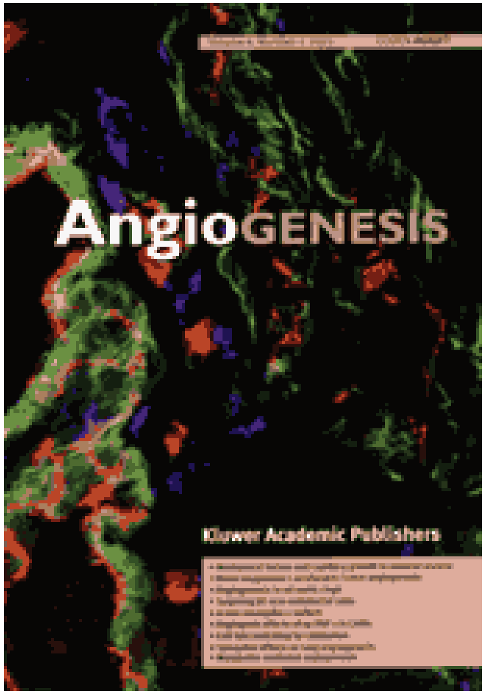
$$\lambda_B(\sigma_B - \sigma, P_B - P, \mathbf{x}, t) = \lambda_B h(\sigma_B - \sigma) \cdot (P_B - P)_+$$

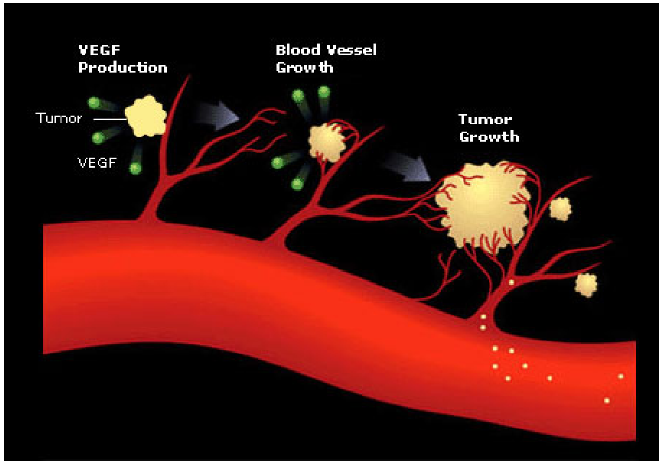
$$h(\sigma_B - \sigma) = (\sigma_B - \sigma)\delta_{Capillary}$$

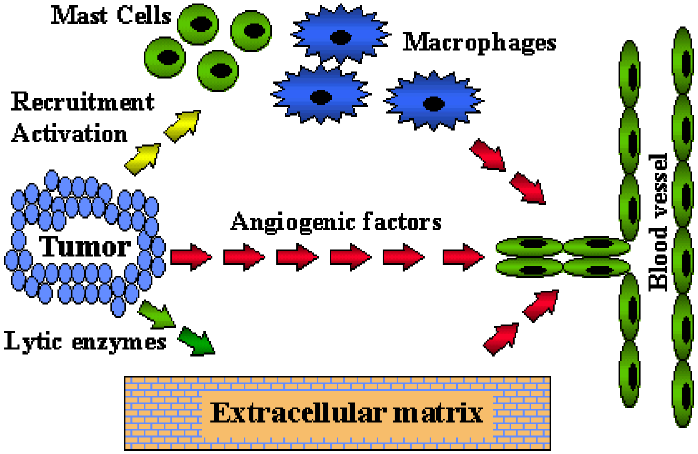
- Avascular, angiogenesis and fully vascularized growth

→ • Nonlinear interaction between developing vasculature and tumor growth

Angiogenesis







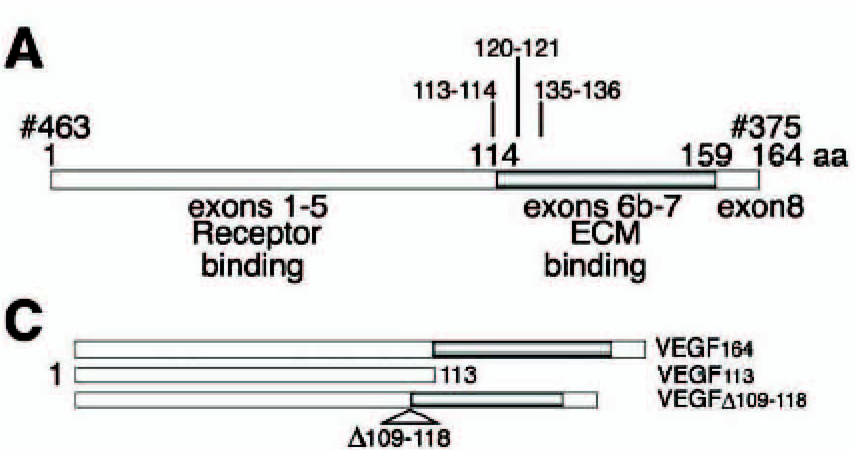
Angiogenic factors:

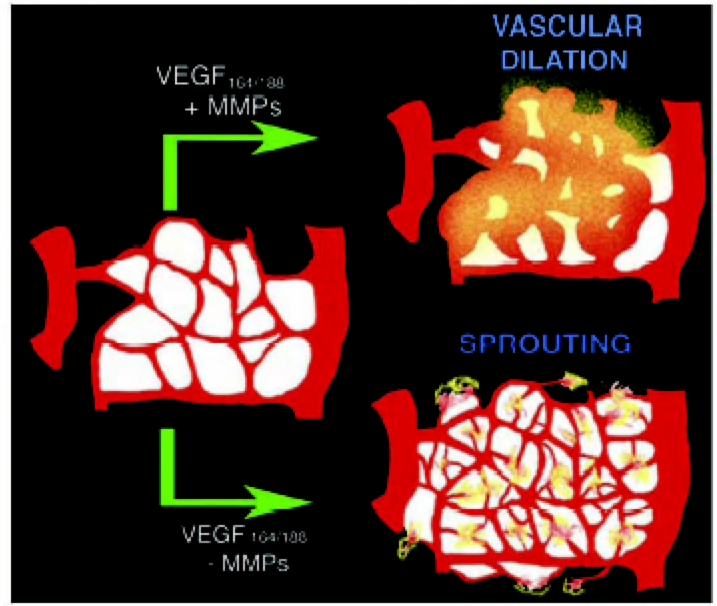
- VEGF (Vascular Endothelial cell Growth Factor)
- FGF (Fibroblast Growth Factor)
- Angiogenin
- TGF (Transforming Growth Factor),….

