Slides, videos, links and more:
https://github.com/physicell-training/ws2022

Session 0: Introduction to Agent-Based Modeling and PhysiCell

Paul Macklin, Ph.D.
@MathCancer

PhysiCell Project

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Goals

- Learn the motivation for and 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

From single cells to 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

Source: Hanahan (2022)
DOI: 10.1158/2159-8290.CD-21-1059

Multicellular systems biology seeks to *understand* these systems.
Multicellular systems engineering seeks to *control* them.

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

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 ($\rho_{\max}$).

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

- **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 ($t + \Delta t$), each cell has a probability $P = r\Delta t$ of a birth event that increases X by one.

What is an agent-based model?

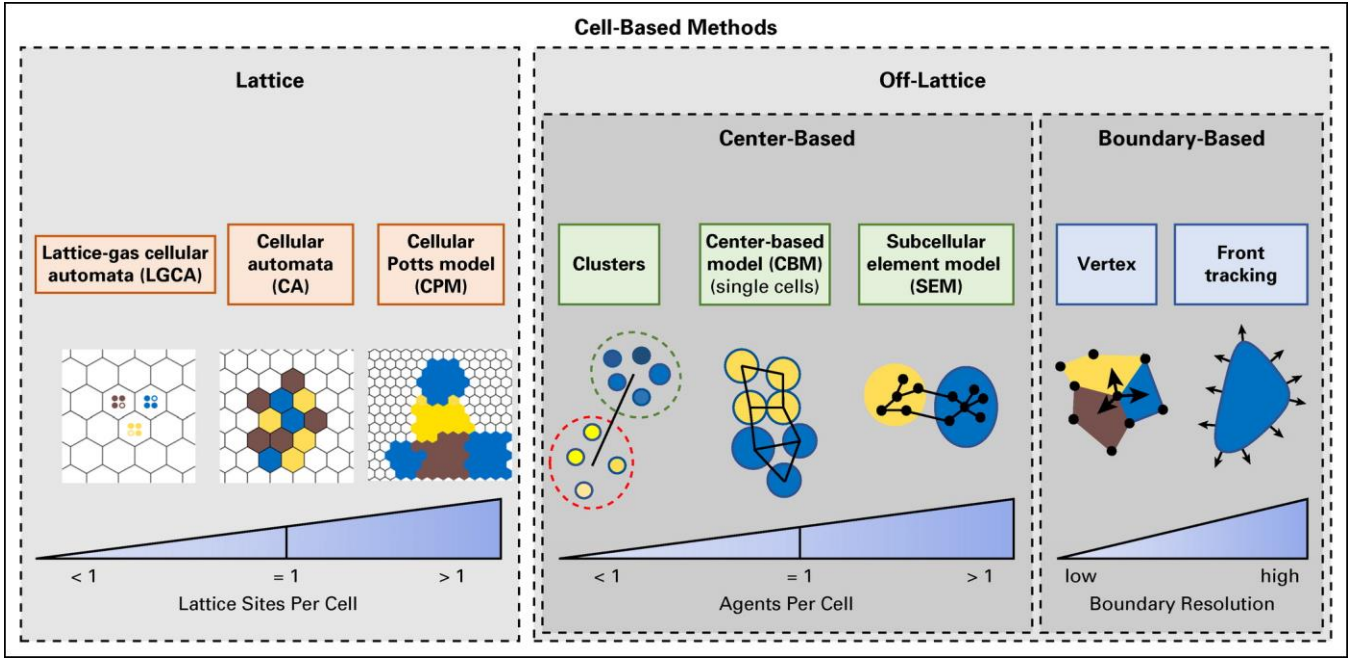
- An **agent-based model** (in biology) is a type of discrete model that simulates individual cells.
  - Also referred to as **individual-based models** or **cell-based models**.
- Agent-based models are often combined with continuum models of the microenvironment (e.g., partial differential equations 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.

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 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 μm resolution

Features:

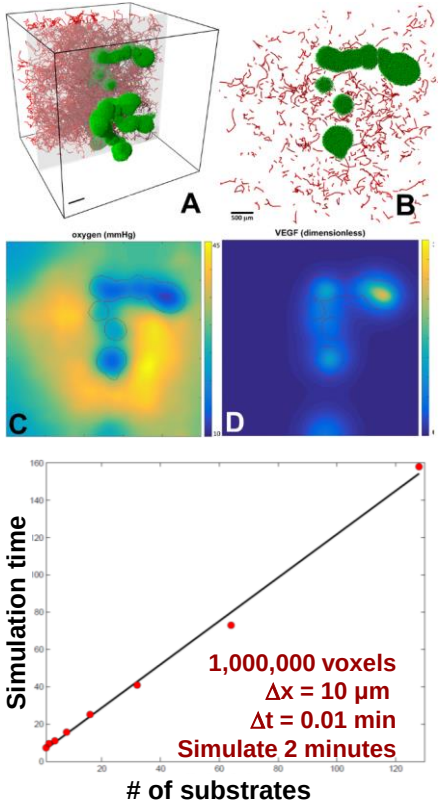
- Off-lattice cell secretion and uptake
- 2^{nd}-order accurate (space), 1^{st}-order accurate (time), numerically stable

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



PhysiCell: A multicellular framework

Design goal: Simulate 10^6 or more cells in 2D or 3D on desktops or single HPC nodes

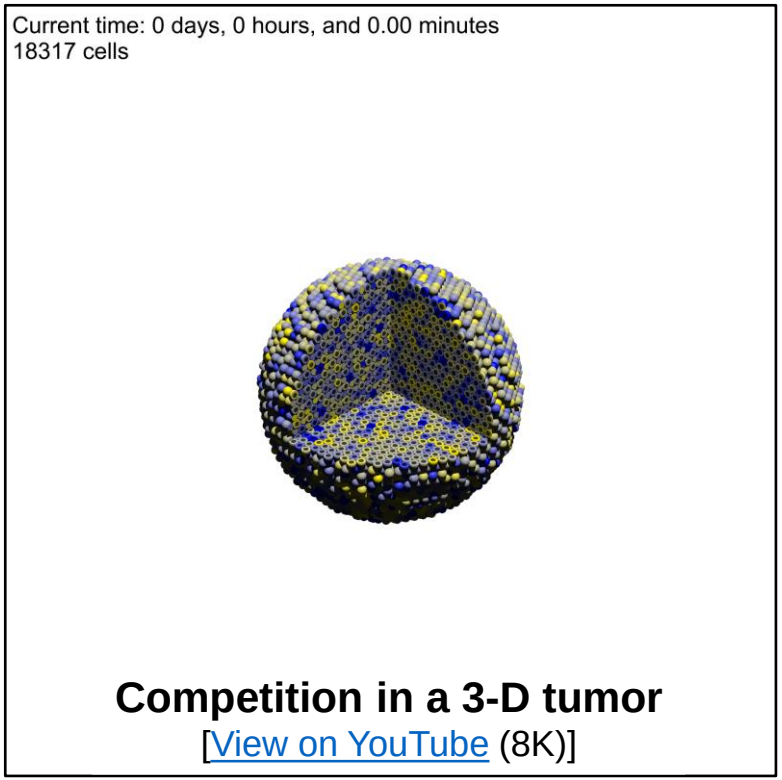
Features:

- 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

2019 PLoS Computational Biology Research Prize *for* Public Impact

Method:

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



Competition in a 3-D tumor

[View on YouTube (8K)]

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

DOI: 10.1371/journal.pcbi.1005991

Try this model yourself!

nanohub.org/tools/pc4heterogen

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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) : more on the next slide**
  - Custom variables
  - Functions that act upon the phenotype, variables, and state **(script)**

Key parts of a PhysiCell model (3)

- Our entire workflow is centered around the cell's **behavioral phenotype**
  - Cell cycle
  - Death
  - Volume
  - Mechanics
  - Motility
  - Secretion
  - Cell-cell interactions

New in 2022!

