

# Introduction to Agent-Based Modeling for Cancer Immunology with PhysiCell



Joint work with  
[Elana Fertig](#)

**Paul Macklin, Ph.D.**

Intelligent Systems Engineering  
Indiana University

June 13, 2024

# Thank you to our sponsors!



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# Thank you to collaborators: cell grammar

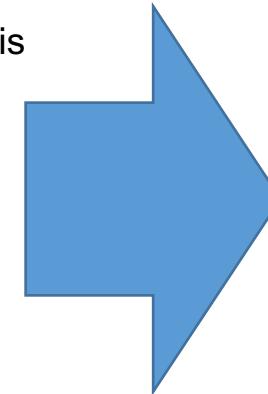
- Johns Hopkins University
  - Elana Fertig\*
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  - Elizabeth Jaffee
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  - **Students (Macklin lab):**
    - Furkan Kurtoglu, Elmar Bucher, John Metzcar, Aneequa Sundus
  - **Alumni:**
    - Yafei Wang, Michael Getz

# Thank you to collaborators: PhysiCell & PhysiBoSS

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  - Alfonso Valencia
- Univ. Paris Descartes
  - Gautier Stoll

# From single cells to cancer ecosystems

- Single-cell behaviors:
  - Growth
  - Division
  - Differentiation
  - Death
  - Consumption
  - Metabolism
  - Secretion
  - Signaling
  - Mutations
  - Motility
- Cell-cell interactions:
  - Adhesion
  - Mechanics
  - Predation / Phagocytosis
  - Effector attack
  - Fusion
  - Contact communication
- Physical constraints:
  - Diffusion limits
  - Mechanical barriers



Multicellular cancer ecosystem



Multicellular systems biology seeks to *understand* these systems.  
Multicellular systems engineering seeks to *control* them.

Source: Hanahan (2022)  
DOI: [10.1158/2159-8290.CD-21-1059](https://doi.org/10.1158/2159-8290.CD-21-1059)

**Scientists use [models\*] to  
detangle complex systems.**

\* animal, *in vitro*, engineered, mathematical, conceptual ...

**We use agent-based models as our virtual laboratory.**

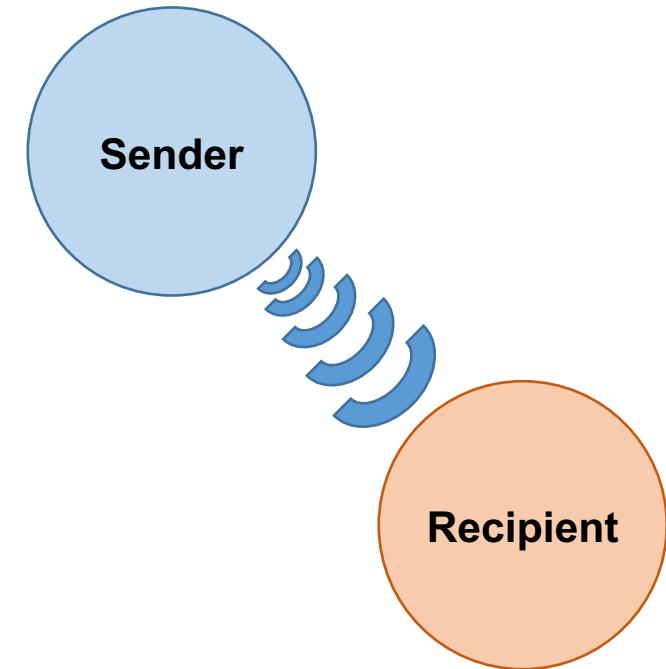
# First, a conceptual model

# Signal-Response as a Conceptual Framing

- Much of the complexity of this system can be decomposed into pairwise interactions between a **sender** and a **recipient**

- A **signal** is a stimulus that can elicit a behavioral **response**:

- A macrophage (**sender**) secretes IL-6 (**signal**) that drives chemotaxis (**response**) in a CD8 T cell (**recipient**)
- An epithelial cell (**sender**) exerts pressure (**signal**) that decreases cycle entry (**response**) in another epithelial cell (**recipient**)



# **Agent-based models are well-suited to this framing**

# Agent-based models: overview

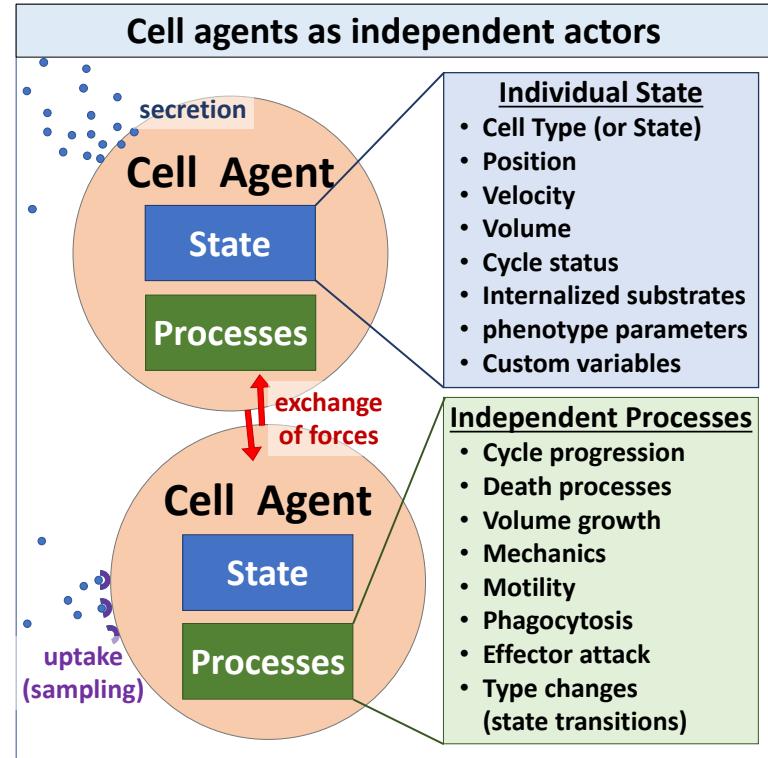
- Each cell is an **independent agent** with:

- **Individual state**

- Type
    - Position
    - Velocity
    - Phenotype parameters
    - Custom variables

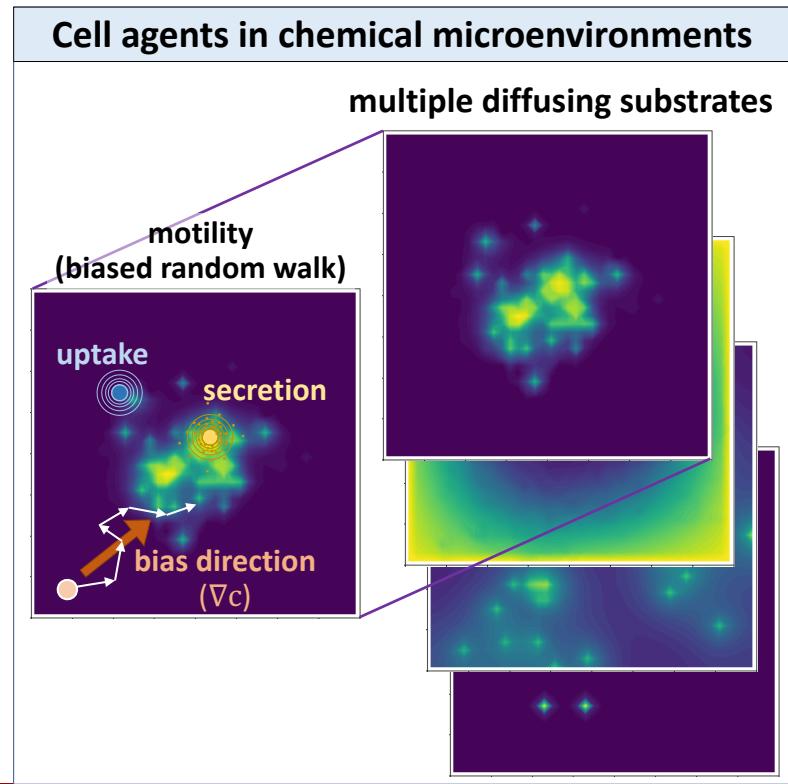
- **Independent processes**

- Cycle and death processes
    - Volume growth
    - Mechanics and motility
    - Secretion and uptake / sampling
    - Phagocytosis, effector attack
    - State transitions (change of type)
    - Custom processes



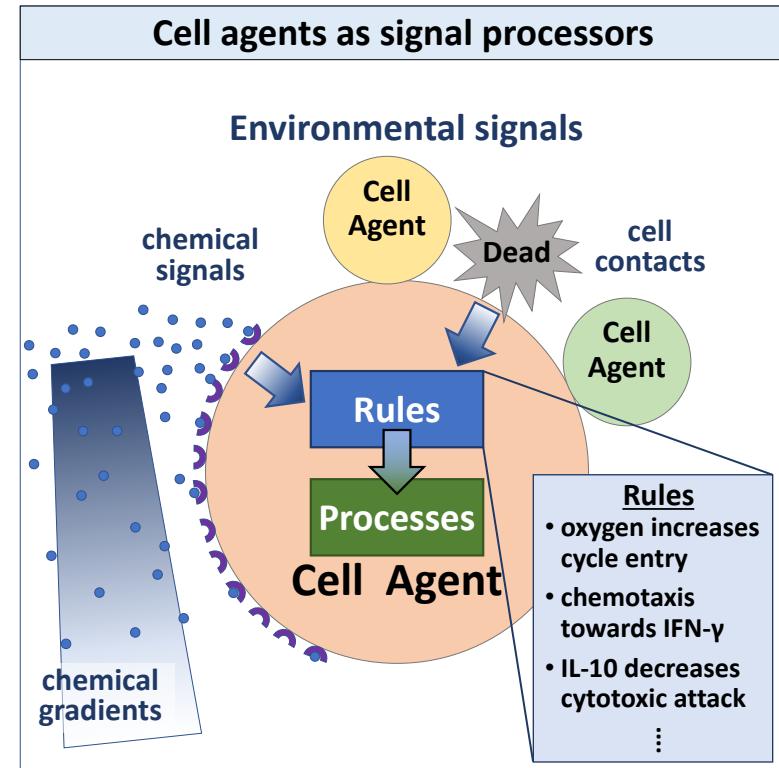
# Cell agents live in a virtual environment

