

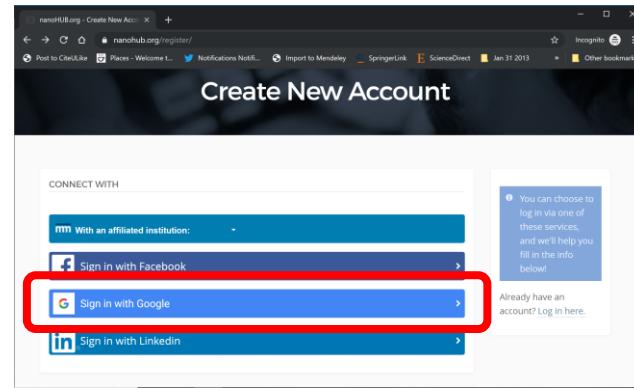
nanoHUB Account

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

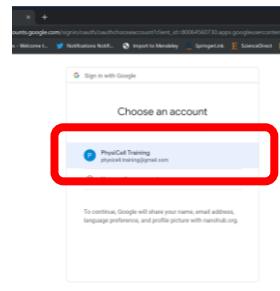
Steps:

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 nanoHIB account)
5. Finish filling in details, and you're done!
6. Use your google account to sign in in the future.

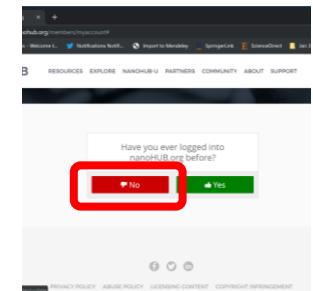
2



3



4



Introduction to agent-based modeling in biology: Part 2 (Python-based)

Lecture materials and code are available at:



Paul Macklin, Ph.D

Intelligent Systems Engineering
Indiana University

February 18, 2021

Last time

- Introduced multicellular systems biology
 - Many cells interacting in a chemical environment
 - Virtual "laboratory" must simulate both cells and environment
- Agent-based models simulate individual cells as software objects
- We built a basic agent-based model in Python
 - What's a software class?
 - Environment class with diffusion/decay
 - Cell class with basic mechanics, birth/death, and environment coupling

**Today, we explore a more
established agent-based
model framework.**

Simulation toolbox

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:

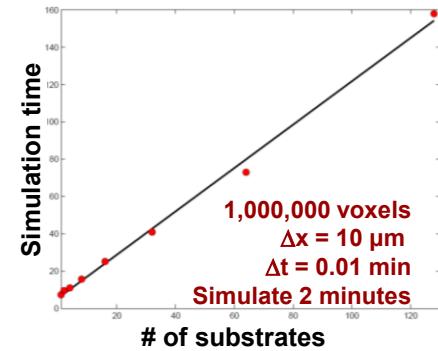
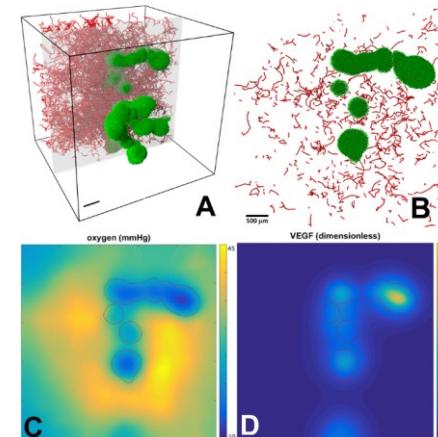
- Off-lattice cell secretion and uptake
- 2nd-order accurate (space), 1st-order accurate (time), numerically stable

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:

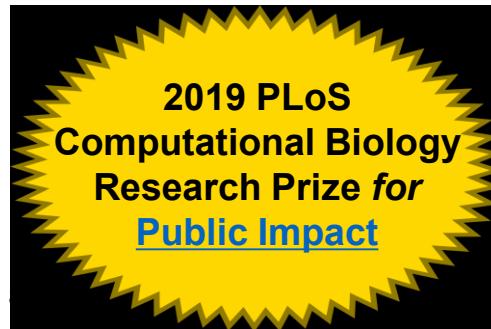
- Off-lattice cell positions
- Mechanics-based cell movement
- Cell processes (cycling, motility, ...)
- Signal-dependent phenotype
- Can dynamically attach custom data functions on a cell-by-cell basis
- **Deployed from Raspberry Pi to Crays**

Method:

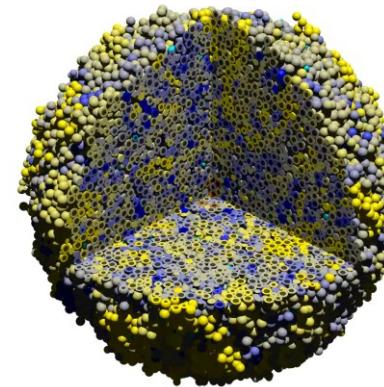
- Standard C++11, cross-platform
- OpenMP parallelization
- $O(n)$ cost scaling in # cells

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



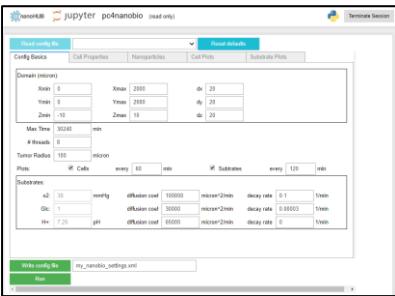
Try this model yourself!

nanohub.org/tools/pc4heterogen

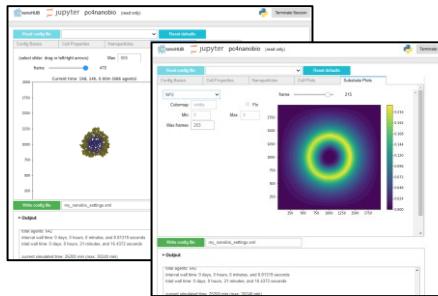
Competition in a 3-D tumor
[View on YouTube](#) (8K)

Jupyter-based GUIs

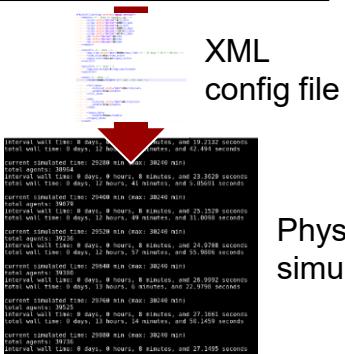
Goal: Make PhysiCell-powered simulators user-friendly, shareable, and available without installing / compiling.



GUI:
settings
Jupyter
notebook



GUI:
output
Jupyter
notebook



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!"