ECM/MMP Regulation of VEGF

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

VEGF-A isoforms





soluble

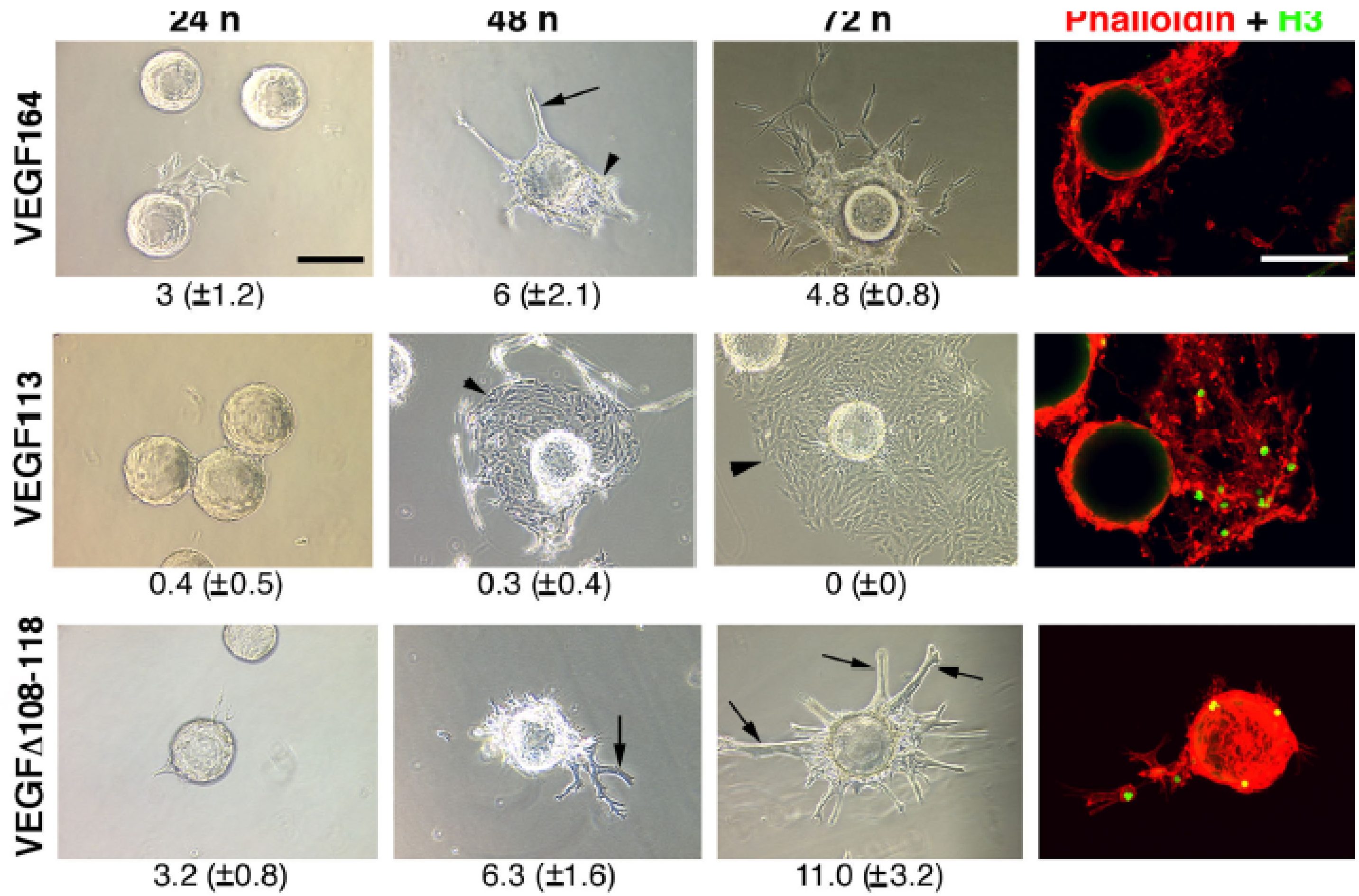
insoluble

- 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

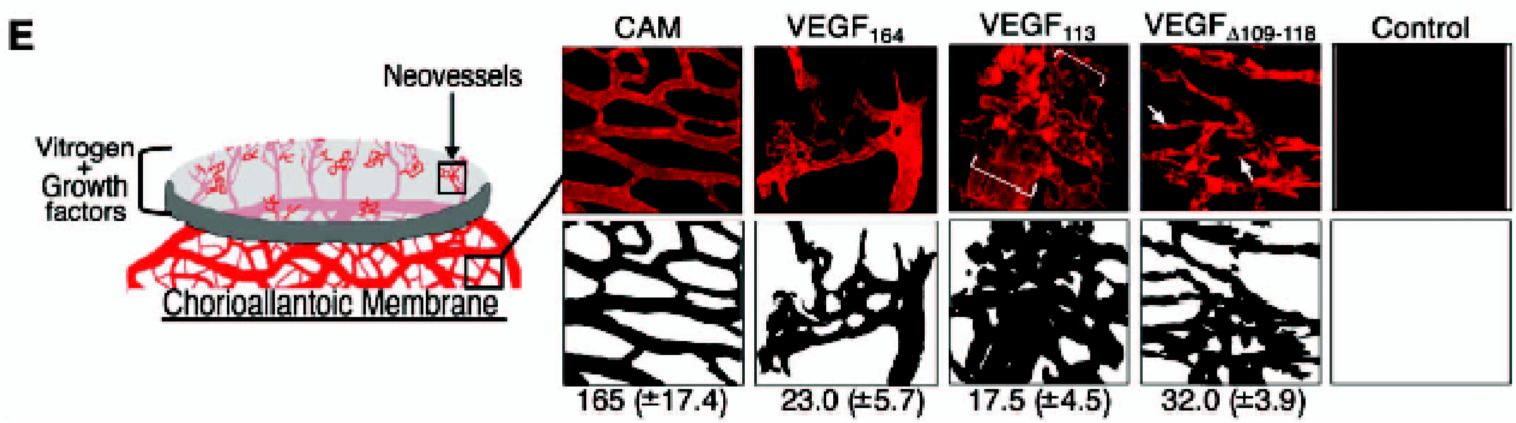


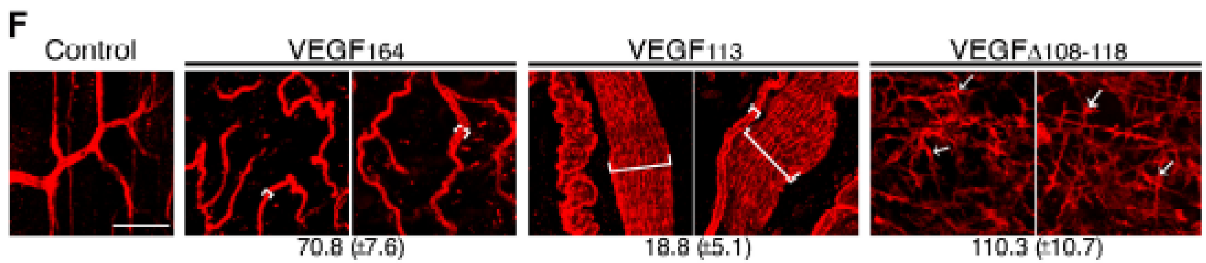
(stain to measure proliferation)

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

Effect on Vessel Morphology

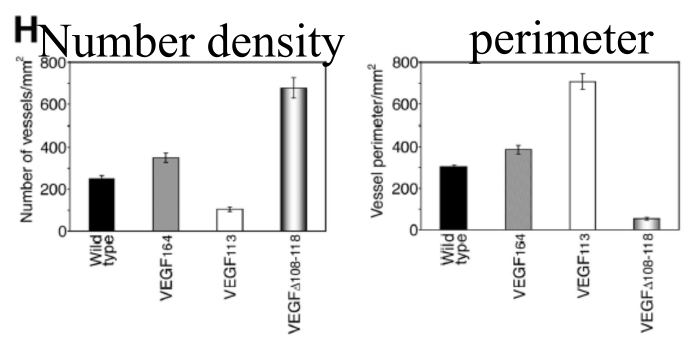
Wild Soluble Insoluble





(diameters) $15\mu m$ $109\mu m$ $16\mu m$

Number density perimeter

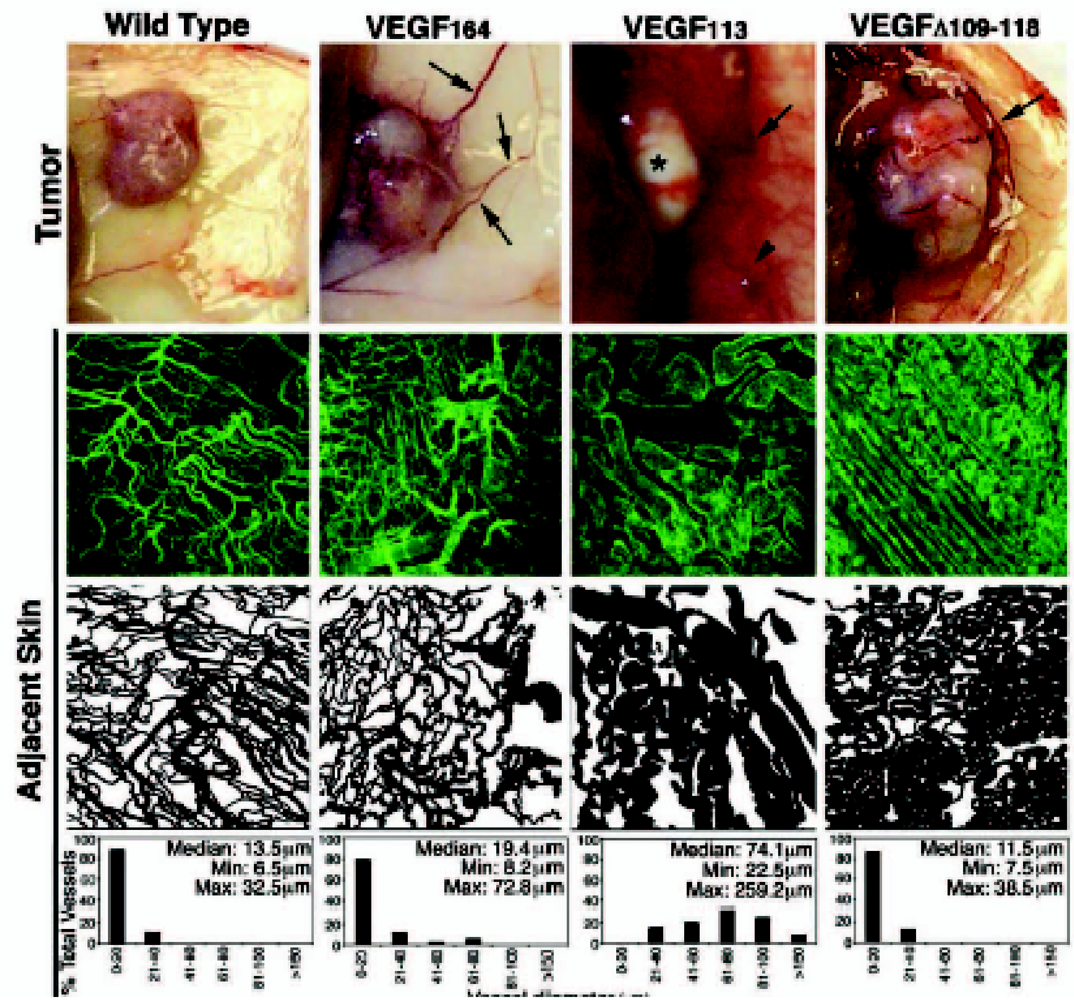


- Morphology strongly depends on type

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, Sun, et al BMB 2005,…

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)

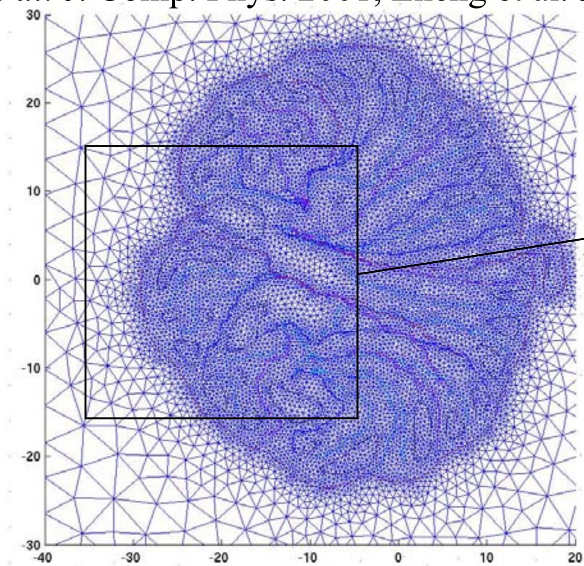
Zheng, Wise, Cristini,. Bull. Math. Biol. 2005

