

Detangling complex multicellular systems with agent-based modeling

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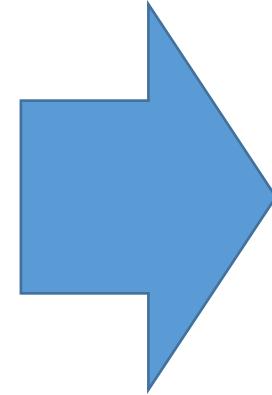
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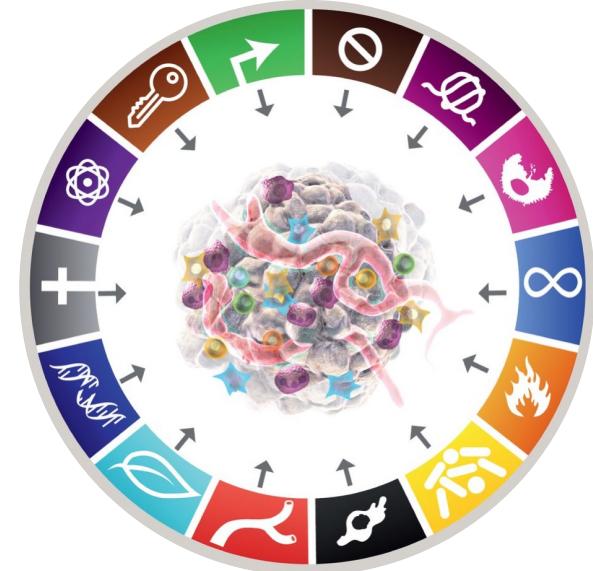
- Jayne Koskinas Ted Giovanis Foundation for Health and Policy
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From single cells to cancer ecosystems

- 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.**

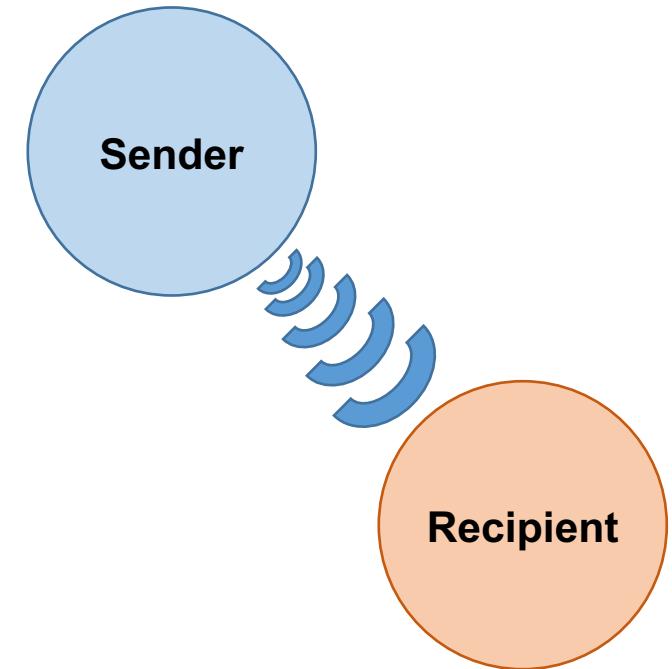
* animal, *in vitro*, engineered, mathematical, conceptual ...

We use agent-based models as our virtual laboratory.

First, a conceptual model

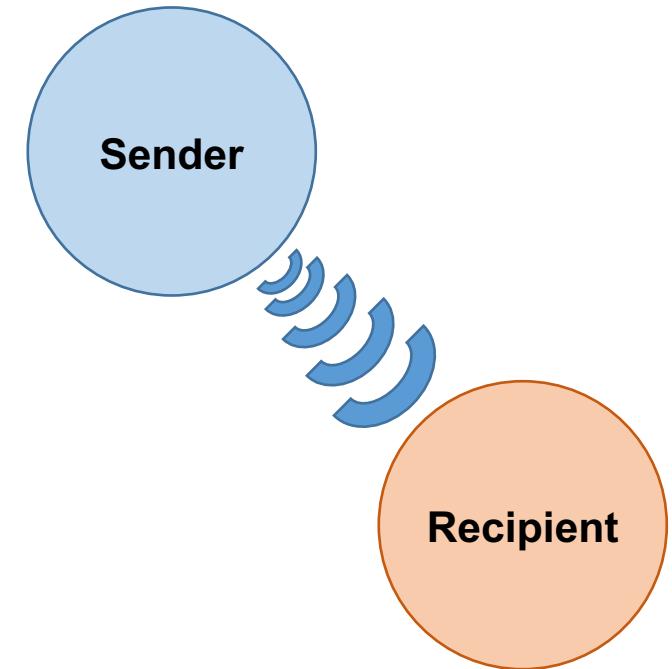
Signal-Response as a Conceptual Framing

- 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**)



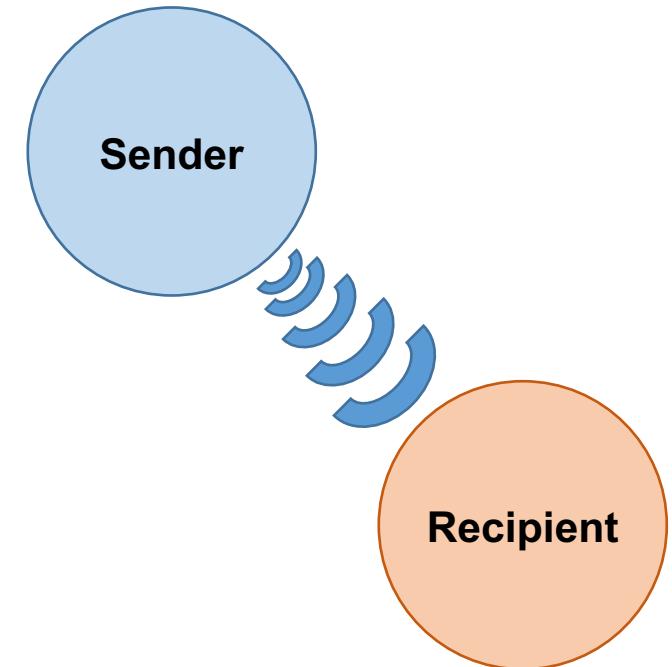
Typical signals

- **Chemical:**
 - extracellular concentration
 - concentration gradient
 - intracellular concentration (sender = recipient)
- **Physical:**
 - Contact with ECM
 - ◆ Sometimes specific to basement membrane vs 3D matrix
 - Compression / pressure
 - Strain / stretch
 - Contact with a (specific type of) cell
 - Extracellular fluid flow
- **Cell status:**
 - Live or dead
 - Damage
 - ◆ Possibly multiple / specific types!
 - Polarization (orientation)
 - Others?