- Cells can secrete or consume
- Substrates diffuse and decay
- Cells can sample substrates
- Cells can perform biased random walks (e.g., chemotaxis)



# Cell agents are signal processors

- Cells interact through chemical and physical **signals** (or stimuli)
  - Secreted chemical signals & gradients
  - ECM properties
  - Contact with a live or dead cell
  - ...
- Signals drive changes in **behavior**
  - Increased or decreased rates of cycling or death
  - Changes in motility, secretion, phagocytosis, ...
- Signal-behavior relationships are **agent rules**



# Our virtual laboratory

# BioFVM: Simulating 3-D biotransport

**Design goal:** Simulate multiple diffusing substrates in 3D with desktops or single HTC/HPC nodes

**Typical use:**  $pO_2$ , glucose, metabolic waste, signaling factors, and a drug, on  $10 \text{ mm}^3$  at  $20 \mu\text{m}$  resolution

## Features:

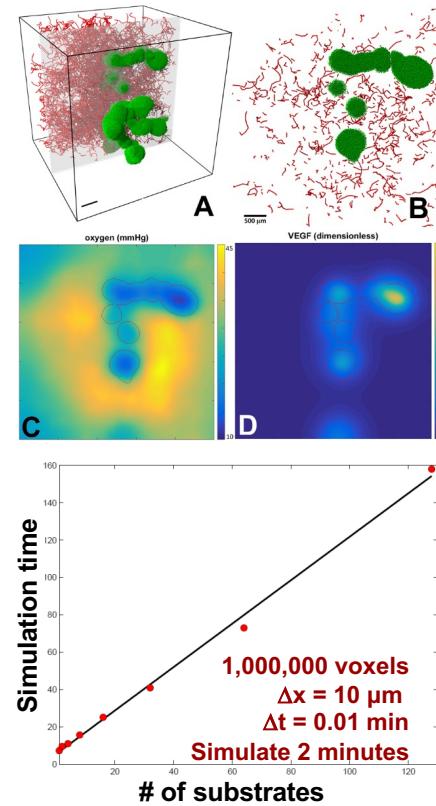
- Off-lattice cell secretion and uptake
- 2<sup>nd</sup>-order accurate (space), 1<sup>st</sup>-order accurate (time), numerically stable

## Method:

- Operator splitting, LOD, customized Thomas solvers, etc.
- Standard C++11, cross-platform
- OpenMP parallelization
- $O(n)$  cost scaling in # substrates, # voxels
- Easy to simulate 5-10 substrates on  $10^6$  voxels

**Reference:** Ghaffarizadeh et al., *Bioinformatics* (2016)

**DOI:** [10.1093/bioinformatics/btv730](https://doi.org/10.1093/bioinformatics/btv730)



# *PhysiCell*: A multicellular framework

**Design goal:** Simulate  $10^6$  or more cells in 2D or 3D on desktops or single HPC nodes

## **Features:**

- Fully coupled diffusion solvers
- Mechanics-based cell movement
- Cell processes (cycling, motility, ...)
- Signal-dependent phenotype
- Can dynamically attach custom data and functions on a cell-by-cell basis

## **Method:**

- Standard C++11, cross-platform
- OpenMP parallelization
- $O(n)$  cost scaling in # cells

**Reference:** Ghaffarizadeh et al.,

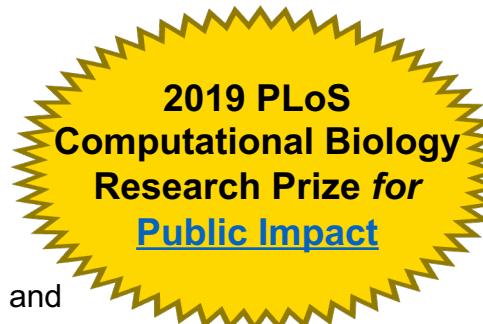
PLoS Comput. Biol. (2018)

**DOI:** [10.1371/journal.pcbi.1005991](https://doi.org/10.1371/journal.pcbi.1005991)

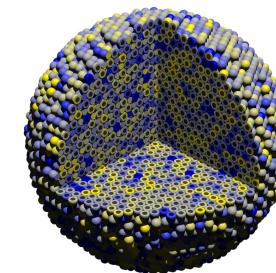


Try this model yourself!

[nanohub.org/tools/pc4heterogen](https://nanohub.org/tools/pc4heterogen)



Current time: 0 days, 0 hours, and 0.00 minutes  
18317 cells



**Competition in a 3-D tumor**  
[View on YouTube](#) (8K)

# PhysiBoSS: PhysiCell + MaBoSS

**Design goal:** Directly integrate Boolean signaling networks in each cell agent

## MaBoSS (from Institut Curie):

- Continuous-time Markovian simulator for Boolean models
- Describe the cell's intracellular signaling and regulatory networks.

## Method:

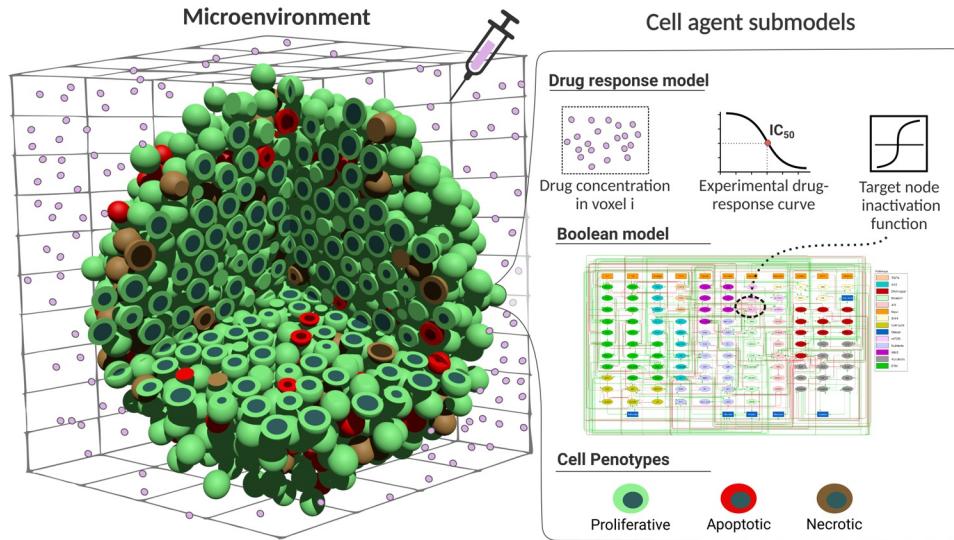
- Each PhysiCell agent has a MaBoSS model and data
- PhysiCell sends cell and tissue data to MaBoSS as inputs
- MaBoSS advances solution a fixed time
- MaBoSS sends outputs to key PhysiCell agent parameters

**Reference 1:** Letort et al., Bioinformatics (2019)

**DOI:** [10.1093/bioinformatics/bty766](https://doi.org/10.1093/bioinformatics/bty766)

**Reference 2:** Ponce-de-Leon et al., npj Sys. Biol. Appl. (2023)

**DOI:** [10.1038/s41540-023-00314-4](https://doi.org/10.1038/s41540-023-00314-4)



**PhysiBoSS simulation of combination therapies in LNCaP**

# Key modeling step: $\mathbf{b} = \mathbf{f}(\mathbf{s})$

- A key modeling step for ABMS is defining the functional relationship  $\mathbf{f}$  between a set of signals  $\mathbf{s}$  and a set of behaviors  $\mathbf{b}$ :

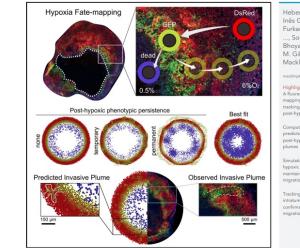
$$\mathbf{b} = \mathbf{f}(\mathbf{s})$$

- Traditionally, ABMs write  $\mathbf{f}$  as hand-written custom code.
- Boolean networks, ODEs, FBA, and NN models are sophisticated forms of  $\mathbf{f}$ .
  - Requires:
    - Mapping quantities in the ABM framework to inputs of  $\mathbf{f}$
    - Mapping outputs of  $\mathbf{f}$  to parameters in the ABM
- More recently, we defined an intermediate level  $\mathbf{f}$  via a grammar. More later.

# PhysiCell as a virtual laboratory

- Choose important chemical signals
  - These become diffusible chemical fields
- Choose important cell types
  - These become our cell definitions
- Clearly state our biological hypotheses as signal-response statements
  - These become our agent rules
- Perform virtual experiments to ask ***what if*** questions
  - What hypotheses does it take to match reality?
    - Which rules are the most important?
    - Which rules can be tuned to steer the system?

# Examples



# Example: Exploring phenotypic persistence in hypoxic breast cancer

# Fate-mapping intratumoral hypoxia

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## Fate-mapping post-hypoxic tumor cells reveals a ROS-resistant phenotype that promotes metastasis

Inés Godet, Yu Jung Shin, Julia A. Ju, I Chae Ye, Guannan Wang & Daniele M. Gilkes 

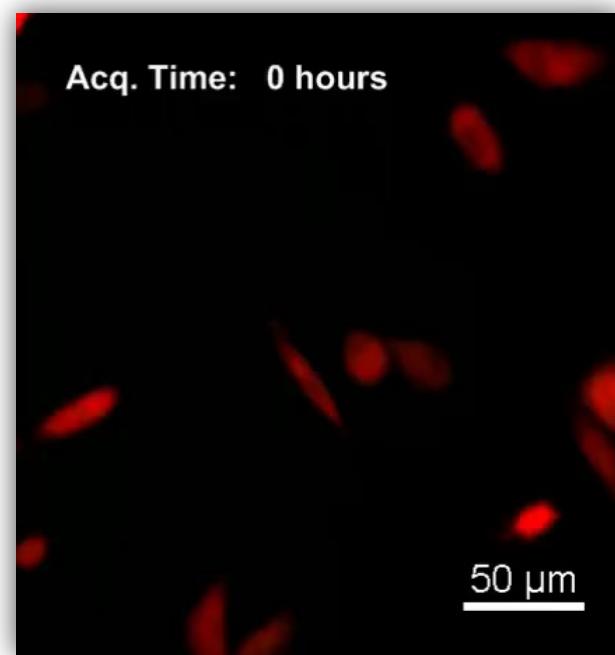
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Sections  Figures  References   
Abstract

