

PhysiCell Mini-Workshop

Part 1: Intro to Agent-Based Modeling

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Link

<https://github.com/PhysiCell-Training/nw2023>

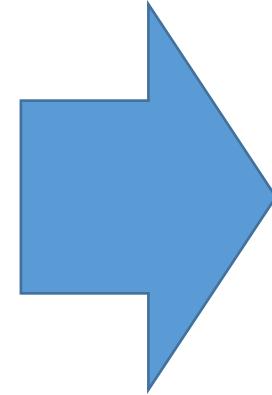
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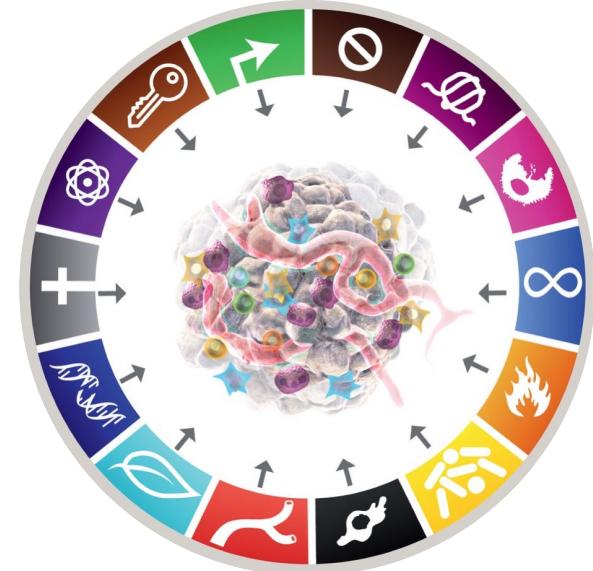
- Jayne Koskinas Ted Giovanis Foundation for Health and Policy
- National Cancer Institute (U01CA232137)
- Administrative supplement to NCI U01CA232137 (Year 2)
- National Science Foundation (1720625, 1818187)
- NCI / DOE / Frederick National Lab for Cancer Research (21X126F)
- DOD / Defense Threat Reduction Agency (HDTRA12110015)
- NIH Common Fund (3OT2OD026671-01S4)

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
 - 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.**

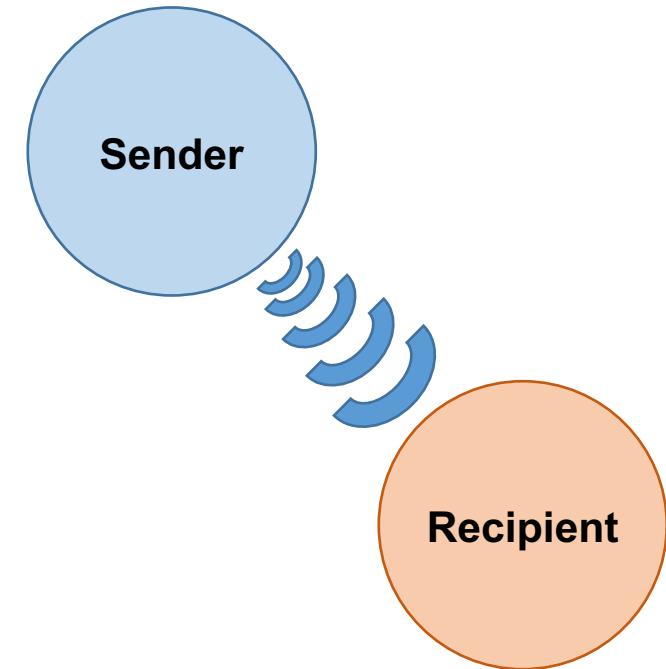
* animal, *in vitro*, engineered, mathematical, conceptual ...

We use agent-based models as our virtual laboratory.

