

# **PhysiCell Mini-Workshop**

## **Part 2: Live modeling with PhysiCell**

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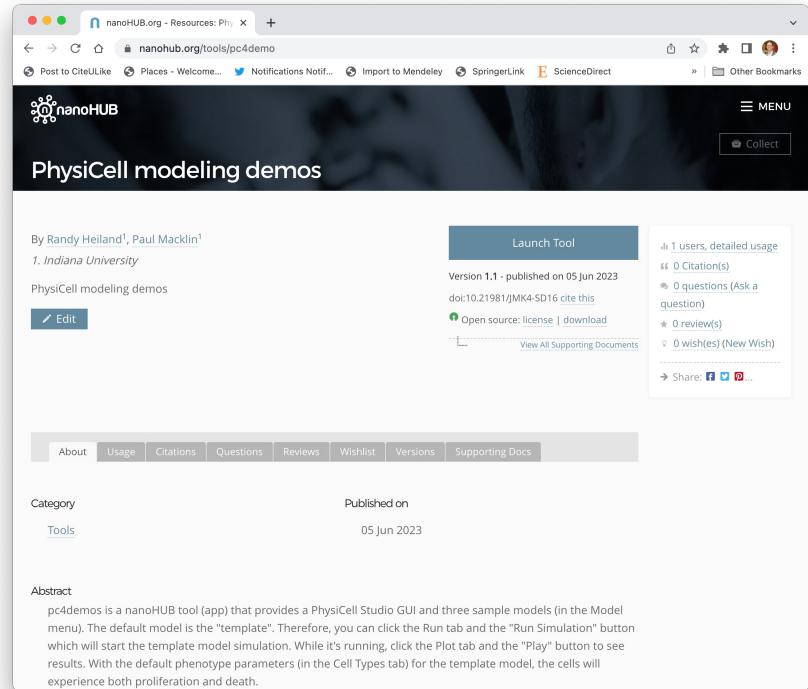
June 8, 2023

# Link

<https://github.com/PhysiCell-Training/nw2023>

# Cloud-hosted PhysiCell

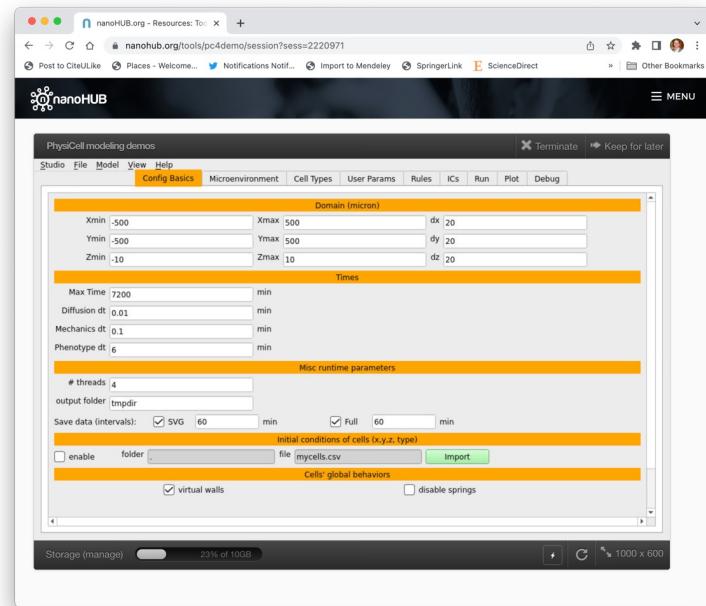
- Login to nanohub.org
- Go to:
  - <https://nanohub.org/tools/pc4demo>
- Click the blue "run tool" button



# Cloud-hosted PhysiCell: Overview

A graphical user interface (GUI) application to make it easier to explore 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.



<https://nanohub.org/tools/pc4demo>

# Iterative modeling example

- 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 hypoxia-driven necrosis
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# Initial tumor and oxygen consumption

# Growing tumor with oxygen: 1

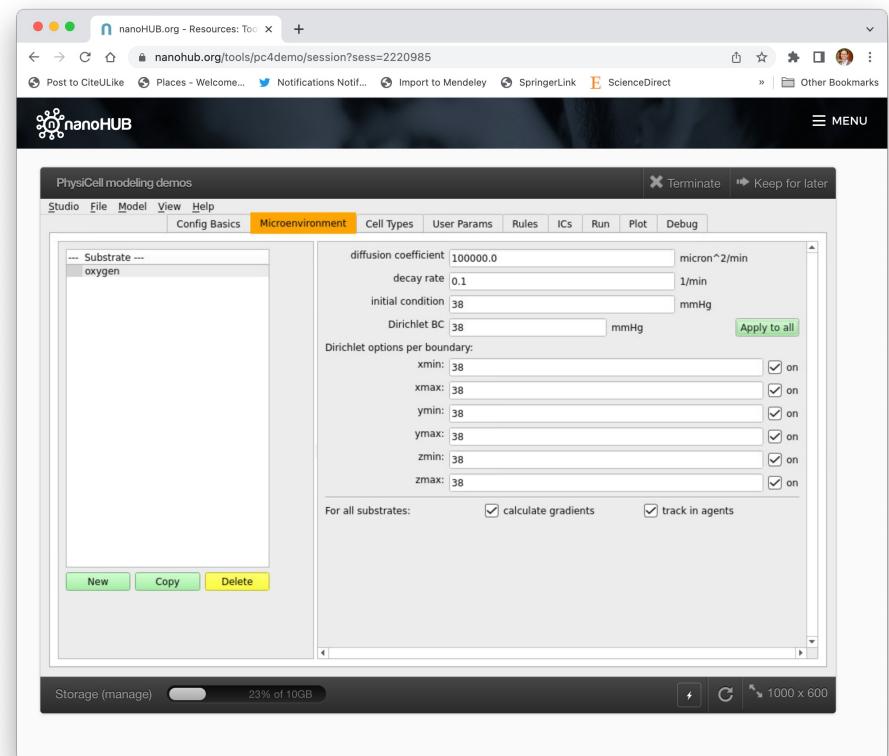
- First, we add oxygen in the **Microenvironment** tab
- We use the **diffusion length scale** from physics / applied mathematics:
  - Penetration into a tissue is competition between effects:
    - ◆ Diffusion ( $D$ ) increases spread
    - ◆ Uptake ( $U$ ) and decay ( $\lambda$ ) tend to halt spread

