

# PhysiCell Essentials for SMB 2025:

## Hands-on Modeling (Part 1)

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# SMB 2025 Course Materials

- GitHub repository
  - All slides
  - Cell supplementary materials
    - reference cell behaviors
    - reference parameter values (and scientific rationale)
    - and more

<https://github.com/physicell-training/smb2025>



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# PhysiCell SMB2025 Curriculum

- **PhysiCell Essentials Short Course – SMB 2025 Edition**

- **Prerequisites:**

- Basic knowledge of cell biology, concepts of mathematical functions

- **Software requirements:**

- Web browser access, OR installation of PhysiCell Studio

- **Curriculum:**

- *Optional Background: Introduction*

- *Optional: Desktop Installation of PhysiCell Studio*

- **Hands-on work Part 1: Background, Getting Started, and Initial Cancer Model (this session)**

- Hands-on work Part 2: Model Extension to Cancer Chemotherapy & Immunology



# Session Goals

- Starting PhysiCell Studio on Galaxy
- Background
  - Essential points on Agent-based models (ABMs)
  - Cell behaviors, phenotype, and signals
  - Cell rules (using our recent cell behavior grammar)
  - Typical modeling process
- First hands-on model (live modeling)
  - Tumor growth with EMT and MET



# PhysiCell Studio (on Galaxy)

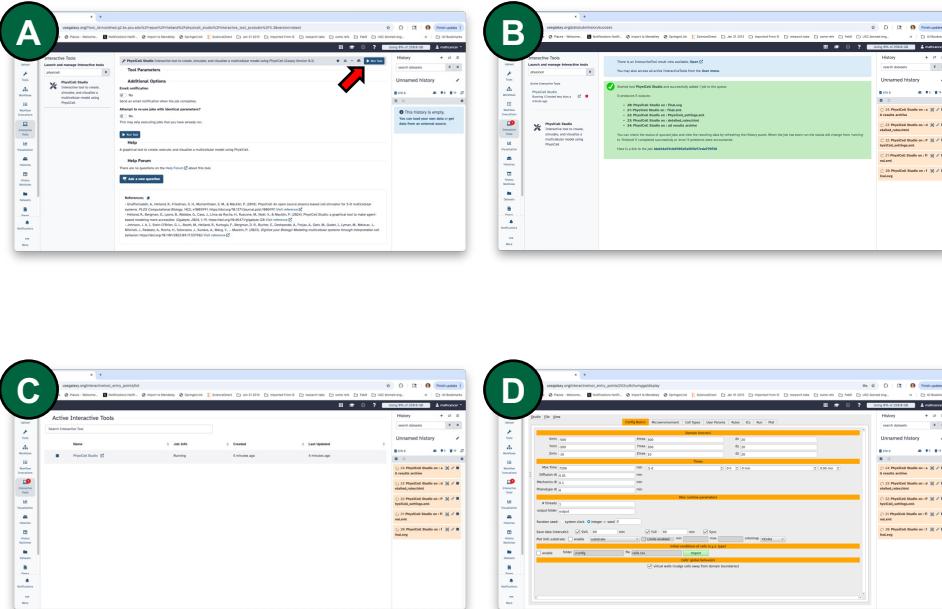


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# Starting PhysiCell Studio on Galaxy

1. Start at UseGalaxy.org
  - Visit <https://usegalaxy.org>
  - If new: Create and validate an account.
  - Sign in with your account
2. Find PhysiCell Studio
  - Click the "all tools" or "interactive tools" search bar on the left
  - Search for "PhysiCell" to find **PhysiCell Studio** as an interactive tool
3. Run (activate) PhysiCell Studio
  - Click the blue "Run Tool" button  at the top (See A.)
  - Wait for studio to activate (watch for 1 on the left side). (See B.)
4. Open the running studio for use
  - Click on "interactive tools" on the left menu.
  - Click once more to collapse the menu. (See C.)
  - When PhysiCell Studio appears in the active list, click to interact. (See D.)
  - Optionally, click the three dots on left and choose **remote rescaling**
5. Further notes and documentation:
  - <https://physicell-studio.readthedocs.io/en/latest/galaxy.html>



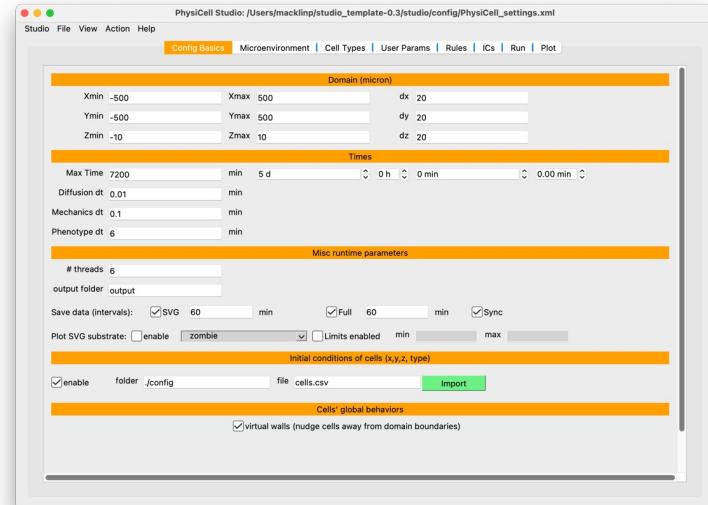
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# PhysiCell Studio: Overview

A graphical user interface (GUI) application to make it easier to build and explore PhysiCell models

- Config basics:** Domain size, simulation duration, output
- Microenvironment:** Diffusing substrates, boundary conditions
- Cell types:** Define cell types and their base phenotypes
- User params:** Model-specific parameters
- Rules:** Hypothesis-based cell behaviors
- ICs:** Initial cell positions
- Run:** Use this to start executing the model
- Plot:** Plot cells and diffusible substrates



Galaxy: [ [Click here](#) ]

NanoHub backup: <https://nanohub.org/tools/pcstudio>

Galaxy: [ [Click here](#) ]



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# Background

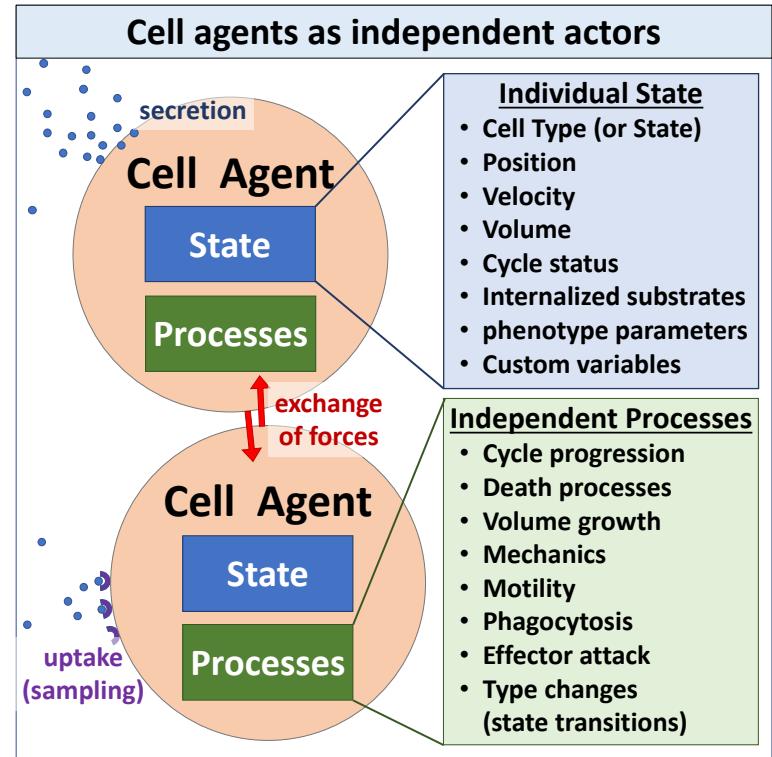


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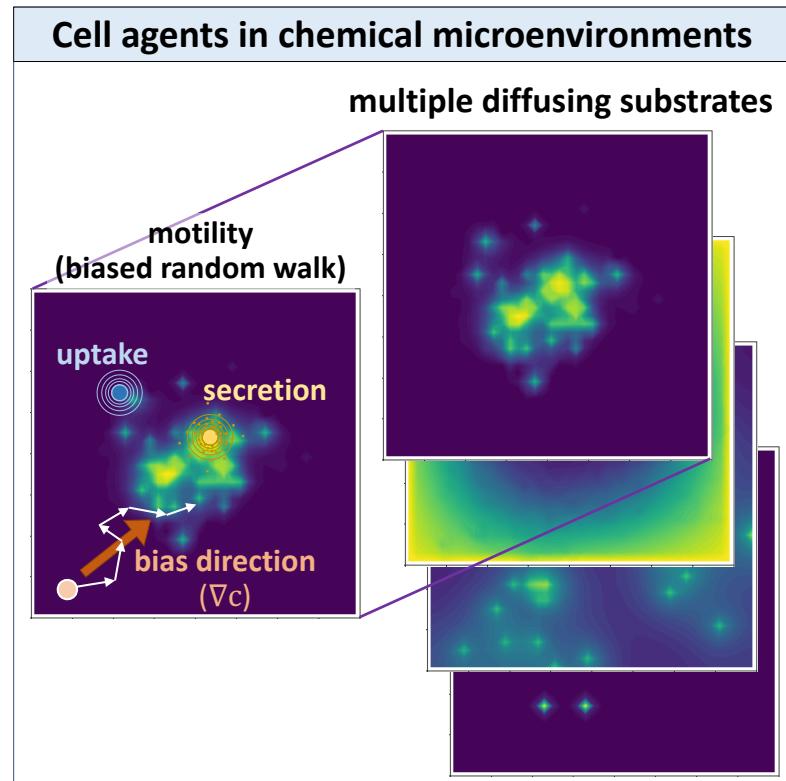
# Agent-based models: overview