First, a conceptual model

Signal-Response as a Conceptual Framing

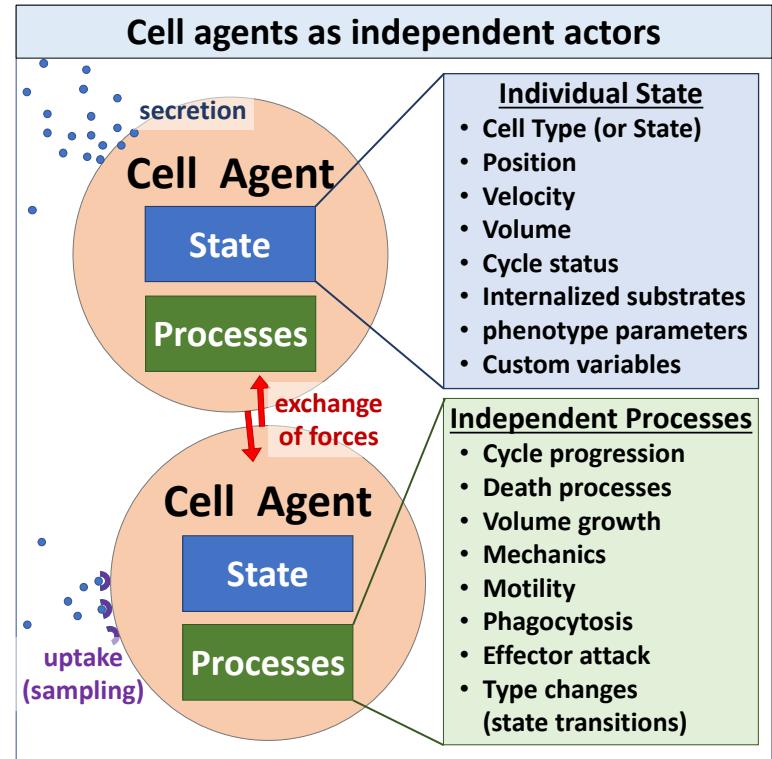
- Much of the complexity of this system can be decomposed into pairwise interactions between a **sender** and a **recipient**
- A **signal** is a stimulus that can elicit a behavioral **response**:
 - A macrophage (**sender**) secretes IL-6 (**signal**) that drives chemotaxis (**response**) in a CD8 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

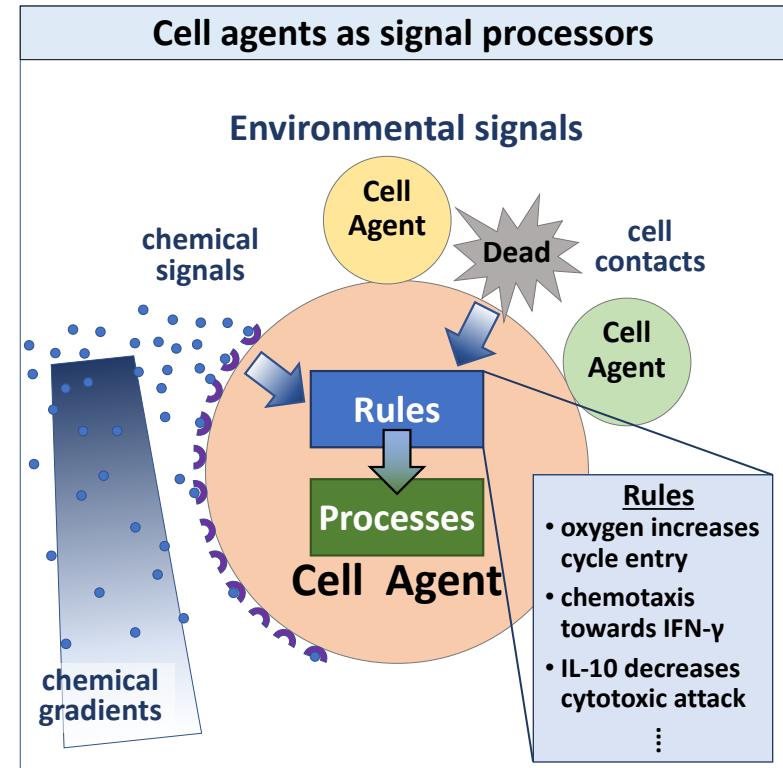
Agent-based models: overview

- 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 are signal processors

- Cells interact through chemical and physical **signals** (or stimuli)
 - Secreted chemical signals
 - Chemical gradients
 - 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 mm^3 at $20 \mu\text{m}$ resolution

Features:

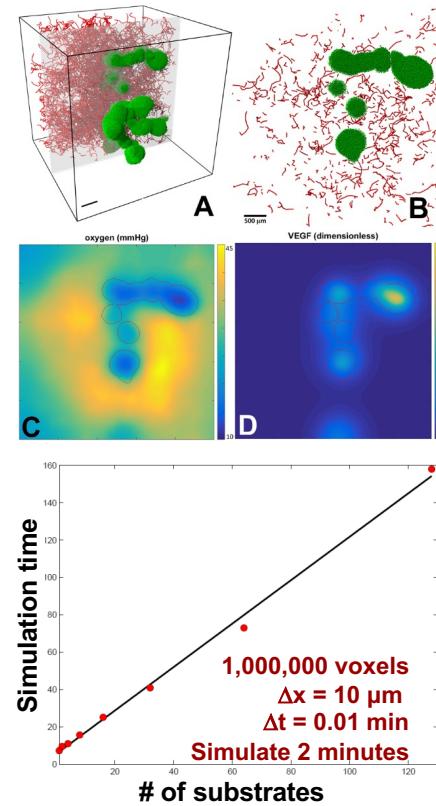
- Off-lattice cell secretion and uptake
- 2nd-order accurate (space), 1st-order accurate (time), numerically stable