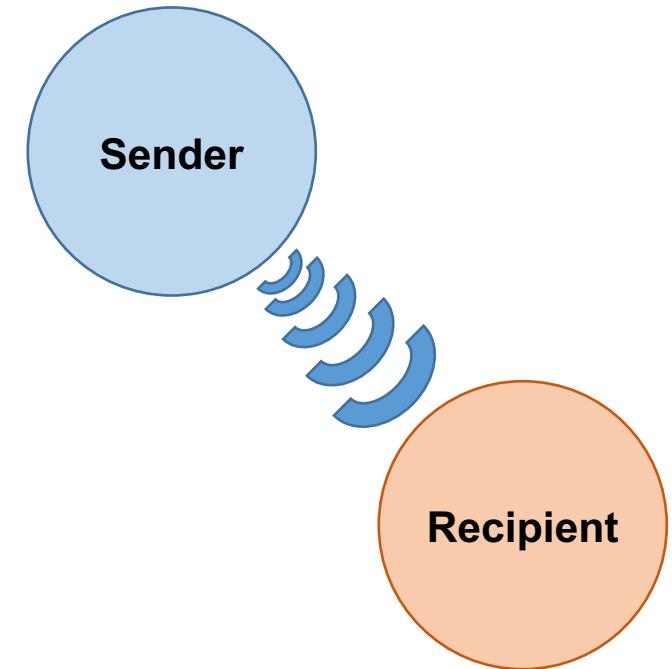
A broad range of responses

- Cycling
 - Cycle entry and transition rates
- Death
 - Specific death rates
- Motility
 - Migration speed, bias, and persistence time
 - Chemotactic sensitivities to specific substrates
- Mechanics
 - Elastic modulus
 - Expression of adhesion molecules
 - Adhesive affinity to specific cell types
- Chemical communication
 - Uptake / sampling rates
 - Secretion rates



and more responses ...

- Phagocytosis / predation
 - Rate of phagocytosing debris
 - Rate of phagocytosing dead cells
 - May include rate of phagocytosing live cells (e.g., amoebas)
- Effector attack
 - Rate of attacking (or attempting to attack) specific cell types
 - Rate of causing damage
- Immunogenicity
 - Relative recognition as a target for effector cells
- Fusion
 - Rate of merging with specific cell types
- Transformation (e.g., differentiation)
 - Rate of transforming into different cell types



Agent-based models are well-suited to this framing

Agent-based models: overview

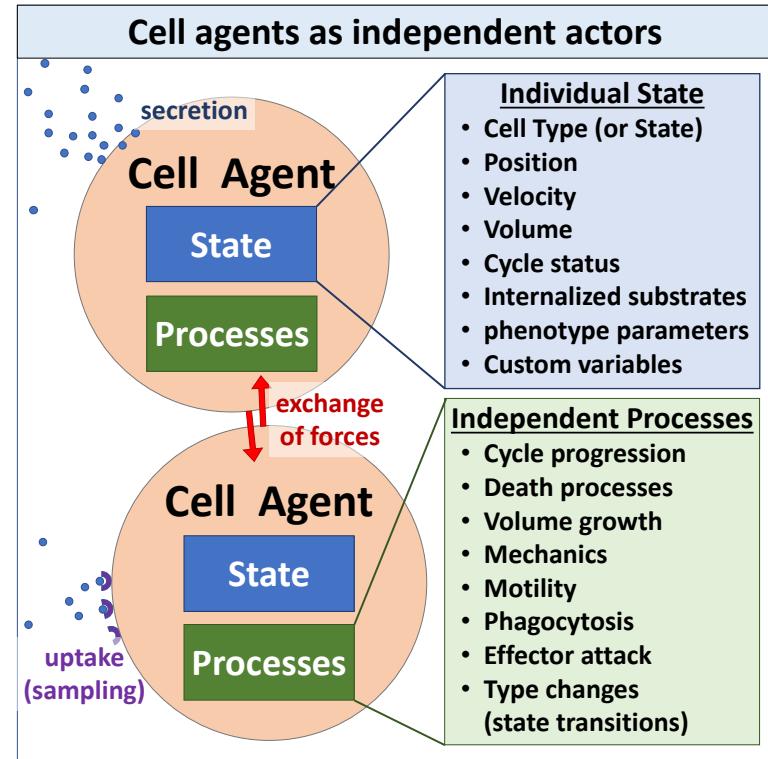
- Each cell is an **independent agent** with:

- **Individual state**

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

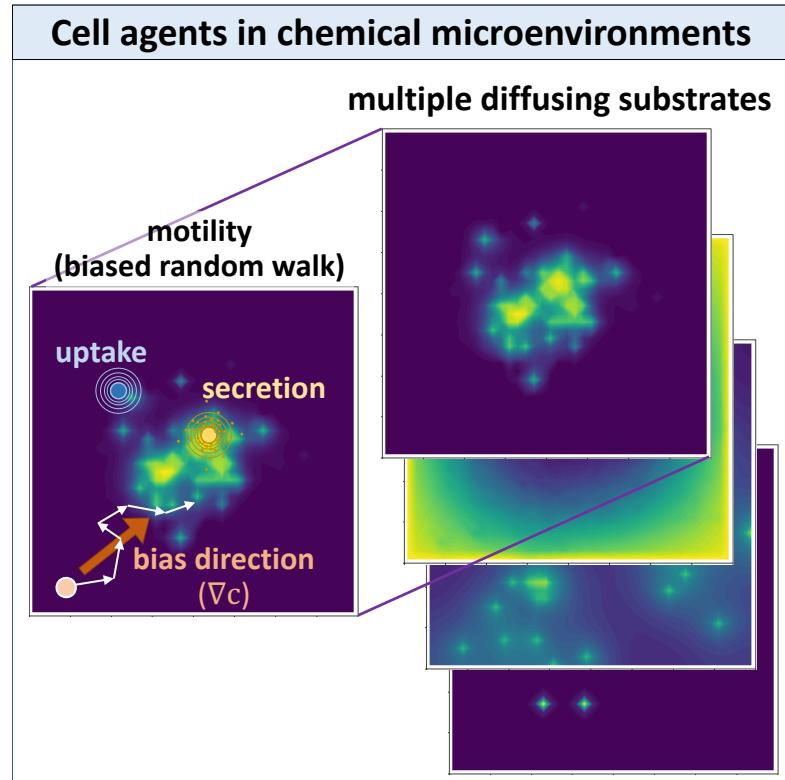
- **Independent processes**

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



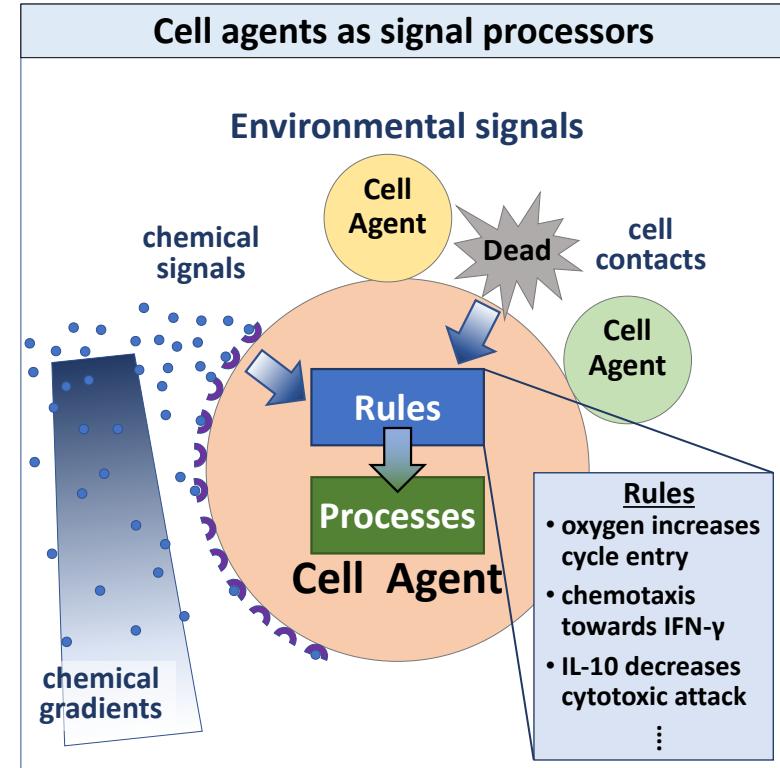
Cell agents live in a virtual environment

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



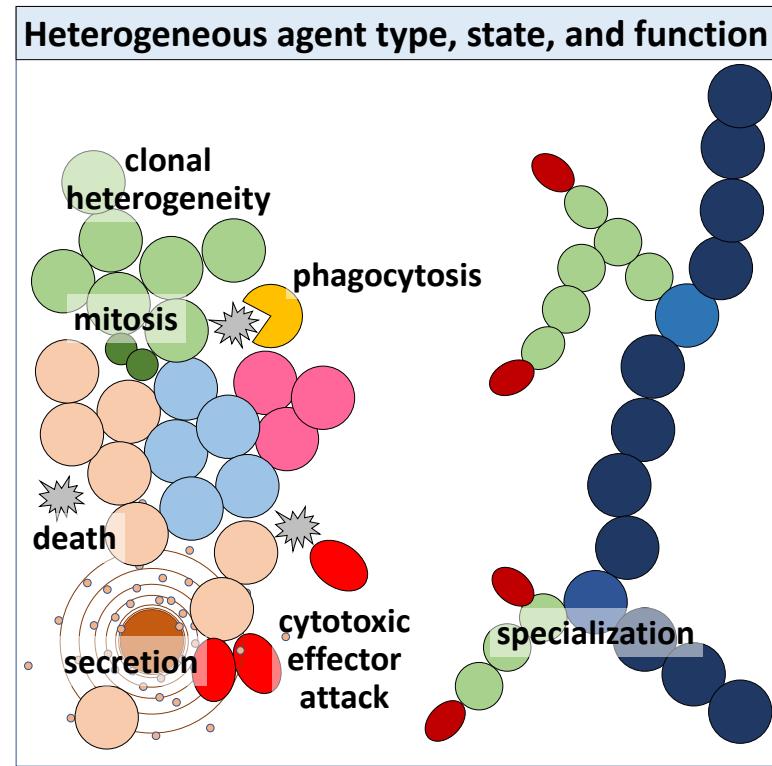
Cell agents are signal processors

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



Cell agents capture heterogeneity

- Cell agents are **heterogeneous**:
 - Populations of multiple cell types
 - Many behaviors across the population
 - Specialized roles and coordination



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:

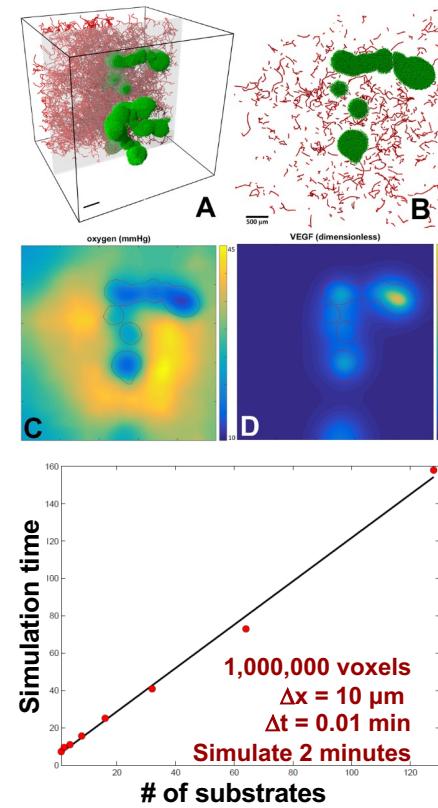
- Off-lattice cell secretion and uptake
- 2nd-order accurate (space), 1st-order accurate (time), numerically stable