- Each cell is an **independent agent** with:
  - **Individual state**
    - Type
    - Position
    - Velocity
    - Phenotype parameters
    - Custom variables
  - **Independent processes**
    - Cycle and death processes
    - Asymmetric division
    - Volume growth
    - Mechanics and motility
    - Secretion and uptake / sampling
    - Phagocytosis
    - Effector attack
    - Cell integrity / damage responses
    - State transitions (change of type)
    - Fusion



# Cell agents live in a virtual environment

- Cells can secrete or consume chemical substrates
- Substrates diffuse and decay
- Cells can sample substrates
- Cells can perform biased random walks that may align with gradients (e.g., chemotaxis)
- Can also add additional mechanical detail (e.g., viscoelastic ECM models)

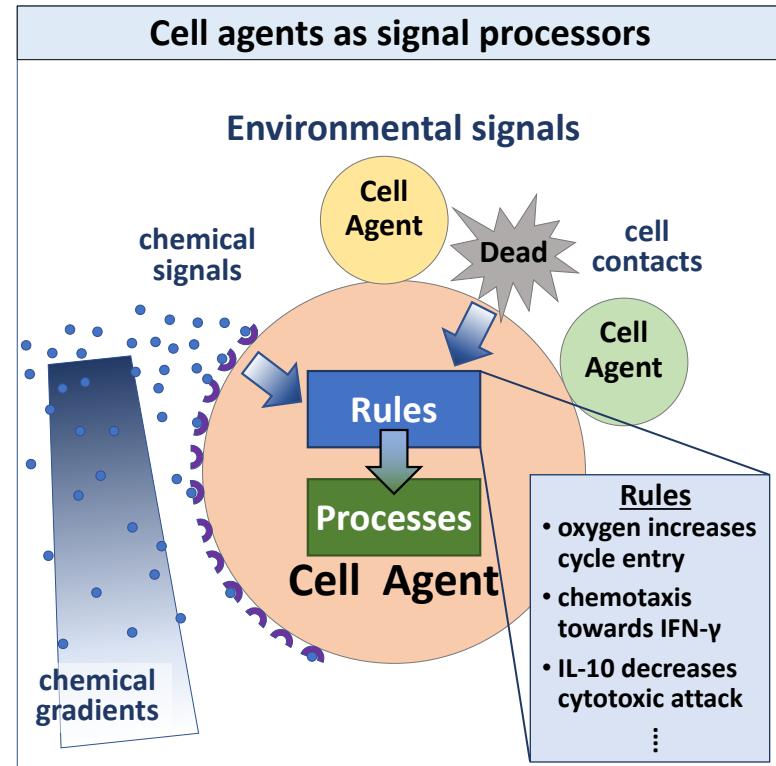


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# Cell agents are signal processors

- Cells interact through chemical and physical **signals** (or stimuli)
  - Secreted chemical signals & gradients
  - ECM properties
  - Contact with a live or dead cell
  - ...
- Signals drive changes in **behavior**
  - Increased or decreased rates of cycling or death
  - Changes in motility, secretion, phagocytosis, ...
- Signal-behavior relationships are **agent rules**



# PhysiCell: A multicellular framework

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

## Features:

- Fully coupled diffusion solvers
- Mechanics-based cell movement
- Cell processes (cycling, motility, ...)
- Signal-dependent phenotype
- Most models: Simple rules-based models
- Advanced users: can write custom C++ additions
- Subcellular models via PhysiBoSS (Boolean networks), LibRoadrunner (SBML ODE models), etc.



## Method:

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



Try this model yourself!

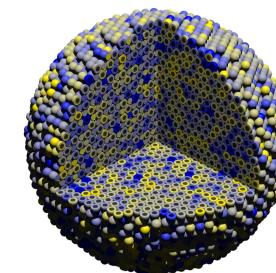
[nanohub.org/tools/pc4heterogen](https://nanohub.org/tools/pc4heterogen)

## References:

Ghaffarizadeh et al., PLoS Comput. Biol. (2018). DOI: [10.1371/journal.pcbi.1005991](https://doi.org/10.1371/journal.pcbi.1005991)

Johnson et al. Cell (2025, in press).

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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# Reference Behavior Models

- All core cell behavior reference models updated in 2025 *Cell* paper:
  - Cycling, asymmetric division, death, migration, secretion/uptake, phagocytosis, effector attack, cell integrity/damage response, fusion
- Supplementary Materials give:
  - Full description for each reference behavior
  - Controllable behavioral parameters
  - Recommended values (and scientific rationale for these values)
- Copy found in the SMB 2025 GitHub Repository
  - <https://github.com/physicell-training/smb2025>



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# Built-in Reference Cell Behaviors

PhysiCell has built-in reference models for key cell processes (behaviors).

Combine and modulate these to create models.

- Cycling (and division)
  - Asymmetric Division
- Apoptotic and necrotic death
- Volume changes
- Secretion and uptake
- Cell-cell adhesion and "repulsion"
- Migration
- Type changes / differentiation
- Phagocytosis
- Fusion
- Effector attack
- Cell integrity



# Reference behavior models: 1

- **Cycling**

- Transition between cycle phases
- Divide into two cells at end of last phase

- **Key parameter(s):**

- cycle entry
  - » (rate of moving from phase 0 to phase 1 (1/min))

- **A bit more detail:**

- Each exit rate  $r_i$  is the transition rate to the next phase

$$r_{i,i+1}$$

- The mean duration  $T_i$  of a phase is related to the exit rate by

$$T_i = \frac{1}{r_i}$$

- **Several built-in models:**

- "Live" (single-phase)
- Quiescent → Cycling
- G0/G1 → S → G2/M
- G0/G1 → S → G2 → M
- Ki67<sup>-</sup> → Ki67<sup>+</sup>
- Ki67<sup>-</sup> → Ki67<sup>+</sup> (pre-mitotic) → Ki67<sup>+</sup> (post-mitotic)



# Reference behavior models: 2

- **Asymmetric division** (from parent type A to daughters A and B)
  - At division, randomly select one daughter cell of type A
  - **Key parameter(s):**
    - Asymmetric division probabilities (dimensionless)
    - **Example:** For cell type A, **asymmetric division to cell type B** is the probability that division yields one daughter cell of type A, and one of type B
- **Apoptosis** (prototypical non-inflammatory death)
  - Gradually shrink, get removed. Relatively short time scale.
  - **Key parameter(s):**
    - apoptotic death rate (rate of starting apoptosis) (1/min)
- **Necrosis** (prototypical inflammatory death)
  - First swell, burst, then shrink. Relatively long time scale
  - **Key parameter(s):**
    - necrotic death rate (rate of starting necrosis) (1/min)



# Reference behavior models: 3

- **secretion, uptake, and export**
  - cells can secrete, uptake (consume), and export diffusible substrates
  - **Key parameter(s):**
    - secretion rates (1/min)
    - secretion targets (substrate/micron<sup>3</sup>)
    - uptake rates (1/min)
    - (net) export rates (substrate/min)

$$\frac{\partial \rho}{\partial t} = D \nabla^2 \rho - \lambda \rho + \sum_{\text{cells } i} \left( \delta(\mathbf{x} - \mathbf{x}_i) V_i \left[ \underbrace{S_i(\rho_i^* - \rho)}_{\text{secretion}} - \underbrace{U_i \rho}_{\text{uptake}} \right] + \delta(\mathbf{x} - \mathbf{x}_i) \underbrace{\tilde{E}_i}_{\text{export}} \right)$$



# Reference behavior models: 4

- **motility**

- biased random walk:

- Move some time along a bias direction, then resample, move again

- **Key parameter(s):**

- migration speed (micron/min)
    - persistence time (min)
    - bias (directedness) (dimensionless)

