

PhysiCell Essentials for SMB 2025:

Hands-on Modeling (Part 2)

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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: Getting Started, and Initial Cancer Model (this session)

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



Session Goals

- First hands-on model (live modeling, continued)
 - Cytotoxic chemotherapy (drug and cell death response)
 - Cell debris (released by dead cells)
 - Macrophages
 - Inflammation (M1-like macrophages, secreted inflammatory factors)
 - Cytotoxic T cells
 - Model exploration and what-ifs (based on time and interests)



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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Adding chemotherapy



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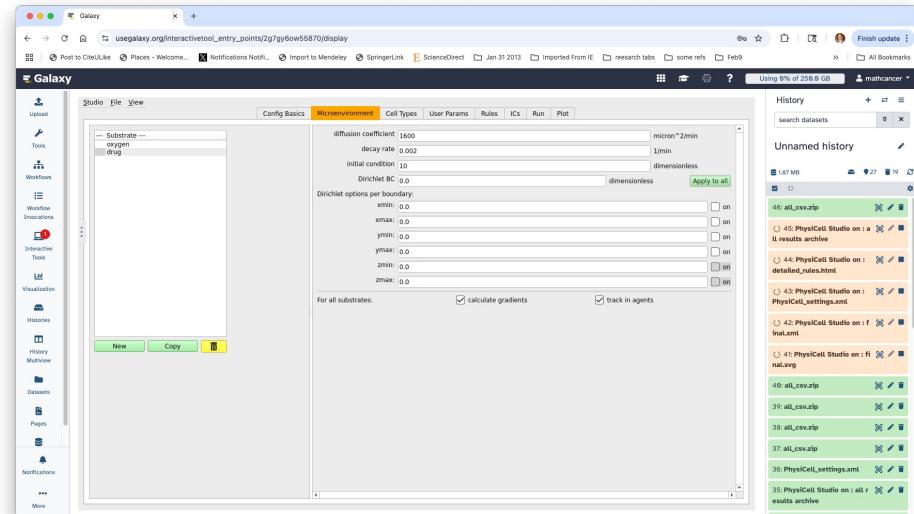
Iterative modeling example

- In the last session, we iteratively built 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 this session, we extend this model to include therapy and immune interactions:
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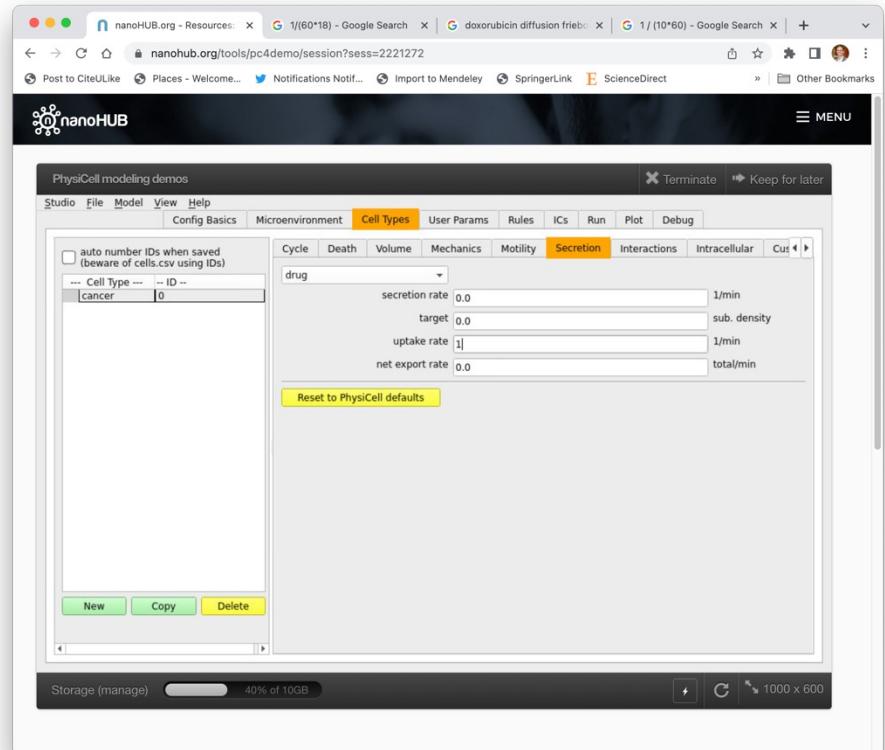
Cytotoxic drug: 1

- 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
 - Make sure the Dirichlet conditions have a (zero) value, but not enabled.