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 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)

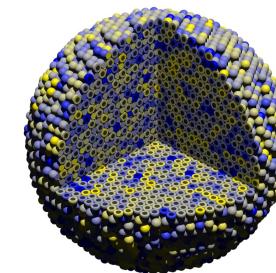


Try this model yourself!

nanohub.org/tools/pc4heterogen

2019 PLoS
Computational Biology
Research Prize for
Public Impact

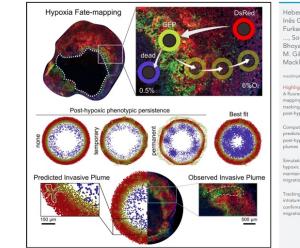
Current time: 0 days, 0 hours, and 0.00 minutes
18317 cells



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

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 can be tuned to steer the system?



Example: Exploring phenotypic persistence in hypoxic breast cancer

Fate-mapping intratumoral hypoxia

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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 

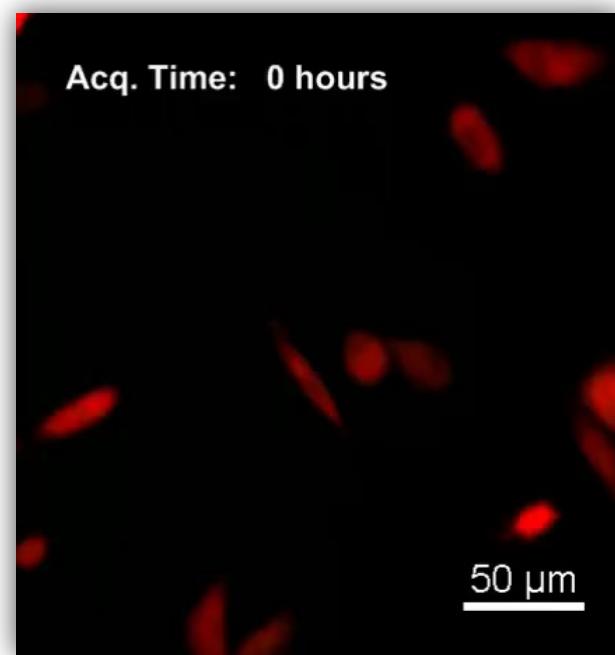
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Sections  Figures  References 
Abstract

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

Do they resume their old program?

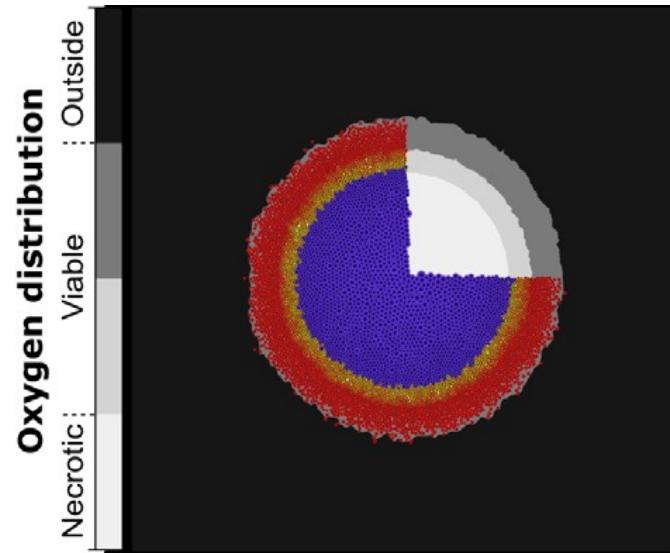
How soon?



Daniele Gilkes Lab, Johns Hopkins

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:

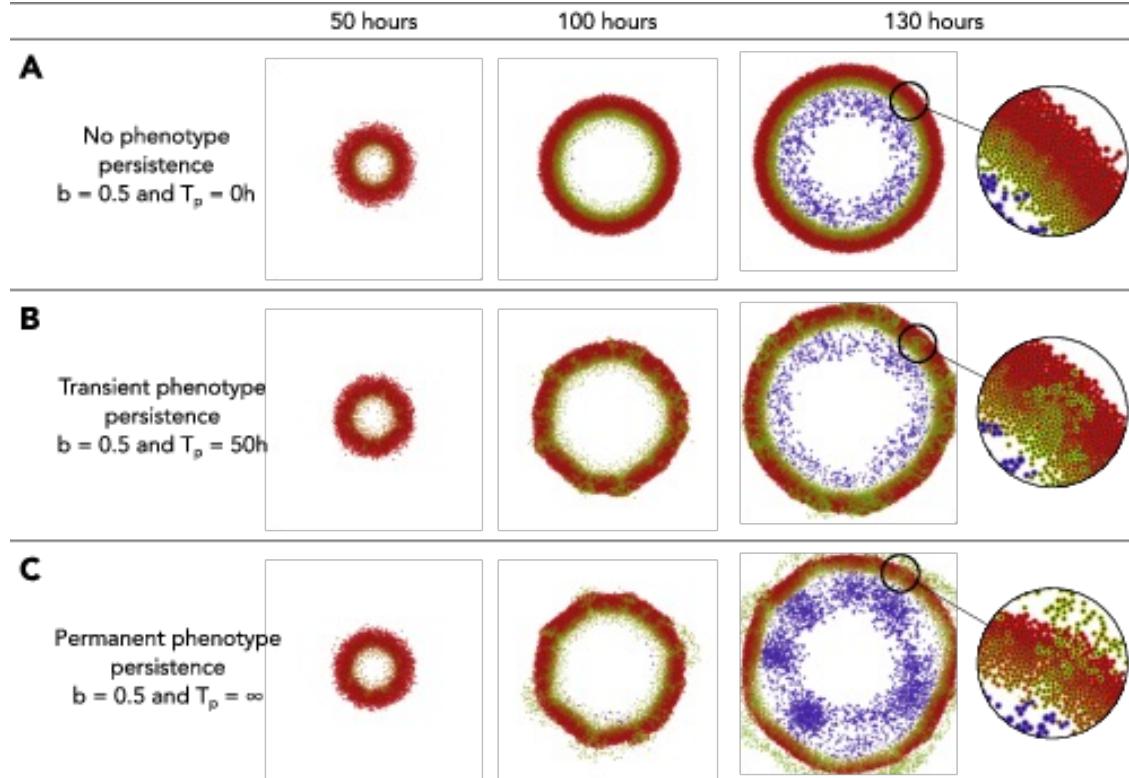
- T_p : duration of hypoxic response

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)

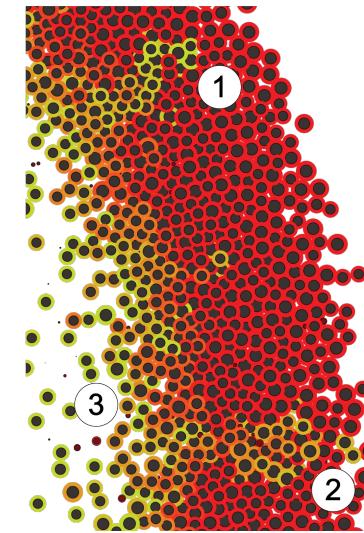
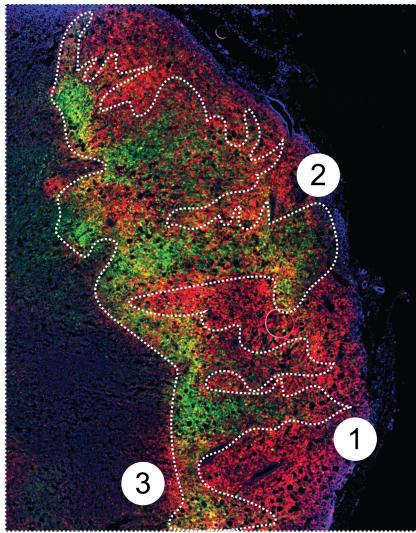
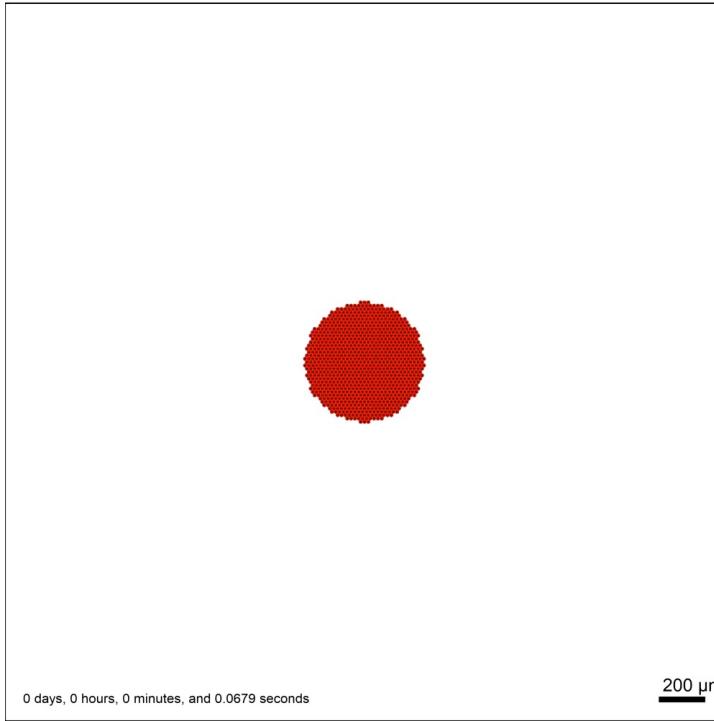
With persistence ($T_p > 0$) – Rows B & C

- 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 μm
889 agents



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

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



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Indiana U.