- **chemotaxis**

- bias direction is a weighted sum of chemical gradients

- **Key parameter(s):**

- weights (-1 to 1) for each chemical gradient (dimensionless)
      - » positive (> 0) weight: movement along this gradient
      - » negative (< 0) weight: movement against this gradient
      - » zero (0) weight: no migration along this gradient



# Reference behavior models: 5

- **cell-cell adhesion (basic)**

- Use potential functions for an attractive force

- **Key parameter(s):**

- adhesive affinity (dimensionless)
    - adhesion strength (micron/min)
    - max (relative) adhesion distance (dimensionless; a multiple of cell's effective radius)

- **cell-cell adhesion (elastic / advanced)**

- form and break spring links to contacting cells

- **Key parameter(s):**

- adhesive affinity (dimensionless)
    - elastic constant (1/min)
    - attachment rate (1/min)
    - detachment rate (1/min)
    - maximum number of adhesions (dimensionless)



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# Reference behavior models: 6

- **resistance to deformation and overlap**

- Use potential function as a "repulsive" force
- **Key parameter(s):**
  - repulsive strength (micron/min)

- **transition / transformation (type change)**

- Transition from type  $i$  to type  $j$  (1/min)
  - Differentiation, Transdifferentiation, mutation, ...
- **Key parameter(s):**
  - transition rates
  - **Example:** For cell type A, **transition to cell type B** is the rate at which the type can transform into cell type B

- **fusion**

- cells  $i$  and  $j$  combine volumes, re-center position
- **Key parameter(s):**
  - fusion rates (type  $i$  to type  $j$ ) (1/min)
  - **Example:** For cell type A, **fuse to cell type B** is the rate at which the cell can fuse with a cell of type B



# Reference behavior models: 7

- **phagocytosis**

- Cell  $i$  consumes cell  $j$  (and acquires its volume)
- Cell  $i$  uses its built-in volume model to return to its original volume

- **Key parameter(s):**

- rates of phagocytosing dead cells (1/min)
  - » (separate rates for apoptotic, necrotic, and other dead cells)
- rates of phagocytosing live cell types (1/min)

- **effector attack**

- Cell  $i$  attacks (damages) cell  $j$ 
  - rate of initiating attack is a function of attack rate of  $i$  on  $j$  and immunogenicity of  $j$  to  $i$
  - the attack increases damage of  $j$
  - cells form (spring) adhesion during attack.
  - Attack has stochastic duration
  - requires an additional hypothesis to cause death in cell  $j$

- **Key parameters:**

- attack rates (one per live cell type) (1/min)
- immunogenicities (dimensionless) ← not currently accessible in Studio
- attack damage rate (1/min)
- attack duration (min)



# Reference behavior models: 8

- **cell integrity**

- Cell  $i$  can undergo and repair (generic) damage
  - damage rate (e.g., from a drug or alpha particles)
    - » Can use to increase cell death, increase mutations, block cell cycle, ...
  - damage repair rate

- **Key parameter(s):**

- damage rate (1/min)
- damage repair rate (1/min)

$$\frac{d[\text{Damage}]}{dt} = [\text{damage rate}] + [\text{damage from effector attack}] - [\text{damage repair rate}][\text{Damage}]$$

- **reference behavior models in development**

- Polarized cell adhesion and division
- ECM interactions
- Spontaneous variation
- (and also built-in lineage tracking)



# Cell Phenotype

- The cell's key parameters are organized according to these processes:
  - Cycle
  - Death
  - Volume (and Geometry)
  - Mechanics
  - Motility
  - Secretion (and Uptake)
  - Interactions
  - Transformations
  - Integrity
- Think of it as a **vector of phenotypic properties  $p(t)$  that vary in time.**
- Each cell has a "base" phenotype  $p_0$  (inherited from its cell definition)



# Built-In Signals

- Based on the cell types and diffusible substrates in a simulation, we auto-generate a dictionary of available signals
- With standardized access, it's much easier to write cell rules
- This allows for a controlled vocabulary (an ontology)

Signal name	Biophysical meaning
{substrate X}	extracellular concentration of chemical factor X
intracellular {substrate X}	intracellular concentration of chemical factor X
{substrate X} gradient	slope of the extracellular concentration field of factor X
pressure	mechanical pressure (from other cells in close proximity)
volume	the cell's current total volume
contact with {cell type X}	number of cells of type X that are in physical contact
contact with live cell	number of live cells that are in physical contact
contact with dead cell	number of dead cells that are in physical contact
contact with basement membrane	1 if in contact with basement membrane. 0 otherwise.
damage	amount of damage (of any type)
dead	1 if the cell is dead (or dying). 0 otherwise.
total attack time	total amount of time the cell has been attacked.
time	current simulation time
custom:{X}	use a custom variable or symbol X to drive cell behavior



# Signal-Based Behavioral Responses

- If signal  $S$  increases / decreases behavior  $B$ 
  - Vary behavioral parameter  $p$  with base value  $p_0$  and maximal response value  $p_M$

$$p(s) = p_0 + (p_M - p_0)R(s) = (1 - R(s)) \cdot p_0 + R(s) \cdot p_M$$

- We generally use **Hill response functions**:

$$R(s) = \frac{s^h}{s_{\text{half}}^h + s^h} = \frac{\left(\frac{s}{s_{\text{half}}}\right)^h}{1 + \left(\frac{s}{s_{\text{half}}}\right)^h} \quad \text{if } s \geq 0, \quad \text{and } H(s) = 0 \text{ if } s < 0.$$



# Key Modeling steps

## 1. Plan the modeling problem.

- What are the important things we want to learn?
- What cell types are important?
  - What are their key behaviors?
  - What diffusible factors drive their behaviors?
  - Any other important interactions?
- Can we estimate parameters (at least to order of magnitude)?
- Can we build the model sequentially? (Add components one at a time?)

## 2. Set up diffusing factors.

## 3. Set up cell types.

## 4. Add rules.

## 5. Simulate and assess.

## 6. Iterate and improve.



# Iterative modeling example

- In this session, we'll iteratively build a simple tumor model, bit-by-bit:
  1. **Growing tumor with oxygen consumption**
  2. Add a mechanofeedback on cycling
  3. Add oxygen-driven cycling
  4. Add an oxygen-based switching to/from an invasive phenotype (EMT and MET)
- In the next session, we'll extend this model to include therapy and immune interactions:
  1. Add a chemotherapy
  2. Add release of debris from dead cells
  3. Add macrophages
  4. Add inflammation
  5. Add effector T cells
  6. Improvised modeling / exploration



# Initial tumor and oxygen consumption



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# Growing tumor with oxygen: 1

- First, we add oxygen in the **Microenvironment** tab
- We use the **diffusion length scale** from physics / applied mathematics:
  - Penetration into a tissue is competition between effects:
    - Diffusion ( $D$ ) increases spread
    - Uptake ( $U$ ) and decay ( $\lambda$ ) tend to halt spread

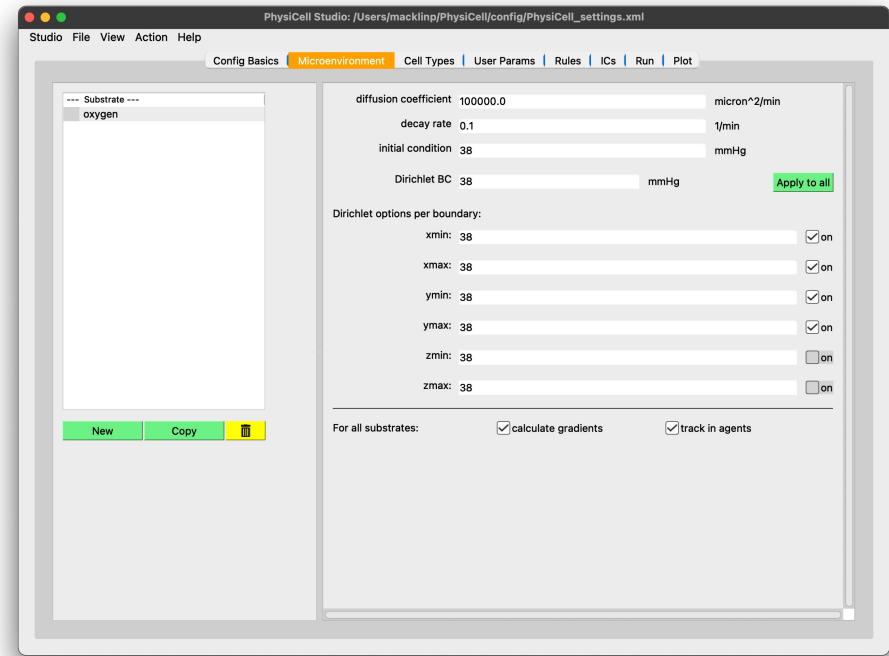
$$L = \sqrt{\frac{D}{U + \lambda}}$$

- Literature for oxygen:
  - $D \sim 10^5 \frac{\mu\text{m}^2}{\text{min}}$
  - $L \sim 100 \mu\text{m}$  in dense tissues
  - We'll assume  $L$  is tenfold larger in cell-free tissue, so  $\lambda \sim 0.1 \text{ min}^{-1}$
  - In physioxic tissues,  $\text{pO}_2 \sim 5\% = 38 \text{ mmHg}$



