Multicell Modeling using CompuCell3D

James A. Glazier
Biocomplexity Institute
Indiana University
Bloomington, IN 47405
USA

International Workshop on Virtual Tissues
Research Triangle Park, NC
Tuesday, April 21, 2009

Support: Work started in 1991 in the Sawada Laboratory at Tohoku University, supported by NSF/JSPS. CompuCell3D Initially developed in collaboration with J. Izaguirre and M. Alber at the University of Notre Dame with support from the NSF. Recent support from NIH, Indiana University.

For papers on these projects, please visit http://www.biocomplexity.indiana.edu

To download software for model building, please visit http://www.compucell3d.org

Biocomplexity of Development

- **How** does the pattern of gene expression act through physical and chemical mechanisms to result in the structures we observe? Genetics is just the beginning.
- Same mechanisms occur repeatedly in different developmental examples.
- Begin by using phenomenological descriptions. In many cases very complex pathways have fairly simple effects under conditions of interest.

Multicell Models

- Distinguish two questions:
  - How does genetics drive cell phenomenology?
  - How does cell phenomenology drive tissue-level patterning?
- Most mammalian cells are fairly limited in their behaviors. They can:
  - Grow,
  - Divide,
  - Change Shape,
  - Move Spontaneously
  - Move in Response to External Cues,
  - Stick,
  - Absorb,
  - Secrete,
  - Exert Forces
  - Change their local surface properties
  - (Send Electrical Signals)

  A long list, but not compared to ~10^{10} gene-product interactions.
- Many cells have relatively simple phenomenological behaviors most of the time.

Microsoft Word is NOT a Novel

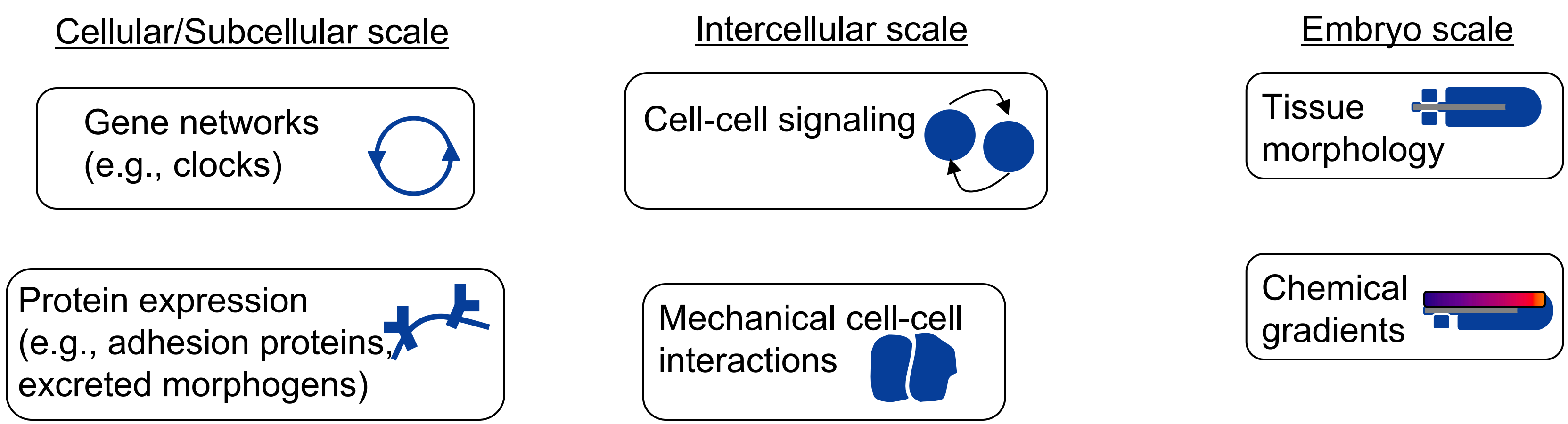
(Though it may be worth writing a novel about its inconveniences)

- It IS a Tool for writing.
- Life would be even worse if you had to rewrite the word processor every time you wanted to write a letter.
- (The Novel is the Hard Part).
- Similar tools exist in Molecular Dynamics, Finite Element simulations…
- NOT for Multiscale Multi-Cell modeling.

Purpose of CompuCell3D Project

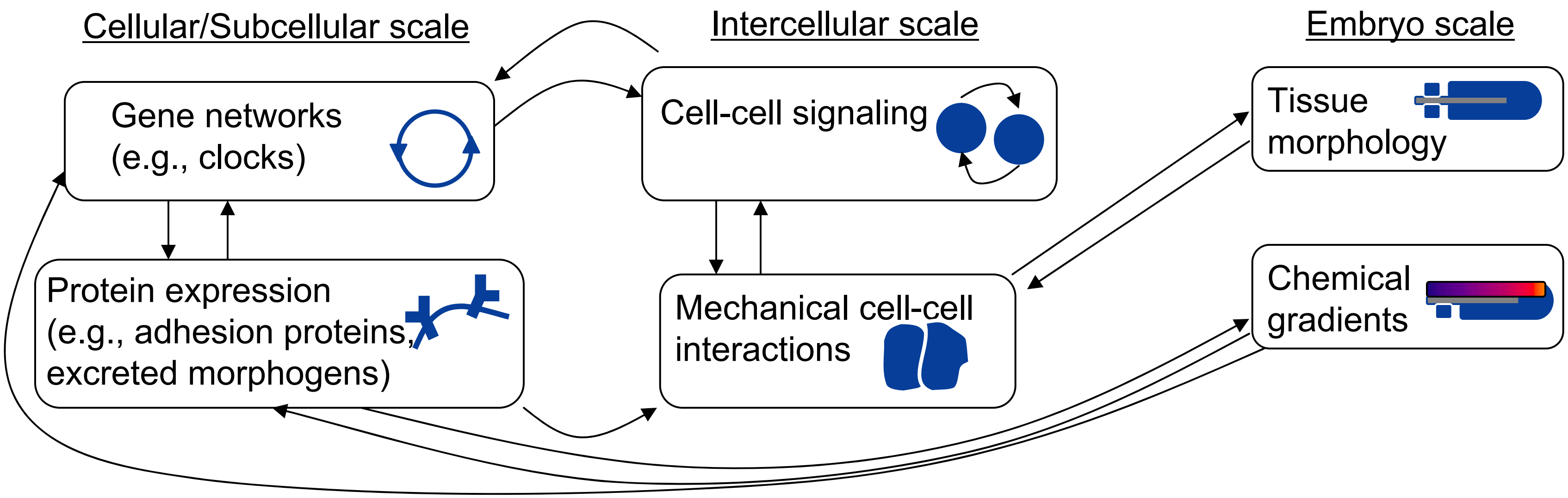
- Make Multi-Cell modeling Accessible to biologists, not just to programmers, physicists, mathematicians and engineers.
- Create a Standard Language to describe Multi-Cell simulations to allow them to be published, shared, reused, adapted and verified.
- Allow reuse of new tools by allowing their integration via standard APIs.
- Solution—create an OPEN SOURCE, PLATFORM INDEPENDENT simulation environment which separated model implementation from model description.

Motivation: Modeling Developmental Phenomena at Multiple Scales



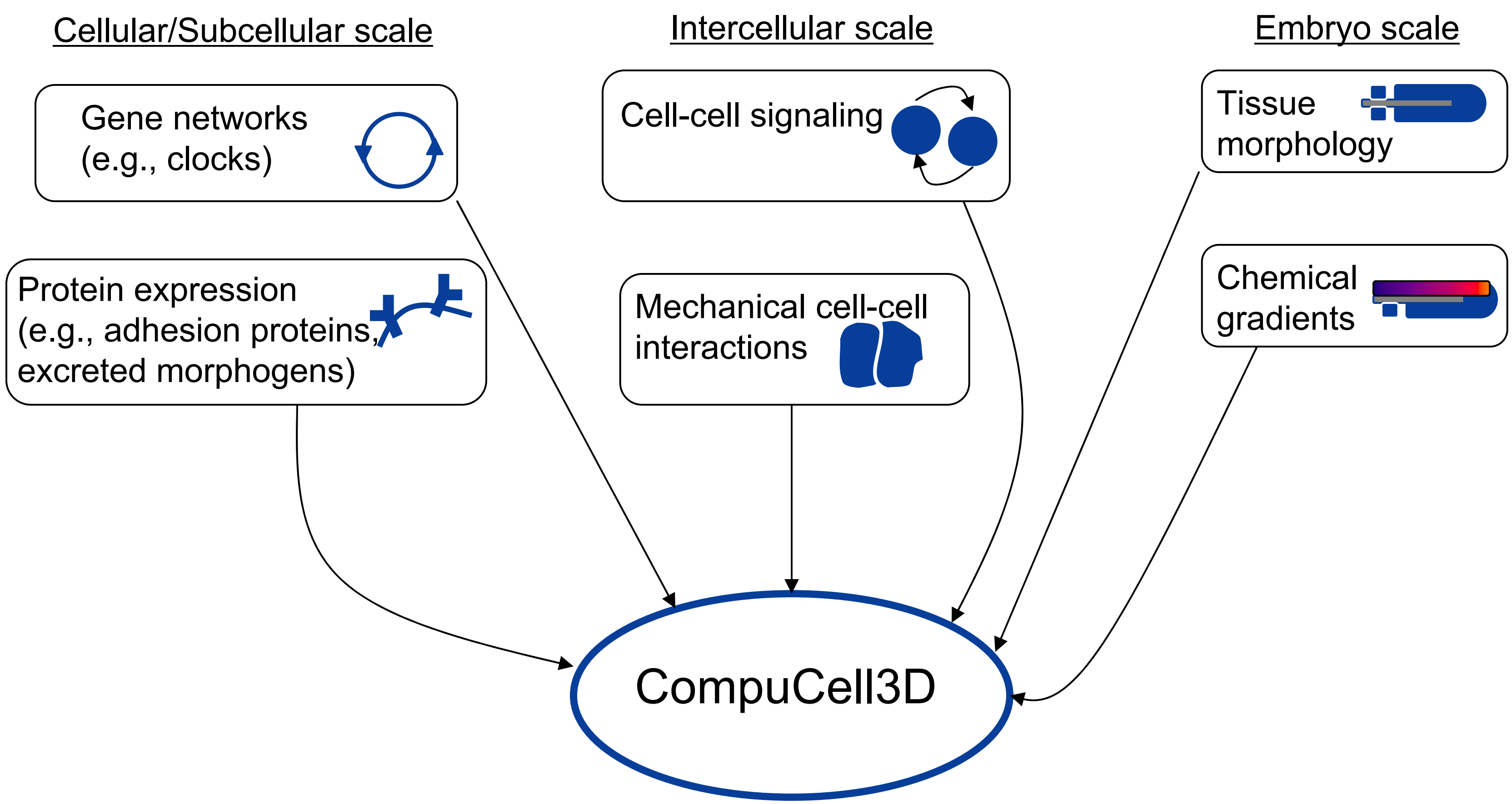
- Phenomena of development occur at multiple scales. To date, most models have focused on handling a single scale (e.g., *segmentation clock* models at the subcellular scale) or the interface between two scales (e.g., *clock and wavefront* models connecting subcellular and embryo scales).

Motivation: Modeling Developmental Phenomena at Multiple Scales



- Combining models at these interconnected scales is daunting.
- However, as understanding of the nature of developmental phenomena at and between scales increase, it has become necessary and important.

Motivation: Modeling Developmental Phenomena at Multiple Scales



- The use of CompuCell3D as a framework makes handling and combining multiple scales tractable.

CompuCell3D

- **Open-Source, Platform-Independent Simulation Environment which allows Complex Simulation Specification and Execution using a Standard Language.**
- **Makes Simulation Development Fast, Extensible, Sharable, Easy to Validate and Publish.**
- **Usable by Nonspecialists.**

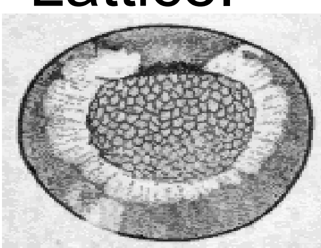
- **Try Going to www.compucell3d.org and Installing it on your Computer Now! (You may need to Install Python First www.Python.org).**

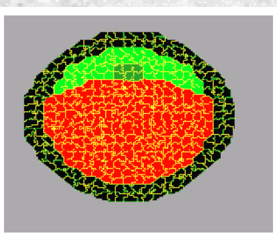
GGH Model Components

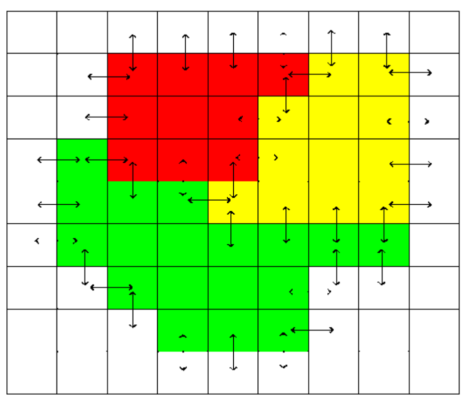
- Objects/Representations
- Object Properties/Interactions
- Dynamics
- ‘Tweaks’
- Initial and Boundary Conditions

GGH Objects/Representation

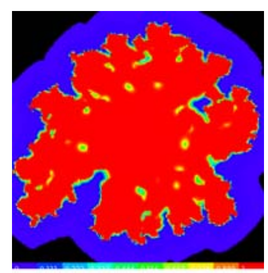
- Fundamental Entities are **Cells** and **Generalized Cells** (*e.g.* mesenchymal cells, epithelial cells, ECM, medium…), represented on the primary **Cell Lattice** (usually a square lattice with third or fourth neighbor interactions). We denote lattice position by $\vec{i}$
- Cells have **Internal States** and **Types** which describe their properties.
- Have **External Chemical Fields** represented on **Auxiliary Lattices** with same geometry as the Cell Lattice.