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

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

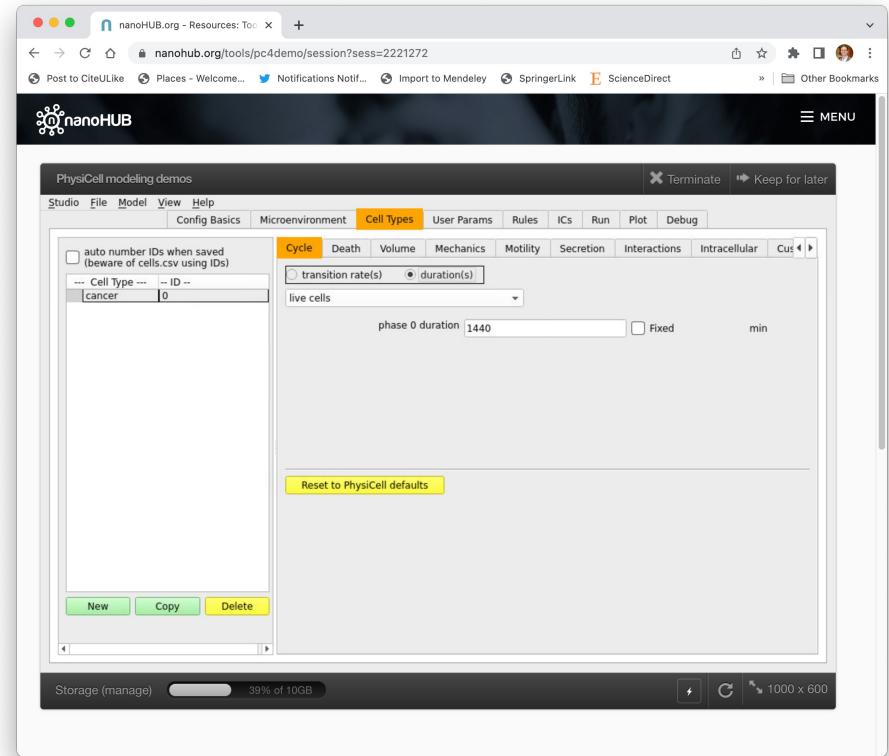
# Growing tumor with oxygen: 2

- 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



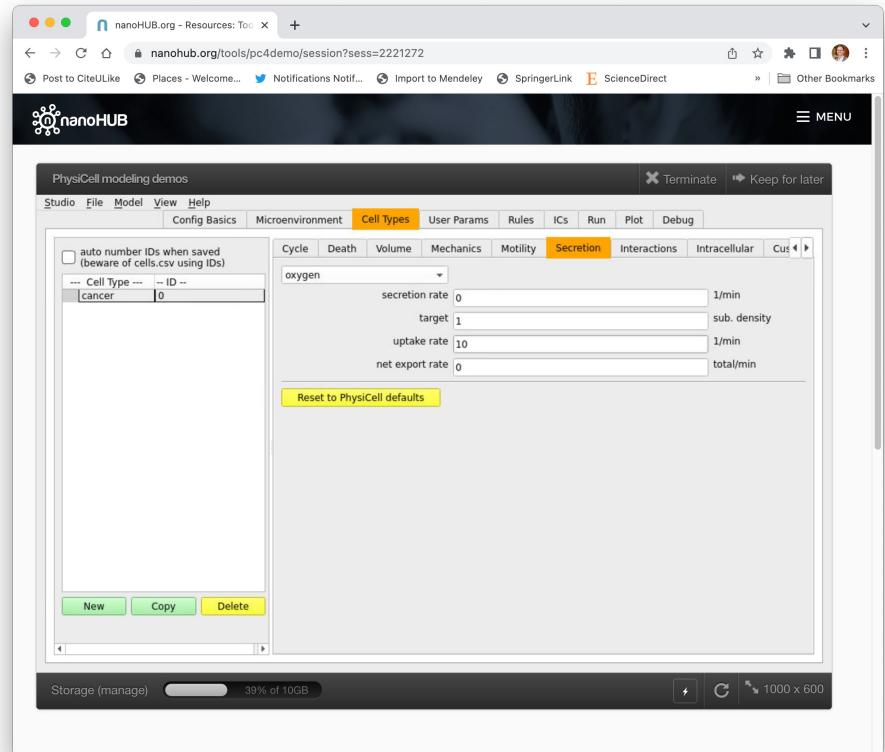
# Setting up cancer cells: 1

- 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



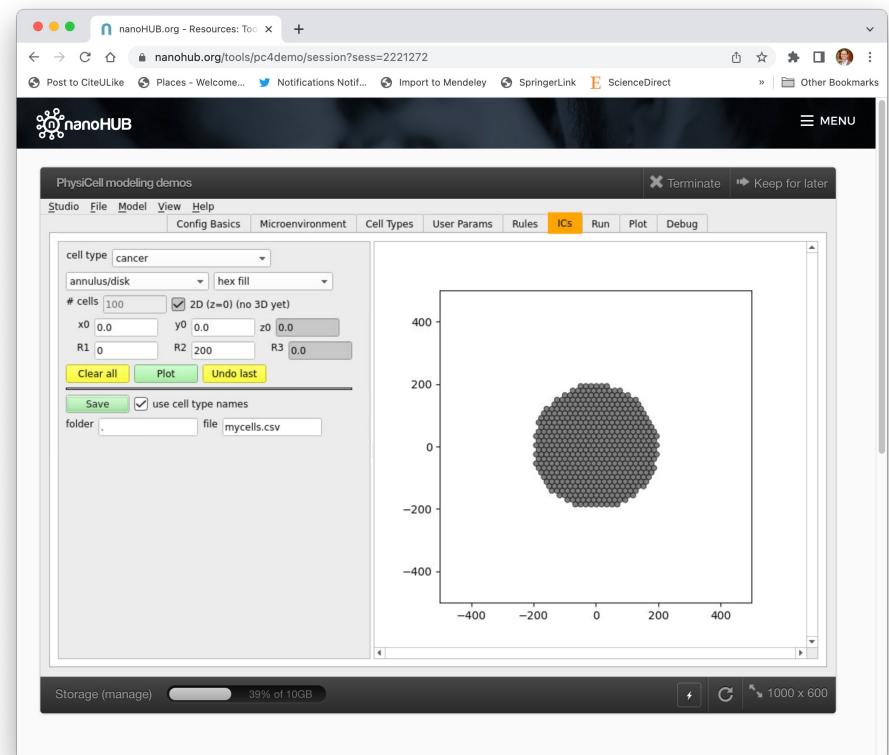
# Setting up cancer cells: 2

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



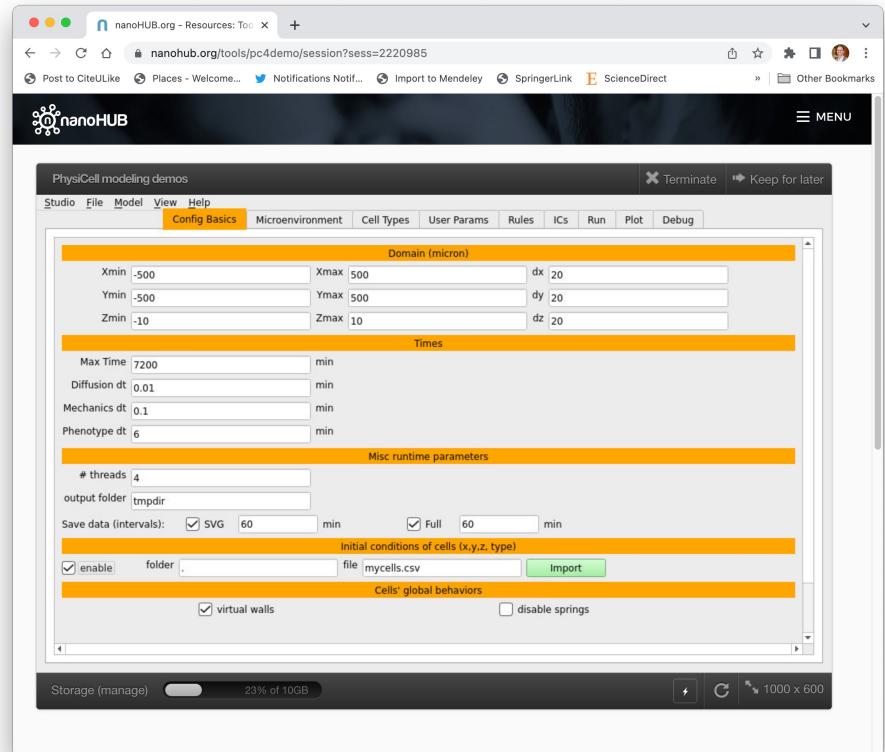
# Set up an initial state: 1

- 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**

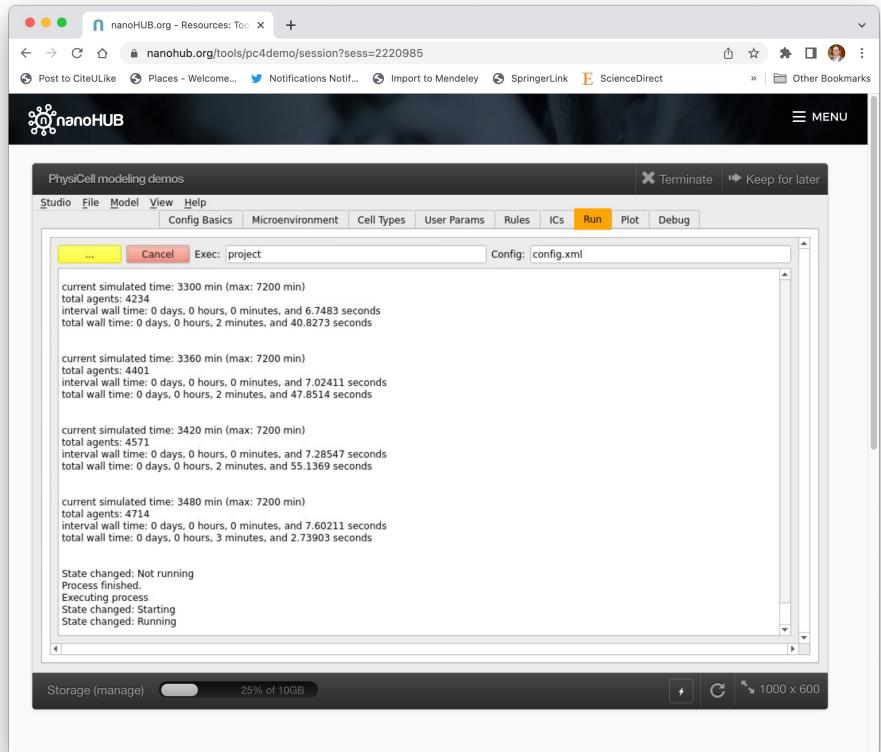
The screenshot shows a web browser window for nanoHUB.org. The URL is [nanohub.org/tools/pc4demo/session?sess=2220985](https://nanohub.org/tools/pc4demo/session?sess=2220985). The page title is "PhysiCell modeling demos". The "User Params" tab is selected in the navigation bar. A table displays parameter 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 button labeled "click row # to Delete".

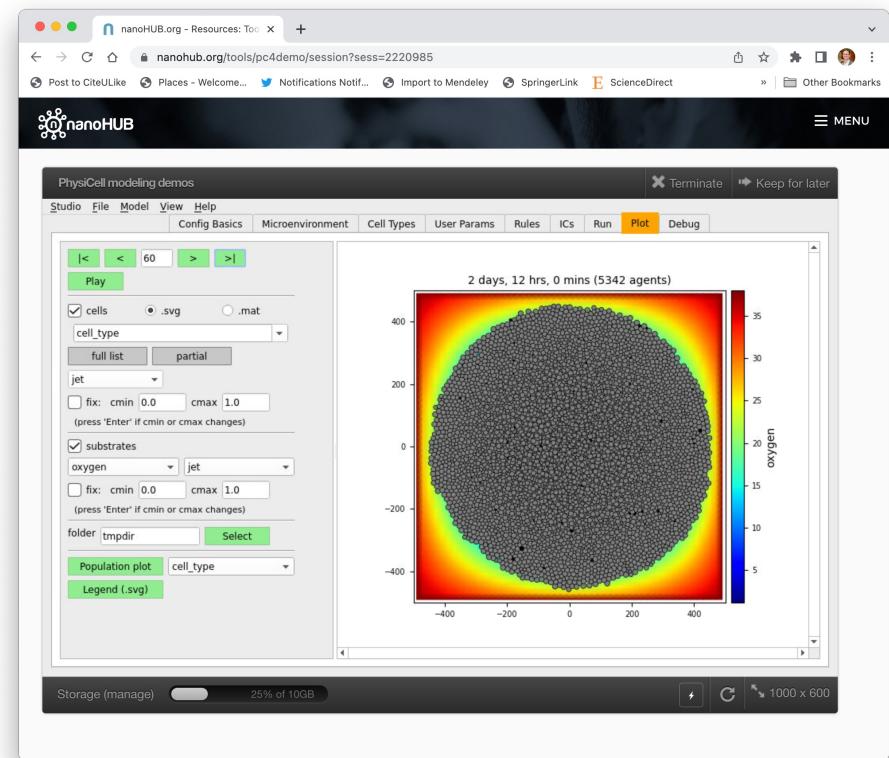
# Run the model!

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



# 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:

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3. Add oxygen-driven cycling
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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

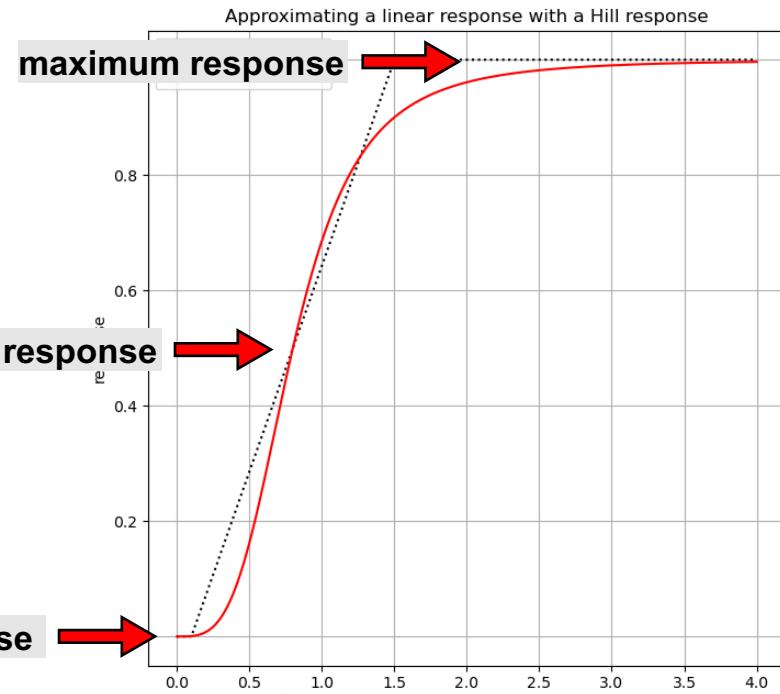
# Hill response functions

- 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

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

half of maximum response

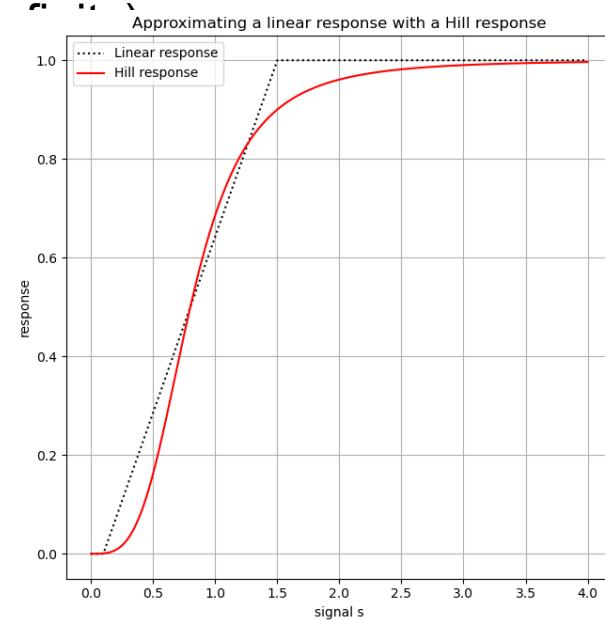
minimum response



# Hill response functions

- A widespread sigmoidal response curve in PKPD and systems biology
  - Varies from 0 (at signal=0) to 1 (as signal → ∞)
  - Complete characterized by:
    - ◆ half-maximum: Input value where curve reaches 0.5
    - ◆ Hill power: How steeply it approaches 1

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



# Our mathematics

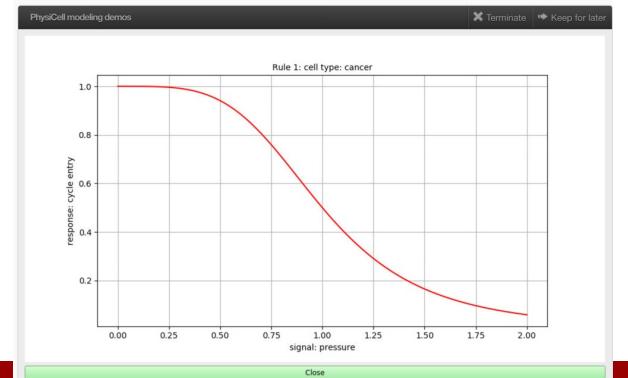
- Mathematical form of pressure:

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

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

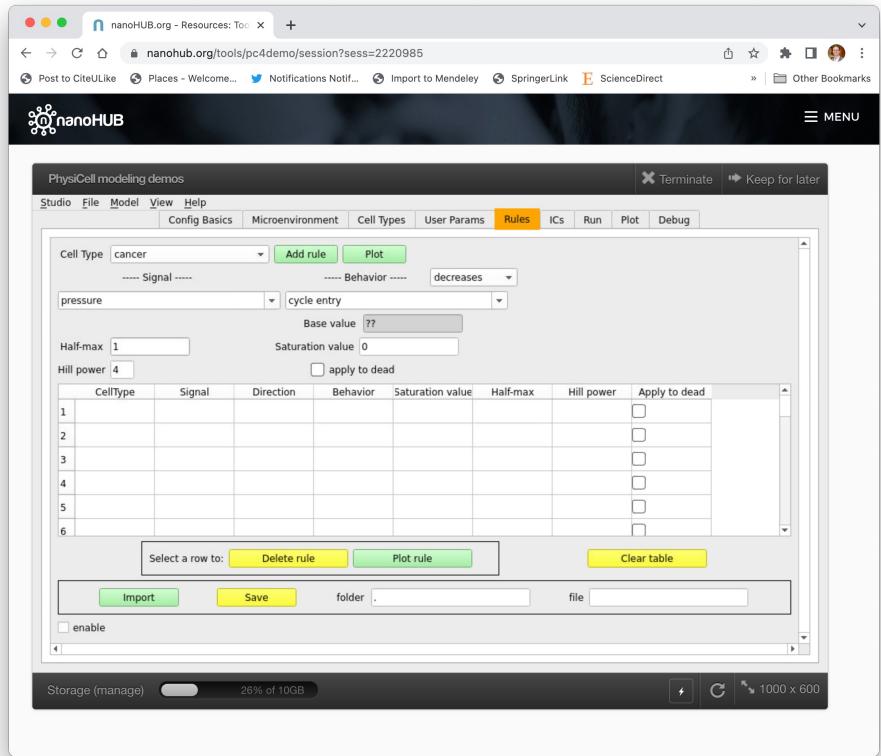
- We'll suppose cancer cells can accept some compression