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:

- Off-lattice cell positions
- 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.,

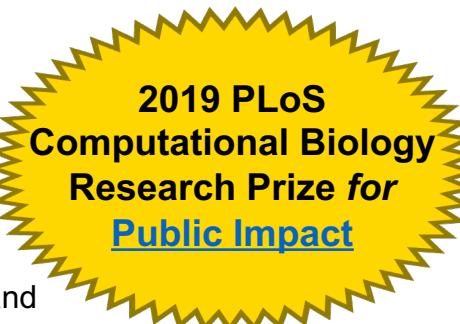
PLoS Comput. Biol. (2018)

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

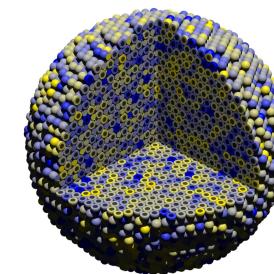


Try this model yourself!

nanohub.org/tools/pc4heterogen



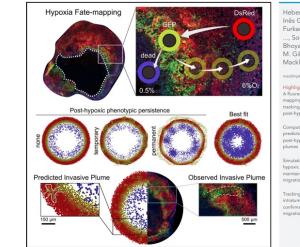
Current time: 0 days, 0 hours, and 0.00 minutes
18317 cells



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

PhysiCell as a virtual laboratory

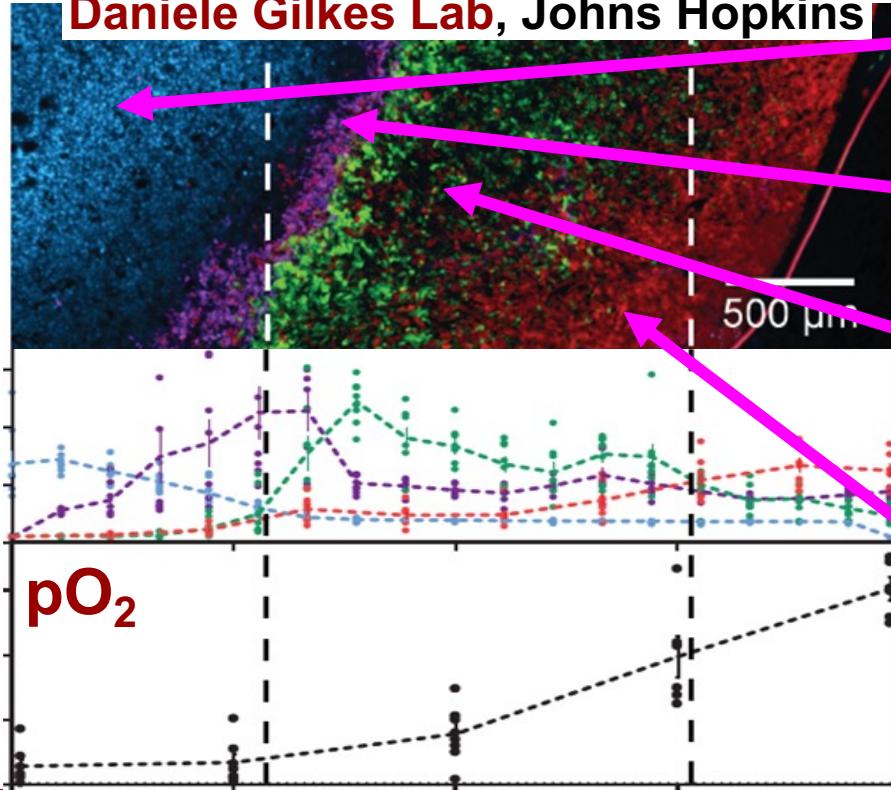
- Choose important chemical signals
 - These become diffusible fields
- Choose important cell types
 - These become our cell definitions
- Clearly state biological hypotheses as signal-response statements
 - These become our agent rules
- Perform virtual experiments to pose ***what if*** questions
 - If this set of hypotheses is right, what are the emergent behaviors?
 - ◆ Do the emergent behaviors match experimental observations?
 - 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

Hypoxic and post-hypoxic cells

Daniele Gilkes Lab, Johns Hopkins



Necrotic cells

Newly hypoxic

(Post-)hypoxic and motile

- hypoxic long enough for GFP

Normoxic

What rules lead to these patterns?

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 

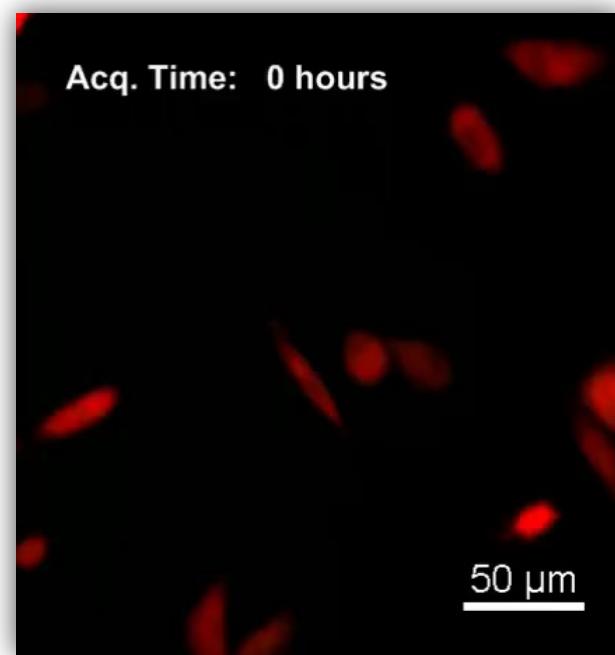
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Sections  Figures  References 
Abstract

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

Do they resume their old program?

