New Developments in Virtual Tissue Simulation of Tissues

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Outline

- **Background on Virtual Tissues**
- **Examples of Virtual Tissue Applications**
- **CompuCell3D (CPM/GGH Models)**
- **Tissue Forge (Center and Vertex Models)**
- **Surrogates for Faster Diffusion Solvers**

We've seen several talks (*e.g*. Ruth Baker) applying multicellular agent-based models

Talk today about tools to make the construction of such models easier

Questions on Tissue Develoment, Homeostasis, Failure and Control

Development: How does a fertilized egg organize into an adult?

Homeostasis: How does an organism maintain itself?

Developmental Diseases: How does failure of homeostasis lead to pathology?

Infectious Diseases: How do pathogens and host interact?

Medicine/Bioengineering: How can we control, repair or create new forms of these processes?

Toxicology: How does molecular level perturbation lead to systems level pathology?

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

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

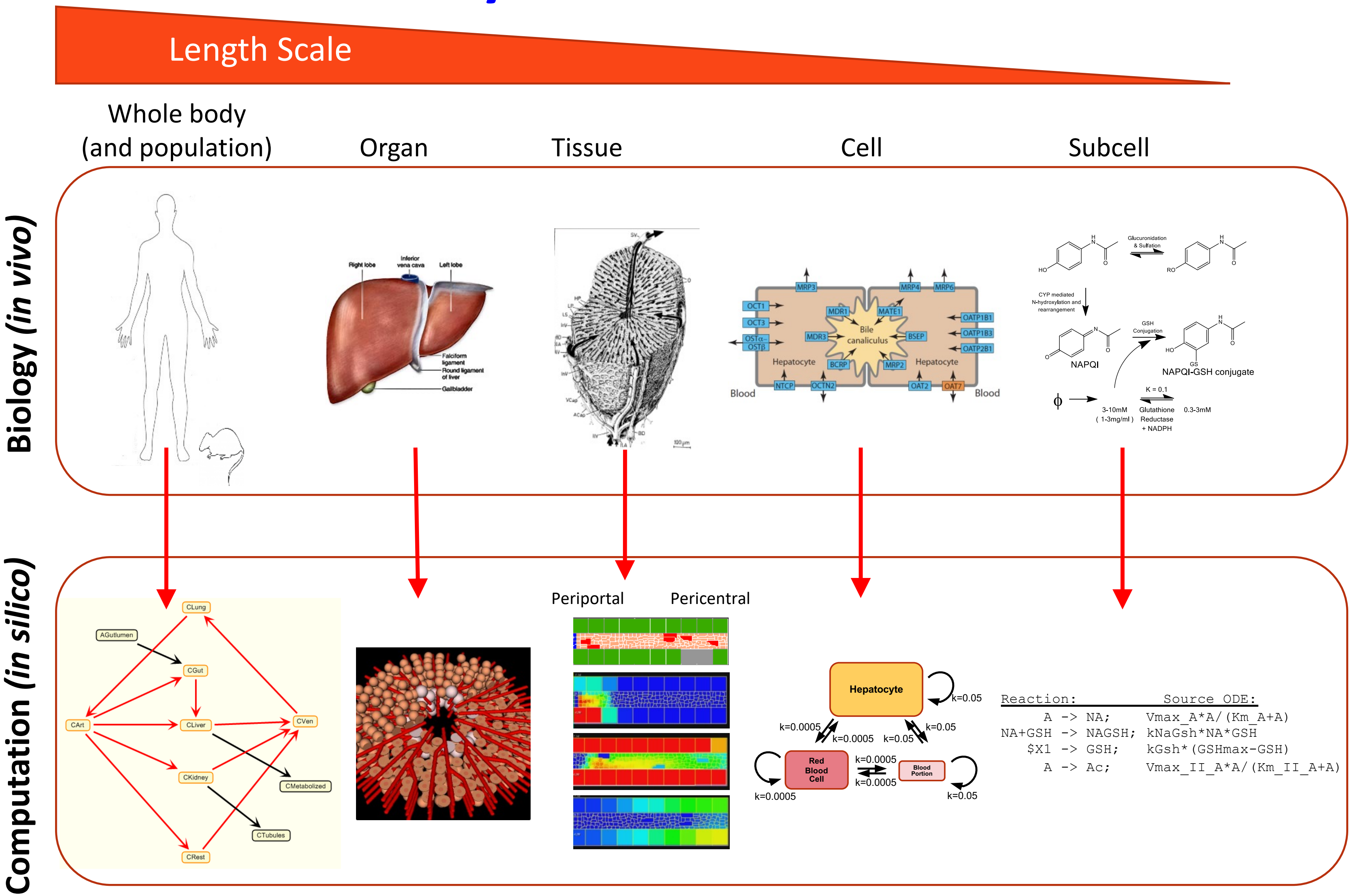
All of these exhibit complex interplay of physical and biochemical mechanism

To control we need to be able to predict

Multicellular Virtual Tissues

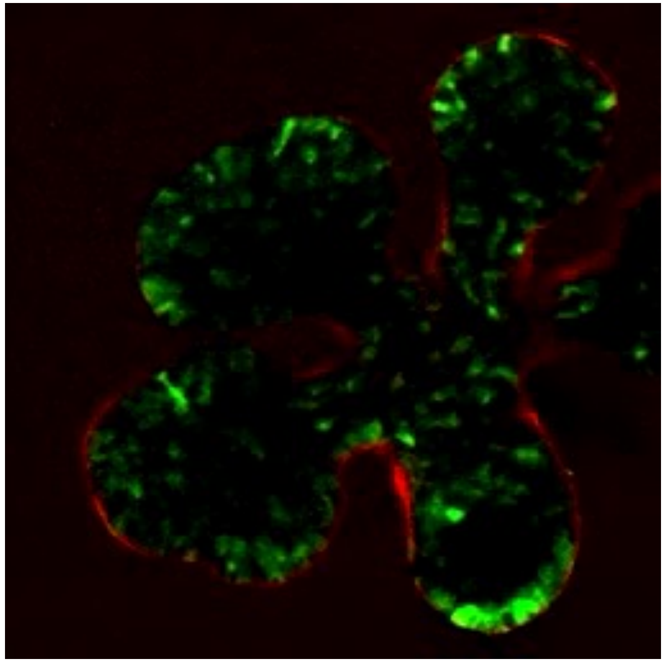
- **Mechanistic Dynamic Agent-Based Multiscale Models**
- **Focus on Emergent Spatiotemporal Phenomena resulting from Interactions between Agents (Objects)**
- **Mechanism driven**
- Additive (start with nothing and add)
- Cell to Organism Focus
- Based on quantitative Submodels of Object Behaviors (Births, Deaths, Forces, Shape Changes and Movements,…)
- Output Spatial Time Series (Movies)

Many Layers of Interaction and Feedback between Molecular Action and Systemic Outcomes



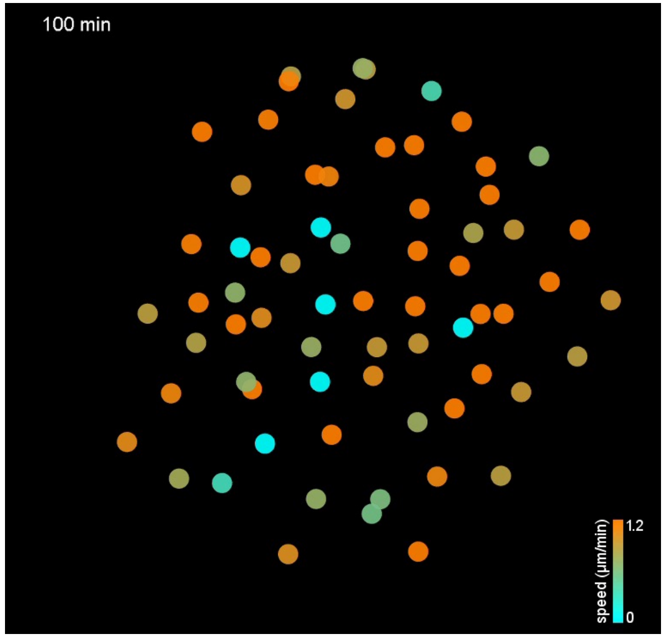
Biological Organization is Highly Dynamic and Crosses Scales—Development

Branching Morphogenesis *in vitro*



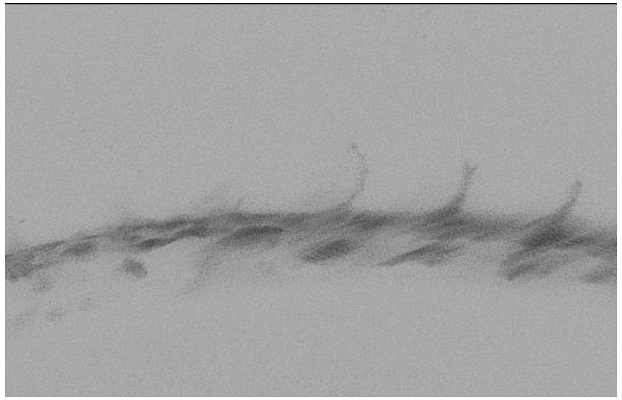
Larsen *et al.*, “Cell and fibronectin dynamics during branching morphogenesis,” *Cell Sci* **119**: 3376.

Early Development of Zebrafish

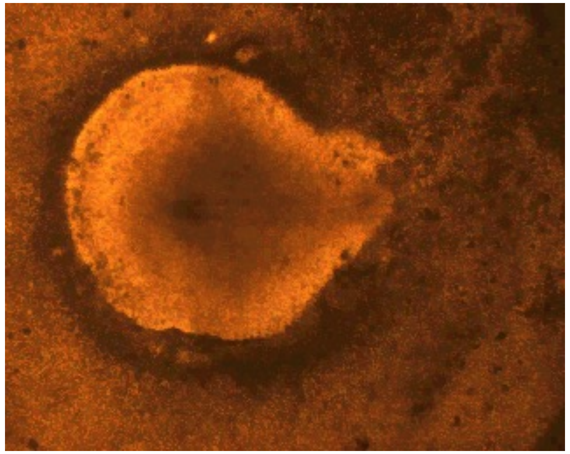


P. J. Keller, *et al.*, “Reconstruction of zebrafish early embryonic development by scanned light sheet microscopy,” *Science* **322**, 1065 (2008).

Intersegmental Vessel Growth in Zebrafish

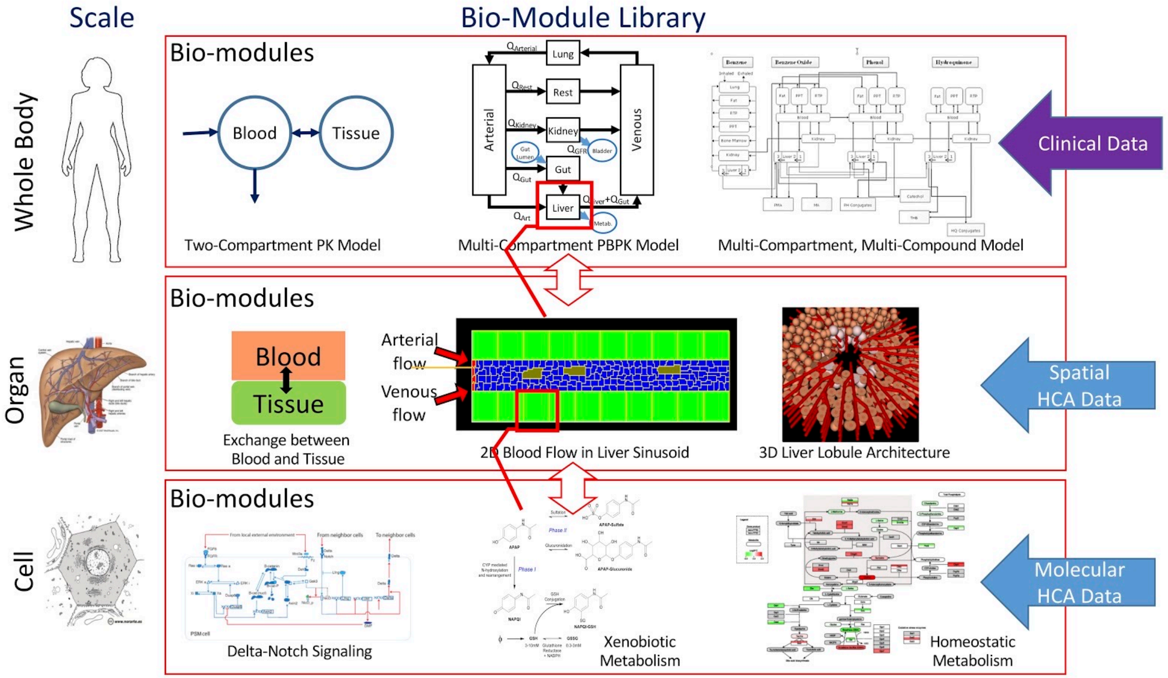


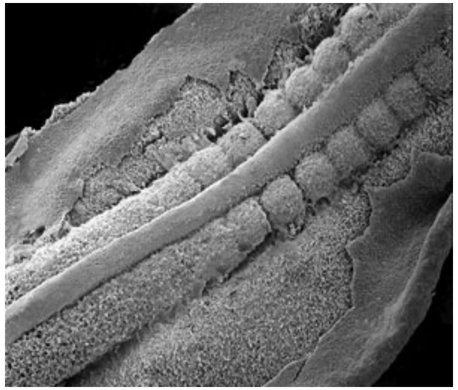
Segmentation of Chick Embryo



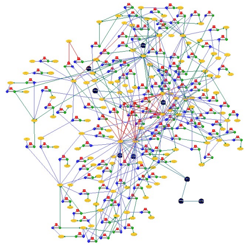
Virtual Tissues—Cell Behaviors Are Central

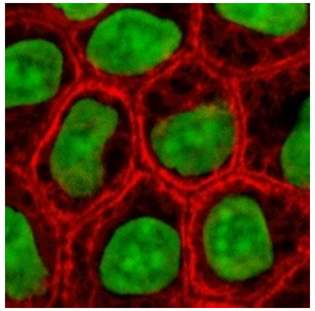
Spatial Computer Simulations to Explain How Interacting Chemical, Physical and Biological Mechanisms lead to Outcomes





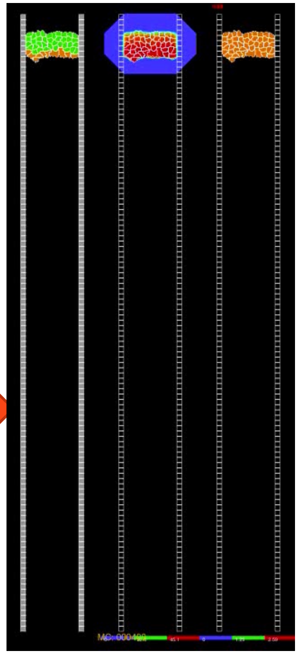
Dynamic Network/ ODE/Gillespie Level





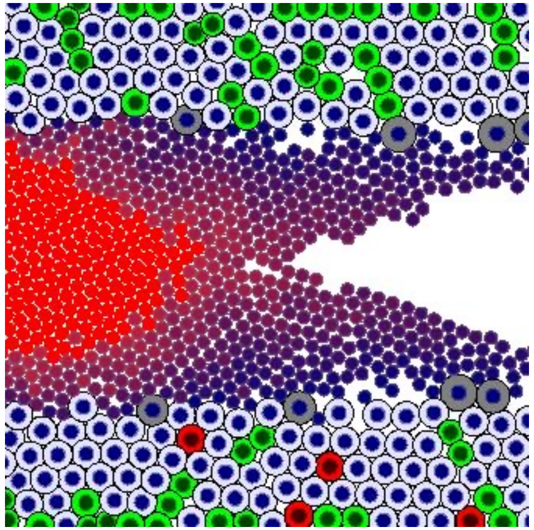
Multi-Cellular/Potts Level

Diffusive Signaling/ PDE Level

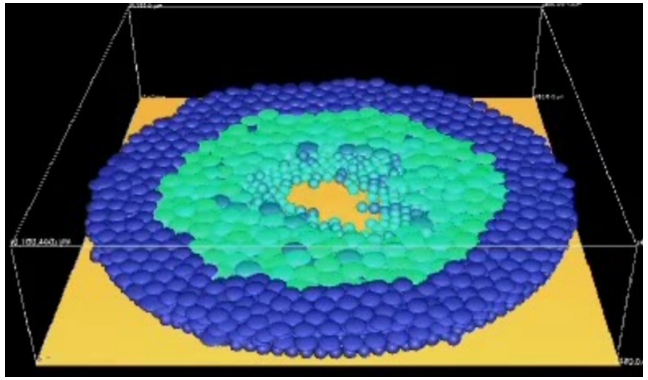


Virtual Tissues representing individual cells particularly helpful when cells move, change shape or individual cell behaviors are critical: *e.g.* cancer metastasis, wound healing, neoangiogenesis,…

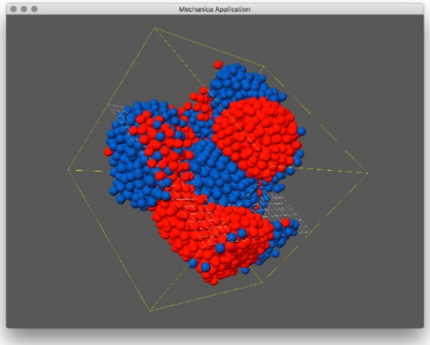
Many Ways to Represent Cells—Center Models



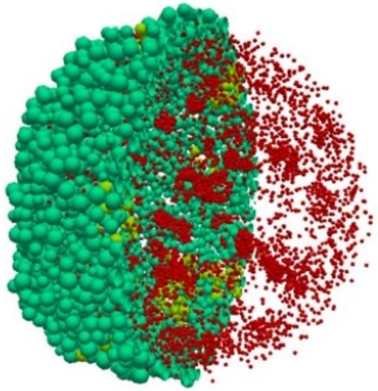
PhysiCell simulation of Ductal Carcinoma in situ (DCIS)



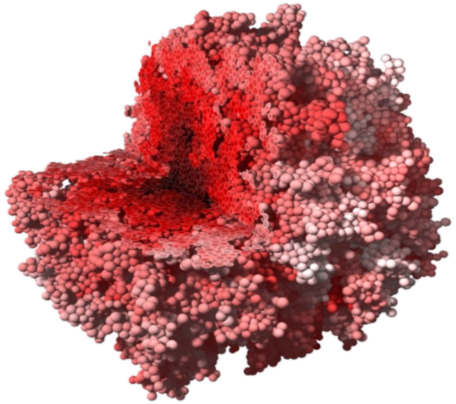
Episim simulation of extending shield mechanism (ESM)



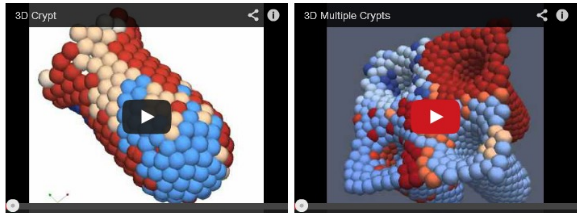
Center-model simulation of cell sorting Using Mechanica, Our New Software



Biocellion simulation of avascular tumor growth

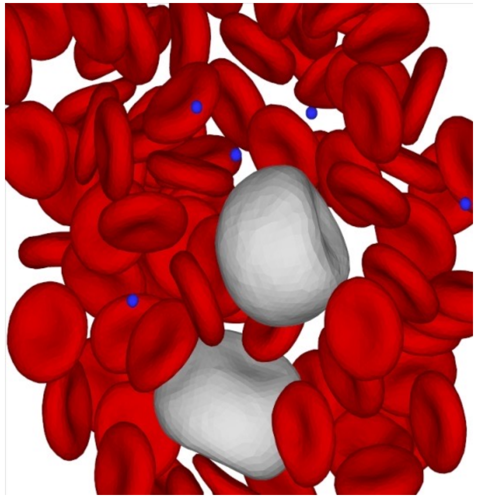


CellSys Simulation of multi-cellular population growth

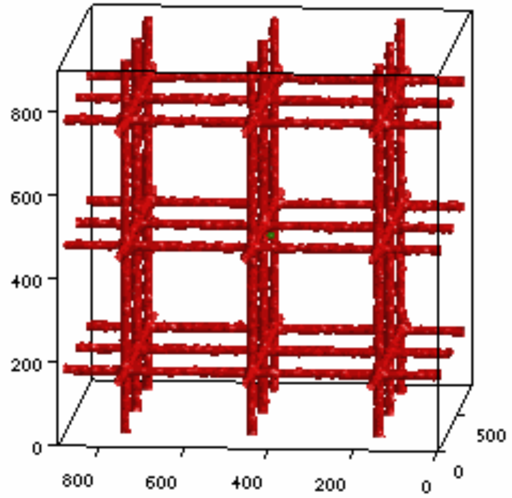


CHASTE simulation of colonic crypts
http://www.cs.ox.ac.uk/chaste/

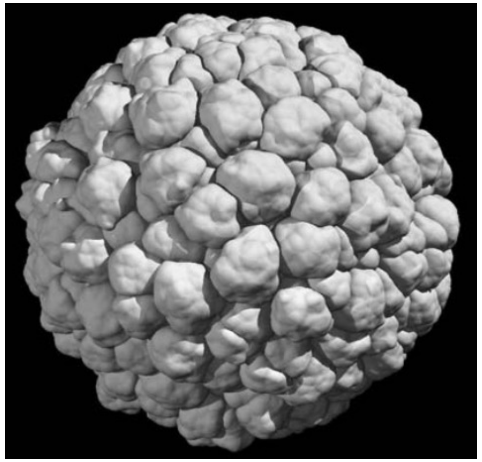
Many Ways to Represent Cells—Explicit Cell Shape