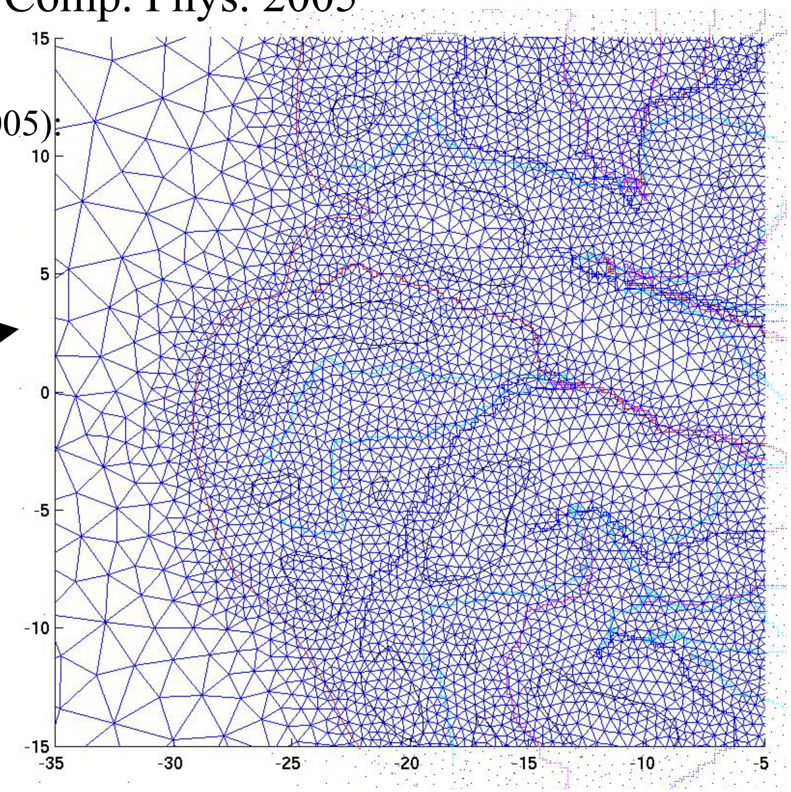
Zheng, Anderson, Cristini, J. Comp. Phys. 2005

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):





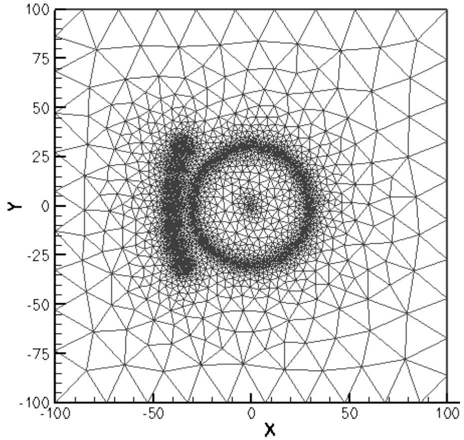
Mesh: System of springs (energy)

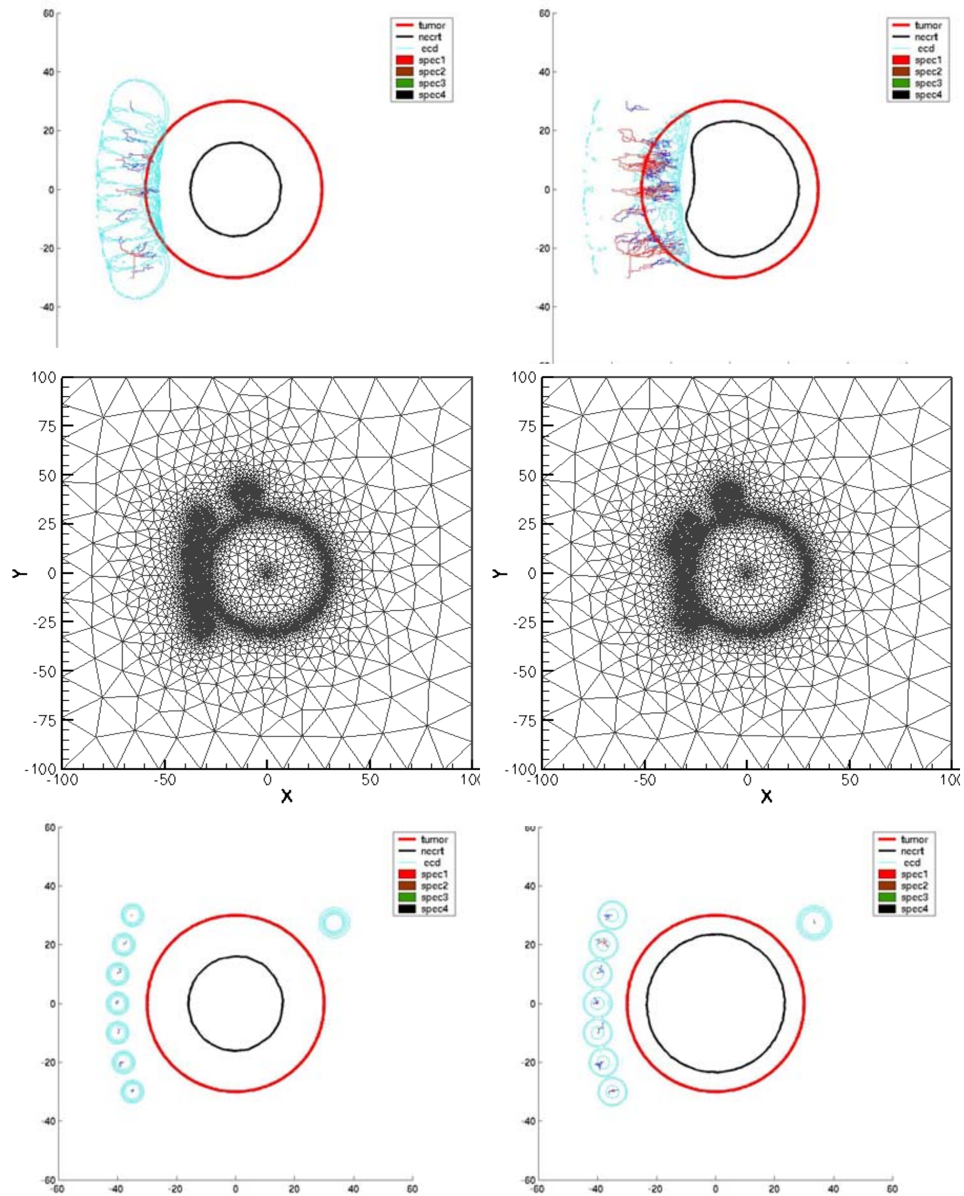
Local Operations → Minimum energy → Optimal mesh

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

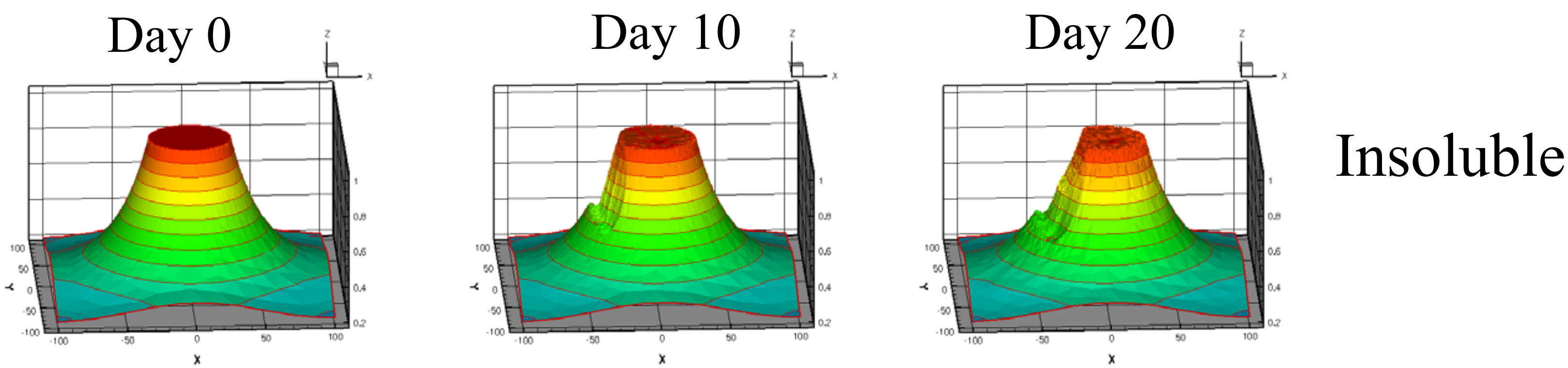
Soluble

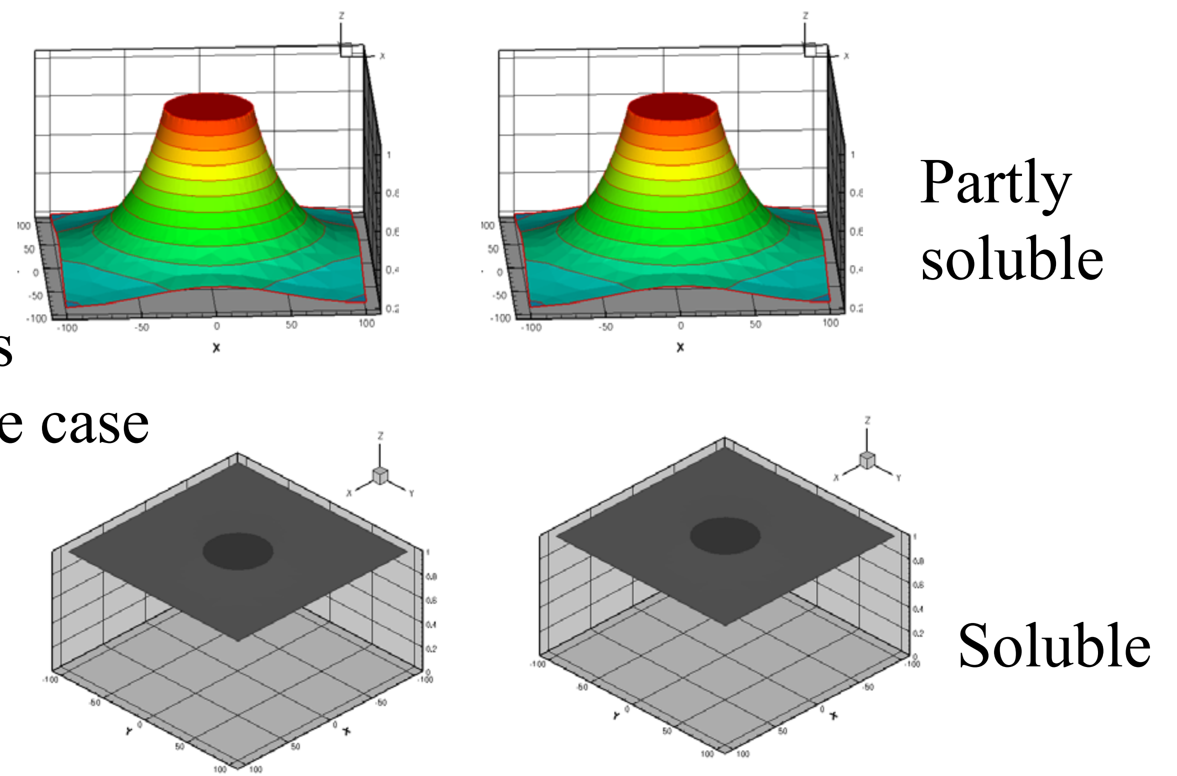
•Chemotaxis/ Branching enhanced with insoluble VEGF

