

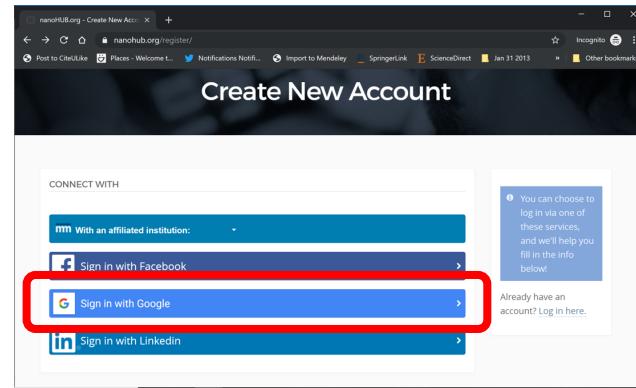
nanoHUB Account

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

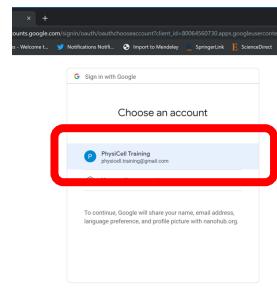
• Steps:

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.

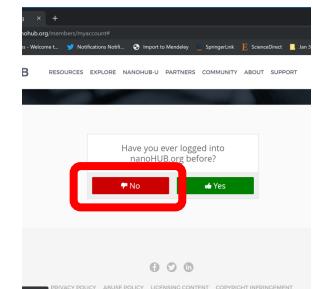
2



3



4



Computational Models of Immune Dynamics

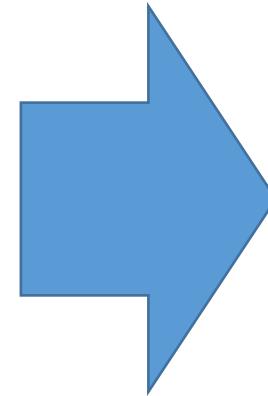
Paul Macklin, Ph.D.

Intelligent Systems Engineering
Indiana University

July 11, 2022

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



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

Source: Hanahan (2022)
DOI: [10.1158/2159-8290.CD-21-1059](https://doi.org/10.1158/2159-8290.CD-21-1059)

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

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

Key parts of a multicellular virtual laboratory

- **Model multiple diffusing chemical factors**
 - Growth substrates and metabolites
 - Signaling factors
 - Drugs and therapeutic compounds
- **Model many cells in these chemical environments**
 - Environment-dependent behavior (including molecular-scale "logic")
 - Mechanical interactions
 - Heterogeneity:
 - ◆ individual states
 - ◆ individual parameter values
 - ◆ individual biological rules
- **Explore the models in high throughput**
 - Discover the rules that best match observations.
 - Identify and exploit weaknesses that can steer the system and restore control

BioFVM: Simulating 3-D biotransport

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

Typical use: pO_2 , glucose, metabolic waste, signaling factors, and a drug, on 10 mm^3 at $20 \mu\text{m}$ resolution

Features:

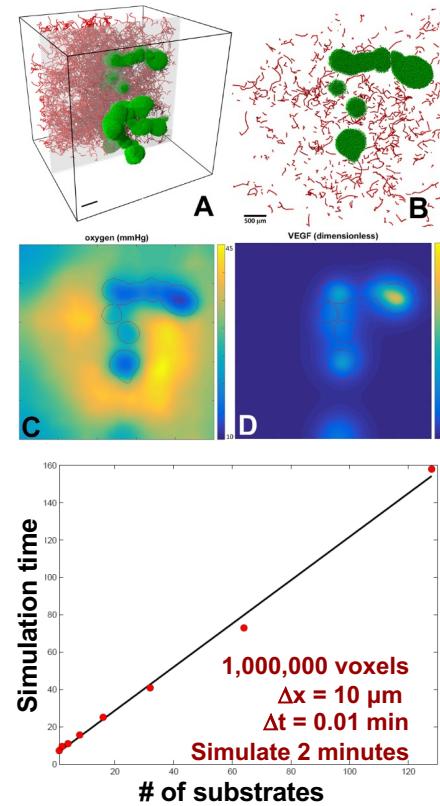
- Off-lattice cell secretion and uptake
- 2nd-order accurate (space), 1st-order accurate (time), numerically stable