Cytotoxic drug: 2

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



Cytotoxic drug: 3

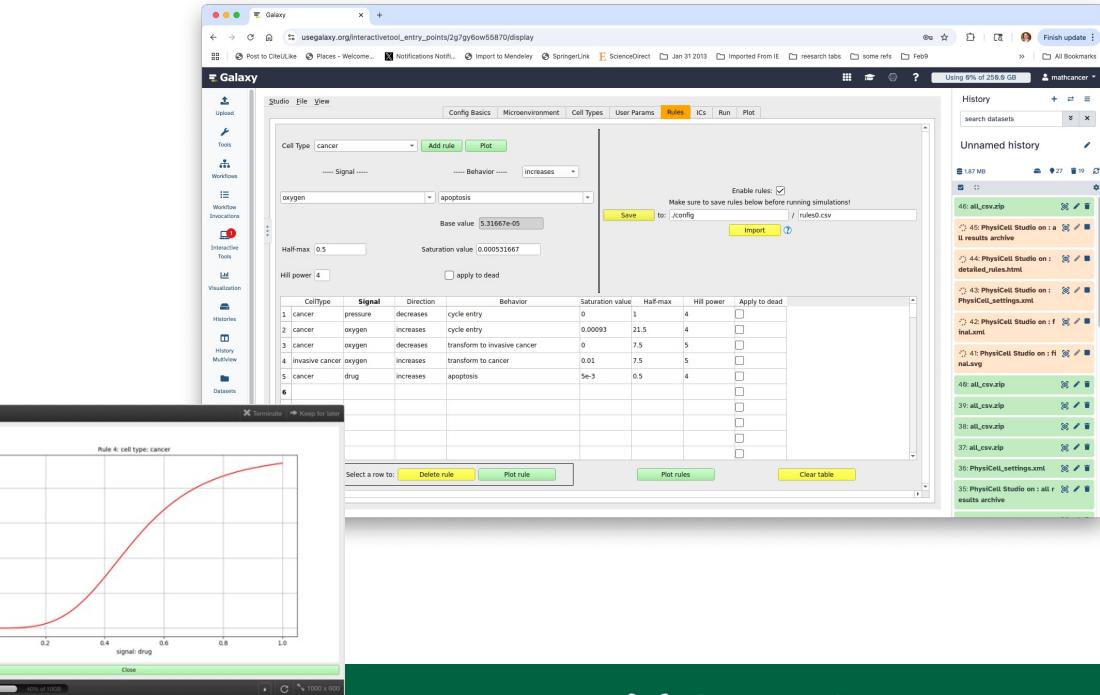
- Now, we add a cytotoxic response

- 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
- Click on **add rule**

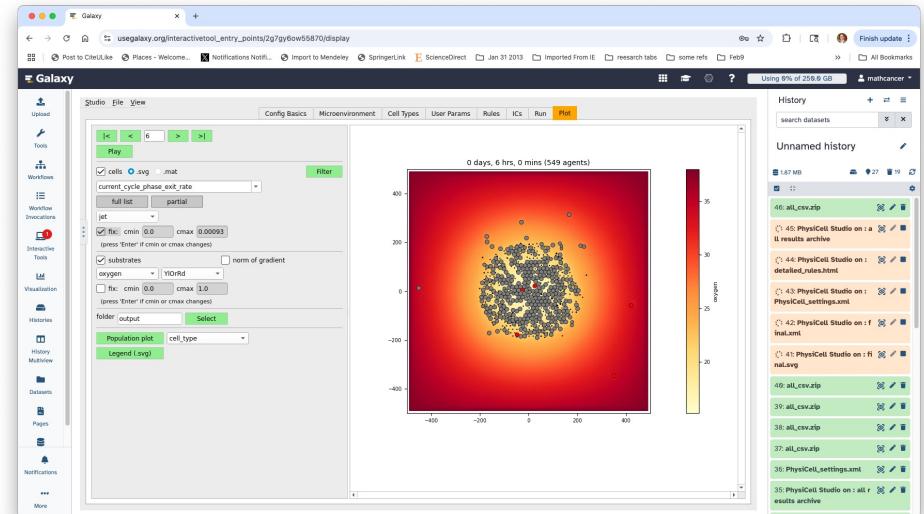
- No effect on invasive cells

- 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
- **Observe:**
 - Lots of death at first
 - Steep drug gradient
 - Drug quickly removed due to fast drug uptake
 - Tumor recovers
- Better modeling in future:
 - Time-varying boundary conditions



