A Briefer than Usual Introduction to Virtual Tissue Modeling with Compucell3D

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Cooperation and the Evolution of Multicellularity
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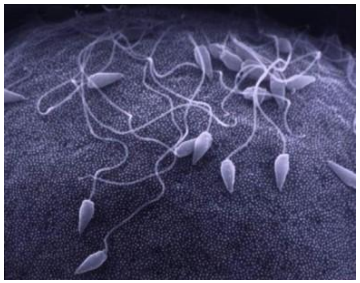
Support: EPA, NIH, NSF, Indiana University.

For papers on these projects, please visit http://www.biocomplexity.indiana.edu
To download software for model building, please visit http://www.compucell3d.org

Key Biological Questions

Development: How does Fertilized Egg Self-Organize into an Organism **without** a road map or plan?



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http://www.stanford.edu/group/Urchin/LP/
[Lauren Palumbi]

http://www.kvarkadabra.net/images/articles/Regeneracija-organov_1_original.jpg

Homeostasis: How does an Organism Maintain itself without an absolute standard of reference?

→

Key Biological Questions

Developmental Diseases: How does Failure of Homeostasis Lead to Redeployment of Developmental Mechanisms in Pathological Ways?

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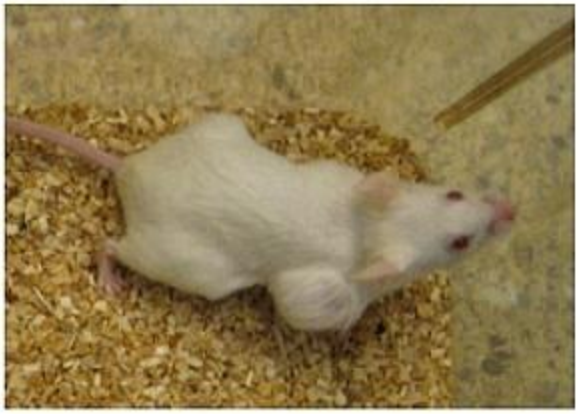


e.g., liver cirrhosis, cancer, diabetic retinopathy, polycystic kidney disease, osteoporosis,..

Promise of Mathematical/Mechanistic Understanding

- Fundamental understanding and control of developmental mechanisms, leading to:
  - Improved treatment regimes for cancer (ranging from more accurate tumor resection to more effective and less toxic therapies).
  - Control of stem and other human-derived cells for engineering of tissue replacements both *in vivo* and *in vitro.*
  - Induction of epimorphic regeneration *in situ*.
  - Treatments of degenerative diseases.
  - Prediction of chemical developmental toxicities.
  - …

CompuCell3D Platform for Virtual Tissue Construction

- Building Virtual Tissues from scratch is difficult, time consuming and error prone.
- CompuCell3D aims to:
  - make model coding so easy, that understanding the Biology becomes the **hard** part of building multiscale, multicell biological models.
  - support modeling at scales from subcellular reaction networks, through individual cell behaviors to continuum tissue mechanics and PDEs.
  - make model specifications compact, reusable, sharable and verifiable.

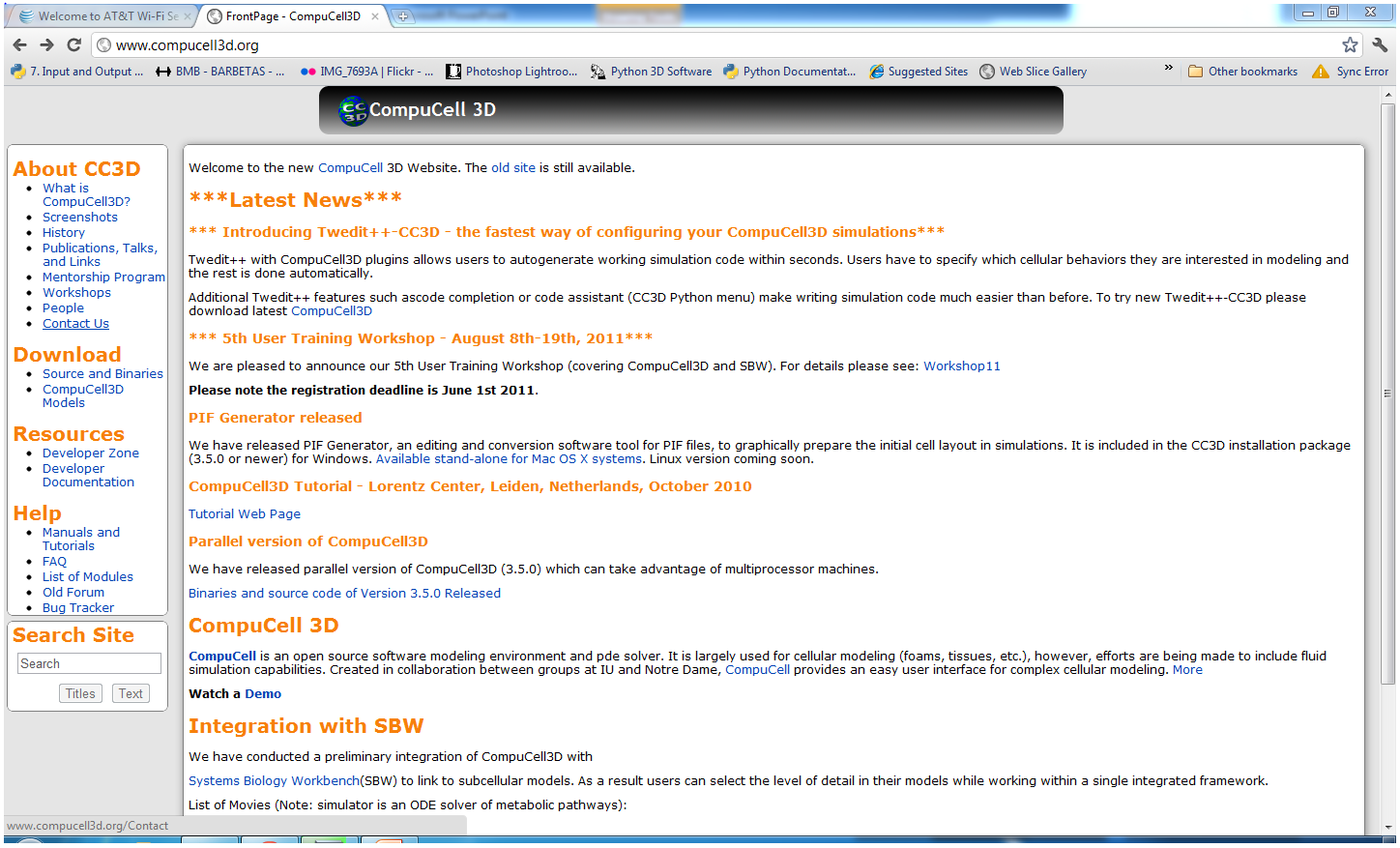
www.compucell3d.org

What is CompuCell3D (*CC3D*)?

- **Platform** for Multiscale, Multicell Model Definition and Execution.
- Open Source.
- Free.
- Sharable.
- Extensible (can add your own code).
- Runs on Macs, Linux, Windows.
- One-button installer for Windows and Macs.
- Automatically takes advantage of multi-core architectures
- Can interface with other code-bases.

Installing CC3D

- http://www.compucell3d.org/



Installing CC3D

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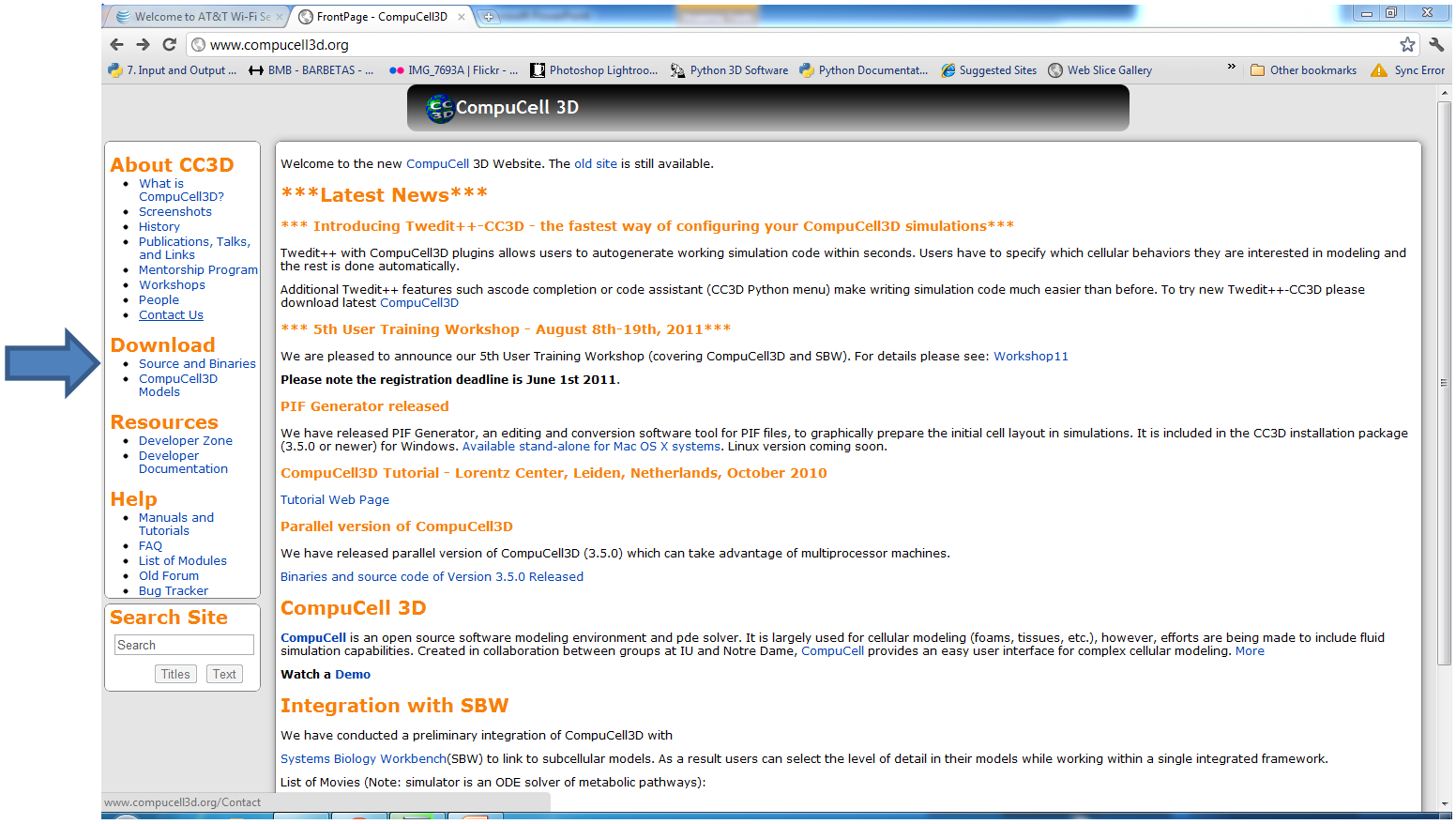
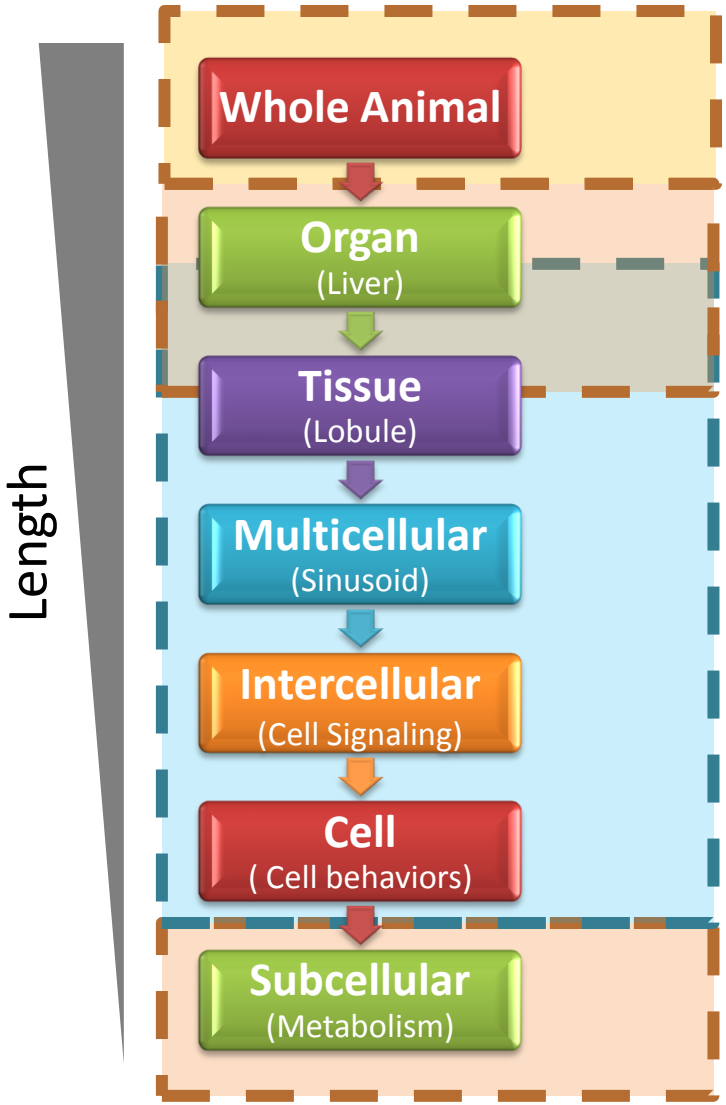


Bioinformatics Complements Mechanistic Virtual Tissue Modeling

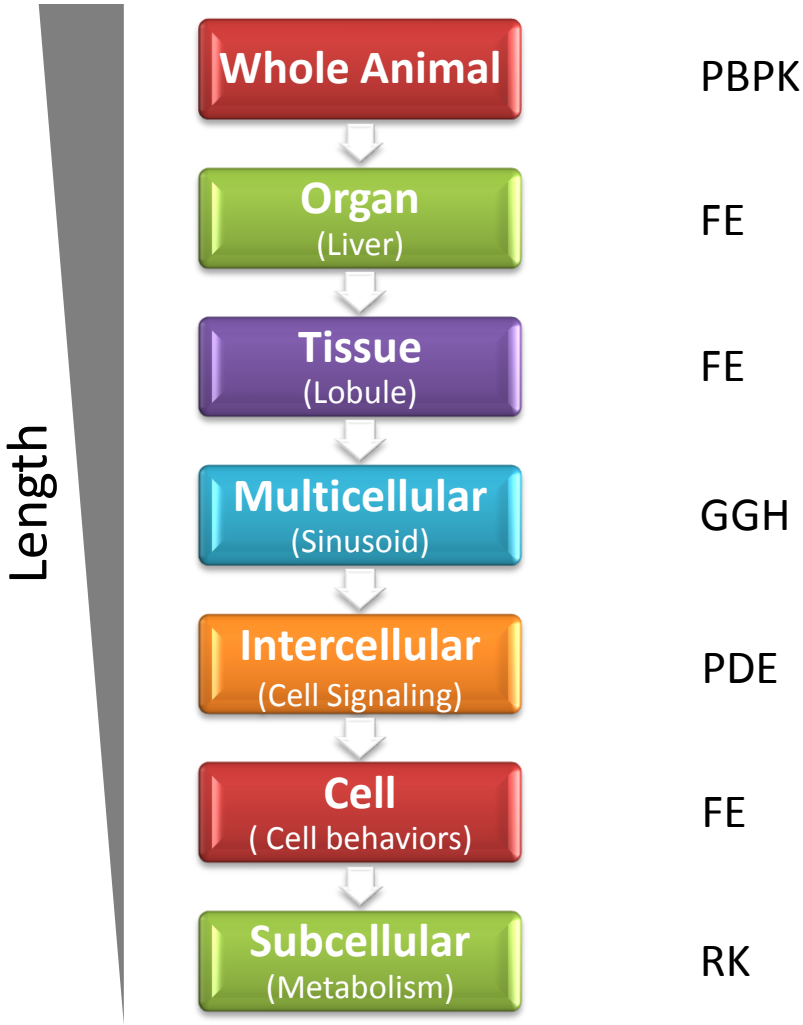
- Bioinformatics
  - Subtractive (start with everything and reduce)
  - Statistical Inference
  - Molecular Focus
  - Data Oriented
  - Output Primarily non-Spatial Correlations
- Mechanistic Modeling
  - Additive (start with nothing and add)
  - Based on Physical Behaviors
  - Cell and Tissue Focus
  - Process (Mechanism) Oriented
  - Output Primarily Spatial Time Series (Movies)

