

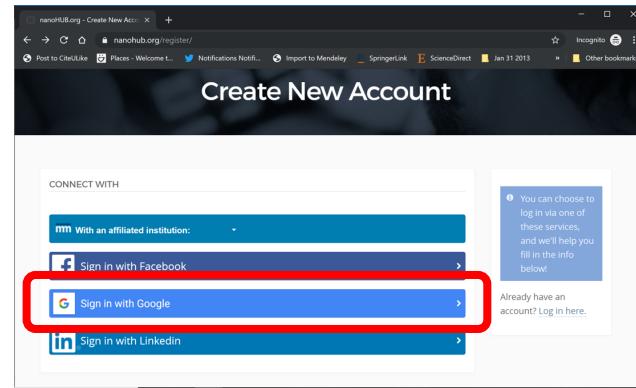
nanoHUB Account

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

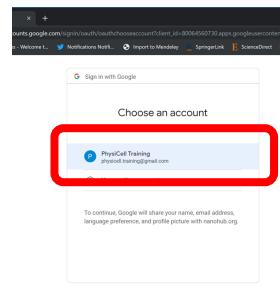
• Steps:

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.

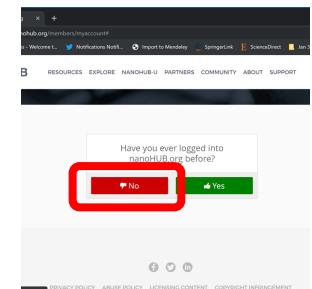
2



3



4



Computational Models of Immune Dynamics

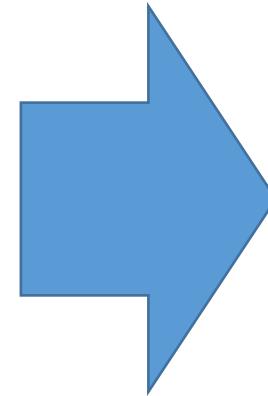
Paul Macklin, Ph.D.

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:

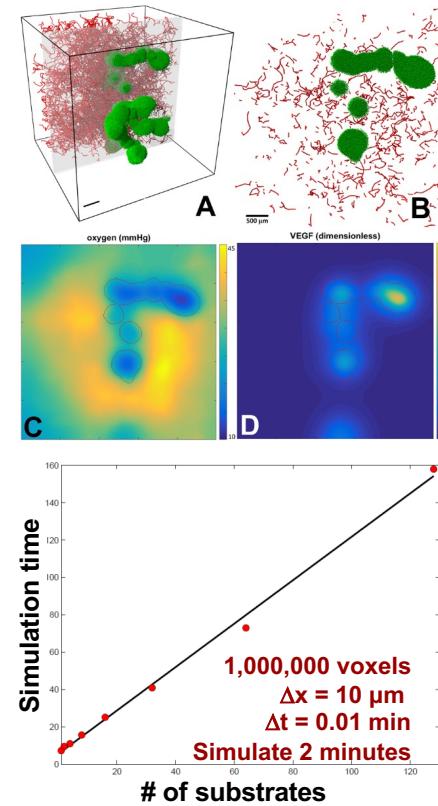
- Off-lattice cell secretion and uptake
- 2nd-order accurate (space), 1st-order accurate (time), numerically stable

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)

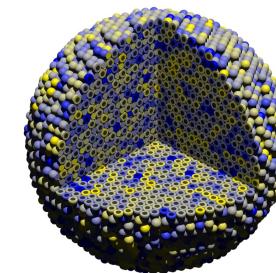


Try this model yourself!

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:

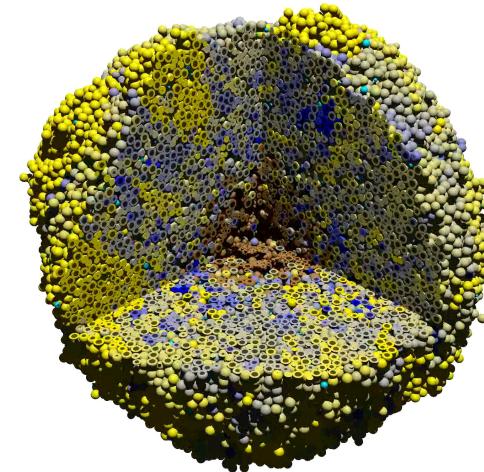
- [Ghaffarizadeh et al. \(2018\)](#)
- [Ozik et al. \(2018\)](#)
- [Ozik et al. \(2019\)](#)



Try this model yourself! (2D)

nanohub.org/tools/pc4cancerimmune

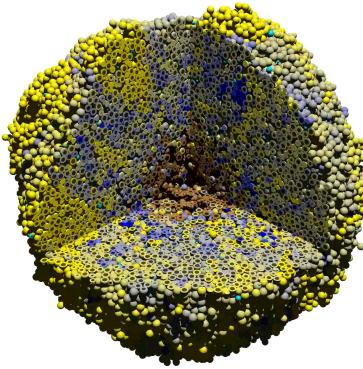
Current time: 13 days, 0 hours, and 0.00 minutes
95309 agents



High-throughput investigations on HPC

3-D tumor-immune model

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

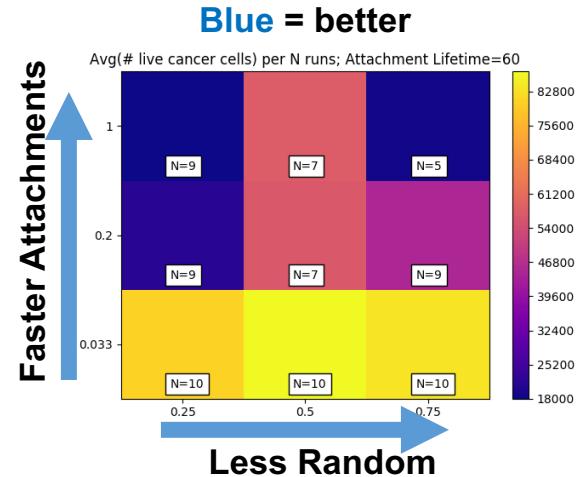


Explore 3 parameters:

- 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

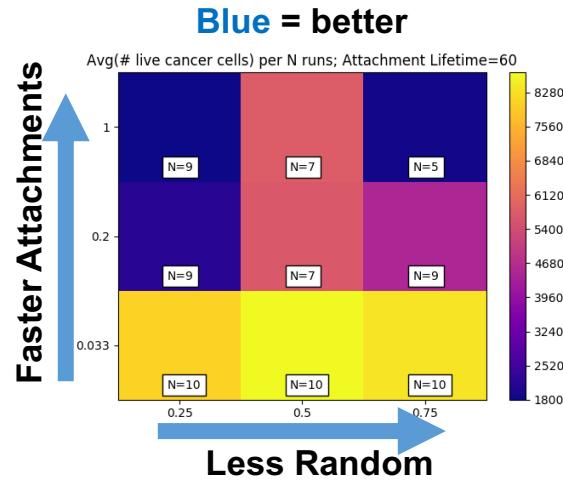


Reference:

[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

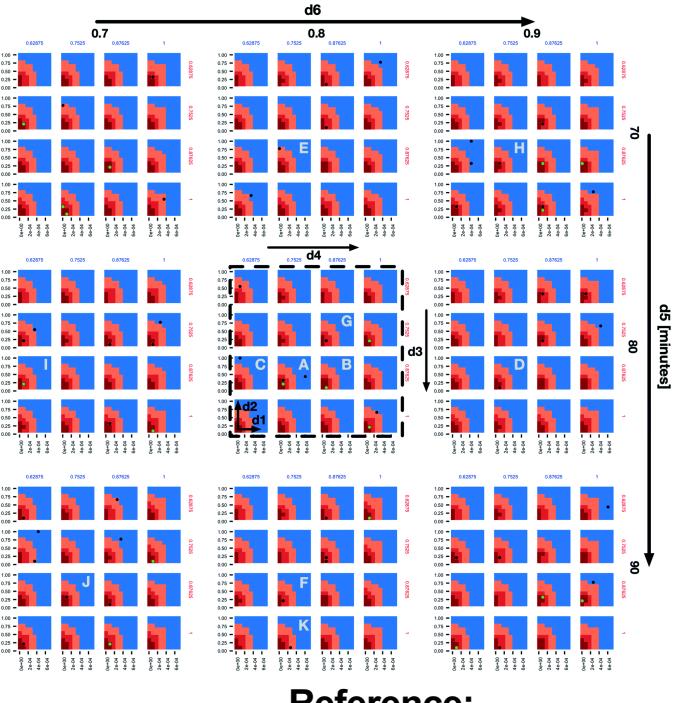
- For each design scenario (e.g., control), build a binary DT classifier:
 - **True**: points that meet the design goal (e.g., $N_{\text{final}} \leq N_{\text{start}}$)
 - **False**: points that don't meet the design goal (e.g., $N_{\text{final}} > N_{\text{start}}$)
- **Run** 1000 simulations at a time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