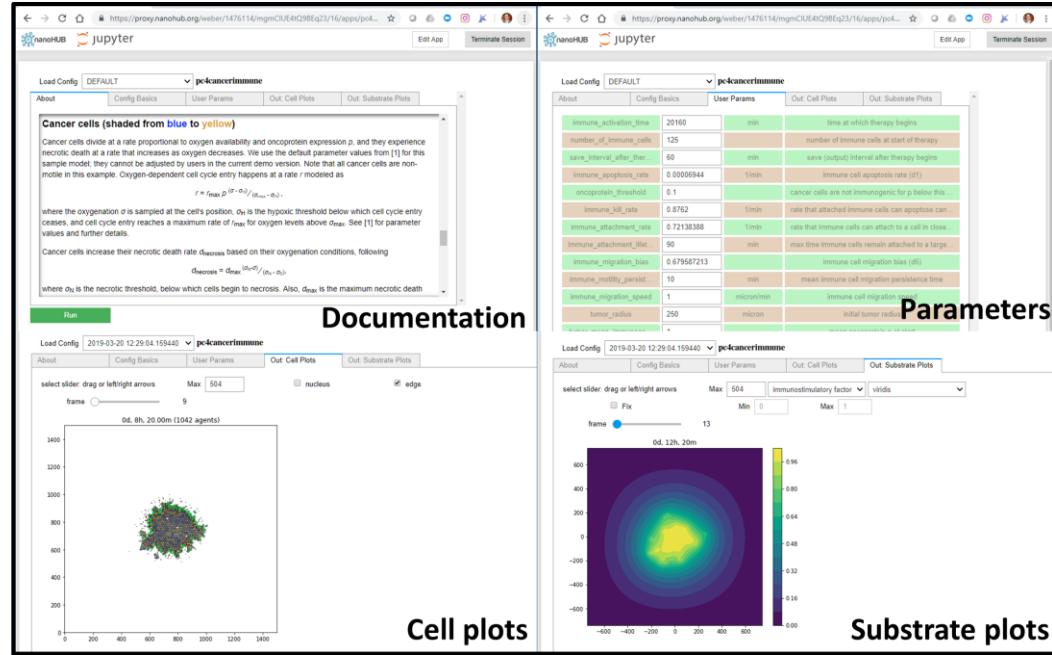
- With xml2jupyter, we can automatically create a Jupyter-based GUI for a PhysiCell model, and host it on nanoHUB as an interactive model.
- The apps can easily be **included in talks, posters, and presentations.**
- We include **publication companion apps** in every paper to help readers explore and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

This should be standard practice.



Try this model yourself! (2D)

nanohub.org/tools/pc4cancerimmune

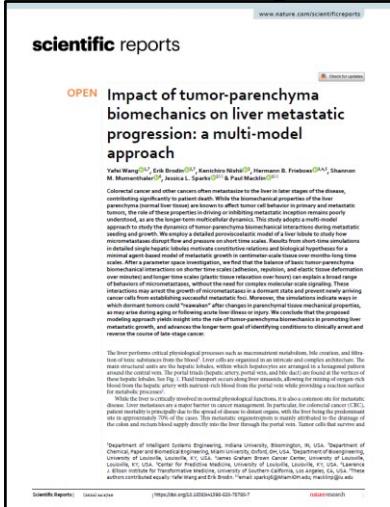


Detailed examples

Work led by:
Yafei Wang

Example 1:

liver parenchyma interactions in CRC micrometastases



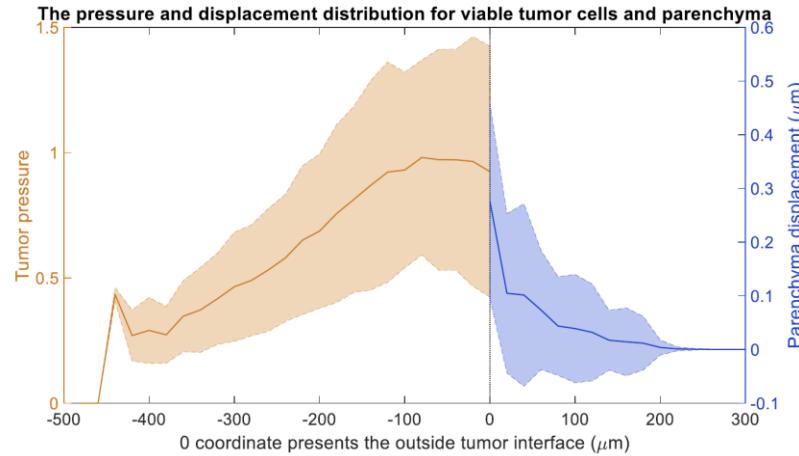
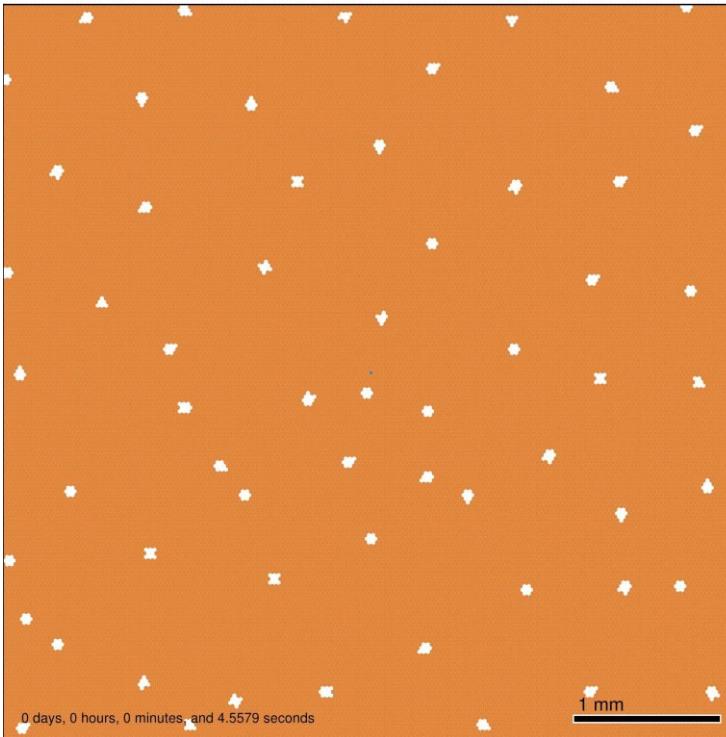
Wang et al. *Sci. Rep.* (2021)
Open Access: <https://doi.org/10.1038/s41598-020-78780-7>

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

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

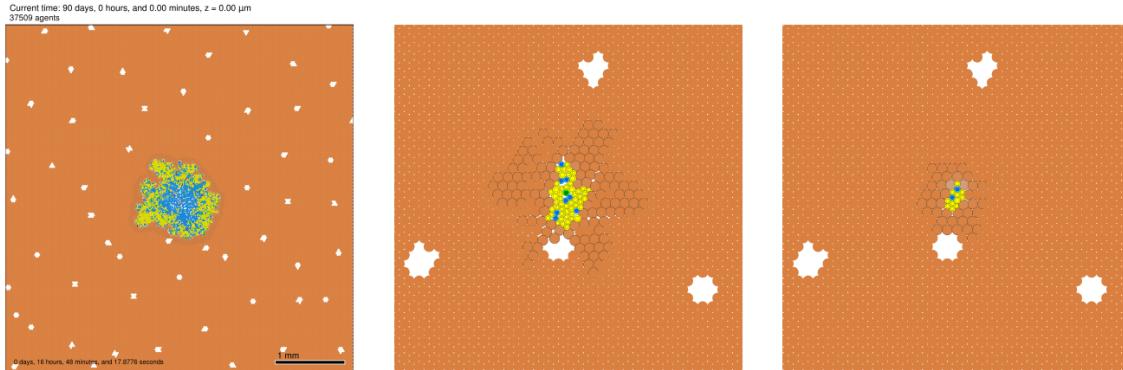


Try this model yourself!

