

Slides, videos, links and more:

<https://github.com/physicell-training/ws2023>

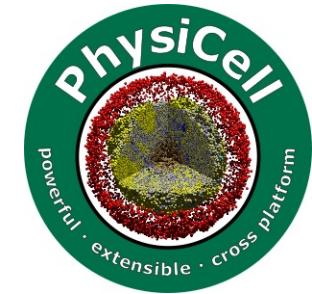
Session 4: Introduction to Agent-Based Modeling and PhysiCell



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 @MathCancer

PhysiCell Project

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Session Goals

- Gain familiarity in using *PhysiCell Studio*
- Build a first model:
 - Tumor growth model
 - ◆ Mechanofeedback
 - ◆ Oxygen-based cycling
 - ◆ Oxygen-based necrosis

Assumed directory structures

- Here's how I'm structuring for this workshop:
 - Home directory
 - ◆ PhysiCell ← Downloaded PhysiCell 1.13.1, unzipped in home directory
 - ◆ PhysiCell-Studio-2.27.5 ← Downloaded PhysiCell Studio, unzipped in home directory
 - ◆ pcStudio ← Symbolic link to PhysiCell-Studio-2.27.5
- Command to create the symbolic link (MacOS and Linux):
 - In –s PhysiCell-Studio-2.27.5 pcStudio
- If you can't create the symbolic link, you can "brute force" it by renaming PhysiCell-Studio-2.27.5 (or your version) to pcStudio

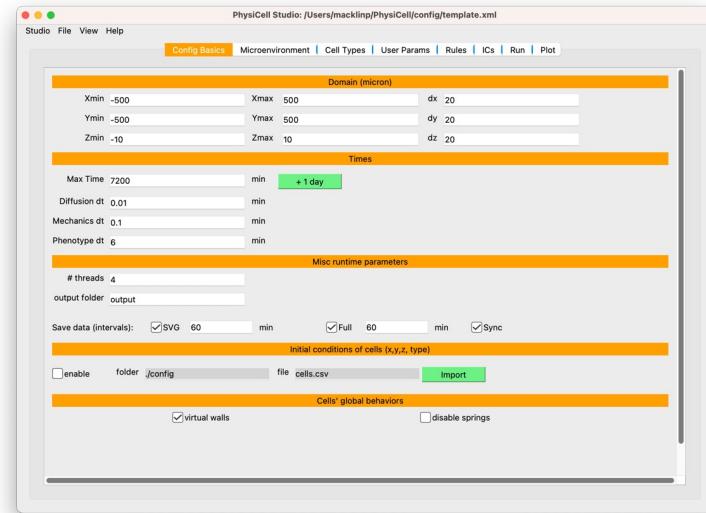
Getting started

- Enter the PhysiCell directory
 - cd PhysiCell
- Populate the template project
 - make template
- Compile the template project
 - make
- Open PhysiCell Studio
 - python/pcStudio/bin/studio.py

PhysiCell Studio: Overview

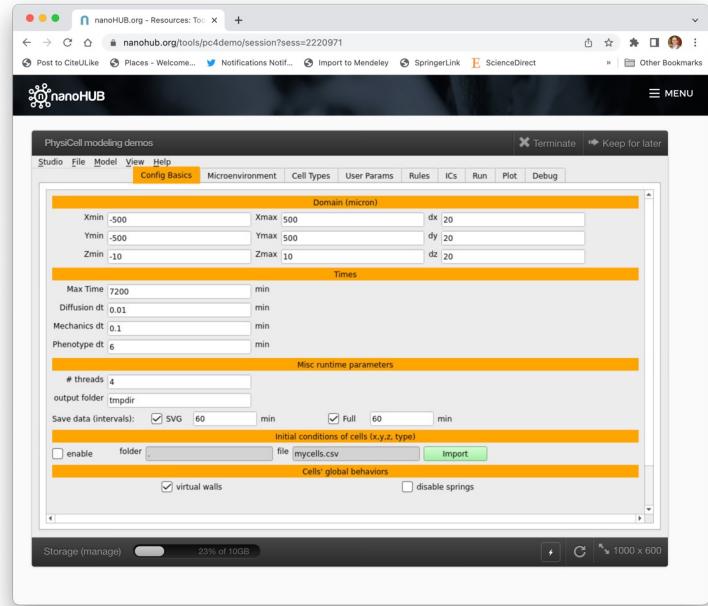
A graphical user interface (GUI) application to make it easier to model with PhysiCell

- 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
- Debug:** There are no bugs.



Cloud-hosted PhysiCell Studio: A backup

- A "zero-install" version of PhysiCell Studio now works in the cloud.
- This can be very handy for quickly trying new models.
- This version can be ideal for education, particularly for users without C++ / Python knowledge or a working dev environment.
- PhysiCell Studio on the Desktop will generally be more up-to-date than the cloud version



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

Iterative modeling example

- We'll iteratively build a simple tumor model, bit-by-bit:

- **Session 4:**

- 1. **Growing tumor with oxygen consumption**
 - 2. Add a mechanofeedback on cycling
 - 3. Add oxygen-driven cycling
 - 4. Add hypoxia-driven necrosis

- **Session 5:**

- 5. Add a cytotoxic drug
 - 6. Add release of dead cell debris
 - 7. Add macrophages
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- **Session 6:**

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Initial tumor and oxygen consumption