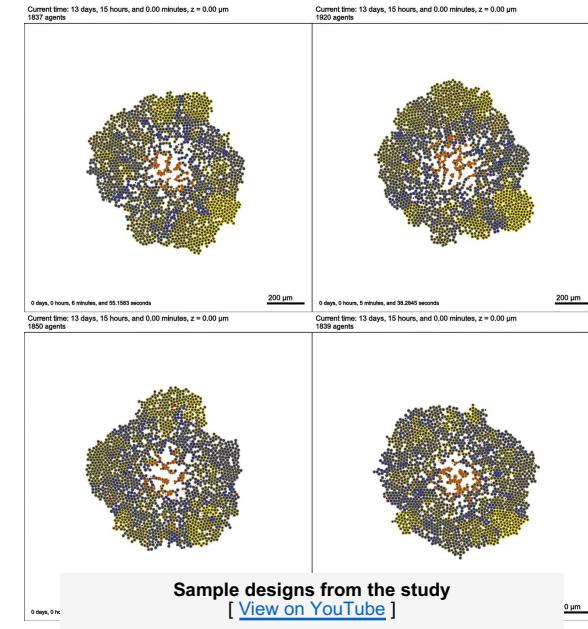


Reference:
[Ozik et al. \(2019\)](#)

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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Michael Getz
Indiana U.

** equal contribution
† in manuscript
*** corresponding author: macklin@iu.edu, [@MathCancer](https://MathCancer.org)



Yafei Wang
Indiana U.



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

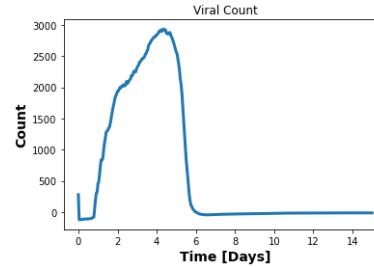
Iterative progress

- **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**

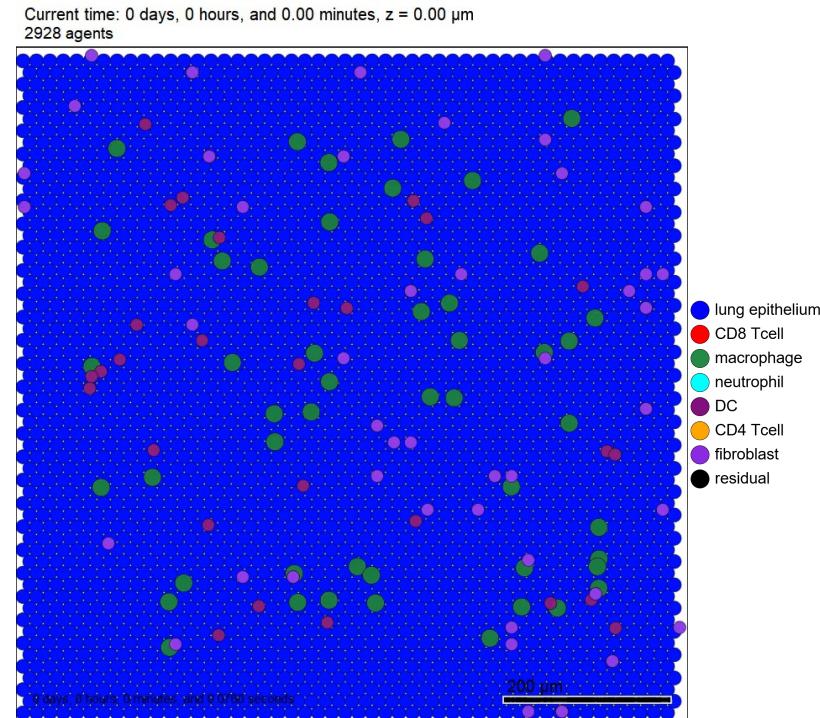
v5: neutralizing antibodies clear the infection

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

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



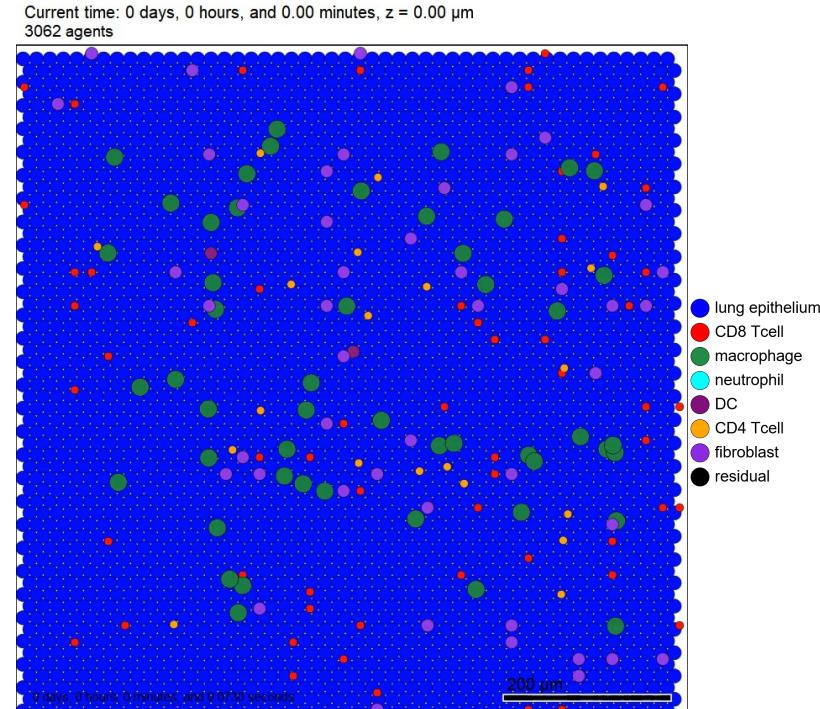
- **This immune model is sufficiently complete to clear a SARS-CoV-2 infection**



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.



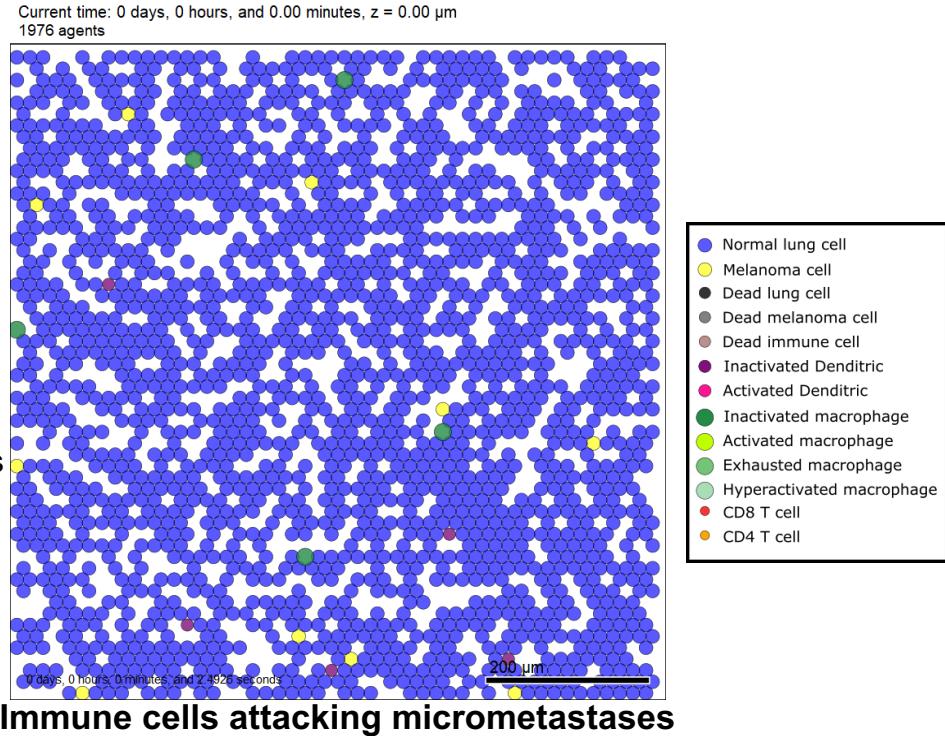
Trained immune system facing future exposure