**What are the rules of hypoxic cancer cells after they escape hypoxia?**

**Do they resume their old program?**

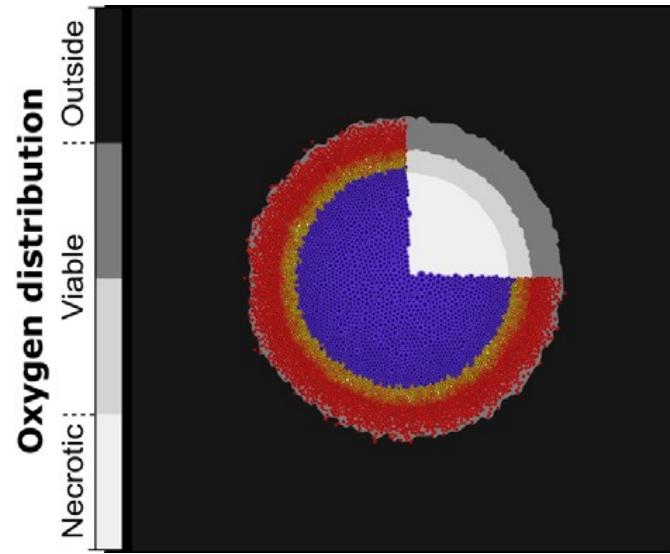
**How soon?**



Daniele Gilkes Lab, Johns Hopkins

# Model overview

- Simulate oxygen diffusion and uptake
- Proliferation and necrosis vary with  $pO_2$  and mechanical pressure
- Live cells are **normoxic (RFP)** or **hypoxic (GFP)**.
- Model transition from **RFP** to **GFP** via ODEs
- **GFP** cells migrate up  $pO_2$  gradients
  - **Phenotypic persistence:** How long do **GFP** cells keep their migratory behavior after leaving hypoxic regions



# Phenotypic persistence drives invasion

## Phenotypic Persistence:

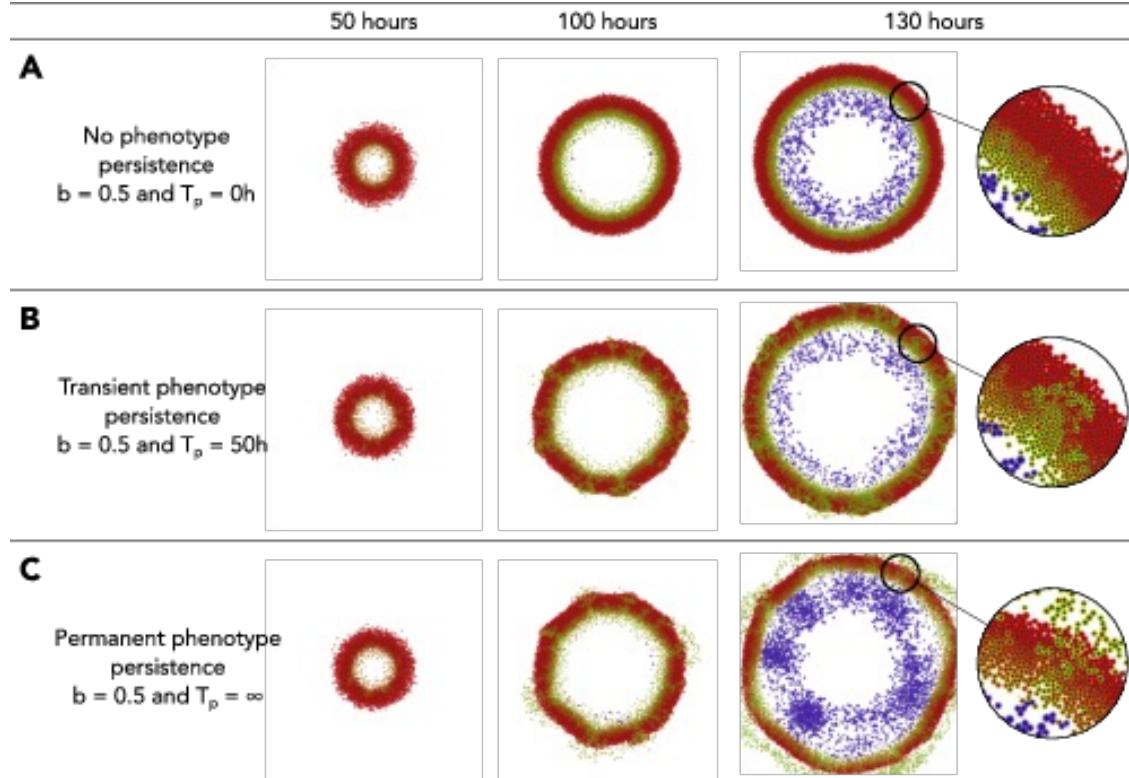
- $T_p$ : duration of hypoxic response

## Without persistence ( $T_p = 0$ ) – Row A

- Migration halts at perinecrotic boundary
- Tumors maintain a concentric structure:
  - Oxygenated viable rim (red)
  - hypoxic (or formerly hypoxic) annulus (green)
  - Necrotic core (purple)

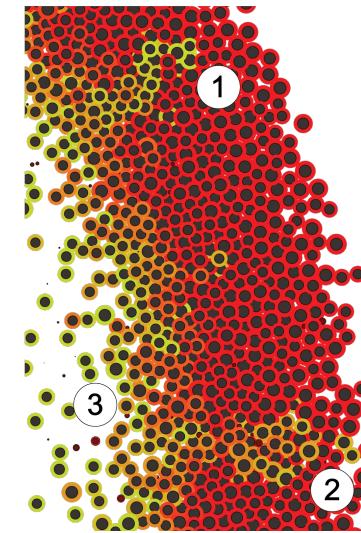
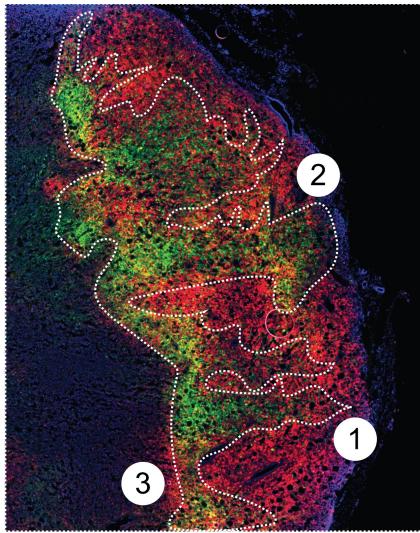
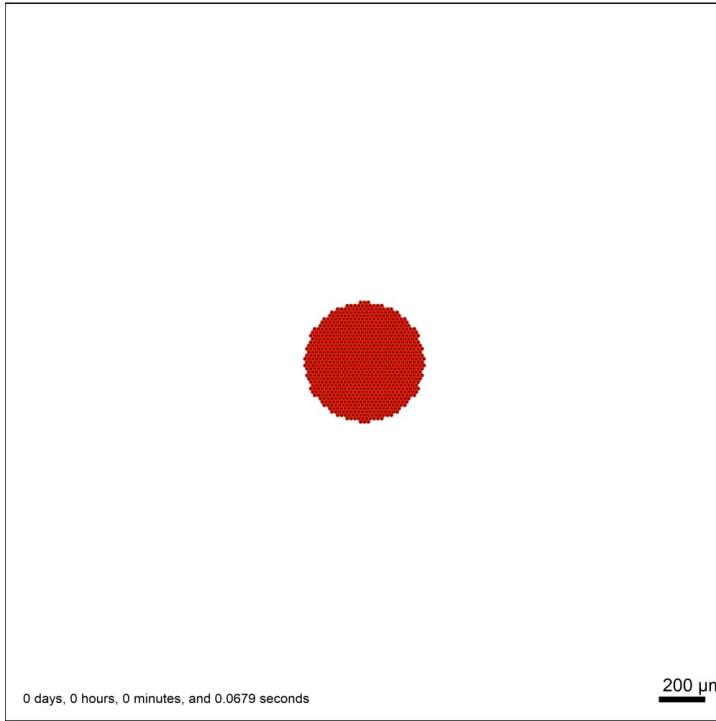
## With persistence ( $T_p > 0$ ) – Rows B & C

- Hypoxic cells can continue migrating
- Hypoxic cells "punch through" the oxygenated tumor region
- Cells act individually, but it *looks* like collective behavior.
  - Risk of over-interpreting single snapshots!



# Mathematical model explains biological observations

Current time: 0 days, 0 hours, and 0.00 minutes, z = 0.00  $\mu\text{m}$   
889 agents



Try this model yourself!  
[nanohub.org/tools/pc4tumorhypoxia](http://nanohub.org/tools/pc4tumorhypoxia)

# Example: Iterative development of a SARS- CoV-2 tissue model

# Thank you to our coalition!

**Multinational:**  
U.S.  
Canada  
United Kingdom

**Federal partners:**  
Veterans Affairs  
Argonne National Lab

**Across Indiana:**  
Luddy School (lead)  
UITs  
IU Health  
Purdue

**Industry:**  
Pfizer  
  
...

## Rapid community-driven development of a SARS-CoV-2 tissue simulator

Michael Getz<sup>1,\*\*</sup>, Yafei Wang<sup>1,\*\*\*</sup>, Gary An<sup>2,\*</sup>, Andrew Becker<sup>2,\*</sup>, Chase Cockrell<sup>2,\*</sup>, Nicholson Collier<sup>3,4,\*</sup>, Morgan Craig<sup>5,6,\*</sup>, Courtney L. Davis<sup>7,\*</sup>, James Faeder<sup>8,\*</sup>, Ashlee N. Ford Versypt<sup>9,10,\*</sup>, Juliano F. Gianlupi<sup>1,\*</sup>, James A. Glazier<sup>1,\*</sup>, Sara Hamis<sup>11,\*</sup>, Randy Heiland<sup>1,\*</sup>, Thomas Hillen<sup>12,\*</sup>, Dennis Hou<sup>13,\*</sup>, Mohammad Aminul Islam<sup>9,\*</sup>, Adrienne Jenner<sup>5,6,\*</sup>, Furkan Kurtoglu<sup>1,\*</sup>, Bing Liu<sup>8,\*†</sup>, Fiona Macfarlane<sup>1,\*</sup>, Pablo Maygrunder<sup>14,\*</sup>, Penelope A Morel<sup>15,\*</sup>, Aarthi Narayanan<sup>16,\*</sup>, Jonathan Ozik<sup>3,4,\*</sup>, Elsje Pienaar<sup>17,\*</sup>, Padmini Rangamani<sup>18,\*</sup>, Jason Edward Shoemaker<sup>19,\*</sup>, Amber M. Smith<sup>20,\*</sup>, Paul Macklin<sup>1,\*\*\*</sup>

<sup>1</sup> Department of Intelligent Systems Engineering, Indiana University, Bloomington, IN USA

<sup>2</sup> The University of Vermont Medical Center, Burlington, VT USA

**40+ regular contributors from 20+ institutions**

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<sup>18</sup> Department of Chemical and Biomolecular Engineering, Purdue University, West Lafayette, IN USA

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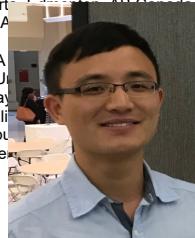
**Michael Getz**  
Indiana U.

