

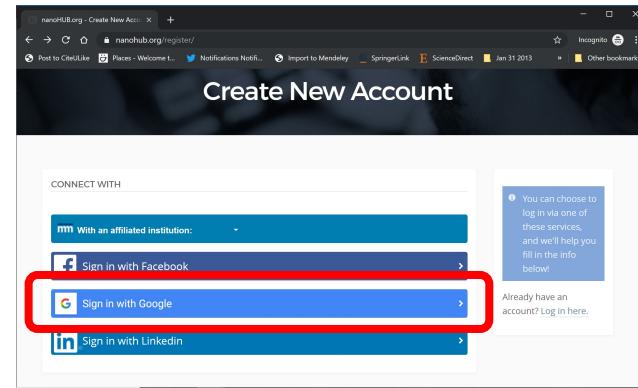
nanoHUB Account

- This talk's online PhysiCell models are cloud-hosted on nanoHUB.org.
- nanoHUB is **free**, but it requires a one-time registration.

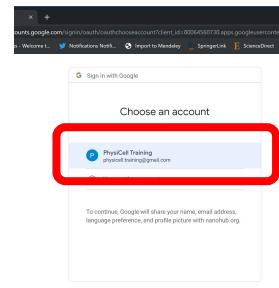
• Steps:

1. Visit <https://nanohub.org/register>
2. Choose "Sign in with Google"
3. Choose a Google account
4. Click "No" (so it doesn't try to associate with some other nanoHUB account)
5. Finish filling in details, and you're done!
6. Use your google account to sign in in the future.

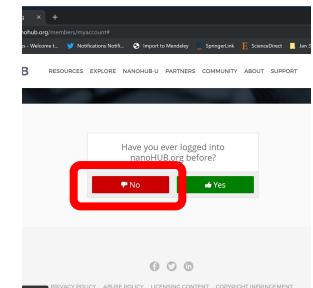
2



3



4



Open source multiscale agent-based modeling of cancer

Lecture materials and code are available at:



[\[link\]](#)

Paul Macklin, Ph.D.

Intelligent Systems Engineering
Indiana University

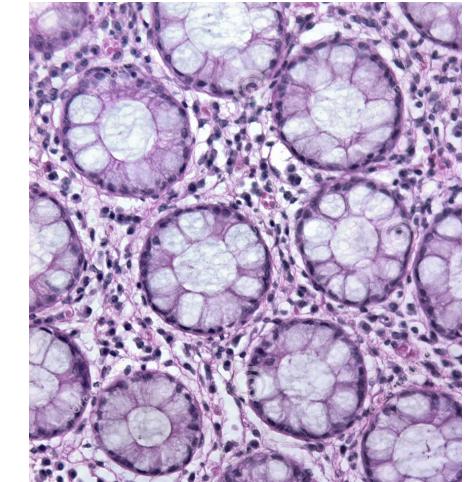
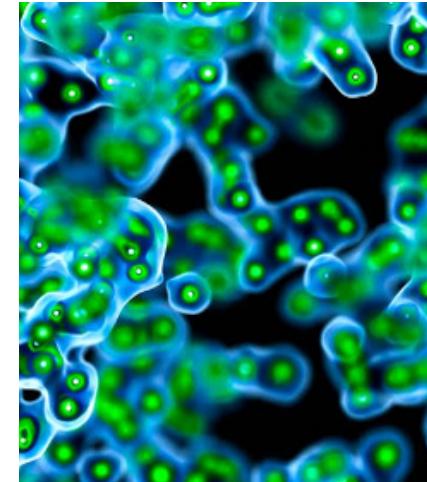
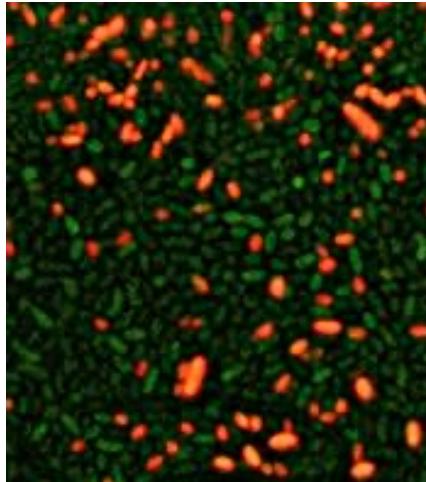
February 7, 2022

Simple single-cell behaviors ...

- **growth**: Cell volume increases as it progresses through the cell cycle.
- **division**: Cells reproduce by dividing in half into daughter cells.
 - These cells may or may not be identical!
- **death**: Cells can die by a variety of mechanisms. They don't disappear immediately, but instead shrink and continue to interact with other cells.
 - **apoptosis**: An orderly, planned shutdown process (that still requires and consumes energy!)
 - **necrosis**: A disorderly, unplanned shutdown process, often from energy depletion.
- **adhesion**: Cells can stick to other cells or to fibers in their environment.
- **resistance to deformation**: Cells are largely incompressible and viscoelastic. They exert resistant forces on other cells and the environment.
- **motility**: Cells actively move through the environment in a biased random walk.
- **secretion**: Cells can secrete chemical factors to communicate.
- **uptake**: Cells can consume chemical factors (e.g., oxygen)
- **sampling**: Cells can sample chemical factors and other physical properties in their immediate surroundings.

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.

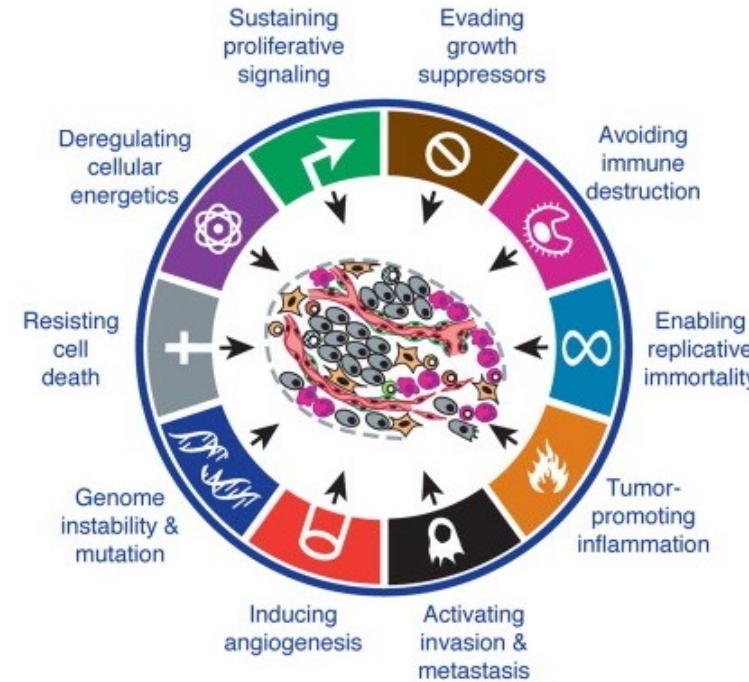
Health is a **complex system**:

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)

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

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

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:

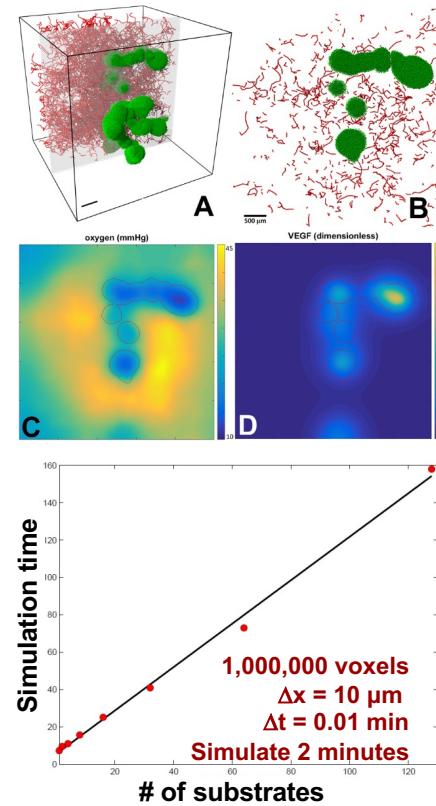
- Off-lattice cell secretion and uptake
- 2nd-order accurate (space), 1st-order accurate (time), numerically stable

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:

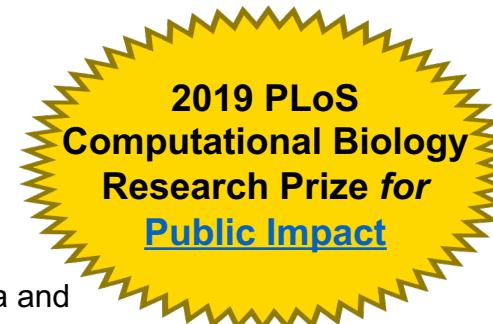
- Off-lattice cell positions
- Mechanics-based cell movement
- Cell processes (cycling, motility, ...)
- Signal-dependent phenotype
- Can dynamically attach custom data and functions on a cell-by-cell basis
- **Deployed from Raspberry Pi to Crays**

Method:

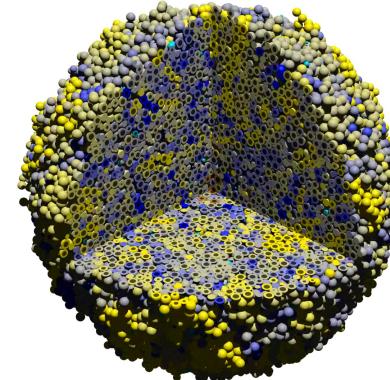
- Standard C++11, cross-platform
- OpenMP parallelization
- $O(n)$ cost scaling in # cells

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

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



Current time: 7 days, 0 hours, and 0.00 minutes
53916 cells



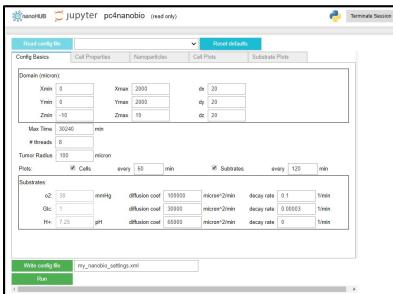
Competition in a 3-D tumor
[View on YouTube](#) (8K)



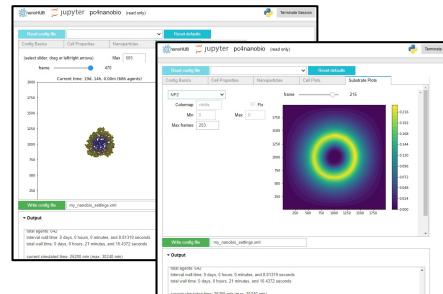
Try this model yourself!
nanohub.org/tools/pc4heterogen

Jupyter-based GUIs

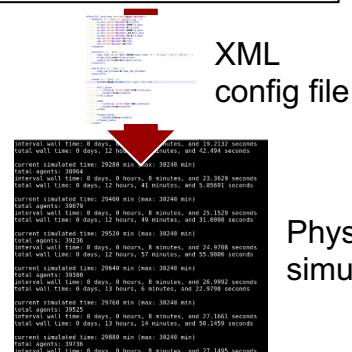
Goal: Make PhysiCell-powered simulators user-friendly, shareable, and available without installing / compiling.