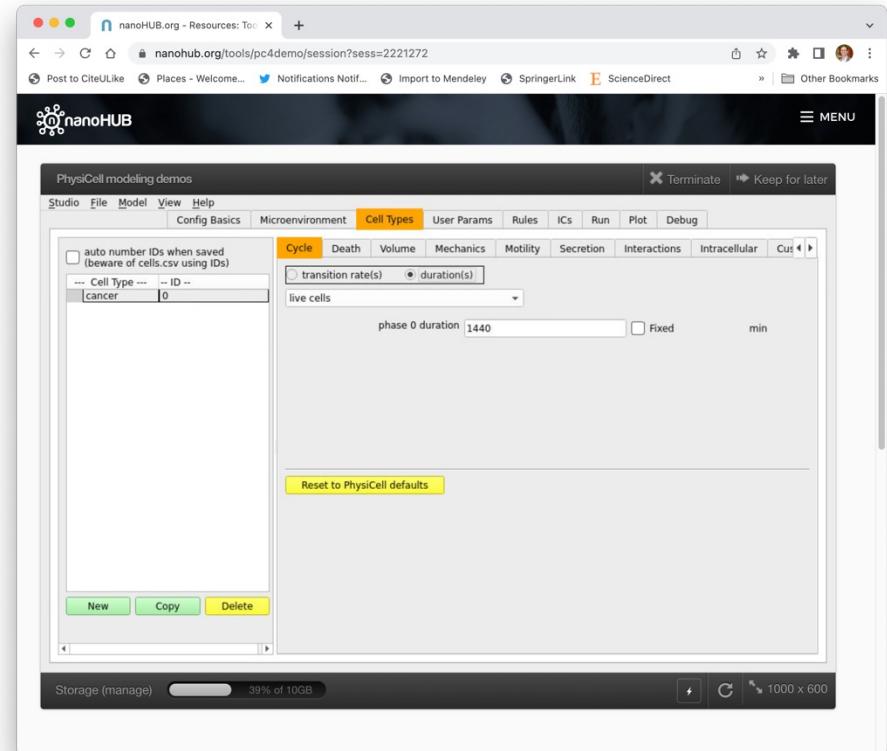
# Growing tumor with oxygen: 2

- Go to **Microenvironment** tab
  - double-click **substrate**
  - rename it to **oxygen**
  - set the **decay rate** to 0.1
  - set the **initial condition** to 38 mmHg
  - set the **boundary condition** to 38 mmHg
    - Hint: use the **apply to all** button
    - Make sure they enabled on X and Y



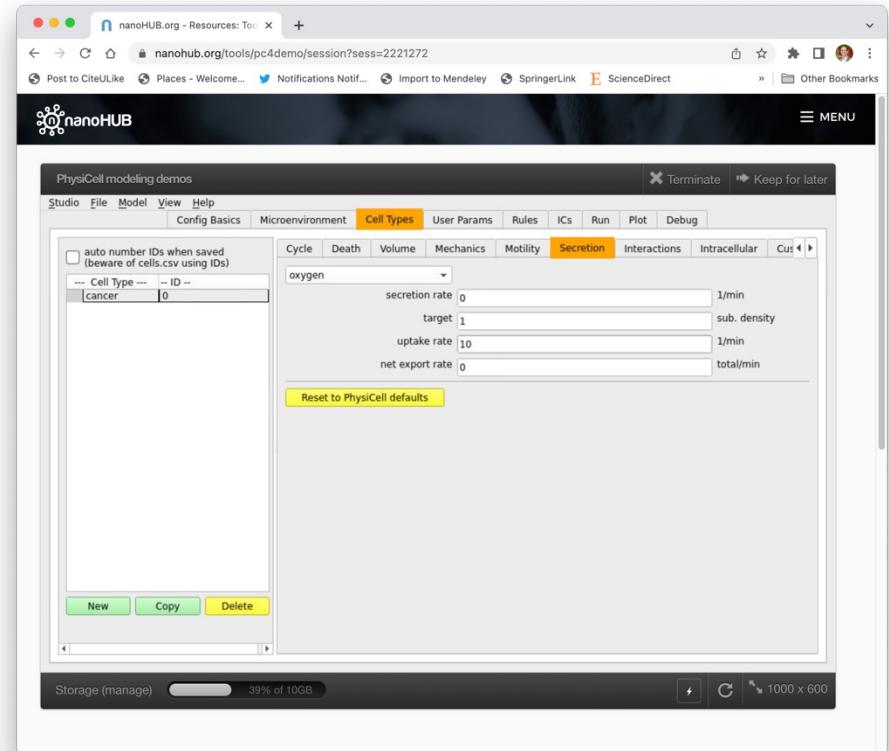
# Setting up cancer cells: 1

- Set the name
  - Go to **Cell Types** tab
  - double-click **default**
  - rename it to **cancer**
- Set cycling to ~24 hour cycle
  - Go to **cycle**
  - Choose the simpler **live cells** model
  - Use the **duration** representation
  - Set mean duration to 1440 min = 24 h



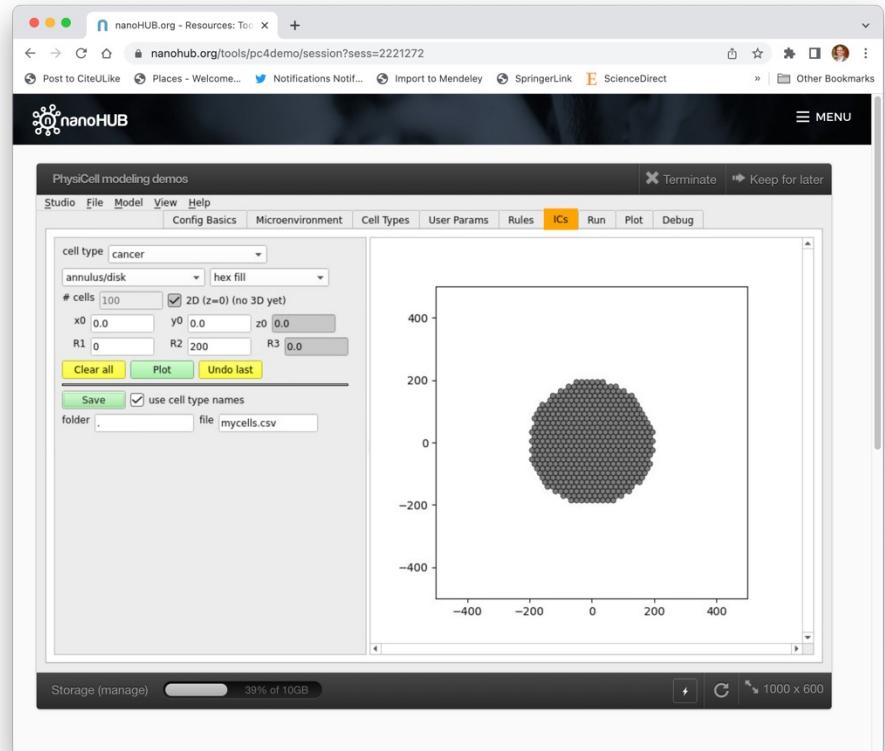
# Setting up cancer cells: 2

- Set up oxygen consumption
  - Go to **secretion**
  - Choose **oxygen** from the drop-down
  - Set **uptake** to 10
    - Chosen for a 100 micron length scale