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

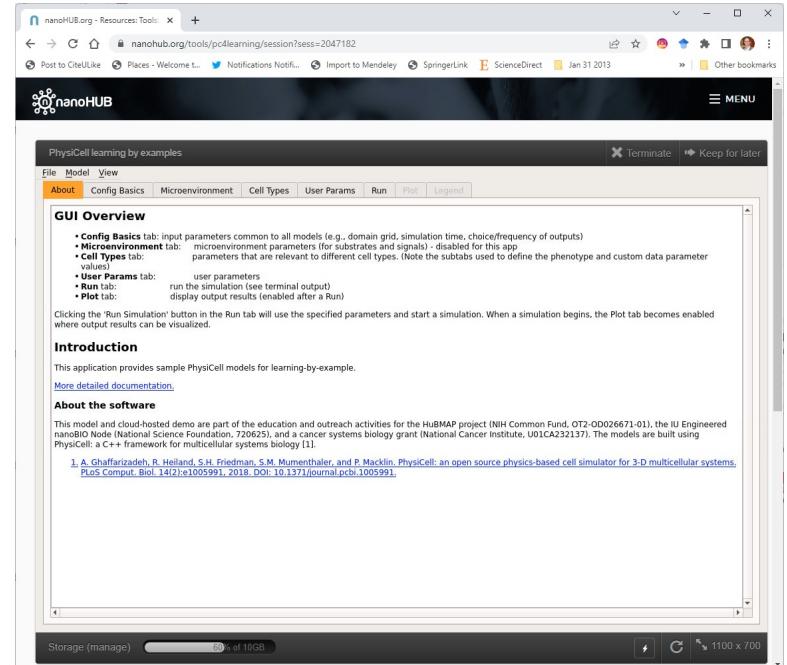
- Adapt and reuse:
 - Tumor growth model
 - Local immune dynamics:
 - ◆ Focused on macrophages, dendritic cells, CD4+ & CD8+ T cells
 - Immune cell trafficking
 - Lymph node T cell expansion
- Value of modular immune models:
 - Advances in one project help all the others
 - ◆ First cancer immune projects 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

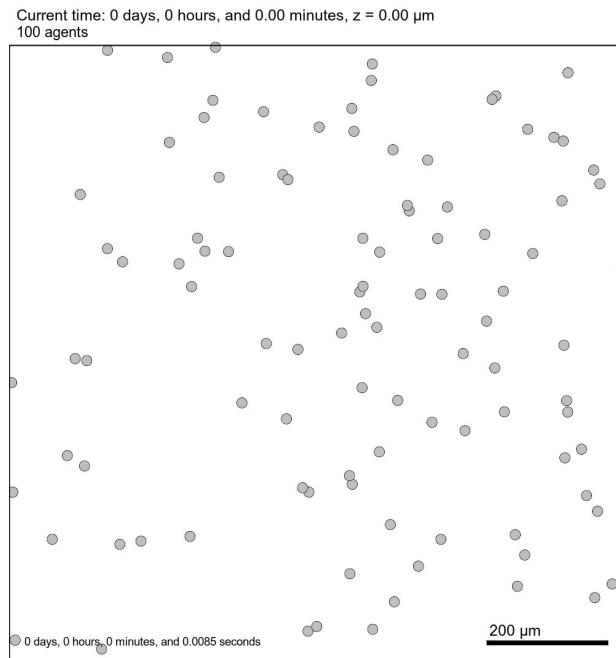
Real-time immune modeling

- 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

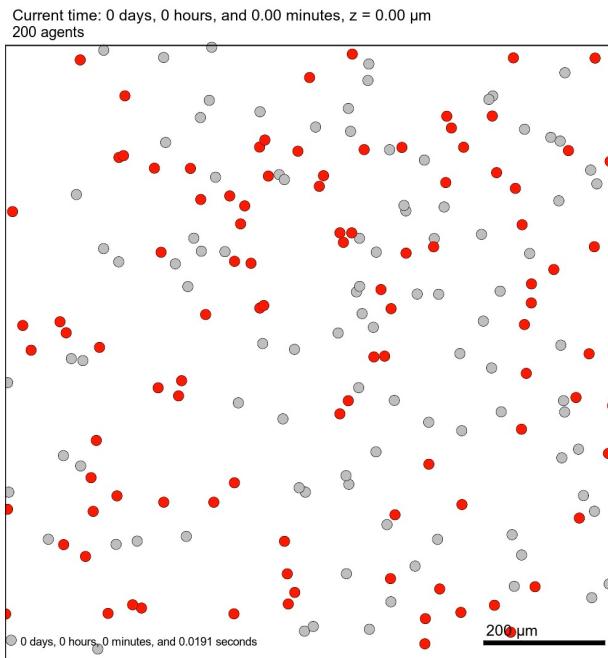


Iterative results: Walk-through takes ~15 min

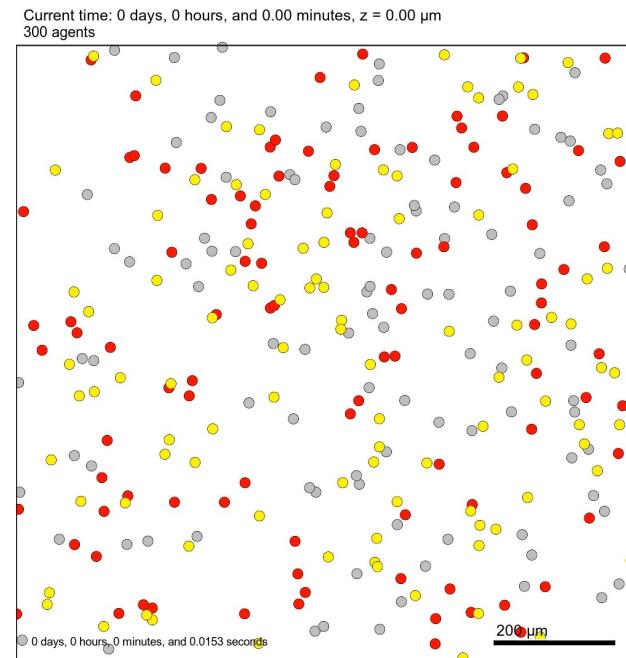
v1: bacteria only



v2: +macrophages



v3: +neutrophils



See full walk-through here!

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

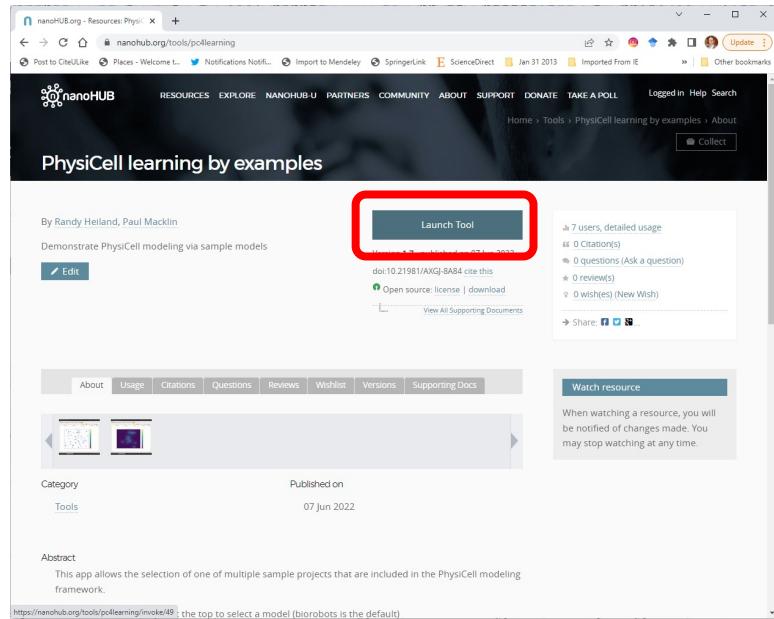


Checklist

- Use online simulator: <http://nanohub.org/tools/pc4learning>
- Build iteratively:
 - Set the domain
 - Add diffusing substrates
 - Add bacteria and test
 - Add macrophages and test
 - Add neutrophils and test