- 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



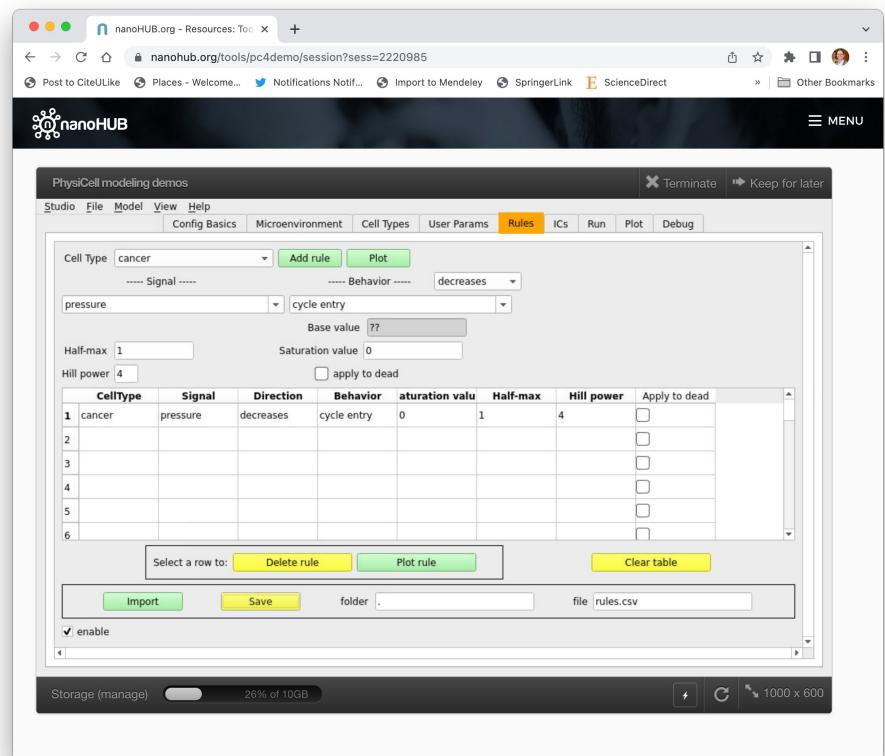
# Add the rule: 1

- 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**



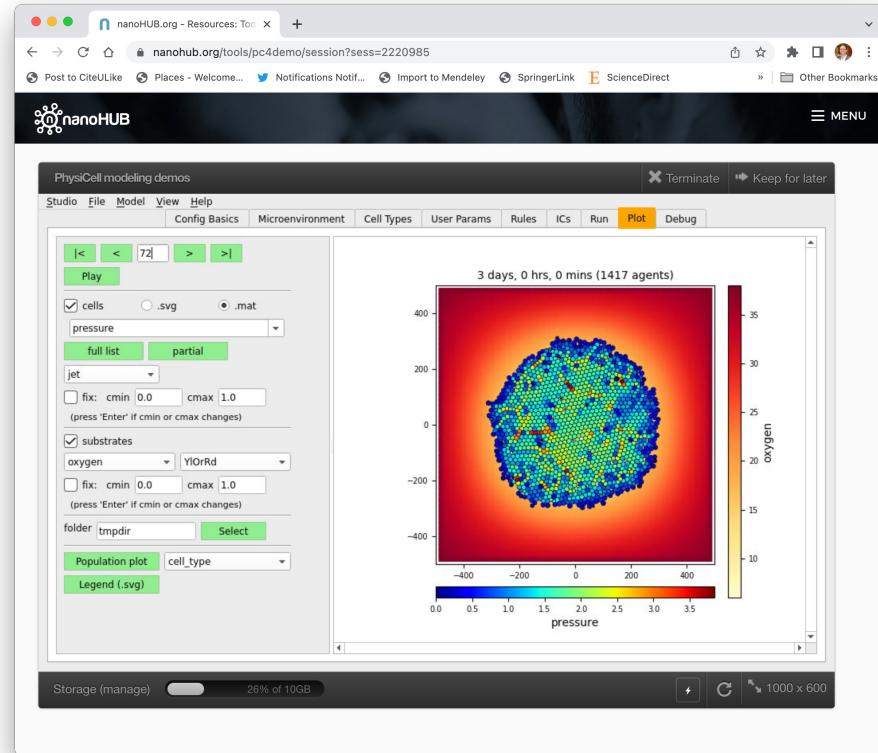
# Add the rule: 2

- 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



# 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

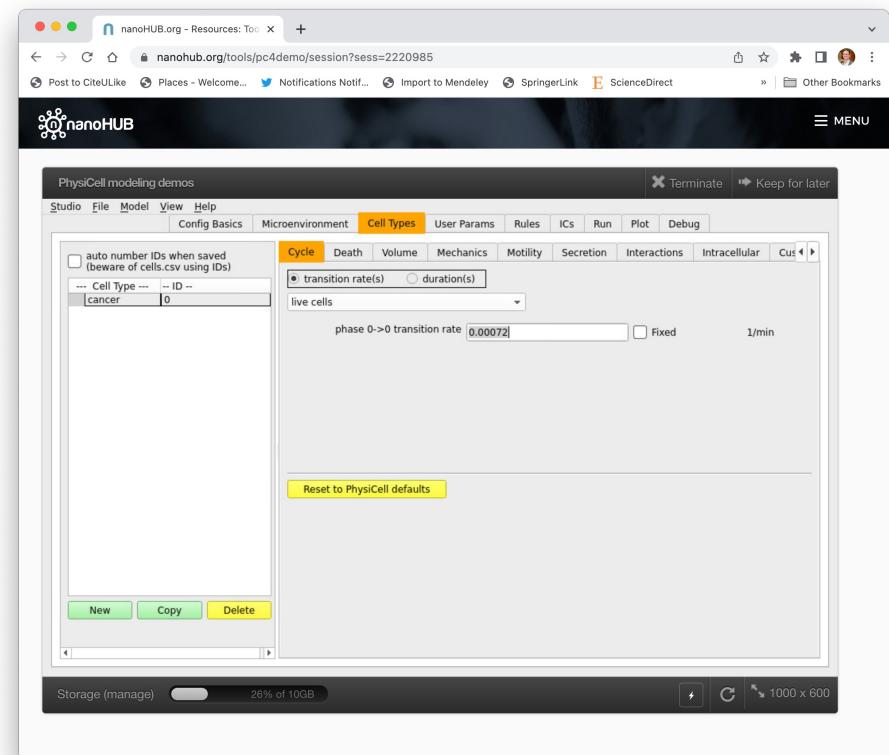
# Iterative modeling example

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

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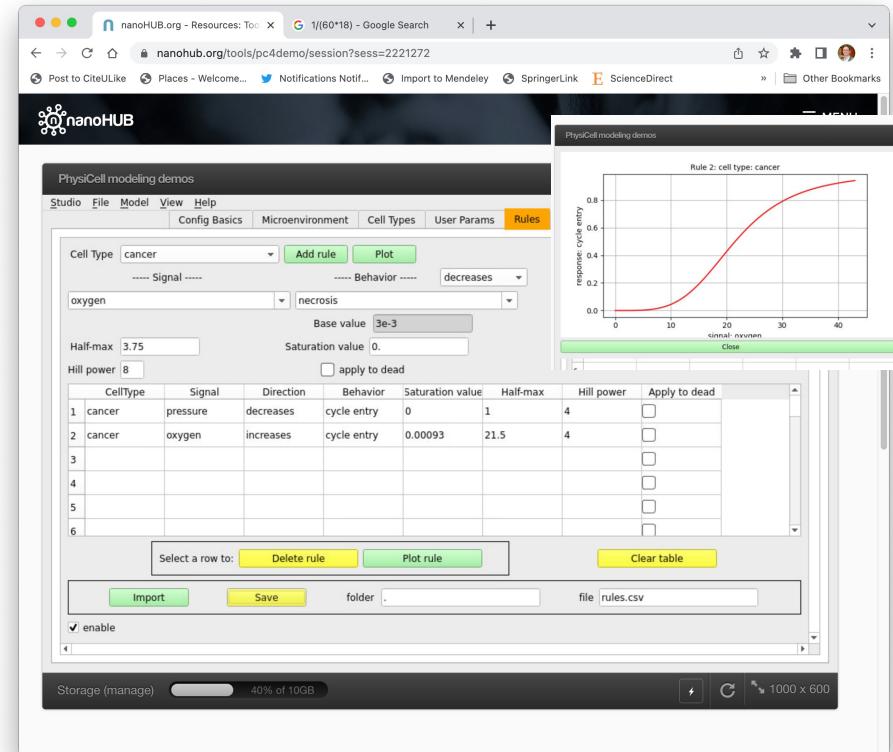
# Oxygen-based cycling setup: 1

- 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

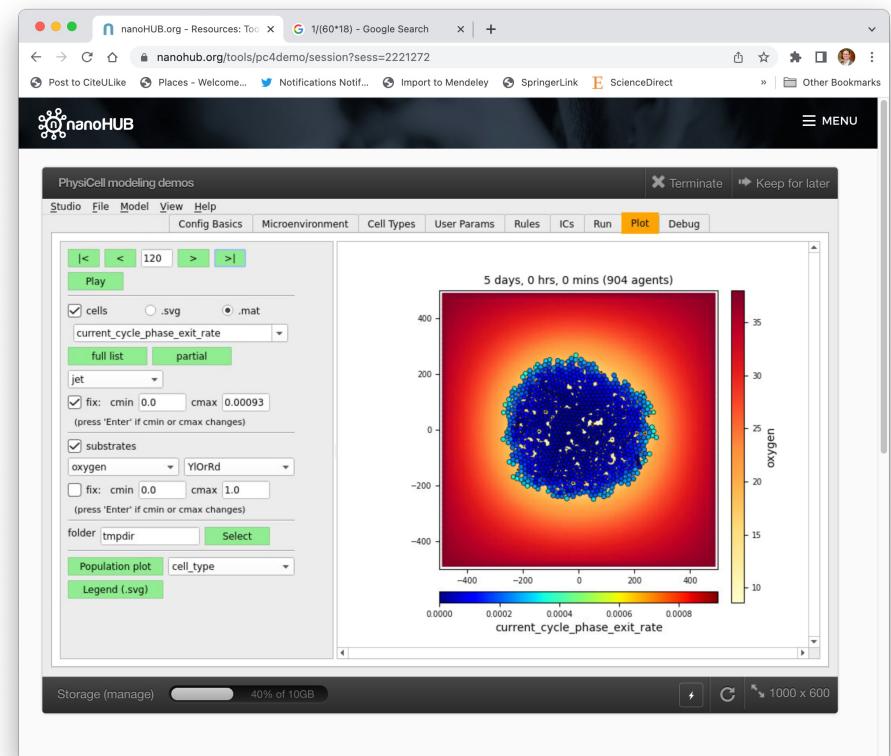
- Go to the **rules** tab
  - Select **cancer** cell
  - Choose **oxygen** as the signal
  - Choose **cycle entry** as the behavior
  - Choose **increases** as the response
  - Choose **0.00093** as the saturation value of the behavior
    - ◆ This sets a max cycle time of around 18 hours
  - Choose **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



# Hypoxia-driven necrosis

# Iterative modeling example

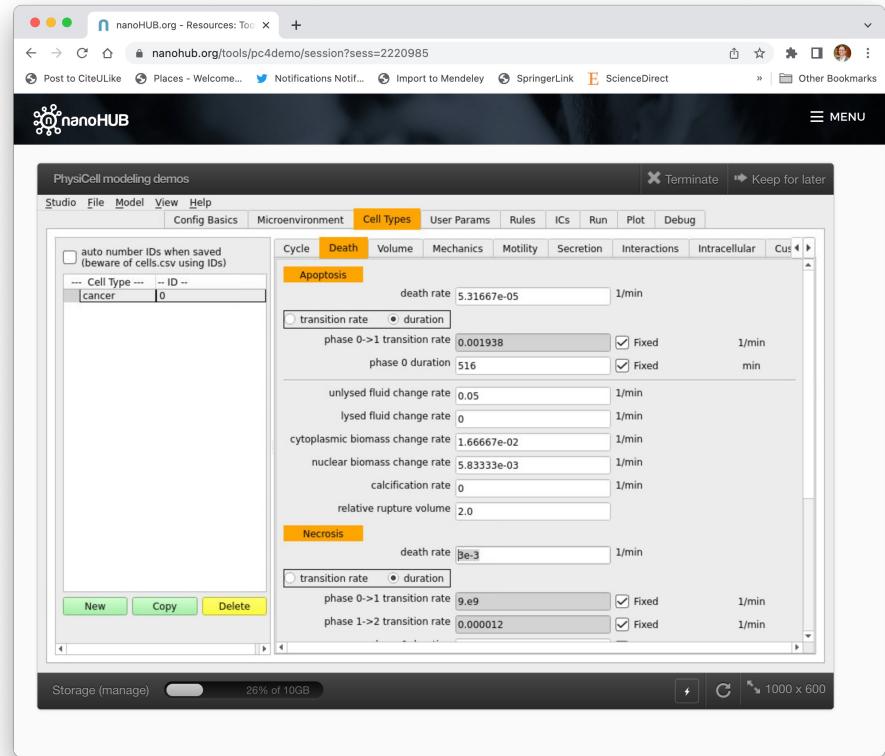
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# Some rephrasing first

- The statement we'd like to make:
  - Increasing hypoxia increases necrosis
  - But there is now "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

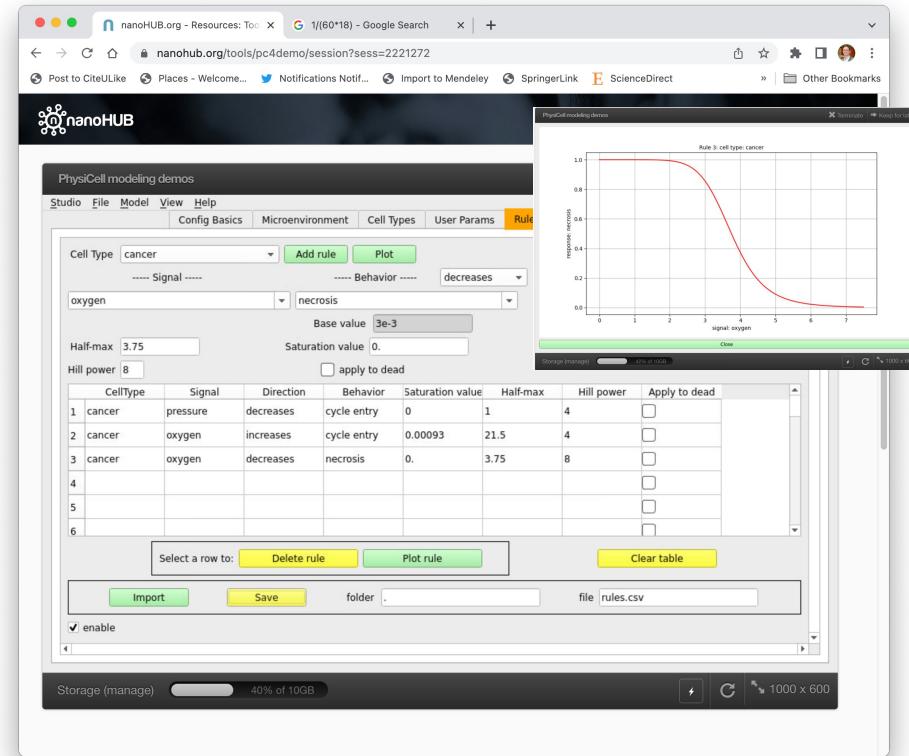
# Hypoxia-driven necrosis: 1

- 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  $\frac{1}{3 \times 10^{-3} \text{ min}^{-1}} \sim 333 \text{ min}$