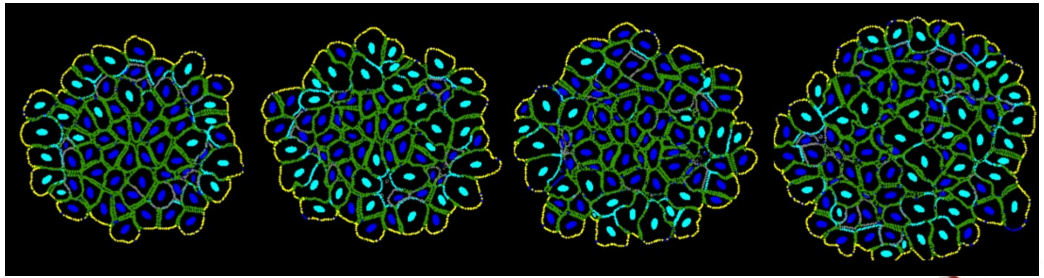
Simulating (Red) Blood Cell morphology, homeostasis and disease, *e.g*. sickle cell anemia, using DPD approach. G Karniadakis Brown University



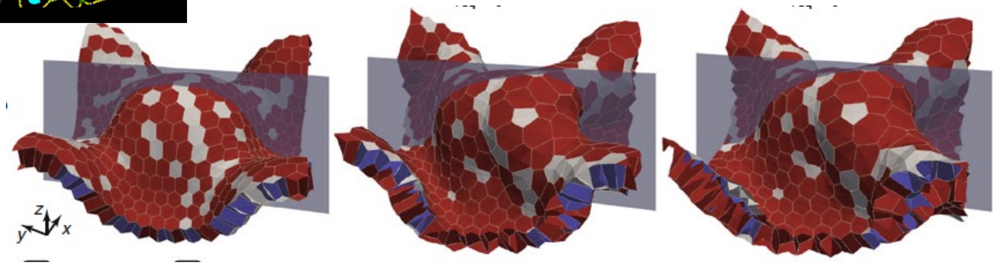
3D Multi-Cell Simulation of Tumor Growth and Angiogenesis using CompuCell3D



Modeling cellular aggregate using SEM, Tim Newman



Modeling tumor growth ,Kasia Rejniak, Moffitt Center, Tampa



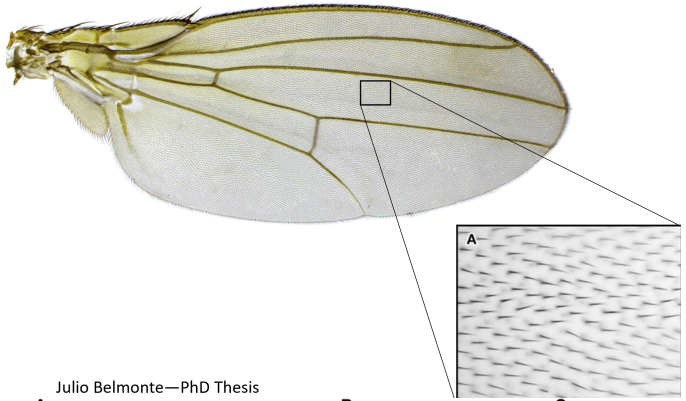
Modeling epithelial sheets, Satoru Okuda

Sample Virtual Tissue Applications

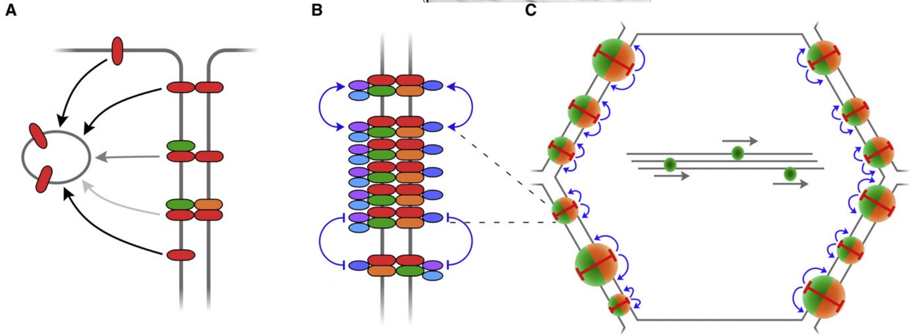
Problems addressed range from basic research on fundamental mechanisms of development to cancer modeling, toxicology and drug discovery

Drosophila Melanogaster Wing Hair Patterning

How does the orientation of cell hairs propagate across a growing wing?



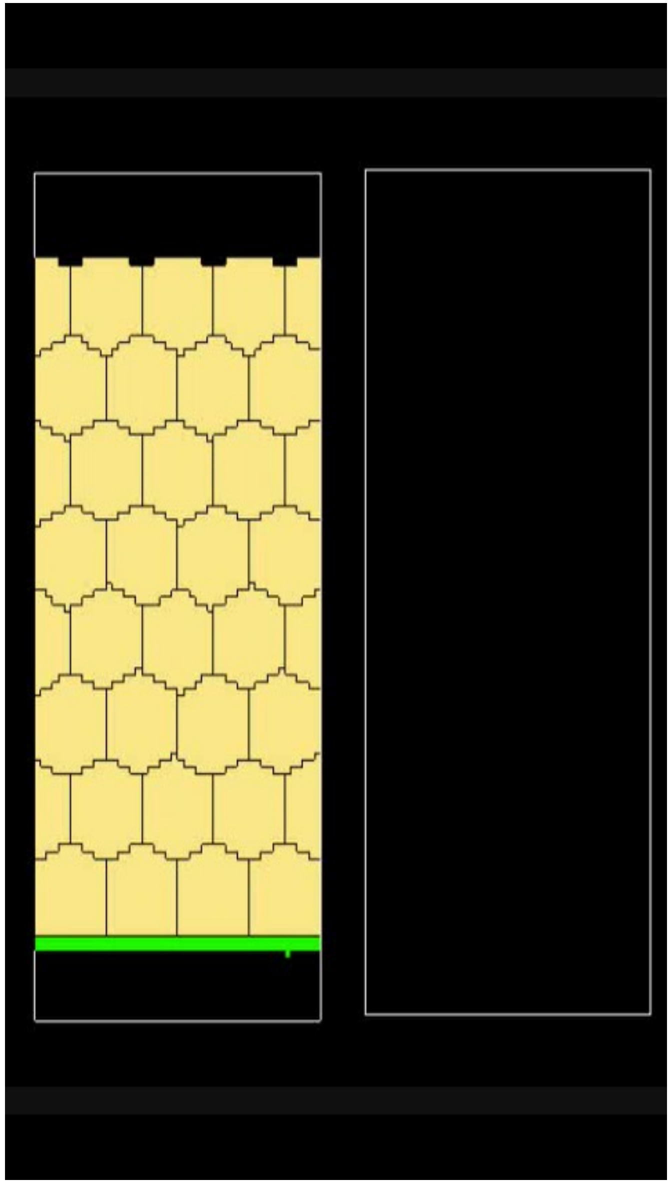
Julio Belmonte—PhD Thesis



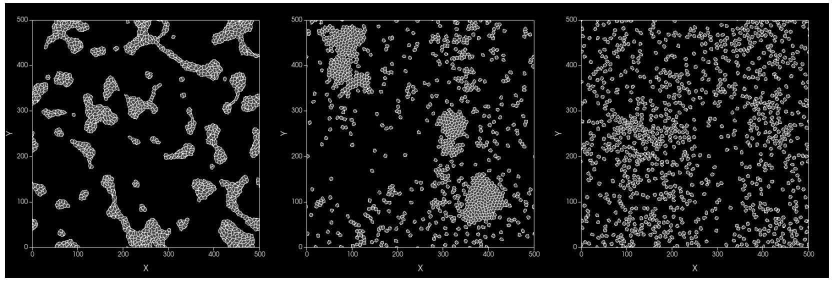
- 6 domain types:
- Cyto
- Lateral
- Fmi-Vg
- Fmi-Fz
- Fmi-Vg-Pk
- Fmi-Fz-Dg-Dsh

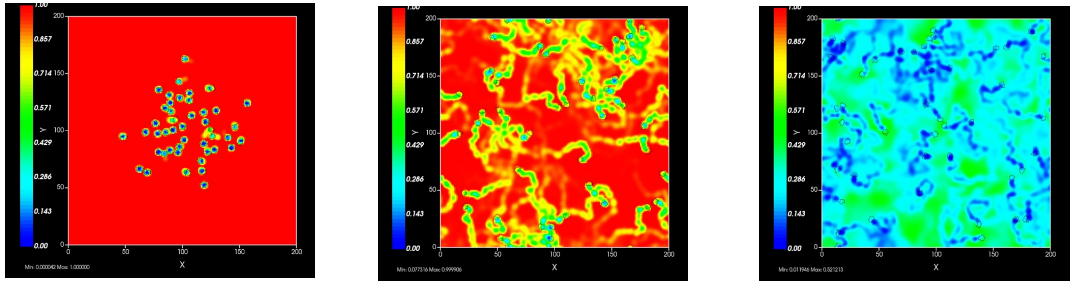
- Fmi-Fz, Fmi-Vg, **Lateral** mix at cell surface
- Fmi-Fz – Fmi-Vg (weakly across cells)

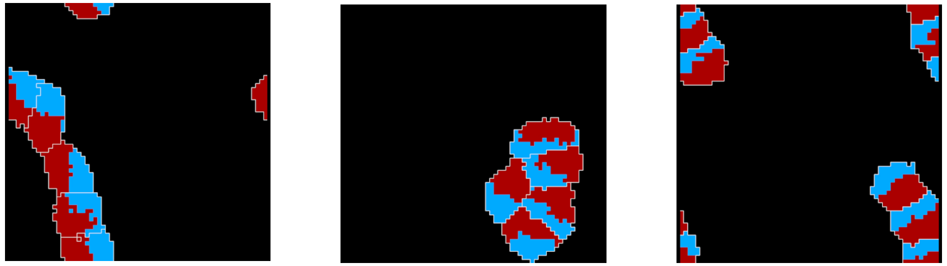
- Signal – Fmi-Vg → Signal – Fmi-Vg-Pk
- Fmi-Vg-Pk *repels* Fmi-Fz
- Fmi-Fz → Fmi-Fz-Dg-Dsh
- Fmi-Fz-Dg-Dsh *signals to* Fmi-Vg (on other cell)

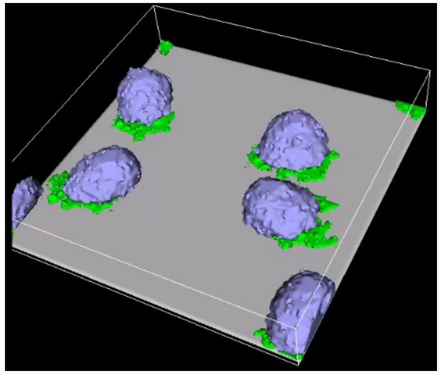


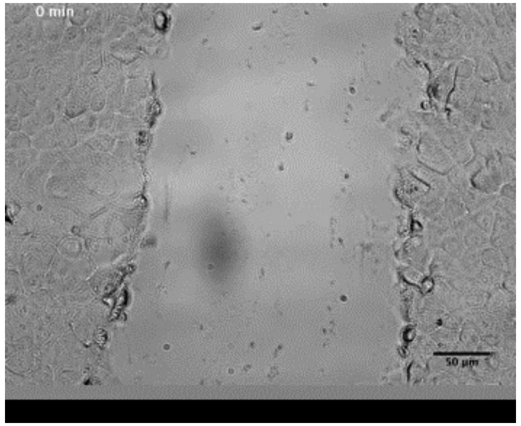
Modeling Collective Cell Migration in CompuCell3D





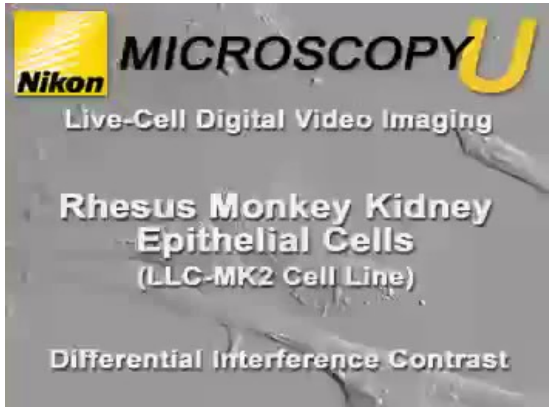






Wound healing

Megha Vaman Rao (2016) 10.1091/mbc.E16-06-0429



https://www.microscopyu.com/galleries/popups/diverter?s=rhesus-monkey-kidney-epithelial-cells-llc-mk2-line

Juliano F. Gianlupi, Gilberto L. Thomas, Pedro Cenci Dal-Castel

Capillary Development

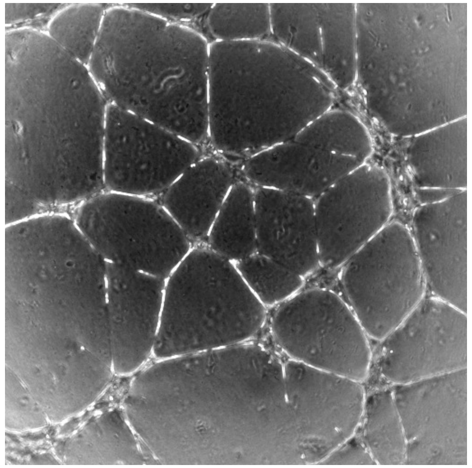
Biological System

Umbilical Vein Endothelial Cells (HUVECs) on Matrigel

What Mechanisms give rise to these patterns?

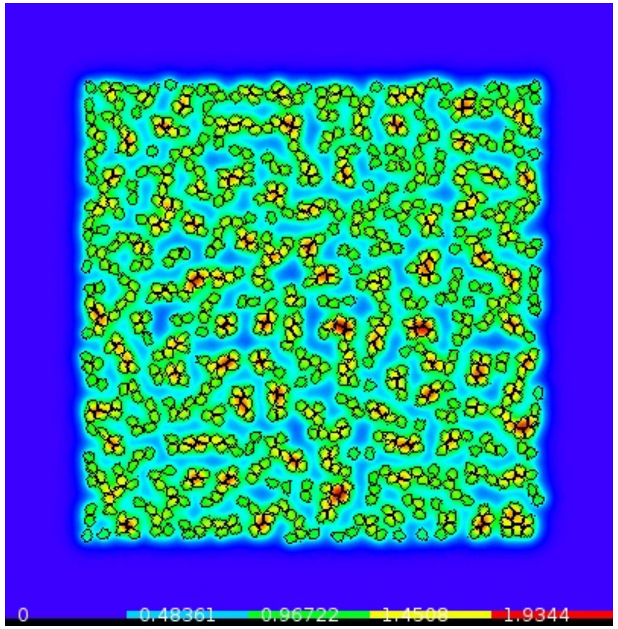
Result: Very Short-Range Chemotaxis + Contact Inhibition can explain both angiogenesis and vasculogenesis.

Works in 2D and 3D.

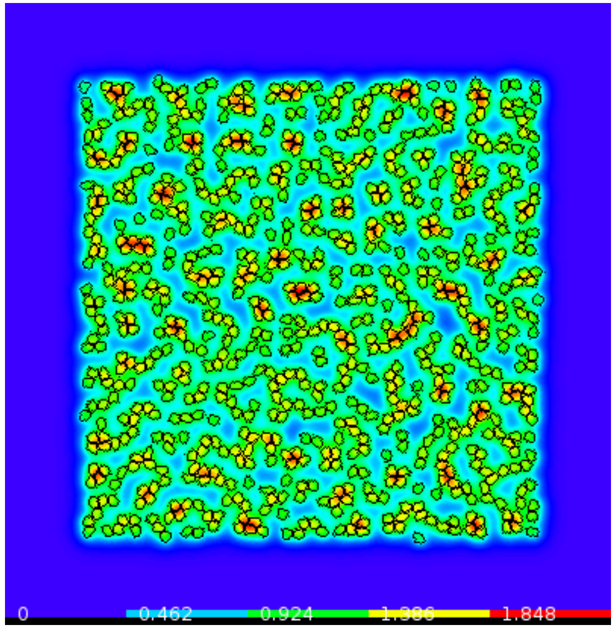


Movie 1: D. Ambrosi et al., Phys. Rev. Letters **90**, 118101

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



No Contact Inhibition



Contact Inhibition

Key Physics:

Cell Diffusion

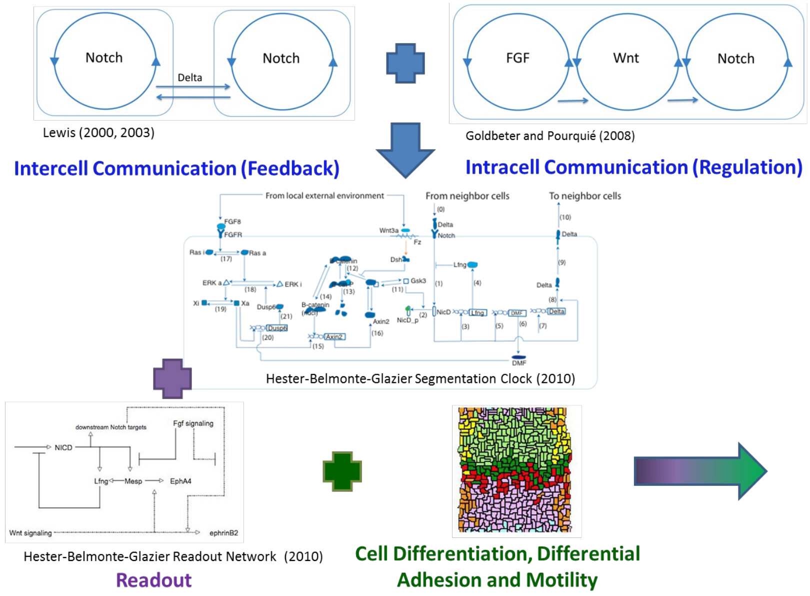
VEGF-A Diffusion

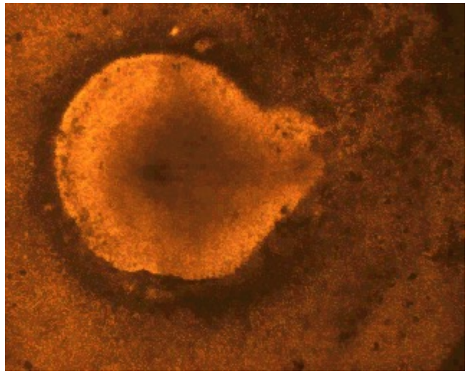
Chemical Potential Response of Cells

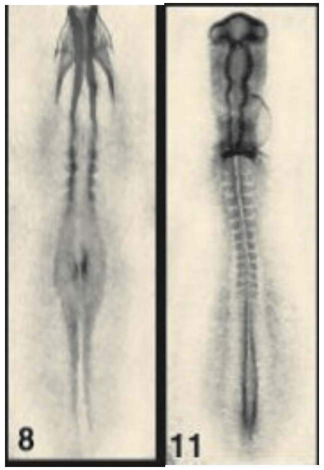
(Constant Pressure –Liquid Like vs Variable Pressue)

Segmentation

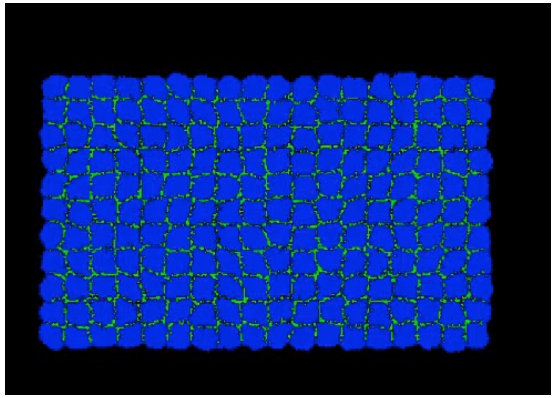
How does the periodic pattern of the vertebrae form in the early embryo?