Method:

- Operator splitting, LOD, customized Thomas solvers, etc.
- Standard C++11, cross-platform
- OpenMP parallelization
- $O(n)$ cost scaling in # substrates, # voxels
- Easy to simulate 5-10 substrates on 10^6 voxels

Reference: Ghaffarizadeh et al., *Bioinformatics* (2016)

DOI: [10.1093/bioinformatics/btv730](https://doi.org/10.1093/bioinformatics/btv730)



PhysiCell: A multicellular framework

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

Features:

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

Method:

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

Reference: Ghaffarizadeh et al.,

PLoS Comput. Biol. (2018)

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

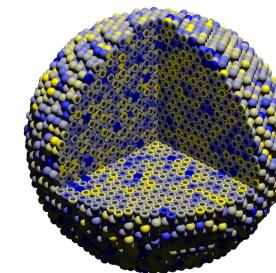


Try this model yourself!

nanohub.org/tools/pc4heterogen

2019 PLoS
Computational Biology
Research Prize for
Public Impact

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



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

Example: 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; blue are least immunogenic

Immune cells (red):

- Biased random walk towards tumor
- Test for contact with cells and adhere
- Attempt to induce apoptosis
 - success depends on immunogenicity
- Eventually detach from cell, continue search

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

References:

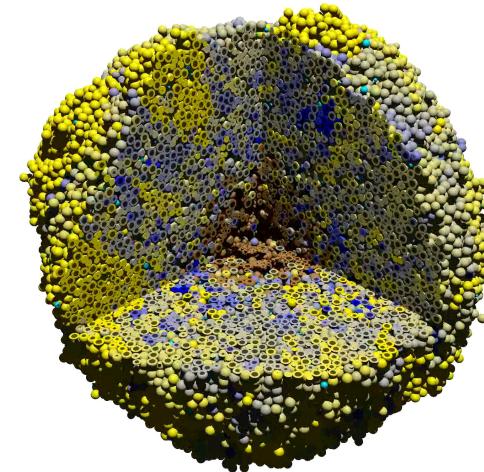
- [Ghaffarizadeh et al. \(2018\)](#)
- [Ozik et al. \(2018\)](#)
- [Ozik et al. \(2019\)](#)



Try this model yourself! (2D)

nanohub.org/tools/pc4cancerimmune

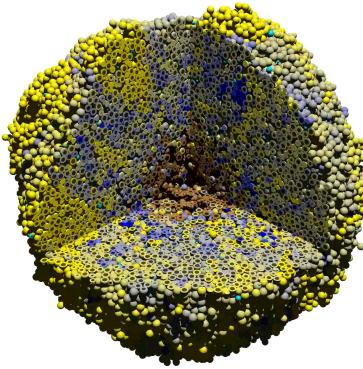
Current time: 13 days, 0 hours, and 0.00 minutes
95309 agents



High-throughput investigations on HPC

3-D tumor-immune model

Current time: 13 days, 0 hours, and 0.00 minutes
95309 agents

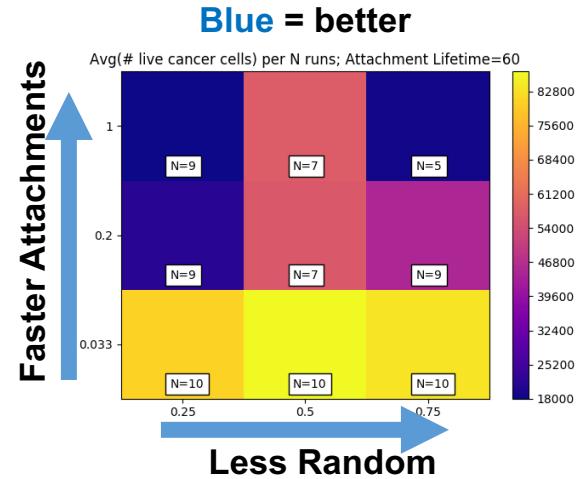


Explore 3 parameters:

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

HTC is the only feasible path

ANL: Do all 270 runs over a weekend

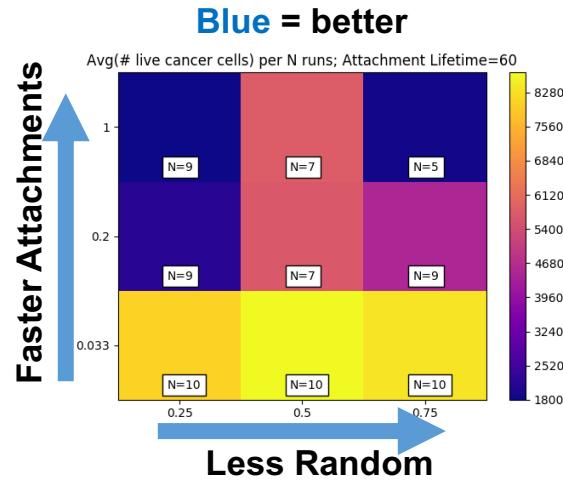


Reference:

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

Lessons from physical interactions (1)

- If interactions start / stop slowly, even perfect T cells aren't effective.
- **Good strategy #1:**
Direct "swarming" from one attractive target to the next with fast kills.
- **Good strategy #2:**
Random migration to increase cell mixing.
- Intermediate strategies aren't as good



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

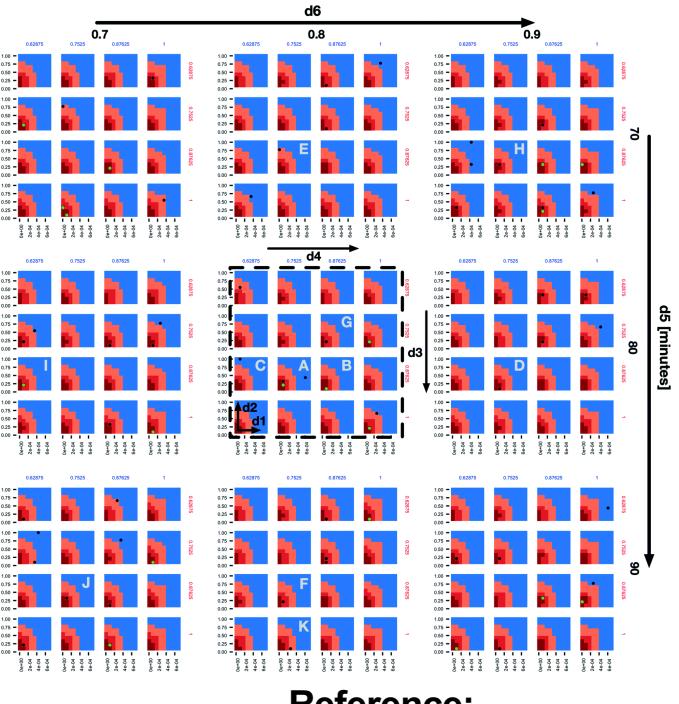
- For each design scenario (e.g., control), build a binary DT classifier:
 - **True**: points that meet the design goal (e.g., $N_{\text{final}} \leq N_{\text{start}}$)
 - **False**: points that don't meet the design goal (e.g., $N_{\text{final}} > N_{\text{start}}$)
- **Run** 1000 simulations at a time 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. \(2019\)](#)

Lessons from physical interactions (2)

- Most important parameters:
 - How many kills before a cell wears out or inactivates?
 - How easily can an immune cell recognize a cancer cell?
- Best responses were often on the EDGES of the design space:
 - Edges are biological & clinical constraints
 - ◆ Biological: How fast can a cell move? How fast can it kill?
 - ◆ Clinical: How much non-specificity can the patient handle?
- 100% elimination may be a fragile strategy:
 - Design space shrinks rapidly as we move from 90% kill to 99% kill
 - Long-term control may be a more robust strategy