Growing tumor with oxygen: 1

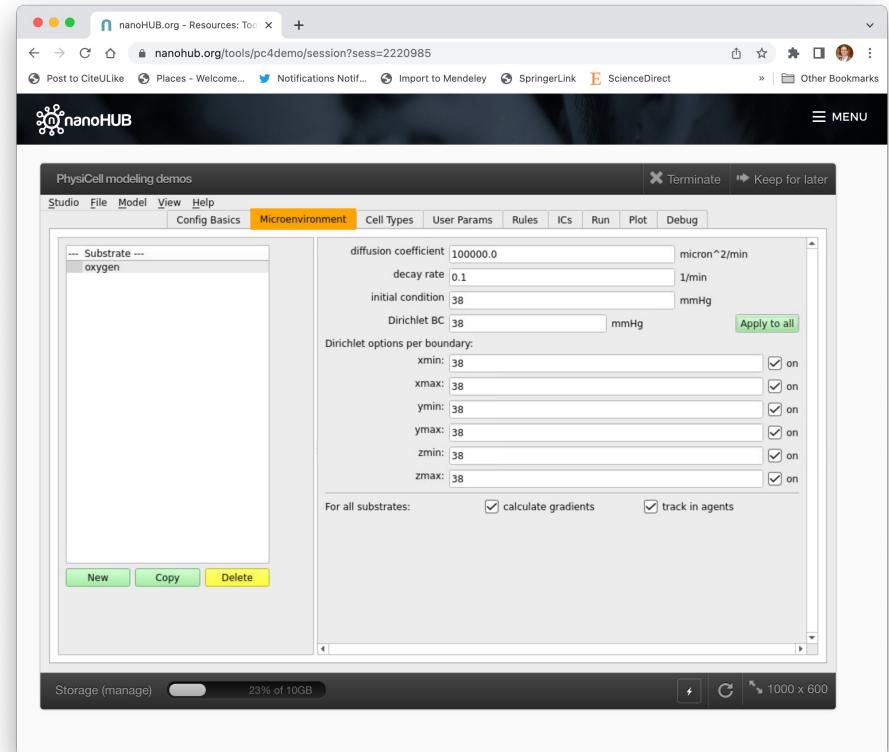
- First, we add oxygen in the **Microenvironment** tab
- We use the **diffusion length scale** from physics / applied mathematics:
 - Penetration into a tissue is competition between effects:
 - ◆ Diffusion (D) increases spread
 - ◆ Uptake (U) and decay (λ) tend to halt spread

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

- 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 smaller in cell free, so $\lambda \sim 0.1 \text{ min}^{-1}$
 - ◆ In physioxic tissues, $\text{pO}_2 \sim 5\% = 38 \text{ mmHg}$