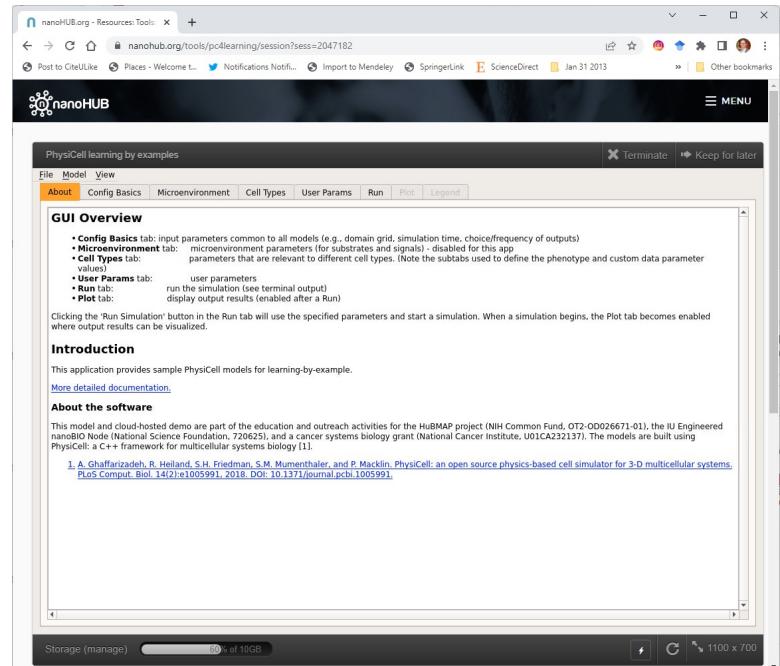
Start the online simulator

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



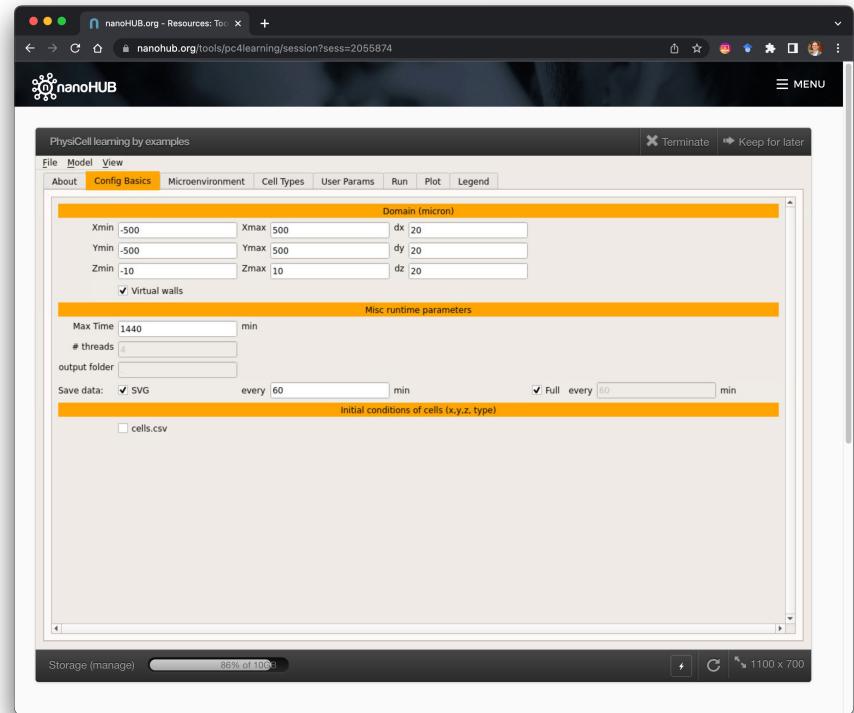
App navigation

- **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



Set up the domain

- Go to the **config basics** tab
- Choose domain settings (in μm)
 - leave $Z_{\min} = -\frac{1}{2}\Delta z$ and $Z_{\max} = \frac{1}{2}\Delta z$ for 2D models
 - Use “virtual walls” to apply a force to keep cells from leaving the domain
- Choose time settings (in min):
 - Set max simulation time to **1440** min (1 day)
- Choose save settings:
 - SVG: required for plotting cell positions
 - ◆ Save every 60 minutes (default setting)
 - Full: required for plotting diffusing substrates

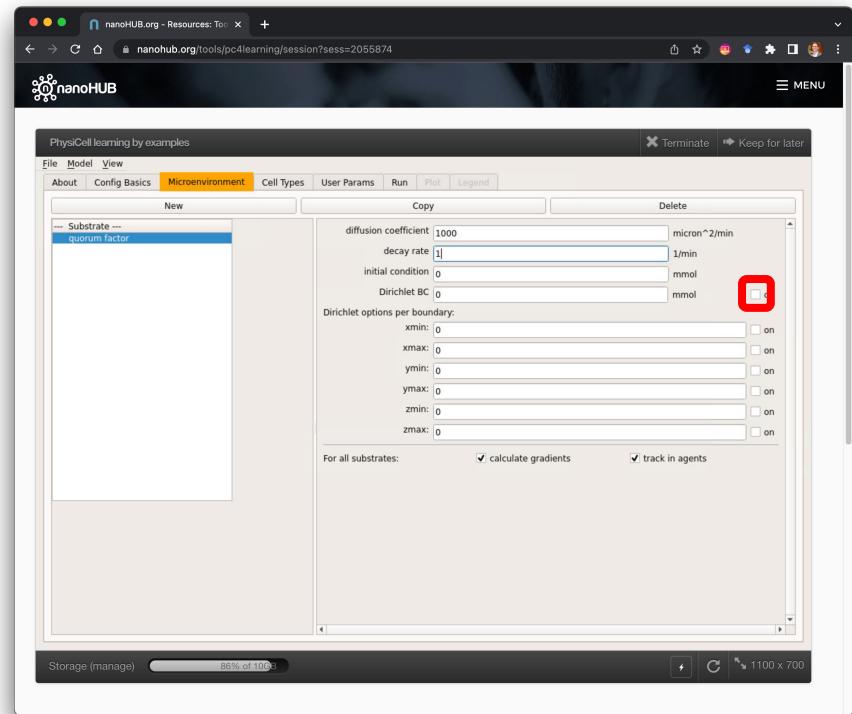


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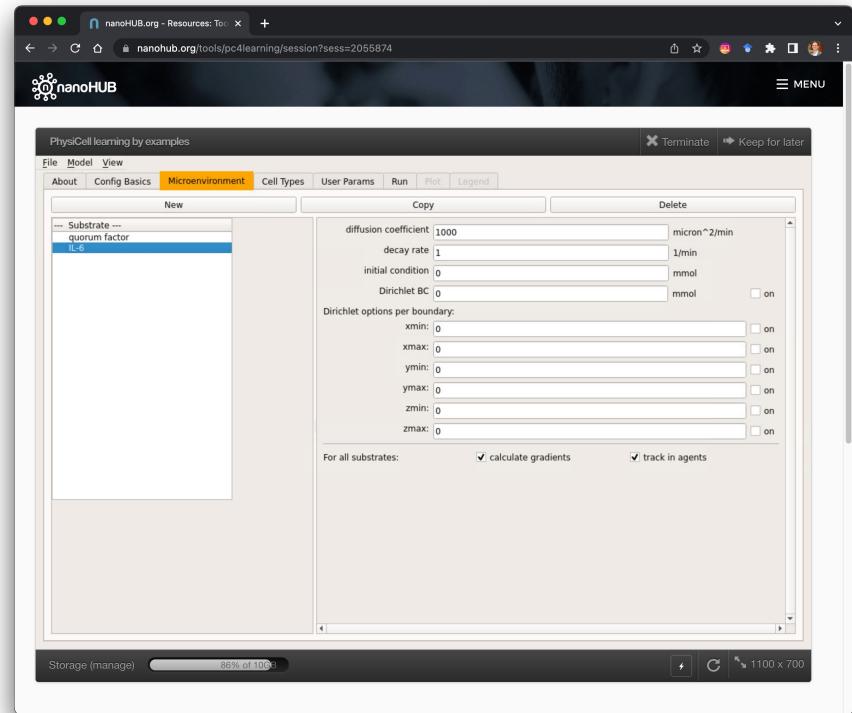
Define substrates (1)

- Go to the **microenvironment** tab
- Double-click **substrate**
 - Rename to **quorum factor**
 - Set diffusion at $1000 \mu\text{m}^2/\text{min}$
 - Set decay at 1 min^{-1}
 - ◆ 100 mm diffusion length scale
 - **Disable** Dirichlet boundary conditions
 - Set initial condition to 0



Define substrates (2)