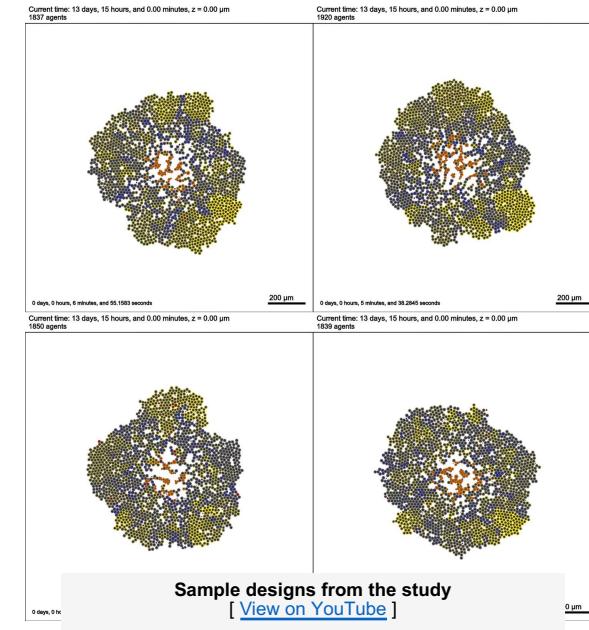


Reference:
[Ozik et al. \(2019\)](#)

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



Sample designs from the study
[[View on YouTube](#)]



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

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

Example: Iterative development of a SARS- CoV-2 tissue model

Thank you to our coalition!

Multinational:
U.S.
Canada
United Kingdom

Federal partners:
Veterans Affairs
Argonne National Lab

Across Indiana:
Luddy School (lead)
UITs
IU Health
Purdue

Industry:
Pfizer

...

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

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

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



Yafei Wang
Indiana U.



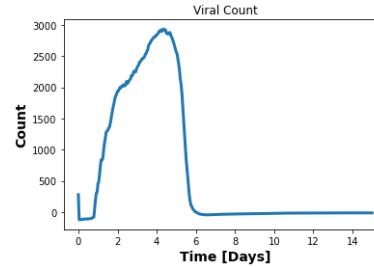
Iterative progress

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

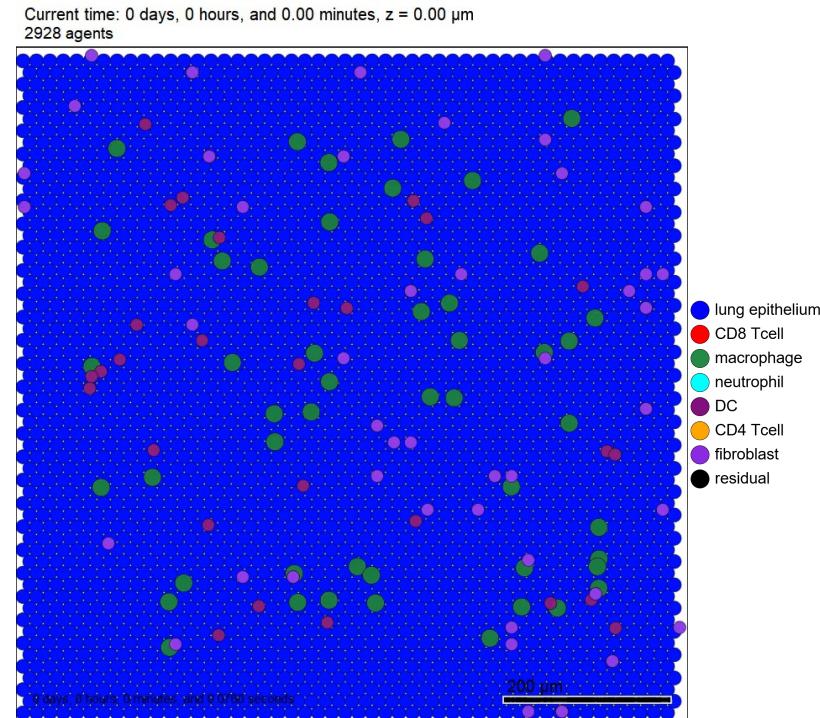
v5: neutralizing antibodies clear the infection