•Qualitative agreement with experiments

Mechanism

Distribution of VEGF:



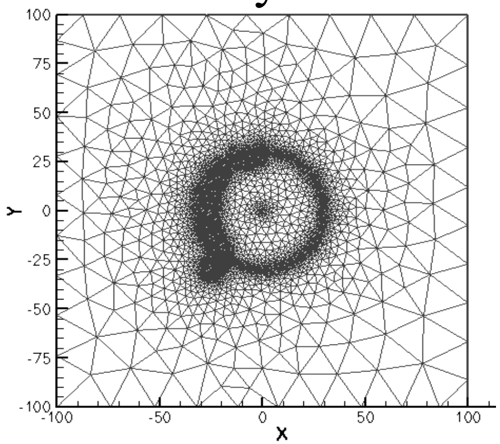


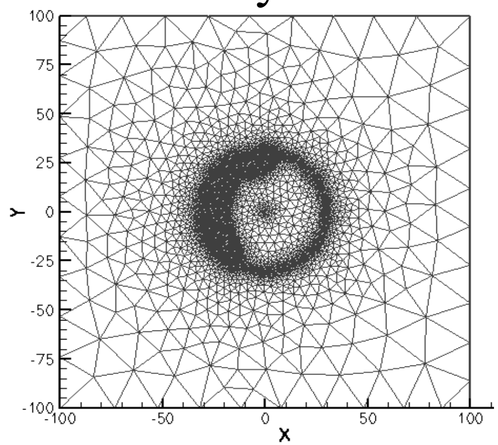
- Uptake of ECM-bound VEGF-A by EC produces large gradient in insoluble case
- Gradients enhance chemotaxis

Later times

Day 45 | Day 70

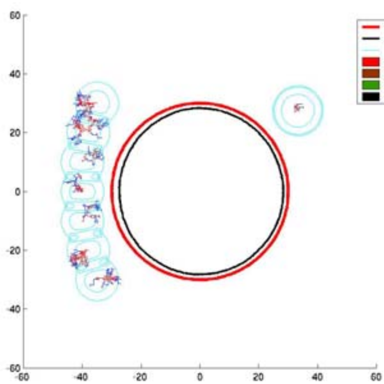
Partly Soluble

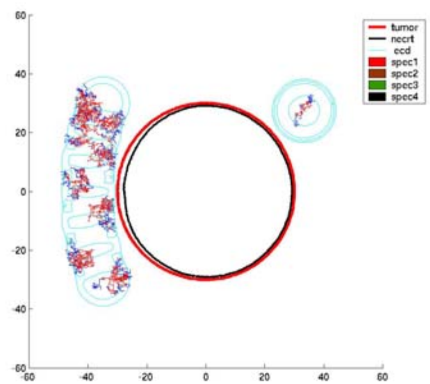




- Brush-border effect
- penetration

Soluble



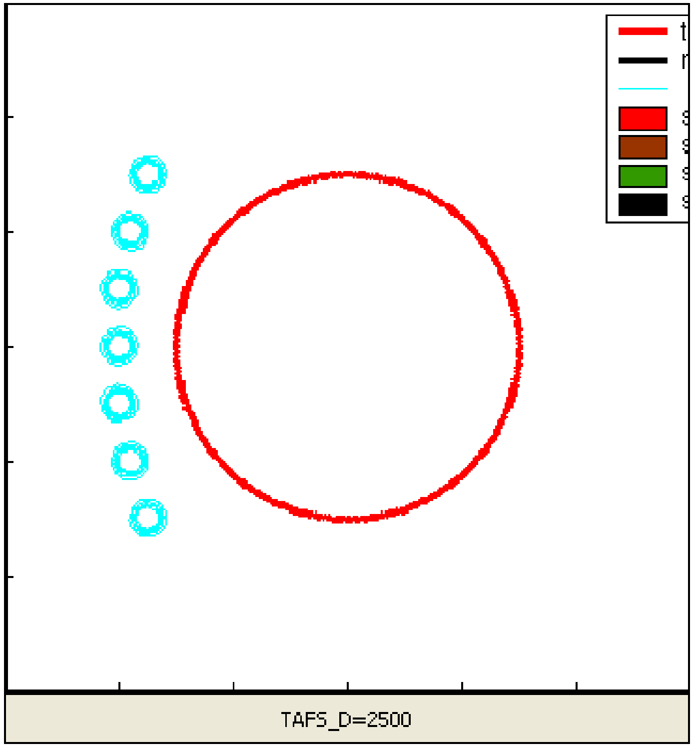


- Irregular vascular development
- No penetration

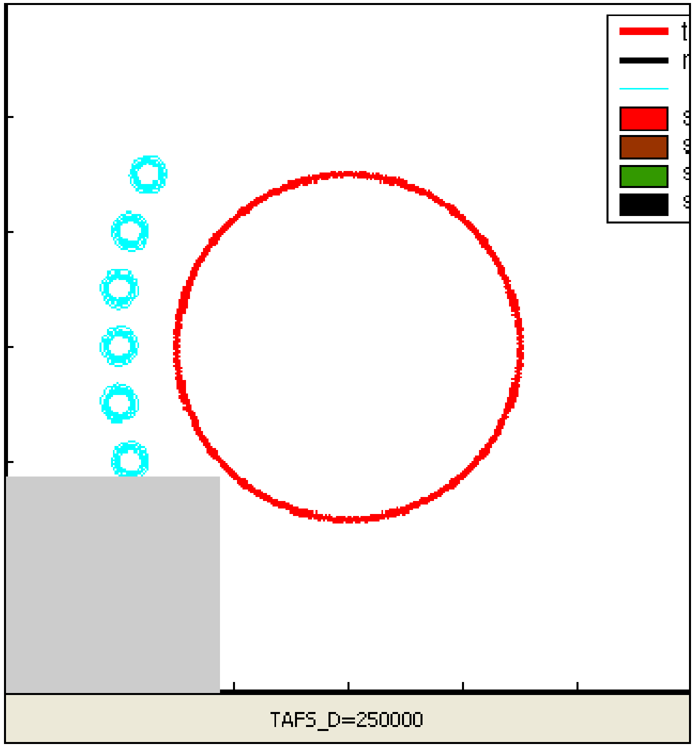
- Qualitative agreement with experiment
- Experimental results consistent with increased D_c and/or decreased β_c

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

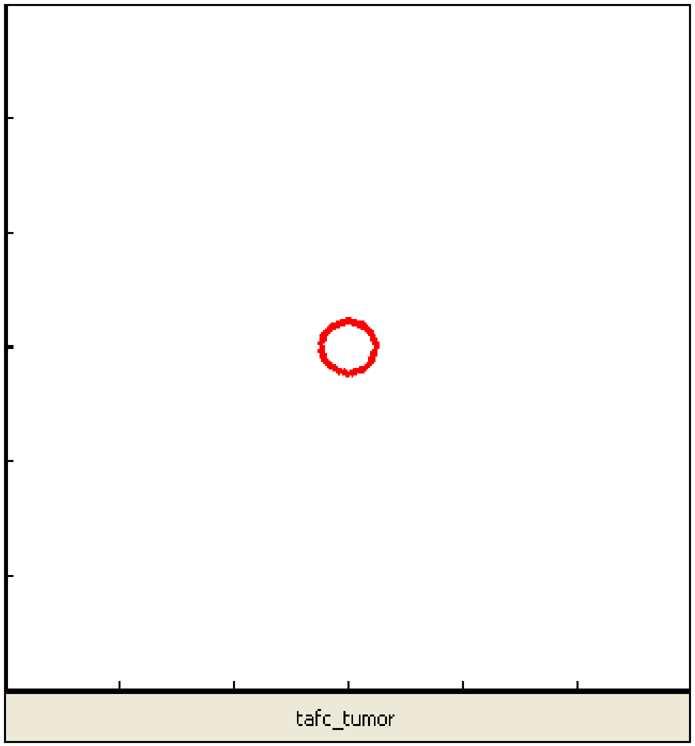
Soluble

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

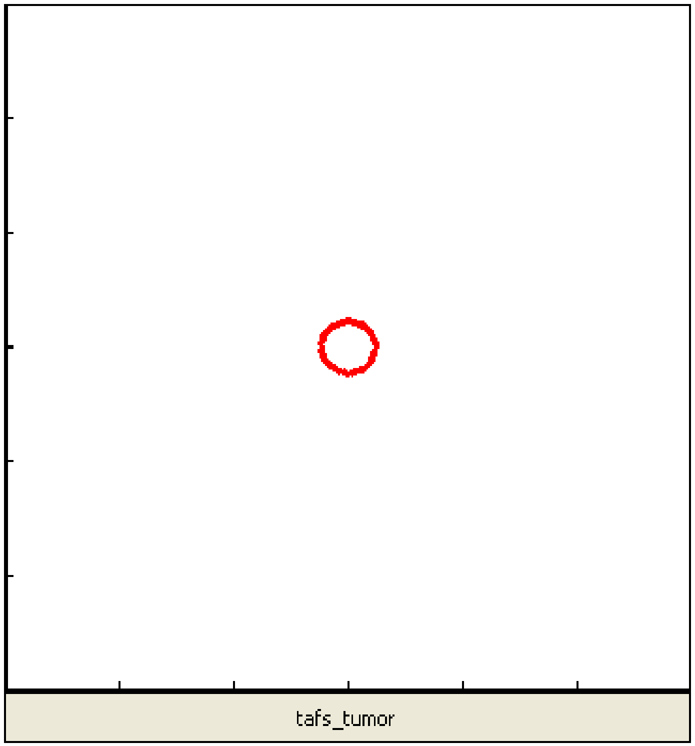
- Variable diffusion for insoluble TAF
- Test coupling with full tumor model
  - -tumor and vessel development nonlinearly coupled