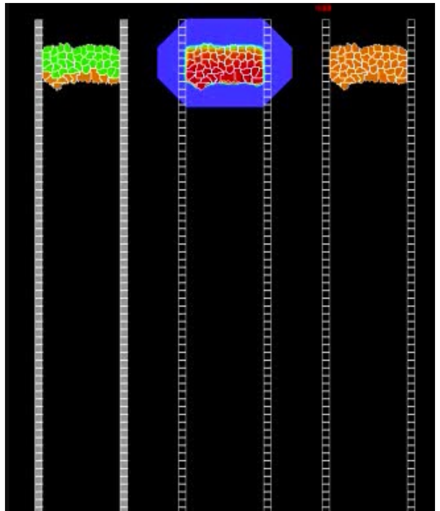






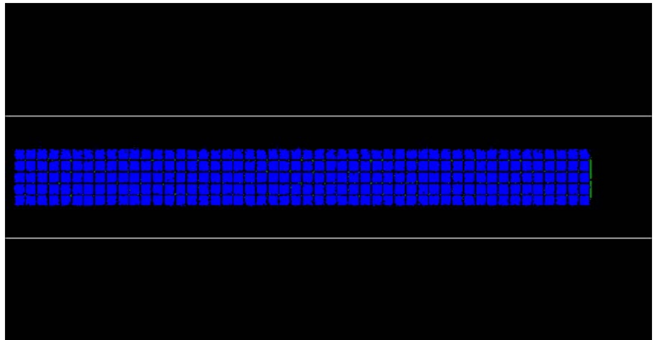
HH staged chick embryos, fixed (Wiley)





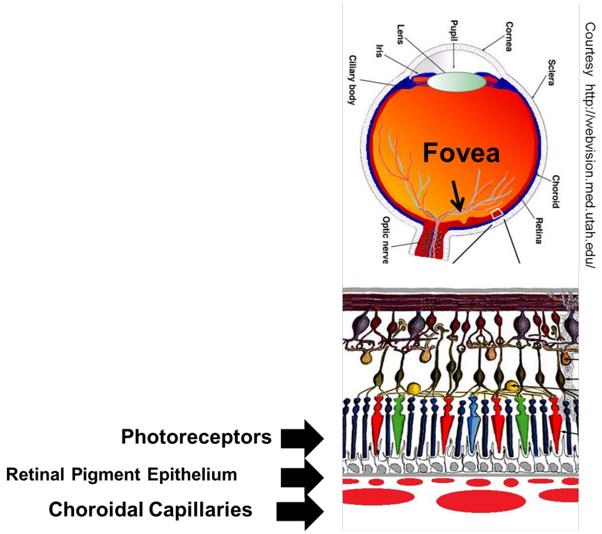
Hester SD, *et al.* (2011). A **Multi-cell, Multi-scale Model of Vertebrate Segmentation and Somite Formation**. *PLoS Comput Biol* **7**, e1002155. doi:10.1371/journal.pcbi.1002155

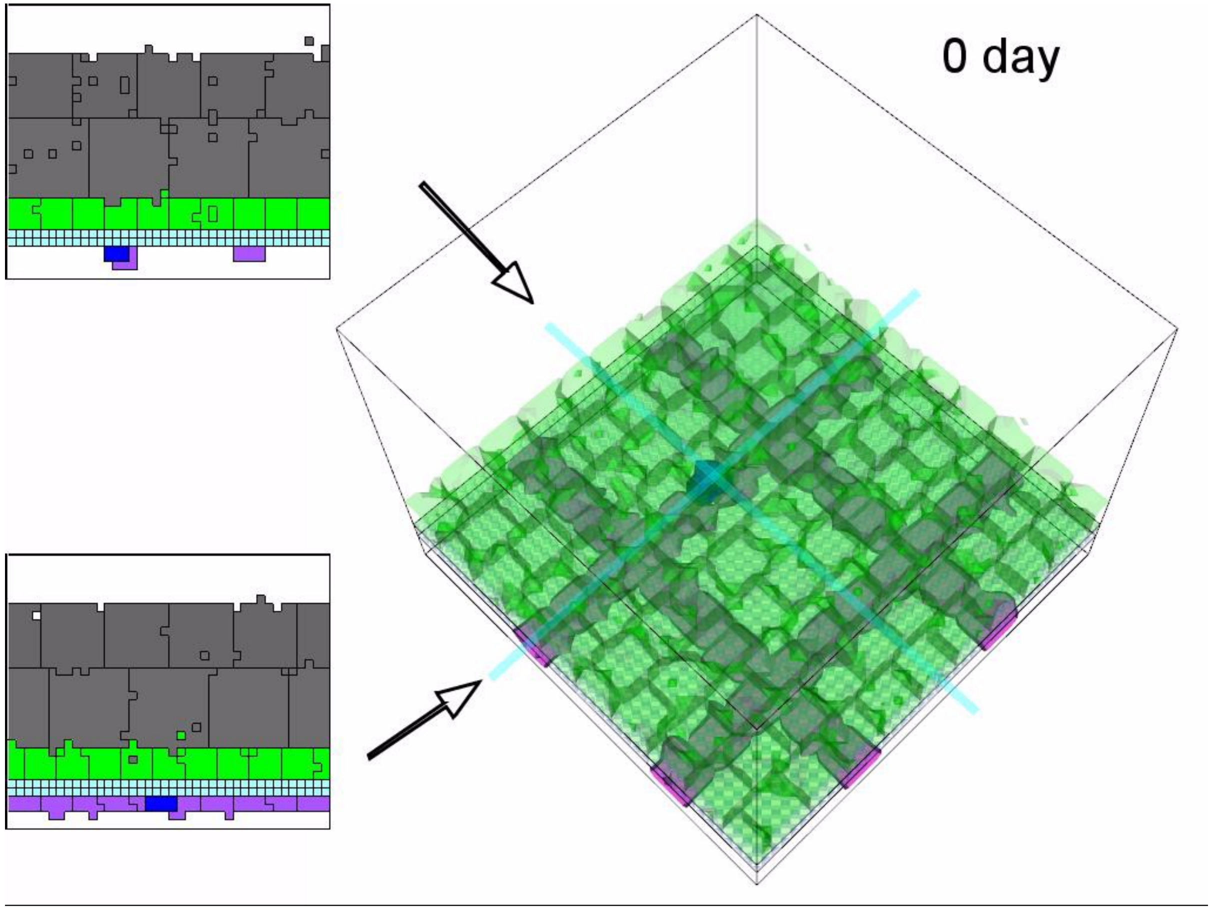
S. Dias AS, *et al.* (2014). **Somites Without a Clock.** *Science* **343**, 791-795.



Why do blood vessels sometimes invade the retina during aging?

Model of Choroidal Neovascularization (CNV) in Wet Aged-Related Macular Degeneration (AMD)

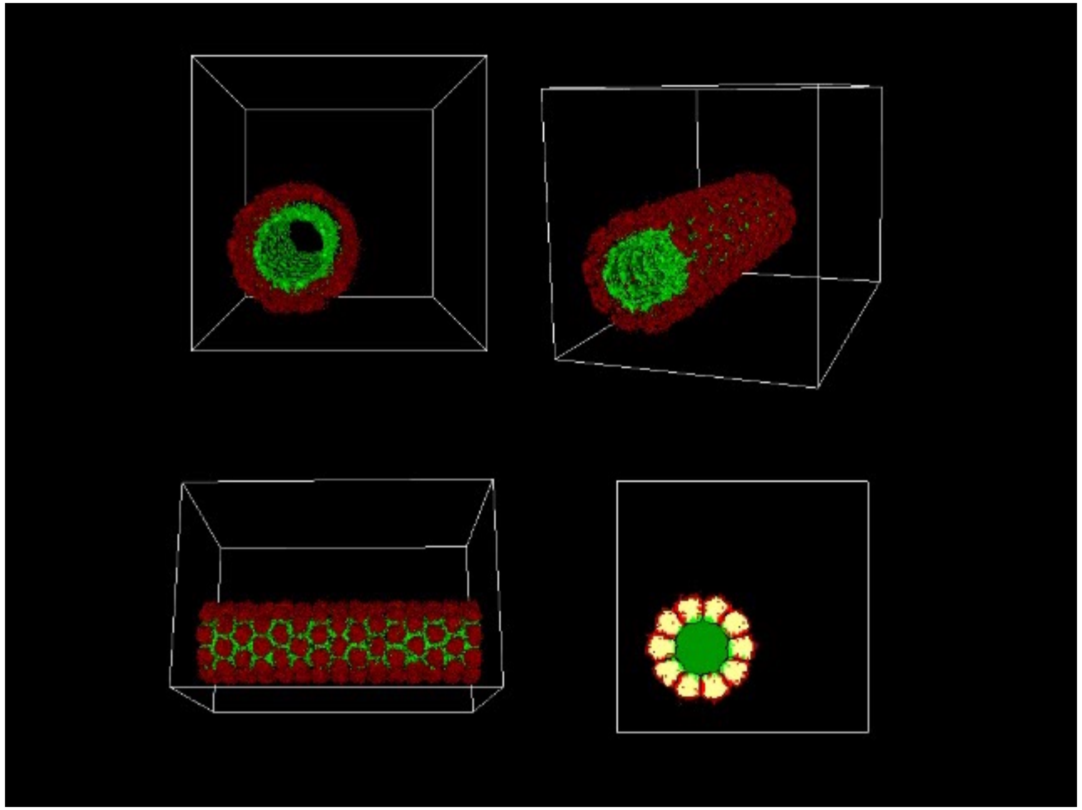




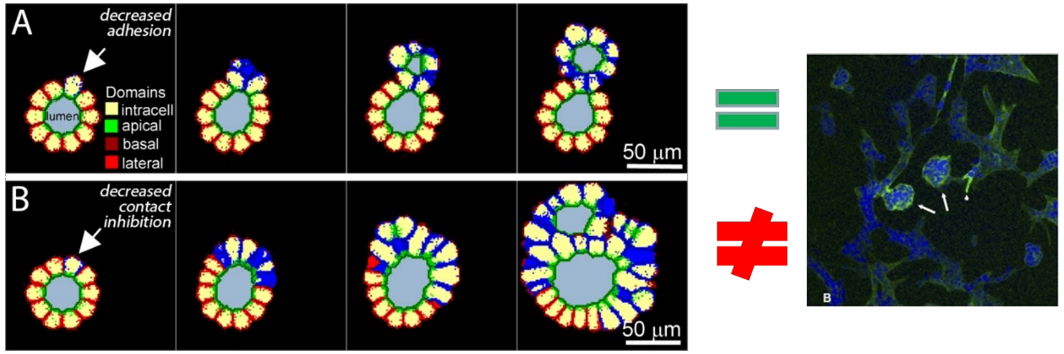
Shirinifard A, Glazier JA, Swat M, Gens JS, Family F, *et al.* (2012) **Adhesion Failures Determine the Pattern of Choroidal Neovascularization in the Eye: A Computer Simulation Study**. *PLoS Comput Biol* **8**: e1002440. doi:10.1371/journal.pcbi.1002440

What causes some people to suffer from uncontrolled and lethal overgrowth of their kidneys?

Model of ADPKD - Autosomal Dominant Polycystic Kidney Disease

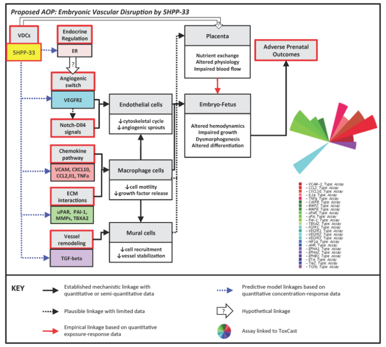


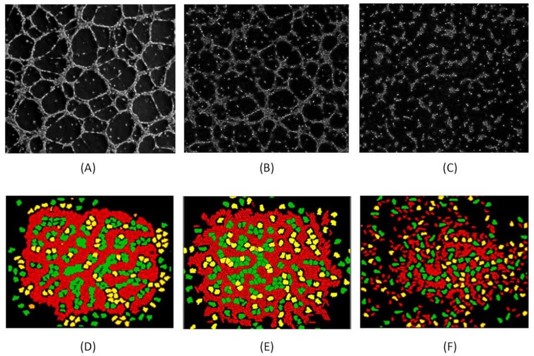
Belmonte JM, Clendenon SG, Oliveira GM, Swat MH, Greene EV, Jeyaraman S, Glazier JA, Bacallao RL, **Virtual-Tissue Computer Simulations Define the Roles of Cell Adhesion and Proliferation in the Onset of Kidney Cystic Disease**, *Molecular Biology of the Cell* (2016), doi: 10.1091/mbc.E16-01- 0059



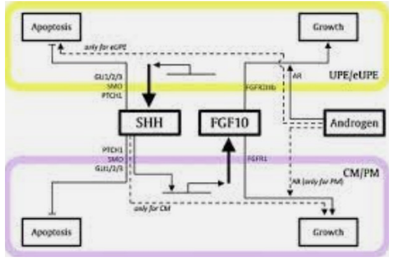
Developmental Toxicology Studies Using CompuCell3D

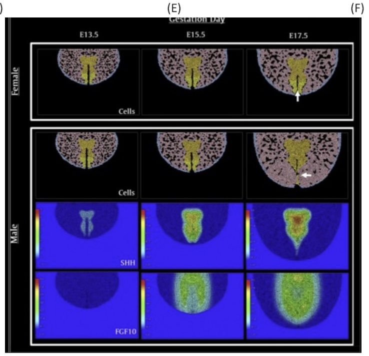
N Kleinstreuer, *et al.*, **A computational model predicting disruption of blood vessel development.** *PLoS computational biology* **9** (2013), e1002996.



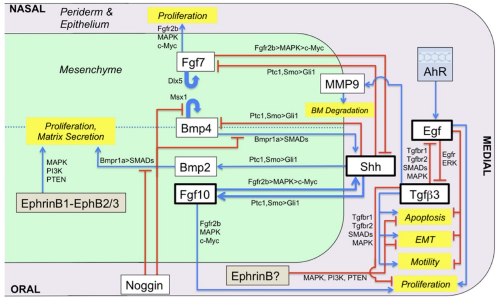


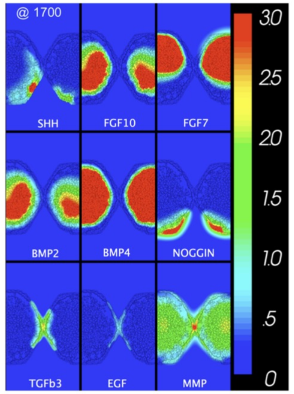
MC Leung, *et al.*, **Computational modeling and simulation of genital tubercle development.** *Reproductive Toxicology* **64**, (2016) 151-161.



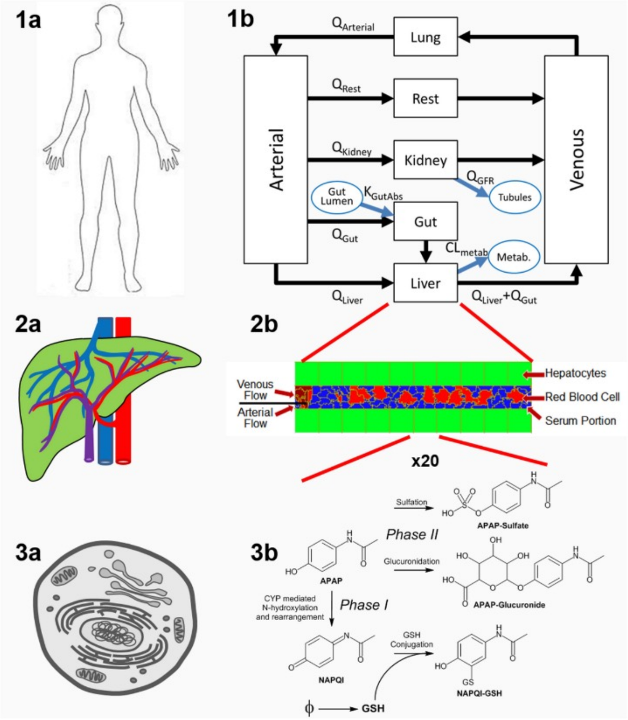


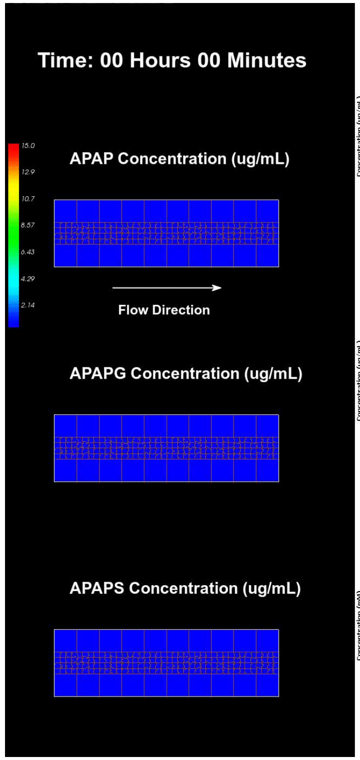
MS Hutson, *et al.*, **Computational Model of Secondary Palate Fusion and Disruption.** *Chemical Research in Toxicology* **30** (2017),965-979, DOI: 10.1021/acs.chemrestox.6b00350

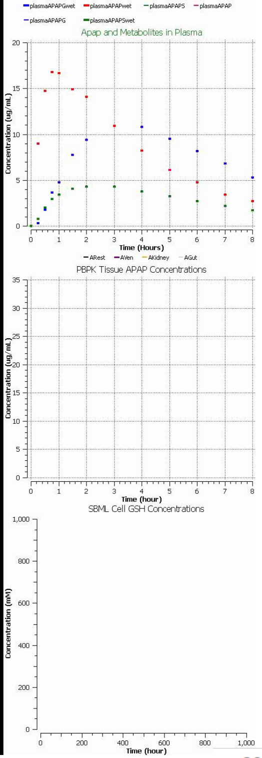




Hepatotoxicity: Simulation of Xenobiotic Uptake, Distribution, Metabolism, Clearance and Damage







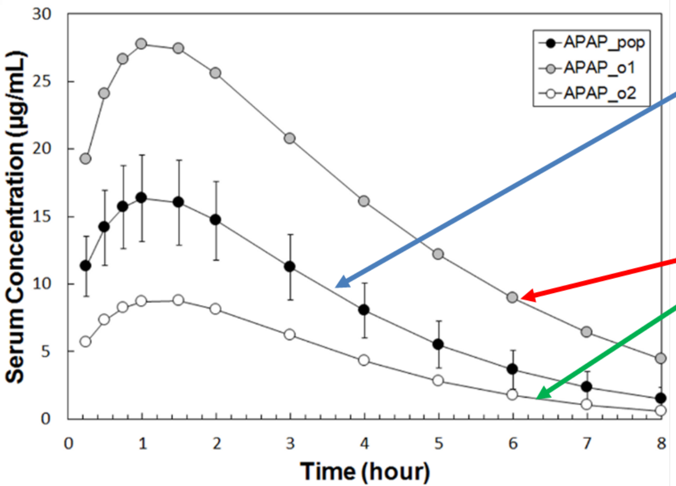
JP Sluka, et al., "A Liver-Centric Multiscale Modeling Framework for Xenobiotics," *PLoS ONE* **11** (2016), e0162428

X Fu, et al., "Modeling of xenobiotic transport and metabolism in virtual hepatic lobule models," *PLoS ONE* **13** (2018), e0198060

KW Dunn, et al., "Mitochondrial depolarization and repolarization in the early stages of acetaminophen hepatotoxicity in mice," *Toxicology* **439**, 152464 (2020)

Validation of the model using human data on serum concentration of acetaminophen and its metabolites

Critchley *et al.* 2005. "Differences in the single-oral-dose pharmacokinetics and urinary excretion of paracetamol and its conjugates between Hong Kong Chinese and Caucasian subjects."



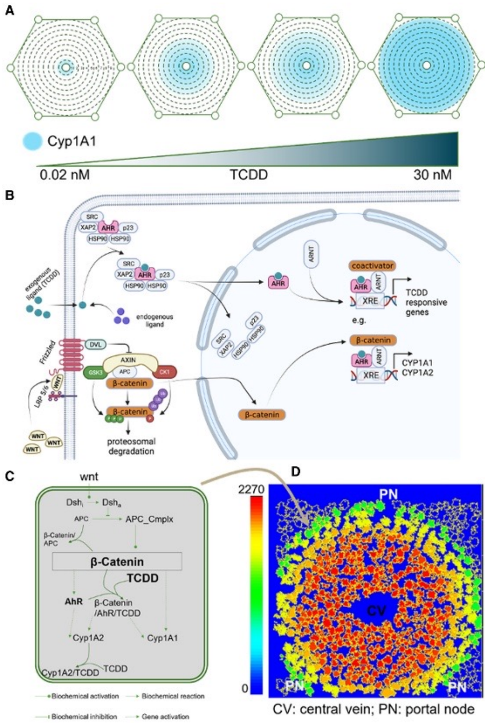
The average population response and its variance agree with clinically measured variability in ADME data for APAP

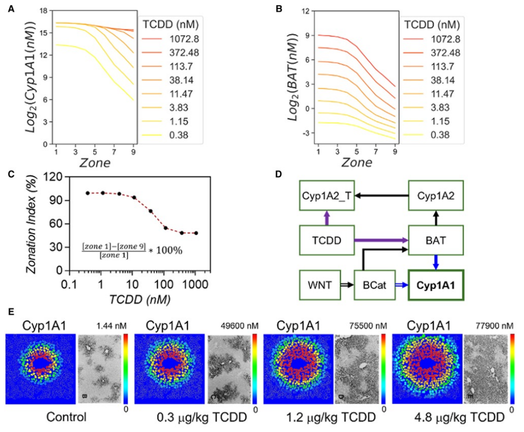
Outliers have greatly different serum concentrations, both higher and lower

Computational Toxicology Studies Using CompuCell3D—Liver Zonation

Y Yang, *et al*., **A Negative Feedback Loop and Transcription Factor Cooperation Regulate Zonal Gene Induction by 2, 3, 7, 8-Tetrachlorodibenzo-p-Dioxin in the Mouse Liver.** *Hepatology communications* **6** (2022) 750-764**.**

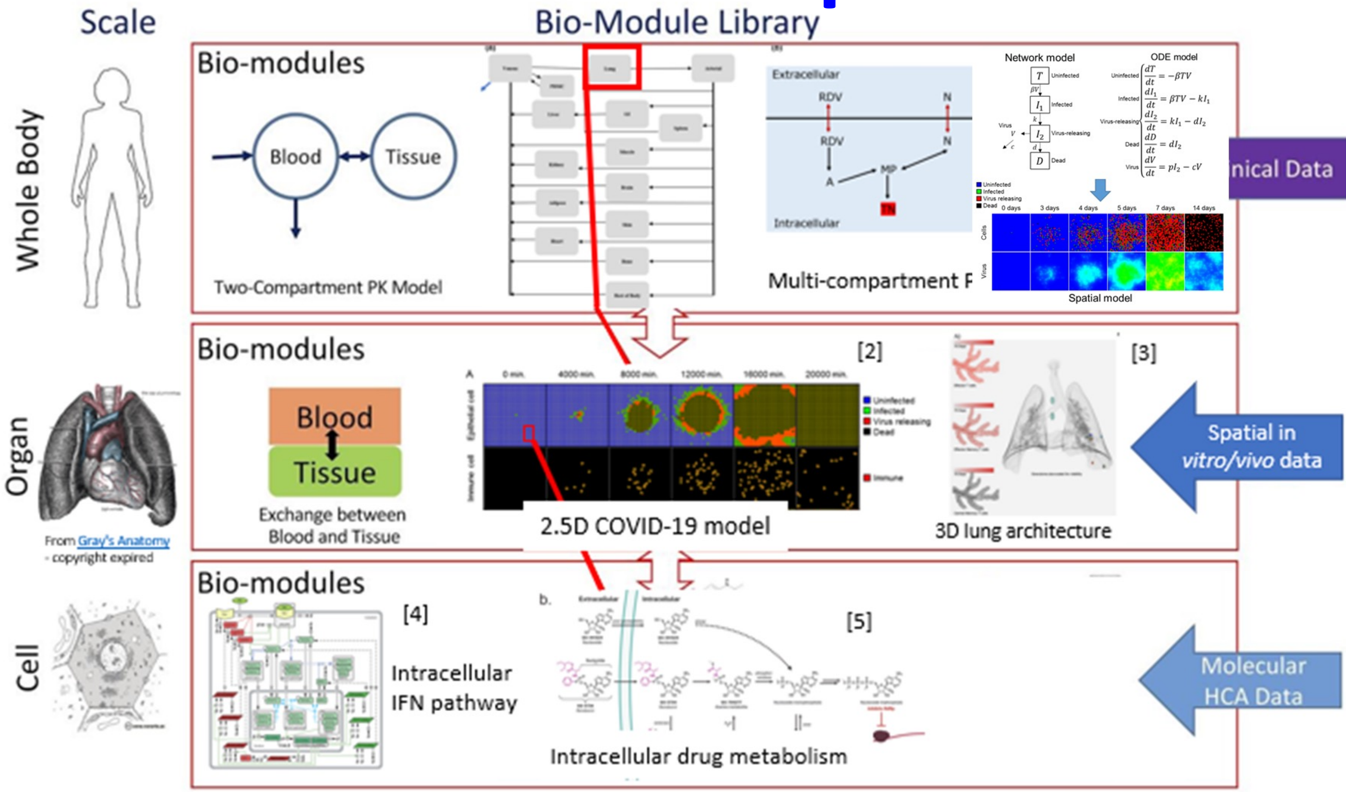
The cytochrome P450 (Cyp) proteins Cyp1A1 and Cyp1A2 are strongly induced in the mouse liver by the potent environmental toxicant 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin (TCDD), acting through the aryl hydrocarbon receptor (AHR). **The induction of Cyp1A1 is localized within the centrilobular regions of the mouse liver at low doses of TCDD, progressing to pan-lobular induction at higher doses.** Even without chemical perturbation, metabolic functions and associated genes are basally zonated in the liver lobule along the central-to-portal axis. To investigate the mechanistic basis of spatially restricted gene induction by TCDD, we have developed a multiscale computational model of the mouse liver lobule with single-cell resolution. **The spatial location of individual hepatocytes in the model was calibrated from previously published high-resolution images. A systems biology model of the network of biochemical signaling pathways underlying Cyp1A1 and Cyp1A2 induction was then incorporated into each hepatocyte in the model. Model simulations showed that a negative feedback loop formed by binding of the induced Cyp1A2 protein to TCDD, together with cooperative gene induction by the β-catenin/AHR/TCDD transcription factor complex and β-catenin, help produce the spatially localized induction pattern of Cyp1A1.** Although endogenous WNT regulates the metabolic zonation of many genes, it was not a driver of zonal Cyp1A1 induction in our model.