Biology occurs across multiple spatial and temporal scales

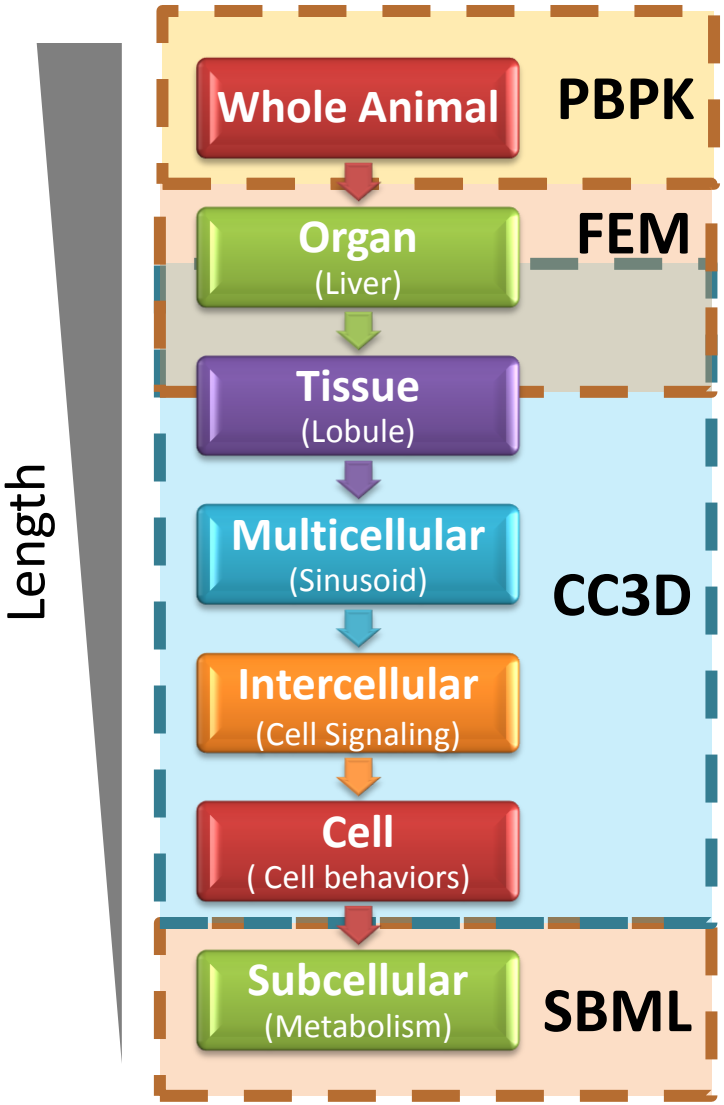
- Distance scales range from sub-nanometer to meters.
- Time scales range from seconds to decades.



Computational Biology models often target a single spatial and temporal scale



Virtual Tissues Integrate Across Scales

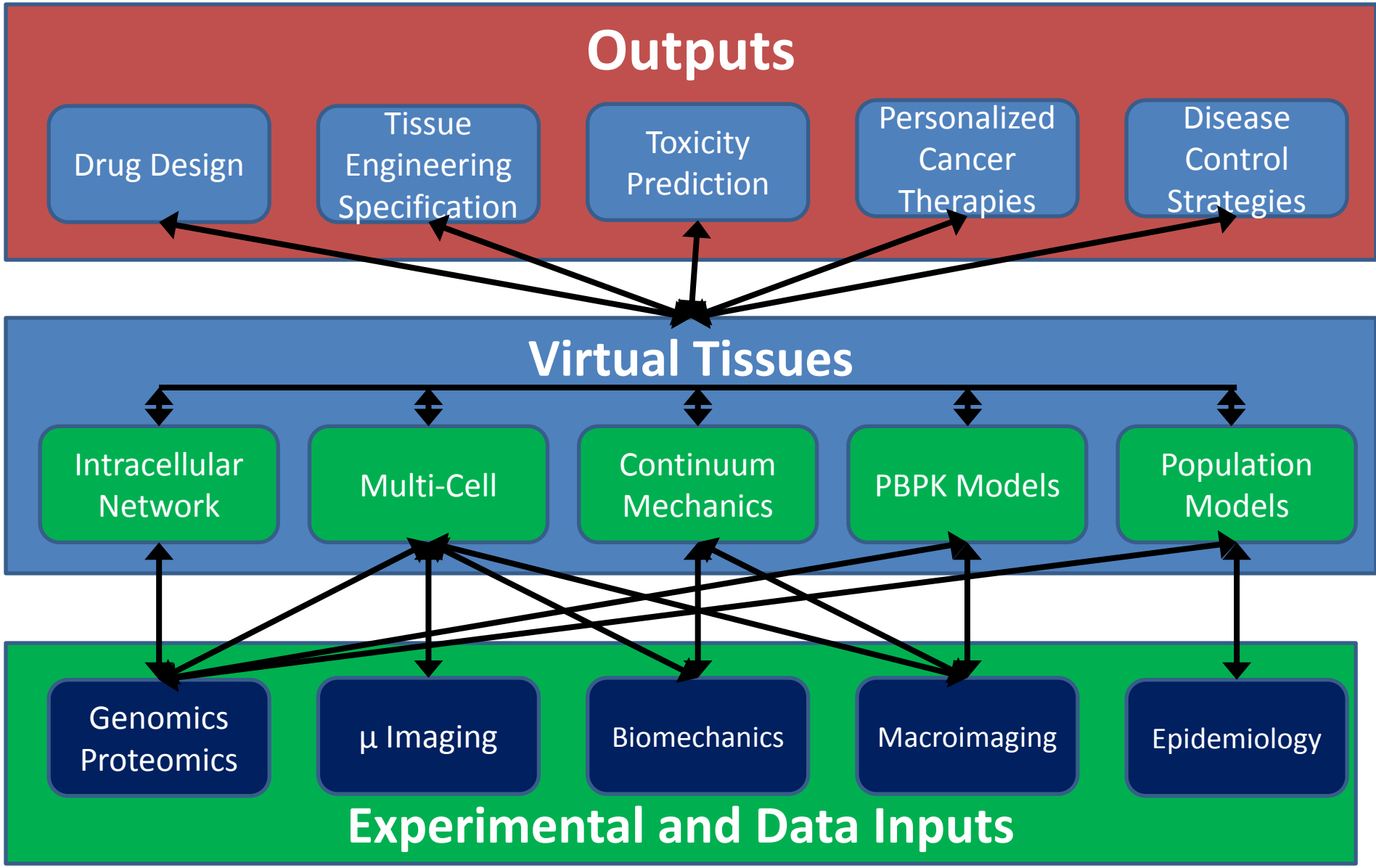


Why Bother?

- **Sometimes molecular or bioinformatics models are adequately predictive**
- **Often can't predict tissue/organ/organism-level effect from study of perturbations inside a single cell**
  - **Sub-detection molecular changes may have macroscopic phenotypic consequences because of amplification (*e.g.* arsenic in zebrafish Intersegmental blood vessel growth)**
  - **Significant molecular changes inside a cell may have negligible phenotypic consequences because of tissue-level compensation**
- **Multiscale models can explore these higher-level effects**

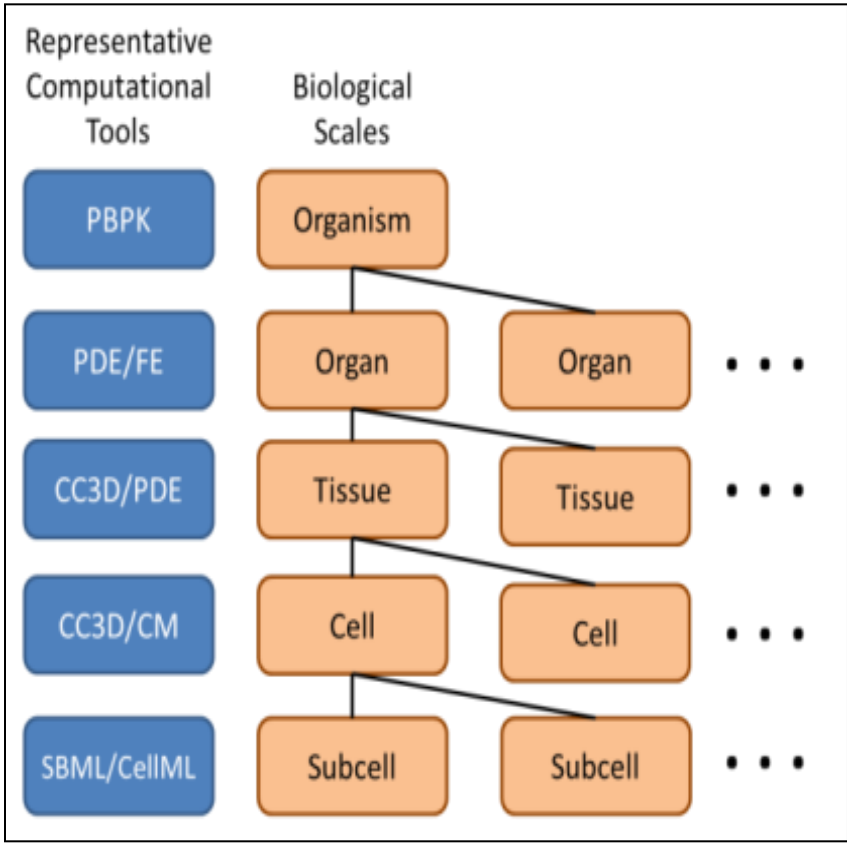
- **Often have adequate molecular detail, while equally crucial data of other types are unavailable**
- **Building multiscale Virtual Tissue models may help identify this missing information**

Virtual Tissues as Platforms for Information Integration



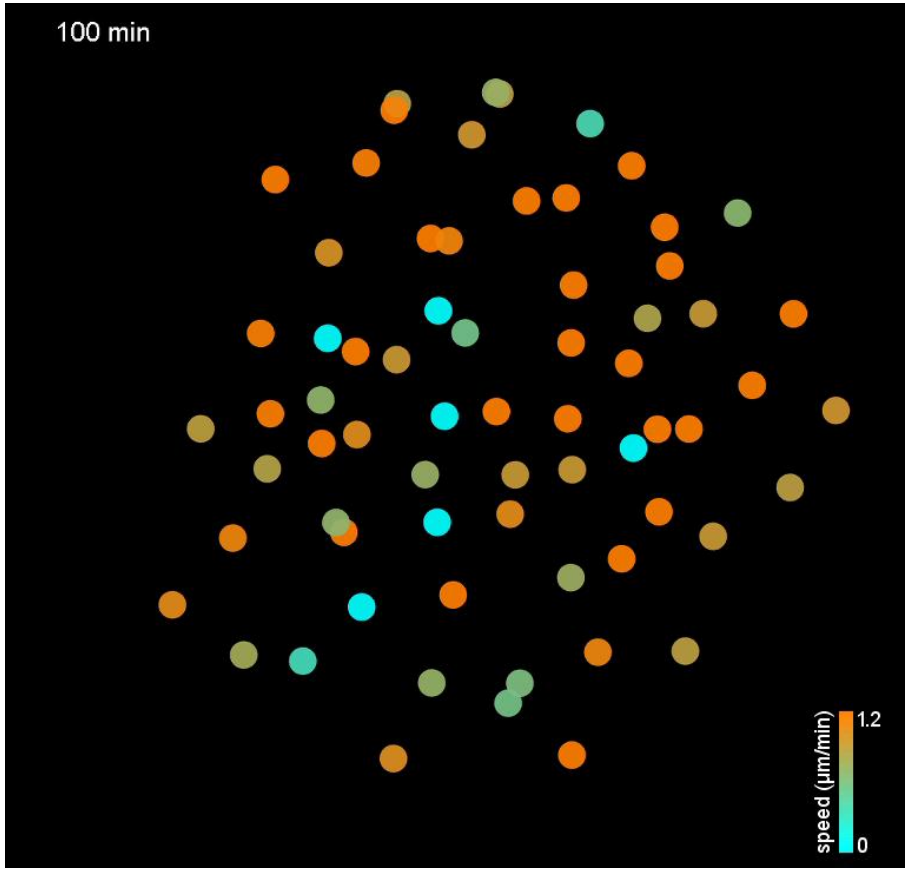
Virtual Tissues

- **Multiscale simulations of tissue function, development, disease and homeostasis integrating, subcellular, cellular, multicellular and tissue-level submodels.**
- **Integrated frameworks for organizing experiment, simulation and clinical development.**
- **Models capture the flow of molecular information across biological networks and process this information into higher-order responses.**
- **Responses depend on network topology, system state dynamics, and collective cellular behavior.**
- **Include multi-cellular behaviors that can result in emergent properties (*e.g.*, functions, phenotypes) not specified *a priori.***



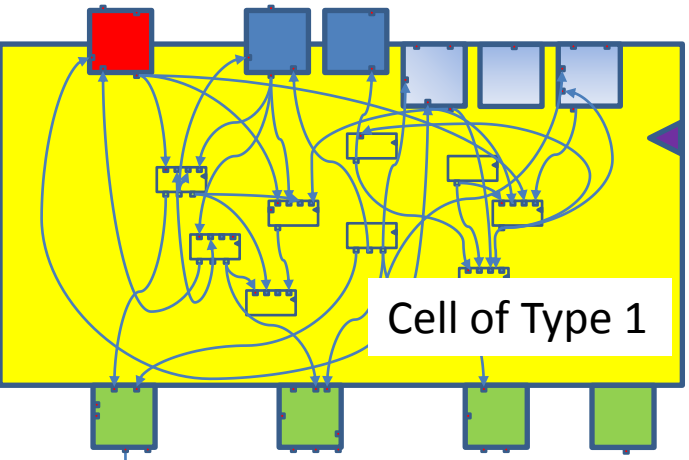
Virtual Tissues Dream

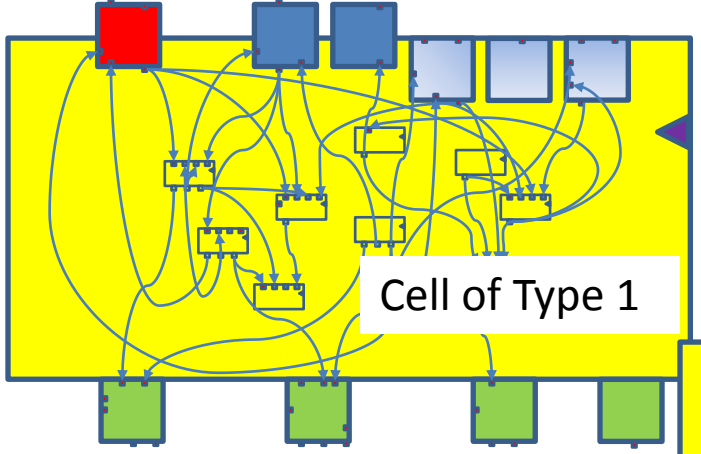
- Annotated Experimental Images ARE the Simulation.
- A Virtual Tissue Environment:
  - Reads an Annotated Image to Identify the Locations and Identity of Components.
  - Builds the Simulation by Populating the Simulation Representation of the Image with Components from the Cell Type Repository and Other Repositories.
  - Executes the Simulation using Standardized Specifications of Organ, Multi-cell, Subcell Behaviors of the Components.
  - Outputs the Simulation Results as Annotated Simulation Images for Analysis and Comparison with Experiment.
  - Functions as a Variable Power Microscope, Handling Refinement/Coarse Graining Automatically.
  - Simulates all Cells in Embryo, Tissue,…
- Ironically harder to track cells in an embryo than to position atoms in a virus!

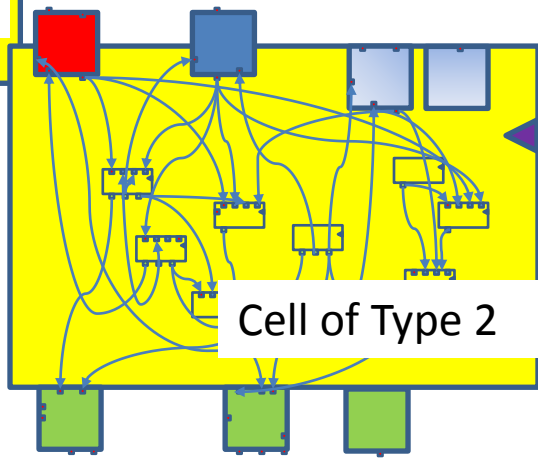


Reconstructed zebrafish embryonic development from P. J. Keller, *et al.,* "Reconstruction of zebrafish early embryonic development by scanned light sheet microscopy," *Science* **322**, 1065 (2008).