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

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



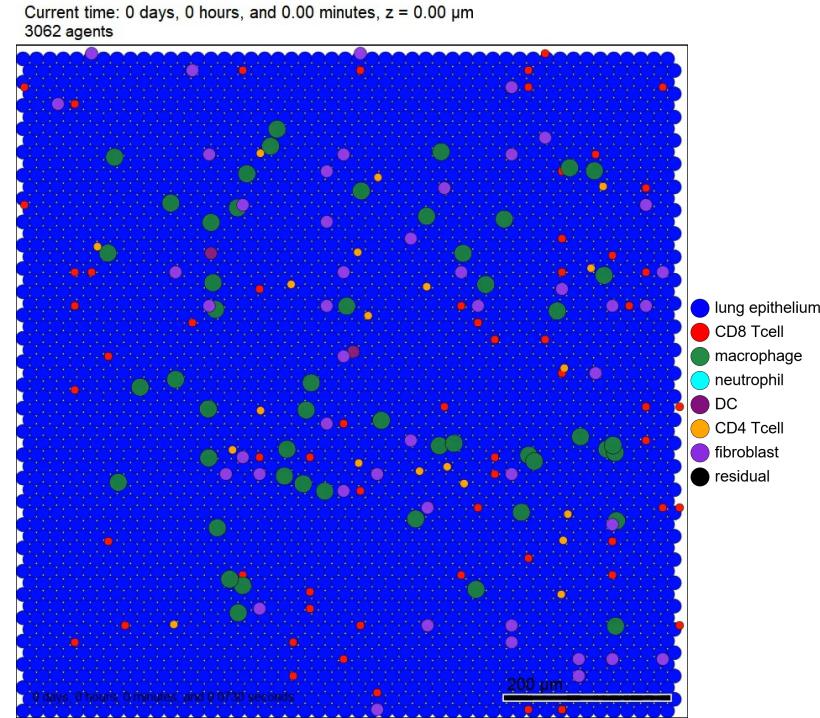
- **This immune model is sufficiently complete to clear a SARS-CoV-2 infection**



A naïve immune system can adapt to halt the infection

v5: prior immune responses are protective

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



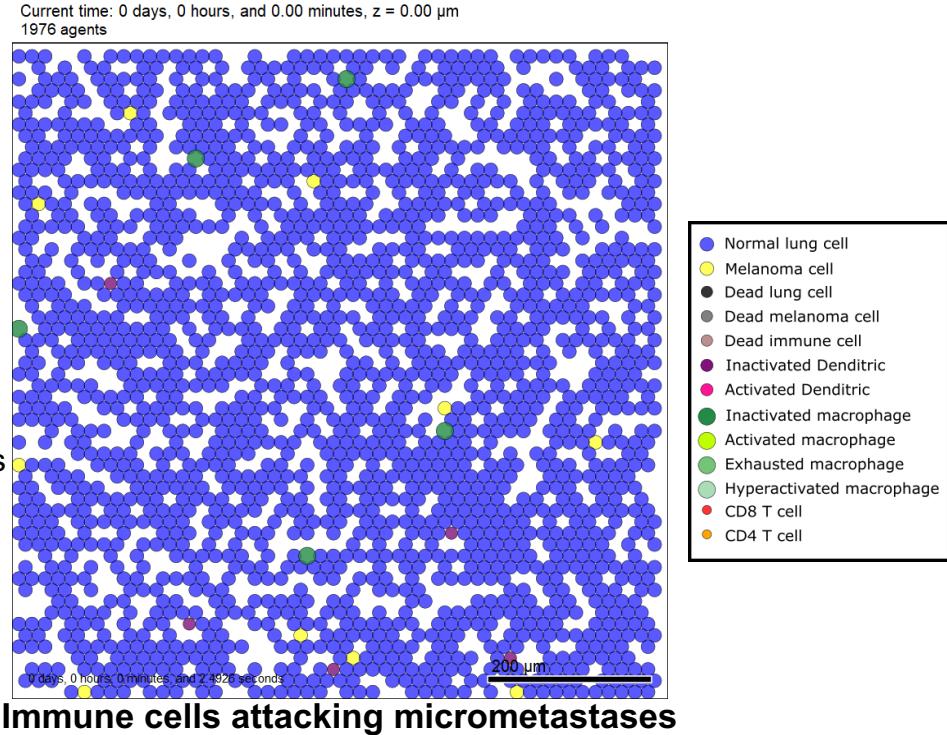
Trained immune system facing future exposure

Some lessons

- Interferon response as first-line defense until the cavalry arrives
- Iterative process often reveals missing hypotheses
 - **Example:** macrophages:
 - ◆ Macrophages acquire the cell's contents and grow
 - ◆ To avoid reaching ridiculous sizes, need one of these:
 - (1) very fast "digestion" of phagocytosed contents, OR
 - (2) a "cool down" period or pause once too big, OR
 - (3) fast wear out after phagocytosing too much
 - **Example:** autoimmune-like behavior
 - ◆ If phagocytosing *any* dead-cell triggers pro-inflammatory secretion, then need:
 - (1) only trigger secretion if cell has viral proteins OR
 - (2) only slow secretion, so need to encounter many dead cells to trigger inflammation
- Far more knowledge on how the immune system ramps up
 - Harder to find knowledge on how it winds down after eliminating the infection