- **Signals**
  - Things in the environment that can influence cell phenotype
  - The **inputs** to cell rules

- **Behaviors**
  - Elements of cell phenotype that can be modulated
  - The **outputs** to cell rules

- **Dictionaries**
  - Auto-generated by PhysiCell at the start of your simulation
  - **Signal dictionary**: Easily get any cell signal by its "plain English" name
  - **Behavior dictionary:** Easily get / set any cell behavior by its "plain English" name
    - ♦ One dictionary to access the individual cell's ***current*** behavior
    - ♦ One dictionary to access the individual cell's ***reference*** behavior (from its cell definition)

A note about time steps

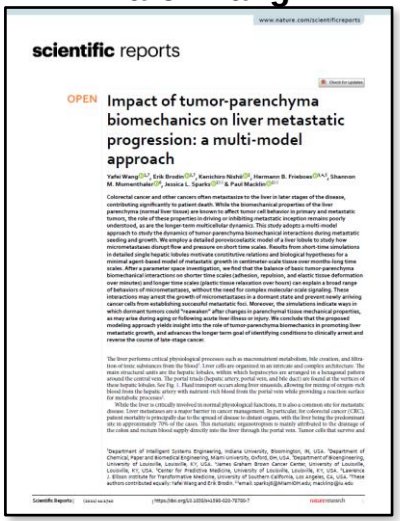
- PhysiCell is designed to account for the multiple time scales inherent to these problems, and has 3 time scales:
  - $\Delta t_{\text{diffusion}}$ diffusion, secretion, and uptake (default: 0.01 min)
  - $\Delta t_{\text{mechanics}}$ cell movement (default: 0.1 min)
  - Δt_{cell} phenotype and volume changes (default: 6 min)

- This allows some efficiency improvements: not all functions need to be evaluated at each time step.

- Intracellular models can have their own step sizes

Some recent examples

Work led by:
Yafei Wang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OPEN

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

Yafei Wang[1,2], Erik Brodin[1,2], Kenichiro Nishii[1,2], Hermann B. Frieboes[3,4,5], Shannon M. Mumenthaler[6], Jessica L. Sparks[1,2,7] & Paul Macklin[1,2]*

Colorectal cancer and other cancers often metastasize to the liver in later stages of the disease, contributing significantly to patient death. While the biomechanical properties of the liver parenchyma (normal liver tissue) are known to affect tumor cell behavior in primary and metastatic tumors, the role of these properties in driving or inhibiting metastatic inception remains poorly understood, as are the longer-term multicellular dynamics. This study adopts a multi-model approach to study the dynamics of tumor-parenchyma biomechanical interactions during metastatic seeding and growth. We employ a detailed poroviscoelastic model of a liver lobule to study how micrometastases disrupt flow and pressure on short time scales. Results from short-time simulations in detailed single hepatic lobules motivate constitutive relations and biological hypotheses for a minimal agent-based model of metastatic growth in centimeter-scale tissue over months-long time scales. After a parameter space investigation, we find that the balance of basic tumor-parenchyma biomechanical interactions on shorter time scales (adhesion, repulsion, and elastic tissue deformation over minutes) and longer time scales (plastic tissue relaxation over hours) can explain a broad range of behaviors of micrometastases, without the need for complex molecular-scale signaling. These interactions may arrest the growth of micrometastases in a dormant state and prevent newly arriving cancer cells from establishing successful metastatic foci. Moreover, the simulations indicate ways in which dormant tumors could "reawaken" after changes in parenchymal tissue mechanical properties, as may arise during aging or following acute liver illness or injury. We conclude that the proposed modeling approach yields insight into the role of tumor-parenchyma biomechanics in promoting liver metastatic growth, and advances the longer-term goal of identifying conditions to clinically arrest and reverse the course of late-stage cancer.

The liver performs critical physiological processes such as macronutrient metabolism, bile creation, and filtration of toxic substances from the blood[1]. Liver cells are organized in an intricate and complex architecture. The main structural units are the hepatic lobules, within which hepatocytes are arranged in a hexagonal pattern around the central vein. The portal triads (hepatic artery, portal vein, and bile duct) are found at the vertices of the hexagonal lobule[2]. The liver receives a dual blood supply: oxygen-rich blood from the hepatic artery and blood from the hepatic artery with nutrient-rich blood from the portal vein while providing a nucleus surface for metabolic processes[3].

While the liver is critically involved in normal physiological functions, it is also a common site for metastatic disease. Liver metastases are a major barrier in cancer management. In particular, for colorectal cancer (CRC), patient mortality is principally due to the spread of disease to distant organs, with the liver being the predominant site in approximately 70% of the cases. This metastatic organotropism is mainly attributed to the drainage of the colon and rectum blood supply directly into the liver through the portal vein. Tumor cells that survive and

[1]Department of Intelligent Systems Engineering, Indiana University, Bloomington, IN, USA. [2]Department of Chemical, Paper and Biomedical Engineering, Miami University, Oxford, OH, USA. [3]Department of Bioengineering, University of Louisville, Louisville, KY, USA. [4]James Graham Brown Cancer Center, University of Louisville, Louisville, KY, USA. [5]Center for Predictive Medicine, University of Louisville, Louisville, KY, USA. [6]Lawrence J. Ellison Institute for Transformative Medicine, University of Southern California, Los Angeles, CA, USA. *These authors contributed equally: Yafei Wang and Erik Brodin. *email: sparksjl@MiamiOH.edu; macklinp@iu.edu

Scientific Reports | (2021) 11:2769 | https://doi.org/10.1038/s41598-020-78780-7 nature research

Example:

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) metastates?