Mockup of Virtual Tissue Framework



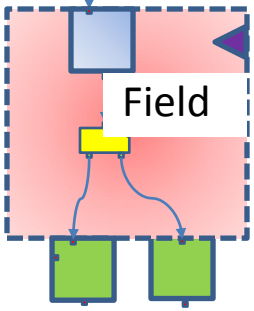


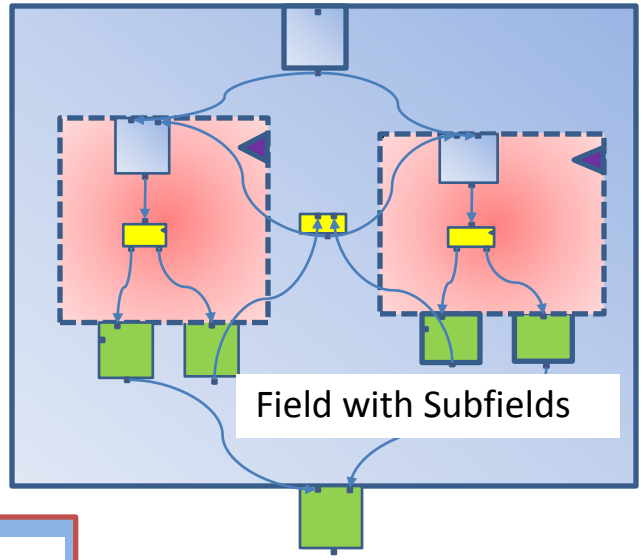


Metadata

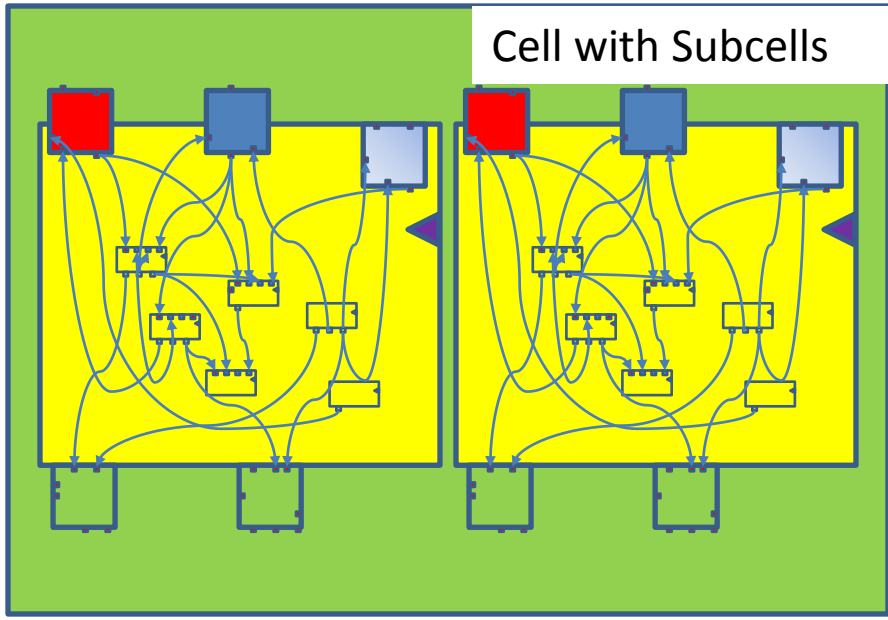
Generic Python Box

Generic Math Box



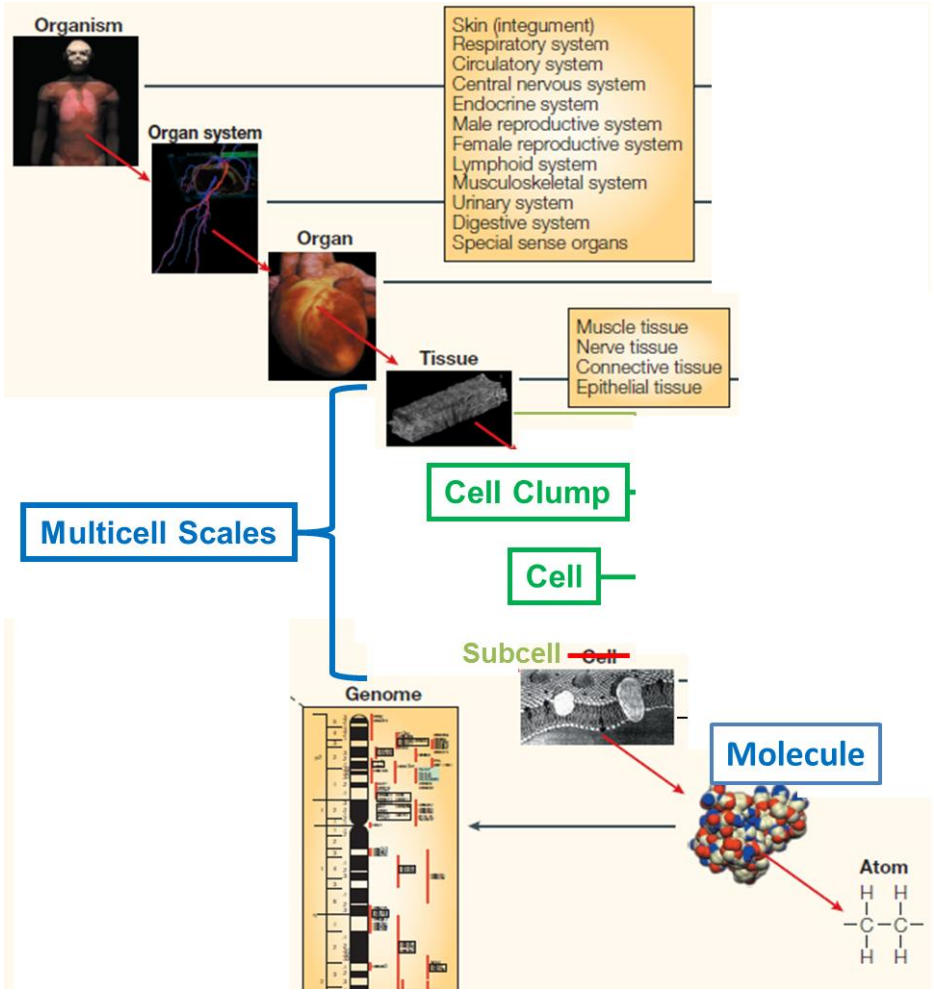


Scalar



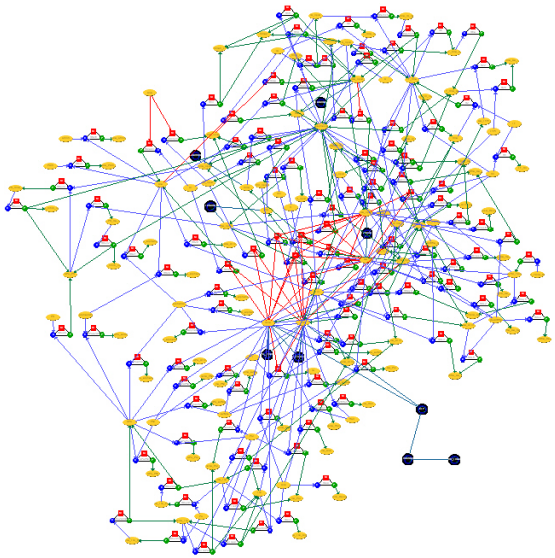
Scales Considered Determine Methodologies

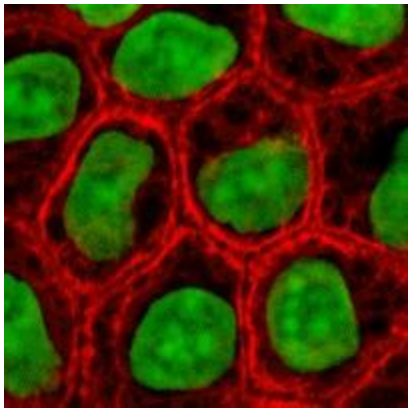
- Human Brain—Many cm^3—Continuum Mechanics and PDE Methods
- Small Embryos, Adult Tissue Samples, Embryonic Organs—Several mm^3—MultiCell Methods
- One or a Few Cells—a few thousand μm^3—Macromolecular Methods
- Macromolecular Assemblies—a few thousand nm^3—Molecular Dynamics Methods
- Subcellular (Non-spatial)—Reaction Kinetics and Stochastic Methods

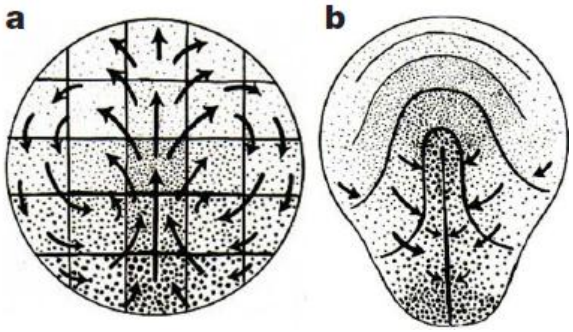


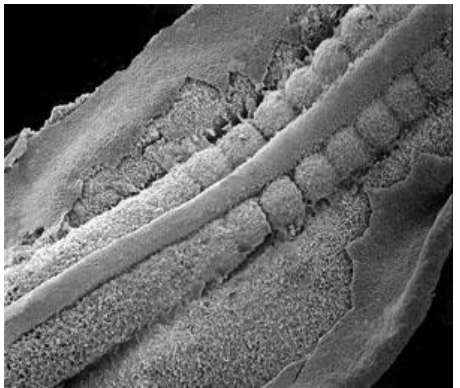
Multicell Modeling

- Separate Analysis into Three Components
  - From molecular event to molecular network behavior
  - From network behavior to cell behaviors
  - From cell behavior to tissue behaviors









Multicell Methodologies

- Many Approaches—Different Advantages and Disadvantages
- In Rough Order of Degree of Spatial Detail
  - *Cellular Automata*
  - *Flock Models* (*SWARM*)
  - *Center Models* (Molecular Dynamics, one atom per cell)
  - ***GGH (CPM) Lattice Models*** (***CompuCell3D***, Glazier; Paulien Hogeweg, Utrecht U.; ***Tissue Simulation Toolkit,*** Roeland Merks, Amsterdam; Yi Jiang, LANL)
  - **Vertex Models**
  - **Multielement Models** (Molecular Dynamics + Finite Element, many atoms per cell; Tim Newman, Arizona State U)
  - **Immersed Boundary Models** (Kasia Resniak, Moffit Cancer Center)
  - **Finite Element Models** (Drasdo, Paris)
  - …

Key:

BOLD=Cells have explicit shapes

Red—Lattice Techniques

Green—Off Lattice

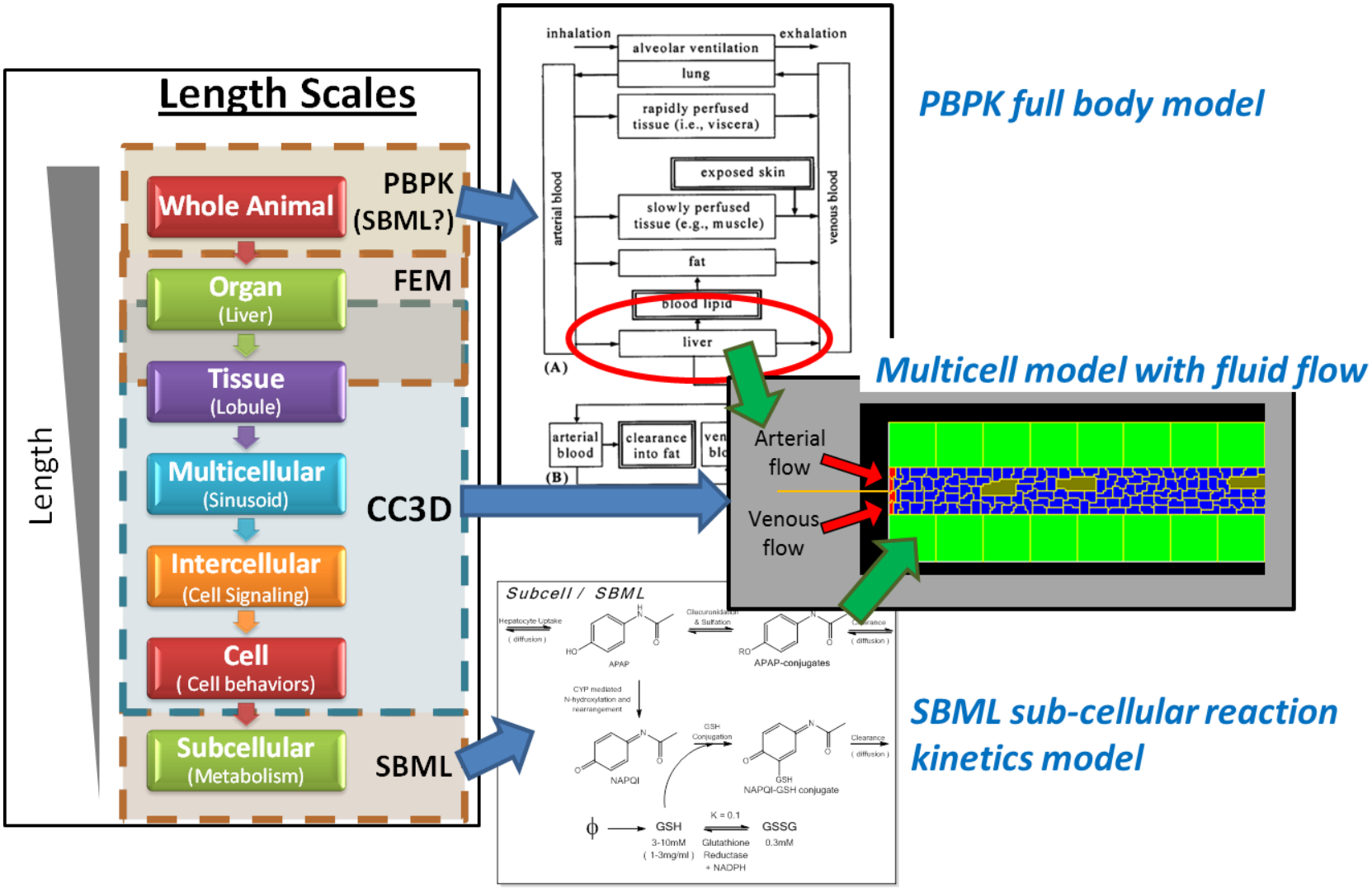
Shadow—Slow

Italics—Fast

Dashed Underline—Generic Modeling Environments Available

Underline—Specialized Open Source Modeling Environment Available

Multiscale, Multicell Virtual Tissue

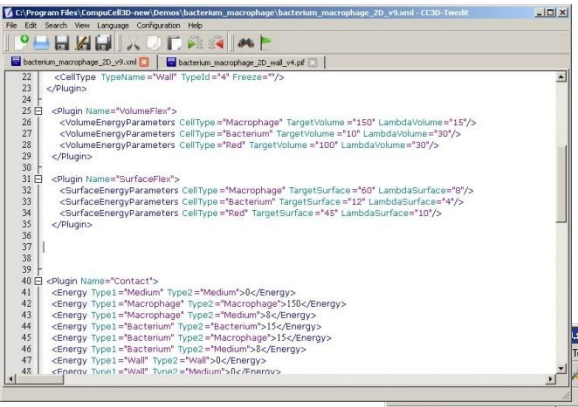


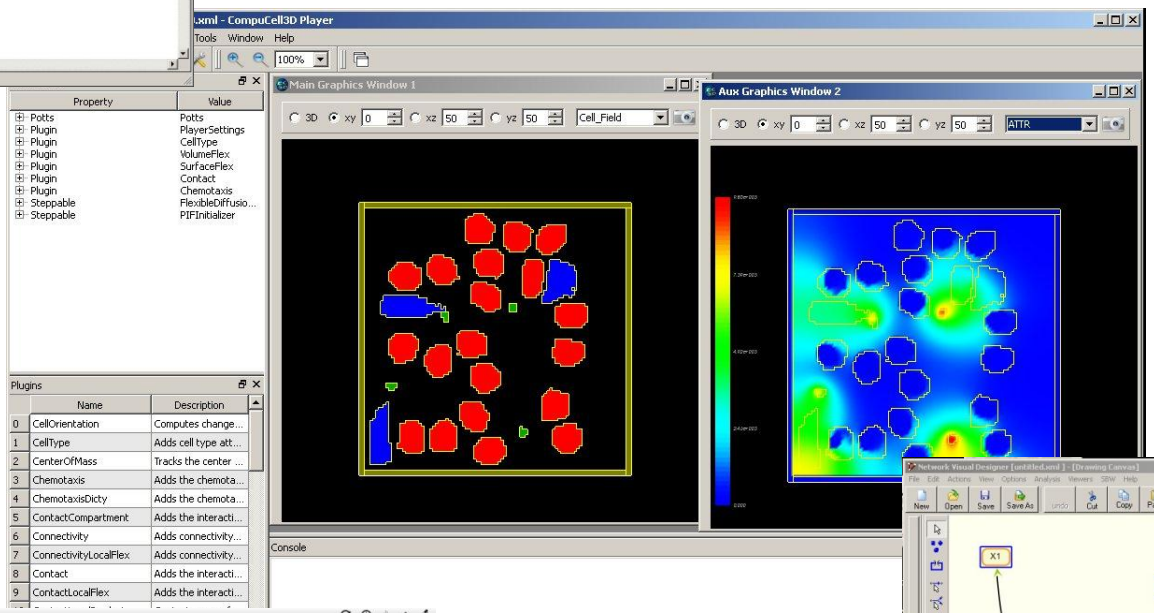
CompuCell3D - Simulation Environment for Multi-Cell, Multi-Scale Models