\*\* equal contribution  
† in manuscript  
\*\*\* corresponding author: [macklin@iu.edu](mailto:macklin@iu.edu), [@MathCancer](https://MathCancer.org)

Note: This is a rapid prototyping project. For the very latest, see <http://COVID-19.physicell.org>



**Yafei Wang**  
Indiana U.



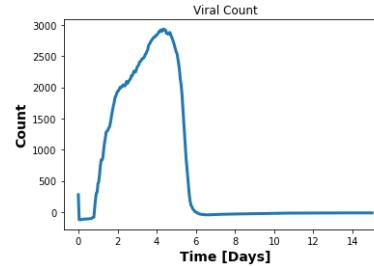
# Iterative progress

- **v1: initial prototype**
  - viral replication dynamics, viral transport, cell death response
- **v2: add ACE2 receptor dynamics, ACE2-based viral entry**
  - random viral seeding with multiplicity of infection (MOI)
- **v3: add immune response**
  - macrophages activate, begin inflammation, immune cell recruitment, CD8+ T cells
- **v4: add lymph node compartment and fibrosis**
  - dendritic cells move to lymph node, start immune expansion, recruitment
- **v5: add neutralizing antibodies**

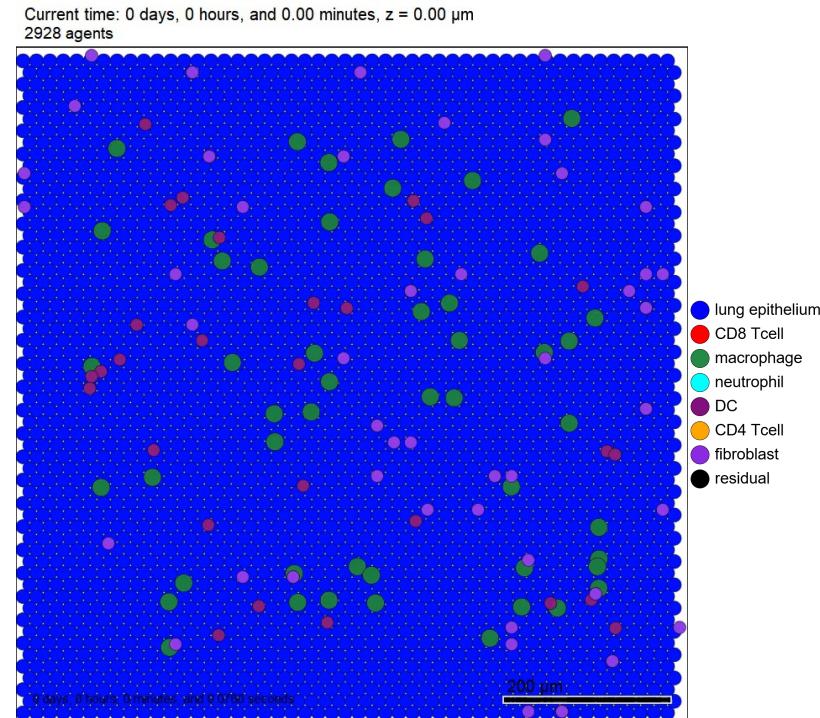
# v5: neutralizing antibodies clear the infection

- **v5 model (released Fall 2021)**

- Neutralizing antibody production
- Neutralizing antibody binds intracellular virus to prevent entry.
- Negative feedbacks:
  - anti-inflammatory signals



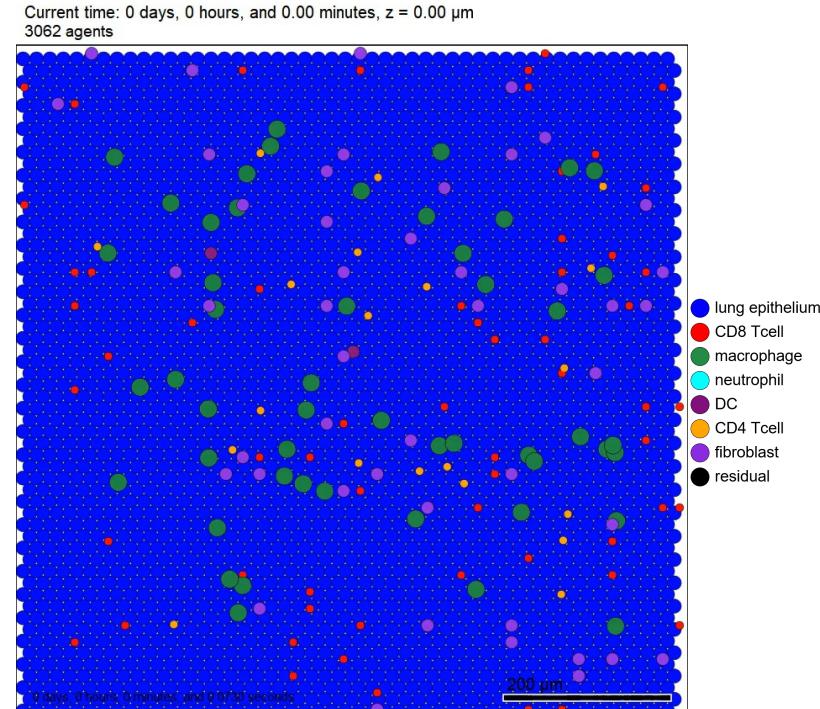
- **This immune model is sufficiently complete to clear a SARS-CoV-2 infection**



A naïve immune system can adapt to halt the infection

# v5: prior immune responses are protective

- The prior immune response is persistent:
  - Elevated "trained" CD8 T cells
  - Elevated neutralizing antibodies
- The prior immune response is protective:
  - Expose lung tissue to more virion
  - Brief immune activation
  - Much more limited tissue damage
  - Complete viral clearance
- This immune model is sufficiently complete to show future protection after successful immune responses.



Trained immune system facing future exposure

# Rethinking modeling

# Key computational modeling steps

## 1. Formulate hypotheses:

- How do biophysical signals drive cell behaviors?
- Requires a conversation between biologists and mathematicians

## 2. Transform hypotheses into mathematics

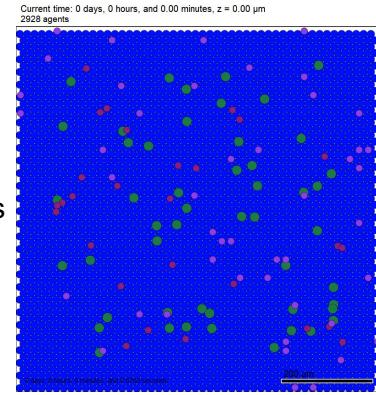
- Typically performed manually for each hypothesis

## 3. Implement mathematical statements as code

- C++, Python, Java, ...
- Typically **hand-written code**

# Sample: COVID-19 macrophage model

- Macrophage hypotheses
  - 5.MPhi.1 Resident (unactivated) and newly recruited macrophages move along debris gradients.
  - 5.MPhi.2 Macrophages phagocytose dead cells. Time taken for material phagocytosis is proportional to the size of the debris
  - 5.MPhi.3 Macrophages break down phagocytosed materials
  - 5.MPhi.4 After phagocytosing dead cells, macrophages activate and secrete pro-inflammatory cytokines
  - 5.MPhi.5 Activated macrophages can decrease migration speed
  - 5.MPhi.6 Activated macrophages have a higher apoptosis rate
  - 5.MPhi.7 Activated macrophages migrate along chemokine and debris gradients
  - 5.MPhi.8 Macrophages are recruited into tissue by pro-inflammatory cytokines
  - 5.MPhi.9 Macrophages can die and become dead cells only if they are in an exhausted state
  - 5.MPhi.10 Macrophages become exhausted (stop phagocytosing) if internalised debris is above a threshold
  - 5.MPhi.11 CD8<sup>+</sup> T cell contact stops activated macrophage secretion of pro-inflammatory cytokine and switches to M2 phase, secreting anti-inflammatory cytokine.
  - 5.MPhi.12 CD4<sup>+</sup> T cell contact induces activated macrophage phagocytosis of live infected cell



**PhysiCell model  
of COVID19**

**These hypotheses become hand-coded functions in C++.**

# Code profiling: identify bottlenecks

- Software analysis: code profiling:
  - For a simulation run, where do we spend the most time?
  - Use this to focus optimization
- Profiling by Sunita Chandrasakaran's group (U. Delaware):
  - 65% of computation time is spent on diffusion
  - If we can accelerate diffusion 10x:

$$\text{Time}_{\text{new}} = \left( \frac{1}{10} \cdot 0.65 + 0.35 \right) \text{Time}_{\text{old}} \approx 0.42 \text{Time}_{\text{old}}$$

- If we can accelerate diffusion 100x:

$$\text{Time}_{\text{new}} = \left( \frac{1}{100} \cdot 0.65 + 0.35 \right) \text{Time}_{\text{old}} \approx 0.36 \text{Time}_{\text{old}}$$

- If we can accelerate diffusion 1000x:

$$\text{Time}_{\text{new}} = \left( \frac{1}{1000} \cdot 0.65 + 0.35 \right) \text{Time}_{\text{old}} \approx 0.35 \text{Time}_{\text{old}}$$

- Notice the **rapidly diminishing returns!** **Key lessons:**
  - Once the bottleneck is gone, move on to the next one!
  - This is the economics of code optimization! (Decreasing marginal utility)

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Kara Morris, kmorris@usf.edu

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SPECIAL TRACK: SOFTWARE ENGINEERING

**OpenACC Acceleration of an Agent-Based Biological Simulation Framework**

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Robert Seales, NVIDIA Corporation, Santa Clara, CA, 95051, USA  
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Computational biology has increasingly turned to agent-based modeling to explore complex biological systems. Biological diffusion (diffusion, decay, secretion, and uptake) is a key driver of many processes in these systems. GPU computation can vastly accelerate the diffusion and uptake processes in the partial differential equations required to model biological transport in an agent-based modeling system. In this article, we utilize OpenACC to accelerate the diffusion portion of PhysCell, a cross-platform agent-based biosimulation framework. We demonstrate an almost 40% speedup on the state-of-the-art NVIDIA Ampere 100 GPU compared to a serial run on AMD's EPYC 7742. We also demonstrate a 10x speedup on a standard Intel Xeon E5-2695 v4 CPU. By utilizing OpenACC for both the CPUs and the GPUs, we maintain a single source code base, thus creating a portable yet performance solution. With the simulator's most significant computational bottleneck significantly reduced, we can continue cancer simulations over much longer times.

