

PhysiCell Mini-Course

Session 2: Cancer Modeling

Paul Macklin, Ph.D.

Intelligent Systems Engineering
Indiana University

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Session Goals

- Work on sample cancer model with key modeling concepts
 - Show mechanofeedbacks
 - Show how to model drugs
 - Show phagocytosis, effector attack, and transformation
 - Transient vs. sustained response

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 a cytotoxic drug
4. Add release of dead cell debris
5. Add macrophages
6. Add pro-inflammatory factor
7. Add effector T cells
8. Improvised modeling / exploration

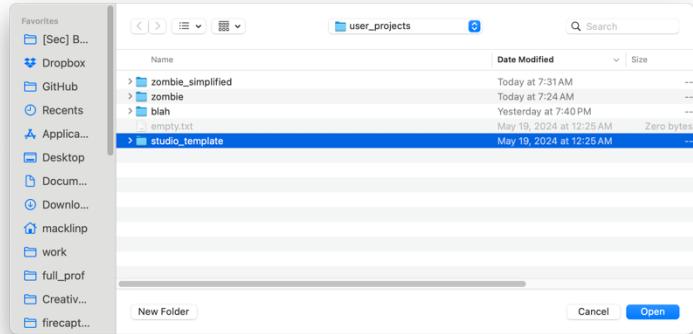


LUDDY

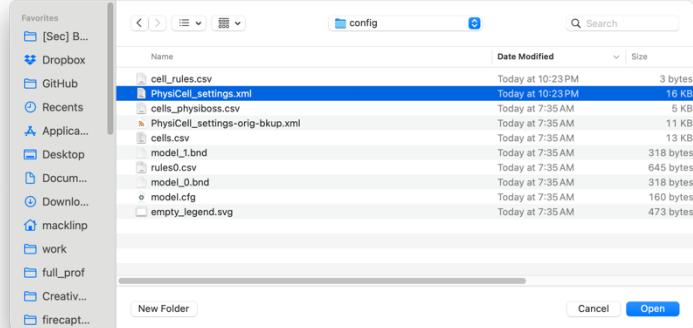
SCHOOL OF INFORMATICS, COMPUTING, AND ENGINEERING

Load the blank template project

- Let's get the (blank) template project
 - File → Load user project
 - Choose **studio_template**
 - This loads all the files into the right place



- Next let's load it into the studio:
 - File → open
 - Browse to **config**
 - Load **PhysiCell_settings.xml**



Initial tumor and oxygen consumption

Growing tumor with oxygen: 1

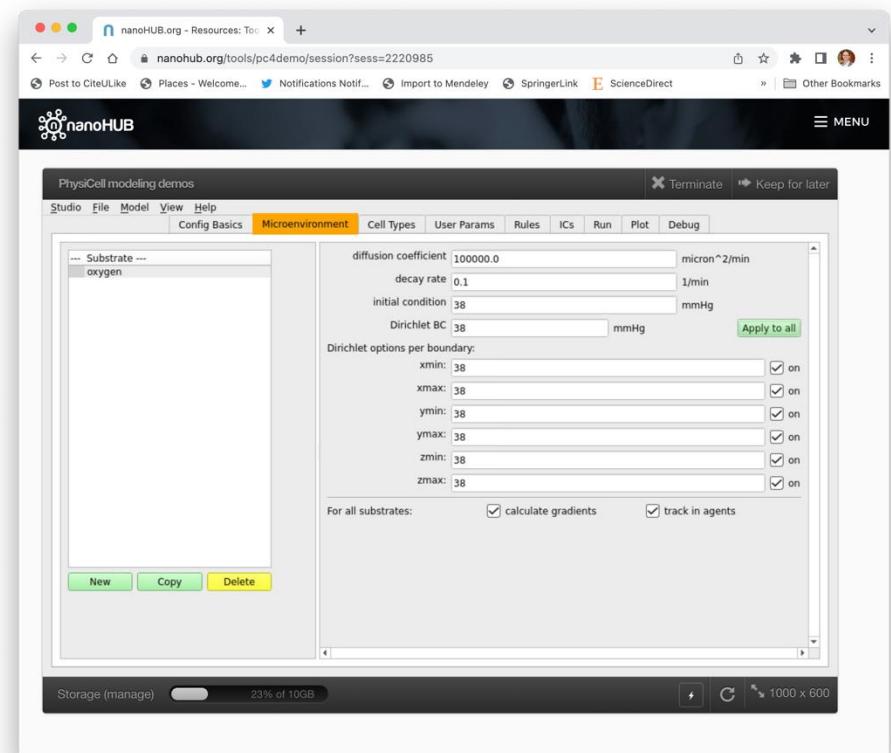
- First, we add oxygen in the **Microenvironment** tab
- We use the **diffusion length scale** from physics / applied mathematics:
 - Penetration into a tissue is competition between effects:
 - Diffusion (D) increases spread
 - Uptake (U) and decay (λ) tend to halt spread

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

- 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, $\text{pO}_2 \sim 5\% = 38 \text{ mmHg}$