Release of dead cell debris



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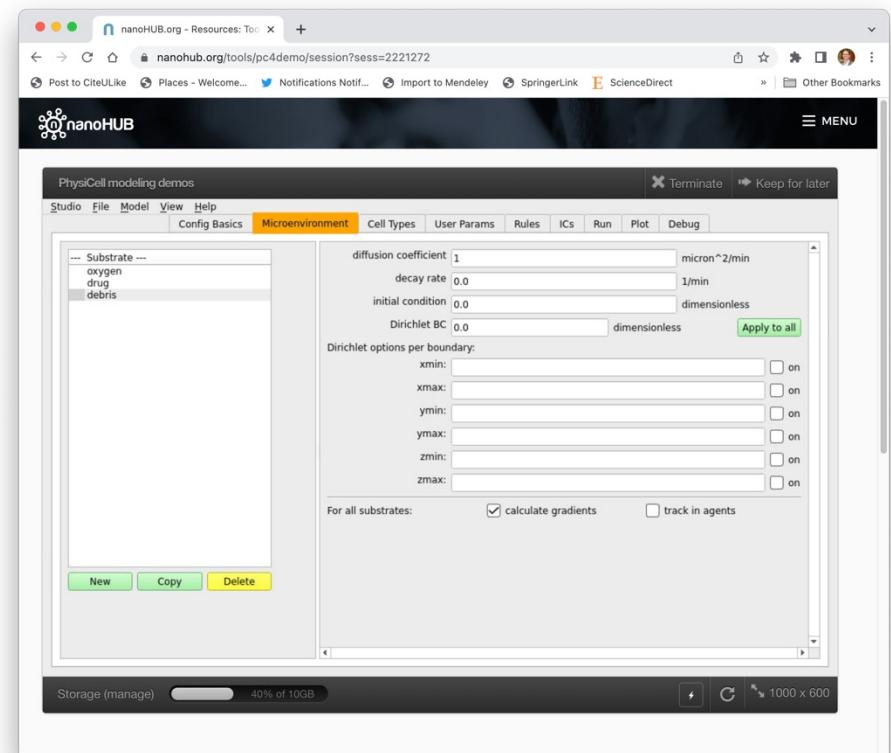
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Debris release: 1

- 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**
- Make sure all fields are populated



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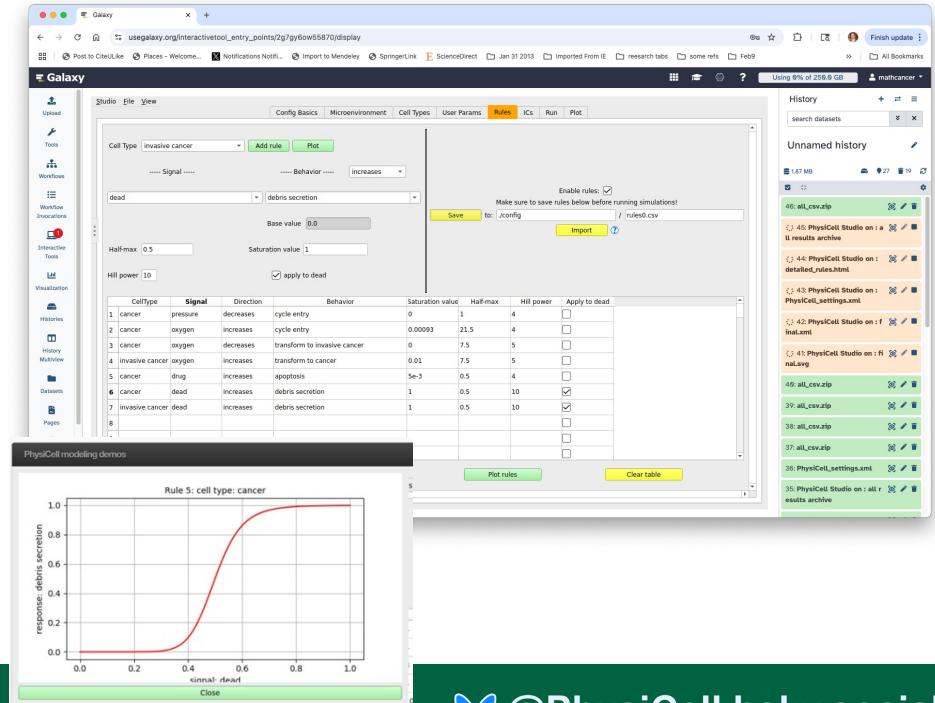
Debris release: 2

- 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

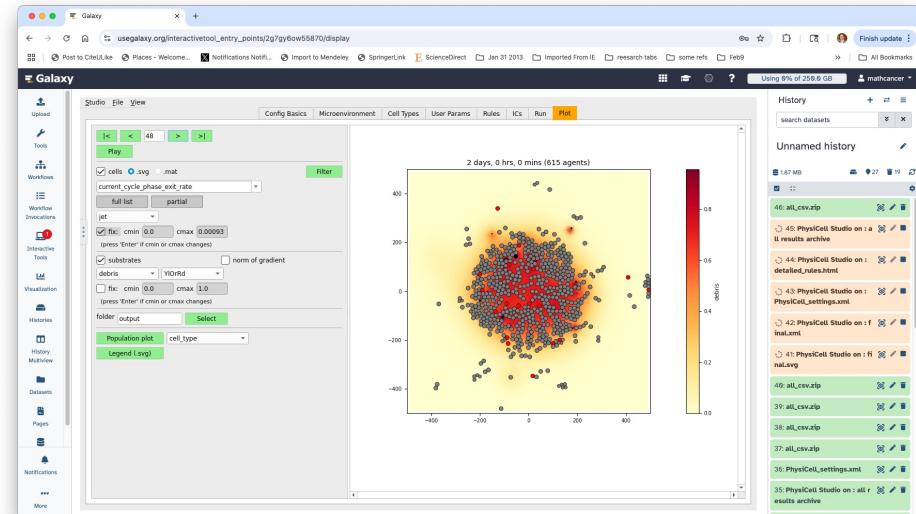
- Click on **save**

- Repeat this for invasive cancer
- 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