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

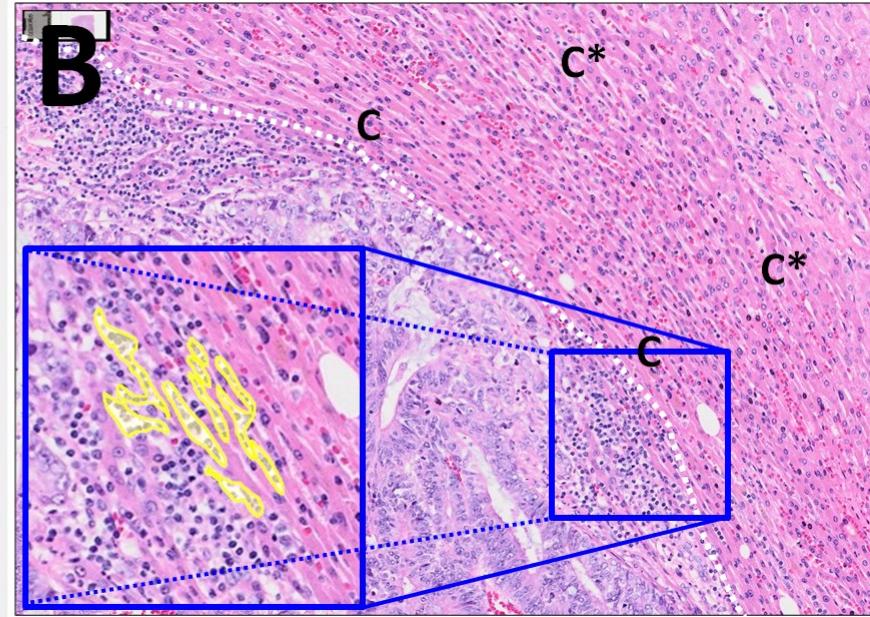
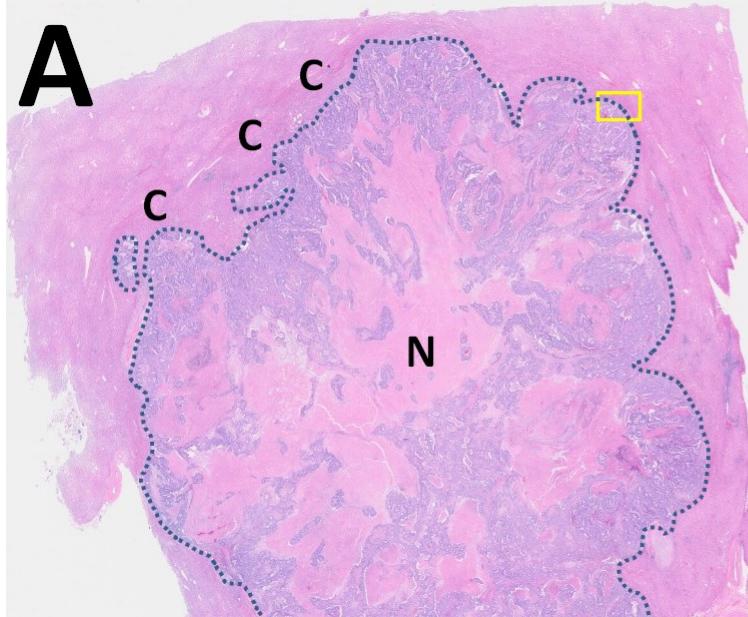
(b) $r_E=0.2$, $r_P=0.0005$,
 $d_{\max}=3$



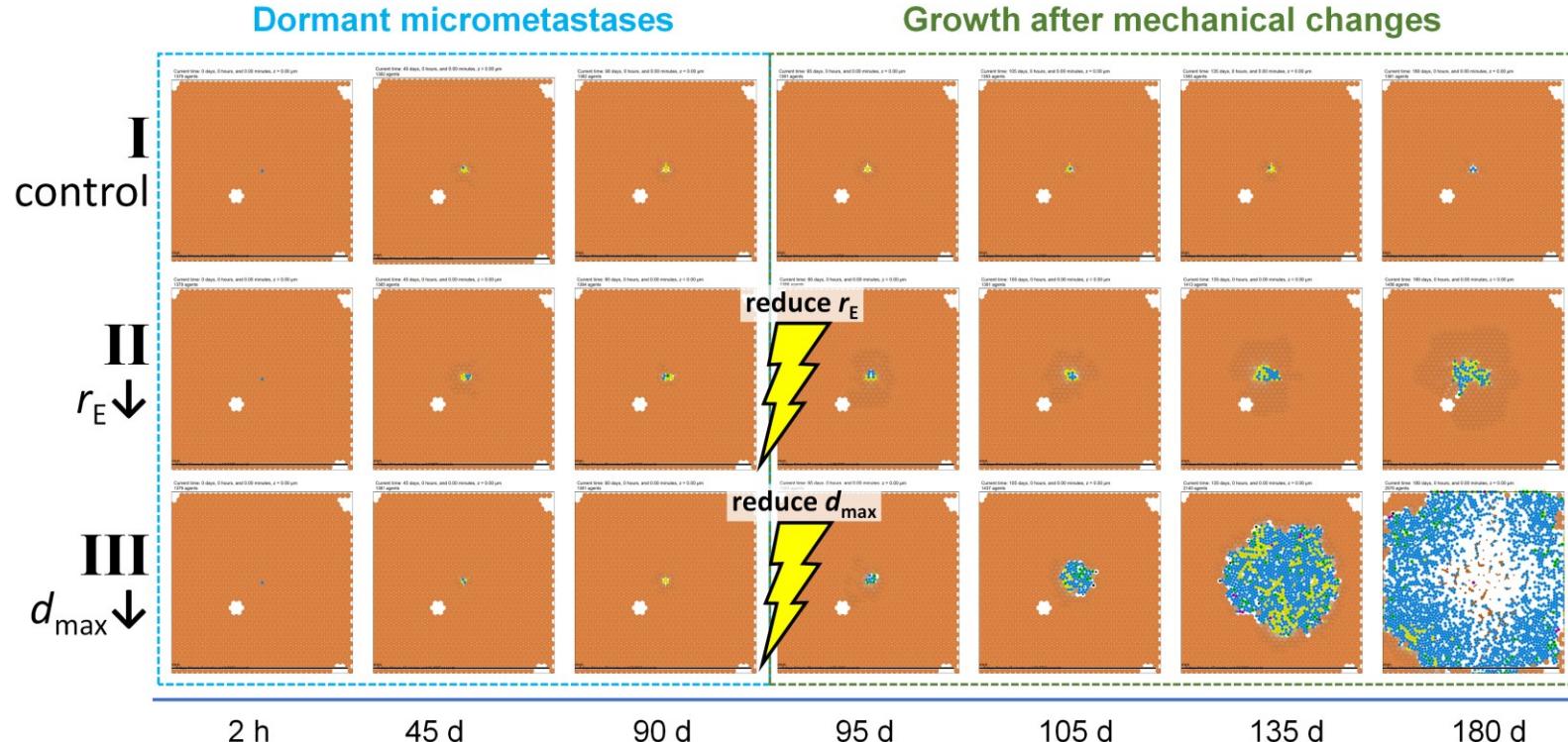
Try this model yourself!

nanohub.org/tools/pc4livermedium

Comparison with a typical clinical sample



Tissue changes can reawaken a tumor



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SCHOOL OF INFORMATICS, UIUC



Try this model yourself!