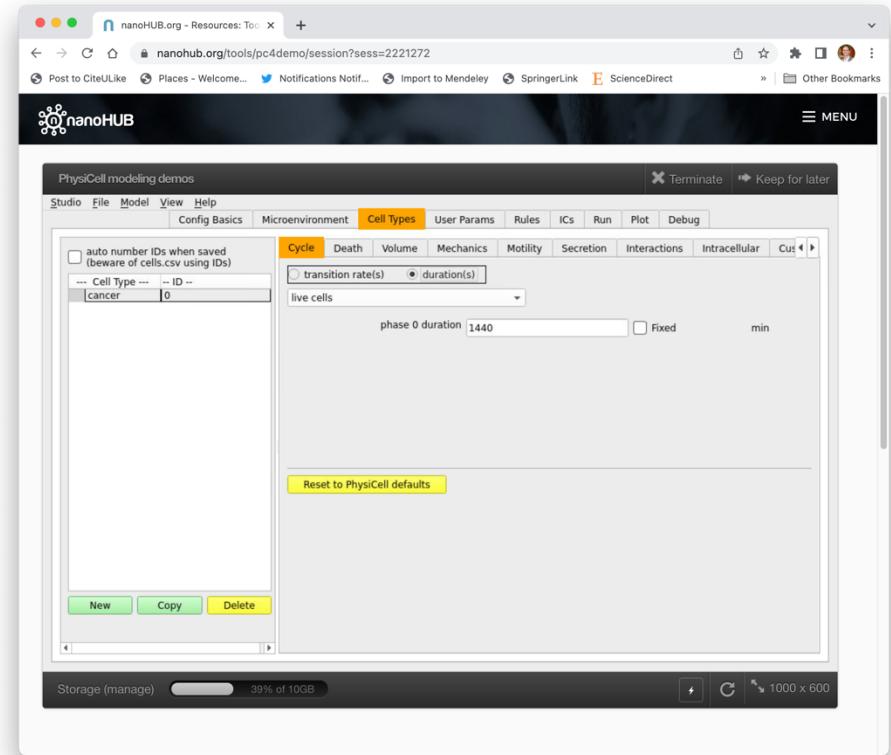
Growing tumor with oxygen: 2

- 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



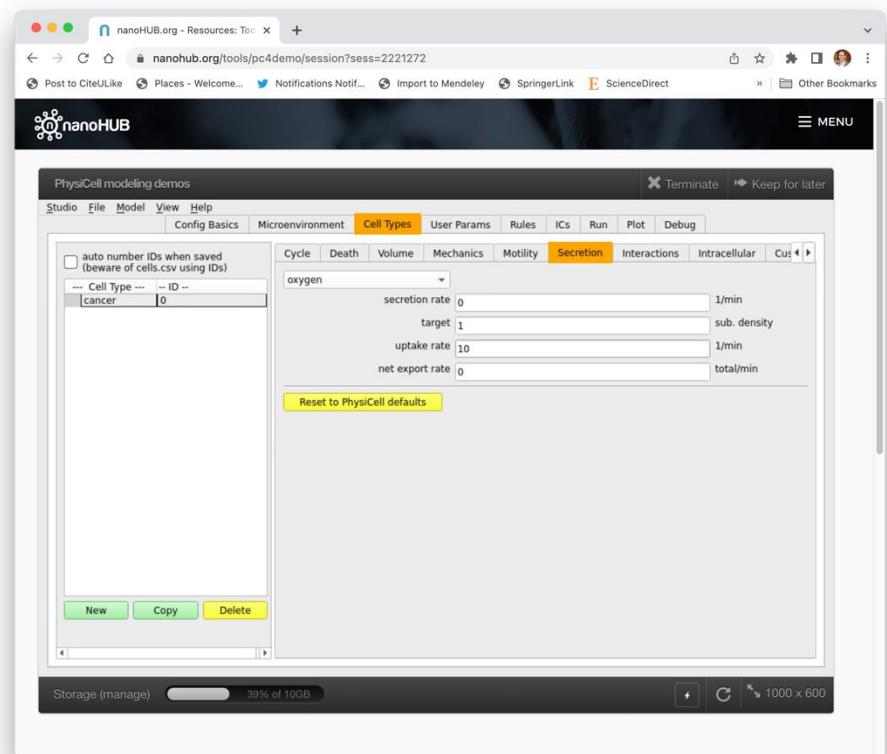
Setting up cancer cells: 1

- 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



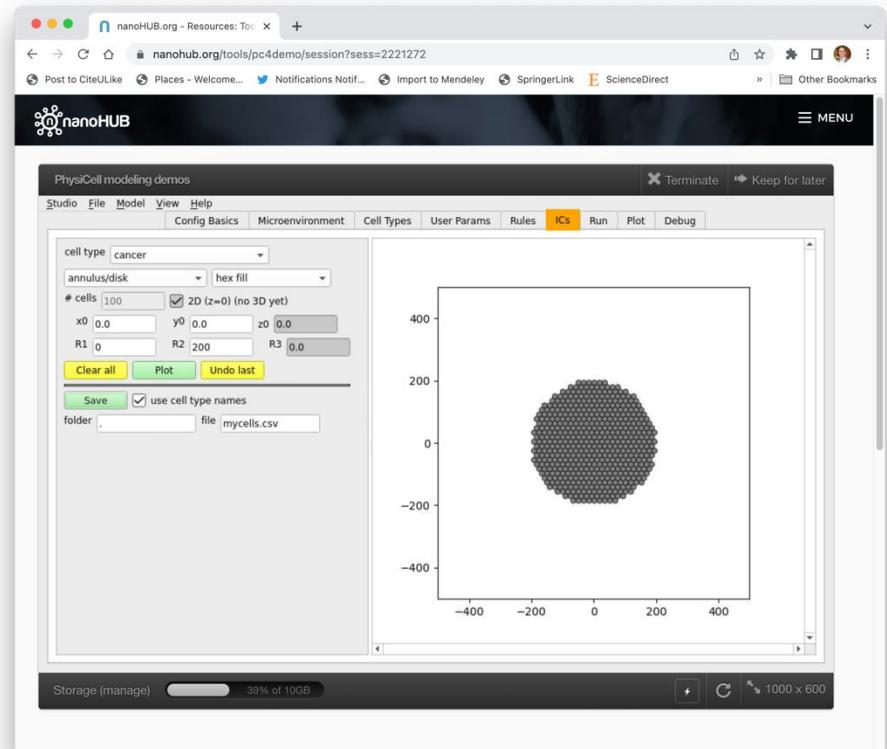
Setting up cancer cells: 2

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



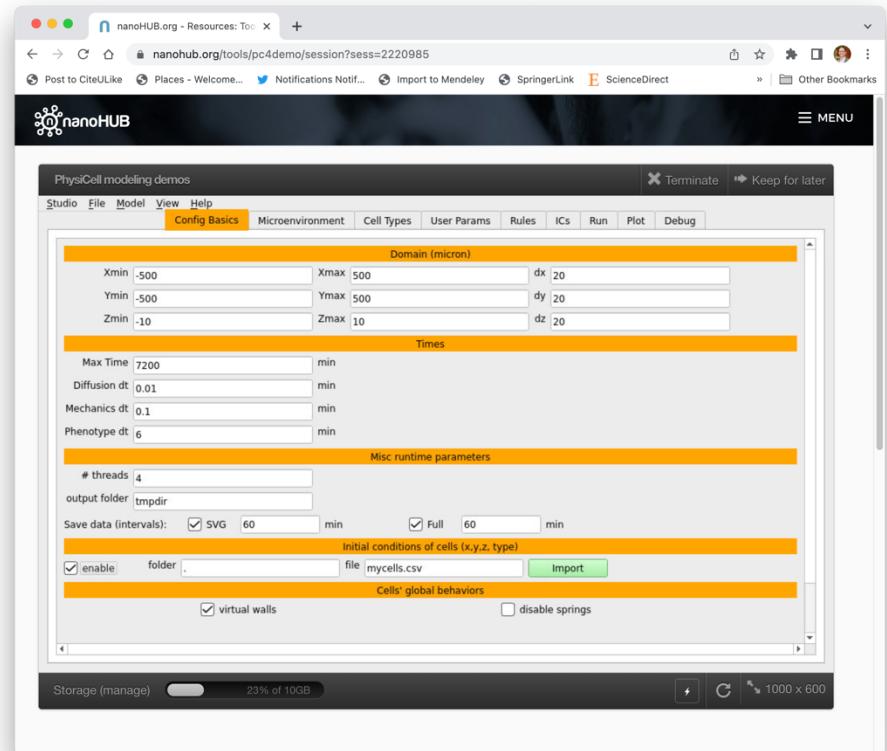
Set up an initial state: 1

- 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**

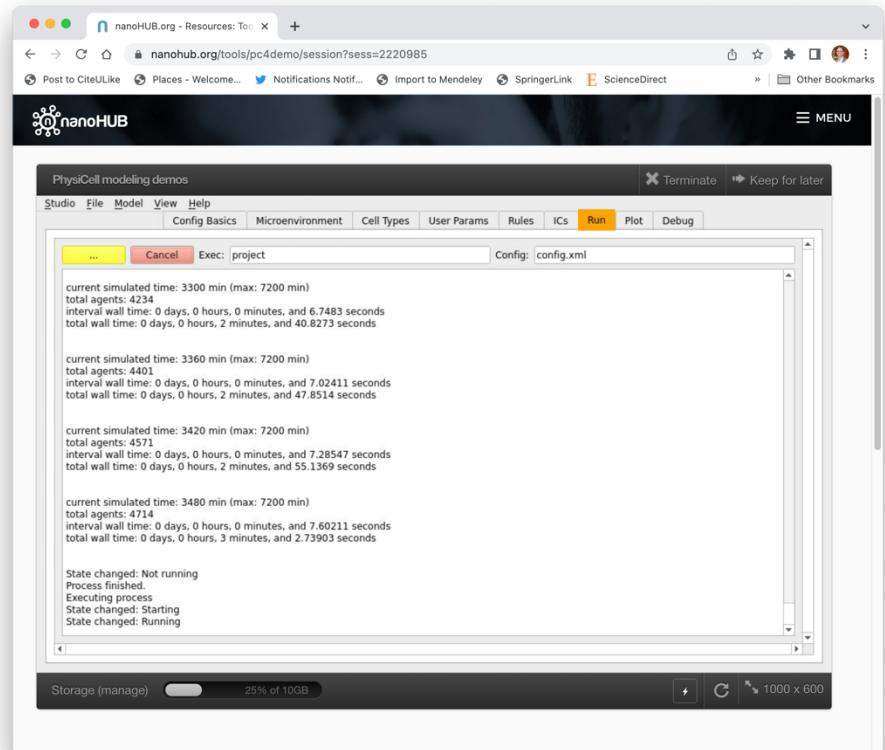
The screenshot shows a web browser window for nanoHUB.org. The URL is nanohub.org/tools/pc4demo/session?sess=2220985. The page title is "PhysiCell modeling demos". The "User Params" tab is selected in the navigation bar. A table lists parameters:

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			

At the bottom, there is a "Delete" button and a message: "click row # to [Delete]".

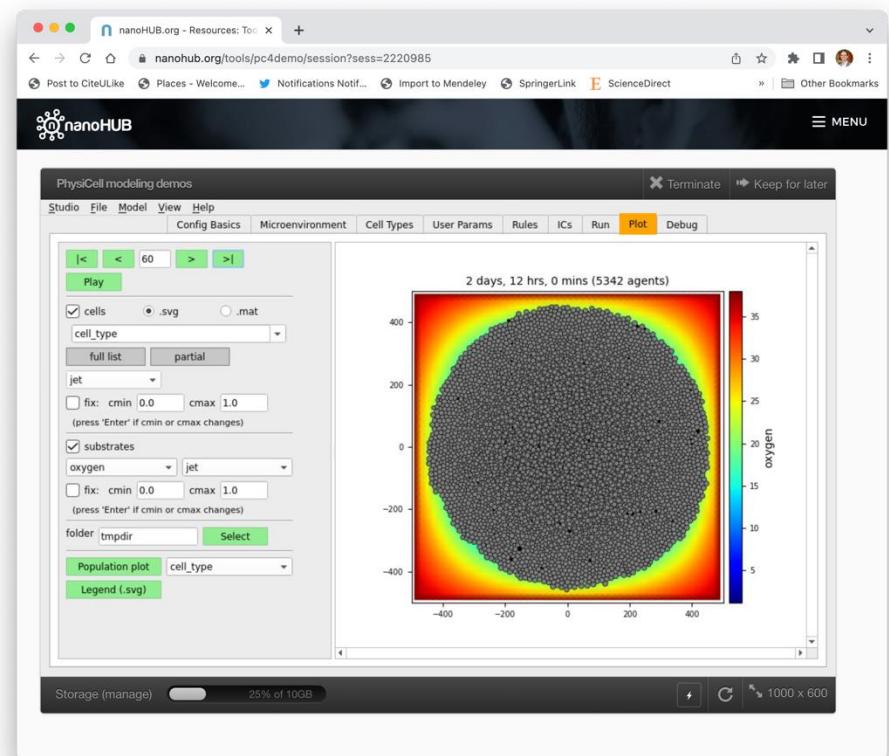
Run the model!

- 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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8. Add pro-inflammatory factor
9. Add effector T cells

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

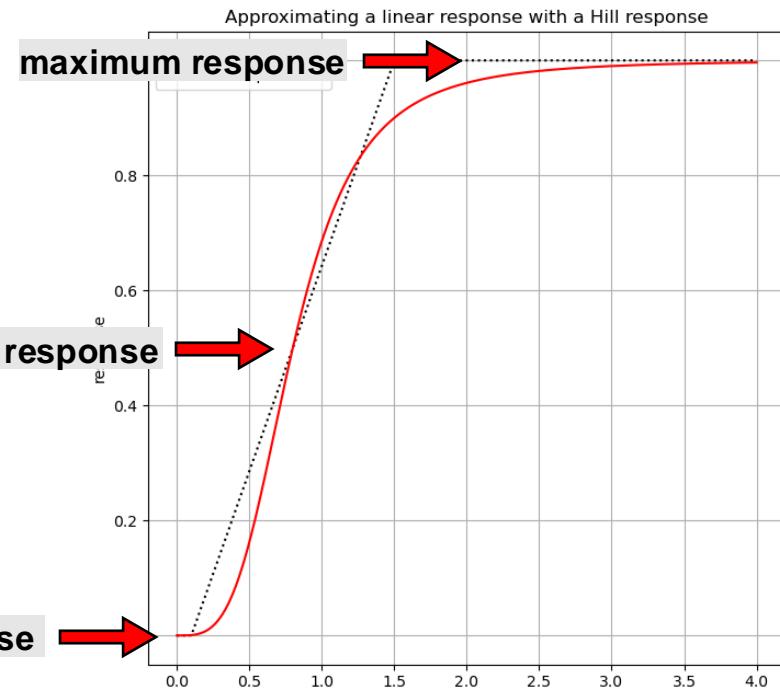
Pressure

- 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

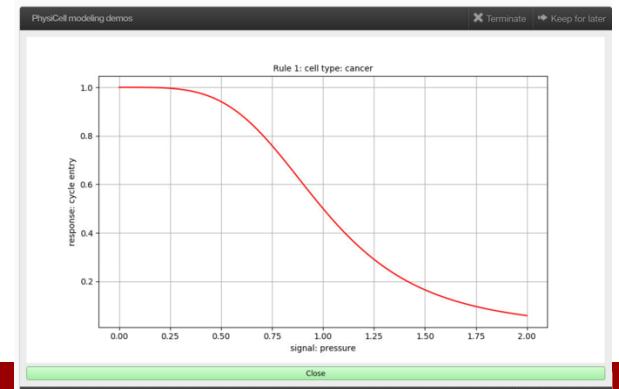
$$H(s; s_{\text{half}}, h) = \frac{s^h}{s_{\text{half}}^h + s^h} = \frac{\left(\frac{s}{s_{\text{half}}}\right)^h}{1 + \left(\frac{s}{s_{\text{half}}}\right)^h} \quad \text{if } s \geq 0, \quad \text{and } H(s) = 0 \text{ if } s < 0.$$



Our mathematics

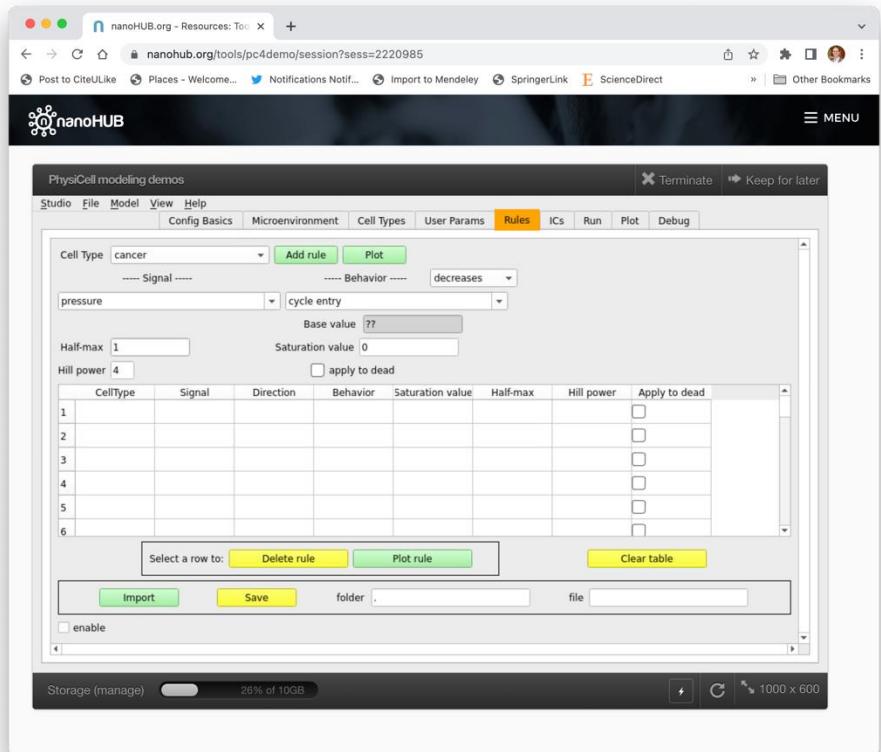
- Mathematical form of pressure:
 - Based on potentials
 - Nondimensionalized to 1 for 3D confluent tissues
 - Nondimensionalized to 0.5 for 2D confluent tissues
- We'll suppose cancer cells can accept some compression
 - Use a **half-max** of 1:
 - Once pressure hits 1.0, a sharp decrease in cycling
 - 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

