# Session 0: Introduction to Agent-Based Modeling and PhysiCell



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• @MathCancer

# PhysiCell Project

July 18, 2022





# **Course goals**

#### Workshop:

- Learn about agent-based modeling in biology
- Learn about key cell interactions in multicellular systems biology
- Learn to build and explore PhysiCell models

#### **Hackathon:**

- Form a new team and build one of:
  - A PhysiCell model of a multicellular system. OR
  - A PhysiCell tool that helps the community.
- Make new connections across the cancer modeling community
- Identify new leaders in the PhysiCell community



# **Session 0 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

- Diffusion limits
- Mechanical barriers





Multicellular systems biology seeks to *understand* these systems.

Multicellular systems engineering seeks to *control* them.

#### Multicellular cancer ecosystem



Source: Hanahan (2022)

**DOI**: <u>10.1158/2159-8290.CD-21-1059</u>

## How do we understand these multiscale systems?

#### Interconnected systems and processes:

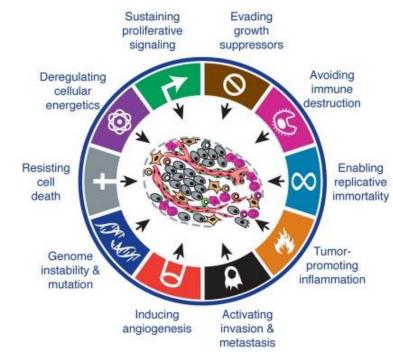
- Single-cell behaviors
- Cell-cell communication
- Physics-imposed constraints (e.g., diffusion)
- Systems of systems (e.g., immune system)
   In diseases, these systems become dysregulated.

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  $\rho$  modeled with exponential growth.

$$\frac{d\rho}{dt} = r\rho$$

- **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.

$$P[X(t + \Delta t) = n + 1 \mid X(t) = n] = r\Delta t$$

# 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**

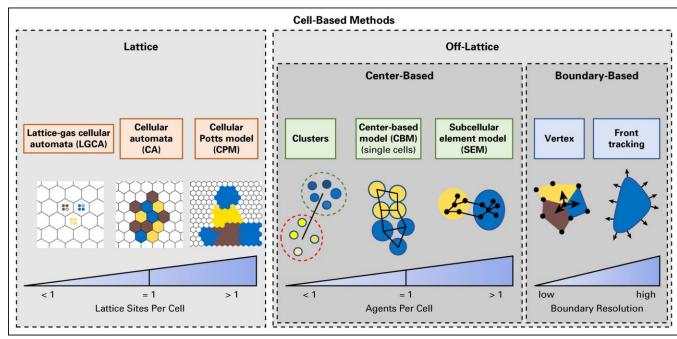
- Read parameters
- Set up microenvironment
  - Create meshes, initialize chemical substrates, diffusion solvers, etc.
- Set up cell agents
  - Define all cell types
  - Instantiate cells
- For each time:
  - Update microenvironment
    - ♦ Solve reaction-diffusion equations (as needed)
    - ♦ Solve 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

<u>Design goal:</u> Simulate multiple diffusing substrates in 3D with desktops or single HTC/HPC nodes

Typical use: pO<sub>2</sub>, glucose, metabolic waste, signaling factors, and a drug, on 10 mm<sup>3</sup> at 20 µm resolution

#### **Features:**

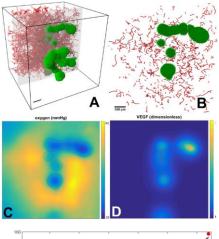
- · Off-lattice cell secretion and uptake
- 2<sup>nd</sup>-order accurate (space), 1<sup>st</sup>-order accurate (time), numerically stable

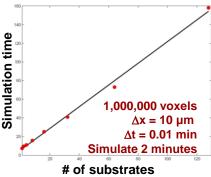
#### **Method:**

- 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<sup>6</sup> voxels

Reference: Ghaffarizadeh et al., Bioinformatics (2016)

DOI: 10.1093/bioinformatics/btv730





# PhysiCell: A multicellular framework

**Design goal**: Simulate 10<sup>6</sup> or more cells in 2D or 3D on desktops or single HPC nodes

#### Features:

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

#### Method:

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

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

DOI: 10.1371/journal.pcbi.1005991



Try this model yourself!