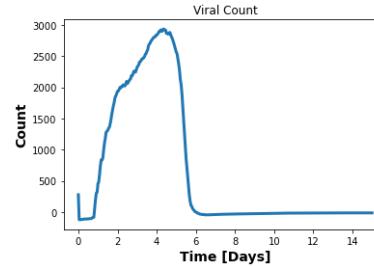
Iterative progress

- **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**

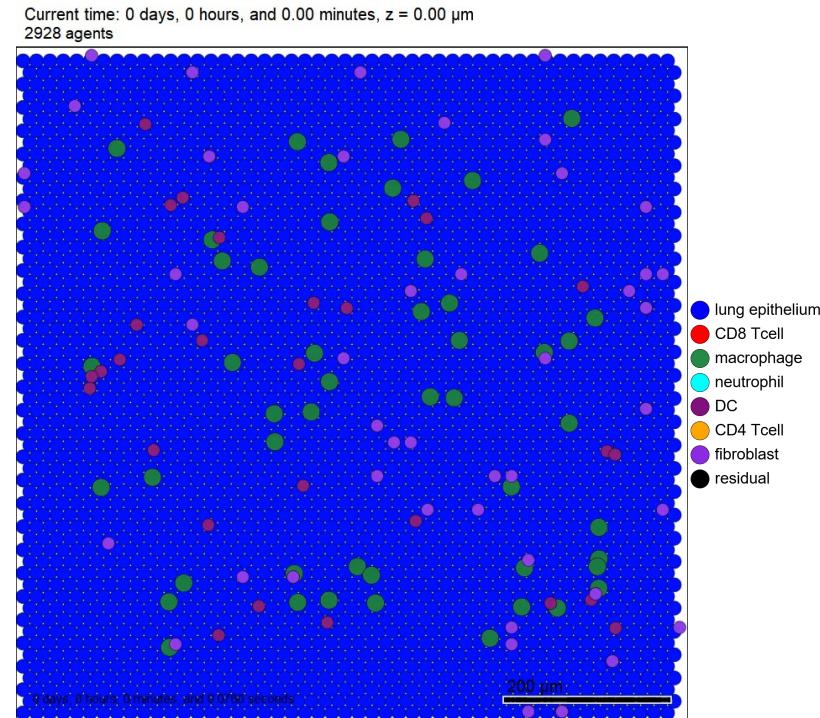
v5: neutralizing antibodies clear the infection

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

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



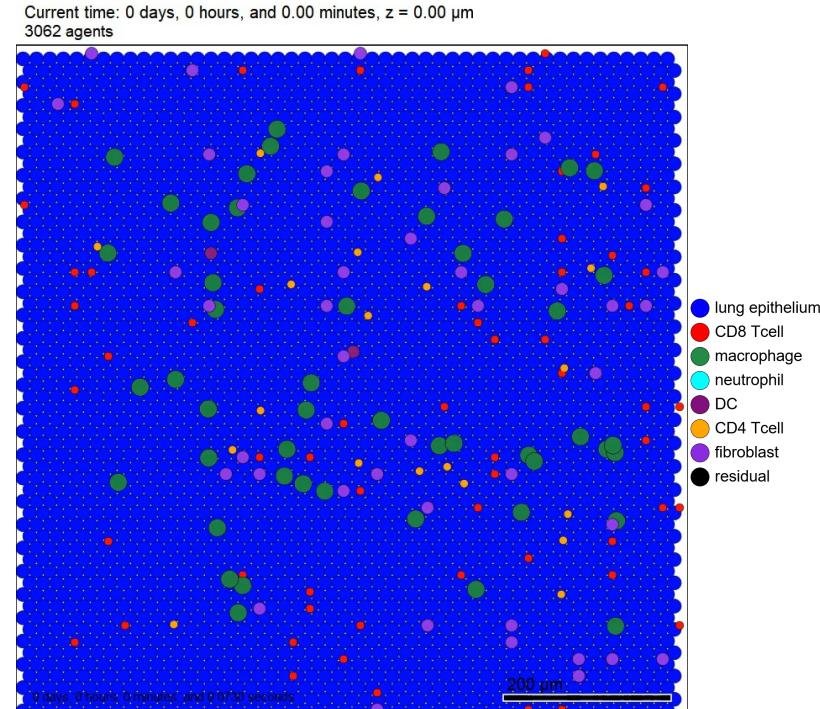
- **This immune model is sufficiently complete to clear a SARS-CoV-2 infection**



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

Cell rules: A signal-response grammar

Goal: Create a modeling 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

What do we need?