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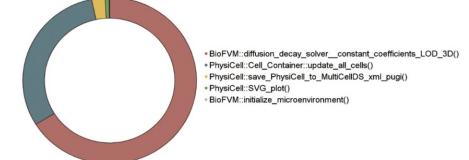
Therefore, most modern agent-based biological modeling systems are hybrid, where discrete cell agents with their own local equations (PDEs) interact with continuous diffusible substrates, such as

$$\frac{\partial p}{\partial t} = D\nabla^2 p - \lambda p = \sum_{i=1}^n (x_i - x_c) V_i(S_i(p_i) - U_i(p))$$

where  $p$  is a vector of diffusible substrates, and each cell agent has position  $x$ , and volume  $V$ , a vector of production rates  $S$ , a vector of consumption rates  $U$ , and a vector of extracellular substrate vector  $\mu$ . (Vector dot products are taken elementwise, and  $\delta$  is the Dirac delta function.) Numerical solution of these coupled PDEs and ODEs can be solved with relatively small step size  $\Delta t$ , making the solution of the coupled simulation PDEs a major bottleneck in hybrid agent-based modeling. This, in turn, can hinder high-throughput simulation model exploration (e.g., newer model calibration techniques like

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Date of current version: 1 May 2023.

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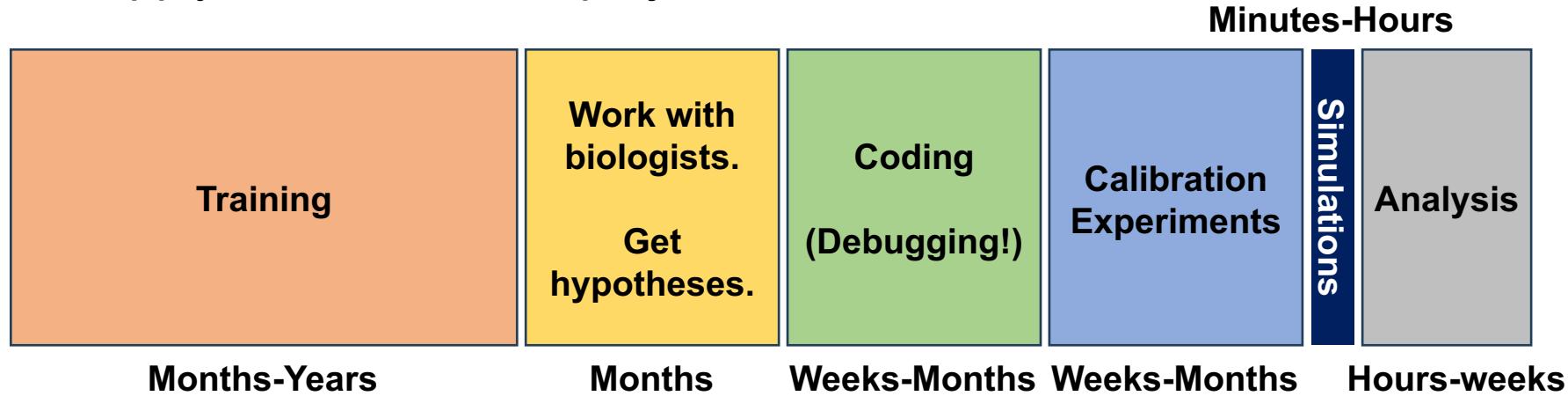


# Let's generalize this analysis

1. Identify the biggest bottleneck
2. Improve that speed by 1-2 orders of magnitude, but no more!
3. After that, move on to the next bottleneck.

# "Code profiling" for scientific projects

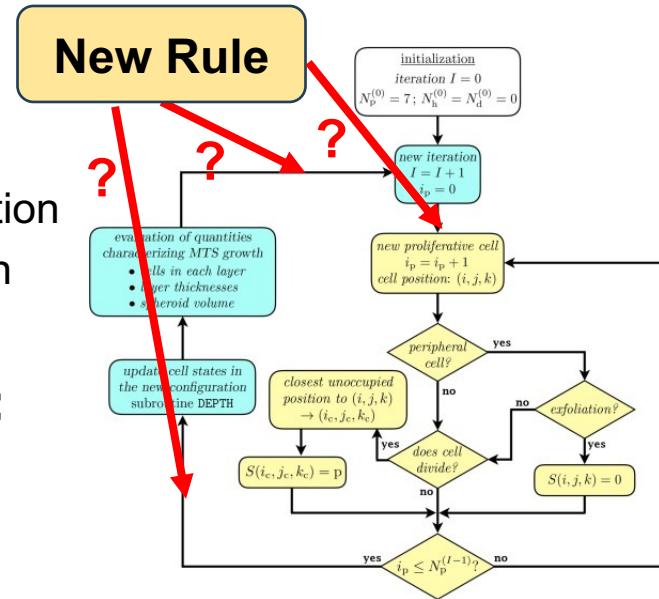
- Let's apply this to scientific projects.



- As numerical analysts, **what are we *most tempted* to improve?**
- With a holistic viewpoint, **where *should* we improve?**

# Problems with hand-written models

- Many models re-implement recurring elements
  - Does not leverage prior modeling
  - Increases likelihood of errors
  - **Large coding effort** discourages multidisciplinary participation
  - Variations in implementation add complexity to interpretation
- **Perhaps most importantly, as complexity grows:**
  - Hard to understand the full model
  - Hard to communicate the current biological hypotheses
  - Hard to integrate new biological hypotheses
  - Hard for domain experts to participate in real time



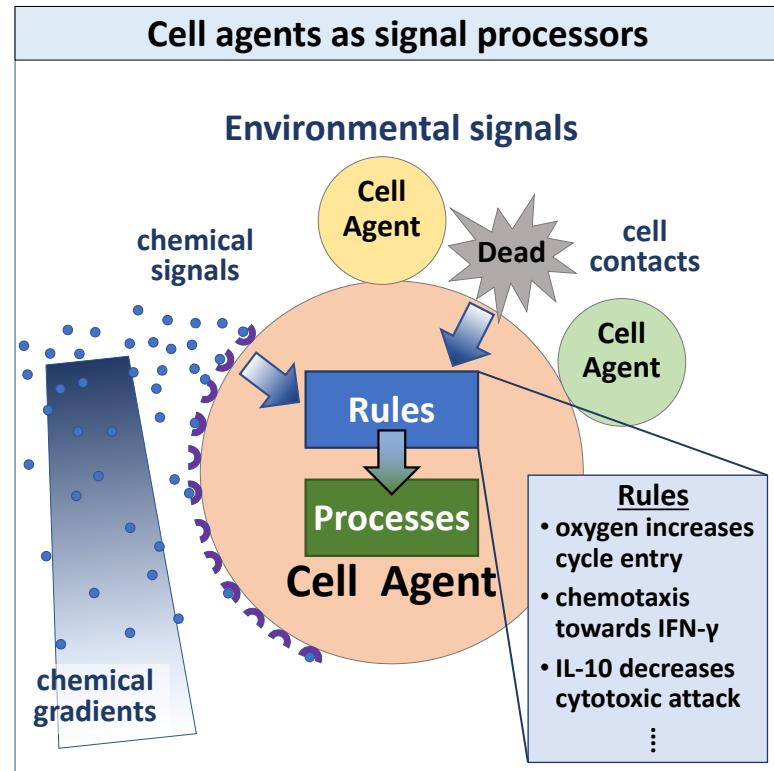
DOI: 10.1016/j.ejmp.2020.07.026

# Creating a model grammar

- **Goal:** Create a formal language for cell rules that:
  - Can be written in human-readable "plain English"
    - Facilitates tools for easy model construction
    - ***Turns model building into knowledge mapping***
  - Can readily be "translated" to a standard mathematical form
    - Model can parse the rules without hand-coding
    - More reusable, maintainable model
  - Can easily integrate new knowledge with prior knowledge
  - Can combine data-driven and knowledge-driven workflows

# Key elements for a computable model grammar

- A "dictionary" of signals (stimuli)
- A "dictionary" of reference behaviors
- A grammar to connect signals to behavioral responses
- Map grammar statements onto mathematics and code



# A dictionary of signals

- A dictionary of signals that can be used as inputs for hypothesis statements
- **Diffusible chemical substrates**
  - extracellular and intracellular concentrations
  - extracellular gradients
- **Cell mechanics / physics**
  - Cell pressure
  - Cell volume
- **Contact**
  - # of contacts with live and dead cells
  - Number of contacts with each cell type
  - Contact with basement membrane
- **Live / dead status**
  - Dead, apoptotic, necrotic
- **Damage** (e.g., from effector attack)
- **Custom symbols**

Each symbol uniquely maps to a mathematical quantity at a cell's position

# Signal mappings

dictionary symbol	synonyms	accessible variable (and notes)
X		extracellular diffusible substrate X at cell location
intercellular X	internalized X	total internalized substrate X in the cell
X gradient	grad(X), gradient of X	norm of the gradient of extracellular diffusible substrate X
volume		total cell volume
pressure		(nondimensionalized) mechanical pressure acting upon the cell
contact with Y	contact with cell type Y	number of live cells of type Y in physical contact with the cell
contact with live cell	contact with live cells	number of live cells in physical contact with the cell
contact with dead cell	contact with dead cells	number of dead cells in physical contact with the cell
contact with basement membrane	contact with BM	1 if in contact with a basement membrane, and 0 otherwise (reserved symbol for future reference models)
damage		total cell damage (see <b>effector attack</b> above)
total attack time		total accumulated attack time on the cell by effector cells (see <b>effector attack</b> above)
dead	is dead	1 if the cell is dead, and 0 otherwise
apoptotic	is apoptotic	1 if the cell is apoptotic, and 0 otherwise (or if the cell is undergoing a non-necrotic cell death)
necrotic	is necrotic	1 if the cell is necrotic, and 0 otherwise
time	current time, global time	current elapsed simulation time
custom:Z	custom: Z, custom Z	access to a cell's custom parameter Z

**Table 8.** A list of symbols in our vocabulary of signals that can be used to drive behavioral or state changes in cells. Here,  $X$  is any diffusible substrate,  $Y$  is a cell type, and  $Z$  is a customized cell parameter (or variable).