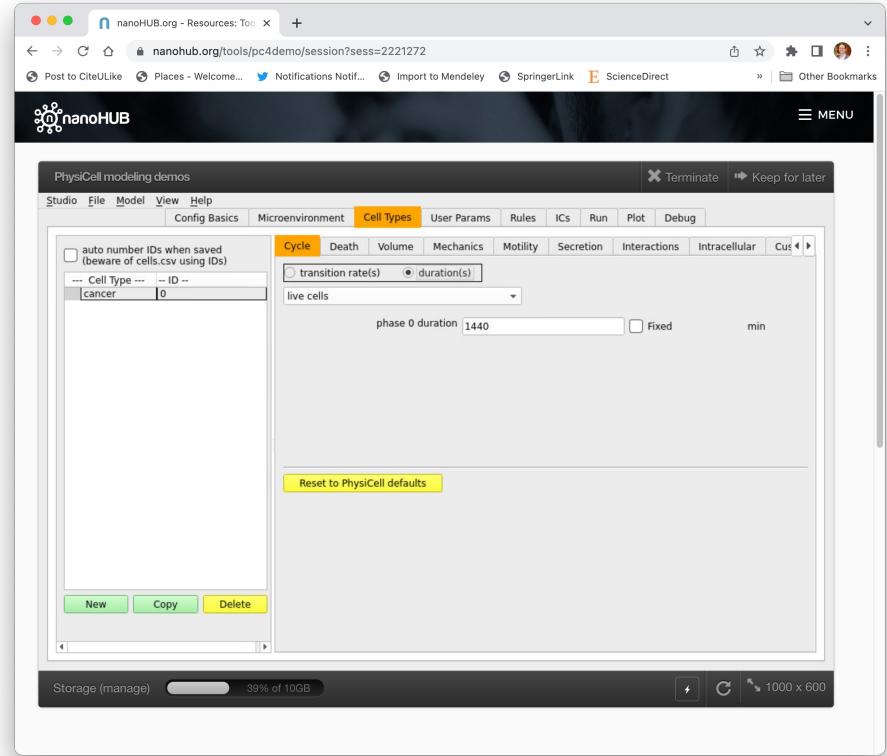
Growing tumor with oxygen: 2

- 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



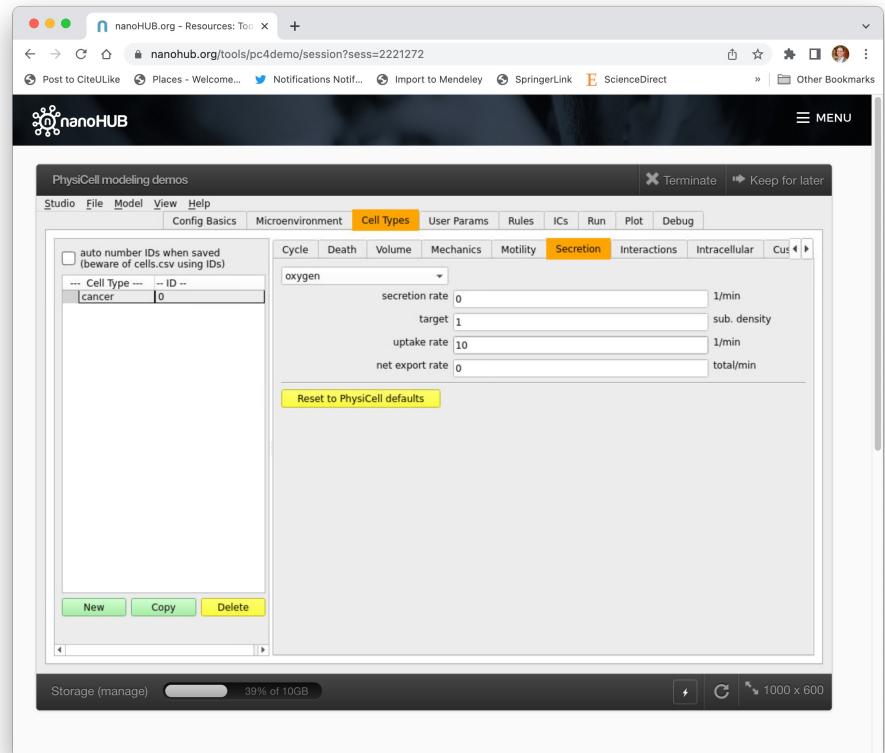
Setting up cancer cells: 1

- 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



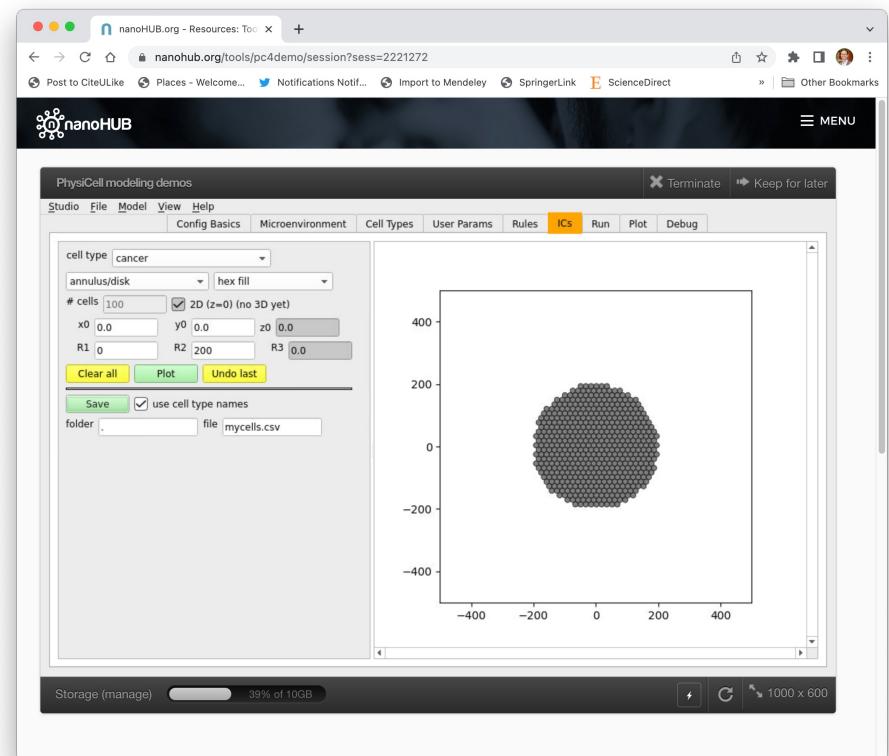
Setting up cancer cells: 2

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



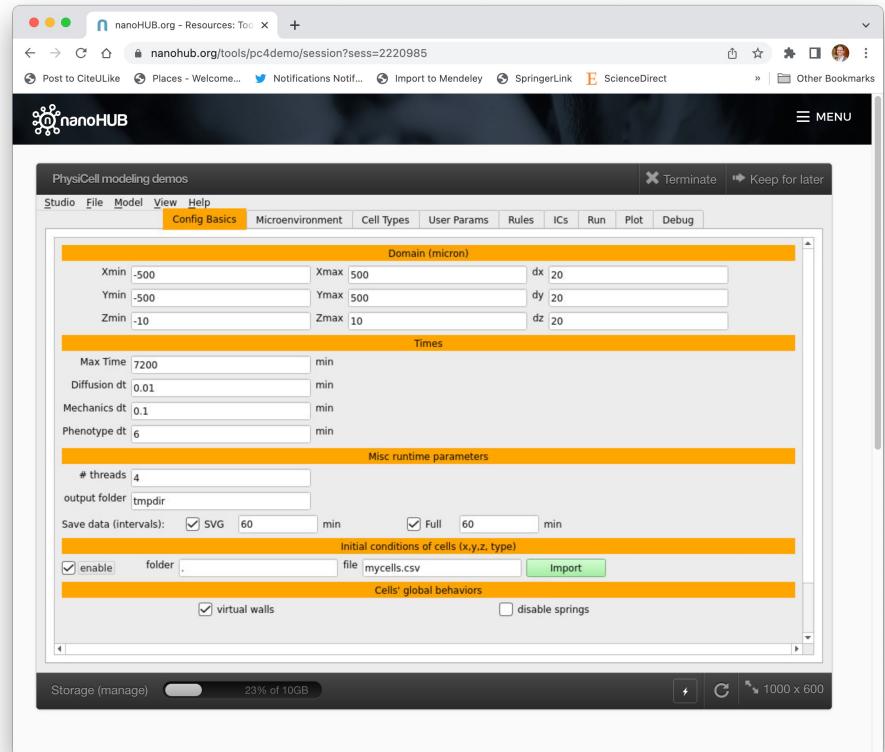
Set up an initial state: 1

- 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 (R_1) = 0
 - Choose max radius (R_2) = 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 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. The page title is "PhysiCell modeling demos". The "User Params" tab is selected in the navigation bar. A table displays parameter settings:

Name	Type	Value	Units	Desc
1 random_seed	int	0	dimensionless	
2 number_of_cells	int	0	none	(reach cell type)
3	double			
4	double			
5	double			
6	double			
7	double			
8	double			
9	double			
10	double			
11	double			
12	double			
13	double			

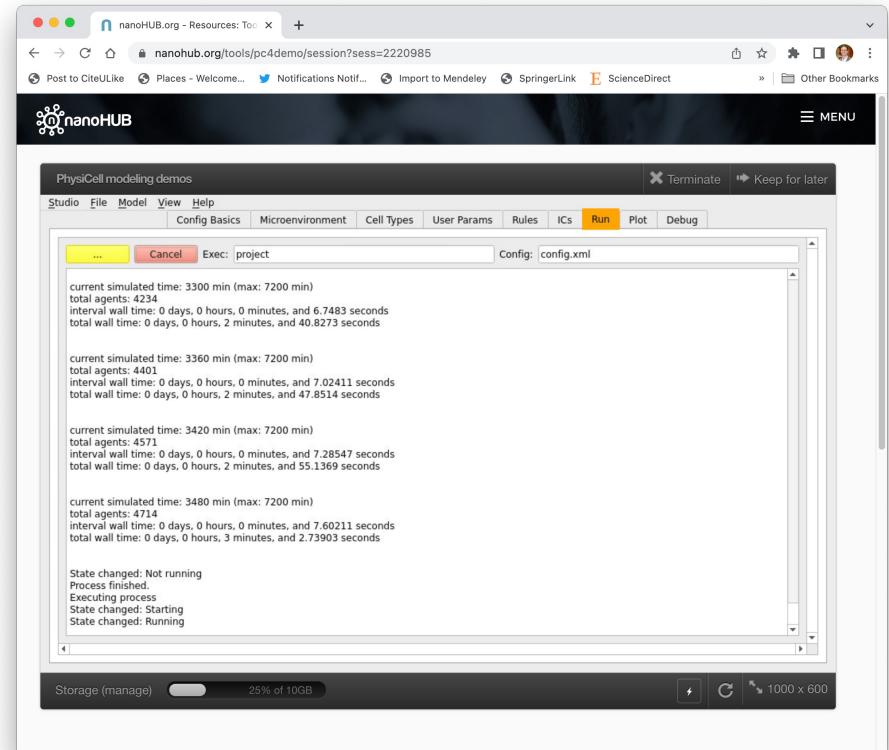
Below the table, there is a note: "click row # to Delete".