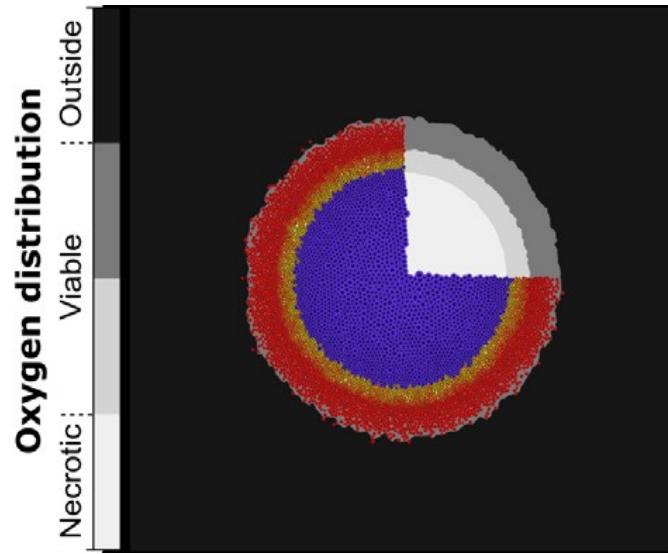
How soon?



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 **GFP** cells keep their migratory behavior after leaving hypoxic regions



Phenotypic persistence drives invasion

Phenotypic Persistence:

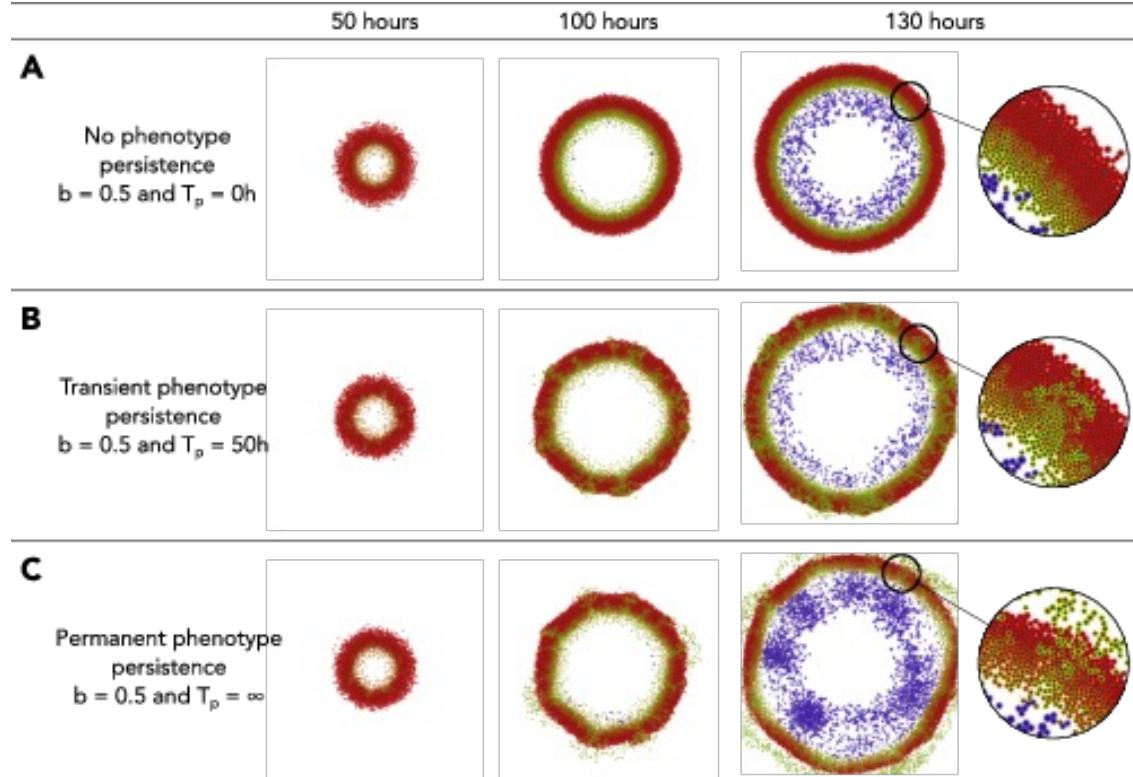
- T_p : duration of hypoxic response

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)

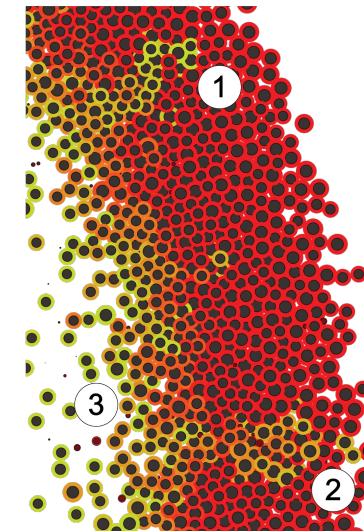
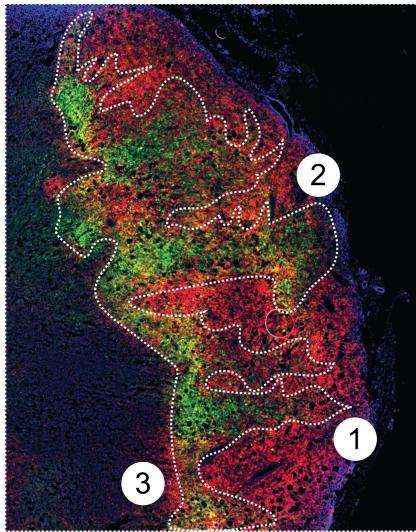
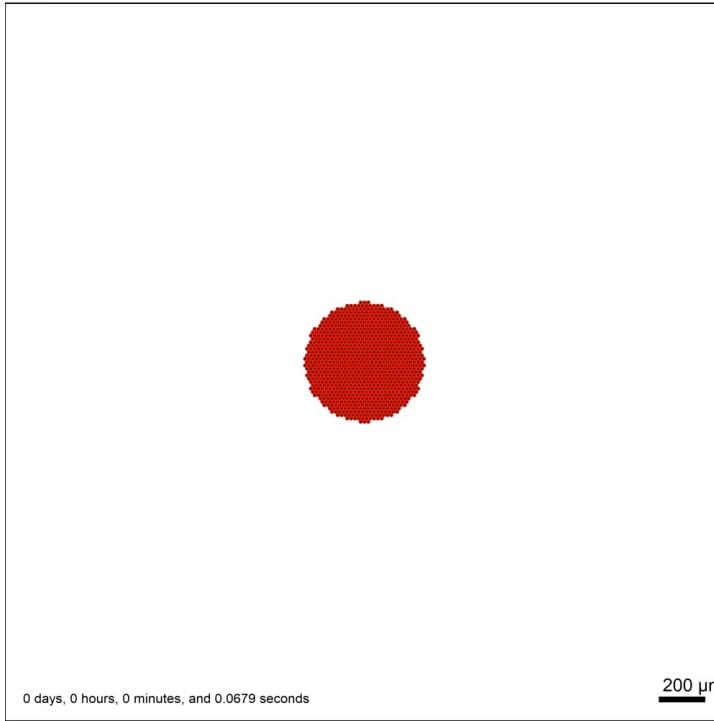
With persistence ($T_p > 0$) – Rows B & C

- 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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Indiana U.