GUI:
settings
Jupyter
notebook



GUI:
output
Jupyter
notebook



PhysiCell
simulation



Simulation
data

The Jupyter notebook and executable can be **cloud-hosted as an app**. This allows **model sharing** for broad audiences.

Use case: "Try this model yourself!"

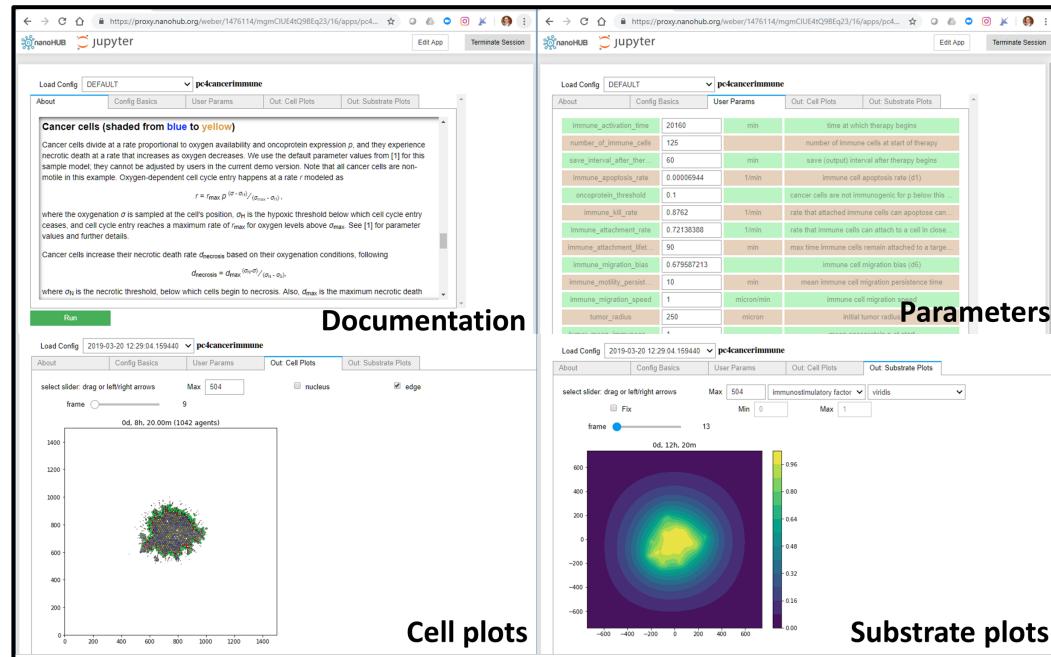
- With `xml2jupyter`, we can automatically create a Jupyter-based GUI for a PhysiCell model, and host it on nanoHUB as an interactive model.
- The apps can easily be **included in talks, posters, and presentations.**
- We include ***publication companion apps*** in every paper to help readers explore and understand the method.

This should be standard practice.



Try this model yourself! (2D)

nanohub.org/tools/pc4cancerimmune



Example: 3-Types model

- In physics, the **3-body problem** shows how 3 objects with very simple interactions (gravitation) can demonstrate chaotic behavior.
- **Let's build a similar system for biology!**
- **3 cell types (A,B,C)** each secrete their own chemical factor
 - **visualization:** assume each cell fluoresces proportionally to its signal
- Each cell type can:
 - **divide** and **die** in response to resource (R), A, B, C, and pressure
 - **move** in response to A, B, C, and R
 - **secrete** (or not secrete) in response to A, B, C, and R
- ***What can happen in this general system?***



Try this model yourself!

<https://nanohub.org/tools/pc3types>

Mathematics: Hill Functions

- Let's define a **Hill function** $H(s)$:

$$H(s) = \frac{s^n}{s^n + h^n}$$

Hill power

half-max

- Let's write:

U = sum of promoter signals

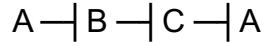
D = sum of inhibitor signals

- We can use these signals to control a parameter p via a Hill function:

$$p = \left[p_0 + \overbrace{(p_{\max} - p_0)H(U)}^{p \rightarrow p_{\max} \text{ as } U \rightarrow \infty} \right] \left[\overbrace{\frac{1}{1 - H(D)}}^{p \rightarrow 0 \text{ as } D \rightarrow \infty} \right]$$

pc3types example: repressilator

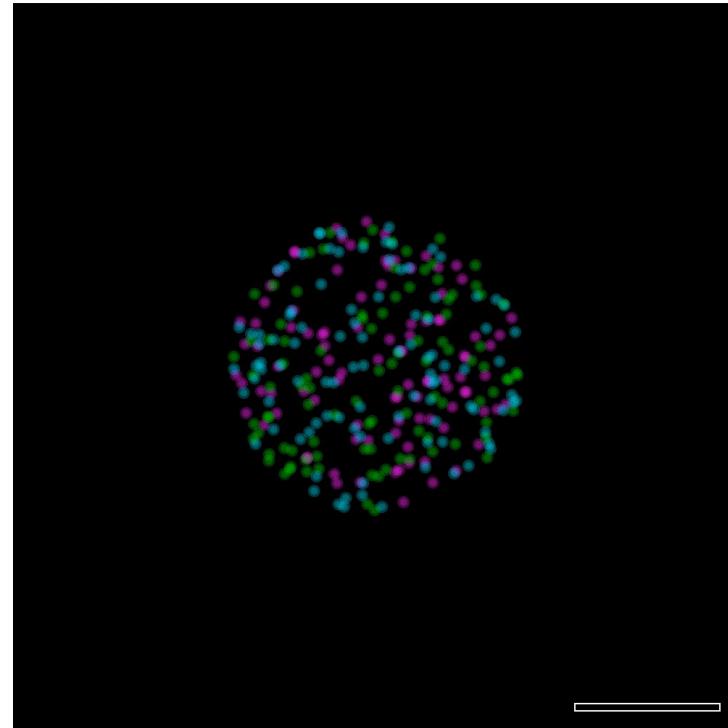
The **repressilator** is the first synthetic biological oscillator:



Let's make a multicellular repressilator!

1. Set A, B, and C diffusion coefficients to 100
 - slow down the dynamics
2. Set A, B, and C decay rates to 0.01
 - keep ~100 μm diffusion length scale
3. Set cell outputs to every 5 minutes (optional)
 - optional: resolve time dynamics more smoothly
4. **Type A rules:**
 - Use 100 cells, all within 200 microns of origin
 - C inhibits secretion
5. **Type B rules:**
 - Use 100 cells, all within 200 microns of origin
 - A inhibits secretion
6. **Type C rules:**
 - Use 100 cells, all within 200 microns of origin
 - B inhibits secretion

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



Exercise: tumor competition

- Let's look at 2 tumor sub-clones:
- Population A:
 - Regular proliferation and death
- Population B:
 - Increased proliferation
 - Cost: more sensitive to resource depletion

Build the model

- Cell Type A:
 - Use default parameters
- Cell Type B:
 - double B_base_cycle to 0.00144
 - double B_max_cycle to 0.0144
 - increase B_necrosis_threshold to 0.6
- set to no Type C cells
 - number_of_C = 0

Run the model

- How do pink (Type A) and green (Type B) cells compete in high-resource regions?
- How do pink (Type A) and green (Type B) cells compete in low-resource regions?

Exercise: tumor co-option of stromal cells

- Let's look at two interacting cell populations:
 - Tumor cells attract stromal cells and "convince" them to secrete a growth factor.
- Population A (tumor):
 - Secretes signal A
 - Signal B **promotes** proliferation
 - No proliferation without signal B
- Population B (stromal):
 - No proliferation without signal A
 - Chemotaxis towards Signal A (and stops in regions of high signal A)
 - Signal A **promotes** secretion of Signal B

Build the model (1)

- Cell Type A:
 - Cycling
 - ◆ A_base_cycle = 0 (no proliferation without signal B)
 - ◆ A_max_cycle = 0.00072 (slow the kinetics down a bit)
 - ◆ A_cycle_B = promote (signal B enables proliferation)
- Cell Type B:
 - Cycling
 - ◆ B_base_cycle = 0
 - ◆ B_max_cycle = 0.000072 (less proliferation than tumor cells)
 - ◆ B_cycle_A (signal A promotes proliferation)
 - Secretion
 - ◆ B_base_secretion = 0 (no secretion without signal A)
 - ◆ B_signal_A = promote (signal A stimulates secretion)
 - Motility
 - ◆ B_speed_base = 0.5 (increase the base speed a bit)
 - ◆ B_speed_A = inhibit (slow down when you reach the tumor)

Build the model (2)

- Now, switch to the cell types tab, and select Type B
- Let's turn on chemotaxis
- Cell Type B:
 - phenotype:motility
 - ◆ enabled = on (turn on motility)
 - ◆ chemotaxis:
 - » enabled = on (use chemotaxis to guide migration)
 - » substrate = signal A (chemotaxis towards tumor cells)
 - » direction = 1 (move up the gradient towards stronger signal A)

Run the model

- Set 25 initial type A cells, and 1 initial type B cell. 0 Type C cells.
 - Where do green (type B) cells end up?
 - Where do you see the most pink cells (Type A)?
- Increase to 5 initial type B cells.
 - Where do green (type B) cells end up?
 - Where do you see the most pink cells (Type A)?
- Increase B_cycle_max to 0.00018. What happens?
- Set 0 initial Type B cells. What happens?