Using Agent-Based Models to Explore the Effects of Spatial Heterogeneity on Infection and Immune Response

- Sego, Aponte-Serrano, Gianlupi, Glazier, *BMC Biol.*, 2021
- ODE models well describe many biological phenomena but only tell part of a story
  - *E.g.*, in predator-prey, where are the predators and the prey?
- A complete picture of many biological problems involves modeling processes at multiple scales
  - *E.g.*, from subgenomic viral replication to population dynamics
- Cellularization: relating spatiotemporal, multicellular models to non-spatial ODE models
- ABMs can improve clinical application of drugs by exploring the multicellular scale and heterogeneity among cells



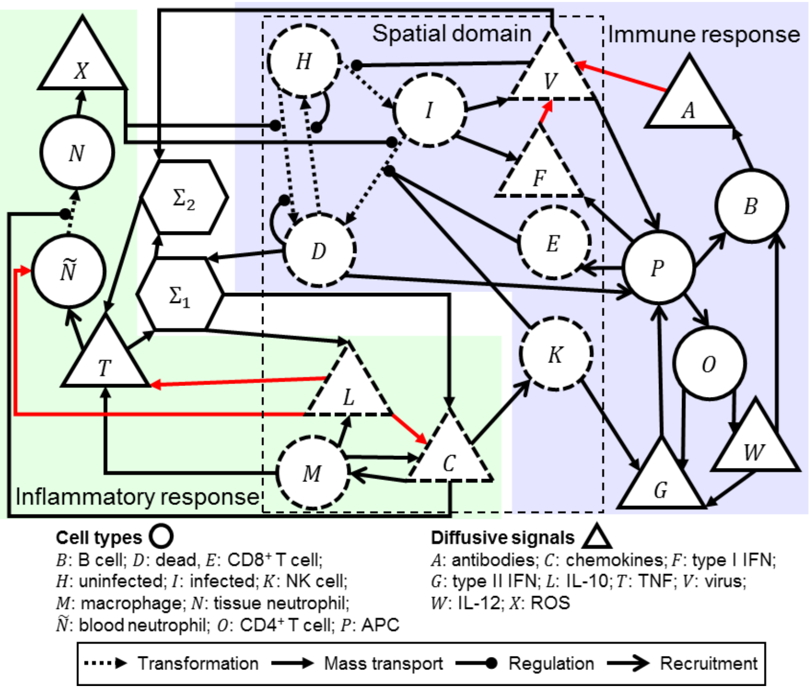
T. J. Sego, …. "Generation of multicellular spatiotemporal models of population dynamics from ordinary differential equations, with applications in viral infection." *BMC biology* **19** (2021): 1-24.

T. J. Sego, …. "A multiscale multicellular spatiotemporal model of local influenza infection and immune response." *JTVB* **532** (2022): 110918.

J Ferrari Gianlupi, T…. "Multiscale Model of Antiviral Timing, Potency, and Heterogeneity Effects on an Epithelial Tissue Patch Infected by SARS-CoV-2." *Viruses* **14** (2022): 605.

Constructing an Immune Response Model Based on a Validated Network Model of Influenza

- Sego, Mochan, Ermentrout, Glazier. *J. Theor. Biol.*, 2022
- Cell types
  - Antigen-presenting cell, B cell, $CD4^+$ and $CD8^+$ T cell, epithelial, macrophage, natural killer, blood and tissue neutrophils
- Species
  - Antibodies, chemokines, types I and II interferons, interleukins 10 and 12, tumor necrosis factor, reactive oxygen, virus



Schematic of cellularized influenza model.

$$
\begin{aligned}
\frac{d\tilde{N}}{dt} &= \frac{b_{nt}T}{a_{nt}+a_{nl}L+T} - \frac{g_{nc}\tilde{N}C}{C+a_{nc}} - \mu_n\tilde{N} \\
\frac{dN}{dt} &= \frac{g_{nc}\tilde{N}C}{C+a_{nc}} - \mu_n N \\
\frac{dM}{dt} &= \frac{b_{mc}C^{h_m}}{C^{h_m}+a_{mc}^{h_m}} - \mu_m(M-b_m) \\
\frac{dL}{dt} &= \frac{b_l M\Sigma_1}{\Sigma_1+\frac{g_1L+g_2}{L+d_2}} - \mu_l(L-b_{lh}(1-R)H) \\
\frac{dT}{dt} &= \frac{b_t M\Sigma_2}{\Sigma_2+\left(\Sigma_2+\frac{g_1L+g_2}{L+d_2}\right)\left(\frac{k_2+Lk_1}{L+d_1}\right)} - \mu_t T \\
\frac{dX}{dt} &= \frac{b_{xn}N}{N+a_{xn}} - g_{xi}IX - g_{xh}HX - \mu_x X \\
\frac{dA}{dt} &= b_a + b_{ab}B - g_{av}AV - \mu_a A \\
\frac{dC}{dt} &= \frac{b_c M\Sigma_1}{\Sigma_1+\frac{g_1L+g_2}{L+d_2}} - \mu_c C \\
\frac{dI}{dt} &= g_{hv}VH - \frac{g_{ix}IX^{h_x}}{X^{h_x}+a_{ix}^{h_x}} - g_{ik}RIK - g_{Ie}RIE - \mu_i(1-R)I \\
\frac{dH}{dt} &= \frac{b_h(1-R)HD(H-\theta)}{\text{total cells}} - g_{hv}VH - \frac{g_{hx}HX^{h_x}}{X^{h_x}+a_{hx}^{h_x}} \\
\frac{dF}{dt} &= b_{fi}(1-R)I + b_{fp}P - g_{fi}IF - \mu_f F \\
\frac{dV}{dt} &= g_{vi}(1-R)I - g_{vh}HV - g_{va}VA - \frac{g_v V}{1+a_v V} - \mu_v V
\end{aligned}
$$

$$
\begin{aligned}
\frac{dDH}{dt} &= \frac{g_{hx}HX^{h_x}}{X^{h_x}+a_{hx}^{h_x}} - \frac{b_h(1-R)HDH(H-\theta)}{\text{total cells}} \\
\frac{dE}{dt} &= \frac{b_{ep}P^{h_e}}{P^{h_e}+a_{ep}^{h_e}} - b_{ei}RIE - \mu_e E \\
\frac{dB}{dt} &= b_b + b_{bp}WP(b_0-B) - \mu_b B \\
\frac{dK}{dt} &= \frac{b_{kc}C^{h_k}}{C^{h_k}+a_{kc}^{h_k}} - g_{ki}RIK - \mu_k(K-b_k) \\
\frac{dP}{dt} &= p_0\left(\frac{g_{pv}V}{(a_{pv}+V)} + g_{pi}DI\right)\left(g_p+\frac{b_{pg}G}{a_{pg}+G}\right) - \mu_p(P-b_p) \\
\frac{dW}{dt} &= \frac{b_{wo}O}{(a_{wo}+O)}P - \mu_w W \\
\frac{dG}{dt} &= \frac{b_{go}W}{a_{go}+W}O + \frac{b_{gk}W}{a_{gk}+W}K - \mu_g G \\
\frac{dO}{dt} &= \frac{b_{op}P^{h_o}}{P^{h_o}+a_{op}^{h_o}} - \mu_o O
\end{aligned}
$$

$$D = \text{total cells} - H - I$$

$$\Sigma_1 = a_{11}T + a_{12}D$$

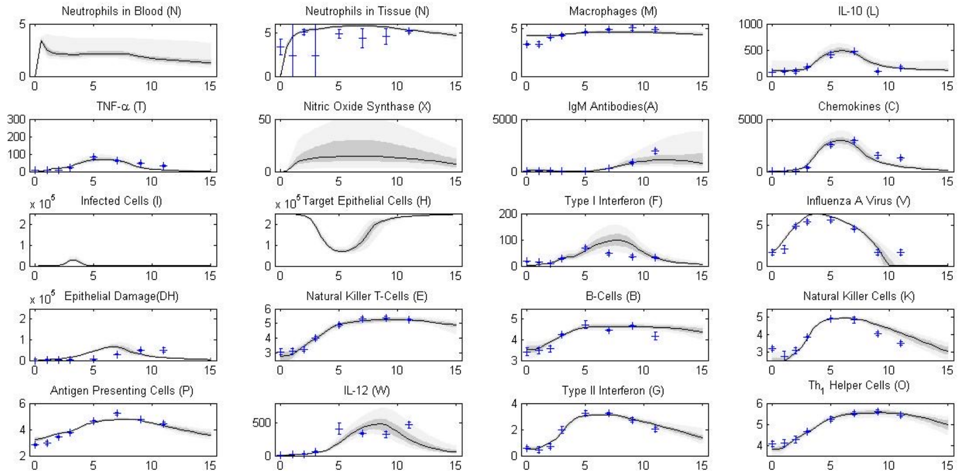
$$\Sigma_2 = \Sigma_1 + \frac{a_{21}V}{a_{22}+V}$$

$$DI = \text{total cells} - H - I - DH$$

$$R = \frac{F}{a_{rf}+F}$$

Price, Mochan et. al, J Theor. Biol., 2015

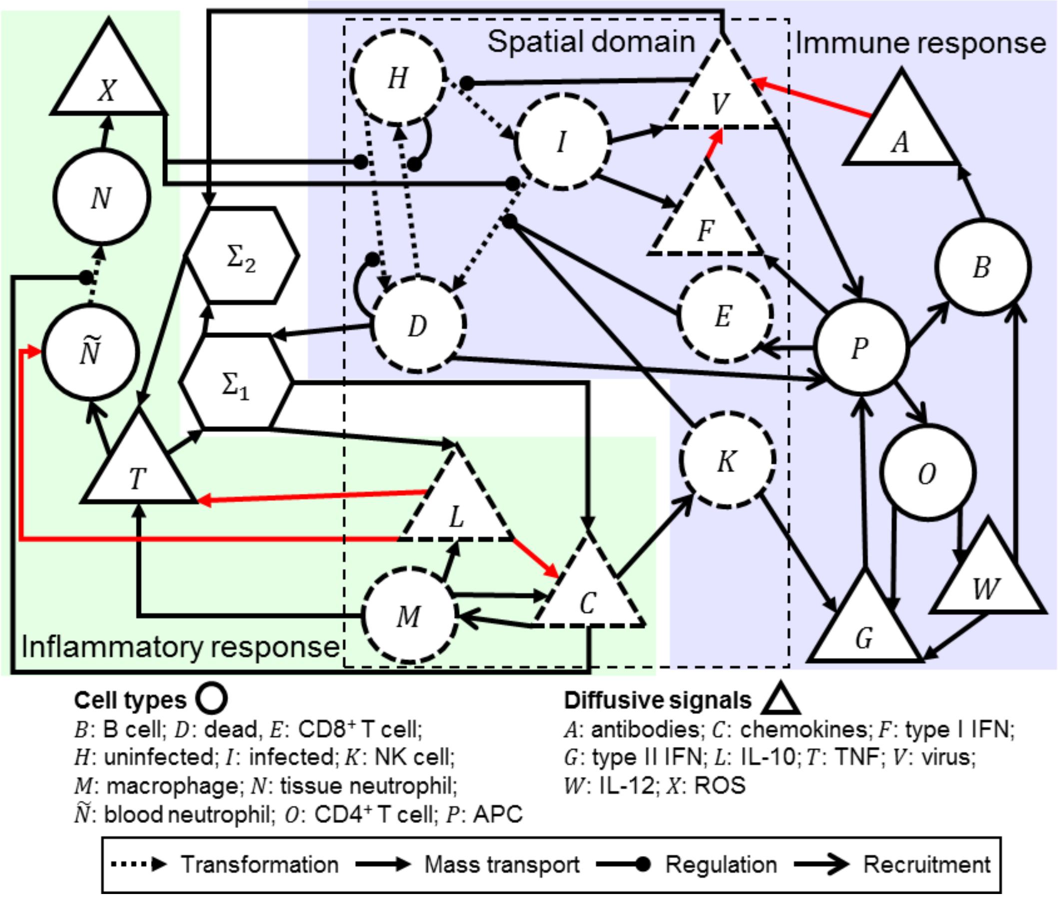
Experimental Validation of Network Model



Price, Mochan et. al, J Theor. Biol., 2015

Influenza Model Overview

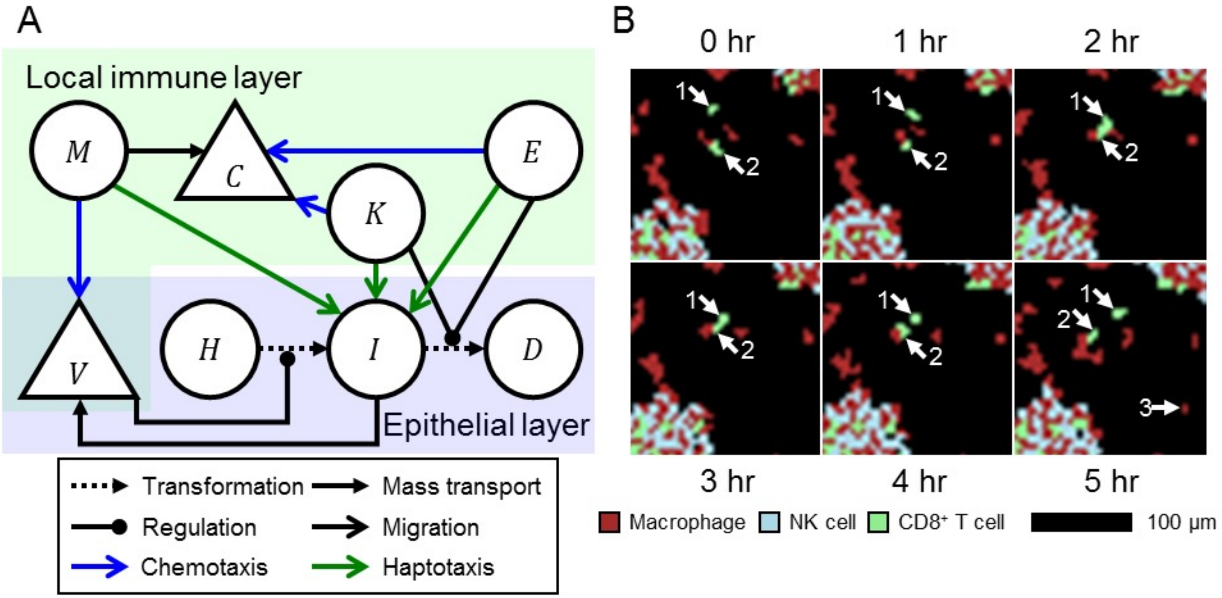
- Spatial model: local site of infection
- Spatial cell types:
  - CD8$^+$ T cell, epithelial, macrophage, NK cell
- Spatial species:
  - Chemokines, type I IFN, IL-10, virus
  - Assumed homogeneous: antibodies, ROS
- Organism-level cell types:
  - APC, B cell, CD4$^+$ T cell, blood and tissue neutrophil
- Organism-level species:
  - Type II IFN, TNF, IL-12

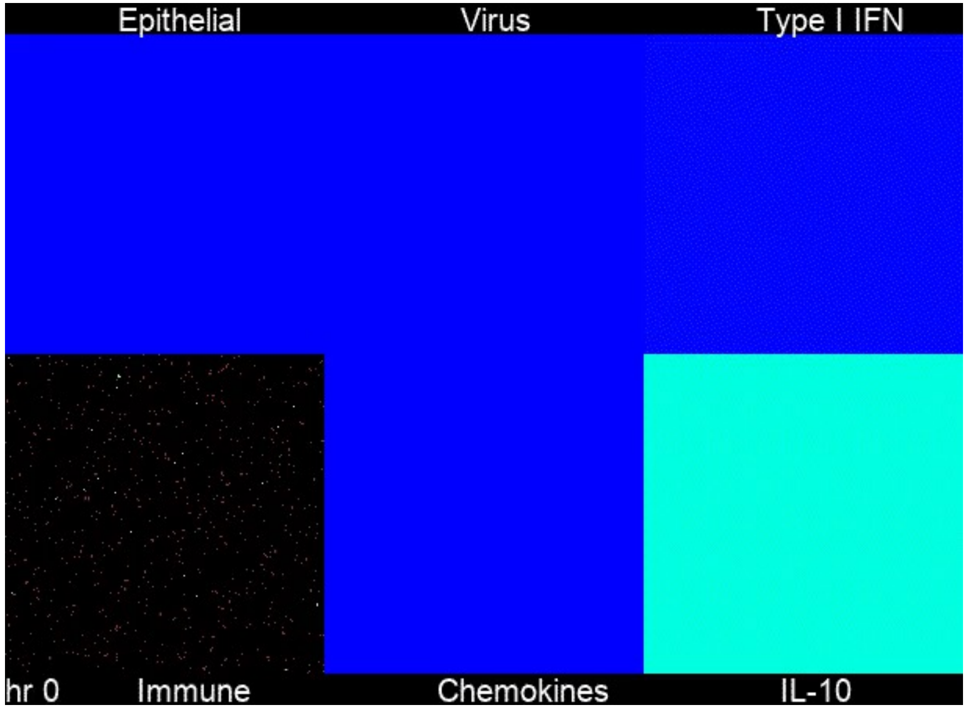


Introducing Cell Locomotion Absent in Homogeneous Model

- Non-spatial model: NK and CD8$^+$ T cells kills by virtue of existing
- NK and CD8$^+$ T cells kill by contact-mediated interactions
- Macrophages phagocytose virus and release inflammatory recruitment signals

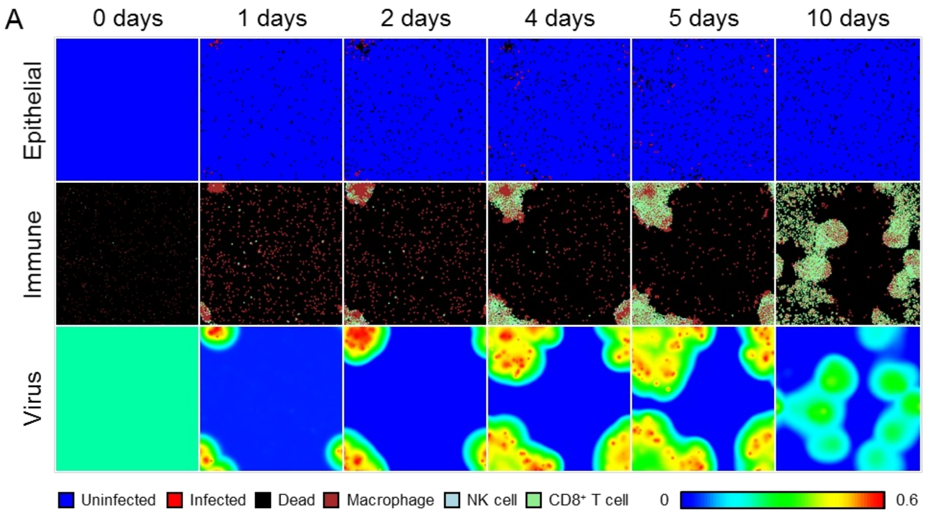
- Chemotaxis
  - Infected cells release virus: recruits macrophages
  - Macrophages release chemokines: recruits NK and CD8$^+$ T cells
- Haptotaxis
  - Infected cell targeting: preferential attachment of immune cells to infected cells
  - Prevent excessive aggregation: preferential attachment of heterotypic immune cell contacts