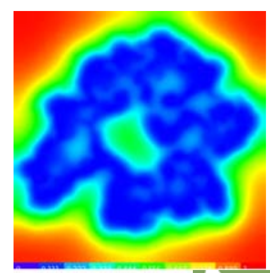




ECM



MDE

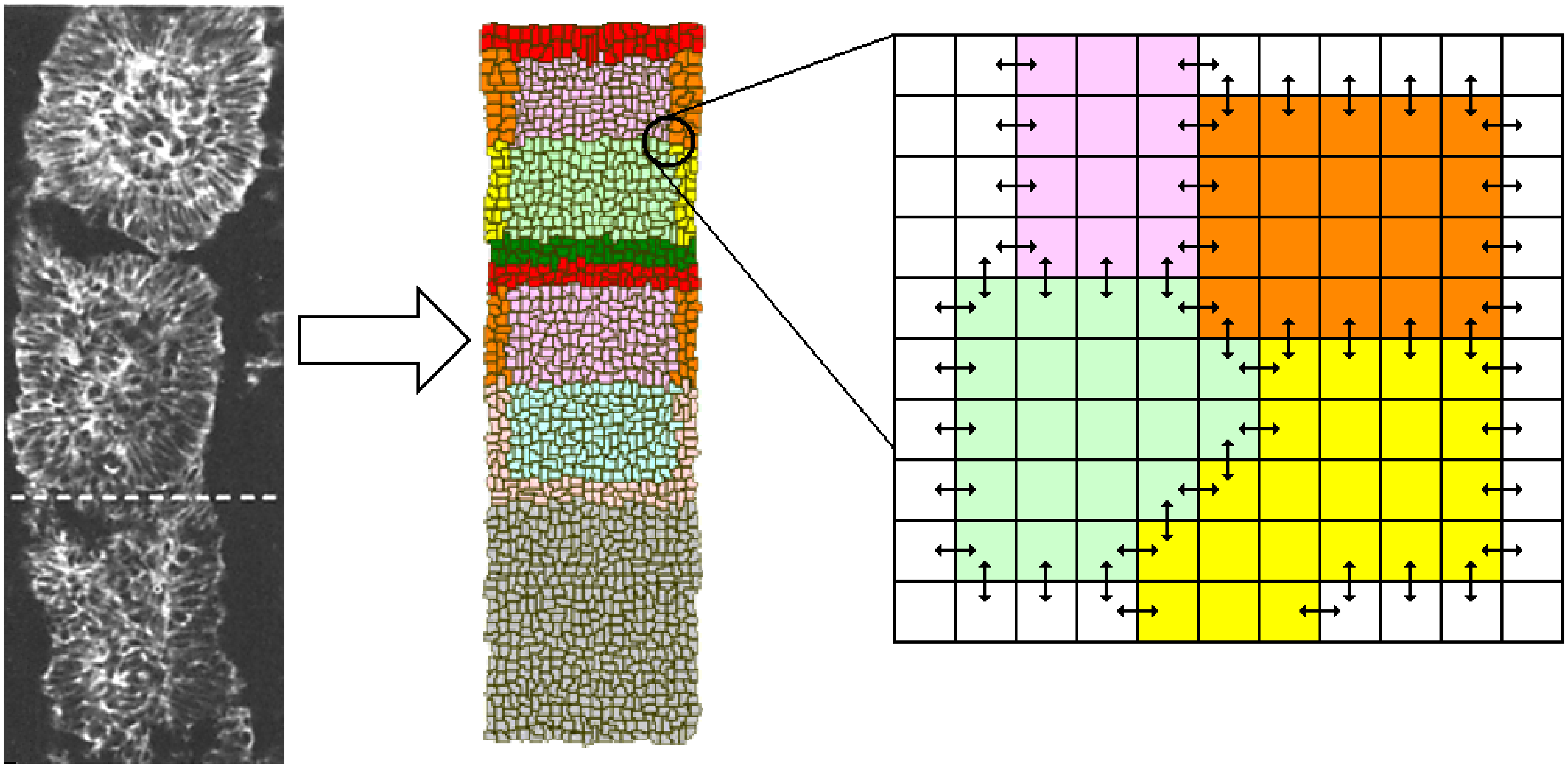


nutrien

GGH Cell Properties/Interactions

- Most biological properties of Cells and their interactions with each other and with Fields are Encapsulated in the Effective Energy, H.
- H is the sum of many separate terms.
- Each term in H encapsulates a single biological mechanism.
- Cell Properties described as **Constraints**.

GGH Model



$$E = \sum_{x,x'} J_{\tau(\sigma(x)),\tau(\sigma(x'))}(1-\delta_{\tau(\sigma(x)),\tau(\sigma(x'))}) + \lambda_s (s_\sigma - S_\sigma)^2 + \lambda_v (v_\sigma - V_\sigma)^2$$

$$\begin{aligned} P(\Delta E) &= 1,\ \Delta E \leq 0 \\ P(\Delta E) &= e^{-\Delta E/kT},\ \Delta E > 0 \end{aligned}$$

Available Mechanisms in CompuCell3D

- Control of Cell Differentiation, Signaling, Growth, … via Coupled ODEs
- Reaction-Diffusion Equations (PDEs)
- Cell Adhesion
- Membrane Areas
- Mitosis
- Apoptosis
- Secretion and Absorption of Materials
- Viscosity
- Chemotaxis
- Haptotaxis
- Rigid-Body Motion
- Inertial/Persistent Motion
- Explicit External Forces
- Gravity
- Compartmental Cell Models
- Cell Polarity
- Complex Cell Shapes and Cell-Shape Changes.
- …..

Building A Model

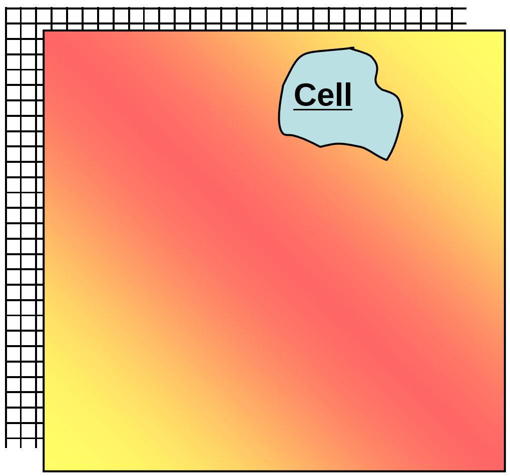
- Define Objects (Cells, Cell Types and Fields).
- Define Energy Terms.
- Define Initial Conditions.
- Pick Parameter Values (Hard, but some rules of thumb).

- Run…

CC3DML

The most commonly needed functions are predefined in CC3D and are specified using a specific eXtended Markup Language (XML).

Define Cell Lattice and Simulation Parameters



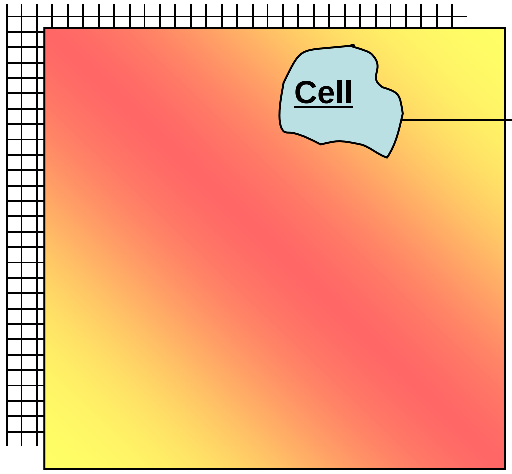

```
< CompuCell3D>
 <Potts>
   <Dimensions x=“100" y=“100"
z=“1"/>
   <Steps>10</Steps>
   <Temperature>2</Temperature>
   <Flip2DimRatio>1</Flip2DimRatio>
 </Potts>

…

</CompuCell3D>
```

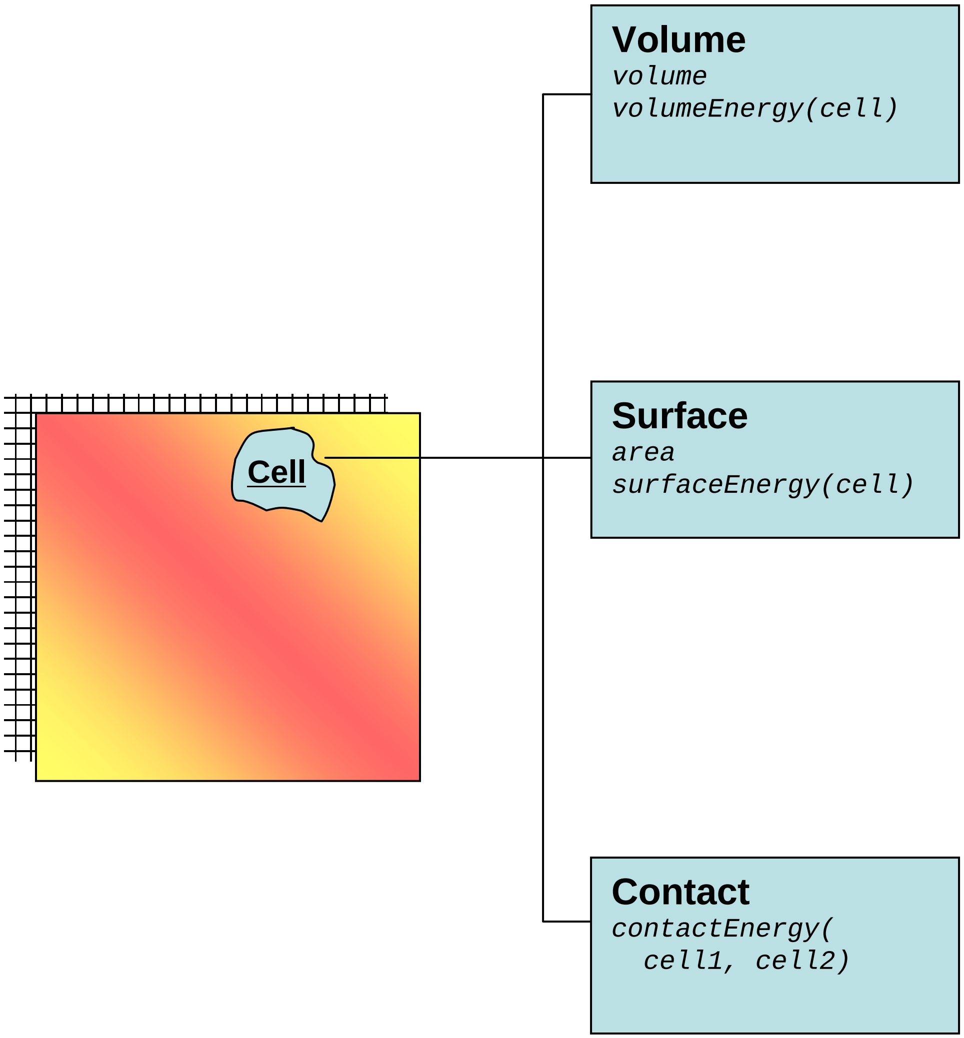
Define Cell Types Used in the Simulation

Each CC3DML file must list all Cell Types that will used in the simulation



<Plugin Name="CellType">
<CellType TypeName="Medium" TypeId="0"/>
<CellType TypeName=“Light" TypeId="1"/>
<CellType TypeName=“Dark" ="2"/>
</Plugin>

