

PhysiCell Essentials Short Course:

Introduction to Agent-Based Modeling and PhysiCell

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PhysiCell Curriculum

- **PhysiCell Essentials Short Course (this short course)**

- **Prerequisites:**

- Basic knowledge of cell biology, concepts of mathematical functions

- **Software requirements:**

- Web browser access, OR installation of PhysiC

- **Curriculum:**

- **Introduction (this session)**

- *Optional: Desktop Installation of PhysiCell Studio*

- Hands-on work Part 1: Getting Started, and Villager/Zombie Model

- Hands-on work Part 2: Cancer Chemotherapy & Immunology Models

- *Optional: Notes and Tips on Parameter Estimates*

- **Integration of Boolean Networks with PhysiBoSS**

- Learn how to integrate Boolean signaling networks into PhysiCell Models

- **Advanced PhysiCell Modeling**

- Learn about creating non-standard model components and visualization in C++

- Learn about C++ extensions for ODE models, ECM fibers, and more.

- **PhysiCell for Developers**

- Learn about PhysiCell core C++ structure, and contributing to PhysiCell core and extensions



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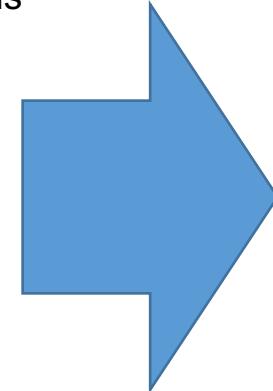
Session Goals

- Introduce multicellular systems biology
- Introduce concepts of **signal-response** cell interactions
- Introduce agent-based models (ABMs)
- Introduce key components of the PhysiCell modeling framework
- Show examples of agent-based modeling
- Introduce next-generation concepts for agent-based (bio)modeling

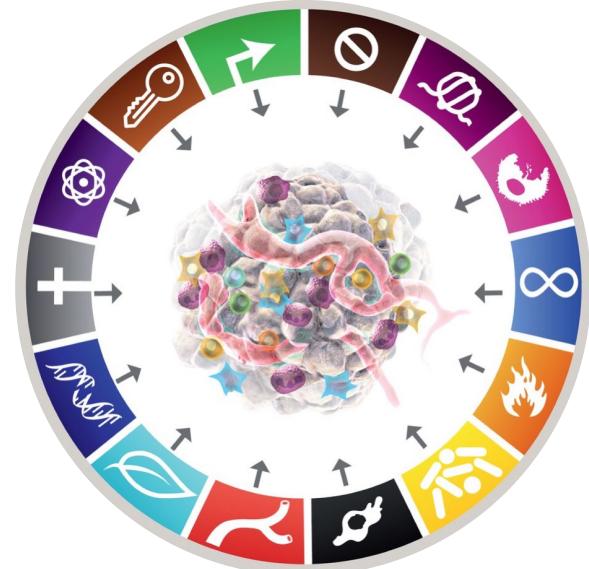


From single cells to tissue ecosystems

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



Multicellular tissue ecosystem



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



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Scientists use [models*] to detangle complex systems.

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

We use agent-based models as our virtual laboratory.



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First, a conceptual model

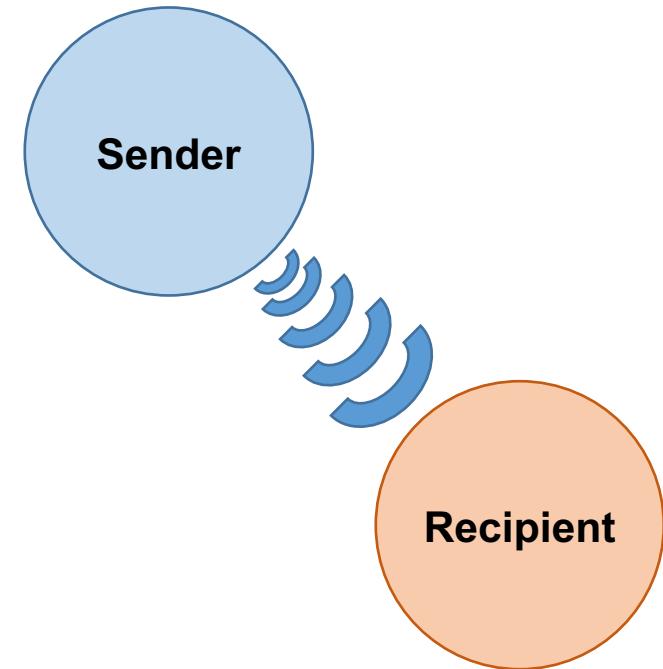


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Signal-Response as a Conceptual Framing

- 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** in the recipient:
 - 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



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Agent-based models: overview

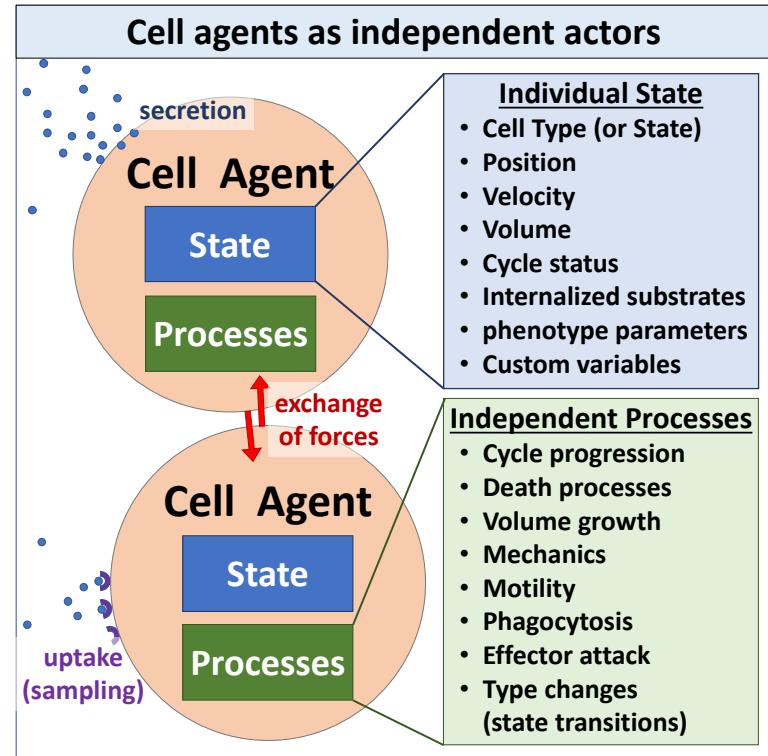
- Each cell is an **independent agent** with:

- **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



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Types of cell-based models

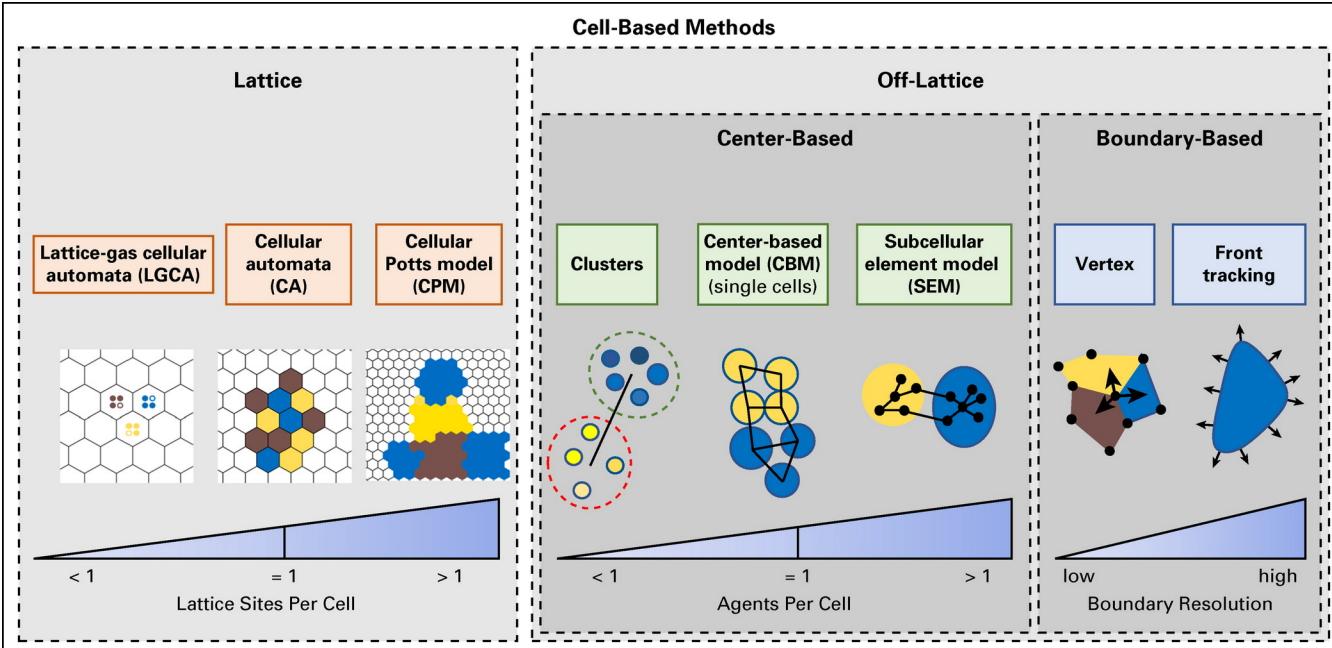
- **lattice-bound:**
cell position and sizes align with a regular lattice

- resolution:

- many cells / site:
» lattice gas
- 1 site / cell
» cellular automaton
- many sites / cell
» cellular Potts

- **off-lattice:**
cells can take any position and size

- **center-based**
- boundary-based

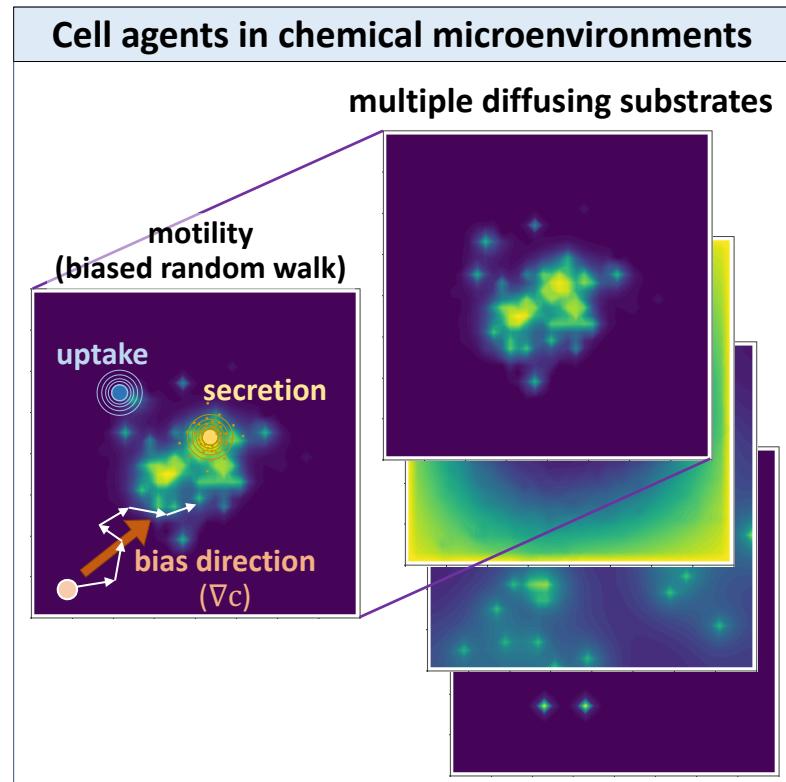


J. Metzcar, Y. Wang, R. Heiland, and P. Macklin. A review of cell-based computational modeling in cancer biology. *JCO Clinical Cancer Informatics* 3:1-13, 2019 (invited review). DOI: [10.1200/CCI.18.00069](https://doi.org/10.1200/CCI.18.00069).



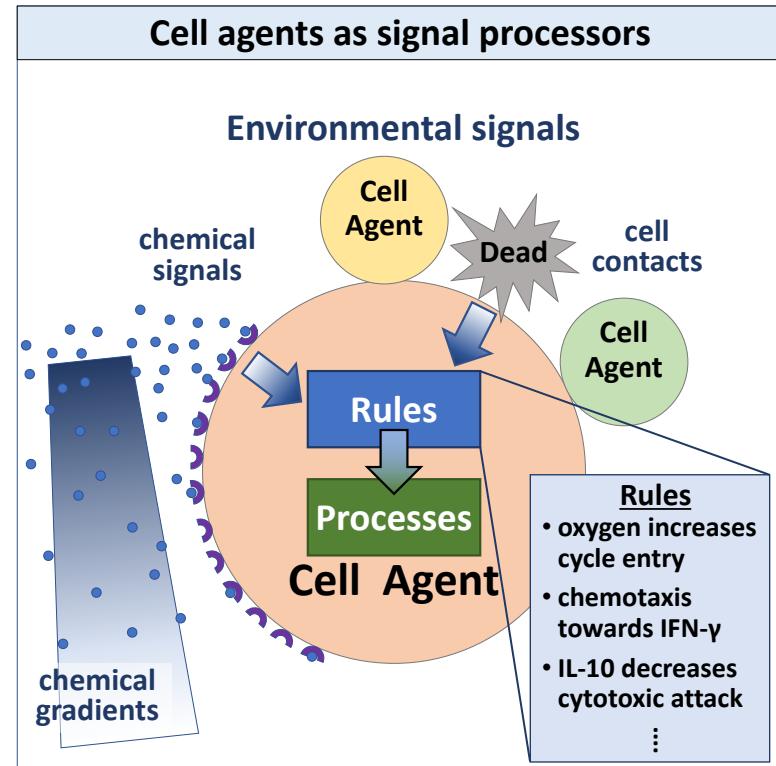
Cell agents live in a virtual environment

- Cells can secrete or consume chemical substrates
- Substrates diffuse and decay
- Cells can sample substrates
- Cells can perform biased random walks that may align with gradients (e.g., chemotaxis)
- Can also add additional mechanical detail (e.g., viscoelastic ECM models)



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**



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 custom code.
- Boolean networks, ODEs, FBA, and NN models are sophisticated forms of \mathbf{f} .
- All these functional relationships require:
 - Mapping quantities in the ABM framework to inputs of \mathbf{f}
 - Computing \mathbf{f}
 - Mapping outputs of \mathbf{f} to parameters in the ABM
- More recently, we defined an intermediate level \mathbf{f} via a grammar.
 - **Most models can be written in this grammar, making modeling faster, reusable, and reproducible.**



Parallel Notions to Continuum Models

- **Continuum models:**

- A general form applies to a broad class of problems.
 - *Example:* Conservation of mass, momentum, and energy
- Constitutive laws (extra hypotheses) adapts the general form to *specific* problems.
 - *Example:* Darcy's law for pressure-driven flows

- **Agent-based models:**

- Agents have general forms for cycling, death, secretion, migration,
- Extra (time & space-dependent) rules trigger and regulate these core (sub)-models
 - These are the **constitutive laws** for ABMs.