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



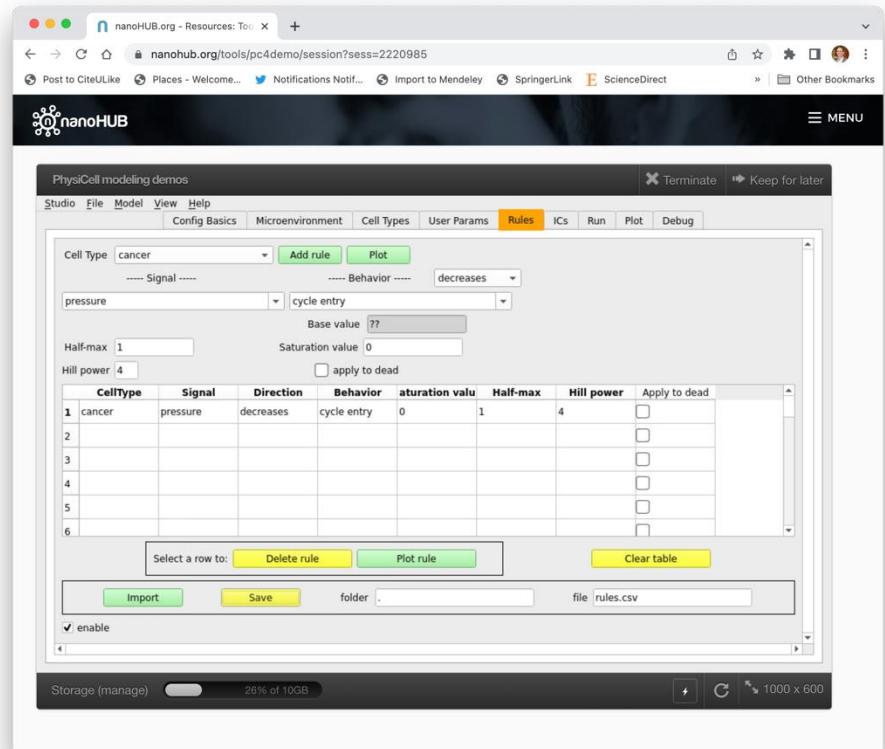
Add the rule: 1

- 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**



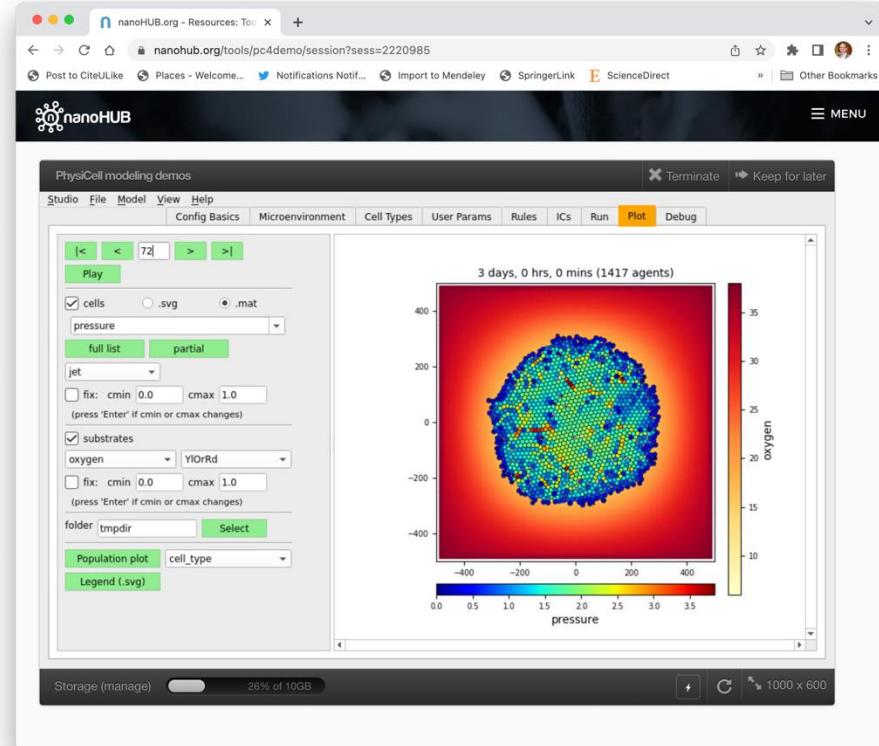
Add the rule: 2

- 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

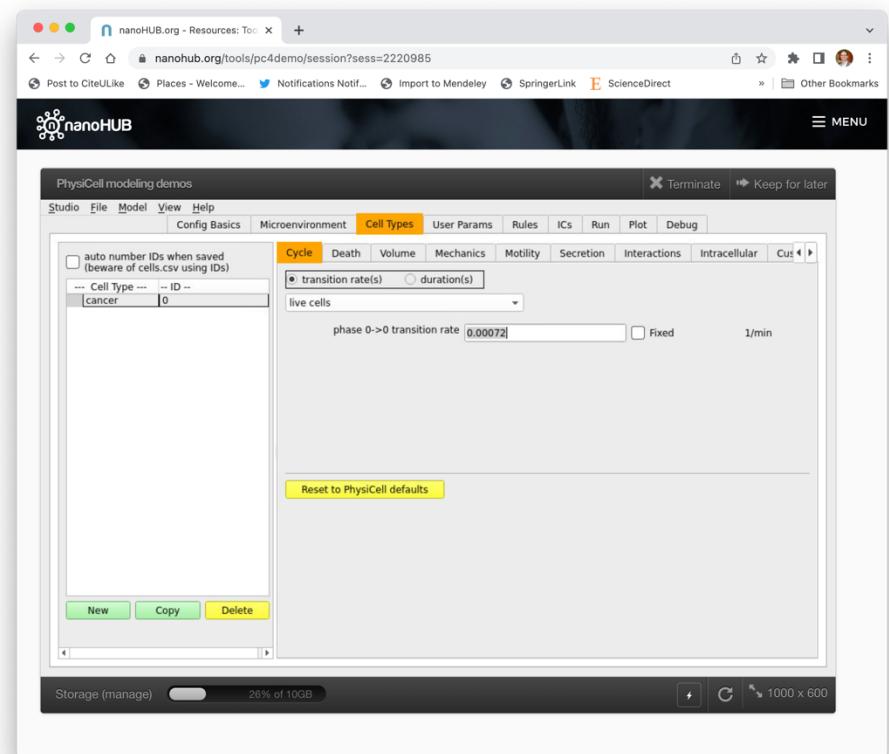
Iterative modeling example

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

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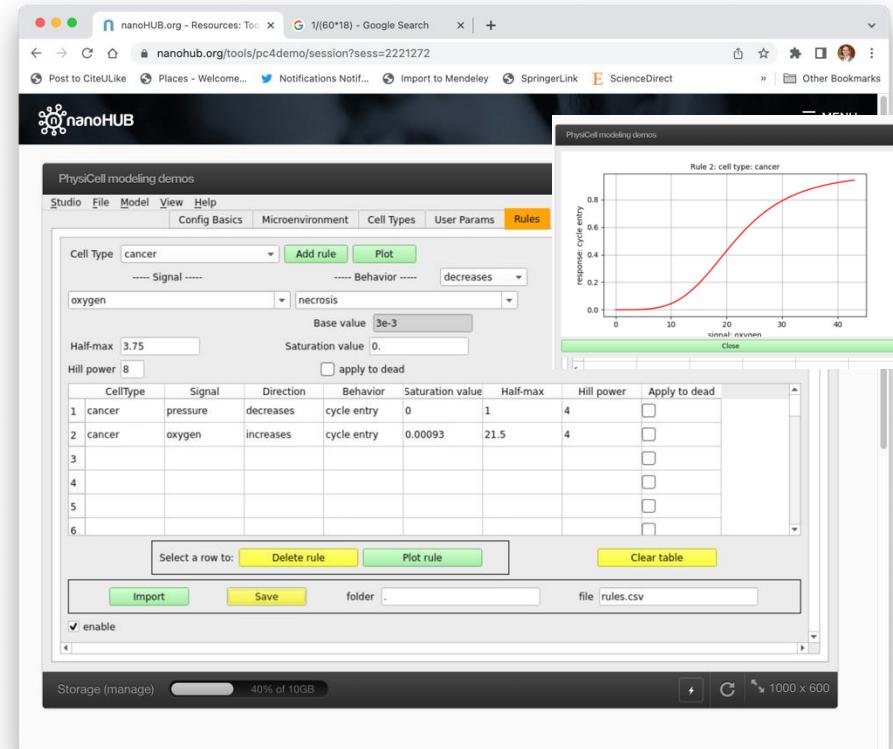
Oxygen-based cycling setup: 1

- 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



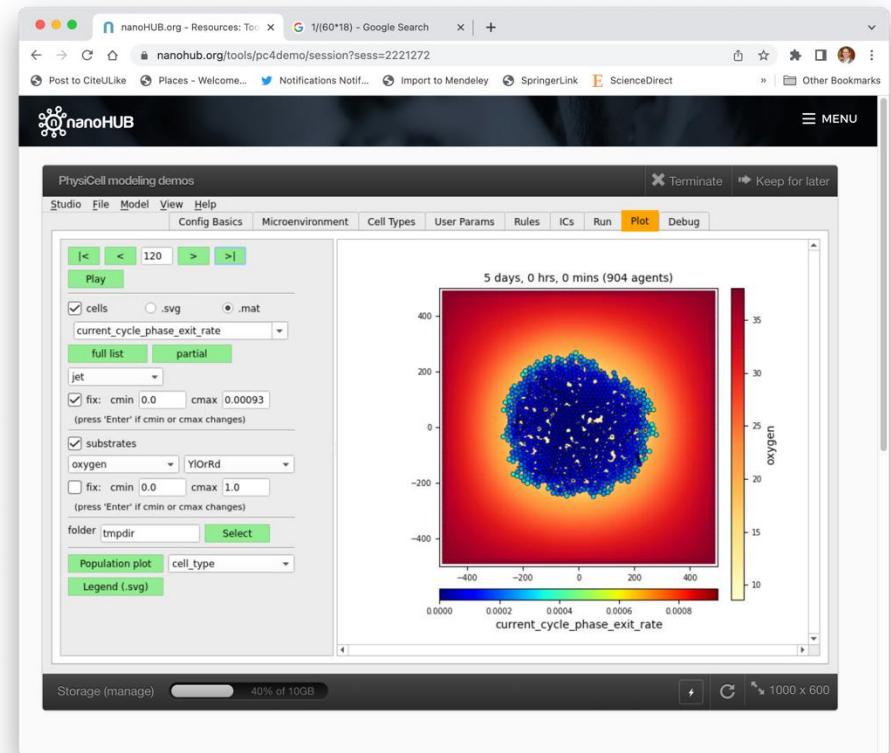
Oxygen-based cycling setup: 2

- 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**



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

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

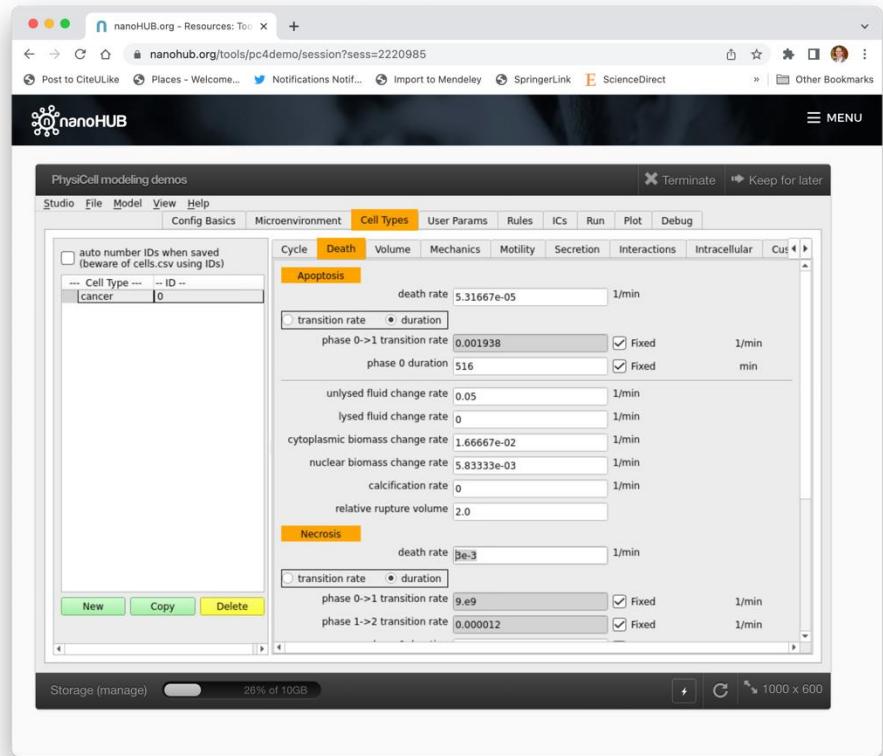
1. Growing tumor with oxygen consumption
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Some rephrasing first