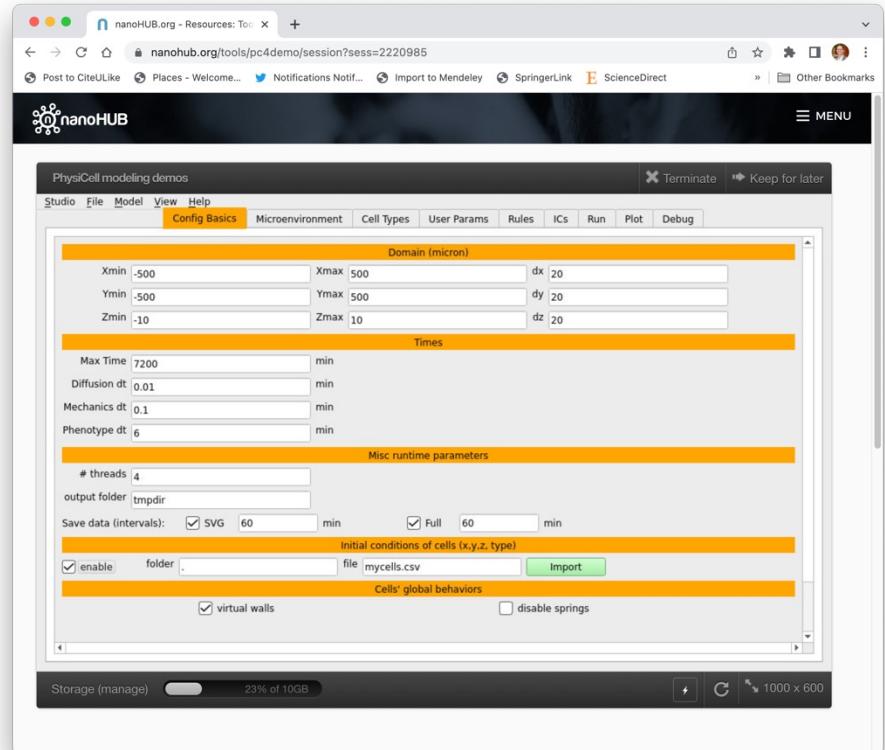
# Set up an initial state: 1

- We want a packed 400 micron circle of cancer cells
  - Go to the **ICs** tab
  - Choose **cancer** cell type
  - Choose **annulus/disk**
  - Choose **hex fill**
  - Choose min radius (R1) = 0
  - Choose max radius (R2) = 200
  - Click **plot**
  - Click **save**



# Set up an initial state: 2

- Make sure PhysiCell uses the initial list of cells
  - Go to **config basics**
  - Browse to **initial conditions of cells**
  - Set the **enabled** box
- Set to **4 threads** for faster runs.



# Set up an initial state: 3

- Make sure PhysiCell doesn't randomly place other cells
  - Go to **User Params** tab
  - Go to the **number\_of\_cells** variable
  - Set the value to **0**

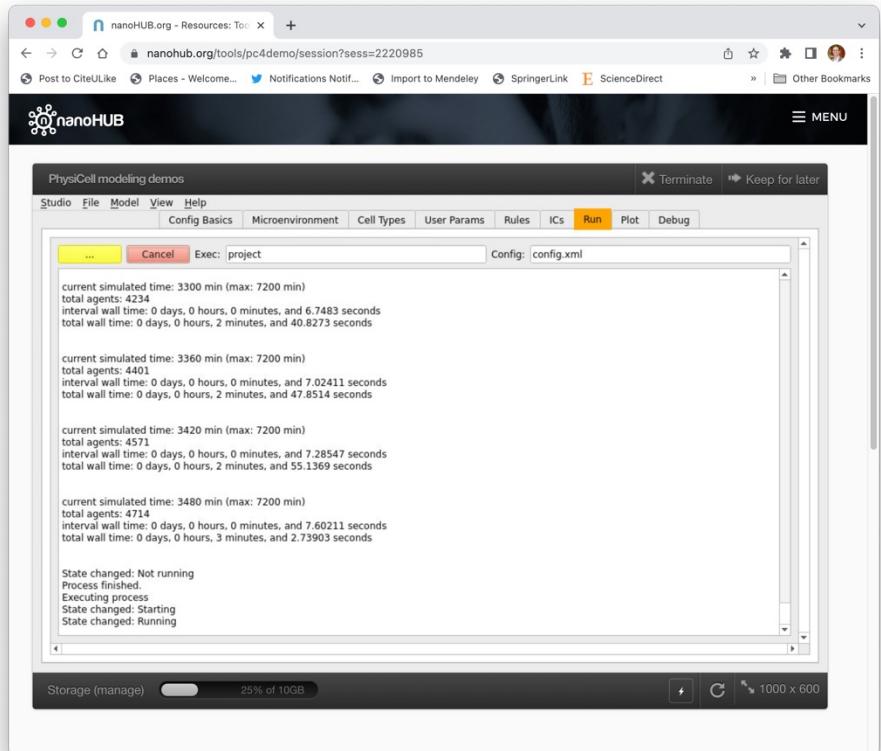
The screenshot shows a web browser window for nanoHUB.org. The URL is [nanohub.org/tools/pc4demo/session?sess=2220985](https://nanohub.org/tools/pc4demo/session?sess=2220985). The page title is "PhysiCell modeling demos". The "User Params" tab is selected in the navigation bar. A table lists parameters with their types, values, units, and descriptions. The "number\_of\_cells" parameter is highlighted with a yellow border, showing its value is 0. A note at the top of the table says "(Note: validation check performed at Save or Run)".

Name	Type	Value	Units	Desc
1 random_seed	int	0	dimensionless	
2 number_of_cells	int	0	none	number of cells per each cell type
3	double			
4	double			
5	double			
6	double			
7	double			
8	double			
9	double			
10	double			
11	double			
12	double			
13	double			



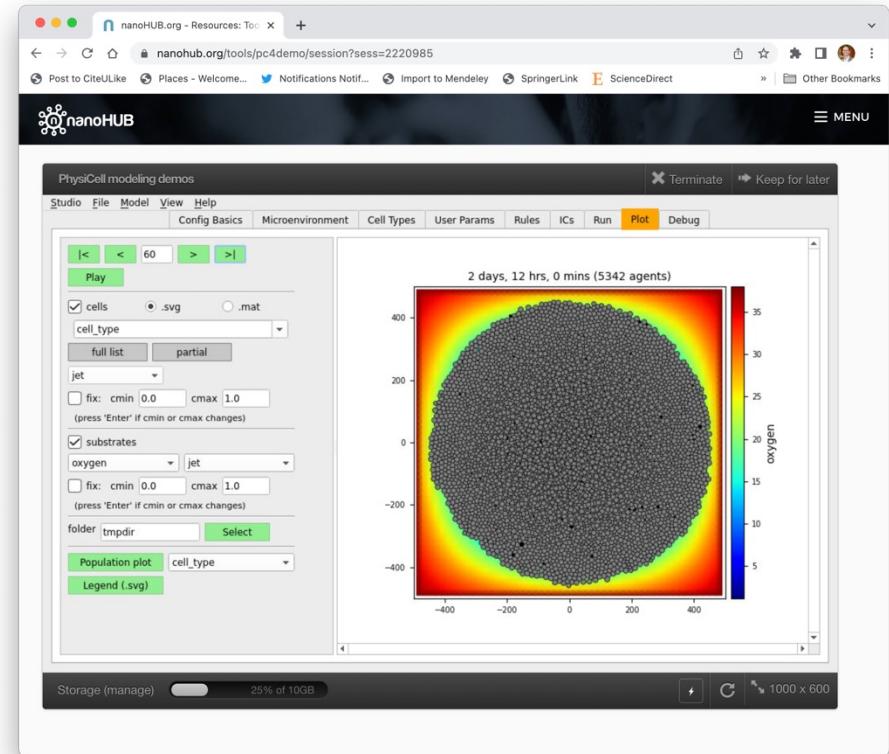
# Run the model!

- Go to the **Run** tab
- Click the **run simulation** button
  - Click **cancel** if you ever need to interrupt it



# View and explore the simulation

- Go to the **Plot** tab
- To navigate times:
  - Click |< to go to the beginning
  - Click > to go forward by one frame
  - Click < to go back by one frame
  - Click >| to go to the last frame
- Click **cells** to toggle cell plots on or off
  - For now, use **SVG** coloring
  - We'll show how to change cell coloring soon
- Click **substrates** to toggle plots of diffusible substrates
  - Choose the field from the first drop-down
  - Choose the color map from the second



# Iterative modeling example

- In this session, we'll iteratively build a simple tumor model, bit-by-bit:
  1. Growing tumor with oxygen consumption
  2. **Add a mechanofeedback on cycling**
  3. Add oxygen-driven cycling
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  5. Add effector T cells
  6. Improvised modeling / exploration



# Let's improve the biology

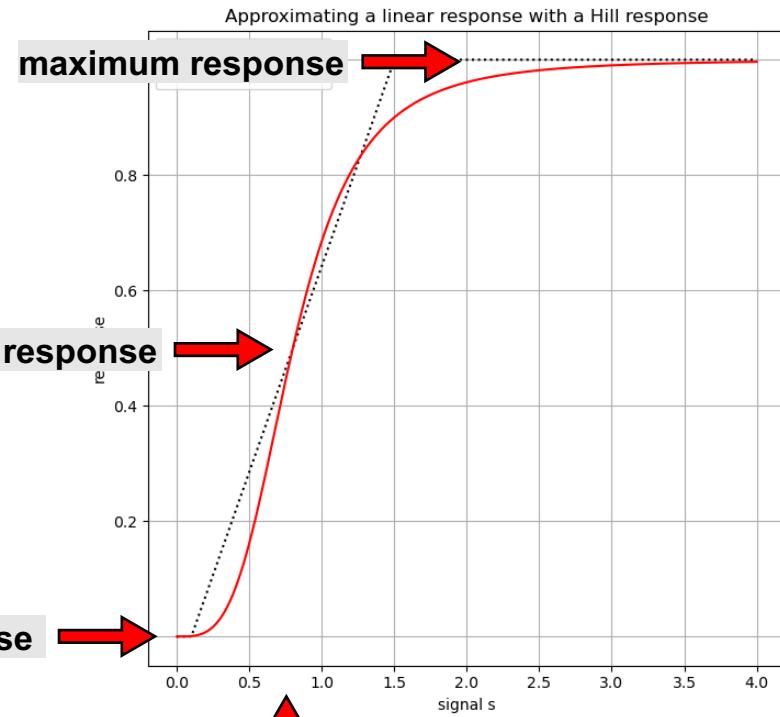
- Notice a **non-physical behavior**
  - All cells proliferate regardless of available space.
  - Non-physical (physically impossible) overlap of cells
- Non-physical behaviors (or a failure to match reality) leads us to conclude that either:
  - Our hypotheses are wrong, OR
  - We are missing a hypothesis
- We'll add a new hypothesis:
  - mechanical pressure (compression) reduces cell cycling