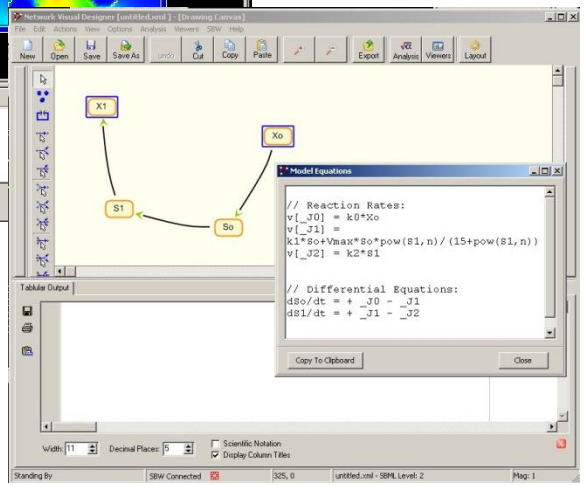
Python and XML model scripting

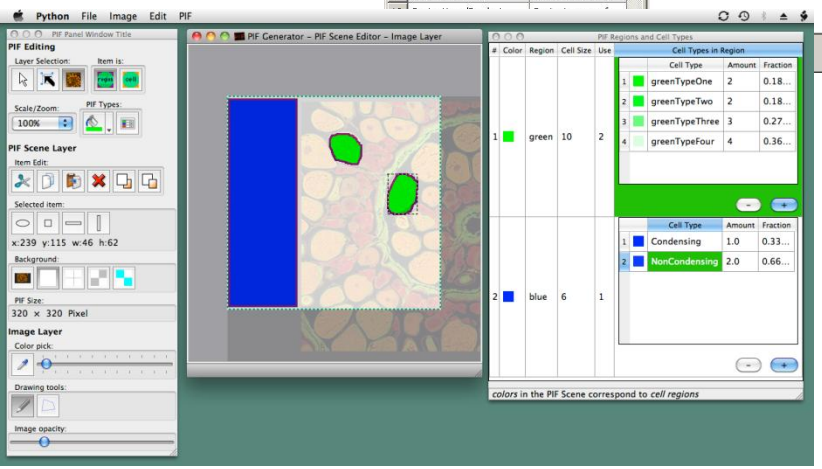
Graphical specification of initial conditions

SBML models (e.g. defined using SBW)









www.compucell3d.org

Available Mechanisms in CompuCell3D

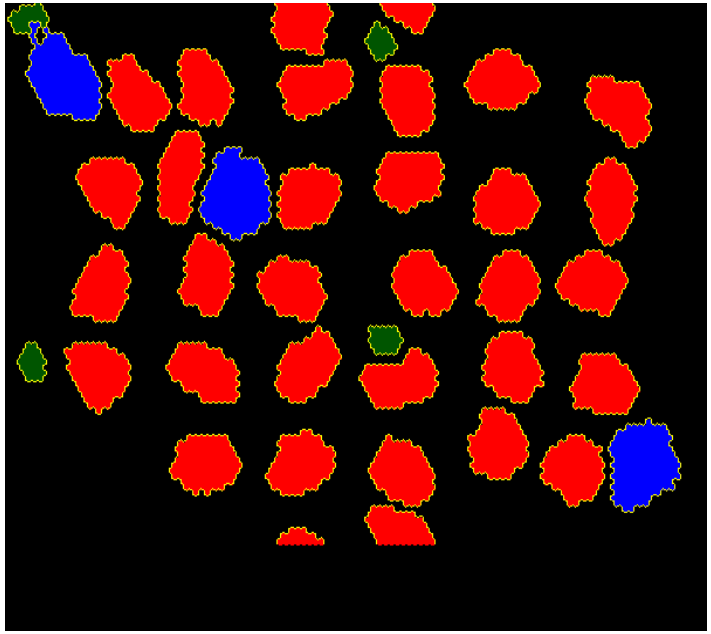
- Control of Cell Differentiation, Signaling, Growth, … via Coupled ODEs (RK)
- Reaction-Diffusion Equations (PDEs)
- Cell Adhesion
- Membrane Areas
- Mitosis
- Apoptosis
- Secretion and Absorption of Materials
- Viscosity
- Chemotaxis
- Haptotaxis
- Rigid-Body Motion (FE)
- Links (FE)
- Inertial/Persistent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

Sample Models Written in CC3D

- Gastrulation (Octavian Voicelescu—Cambridge, Kees Wejier—Dundee)
- Somitogenesis (Claudio Stern—UCL, James Sharpe—Barcelona)
- Early Limb Development (Tom Knudsen—EPA)
- Angiogenesis (Tom Knudsen and Nicole Kleinstreur—EPA)
- Liver Lobule (Imran Shah—EPA, Sudin Bhattacharya—Hamner Institute)
- *Drosophila* Eye Development
- Colonic Crypt Stem Cell Maintenance
- Tumor Vascularization (Mark Chaplain—Dundee)
- Optimizing Radiation Therapy for Solid Tumors (Dan Lea—London)
- Somatic Evolution in Tumors
- MDCK Cell Dynamics
- Modeling Engineered Tissues
- Biofilm Growth
- *Myxobacteria* Dynamics
- *Dictyostelium* Development

Simple cell-agent based model

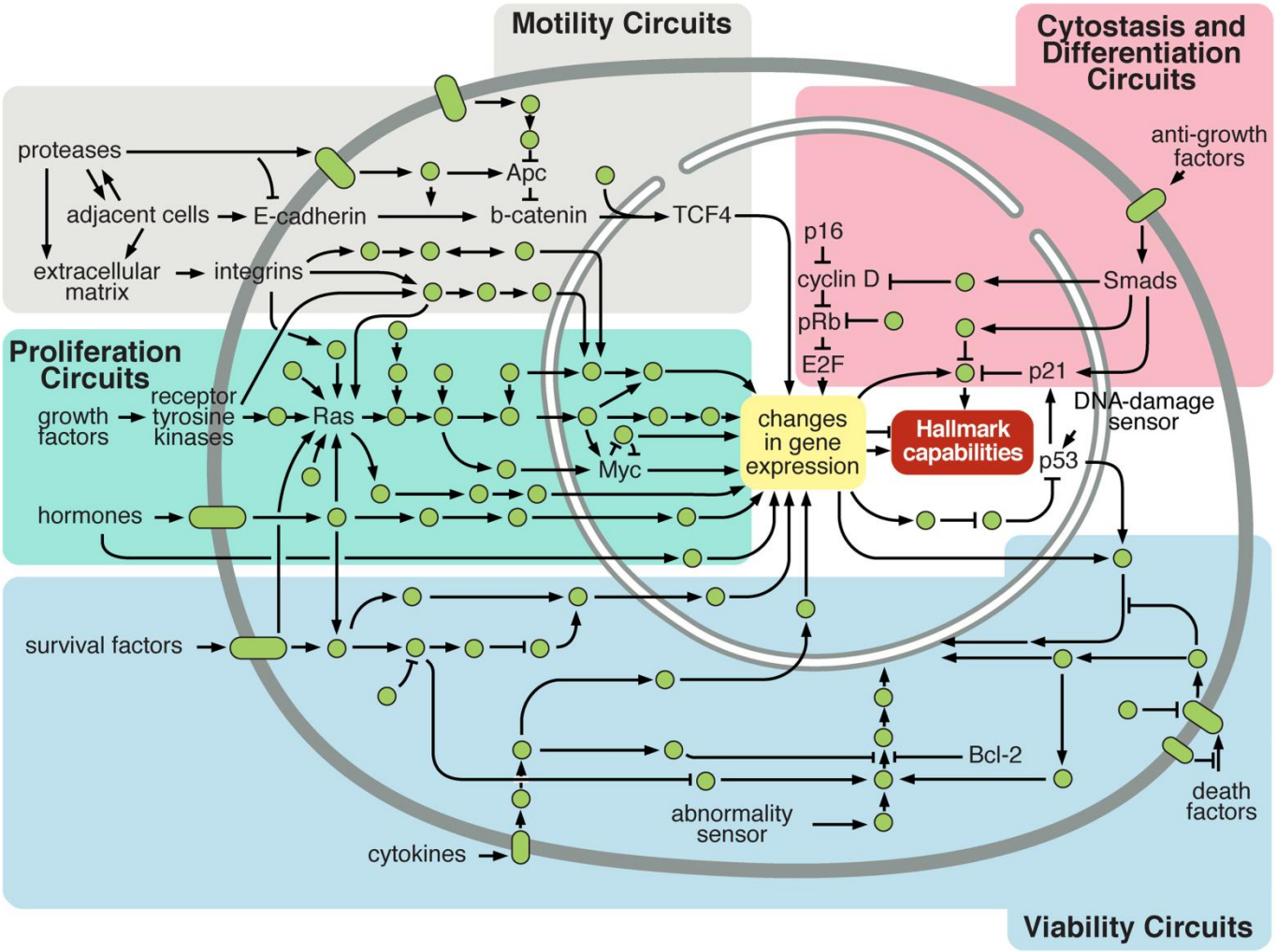
macrophage navigating RBCs toward a microbial pathogen



simple CompuCell3D model

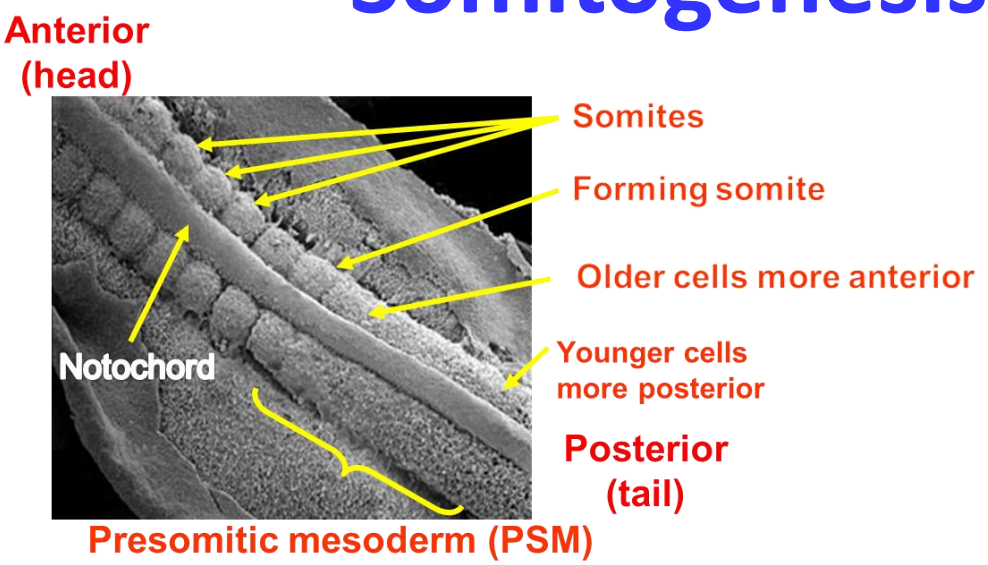
Slide from Dr. Thomas Knudsen (EPA)

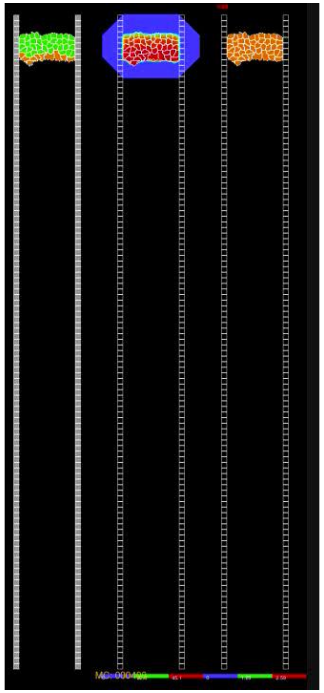
Key Intracellular Regulatory Circuits and Intercellular Signaling Pathways

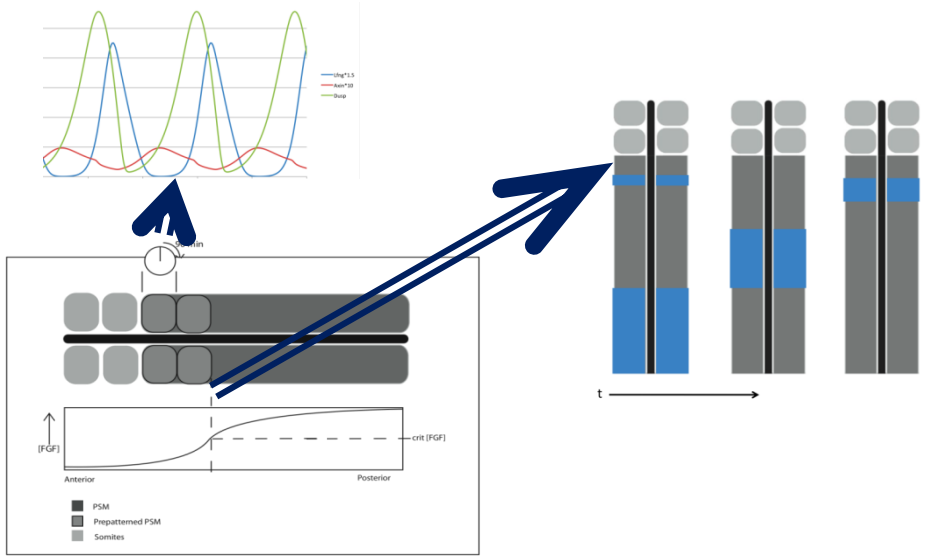


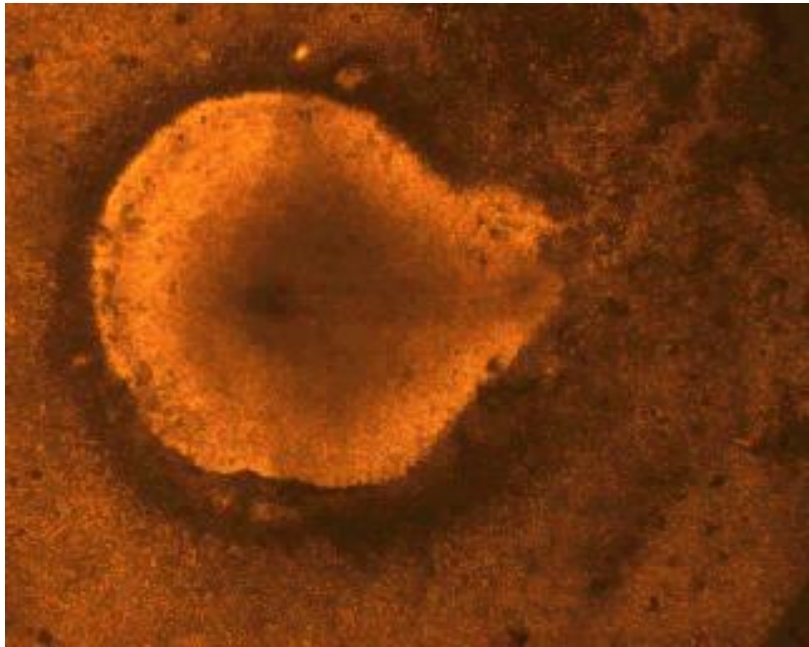
Slide from Dr. Thomas Knudsen (EPA)