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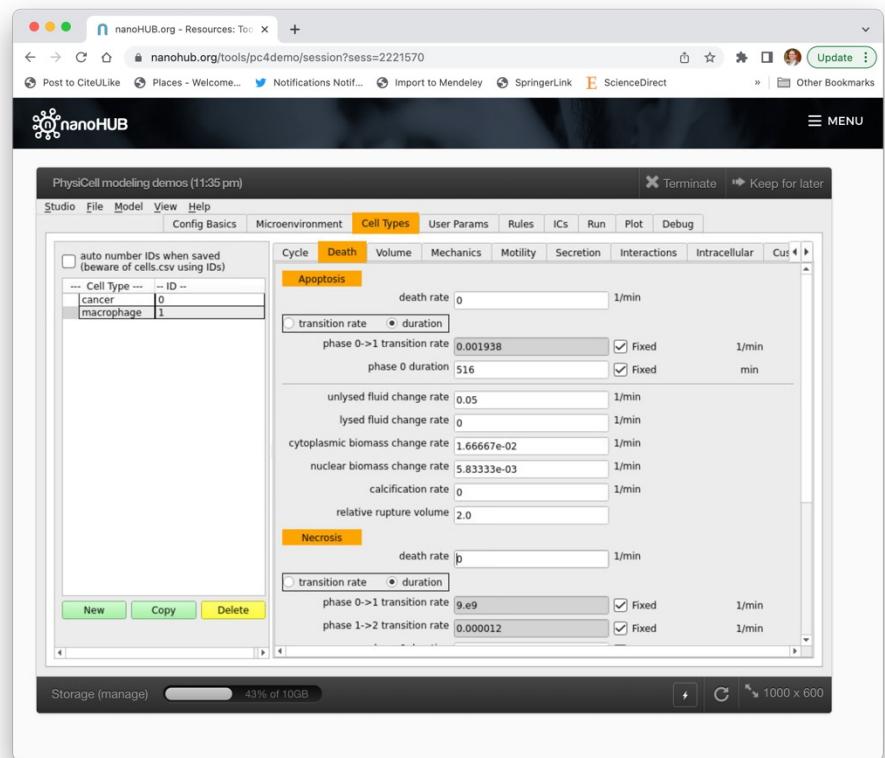
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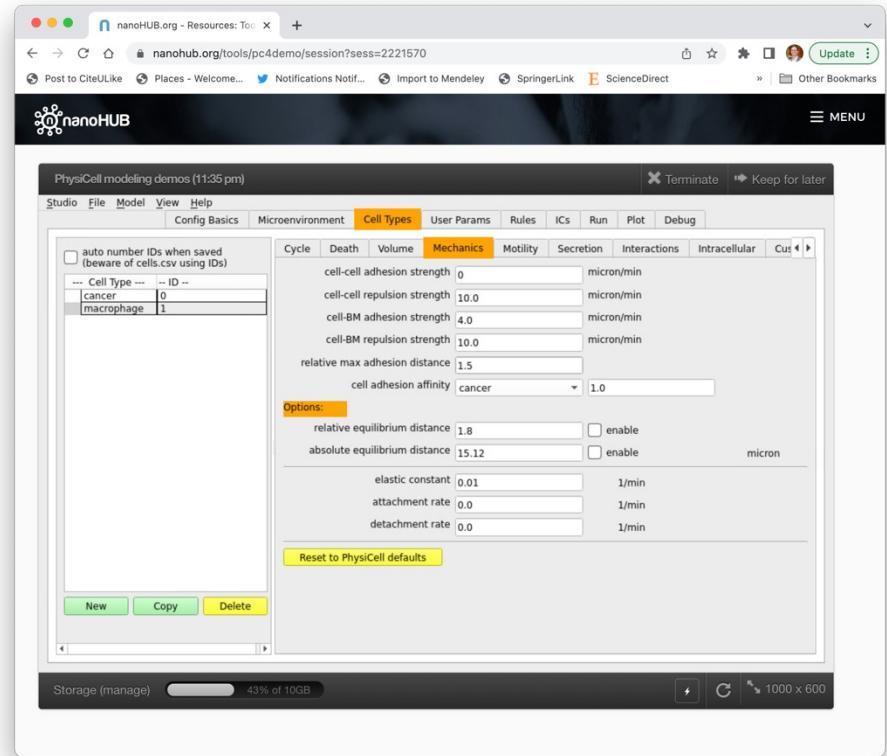
Macrophages: 1

