

Slides, videos, links and more:

<https://github.com/physicell-training/ws2021>

Session 0: Introduction to Agent-Based Modeling and PhysiCell

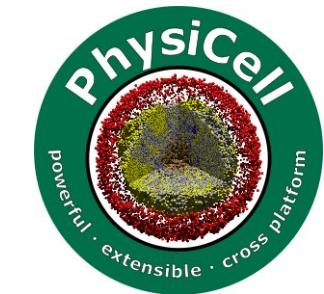


Paul Macklin, Ph.D.

 @MathCancer

PhysiCell Project

July 15, 2021



Goals

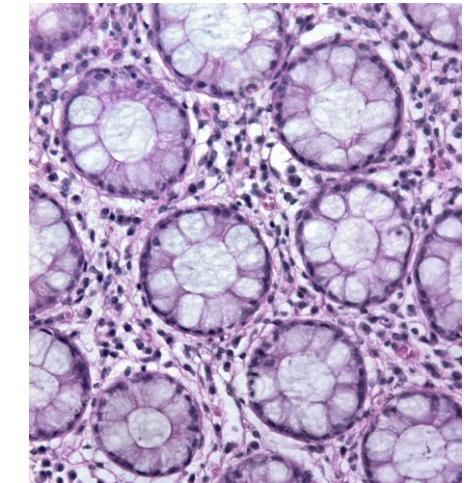
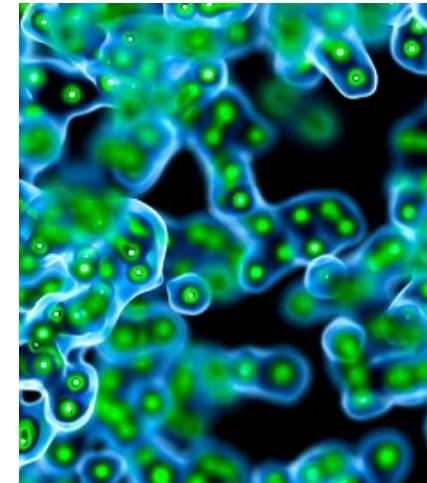
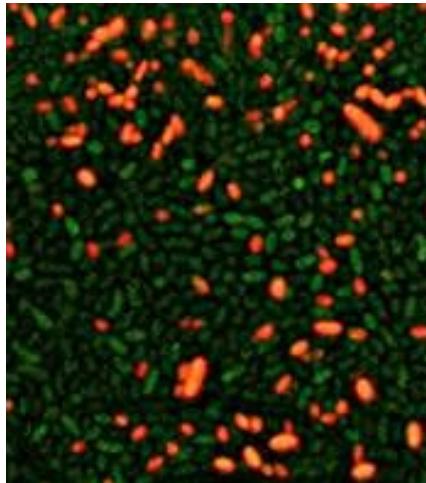
- Learn the concepts of agent-based modeling
- Briefly survey the main types of agent-based modeling approaches
- Learn about PhysiCell's agent modeling approaches
- See some examples

Simple single-cell behaviors ...

- Growth
- Division
- Death
- Adhesion
- Mechanics
- Motility
- Secretion
- Uptake
- Sampling
- Predation
- Differentiation
- ...

Give rise to complex systems

- ***Multicellular systems***—composed of multiple cells of multiple types—can exhibit remarkable diversity, with complex emergent behaviors.



How do these systems self-organize and sustain themselves?

How do we understand these multiscale systems?

Interconnected systems and processes:

- Single-cell behaviors
- Cell-cell communication
- Physics-imposed constraints (e.g., diffusion)
- Systems of systems (e.g., immune system)

In diseases, these systems become dysregulated.

Treatments target parts of these systems.

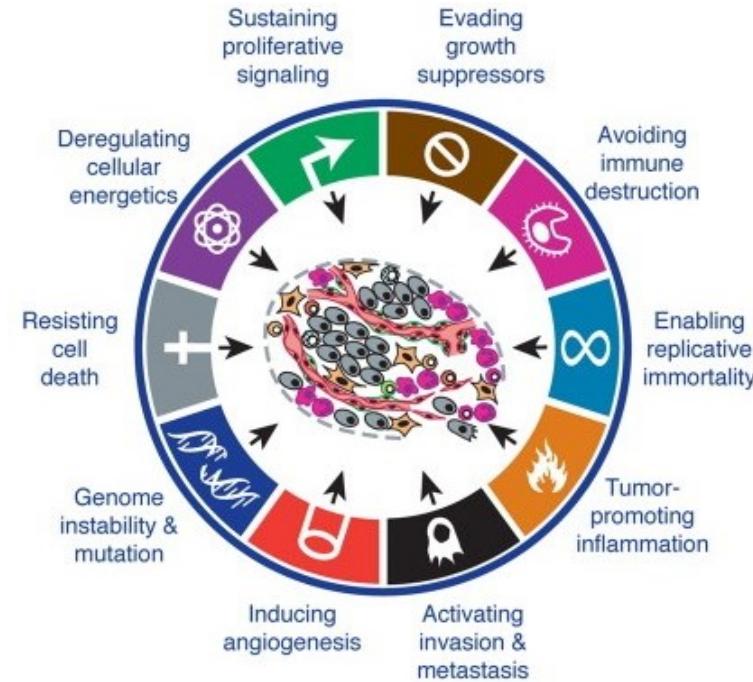
Health is a **complex system**:

changing one part can have **surprising effects!**

Modeling can help **understand** this system.

This is **multicellular systems biology**.

If we can **control** these systems, we've arrived at
multicellular systems engineering.



Source: Hanahan & Weinberg (2011)
DOI: [10.1016/j.cell.2011.02.013](https://doi.org/10.1016/j.cell.2011.02.013)

Analogy: multicellular biology as a play

- The **microenvironment** is the **stage**.
- The **cells** are the **actors**.
- The **cell actors** follow their own **scripts**.
- **BUT:**
 - The scripts change based on the stage. (microenvironment-dependent phenotype)
 - The actors' dialog is critical. (cell-cell communication)
 - The actors can tear up and remodel the stage. (tissue remodeling)
 - The actors can ignore their scripts and ad lib. (Mutations, evolution)

It's our job as scientists to figure out each actor's script by watching the play.

Clinicians and engineers want to rewrite the script.

Agent-based modeling is a modeling paradigm for these complex multicellular systems:

Cells are *software agents* that move and live a *virtual tissue environment*.

What is a discrete model?

- “**Discrete**” applies to discrete mathematics.
- **Continuum models** describe *continuous variables* with continuous (and differentiable) operations. The variables take continuous values. (e.g., positive real numbers)
 - **Example:** a cell population density ρ modeled with the Fisher's equation with diffusion (D) and a birth rate (r) up to a carrying capacity (ρ_{\max}).

$$\frac{\partial \rho}{\partial t} = D \nabla^2 \rho + r \rho \left(1 - \frac{\rho}{\rho_{\max}}\right)$$

- **Discrete models** describe *distinct individuals* with discrete events. The variables tend to take discrete values. (e.g., Boolean or integer variables)
 - **Example:** A cell population $X(t)$ models birth events as a Poisson process with rate r : Between now (t) and the next time step ($t + \Delta t$), there is a probability $P = r\Delta t$ of a birth event that increases X by one.

What is an agent-based model?

- An **agent-based model** (in biology) is a type of discrete model that simulates individual cells.
 - Also referred to as **individual-based models** or **cell-based models**.
- Agent-based models are often combined with continuum models of the microenvironment (e.g., partial differential equations for signaling factors), resulting in **hybrid discrete-continuum (HDC) models**.
- **Object-oriented programming (OOP)** is ideal for agent-based modeling:
 - Modeling work focuses on individual cells
 - Each cell is an independent *agent* that carries its own data, and has its own behavioral rules
 - **Use OOP:** Define a cell *class* with member data and methods. Each cell is an instance of that class.
- Agent-based models are a little closer to the biology:
 - Focus on modeling cells and their changing behavior.
 - Specific problems are then a matter of choosing the right rules.
 - You can tailor the level of detail: add molecular-scale biology to each cell if you need it.

Typical ABM program flow

- Read parameters
- Set up microenvironment
 - Create meshes, initialize chemical substrates, diffusion solvers, etc.
- Set up cell agents
 - Define all cell types
 - Instantiate cells
- For each time:
 - Update microenvironment
 - ◆ Solve reaction-diffusion equations (as needed)
 - ◆ Solve tissue mechanics (as needed)
 - Update each cell's state
 - ◆ Sample environment
 - ◆ Run signaling model (as needed)
 - ◆ Update behavioral parameters based on signaling model and sampled environment
 - ◆ Run cell process models (growth, cycling, death, ...)
 - Calculate cell velocities
 - Update cell positions
 - Advance time

Types of cell-based models

- **lattice-bound**

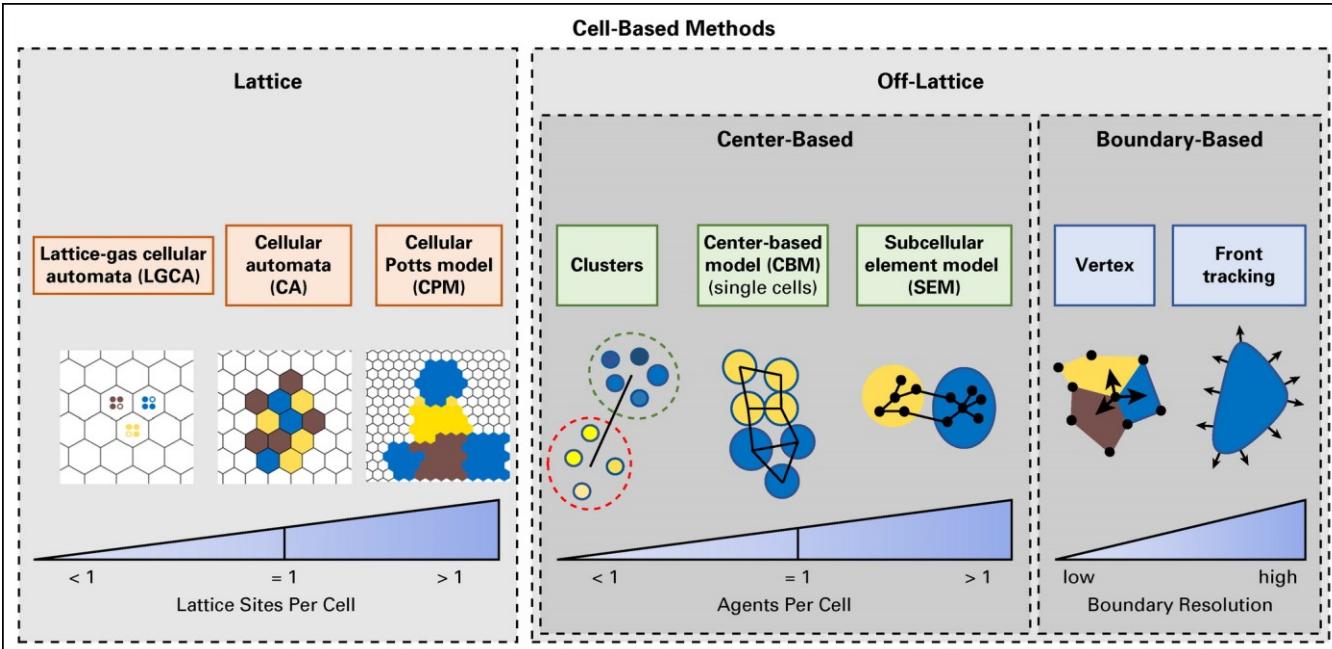
- resolution:

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

- **off-lattice**

- **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).