- Select **quorum factor** is selected
- Click **copy**
- Rename to **IL-6**

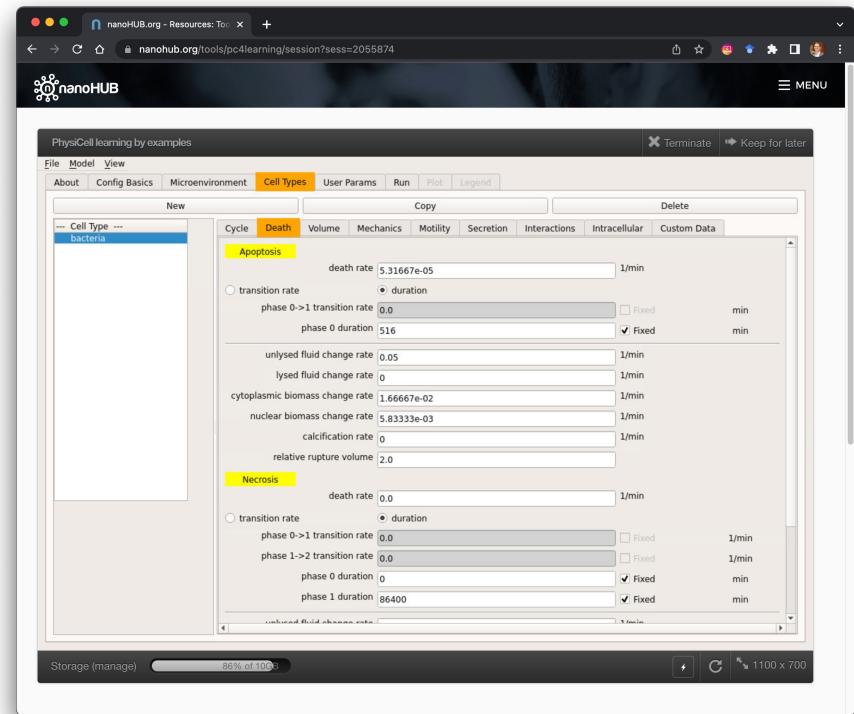


Checklist

- Use online simulator: <http://nanohub.org/tools/pc4learning>
- Build iteratively:
 - Set the domain
 - Add diffusing substrates
 - Add bacteria and test
 - Add macrophages and test
 - Add neutrophils and test

Define bacteria (1)

- Go to the **cell types** tab
- Double-click on **default**
 - Rename to **bacteria**
- Let's set a moderate 10-hour cycle
 - Go to **Cycle**
 - ◆ Set the cycle model type to **live cells**
 - ◆ Set the cycle **duration** to **600 min**



Define bacteria (2)

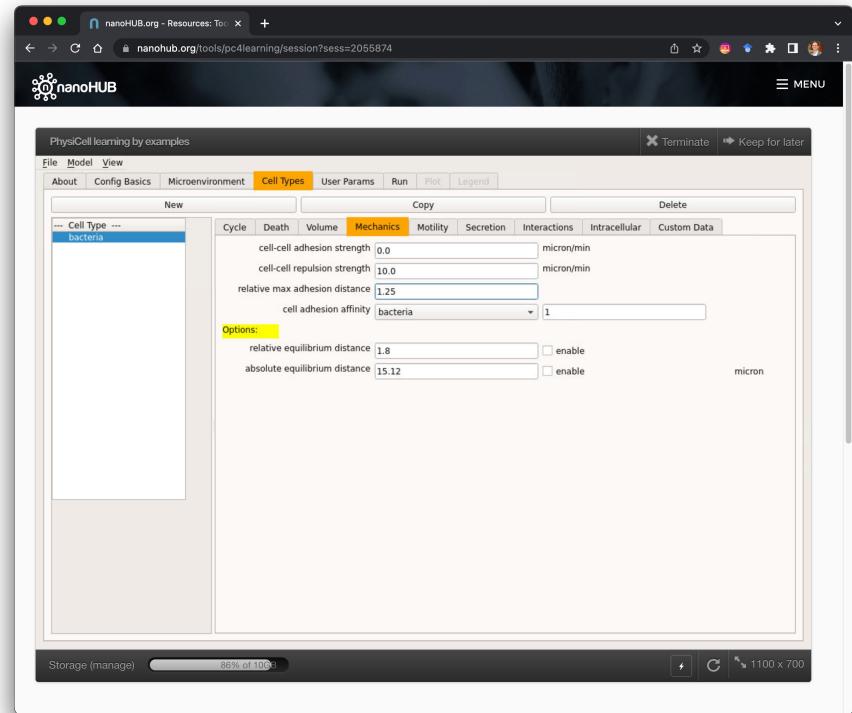
- Let's set a low background death
 - Go to **Death**
 - Set the **apoptosis** rate to **0.0002**

The screenshot shows the PhysiCell learning by examples interface on nanoHUB.org. The 'Cell Types' tab is selected, showing parameters for 'bacteria'. The 'Apoptosis' section is active, displaying a death rate of 0.0002 1/min. Other parameters shown include transition rates, fluid change rates, biomass change rates, and calcification rates for both apoptosis and necrosis.

Category	Parameter	Value	Unit	
Apoptosis	death rate	0.0002	1/min	
	transition rate	phase 0->1 transition rate	0.0	1/min
Necrosis	duration	phase 0 duration	516	min
	unlysed fluid change rate	0.05	1/min	
	lysed fluid change rate	0	1/min	
	cytoplasmic biomass change rate	1.66667e-02	1/min	
	nuclear biomass change rate	5.83333e-03	1/min	
	calcification rate	0	1/min	
relative rupture volume	2.0			
	death rate	0.0	1/min	
transition rate	phase 0->1 transition rate	0.0	1/min	
duration	phase 1->2 transition rate	0	1/min	
phase 0 duration	0	min		
phase 1 duration	86400	min		

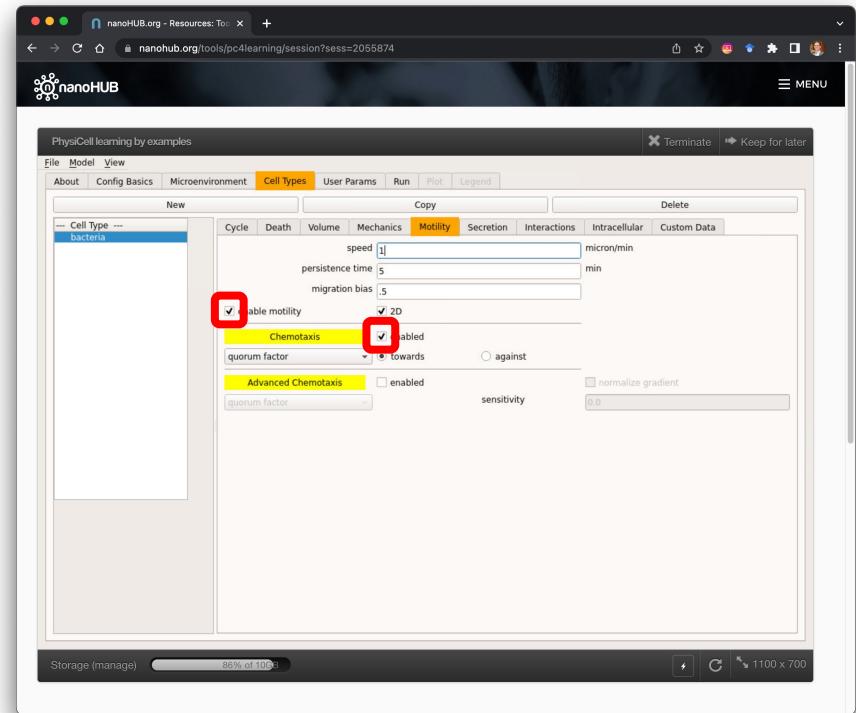
Define bacteria (3)

- Make them non-adhesive
 - Go to **Mechanics**
 - ◆ Set **cell-cell adhesion** to 0



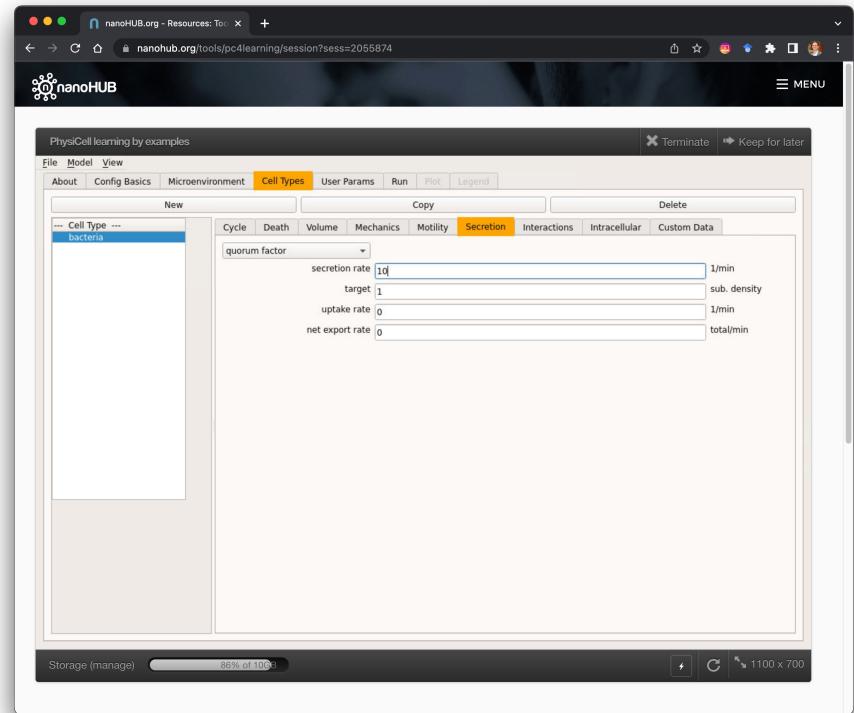
Define bacteria (4)