Complex cell-agent based model: Somitogenesis

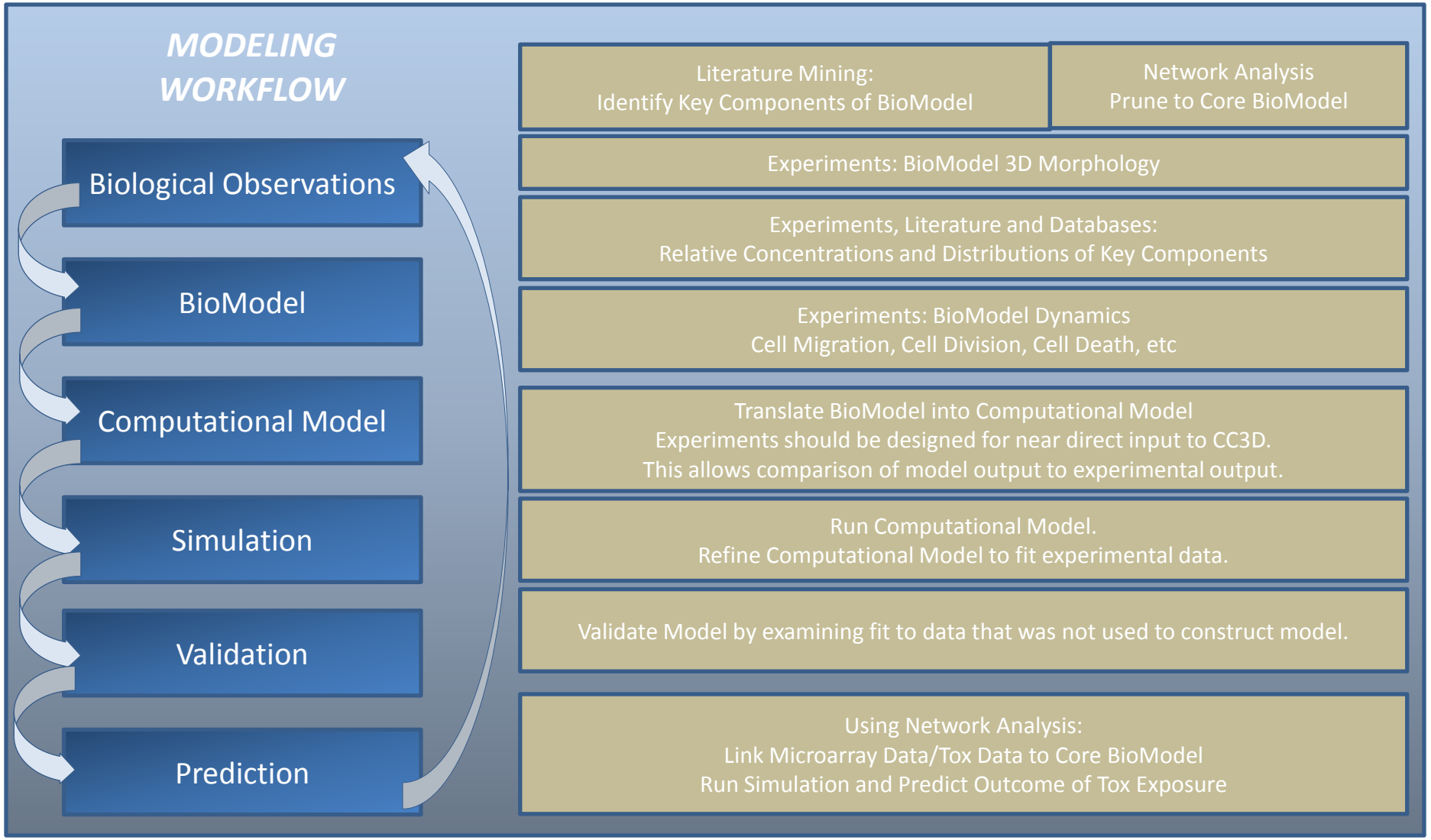








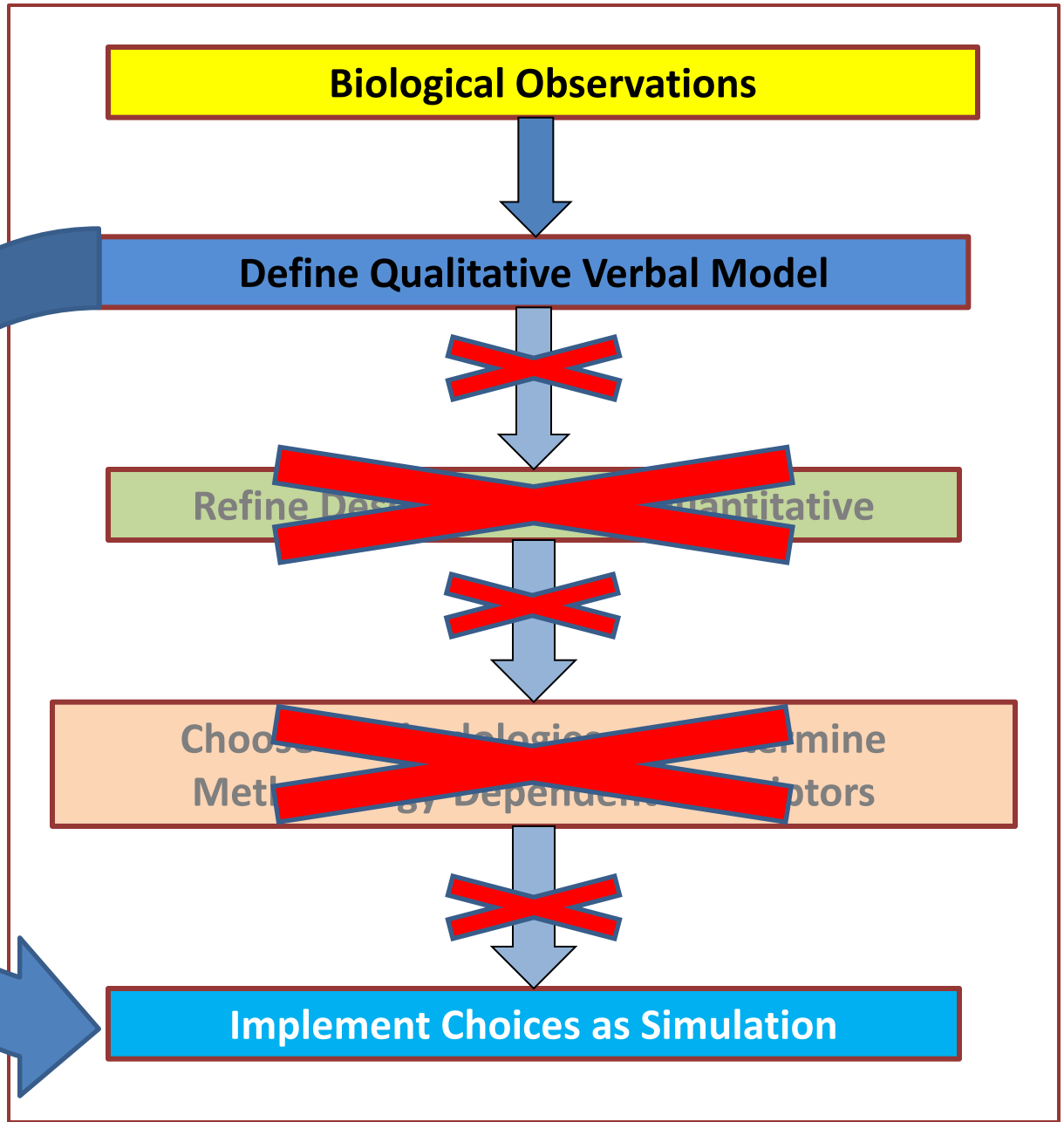
Building a Model


MODELING WORKFLOW
Biological Observations
BioModel
Computational Model
Simulation
Validation
Prediction
Literature Mining:
Identify Key Components of BioModel
Network Analysis
Prune to Core BioModel
Experiments: BioModel 3D Morphology
Experiments, Literature and Databases:
Relative Concentrations and Distributions of Key Components
Experiments: BioModel Dynamics
Cell Migration, Cell Division, Cell Death, etc
Translate BioModel into Computational Model
Experiments should be designed for near direct input to CC3D.
This allows comparison of model output to experimental output.
Run Computational Model.
Refine Computational Model to fit experimental data.
Validate Model by examining fit to data that was not used to construct model.
Using Network Analysis:
Link Microarray Data/Tox Data to Core BioModel
Run Simulation and Predict Outcome of Tox Exposure

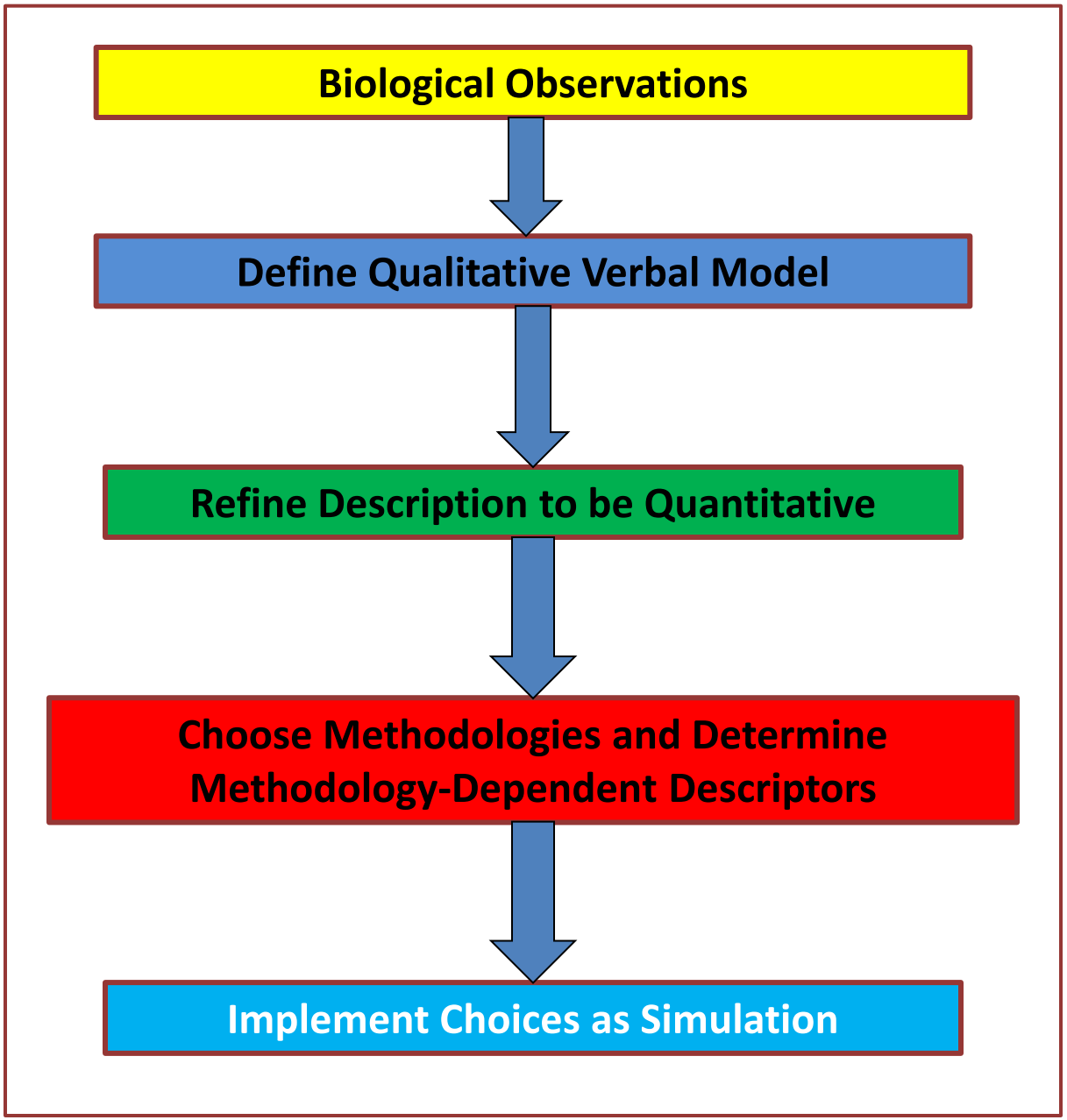
How to Start Building a Model?

- Experimentalists—Think at 20x Objective Scale.
  - How would you Describe the Key Components of Your Problem to:
  - Someone Who Doesn't Know about It?
  - Someone Who Wants to Develop a Biological Model of It?
  - Someone Wanting to Build a Simulation of It?
- Simulators—What Questions Do you Need to Answer about a Biological Problem to Build a Simulation?

