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 Development, 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?

*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

Length Scale

Whole body
(and population)

Organ

Tissue

Cell

Subcell

Biology (in vivo)

Computation (in silico)

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

\[
\text{Reaction: } A -\rightarrow \text{Na; } V_{\text{max}}\text{A}\frac{A}{K_{\text{m}}\text{A}+A}
\]

\[
\text{Source ODE: } \text{A} \rightarrow \text{Na; } V_{\text{max}}\text{A}\frac{A}{K_{\text{m}}\text{A}+A}
\]

\[
\text{NA+GSH} -\rightarrow \text{NAGSH; } k_{\text{NaGsh}}\text{NA}\text{GSH}
\]

\[
\text{$X_1$ -\rightarrow \text{GSH; } k_{\text{Gsh}}\text{GSH}_{\text{max}}-\text{GSH}}
\]

\[
\text{ Reaction: Source ODE: } A \rightarrow \text{Na; } V_{\text{max}}\text{A}\frac{A}{K_{\text{m}}\text{A}+A}
\]

\[
\text{NA+GSH} \rightarrow \text{NAGSH; } k_{\text{NaGsh}}\text{NA}\text{GSH}
\]

\[
\text{GSH}_{\text{max}} \rightarrow \text{GSH; } k_{\text{Gsh}}\text{GSH}_{\text{max}}-\text{GSH}
\]

\[
\text{A} \rightarrow \text{Ac; } V_{\text{max}}\text{II}\text{A}\frac{A}{K_{\text{m}}\text{II}\text{A}+A}
\]

\[
\text{ Reaction: Source ODE: } A \rightarrow \text{Na; } V_{\text{max}}\text{II}\text{A}\frac{A}{K_{\text{m}}\text{II}\text{A}+A}
\]

\[
\text{NA+GSH} \rightarrow \text{NAGSH; } k_{\text{NaGsh}}\text{NA}\text{GSH}
\]

\[
\text{GSH}_{\text{max}} \rightarrow \text{GSH; } k_{\text{Gsh}}\text{GSH}_{\text{max}}-\text{GSH}
\]
Biological Organization is Highly Dynamic and Crosses Scales—Development

Branching Morphogenesis *in vitro*


Early Development of Zebrafish


Segmentation of Chick Embryo

Intersegmental Vessel Growth in Zebrafish
Virtual Tissues—Cell Behaviors Are Central

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

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

PhysCell simulation of Ductal Carcinoma in situ (DCIS)

Episim simulation of extending shield mechanism (ESM)

Biocellion simulation of avascular tumor growth

CellSys Simulation of multicellular population growth

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

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

- 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)
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.

No Contact Inhibition

Contact Inhibition

Key Physics:

Cell Diffusion
VEGF-A Diffusion
Chemical Potential Response of Cells
(Constant Pressure – Liquid Like vs Variable Pressure)
Segmentation

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


HH staged chick embryos, fixed (Wiley)
Why do blood vessels sometimes invade the retina during aging?

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

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

Model of ADPKD - Autosomal Dominant Polycystic Kidney Disease


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

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


KW Dunn, et al., “Mitochondrial depolarization and repolarization in the early stages of acetaminophen hepatotoxicity in mice,” *Toxicology* 439, 152464 (2020)
Computational Toxicology Studies Using CompuCell3D—Liver Zonation


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

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


• 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

\[
\begin{align*}
\frac{dR}{dt} &= \frac{h_R R}{C + \alpha_R} - \mu_R R \\
\frac{dN}{dt} &= \frac{h_N N}{C + \alpha_N} - \mu_N N \\
\frac{dM}{dt} &= \frac{h_M M}{C + \alpha_M} - \mu_M M \\
\frac{dL}{dt} &= \frac{h_L L}{C + \alpha_L} - \mu_L L \\
\frac{dH}{dt} &= \frac{h_H H}{C + \alpha_H} - \mu_H H \\
\frac{dV}{dt} &= \frac{h_V V}{C + \alpha_V} - \mu_V V
\end{align*}
\]