** equal contribution
† in manuscript
*** corresponding author: 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.



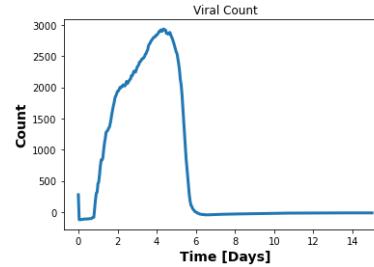
Iterative progress

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

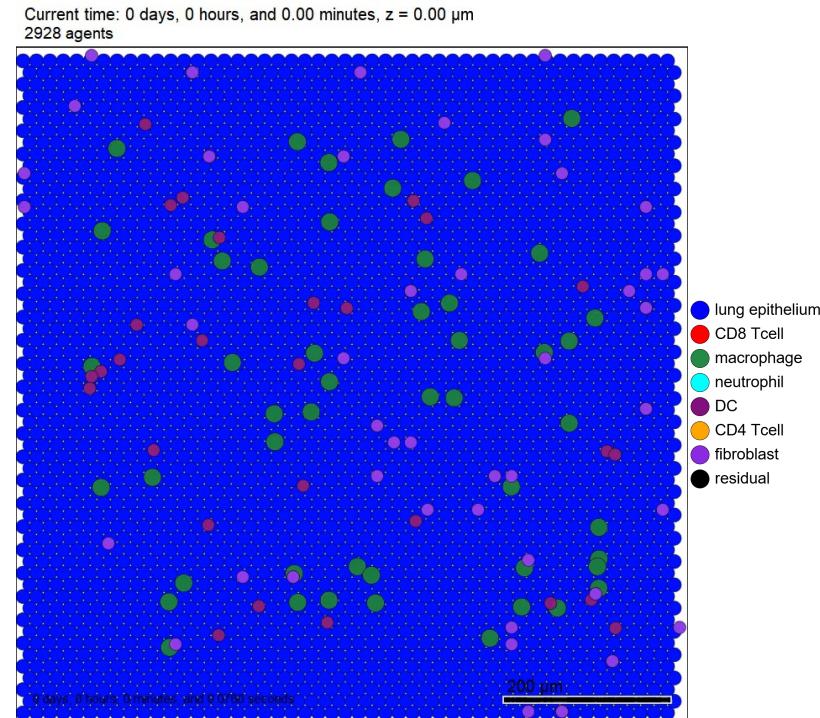
v5: neutralizing antibodies clear the infection

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

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



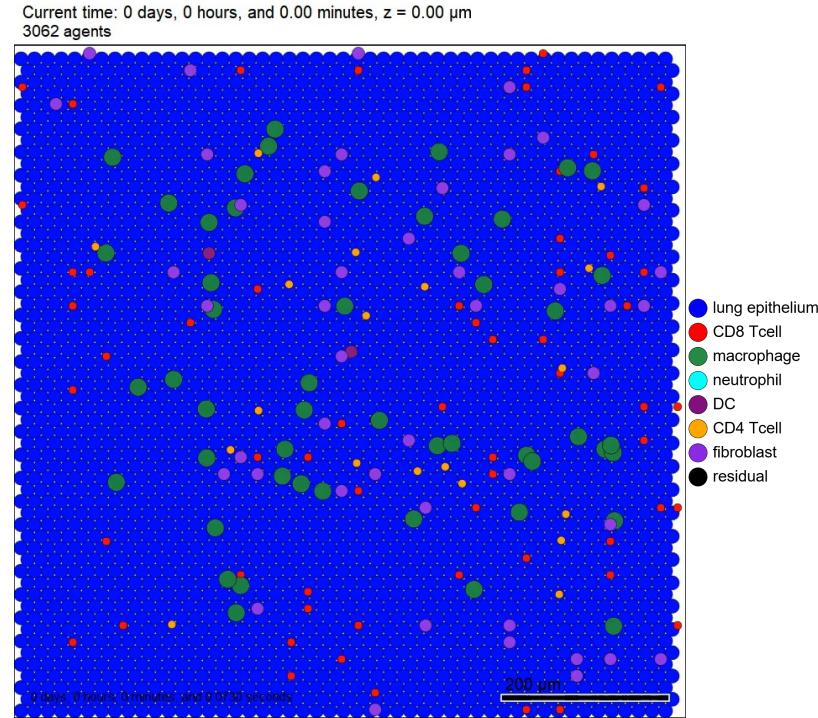
- **This immune model is sufficiently complete to clear a SARS-CoV-2 infection**