Run the model!

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

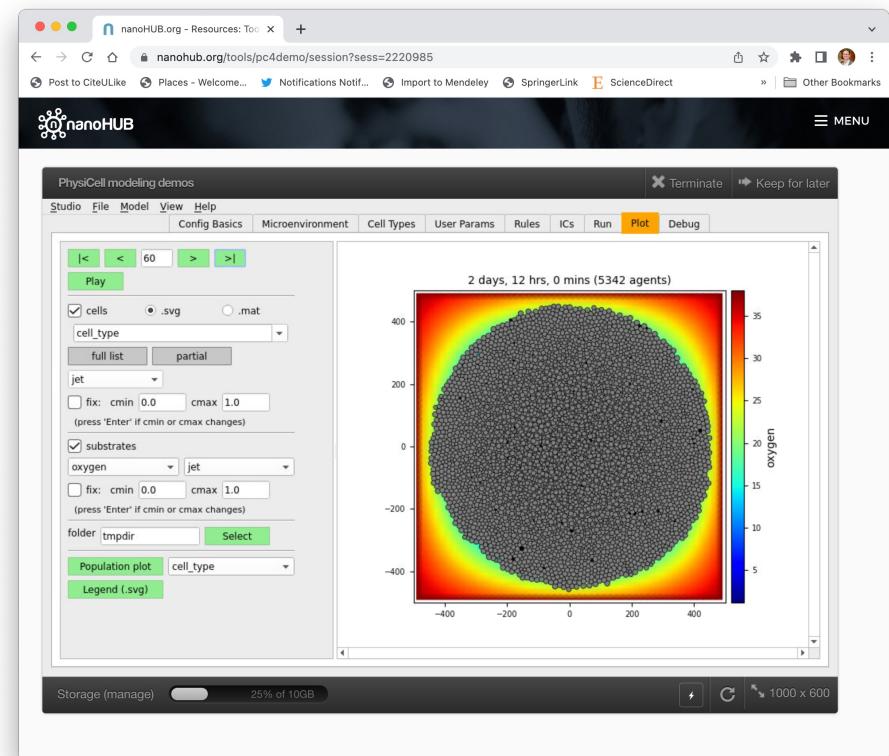
This code is **session04_1**

- Get **session04_1.zip** from the repo
- Save to `user_projects`
- make unpack PROJ=session04_1
- make



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



Adding a pressure mechanofeedback

Iterative modeling example

- We'll iteratively build a simple tumor model, bit-by-bit:

- **Session 4:**

- 1. Growing tumor with oxygen consumption
 - 2. **Add a mechanofeedback on cycling**
 - 3. Add oxygen-driven cycling
 - 4. Add hypoxia-driven necrosis

- **Session 5:**

- 5. Add a cytotoxic drug
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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

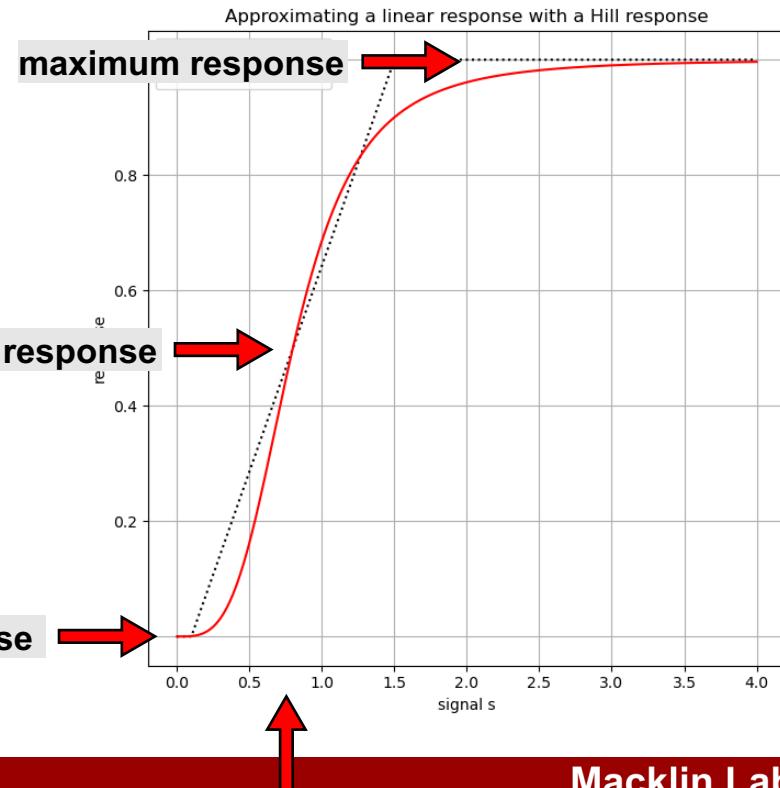
Pressure

- Mathematical form of pressure:
 - Based on potentials
 - Nondimensionalized to 1 for 3D confluent tissues
 - Nondimensionalized to 0.5 for 2D confluent tissues
- We'll suppose cancer cells can accept some compression

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)
 - Complete 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

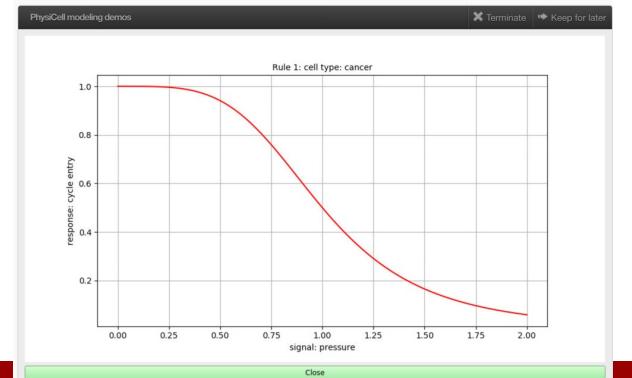
- Mathematical form of pressure:

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

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

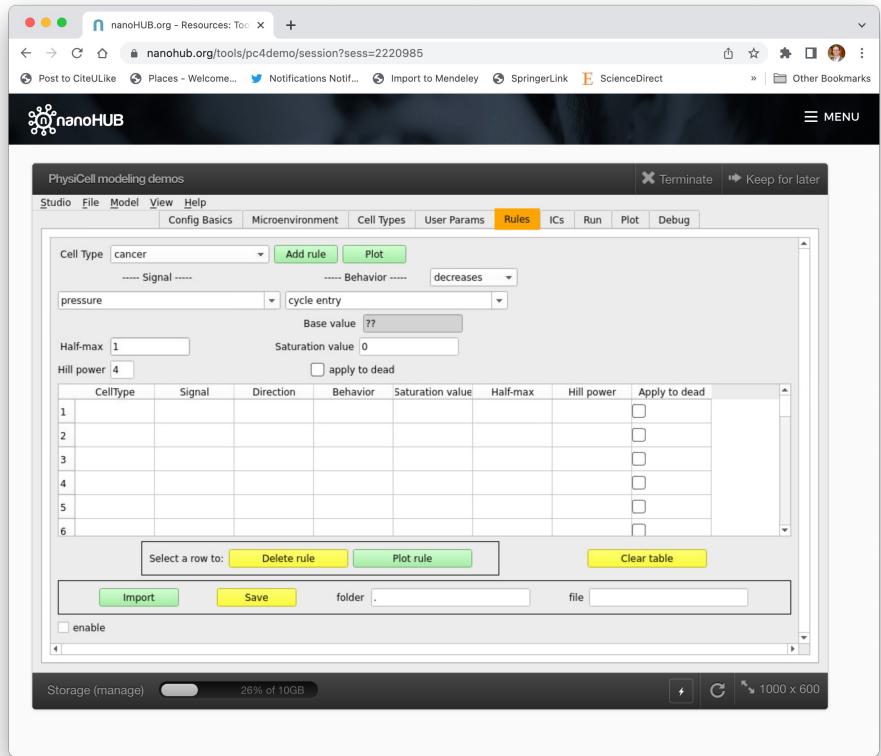
- We'll suppose cancer cells can accept some compression

- Use a **half-max** of 1:
 - ◆ Once pressure hits 1.0, a sharp decrease in cycling
 - 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**

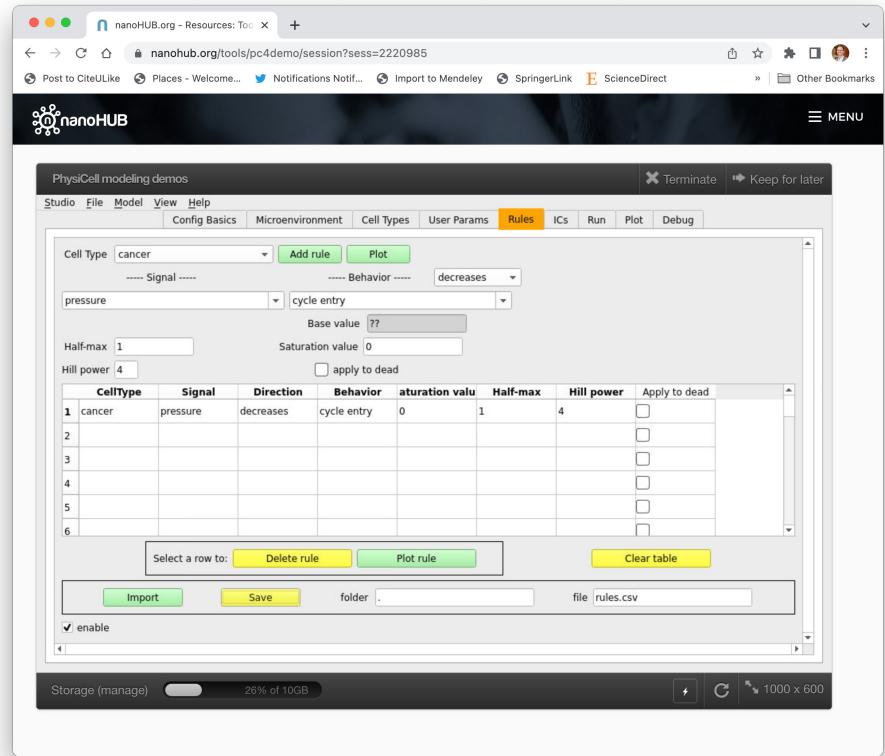


Add the rule: 2

- 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

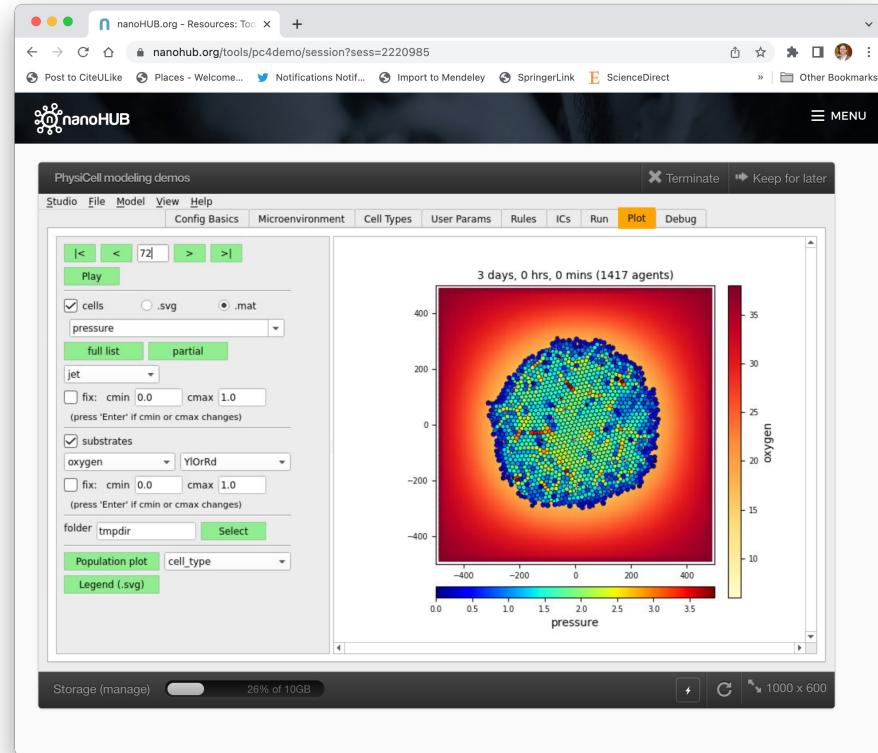
This code is **session04_2**

- Get **session04_2.zip** from the repo
- Save to **user_projects**
- make unpack PROJ=session04_2
- make