Where does PhysiCell fit in?

- PhysiCell is an **off-lattice, center-based** modeling platform
 - **Spatial resolution:** one agent per cell
 - **Trick:** Use bigger agents to model cell collections or pieces of tissue.
 - **Trick:** Use smaller agents to model cell parts
- PhysiCell couples with PDE models of the microenvironment, making it a **hybrid discrete-continuum approach.**
 - Since most useful agent-based models are coupled to PDE models of the microenvironment, we simply refer to them as agent-based models.
- PhysiCell uses ODEs and other technical to model dynamical details in individual cells. This makes it **multiscale.**

BioFVM: Simulating the 3-D microenvironment

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:

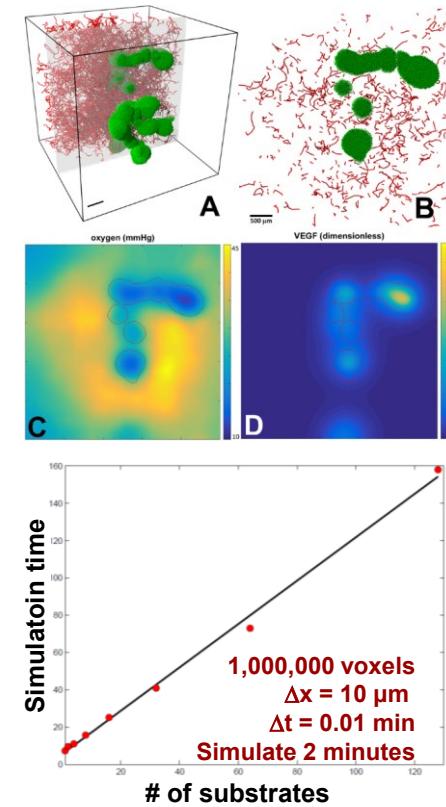
- Off-lattice cell secretion and uptake
- 2nd-order accurate (space), 1st-order accurate (time), numerically stable

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 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)

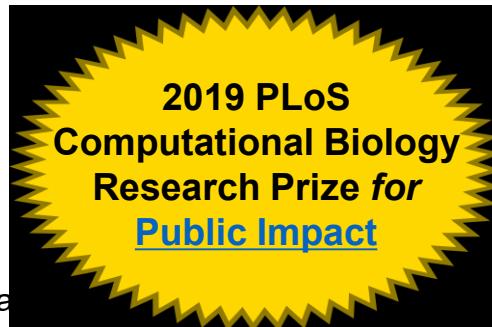


PhysiCell: A multicellular framework

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
- **Deployed from Raspberry Pi to Crays**



Method:

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

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

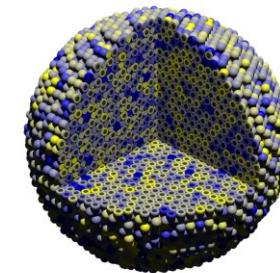
DOI: [10.1371/journal.pcbi.1005991](https://doi.org/10.1371/journal.pcbi.1005991)



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)]

Key parts of a PhysiCell model (1)

- **Microenvironment (stage):**

- diffusing substrates
 - ◆ diffusion coefficient
 - ◆ decay rate
 - ◆ boundary conditions
 - ◆ Defined in XML configuration file

- **Cell Definitions (types of players):**

- name
- default phenotype (more on next page)
- defined in XML configuration file

Key parts of a PhysiCell model (2)

- **Cell agents (individual players):**
 - Which cell type? (The cell agent is initialized based on a cell definition.)
 - State variables:
 - ◆ position
 - ◆ mechanical pressure
 - ◆ interaction list (optional)
 - **Phenotype (the script)**
 - ◆ Cell cycle
 - ◆ Volume
 - ◆ Death
 - ◆ Motility
 - ◆ Mechanics
 - ◆ Substrate uptake & release
 - Custom variables
 - Custom functions that act upon the phenotype, variables, and state (**script**)

- live in a microenvironment
- single-cell biological behaviors
- cell functions model biological hypotheses to trigger core behaviors
- cell-cell interactions

A note about time steps

- PhysiCell is designed to account for the multiple time scales inherent to these problems, and has 3 time scales:
 - $\Delta t_{\text{diffusion}}$ diffusion, secretion, and uptake (default: 0.01 min)
 - $\Delta t_{\text{mechanics}}$ cell movement (default: 0.1 min)
 - Δt_{cell} phenotype and volume changes (default: 6 min)
- This allows some efficiency improvements: not all functions need to be evaluated at each time step.

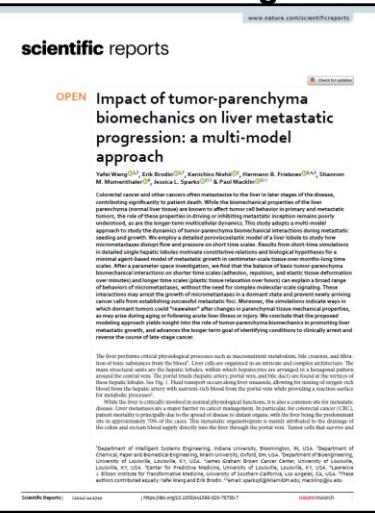
Some recent examples

Work led by:
Yafei Wang

Example 1:

tumor-parenchyma interactions in micrometastases

Wang et al. *Sci. Rep.* (2021)
Open Access: <https://doi.org/10.1038/s41598-020-78780-7>

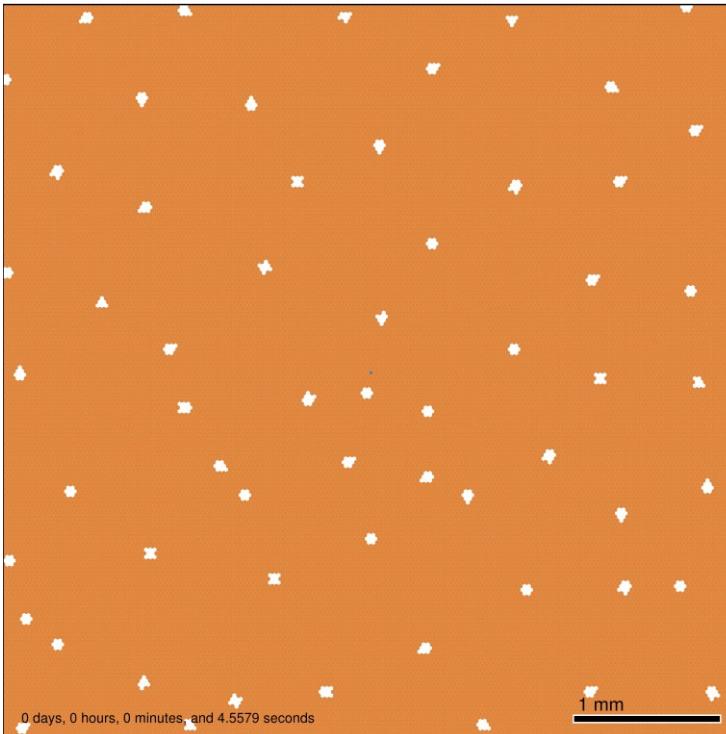


How can liver parenchyma impact colorectal cancer (CRC) metastases?

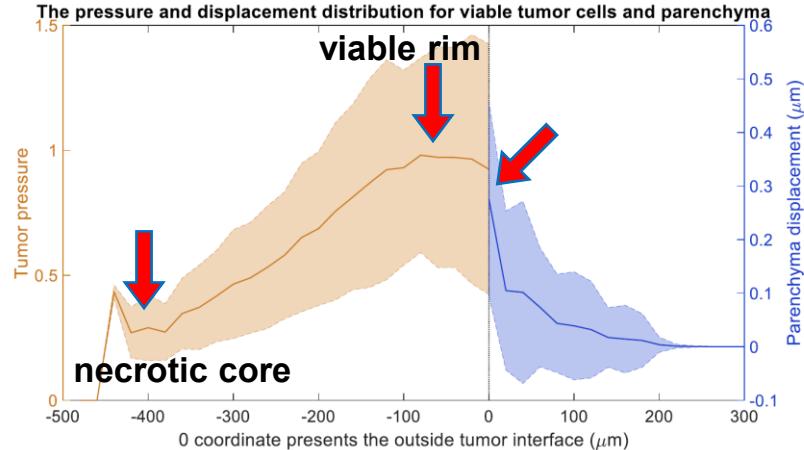
- **How can a micrometastasis clear space for expansion?**
 - Displacement and compression of liver parenchyma
 - Compressive forces on the micrometastasis
- Key model elements: **biomechanical tumor-parenchyma feedbacks**
 - Parenchyma → Tumor:
 - ◆ Pressure (compression) down-regulates tumor cell proliferation
 - Tumor → Parenchyma:
 - ◆ Parenchyma agents use plastic-elastic model
 - » Elastic restorative force on short time scales
 - » Plastic reorganization on long time scales
 - » Apoptosis under sustained deformation