nanohub.org/tools/pc4livermedium

Macklin Lab
Twitter: @MathCancer
MathCancer.org

Example 2:

Cancer-immune contact interactions

Simple model of cancer-immune interactions

Heterogeneous tumor cells (blue to yellow):

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

Immune cells (red):

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

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

References:

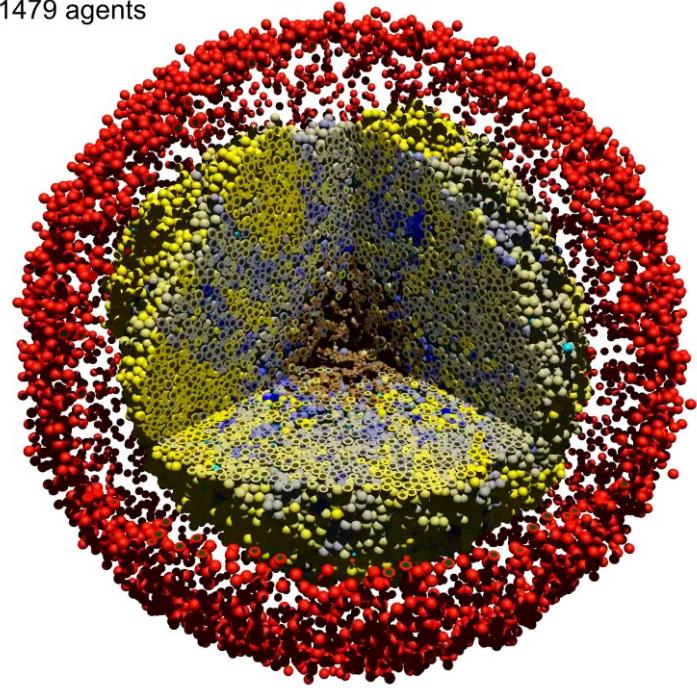
- [Ghaffarizadeh et al. \(2018\)](#)
- [Ozik et al. \(2018\)](#)
- [Ozik et al. \(2019\)](#)



Try this model yourself! (2D)

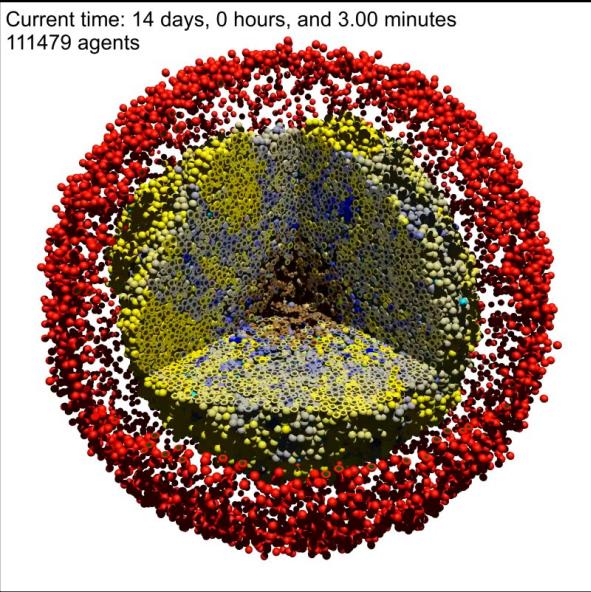
nanohub.org/tools/pc4cancerimmune

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



High-throughput investigations on HPC

3-D tumor-immune model

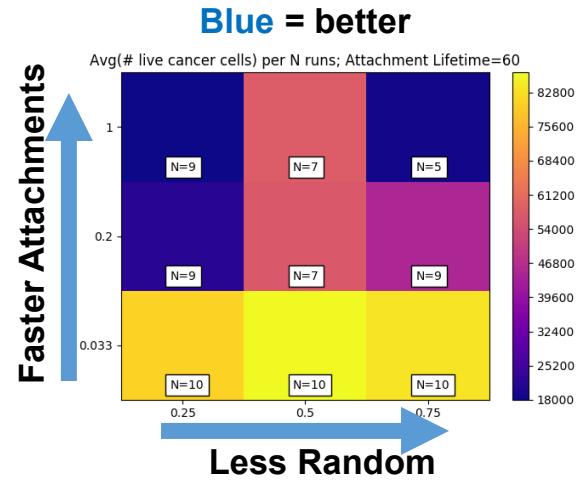


Explore 3 parameters:

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

HTC is the only feasible path

ANL: Do all 270 runs over a weekend



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

Higher-dimensional design spaces

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

Cancer control

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

Cancer remission

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

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

Treatment optimization:

4) Can we minimize N_{final} ?

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

Using active learning

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

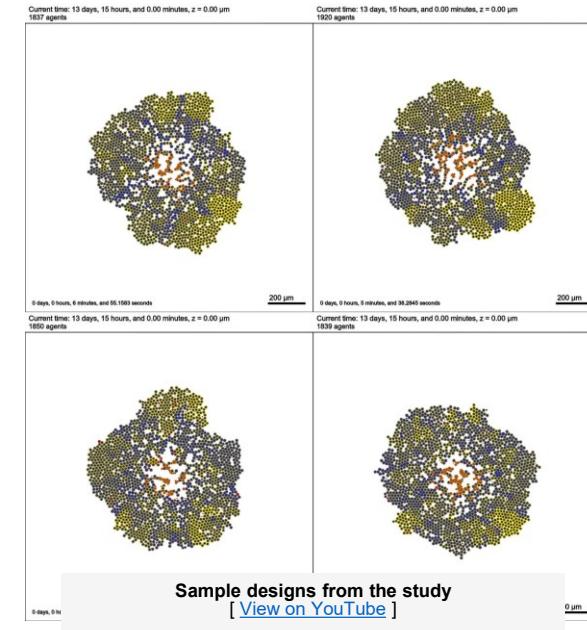
Reference:

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

How does HPC+ML enable new science?

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

Machine learning helps us interpret the agent-based model results



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

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

Example 3:

**Rapid 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^{11,*}, 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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² The University of Vermont Medical Center, Burlington, VT USA

40+ regular contributors from 20+ institutions

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¹⁴ Citzit, Inc., Pittsburgh, PA USA

¹⁵ Department of Biostatistics, University of Pittsburgh, Pittsburgh, PA USA

¹⁶ Department of Infectious Disease, George Mason University, Fairfax, VA USA

¹⁷ Department of Biostatistics and Bioinformatics, School of Public Health, Georgia Institute of Technology, Atlanta, GA USA

¹⁸ Department of Chemical and Biomolecular Engineering, Purdue University, West Lafayette, IN USA

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^{***} corresponding author: macklin@iu.edu, [@MathCancer](https://MathCancer.org)

**Michael Getz
Indiana U.**

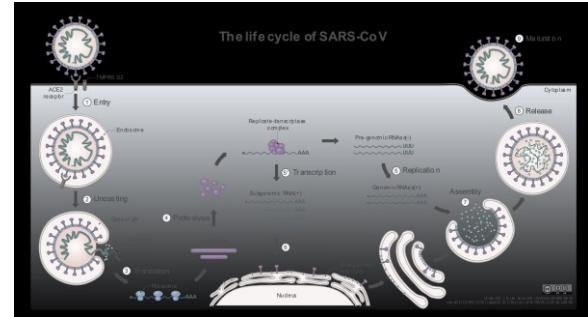


**Yafei Wang
Indiana U.**

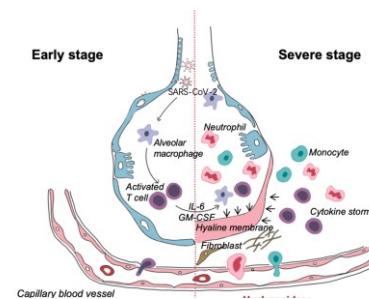
Note: This is a rapid prototyping project. For the very latest, see <http://COVID-19.physicell.org>