Define Energy Terms of the Effective Energy and their Parameters




```
<Plugin Name="Volume">
<TargetVolume>25</TargetVolume>
<LambdaVolume>1.0</LambdaVolume>
</Plugin>
```

```
<Plugin Name="Surface">
 <TargetSurface>21</TargetSurface>
 <LambdaSurface>0.5</LambdaSurface>
</Plugin>
```

```
<Plugin Name="Contact">
  <Energy Type1="Medium" Type2="Medium">0
  </Energy>
  <Energy Type1="Light" Type2="Medium">0
  </Energy>
  <Energy Type1="Dark" Type2="Medium">0.1
  </Energy>
  <Energy Type1="Light" Type2="Light">0.5
  </Energy>
  <Energy Type1="Dark" Type2="Dark">3.0
  </Energy>
  <Energy Type1="Light" Type2="Dark">0.5
  </Energy>
</Plugin>
```

Adding Subcellular Reaction Networks

- Use your favorite Subcellular model package (SBW, Fortran, C++, Mathematica, Matlab,…)
- Use standard Python glue files to run network inside each CC3D cell.
- Working for full interoperability between SBW and CC3D via CC3DML and SBML extensions…

Python Scripting

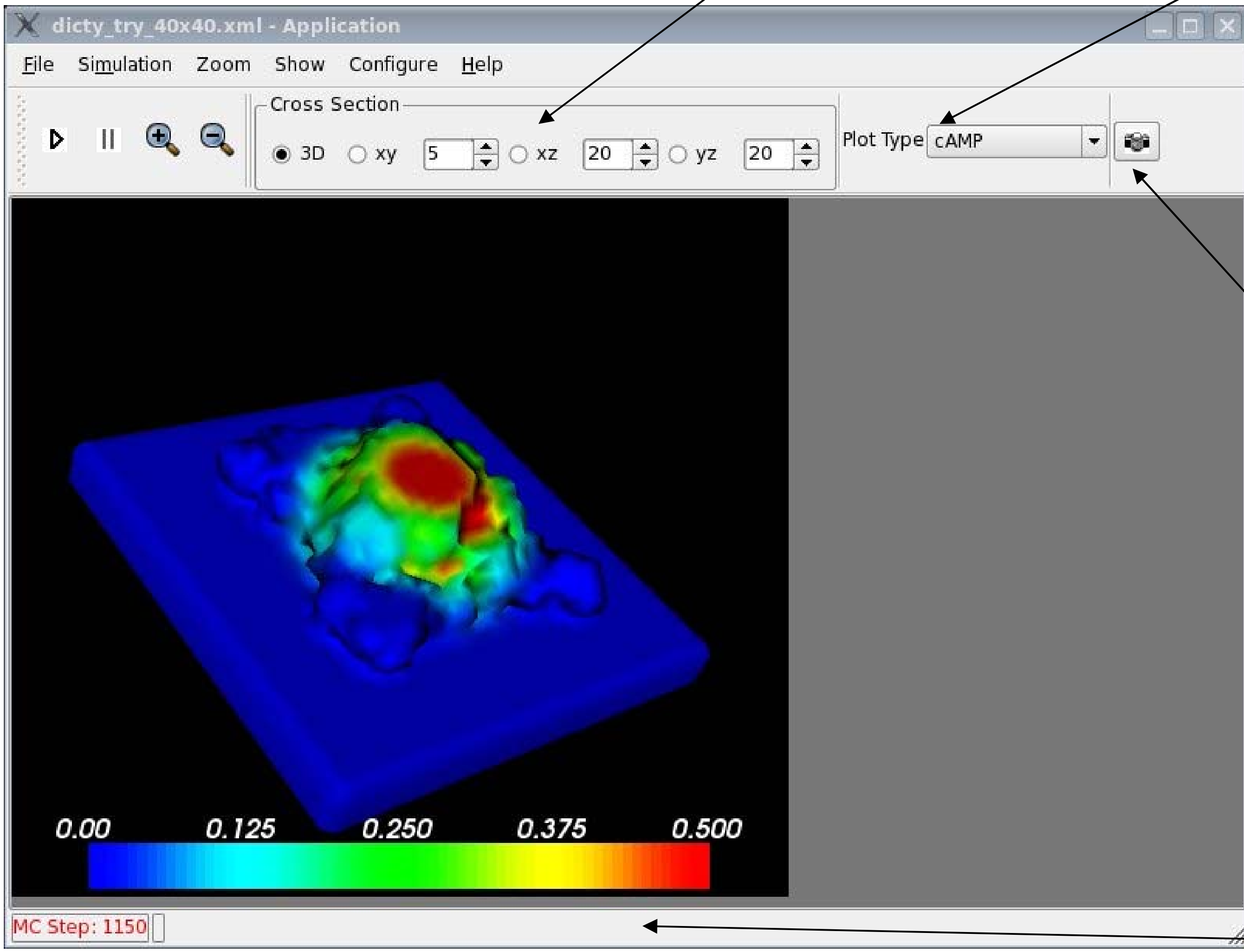
For more complex cell behaviors, CompuCell3D supports Python scripting (will have Java soon as well).

Simple example to print cell id, cell type and cell volume for every cell in the simulation (user code in blue, template code in grey).

```
class InfoPrinterSteppable(SteppablePy):
   def __init__(self,_simulator,_frequency=10):
      SteppablePy.__init__(self,_frequency)
      self.simulator=_simulator
      self.inventory=self.simulator.getPotts().getCellInventory()
      self.cellList=CellList(self.inventory)
   def start(self):
      print "This function is called once before simulation“\
   def step(self,mcs):
      print "This function is called every 10 MCS“
      for cell in self.cellList:
         print "CELL ID=",cell.id, " CELL TYPE=",cell.type," volume=",cell.volume
```

Running the Simulation

Steering bar allows users to start or pause the simulation, zoom in , zoom out, to switch between **2D and 3D** visualization, change **view modes** (cell field, pressure field , chemical concentration field, velocity field etc..)



Player can output multiple views during single simulation run – **Add Screenshot** function

Information bar

Tumors

Biomedical Background

- **Issue:** Most Tumors are Only Dangerous when:
  - They become **neovascularized** (induce growth of new blood vessels to provide nutrients).
  - They **metastasize** (their cells migrate--usually via the blood stream) to form numerous secondary tumors.

- **Idea:** ~20 years ago—use drugs to block neoangiogenesis (*e.g*. Avastin).

- **Result:** Sometimes it works, sometimes the antiangiogenic drug **induces metastasis** (makes things **much worse**).

Start with Anderson Tumor Model

Cell Types:

- normal (Motile, Adhere Strongly, chemorepelled by ECM, divide, consume nutrients, secrete MDE, mutate).
- quiescent (Induced by pressure, Motile, Adhere Strongly, chemorepelled by ECM, consume nutrient, do not divide).
- mutated (Motile, Adhere Weakly, chemorepelled by ECM, divide, consume nutrients, secrete MDE).
- necrotic (Passive, gradually shrink).

Fields:

- nutrient (aggregates Oxygen if needed, glucose, *etc*…).
- surrounding tissue (ECM) (aggregates non-cellular material and normal cells, *etc*…).
- matrix degrading enzyme (MDE) (aggregates lactic acid and MMPs).

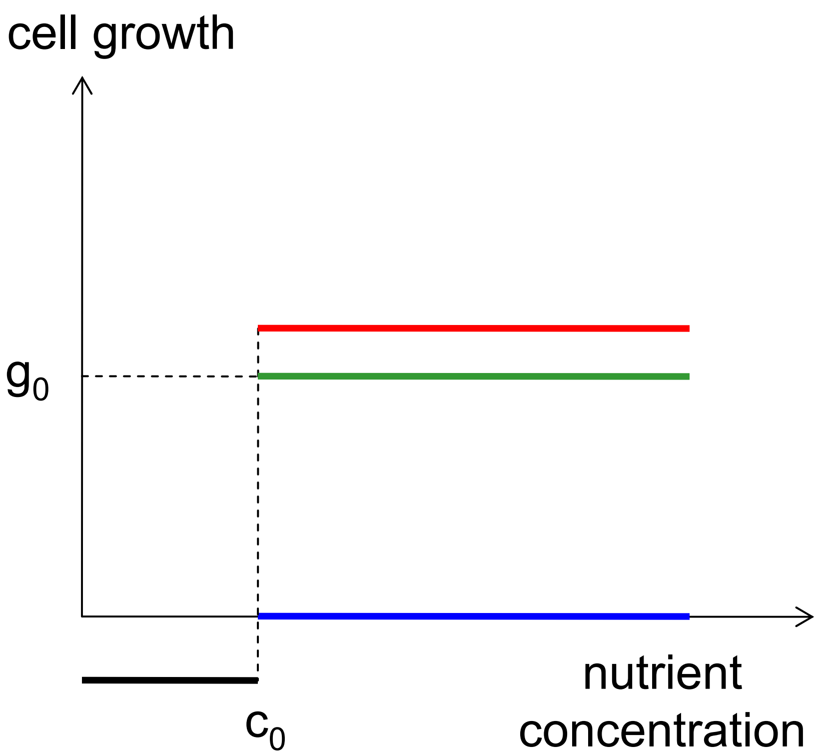
Reaction-diffusion equations for Fields:

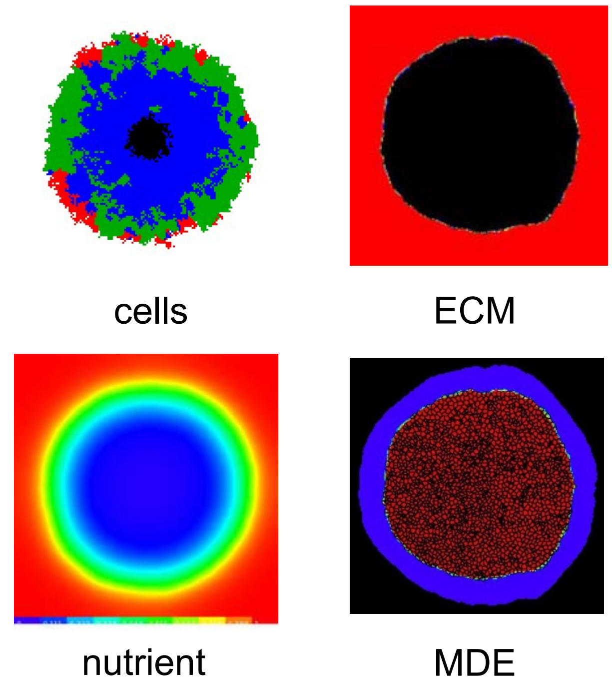
Nutrient: concentration change = diffusion + production by ECM – uptake by tumor cells – decay

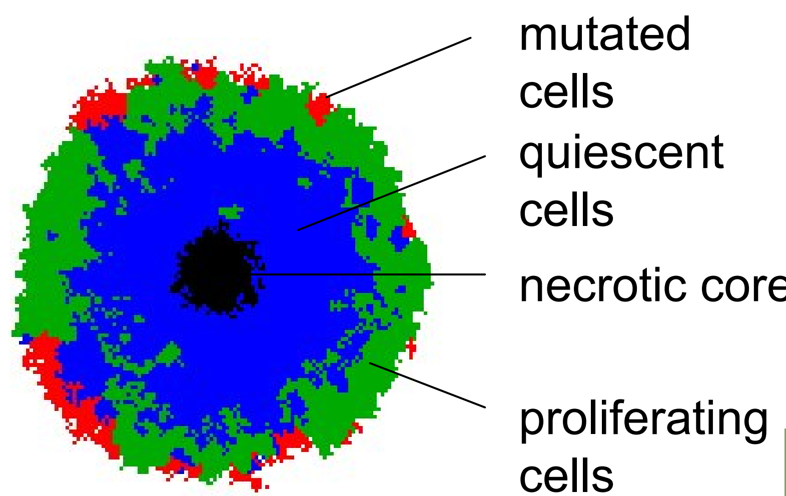
MDE: concentration change = diffusion + production by cells – decay