- Make them chemotactic
 - Go to **Motility**
 - ◆ Set **speed** to 1
 - ◆ Set **persistence time** to 5
 - ◆ Set **bias** to 0.5
 - ◆ Check the box to enable motility
 - ◆ Check the box to enable chemotaxis
 - ◆ Select **quorum factor**



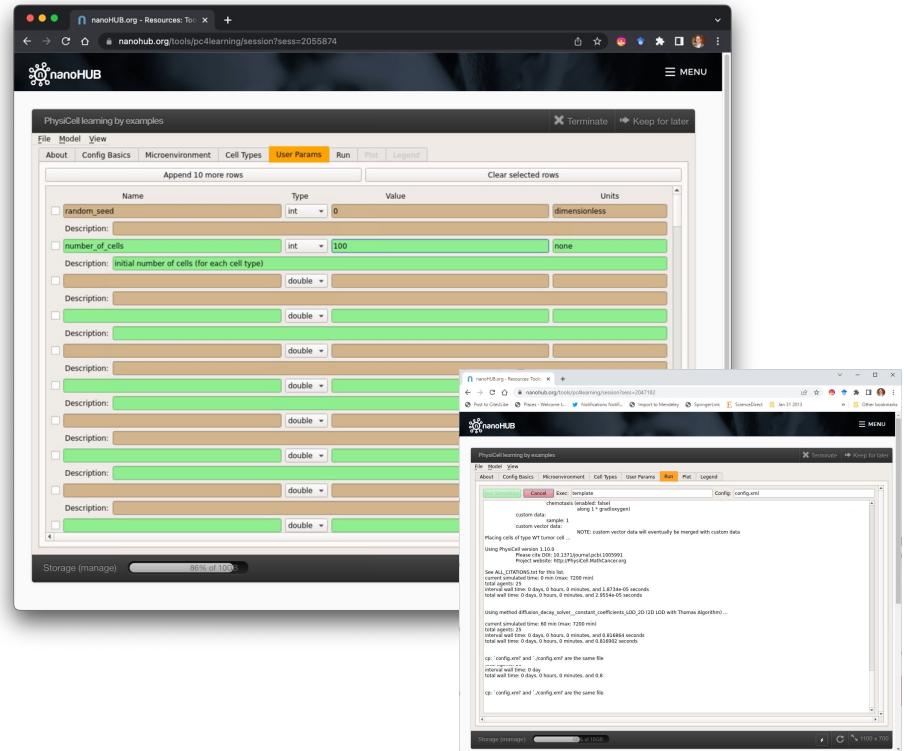
Define bacteria (5)

- Make them secrete quorum factor
 - Go to **Secretion**
 - ◆ Choose **quorum factor** from the drop-down menu
 - ◆ Set **secretion rate** to 10
 - ◆ Set **target** to 1



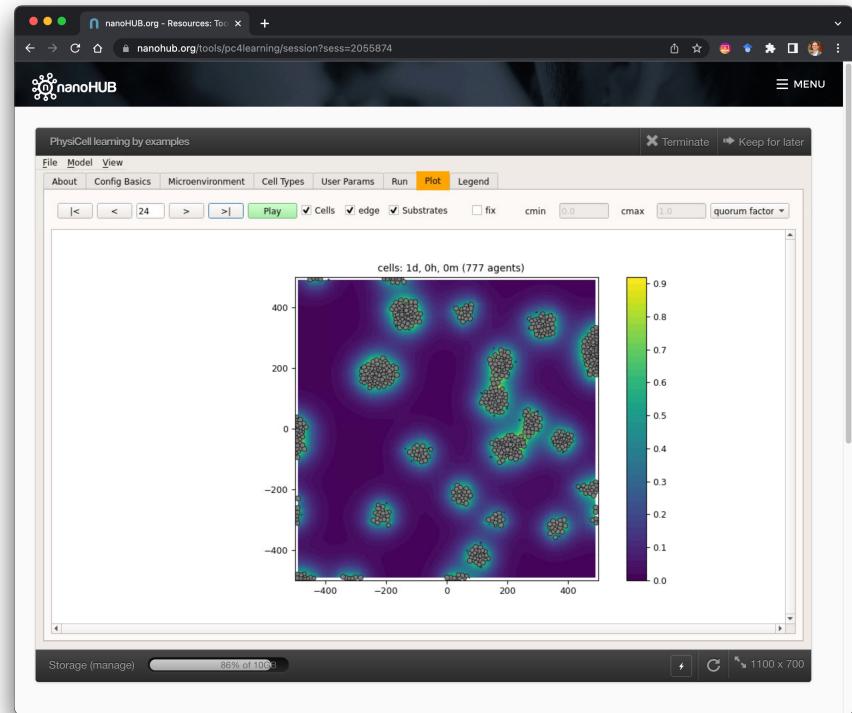
Test the model!

- Go to the **user params** tab
 - Set **number of cells** to 100
 - Go to the **run** tab
 - Click **run simulation**



View the results

- Go to the **plot** tab
 - Click **play** to automatically animate
 - Click **pause** to stop playback
 - Click **<** or **>** to advance by 1 frame
 - Click **|< or >|** to go to the start or end
- Check **substrates** to plot substrates below the cells
 - Use the drop-down to choose the **quorum factor**



Checklist

- Use online simulator: <http://nanohub.org/tools/pc4learning>
- Build iteratively:
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 - Add bacteria and test
 - Add macrophages and test
 - Add neutrophils and test

Define macrophages (1)

- Go to the **cell types** tab
- Select **bacteria** and click **copy**
- Double-click the new type
 - Rename to **macrophage**
- Let's disable cycling and apoptosis
 - Go to **Cycle**
 - ◆ Set the cycle **duration** to **9e9 min**
 - Go to **Death**
 - ◆ Set the **apoptotic death rate** to **0**

The screenshots illustrate the process of defining a macrophage cell type in the PhysCell software. In the top window, the 'Cell Types' tab is active, showing a list of cell types including 'bacteria' and 'macrophage'. In the bottom window, the 'Death' tab is active for the 'macrophage' cell type, where the 'death rate' is explicitly set to 0. Other parameters shown include 'phase 0 duration' (set to 9e9 min), various fluid and biomass change rates, and calcification rates.

Define macrophages (2)

- Let's increase the range of mechanical interactions
 - Go to **Mechanics**
 - ◆ Set **relative max adhesion distance** to 1.5
 - » (this is a multiple of cell radius)
- Let's enable chemotaxis towards quorum factor, but more random
 - Go to **Motility**
 - ◆ Set **migration bias** to 0.25

The image displays two side-by-side screenshots of the PhysCell software interface on nanoHUB.org. Both screenshots show the 'PhysCell learning by examples' tool with the 'Cell Types' tab selected.

Screenshot 1 (Top): Mechanics Tab

This screenshot shows the 'Mechanics' tab selected. The 'relative max adhesion distance' field is highlighted with a red box and contains the value '1.5'. Other visible parameters include 'cell-cell adhesion strength' (0.0), 'cell-cell repulsion strength' (0.0), 'cell adhesion affinity' (1), and 'relative equilibrium distance' (1.8). The 'absolute equilibrium distance' is set to 15.12 micrometers.