Fully coupled model

Insoluble



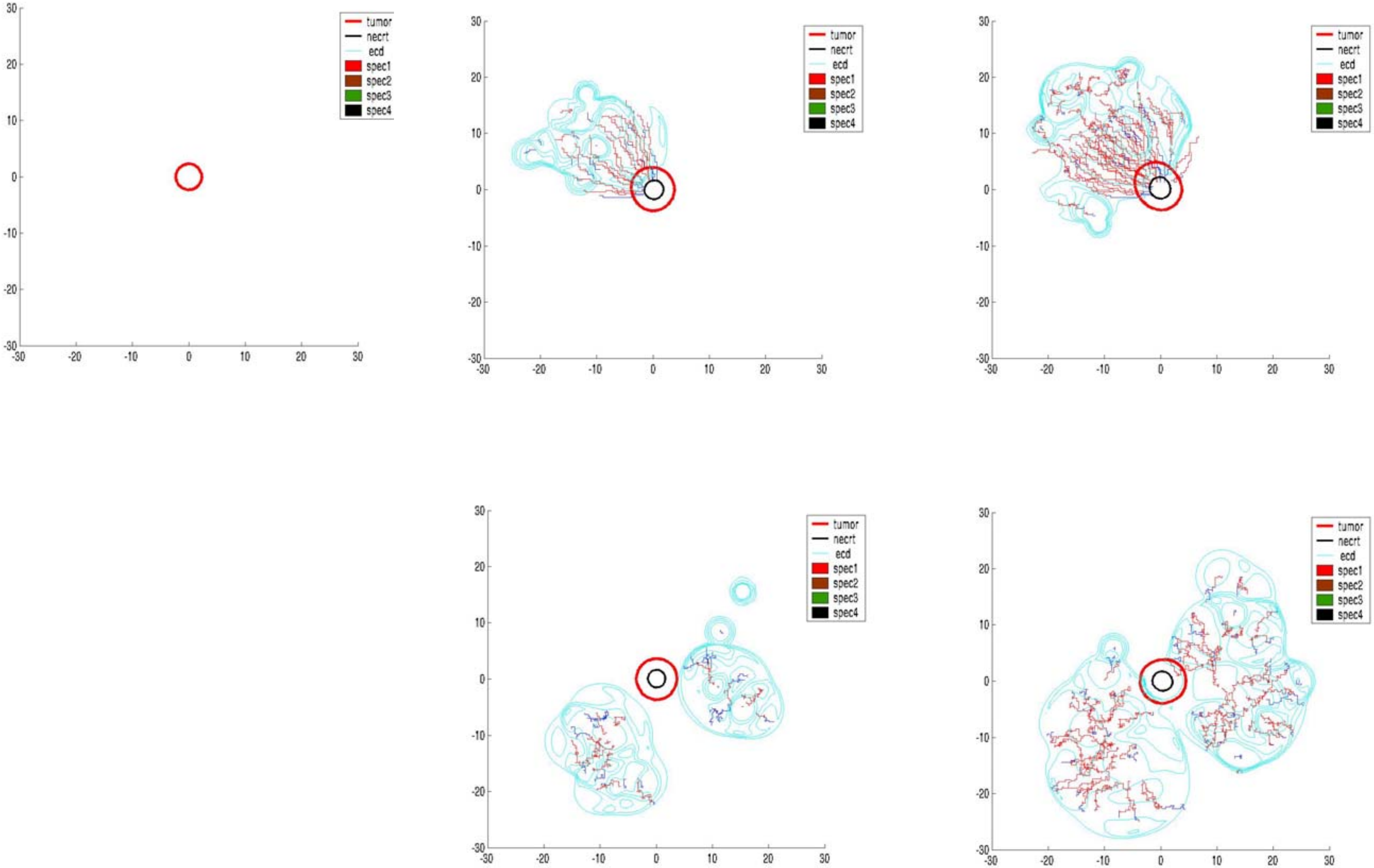
Soluble



- Brush-border effect
- Penetration
- Growth of tumor

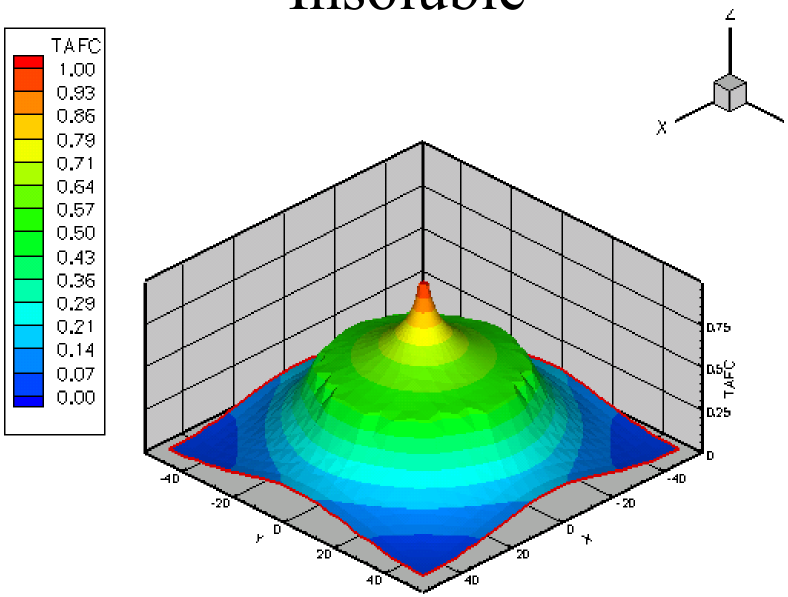
- Irregular vascular development
- little penetration
- Less growth

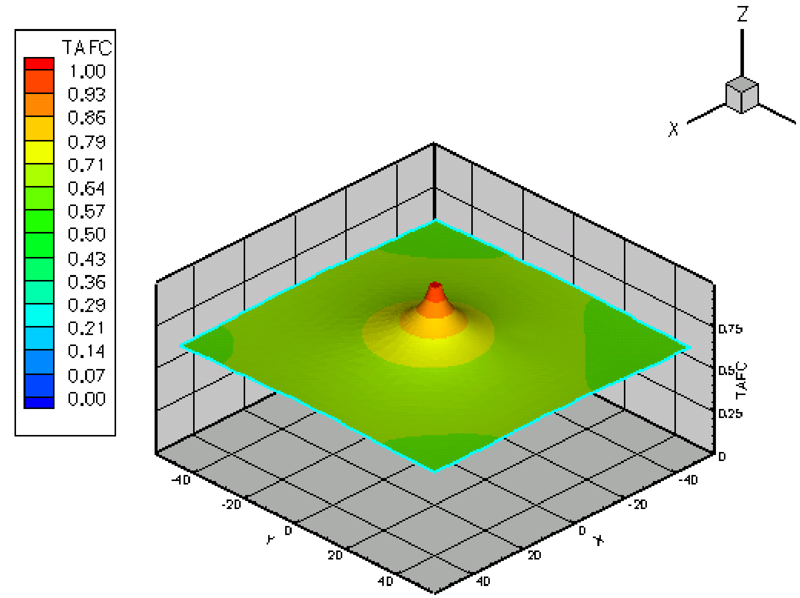
Stills


tumor
necrt
ecd
spec1
spec2
spec3
spec4
30
20
10
0
-10
-20
-30
-30
-20
-10
0
10
20
30