- 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

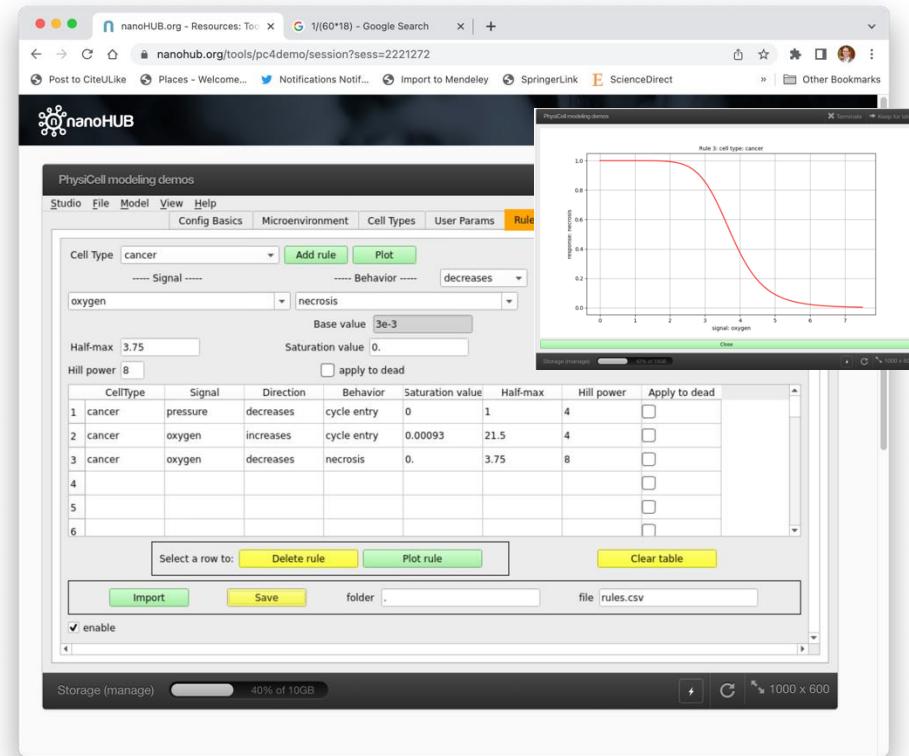
Hypoxia-driven necrosis: 1

- 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

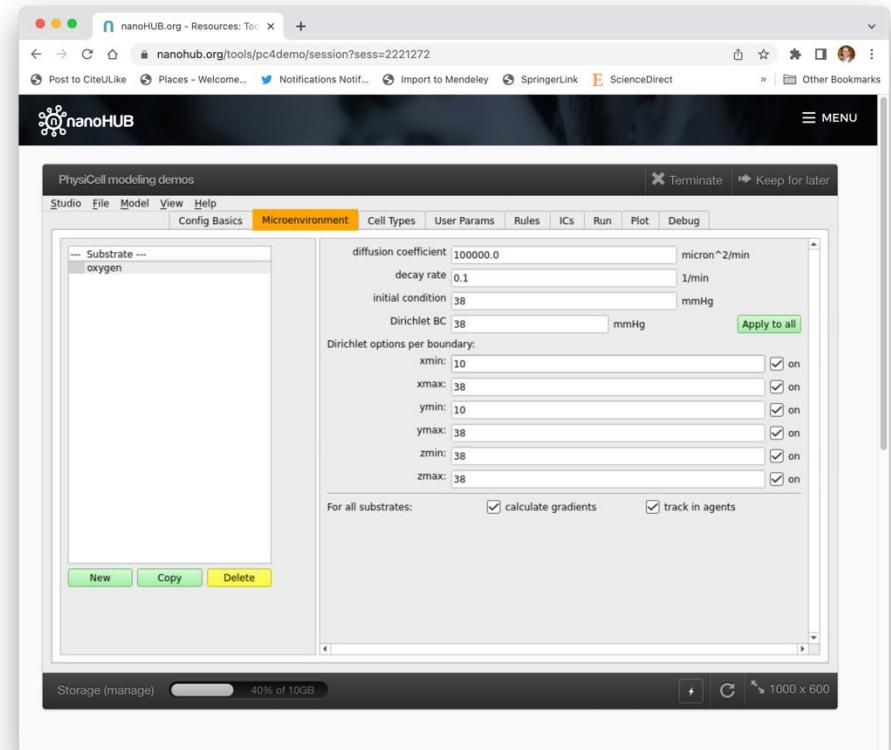
- Go to the **rules** tab
 - Select **cancer** cell
 - Choose **oxygen** as the signal
 - Choose **necrosis** as the behavior
 - Choose **decreases** as the response
 - Choose **0.0** as the saturation value of the behavior
 - Choose **3.75 mmHg** as the half-max
 - Choose **8** as the Hill power
 -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



- 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 boundary value to 10 on the lower bounds.

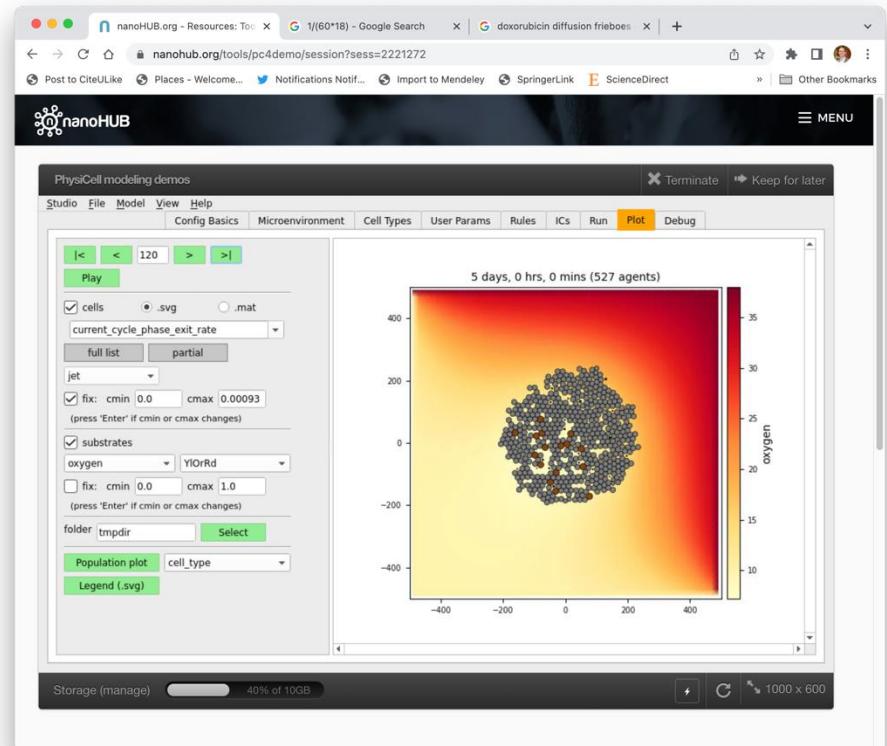


Run and Visualize

- 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



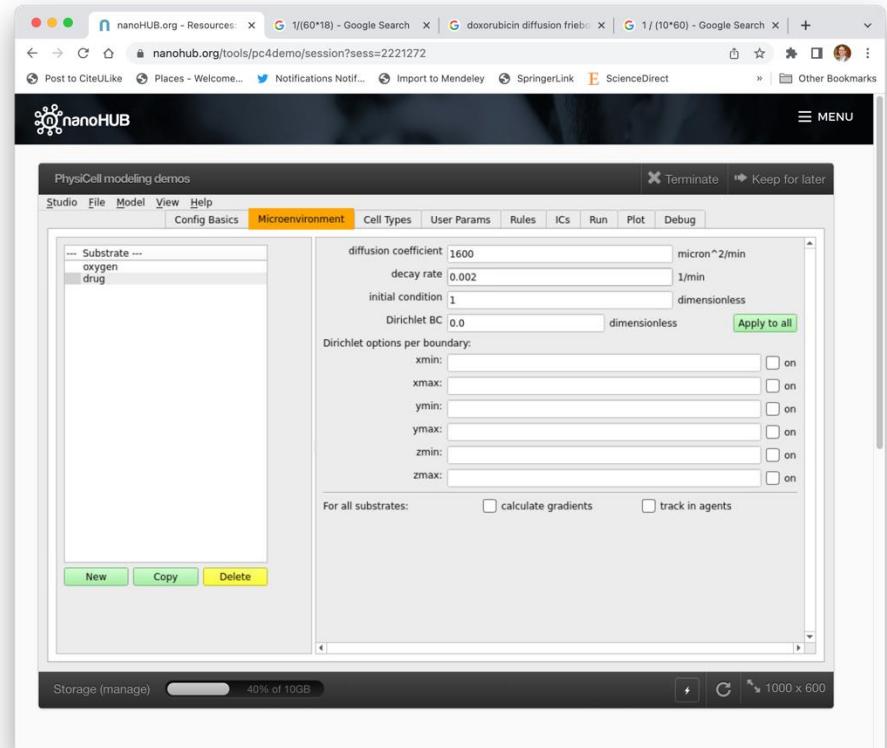
Cytotoxic drug

Iterative modeling example

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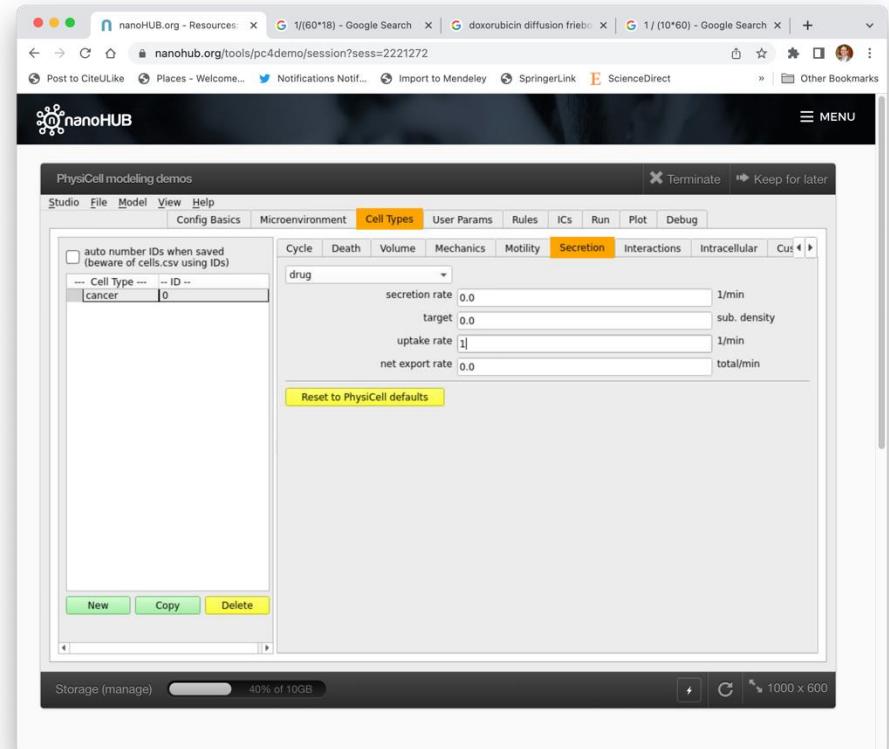
Cytotoxic drug: 1