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.
- 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

Iterative modeling example

- We'll iteratively build a simple tumor model, bit-by-bit:

- **Session 4:**

- 1. Growing tumor with oxygen consumption
 - 2. Add a mechanofeedback on cycling
 - 3. Add oxygen-driven cycling**
 - 4. Add hypoxia-driven necrosis

- Session 5:

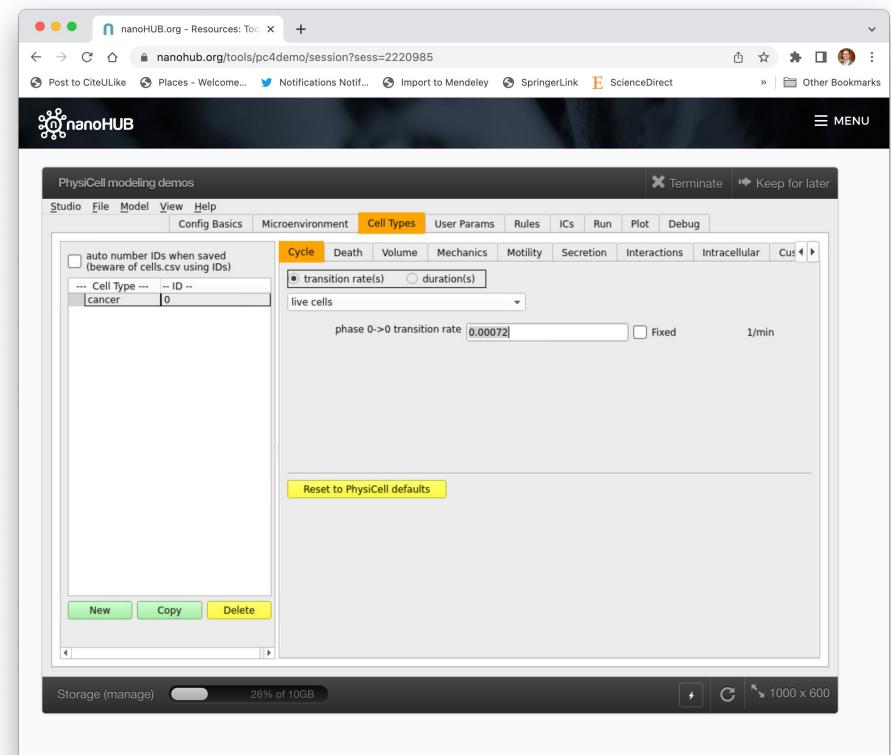
- 5. Add a cytotoxic drug
 - 6. Add release of dead cell debris
 - 7. Add macrophages
 - 8. Add M1/M2 macrophage polarization

- Session 6:

- 8. Add pro-inflammatory factor
 - 9. Add effector T cells
 - 10. Add anti-immune mutations
 - 11. Add anti-anti-immune treatment