- Prior work mostly investigated:
  - Signaling impact of ECM
  - Signaling impact of liver cells
  - All at single-cell level

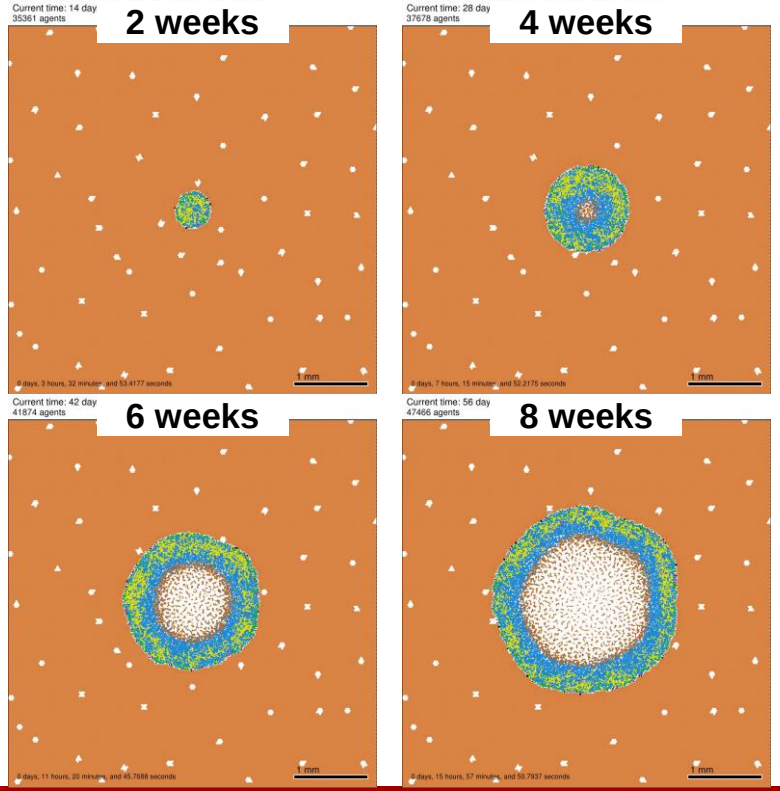
- What about the larger-scale tumor-parenchyma interactions?
  - Displacement and compression of liver parenchyma
  - Compressive forces on the micrometastasis

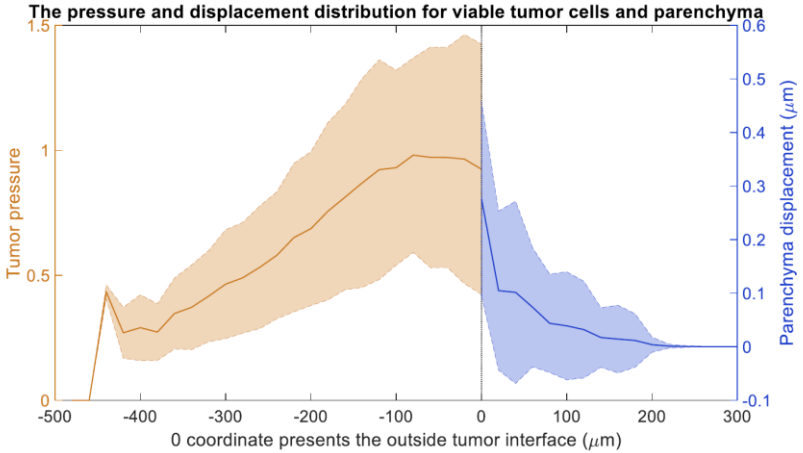
$$b = b_M \cdot \left(\frac{\sigma - \sigma_{\text{hypoxic}}}{\sigma_{\text{sat}} - \sigma_{\text{hypoxic}}}\right) \cdot \left(1 - \frac{p}{p_{\max}}\right)$$

- 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

$$p = k \sum_j \left|\nabla\psi(x_i, x_j)\right|$$

Growth with feedback



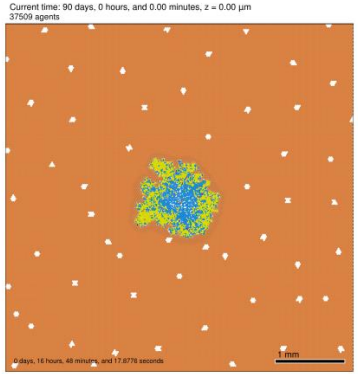


Try this model yourself!

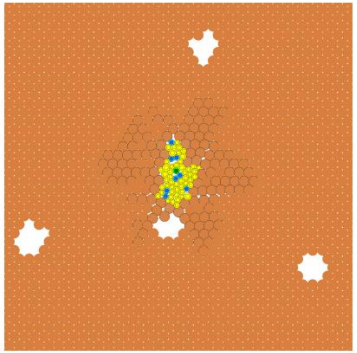
nanohub.org/tools/pc4livermedium

Tumor dormancy in some tissues

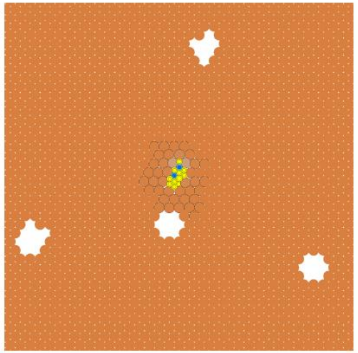
- If tissue has:
  - large elastic force (large r_E)
  - slow plastic relaxation (small r_P)
  - tolerance of deformation (large d_{max})
- Then:
  - Compressed tissue surrounds tumor (encapsulation)
  - Most cells are pressure-arrested, leading to **tumor dormancy**