- Repertoire of standard cell process (behavior) models
- Dictionary of signals (stimuli) that modulate behaviors
- Interpretable grammar to write signal-behavior relationships
- Automated mapping of the grammar onto mathematics and code

Reference behavior models: 1

- **Cycling**
 - Transition between cycle phases
 - Divide into two cells at end of last phase
 - Key parameter: cycle entry (rate of moving from phase 0 to phase 1)
- **Apoptosis** (prototypical non-inflammatory death)
 - Gradually shrink, get removed
 - Key parameter: apoptotic death rate (rate of starting apoptosis)
- **Necrosis** (prototypical inflammatory death)
 - First swell, burst, then shrink
 - Key parameter: necrotic death rate

Reference behavior models: 2

- **motility**

- biased random walk:
 - ◆ Move some time along a bias direction, then resample, move again
- Key parameters: migration speed, persistence time, bias (directedness)

- **chemotaxis (basic)**

- bias direction is along or against a chemical gradient
- Key parameter: which chemical gradient

- **chemotaxis (advanced)**

- bias direction is a weighted sum of chemical gradients
- Key parameter: weights (-1 to 1) of each chemical gradient

Reference behavior models: 3

- **cell-cell adhesion (basic)**
 - Use potential functions for an attractive force
 - Key parameters: adhesive affinity, adhesion strength, max (relative) adhesion distance
- **cell-cell adhesion (elastic / advanced)**
 - form and break spring links to contacting cells
 - Key parameter: adhesive affinity, elastic constant, attachment rate, detachment rate, maximum number of adhesions
- **resistance to deformation and overlap**
 - Use potential function as a "repulsive" force
 - Key parameter: repulsive strength

Reference behavior models: 4

- **transformation (type change)**
 - Transition from type i to type j
 - ◆ Differentiation, Transdifferentiation, mutation, ...
 - Key parameters: transition rates
- **fusion**
 - cells i and j combine volumes, re-center position
 - Key parameter: fusion rates (type i to type j)
- **phagocytosis**
 - Cell i consumes cell j (and acquire volume)
 - Key parameter: rate of phagocytosing dead cells, rates of phagocytosing live cell types

Reference behavior models: 5

- **effector attack**

- Cell i attacks (damages) cell j
 - ◆ rate of attacking a function of attack rate of i on j and immunogenicity of j to i
 - ◆ the attack increases damage of j
 - ◆ requires an additional hypothesis to cause death in cell j
- Key parameters: attack rates, immunogenicities

- **secretion**

- cells can secrete, uptake (consume), and export diffusible substrates
- Key parameter: secretion rates, secretion targets, uptake rates, export rates

$$\frac{\partial \rho}{\partial t} = D\nabla^2 \rho - \lambda\rho + \sum_{\text{cells } i} \left(\delta(\mathbf{x} - \mathbf{x}_i) V_i \left[\overbrace{S_i(\rho_i^* - \rho)}^{\text{secretion}} - \overbrace{U_i \rho}^{\text{uptake}} \right] + \delta(\mathbf{x} - \mathbf{x}_i) \overbrace{\tilde{E}_i}^{\text{export}} \right)$$

Signal Dictionary

- Based on the cell types and diffusible substrates in a simulation, we can auto-generate dictionaries of available signals
- With standardized access, it's much easier to write cell rules
- This allows for a controlled vocabulary (an ontology)

Signal name	Biophysical meaning
{substrate X}	extracellular concentration of chemical factor X
intracellular {substrate X}	intracellular concentration of chemical factor X
{substrate X} gradient	slope of the extracellular concentration field of factor X
pressure	mechanical pressure (from other cells in close proximity)
volume	the cell's current total volume
contact with {cell type X}	number of cells of type X that are in physical contact
contact with live cell	number of live cells that are in physical contact
contact with dead cell	number of dead cells that are in physical contact
contact with basement membrane	1 if in contact with basement membrane. 0 otherwise.
damage	amount of damage (of any type)
dead	1 if the cell is dead (or dying). 0 otherwise.
total attack time	total amount of time the cell has been attacked.
time	current simulation time
custom:{X}	use a custom variable or symbol X to drive cell behavior

Behavior Dictionary

- With standardized forms, behaviors are fully controlled by well-defined parameters
- A full dictionary of available behaviors is auto-generated based on the types of cells and diffusible substrates
- This allows for a controlled vocabulary (an ontology)