Our virtual laboratory



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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 mm^3 at $20\text{ }\mu\text{m}$ resolution

Features:

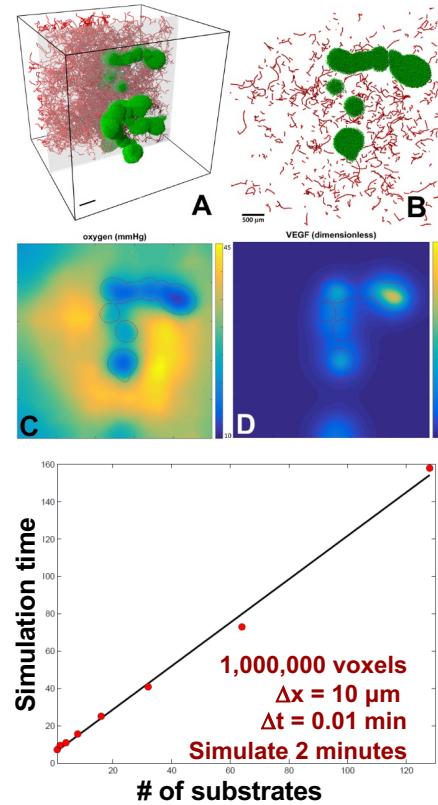
- Off-lattice cell secretion and uptake
- 2nd-order accurate (space), 1st-order accurate (time), numerically stable

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 10+ diffusing substrates on 10^6 voxels

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

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



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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:

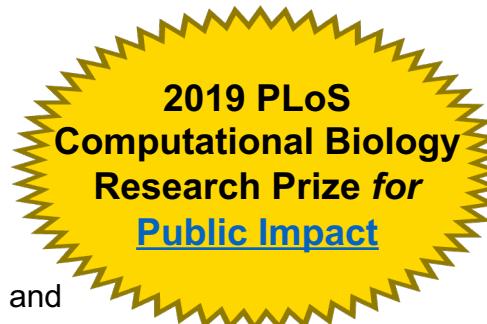
- Standard C++11, cross-platform
- OpenMP parallelization
- $O(n)$ cost scaling in # cells

Reference: Ghaffarizadeh et al.,
PLoS Comput. Biol. (2018)

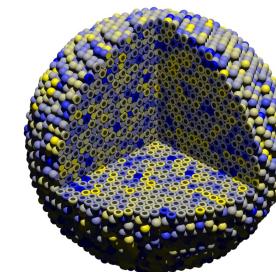
DOI: [10.1371/journal.pcbi.1005991](https://doi.org/10.1371/journal.pcbi.1005991)



Try this model yourself!
nanohub.org/tools/pc4heterogen



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



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



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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:

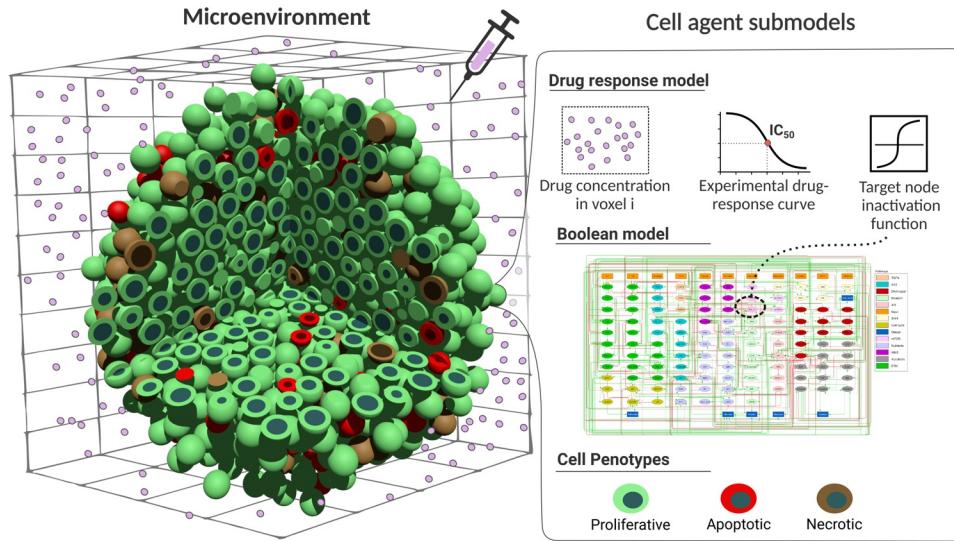
- Each PhysiCell agent has a MaBoSS model and data
- PhysiCell sends cell and tissue data to MaBoSS as inputs
- MaBoSS advances solution a fixed time
- MaBoSS sends outputs to key PhysiCell agent parameters

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



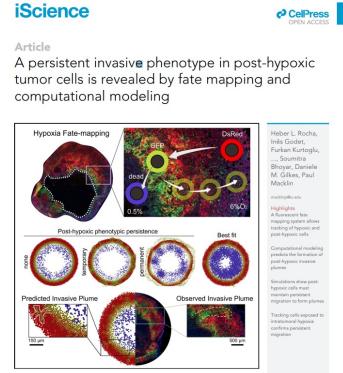
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PhysiCell as a virtual laboratory

- Choose important chemical signals
 - These become diffusible 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 (and parameters) can be tuned to steer the system?





Example: Exploring phenotypic persistence in hypoxic breast cancer



Fate-mapping intratumoral hypoxia

nature communications

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Article | Open Access | Published: 24 October 2019

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 

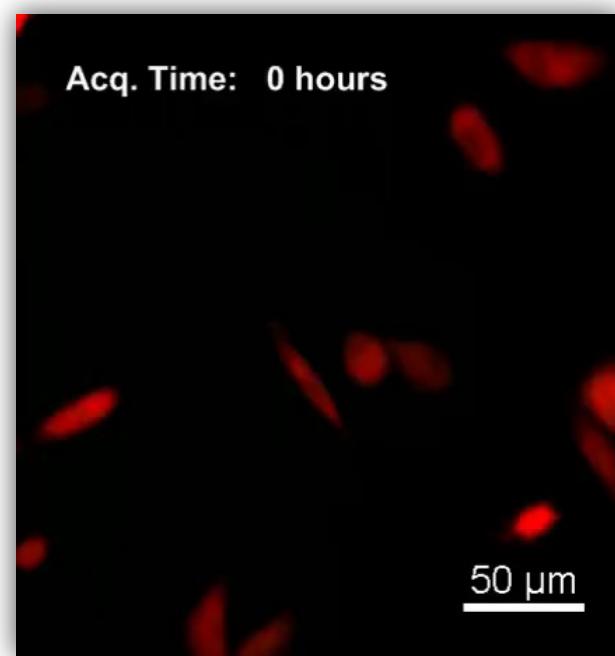
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Sections  Figures  References 
Abstract

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

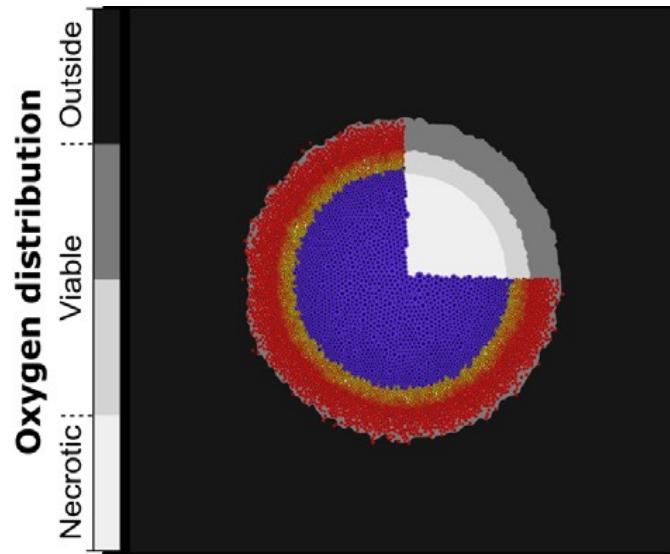


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Model overview

- 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:

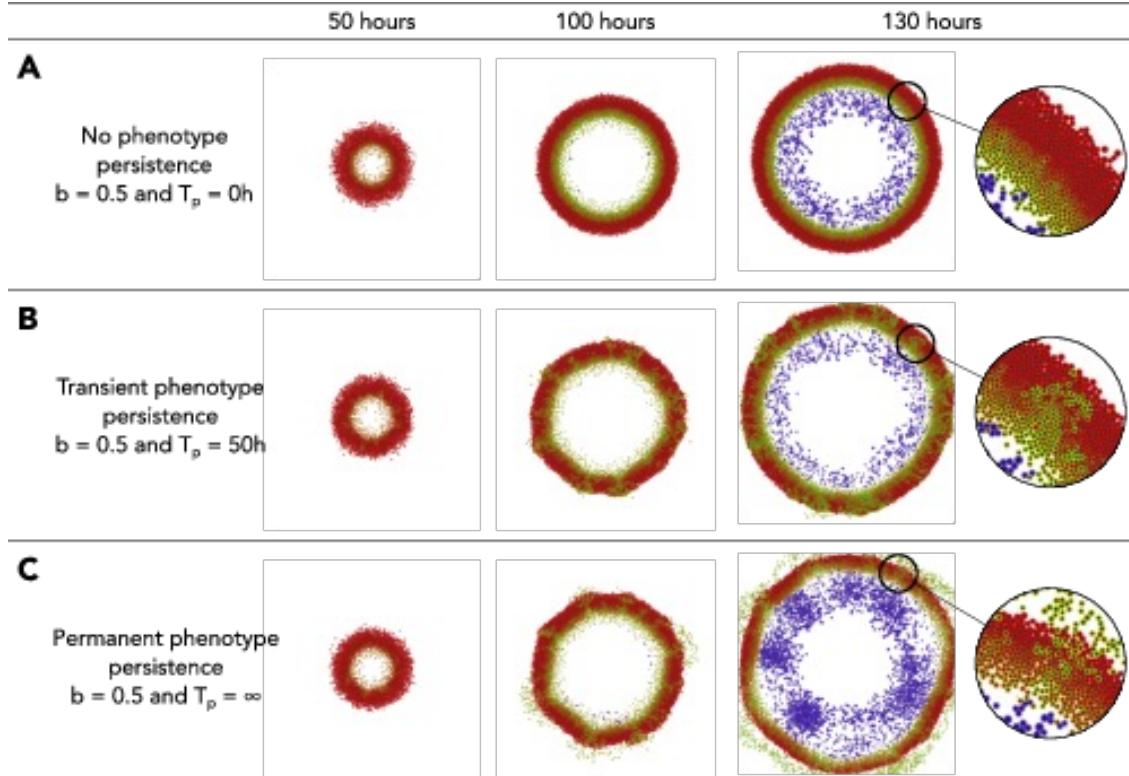
- T_p : duration of hypoxic response

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!

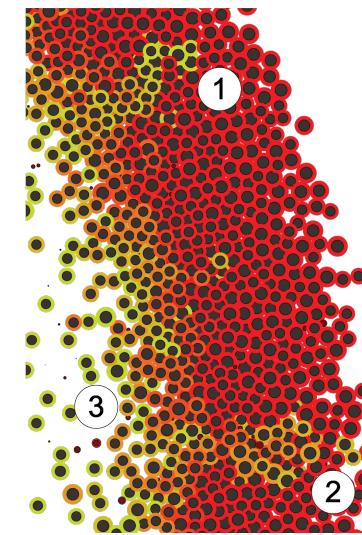
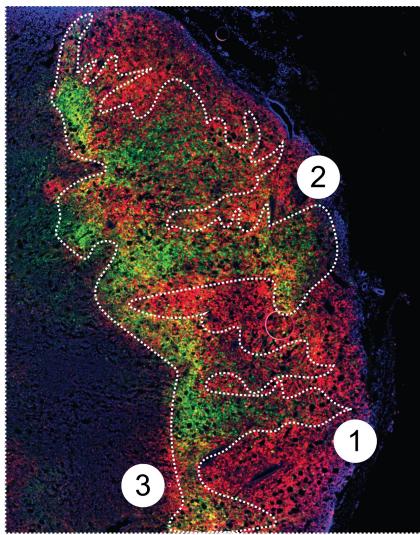
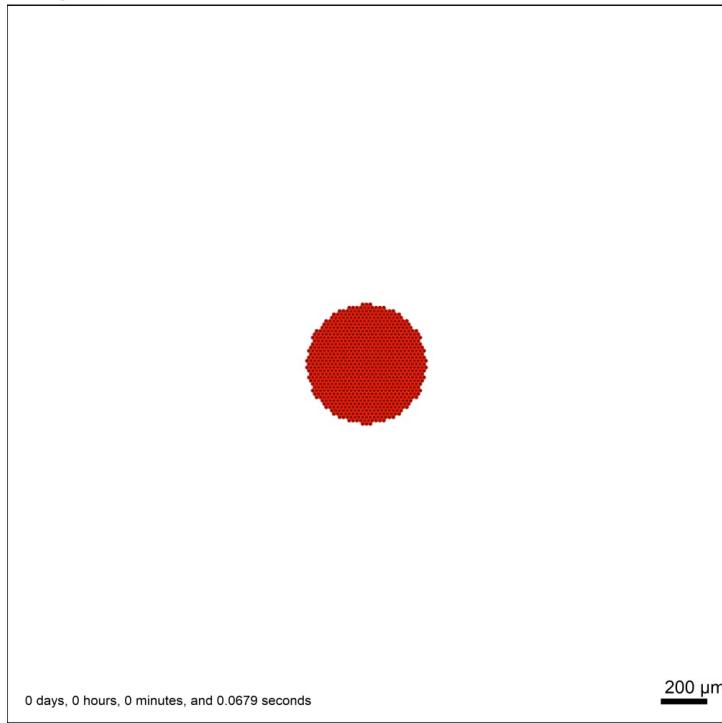


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Mathematical model explains biological observations

Current time: 0 days, 0 hours, and 0.00 minutes, z = 0.00 μm
889 agents



Try this model yourself!
nanohub.org/tools/pc4tumorhypoxia



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Takeaway:

**Simulation models + novel
imaging can explain biology
better together than separately**



Rethinking modeling



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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

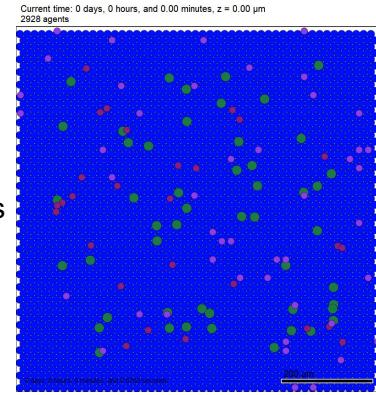
3. Implement mathematical statements as code

- 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⁺ T cell contact stops activated macrophage secretion of pro-inflammatory cytokine and switches to M2 phase, secreting anti-inflammatory cytokine.
 - 5.MPhi.12 CD4⁺ T cell contact induces activated macrophage phagocytosis of live infected cell