ECM: concentration change = – degradation by MDE

CONSTANT GROWTH RATE ABOVE THRESHOLD



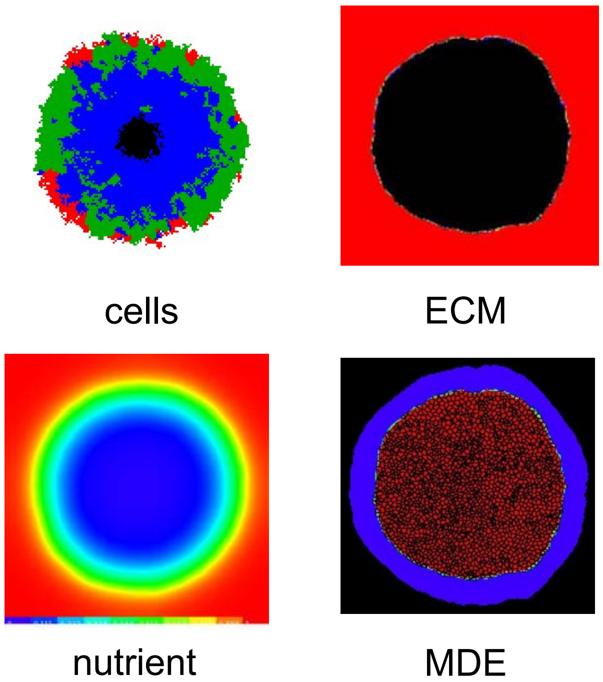


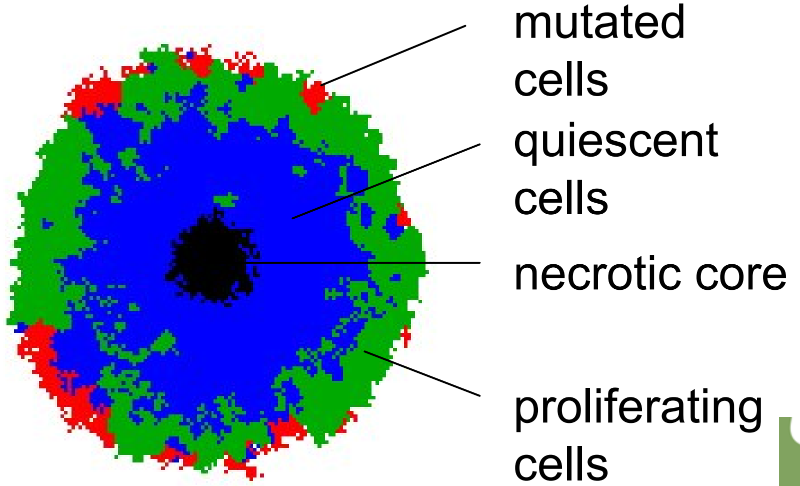


Benign Tumor

Sufficient supply of nutrients

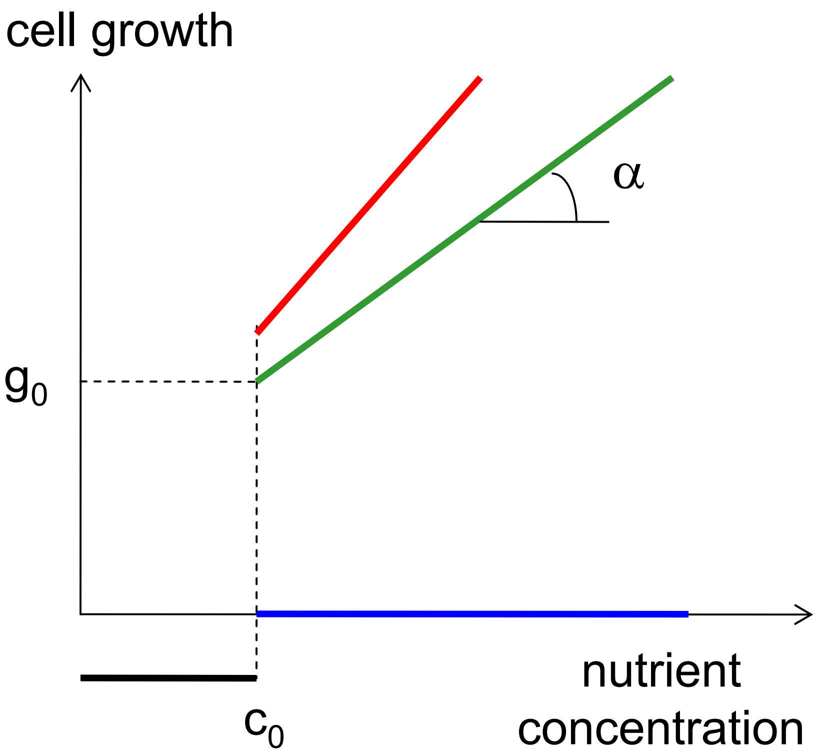
CONSTANT GROWTH RATE ABOVE THRESHOLD

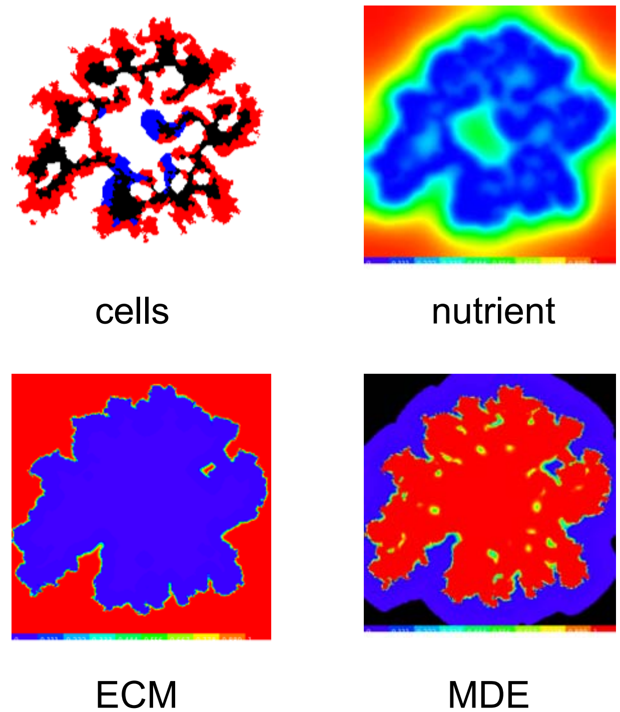




Benign Tumor
Sufficient supply of nutrients

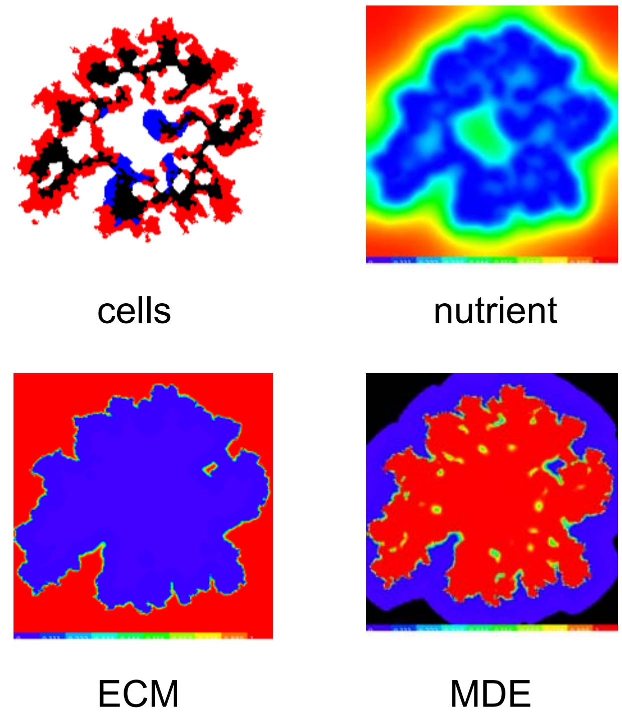
GROWTH RATE PROPORTIONAL TO NUTRIENT CONCENTRATION ABOVE THRESHOLD





Malignant Tumor
Sensitivity of growth to nutrient supply leads to fingering instabilities (and possibly metastasis)

GROWTH RATE PROPORTIONAL TO NUTRIENT CONCENTRATION ABOVE THRESHOLD



Malignant Tumor

Sensitivity of growth to nutrient supply leads to fingering instabilities (and possibly metastasis)

Suggests that Growth rate/properties of cells can determine invasiveness. Tissue inhomogeneity NOT needed.

Now simplify much further:

One cell type.

One diffusing field (nutrient).

Two parameters:

G —The Dimensionless ratio between nutrient diffusion and growth rate (determines if growing periphery of tumor is nutrient limited).

γ —The effective tumor surface tension (aggregates many things but effectively ratio between tumor-cell-tumor-cell binding and tumor-cell-ECM binding, *i.e*. cadherins/integrins. ↑Integrin, ↓cadherin $\Rightarrow \downarrow \gamma$.

	G=4	G=8	G=12	G=16	G=20	G=24
γ=6						
γ=4						
γ=2						
γ=0						

Result and Sample Clinical Deduction

1) Competition for nutrients as measured by *G*, controls tumor morphology (spherical benign vs. fingering malignant). (Agrees with *in vitro* experiments as reported in P. Macklin, J. Lowengrub, *J. Theor. Biol.* (2007)).

2) For Fixed *G*, smaller γ are more invasive.

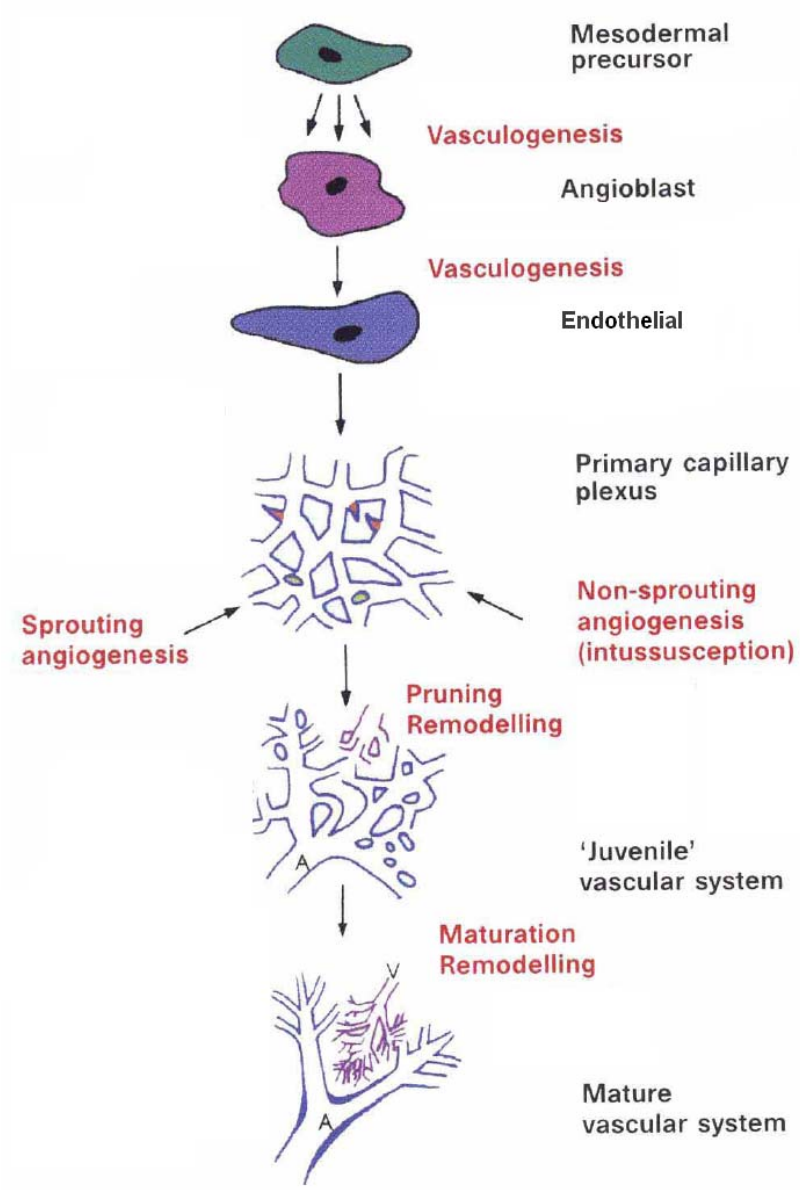
3) Small γ tumors are more sensitive to nutrient limitation than large-γ tumors.

4) Can INFER G and γ from Tumor Morphology.

Implication: If Tumor has morphology in high *G*, γ range, then antiangiogeneic therapy may be helpful. If in low *G*, γ range, antiangiogenic therapy is likely to promote metastasis.