- 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



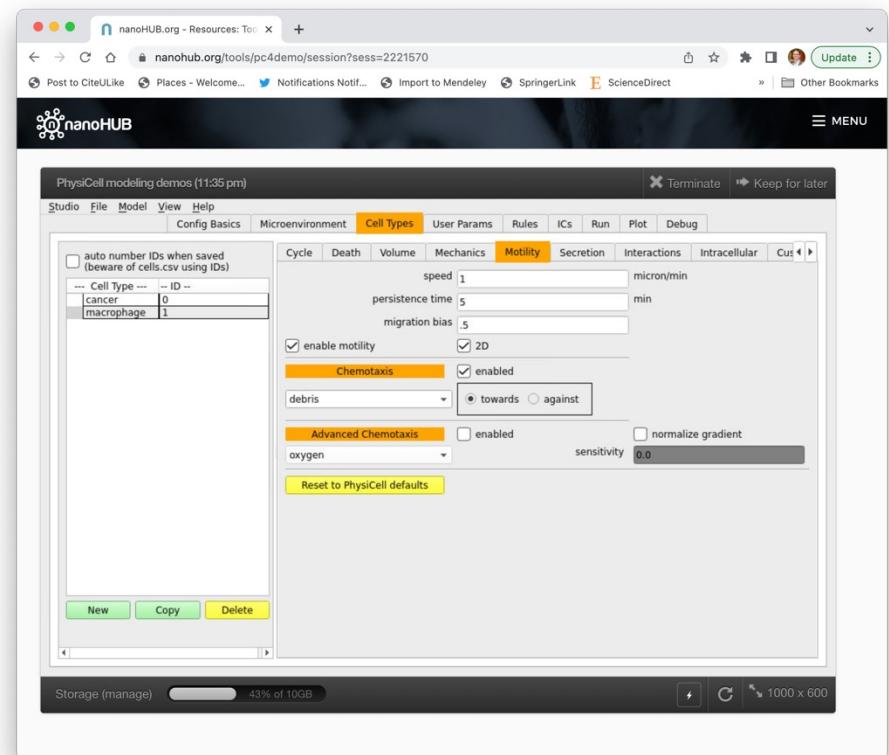
Macrophages: 2

- 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



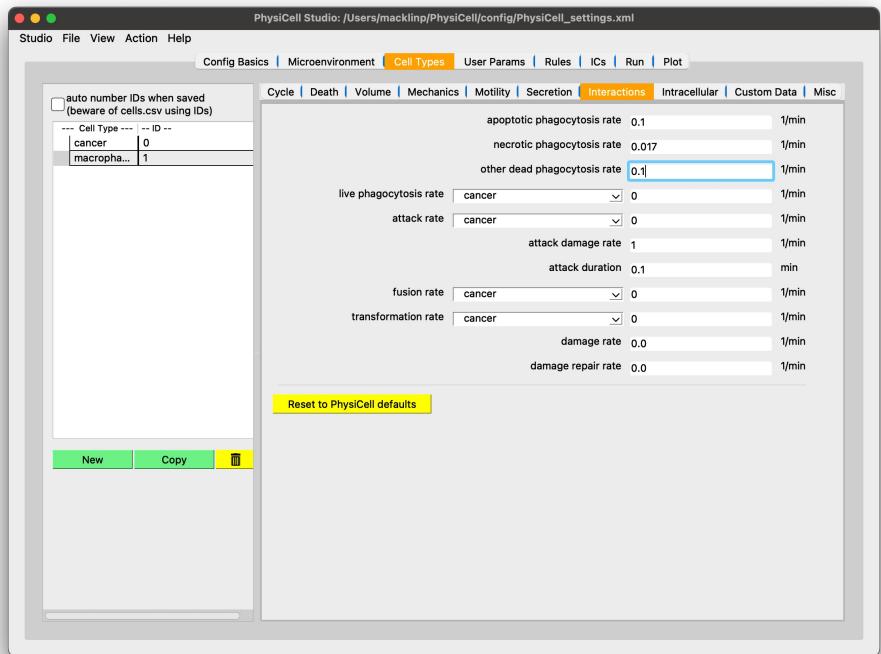
Macrophages: 3

- 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**



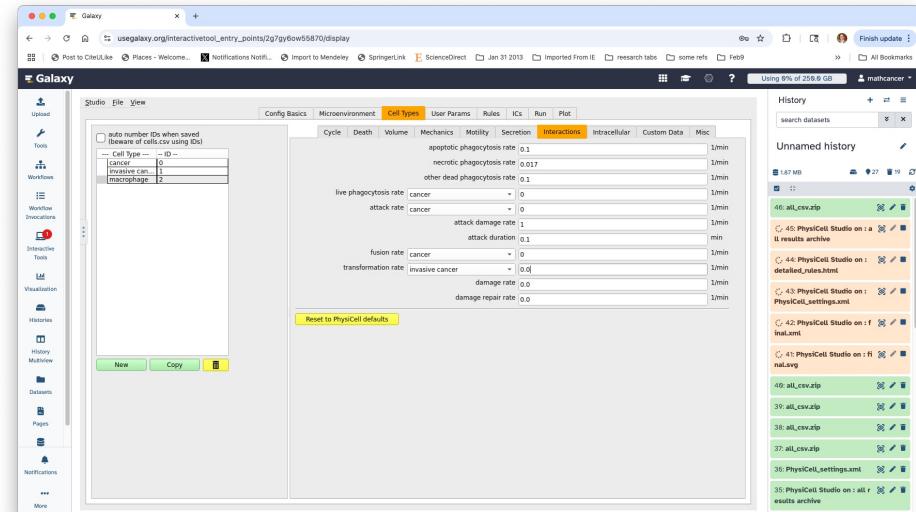
Macrophages: 4

- We want macrophages to phagocytose dead cells
 - Go to interactions
 - Set **apoptotic phagocytosis rate** to 0.1
 - Set **necrotic phagocytosis rate** to 0.017
 - Set **other dead phagocytosis rate** to 0.1