Growth with feedback

Current time: 0 days, 0 hours, and 0.00 minutes, z = 0.00 μm
34887 agents



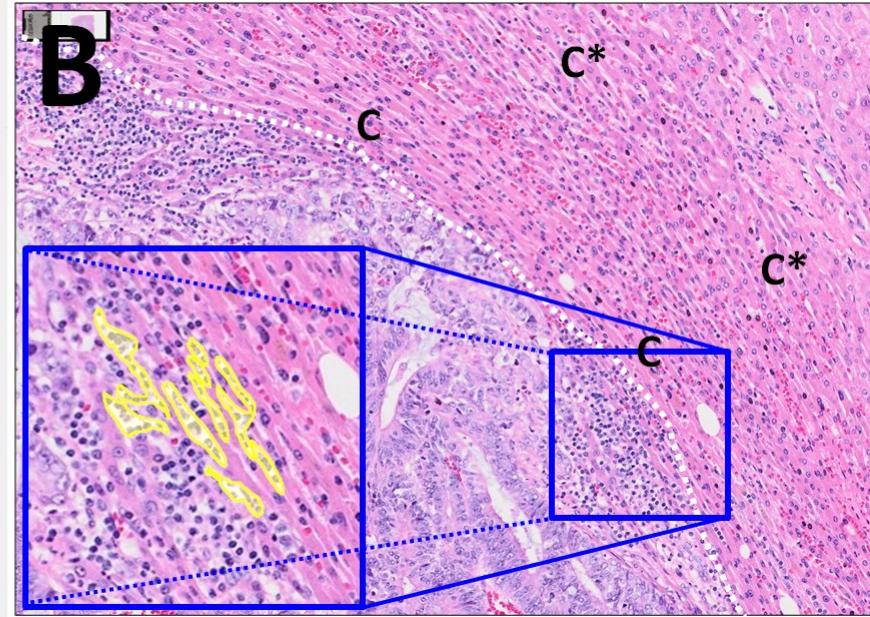
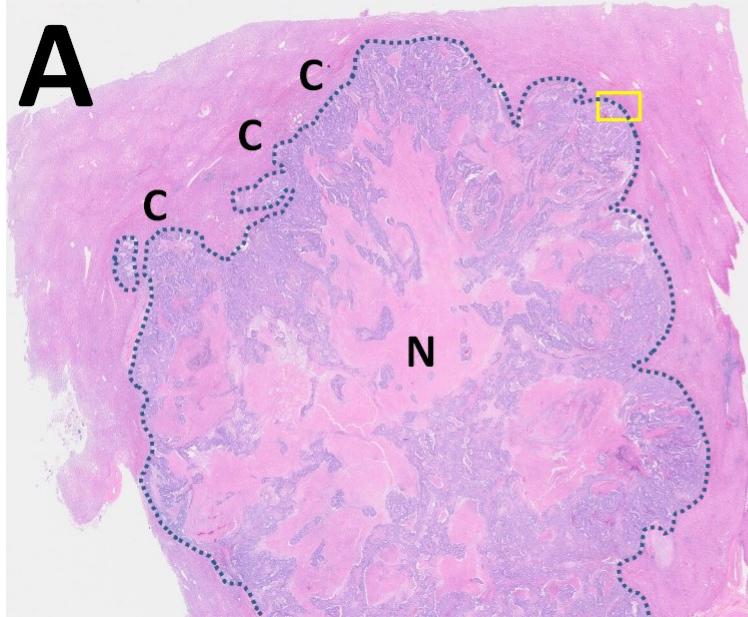
**Yellow tumor cells
have arrested cycling
due to high pressure.**



Try this model yourself!

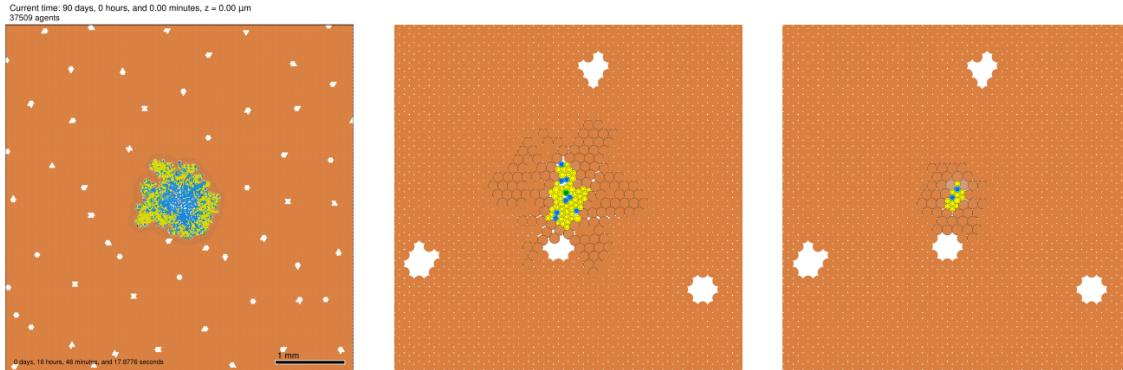
nanohub.org/tools/pc4livermedium

Comparison with a typical clinical sample



Tumor dormancy in some tissues

- If tissue has:
 - large elastic force
(large r_E)
 - slow plastic relaxation
(small r_P)
 - tolerance of deformation
(large d_{\max})
- Then:
 - Compressed tissue surrounds tumor (encapsulation)
 - Most cells are pressure-arrested, leading to **tumor dormancy**



(a) $r_E=0.2$, $r_P=0.001$,
 $d_{\max}=1.5$

(a) $r_E=0.2$, $r_P=0.001$,
 $d_{\max}=3$

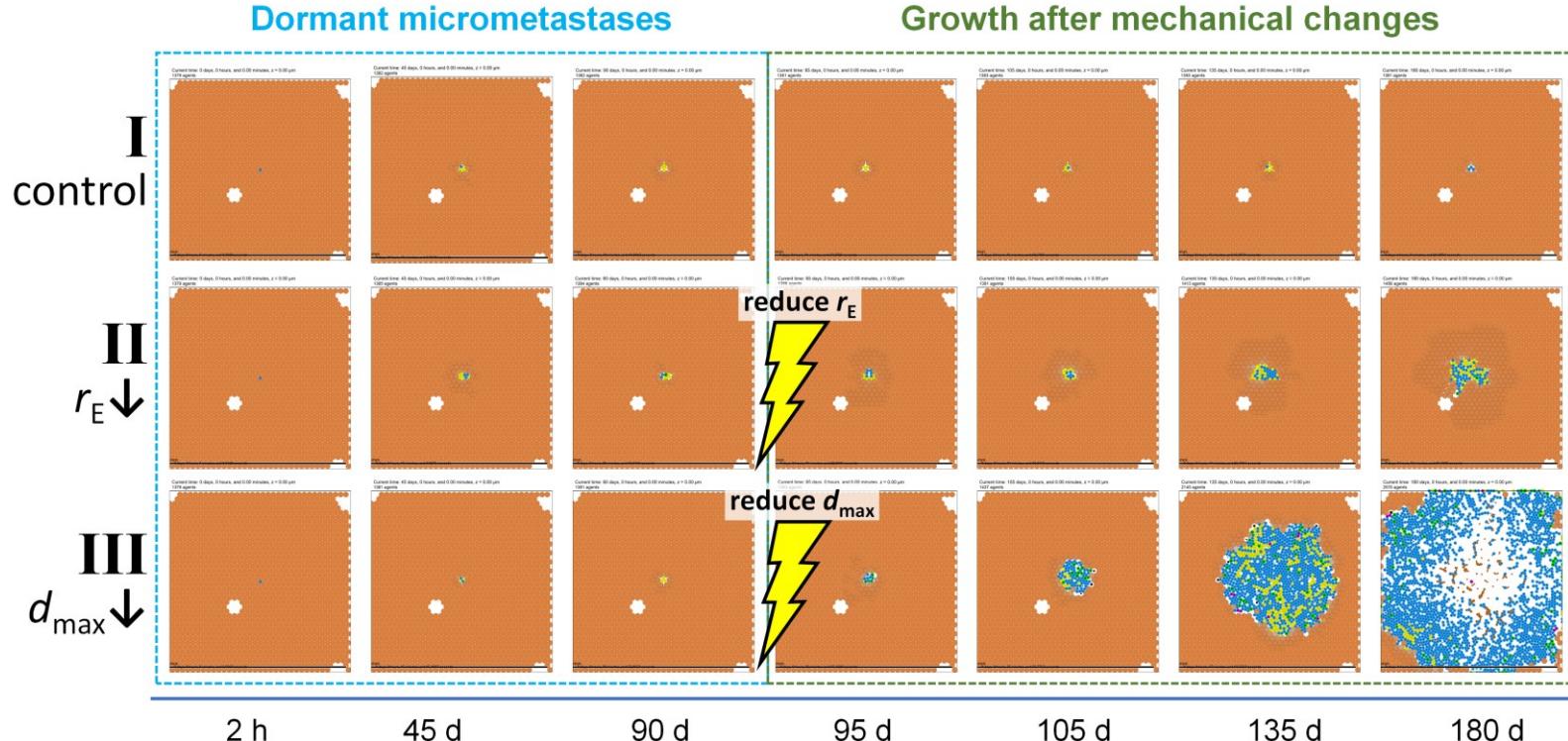
(b) $r_E=0.2$, $r_P=0.0005$,
 $d_{\max}=3$



Try this model yourself!

nanohub.org/tools/pc4livermedium

Tissue changes can reawaken a tumor



Example 2:

Cancer-immune contact interactions

Simple model of cancer-immune interactions

Heterogeneous tumor cells (blue to yellow):

- Cycle entry rate scales with O₂
- Cells necrose in very low O₂
- Yellow cells are most proliferative;
 - blue are least proliferative
- Yellow cells are most immunogenic
 - simplified model of MHC

Immune cells (red):

- Biased random walk towards tumor
- Test for contact with cells
- Form adhesion
- Attempt to induce apoptosis
 - (e.g., FAS receptor)
 - success depends on immunogenicity
- Eventually detach from cell, continue search

Movie: [[View on YouTube](#) (4K)]

References:

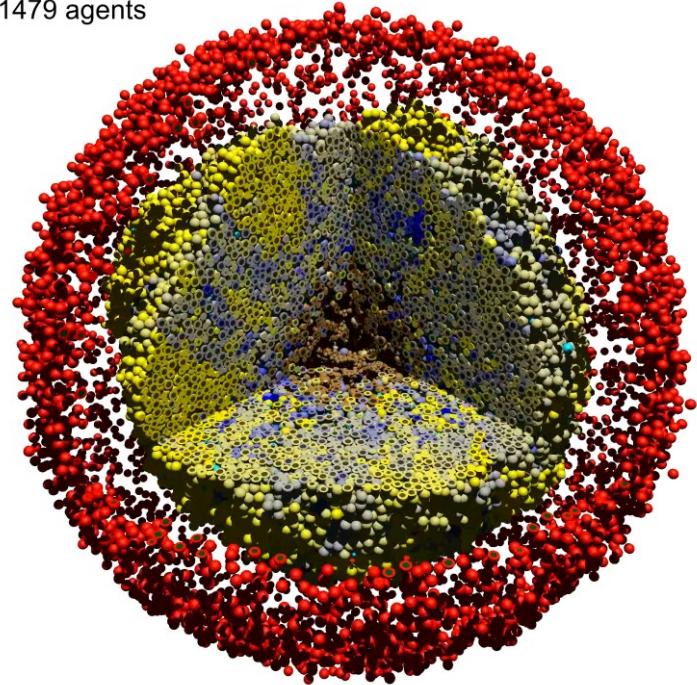
- [Ghaffarizadeh et al. \(2018\)](#)
- [Ozik et al. \(2018\)](#)
- [Ozik et al. \(2019\)](#)