**PhysiCell model
of COVID19**

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

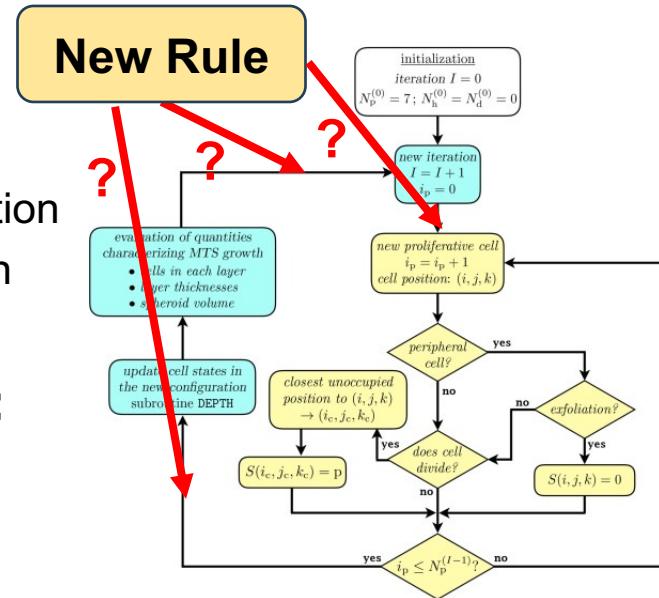


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Problems with hand-written models

- 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



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, kmmorris@duke.edu

SPECIAL TRACK: SOFTWARE ENGINEERING

OpenACC Acceleration of an Agent-Based Biological Simulation Framework

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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 part of these models. GPU acceleration vastly speeds up the diffusion and uptake processes in the partial differential equations required for biological transport in an agent-based biological modeling system. In this article, we utilize OpenACC to accelerate the diffusion portion of PhysiCell, 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 single-core Intel Xeon W-2135 processor. 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.

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 biological tissues. Blood vessel release nutrients and waste products to cells, and other cells move metabolites that diffuse through tissues to be consumed by cells and then absorb diffusible waste products while cells secrete waste products. Cells must interact to communicate and coordinate their behaviors. See Figure 1 for a typical 3-D simulation model.

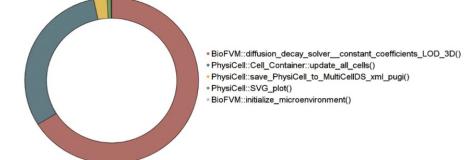
Therefore, most modern agent-based biological modeling systems are hybrid, they use discrete cell agents with continuous partial differential equations (PDEs) to represent biological transport, such as

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

where p is a vector of diffusible substrates, and each cell agent has position x , and volume V , a vector of production rates S , and a vector of consumption rates U . The extracellular substrate vector λ , (vector dot products are taken elementwise, and δ is the Dirac delta function.) Numerical simulation of these coupled PDEs can be solved with relatively small step sizes Δt , making the solution of the coupled reaction PDEs a major bottleneck in hybrid agent-based biological models that can limit the maximum size and duration of simulations. This, in turn, can hinder high-throughput simulation model exploration (e.g., never-before calibration techniques like

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Date of current version: 1 May 2023.

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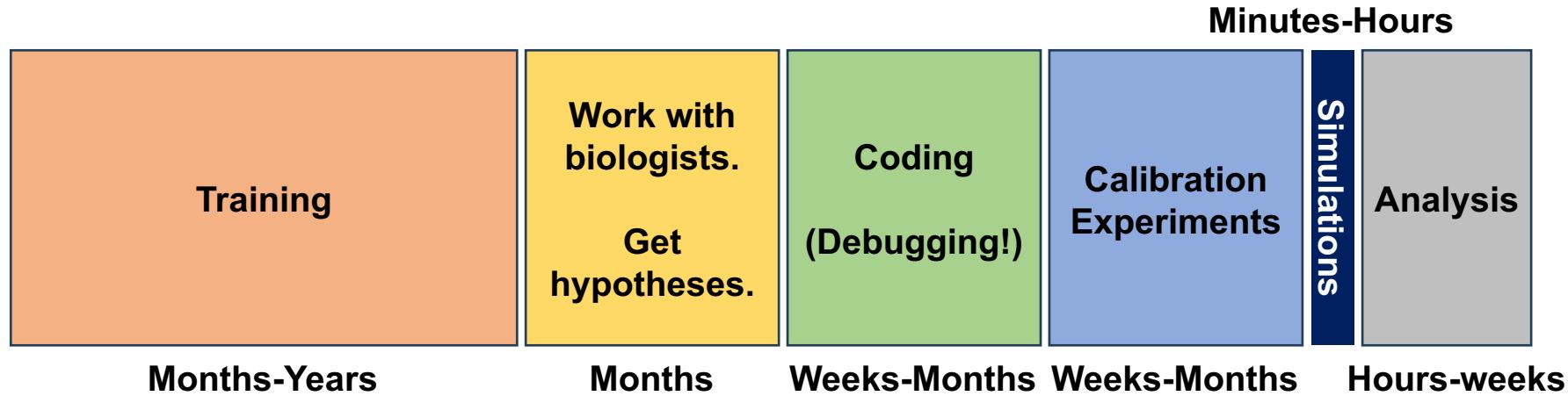
Let's generalize this analysis

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.



- Improving **simulation speed** speeds up investigations.
- We also need to speed up the **learning and development bottlenecks!**



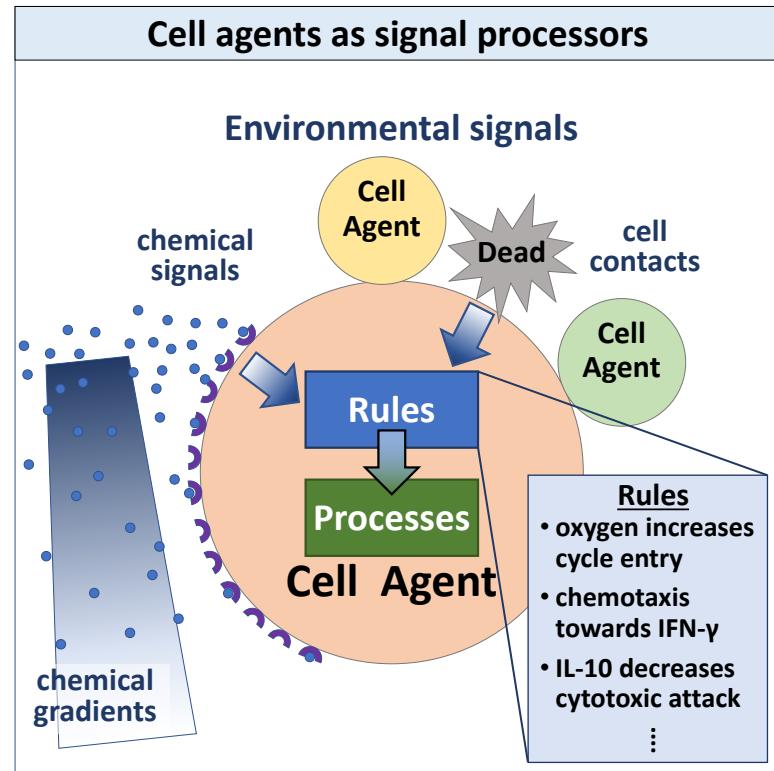
Creating a computable model grammar

- **Goal:** Create a 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



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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**
 - Number of contacts with each cell type
 - # of contacts with live and dead cells
 - Contact with basement membrane
- **Attack and damage interactions**
 - Accumulated damage
 - Cumulative attack time
 - Attack status
 - Am I attacking?
 - How much damage have I delivered?
- **Live / dead status**
 - Dead, apoptotic, necrotic
- **Global information**
 - Current simulation time (for event timing)
- **Custom symbols**