# Hill response functions

- A widespread sigmoidal response curve in PKPD and systems biology
  - Varies from 0 (at signal=0) to 1 (as signal  $\rightarrow$  infinity)
  - Completely characterized by:
    - half-maximum: Input value where curve reaches half of max effect
    - Hill power: How steeply it approaches 1

$$H(s; s_{\text{half}}, h) = \frac{s^h}{s_{\text{half}}^h + s^h} = \frac{\left(\frac{s}{s_{\text{half}}}\right)^h}{1 + \left(\frac{s}{s_{\text{half}}}\right)^h} \quad \text{if } s \geq 0, \quad \text{and } H(s) = 0 \text{ if } s < 0.$$



# Our mathematics

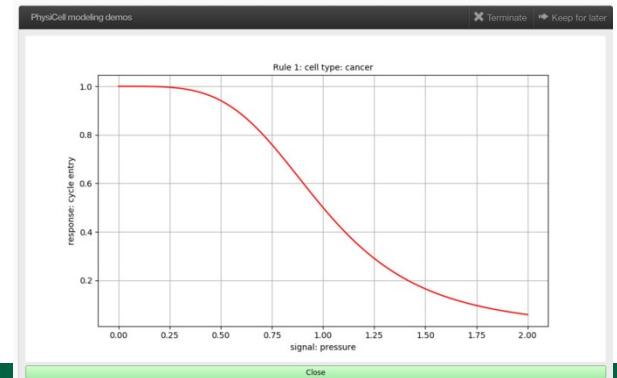
- Mathematical form of pressure:

- Based on potentials
  - Nondimensionalized to 1 for 3D confluent tissues
  - Nondimensionalized to 0.5 for 2D confluent tissues

$$\frac{p^4}{1^4 + p^4}$$

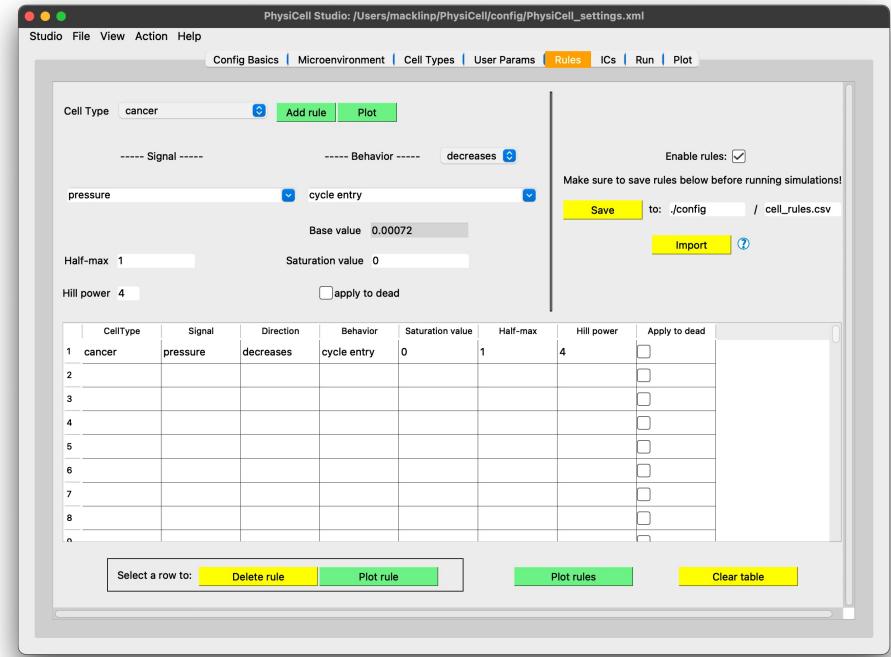
- We'll suppose cancer cells can accept some compression

- Use a **half-max** of 1:
    - Once pressure hits 1.0, cycling is already halved
  - Use a **saturation value** of 0:
    - As pressure increases, cycling goes to 0
  - Use a strong **Hill parameter** of 4
    - Spreads the response over pressures from 0 to 2



# Add the rule: 1

- Go to the **rules** tab
  - Select **cancer** cell
  - Choose **pressure** as the signal
  - Choose **cycle entry** as the behavior
  - Choose **decreases** as the response
  - Choose **0** as the saturation value of the behavior
  - Choose **4** as the Hill power
  - Choose **1** as the half-max
  - Then, click **add rule**
  - Click **save** on the right.



# Add the rule: 2

- Make sure we use the rule
  - At the bottom, use a name **rules.csv**
  - Click the **save** button
  - Click the **enable** checkbox
- Run the model as before

The screenshot shows the nanoHUB.org interface for PhysiCell modeling. The 'Rules' tab is active. A table defines rules for 'cancer' cells:

Cell Type	Signal	Direction	Behavior	saturation value	Half-max	Hill power	Apply to dead
1 cancer	pressure	decreases	cycle entry	0	1	4	<input type="checkbox"/>
2							<input type="checkbox"/>
3							<input type="checkbox"/>
4							<input type="checkbox"/>
5							<input type="checkbox"/>
6							<input type="checkbox"/>

Buttons at the bottom include 'Import', 'Save', 'Plot rule', 'Clear table', and a file input field set to 'rules.csv'. A checkbox labeled 'enable' is checked.

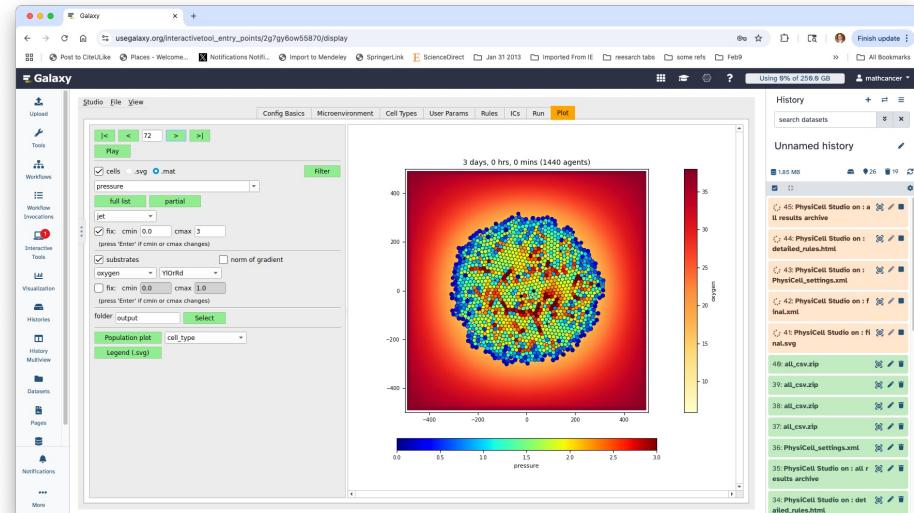


# Visualization

- Now, let's color cells by their color
  - Go to **Plot**, then **cells**
  - Choose **mat** instead of **SVG**
  - Choose **pressure** from the drop-down.
    - I suggest a **jet** coloring
    - I suggest fixing the range 0 to 3.

- Options:
  - Click **full list** to see a list of all possible variables we can use to color the cells
  - Choose color maps and ranges, etc.