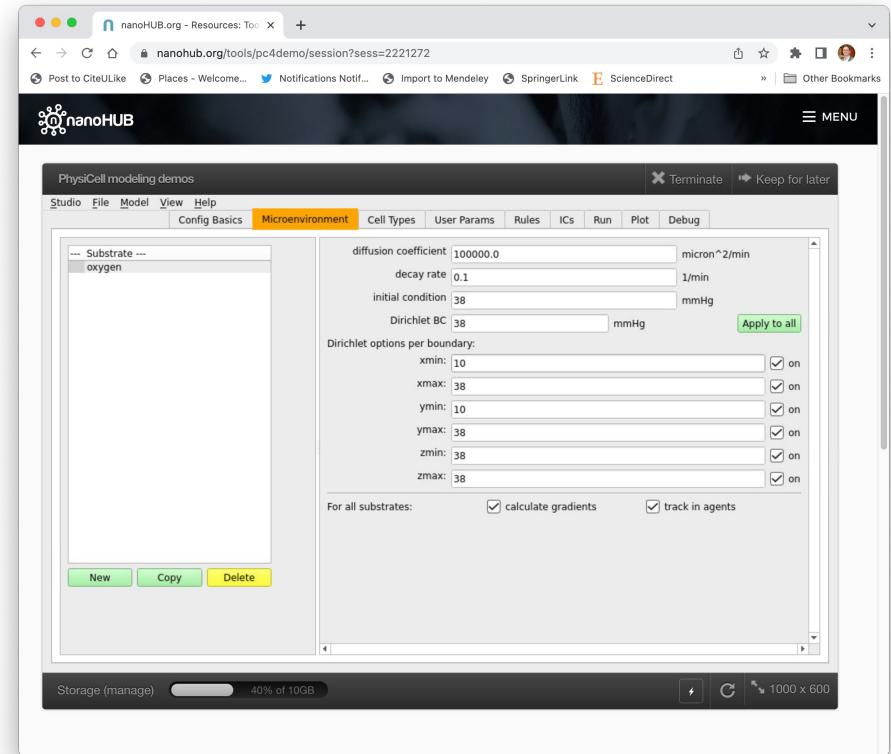
# Hypoxia-driven necrosis: 2

- 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**



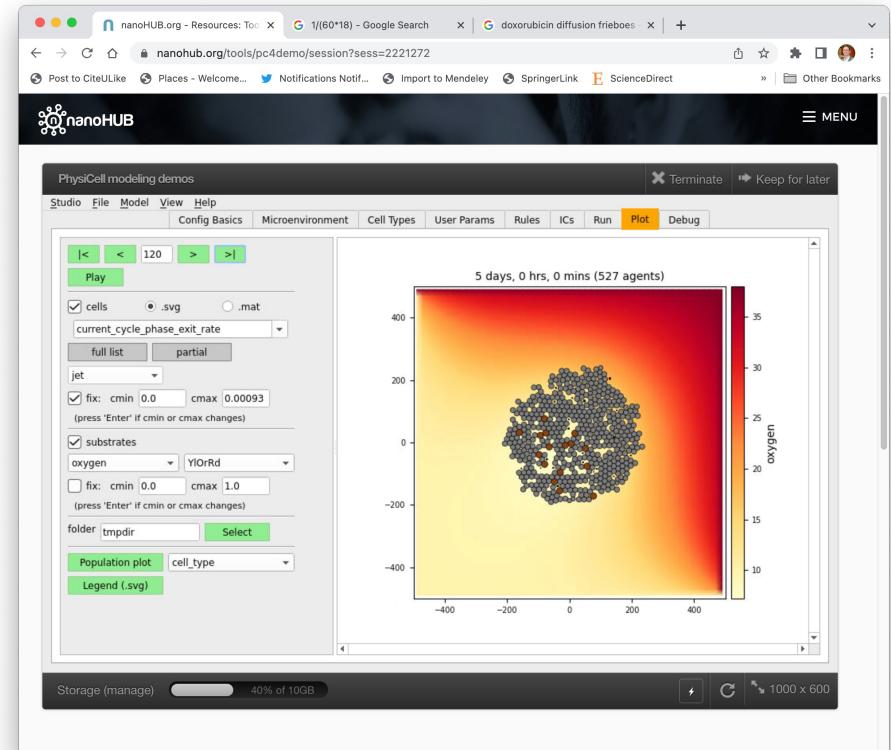
# Let's try a more interesting boundary

- Let's set oxygen on the lower x and y boundaries
  - Got to **microenvironment**
  - Look at **oxygen**
  - Set the



# 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



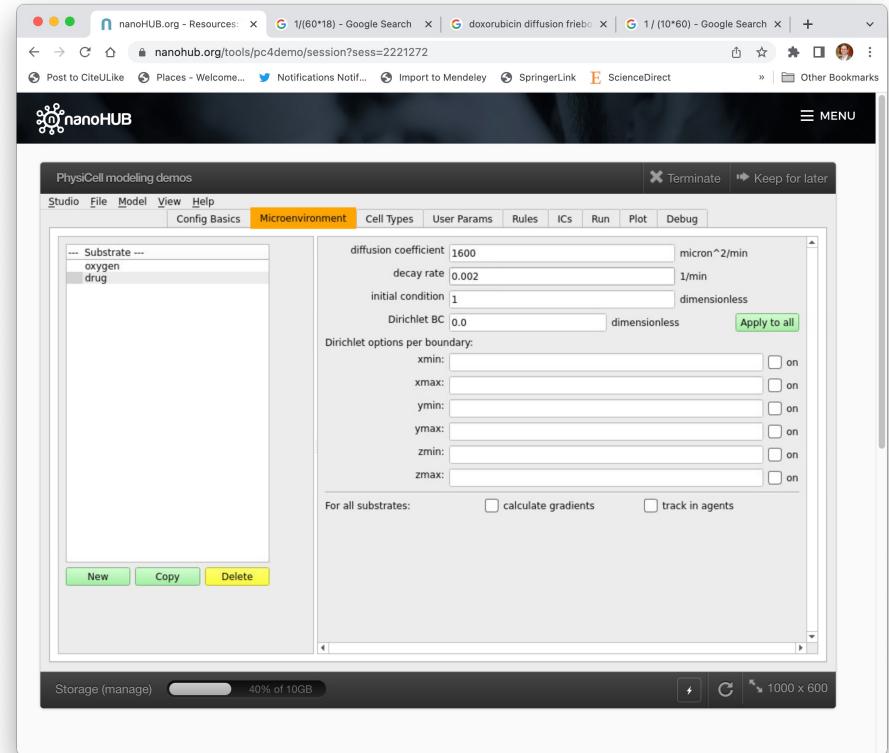
# Cytotoxic drug

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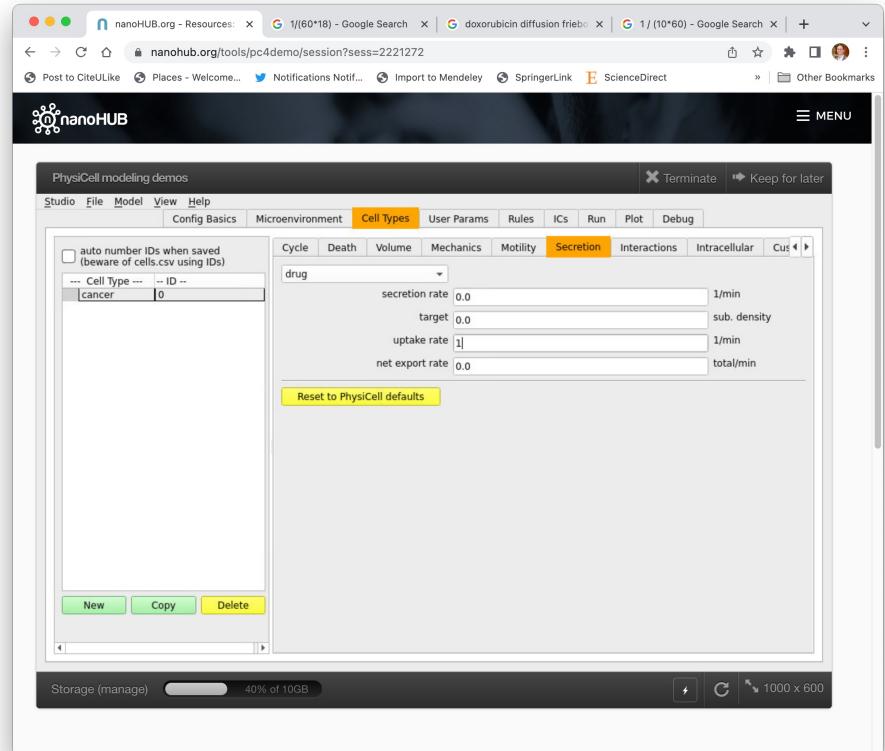
# Cytotoxic drug: 1

- First, we add a diffusible drug (e.g., to doxorubicin)
  - Go to the **microenvironment** tab
  - Click on **new**
  - Double-click and rename to **drug**
  - Set diffusion to **1600**
  - Set decay (removal) to **0.002**
    - ◆ Most doxorubicin eliminated from tissue by 30 hours. Call this 3 half lives.
  - Set the initial condition to **10**
    - ◆ A single initial bolus of drug



# Cytotoxic drug: 2

- Now, we use a cell uptake
  - Go to **cell types**
  - Go to **secretion**
  - Select **drug**
  - Set uptake to 1
    - ◆ Use this to give a 40 micron length scale



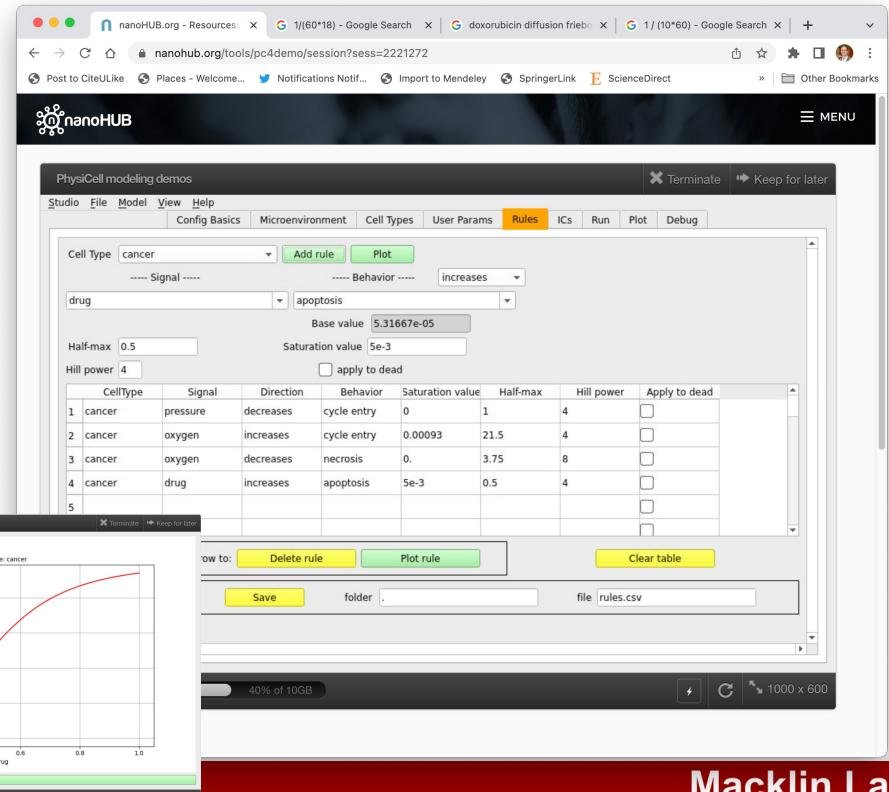
# Cytotoxic drug: 3

- Now, we add a cytotoxic response

- Go to rules
- Add a new rule

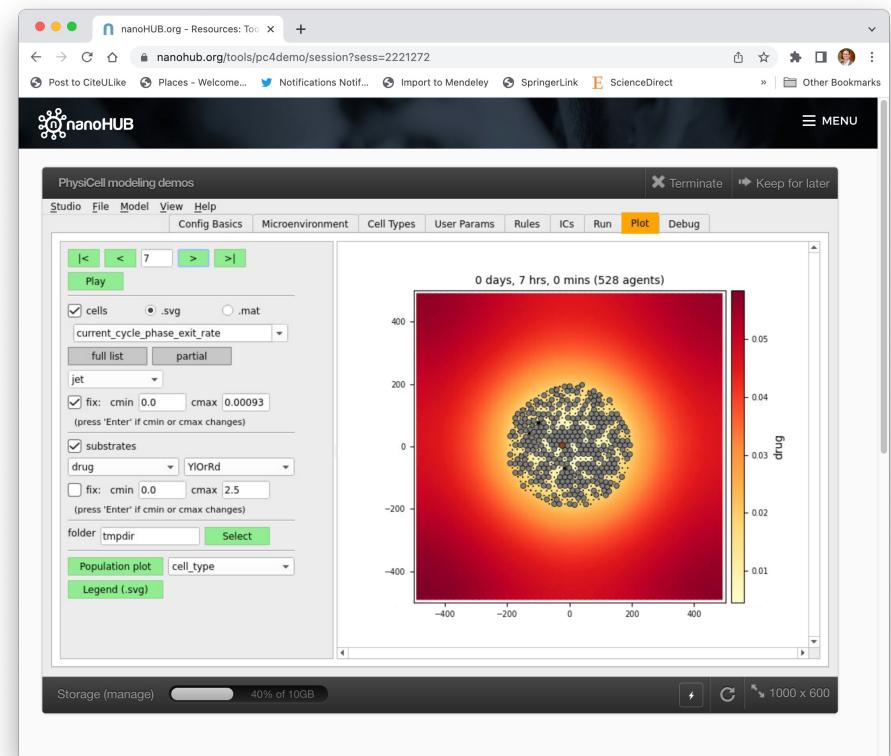
- ◆ cell type: cancer
- ◆ signal: drug
- ◆ response: increases
- ◆ behavior: apoptosis
- ◆ half-max: 0.5
- ◆ Hill power: 4
- ◆ saturation value: 5e-3
  - » 100x increase over base death

- Make sure to click save!