Examples

Work led by:
Yafei Wang

www.nature.com/scientificreports/ Check for updates

OPEN Impact of tumor-parenchyma biomechanics on liver metastatic progression: a multi-model approach

Yafei Wang^{1,2}, Erik Brodin^{3,4}, Kenichiro Nishi⁵, Hermann B. Friedl^{6,7,8}, Shannon M. Monteith⁹, Jessica L. Sparks¹⁰ & Paul Macklin^{1,2}

Cancerous cancer and other cancers often metastasize to the liver in later stages of the disease, constituting a major challenge to cancer treatment. Metastatic cancer cells that have spread to the liver parenchyma (internal liver tissue) are known to affect tumor behavior in primary and metastatic tumors. However, the mechanisms through which tumor cells interact with liver parenchyma are poorly understood, as are the longer-term metastatic dynamics. This study adopts a multi-model approach to predict tumor behavior in the liver parenchyma. We propose a mechanobiological model of tumor-parenchyma interactions that consider the mechanical properties of the liver parenchyma and their effect on tumor seeding and growth. We employ a detailed porous media model of a liver lobule to study how mechanical properties of the liver parenchyma affect tumor growth and metastasis. Constitutive relations in detailed single hepatic lobules illustrate constitutive relations and biological hypotheses for a mechanobiological model of tumor-parenchyma interactions at different time scales. After a parameter space investigation, we find that the balance of basic tumor-parenchyma interactions and mechanical properties of the liver parenchyma at different time scales (from minutes to longer time scales (hepatocyte relaxation over hours)) can explain a broad range of behaviors of micrometastases, without the need for complex molecule-scale signaling. These results provide a mechanobiological framework for understanding the conditions required for cancer cells from establishing successful metastatic foci. Moreover, the simulations indicate ways in which mechanical properties of the liver parenchyma may influence tumor behavior and progression, which may arise during aging or following acute liver illness or injury. We conclude that the proposed model provides a mechanobiological framework for understanding the conditions required for liver metastatic growth, and advances the longer term goal of identifying conditions to clinically arrest and prevent liver metastatic progression.

The liver performs critical physiological processes such as macromolecular metabolism, bile creation, and filtration of toxic substances from the blood. Liver cells are organized in an intricate and complex architecture. The liver is divided into lobules, which are further subdivided into acini. Hepatocytes are the main parenchymal cells that surround the central vein. The portal triads (hepatic artery, portal vein, and bile duct) are found at the vertices of the lobules. The hepatic artery and portal vein enter the liver via the hepatic artery and portal vein, respectively. Blood from the hepatic artery with nutrient rich blood flows from the portal vein while providing a reactive surface for oxygen exchange. The liver is primarily involved in normal physiological functions. It also consumes bile for metabolic function. Liver diseases can lead to various complications. For example, liver metastasis (Liu et al., 2021), patient mortality is principally due to the spread of disease to distant organs, with the liver being the predominant site of metastasis. The liver is a common site for metastasis due to its large blood supply and ability to receive blood from the colon and rectum. Blood supply directly from the liver through the portal vein. Tumor cells that survive and

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Scientific Reports | (2021) 11:10382 | DOI: 10.1038/s41598-020-78780-7

SEARCH

Example 1:

liver parenchyma interactions in CRC micrometastases

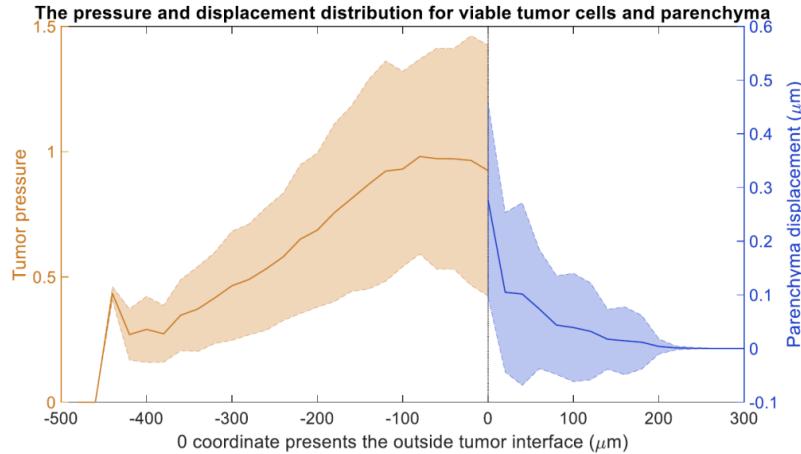
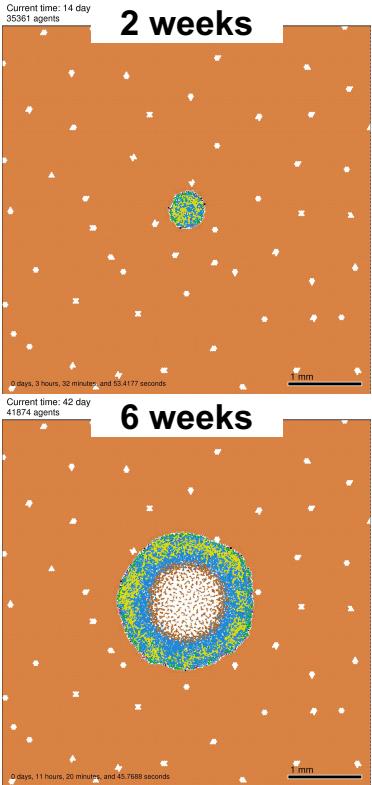
Wang et al. *Sci. Rep.* (2021)

Open Access: <https://doi.org/10.1038/s41598-020-78780-7>

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

- Prior work mostly investigated:
 - Signaling impact of ECM
 - Signaling impact of liver cells
 - All at single-cell level
- What about the larger-scale tumor-parenchyma interactions?
 - Displacement and compression of liver parenchyma
 - Compressive forces on the micrometastasis
- Key model elements:
 - Pressure (compression) down-regulates tumor cell proliferation
 - 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

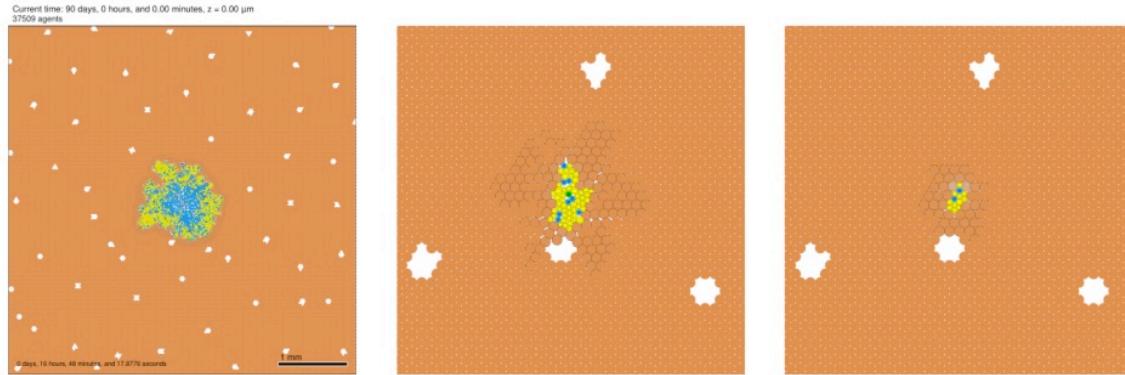


Try this model yourself!

nanohub.org/tools/pc4livermedium

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

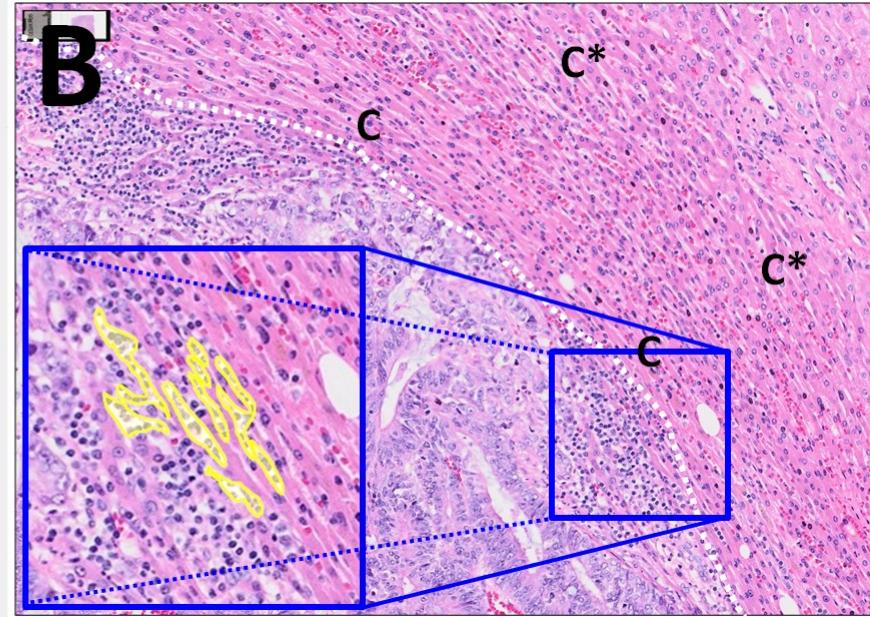
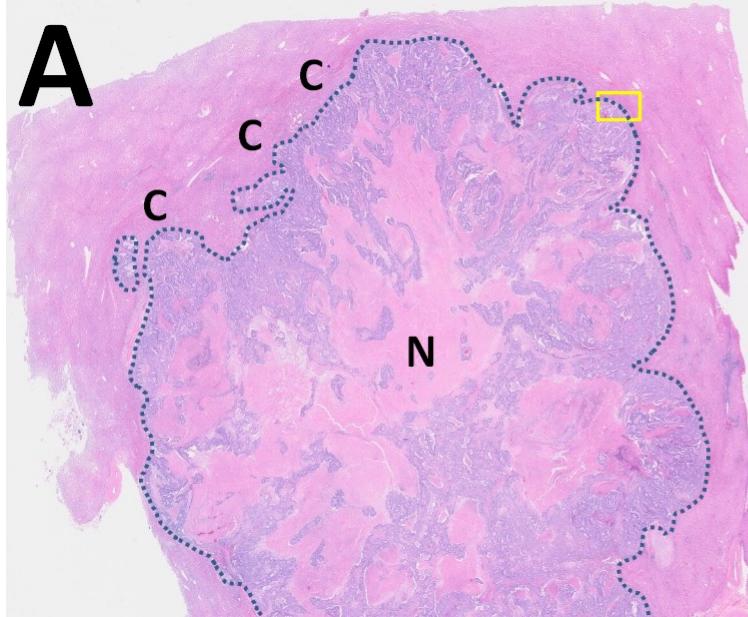
(b) $r_E=0.2$, $r_P=0.0005$,
 $d_{\max}=3$