Try this model yourself! (2D)

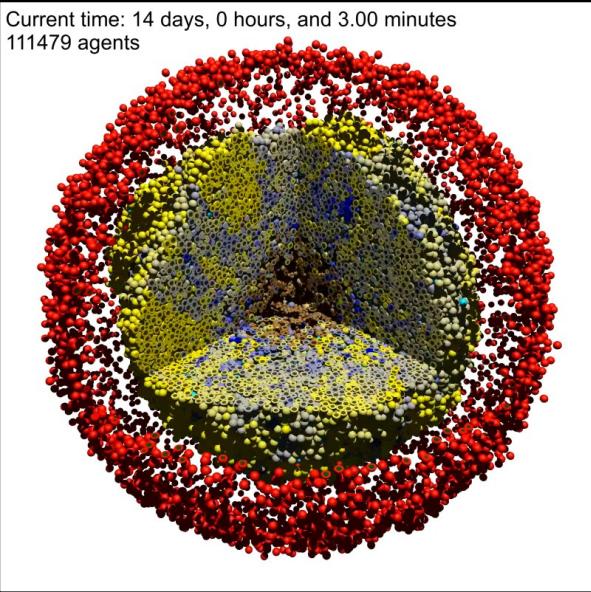
nanohub.org/tools/pc4cancerimmune

Current time: 14 days, 0 hours, and 3.00 minutes
111479 agents



High-throughput investigations on HPC

3-D tumor-immune model

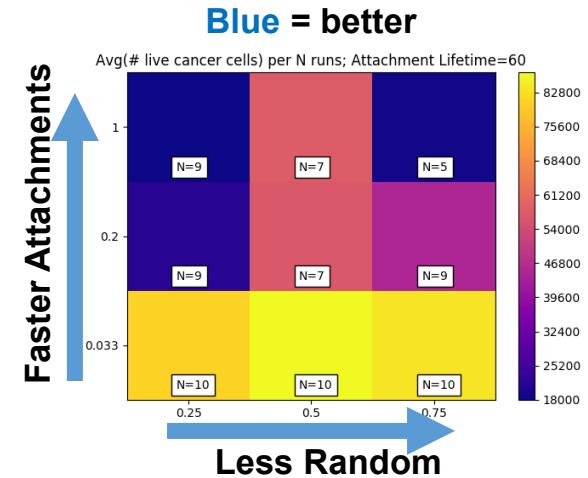


Explore 3 parameters:

- migration bias
- attachment rate
- attachment lifetime
- 27 parameter sets
- 10 replicates per set
- ~2 days per run
- ~1.5 years of computing

HTC is the only feasible path

ANL: Do all 270 runs over a weekend



Reference:
[Ozik et al. \(2018\)](#)

PhysiCell Project
PhysiCell.org
 [@PhysiCell](#)

Higher-dimensional design spaces

- As the number of design parameters increases, this becomes a high-dimensional design space.
- We focus exploration with a nested series of design goals:

Cancer control

1) Number of tumor cells at end (N_{final}) doesn't exceed initial count (N_{initial})

Cancer remission

2) Can we reduce cancer cells by 90% ($N_{\text{final}} \leq 0.1 N_{\text{initial}}$)?

3) Can we reduce cancer cells by 99% ($N_{\text{final}} \leq 0.01 N_{\text{initial}}$)?

Treatment optimization:

4) Can we minimize N_{final} ?

- We can't explore the entire space by brute force, even on HPC

Using active learning

- For each design scenario (e.g., 10% scenario), build a binary DT classifier:
 - **True**: points that meet the design goal (e.g., $N_{\text{final}} \leq 0.1 N_{\text{start}}$)
 - **False**: points that don't meet the design goal (e.g., $N_{\text{final}} > 0.1 N_{\text{start}}$)
- Run 1000 simulations at a time on HPC to build the classifier:
 - 50 points in the 6-parameter space
 - 20 replicates per sample
 - Classify samples as true/false
- **Active learning** helps us choose samples that refine the decision boundary

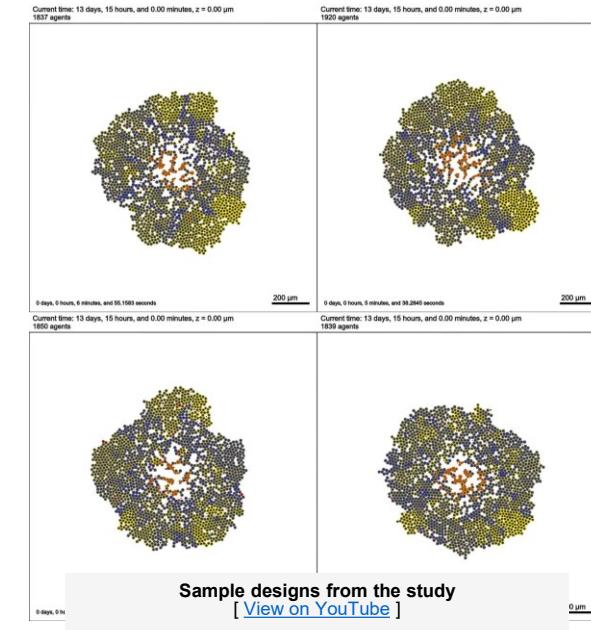
Reference:

Bonus: Use the Gini coefficients to **rank** the parameters [Ozik et al. \(2019\)](#)

How does HPC+ML enable new science?

- HPC gives the **topology** of a design space:
 - Each design scenario is an isosurface.
 - Finding multiple surfaces gives the topology.
 - More **aggressive treatment goals** drastically **shrink the viable design space**
- HPC+ML makes it **feasible to** find several design surfaces to **see the topology**
 - ~ 30,000 to 40,000 simulations per contour
 - **Active learning:** Reduced from 10^7 to 10^4 simulations
 - ~ 48,000 core hours for each surface
 - ~ 250 days (nonstop) on high-end workstation
 - ~ 2 weeks (nonstop) on a smallish cluster
 - ~ 12 hours on a Cray at ANL

Machine learning helps us interpret the agent-based model results



Try this model yourself!
nanohub.org/tools/pc4cancerimmune

Reference:
[Ozik et al. \(2019\)](#)

Work led by:
Michael Getz

Example 3:

iterative development of a SARS-CoV-2 tissue simulator

Getz et al. *bioRxiv*. (2021)
Preprint: <https://doi.org/10.1101/2020.02.19.200780>



Collaborative, Iterative Progress

Approach

- **Rapid prototyping**
 - Build, test, and refine
- **Multidisciplinary team**
 - Domain experts guide modelers
 - Subteams work in parallel
 - Integration team coordinates the work
- **Rapid communication**
 - Preprints (open science)
 - Cloud-hosted models for live demos to team experts
- **Open source software**

Progress

Phase I (community building)

- **v1 prototype** (March 2020) built in 12 hours
- **v2 model** (April) added ACE2 receptor trafficking

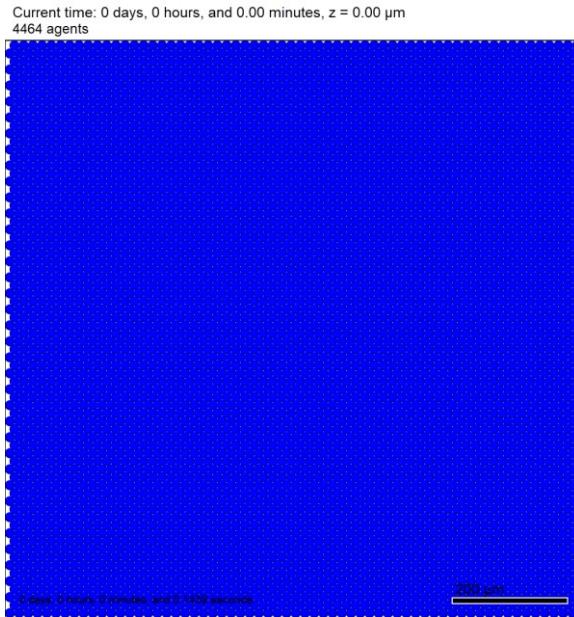
Phase II (community-driven) (current)

- **v3 model** (May-July 2020) added tissue immune responses
- **v4 model** (August-November 2020) added:
 - interferon signaling
 - pyroptosis
 - systems-scale immune model
 - immune cell trafficking
 - improved tissue immune model
 - better receptor-virus binding
 - better viral replication
 - tissue fibrosis.
- **v5 model** (November 2020-July 2021) added:
 - neutralizing antibodies
 - "bystander" killing by ROS
 - anti-inflammatory signals
 - improved tissue immune model
 - better receptor-virus binding
 -

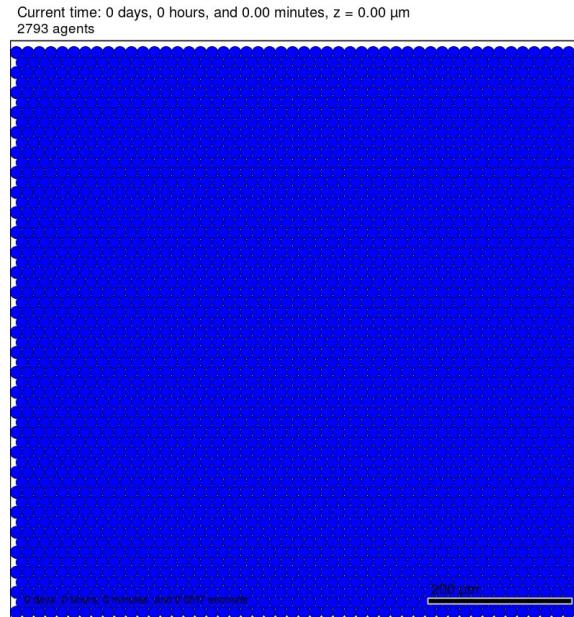
Iterative modeling progress

Versions 1 to 3

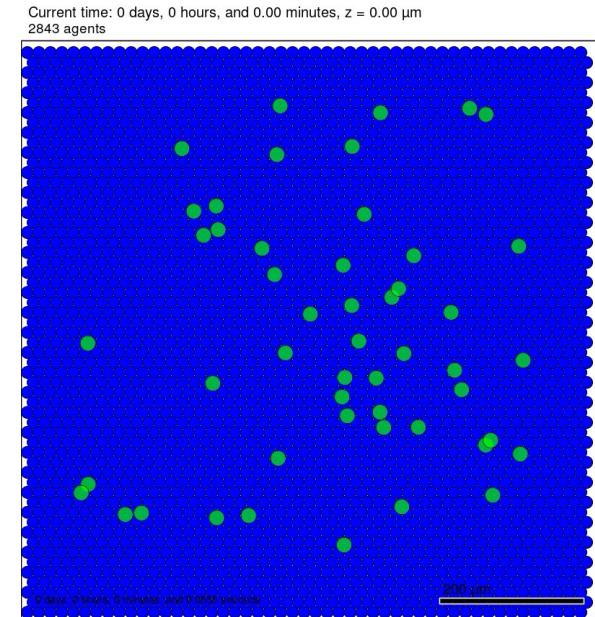
v1: prototype



v2: +ACE2
+random virion seeding



v3: +tissue immune



Version 4

multiscale immune model advances

Improved macrophages:

- Macrophages exhaustion & death
- Phenotype changes from CD8+ T cell contact
 - Stop secreting pro-inflammatory cytokine
- Enable phagocytosis of live infected cells

Dendritic cells:

- Resident DCs activated by virus or infected cells
- DCs traffick to lymph node to drive T cell expansion

More T cell types

Epithelial cells present antigens

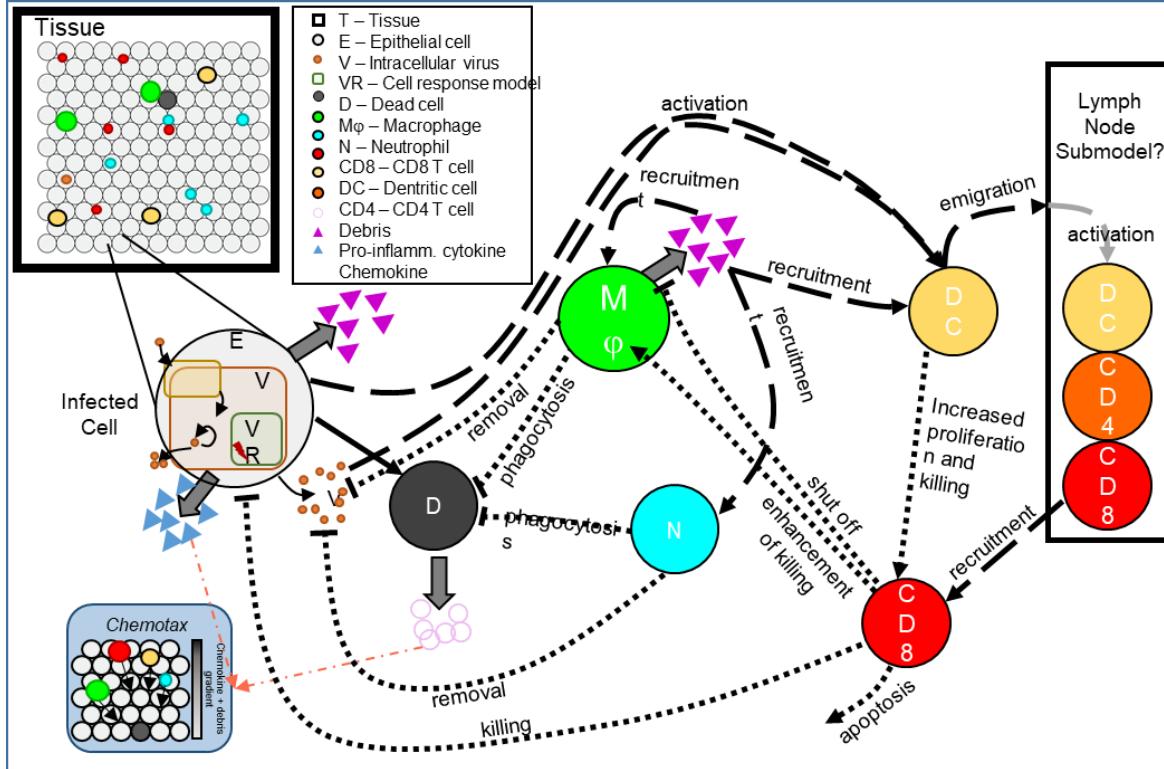
Systems-scale model of immune activation



systems scale:
Tarunendu Mapder
IUPUI

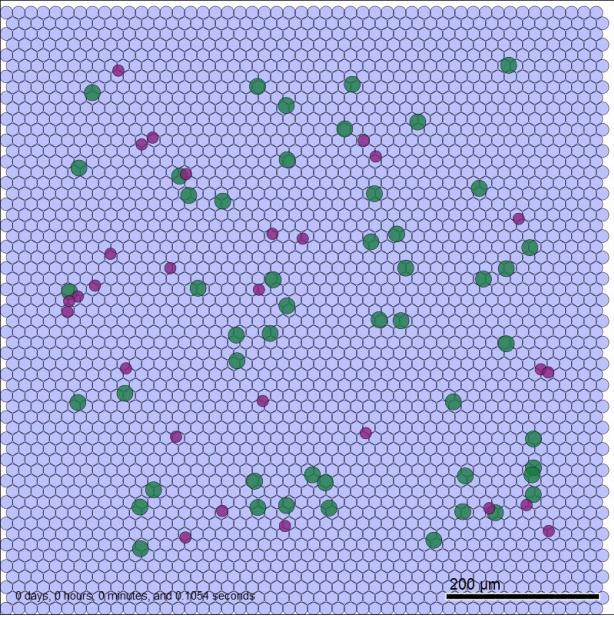


tissue scale:
Adrienne Jenner
U. Montreal



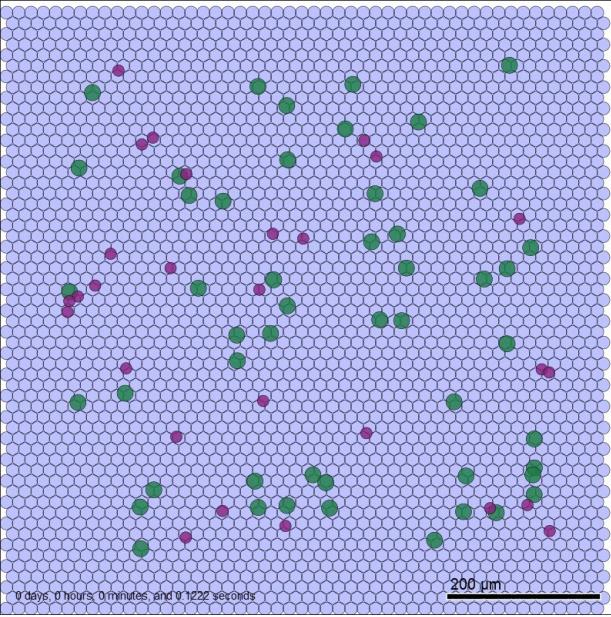
Type I interferons slow progression

Current time: 0 days, 0 hours, and 0.00 minutes, z = 0.00 μm
2871 agents



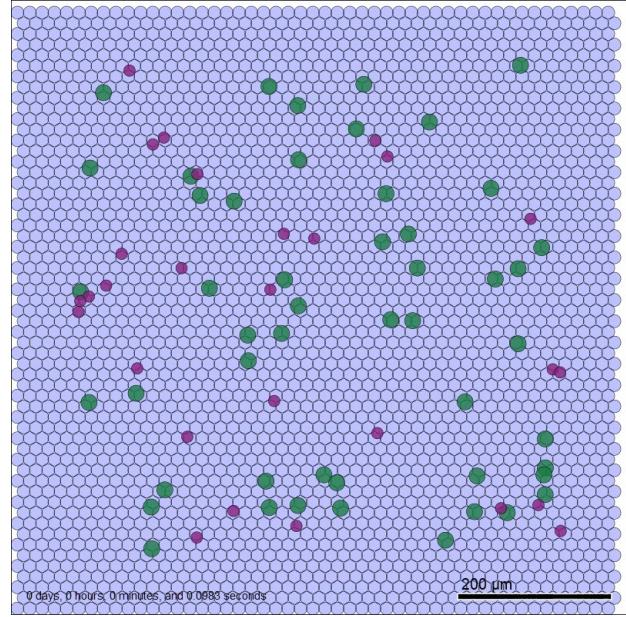
no interferon secretion

Current time: 0 days, 0 hours, and 0.00 minutes, z = 0.00 μm
2871 agents



low interferon secretion

Current time: 0 days, 0 hours, and 0.00 minutes, z = 0.00 μm
2871 agents



10x interferon secretion

- Uninfected cell
- Infected cell
- Dead cell
- Macrophage (inactive)
- Macrophage (active)
- Macrophage (exhausted)
- Macrophage (hyperactive)
- Neutrophil
- CD8 T cell
- CD4 T cell
- DC (inactive)
- DC (active)