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



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
 - Asymmetric division
- **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
- **Transition / Type change / 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
 - Apoptotic & Necrotic rates can differ!
 - Rate of ingesting live cells (one rate for each type)
- **Effector Attack**
 - Rate of initiating attacks on live cells (one for each type),
 - Immunogenicity (one for each cell type)
 - Duration of attacks, rate of causing damage during attack
- **Damage and Repair**
 - Damage rate (e.g., via doxorubicin)
 - Repair rate
- **Custom symbols**

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



Example Reference Behavior Models

- **Migration**

- Choose migration bias \mathbf{d}_{bias} :

- Uses chemotactic sensitivities (s_i) to each chem gradient (∇c_i):

$$\mathbf{d}_{\text{bias}} = \frac{\sum_i s_i \nabla c_i}{|\sum_i s_i \nabla c_i|}$$

- Choose migration direction:

- Uses speed s , bias b , and bias direction \mathbf{d}_{bias} :

$$\mathbf{v}_{\text{migration}} = s \frac{(1 - b)\xi + b \mathbf{v}_{\text{bias}}}{|(1 - b)\xi + b \mathbf{v}_{\text{bias}}|}$$

- Continue with persistence time T_{persist} :

$$P(\text{choose new direction in } [t, t + \Delta t]) = \frac{\Delta t}{T_{\text{persist}}}$$

- **(Effector) Attack**

- If attacker cell i is not attacking a cell

- Determine whether to attack a neighbor j :
 - » Uses rate of cell i attacking cell of type j ($r_{A,ij}$)
 - » Uses immunogenicity of j to cell i (I_{ji})

$$\text{Prob}(i \text{ attacks } j \text{ in } [t, t + \Delta t]) = r_{A,ij} I_{ji} \Delta t$$

- While attacking:

- Form mechanical adhesion (spring link)
 - Cause damage in target cell
 - » rate of causing attack damage ($r_{D,i}$)

$$\frac{dD_j}{dt} = r_{Di}$$

- Determine whether to end attack:

$$P(\text{end attack in } [t, t + \Delta t]) = \frac{\Delta t}{T_{\text{attack}}}$$

- In the target cell:

- Requires a damage response rule ("Damage increases apoptosis")



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
 - Radioisotope edition:
 - For malignant epithelial cells, internalized radioisotope increases alpha particle secretion (release)
 - For malignant epithelial cells, alpha particles increase damage rate
 - For malignant epithelial cells, damage 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

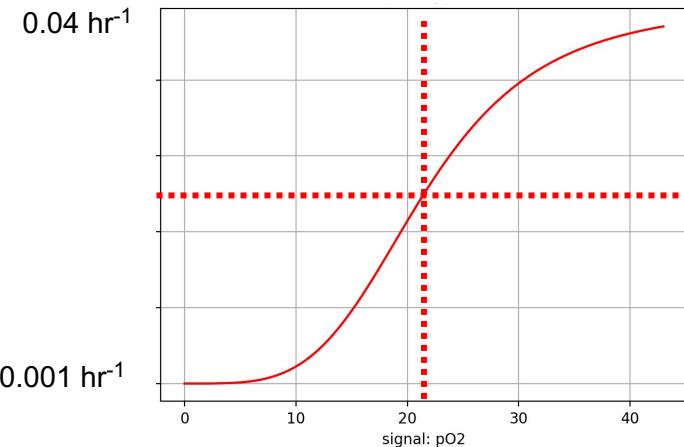
$$p(s) = p_0 + (p_M - p_0)R(s) = (1 - R(s)) \cdot p_0 + R(s) \cdot p_M$$

- 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:**

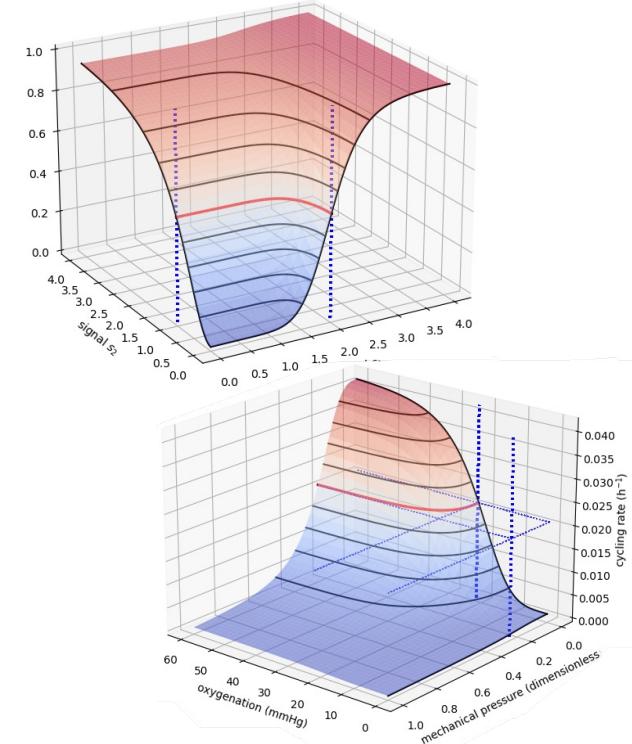
$$U = H_M(\mathbf{u}; \mathbf{u}_{\text{half}}, \mathbf{p}) = \frac{\left(\frac{u_1}{u_1^*}\right)^{p_1} + \left(\frac{u_2}{u_2^*}\right)^{p_2} + \cdots + \left(\frac{u_m}{u_m^*}\right)^{p_m}}{1 + \left(\frac{u_1}{u_1^*}\right)^{p_1} + \left(\frac{u_2}{u_2^*}\right)^{p_2} + \cdots + \left(\frac{u_m}{u_m^*}\right)^{p_m}}$$

- **Total down response:**

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

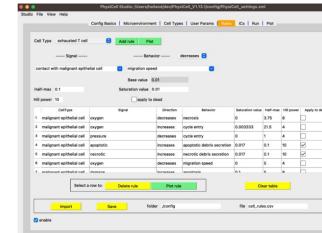
- **Integrated response:**

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

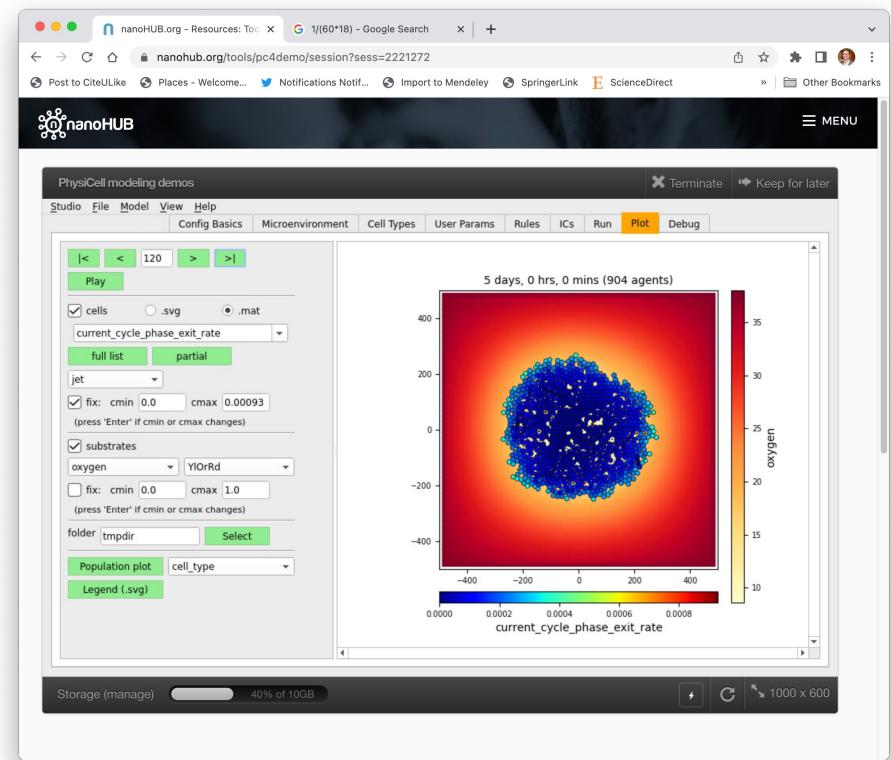


Building models *on-the-fly* in the cloud

- 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 can be minutes instead of weeks or months.