**2019 PLoS** 

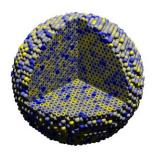
Computational Biology

Research Prize for

**Public Impact** 

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)]



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MathCancer.org

# 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 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)

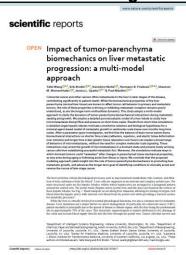
•  $\Delta t_{\text{cell}}$  phenotype and volume changes (default: 6 min)

• 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



# Example: liver parenchyma interactions in CRC micrometastases

Wang et al. Sci. Rep. (2021)

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





# 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

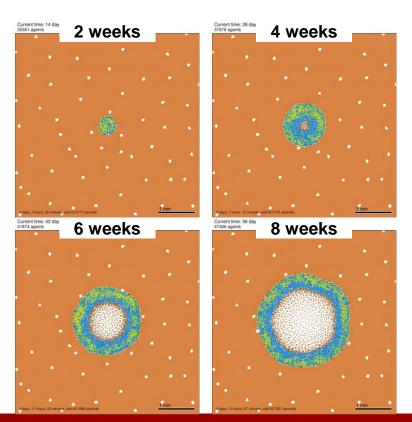
- Pressure (compression) down-regulates tumor cell proliferation
- Parenchyma agents use plastic-elastic model
  - ♦ Elastic restorative force on short time scales
  - Plastic reorganization on long time scales
  - ♦ Apoptosis under sustained deformation

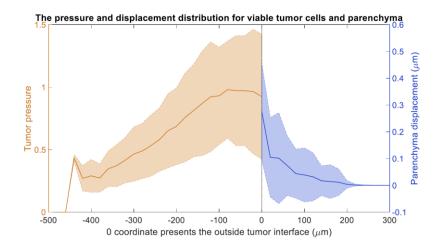
$$b = b_M \cdot \left(\frac{\sigma - \sigma_{\text{hypoxic}}}{\sigma_{\text{sat}} - \sigma_{\text{hypoxic}}}\right) \cdot \left(1 - \frac{p}{p_{\text{max}}}\right)$$

$$p = k \sum_{i} |\nabla \psi(x_i, x_j)|$$



## **Growth with feedback**







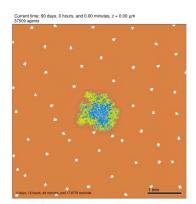
#### Try this model yourself!

nanohub.org/tools/pc4livermedium

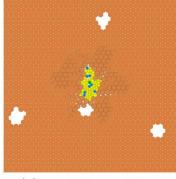
# **Tumor dormancy in some tissues**

#### If tissue has:

- large elastic force (large r<sub>F</sub>)
- slow plastic relaxation (small r<sub>P</sub>)
- tolerance of deformation (large d<sub>max</sub>)
- Then:
  - Compressed tissue surrounds tumor (encapsulation)
  - Most cells are pressurearrested, leading to tumor dormancy



(a)  $r_{\rm E}$ =0.2,  $r_{\rm P}$ =0.001,  $d_{\rm max}$ =1.5



(a)  $r_{\rm E}$ =0.2,  $r_{\rm P}$ =0.001,  $d_{\rm max}$ =3



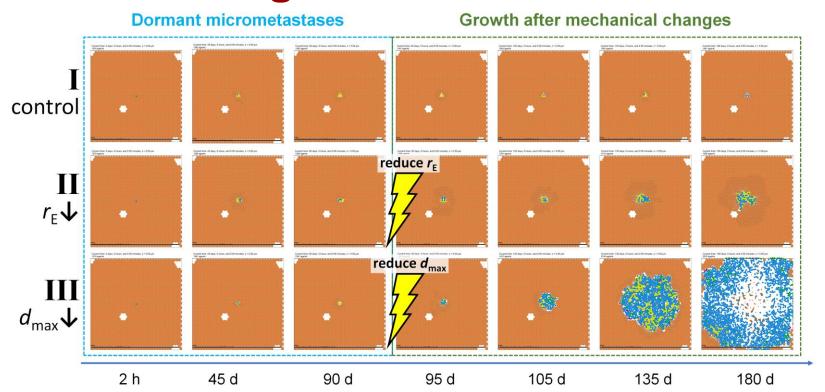
(b)  $r_{\rm E}$ =0.2,  $r_{\rm P}$ =0.0005,  $d_{\rm max}$ =3