# 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:
  - Lots of death at first
  - Steep drug gradient
  - Drug quickly removed due to fast drug uptake
- Better modeling in future:
  - Time-varying boundary condition for circulating drug



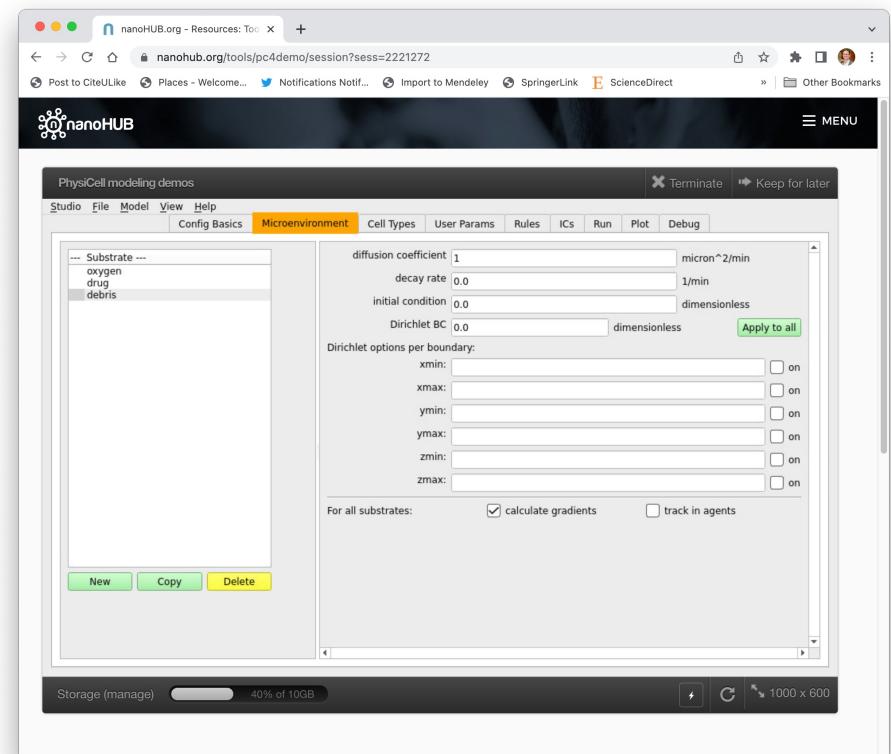
# Release of dead cell debris

# Iterative modeling example

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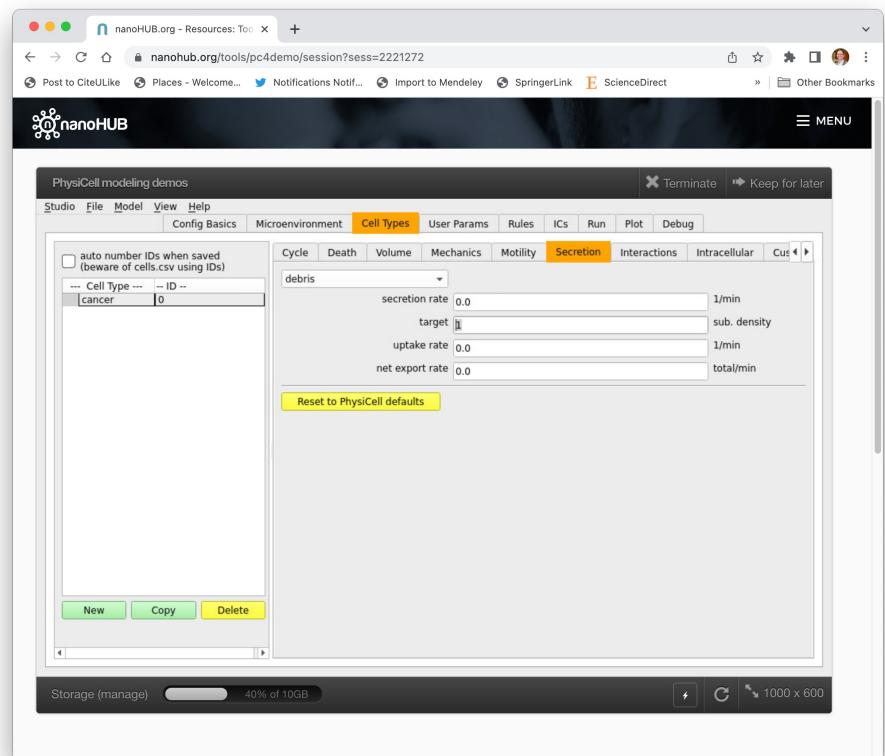
# Debris release: 1

- First, we add a diffusible debris
  - Go to the **microenvironment** tab
  - Click on **new**
  - Double-click and rename to **debris**
  - Set diffusion to **1**
  - Set decay (removal) to **0**
  - Set the initial condition to **0**



# Debris release: 2

- Now, we use a cell release target
  - Go to **cell types**
  - Go to **secretion**
  - Select **debris**
  - Set target to **1**

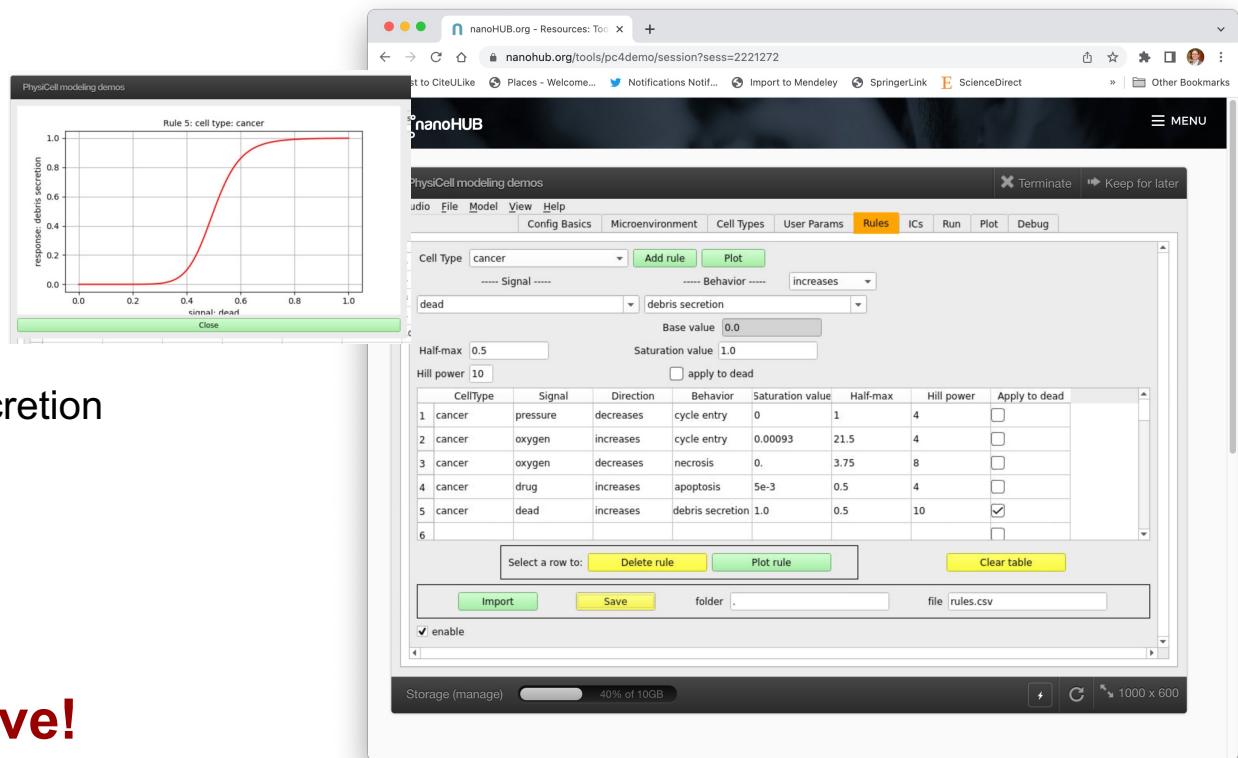


# Debris release: 3

- Now, we add a rule

- Go to rules
- Add a new rule

- ◆ cell type: cancer
- ◆ signal: dead
- ◆ response: increases
- ◆ behavior: debris secretion
- ◆ half-max: 0.5
- ◆ Hill power: 10
- ◆ saturation value: 1
- ◆ Applied to dead: true



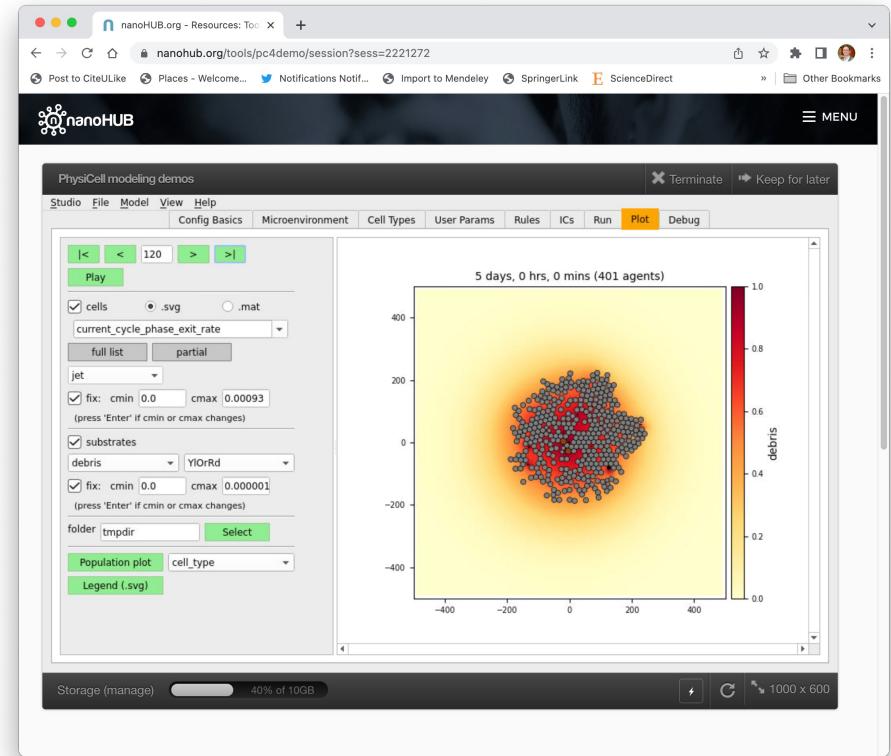
- Make sure to click save!

# Run and Visualize

- Let's color cells by standard again:

- Go to **cells** and select **SVG**
- Apoptotic cells are black
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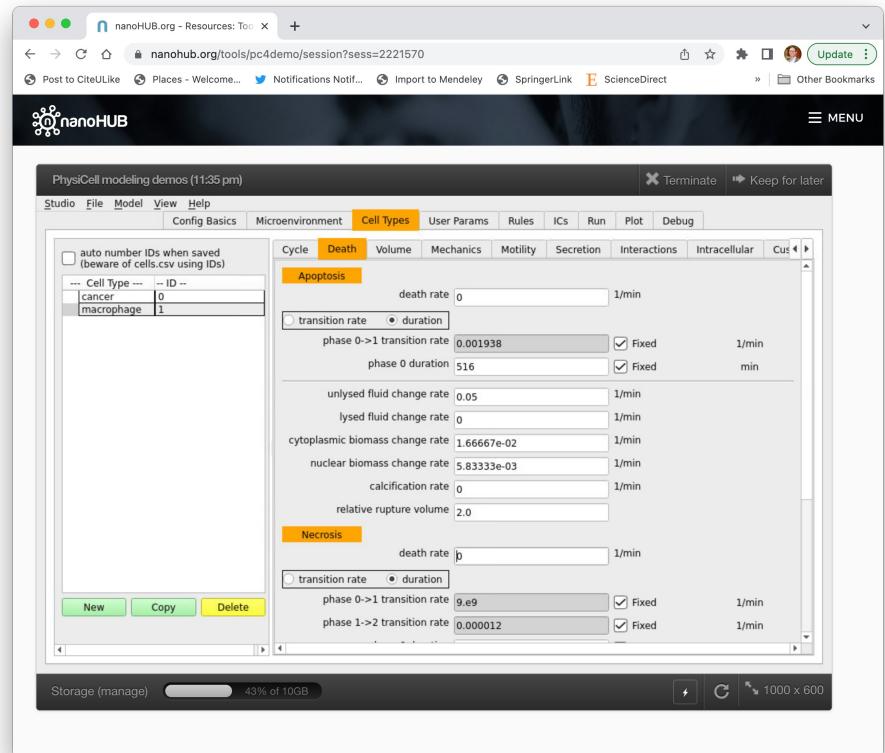
- Notice:
  - Cell debris starts to accumulate
- Future:
  - We can have apoptotic and necrotic cells release separate debris



# Macrophages

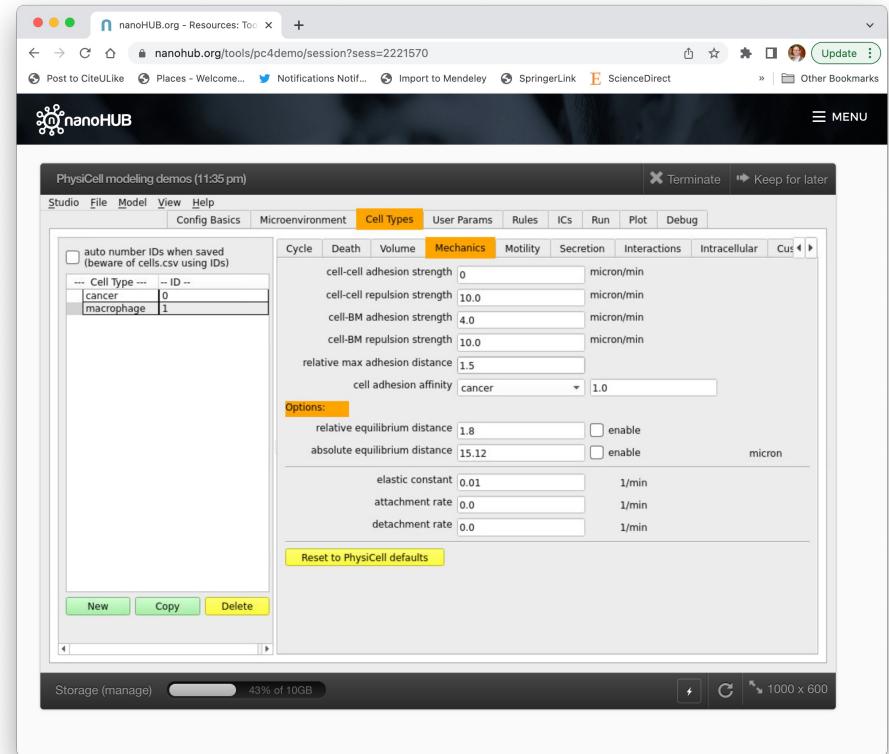
# Macrophages: 1

- First, we add a new cell type
  - Go to the **Cell types** tab
  - Select on **cancer**
  - Choose **copy**
  - Double-click and rename to **macrophage**
- Turn off death
  - Go to **death**
  - Set apoptosis **death rate** to 0
  - Set necrosis **death rate** to 0