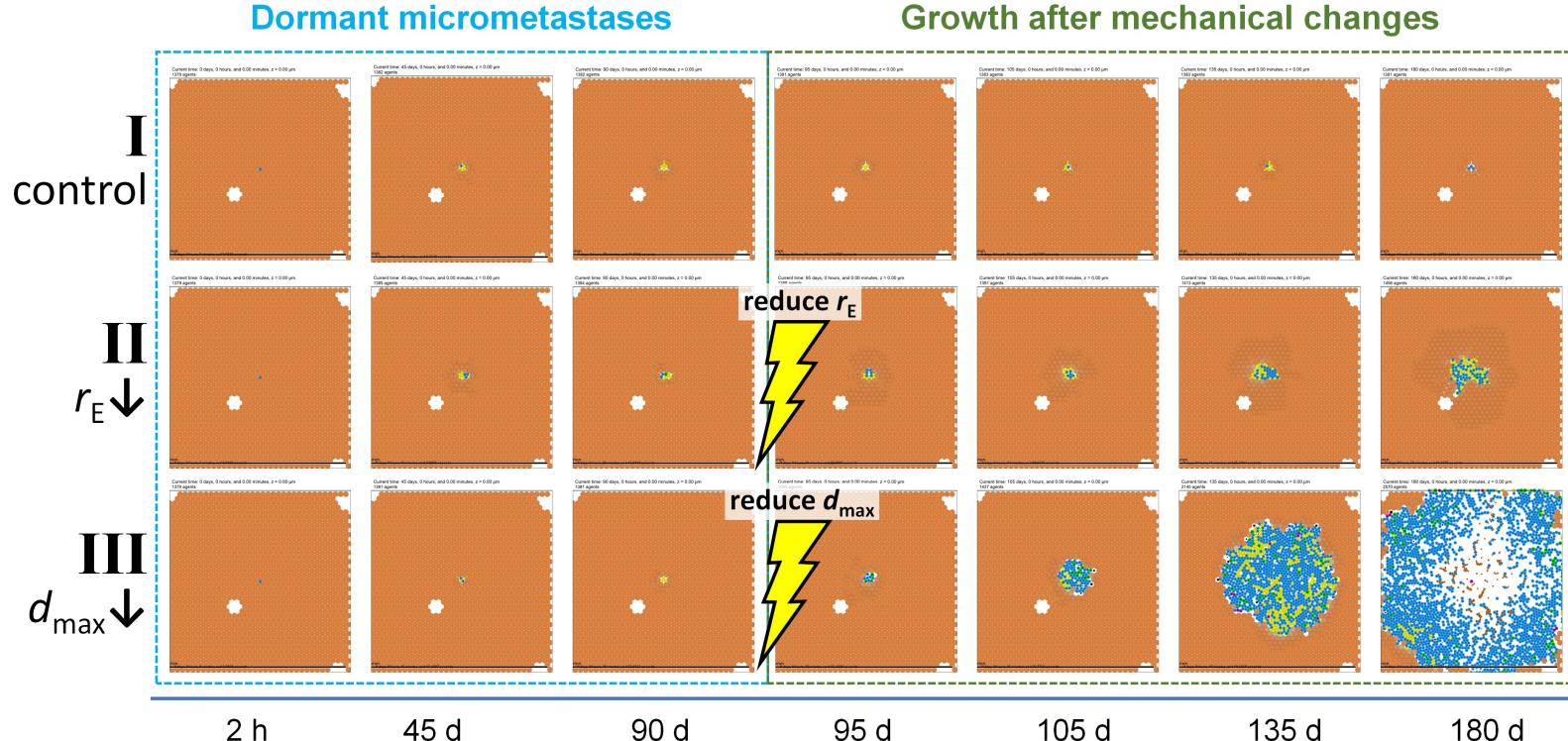
Try this model yourself!

nanohub.org/tools/pc4livermedium

Comparison with a typical clinical sample



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:

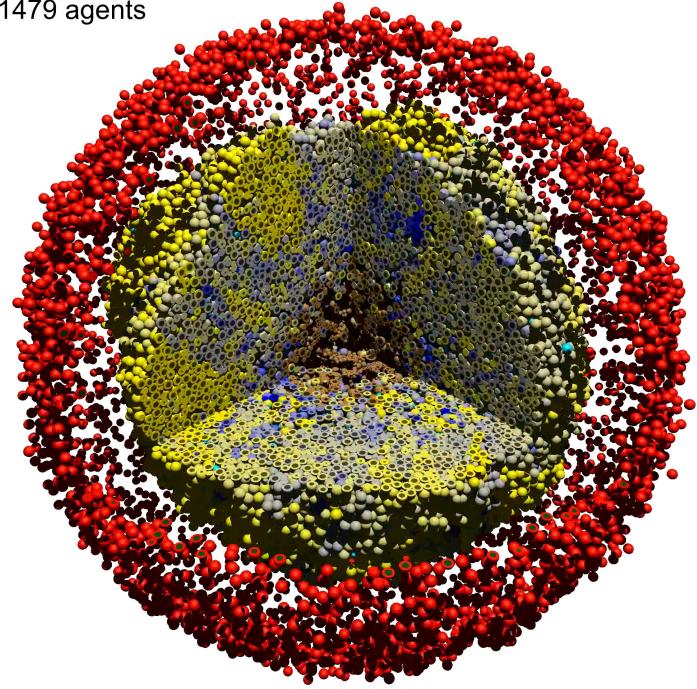
- [Ghaffarizadeh et al. \(2018\)](#)
- [Ozik et al. \(2018\)](#)
- [Ozik et al. \(2019\)](#)



Try this model yourself! (2D)

nanohub.org/tools/pc4cancerimmune

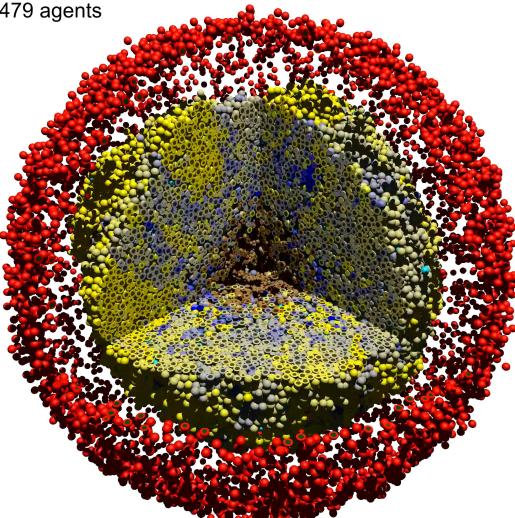
Current time: 14 days, 0 hours, and 3.00 minutes
111479 agents



High-throughput investigations on HPC

3-D tumor-immune model

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

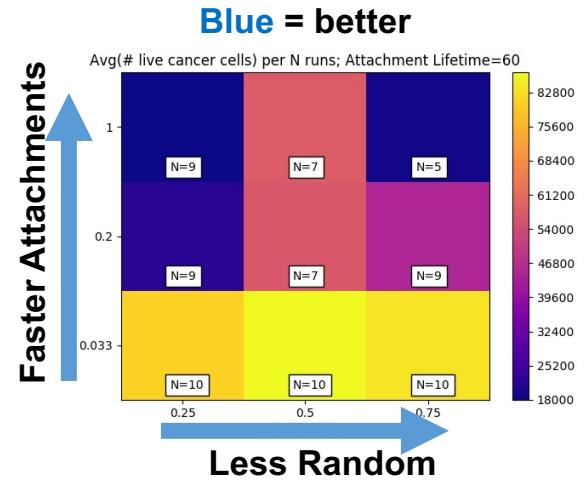


Explore 3 parameters:

- 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. \(2018\)](#)

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

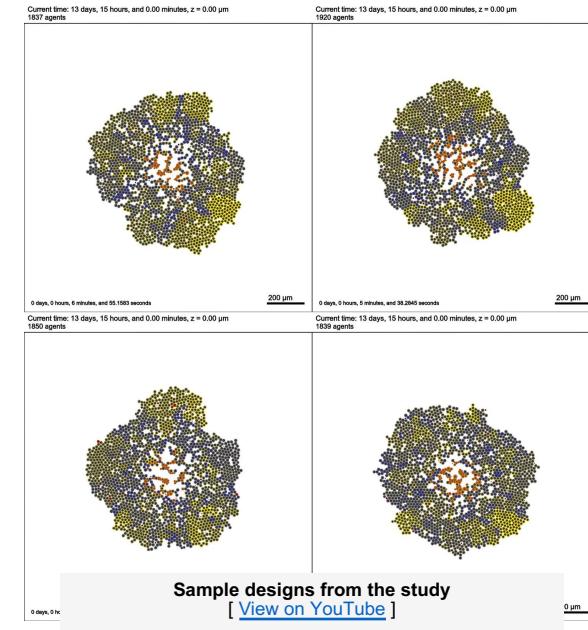
Bonus: Use the Gini coefficients to **rank** the parameters

Reference:
[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. \(2019\)](#)

Example 3:

**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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** equal contribution
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Yafei Wang
Indiana U.