(Re)adapting to cancer

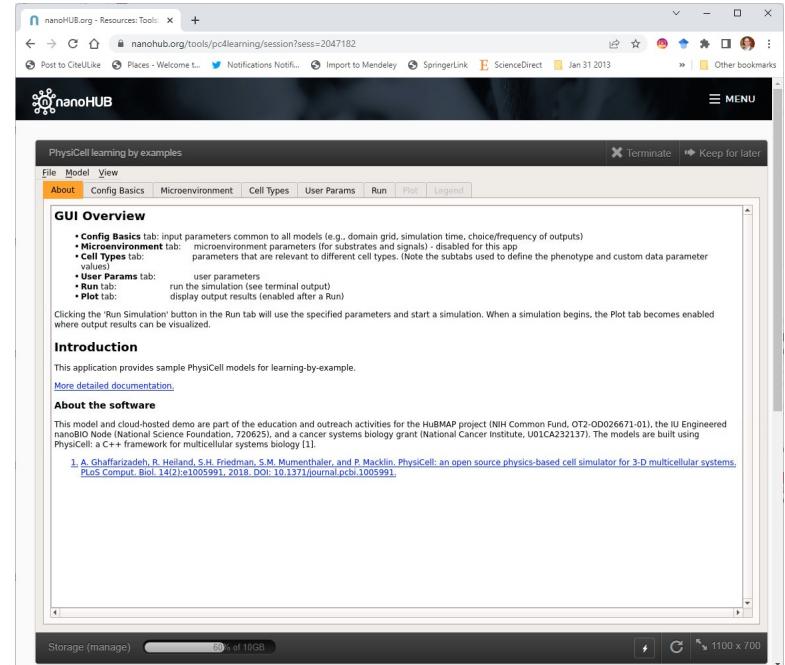
- Adapt and reuse:
 - Tumor growth model
 - Local immune dynamics:
 - ◆ Focused on macrophages, dendritic cells, CD4+ & CD8+ T cells
 - Immune cell trafficking
 - Lymph node T cell expansion
- Value of modular immune models:
 - Advances in one project help all the others
 - ◆ First cancer immune projects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



(Almost) live demo

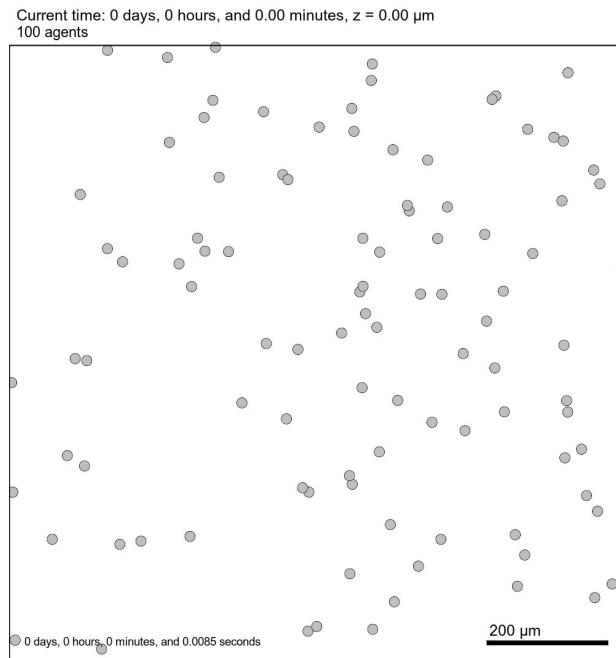
Real-time immune modeling

- Let's build a simple immune model in real time
- **Bacteria:**
 - Cycle, apoptosis, secrete quorum factor
 - Random motility towards quorum factor
- **Macrophages:**
 - Attracted to bacteria
 - Phagocytose dead cells
 - Secrete pro-inflammatory factor (e.g., IL-6)
- **Neutrophils:**
 - Attracted to pro-inflammatory factor
 - Phagocytose live bacteria