COVID-19 is a multiscale problem

- At the **subcellular level**:
 - Viral binding and endocytosis (virus entry)
 - Viral replication and exocytosis (virus release)
 - ACE2 receptor trafficking
 - Signaling responses
- At the **cell level**:
 - Infected cells will die, but they can “warn” other cells (interferons)
 - Immune cells phagocytose dead cells
 - Immune cells attack infected cells
- At the **tissue level**:
 - Virus spreads through the tissue
 - The infected regions spreads
 - Tissue damage spreads
 - Immune cells coordinate with secreted factors
- At the **systems level** (a sampling):
 - Immune cells send signals to lymphatic system
 - Immune response ramps up (immune expansion, antibodies)
 - More immune cells arrive at site of infection



Source: [wikimedia.org](https://commons.wikimedia.org)



Source DOI: [10.1038/s41418-020-0530-3](https://doi.org/10.1038/s41418-020-0530-3)

Collaborative, Iterative Progress

Approach

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

Progress

Phase I (community building)

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

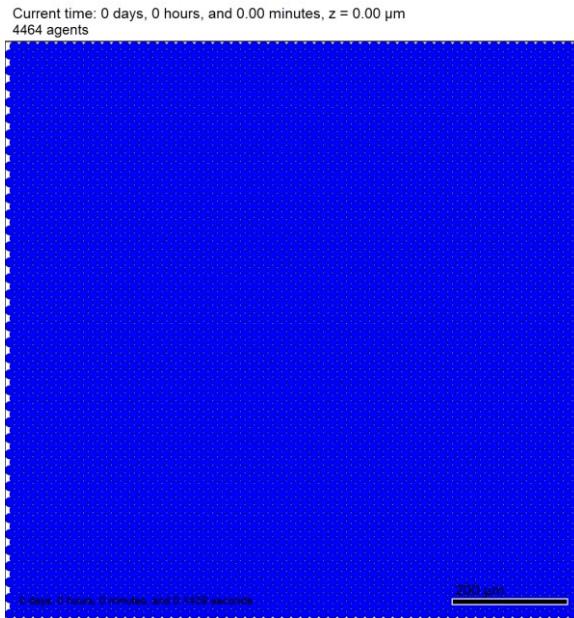
Phase II (community-driven) (current)

- **v3 model** (May-July) added tissue immune responses
- **v4 model** (August-October) is adding
 - interferon signaling
 - pyroptosis
 - systems-scale immune model
 - immune cell trafficking
 - improved tissue immune model
 - better receptor-virus binding
 - better viral replication
 - tissue fibrosis.

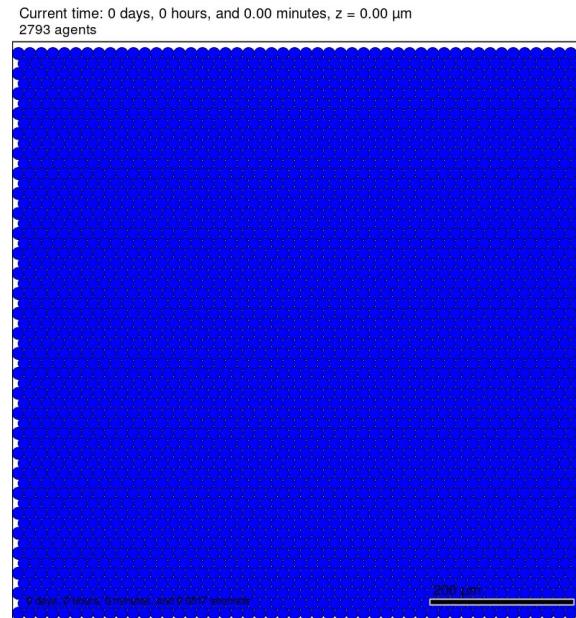
Iterative modeling progress

Versions 1 to 3

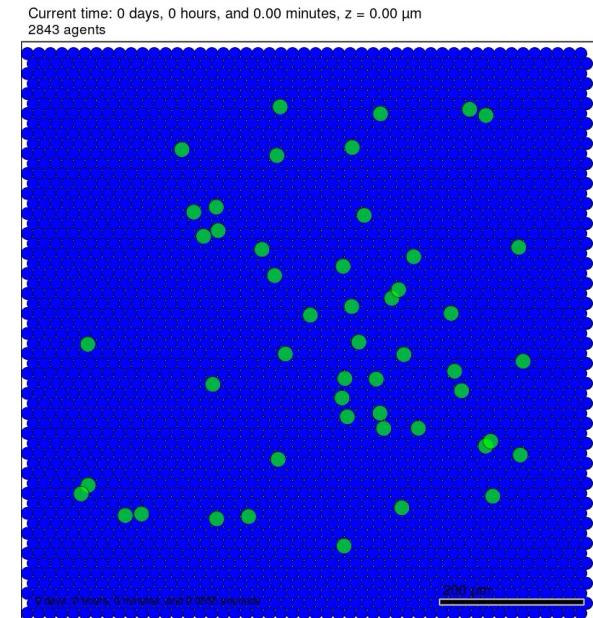
v1: prototype



v2: +ACE2
+random virion seeding



v3: +tissue immune



Version 4

(v4 preprint on the way!)

multiscale immune model advances

Improved macrophages:

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

Dendritic cells:

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

More T cell types

Epithelial cells present antigens

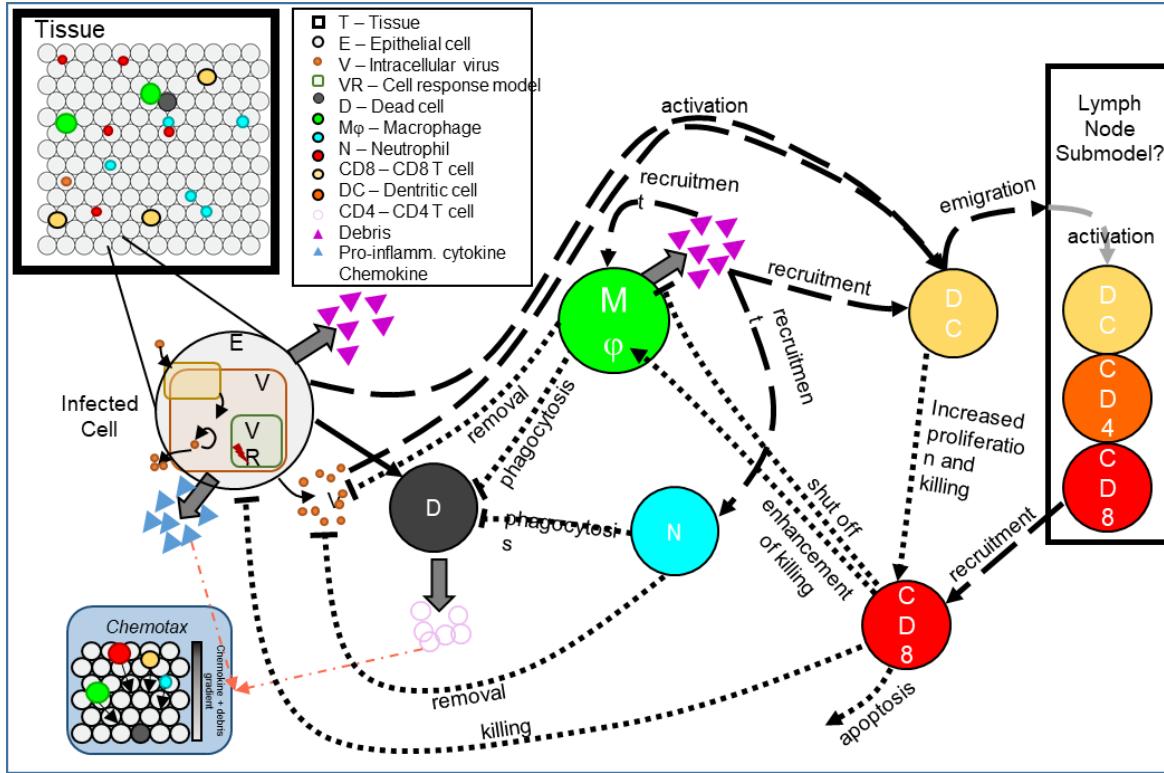
Systems-scale model of immune activation



systems scale:
Tarunendu Mapder
IUPUI

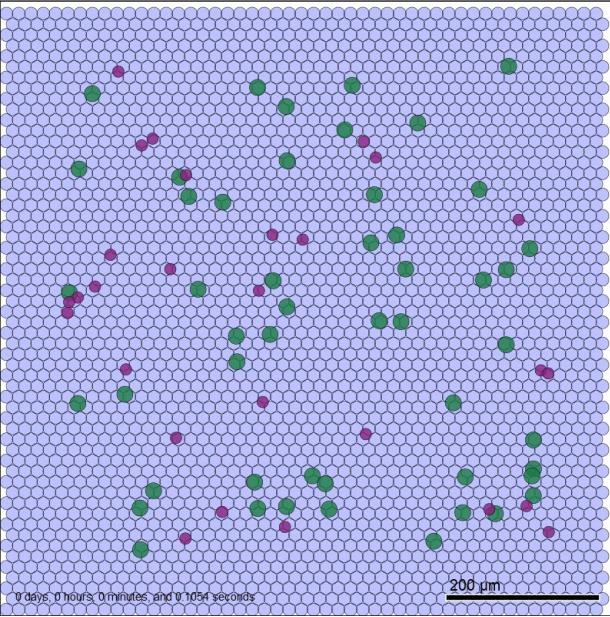


tissue scale:
Adrienne Jenner
U. Montreal

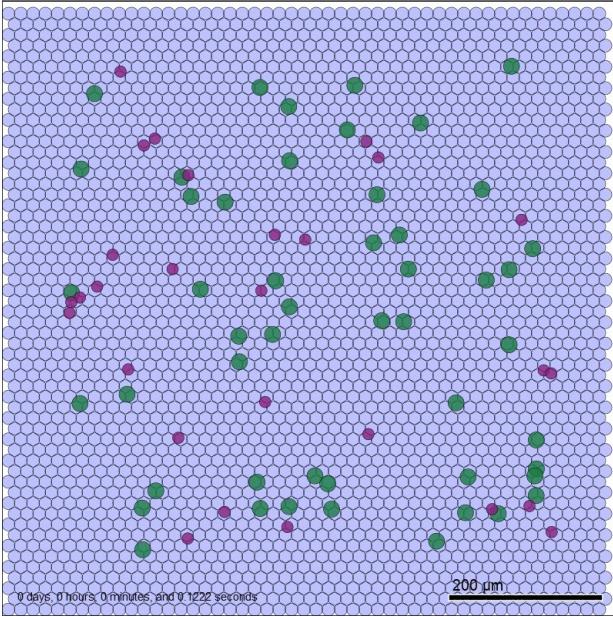


Type I interferons slow progression

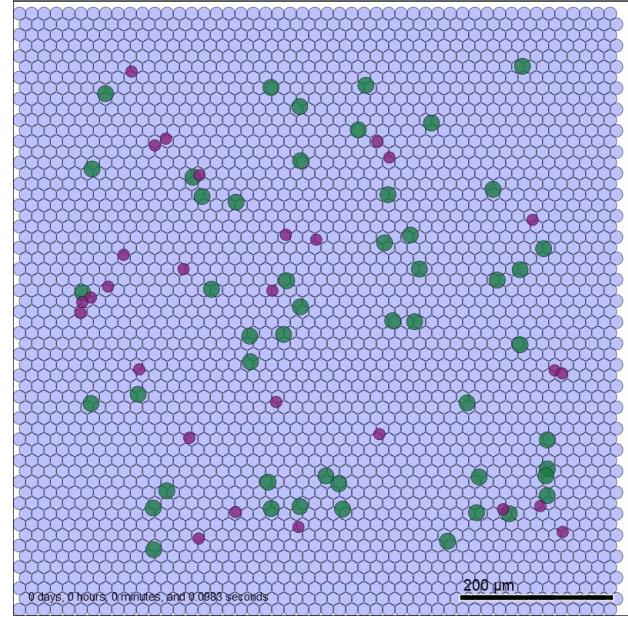
Current time: 0 days, 0 hours, and 0.00 minutes, z = 0.00 μm
2871 agents