Try this model yourself!

nanohub.org/tools/pc4livermedium

# Tissue changes can reawaken a tumor







Try this model yourself!

nanohub.org/tools/pc4livermedium



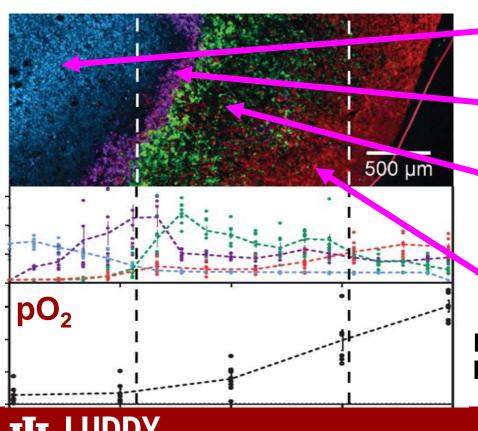
# Example: hypoxia-driven breast cancer invasion

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** 

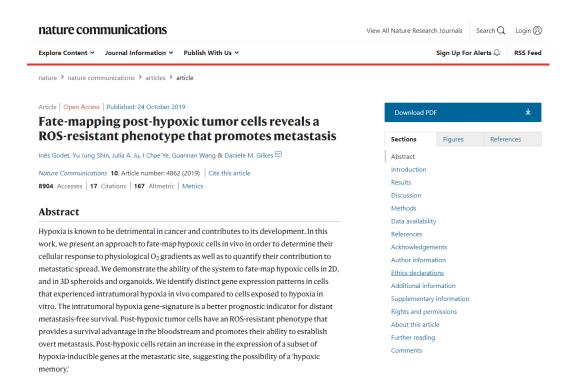
How do cancer cells behave after leaving hypoxic regions?

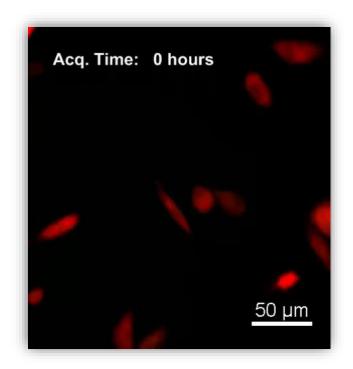


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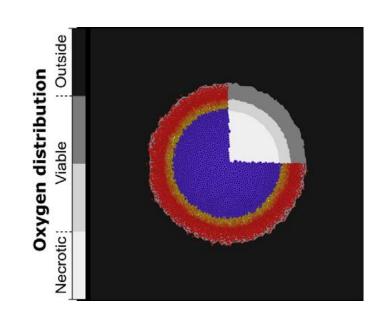
# Fate-mapping intratumoral hypoxia





#### **Model overview**

- Simulate oxygen diffusion and uptake
- Proliferation and necrosis vary with pO<sub>2</sub> and pressure
- Live cells are normoxic (RFP) or hypoxic (GFP)
- Model transition from RFP to GFP via ODEs
- GFP cells migrate up pO<sub>2</sub> gradients
  - Phenotypic persistence: How long GFP cells keep their migratory behavior after leaving hypoxic regions