# A dictionary of behaviors

- Based on years of modeling, we created a "dictionary" of standardized behaviors ***and well-defined reference models***
- **Cycling**
  - Exit rates from each cycle phase
- **Death**
  - Apoptotic and necrotic death rates
- **Transport**
  - Secretion, uptake, and export rates
- **Migration and chemotaxis**
  - Migration speed, bias, persistence time
  - Chemotactic sensitivities (to each diffusible factor)
- **Mechanics and Adhesion**
  - Adhesion and repulsion potential coefficients
  - Adhesion affinities (to each cell type)
  - Elastic adhesion constant, maximum number of adhesions
  - Rate of forming and breaking elastic adhesions
- **Transformation**
  - Rate of transforming (to each cell type)
- **Fusion**
  - Rate of fusing (combining with) each cell type
- **Phagocytosis (or ingestion / predation)**
  - Rate of ingesting dead cells
  - Rate of ingesting live cells (one rate for each type)
- **Effector Attack**
  - Rate of attacking live cells (one for each type), Immunogenicity (one for each cell type)
  - Rate of causing damage during attack
- **Custom symbols**

Each symbol uniquely maps to a mathematical parameter in a reference process model.

# Sample behavior mappings

dictionary symbol	synonyms	controllable phenotype parameter
migration speed		$s$
migration bias		$b$
migration persistence time		$T_{\text{persist}}$
chemotactic response to $X$	chemotactic sensitivity to $X$	$\omega_i$

dictionary symbol	synonyms	controllable phenotype parameter
transform to X	transform to cell type X	$r_{T,ij}$
fuse to X	fuse to cell type X	$r_{F,ij}$
phagocytose dead cell	phagocytosis of dead cell, phagocytosis of dead cells	$r_{PD,i}$
phagocytose X	phagocytose cell type X, phagocytosis of X	$r_{PL,ij}$
attack X	attack cell type X	$r_{A,ij}$
immunogenicity to X	immunogenicity to cell type X	$g_{A,ij}$
damage rate		$r_{\text{damage}}$

# Hypothesis statements

- For [cell type T], [S] increases / decreases [B] **[optional arguments]**
  - **Cell type T** is as cell type defined in the simulation model
  - **S** is a signal in our signal dictionary
  - **B** is a behavioral parameter in our behavior dictionary
- **Examples:**
  - For M0 macrophages, necrotic cell debris increases transformation to M1 macrophages
  - For malignant epithelial cells, doxorubicin increases apoptosis

# Mathematical Mapping

- If signal  $S$  increases / decreases behavior  $B$ 
  - Vary behavioral parameter  $p$  with base value  $p_0$  and maximal response  $p_M$

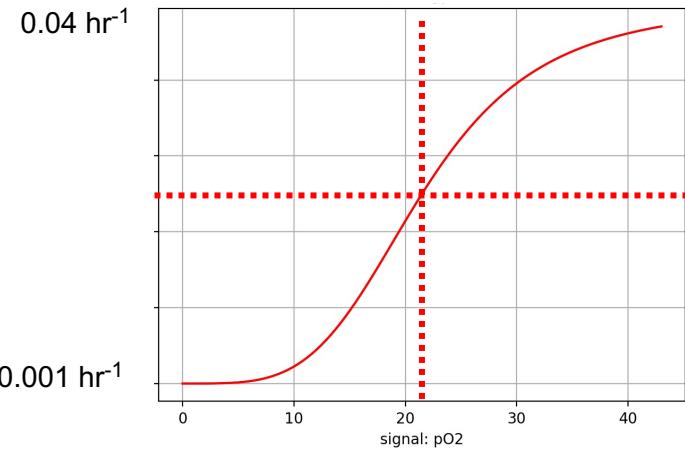
$$p(s) = p_0 + (p_M - p_0)R(s) = (1 - R(s)) \cdot p_0 + R(s) \cdot p_M$$

- We generally use **Hill response functions**:

$$R(s) = \frac{s^h}{s_{\text{half}}^h + s^h} = \frac{\left(\frac{s}{s_{\text{half}}}\right)^h}{1 + \left(\frac{s}{s_{\text{half}}}\right)^h} \quad \text{if } s \geq 0.$$

- **Example:** Oxygen increases cycle entry

$$r_{01} = 0.001 + (0.042 - 0.001) \frac{(pO_2)^4}{21.5^4 + (pO_2)^4}$$



# Integrating many hypotheses

- **Multivariate Hill response functions**

- Can integrate multiple signals with independent half-maxes and Hill powers
- Reduce back down to original Hill function if all but one input is zero

- **Total up response:**

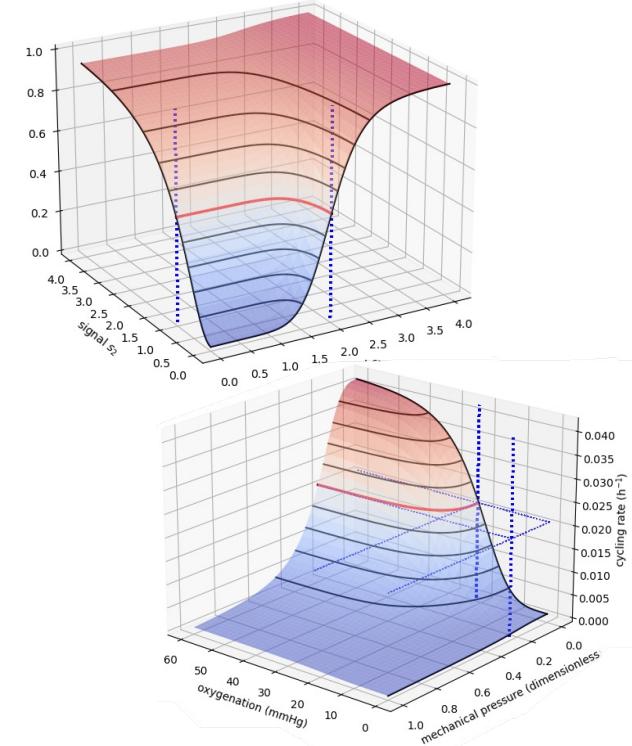
$$U = H_M(\mathbf{u}; \mathbf{u}_{\text{half}}, \mathbf{p}) = \frac{\left(\frac{u_1}{u_1^*}\right)^{p_1} + \left(\frac{u_2}{u_2^*}\right)^{p_2} + \cdots + \left(\frac{u_m}{u_m^*}\right)^{p_m}}{1 + \left(\frac{u_1}{u_1^*}\right)^{p_1} + \left(\frac{u_2}{u_2^*}\right)^{p_2} + \cdots + \left(\frac{u_m}{u_m^*}\right)^{p_m}}$$

- **Total down response:**

$$D = H_M(\mathbf{d}; \mathbf{d}_{\text{half}}, \mathbf{q}) = \frac{\left(\frac{d_1}{d_1^*}\right)^{q_1} + \left(\frac{d_2}{d_2^*}\right)^{q_2} + \cdots + \left(\frac{d_n}{d_n^*}\right)^{q_n}}{1 + \left(\frac{d_1}{d_1^*}\right)^{q_1} + \left(\frac{d_2}{d_2^*}\right)^{q_2} + \cdots + \left(\frac{d_n}{d_n^*}\right)^{q_n}}.$$

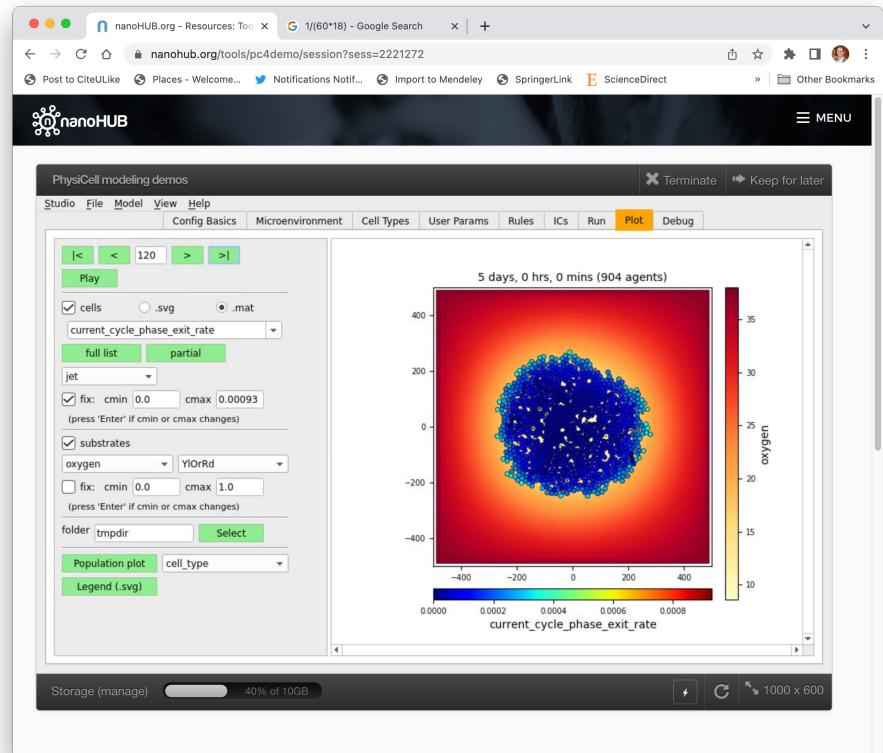
- **Integrated response:**

$$p(\mathbf{u}, \mathbf{d}) = (1 - D) \cdot [(1 - U) \cdot p_0 + U \cdot p_M] + D \cdot p_m$$



# Building models *on-the-fly* in the cloud

- The language is constrained enough to create a data format.
- A fixed data format makes GUIs possible.
- We can bundle this as a cloud-hosted app.
  - <http://nanohub.org/tools/pcstudio>
- Now, **in real time**:
  - Choose cell types and diffusing factors
  - Write rules
  - Simulate and visualize
  - Ask biologist for feedback
  - Write more rules
  - Simulate, visualize, and repeat



**The modeler-biologist  
feedback loop is now minutes  
instead of weeks.**

# Automated model annotation

- We auto-generate formatted HTML tables as we parse the rules
  - (We can generate LaTeX, DOCX, etc. too ... )
- Thus, the underlying hypotheses are summarized for inclusion in the methods section for later papers.