\[
\begin{align*}
\frac{dDH}{dt} &= \frac{g_{DH} X}{X^{n_D} + \alpha_{DH}} - \mu_{DH} H \\
\frac{dB}{dt} &= \frac{g_{DB} P}{P^{n_D} + \alpha_{DB}} - \mu_{DB} B \\
\frac{dP}{dt} &= \left( \frac{g_P V}{(G + V) + g_D} \right) \left( \frac{g_{HP} P}{G + V} \right) - \mu_P P \\
\frac{dW}{dt} &= \frac{g_{WO} O}{O^{n_O} + \alpha_{WO}} - \mu_{WO} W \\
\frac{dO}{dt} &= \frac{g_{PO} P}{P^{n_O} + \alpha_{PO}} - \mu_{PO} O
\end{align*}
\]

\[
D = \text{total cells} - H - I
\]

\[
\begin{align*}
\Sigma_1 &= \alpha_I T + \alpha_I D \\
\Sigma_2 &= \Sigma_1 + \frac{g_V V}{G + V} \\
\Sigma_3 &= \Sigma_2 + \frac{g_F F}{G + V} \\
\Sigma_4 &= \Sigma_3 + \frac{g_I I}{G + V} \\
\Sigma_5 &= \Sigma_4 + \frac{g_P P}{G + V}
\end{align*}
\]

Experimental Validation of Network Model

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](https://nanohub.org/tools/cc3dbase4x)
- Download at [https://compucell3d.org/](https://compucell3d.org/)

CC3D simulation of somitogenesis
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
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
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

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)
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

Phenotypes
- Non-expressing
- Delta-expressing
- Notch-expressing

Boolean states
- False
- True

 Phenotypes
<table>
<thead>
<tr>
<th>Cells</th>
<th>NICD</th>
<th>CycE</th>
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</tbody>
</table>

Network coupling cell cycle and delta-notch signaling

Cell
- Delta
- Notch
- NICD
- Rb
- CycA
- CycB

Sample code of MaBoSS in CompuCell3D

```
def step(self, mcs):
    # Called every simulation step
    param mcs: step number
    ***
    for cell in self.cell_list:
        mboss_model = cell.mboss.cell_cycle
        for neighbor in cell.get_neighbor(data_list):
            if neighbor:
                mboss_model.symbol_table['delta_ex'] = float(num_delta_ex) * area_to_delta
        self.mboss.run_simulation()
        get a cell's MaBoSS node state
        Set a cell's MaBoSS parameter
        Integrate all MaBoSS simulations
        Loop over every cell
```

Notch
- expressing
- Delta
- expressing
- Non expressing

Phenotypes

Delta
- expressing
- not expressing

Phenotypes

Cell
- cycle
- 
- Rb
- 
- 

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

CompuCellSetup.register_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

Later Treatment

Higher Potency

Massively parallel execution of viral infection and therapy
Flexible and It Works...

2023


2022


2021


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
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

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
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

Gastrulation simulation using the Tissue Forge cell polarity extension module

Center-model simulation of gastrulation in sea urchin

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

Total force: \( f_i \); mass or damping: \( m \); particle position: \( r_i \).
Particle Interactions

Potentials, Forces and Bonds

Potentials describe implicit forces

\[ f_i = -\frac{\partial U}{\partial \mathbf{r}_i} \]

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: \( \mathbf{r}_i \); potential: \( U \).
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
\[
- \frac{\partial U_{DPD}^i}{\partial r_i} = F_i^C + F_i^D + F_i^R
\]

Cargo diffusion: inter-particle diffusion
\[
S(A) \leftrightarrow S(B); k \left(1 - \frac{r(A, B)}{r_c}\right)(S(A) - S(B))
\]

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 capabilities
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)

Input: We concatenate Secretion and Uptake
Output: We used MSE to train the models to predict the steady state diffusion field.

Input: We concatenate Secretion, Uptake and Cell type
Output
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

MAE

- $10^{-4.0}$
- $10^{-3.5}$
- $10^{-3.0}$
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, Biomedical Programs
  Grant Nr. ACC- APG- RTF W911NF
- University of Florida Health

May 15-June 2, 2023

**Using digital twins in viral infection**

Personalized computer simulations of infection could allow more effective treatments

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

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/](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)
Links and Disclosures

• You can download CompuCell3D software from www.compucell3d.org or run them on line at https://nanohub.org/tools/cc3dcovid19

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