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

Collaborative, Iterative Progress

Approach

- **Iterative 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-present) added: neutralizing antibodies • "bystander" killing by ROS • anti-inflammatory signals • improved tissue immune model • better receptor-virus binding •

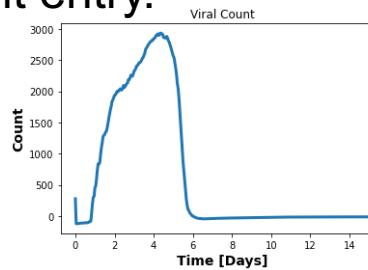
Iterative progress

- **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**

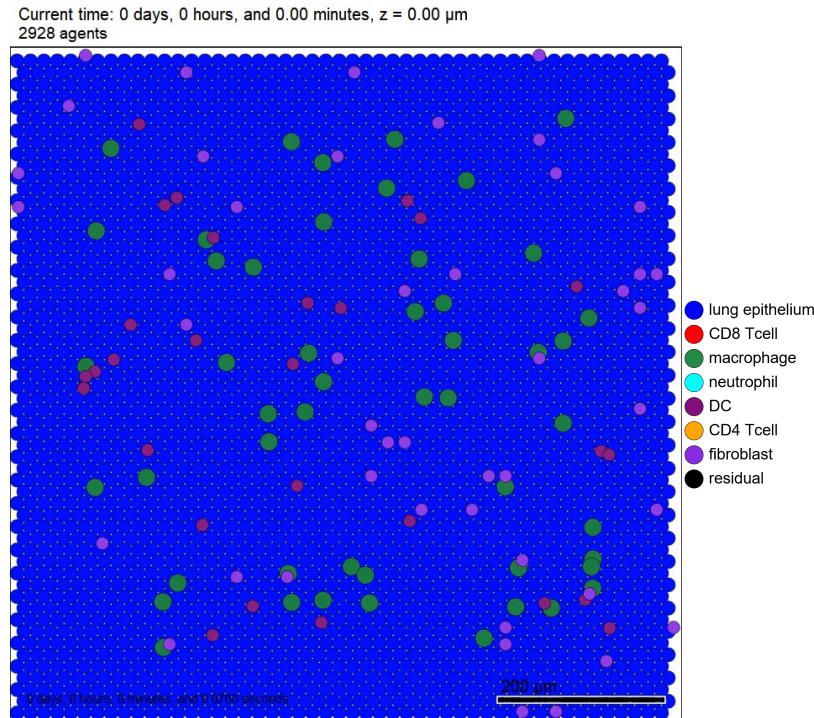
v5: neutralizing antibodies clear the infection

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

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



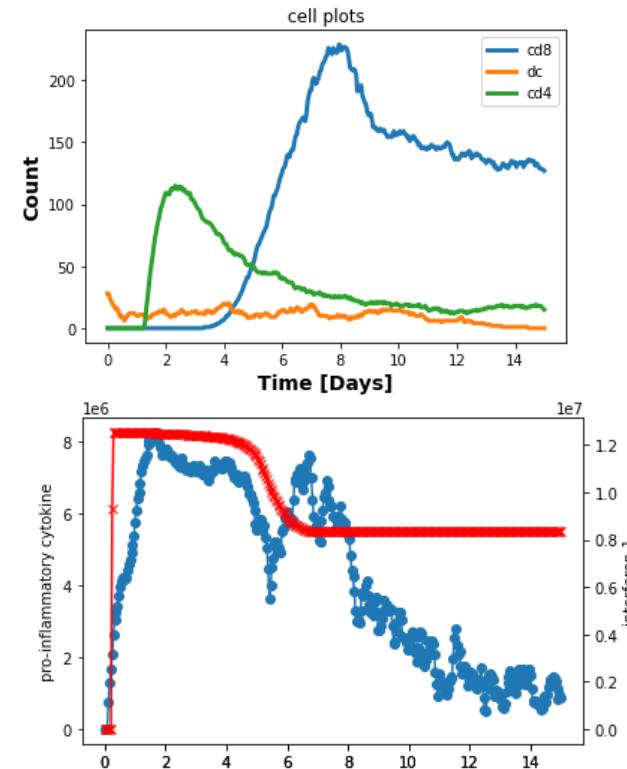
- **This immune model is sufficiently complete to clear a SARS-CoV-2 infection**



A naïve immune system can adapt to halt the infection

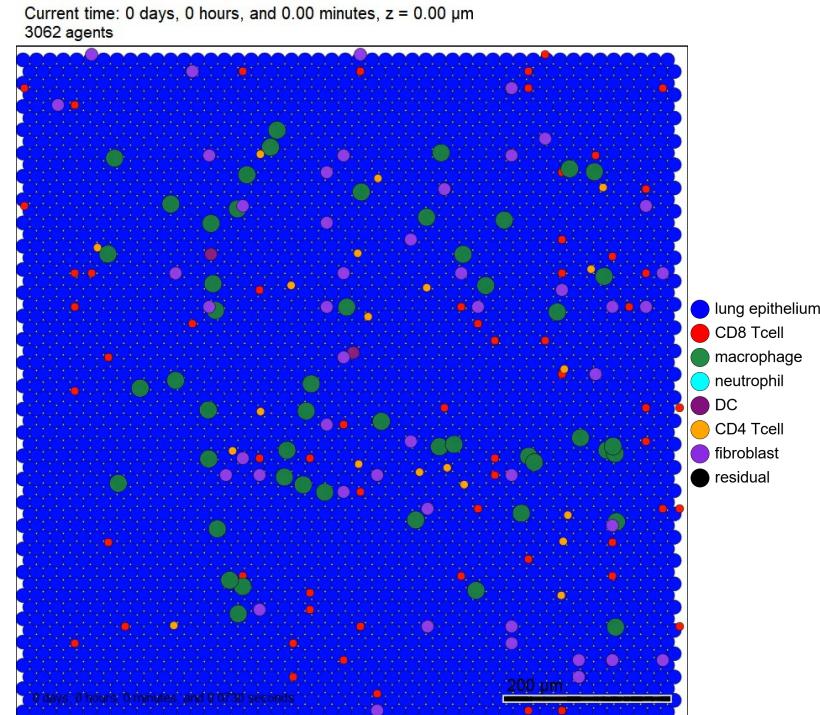
v5: immune system "cooldown" after clearance

- After viral clearance:
 - Inflammatory signals decrease
 - CD4 T cell, dendritic cell and macrophage cell counts decrease to a steady level
 - CD8 T cells decrease from their peak value but only slowly decrease
- Work remaining:
 - Need negative feedbacks on interferon



v5: prior immune responses are protective

- The 1st immune response is persistent:
 - Elevated "trained" CD8 T cells
 - Elevated neutralizing antibodies
- The first 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 of prior successful immune responses.



Trained immune system facing future exposure

Next steps

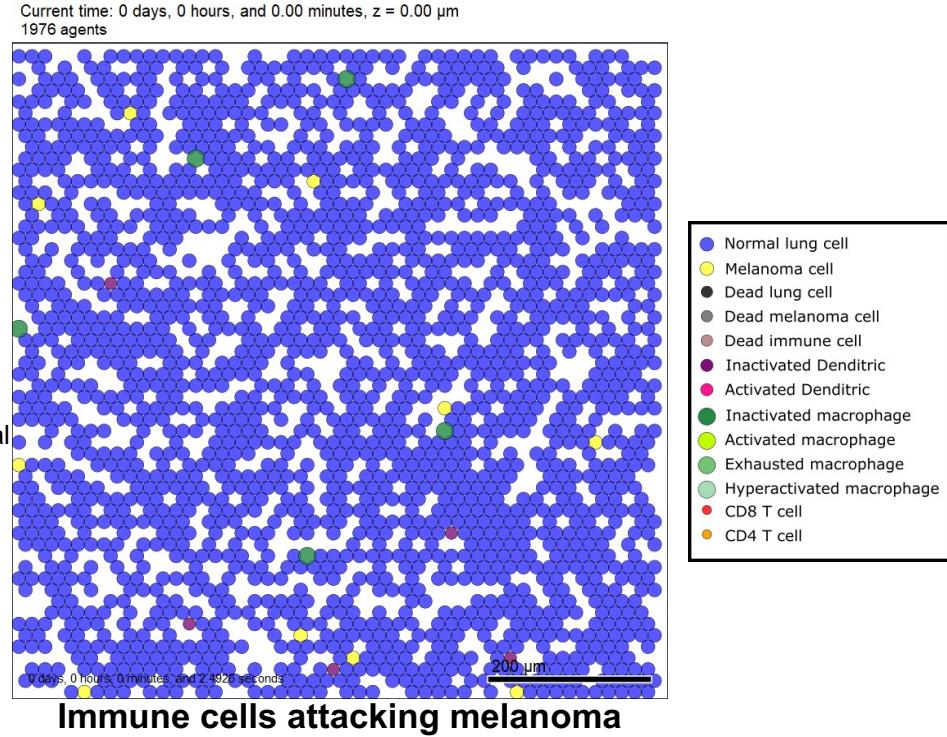
- Write final paper for peer-reviewed submission
- **Pivot to Phase III**
 - Refine cloud-hosted model
 - ◆ Focus: user-friendly interface
 - Refine documentation, training materials
 - Increase outreach activities
 - Support partners
 - ◆ Major EU center using the covid19 model + scRNASeq + Boolean



Scientific Impact: PerMedCOE (an EU Center of Excellence) and DiseaseMap use the model

Cancer Patient Digital Twins

- **DOE + NCI pilot project** to adapt the covid19 immune component to cancer
- Using this detailed model:
 - Massively explore model: 100k simulations on HPC
 - Cluster trajectories to look for parameter-outcome relationships
 - Assess impact on precision & predictive medicine
 - ◆ Are exceptional responders a distinct population or a lucky random fraction?
 - ◆ How soon can good and bad responses be identified with identical starting conditions?
 - ◆ Can we find "patient templates" for predictive medicine?
- New pilot (IU Luddy Faculty Fellowship):
 - ABM generates synthetic data
 - Test data assimilation methods
 - ◆ ODE models, RNNs
 - Understand impact of sampling, uncertainty

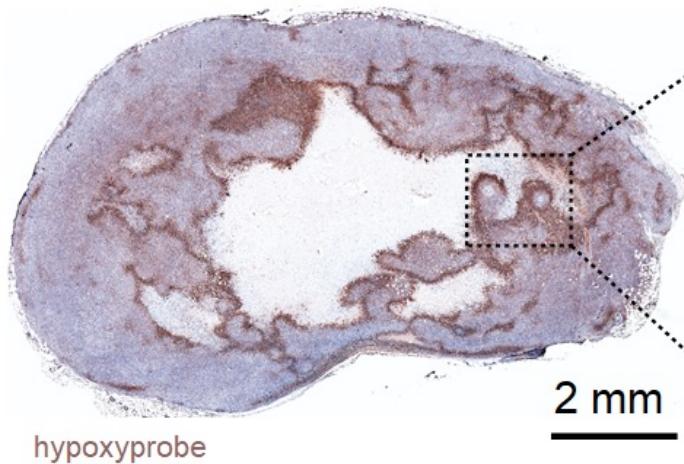


Example 4:

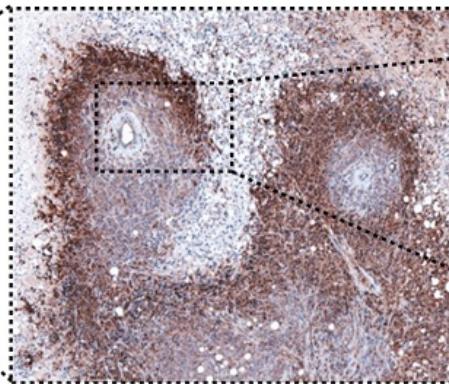
**hypoxia-driven breast
cancer invasion**

Intratumoral hypoxia

Mouse tumor



Blood vessels

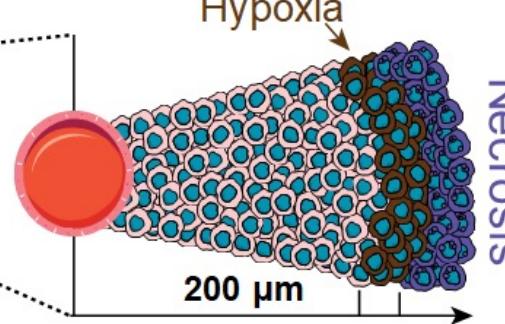


Hypoxia

Necrosis

200 μm

Oxygenated cells



Fate-mapping intratumoral hypoxia

nature communications

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Article | Open Access | Published: 24 October 2019

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

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

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

8904 Accesses | 17 Citations | 167 Altmetric | Metrics

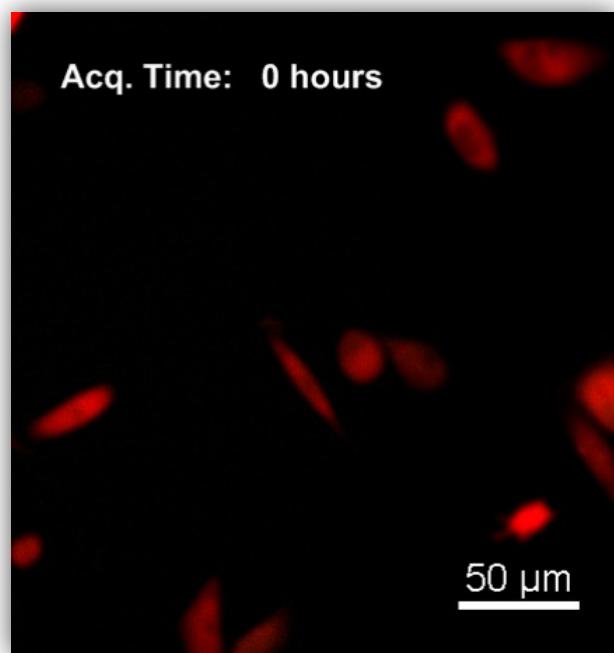
Abstract

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.'

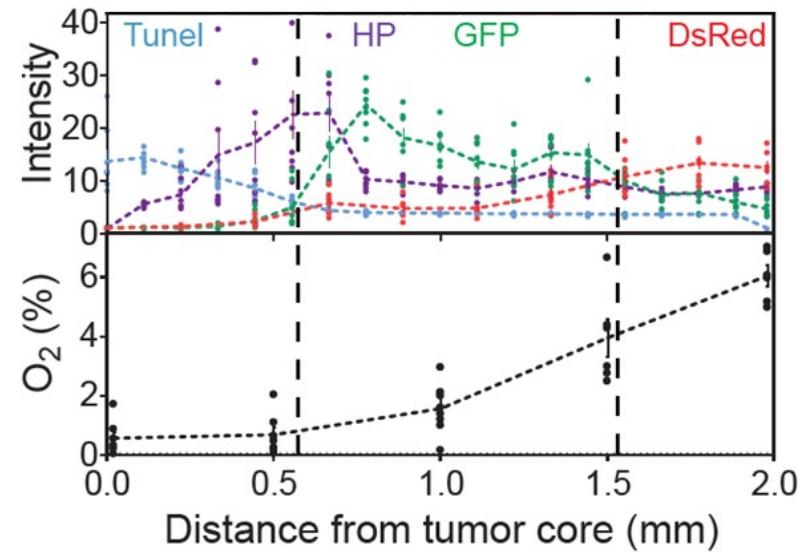
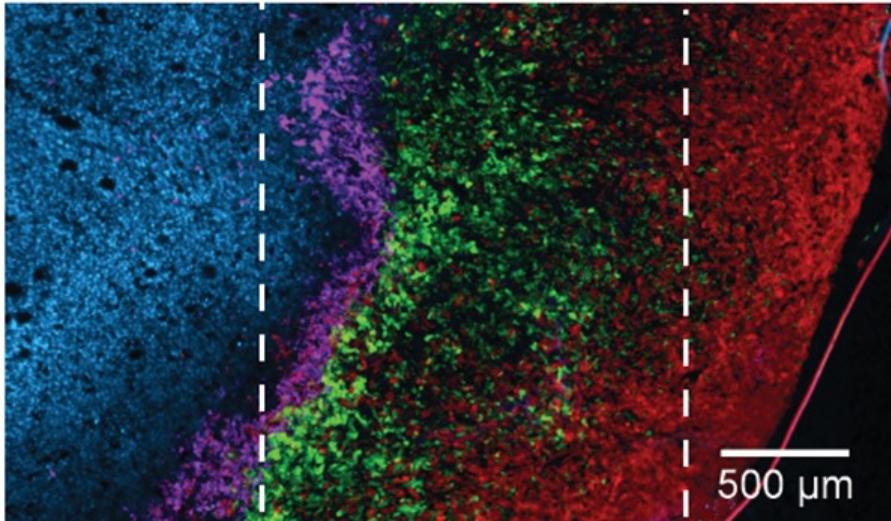
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Hypoxic and post-hypoxic cells



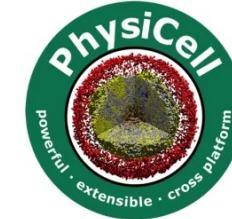
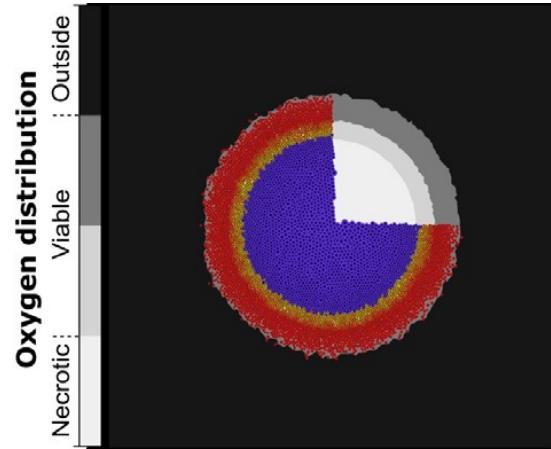
Questions

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

How persistent is their response to hypoxic stress?

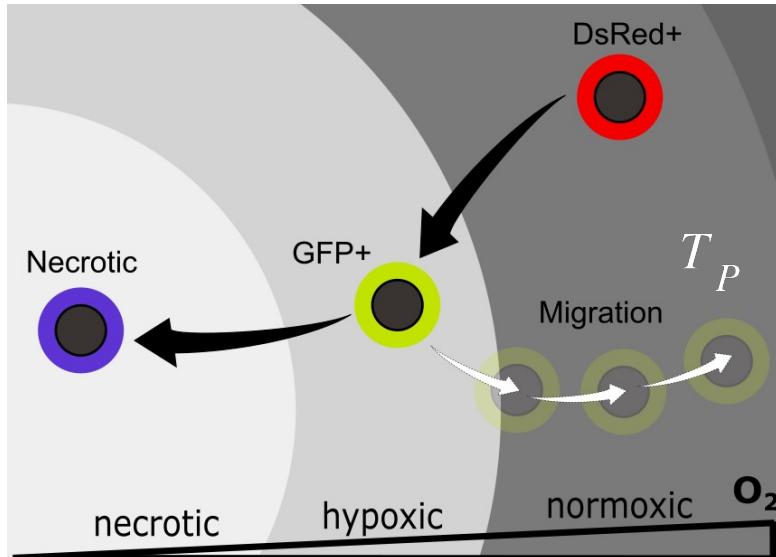
Hypoxia computational model

- 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](#).



Phenotypic transitions

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



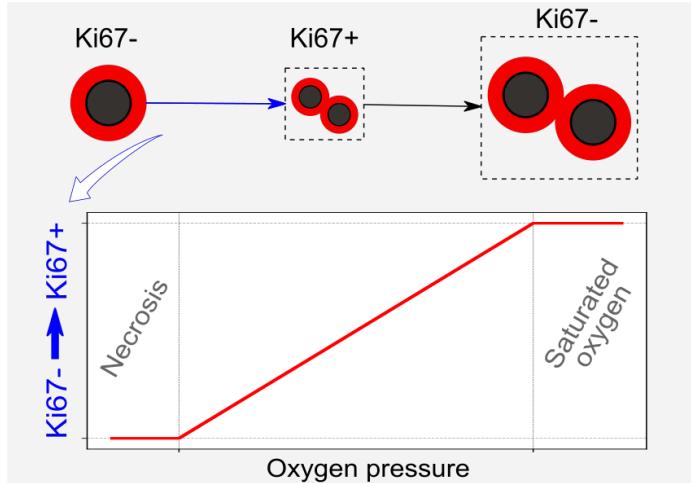
Simple ODE model for protein expression based on the "genes"