Screenshot 2 (Bottom): Motility Tab

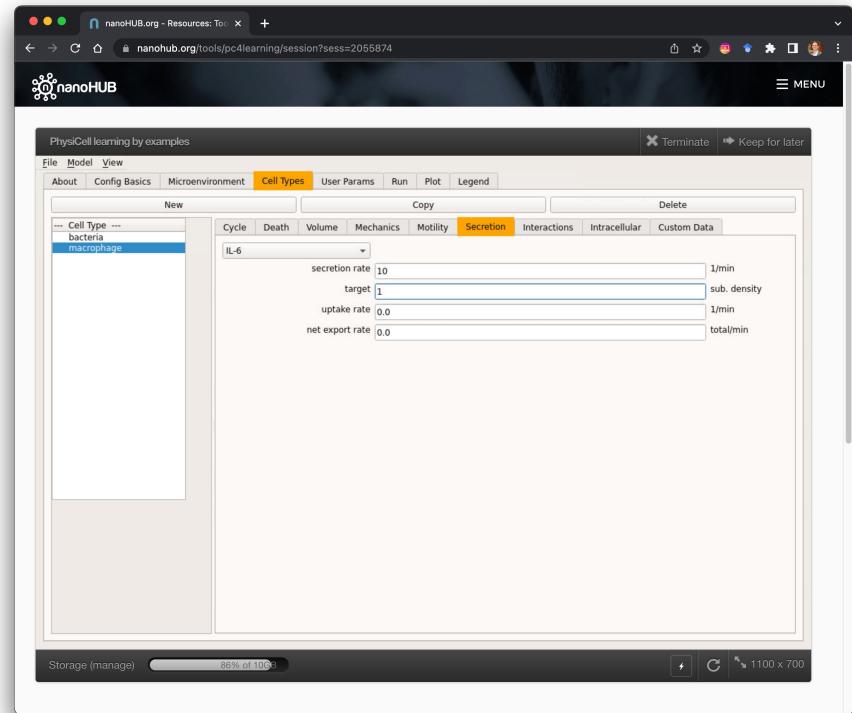
This screenshot shows the 'Motility' tab selected. The 'migration bias' field is highlighted with a red box and contains the value '0.25'. Under the 'Chemotaxis' section, 'enabled' is checked, and 'towards' is selected. The 'Advanced Chemotaxis' section is also visible. A 'Storage (manage)' bar at the bottom indicates 0% of 100 MB used.

Define macrophages (3)

- Let's secrete IL-6 and not quorum factor

- Go to **Secretion**

- Choose **quorum factor** from the drop-down
 - Set **secretion rate** to 0
- Choose **IL-6** from the drop-down
 - Set **secretion rate** to 10
 - Set **target** to 1



Define macrophages (4)

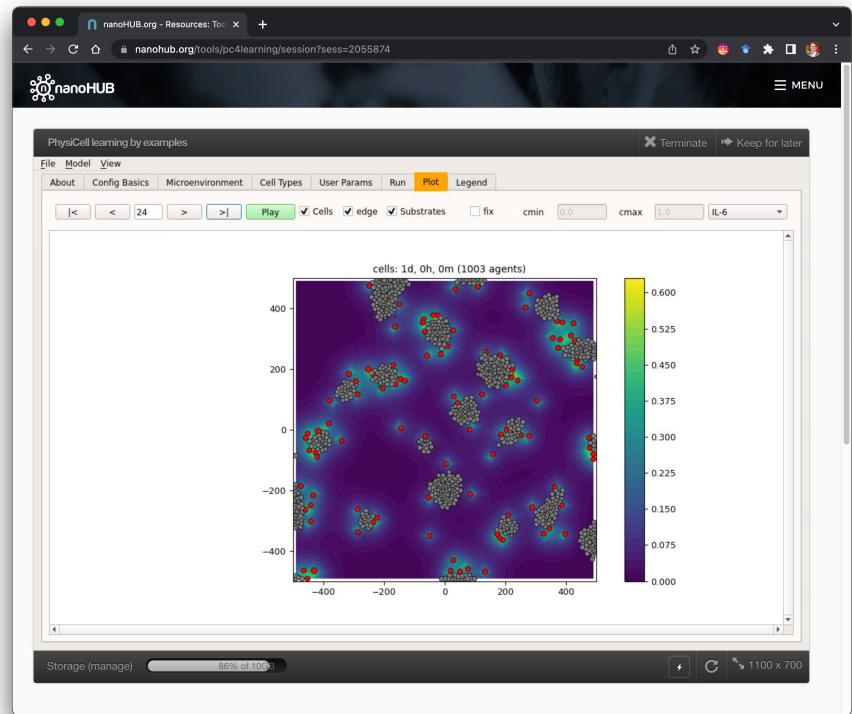
- Let's enable phagocytosis of dead cells
 - Go to **Interactions**
 - Set **dead phagocytosis rate to 0.1**

The screenshot shows the PhysiCell learning by examples interface on nanoHUB.org. The 'Cell Types' tab is selected, and a macrophage is chosen as the cell type. In the 'Secretion' tab, the parameter 'IL-6' is selected. The settings are as follows:

Parameter	Value	Unit
secretion rate	10	1/min
target	1	sub. density
uptake rate	0.0	1/min
net export rate	0.0	total/min

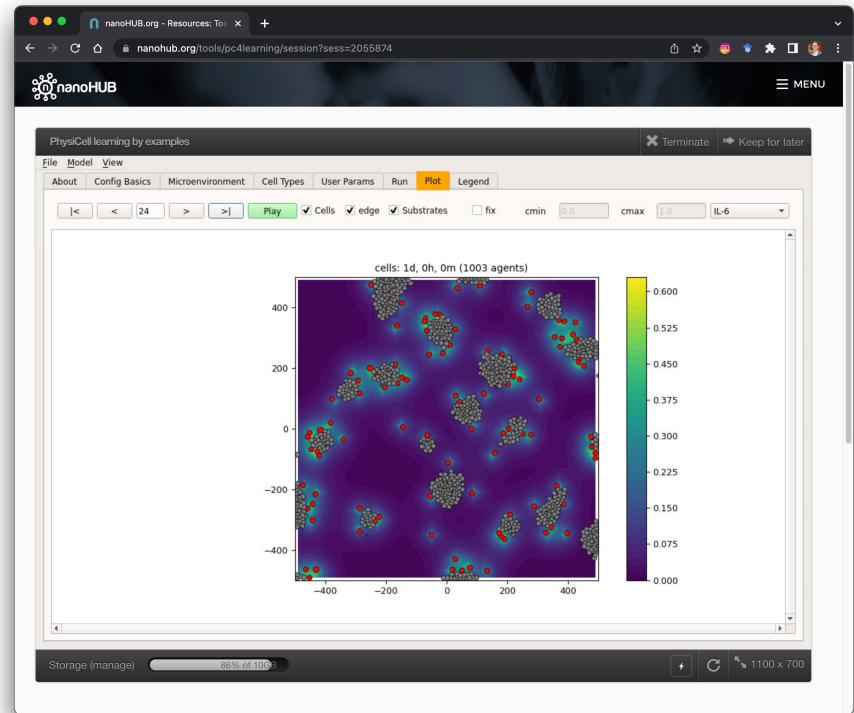
Test the model!

- Go to the **run** tab
 - Click **run simulation**
- Go to the **plot** tab
 - View the results!
- Click the **legend** tab to see cell colors defined
 - grey: **bacteria**
 - red: **macrophages**



Test the model: animation

- Go to the **run** tab
 - Click **run simulation**
- Go to the **plot** tab
 - View the results!
- Click the **legend** tab to see cell colors defined
 - grey: **bacteria**
 - red: **macrophages**

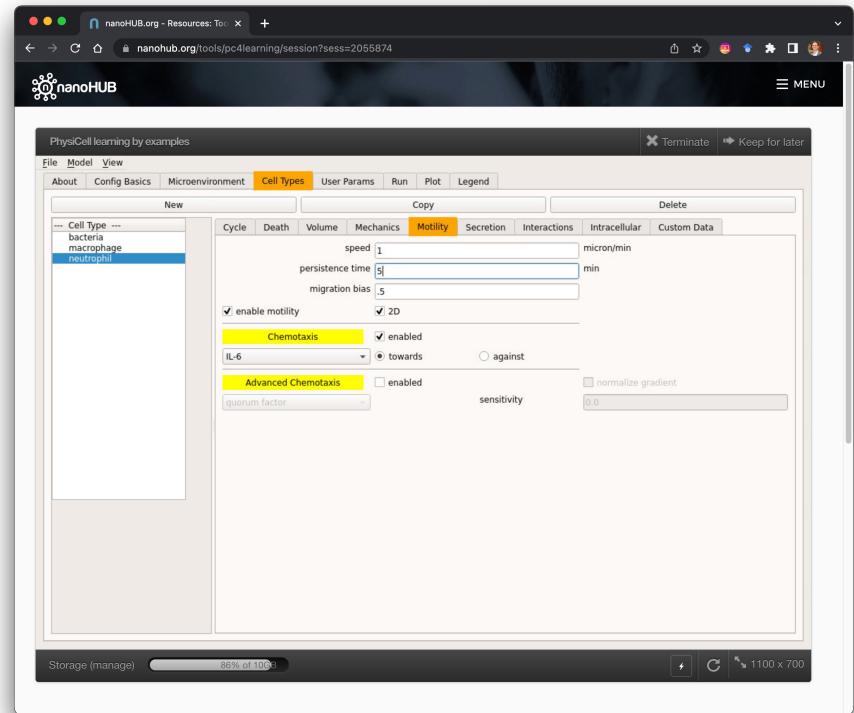


Checklist

- Use online simulator: <http://nanohub.org/tools/pc4learning>
- Build iteratively:
 - Set the domain
 - Add diffusing substrates
 - Add bacteria and test
 - Add macrophages and test
 - Add neutrophils and test

Define neutrophils (1)

- Go to the **cell types** tab
- Select **macrophage**, click **copy**
- Double-click the new type
 - Rename to **neutrophil**
- Let's switch chemotaxis to IL-6
 - Go to **Motility**
 - ◆ Set **migration bias** to **0.5**
 - ◆ Go to **chemotaxis**
 - » Choose **IL-6** from the drop-down



Define neutrophils (2)

- Let's disable secretion
 - Go to **Secretion**
 - ◆ Choose **IL-6** from the drop-down
 - ◆ Set **secretion rate** to **0**

The screenshot shows a web-based application window titled "PhysiCell learning by examples" on the nanoHUB.org platform. The URL in the address bar is nanohub.org/tools/pc4learning/session?sess=2055874. The main menu at the top includes File, Model, View, About, Config Basics, Microenvironment, Cell Types (which is highlighted in yellow), User Params, Run, Plot, and Legend.