Now Add Vasculogenesis

- Vasculogenesis
  - The formation of early vascular plexus from in situ differentiated **Endothelial Cells** (***ECs***)
- Angiogenesis
  - The formation of new blood vessels from pre-existing ones
    - Sprouting Angiogenesis
    - Non-sprouting Angiogenesis (**Intussusceptive angiogenesis**)



Werner Risau, *Nature* **386**, 671 - 674 (1997)

A4

Vascular Development

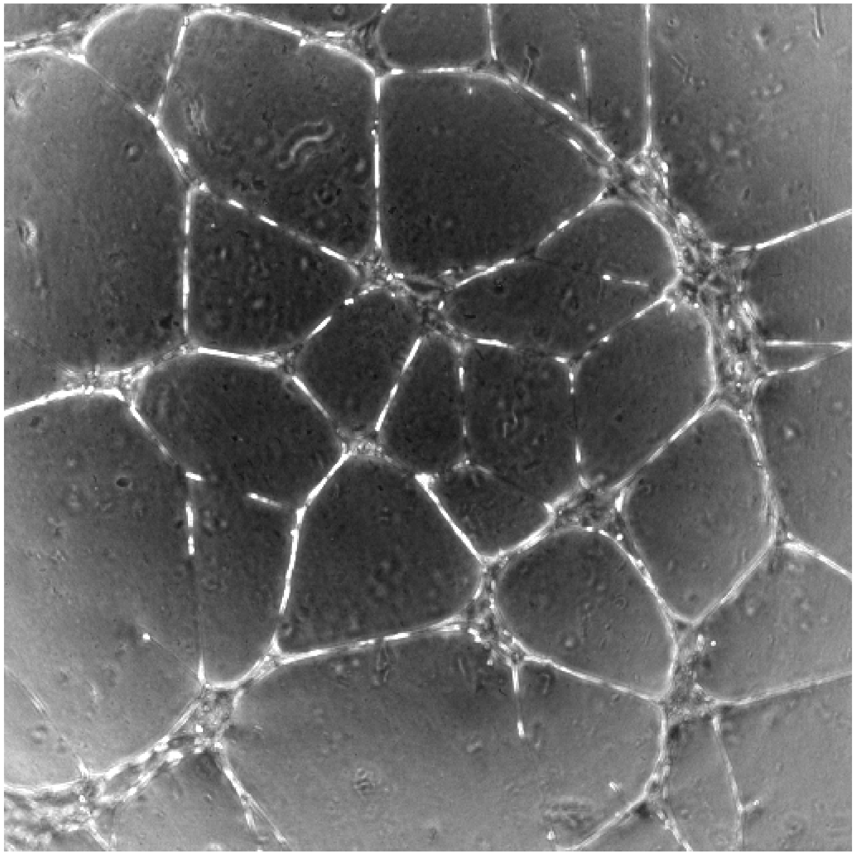
Biological System
- Umbilical Vein Endothelial Cells (HUVECs) on Matrigel

Can We Reproduce *in vitro* vasclar Patterning?

Can We determine the chemoattractant?

Can we Define the roles of Contact inhibition and Cell Elongation?

Can the Same Model reproduce Both Vasculogenesis (random initial conditions) and Angiogenesis (Sprouting)?



Movie 1

Movie 1: D. Ambrosi et al., Phys. Rev. Letters **90**, 118101

Slide 33

A4 We are starting with a very simple model and gradually add more details.

The biological system, HUVEC culture on matrige, is essentially a 2D system,and no ECM envoled

Cell elongation is implemented in GG CPM, but we don't have in the current model

Some of this mechanis

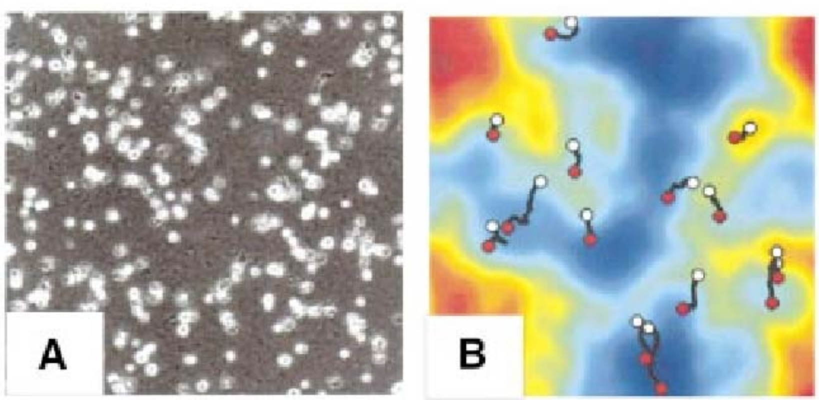
Abbas, 12/13/2006

Vasculogenesis based on

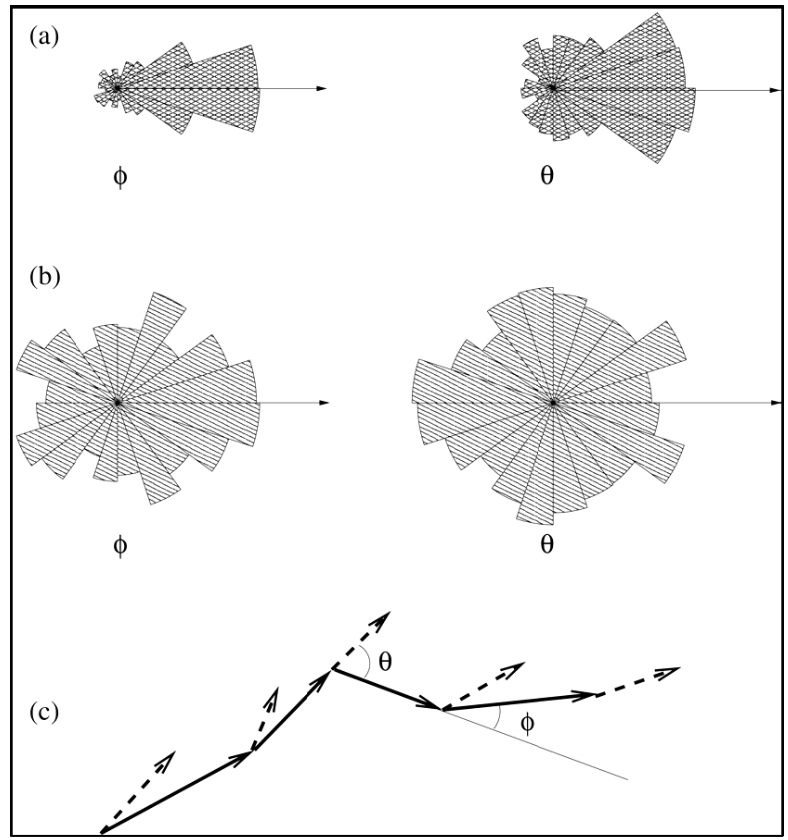
Chemotaxis Hypothesis

(Gamba *et al.* 2003; Serini *et al.*, 2003)

- Cells migrate to higher concentrations of cells
- Saturation of **VEGF-A gradients** inhibits directional cell migration
- ECs produce VEGF-A during first hour of vascular development



Red circles: starting point. White circles: arrival point.



Solid arrows represent cell displacements; dashed arrows represent chemoattractant Gradients.

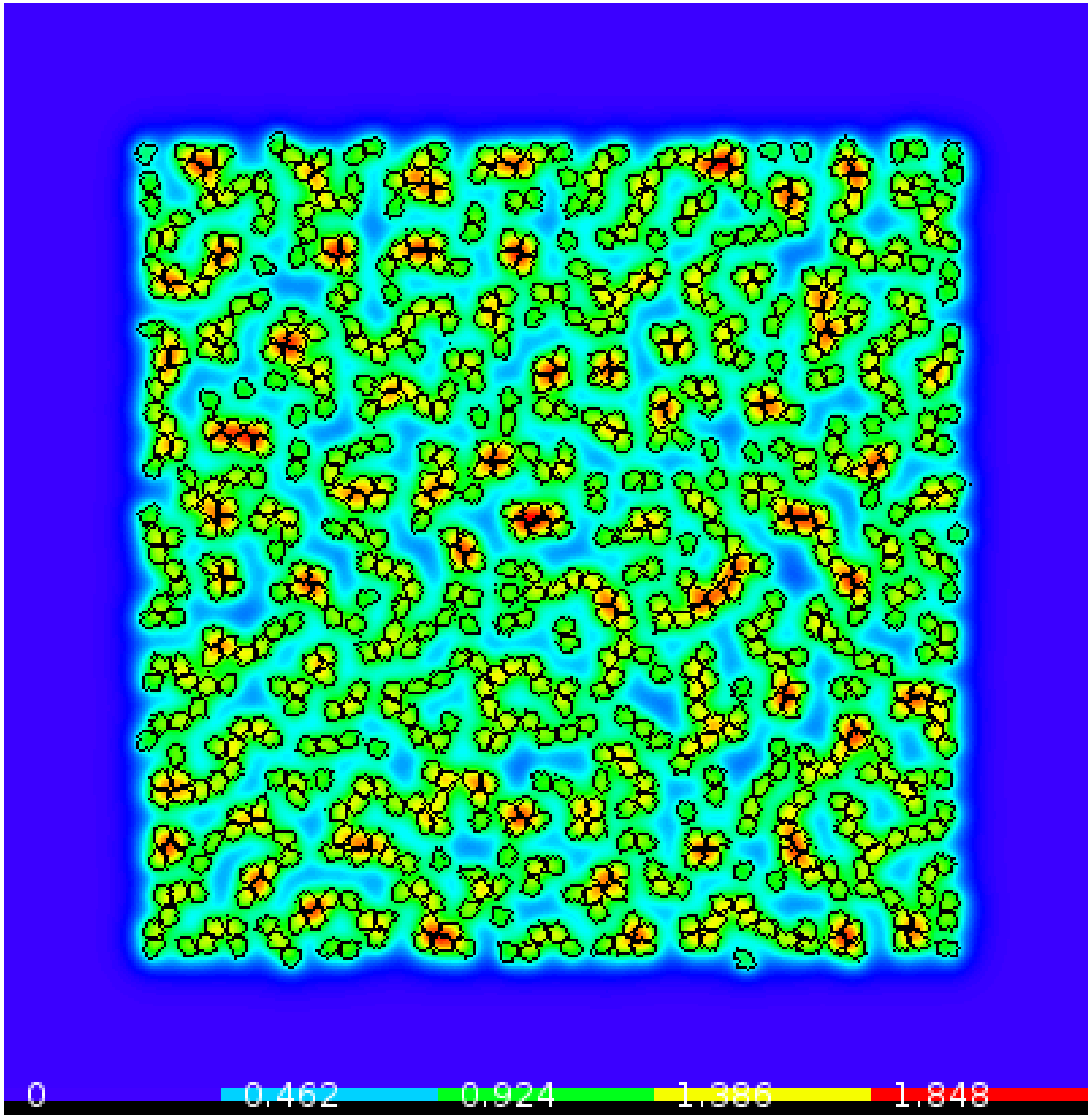
Contact Inhibition of Motility

"Context-dependent" effect of VEGF-A (Vascular-endothelial growth-factor A: stimulates vasculogenesis)

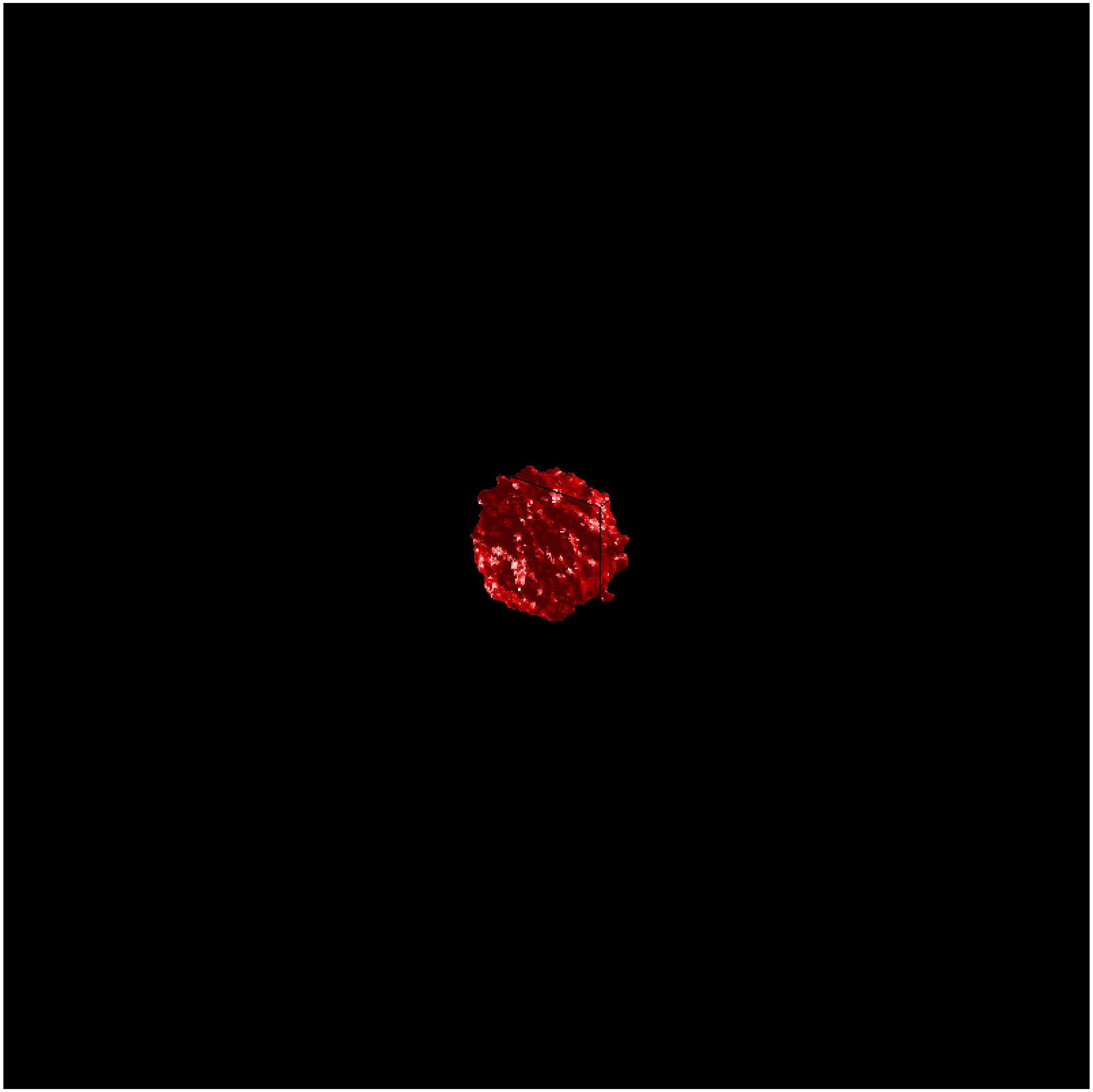
- VE-Cadherin clusters at adherens junctions between endothelial cells
- VE-Cadherin-binding → dephosporylation of VEGFR-2
- VEGF-A signaling:
  - in presence of VE-Cadherin: AKT/PKB ↑
    - cell survival
  - In absence of VE-Cadherin: ERK/MAPK ↑
    - Actin polymerization: cell motility / filopodia

In model: suppress chemotaxis at cell interfaces

Contact-Inhibited Chemotaxis Simulation



3D Vasculogenesis simulations



Simplified Vascular Tumor Growth

What is effect of Tumor-Blood Vessel adhesivity on tumor invasiveness?