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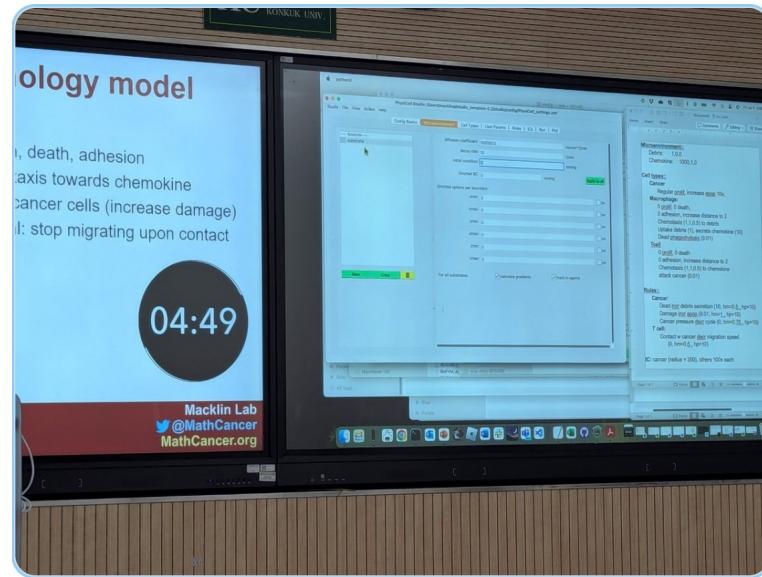
New Possibilities with PhysiCell Studio

- Interactive model editing & exploration
- Interdisciplinary instruction
 - No installation required
 - No coding required
 - **Afternoon short course:**
 - Get started with basic tumor-immune and chemotherapy models
 - **Weeklong hackathons:**
 - **Day 1:** Learn overall model framework
 - **Days 2-5:** Mentored hackathon, daily starter model demos
- Live modeling in talks
 - 5-minute demo at SMB 2024! ☺

Heiland et al., **PhysiCell Studio: a graphical tool to make agent-based modeling more accessible.** GigaByte (2024). DOI: [10.46471/gigabyte.128](https://doi.org/10.46471/gigabyte.128)



If you were wondering how to make your talk more stressful, I imagine putting a live countdown on your slides is one way to do it #smb2024



Automated model annotation

- We auto-generate formatted tables as we parse the rules
- The underlying hypotheses are summarized for inclusion in the methods section for later papers.
 - Easier for future scientists to understand the model assumptions.
 - Easier to reuse in future models.
 - Also helpful for internal QC!

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 w/ dead cell increases transform to M1 mac
- contact w/ 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
- dead increases debris secretion



In CD8 T cells:

- IFN-gamma increases cycle entry
- IL-10 decreases attack tumor
- IL-10 decreases migration speed
- contact w/ 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:

U. Maryland:

- Elana Fertig
- Daniel Bergman

Johns Hopkins:

- Genevieve Stein-O'Brien
- Jeanette Johnson

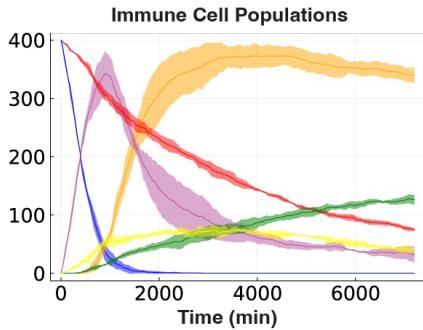
OHSU:

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

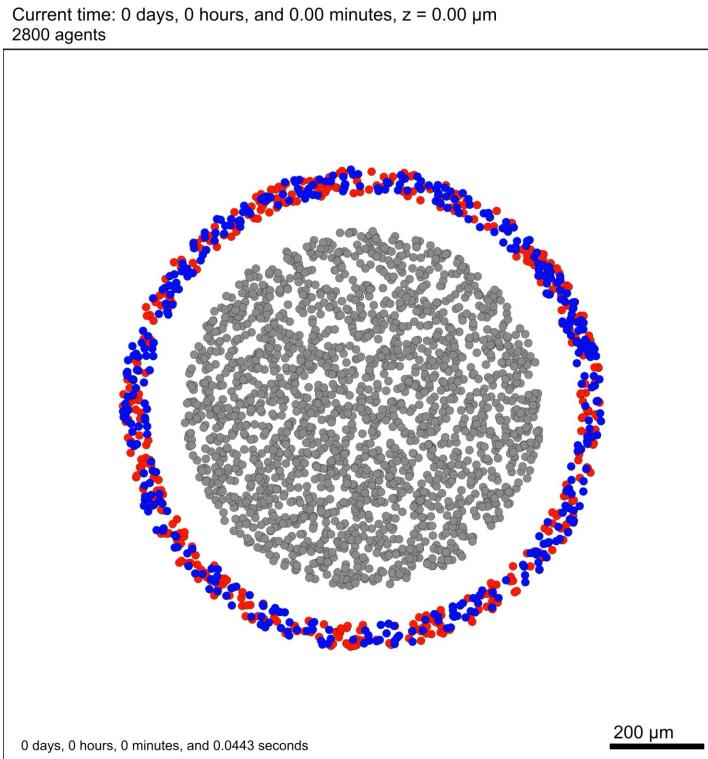


Example: tumor-immune

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



Johnson et al, *BioRxiv*, 2023



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We can use the language to
connect genomics with
dynamical modeling