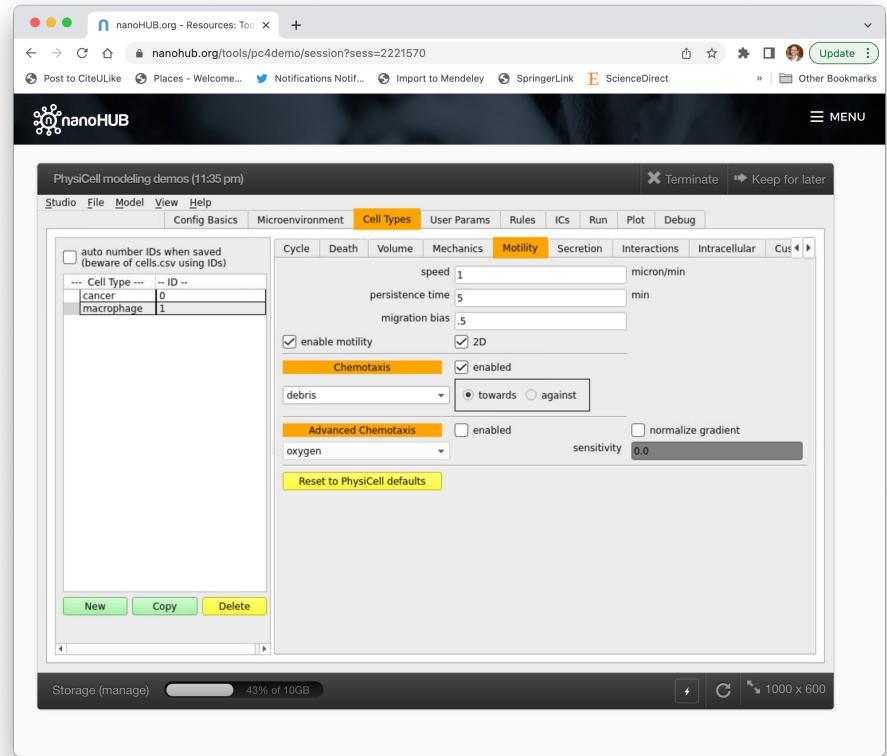
# Macrophages: 2

- Now, we want them to consume debris
  - Go to **secretion**
  - Set **oxygen uptake** at 10
  - Set **drug uptake** at 0
  - Set **debris uptake** at 1
- Macrophages should not be adhesive, and stretch farther
  - Go to **mechanics**
  - Set **cell-cell adhesion strength** to 0
  - Set **relative max adhesion distance** to 1.5



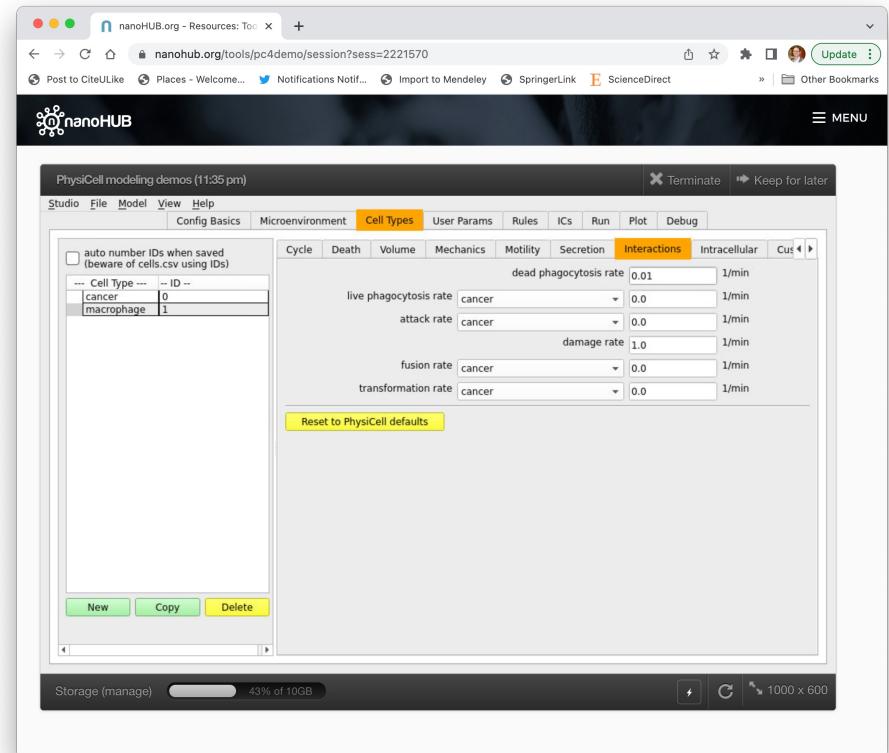
# Macrophages: 3

- Now, we want to enable motility as a biased random walk
  - Go to **motility**
  - Set **speed** to 1 micron/min
  - Set **persistence time** at 5 min
  - Set **migration bias** at 0.5
  - Click to **enable motility**
- Next, we want that random walk to be chemotaxis towards debris
  - click to **enable chemotaxis**
  - set the direction to be **towards debris**



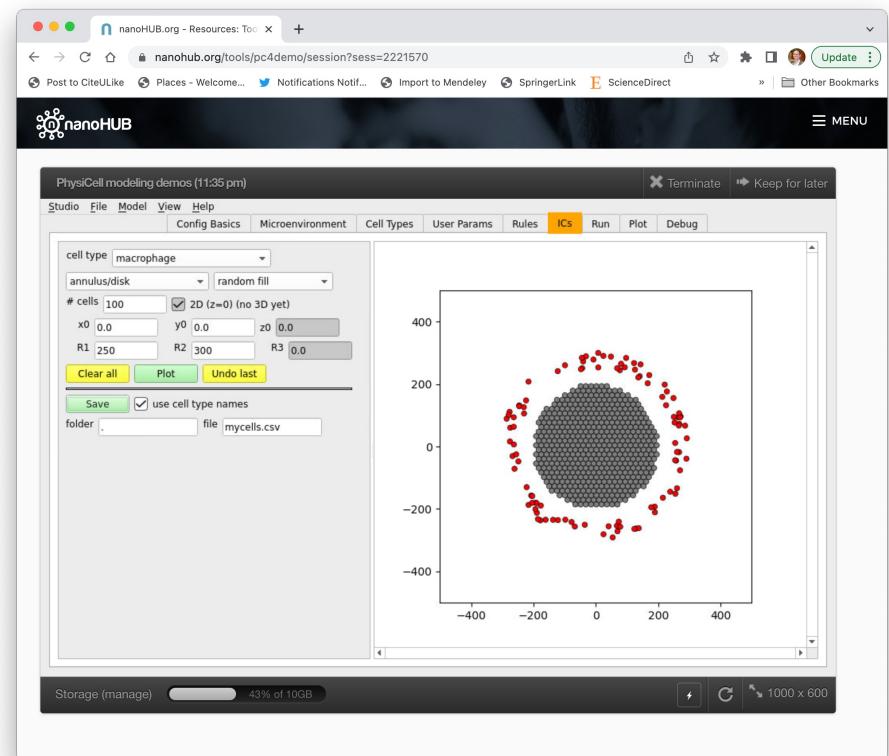
# Macrophages: 4

- Lastly, we want macrophages to phagocytose dead cells
  - Go to **interactions**
  - Set **dead phagocytosis** to 0.01



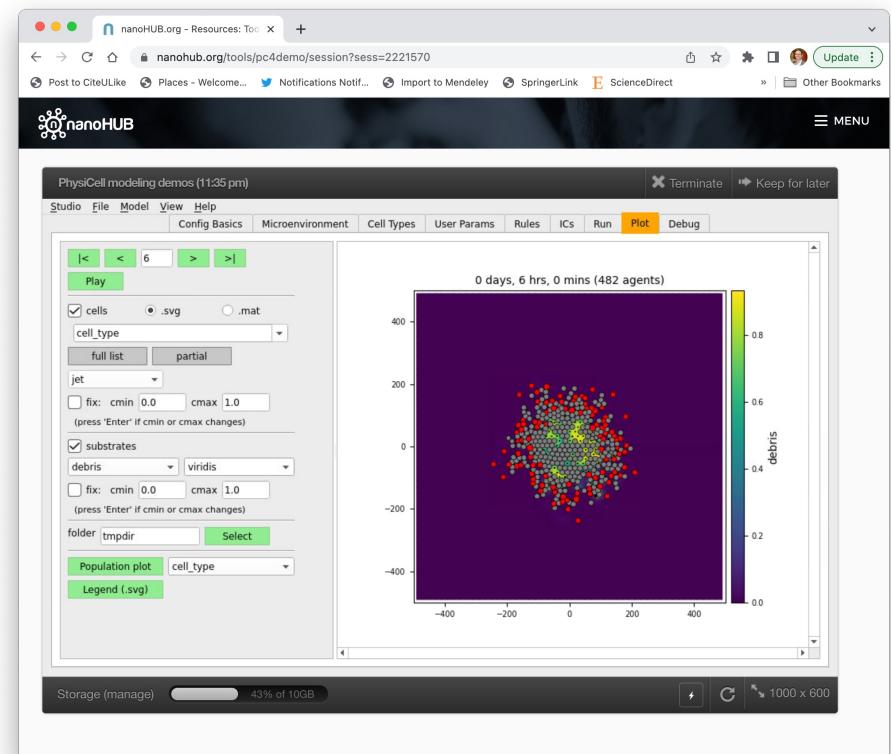
# Macrophages: 5

- Lastly, we need to add some macrophages to our environment!
  - Go to **ICs**
  - Choose **macrophage**
  - Choose **random fill**
  - Place **100** cells
  - Set min radius **R1** to 250
  - Set max radius **R2** to 300
  - Click **plot**
  - Click **save**



# 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:
  - Cell debris removed by macrophages!



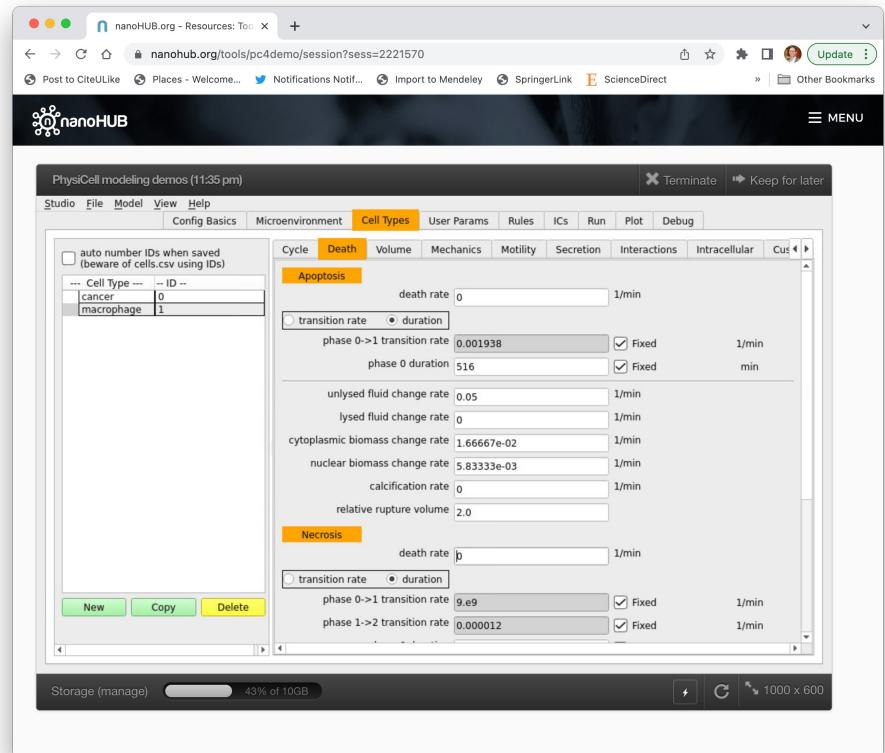
# Macrophages

# Iterative modeling example

- 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 hypoxia-driven necrosis
  5. Add a cytotoxic drug
  6. Add release of dead cell debris
  - 7. Add macrophages**
  8. Add pro-inflammatory factor
  9. Add effector T cells

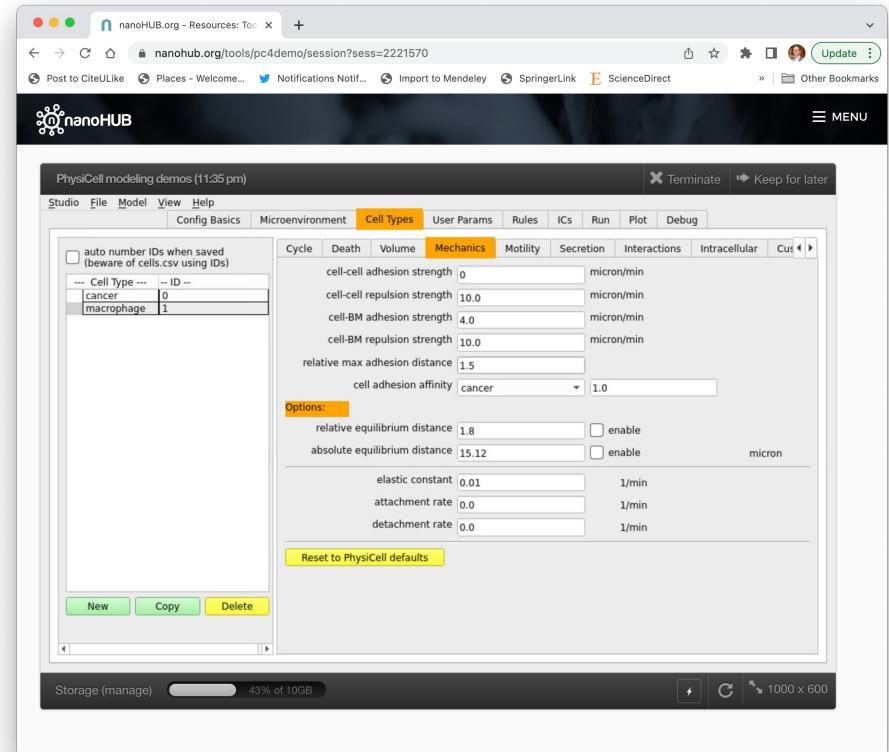
# Macrophages: 1

- First, we add a new cell type
  - Go to the **Cell types** tab
  - Select on **cancer**
  - Choose **copy**
  - Double-click and rename to **macrophage**
- Turn off death
  - Go to **death**
  - Set apoptosis **death rate** to 0
  - Set necrosis **death rate** to 0