(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

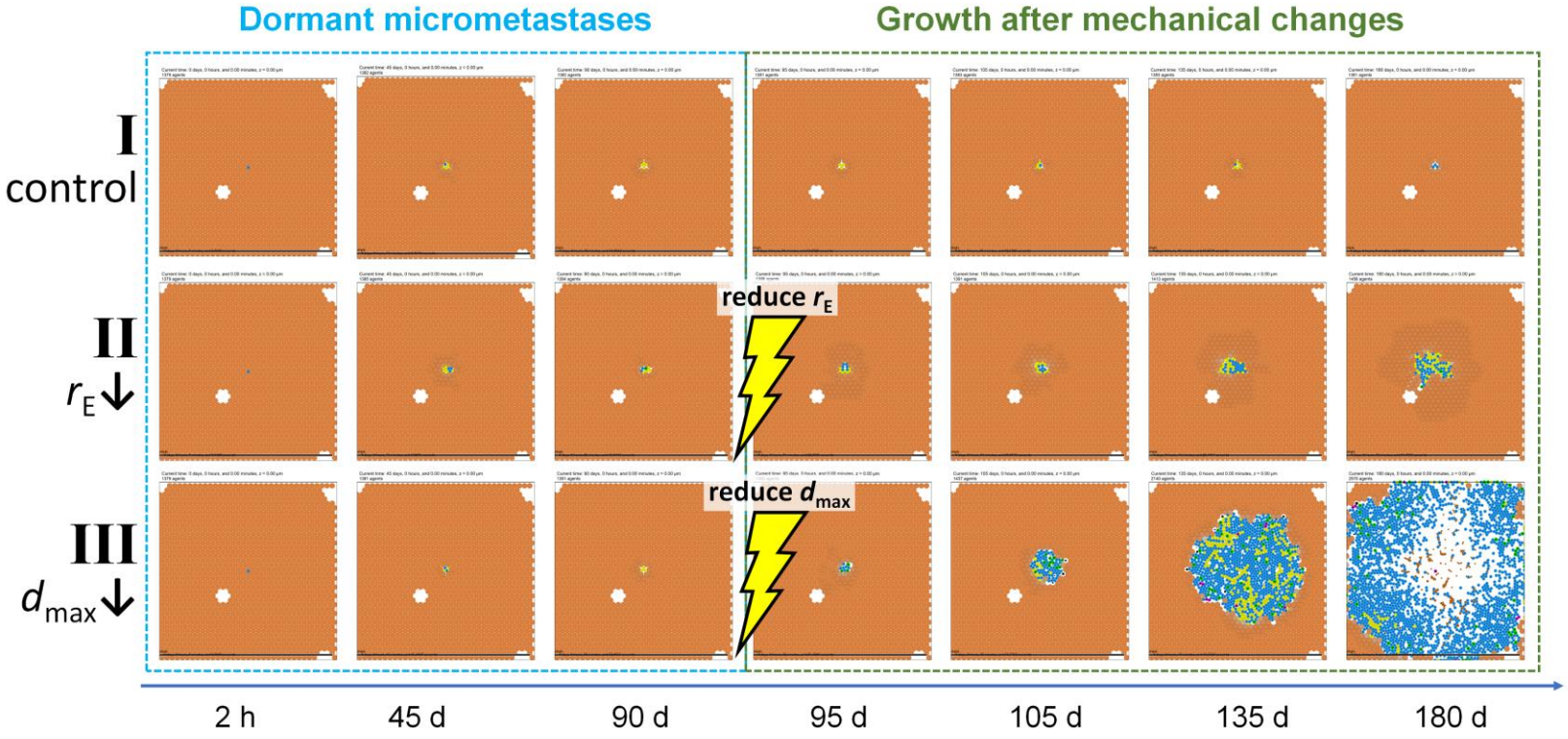


(b) r_E=0.2, r_P=0.0005, d_{max}=3

Try this model yourself!

nanohub.org/tools/pc4livermedium

Tissue changes can reawaken a tumor



Try this model yourself!

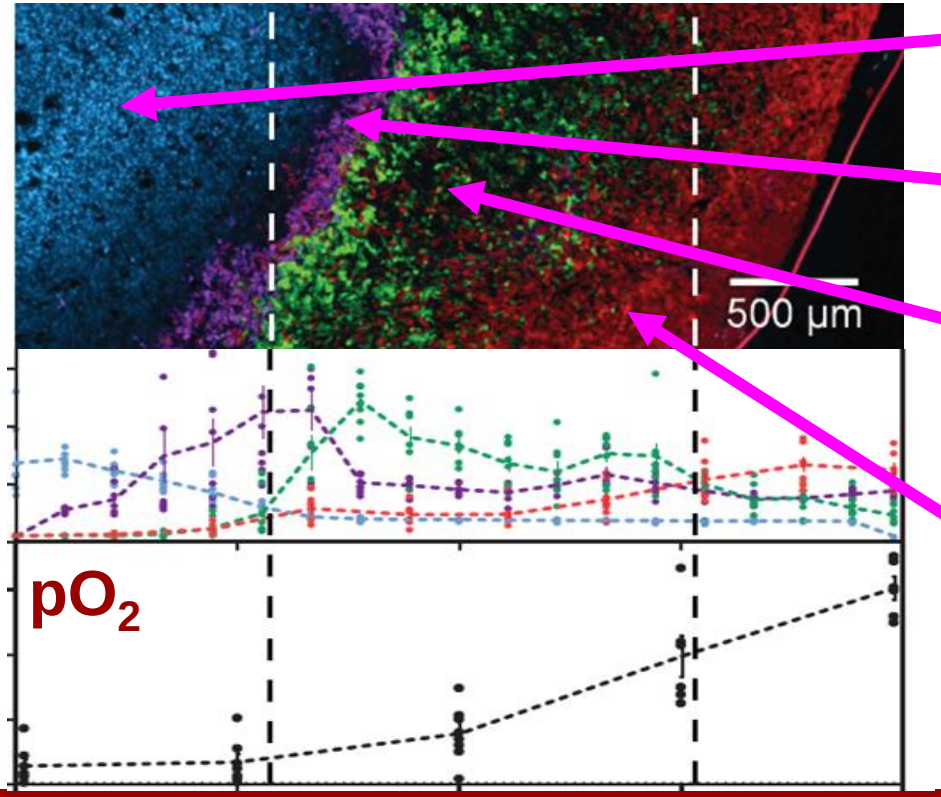
nanohub.org/tools/pc4livermedium

Example:

hypoxia-driven breast cancer invasion

Rocha et al., *iScience* (2021)
DOI: 10.1016/j.isci.2021.102935

Hypoxic and post-hypoxic cells



Necrotic cells

Newly hypoxic

(Post-)hypoxic and motile

- hypoxic long enough for GFP

Normoxic

How do cancer cells behave after leaving hypoxic regions?

Fate-mapping intratumoral hypoxia

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Article | Open Access | Published: 24 October 2019

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

Inês 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 O_2 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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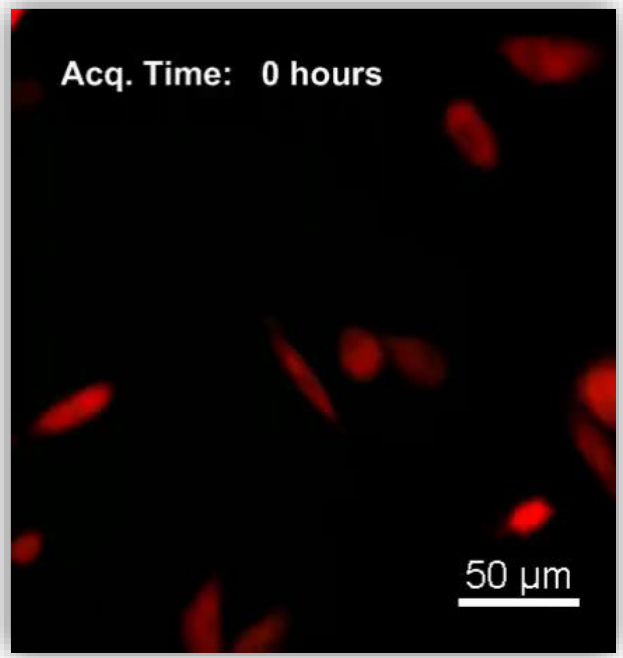
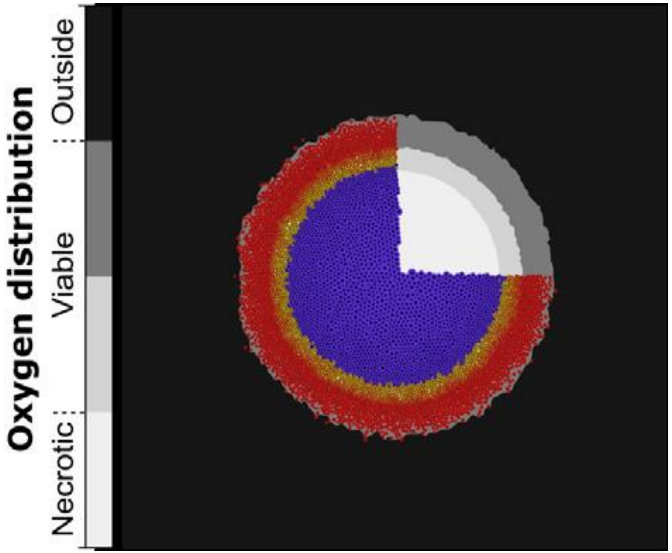
Sections | Figures | References