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



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



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

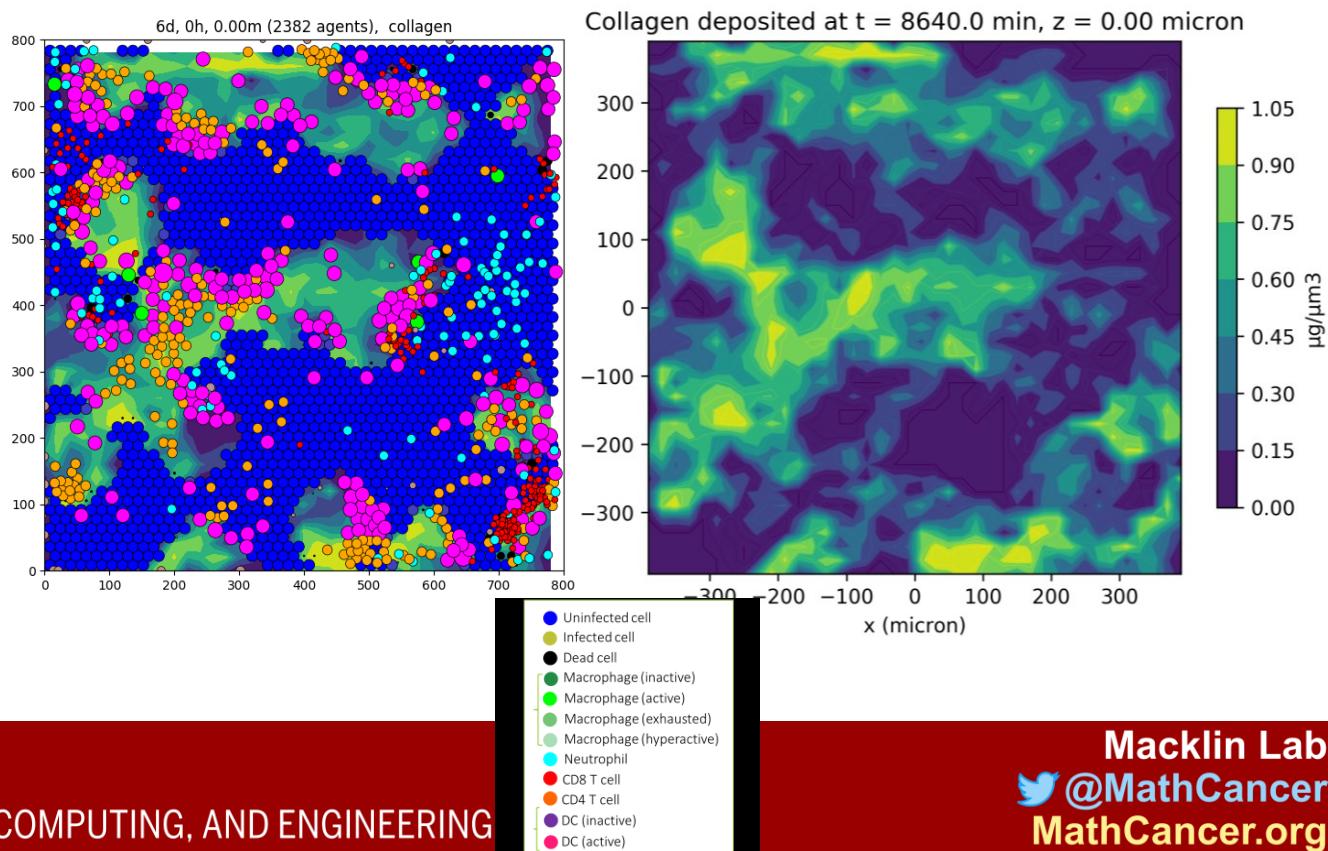
Preliminary work: coupled fibrosis

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

Hohammad Aminul
Islam
Oklahoma State



Ashlee N. Ford-
Versypt
Oklahoma State



Next steps

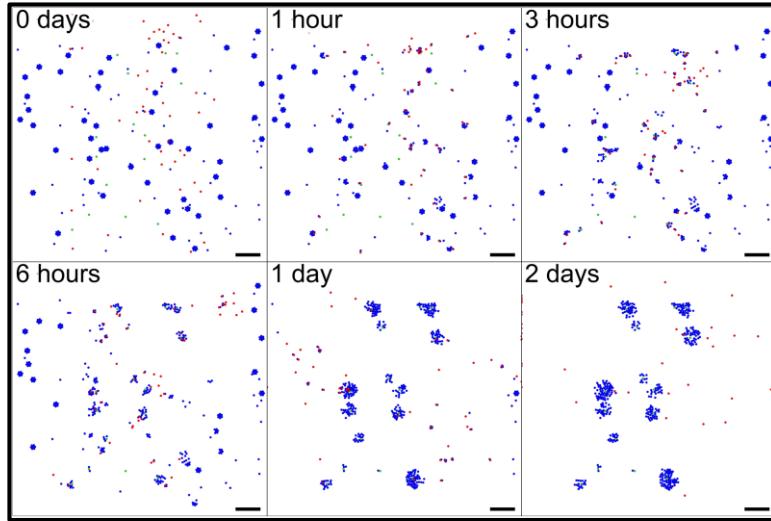
- v5 model
 - Negative feedbacks (anti-inflammation signals)
 - Antibodies
 - "bystander" effects (collateral damage to uninfected cells)
- v6 model (final release candidate)
 - Fine tuning parameters
 - Parameter space exploration on HPC, ML-guided analysis
 - Prototype 3D tissue geometry
 - Pivot to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

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

Let's try some models!

Example: biological cargo delivery system

- **Chemical environment:**
 - two diffusing chemical signals
- **Cell types and rules:**
 - **directors (green):**
 - ◆ secrete director signal to attract workers
 - **cargo (blue):**
 - ◆ **undocked:** secrete cargo signal to attract workers
 - ◆ **docked:** turn off signal
 - **workers (red):**
 - ◆ **undocked:** seek cargo via chemotaxis
 - ◆ **docked:** seek directors via chemotaxis, release cargo in high signal areas



Try this model yourself!

<https://nanohub.org/tools/pc4biorobots>



LUDDY

SCHOOL OF INFORMATICS, COMPUTING, AND ENGINEERING

Macklin Lab
Twitter: @MathCancer
MathCancer.org

pc4biorobots exercises

1. Cargo and workers only

- Set # of directors to zero.
- Set max time to 120 minutes.
- Click run. What happens?
- Plot the cargo signal. How does this explain the behavior?

2. Full model

- Set # of directors to 15
- Set max time to 1000 minutes.
- Click run. What happens?
- Plot the director signal. How does this explain the behavior?

3. Modify workers (1)

- Set drop threshold to 0.1
- Click run. What happens?
- Plot the director signal. How does this explain the behavior?

4. Modify workers (2)

- Set attached migration bias to 0.3.
- Click run. What happens?

*What if we could use this for
cancer treatments?*

pc4cancerbots

- **cancer biorobots:**

- **green:**

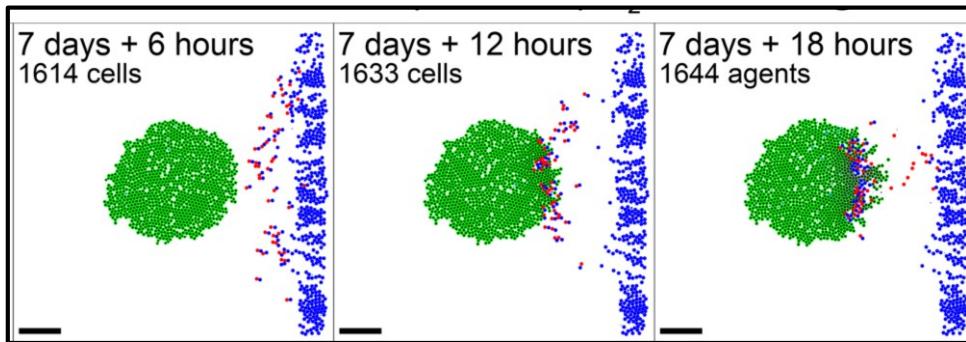
- ◆ cycle entry scales with O₂
 - ◆ O₂ depletion causes necrosis
 - ◆ cumulative drug exposure causes apoptosis

- **blue:**

- ◆ drug-loaded "cargo"

- **red:**

- ◆ worker cells that seek and haul cargo towards hypoxic zones



Try this model yourself!

<https://nanohub.org/tools/pc4cancerbots>

pc4cancerbots exercises (later)

1. Cancer cells only

- Set # injected cells to 0
- Increase tumor radius to 400
- Set max time to 2880 minutes.
- Click run. What happens?
- Plot the oxygen. How does this explain the behavior?

2. Add therapy (full model)

- Set # of injected cells to 500
- Set therapy activation time to 120
- Increase max time to 4320 minutes
- Click run. What happens?
- Plot the therapeutic. How does this explain the behavior?

3. Modify treatment

- Set attached worker migration bias to 0.2
- Click run. What happens?