Behavior name	Biophysical meaning	Parameter
{substrate X} secretion	secretion rate of (extracellular) chemical factor X	S
{substrate X} secretion target	extracellular target concentration for secreted factor X	ρ^*
{substrate X} uptake	uptake rate of chemical factor X	U
{substrate X} export	net export rate of chemical factor X	E
cycle entry	rate of entering the cell cycle	r_{01}
exit from cycle phase {n}	transition rate between the n th and n+1 th cycle phases	$r_{n,n+1}$
apoptosis	rate of beginning apoptotic cell death	d_A
necrosis	rate of beginning necrotic cell death	d_N
migration speed	the cell's (locomotive) migration speed	s
migration bias	the cell's bias to migrate along a selected bias direction	b
migration persistence time	mean time traveled before choosing a new migration direction	$T_{\text{persistence}}$
chemotactic response to {X}	the cell's relative chemotactic affinity for diffusible factor X	c_j
cell-cell adhesion	the strength of cell-cell adhesion	α_{cca}
cell-cell adhesion elastic constant	strength of elastic cell-cell adhesions	ϵ
adhesive affinity to {cell type X}
relative maximum adhesion distance		
cell-cell repulsion		
cell-BM adhesion		
cell-BM repulsion		
phagocytose dead cell		
phagocytose {cell type X}		
attack {cell type X}		
fuse to {cell type X}		
transform to {cell type X}		
custom:{X}		

We use the dictionaries in a grammar

- **Behavior hypotheses**

In {cell type X}:

{signal S} {increases or decreases} {behavior Y} {optional parameters}. {optional statements}.

- **Examples:**

- ◆ Oxygen increases cycle entry.
- ◆ Oxygen increases cycle entry from 7e-6 1/min towards 7e-4 1/min.
- ◆ doxorubicin increases apoptosis towards 0.01 1/min with a Hill response, with half-max 0.1 and Hill power 2.

Mathematical mapping

Using a response function

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

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

Sample rule

- **Oxygen increases cycle entry** from 0.001 hr^{-1} towards 0.042 hr^{-1} with a Hill response function, with half-max 21.5 mmHg and Hill power 4.

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

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:**

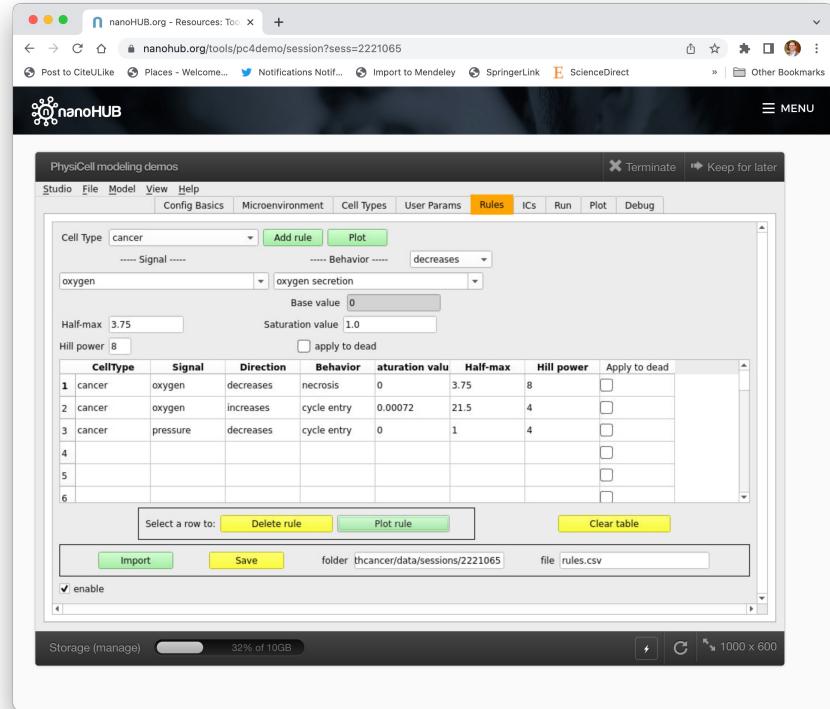
$$p(\mathbf{u}, \mathbf{d}) = (1 - D) \cdot [(1 - U) \cdot p_0 + U \cdot p_M] + D \cdot p_m$$

- **Weaknesses:**

- Only additive effects. (Remember our goal: hit many use cases, improve over time.)
- Possible extensions: more complex signals (AND, OR, NOR, NAND ...)