Model overview

- Simulate oxygen diffusion and uptake
- Proliferation and necrosis vary with pO_2 and 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:

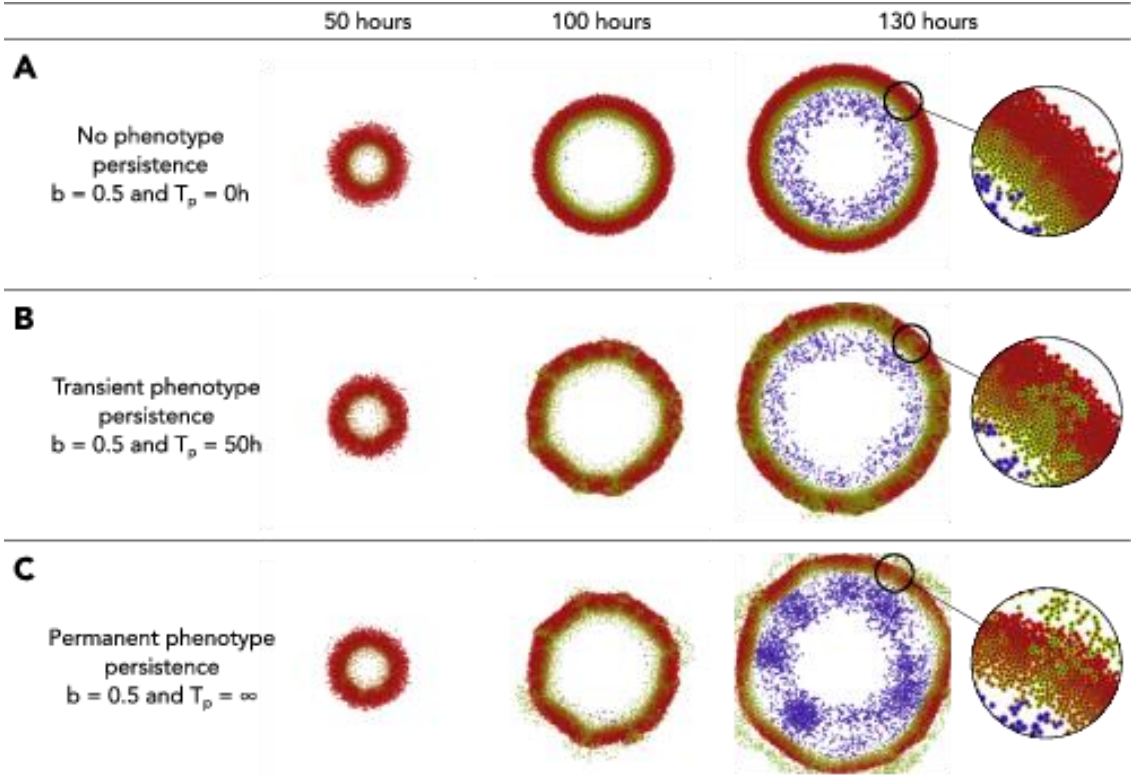
- T_p : duration of hypoxic response

Without persistence ($T_p = 0$) – Row A

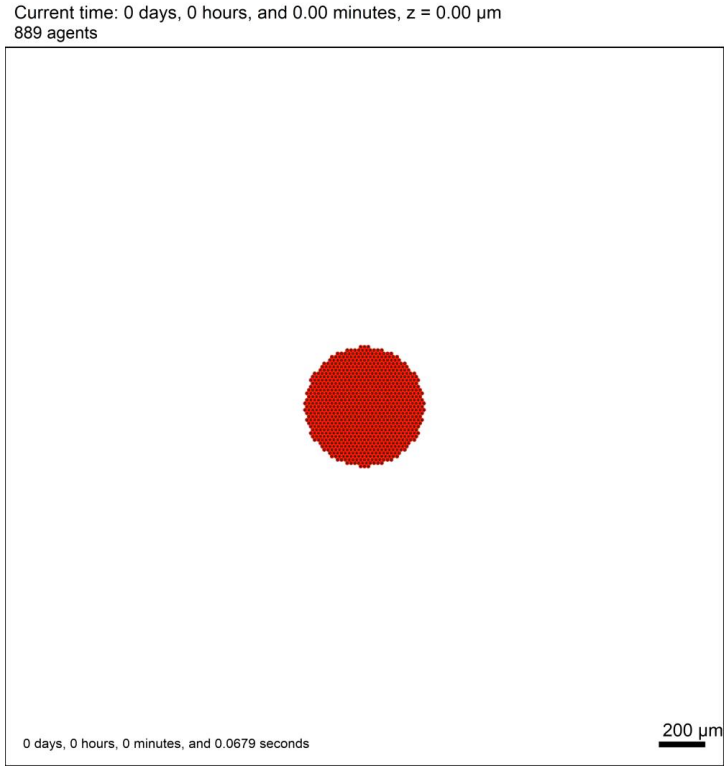
- Migration halts at perinecrotic boundary
- Tumors maintain a concentric structure:
  - Oxygenated viable rim (red)
  - hypoxic (or formerly hypoxic) annulus (green)
  - Necrotic core (purple)

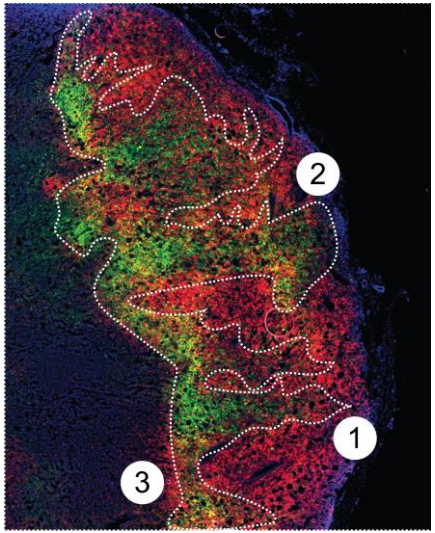
With persistence ($T_p > 0$) – Rows B & C

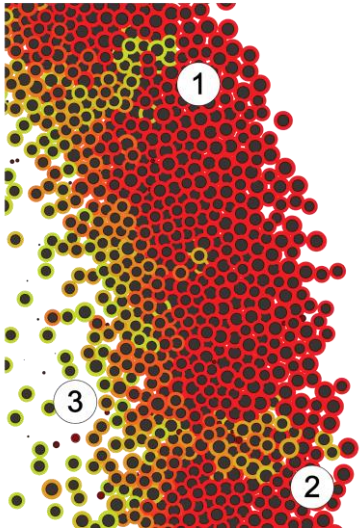
- Hypoxic cells can continue migrating
- Hypoxic cells "punch through" the oxygenated tumor region