4. Modify treatment (on your own)

- Set cargo release o2 threshold to 15
- Increase max time to 14400 minutes
- Click run. What happens?

**This is a key strength of
simulation models:**

**We can explore new ideas
before committing time and
resources.**

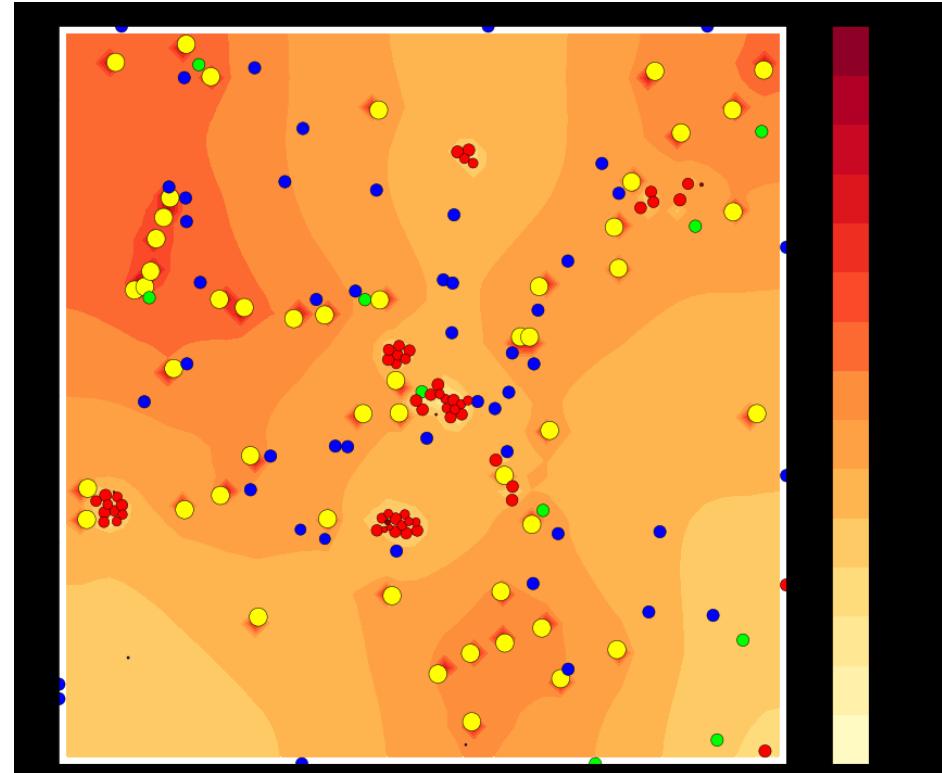
pcISA: an adversarial multicellular system

- What are the dynamics of an adversarial system?
- **suppliers (e.g., blood vessels)**
 - supply growth substrates
- **Invaders (e.g., bacteria)**
 - grow near vessels
 - avoid dead cells
 - avoid attackers
- **Scouts (e.g., macrophages)**
 - look for invaders, release signal
- **Attackers (e.g., T cells)**
 - Look for signal, attack invaders



Try this model yourself!

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



pcISA exercises

1. Suppliers and invaders only

- Set # of scouts and # of attackers to 0
- Set max time to 2400 minutes.
- Click run. What happens?
- Plot the resource. How does this explain the behavior?

2. Add scouts

- Set # of scouts to 10
- Click run. What happens? Does plotting the "signal" help explain their behavior?

3. Add attackers (full model)

- Set # of attackers to 50
- Set max time to 7200 minutes.
- Click run. What happens?

4. Modify invaders

- Set invader quorum weight to 0.01
- Click run. What happens?
- Plot the death signal. How does this explain the behavior of invaders after an attack?

5. Modify invaders and scouts (on your own)

- Set invader quorum weight to 1
- Set scout migration bias to 1
- Increase invader max death rate to 0.01
- Click run. What happens?

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
- 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?***

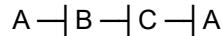


Try this model yourself!

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

pc3types example: repressilator

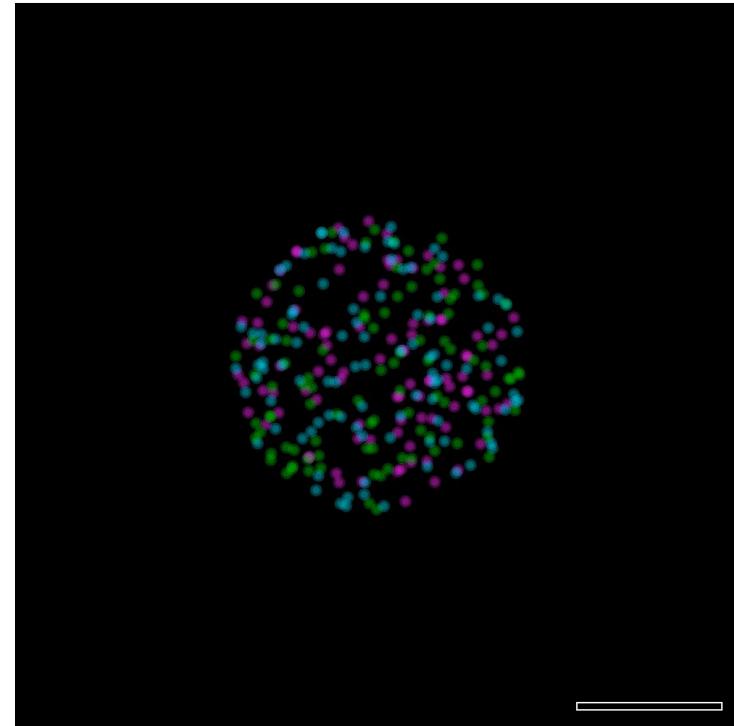
The **repressilator** is the first synthetic biological oscillator:



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



pc3types exercises for later (competitive)

1. Competition for resources (neutral)

- Increase to 75 of A, B, and C cells
- Decrease max time to 5760 minutes (4 days)
- Run with default parameters – what happens?

2. Competition for resources (each type secretes "poisons")

- For type A: B and C promote death (apoptotic death rate 0.001)
- For type B: A and C promote death (apoptotic death rate 0.001)
- For type C: A and B promote death (apoptotic death rate 0.001)

3. Competition for resources (A more aggressive)

- Change Type A's Phase 0->Phase 1 transition rate to 0.005

4. Competition for resources (A more aggressive, B is motile)

- Change Type B's motility to "on", migration bias = 0.5, towards "resource"

pc3types exercises for later (cooperative)

1. A helps B, and B helps C

- Reset to defaults
- Decrease max time to 5760 minutes (4 days)
- Type B: A promotes division
- Type C: B promotes division

2. A helps B, B migrates to A. B helps C.

- Type B: A promotes division, chemotaxis towards A
- Type C: B promote division

3. A helps B, B migrates to A. B helps C. (Version 2)

- Type B: A promotes division, chemotaxis towards A. A inhibits migration
- Type C: B promote division

4. A helps B, B migrates to A. B suppresses proliferation of A.

- Type B: A promotes division, chemotaxis towards A. A inhibits migration
- Type A: B inhibits division
- Type C: B promotes division. chemotaxis away from B. B promotes migration.
- Set diffusion coefficient of factors A, B, C to 100, set decay to 0.04 (length scale = 50 micron)

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>)