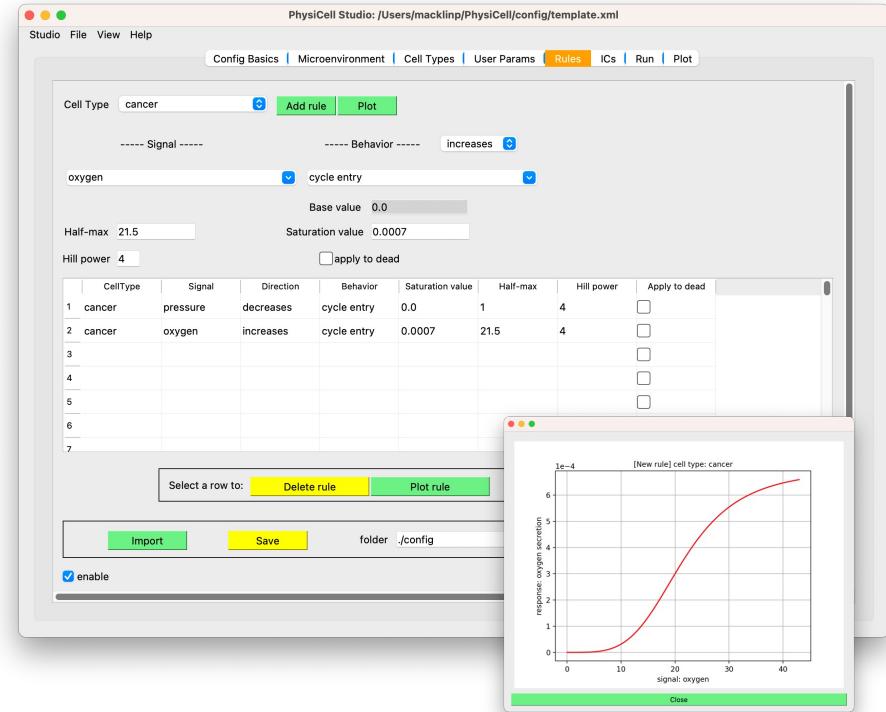
Oxygen-based cycling setup: 1

- 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



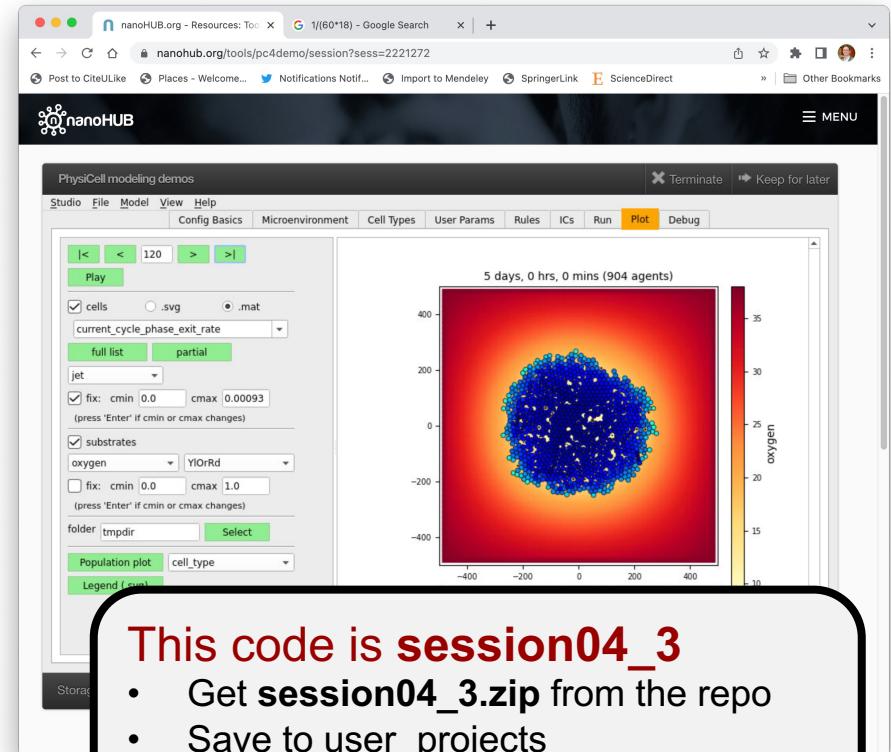
Oxygen-based cycling setup: 2

- 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 **0.0007** 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 0.0007
- 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



This code is **session04_3**

- Get **session04_3.zip** from the repo
- Save to **user_projects**
- make unpack PROJ=session04_3
- make

Hypoxia-driven necrosis

Iterative modeling example

- We'll iteratively build a simple tumor model, bit-by-bit:

- **Session 4:**

1. Growing tumor with oxygen consumption
2. Add a mechanofeedback on cycling
3. Add oxygen-driven cycling

- 4. **Add hypoxia-driven necrosis**

- Session 5:

- 5. Add a cytotoxic drug
 6. Add release of dead cell debris
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 8. Add M1/M2 macrophage polarization

- Session 6:

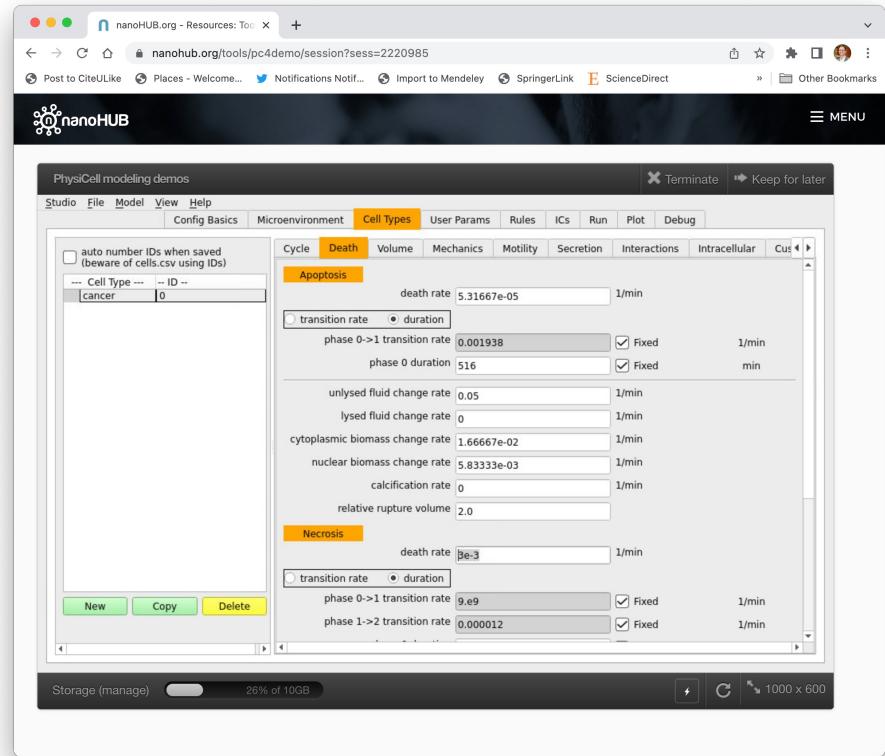
- 8. Add pro-inflammatory factor
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Some rephrasing first

- The statement we'd like to make:
 - Increasing hypoxia increases necrosis
 - But there is no "low oxygen" signal in our dictionary
- So, let's turn this around:
 - Increasing oxygen decreases necrosis
- To make this work:
 - High necrosis in the absence of oxygen (no signal)
 - Oxygen decreases necrosis
 - Almost no necrosis above 5 mmHg

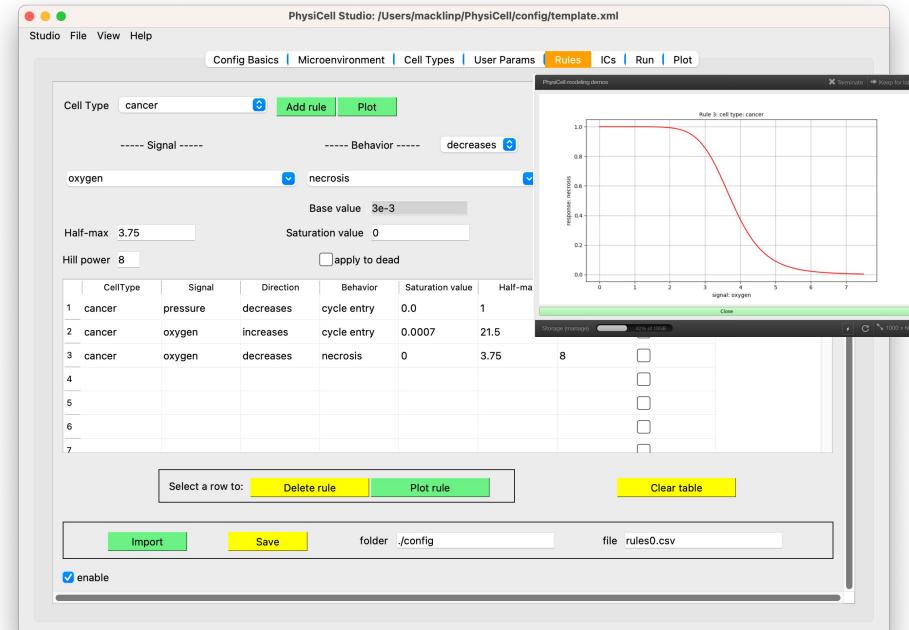
Hypoxia-driven necrosis: 1

- We'll need to modify our base phenotype:
 - Phenotype is the **base behavior** in the absence of other signals
 - High necrosis in the absence of oxygen
 - So, we need to set base necrosis rate high
- Go to **cell types**
 - Choose **cancer**
 - Go to the **death** sub-tab
 - Go to **necrosis**
 - Set the **death rate** to **3e-3**
 - This sets a survival time of $\frac{1}{3 \times 10^{-3} \text{ min}^{-1}} \sim 333 \text{ min}$