- 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

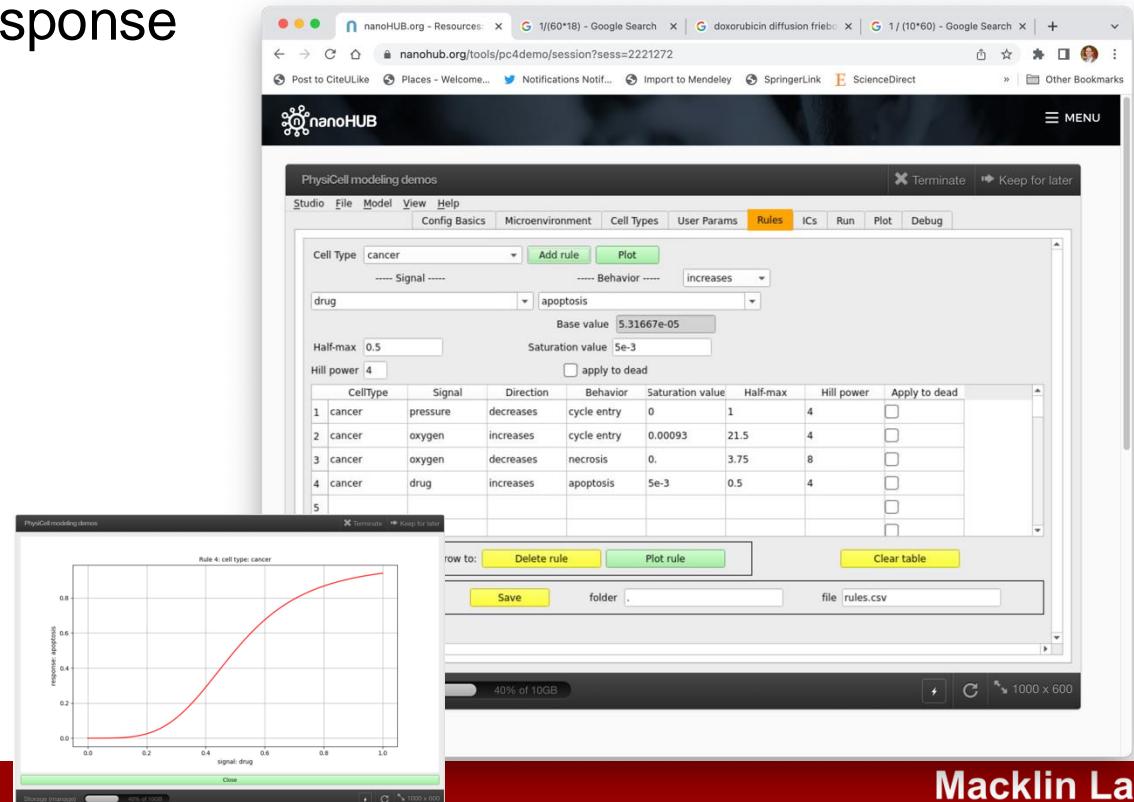


Cytotoxic drug: 3

- Now, we add a cytotoxic response

- Go to rules
- Add a new rule

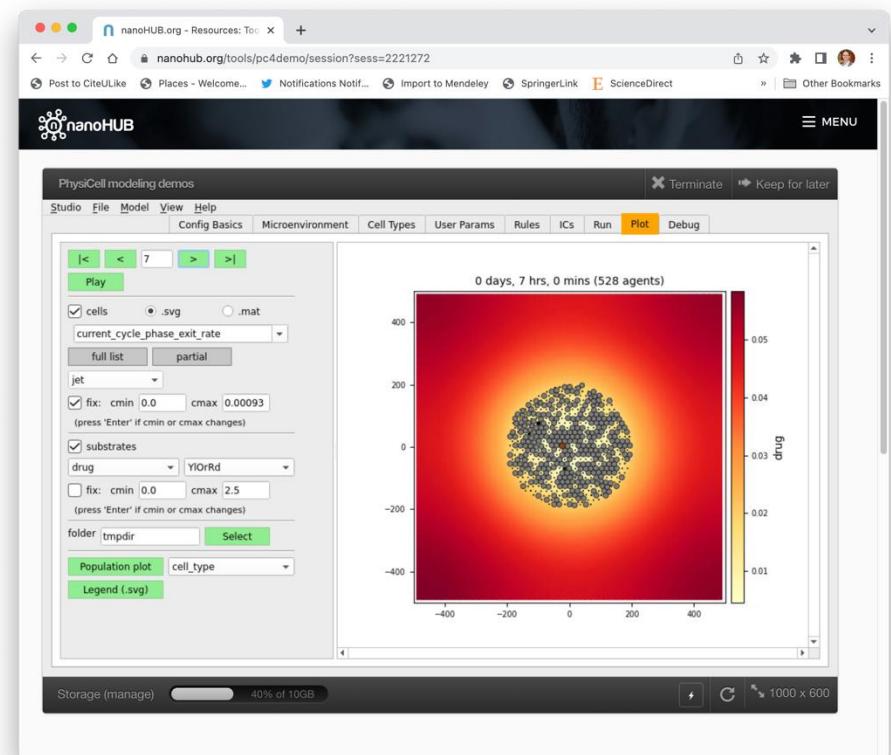
- cell type: cancer
- signal: drug
- response: increases
- behavior: apoptosis
- half-max: 0.5
- Hill power: 4
- saturation value: 5e-3
 - » 100x increase over base death



- 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



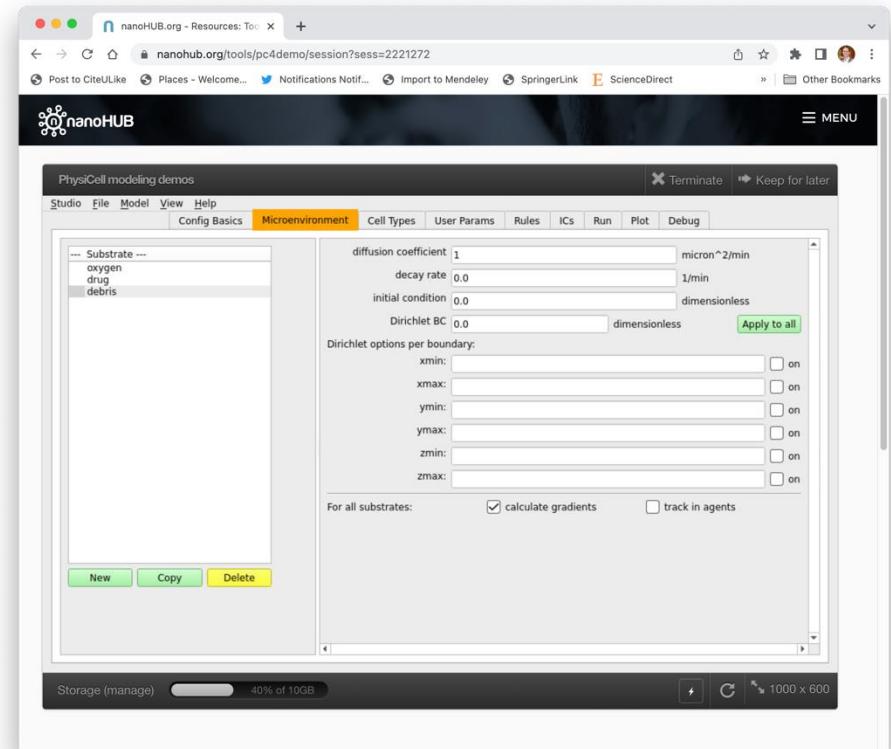
Release of dead cell debris

Iterative modeling example

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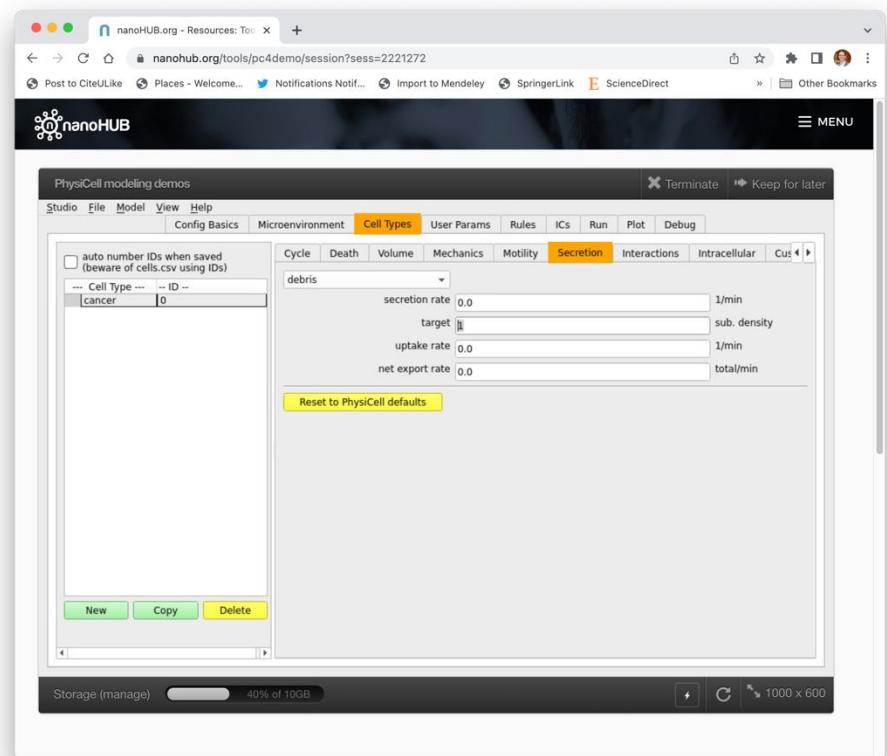
Debris release: 1