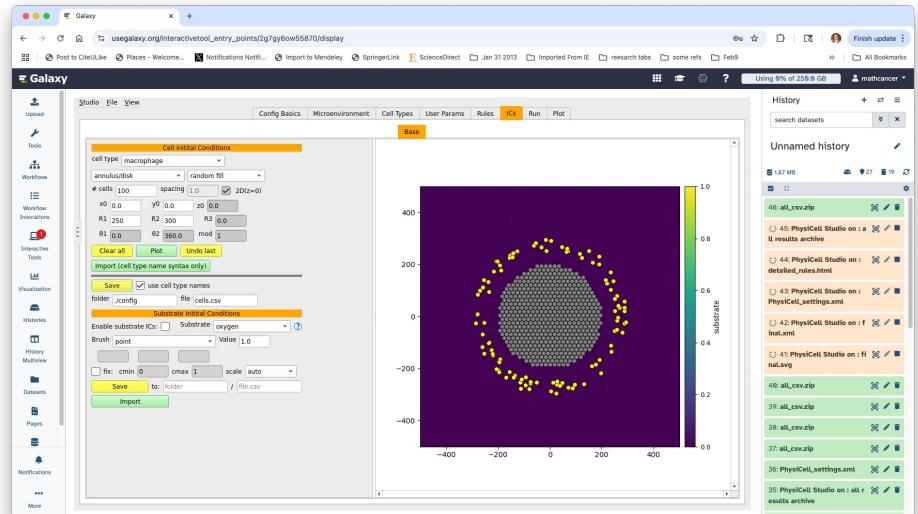
Macrophages: 5

- We don't want macrophages to turn into invasive cancer cells (due to copying the **cancer** cell type)
 - Go to interactions
 - Set transformation rate to invasive cancer to 0.0



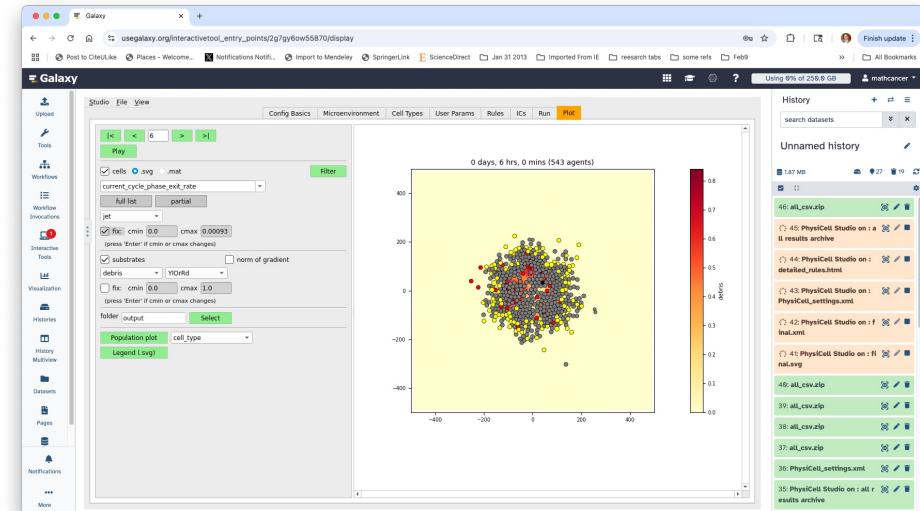
Macrophages: 6

- 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
- **Observe:**
 - Cell debris removed by macrophages!
 - Macrophages eat (engulf) dead cells
 - Macrophages gain volume of the cells they ate, and gradually "digest" it to return to original volume.