More Realistic Model:

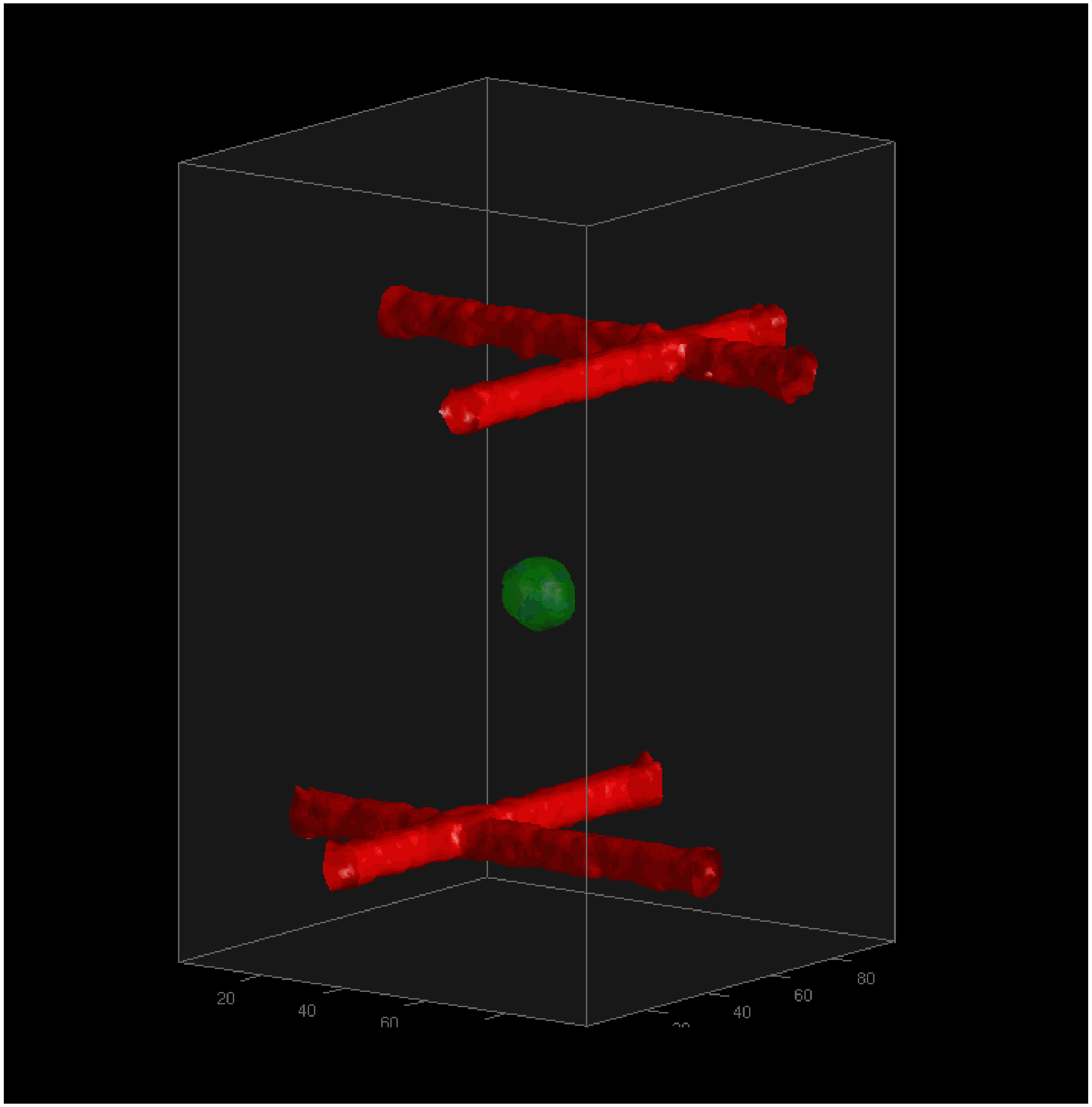
Anderson Tumor Model.
Three-dimensional.
Diffusive Nutrient Supplied by Vasculature.
Hypoxic Tumor Cells Produce Pro-Angiogenic Factor.
Vasculature Modeled as Capillary Plexus Following our Earlier Work but Divide ECs into two classes

- Tip Cells chemotax but do not divide.
- Other ECs divide but do not chemotax.

Neglects Transport Effects in Vasculature (*e.g.* Reduction in Nutrient Supply Downstream), Variations due to Vessel Diameter, Blood Vessel Collapse, *etc*…).

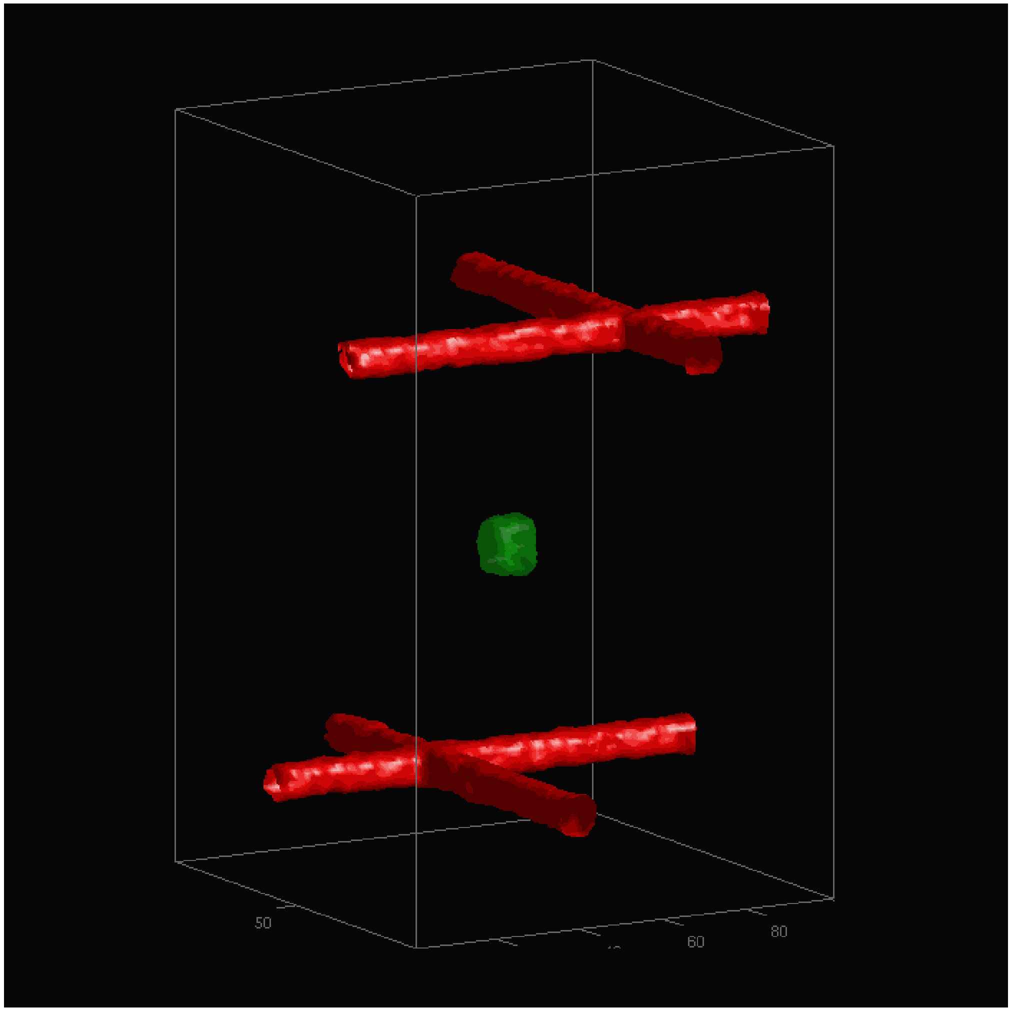
No Flow-Induced Remodeling (Easy to Add).

Tumor-Induced Vascularization (1)



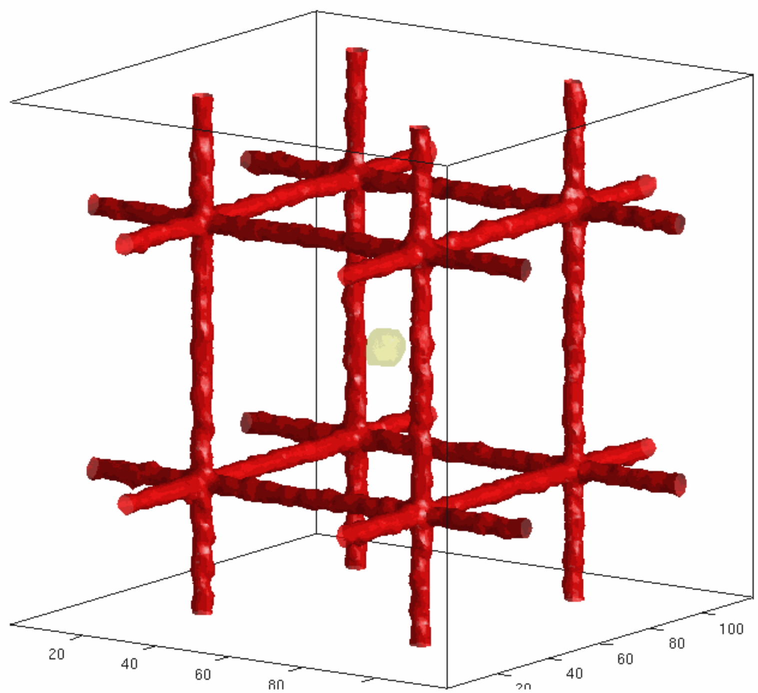
Vasculature Does Not Penetrate Tumor (*e.g.* Glioblastoma)

Tumor-Induced Vascularization (2)



Vasculature Does Penetrate Tumor

Tumor-Induced Vascularization (3)