$$G = (G_0, G_1)$$

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

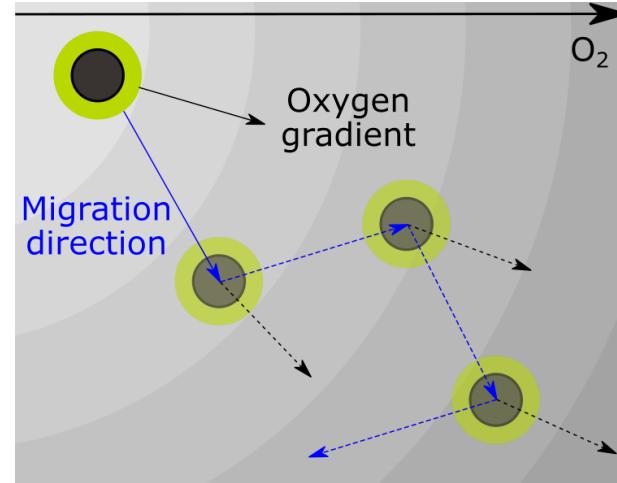
Proliferation and migration

Cell proliferation



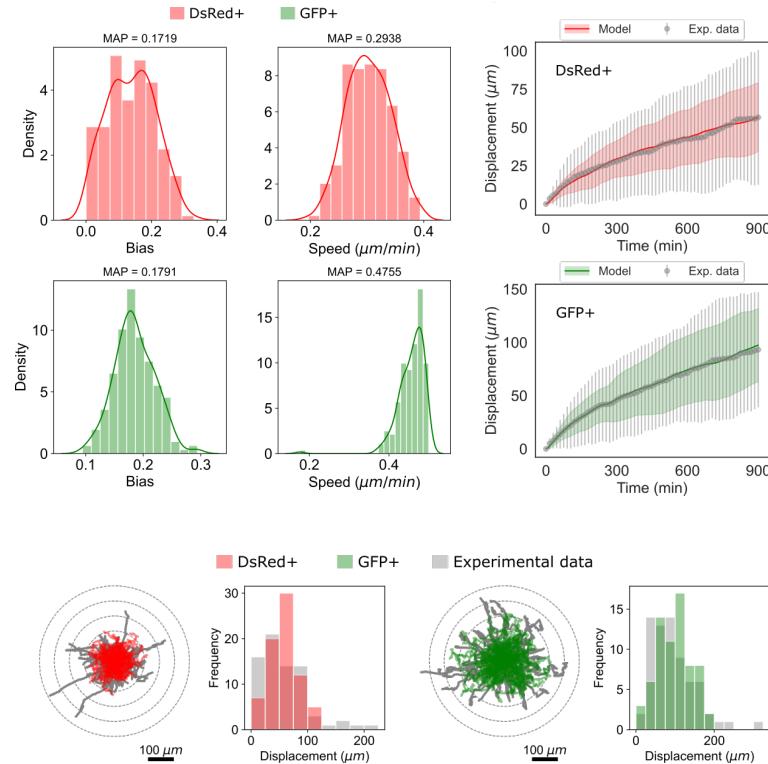
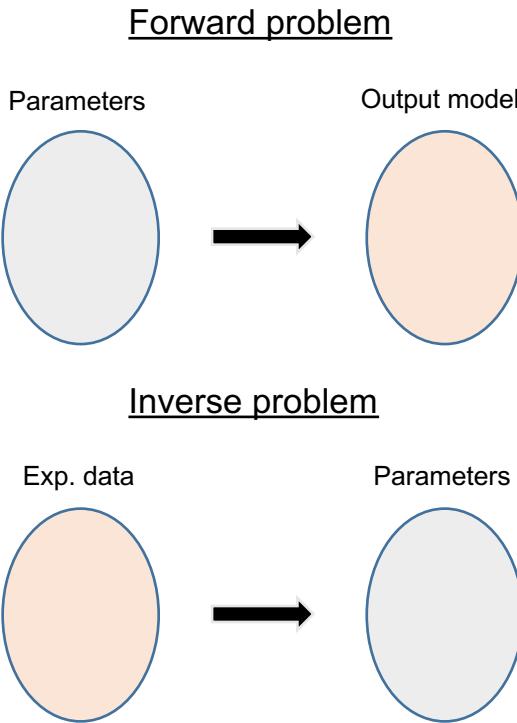
Basic Ki-67 model

Cell migration



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

Biological observations calibrate cellular motility in hypoxia computational model



Phenotypic persistence drives invasion

Phenotypic Persistence:

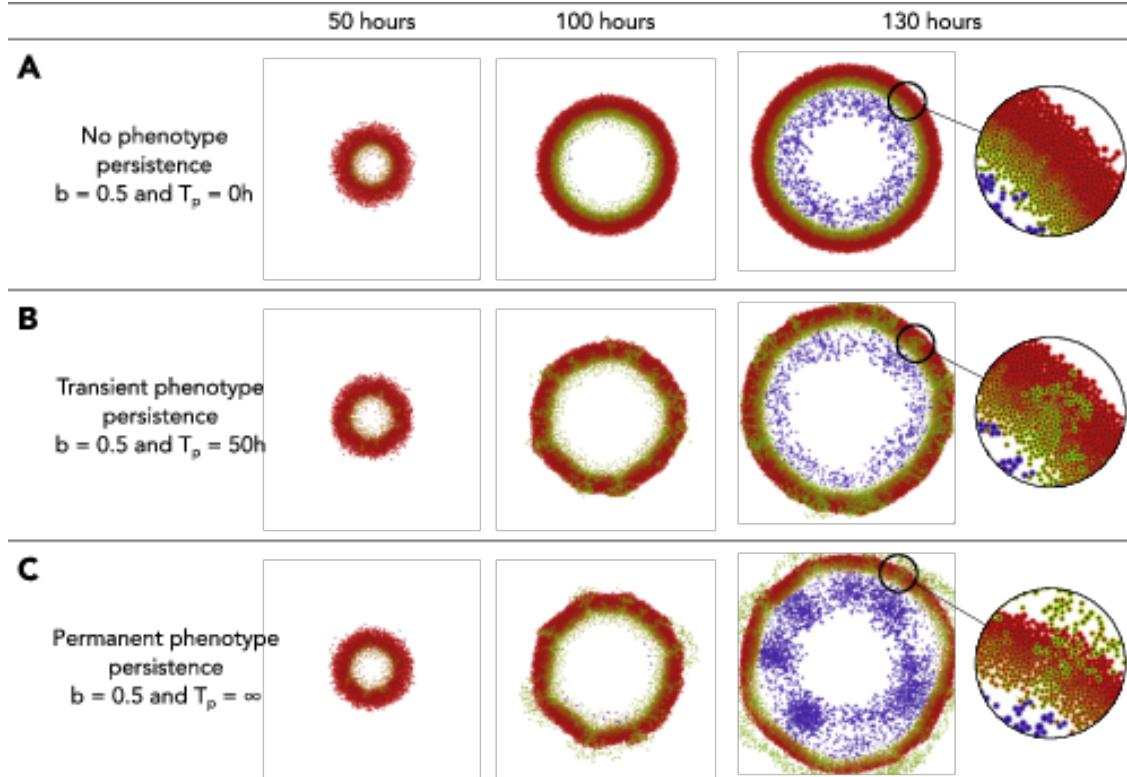
- T_p : duration of hypoxic response

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)

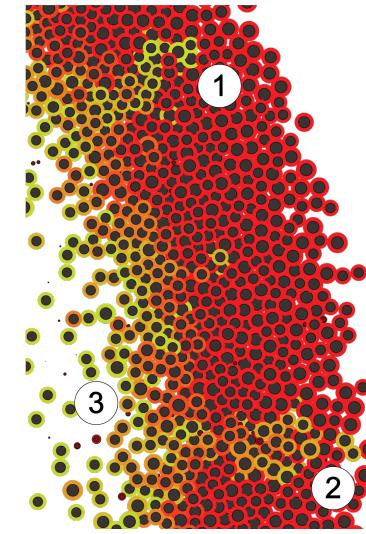
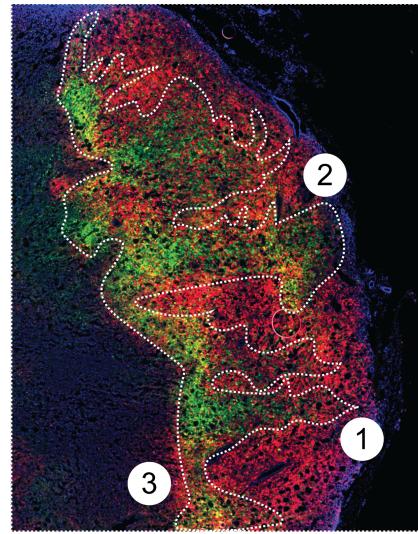
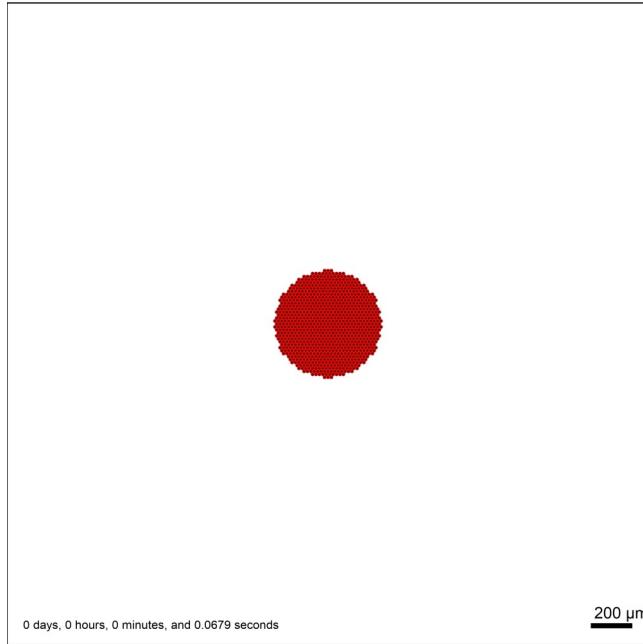
With persistence ($T_p > 0$) – Rows B & C