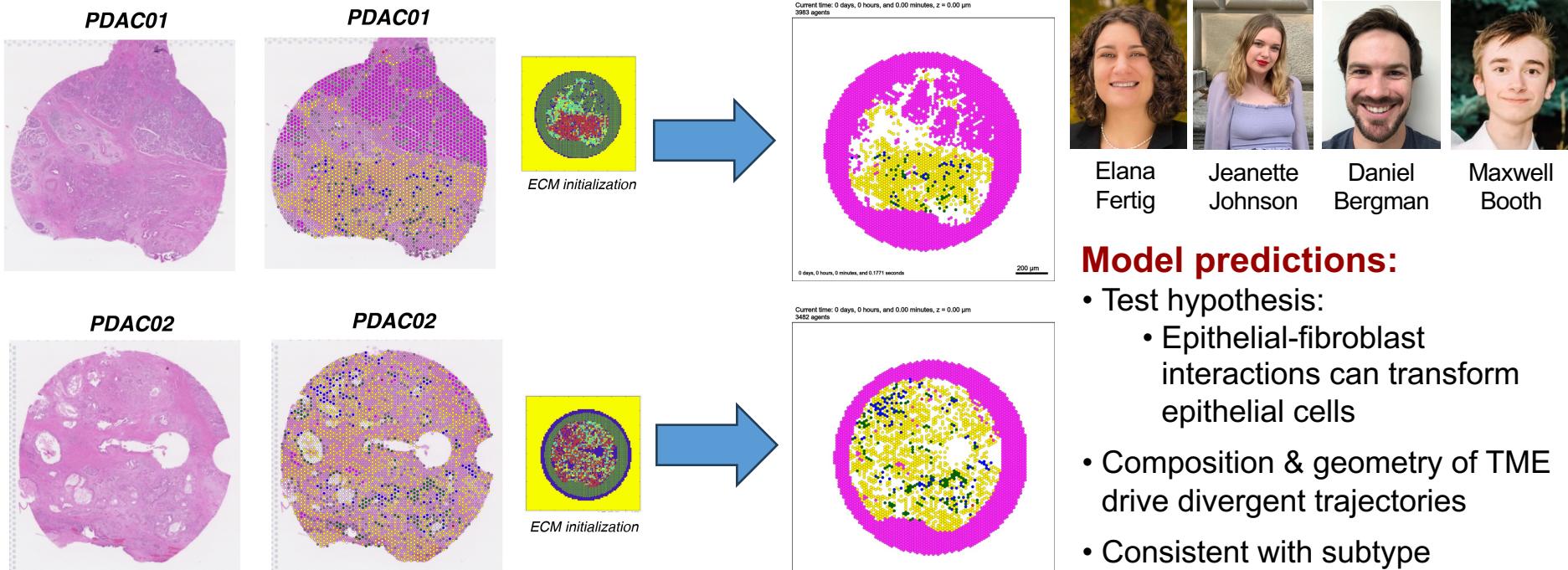


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Creating models from spatial transcriptomic data

CONVERGENCE
INSTITUTE



Johnson et al, *BioRxiv*, 2023

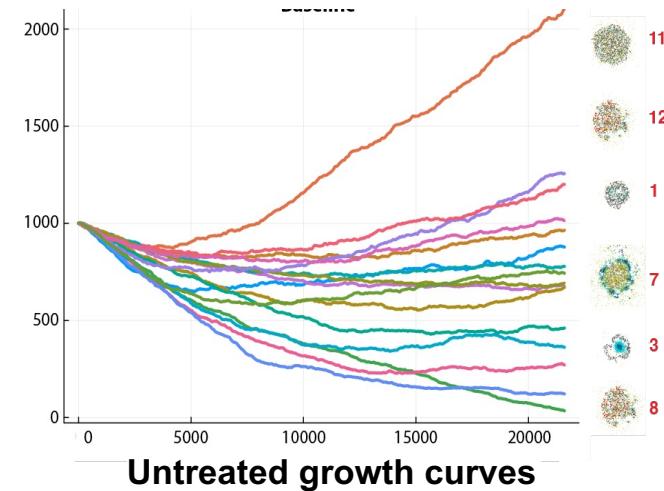
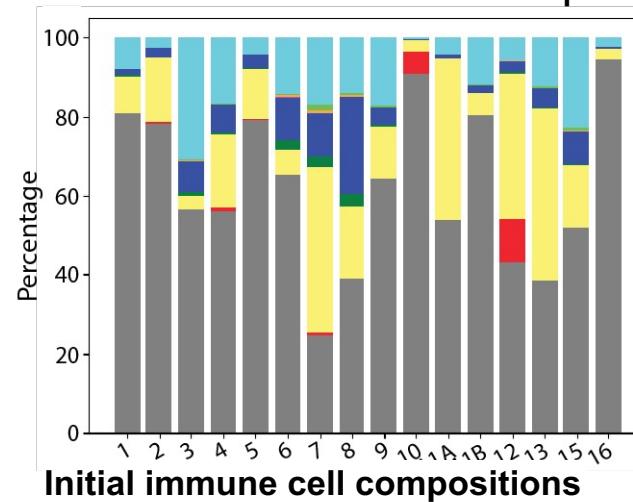


Model predictions:

- 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

Simulating immunotherapy trials (1)

- Initialize to 16 patient tissues
 - Same immune cell rules and parameters for each tissue
 - Set initial immune cell composition to match tissue
 - Simulate immune response sans therapy



Johnson et al, *BioRxiv*, 2023

Differences in immune composition lead to widely divergent growth curves, even without any other biological differences



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Simulating immunotherapy trials (2)

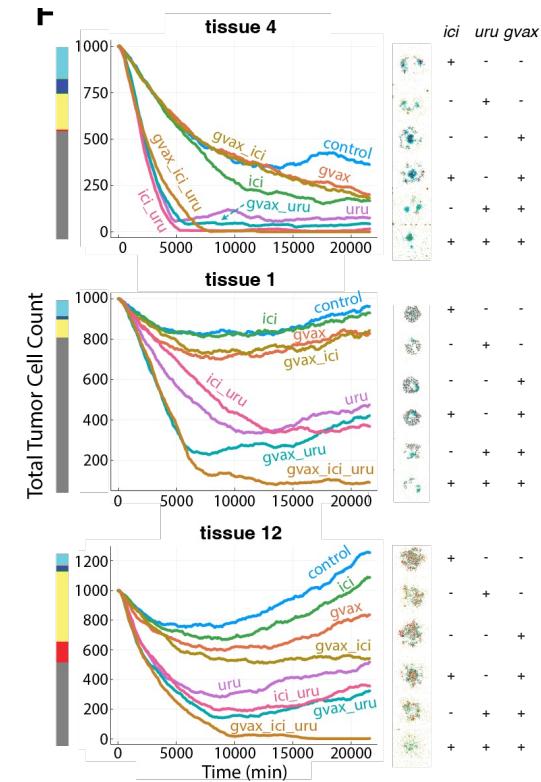
- Simulate immunotherapies in the 16 patients
 - **immune checkpoint inhibitor:** shift T cell population to PDL1 low (more active killing)
 - **CD137 agonist:** shift to T cells that can kill independent of PD1/PDL1
 - **GVAX (vaccine):** attracts more T cells → higher initial T cell population

Combinations increase immune activity and infiltration.

Impact (and best therapy choice) highly dependent on initial immune composition



Elana Fertig
Jeanette Johnson
Daniel Bergman
Johnson et al, BioRxiv, 2023



Ultimately, we envision many paths

- Expert-driven
 - Tap centuries 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!

Preprint with the modeling language and spatial transcriptomics:

Under review at *Cell*

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



The screenshot shows the bioRxiv preprint page for the paper "Digitize your Biology! Modeling multicellular systems through interpretable cell behavior". The page includes the CSHL logo, the bioRxiv header, navigation links, a search bar, and sections for new results, author information, and subject areas. The preprint was posted on September 17, 2023, and includes options to download PDF, print/save, and share. A sidebar on the right lists COVID-19 SARS-CoV-2 preprints from medRxiv and bioRxiv, along with subject areas like Systems Biology and Subject Areas.



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PhysiCell Curriculum: Next Steps

- **PhysiCell Essentials Short Course (this short course)**

- **Prerequisites:**

- Basic knowledge of cell biology, concepts of mathematical functions

- **Software requirements:**

- Web browser access, OR installation of PhysiC

- **Curriculum:**

- Introduction
 - *Optional: Desktop Installation of PhysiCell Studio*
 - **Hands-on work Part 1: Getting Started, and Villager/Zombie Model (next session!)**
 - Hands-on work Part 2: Cancer Chemotherapy & Immunology Models
 - *Optional: Notes and Tips on Parameter Estimates*

- **Integration of Boolean Networks with PhysiBoSS**

- Learn how to integrate Boolean signaling networks into PhysiCell Models

- **Advanced PhysiCell Modeling**

- Learn about creating non-standard model components and visualization in C++
 - Learn about C++ extensions for ODE models, ECM fibers, and more.

- **PhysiCell for Developers**

- Learn about PhysiCell core C++ structure, and contributing to PhysiCell core and extensions



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