Inflammation



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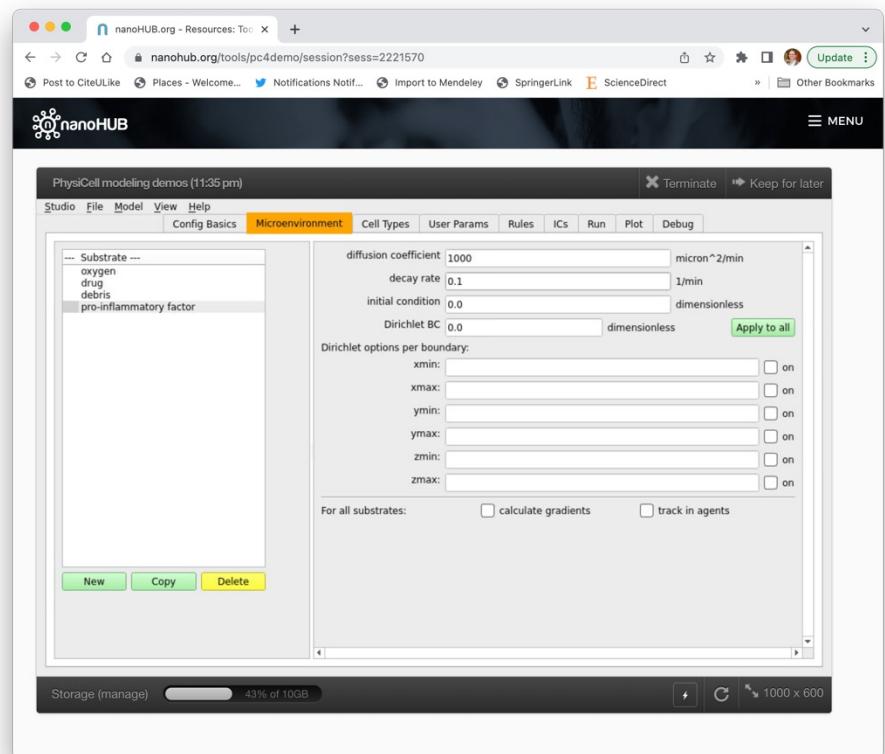
Strategy

- 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



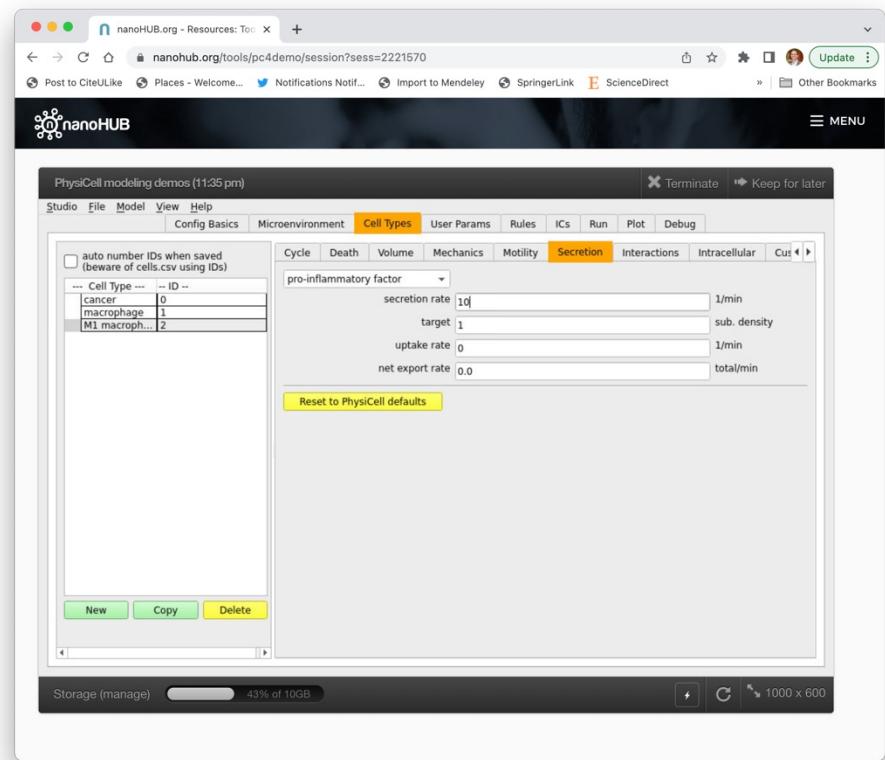
M1 Macrophages: 1

- 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
- Make sure all fields are populated (e.g., with 0.0)