Mathematical model explains biological observations

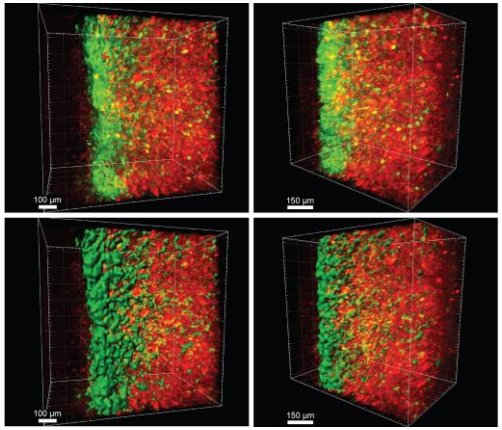


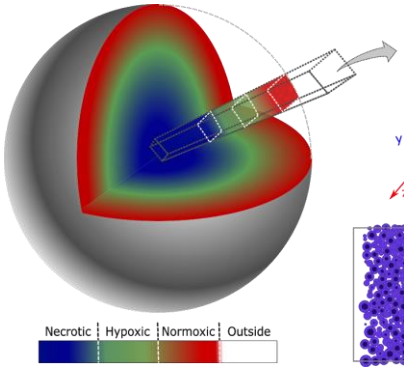


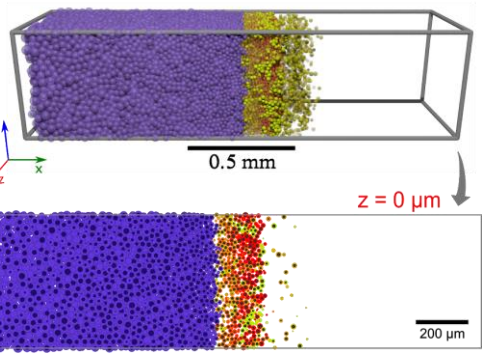


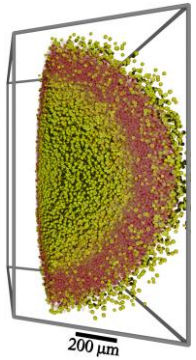
Try this model yourself!
nanohub.org/tools/pc4tumorhypoxia

It also works in 3D









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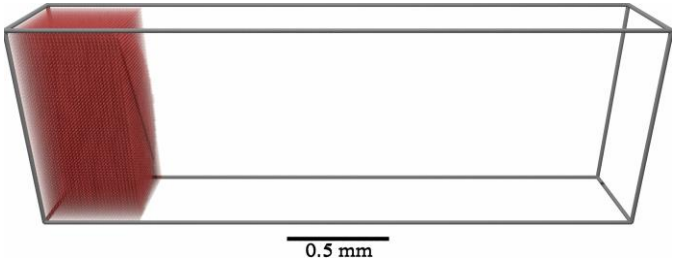
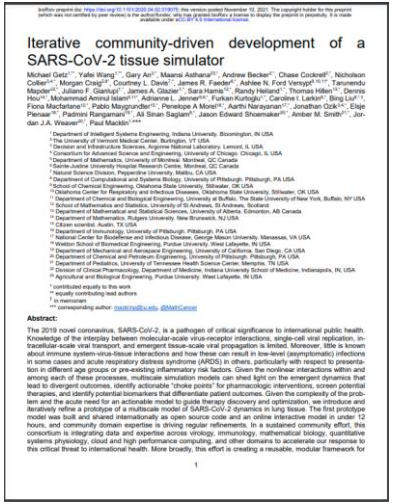


Work led by:
Michael Getz



Iterative community-driven development of a SARS-CoV-2 tissue simulator

Michael Getz[1,*], Yafei Wang[1,*], Gary An[2], Maansi Asthana[3,4], Andrew Becker[2,5], Chase Cockrell[2,6], Nicholson Collier[3,4,*], Morgan Craig[7,8], Courtney L. Davis[9,*], James R. Faeder[9,*], Ashlee N. Ford Versypt[10,11,*], Tarunendu Mapder[12], Juliano F. Gianlupi[13,*], James A. Glazier[14], Sara Hamis[15,*], Randy Heiland[14], Thomas Hillen[16], Dennis Hou[17], Mohammad Aminul Islam[17,*], Adrianne L. Jenner[18,*], Furkan Kurtoglu[1,*], Caroline I. Larkin[19], Bing Liu[1,*], Fiona Macfarlane[20], Pablo Maygrundter[21], Penelope A Morel[14], Aarthi Narayanan[17,*], Jonathan Ozik[3,4,*], Elsje Pienaar[18,*], Padmini Rangamani[22], Ali Sinan Saglam[23], Jason Edward Shoemaker[24], Amber M. Smith[25,*], Jordan J.A. Weaver[20], Paul Macklin[1,***]

[1] Department of Intelligent Systems Engineering, Indiana University, Bloomington, IN USA
[2] The University of Vermont Medical Center, Burlington, VT USA
[3] Decision and Infrastructure Sciences, Argonne National Laboratory, Lemont, IL USA
[4] Consortium for Advanced Science and Engineering, University of Chicago, Chicago, IL USA
[5] Department of Mathematics, University of Montreal, Montreal, QC Canada
[6] Sainte-Justine University Hospital Research Centre, Montreal, QC Canada
[7] Natural Science Division, Pepperdine University, Malibu, CA USA
[8] Department of Computational and Systems Biology, University of Pittsburgh, Pittsburgh, PA USA
[9] School of Chemical Engineering, Oklahoma State University, Stillwater, OK USA
[10] Oklahoma Center for Respiratory and Infectious Diseases, Oklahoma State University, Stillwater, OK USA
[11] Department of Chemical and Biological Engineering, University at Buffalo, The State University of New York, Buffalo, NY USA
[12] School of Mathematics and Statistics, University of St Andrews, St Andrews, Scotland
[13] Department of Mathematical and Statistical Sciences, University of Alberta, Edmonton, AB Canada
[14] Department of Mathematics, Rutgers University, New Brunswick, NJ USA
[15] Citizen scientist, Austin, TX USA
[16] Department of Immunology, University of Pittsburgh, Pittsburgh, PA USA
[17] National Center for Biodefense and Infectious Disease, George Mason University, Manassas, VA USA
[18] Weldon School of Biomedical Engineering, Purdue University, West Lafayette, IN USA
[19] Department of Mechanical and Aerospace Engineering, University of California, San Diego, CA USA
[20] Department of Chemical and Petroleum Engineering, University of Pittsburgh, Pittsburgh, PA USA
[21] Department of Pediatrics, University of Tennessee Health Science Center, Memphis, TN USA
[22] Division of Clinical Pharmacology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA
[23] Agricultural and Biological Engineering, Purdue University, West Lafayette, IN USA

* contributed equally to this work
** equally contributing lead authors
† in memoriam
*** corresponding author: macklinp@iu.edu, @MathCancer

Abstract:

The 2019 novel coronavirus, SARS-CoV-2, is a pathogen of critical significance to international public health. Knowledge of the interplay between molecular-scale virus-receptor interactions, single-cell viral replication, intracellular-scale viral transport, and emergent tissue-scale viral propagation is limited. Moreover, little is known about immune system–virus-tissue interactions and how these can result in low-level (asymptomatic) infections in some cases and acute respiratory distress syndrome (ARDS) in others, particularly with respect to presentation in different age groups or pre-existing inflammatory risk factors. Given the nonlinear interactions within and among each of these processes, multiscale simulation models can shed light on the emergent dynamics that lead to divergent outcomes, identify actionable "choke points" for pharmacologic interventions, screen potential therapies, and identify potential biomarkers that differentiate patient outcomes. Given the complexity of the problem and the acute need for an actionable model to guide therapy discovery and optimization, we introduce and iteratively refine a prototype of a multiscale model of SARS-CoV-2 dynamics in lung tissue. The first prototype model was built and shared internationally as open source code and an online interactive model in under 12 hours, and community domain expertise is driving regular refinements. In a sustained community effort, this consortium is integrating data and expertise across virology, immunology, mathematical biology, quantitative systems physiology, cloud and high performance computing, and other domains to accelerate our response to this critical threat to international health. More broadly, this effort is creating a reusable, modular framework for

Example:
SARS-CoV-2

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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,*], Adrianne Jenner[5,6,*], Furkan Kurtoglu[1,*], Bing Liu[8,*,†], Fiona Macfarlane[11,*], Pablo Maygrundter[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,***]

[1] Department of Intelligent Systems Engineering, Indiana University. Bloomington, IN USA
[2] The University of Vermont Medical Center. Burlington, VT USA

40+ regular contributors from 20+ institutions

[11] School of Mathematics and Statistics, University of St Andrews, St Andrews, Scotland.
[12] Dep… Statistical Sciences, University of Alberta… AB Canada
[13] Dep…ers University. New Brunswick, NJ USA
[14] Citiz…
[15] Dep…ersity of Pittsburgh. Pittsburgh, PA USA
…d Infectious Disease, George Mason U…
…ineering, Purdue University. West Lafay…
…erospace Engineering, University of Cali…
…oleum Engineering, University of Pittsbu…
…ity of Tennessee Health Science Cente…
** equa…
† in me…
*** corresponding author: macklinp@iu.edu, @MathCancer

Michael Getz
Indiana U.

Yafei Wang
Indiana U.

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

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

Some key contact interactions

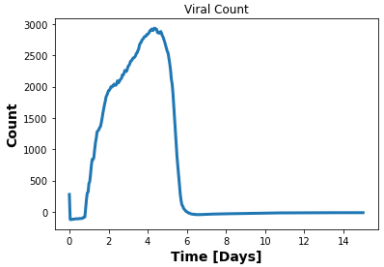
- CD8+ T cell attacks
  - While T cell is in contact with infected cell, increase damage by $r_{\text{damage}}\Delta t$
  - Infected cell has death rate that increases with damage

$$d = d_0 + (d_{\max} - d_0) \cdot \left(\frac{\text{damage}^h}{\text{damage}^h + \text{damage}_{\text{halfmax}}^h} \right)$$

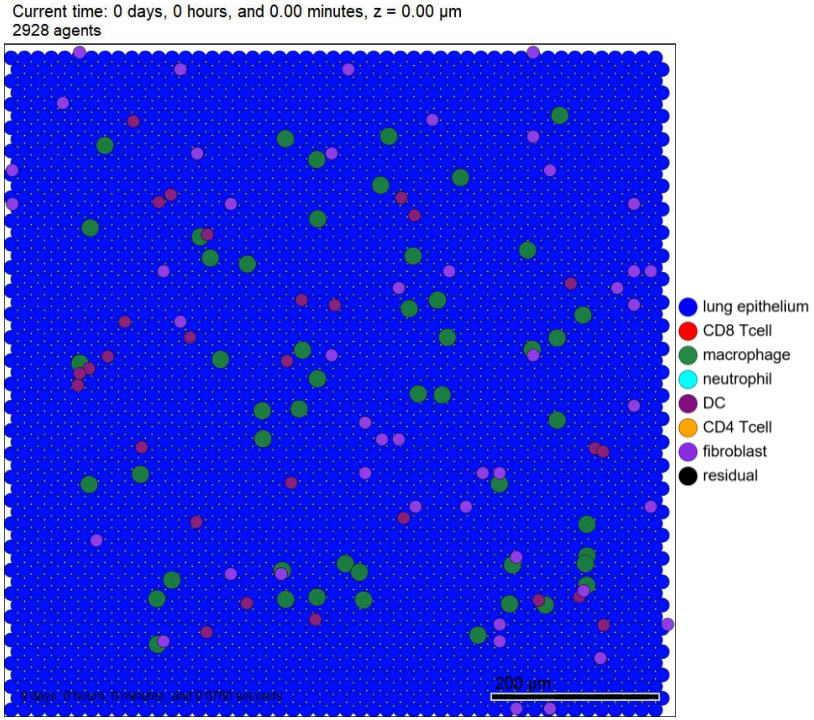
- Macrophages
  - When in contact with a dead cell, phagocytose it with probability $r_{\text{phago}}\Delta t$
  - Acquire volume phagocytosed cell
  - Ingesting infected cell causes secretion of pro-inflammatory signals

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



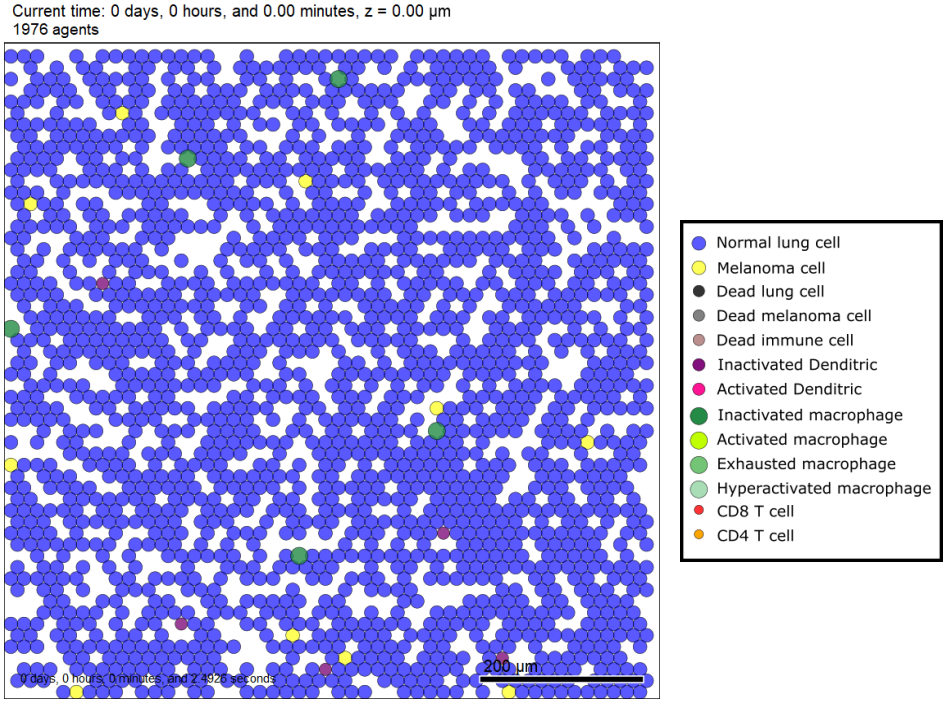
- **This immune model is sufficiently complete to clear a SARS-CoV-2 infection**



A naïve immune system can adapt to halt the infection

(Re)adapting to cancer

- Adapt and reuse:
  - Tumor growth model
  - Local immune dynamics:
    - 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
    - Early 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.