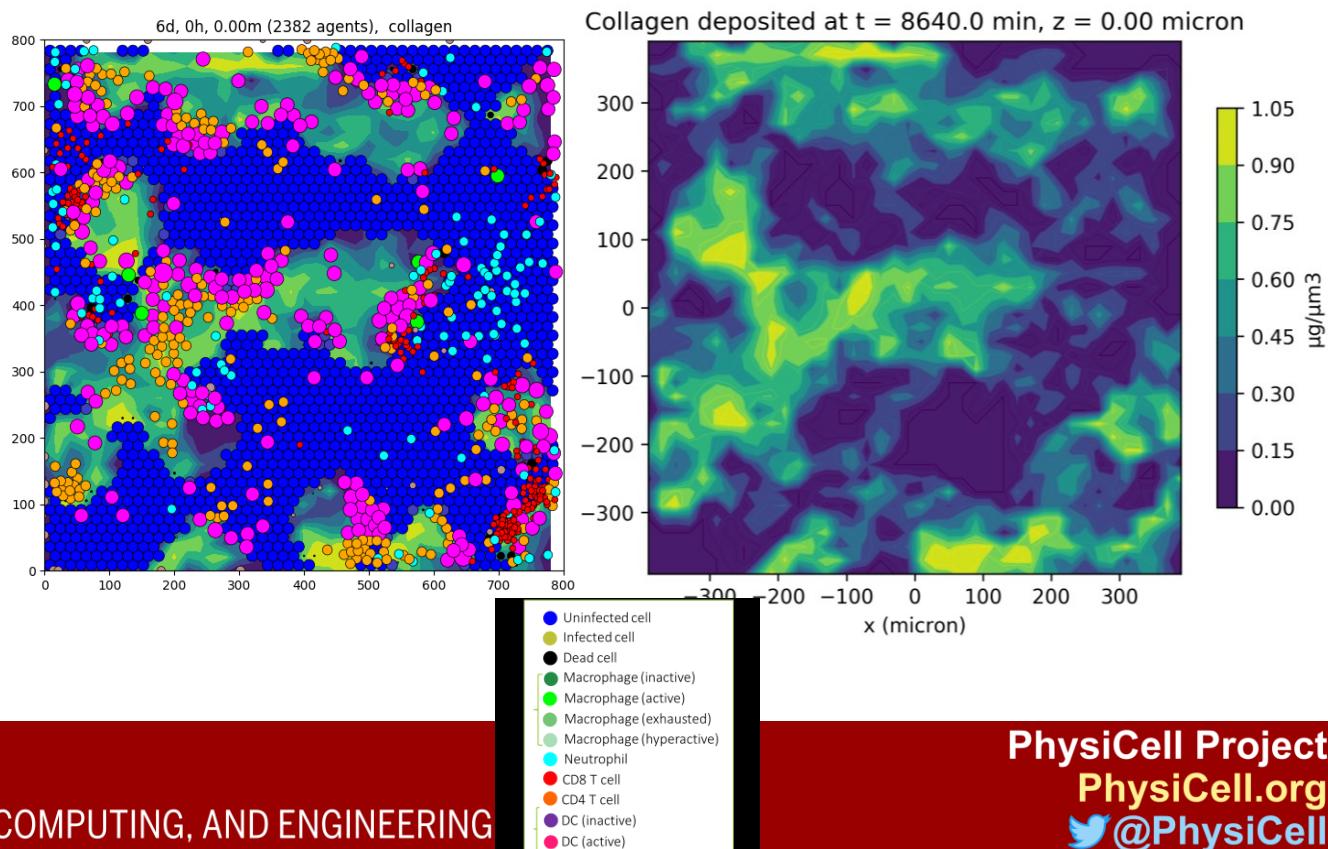
Preliminary work: coupled fibrosis

- Recruited fibroblasts re=seek damage from CD8+ T cells
- Fibroblasts deposit collagen

Hohammad Aminul
Islam
Oklahoma State



Ashlee N. Ford-
Versypt
Oklahoma State



Next steps

- **v5 model (ongoing work, release Summer 2021)**
 - Negative feedbacks (anti-inflammation signals)
 - Antibodies
 - "bystander" effects (collateral damage to uninfected cells)
- **v6 model (final release candidate, release Fall 2021)**
 - Fine tuning parameters
 - Parameter space exploration on HPC, ML-guided analysis
 - Prototype 3D tissue geometry
 - Pivot to Phase III
 - ◆ Documentation and training materials
 - ◆ Long-term support
 - ◆ Data & results clearinghouse

2021: Use the immune model as starting point for **cancer patient digital twin project** in melanoma
(with autologous vaccine immunotherapy)

Work led by:
Heber L. Rocha

A persistent invasive phenotype in post-hypoxic tumor cells is revealed by fate-mapping and computational modeling

Heber L. Rocha^{1,*}, Inés Godoy^{1,†}, Furkan Kurtoglu¹, John Metzcar², Kali Konstantinopoulos³, Soumik Bhayar⁴, Daniel M. Gilkes^{1,3,5*}, and Paul Macklin^{1,2,3,4,6}

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⁶Co-corresponding authors: dgilkes@jhu.edu and macklin@jhu.edu.

*These authors contributed equally to this work.

†Lead contact.

SUMMARY

Hypoxia is a critical factor in solid tumors, which has been associated with cancer progression and aggressiveness. We have developed a hypoxia fate-mapping system to trace post-hypoxic cells within a tumor for the first time. This approach uses an oxygen-dependent fluorescent switch and allowed us to measure key biological features such as oxygen distribution, cell proliferation and migration. We developed a mathematical model to predict the fate of individual cells under hypoxia and normoxia and post-hypoxic cells during tumor progression. The cellular behavior was defined by phenotypic persistence time, cell movement bias and the fraction of cells that respond to an enhanced migratory stimulus. This work can help to better understand the mechanism of tumor invasion. Our results show that a persistent invasive phenotype in post-hypoxic cells develops under hypoxia is required for cellular escape into the surrounding tissue, promoting the formation of invasive structures ("plumes") expanding towards the oxygenated tumor regions.

INTRODUCTION

Intrinsic hypoxia, or oxygen (O_2) deprivation, is associated with an increased risk of metastasis, treatment failure and worse patient outcome (Giles and Semenza, 2013; Mair et al., 2015). Hypoxia occurs in 90% of solid tumors as a result of rapid cancer cell proliferation and insufficient vascularization (Makrilia et al., 2018). Previous studies have shown that the average partial pressure of oxygen (pO_2) in solid tumors in patients with breast cancer was 10 mmHg (1.3% O_2) compared to normal breast tissue where the median pO_2 was 100 mmHg (13.3% O_2) (Fager et al., 2001).

The cellular response to hypoxia is driven by the hypoxia-inducible factors 1 and 2 (HIF-1 and HIF-2). The alpha subunits of HIF-1 and HIF-2 are subject to proteosomal degradation under well-oxygenated conditions, whereas the beta subunits are relatively stable. The HIF-1 and HIF-2 heterodimerize with HIF-1 β (Reya et al., 2001). HIF-1 and HIF-2 heterodimers transcriptionally regulate gene expression when O_2 is limited. Hypoxia has been reported to regulate the expression of more than a

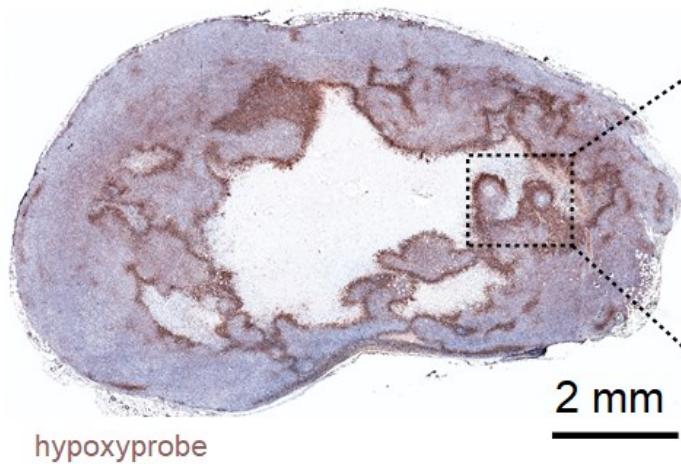
Example 4:

Hypoxia-driven breast cancer invasion

Rocha et al., *iScience* (2021, accepted)
Preprint: <https://doi.org/10.1101/2020.12.30.424757>

Intratumoral hypoxia

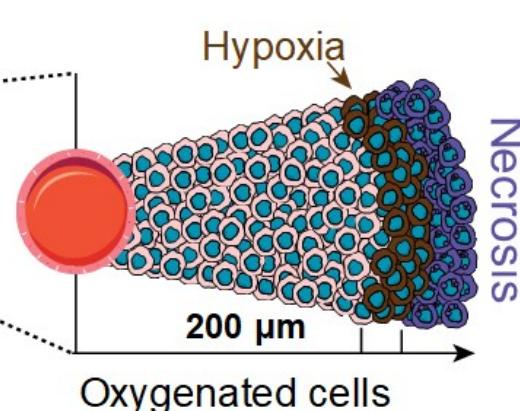
Mouse tumor



Blood vessels



Hypoxia



Necrosis

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

Nature Communications 10, Article number: 4862 (2019) | Cite this article

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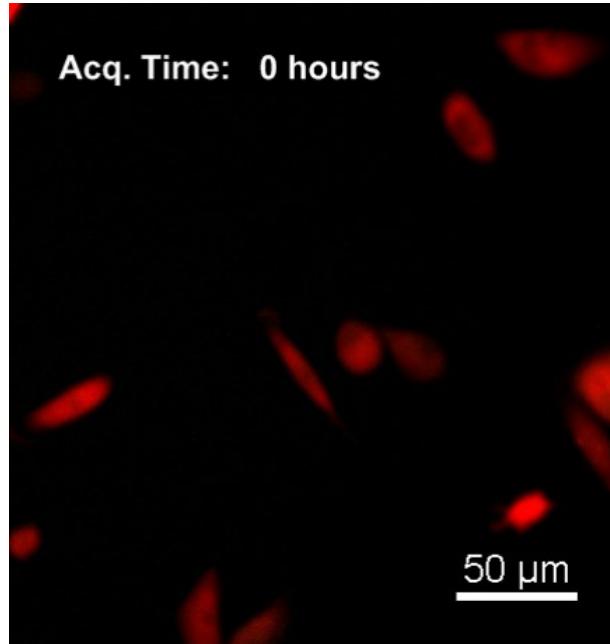
Abstract

Hypoxia is known to be detrimental in cancer and contributes to its development. In this work, we present an approach to fate-map hypoxic cells *in vivo* in order to determine their cellular response to physiological O₂ gradients as well as to quantify their contribution to metastatic spread. We demonstrate the ability of the system to fate-map hypoxic cells in 2D, and in 3D spheroids and organoids. We identify distinct gene expression patterns in cells that experienced intratumoral hypoxia *in vivo* compared to cells exposed to hypoxia *in vitro*. The intratumoral hypoxia gene-signature is a better prognostic indicator for distant metastasis-free survival. Post-hypoxic tumor cells have an ROS-resistant phenotype that provides a survival advantage in the bloodstream and promotes their ability to establish overt metastasis. Post-hypoxic cells retain an increase in the expression of a subset of hypoxia-inducible genes at the metastatic site, suggesting the possibility of a 'hypoxic memory.'