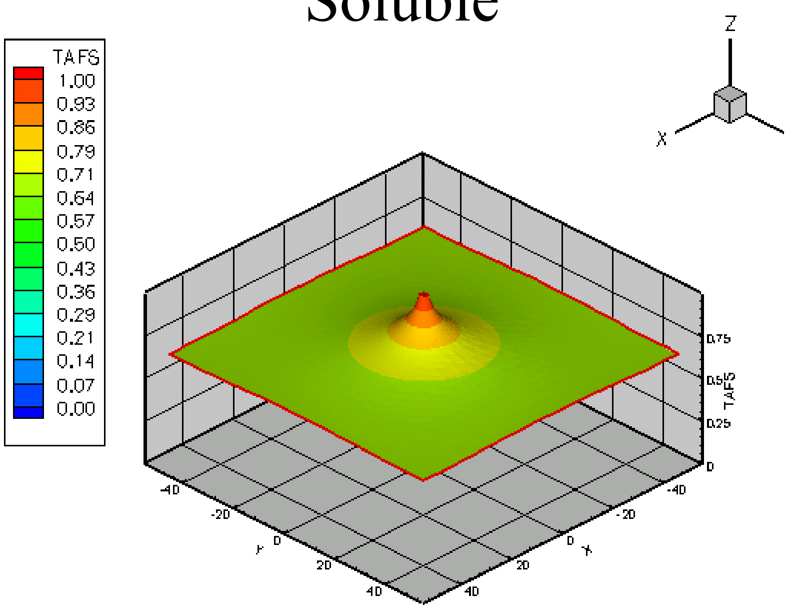
VEGF

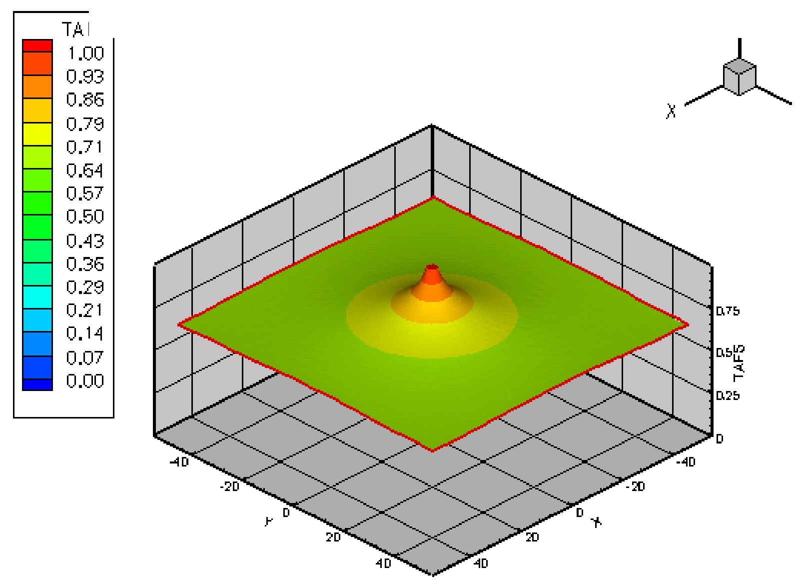
Insoluble





Soluble





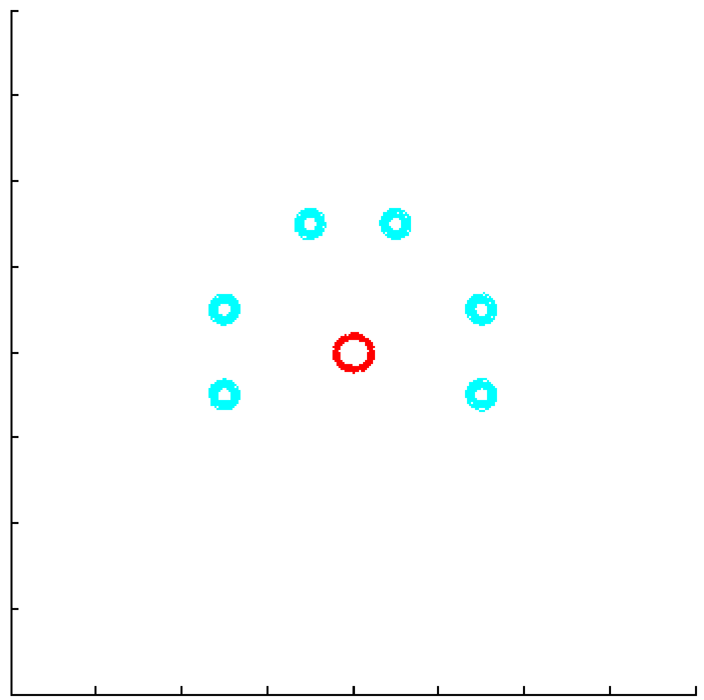
Growth of Glioblastoma Multiforme

(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

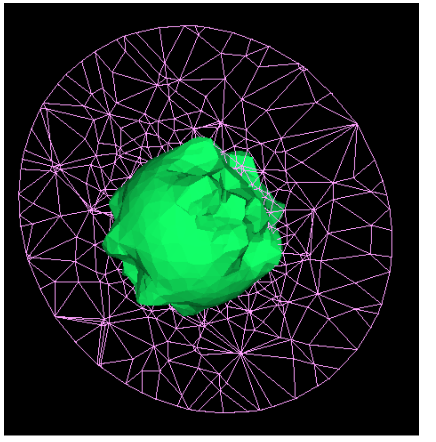
  of VEGF-A

  - Needs further work: MMPs, identification of biophysical mechanisms

  - Vascular remodeling/flow, etc.

Ongoing and Future work

- 3D

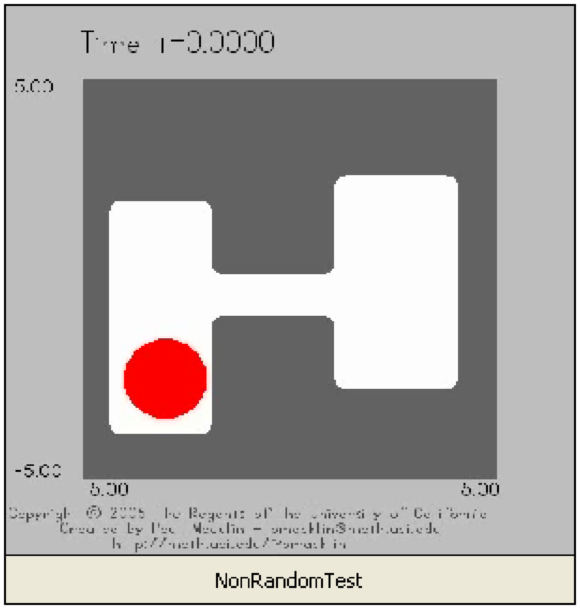


- Direct modeling of VEGF-A/ECM/MMP interaction on neovascular morphology.
- Realistic mechanical/diffusional description of tissue
- Cell-signaling– macro/micro nonlinear coupling
- Stochastic models
- Finite, complex domains

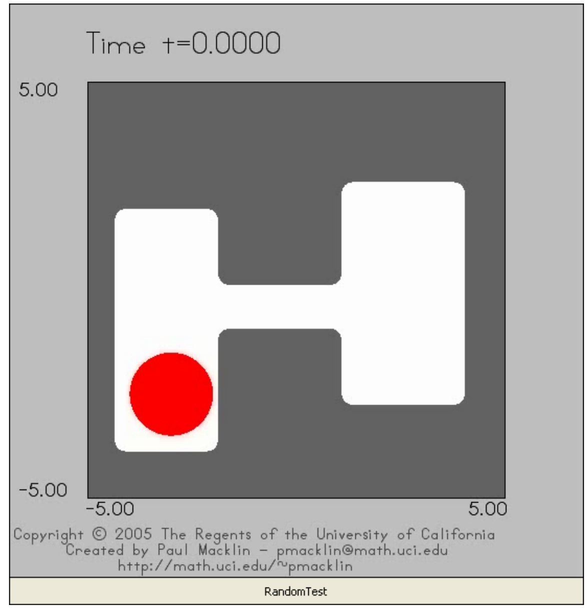
Future work contd.

•Genetic mutations, cell-differentiation and spatial structure

Non-random



Random



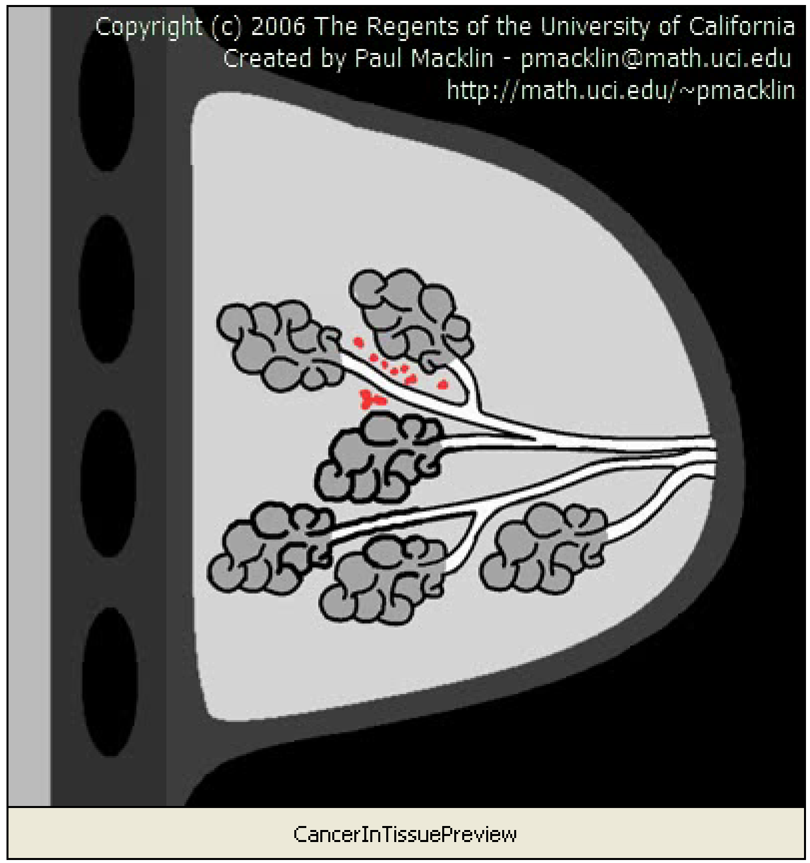
Komarova, Macklin, L.