## Cell Hypothesis Rules (detailed)

In tumor cells:

- oxygen increases cycle entry from 0 towards 0.00072 with a Hill response, with half-max 21.5 and Hill power 4.
- pressure decreases cycle entry from 0 towards 0 with a Hill response, with half-max 1 and Hill power 4.
- oxygen decreases necrosis from 0.0028 towards 0 with a Hill response, with half-max 3.75 and Hill power 8.
- damage increases apoptosis from 7.2e-05 towards 0.072 with a Hill response, with half-max 180 and Hill power 2.
- dead increases debris secretion from 0 towards 0.017 with a Hill response, with half-max 0.1 and Hill power 10. Rule applies to dead cells.
- IFN-gamma decreases migration speed from 0.5 towards 0 with a Hill response, with half-max 0.25 and Hill power 2.

In M0 macrophage cells:

- contact with dead cell increases transform to M1 macrophage from 0 towards 0.05 with a Hill response, with half-max 0.1 and Hill power 10.
- contact with dead cell decreases migration speed from 1 towards 0.1 with a Hill response, with half-max 0.1 and Hill power 4.
- dead increases debris secretion from 0 towards 0.017 with a Hill response, with half-max 0.1 and Hill power 10. Rule applies to dead cells.

In M1 macrophage cells:

- contact with dead cell decreases migration speed from 1 towards 0.1 with a Hill response, with half-max 0.1 and Hill power 4.
- oxygen decreases transform to M2 macrophage from 0.01 towards 0 with a Hill response, with half-max 5 and Hill power 4.
- IFN-gamma increases cycle entry from 7.2e-05 towards 0.00036 with a Hill response, with half-max 0.25 and Hill power 2.
- IFN-gamma increases phagocytose dead cell from 0.01 towards 0.05 with a Hill response, with half-max 0.25 and Hill power 2.
- dead increases debris secretion from 0 towards 0.017 with a Hill response, with half-max 0.1 and Hill power 10. Rule applies to dead cells.

In M2 macrophage cells:

- contact with dead cell decreases migration speed from 1 towards 0.1 with a Hill response, with half-max 0.1 and Hill power 4.
- IFN-gamma decreases cycle entry from 7.2e-05 towards 0 with a Hill response, with half-max 0.25 and Hill power 2.
- IFN-gamma increases phagocytose dead cell from 0.01 towards 0.05 with a Hill response, with half-max 0.25 and Hill power 2.
- dead increases debris secretion from 0 towards 0.017 with a Hill response, with half-max 0.1 and Hill power 10. Rule applies to dead cells.

In naive T cell cells:

- IL-10 decreases transform to CD8 T cell from 0.001 towards 0 with a Hill response, with half-max 0.25 and Hill power 2.
- IFN-gamma increases transform to CD8 T cell from 0.001 towards 0.01 with a Hill response, with half-max 0.25 and Hill power 2.
- dead increases debris secretion from 0 towards 0.017 with a Hill response, with half-max 0.1 and Hill power 10. Rule applies to dead cells.

In CD8 T cell cells:

- IFN-gamma increases cycle entry from 7.2e-05 towards 0.00093 with a Hill response, with half-max 0.25 and Hill power 2.
- IL-10 decreases attack tumor from 0.01 towards 0 with a Hill response, with half-max 0.25 and Hill power 2.
- IL-10 decreases migration speed from 1 towards 0.1 with a Hill response, with half-max 0.25 and Hill power 2.
- contact with tumor decreases migration speed from 1 towards 0.1 with a Hill response, with half-max 0.1 and Hill power 2.
- IL-10 increases transform to exhausted T cell from 0 towards 0.005 with a Hill response, with half-max 0.25 and Hill power 4.
- dead increases debris secretion from 0 towards 0.017 with a Hill response, with half-max 0.1 and Hill power 10. Rule applies to dead cells.

In exhausted T cell cells:

- dead increases debris secretion from 0 towards 0.017 with a Hill response, with half-max 0.1 and Hill power 10. Rule applies to dead cells.

# Example: tumor-immune

## In tumor cells:

- oxygen increases cycle entry
- pressure decreases cycle entry
- oxygen decreases necrosis
- damage increases apoptosis
- dead increases debris secretion
- IFN-gamma decreases migration speed

## In M0 macrophages:

- contact with dead cell increases transform to M1 macrophage
- contact with dead cell decreases migration speed
- dead increases debris secretion

## In M1 macrophages:

- contact with dead cell decreases migration speed
- oxygen decreases transform to M2 macrophage
- IFN-gamma increases cycle entry
- IFN-gamma increases phagocytose dead cell
- dead increases debris secretion

## In M2 macrophages:

- contact with dead cell decreases migration speed
- IFN-gamma decreases cycle entry
- IFN-gamma increases phagocytose dead cell
- dead increases debris secretion

## In naive T cells:

- IL-10 decreases transform to CD8 T cell
- IFN-gamma increases transform to CD8 T cell
- increases debris secretion
- dead

## In CD8 T cells:

- IFN-gamma increases cycle entry
- IL-10 decreases attack tumor
- IL-10 decreases migration speed
- contact with tumor decreases migration speed
- IL-10 increases transform to exhausted T cell
- dead increases debris secretion

## In exhausted T cells:

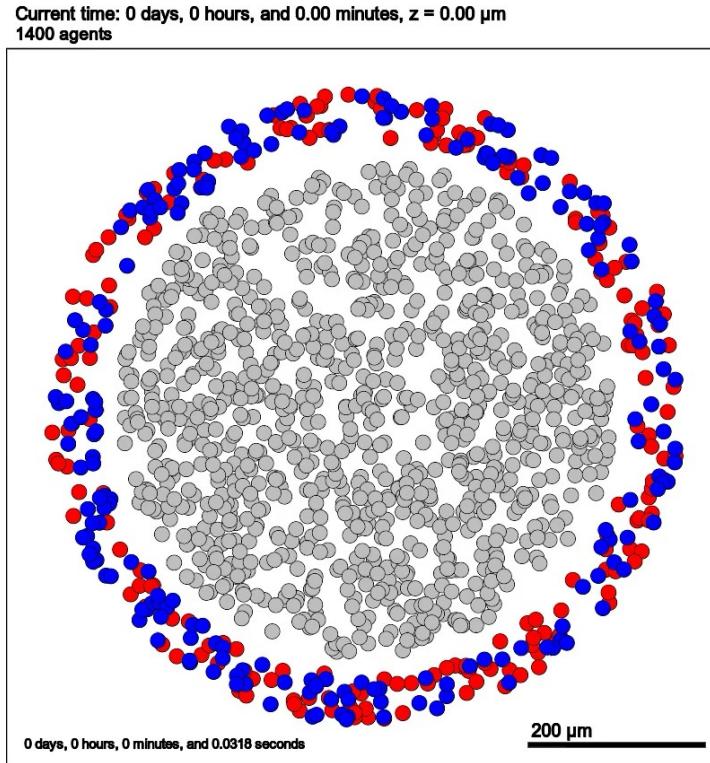
- dead increases debris secretion

## Joint work with OHSU:

- Lisa Coussens
- Joe Gray
- Laura Heiser
- Young Hwan-Chang

# Example: tumor-immune

- tumor
- M0 macrophage
- M1 macrophage
- M2 macrophage
- naive T cell
- CD8 T cell
- exhausted T cell

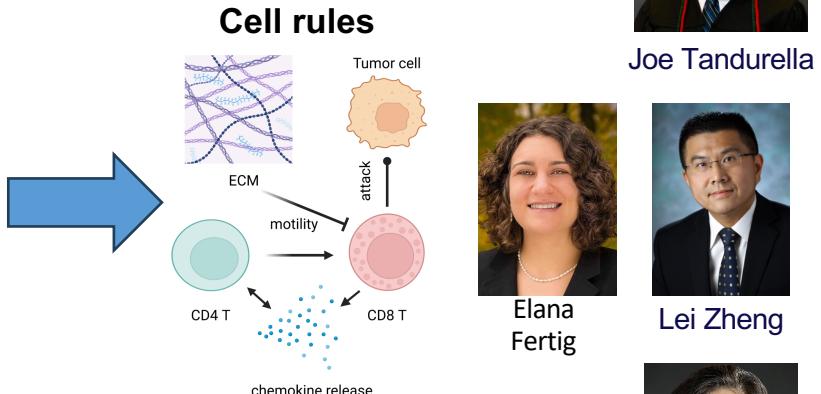
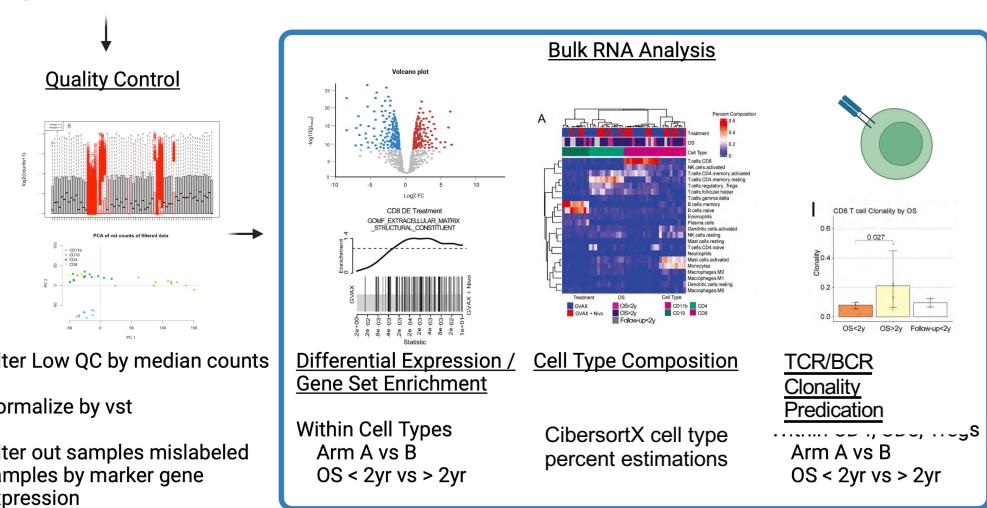
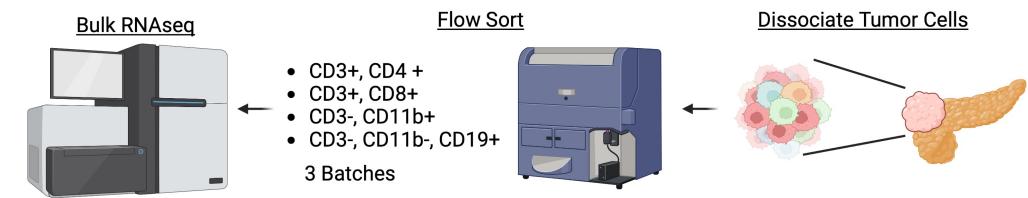