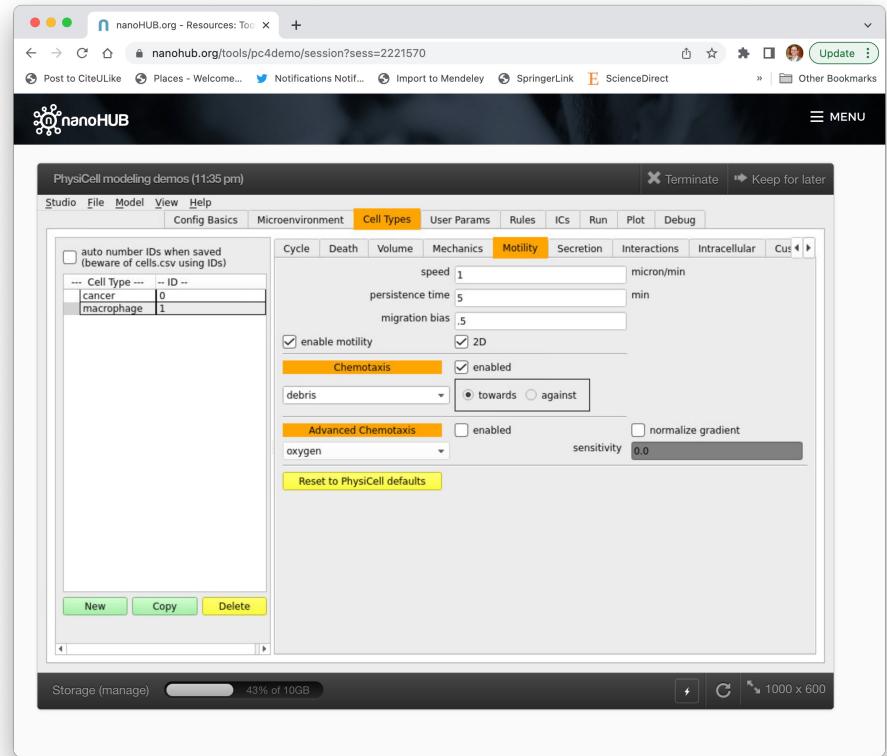
# Macrophages: 2

- Now, we want them to consume debris
  - Go to **secretion**
  - Set **oxygen uptake** at 10
  - Set **drug uptake** at 0
  - Set **debris uptake** at 1
- Macrophages should not be adhesive, and stretch farther
  - Go to **mechanics**
  - Set **cell-cell adhesion strength** to 0
  - Set **relative max adhesion distance** to 1.5



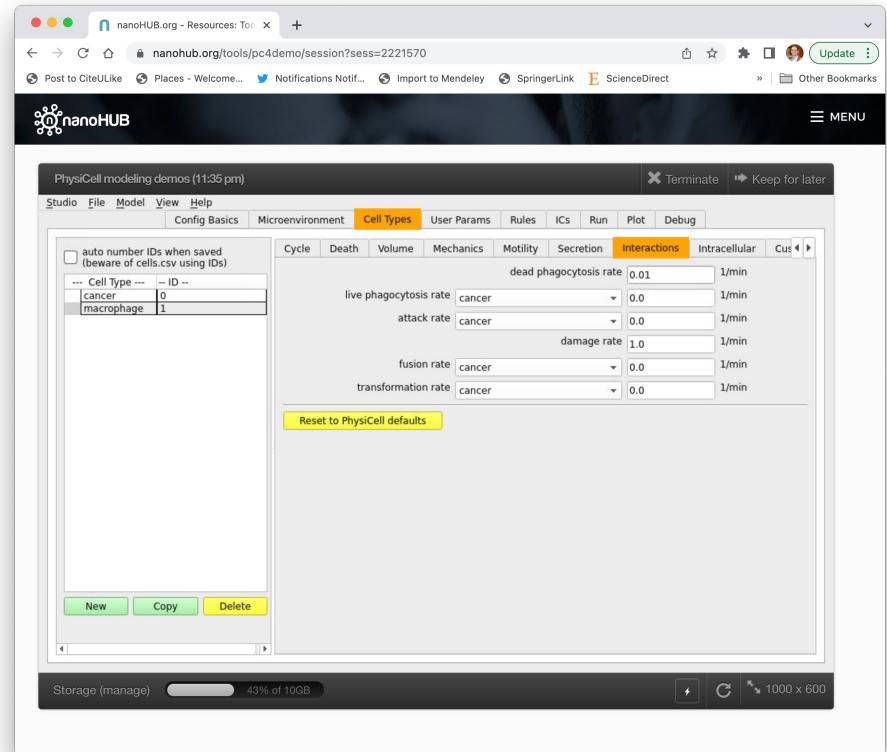
# Macrophages: 3

- Now, we want to enable motility as a biased random walk
  - Go to **motility**
  - Set **speed** to 1 micron/min
  - Set **persistence time** at 5 min
  - Set **migration bias** at 0.5
  - Click to **enable motility**
- Next, we want that random walk to be chemotaxis towards debris
  - click to **enable chemotaxis**
  - set the direction to be **towards debris**



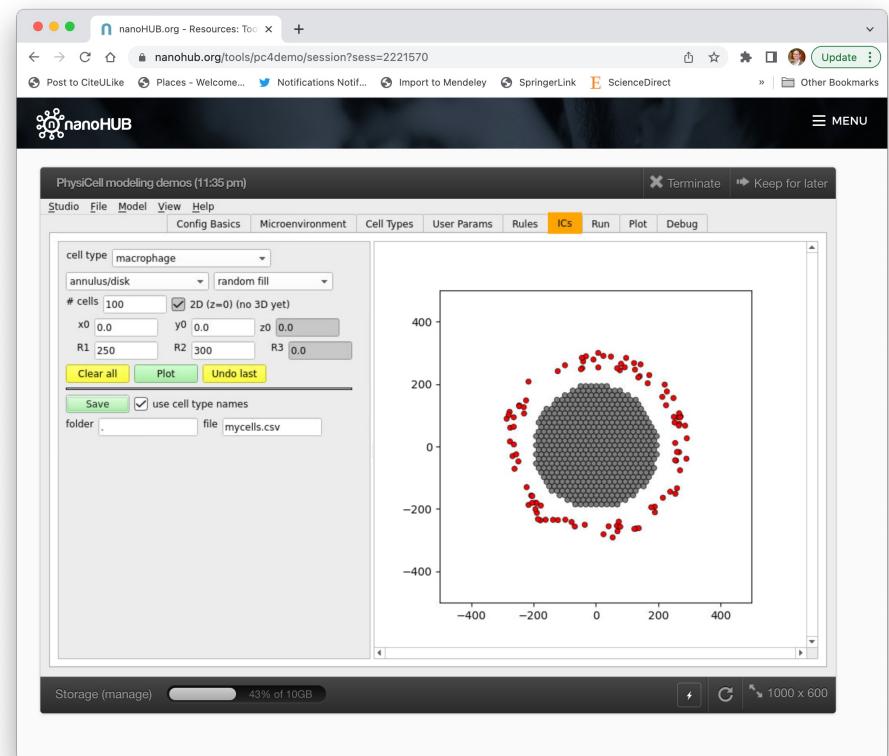
# Macrophages: 4

- Lastly, we want macrophages to phagocytose dead cells
  - Go to **interactions**
  - Set **dead phagocytosis** to 0.01



# Macrophages: 5

- Lastly, we need to add some macrophages to our environment!
  - Go to **ICs**
  - Choose **macrophage**
  - Choose **random fill**
  - Place **100** cells
  - Set min radius **R1** to 250
  - Set max radius **R2** to 300
  - Click **plot**
  - Click **save**

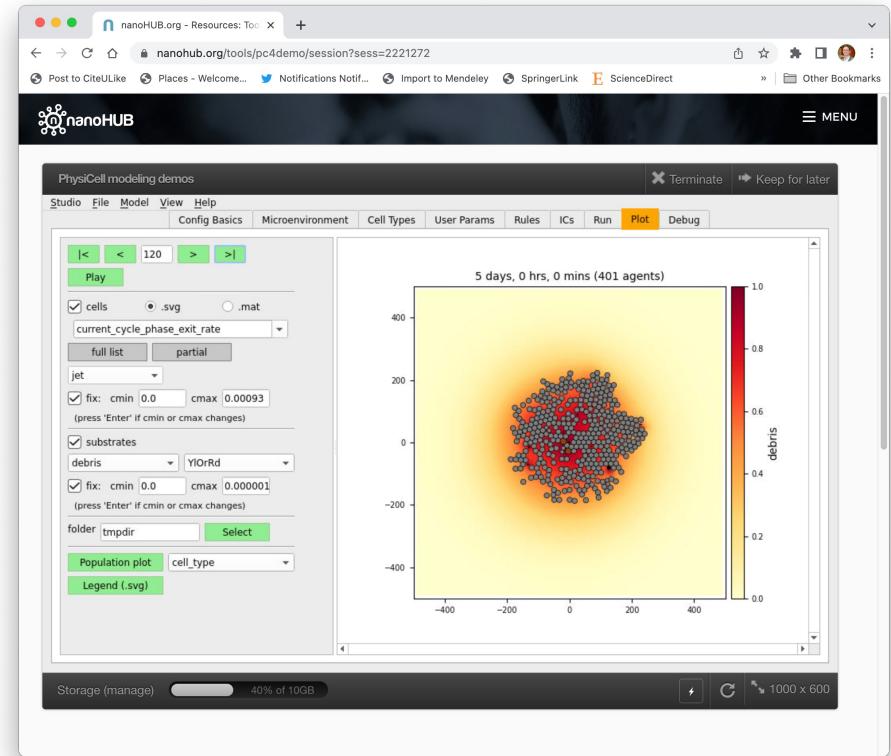


# Run and Visualize

- Let's color cells by standard again:

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

- Notice:
  - Cell debris starts to accumulate
- Future:
  - We can have apoptotic and necrotic cells release separate debris



# Inflammation

# Iterative modeling example

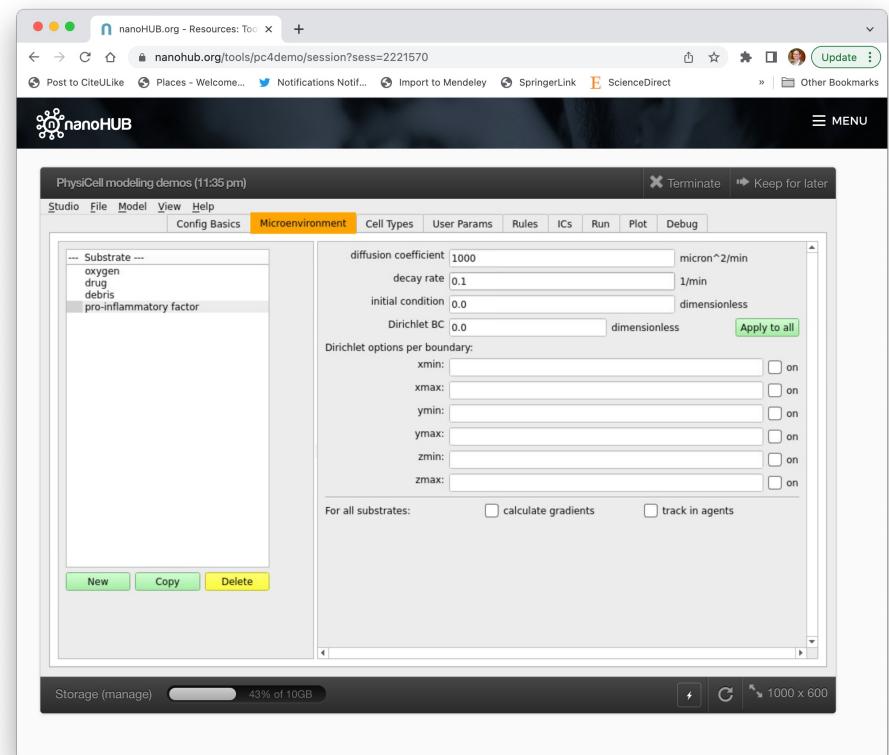
- We'll iteratively build a simple tumor model, bit-by-bit:
  1. Growing tumor with oxygen consumption
  2. Add a mechanofeedback on cycling
  3. Add oxygen-driven cycling
  4. Add hypoxia-driven necrosis
  5. Add a cytotoxic drug
  6. Add release of dead cell debris
  7. Add macrophages
  - 8. Add pro-inflammatory factor**
  9. Add effector T cells

# Strategy

- Let's do 3 things:
  - First, add a pro-inflammatory factor
    - ◆ Give it a 100 micron length scale, and very slow decay / removal
    - ◆  $L = \sqrt{1000 / 0.1}$
  - Second, create a second M1 macrophage cell type
    - ◆ Identical to macrophage, **except** they secrete pro-inflammatory factor
  - Third, make macrophages transform to M1 macrophages
    - ◆ Make it happen when in contact with dead cells

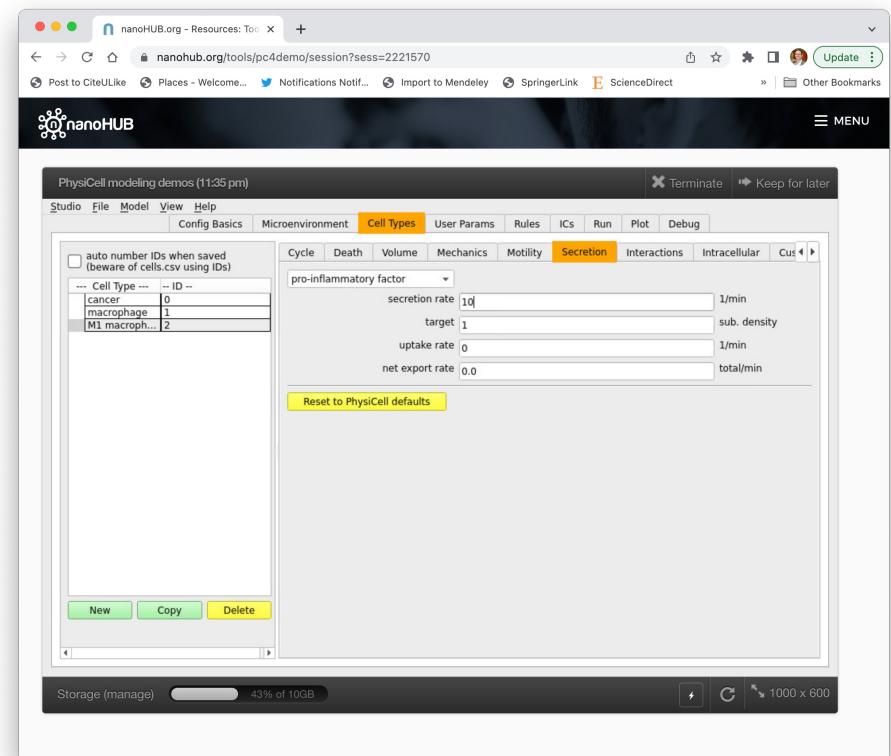
# M1 Macrophages: 1

- First, we add pro-inflammatory factor
  - Go to **microenvironment**
  - Create **new**
  - Rename to **pro-inflammatory factor**
  - Set **diffusion** to 1000
  - Set **decay** to 0.1