- 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**

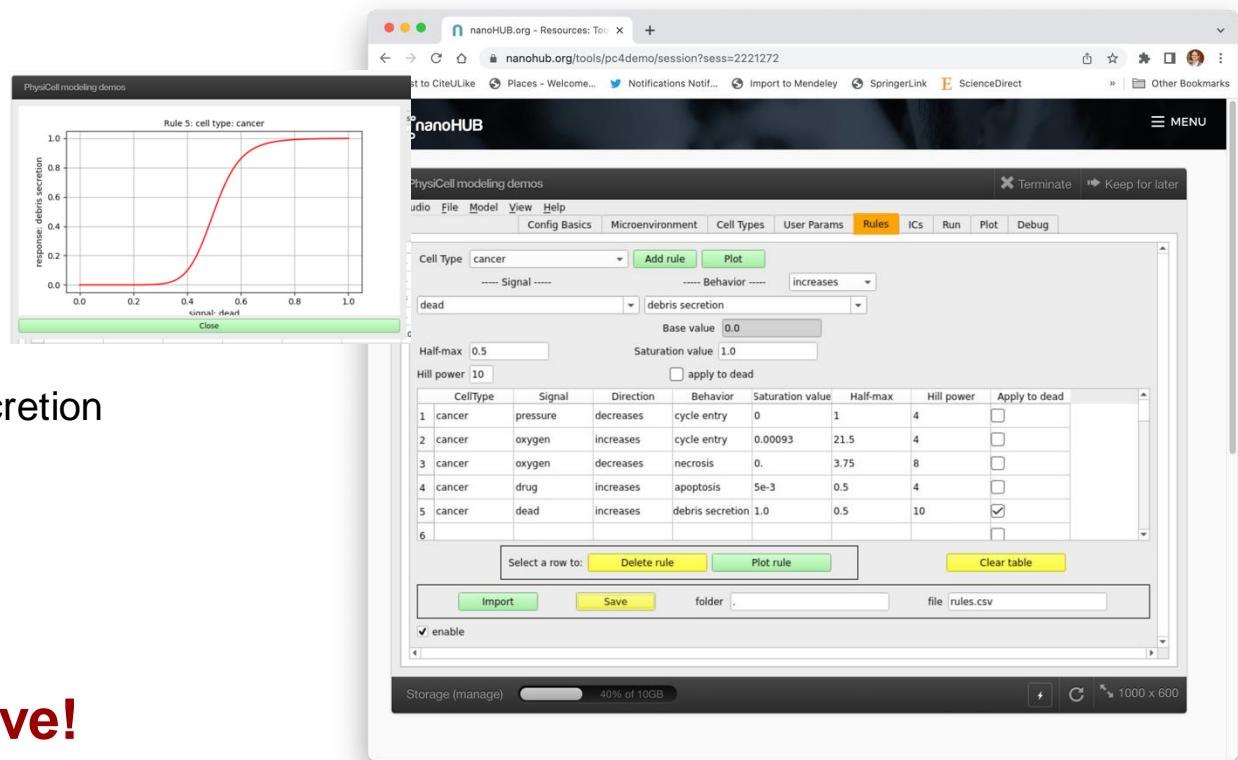


Debris release: 3

- 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



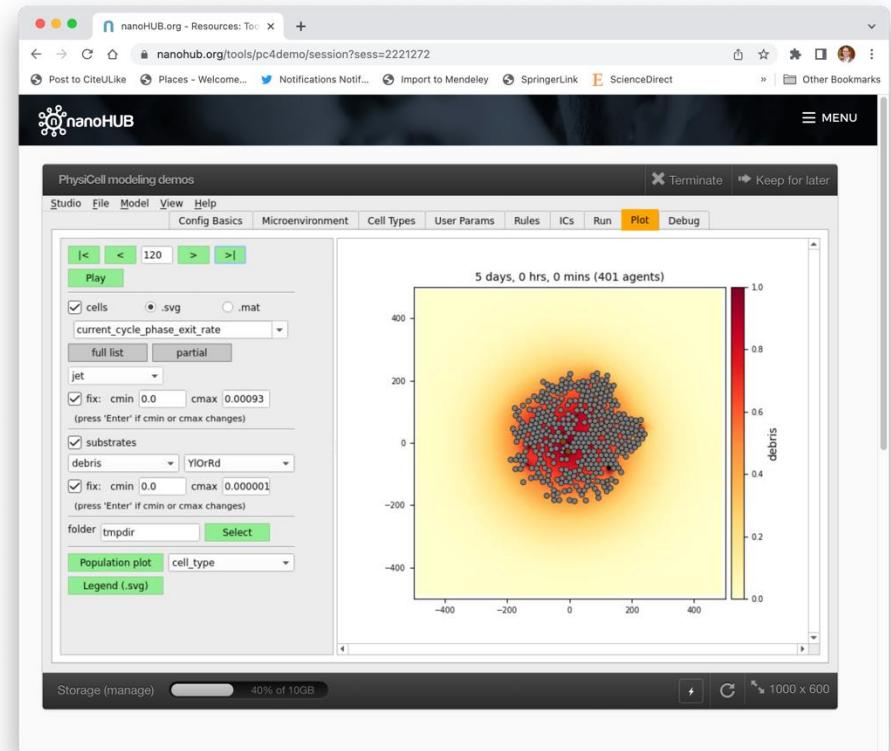
- Make sure to click save!

Run and Visualize

- Let's color cells by standard again:

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

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



Macrophages

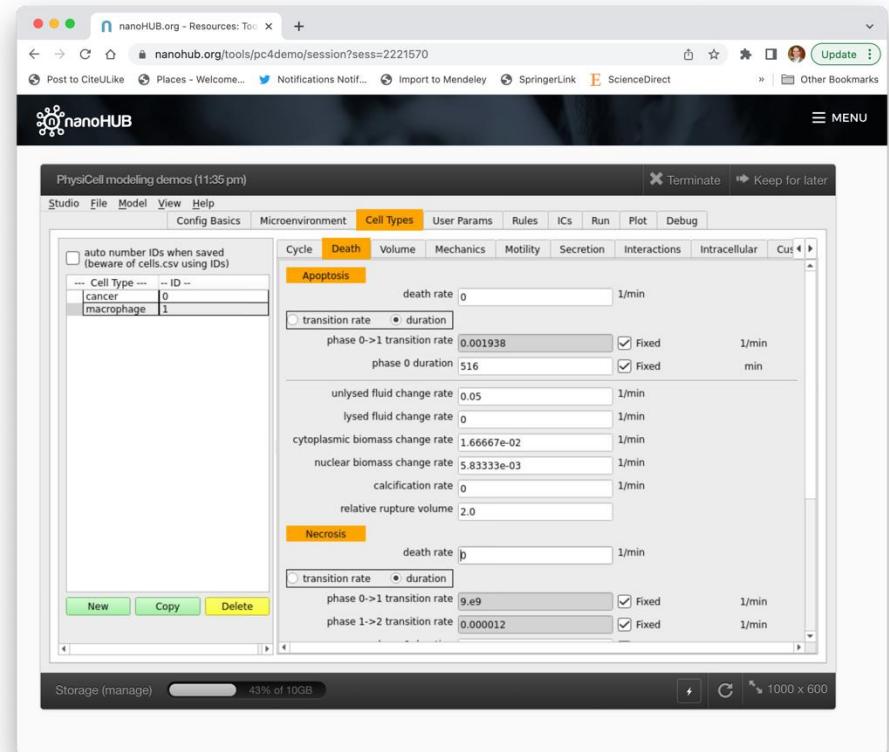
Iterative modeling example

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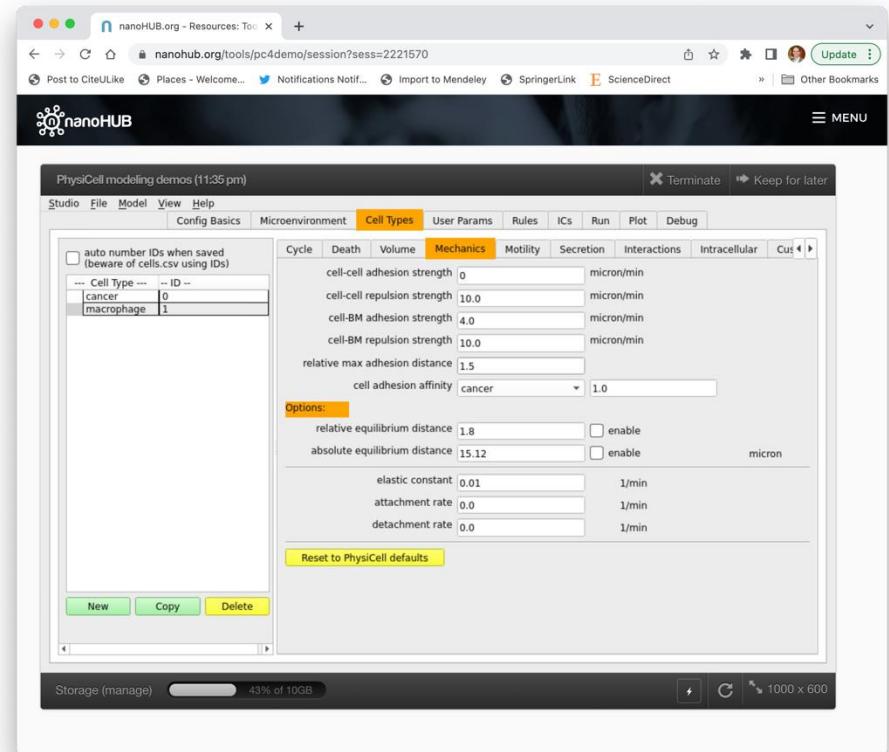
Macrophages: 1