A naïve immune system can adapt to halt the infection

v5: prior immune responses are protective

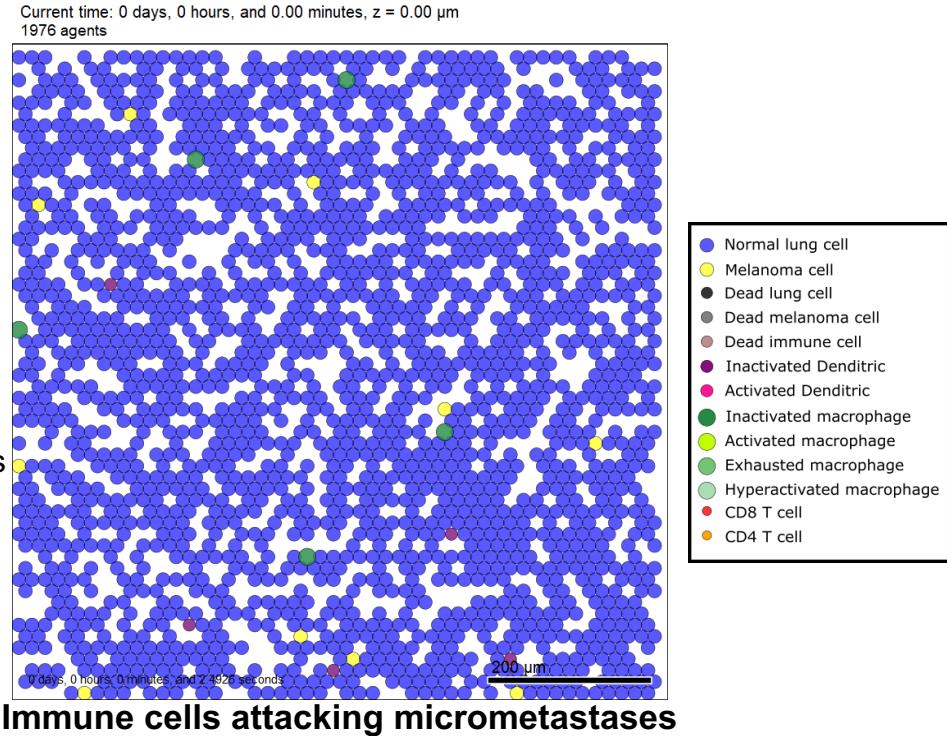
- The prior immune response is persistent:
 - Elevated "trained" CD8 T cells
 - Elevated neutralizing antibodies
- The prior immune response is protective:
 - Expose lung tissue to more virion
 - Brief immune activation
 - Much more limited tissue damage
 - Complete viral clearance
- This immune model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



Trained immune system facing future exposure

(Re)adapting to cancer

- Adapt and reuse:
 - Tumor growth model
 - Local immune dynamics:
 - ◆ Focused on macrophages, dendritic cells, CD4+ & CD8+ T cells
 - Immune cell trafficking
 - Lymph node T cell expansion
- Value of modular immune models:
 - Advances in one project help all the others
 - ◆ First cancer immune projects helped COVID19 models
 - ◆ COVID19 advances useful for cancer models
 - New projects don't start from scratch
- Ongoing work:
 - Explore potential for digital twins
 - Adapt to study vaccine immunotherapies.



Some of the hypotheses

- 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

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

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 and comparisons
- **Perhaps most importantly, as model complexity grows:**
 - Harder to understand the full model
 - Harder to clearly communicate the current biological hypotheses
 - Harder to integrate new biological hypotheses
 - Harder for domain experts to participate in real time

Create a "signal-response" 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 models
- Dictionary of signals (stimuli) that modulate behaviors
- Interpretable grammar to write signal-behavior relationships
- Automated mapping of the grammar onto mathematics and code

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

Dictionary of Behaviors

Behavior Dictionary

- With standardized forms, behaviors are fully controlled by well-defined parameters
- A 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 $n+1^{\text{th}}$ 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}		

Grammar

Now we use the dictionaries in a grammar

- **Base behaviors**

{cell type X}s {optional language smoothing words} {behavior Y} {optional parameters}.

- **Examples:**

- ◆ neutrophils phagocytose bacteria **with value** 0.001 1/min.
- ◆ CD8+ T cells attack tumor cells **with value** 0.01 1/min.
- ◆ tumor cells uptake oxygen **with value** 10 1/min.
- ◆ tumor cells **have** migration speed **with value** 1 micron/min.

- **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.

Joint work with JHU:

- Elana Fertig
- Genevieve Stein-O'Brien

Mathematical mapping

Hill response functions

- A widespread sigmoidal response curve in PKPD and systems biology
 - Varies from 0 (at signal=0) to 1 (as signal \rightarrow infinity)
 - Completely characterized by:
 - ◆ half-maximum: Input value where curve reaches half of maximum effect
 - ◆ Hill power: How steeply it approaches 1

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

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

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

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

Example

- **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.

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

Reconciling competing rules

- Suppose signal s_1 increases p towards p_U and s_2 decreases p towards p_D .

$$p(s_1, s_2) = \left(p_0 + (p_U - p_0) \frac{s_1^p}{(s_1^*)^p + s_1^p} \right) + \left(p_D - \left(p_0 + (p_D - p_0) \frac{s_1^p}{(s_1^*)^p + s_1^p} \right) \right) \frac{s_2^q}{(s_2^*)^q + s_2^q}$$

- We can write this more simply with:

$$U = \frac{s_1^p}{(s_1^*)^p + s_1^p} \quad (\text{up response}), \quad D = \frac{s_2^q}{(s_2^*)^q + s_2^q} \quad (\text{down response})$$

- Write overall response as a bilinear interpolation of responses

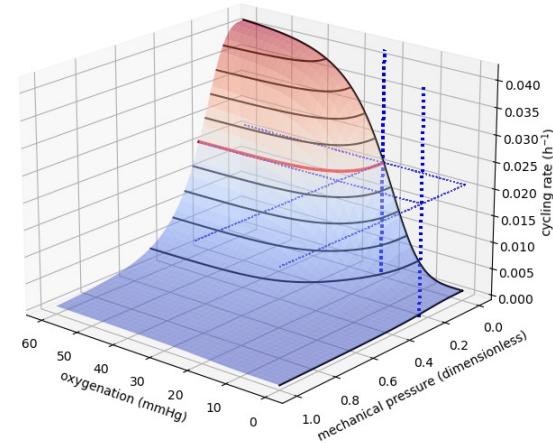
$$p(s_1, s_2) = (1 - D) \cdot [(1 - U) \cdot p_0 + U \cdot p_U] + D \cdot p_D$$

Example: combination rule

- **Oxygen increases cycle entry** from 0.001 hr^{-1} towards 0.02 hr^{-1} with a Hill response function, with half-max 21.5 mmHg and Hill power 4.
- **Pressure decreases cycle entry** from $p_0 = 0.001 \text{ hr}^{-1}$ towards a maximally inhibited rate of $p_M = 0 \text{ hr}^{-1}$.