The "Cell Types" tab is active, showing a list of cell types: bacteria, macrophage, and neutrophil. The "neutrophil" entry is selected. On the right side of the interface, there are several tabs: Cycle, Death, Volume, Mechanics, Motility, Secretion (which is also highlighted in yellow), Interactions, Intracellular, and Custom Data. Under the "Secretion" tab, the "Cell Type" dropdown is set to "IL-6". The configuration parameters are as follows:

- secretion rate: 0 1/min
- target: 1 sub. density
- uptake rate: 0.0 1/min
- net export rate: 0.0 total/min

At the bottom of the application window, there are buttons for Storage (manage) and a progress bar indicating 86% of 100G. The overall size of the window is listed as 1100 x 700 pixels.

Define neutrophils (3)

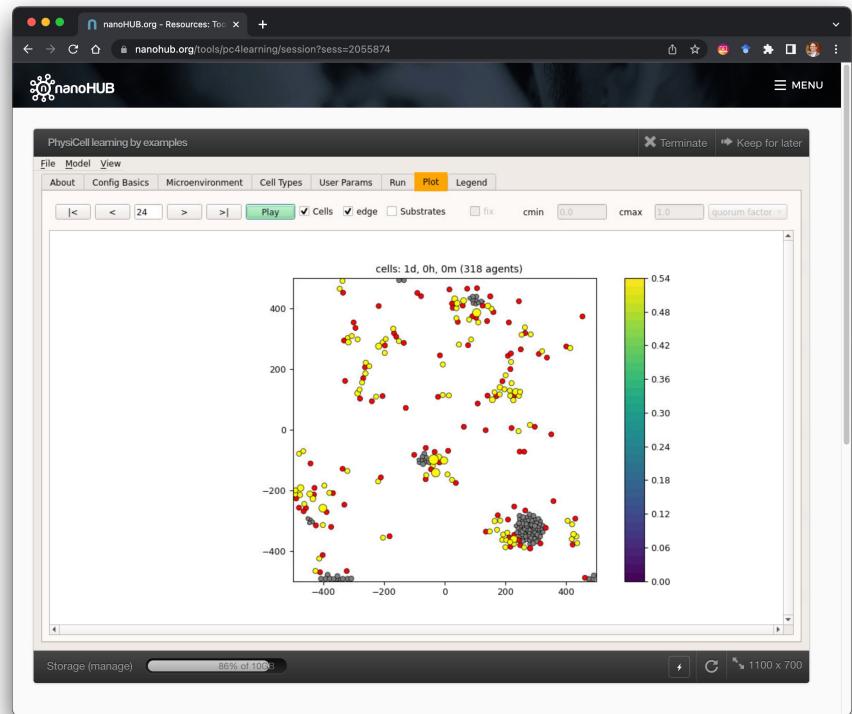
- Let's set up phagocytosis!
 - Go to **Interactions**
 - ◆ Set **dead cell phagocytosis** to 0
 - ◆ Go to **live phagocytosis rate**
 - » Choose **bacteria** in the drop-down
 - » Set the rate to **0.05**

The screenshot shows the nanoHUB.org PhysiCell learning by examples interface. The 'Cell Types' tab is selected. On the left, a sidebar lists 'Cell Type' options: bacteria, macrophage, and neutrophil, with 'neutrophil' currently selected. The main panel displays various parameters under the 'Interactions' tab:

Parameter	Setting	Unit	
dead phagocytosis rate	0	1/min	
live phagocytosis rate	bacteria	0.05	1/min
attack rate	macrophage	0.0	1/min
damage rate	1		1/min
fusion rate	bacteria	0.0	1/min
transformation rate	bacteria	0.0	1/min

Test the model!

- Go to the **run** tab
 - Click **run simulation**
- Go to the **plot** tab
 - View the results!
- Click the **legend** tab to see cell colors defined
 - grey: **bacteria**
 - red: **macrophages**
 - yellow: **neutrophils**



Checklist

- Use online simulator: <http://nanohub.org/tools/pc4learning>
- Build iteratively:
 - Set the domain
 - Add diffusing substrates
 - Add bacteria and test
 - Add macrophages and test
 - Add neutrophils and test

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:

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

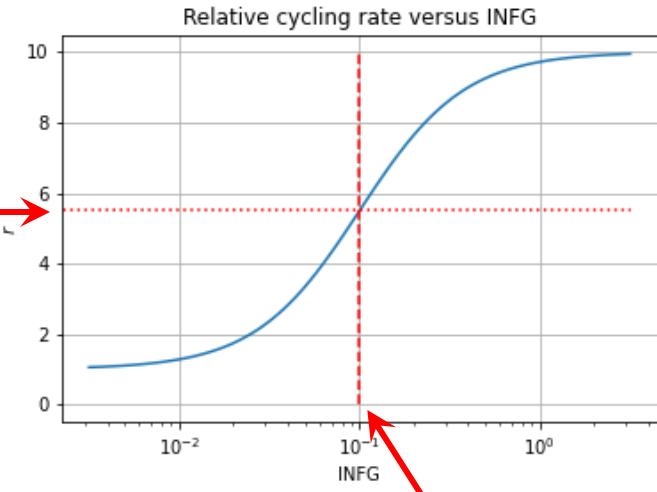
- Refined rule (with parameters):

▪ 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:

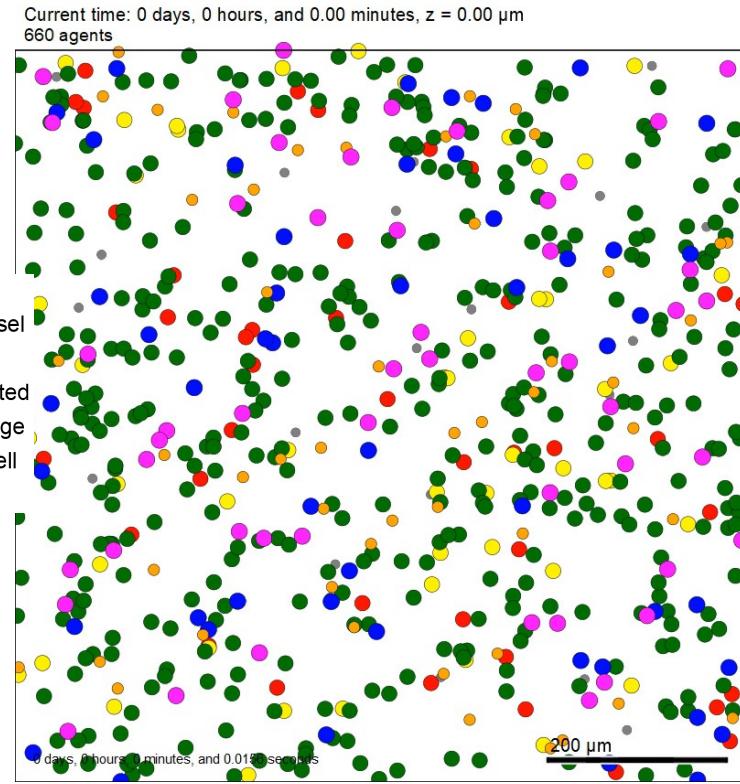
```
<rule>
  <signal name="INFG"/>
  <behavior name="cycle entry"/>
  <response type="increase" form="hill">
    <max_response type="relative">10</max_response>
    <hill_power>1.5</hill_power>
    <half_max>0.1</half_max>
  </response>
</rule>
```

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.

Last Year's Virtual Training Course

15 Virtual Sessions:

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

Sessions include:

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

github.com/PhysiCell-Training/ws2021



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>