•Multiscale Mixture Models

Cell-to-cell adhesion

Modeling growth in real organs

Breast cancer model



Example from Systems Biology

Morphogen gradients

Extra-Cellular Signaling—Morphogen gradients

Key collaborators:

- Arthur Lander Dept. of Cell and Developmental Biology, UCI
- **Fred Wan** Dept. of Mathematics, UCI
- Larry Marsh Dept of Cell and Developmental Biology, UCI
- **Qing Nie** Dept. of Math., UCI
- **Yong-Tao Zhang** Dept. of Math., UCI ---- (U. of Norte Dame, next year)
- **Rui Zhao** Dept. of Math., UCI ---- (MBI, next year)

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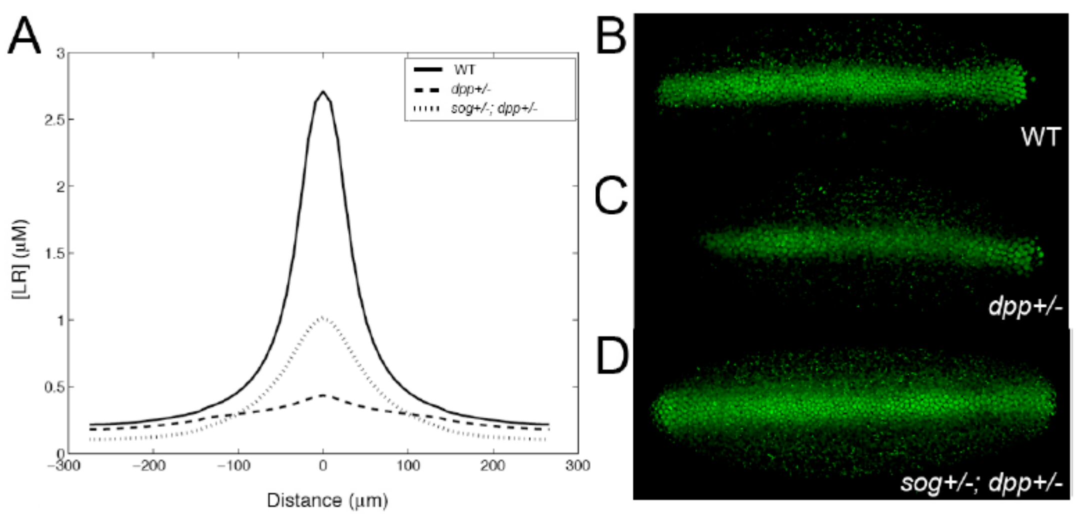
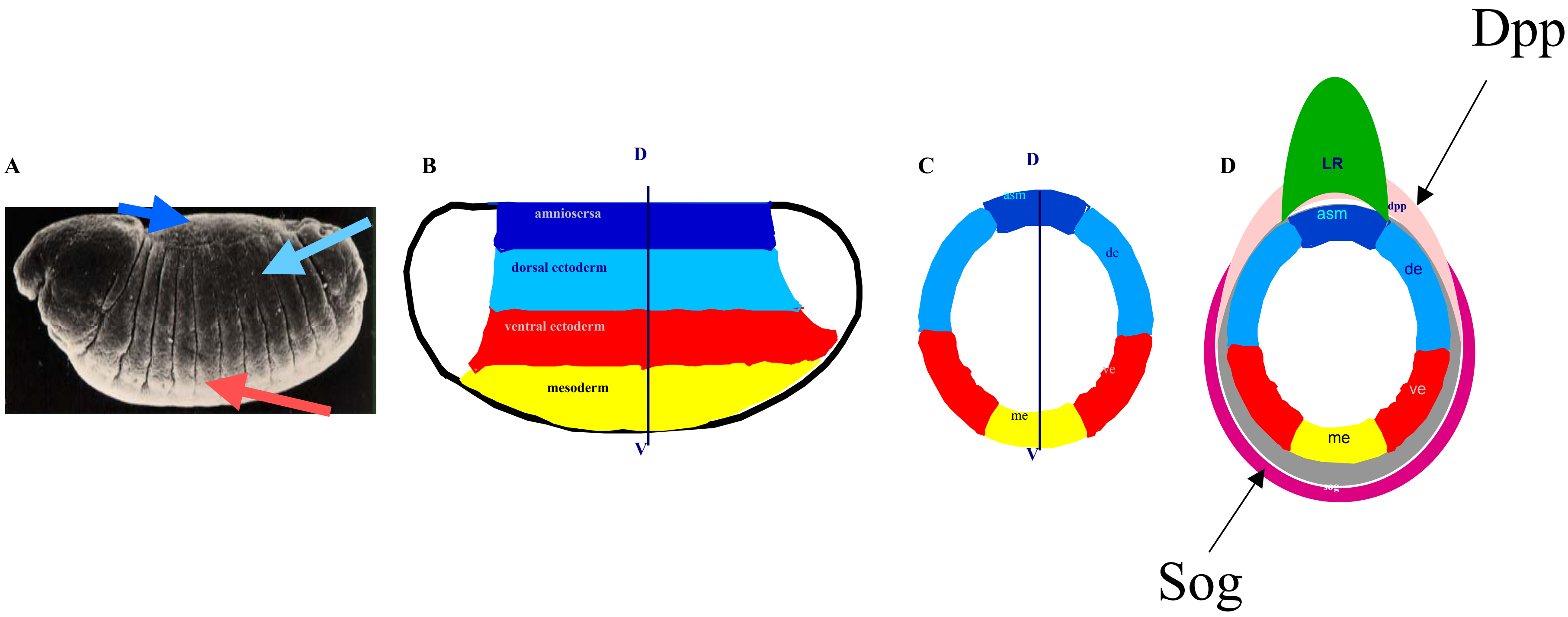
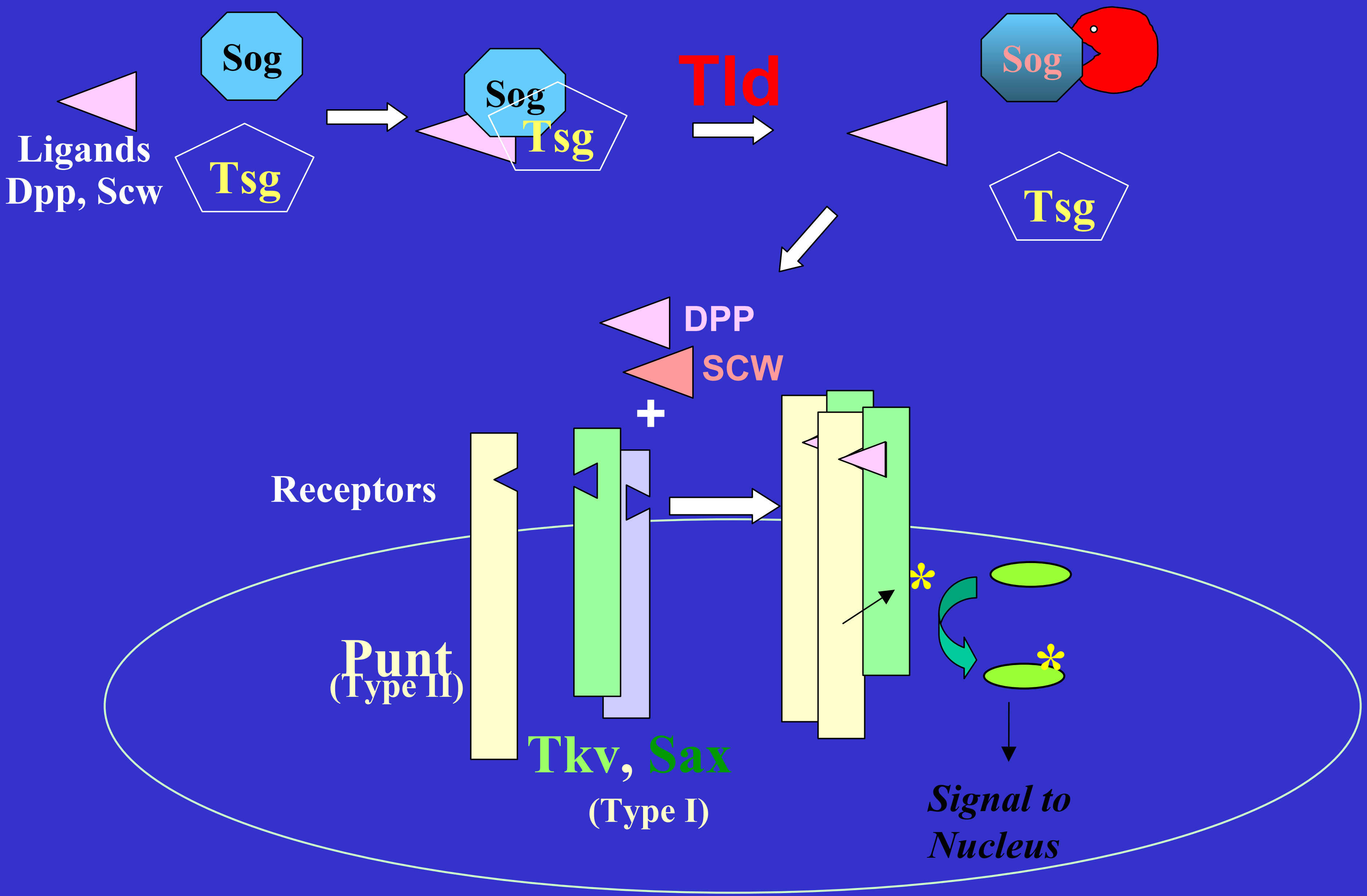