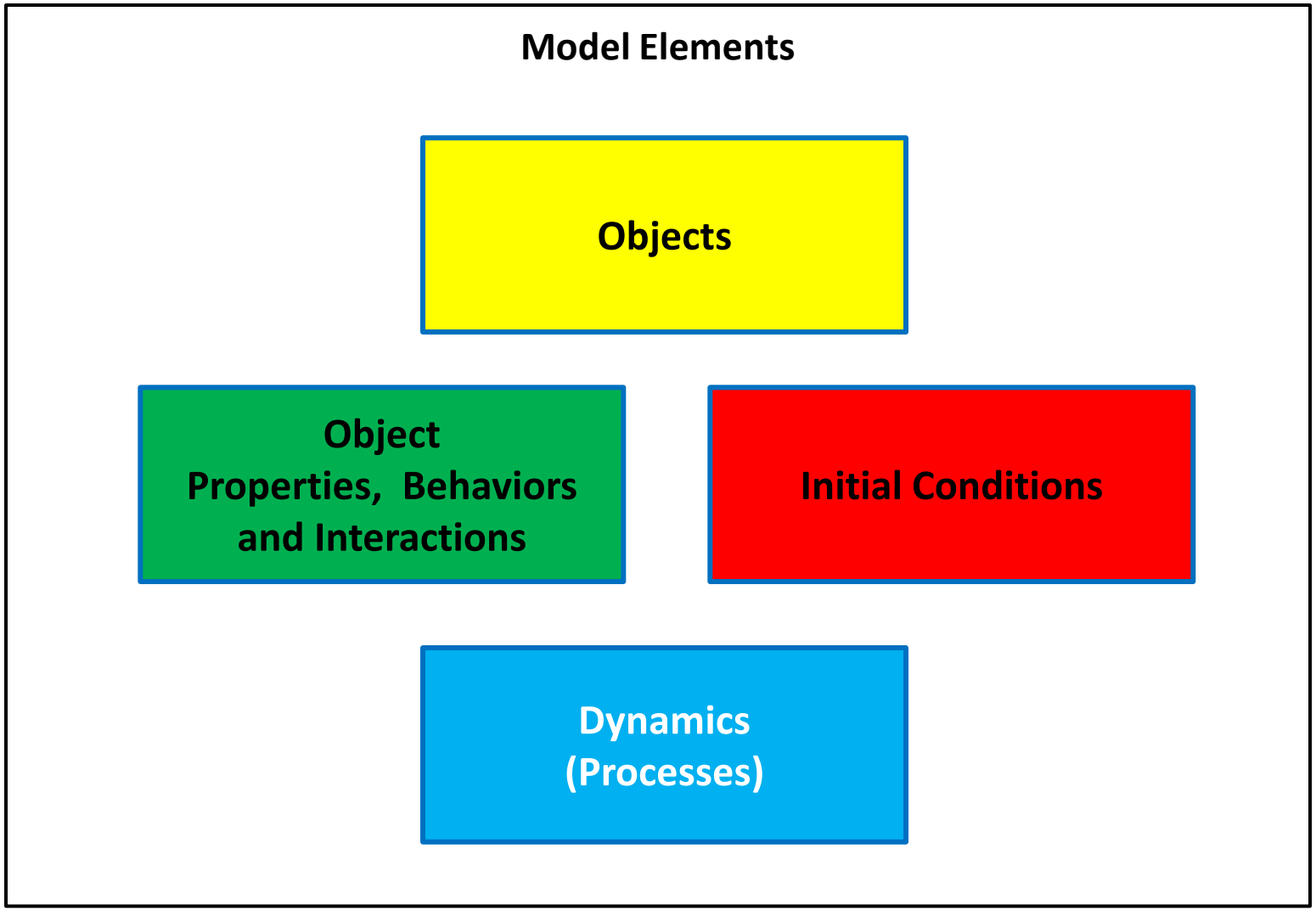
Building a Model—Now



Building a Model—Better



Model Components



Suggestions

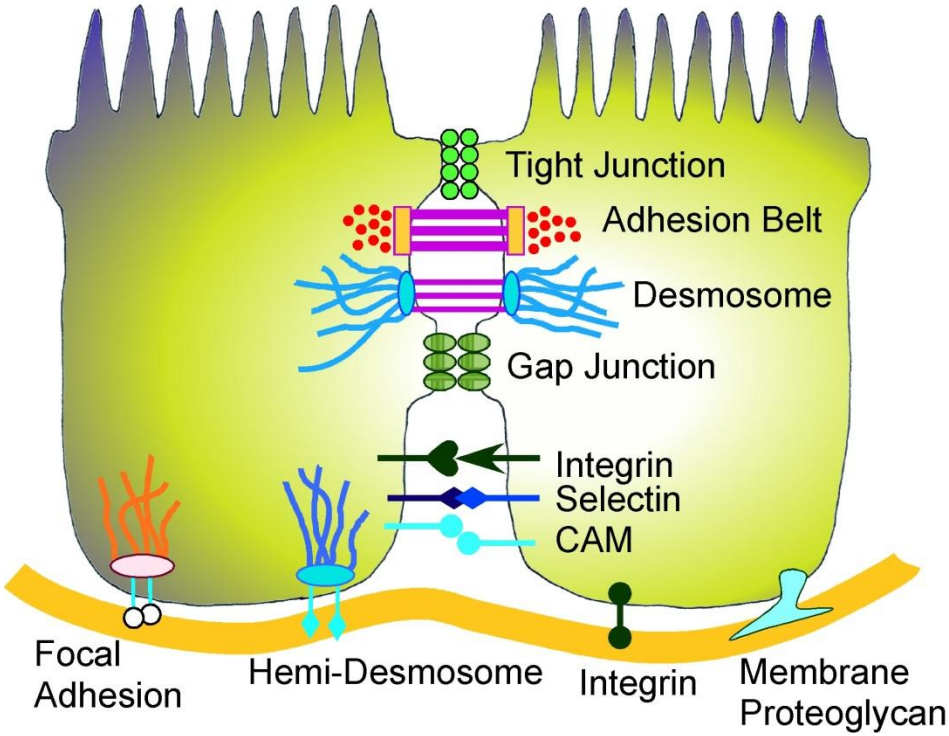
- Think top down.
- Think about how you Describe your Experimental Results/Simulations to Others.
  - What Components/Objects (Cell, ECM…) are Involved?
  - What Behaviors, Morphologies,…are **Crucial** to these Components in your Particular Problem?
    - Start as Generically as Possible.
    - Treat Objects Initially as Black Boxes.
    - Add Detail Hierarchically.
    - Separate Control (Differentiation) from Behaviors.
    - Stop when you become Quantitative.
  - What Spatial Information do you Need?
  - Do all Components of a Given Type Have the Same Behaviors?

Main Processes in Development

- Cell Differentiation
- Cell Adhesion
- Cellular Secretion and Absorption
- Chemical Diffusion
- Cell Polarization
- Cell Movement
- Cell Proliferation and Death

Cellular Adhesion Holds Things Together

- Adhesion binds a cell to a surface, ECM or another cell
- Proper adhesion is essential in maintaining a normal multicellular structure
- Adhesion is accomplished through cell adhesion molecules



Cellular adhesion can link the cytoplasm of cells and and has both static and dynamic functions

Adhesion Questions

- How strongly do cells of one type adhere to cells of another type?
- How strongly do cells of a given type adhere to ECM?
- Are adhesions labile (e.g. single molecule pair, or junctional
- How does cell adhesion change in time?

Secretion and Absorption

- What chemicals do cells secrete and absorb?
- If they diffuse, how rapidly do these chemicals diffuse?
- If they do not diffuse, what are their mechanical properties?
- How stable are they (what is their decay rate)?

Chemical Field Questions

- How do cells move in response to chemical signals in their environment?
- How do cells change type in response to these signals?

Cell Growth and Death Questions

- What signals cause cells to grow?
- What signals cause cells to die?

Be Aware of Feedback Loops

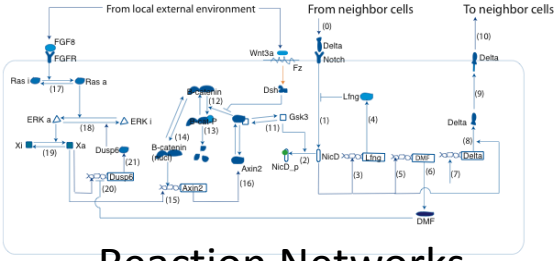
- Not Simply: Signal→Differentiation→Pattern (Known as Prepatterning).
- Cells Create Their Own Environment, by Moving and Secreting New Signals, so Signaling Feeds Back on Itself.
- Hence Self-Organization and Robustness.

Model Components

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

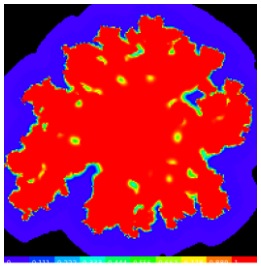
CompuCell3D Objects/Representations

- **Cells** and **Generalized Cells** (*e.g.* mesenchymal cells, epithelial cells, ECM, medium…), represented on the primary **Cell Lattice**
- **Internal States**, **Types** and **Reaction Networks** which control their properties.
- **Fields** represented on **Auxiliary Lattices** with same geometry as the Cell Lattice.
- **Finite Element Links** for the control of Mechanical Properties

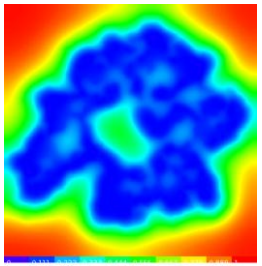


Reaction Networks

ECM

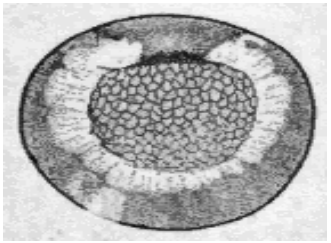


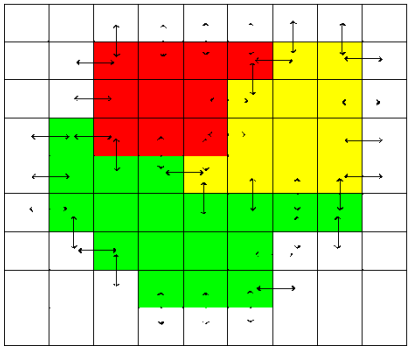
MDE



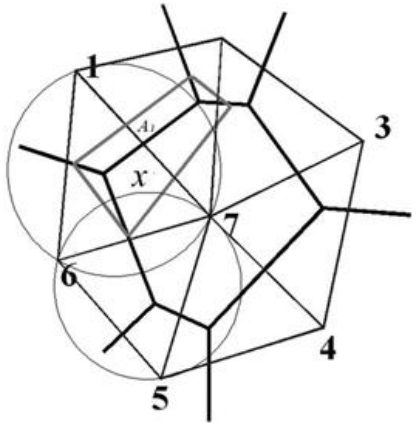
nutrient

Fields





Cell Lattice and Generalized Cells



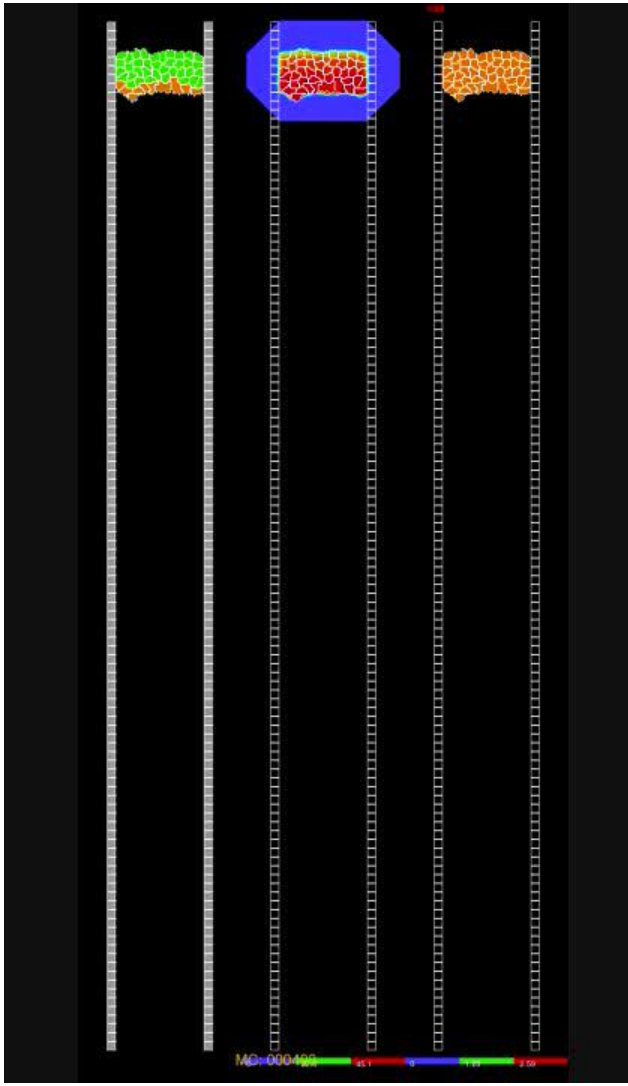
Finite Element Links

CompuCell3D Objects/Representations

- CompuCell3D allows you to define your own additional object classes if needed.

Fields

- A Field is a Lattice of (usually) real numbers denoting.
- Fields can represent ECM, diffusible chemicals, charge,…
- Fields and the Cell Lattice usually occupy the same notional space (no excluded volume). However, see below.
- Fields may be confined to subregions of the Lattice, corresponding to particular areas of the Cell Lattice.
- Fields can be diffusing or non-diffusing in different regions and support spatially varying diffusion and decay constants.
- Other objects can secrete or absorb into fields (at centers, boundaries or throughout volumes).
- Other objects can interact with Fields and Fields can interact with each other (e.g. Reaction-Diffusion equations).
- Multiple Fields can represent textured materials like fibronectin or collagen Extracellular Matrix.



Field Dynamics

- Most Fields evolve via diffusion, secretion and absorption and cells and by decay.

$$\frac{\partial C(\vec{i})}{\partial t} = D_c \nabla^2 C(\vec{i}) - \gamma_c C(\vec{i}) + S_c(\sigma(\vec{i})) - A_c(\sigma(\vec{i}))$$

Diffusion Decay Secretion Absorption

- Sometimes we couple two or more Fields via Reaction-Diffusion Equations of Form:

$$\frac{\partial C_1(\vec{i})}{\partial t} = f(C_1, C_2) + D_{c_1} \nabla^2 C_1(\vec{i}) - \gamma_{c_1} C_1(\vec{i}) + S_{c_1}(\sigma(\vec{i})) - A_{c_1}(\sigma(\vec{i}))$$

$$\frac{\partial C_2(\vec{i})}{\partial t} = g(C_1, C_2) + D_{c_2} \nabla^2 C_2(\vec{i}) - \gamma_{c_2} C_2(\vec{i}) + S_{c_2}(\sigma(\vec{i})) - A_{c_2}(\sigma(\vec{i}))$$

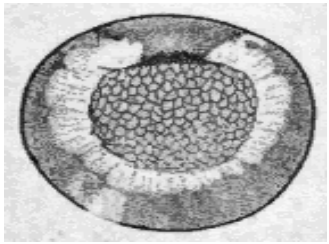
Generalized Cells

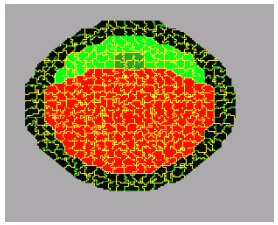
Each Cell has a unique integer Index, σ and consists of all sites on the Cell Lattice containing that Index.

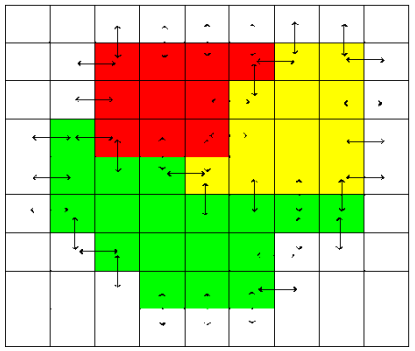
The number of Cell Lattice Sites with Index σ is the Cell's Volume, V.

The number of Lattice Sites with Index σ and, which are next to a Site with a Different Index σ' is the Cell's Surface Area, S.

Each cell also has a Type, τ.







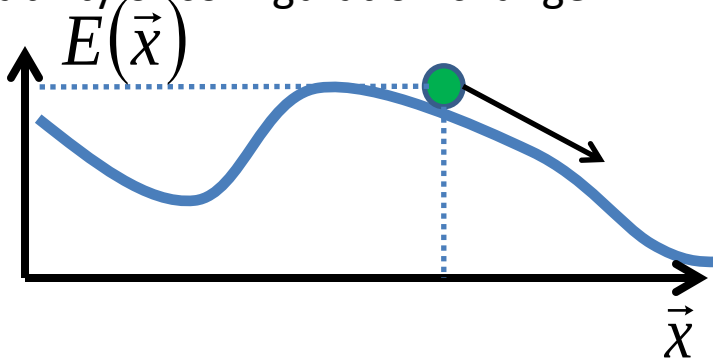
Cell Dynamics

•To simulate the cytoskeleton-driven extension and retraction of cell membranes (including pseudopods, filopodia and lamellipodia). The GGH algorithm tries randomly to extend and retract cell boundaries one pixel at a time.

•At each attempt, it calculates the new configuration Effective Energy and accepts the new configuration according to the Metropolis algorithm: probability of configuration change:

$$P(\Delta E) = e^{-\Delta E/kT}, \Delta E > 0$$

$$P(\Delta E) = 1, \Delta E \leq 0$$



•Result is movement with velocity proportional to the gradient of the Effective Energy, *i.e.*, linear in the applied force.

•Method breaks down if $\Delta H/kT$ too large.

•Configurations evolve to satisfy the constraints.

•When constraints conflict, evolve to balance errors.

•CC3D allows users to define their own acceptance functions.

Cell Properties/Interactions

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

Effective Energy Terms

- The most important Effective Energy Terms describe:
- Interfacial Energy between Cells and other Cells.
- The Effective Chemical Potential which induces Chemotaxis and Haptotaxis.
- Other terms may be useful in particular situations (*e.g.* gravitational potential energy, explicit external forces).