# M1 Macrophages: 2

- First, we add a new cell type
  - Go to the **Cell types** tab
  - Select on **macrophage**
  - Choose **copy**
  - Rename to **M1 macrophage**
- Turn on secretion
  - Go to **secretion**
  - Choose **pro-inflammatory factor**
  - Set **target** to 1
  - Set **secretion rate** to 10



# M1 Macrophage: 3

- Now, we add a rule

- Go to **rules**
- Add a new rule

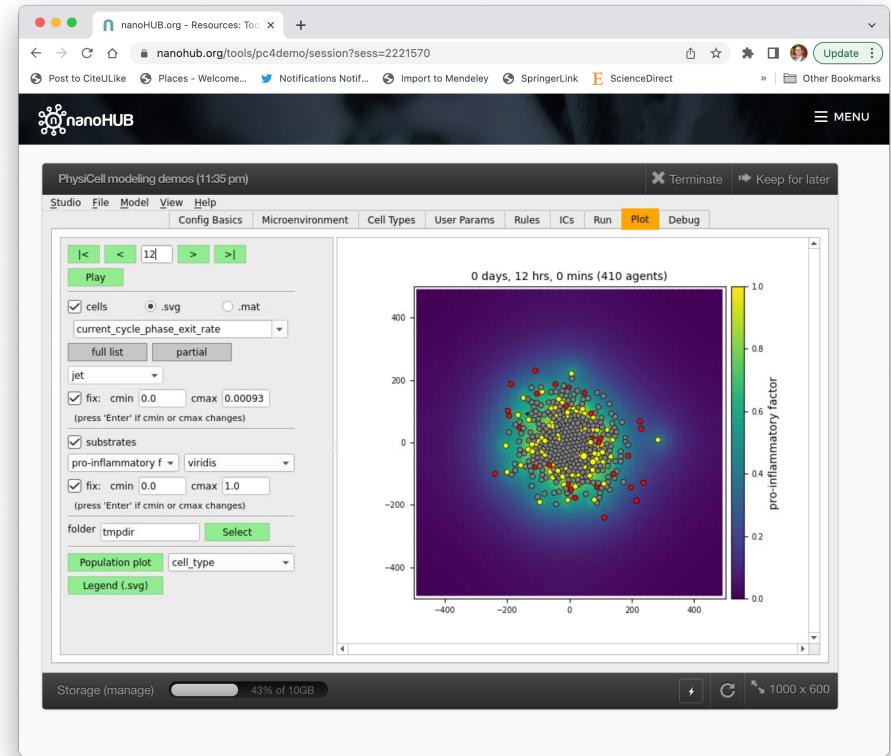
- ◆ cell type: macrophage
- ◆ signal: contact with dead cell
- ◆ response: increases
- ◆ behavior: transform to M1 macrophage
- ◆ half-max: 0.5
- ◆ Hill power: 10
- ◆ saturation value: 0.1
- ◆ Applied to dead: **false**

- Make sure to click save!**



# 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:
  - Cell debris starts to accumulate
- Future:
  - We can have apoptotic and necrotic cells release separate debris



# Effector T cells

# Iterative modeling example

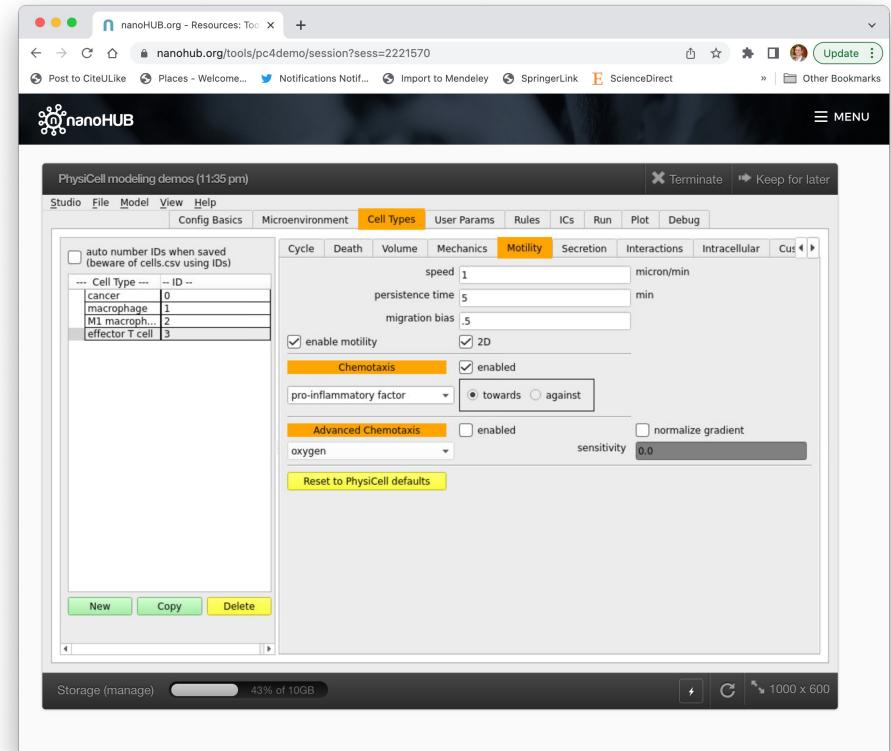
- We'll iteratively build a simple tumor model, bit-by-bit:
  1. Growing tumor with oxygen consumption
  2. Add a mechanofeedback on cycling
  3. Add oxygen-driven cycling
  4. Add hypoxia-driven necrosis
  5. Add a cytotoxic drug
  6. Add release of dead cell debris
  7. Add macrophages
  8. Add pro-inflammatory factor
  - 9. Add effector T cells**

# Strategy

- Let's do 2 things:
  - First, add effector T cells
    - ◆ Identical to Macrophages, **except**
      - » Chemotaxis towards pro-inflammatory factor
      - » Do not consume debris
      - » Do not secrete pro-inflammatory factor
      - » Uptake pro-inflammatory factor
      - » Attack cancer cells
  - Second, make damage cause cancer cell death
    - ◆ Add rule: damage increases apoptosis

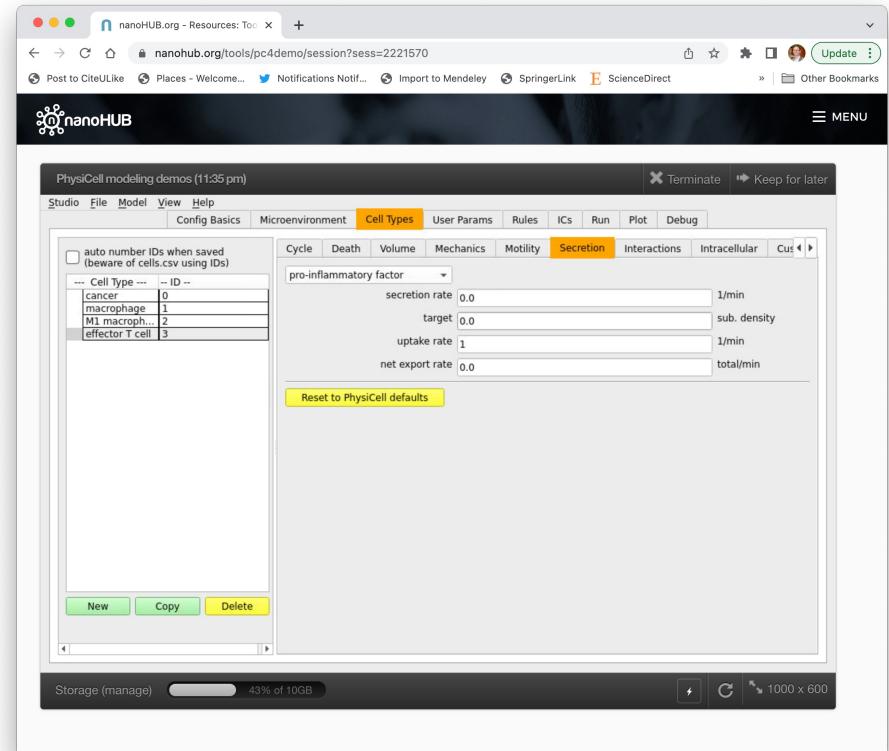
# Effector T cells: 1

- Add the new cell type
  - Go to **cell types**
  - select **macrophage**
  - **copy**
  - Rename to **Effector T cell**
- Change chemotaxis
  - Go to **motility**
  - Go to **chemotaxis**
  - Change drop-down to **pro-inflammatory factor**



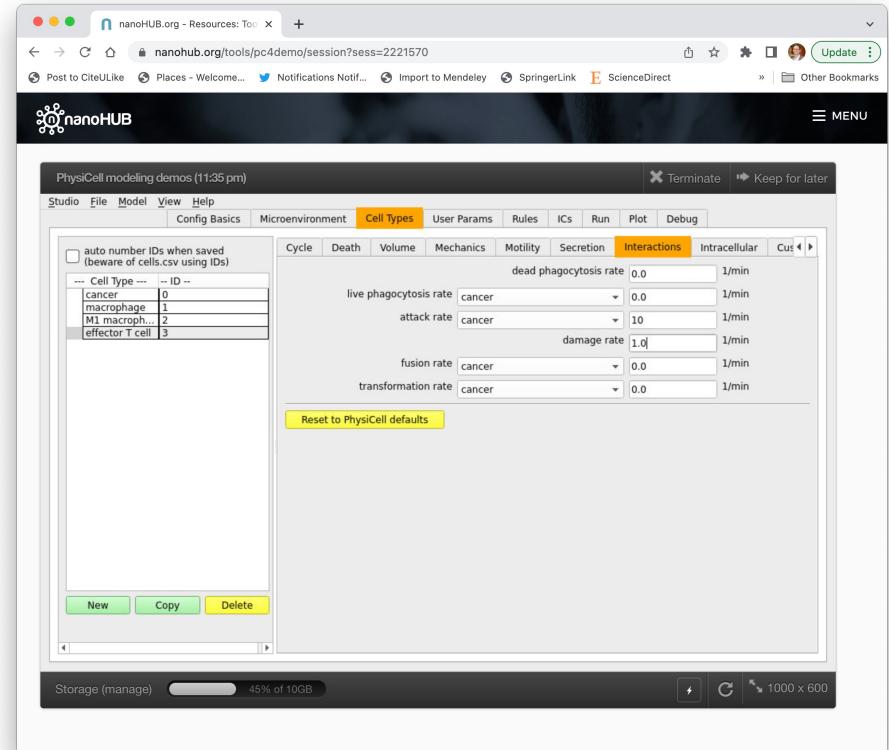
# Effector T cells: 2

- Change secretion
  - Go to **secretion**
  - Choose **debris**
  - Set **uptake** to 0
- Go to **pro-inflammatory factor**
- Set **uptake** to 1



# Effector T cells: 3

- Change interactions
  - Go to **interactions**
  - Set **dead cell phagocytosis** to 0
  - Set **attack rate** for **cancer** to 10



# Effector T cells: 4

- Now, we add a rule

- Go to rules
- Add a new rule

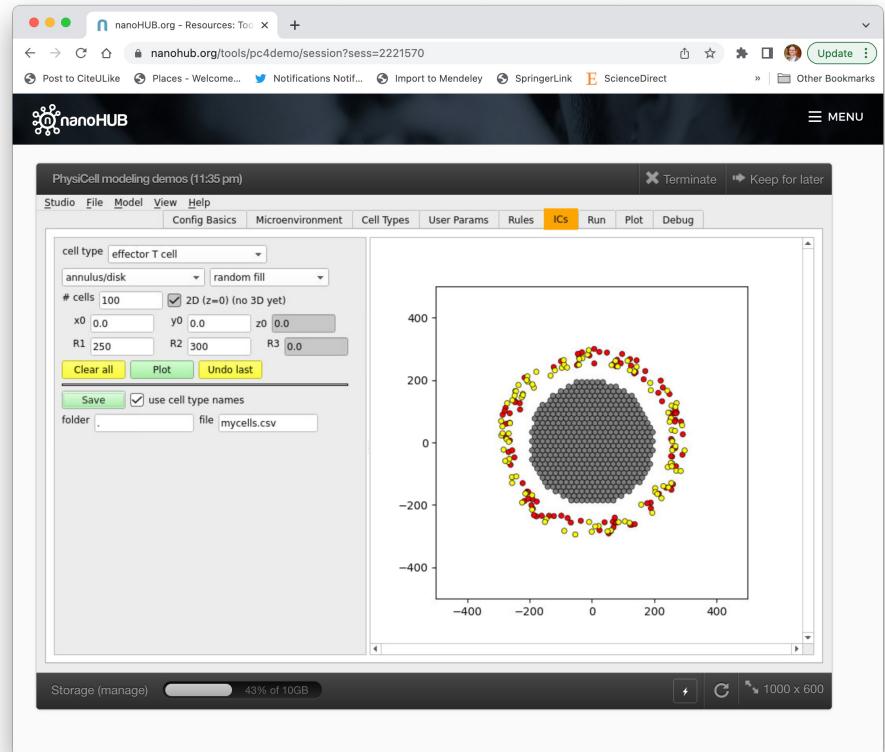
- ◆ cell type: cancer
- ◆ signal: damage
- ◆ response: increases
- ◆ behavior: apoptosis
- ◆ half-max: 5
- ◆ Hill power: 4
- ◆ saturation value: 0.01
- ◆ Applied to dead: false

- Make sure to click save!

Cell Type	Signal	Direction	Behavior	Saturation value	Half-max	Hill power	Apply to dead
3 cancer	oxygen	decreases	necrosis	0	3.75	8	<input type="checkbox"/>
4 cancer	drug	increases	apoptosis	5e-3	0.5	4	<input type="checkbox"/>
5 cancer	dead	increases	debris secretion	1.0	0.5	10	<input checked="" type="checkbox"/>
6 macrophage	contact with dead cell	increases	M1 macrophage	0.1	0.5	10	<input type="checkbox"/>
7 cancer	damage	increases	apoptosis	0.01	5	4	<input type="checkbox"/>
8							

# Effector T cells: 5

- Lastly, add cells!
  - Go to ICs
  - Choose **effector T cell**
  - Annulus/Circle, hex fill, 100 cells
  - Min radius 250
  - max radius 300
  - plot, save



# 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:
  - They attack and kill off cancer cells!
- Future:
  - Factor-dependent attack
  - Tumor evolve resistance
  - T cell exhaustion