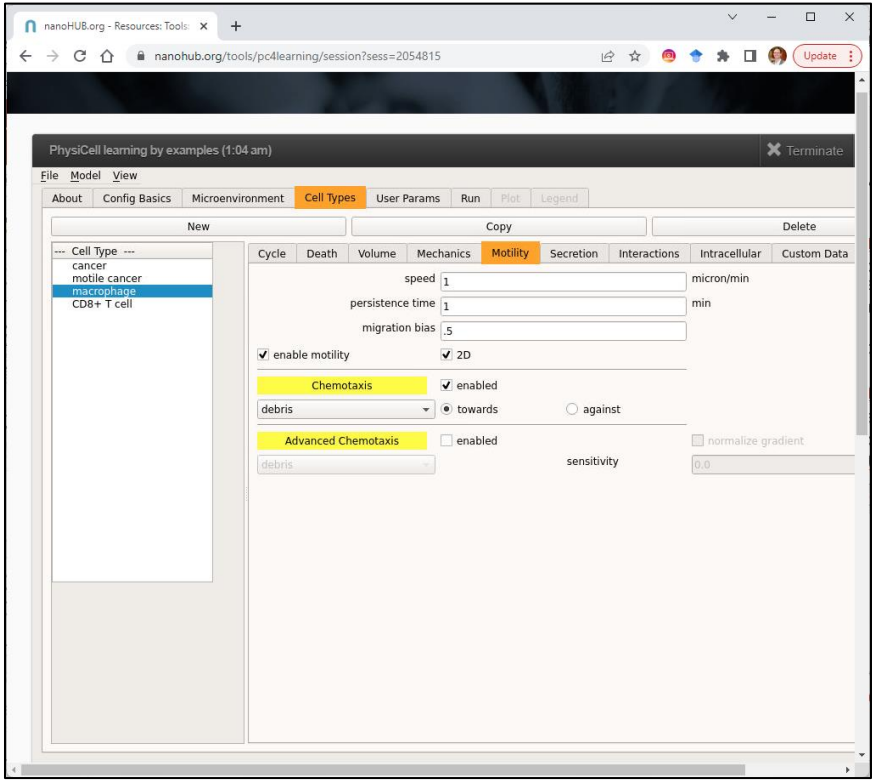
Immune cells attacking micrometastases

pc4learning: an interactive testbed

- Free online PhysiCell simulator hosted on nanoHUB

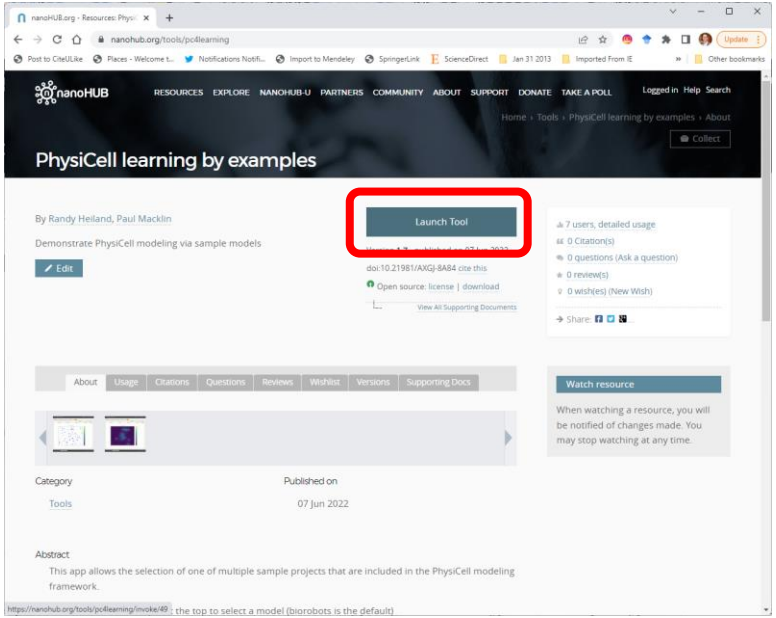
https://nanohub.org/tools/pc4learning

- Use it to explore core features:
  - Microenvironment
  - Cell definitions
  - Phenotype
    - Constant parameters for each cell type
    - Dynamical parameters (cell rules) currently requires C++
  - Run and explore



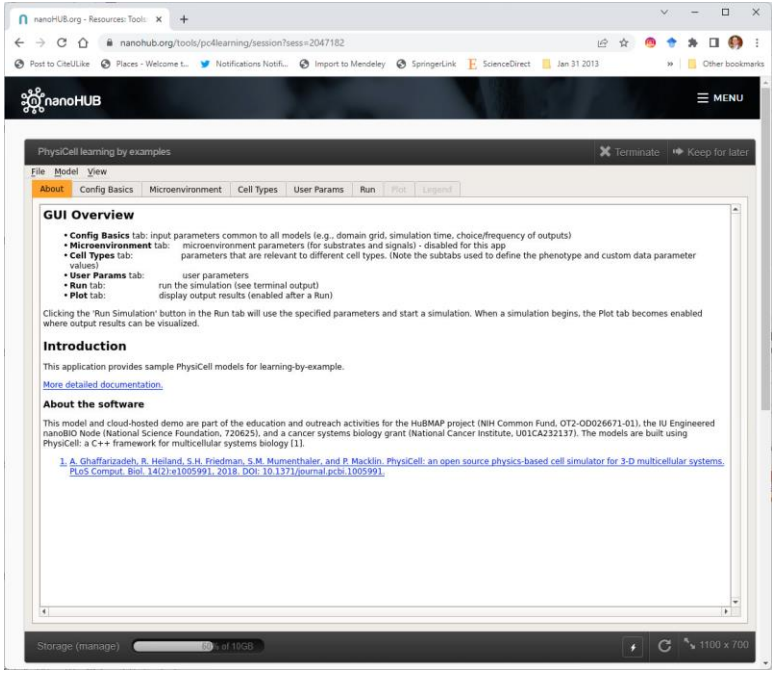
Start the online simulator

- Go to the tool on nanoHUB:
  - https://nanohub.org/tools/pc4learning
- Make sure you're logged on.
- Click the "launch tool" button



App navigation

- **Overview:**
  - basic overview
- **Config basics:**
  - Domain size, Simulation duration, Data output
- **Microenvironment:**
  - Define diffusing substrates and boundary conditions
- **Cell types:**
  - Define cell types, including their base phenotypes (behaviors)
- **User params:**
  - Model-specific parameters
- **Run:**
  - Start running in the cloud and view (virtual) console output
- **Plot:**
  - Plot the cells and diffusing substrates
- **Legend:**
  - Define the coloring of the plotted cell types



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