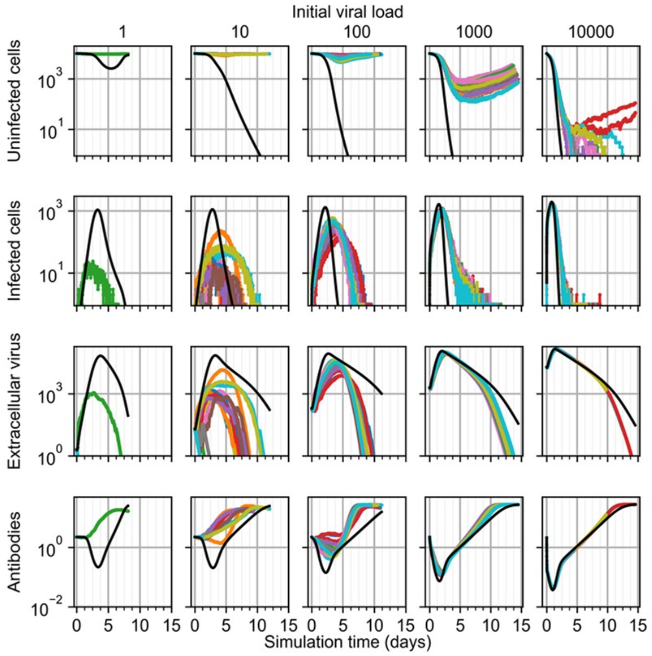




Disagreement Between Non-spatial and Spatial Models

- Published scenario of calibrated non-spatial model: initial viral exposure and lethal outcome
- Spatial implementation: uniform non-zero initial virus
- **Spatial model predicts less spread of infection and more recovery compared to Homogeneous Model for equivalent parameters**
- **Only recover ODE result for very high MOI and high diffusion constants**

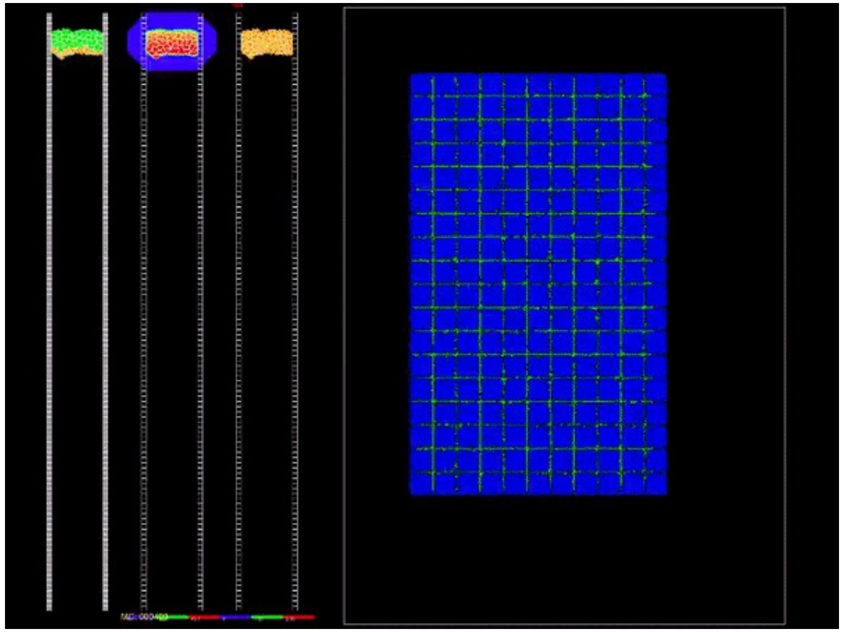




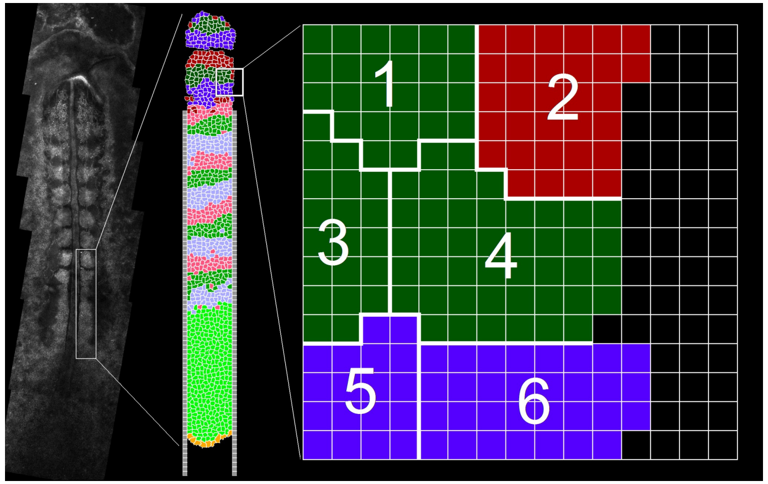
CompuCell3D Simulation Environment

Potts-based multicellular simulation

- Cell-based, stochastic, multicellular modeling (Cellular Potts Model)
- Open source, simulations can be proprietary
- Allows researchers to develop models themselves without requiring excessive computational expertise
- Recent improvements making CC3D more usable in cluster/HPC contexts and making it Python callable so it can be integrated into optimization or sensitivity analysis workflows
- Can call other (Python) packages from
- On-line web-based execution at https://nanohub.org/tools/cc3dbase4x
- Download at https://compucell3d.org/



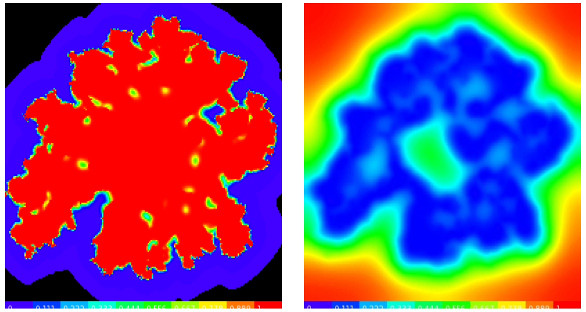
CC3D simulation of somitogenesis



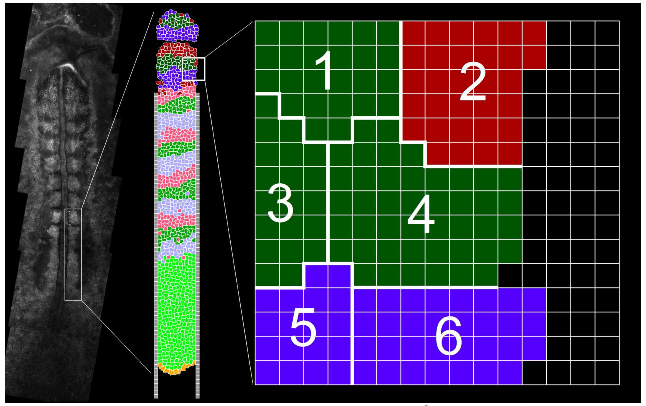
github.com/CompuCell3D/ CompuCell3D

CompuCell3D Supported Concepts

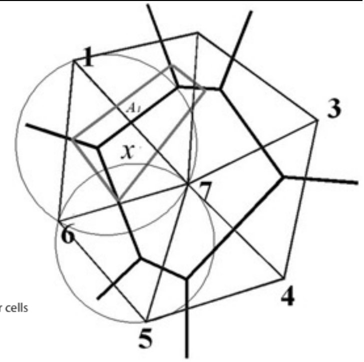
Objects: Fields, Generalized Cells, Links, Networks



Fields:
Properties: Concentration, Diffusion Constants, Decay Constants
Behaviors: Diffusion, Decay,
Interactions: Reaction, Secretion, Absorption, Advection

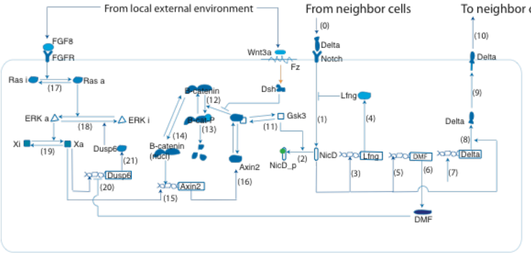


Generalized Cells:
Properties: Volume, Polarity, Surface Area, Inertia, Density, Viscosity, Elasticity, Plasticity, Substructure, Adjacency
Behaviors: Motility, Growth, Division, Death
Interactions: Adhesion, Chemotaxis, Differentiation, Secretion, Absorption



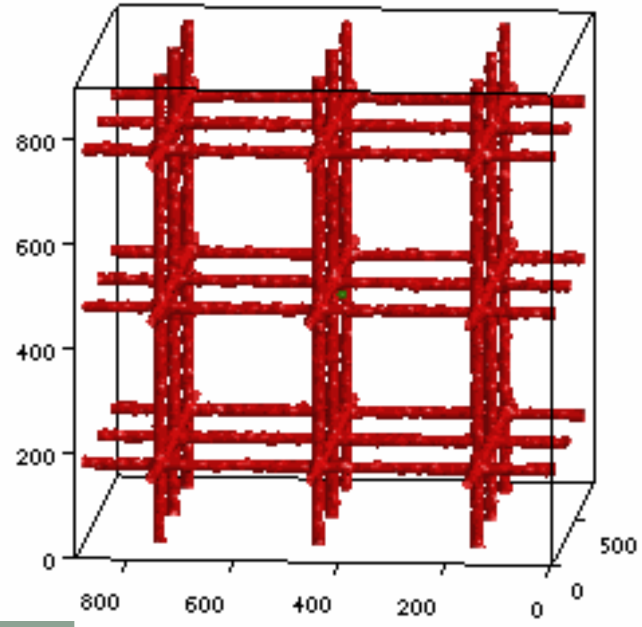
Links:
Properties: Length, Target Length, Elastic Modulus, Yield Strain, Target Angles, Bending Moduli
Behaviors: Creation, Destruction, Change of Target Length
Interactions: Exert Forces on Cells, Pulled on By Cells

Dynamic Networks:
Properties: Values
Behaviors: ODEs, Stochastic Evolution
Interactions: Activation, Inhibition, Reaction, Decay



Virtual Tissue Modeling with CompuCell3D

- CompuCell3D has been used for dozens of applications over the last two decades
  - Somitogenesis
  - Tumor progression
  - Polycystic kidney disease
  - Host-pathogen interactions during viral infection



CC3D simulation of tumor growth and angiogenesis

CompuCell3D

Home
- CC3D Home

Download
- Binaries
- Source Code
- Developer Zone

Help
- Manuals
- Problems?
- CC3D User Forum
- Tutorials
- Training Videos
- F.A.Q.

Demos
- Web Demos (no installation required)
- Model Repository
  - Covid19 on nanoHUB
- Visual Examples

Welcome to CompuCell3D

NEW CC3D Version 4.3.0 (Apr 14 2022)

We are pleased to announce new version 4.3.0 of our software CompuCell3D. This release includes multiple bug fixes and new features. For more info, and to download the latest version, visit the Downloads page.

Improvements and new features

- New, conda-based packaging
- Integrated miniconda - gives users access to the entire Python ecosystem
- One-click configuration for DeveloperZone - enables users to quickly develop C++ plugins and steppables (updated Developers Manual coming soon)
- Integrated C/C++ compilers (Linux, OSX)
- Much easier future upgrades
- Added support for cell link inventory lists in Python
- Added support for relocatability and builds with cc3d as a dependency
- Split code into 3 separate packages - cc3d-core, Player, Twedit
- cc3d core code released under MIT license
- Multiple bug fixes

A **thirtieth anniversary**! Back on March 16th, 1992, François Graner and James Glazier submitted our very first paper on the Cellular Potts Model/Glazier-Graner-Hogeweg model to Physical Review Letters. We had no idea at that point that the method would still be used today and would be implanted in a dozen different modeling frameworks. As of today, that original paper (which appeared on September 28th, 1992) **has been cited more than 1350 times.**
https://journals.aps.org/prl/abstract/10.1103/PhysRevLett.69.2013

VOLUME 69, NUMBER 13 PHYSICAL REVIEW LETTERS 28 SEPTEMBER 1992

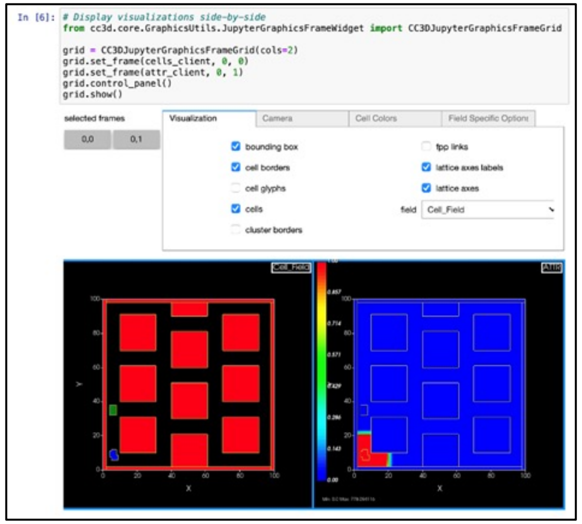
Simulation of Biological Cell Sorting Using a Two-Dimensional Extended Potts Model

François Graner and James A. Glazier[a]

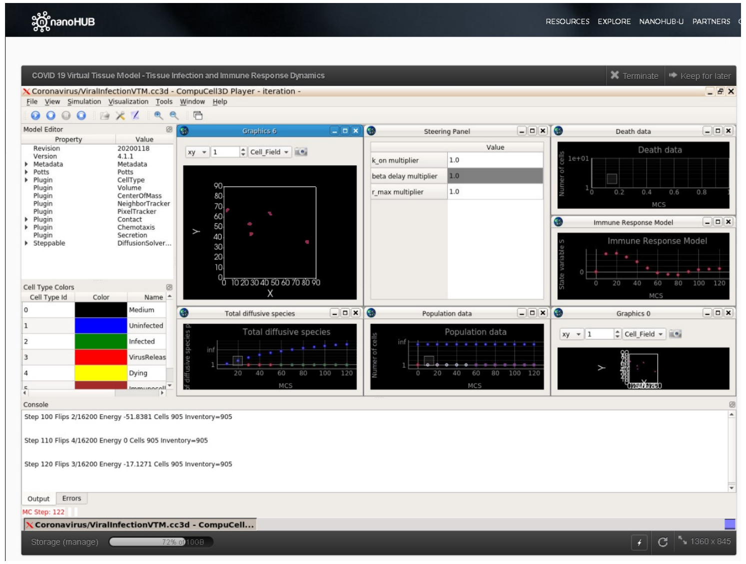
compucell3d.org

Computational performance + Rapid, intuitive, shareable model specification

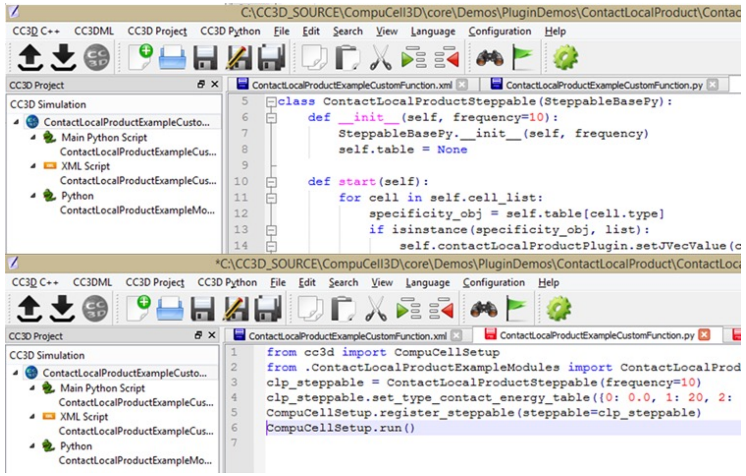
- Model specification
  - Declarative (built-in) + procedural (custom)
  - XML, Python and XML, or all Python (Jupyter)
- Player: interactive execution with real-time rendering
- Twedit++: editor with tools for model development



CC3D in a Jupyter Notebook
(Chung, J. App. Technol. Edu. Sci., 2023)



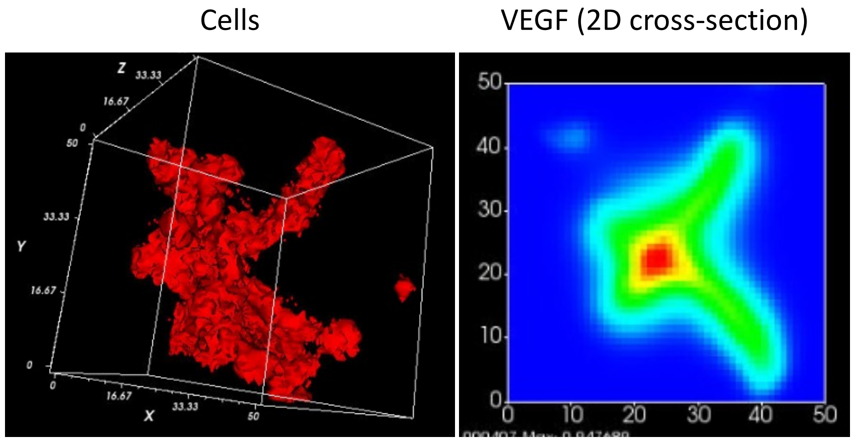
Player: CC3D interactive simulation execution on nanoHUB



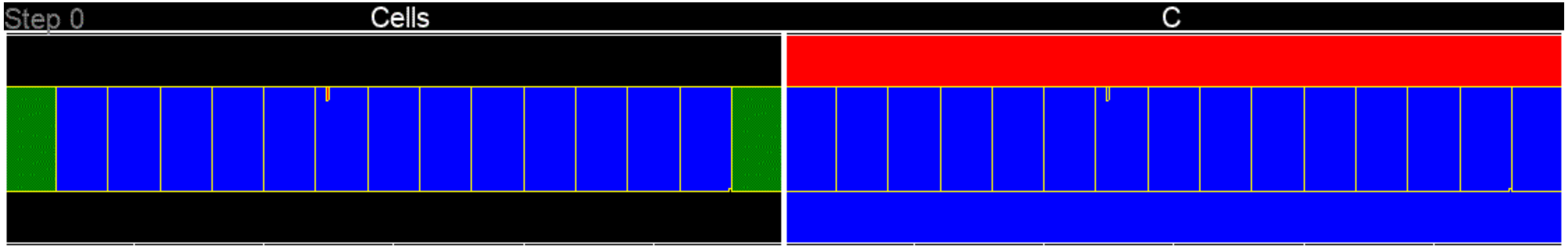
Twedit++: CC3D model editor

In-house PDE solver suite

- String specification of field interactions
- Uptake and release by cell
- Diffusivity and decay by cell phenotype
- Built-in stability and automatic time-stepping
- New Finite-Volume solver and improved FE solvers



Angiogenesis simulation

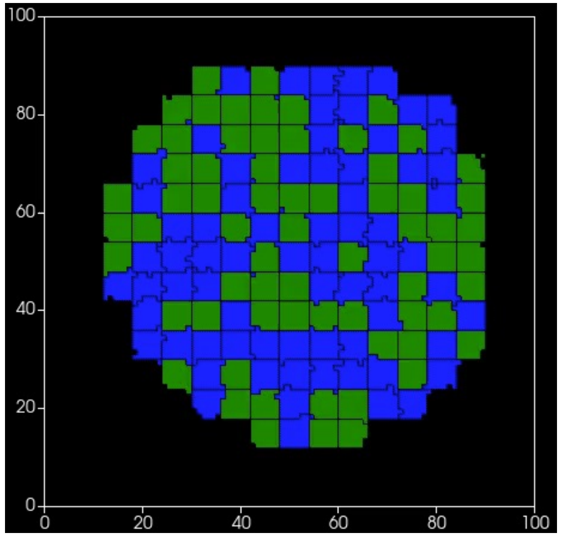


Transcytosis simulation with new transport modeling capabilities in CC3D

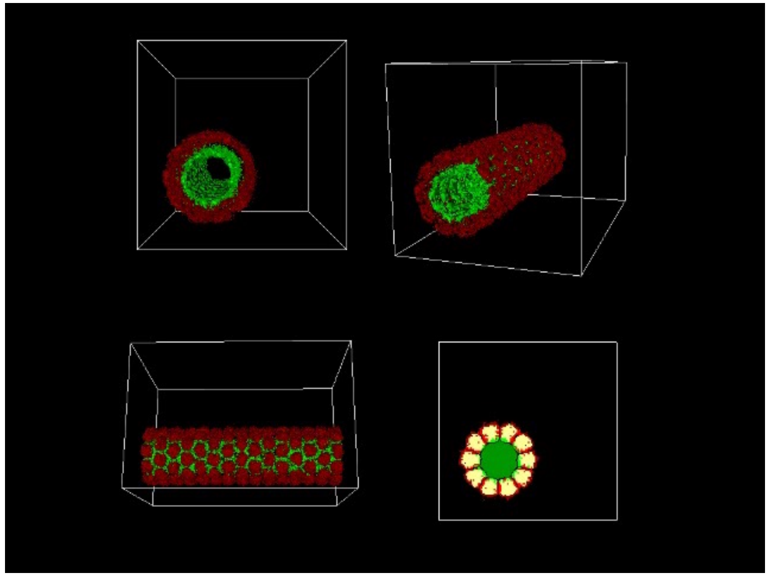
Lots of plugins modeling biological/physical processes!