- Observe:
  - With this feedback, there's much less cycling.
  - Pressure tends to be higher in the center



# Oxygen-based cycling



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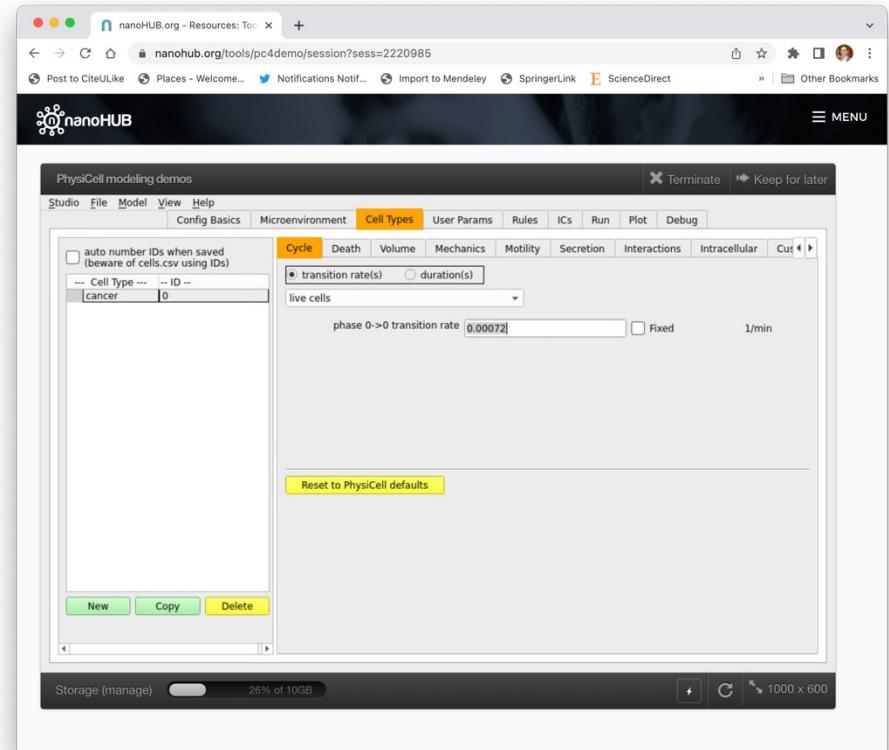
# Iterative modeling example

- In this session, we'll iteratively build a simple tumor model, bit-by-bit:
  1. Growing tumor with oxygen consumption
  2. Add a mechanofeedback on cycling
  - 3. Add oxygen-driven cycling**
  4. Add an oxygen-based switching to/from an invasive phenotype (EMT and MET)
- In the next session, we'll extend this model to include therapy and immune interactions:
  1. Add a chemotherapy
  2. Add release of debris from dead cells
  3. Add macrophages
  4. Add inflammation
  5. Add effector T cells
  6. Improvised modeling / exploration



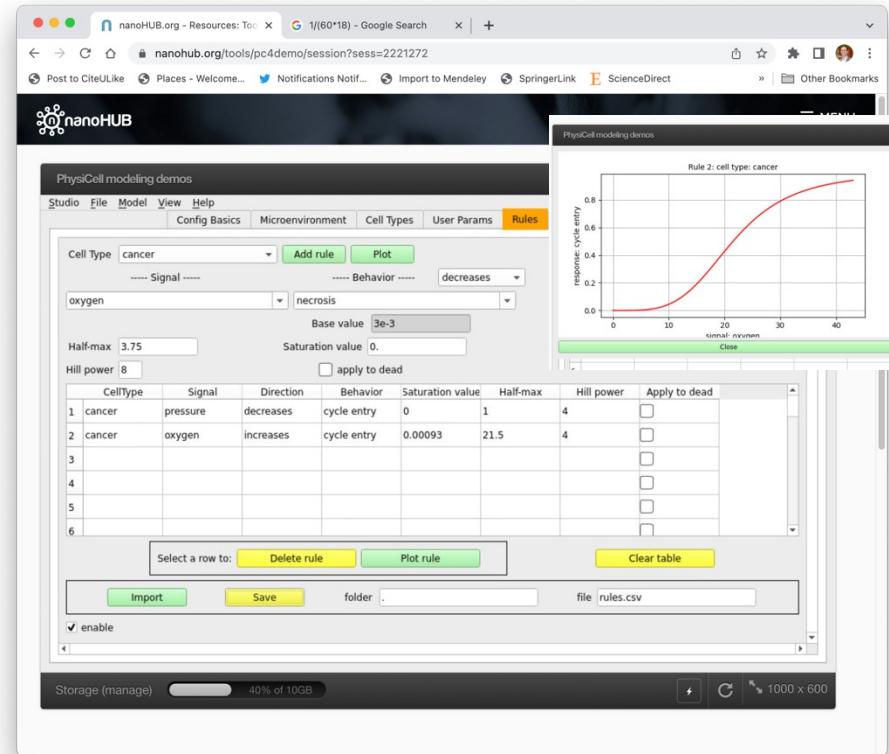
# Oxygen-based cycling setup: 1

- We'll suppose cycle entry increases with oxygen availability
  - This is a sort of proxy for cell energy
- We'll need to modify our base phenotype:
  - Phenotype is the **base behavior** in the absence of other signals
  - No cycling in the absence of oxygen
    - So, we need to set base cycle rate = 0
- Go to **cell types**
  - Choose **cancer**
  - Go to the **cycle** sub-tab
  - View it as a **transition rate**
  - Set the rate to 0



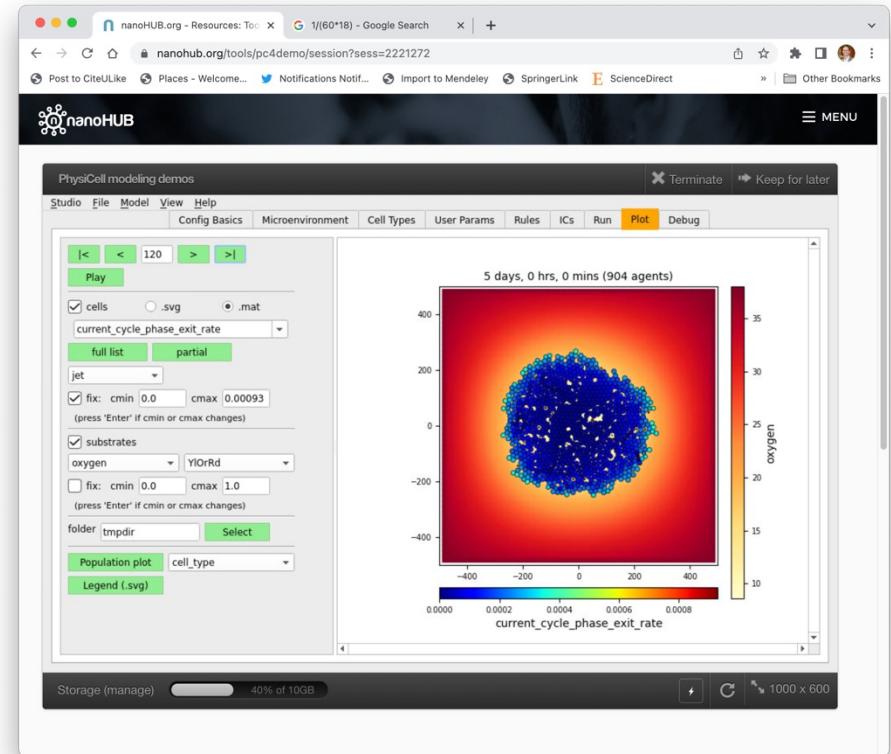
# Oxygen-based cycling setup: 2

- Go to the **rules** tab
  - Select **cancer** cell
  - Choose **oxygen** as the signal
  - Choose **cycle entry** as the behavior
  - Choose **increases** as the response
  - Choose **0.00093** as the saturation value of the behavior
    - This sets a max cycle time of around 18 hours
  - Choose **21.5 mmHg** as the half-max
  - Choose **4** as the Hill power
  - Then, click **add rule**
- Make sure to click the **save** button!



# Run and Visualize

- Let's color cells by cycling:
  - Go to **cells** and select **mat**
  - Use the **full list** drop-down to get more options
  - Use **current\_cycle\_phase\_exit\_rate**
  - Set the range from 0 to 0.00093
- This says how quickly cells are trying to exit the current cycle phase
  - (In this case, phase 0: "live")
  - Notice greatest cycling along the outer periphery



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# **Adding invasive cells (EMT and MET)**



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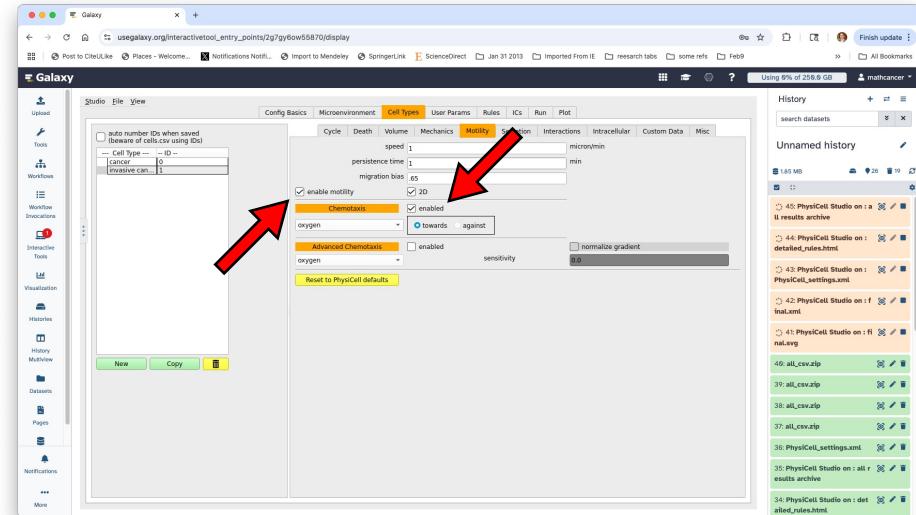
# Iterative modeling example