Vasculature Does Not Penetrate Tumor

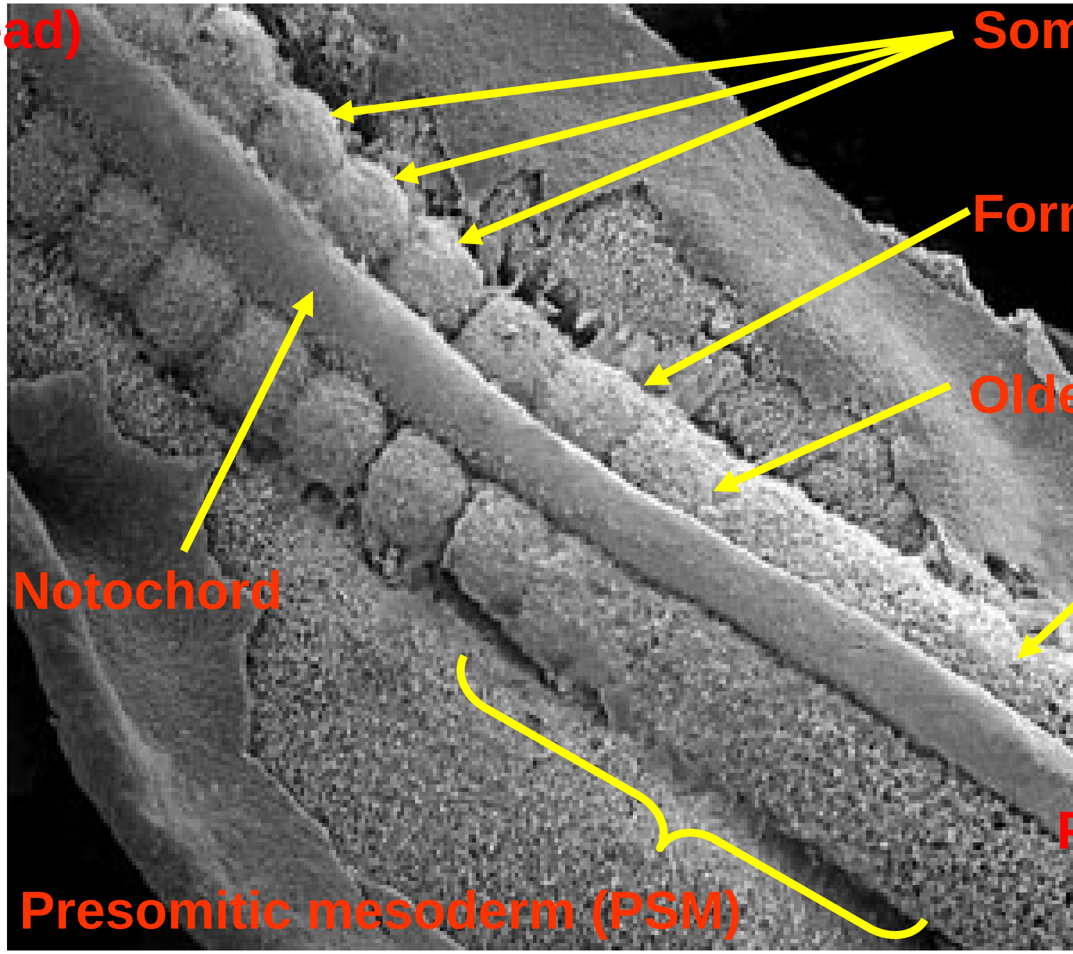
Comments and Next Steps

- Failure of Vasculature to Penetrate Growing Tumor can Actually Increase Tumor Invasiveness/Metastatic Potential.
- Paradox in Somatic Evolution (or Tumor as Ecosystem)—Metastatic Cells mostly Die, so Should be Selected Against.
- Implies Invasiveness Must be Selectively Advantageous but NOT because of Metastatic Potential.
- So Why?

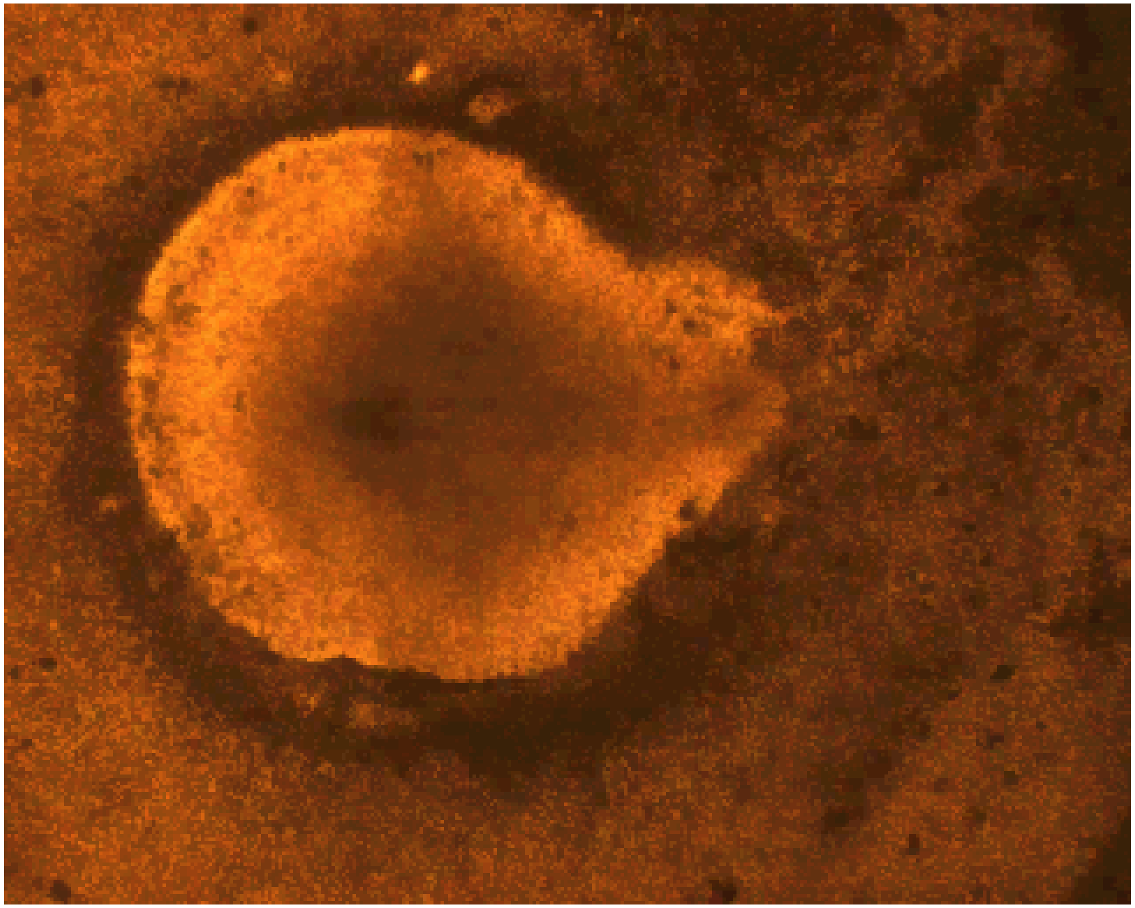
Somatic Evolution Theory

- Tumor Environment Changes in Time (in Particular Necrotic Regions Move Around because neovascular capillaries are easily crushed by pressure due to cell growth).
- Thus cells which can move to avoid necrotic regions selected for.
- These cells **accidentally** promote Metastasis.
- We will test by including heritability variability in invasiveness and vascular collapse.

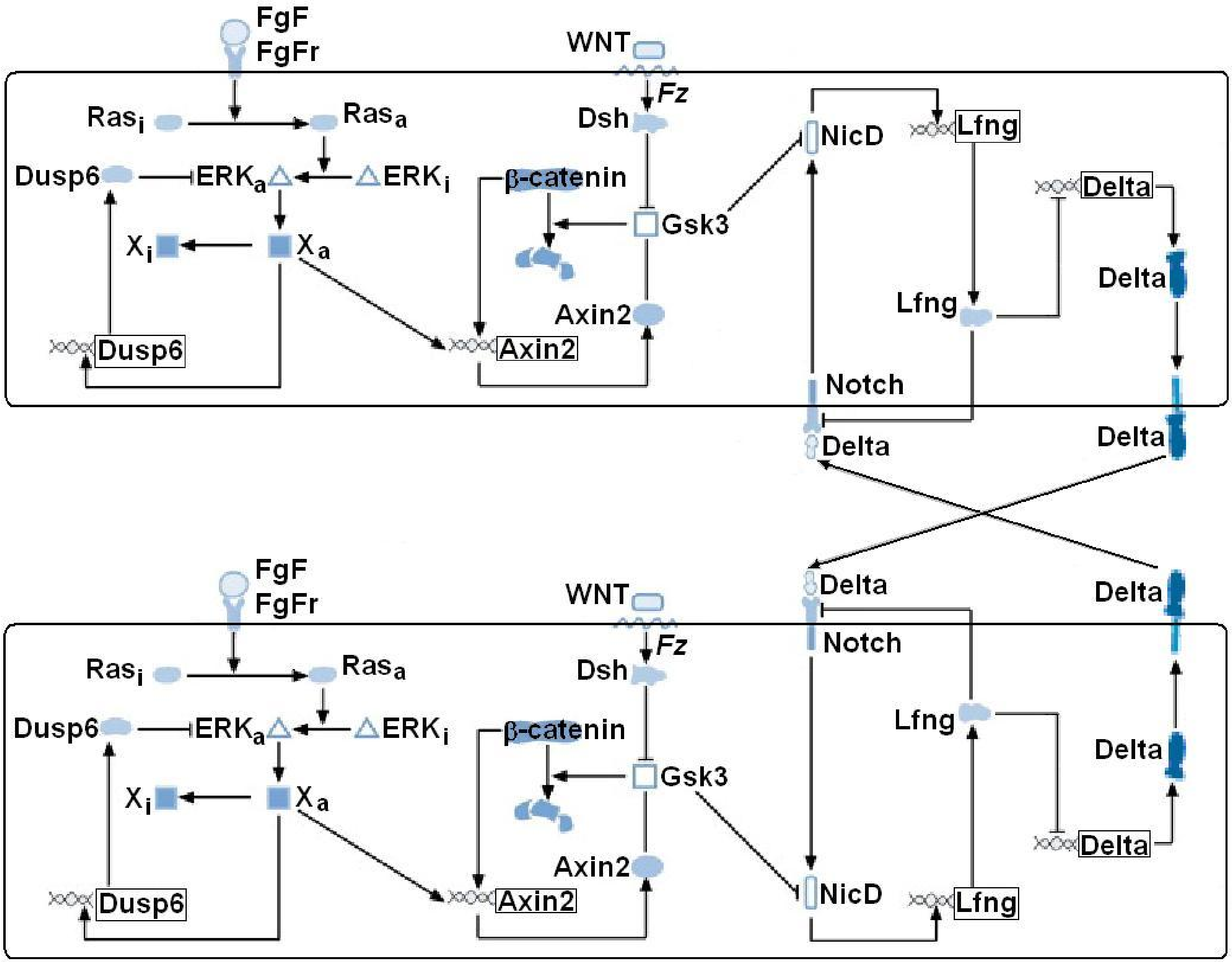
Somitogenesis



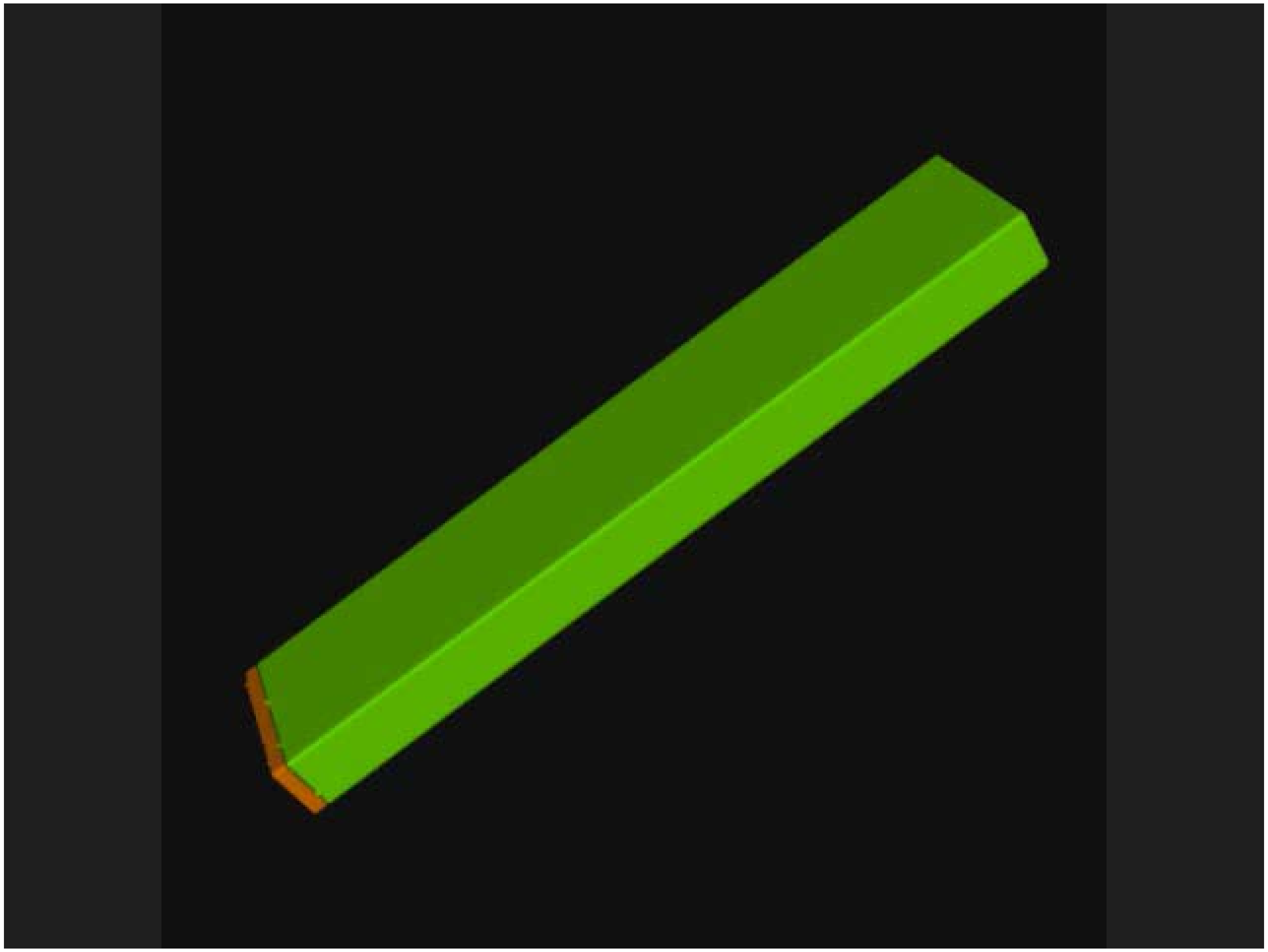
Somitogenesis



Pathways (Lewis *et al.* 2003)