- Cell volume, surface area, shape constraints
- Phenotype- and molecule-specific adhesion (*e.g.*, modeling N-cadherin)
- Compartmental cells (*e.g.*, modeling organelles)
- Complete list: www.compucell3d.org

- **CC3D designed so you can add new mechanisms and functionality to the core codebase (improved support for user-developed C++ functionality)**

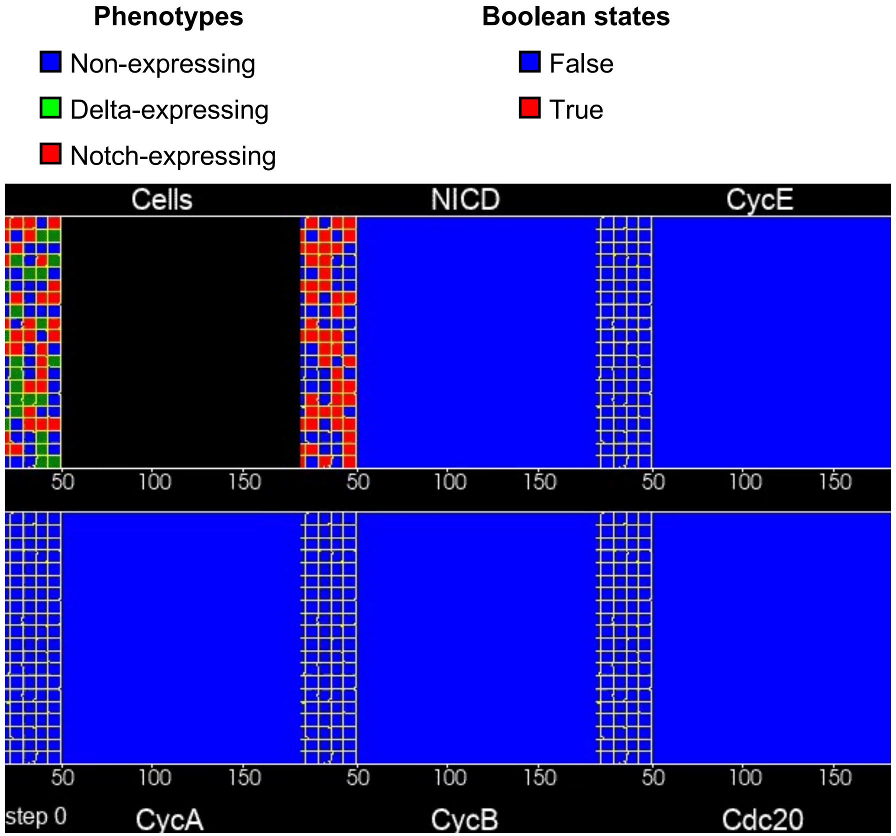


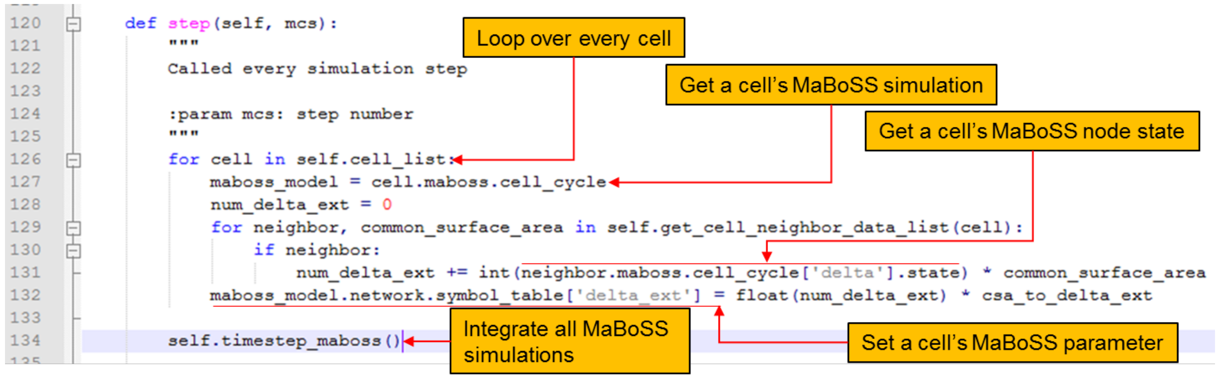
CC3D simulation of cell sorting


CC3D simulation of polycystic kidney disease

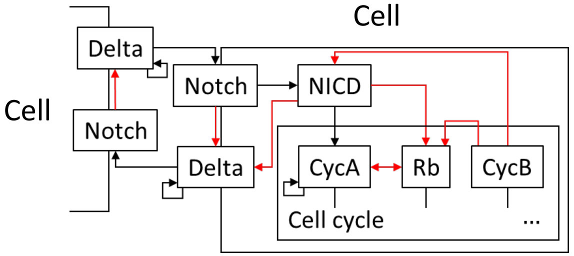
Concurrent multiscale multimethod modeling and interactive simulation

- ODE model specification with Antimony, CellML and SBML
- Boolean network model specification with MaBoSS (New)
- Supports attaching models to individual cells (*e.g.*, intracellular processes) and simulation domains (*e.g.*, systemic processes)





Sample code of MaBoSS in CompuCell3D

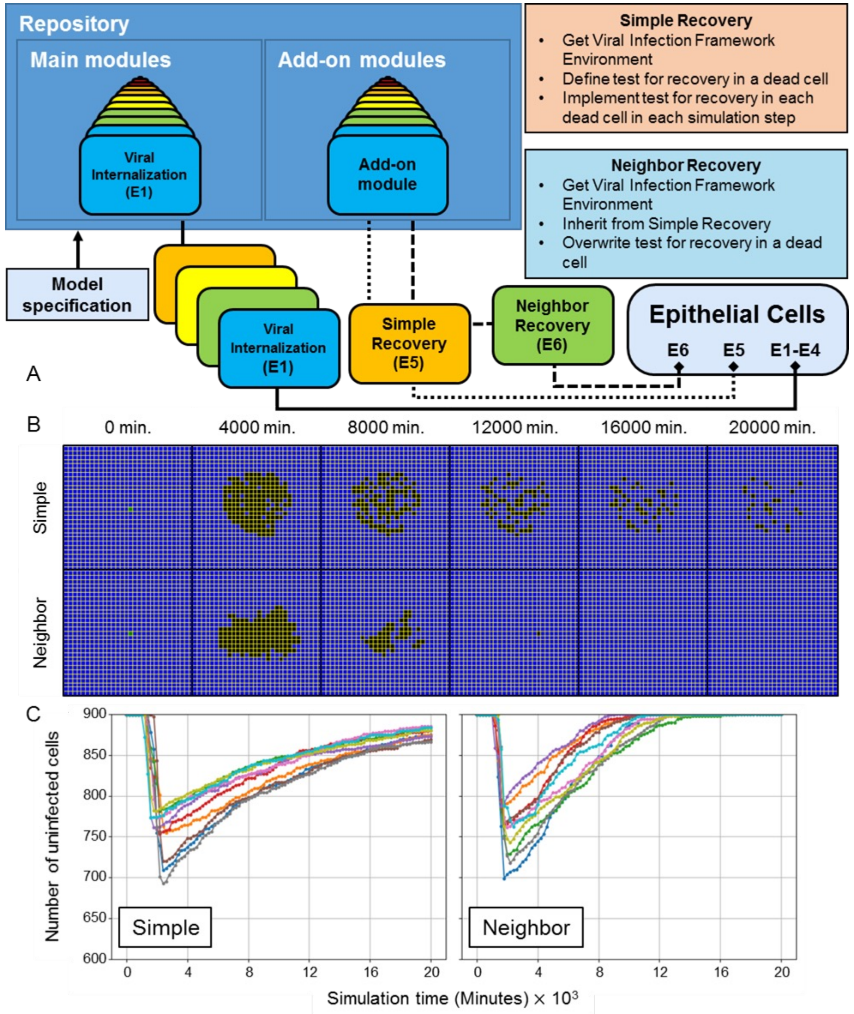


Network coupling cell cycle and delta-notch signaling

Collaborative, Concurrent Model Development (New Component Architecture)

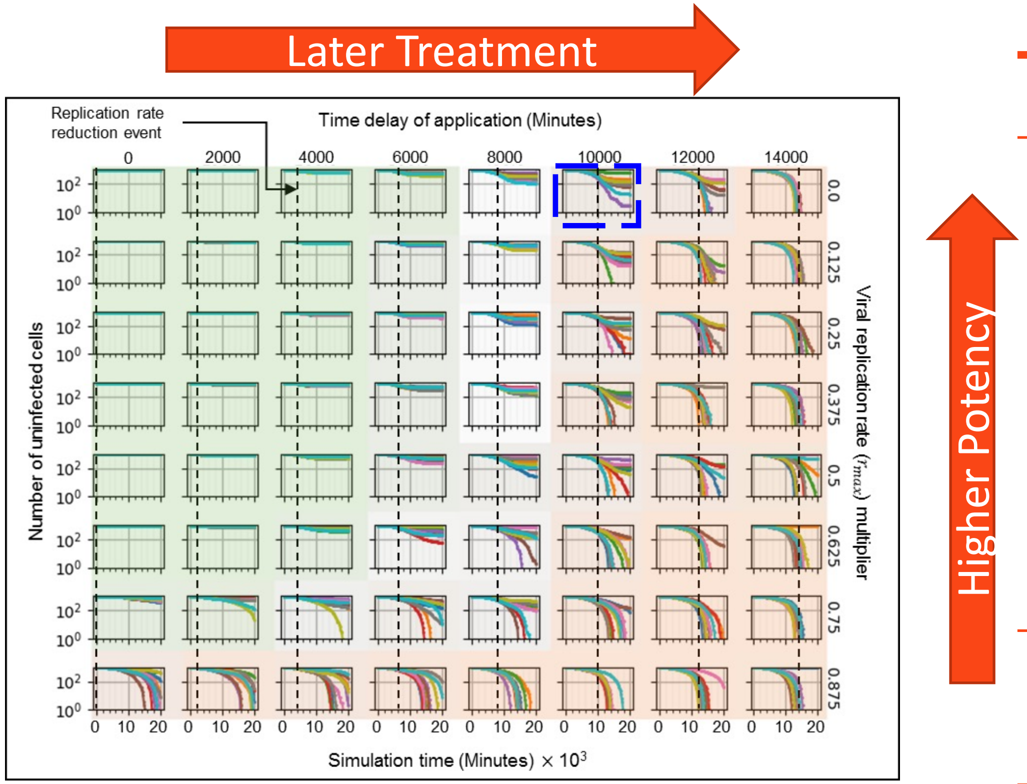
- Simulation framework is designed with *interchangeable*, *shareable*, and *extensible* model modules (architecture like the Python programming language)
- Simulation specification: load a set of model modules
- Built-in support for seamlessly downloading, adding, using and uploading add-on model modules
- Architecture prevents collision during concurrent development
- Framework and library are maintained on GitHub: collaborative public development

```python
from Models.RecoveryNeighbor.RecoverySteppables import NeighborRecoveryDataSteppable

CompuCellSetup.register_steppable(steppable=NeighborRecoveryDataSteppable(frequency=1))

CompuCellSetup.run()
```



Advanced/Integrated Applications (New Chaining of CC3D Simulations, Python Callability and Workflow Integration)

- Cluster execution
- CC3D Python API (*e.g.*, model calibration using PyTorch, integrated applications)
- CC3D Simulation as a Service
    - Live CC3D simulations as interactive, memory-safe Python objects
    - Interacting, multi-site simulations
    - Integrated applications
    - Jupyter support



Massively parallel execution of viral infection and therapy

Flexible and It Works…

2023

1. "Cell Modeling in Jupyter Notebook using CompuCell3D" Trinity Chung, T.J. Sego, James A. Glazier. Journal of Advanced Technological Education (J ATE), Vol. 2, Issue 1, Jan. 30, 2023. DOI:10.5281/zenodo.7600786..

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https://compucell3d.org/Publications

Tissue Forge

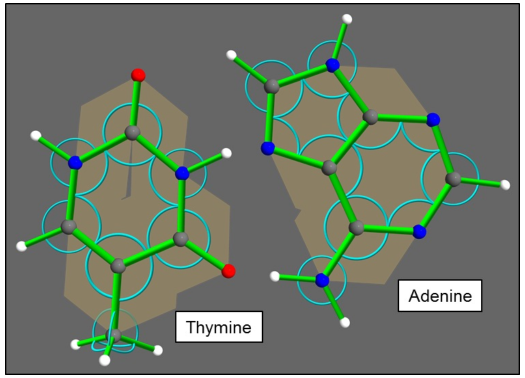
A new Python-scriptable modeling environment for large, multiscale Virtual-Tissue models using center-model and vertex model formalism

Original code developed by Dr. Endre Somogyi, current code developed by Prof. TJ Sego, University of Florida

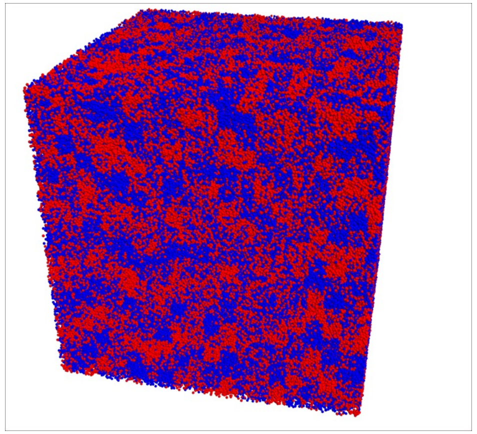
Tissue Forge Simulation Environment

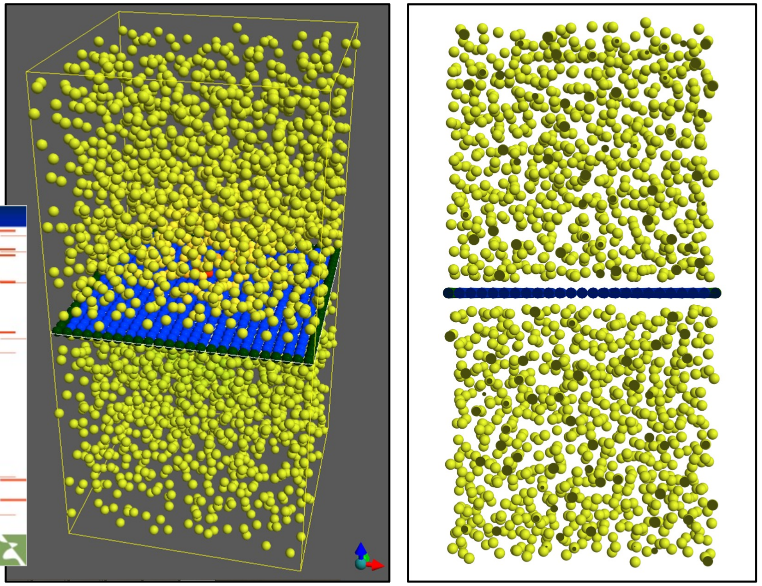
Particle-Based Multiphysics

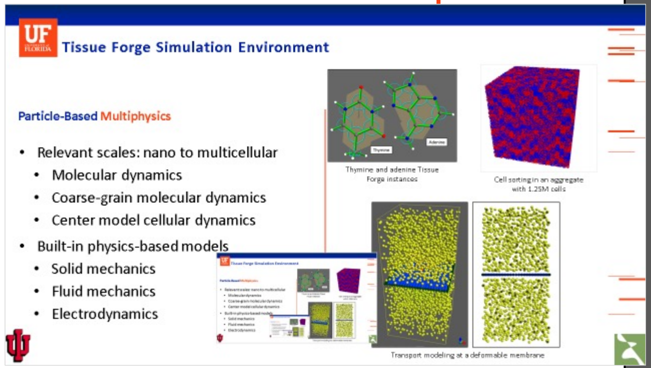
- Relevant scales: nano to multicellular
  - Molecular dynamics
  - Coarse-grain molecular dynamics
  - Center model cellular dynamics
- Built-in physics-based models
  - Solid mechanics
  - Fluid mechanics
  - Electrodynamics



Thymine and adenine Tissue Forge instances


Cell sorting in an aggregate with 1.25M cells

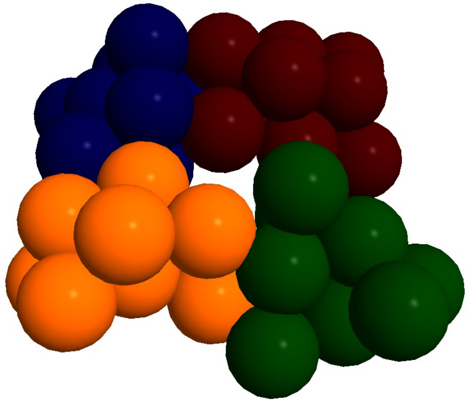

Transport modeling at a deformable membrane



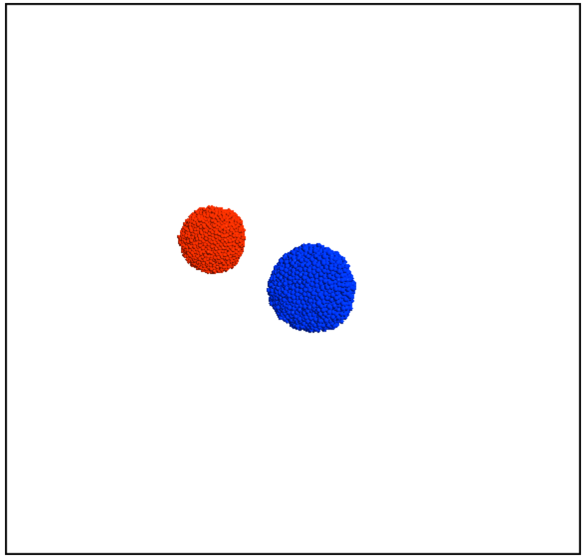
Tissue Forge Simulation Environment

Event- and Agent-based Modeling

- Type-centric model specification
- User-specified events
- Customizable potentials and forces
- Runtime particle creation, destruction and modification



Implementation of Cellular Particle Dynamics (Flenner, Phys. Rev. E, 2012) modeling four aggregating cells

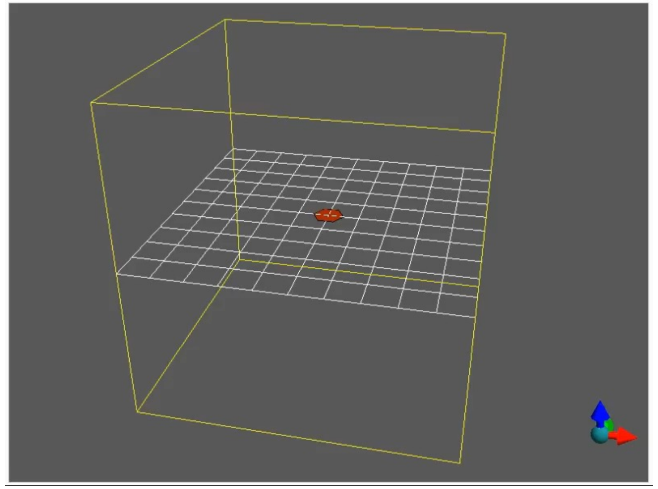


Convection during droplet collision using Smooth Particle Hydrodynamics (Gu, Theor. Appl. Mech. Lett., 2022)

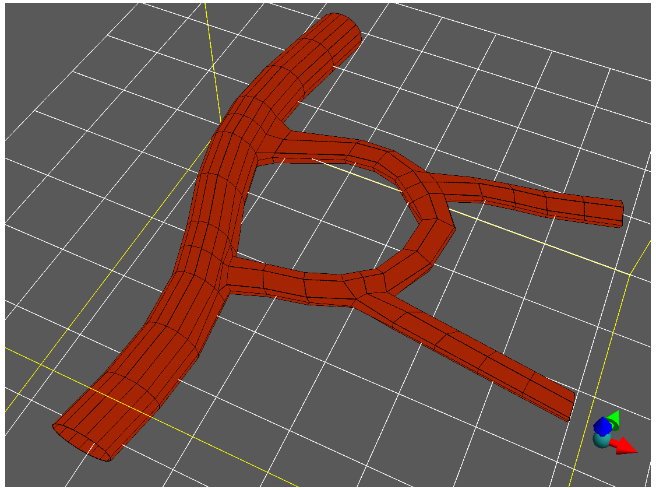
Tissue Forge Simulation Environment

Real-time Interactive Simulation

- Real-time simulation visualization
- Keyboard-driven event handling
- Simulation visualization output
  - Programmatic camera/scene control
  - High-resolution rendering
- Off-screen dynamic GPU acceleration



Interactive two-dimensional simulation of cell splitting using Tissue Forge vertex model extension module

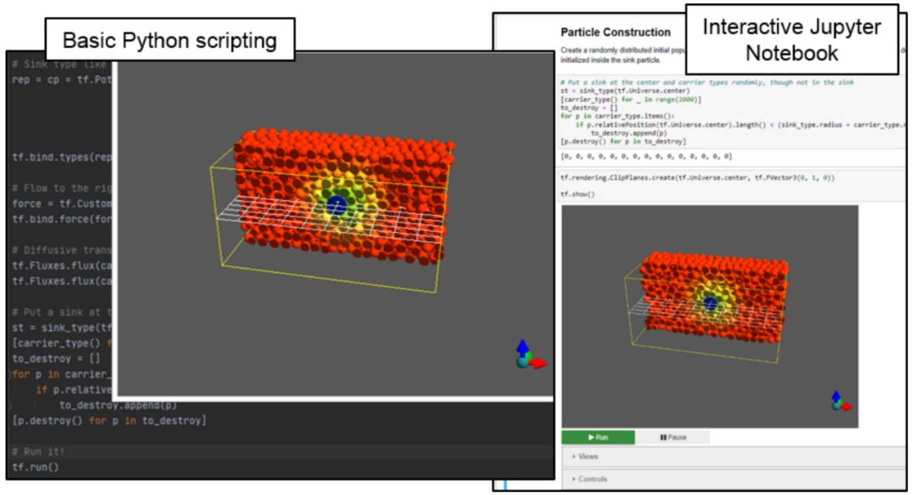


High-resolution rendering of imported Blender mesh of a local vasculature

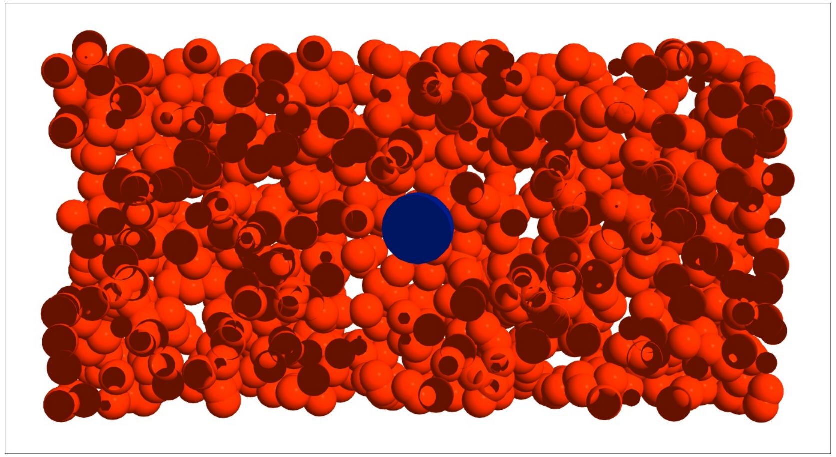
Tissue Forge Simulation Environment

Sharable Biophysics Models

- Language support: C, C++, Python
- Interactive environment support
  - IPython
  - Jupyter
- I/O support for whole simulations and (most) model object states
  - Human-readable JSON
  - 3DF model file format support