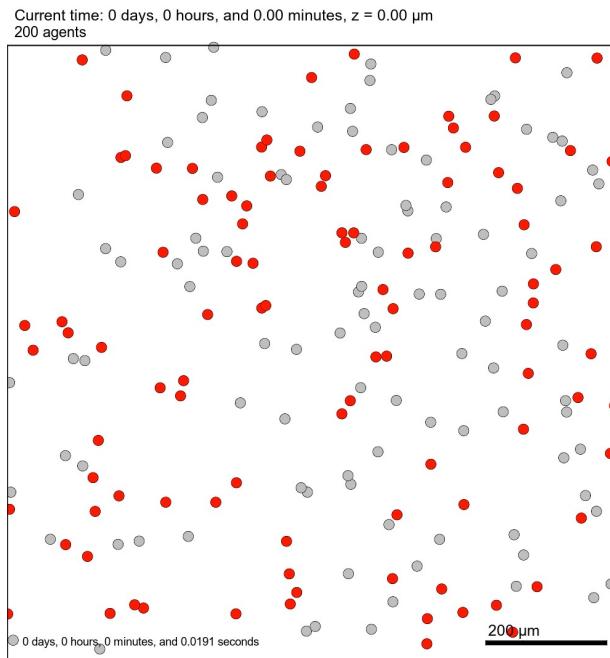


Iterative results: Walk-through takes ~15 min

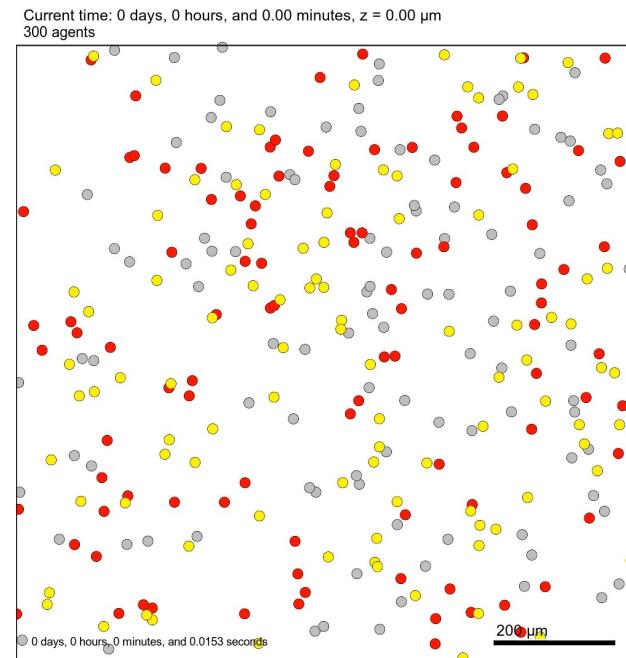
v1: bacteria only



v2: +macrophages



v3: +neutrophils



See full walk-through here!

https://github.com/physicell-training/GRC_immunoengineering_2022



Ongoing work and Opportunities

Problems with hand-coded models

- As (hand-coded) model complexity grows:
 - Harder to understand the full model
 - Harder to clearly communicate the current biological hypotheses
 - Harder for domain experts to participate in real time
- **Goal:** Create a formal language for cell rules that:
 - Can be written in human-readable "plain English"
 - ◆ Facilitates tools for easy model construction
 - ◆ *Turns model building into knowledge mapping*
 - Can readily be "translated" to a standard mathematical form
 - ◆ Model can parse the rules without hand-coding
 - ◆ More reusable, maintainable model

Example: chemokine-driven cycling

- Biological hypothesis statement: INFG promotes cell cycling
- Rule: INFG increases cell cycle entry
- Mathematical translation:

$$r_{\text{cycle}} = r_0 + (10r_0 - r_0) \frac{[\text{INF}G]^{1.5}}{0.1^{1.5} + [\text{INF}G]^{1.5}}$$