3D Version

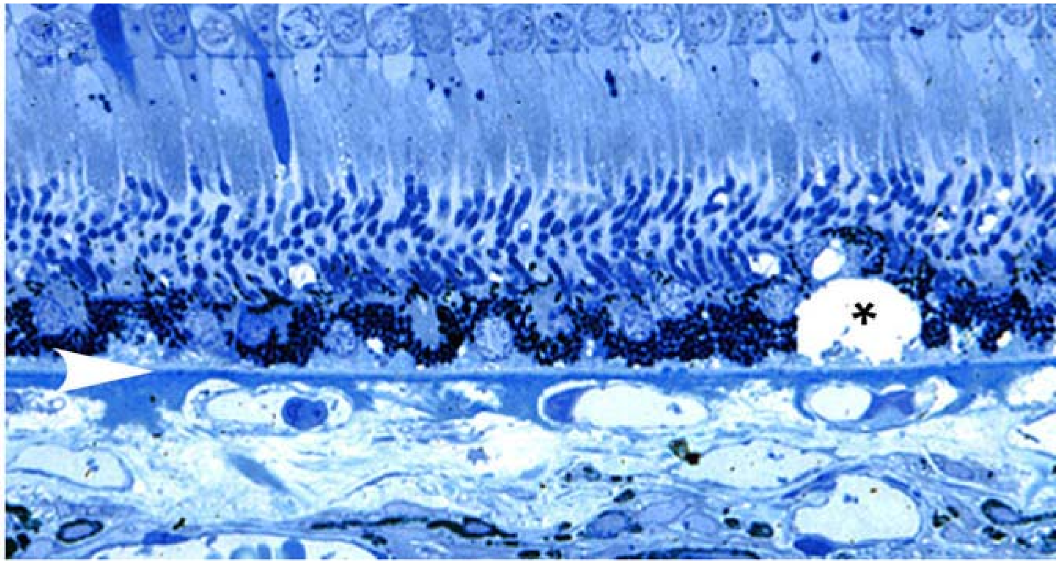


Conclusions

- Observed signaling, chemotaxis and adhesion can reproduce experimental dynamics.

Age-Related Macular Degeneration

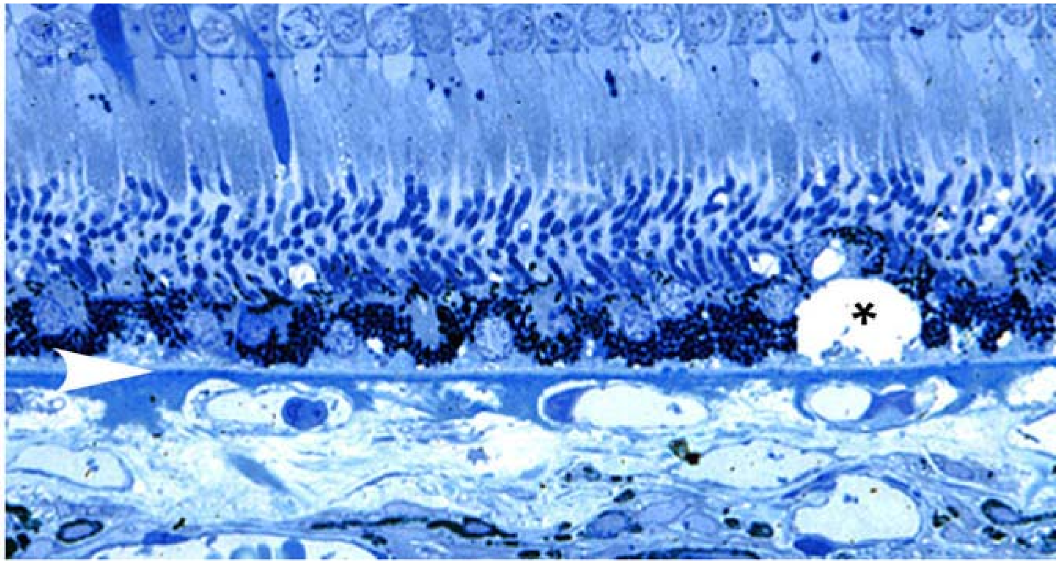
- The receptor cells in the retina have one of the highest metabolic rates in the body.
- Most nutrient and oxygen supplied from behind the retina by the choroid plexus.
- Plexus Separated from Retina by Bruch’s Membrane.



http://webvision.med.utah.edu/imageswv/Hagerman.Fig15.jpg

Age-Related Macular Degeneration

- Deposition of waste between retinal cells and Bruch's membrane can lead to hypertrophy of vasculature.
- Causes deterioration of vision.
- In extreme cases can cause blindness.
- Mechanism and treatment strategy poorly understood.

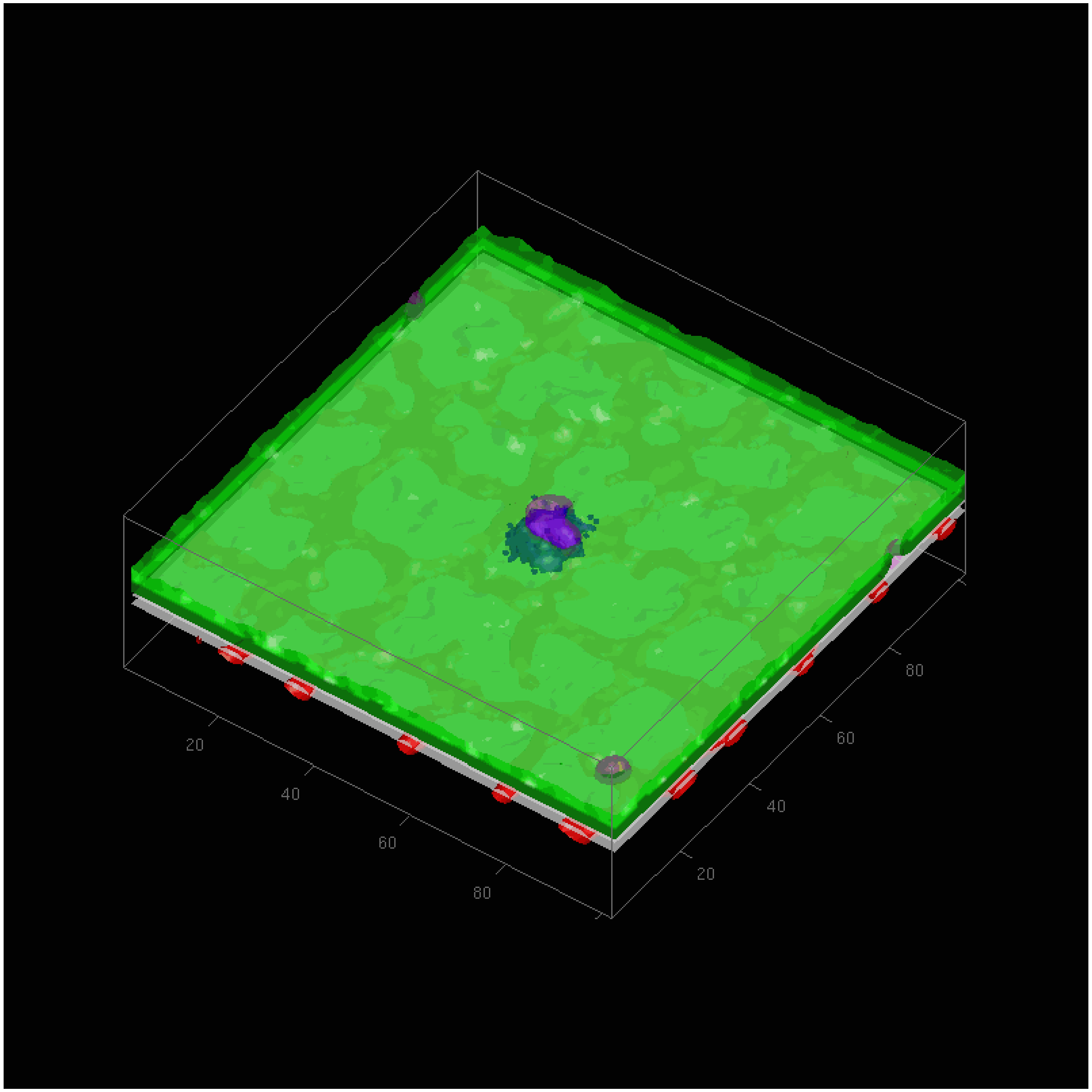


http://webvision.med.utah.edu/imageswv/Hagerman.Fig15.jpg

Age Related Macular Degeneration

- The receptor cells in the retina have one of the highest metabolic rates in the body.
- Most nutrient and oxygen supplied from behind the retina by the choroid plexus.
- Plexus Separated from Retina by Bruch's Membrane.
- Deposition of waste proteins between retinal cells and Bruch's membrane can lead to hypertrophy of vasculature.
- Causes deterioration of vision.
- In extreme cases can cause blindness.
- Mechanism and treatment strategy poorly understood.

Age Related Macular Degeneration



Comments (1)

- CompuCell3D is a General Modeling Framework. Can Combine with Other Simulation Methods.
- Easy to Add Detailed Subcell Models of Pathways, Metabolism…
- Easy to Add Cell Variability, Stem-like Cells…
- Run on Single Laptop.

- Happy to Help Integrate this Method with Your Own Continuum or Subcellular Methods.

Comments (2)

- Lack of Right Kind of Experimental Data:
  - Cell Tracking.
  - Adhesivity Measures.
  - Relationship between *e.g.* cell-surface cadherin densities and adhesion energies/unit area.
  - Tissue Mechanics.
  - Readout Mechanisms connecting Signals→Adhesion and Adhesion→Cell Cycle.

Needs

- Implementation-Independent Cell Behavior Phenomenology Ontology/ML (*e.g.* definitions of “mitosis,” “chemotaxis,”…).
- Standard Linkages to other Packages (*e.g.* Physiome).
- Improved Units Definition.
- Model Validation Tools.
- MPI Support?

CompuCell3D Allows You Easily to Reproduce the Models in this Talk, and Develop Your Own

- **CompuCell3D Training Workshop August 17-21, 2009, in Bloomington Indiana, USA (some funding available).**
- **Looking for new collaborations.**
- **Can support training of people interested in learning to use or enhance CompuCell3D to build specific models.**
- **Looking for collaborations on Ontology/ML development.**
- **Looking for collaborations on Package Interoperabilty.**
- **Hiring Computer Simulation-Oriented Postdoc to Help Develop CC3D.**

If You Want to Learn More

Please Visit Our Web Location

at http://www.compucell3d.org

and Try Downloading it

Yourself!

CompuCell3D Collaboration

University of Notre Dame, Indiana University, Kansas University Medical Center

People: Mark Alber, Ariel Balter, Julio Belmonte, Rajiv Chaturvedi, Nan Chen, Trevor Cickovski, Jeff Coffland, Michael Crocker, Rita deAlmeida, Gabor Forgacs, Tilmann Glimm, Francois Graner, Randy Heiland, George Hentschel, Susan Hester, Chengbang Huang, Jesus Izaguirre, Yi Jiang, Charles Little, Roeland Merks, Charles Moad, Chris Mueller, Stuart Newman, Nikodem Poplawski, Herbert Sauro, Abbas Shirinifard, Andy Somogyi, Maciej Swat, Gilberto Thomas, Benjamin Zaitlen

Funding Agencies and Institutions: NIH/NIGMS, NSF, ICSB Notre Dame, The Biocomplexity Institute Indiana University, Los Alamos National Laboratory, Keck Graduate Center, Washington University, Seattle, Technical University Dresden, Universidade Federal do Rio Grande do Sul, University of Grenoble.

Websites:

http://www.biocomplexity.indiana.edu

http://www.compucell3d.org

Google keyword: CompuCell3D

- **CompuCell3D Training Workshop August 17-21, 2009.**
- **Hiring Computer Simulation-Oriented Postdoc to Help Develop CC3D.**