Energy Terms: Labile Adhesion/Surface Tension

Each unit of Cell Boundary (a Link between Adjacent Lattice Sites containing different Indices) has an associated Adhesion Energy, J, which depends on the Types of the Neighboring Cells: $J\left(\tau\left(\sigma\left(\vec{i}\right)\right),\tau\left(\sigma\left(\vec{i}'\right)\right)\right)$

or the number and types of adhesion molecule on each cell: $f\left(n_j\left(\vec{i}\right),\ldots;n_k\left(\vec{i}'\right),\ldots\right)$

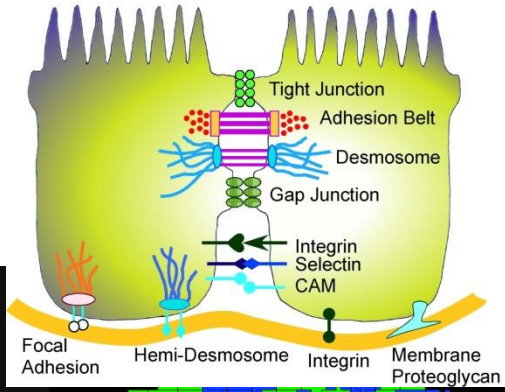
The Total Adhesion Energy, E_{adhesion} is:

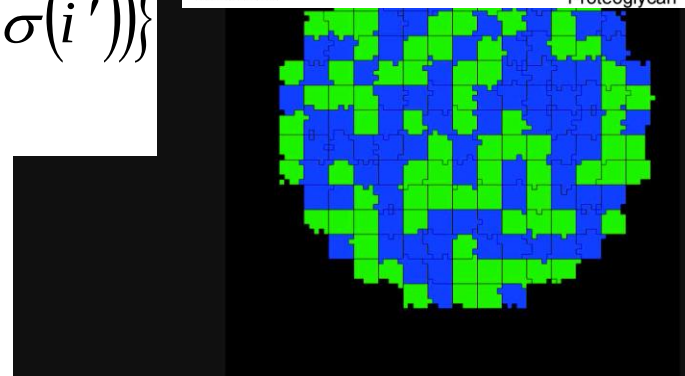
$$E_{\text{adhesion}}=\sum_{\substack{\vec{i},\vec{i}'\\ \text{neighbors}}} J\left(\tau\left(\sigma\left(\vec{i}\right)\right),\tau\left(\sigma\left(\vec{i}'\right)\right)\right)\left\{1-\delta\left(\sigma\left(\vec{i}\right),\sigma\left(\vec{i}'\right)\right)\right\}$$

or

$$E_{\text{adhesion}}=\sum_{\substack{\vec{i},\vec{i}'\\ \text{neighbors}}} f\left(n_j\left(\vec{i}\right),\ldots;n_j\left(\vec{i}'\right),\ldots\right)\left\{1-\delta\left(\sigma\left(\vec{i}\right),\sigma\left(\vec{i}'\right)\right)\right\}$$

Where, $\delta\left(\sigma\left(\vec{i}\right),\sigma\left(\vec{i}'\right)\right)=\begin{cases}1, \sigma\left(\vec{i}\right)=\sigma\left(\vec{i}'\right)\\ 0, \sigma\left(\vec{i}\right)\neq\sigma\left(\vec{i}'\right)\end{cases}$





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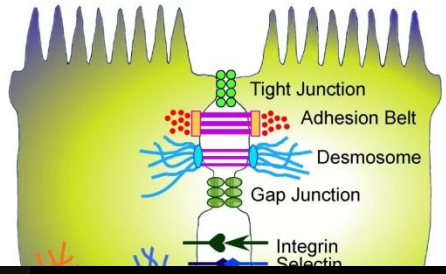
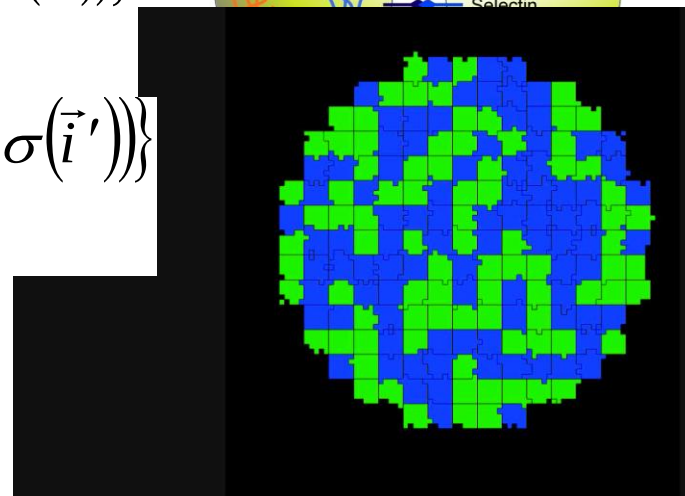




Energy Terms: Chemotaxis

If a Cell is attracted or repelled by a chemical, the response is represented by a Chemotaxis or Haptotaxis Effective Energy, E_{chemo}:

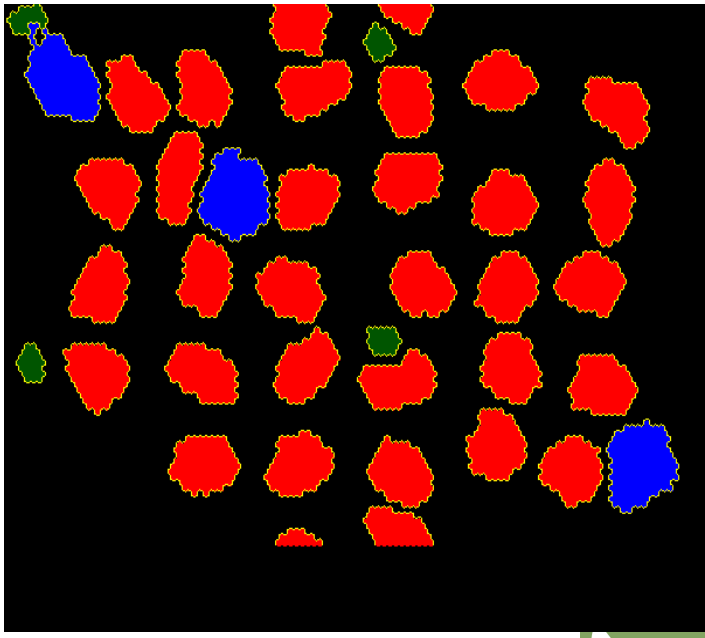
$$E_{\text{chemo}} = \sum_{\vec{i}} \mu\left(\tau\left(\sigma\left(\vec{i}\right)\right)\right) f\left(C\left(\vec{i}\right)\right)$$

μ>0→chemorepulsion,

μ<0→chemoattraction.

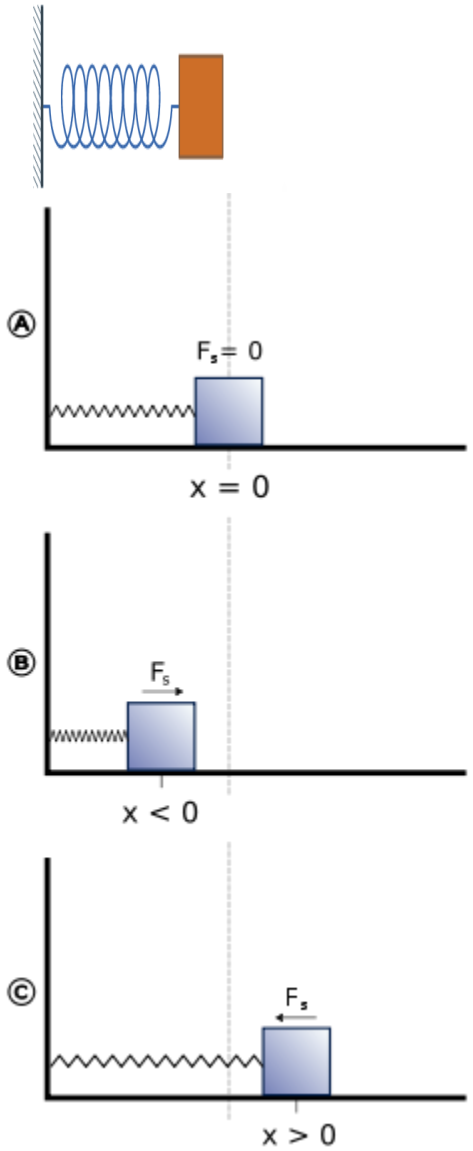
f is the response function of the cell to the chemoattractant.

There may be many such terms, with different responses for each cell or cell type.



Constraints

- What is a Constraint?
- A function that pushes a system back towards some predefined state.
- *E.g.*
  - A mass on a spring
  - A ball rolling in a bowl



Constraints

- A Constraint is a very convenient method for implementing behaviors via an Effective Energy.
- In general, an elastic Constraint has the form:

$$E_{\text{constraint}} = \sum_{\text{objects}} \lambda(\text{object})\left(f(\text{object}) - f_{\text{target}}(\text{object})\right)^2$$

- λ is the Constraint Strength and *f* the Constraint Function. The bigger λ, the smaller the deviations of the behavior of the system from the target.
- Because of the Dynamic Behavior of Metropolis Algorithm ANY behavior can be implemented this way.

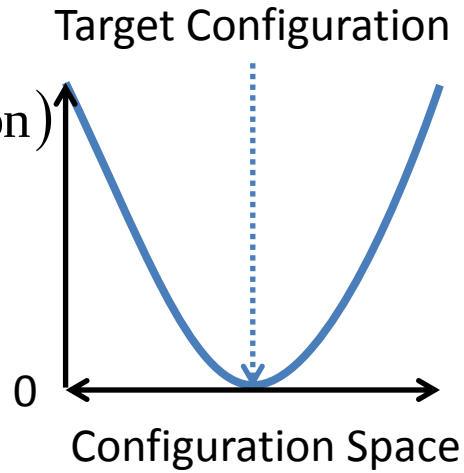
Constraints

- Saw before, the pattern configuration evolves to reduce the Effective Energy at a rate $\left|\nabla E\left(\vec{x}\right)\right|/T$

- For a constraint:

$$E_{\text{constraint}}(\text{configuration})$$

$$E_{\text{constraint}} = \sum_{\text{objects}} \lambda(\text{object})\left(f(\text{object}) - f_{\text{target}}(\text{object})\right)^2$$



- Because the energy function is smooth and has a single minimum, the pattern will evolve from any configuration to try to satisfy the constraint, at a rate proportional to $2\lambda(\text{object})\left(f(\text{object}) - f_{\text{target}}(\text{object})\right)$
- **For multiple incompatible constraints, the selected configuration will be a compromise among the constraints.**

Constraints

- Most Important Constraints:
  - Cell Volume
  - Cell Surface Area
  - Elasticity (Elastic/Plastic Solids/Junctional Adhesion)

Volume Constraints

- Most Cells (except Generalized Cells representing fluid media) have defined volumes.

$$E_{\text{volume}} = \sum_{\sigma} \lambda_{\text{volume}}(\sigma)\left(V(\sigma) - V_{\text{target}}(\sigma)\right)^2$$

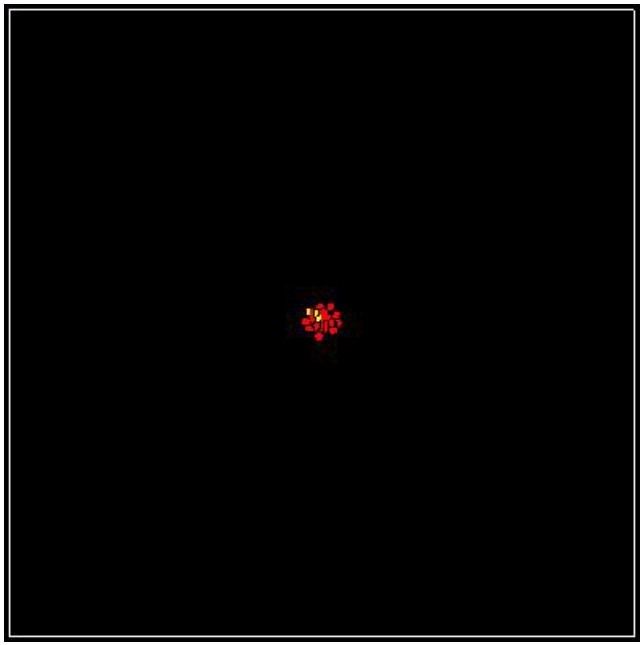
$$\text{Pressure} = 2\lambda_{\text{volume}}(\sigma)\left(V(\sigma) - V_{\text{target}}(\sigma)\right)$$

- *i.e.* the cell obeys the ideal gas law.
- Easy way to implement Cell Growth:

$$\frac{dV_{\text{target}}(\sigma)}{\text{dt}} = f(\text{systemstate}, \text{cell state})$$

- And Cell Death: $V_{\text{target}}(\sigma) = 0$

The rate of cell disappearance proportional to $\lambda_{\text{volume}}(\sigma)$



Elastic/Plastic Solids/Junctional Adhesion

Subdivide the object into subelements, measure the center-of-mass distances between neighboring elements and constrain them to remain equal to their original values using links between subelements.

$$E_{\text{elastic}} = \sum_{\sigma} \sum_{\substack{\mu,\nu=1 \\ \text{neighbors}}}^{m(\sigma)} \lambda_{\text{elastic}}(\sigma,\mu,\nu)\left(\left\|\vec{c}m(\sigma,\mu)-\vec{c}m(\sigma,\nu)\right\| - L_{\text{target}}(\sigma,\mu,\nu)\right)^2.$$

λ_{elastic} is the Young's Modulus of the Solid.

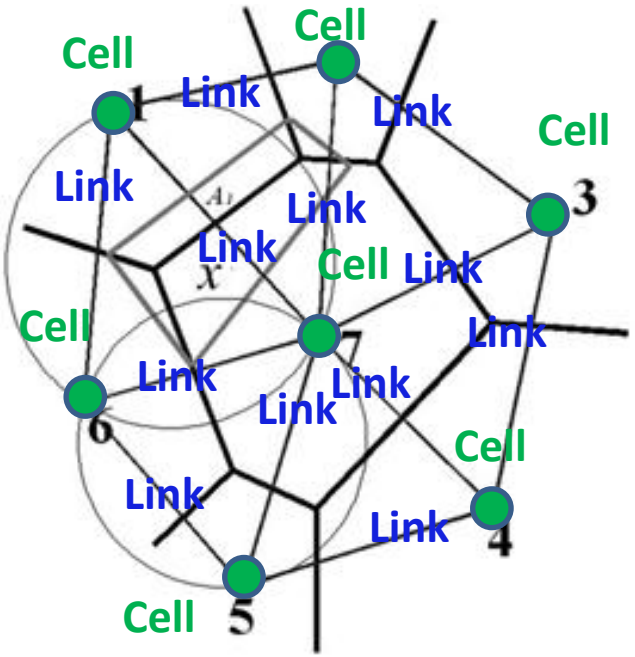
The strain on a link is:

$$\left\|\vec{c}m(\sigma,\mu)-\vec{c}m(\sigma,\nu)\right\| - L_{\text{target}}(\sigma,\mu,\nu)$$

The stress on a link is:

$$\lambda_{\text{elastic}}(\sigma,\mu,\nu)\left(\left\|\vec{c}m(\sigma,\mu)-\vec{c}m(\sigma,\nu)\right\| - L_{\text{target}}(\sigma,\mu,\nu)\right)$$

For a plastic material, define a Yield Strain (or Yield Stress at which the links break.



Model Components

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

Tweaks: Mitosis

Implement by setting a Criterion for Cell Division.

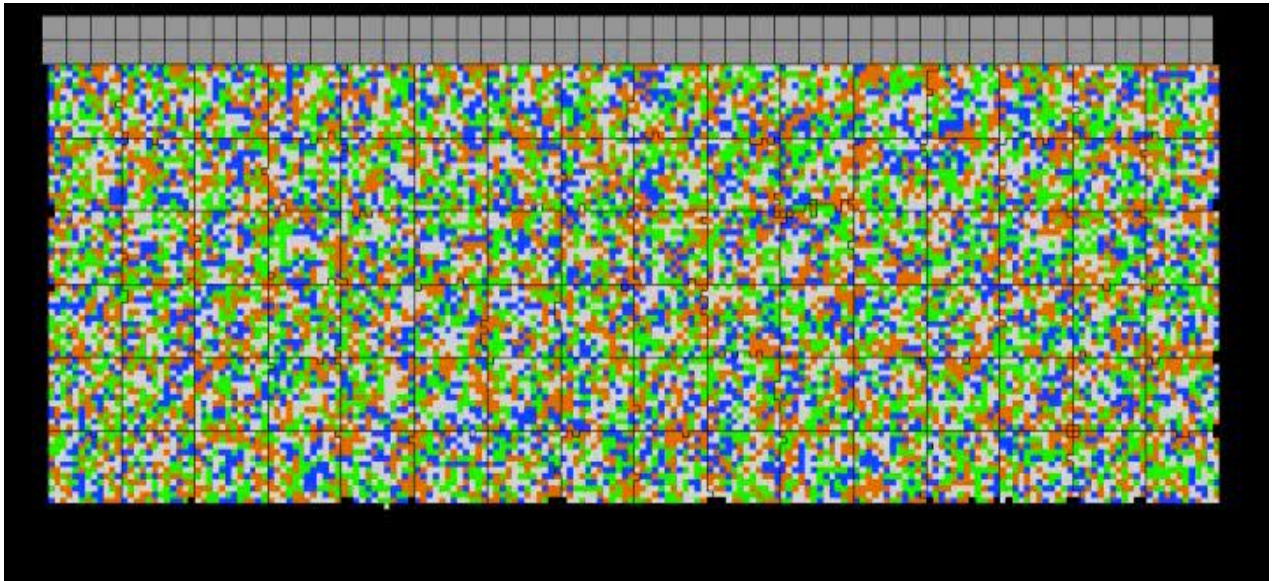
When reached, divide Cell along either random axis (random cell division) or axis with minimal moment of inertia (oriented cell division)

Assign Cell Lattice Sites in one half of Cell to a new unique Index. New Cell Inherits other properties of Parent.