## Phenotypic persistence drives invasion

#### **Phenotypic Persistence:**

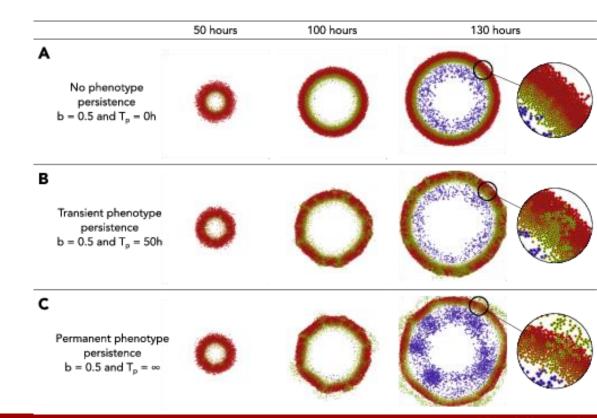
•  $T_p$ : duration of hypoxic response

#### 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

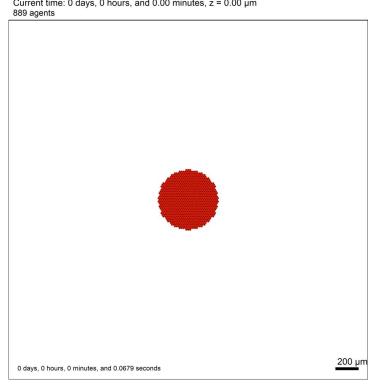
- Hypoxic cells can continue migrating
- Hypoxic cells "punch through" the oxygenated tumor region

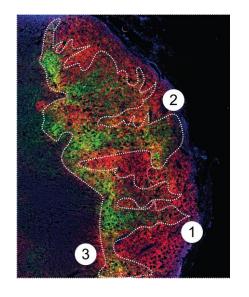


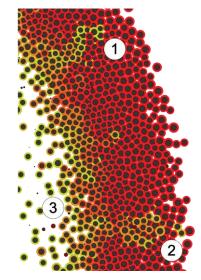


## Mathematical model explains biological observations

Current time: 0 days, 0 hours, and 0.00 minutes,  $z = 0.00 \mu m$ 



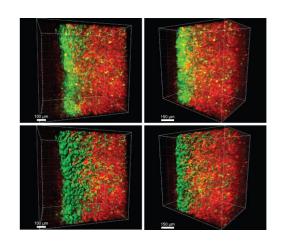


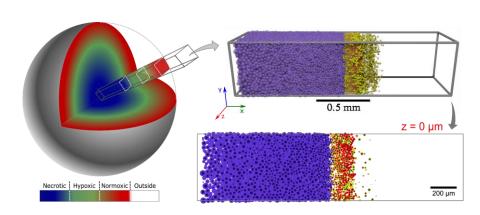




Try this model yourself! nanohub.org/tools/pc4tumorhypoxia

#### It also works in 3D

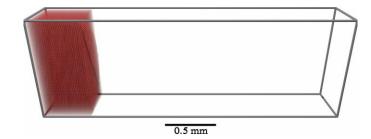






#### Try this model yourself!

nanohub.org/tools/pc4tumorhypoxia



## Work led by: **Michael Getz**

# Iterative community-driven development of a SARS-Cov-2 tissue simulation of the Community-driven development of a SARS-Cov-2 tissue simulation of the Community-driven development of a SARS-Cov-2 tissue simulation of the Community-driven development of the SARS-Cov-2 tissue simulation of the Community-driven development of the SARS-Cov-2 tissue simulation of the Community-driven development developme

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# **Example: SARS-CoV-2**

Getz et al. bioRxiv (2021)

Open Access: <a href="https://doi.org/10.1101/2020.04.02.019075">https://doi.org/10.1101/2020.04.02.019075</a>



# 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

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# Rapid community-driven development of a SARS-CoV-2 tissue simulator

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

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

#### 40+ regular contributors from 20+ institutions



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 cell interactions

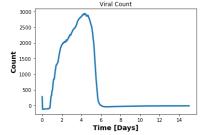
- CD8+ T cell attacks
  - While T cell is in contact with infected cell, increase damage by  $r_{\rm damage} \Delta t$
  - Infected cell has death rate that increases with damage

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

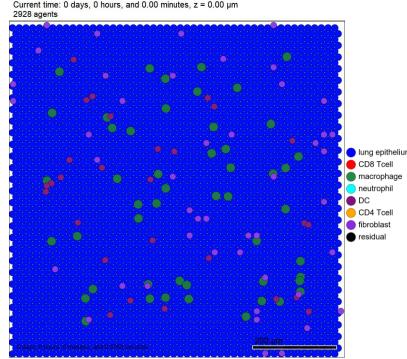
- Macrophages
  - When in contact with a dead cell, phagocytose it with probability  $r_{
    m phago}\Delta t$
  - Acquire volume phagocytosed cell
  - Ingesting infected cell causes secretion of pro-inflammatory signals