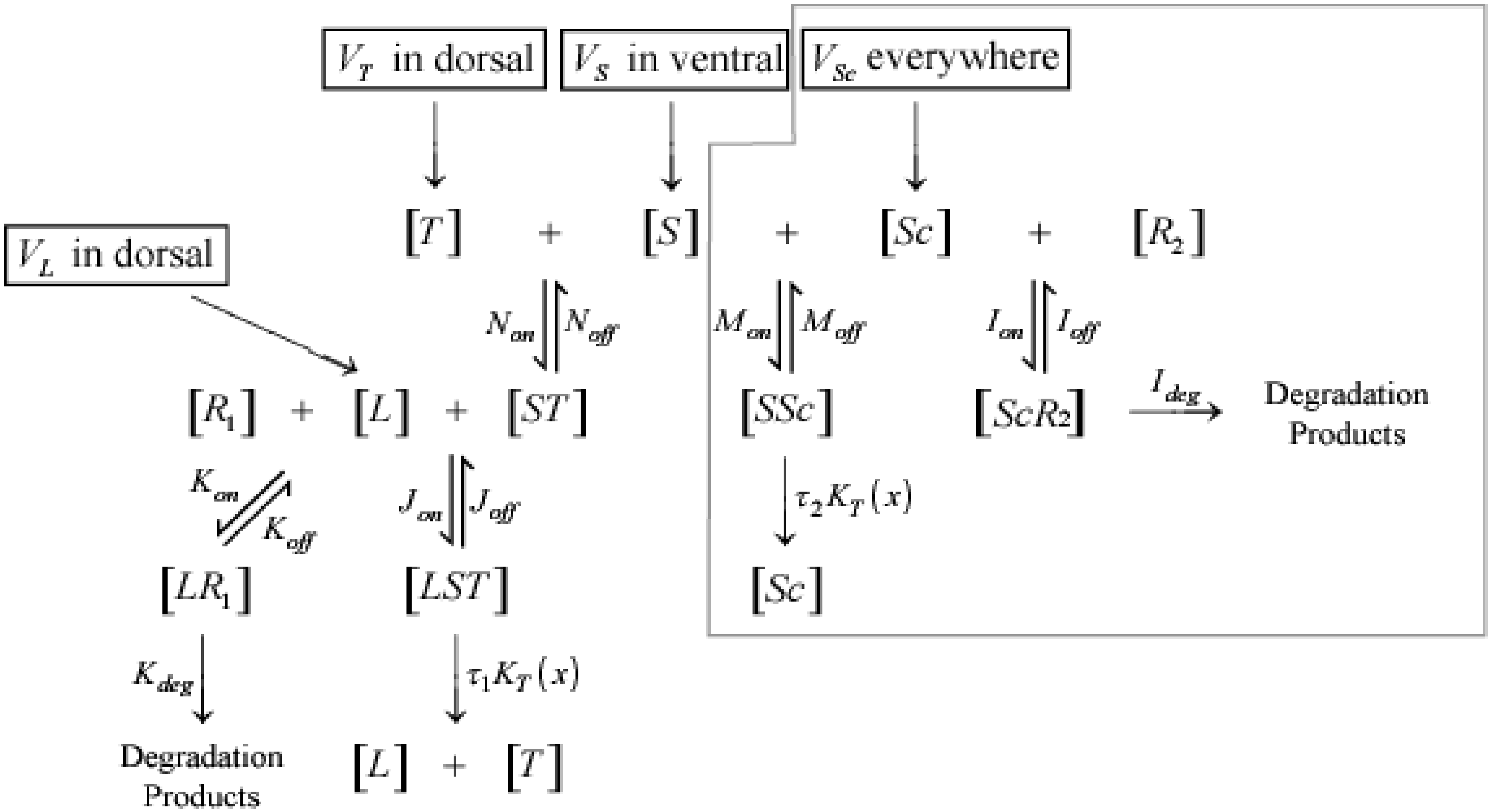
Ventral-Dorsal Patterning of a *Drosophila Embyro*



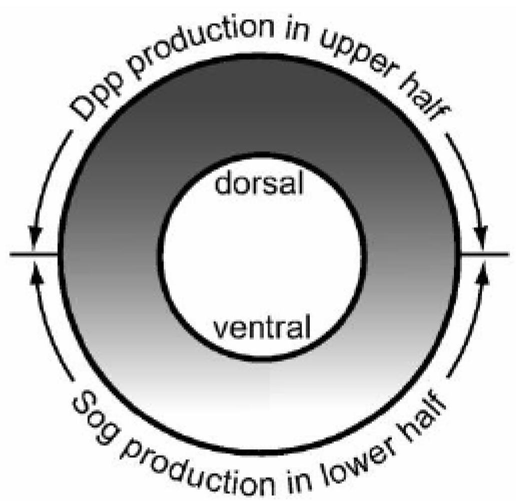
Secreted modulators of Dpp



A Mathematical Description



Model and Equations



$$\frac{\partial[L]}{\partial t} = D_L \frac{\partial^2[L]}{\partial x^2} - k_{on}[L](R_0 - [LR]) + k_{off}[LR]$$
$$- j_{on}[L][ST] + (j_{off} + \tau)[LST] + V_L(x)$$

$$\frac{\partial[LR]}{\partial t} = k_{on}[L](R_0 - [LR]) - (k_{off} + k_{deg})[LR]$$

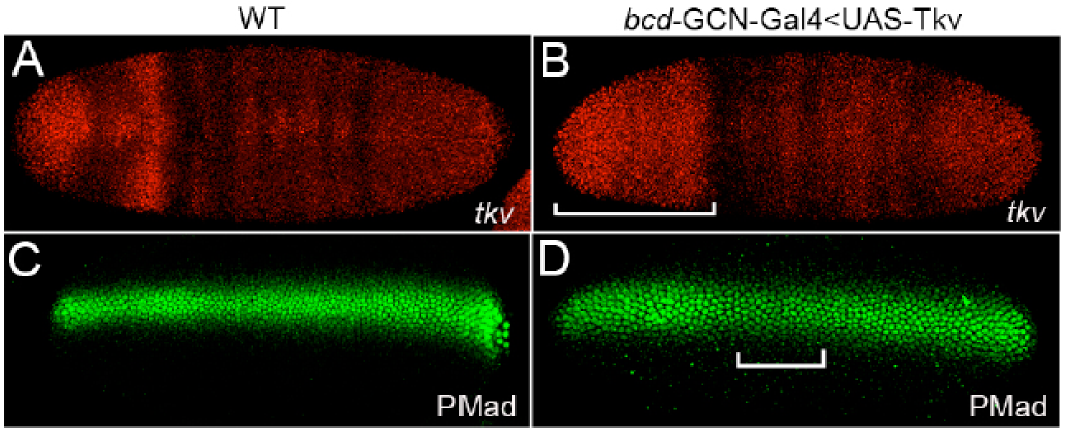
$$\frac{\partial[S]}{\partial t} = D_S \frac{\partial^2[S]}{\partial x^2} - n_{on}[S][T] + n_{off}[ST] + V_S(x)$$

$$\frac{\partial[ST]}{\partial t} = D_{ST} \frac{\partial^2[ST]}{\partial x^2} + n_{on}[S][T] - n_{off}[ST]$$
$$- j_{on}[L][ST] + j_{off}[LST]$$

$$\frac{\partial[T]}{\partial t} = D_T \frac{\partial^2[T]}{\partial x^2} - n_{on}[S][T] + n_{off}[ST] + \tau[LST] + V_T(x)$$

$$\frac{\partial[LST]}{\partial t} = D_{LST} \frac{\partial^2[LST]}{\partial x^2} + j_{on}[L][ST] - (j_{off} + \tau)[LST]$$

Dorsal-Ventral Patterning of *Drosophila*



C. Mizutant, Q. Nie, et al. *Developmental Cell* 8(6), 2005

$$\frac{\partial[L]}{\partial t} = D_L \frac{\partial^2[L]}{\partial x^2} - k_{on}[L](R_0 - [LR]) + k_{off}[LR] - j_{on}[L][ST] + (j_{off} + \tau)[LST] + V_L(x)$$

$$\frac{\partial[LR]}{\partial t} = k_{on}[L](R_0 - [LR]) - (k_{off} + k_{deg})[LR]$$

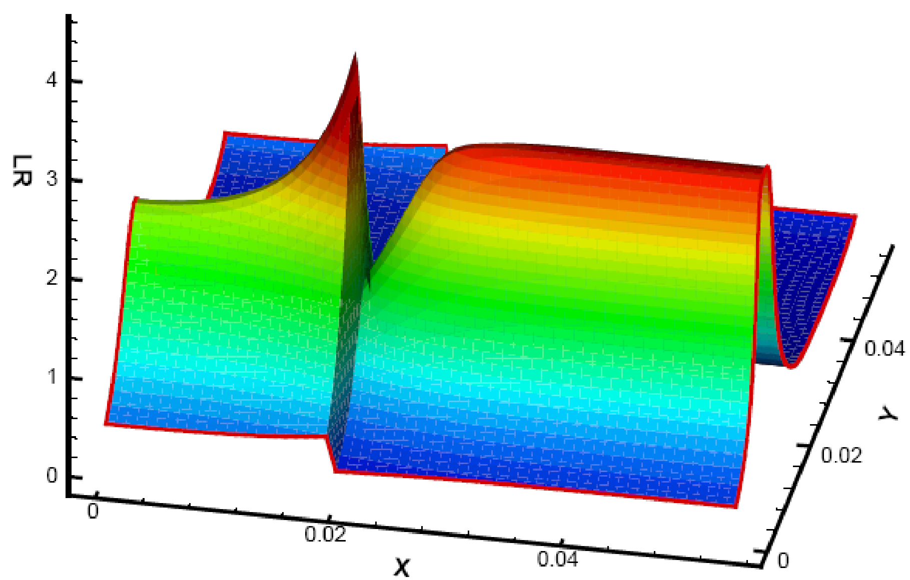
$$\frac{\partial[S]}{\partial t} = D_S \frac{\partial^2[S]}{\partial x^2} - n_{on}[S][T] + n_{off}[ST] + V_S(x)$$

$$\frac{\partial[ST]}{\partial t} = D_{ST} \frac{\partial^2[ST]}{\partial x^2} + n_{on}[S][T] - n_{off}[ST] - j_{on}[L][ST] + j_{off}[LST]$$

$$\frac{\partial[T]}{\partial t} = D_T \frac{\partial^2[T]}{\partial x^2} - n_{on}[S][T] + n_{off}[ST] + \tau[LST] + V_T(x)$$

$$\frac{\partial[LST]}{\partial t} = D_{LST} \frac{\partial^2[LST]}{\partial x^2} + j_{on}[L][ST] - (j_{off} + \tau)[LST]$$

A two-dimensional simulation



New Graduate Programs at UCI

- A new gateway interdisciplinary Ph. D. program on ***Mathematical and Computational Biology*** starts in Fall, 2006

- UCI was awarded $1M from HHMI in 2006 to create an interdisciplinary Ph.D. program on ***Mathematical, Computational and Systems Biology***

  3-year development period and subsequent NIH training grant support

- Continuum and PDE modeling is one of the focus areas in the training program