Graphical model editing

- With a clear model representation, it's also easy to write tools to graphically edit and run models
 - Key to getting multidisciplinary researchers involved!
 - Immediate link between hypothesis statement and visualization



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

Machine-readable version

```
tumor,cycle entry,0,0,7.20E-04,oxygen,increases,21.5,4,0
tumor,cycle entry,0,0,7.20E-04,pressure,decreases,1,4,0
tumor,necrosis,0,2.80E-03,0.00E+00,oxygen,decreases,3.75,8,0
tumor,apoptosis,0,7.2e-5,7.2e-2,damage,increases,180,2,0
tumor,debris secretion,0,0,0.017,dead,increases,0.1,10,1
tumor,migration speed,0,0.5,1,IFN-gamma,decreases,0.25,2,0

M0 macrophage,transform to M1 macrophage,0,0,0.05,contact with dead cell,increases,0.1,10,0
M0 macrophage,migration speed,0.1,1,1,contact with dead cell,decreases,0.1,4,0
M0 macrophage,debris secretion,0,0,0.017,dead,increases,0.1,10,1

M1 macrophage,migration speed,0.1,1,1,contact with dead cell,decreases,0.1,4,0
M1 macrophage,transform to M2 macrophage,0,0.01,0.05,oxygen,decreases,5,4,0
M1 macrophage,cycle entry,0,7.2e-5,3.6e-4,IFN-gamma,increases,0.25,2,0
M1 macrophage,phagocytose dead cell,0,0.01,0.05,IFN-gamma,increases,0.25,2,0
M1 macrophage,debris secretion,0,0,0.017,dead,increases,0.1,10,1

M2 macrophage,migration speed,0.1,1,1,contact with dead cell,decreases,0.1,4,0
M2 macrophage,cycle entry,0,7.2e-5,3.6e-4,IFN-gamma,decreases,0.25,2,0
M2 macrophage,phagocytose dead cell,0,0.01,0.05,IFN-gamma,increases,0.25,2,0
M2 macrophage,debris secretion,0,0,0.017,dead,increases,0.1,10,1

naive T cell,transform to CD8 T cell,0,0.001,0.01,IL-10,decreases,0.25,2,0
naive T cell,transform to CD8 T cell,0,0.001,0.01,IFN-gamma,increases,0.25,2,0
naive T cell,debris secretion,0,0,0.017,dead,increases,0.1,10,1

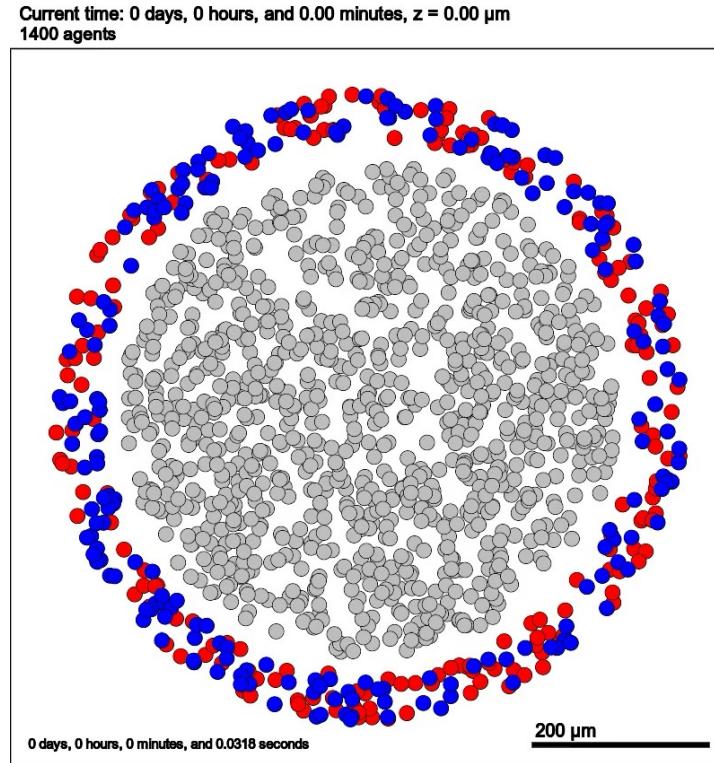
CD8 T cell,cycle entry,0,7.2e-5,9.3e-4,IFN-gamma,increases,0.25,2,0
CD8 T cell,attack tumor,0,0.01,0.05,IL-10,decreases,0.25,2,0
CD8 T cell,migration speed,0.1,1,1,IL-10,decreases,0.25,2,0
CD8 T cell,transform to exhausted T cell,0,0,0.05,IL-10,increases,0.25,2,0
CD8 T cell,migration speed,0.1,1,1,contact with tumor,decreases,0.1,2,0
CD8 T cell,debris secretion,0,0,0.017,dead,increases,0.1,10,1

exhausted T cell,debris secretion,0,0,0.017,dead,increases,0.1,10,1
```

- Joint work with OHSU:**
- Lisa Coussens
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Sample result

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



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Next session

- Introduce cloud-based PhysiCell
 - Build, run, and explore complex models *without coding*
- Iteratively build a tumor-immune model
 - Proliferation and oxygen uptake
 - Mechanofeedback
 - Oxygen-based birth and hypoxia-based necrosis
 - Cytotoxic drug
 - Cell debris and macrophages
 - Inflammation
 - Cytotoxic effector cells