# 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

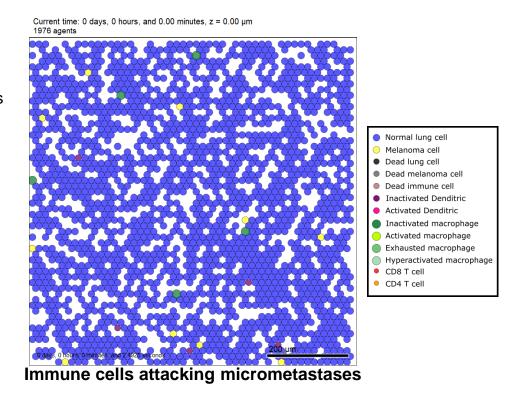


A naïve immune system can adapt to halt the infection



# (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.

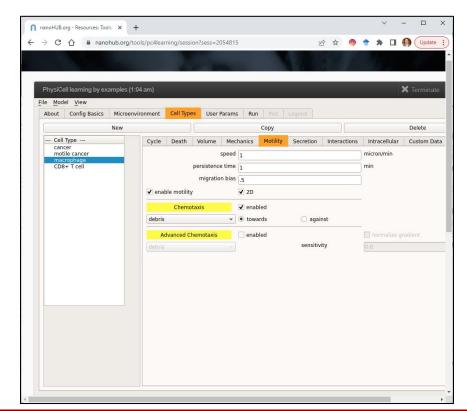


# pc4learning: an interactive testbed

 Free online PhysiCell simulator hosted on nanoHUB

https://nanohub.org/tools/pc4learning

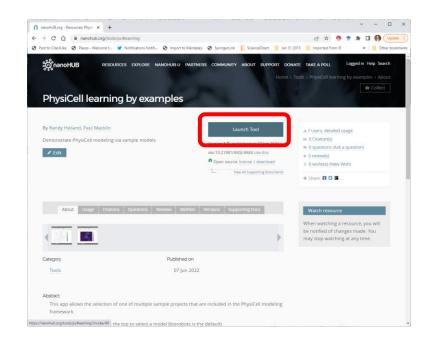
- Use it to explore core features:
  - Microenvironment
  - Cell definitions
  - Phenotype
    - ♦ Constant parameters for each cell type
    - ◆ Dynamical parameters (cell rules) currently requires C++
  - Run and explore



### 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:

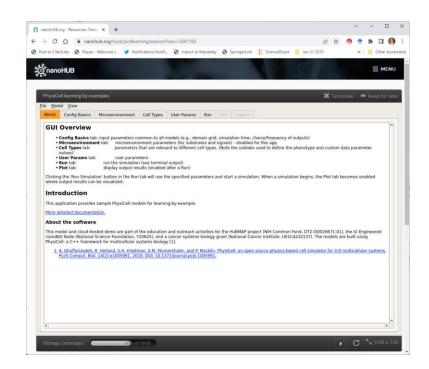
Start running in the cloud and view (virtual) console output

#### Plot:

Plot the cells and diffusing substrates

#### Legend:

Define the coloring of the plotted cell types



### What's new in 2022?

- Streamlined course materials
- New built-in cell interactions
  - phagocytosis, transformation, attack, fusion
- New dictionaries to make modeling faster and easier than ever!
- Better integration of PhysiBoSS and libRoadrunner
  - Full tutorial sessions are part of this year's course
- Community-supported 3D visualization
  - New tutorials integrated in the course!

https://github.com/PhysiCell-Training/ws2022



# **Funding Acknowledgements**











#### **PhysiCell Development:**

- Breast Cancer Research Foundation
- Jayne Koskinas Ted Giovanis Foundation for Health and Policy
- National Cancer Institute (U01CA232137)
- National Science Foundation (1720625, 1818187)

#### **Training Materials:**

Administrative supplement to NCI U01CA232137 (Year 2)

#### Other Funding:

- NCI / DOE / Frederick National Lab for Cancer Research (21X126F)
- DOD / Defense Threat Reduction Agency (HDTRA12110015)
- NIH Common Fund (3OT2OD026671-01S4)