Tissue Forge simulation in a Python script (left) and Jupyter Notebook (right)



Cut-plane view of Tissue Forge simulation of convection around a rigid, fixed sink (blue)

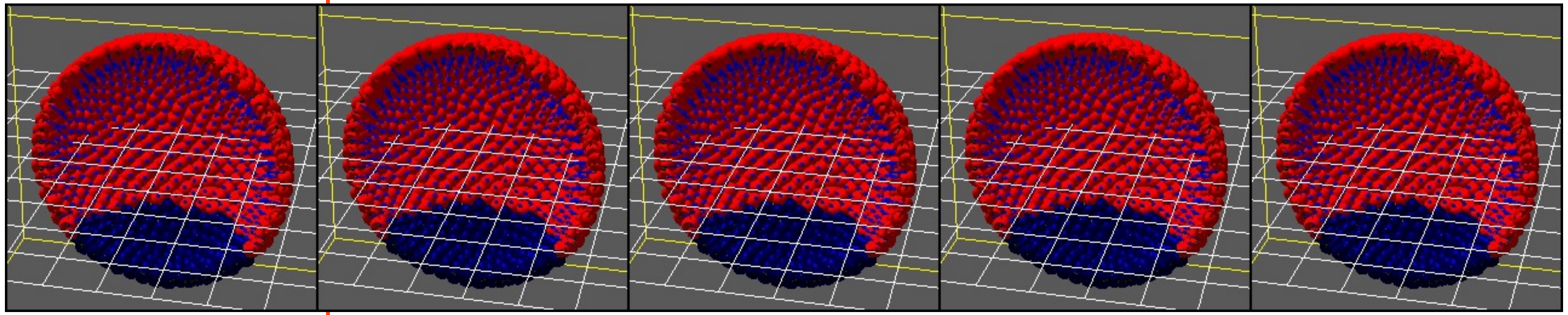
Tissue Forge Simulation Environment

Open-Source and Extensible

- LGPL v3
- Automated build from source
- Robust support for extensions
- Binaries available for Windows,
- Mac and Linux via conda:

conda install –c tissue-forge tissue-forge

Center-model simulation of gastrulation in sea urchin



Gastrulation simulation using the Tissue Forge cell polarity extension module

github.com/tissue-forge/tissue-forge

Particles, Particle Types and Clusters

Type vs. Instance vs. Cluster

- Particle type
  - Dynamic particle definition
  - Factory for creating instances
- Particle
  - Instance of a particle type
  - Uniquely identifiable and modifiable
- Cluster
  - A meta-instance of constituent particles (or other clusters)

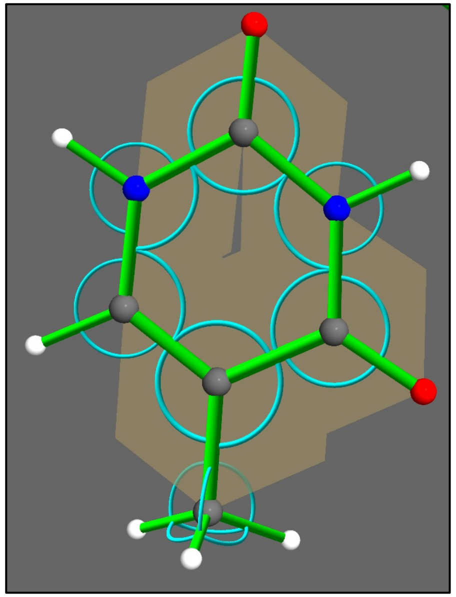
Cluster: thymine molecule

Types:

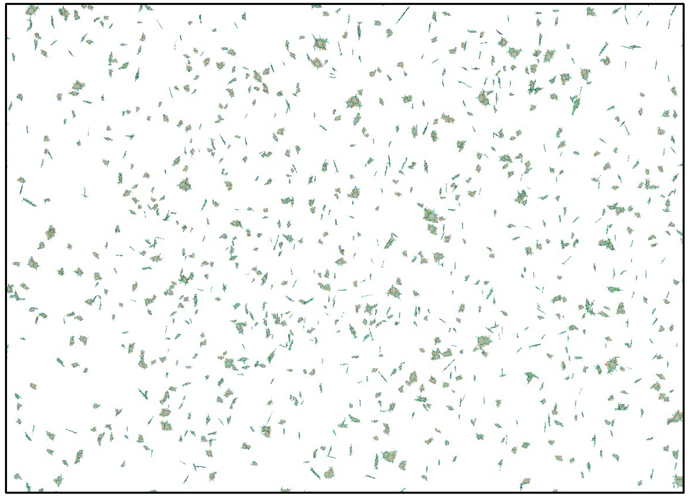
- Hydrogen (white)
- Carbon (gray)
- Nitrogen (blue)
- Oxygen (red)

Instances:

- 6 hydrogen atoms
- 5 carbon atoms
- 2 nitrogen atoms
- 2 oxygen atoms



Tissue Forge thymine instance



Cloud of interacting thymine and adenine instances

Particle Dynamics

Newtonian vs. Langevin

Each particle trajectory updates according to the total force acting on it

- Newtonian dynamics

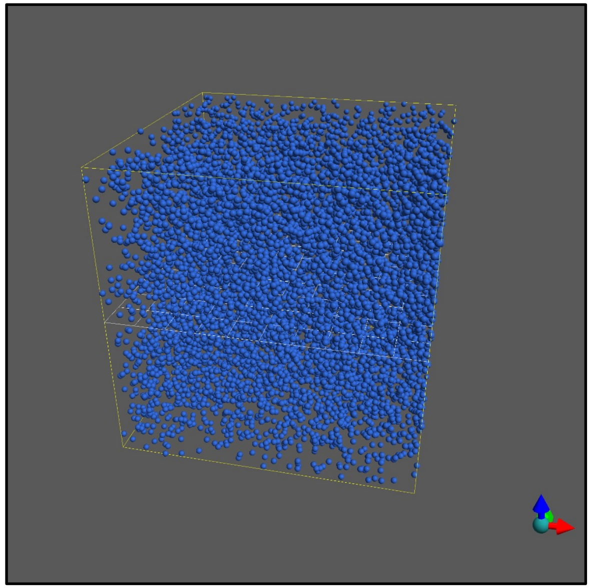
$$f_i = m\ddot{r}_i$$

- Langevin (overdamped) dynamics

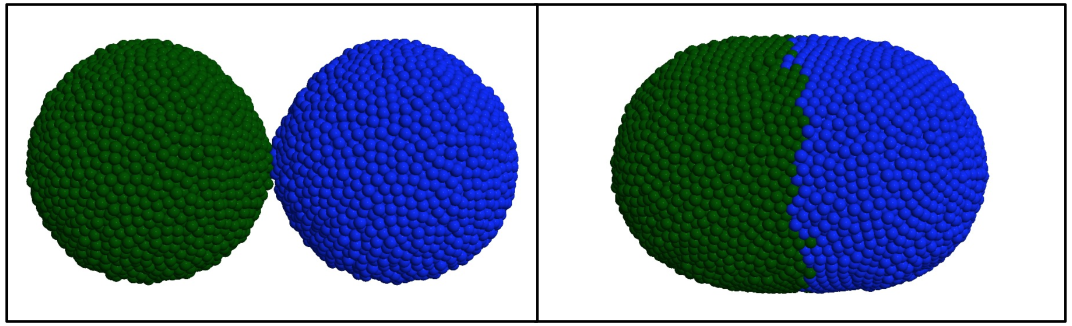
$$f_i = m\dot{r}_i$$

Dynamics are settable by particle type

Argon gas simulation: Newtonian dynamics



Multicellular simulation: Langevin dynamics



Total force: f_i; mass or damping: m; particle position: r_i.

Particle Interactions

Potentials, Forces and Bonds

Potentials describe implicit forces

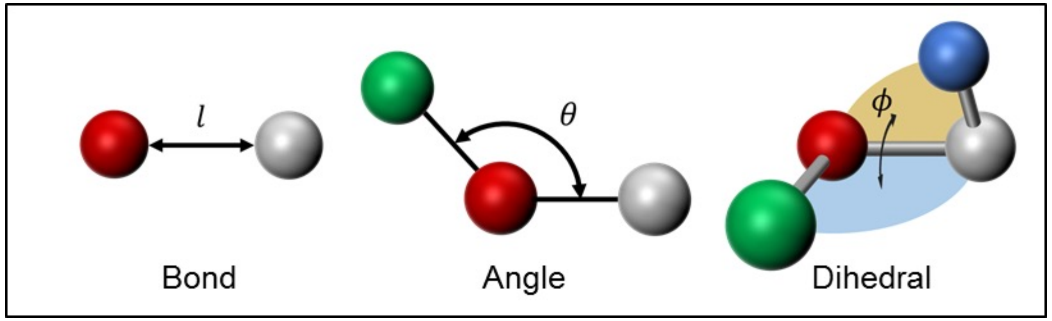
$$f_i = -\frac{\partial U}{\partial r_i}$$

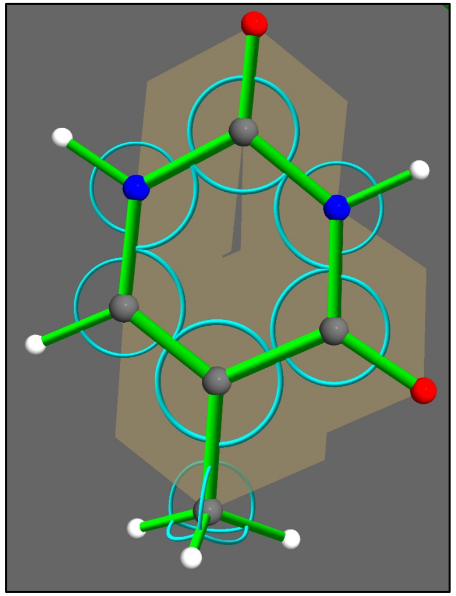
Potentials and forces are applied through **binding**

- Modifiable simulation objects
- Can be added (*e.g.*, $U = U^A + U^B$)
- Forces bound by type (*e.g.*, random noise)
- Potentials bound by types or particles (bonds)
- Potentials bound by inter-cluster and intra-cluster
- Customizable potentials and forces through user functions

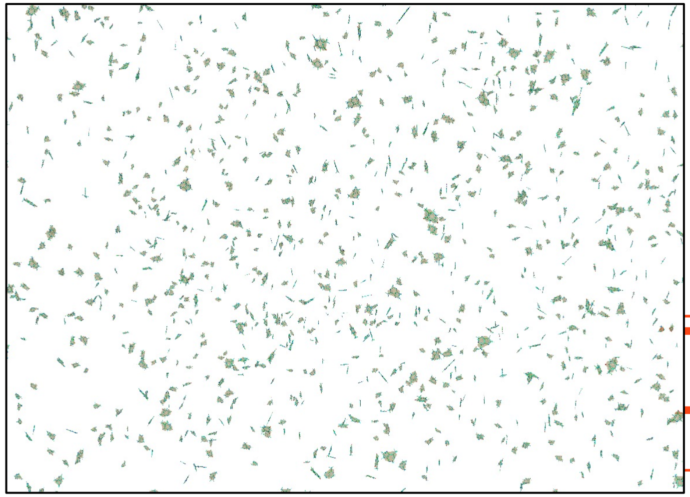
Total force: f_i; particle position: r_i; potential: U.

Supported bonds in Tissue Forge





Tissue Forge thymine instance with bonds (green rods), angles (cyan arcs) and dihedral (gold planes) bonded interactions



Cloud of thymine and adenine molecules interact through inter-cluster interaction potentials

Fluid Mechanics

Particle-based fluid modeling

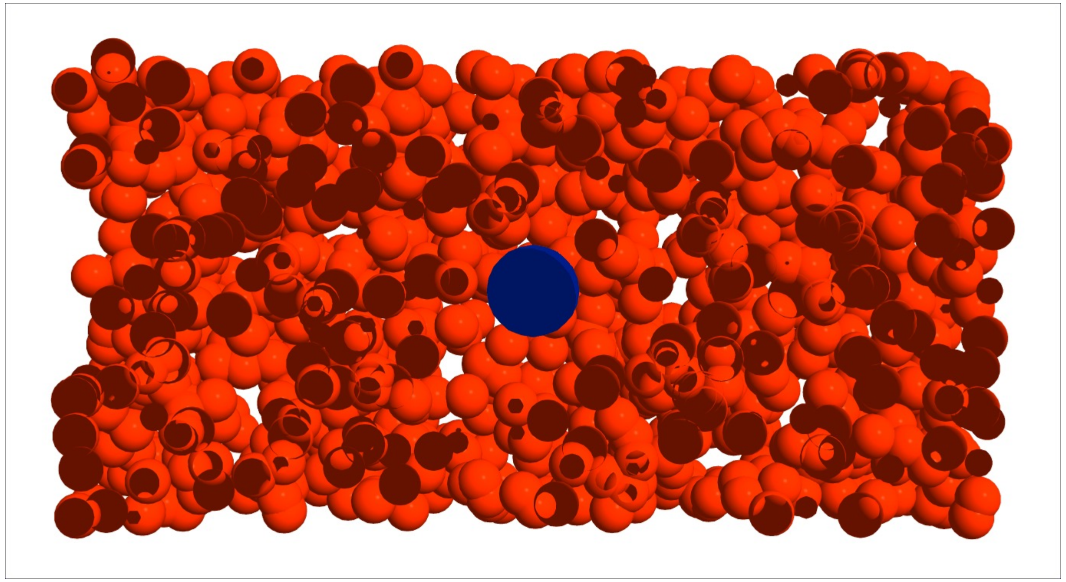
- Particle: parcel of fluid materials
- Cargo: fluid material carries a quantity of "stuff" (e.g., chemical contents)

Material advection: dissipative particle dynamics

$$-\frac{\partial U^{DPD}}{\partial r_i} = F_i^C + F_i^D + F_i^R$$

Cargo diffusion: inter-particle diffusion

$$S(A) \leftrightarrow S(B)\,;\, k\left(1 - \frac{r(A,B)}{r^c}\right)\left(S(A) - S(B)\right)$$



Cut-plane view of Tissue Forge simulation of convection around a rigid, fixed sink (blue)

Conservative force: F_i^C; dissipative force: F_i^D; random force: F_i^R; diffusivity: k; distance between particles A and B: $r(A,B)$; flux cutoff distance: r^c; particle position: r_i; amount of species in particle A and B: $S(A)$ and $S(B)$; Dissipative particle dynamics potential: U^{DPD}

Tissue Forge Next Steps

Full 3D vertex model specification

Integration with subcellular network models

Predefined cell types and multiaxis interaction dependence

More demos of capabilites

Towards Diffusion Solver Surrogates

Solving the diffusion equation is often the most computationally expensive part of Virtual Tissue models, especially for fast diffusing species like Oxygen, Glucose or ions

Gradually building up to ML surrogates for classical diffusion solvers (not there yet)

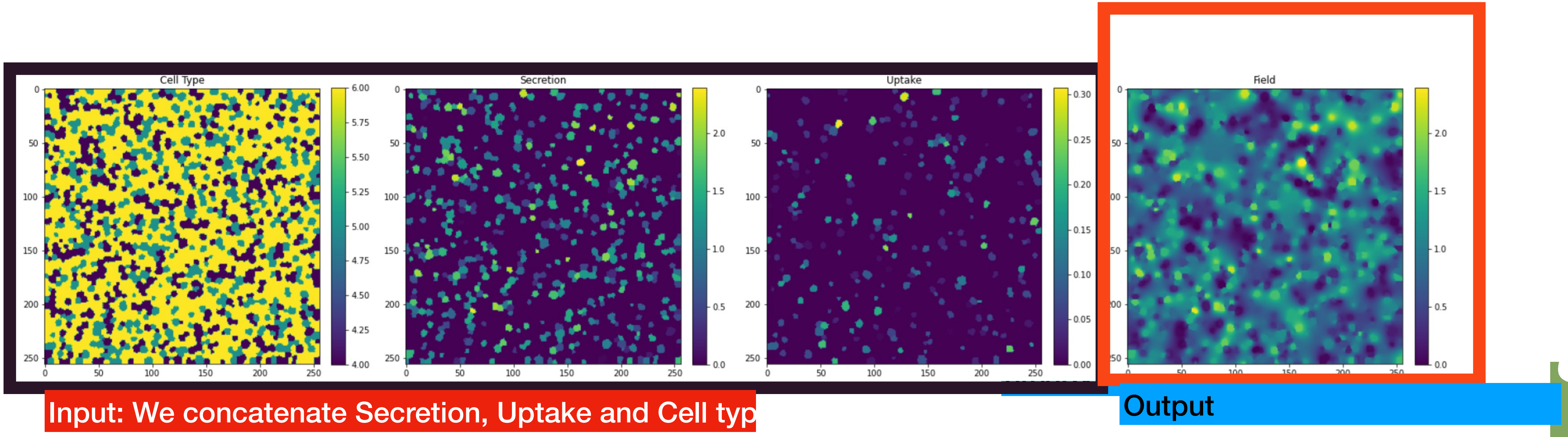
Work by Dr. Javier Toledo (TRIUMF) and Prof. Geoffrey Fox (University of Virginia)

Background

- Steady-state solution for diffusion with multiple sources and sinks in a lattice with periodic boundary conditions
- For now, constant diffusion constant, 2D
- Encoder-decoder performs well, while convolutional neural networks do not (only detect sources and sinks) [Toledo-Marin, G. Fox, J. Sluka, **JAG** *Frontiers in Physiology*, 2021]

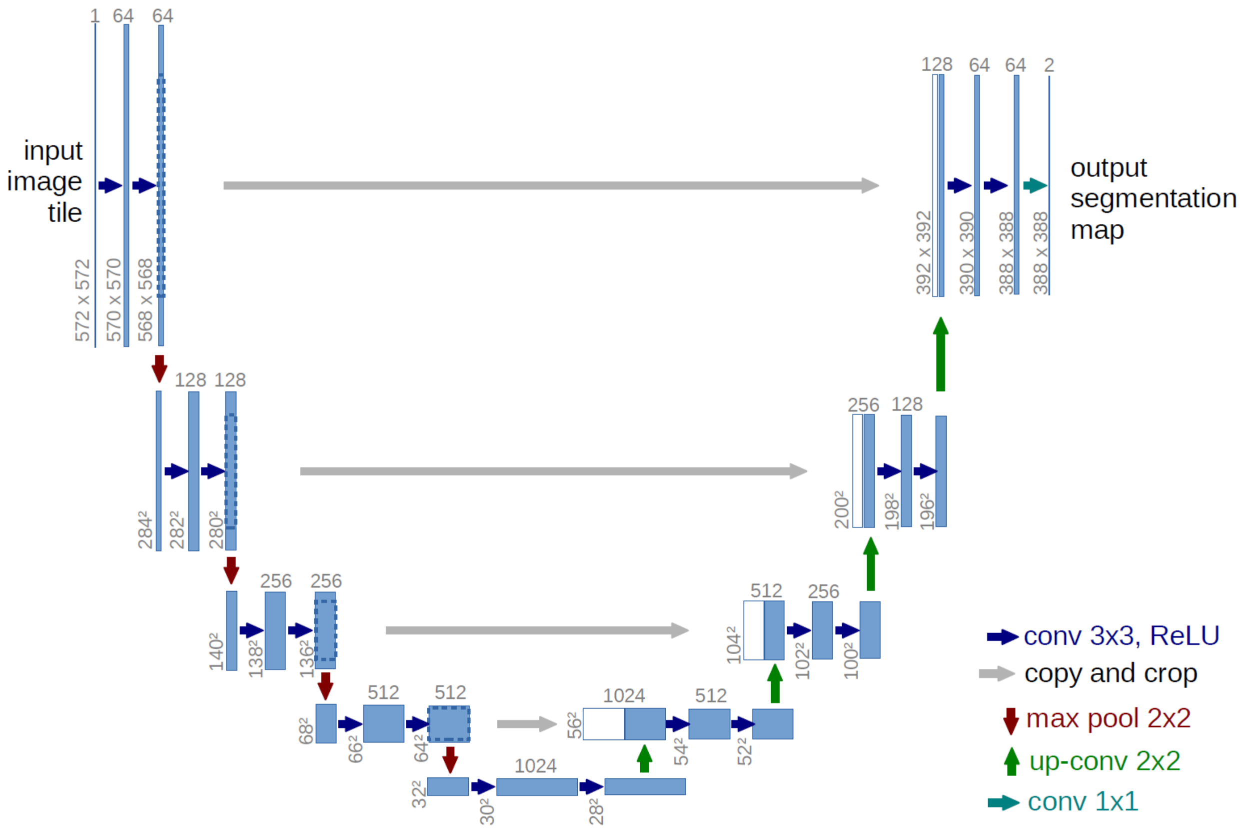
Problem Formulation

- Image-based (direct) method—inputs are 3 channel, secretion (constant value) update rates (first order decay) and locations of sources and sinks
- Variable numbers, locations and sizes of sources and sinks
- Training data pairs inputs triples with steady state fields calculated directly in CC3D (20,000 input-output pairs)