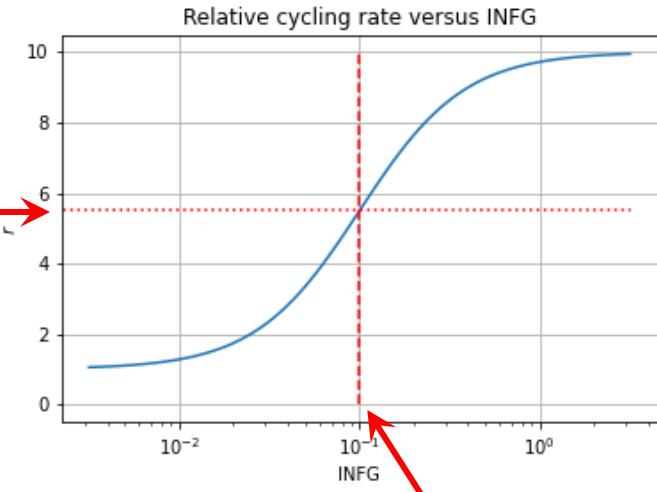
- Refined rule (with parameters):

▪ Hill response function	
▪ Hill power:	1.5
▪ half-max:	0.1
▪ base value:	r_0
▪ tenfold max response:	$r_U = 10 r_0$

- XML markup:

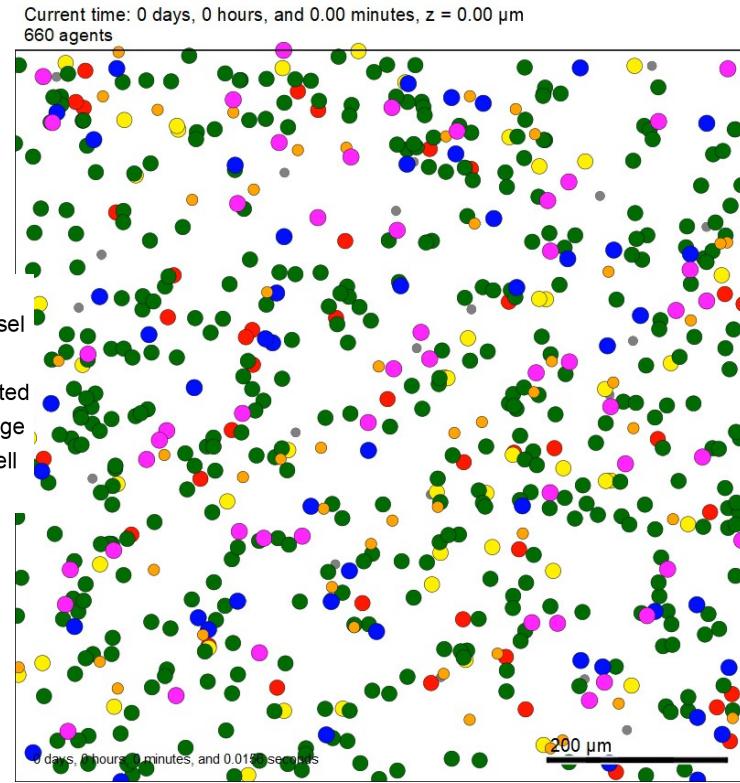
```
<rule>
  <signal name="INFG"/>
  <behavior name="cycle entry"/>
  <response type="increase" form="hill">
    <max_response type="relative">10</max_response>
    <hill_power>1.5</hill_power>
    <half_max>0.1</half_max>
  </response>
</rule>
```

Half of max response



Example: Tissue versus virulent bacteria

- Stem cells
 - Divide, differentiate
 - Killed by toxin
- Differentiated cells
 - Divide
 - Killed by toxin
- Blood vessels
 - Release resource
- Bacteria
 - Colonize near resources (via quorum)
 - Release toxin
 - Killed by damage
- Macrophages
 - Phagocytose dead cells
 - Release pro-inflammatory factor
- CD8+ T cells
 - Attracted to pro-inflammatory factor
 - Damage bacteria
- Neutrophils
 - Attracted to pro-inflammatory factor
 - Phagocytose bacteria



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

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

GOAL: accumulate and curate *knowledge!*

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

PhysiCell 2022 Virtual Workshop

- July 24-30, 2022
- Fully virtual
- **Tutorial sessions open to general public**
- Competitive selection for mentored hackathon



**2022 Virtual PhysiCell
Workshop and
Hackathon**
July 24-30, 2022



- Build and explore multicellular agent-based simulations of cancer and other systems
- Learn to share your models online
- Meet other modelers in the CSBC / PS-ON community
- Compete in an exclusive mentored hackathon
- PhysiCell swag for accepted participants
- Application and full agenda at QR code or:
<https://github.com/PhysiCell-Training/ws2022>