- In this session, we'll iteratively build a simple tumor model, bit-by-bit:
  1. Growing tumor with oxygen consumption
  2. Add a mechanofeedback on cycling
  3. Add oxygen-driven cycling
  4. **Add an oxygen-based switching to/from an invasive phenotype (EMT and MET)**
- In the next session, we'll extend this model to include therapy and immune interactions:
  1. Add a chemotherapy
  2. Add release of debris from dead cells
  3. Add macrophages
  4. Add inflammation
  5. Add effector T cells
  6. Improvised modeling / exploration



# Invasive cells: 1

- First, we add a new cell type
  - Go to the **Cell types** tab
  - Select on **cancer**
  - Choose **copy**
  - Double-click and rename to **invasive cancer**
- Enable migration
  - Go to **motility**
  - Set **migration speed** to 1
  - Set **migration bias** to 0.65
  - Enable **migration**
  - Enable **chemotaxis**
    - Use **towards oxygen**



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# Invasive cells: 2

- Now, make invasive cells less adhesive
  - Go to **mechanics**
  - Set **cell-cell adhesion strength** to **0**
- And make cancer cells switch to invasive cancer cells in low O<sub>2</sub>:
  - Go to **interactions**
  - Select **cancer** cells
  - Set the **transformation rate to invasive cancer** to **0.01**
    - (100 minute mean waiting time)

The screenshot shows the 'Mechanics' tab of the PhysiCell Studio configuration interface. Under the 'cancer' cell type, the 'cell-cell adhesion strength' is set to 0.0. Other parameters like 'cell adhesion affinity' and 'attachment rate' are also visible.

The screenshot shows the 'Interactions' tab of the PhysiCell Studio configuration interface. Under the 'cancer' cell type, the 'transformation rate to invasive cancer' is set to 0.01. Other parameters like 'attack rate' and 'attack damage rate' are also visible.



# Invasive cells: 3

- For cancer cells, oxygen prevents transition to the invasive type:
  - Go to rules
    - Select **cancer** cell
    - Choose **oxygen** as the signal
    - Choose **transform to invasive cancer** as the behavior
    - Choose **decreases** as the response
    - Choose **0** as the saturation value of the behavior
    - Choose **5** as the Hill power
    - Choose **7.5** as the half-max
  - Then, click **add rule**

CellType	Signal	Direction	Behavior	Saturation value	Half-max	Hill power	Apply to dead	
1	cancer	pressure	decreases	cycle entry	0	1	4	<input type="checkbox"/>
2	cancer	oxygen	increases	cycle entry	0.00093	21.5	4	<input type="checkbox"/>
3	cancer	oxygen	decreases	transform to invasive cancer	0	7.5	5	<input type="checkbox"/>
4								<input type="checkbox"/>
5								<input type="checkbox"/>
6								<input type="checkbox"/>
7								<input type="checkbox"/>
8								<input type="checkbox"/>
9								<input type="checkbox"/>
10								<input type="checkbox"/>

▪ Then, click **add rule**



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# Invasive cells: 4

- For invasive cancer cells, oxygen increases transition to the non-invasive invasive type:
  - Go to rules
    - Select **invasive cancer** cell
    - Choose **oxygen** as the signal
    - Choose **transform to invasive cancer** as the behavior
    - Chose **increases** as the response
    - Choose **0.1** as the saturation value of the behavior
    - Choose **5** as the Hill power
    - Choose **7.5** as the half-max
  - Then, click **add rule**
  - Don't forget to **save**

CellType	Signal	Direction	Behavior	saturation value	Half-max	Hill power	Apply to dead	
1	cancer	pressure	decreases	cycle entry	0	1	4	<input type="checkbox"/>
2	cancer	oxygen	increases	cycle entry	0.00093	21.5	4	<input type="checkbox"/>
3	cancer	oxygen	decreases	transform to invasive cancer	0	7.5	5	<input type="checkbox"/>
4	invasive cancer	oxygen	increases	transform to cancer	0.01	7.5	5	<input type="checkbox"/>
5								<input type="checkbox"/>
6								<input type="checkbox"/>
7								<input type="checkbox"/>
8								<input type="checkbox"/>
9								<input type="checkbox"/>
10								<input type="checkbox"/>



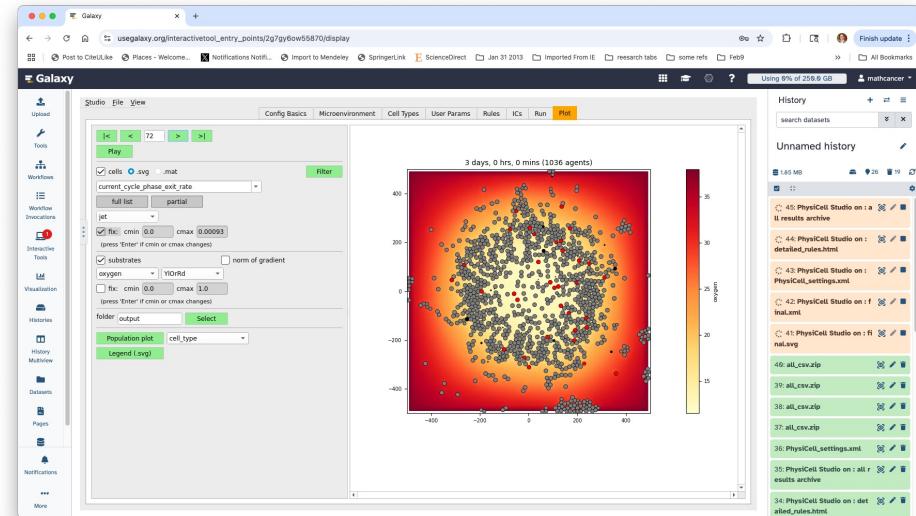
# Run and Visualize

- Now, let's color cells by their color

- Go to Plot, then cells
- Choose SVG

- Observe:

- Invasive cells (red) stream out of low oxygen regions
- Once they reach higher oxygen, they stop and switch back
- These escaped cells nucleate new tumors



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# Acknowledgements

- **Macklin Lab and IU (selected)**
  - **Randy Heiland** : major development of PhysiCell Studio and ports to NanoHub and Galaxy. PhysiCell core developer.
  - **Heber Rocha** : model grammar development, stability analyses on HPC, and more! PhysiCell core developer
  - **Elmar Bucher** Data loading in Python, visualization , ...
  - **Aneequa Sundus** : Training apps, model development, ...
  - **Robert Quick** : Cloud development and allocations
- **Johns Hopkins (selected)**
  - **Genevieve Stein-O'Brien** : CoGAPS, model development
  - **Atul Deshpande** : uncertainty analysis, model selection
  - **Jeanette Johnson** : immunology, simulation model development
- **University of Maryland**
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  - **Daniel Bergman** : model grammar development, simulation model development, PhysiCell Studio. PhysiCell core developer.
- **Oregon Health & Science University (selected)**
  - **Lisa Coussens** : cancer immunology
  - **Laura Heiser** : cancer immunology, modeling
  - **Joe Gray** : cancer biology & physics
  - **Young Hwan Chang** : Image analyses, AI
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    - (Heiser, Macklin, Gilkes, Ewald PIs on several awards)



# PhysiCell Curriculum: Next Steps

- **PhysiCell OpenVT Workshop at SMB 2025**
  - **Prerequisites:**
    - Basic knowledge of cell biology, concepts of mathematical functions
  - **Software requirements:**
    - Web browser access, OR installation of PhysiC
  - **Curriculum:**
    - Hands-on work Part 1: Getting Started, and Villager/Zombie Model
    - **Hands-on work Part 2: Cancer Chemotherapy & Immunology Models**

**Other Virtual Training at <https://physicell.org/Training.html>**

- **PhysiCell Essentials**
- **Integration of Boolean Networks with PhysiBoSS**
  - Learn how to integrate Boolean signaling networks into PhysiCell Models
- **Advanced PhysiCell Modeling**
  - Learn about creating non-standard model components and visualization in C++
  - Learn about C++ extensions for ODE models, ECM fibers, and more.
- **PhysiCell for Developers**
  - Learn about PhysiCell core C++ structure, and contributing to PhysiCell core and extensions



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- Extended version of this mini-course (with more complete background)

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