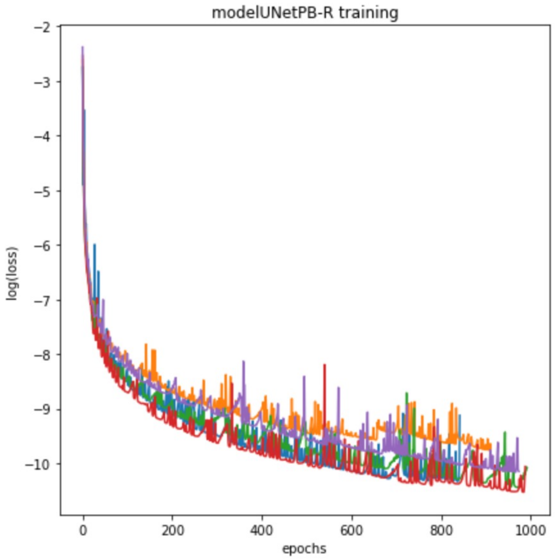


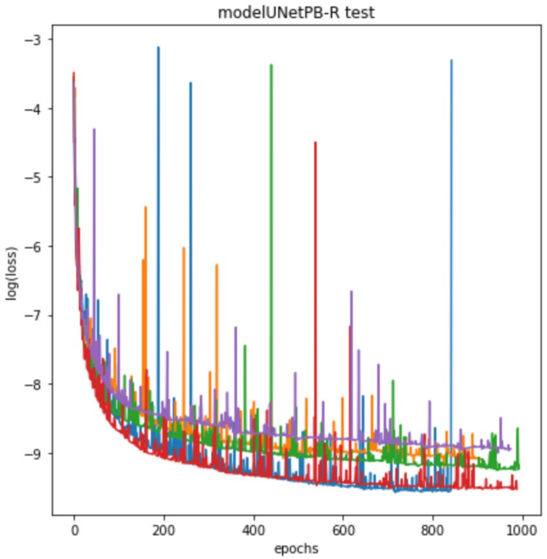
Adopt U-net Architecture

- NN proposed for segmentation in [Ronneberger, Olaf, Philipp Fischer, and Thomas Brox. U-net].
- Combines features of an encoder-decoder architecture and a ResNet.
- Reminiscent of a multigrid method.
- Has been used for different tasks in deep learning…
- We trained different types of UNets, by changing the activation functions to Leaky ReLU and PReLU.
- We also trained models with the bias in the convolutions set to 0



Quality of Results Sensitive to Loss Functions, Training Algorithms and Transfer Functions

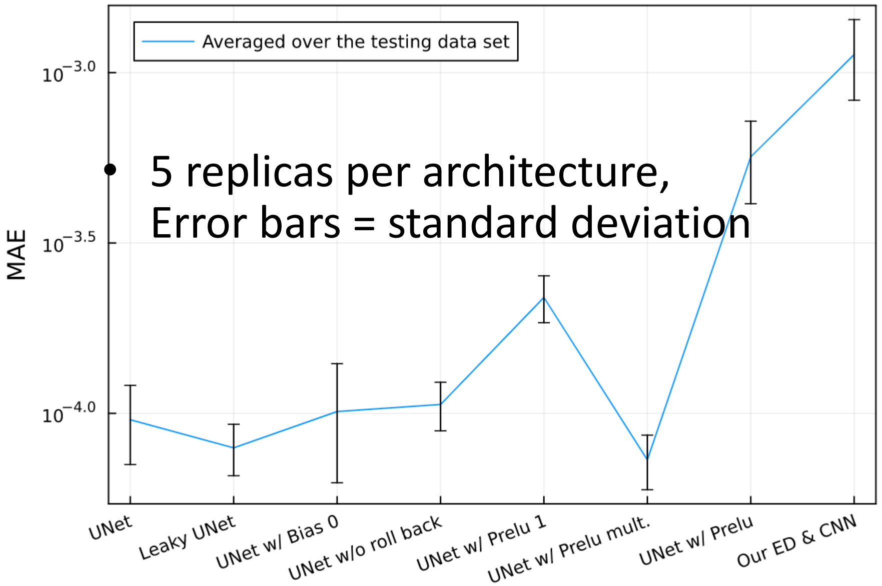




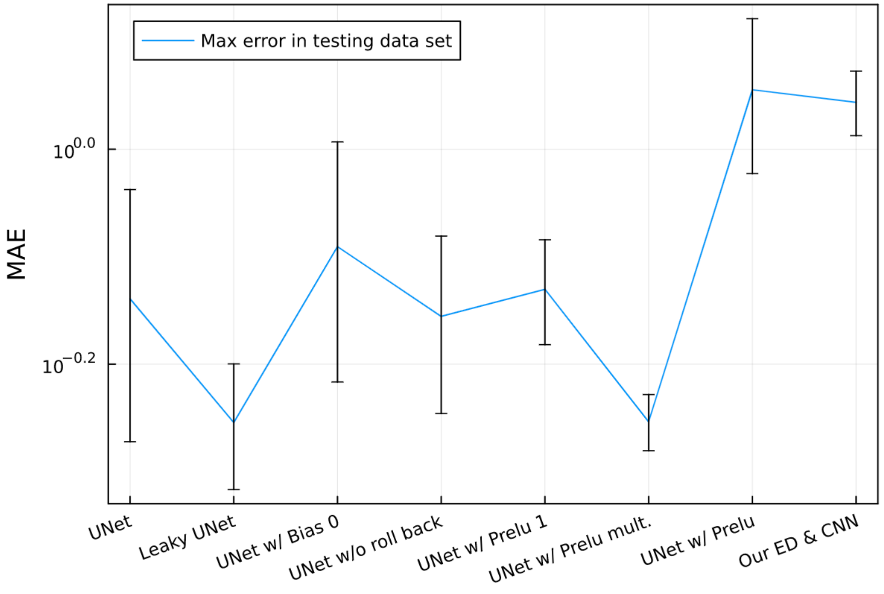
Several Characteristic times:

- **Short relaxation time**
- **Long relaxation time**
- **In-between peak time**
- **Peak relaxation time**

JQ. Toledo-Marin, G. Fox, **JAG** 2023 (in preparation)

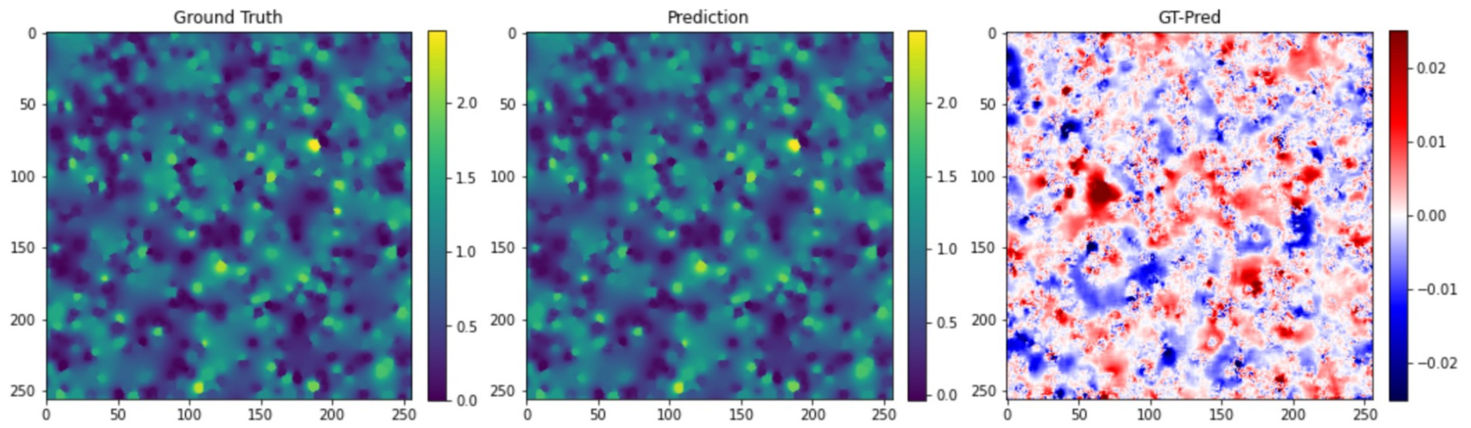


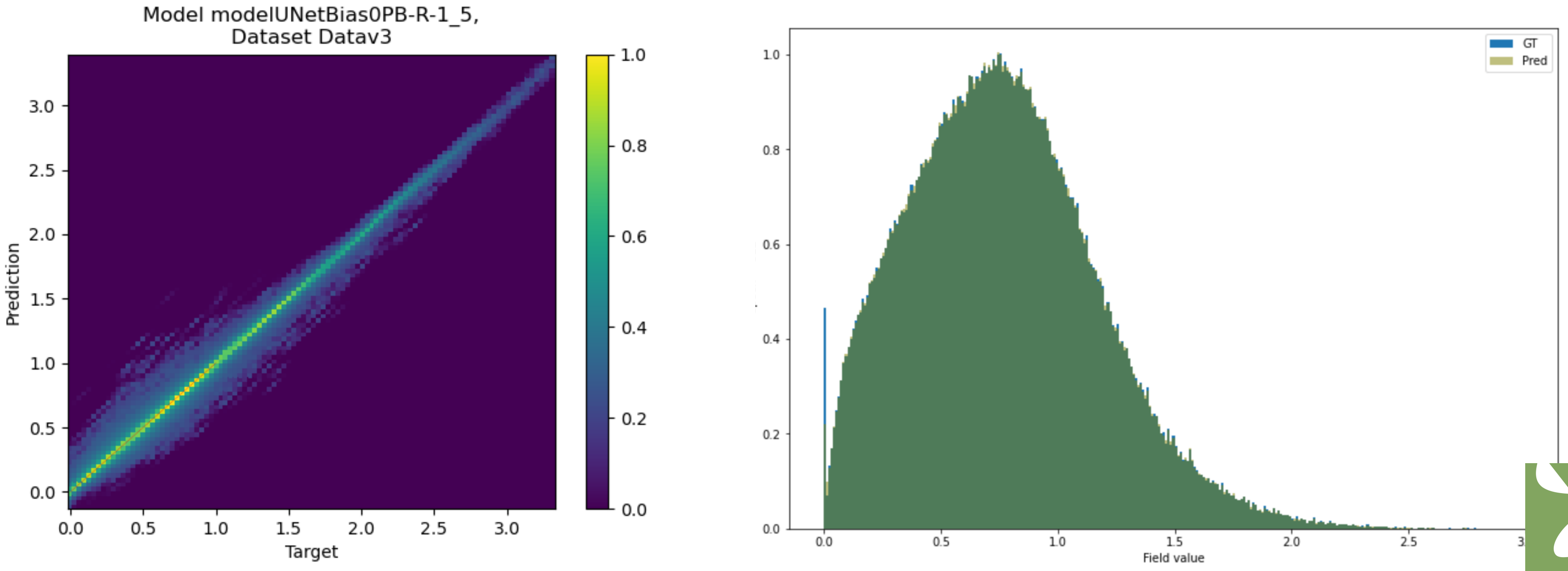
- 5 replicas per architecture, Error bars = standard deviation



Works Remarkably Well

- Negligible mean errors, maximum errors of a few percent of final values





We applied a power of 1/8 to the error grid to be able to visualize better the deviations

Next Steps and Issues

It worked better than we expected!

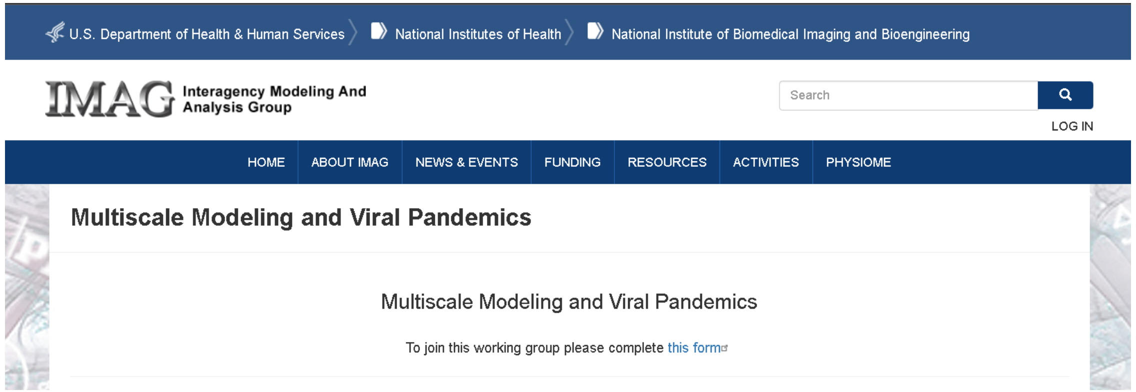
- Dispersed (as opposed to focal) background uptake
- Spatially varying diffusion constants as an extra channel (currently trained for a single global D)
- Time-dependent (time-stepper vs steady-state)
- 3D vs 2D (big lattices, will need to do decimation)
- Integration into CompuCell3D and Tissue Forge
- **Fundamental problem with boundary conditions for real-world field-of-view windows (affects direct methods as well, but worse in ML approaches)**

Building a Community to Develop Biomedical Digital Twin Modeling Technologies

Please join the WG and attend or present in our virtual seminars: https://www.imagwiki.nibib.nih.gov/working-groups/multiscale-modeling-and-viral-pandemics

IMAG/MSM: Working Group on Multiscale Modeling and Viral Pandemics

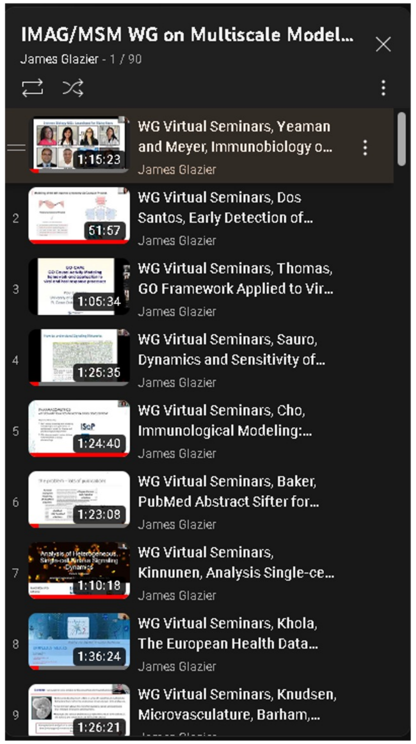
- Started by James Glazier and Reinhard Laubenbacher in Summer, 2020



Through this working group, recognized that developing infrastructure for mechanistic medical digital twins and immune digital twins is an integral part of planning for the next viral pandemic

WG Efforts to Develop Immune Digital Twin

- **Viral Pandemics Working Group IMAG/MSM Wiki**
  https://www.imagwiki.nibib.nih.gov/working-groups/multiscale-modeling-and-viral-pandemics
- Presentations to the Working Group--YouTube videos (~170 total),
  https://www.imagwiki.nibib.nih.gov/content/msm-viral-pandemics-meetings
- Publications
  https://www.imagwiki.nibib.nih.gov/content/viral-pandemics-group-publications-page
- Workshops



Forum On Precision Immunology: Immune Digital Twins

February 23-24, 2023

UF Health Research and Academic Center, Orlando, FL

Sponsors:

- **U.S. Department of Defense, Army Research Office, Biomathematics Program Grant Nr. ACC- APG- RTP W911NF**
- **University of Florida Health**

May 15-June 2, 2023

PERSPECTIVE | INFECTIOUS DISEASE

Using digital twins in viral infection

Personalized computer simulations of infection could allow more effective treatments

REINHARD LAUBENBACHER, JAMES P. SLUKA, AND , JAMES A. GLAZIER Authors Info & Affiliations

SCIENCE • 12 Mar 2021 • Vol 371, Issue 6534 • pp. 1105-1106 • DOI: 10.1126/science.abf3370

Building digital twins of the human immune system: toward a roadmap

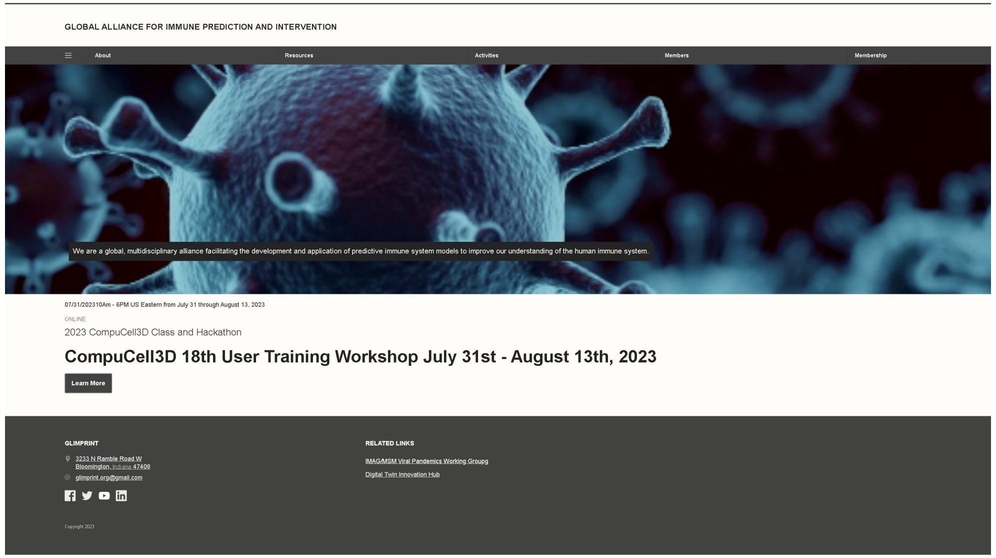
R. Laubenbacher, A. Niarakis, T. Helikar, G. An, B. Shapiro, R. S. Malik-Sheriff, T. J. Sego, A. Knapp, P. Macklin & J. A. Glazier

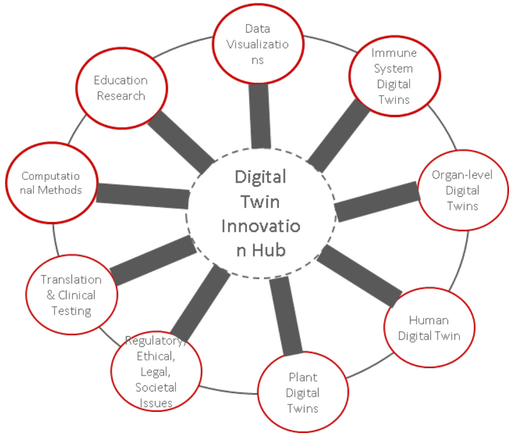
npj Digital Medicine 5, Article number: 64 (2022) | Cite this article

8409 Accesses | 3 Citations | 82 Altmetric | Metrics

JUST BECAUSE IT'S DIFFICULT DOESN'T MEAN WE SHOULDN'T DO IT

- Global Alliance for Immune Prediction and Intervention
  - Non-profit organization to:
    - Facilitate the development and application of predictive immune system models to improve our understanding of systemic immune-related etiologies and pathologies and initiate a new era of novel therapeutic design through systems-based precision medicine
    - Facilitate the development of technological, scientific, regulatory, and social infrastructure and its application in science, medicine, and education
- Please join at http://glimprint.org/
    - **Your suggestions for what we should do to build community much appreciated**





Digital Twin Innovation Hub, Tomas Helikar

Sponsor: University of Nebraska-Lincoln

Indiana University,
Luddy School of Informatics, Computing, and Engineering

Two Tenured Professor Positions in Technology and Research Related to Next-Generation Biomedical Digital Twins

https://indiana.peopleadmin.com/postings/16811

Questions, nominations, and confidential inquiries may be sent to Prof. James A. Glazier (jaglazier@gmail.com)

IMAG/MSM:
Multiscale Modeling And Viral Pandemics

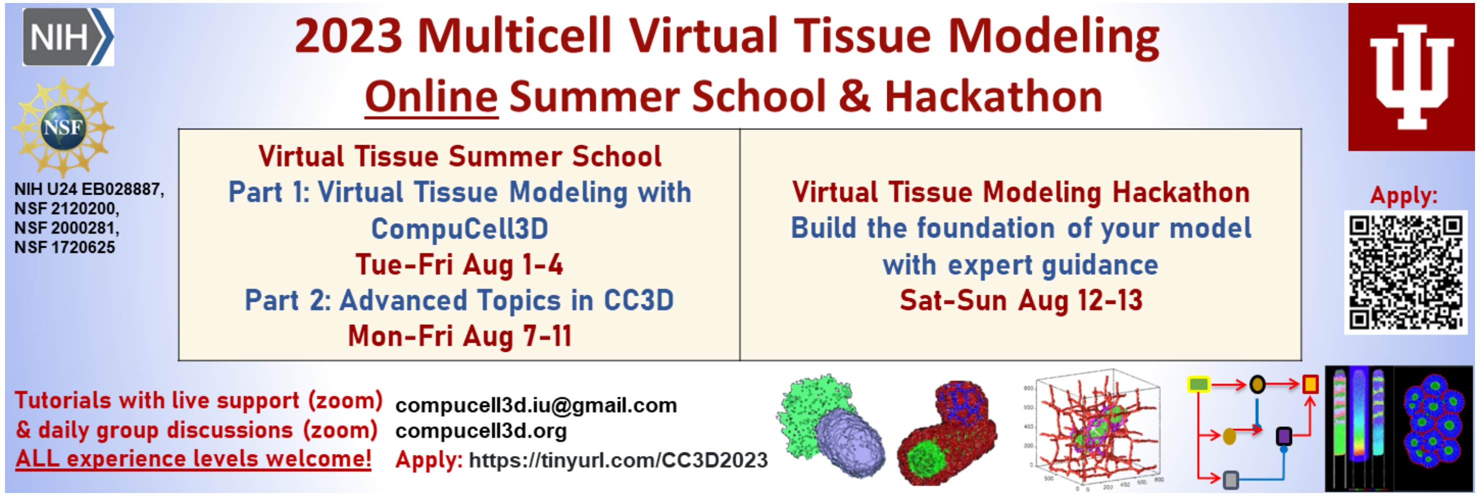
Links and Disclosures

- **You can download CompuCell3D software from www.compucell3d.org or run them on line at https://nanohub.org/tools/cc3dcovid19**
- You Can try Tissue Forge at https://tissue-forge-python-api-documentation.readthedocs.io/en/latest/api_reference.html

Looking for 2 postdocs immediately to work on model building—on corneal homeostasis and damage and on software infrastructure, language specification and model sharing

We'd love to work with you to apply these methods to your problems

2 week, free, on-line course on using CompuCell3D this August—you're welcome to attend



Disclosure: Dr. Glazier and other investigators listed have filed for international patent protection for the ADPKD and Diabetic Retinopathy therapies under development and have financial interest in Apoptocys Inc. and Virtual Tissues For Health LLC, also owns a small amount of stock in Gilead

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