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

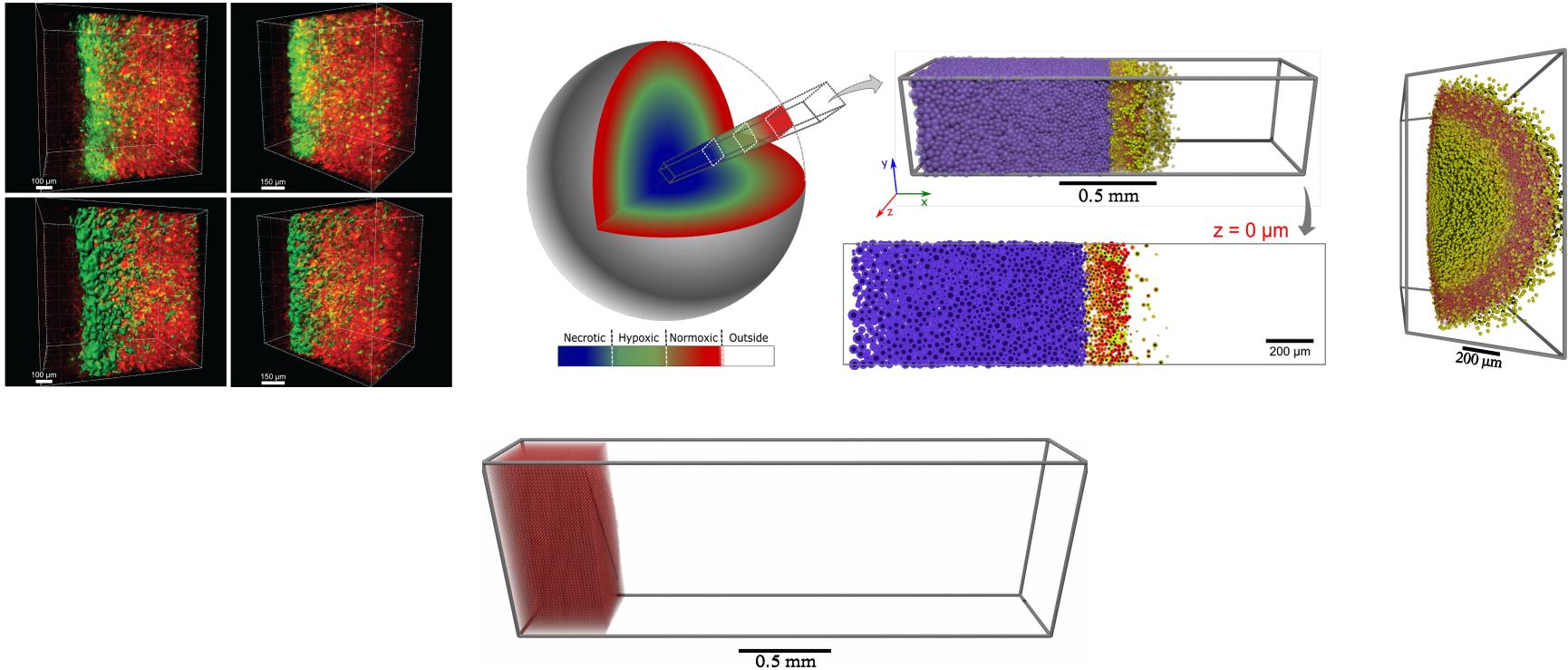


Mathematical model explains biological observations

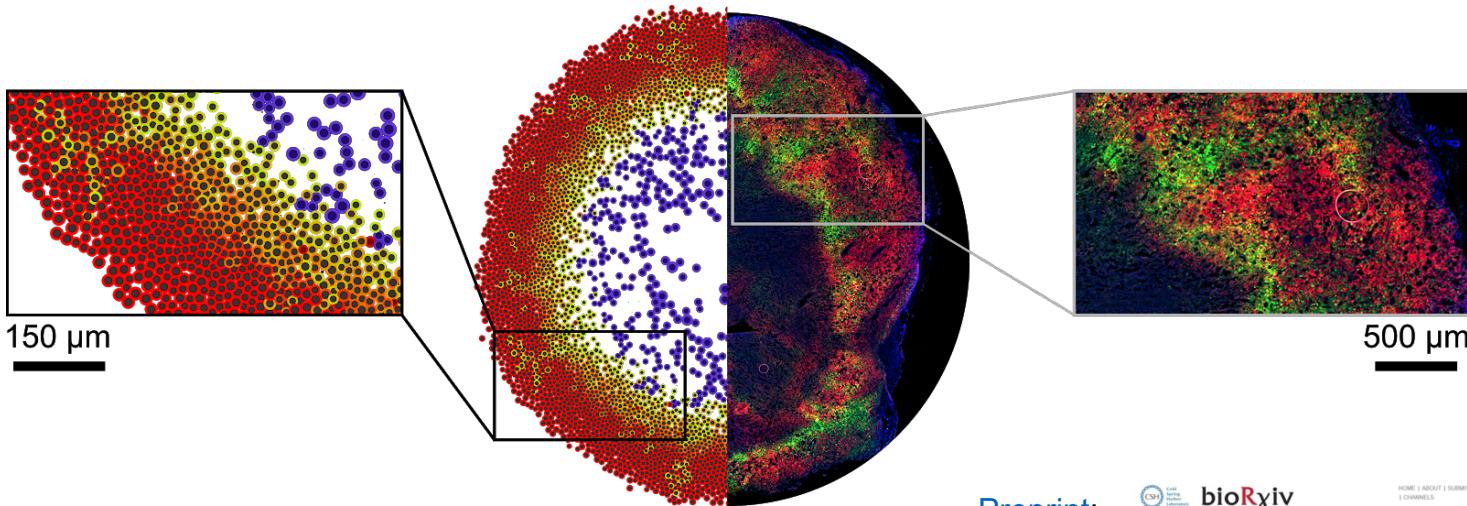
Current time: 0 days, 0 hours, and 0.00 minutes, z = 0.00 μm
889 agents



It also works in 3D



Explore this model



[Preprint:](#)



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bioRxiv is receiving many new papers on coronavirus SARS-CoV-2. A reminder: these are preliminary reports that have not been peer-reviewed. They should not be regarded as conclusive, guide clinical practice/health-related behavior, or be reported in news media as established information.

New Results

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

Helen L. Roche, Indra Goel, Furkan Kurtoglu, John Macklin, Kai Konstantinopoulos, Soumitra Bhayre, Daniela M. Gilkes, Paul Macklin
doi: <https://doi.org/10.1101/2020.12.30.424757>

This article is a preprint and has not been certified by peer review (what does this mean?).

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

2021 Virtual Training Course

15 Virtual Sessions:

- PhysiCell Essentials and Modeling Workflows
- Graphical Model Editor
- Phenotype
- Microenvironment
- Functions
- Chemical Communication / Interactions
- Contact Communication / Interactions
- Intracellular Modeling with ODEs / SBML
- Extensions for high performance computing (HPC)
- Cloud-hosted Model Sharing
- ... and more!

Sessions include:

- Slides (PDF format)
- YouTube recordings
- Source code

github.com/PhysiCell-Training/ws2021



Thank you!

Further reading (1)

- **BioFVM method paper (3-D diffusion)**

A. Ghaffarizadeh, S.H. Friedman, and P. Macklin. BioFVM: an efficient, parallelized diffusive transport solver for 3-D biological simulations. *Bioinformatics* 32(8):1256-8, 2016. DOI: [10.1093/bioinformatics/btv730](https://doi.org/10.1093/bioinformatics/btv730).

- **PhysiCell method paper (agent-based model)**

A. Ghaffarizadeh, R. Heiland, S.H. Friedman, S.M. Mumenthaler, and P. Macklin. PhysiCell: an open source physics-based cell simulator for 3-D multicellular systems. *PLoS Comput. Biol.* 14(2):e1005991, 2018. DOI: [10.1371/journal.pcbi.1005991](https://doi.org/10.1371/journal.pcbi.1005991).

- **PhysiBoSS (PhysiCell + MaBoSS for Boolean networks)**

G. Letort, A. Montagud, G. Stoll, R. Heiland, E. Barillot, P. Macklin, A. Zinovyev, and L. Calzone. PhysiBoSS: a multi-scale agent based modelling framework integrating physical dimension and cell signalling. *Bioinformatics* 35(7):1188-96, 2019. DOI: [10.1093/bioinformatics/bty766](https://doi.org/10.1093/bioinformatics/bty766).

- **xml2jupyter paper (create GUIs for cloud-hosted models)**

R. Heiland, D. Mishler, T. Zhang, E. Bower, and P. Macklin. xml2jupyter: Mapping parameters between XML and Jupyter widgets. *Journal of Open Source Software* 4(39):1408, 2019. DOI: [10.21105/joss.01408](https://doi.org/10.21105/joss.01408).

- **PhysiCell+EMEWS (high-throughput 3D PhysiCell investigation)**

J. Ozik, N. Collier, J. Wozniak, C. Macal, C. Cockrell, S.H. Friedman, A. Ghaffarizadeh, R. Heiland, G. An, and P. Macklin. High-throughput cancer hypothesis testing with an integrated PhysiCell-EMEWS workflow. *BMC Bioinformatics* 19:483, 2018. DOI: [10.1186/s12859-018-2510-x](https://doi.org/10.1186/s12859-018-2510-x).

- **PhysiCell+EMEWS 2 (HPC accelerated by machine learning)**

J. Ozik, N. Collier, R. Heiland, G. An, and P. Macklin. Learning-accelerated Discovery of Immune-Tumour Interactions. *Molec. Syst. Design Eng.* 4:747-60, 2019. DOI: [10.1039/c9me00036d](https://doi.org/10.1039/c9me00036d).

Further reading (2)

- **A review of cell-based modeling (in cancer):**

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).

- **Progress on multicellular systems biology:**

P. Macklin, H.B. Frieboes, J.L. Sparks, A. Ghaffarizadeh, S.H. Friedman, E.F. Juarez, E. Jockheere, and S.M. Mumenthaler. "Progress Towards Computational 3-D Multicellular Systems Biology". In: . Rejniak (ed.), *Systems Biology of Tumor Microenvironment*, chap. 12, pp. 225-46, Springer, 2016. ISBN: 978-3-319-42021-9. (invited author: P. Macklin). DOI: [10.1007/978-3-319-42023-3_12](https://doi.org/10.1007/978-3-319-42023-3_12).

- **Challenges for data-driven multicellular systems biology**

P. Macklin. Key challenges facing data-driven multicellular systems biology. *GigaScience* 8(10):giz127, 2019. DOI: [10.1093/gigascience/giz127](https://doi.org/10.1093/gigascience/giz127)

Some models to explore

On nanoHUB:

- **pc4heterogen**: heterogeneous cancer growth (<https://nanohub.org/tools/pc4heterogen>)
- **pc4cancerbots**: use the "biorobots" as a cell-based cancer therapy (<https://nanohub.org/tools/pc4cancerbots>)
- **pc4cancerimmune**: basic cancer immunotherapy model (<https://nanohub.org/tools/pc4cancerimmune>)
- **trmotility**: learn about biased random cell migration (<https://nanohub.org/tools/trmotility>)
- **pcisa**: learn about an adversarial ecosystem: invader cells are fueled by resource providers, but scout cells seek invaders to recruit attackers, who poison invaders. (<https://nanohub.org/tools/pcisa>)
- **pc4thanos**: Avengers *Endgame* battle using cell rules (<https://nanohub.org/tools/pc4thanos>)
- **pc4covid19**: COVID-19 simulation model (<https://nanohub.org/tools/pc4covid19>)
- **pc4livermedium**: tumor-stroma biomechanical feedbacks (<https://nanohub.org/tools/pc4livermedium>)