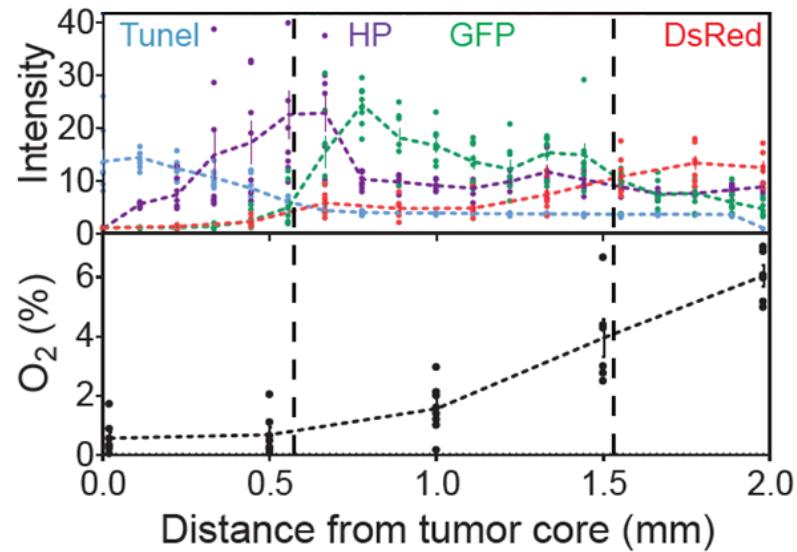
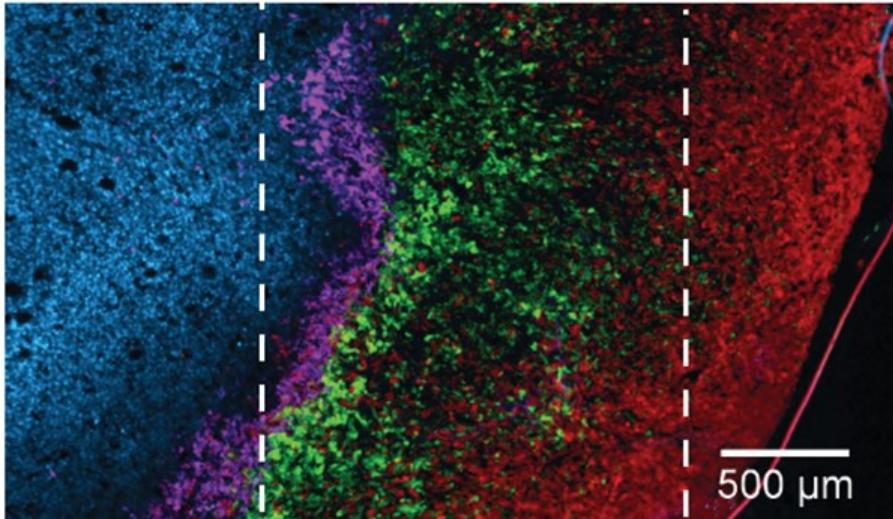
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Hypoxic and post-hypoxic cells



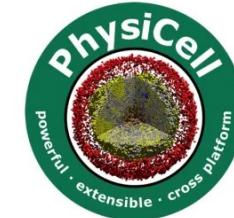
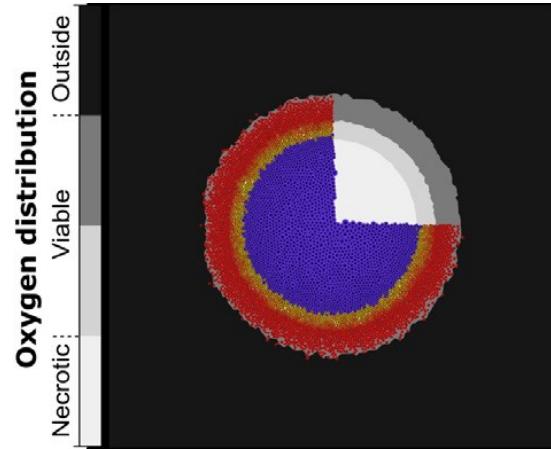
Questions

What are the **rules** of hypoxic cell motility?

How persistent is their response to hypoxic stress?

Hypoxia computational model

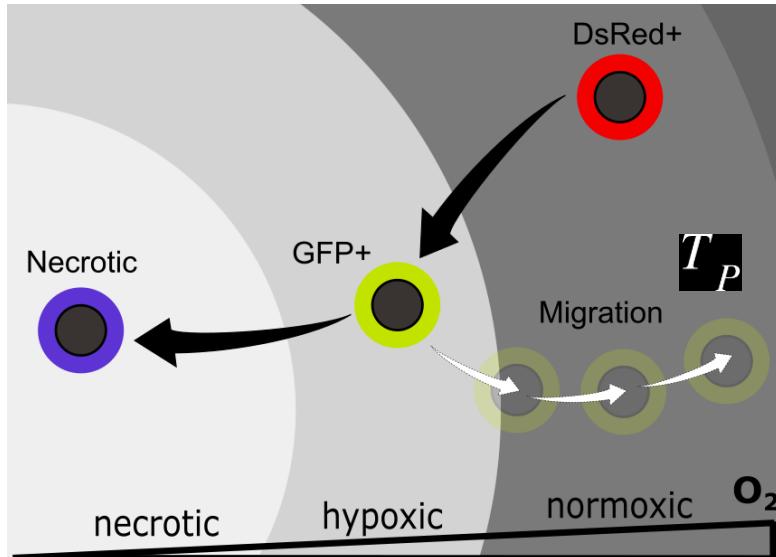
- We used Physicell to develop a mathematical model representative of tumor progression that incorporates the **cell phenotypes**, **location**, and exposure to **oxygen concentrations**.
- Phenotypic states of the cancer cells based on the oxygen distribution: **normoxic**, **hypoxic**, and **necrotic**.
- The oxygen concentration (σ) is distributed in the environment using the standard transport equations from [BioFVM](#) and [PhysiCell](#).



PhysiCell Project
PhysiCell.org
[@PhysiCell](https://twitter.com/PhysiCell)

Phenotypic transitions

Eventually, cells may undergo phenotypic transitions due to their **motility** or **changes in the microenvironment**.



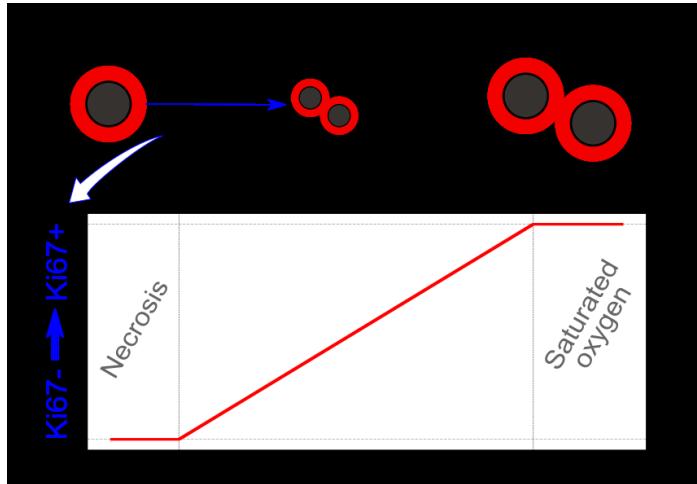
Simple ODE model for protein expression based on the "genes"

$$G_0 \quad G_1$$

$$\frac{d[DsRed]}{dt} = G_0 \alpha_0 (1 - [DsRed]) + \beta_0 (G_0 - [DsRed])$$
$$\frac{d[GFP]}{dt} = G_1 \alpha_1 (1 - [GFP]) + \beta_1 (G_1 - [GFP])$$

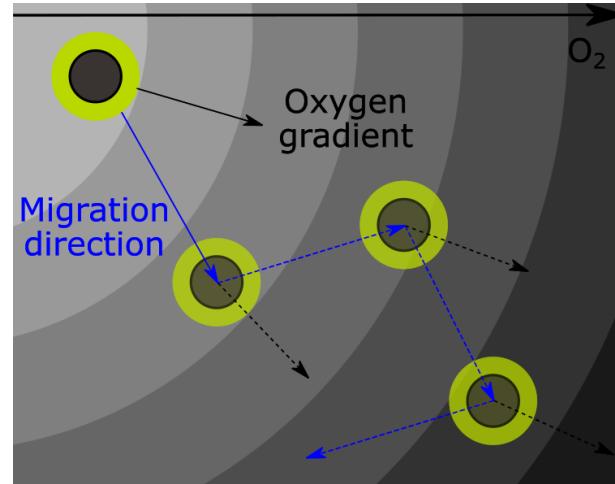
Proliferation and migration

Cell proliferation



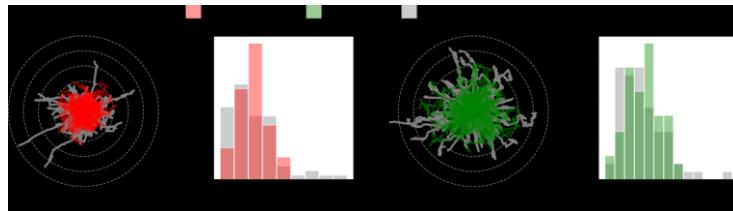
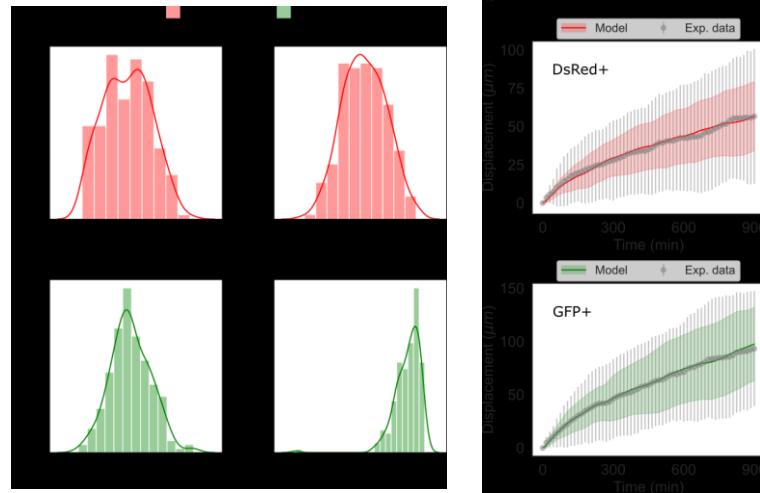
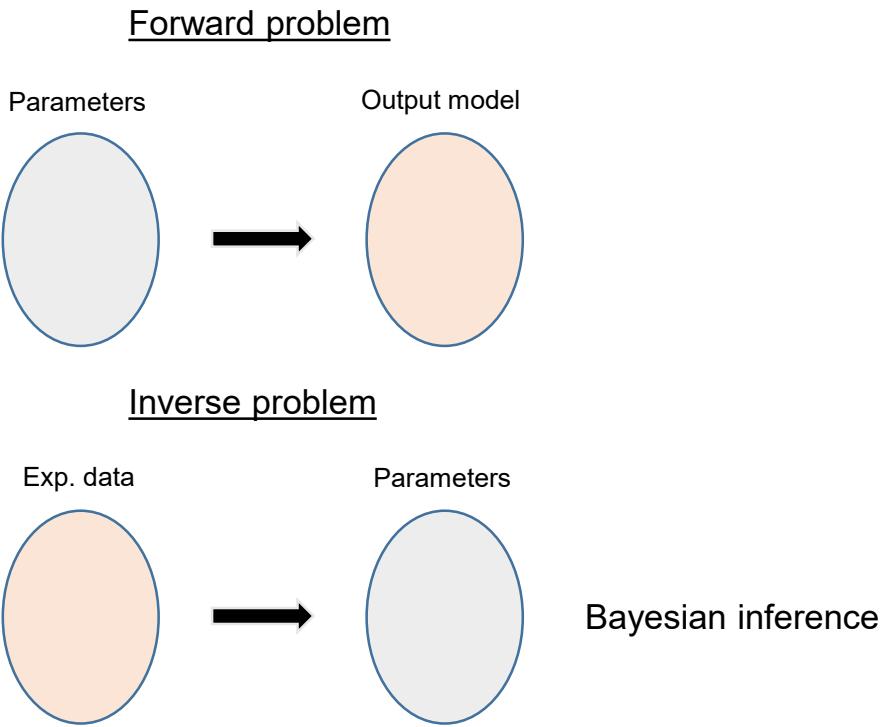
Basic Ki-67 model