Reset $V_{\text{target}}=V_{\text{target}}/2$ for both Cells.

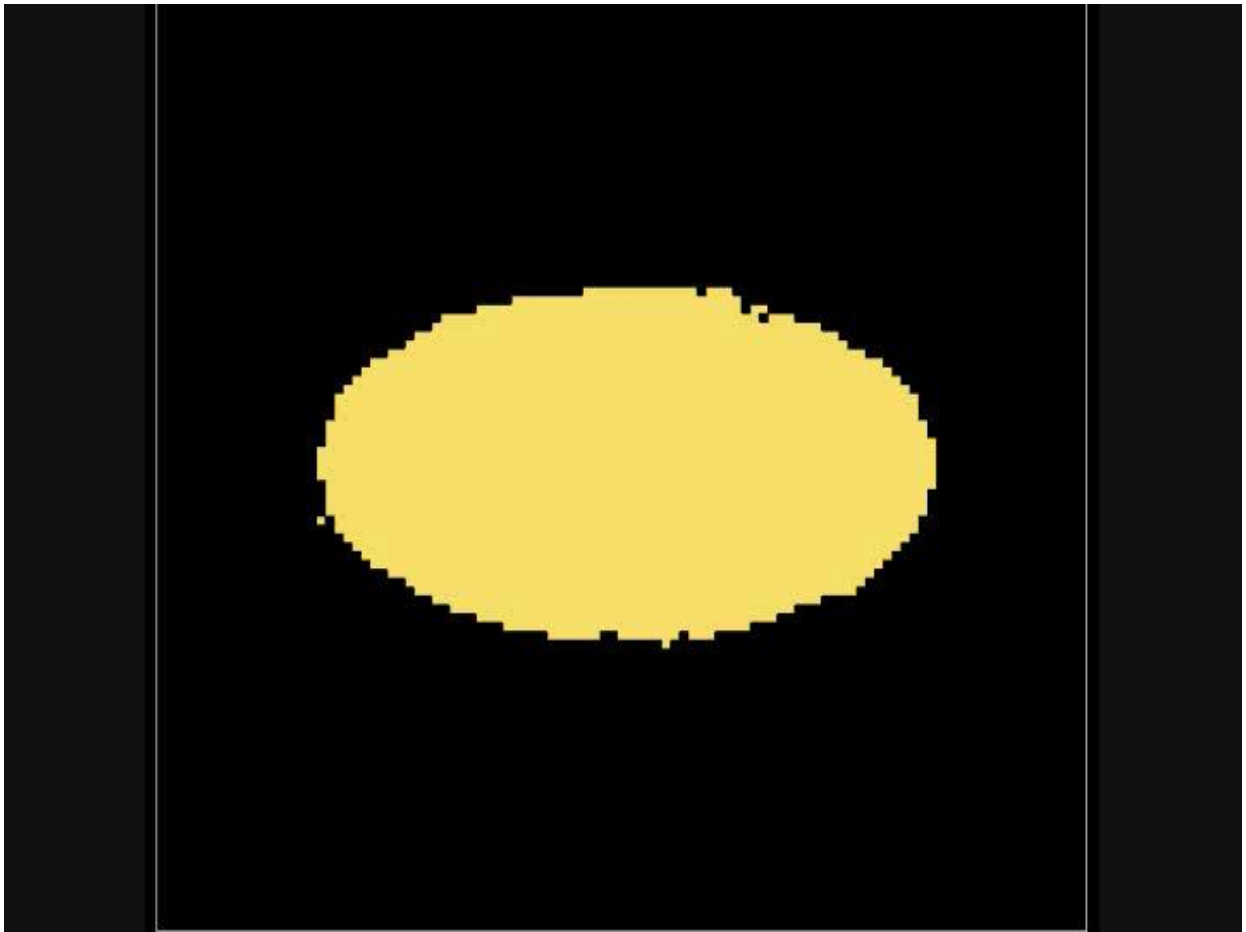
Subcell Spatial Modeling Intracellular Fields:

- While CompuCell3D was originally designed to model multicell phenomena, it can also do subcellular modeling.
- Example: Induction of Planar Polarity Pathway due to contact with an external bounding surface.



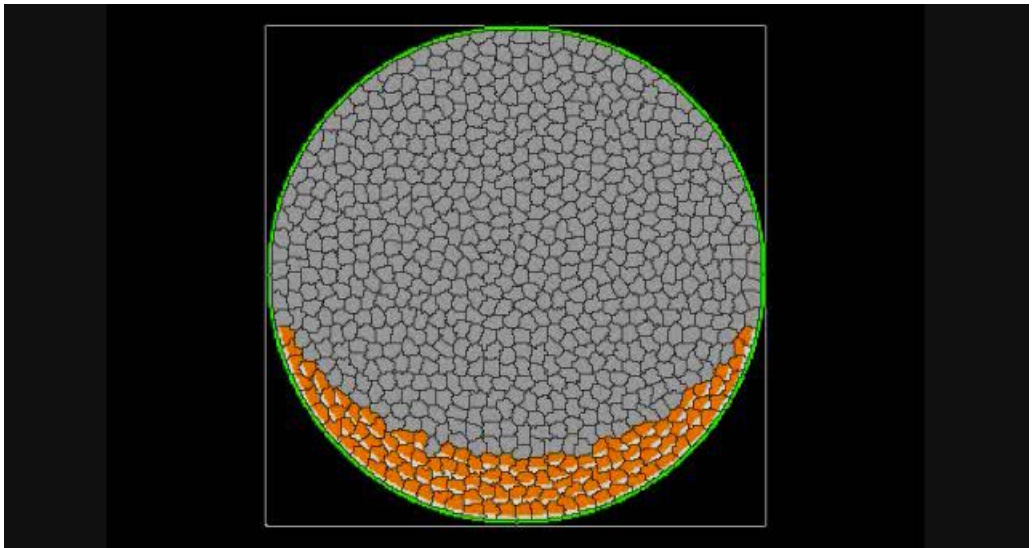
Subcell Spatial Modeling Intracellular Fields:

- PAR-2/PAR-6 Polarization by Centromere from Goehring Lecture



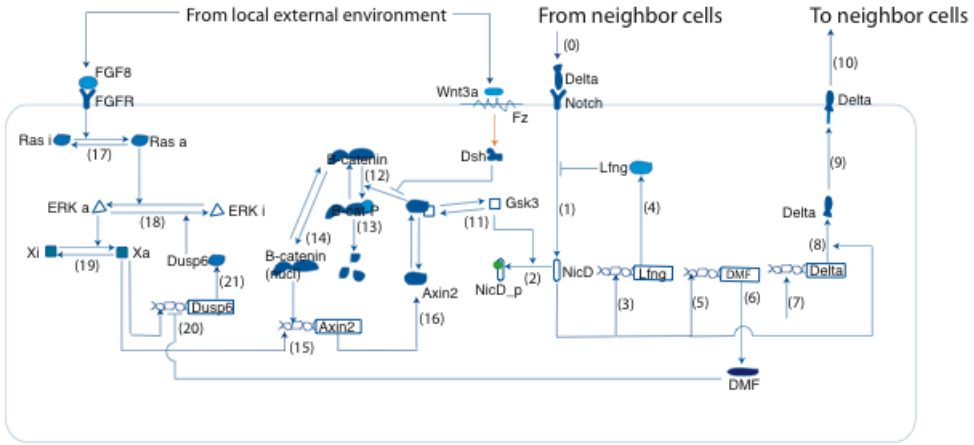
Subcell Spatial Modeling
Compartmental Cells

- The Basic CC3D Cell is an isotropic blob.
- CC3D allows the division of Cells into compartments called SubCells where each SubCell compartment has a different set of properties.
- Example: Gastrulation in chick embryo with convergent extension due to polarized cell-surface properties.



Subcellular or Supercellular Reaction Kinetics Modeling

- CC3D allows you to attach one or more coupled ODE submodels to any Object.
- Usually we use these to implement subcellular functions like Regulatory, Metabolic or Signaling Networks.
- Can also attach to extracellular compartments to allow Physics-Based Pharmaco-Kinetic Modeling (PBPK) modeling.
- These RK networks can control the properties of other Object classes and inquire about the states of other Objects.
- RK models can also couple to each other within or between Objects (e.g. intracellular vs. juxtracrine signaling.
- Examples of Biochemical Kinetics:
  - Cell-Cycle
  - Circadian rhythms
  - Cardiac rhythms
  - cAMP oscillations
  - Delta-Notch patterning
  - WNT pathway
  - FGF pathway
  - Etc…



Subcellular modelling

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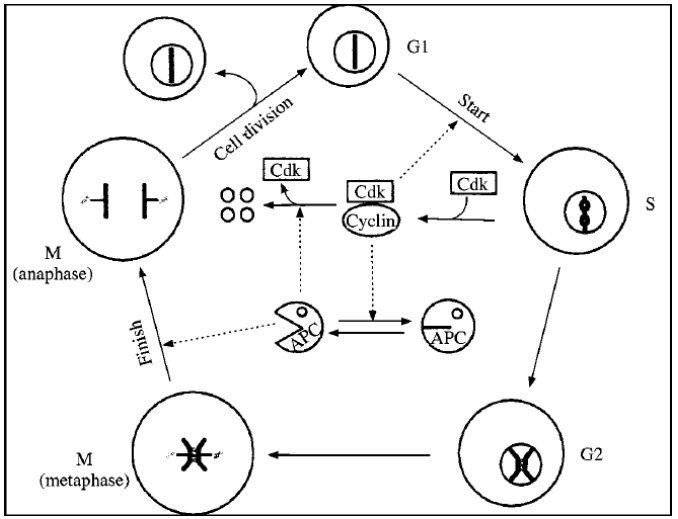
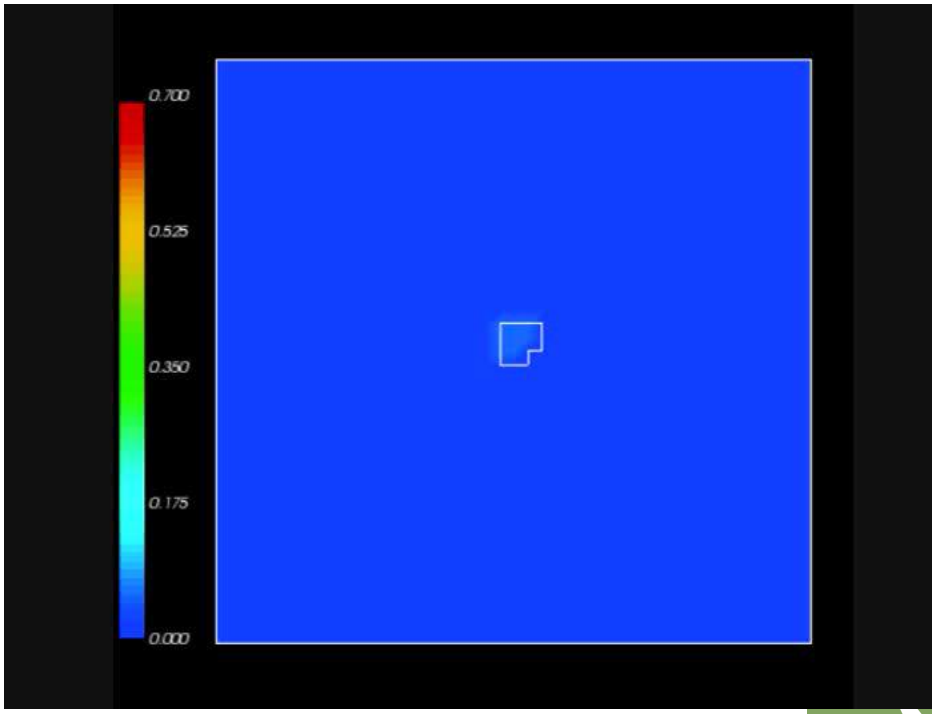
  - Etc…





Subcellular Modelling

- Biochemical Kinetics
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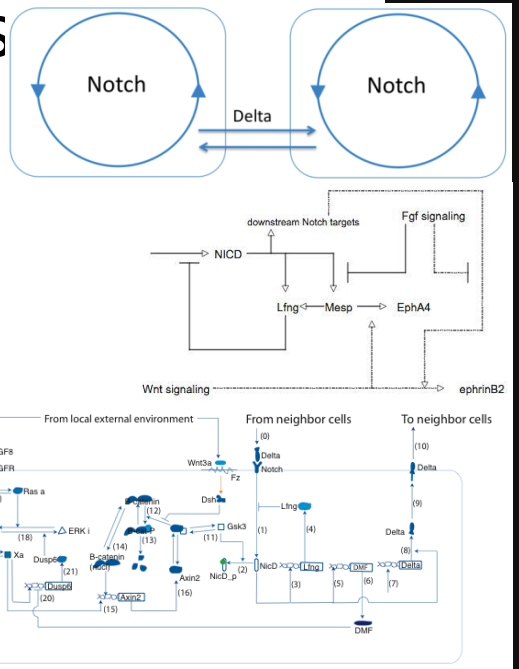
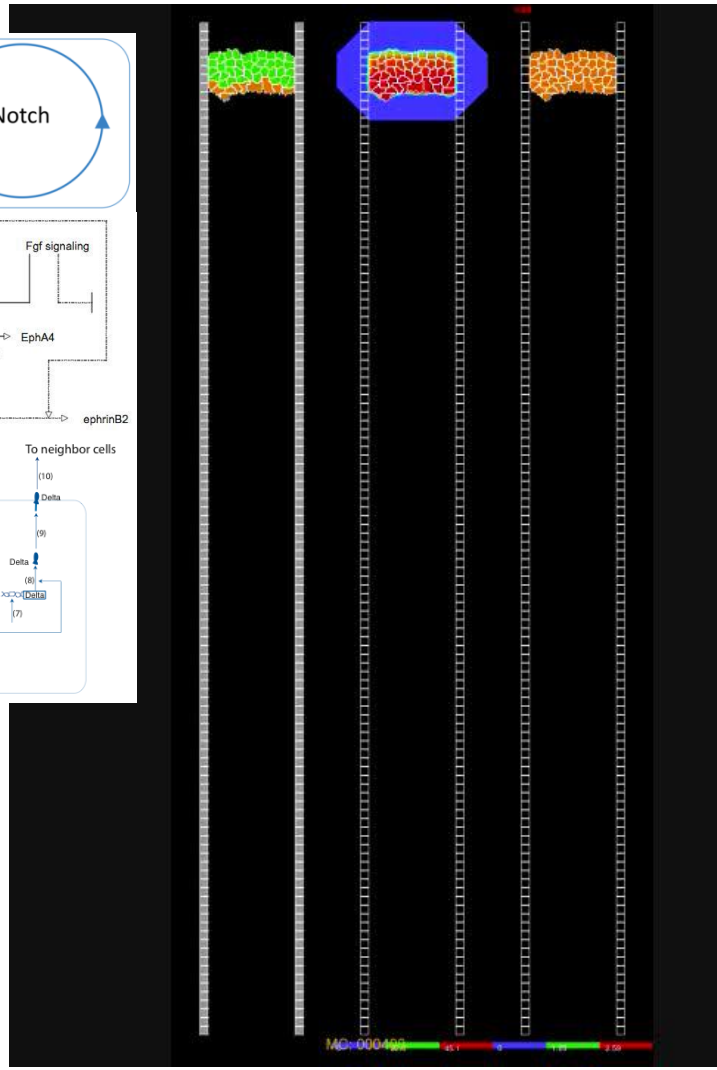
  - WNT pathway
  - FGF pathway
  - Somitogenesis…





Model Components

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

Initial and Boundary Conditions

- Need to Define Initial Configurations for All Lattices and Initial Values for all Internal Variables and Parameters.
- Need to Define Boundary Conditions of Fields and Cell Lattice (Periodic or Fixed, Absorbing or Reflecting, Excluded Volumes/No Excluded Volumes…).

Summary

- Multicell models can connect heterogeneous molecular and cell-level data to predict significant tissue and organ level outcomes.
- Natural framework for studying developmental processes and failures—angiogenesis disruption, gastrulation, limb growth, liver regrowth and disfunction, polycystic kidney disease…
- Models are phenomenological.
- Models can omit key mechanisms.
- Models can only show sufficiency, not necessity.
  - www.compucell3d.org, www.sys-bio.org