Hypoxia-driven necrosis: 2

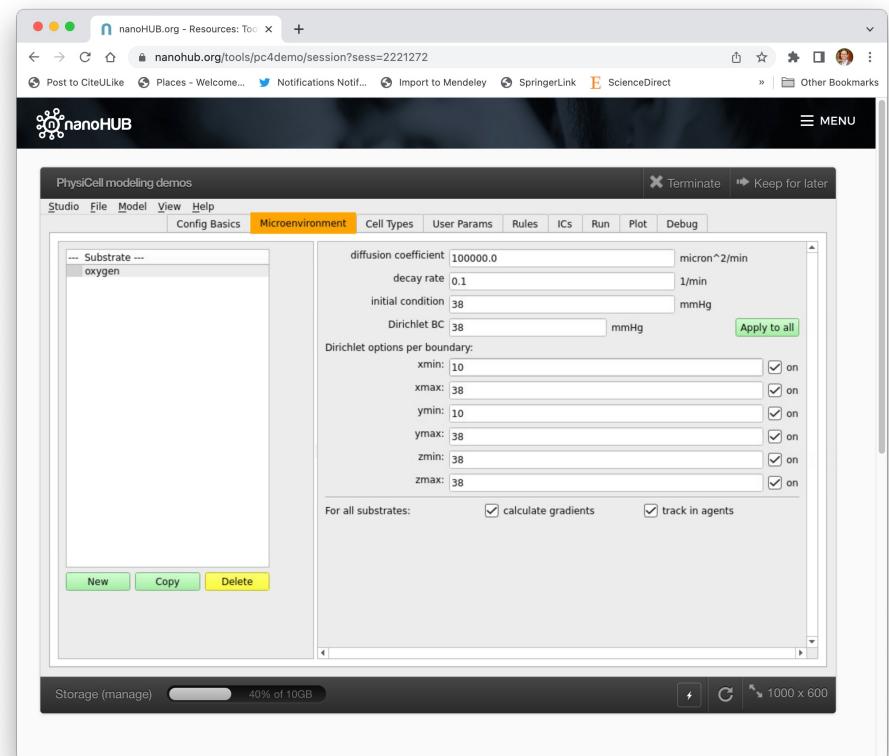
- Go to the **rules** tab
 - Select **cancer** cell
 - Choose **oxygen** as the signal
 - Choose **necrosis** as the behavior
 - Choose **decreases** as the response
 - Choose **0.0** as the saturation value of the behavior
 - Choose **3.75 mmHg** as the half-max
 - Choose **8** as the Hill power
 - Then, click **add rule**



- Make sure to click the **save** button!

Let's try a more interesting boundary

- Let's set oxygen on the lower x and y boundaries
 - Got to **microenvironment**
 - Look at **oxygen**
 - Set the oxygen value to **10 mmHg** at:
 - ◆ x_{min}
 - ◆ y_{min}



Run and Visualize

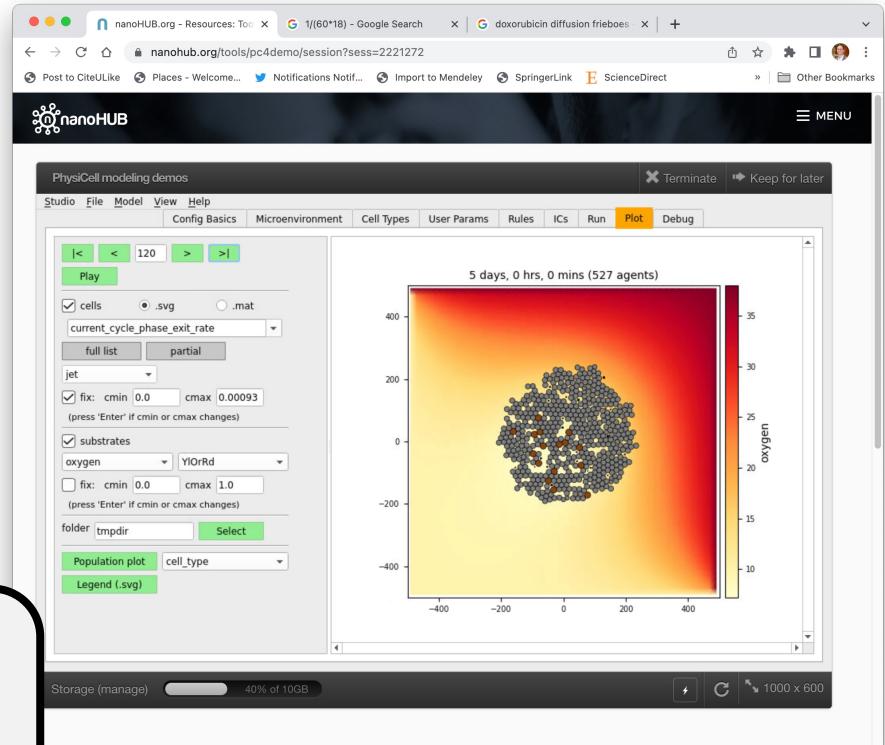
- Let's color cells by standard again:

- Go to **cells** and select **SVG**
- Apoptotic cells are black
- Necrotic cells are brown

- Notice:
 - Cycling is preferential on the side of the tumor with more oxygen
 - Necrosis is preferential on the side with less oxygen

This code is **session04_4**

- Get **session04_4.zip** from the repo
- Save to **user_projects**
- make unpack PROJ=session04_4
- make



Next session

- Add cell debris
 - example of a dead cell rule
- Add macrophages
 - example of phagocytosis
- Add macrophage M1/M2 polarization
 - Example O₂-based behavior
 - Opportunity to talk about transient versus long-term rules

Funding Acknowledgements



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- Breast Cancer Research Foundation
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- National Cancer Institute (U01CA232137)
- National Science Foundation (1720625, 1818187)

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- NIH Common Fund (3OT2OD026671-01S4)