- Joint work with OHSU:**
- Lisa Coussens
  - Joe Gray
  - Laura Heiser
  - Young Hwan-Chang

We can use the language to  
connect genomics with  
dynamical modeling

# Analysis of genomic data can generate cell rules

CONVERGENCE  
INSTITUTE



Joe Tandurella



Elana  
Fertig



Lei Zheng

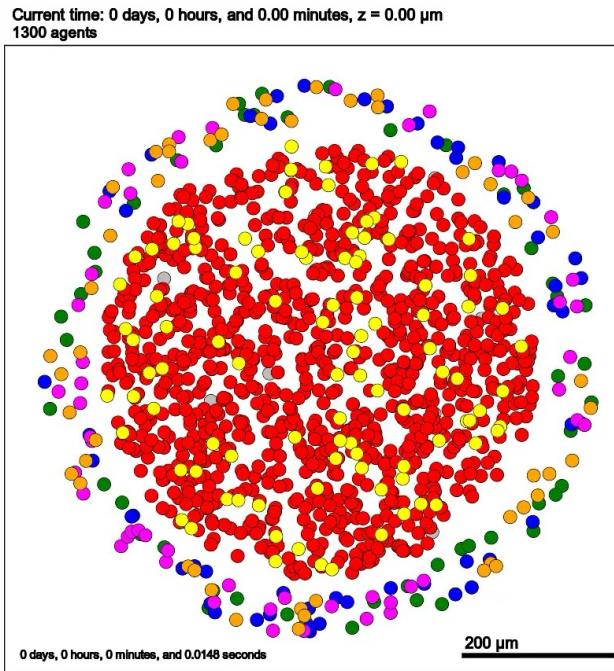
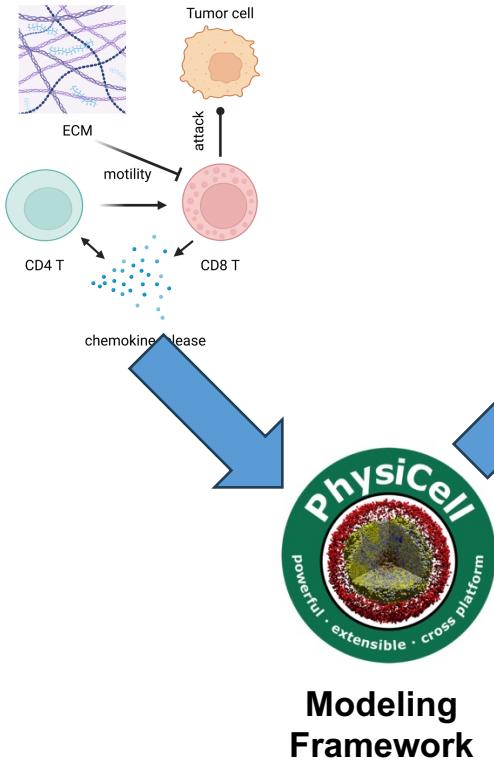


Elizabeth Jaffee

# We can use genomics-derived cell rules in cell agents to simulate evolution of virtual tumors

CONVERGENCE  
INSTITUTE

## Cell rules



Johnson et al, 2023, *BioRxiv*



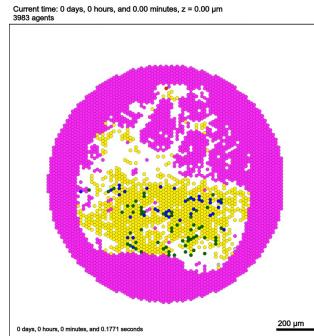
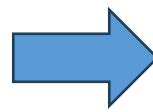
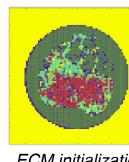
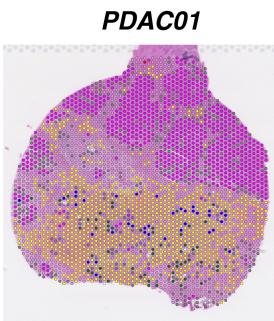
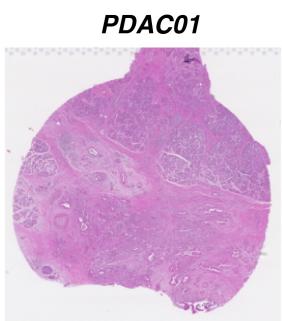
Jeanette  
Johnson

## Model predictions:

- Immune aggregates arise from ICI-induced cell networks
- Cell aggregates block T cell trafficking
- Consistent with (and explains!) clinical observations

# Creating models from spatial transcriptomic data

CONVERGENCE  
INSTITUTE



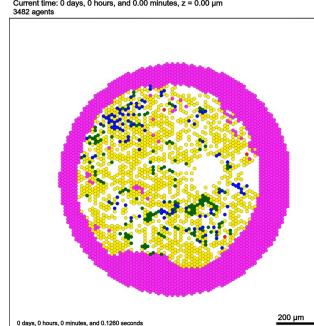
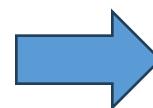
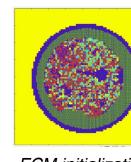
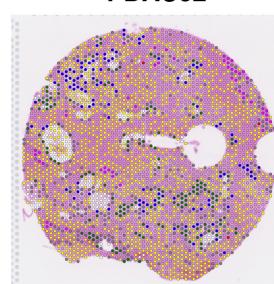
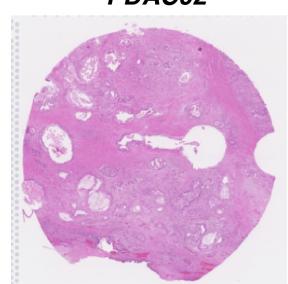
Jeanette  
Johnson



Daniel  
Bergman



Maxwell  
Booth



## Model predictions:

- Test hypothesis:
  - Epithelial-fibroblast interactions can transform epithelial cells
- Composition & geometry of TME drive divergent trajectories
- Consistent with subtype switching in PDAC progression to invasion

# Ultimately, we envision many paths

- Expert-driven
  - Tap decades of learning by biologists and other experts
- Data-driven
  - Automated analysis of scRNASeq data
    - Who is the sender? What signal? (who expresses diffusible and other factors?)
    - Who is the recipient? (Who expresses receptors for the signal?)
    - What is the response? (Can receptor activation be correlated with functional changes?)
- AI-driven Literature Analysis
  - Mine PubMed with NLP, Chat-GPT, etc. to identify relationships
    - Constrained / structured prompts → grammar-formatted rules → human quality control
- All of these paths could be represented in this framing, integrating data-driven and knowledge-driven modeling paths

# New preprint!

This work is available as a preprint on *bioRxiv*.

Under review at *Cell*

DOI: [10.1101/2023.09.17.557982](https://doi.org/10.1101/2023.09.17.557982)

The screenshot shows a web browser displaying a bioRxiv preprint page. The page header includes the bioRxiv logo and navigation links for HOME, SUBMIT, FAQ, BLOG, ALERTS / RSS, ABOUT, and CHANNELS. A search bar is also present. The main content area displays the preprint details:

- Title:** Digitize your Biology! Modeling multicellular systems through interpretable cell behavior
- Posted:** September 17, 2023
- DOI:** <https://doi.org/10.1101/2023.09.17.557982>
- Authors:** Jeanette A.I. Johnson, Genevieve L Stein-O'Brien, Max Booth, Randy Heiland, Furkan Kurtoglu, Daniel Bergman, Elmar Bucher, Atul Deshpande, Andre Forjaz, Michael Getz, Ines Godet, Melissa Lyman, John Metzcar, Jacob Mitchell, Andrew Radatz, Heber L. Rocha, Jacobo Solorzano, Anequa Sundus, Yafei Wang, Daniele M. Gilkes, Luciane T. Kagohara, Ashley L. Kiemien, Elizabeth D. Thompson, Denis Wirtz, Pei-Hsun Wu, Neeha Zaidi, Lei Zheng, Jacqueline W. Zimmerman, Elizabeth M. Jaffee, Young Hwan Chang, Lisa Coussens, Joe Gray, Laura M. Heiser, Elana J. Ferig, Paul Macklin
- Abstract:** Cells are fundamental units of life. Recent technical advances have revolutionized our ability to quantify the state and identity of individual cells, and intercellular regulatory programs. However, these static measurements alone are limited in their ability to predict the complex collective behaviors that emerge from populations of many interacting cells over time. Mathematical models have a proven record of successfully predicting the behaviors of dynamic biological systems, e.g., therapeutic responses in cancer. Simulations from these models

# Today's Sessions

- **Morning:**

- Introduction to Agent-Based Modeling in Cancer
- Agent-Based Models and Digital Twins

- **Afternoon:**

- **Session 1: Getting Started**

- Signals, Behaviors, Phenotype, and Response Functions
- PhysiCell Studio Walk-Through
- Modeling workflow
- First example: Zombies and Villagers

- **Session 2: Cancer Modeling**

- Cancer with mechanofeedback
- Cytotoxic and Cytostatic drugs
- Cell death and macrophages (and phagocytosis)
- T Cells (effector attack)
- Free exploration: "what if" models