- 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



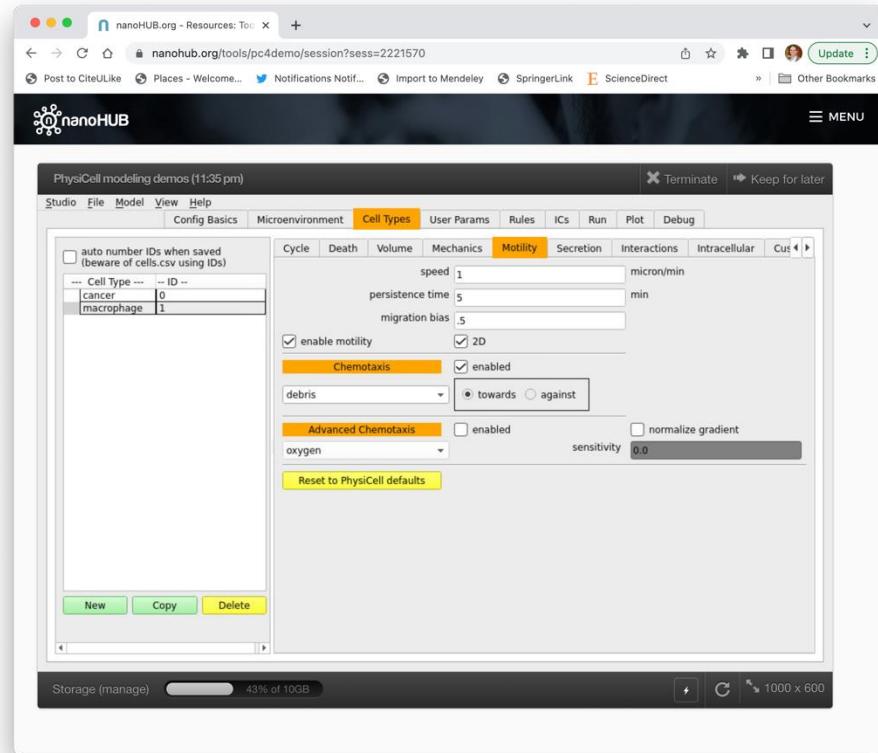
Macrophages: 2

- 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



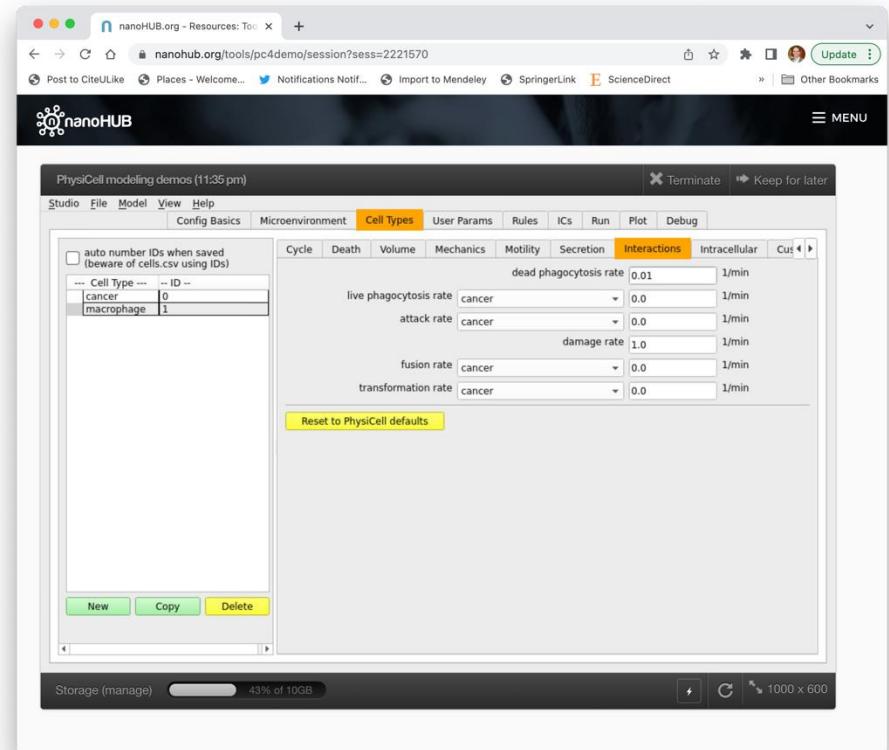
Macrophages: 3

- 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**



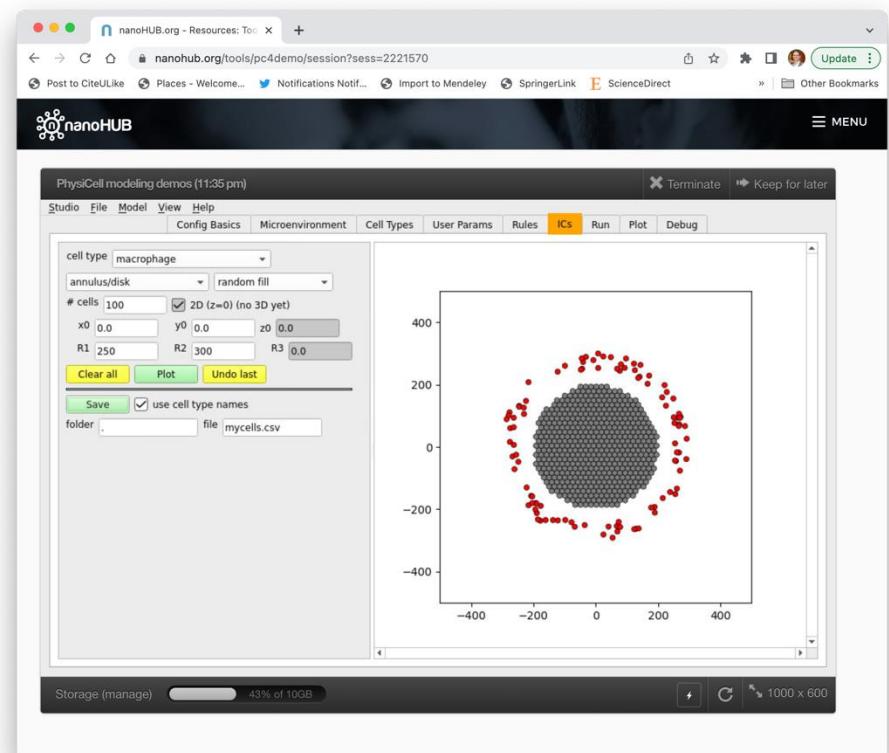
Macrophages: 4

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



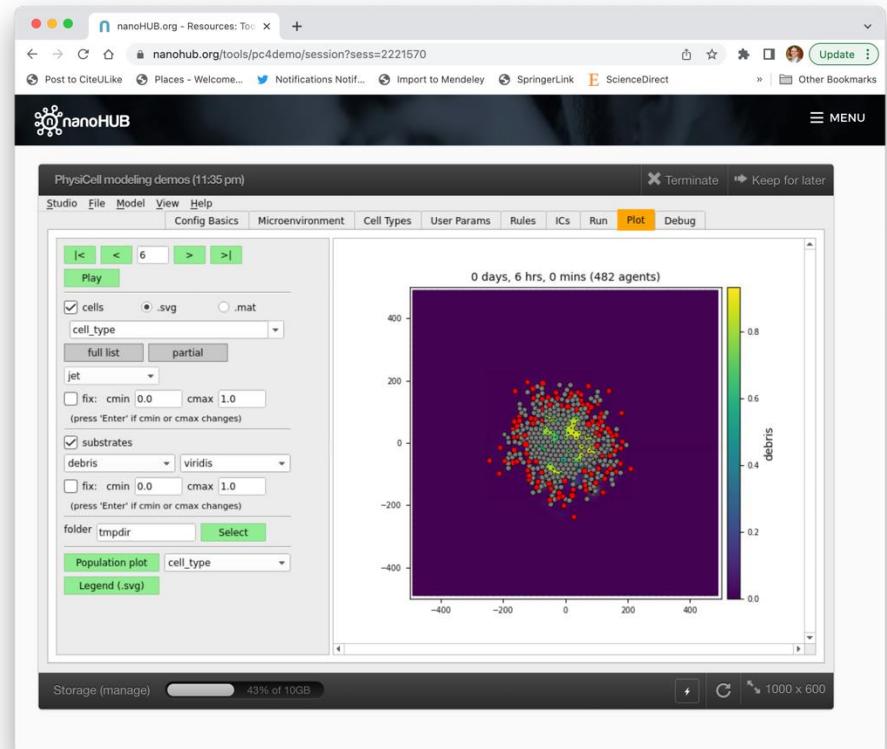
Macrophages: 5

- 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!



Inflammation

Iterative modeling example

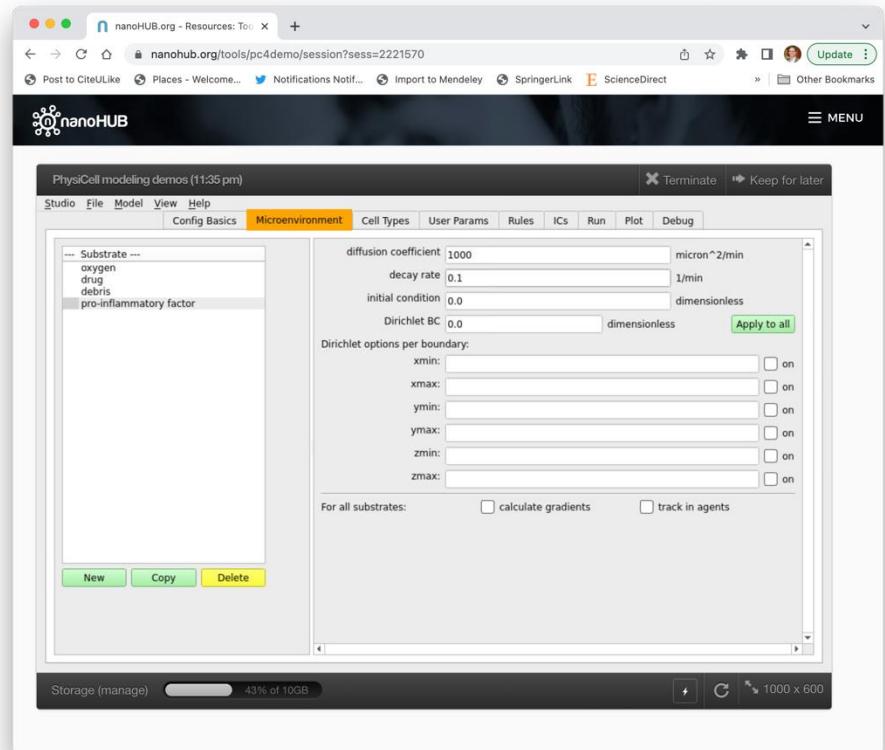
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Strategy

- 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

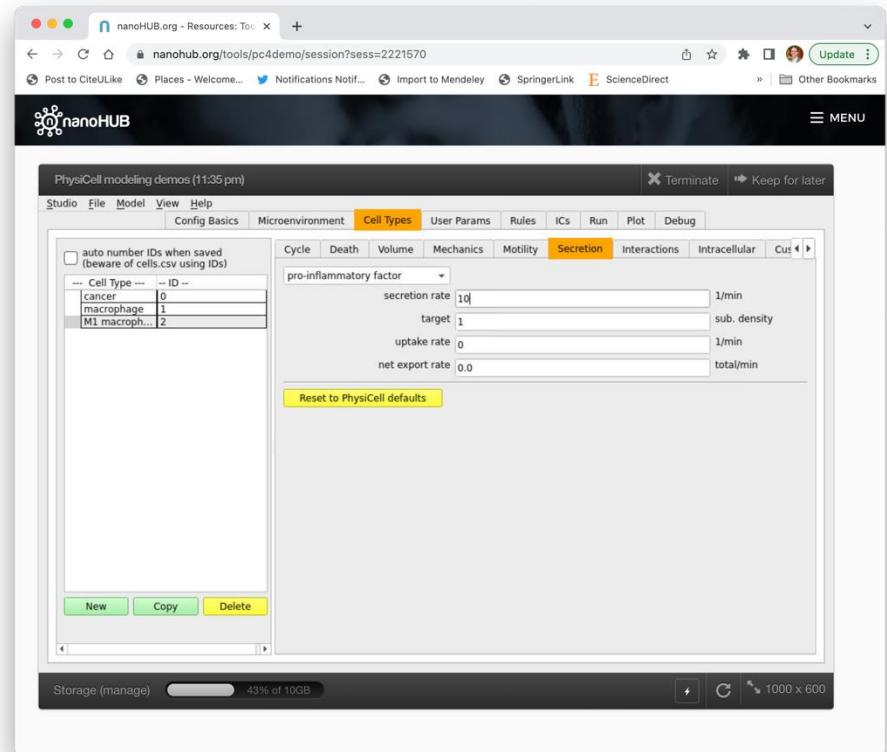
M1 Macrophages: 1

- 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



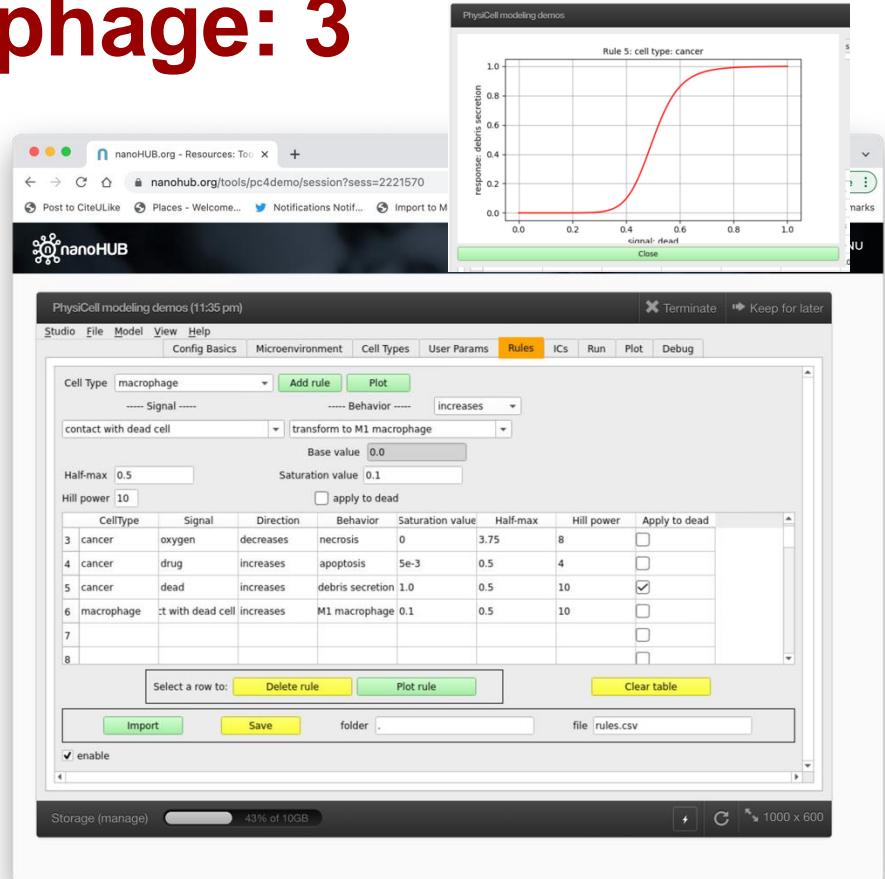
M1 Macrophage: 3

- 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!