$$U = \frac{(pO_2)^4}{21.5^4 + (pO_2)^4}, \quad D = \frac{p^3}{0.25^3 + p^3}$$

$$p(pO_2, p) = (1 - D) \cdot [(1 - U) \cdot 0.001 + U \cdot 0.042].$$



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:**

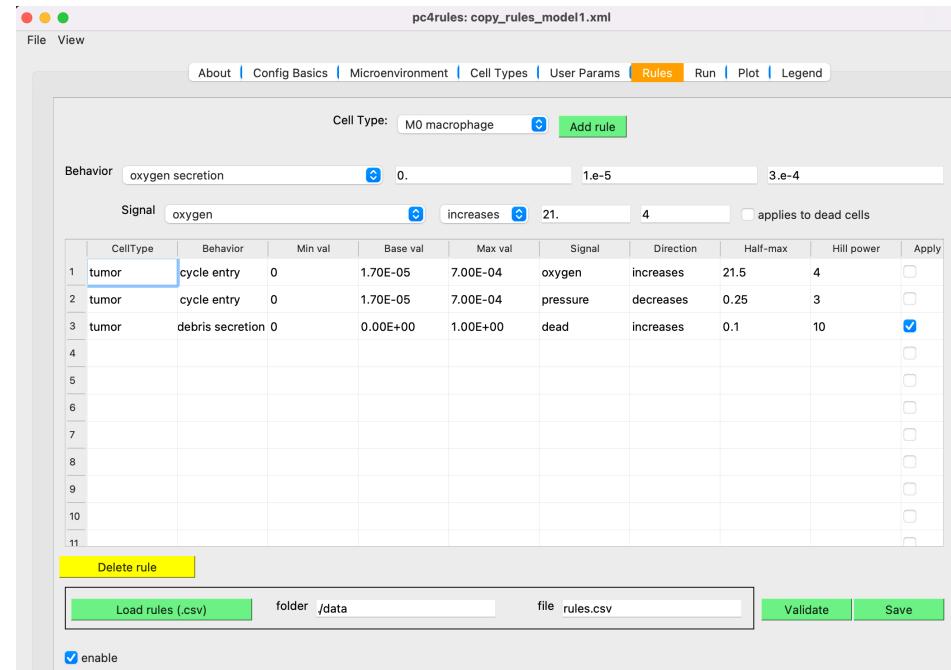
$$p(\mathbf{u}, \mathbf{d}) = (1 - D) \cdot [(1 - U) \cdot p_0 + U \cdot p_M] + D \cdot p_m$$

- **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
 - (Should also generate other forms such as LaTeX, DOCX, PPTX, ...)
- 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

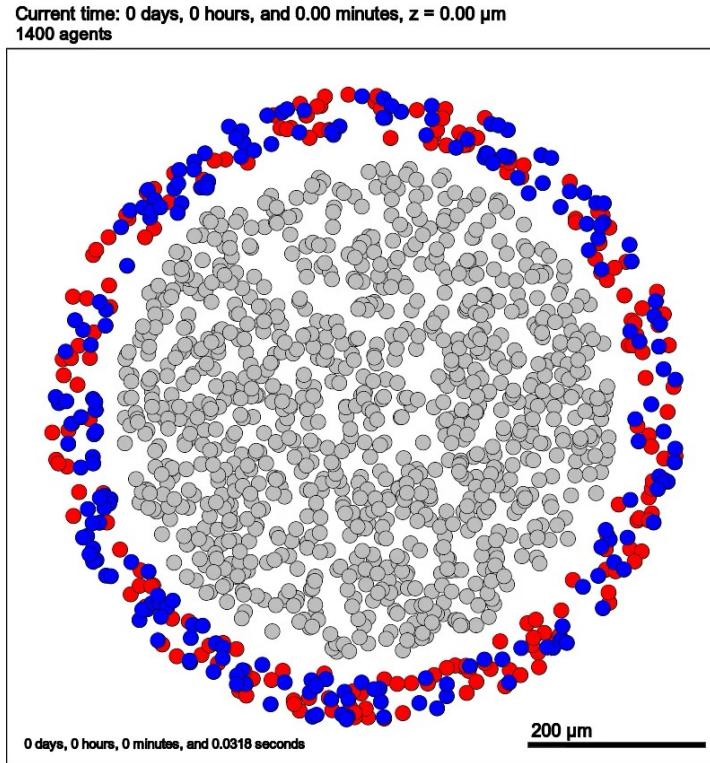
CD8 T cell,cycle entry,0,7.2e-5,9.3e-4,IFN-gamma,increases,0.25,2,0
CD8 T cell,attack tumor,0,0.01,0.05,IL-10,decreases,0.25,2,0
CD8 T cell,migration speed,0.1,1,1,IL-10,decreases,0.25,2,0
CD8 T cell,transform to exhausted T cell,0,0,0.05,IL-10,increases,0.25,2,0
CD8 T cell,migration speed,0.1,1,1,contact 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
 - Joe Gray
 - Laura Heiser
 - Young Hwan-Chang

Sample result

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



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The future is *real time* modeling with knowledge mapping.

1. Meet with domain experts to formulate behavioral hypotheses
2. Immediately import the rules and simulate behavior
3. Assess work with experts *in real time* to improve the hypotheses

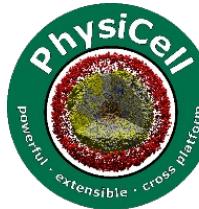
GOAL: accumulate and curate *knowledge!*

Create a community-curated library of *reusable* behavioral hypotheses.

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?)
- Literature-driven
 - Mine PubMed with NLP, Chat-GPT, etc. to identify relationships
- All of these paths could be represented in this framing, integrating data-driven and knowledge-driven modeling paths

Save the date!



2023 Virtual PhysiCell Workshop and Hackathon

July 23-29, 2023

- Build and explore multicellular agent-based simulations of cancer and other systems
- Learn to share your models online
- Meet other modelers in the PhysiCell community
- Compete in an exclusive mentored hackathon
- PhysiCell swag available for accepted participants
- Application and full agenda coming soon at:
<https://github.com/PhysiCell-Training/ws2023>