Cell migration



- Speed (s)
- Bias (b)
- Persistence time (t)

Biological observations calibrate cellular motility in hypoxia computational model



Phenotypic persistence drives invasion

Phenotypic Persistence:

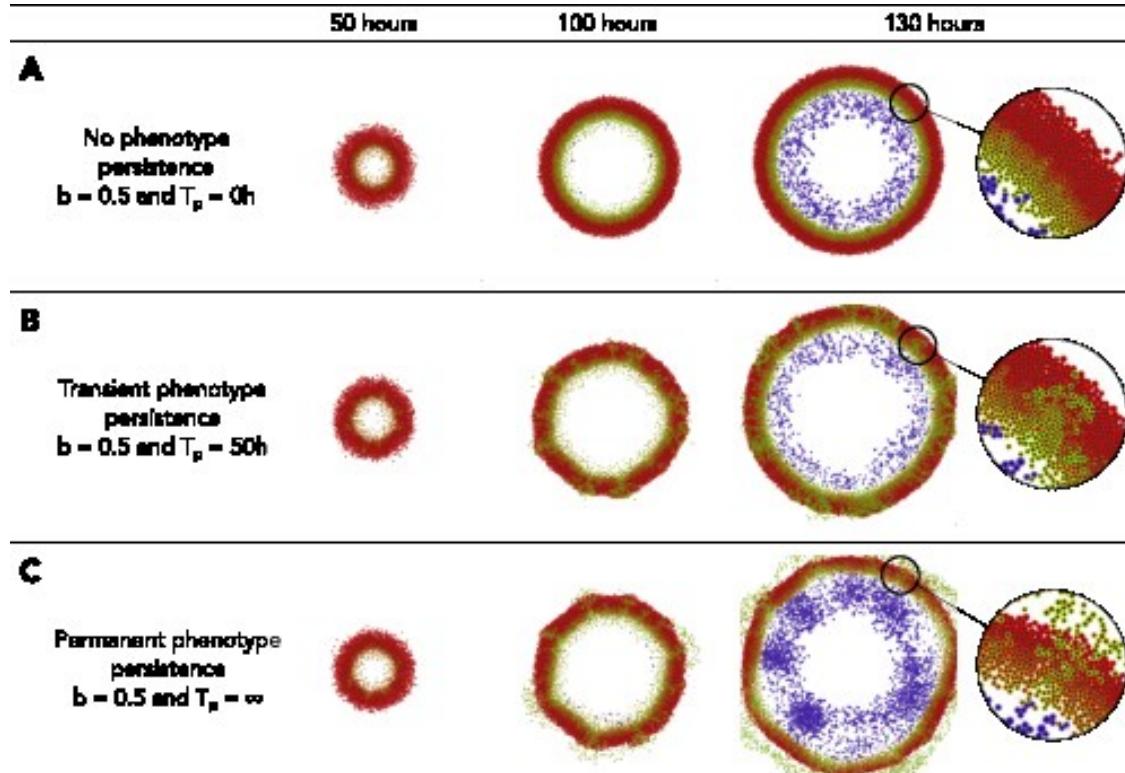
- T_p : duration of hypoxic response

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)

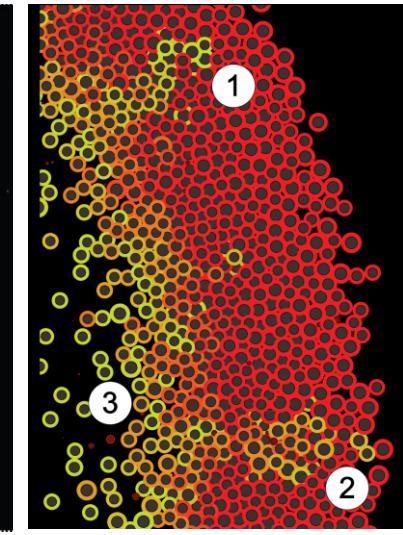
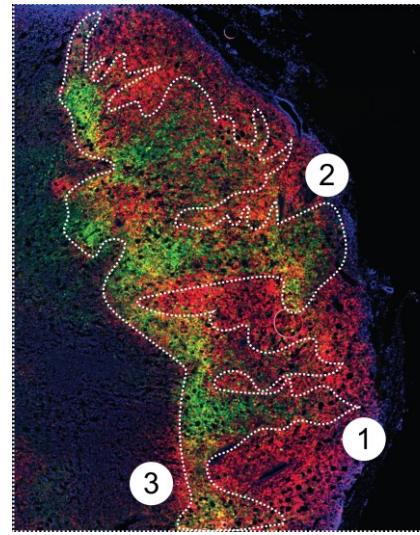
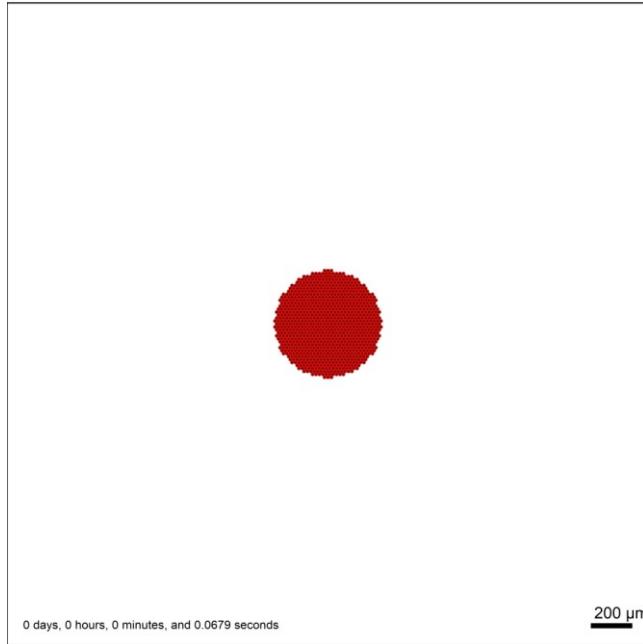
With persistence ($T_p > 0$) – Rows B & C

- Hypoxic cells can continue migrating
- Hypoxic cells "punch through" the oxygenated tumor region

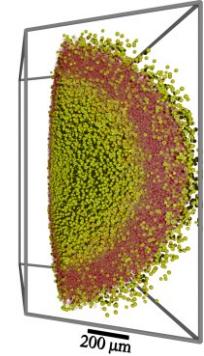
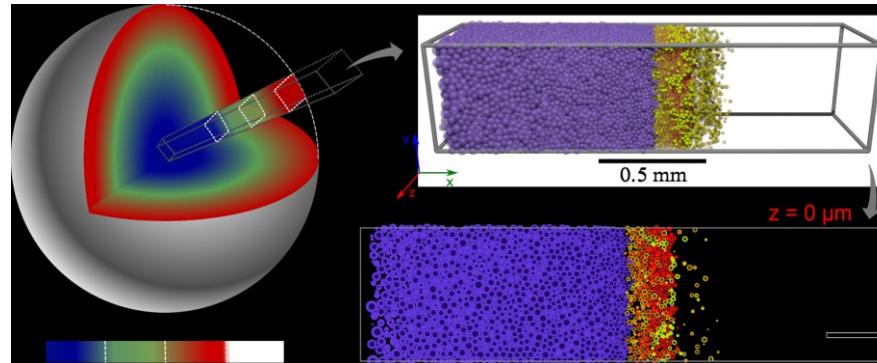
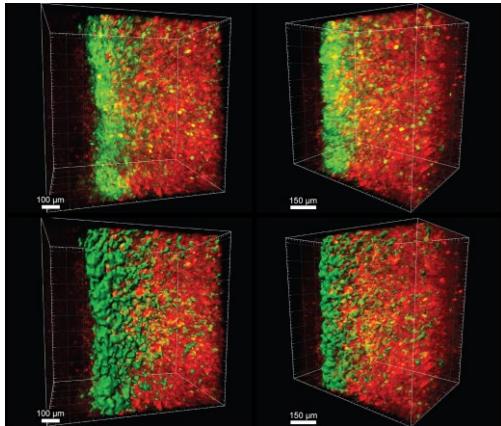


Mathematical model explains biological observations

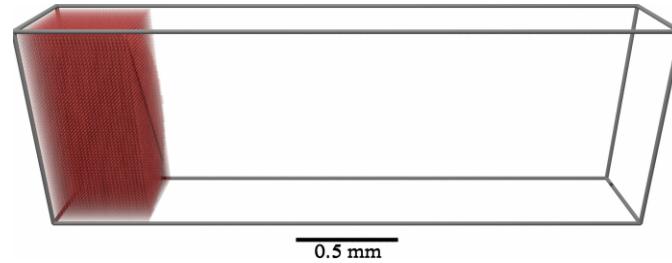
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It also works in 3D



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



Funding Acknowledgements



JAYNE KOSKINAS
TED GIOVANIS

Foundation for
Health and Policy



NATIONAL
CANCER
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BCRF
BREAST
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RESEARCH
FOUNDATION

PhysiCell Development:

- Breast Cancer Research Foundation
- Jayne Koskinas Ted Giovanis Foundation for Health and Policy
- National Cancer Institute (U01CA232137)
- National Science Foundation (1720625)

Training Materials:

- Administrative supplement to NCI U01CA232137 (Year 2)