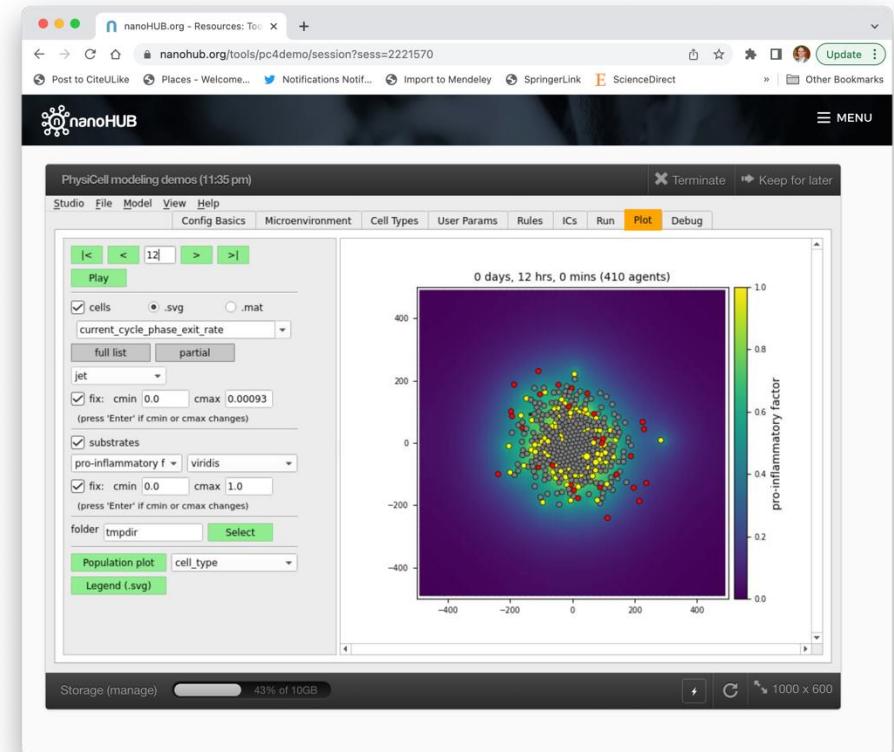


Run and Visualize

- 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

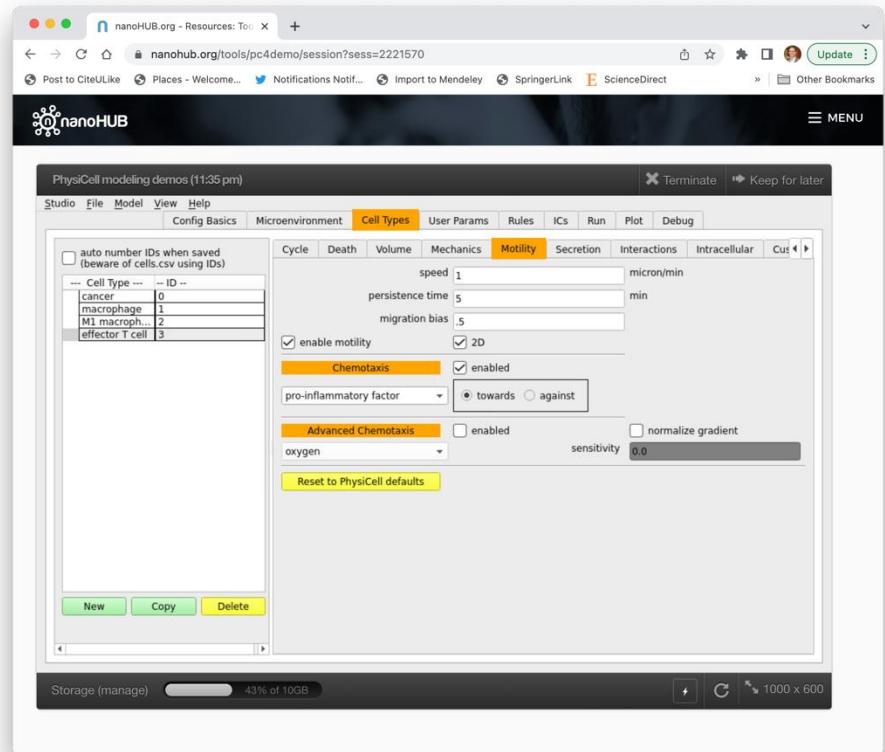
- We'll iteratively build a simple tumor model, bit-by-bit:
 1. Growing tumor with oxygen consumption
 2. Add a mechanofeedback on cycling
 3. Add oxygen-driven cycling
 4. Add hypoxia-driven necrosis
 5. Add a cytotoxic drug
 6. Add release of dead cell debris
 7. Add macrophages
 8. Add pro-inflammatory 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

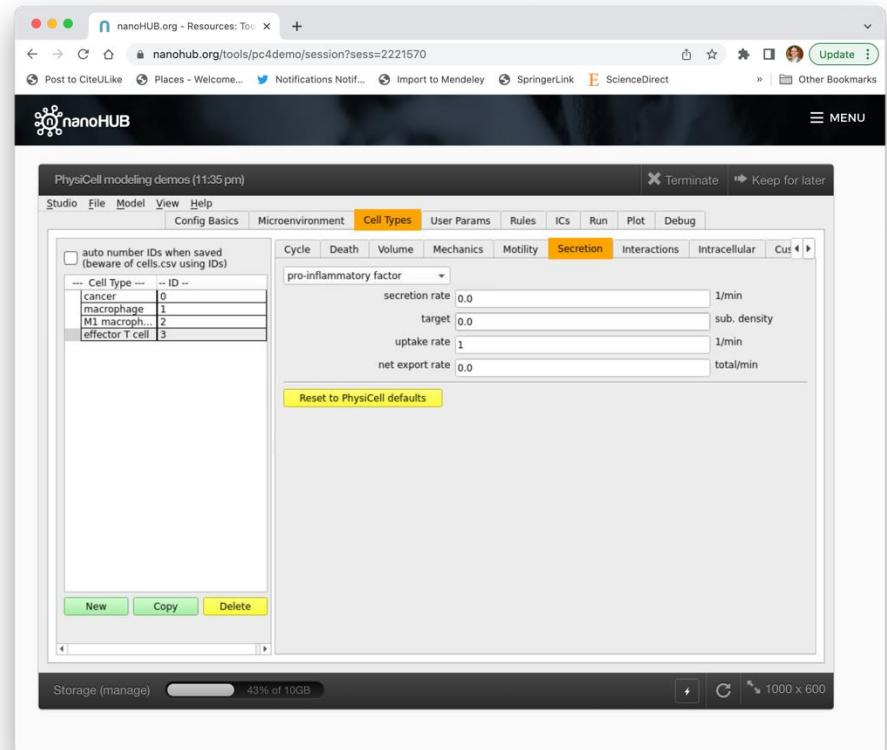
Effector T cells: 1

- 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**



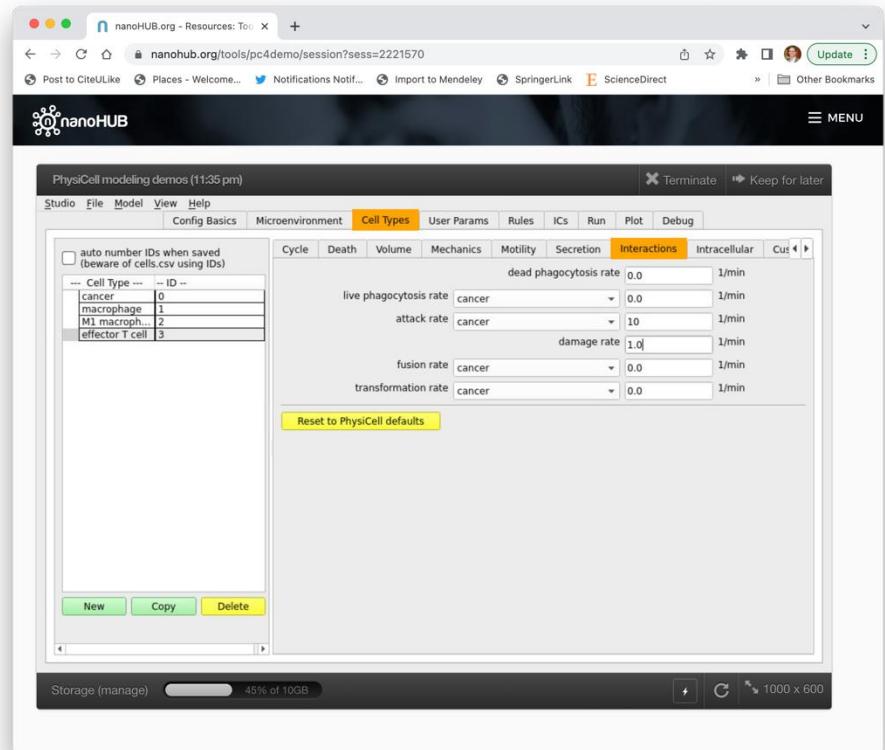
Effector T cells: 2

- 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 **phagocytosis rates** to 0
 - Set **attack rate** for **cancer** to 10
 - Leave **attack damage rate** at 1



Effector T cells: 4

- Now, we add a rule

- Go to rules
- Add a new rule

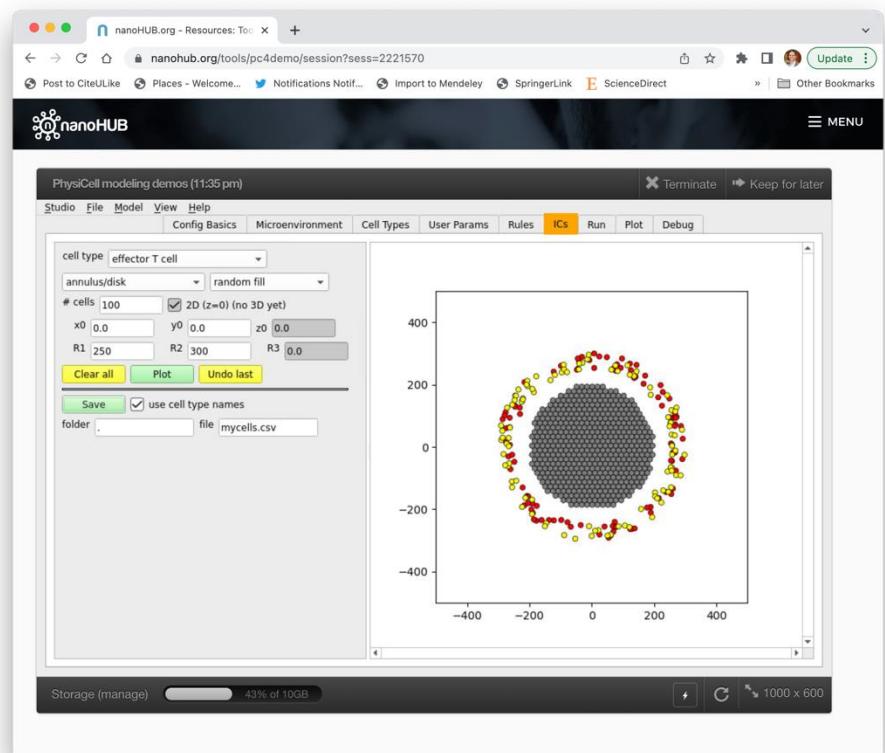
- cell type: cancer
- signal: damage
- response: increases
- behavior: apoptosis
- half-max: 5
- Hill power: 4
- saturation value: 0.01
- Applied to dead: **false**

- Make sure to click save!

CellType	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, **random 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