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



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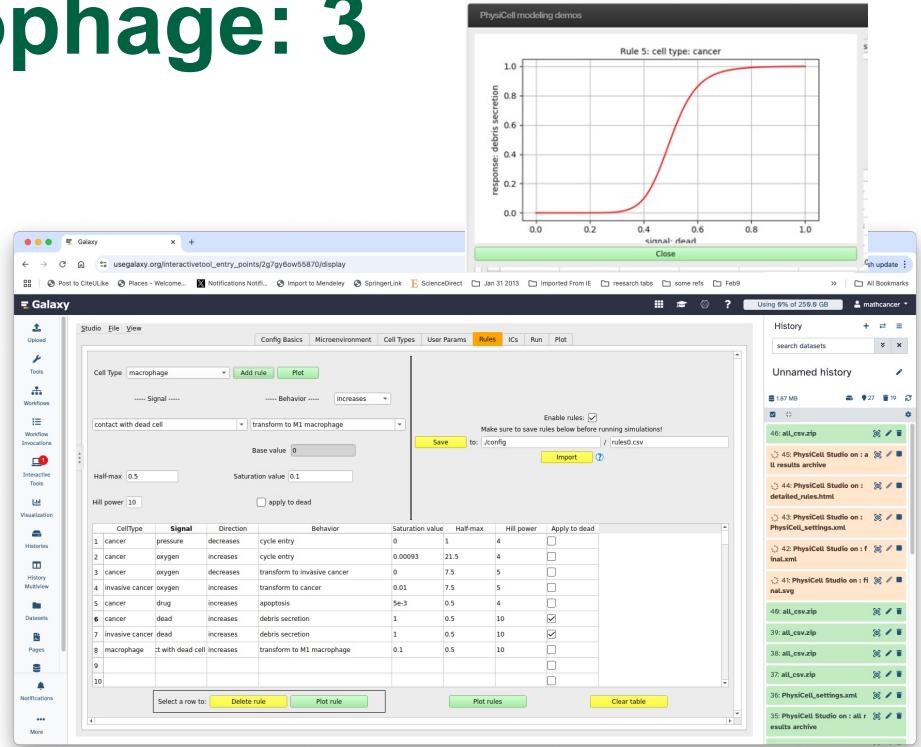
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M1 Macrophage: 3

- 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!

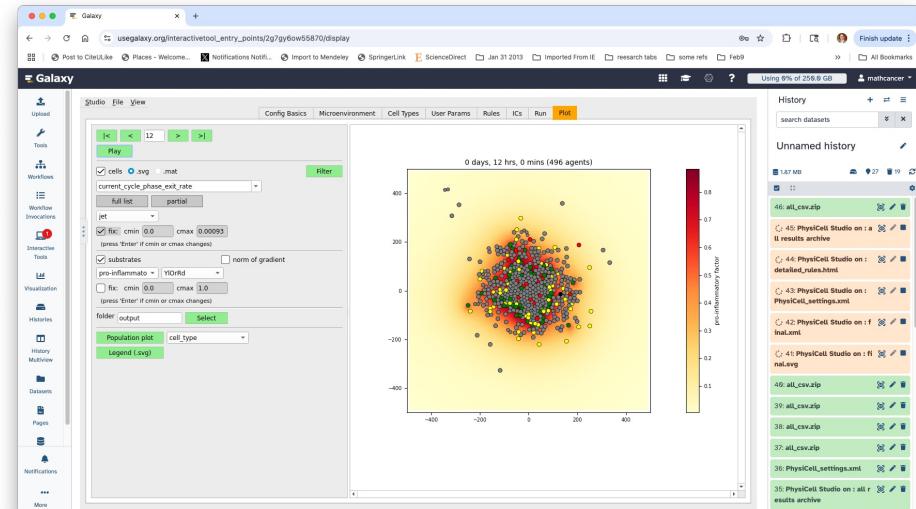


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Run and Visualize

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 - Necrotic cells are brown
- **Observe:**
 - Over time, more macrophages change type
 - Pro-inflammatory factor accumulates near the new macrophages



Effector T cells



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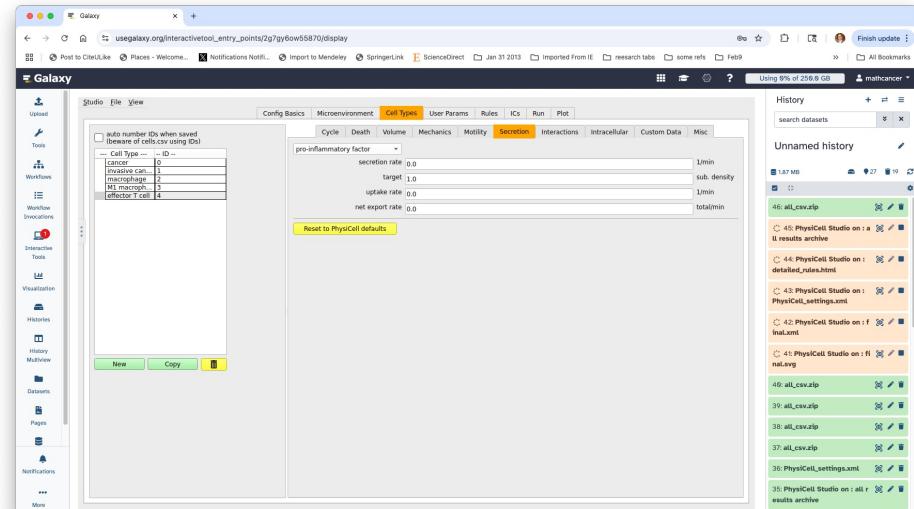
Strategy

- 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**

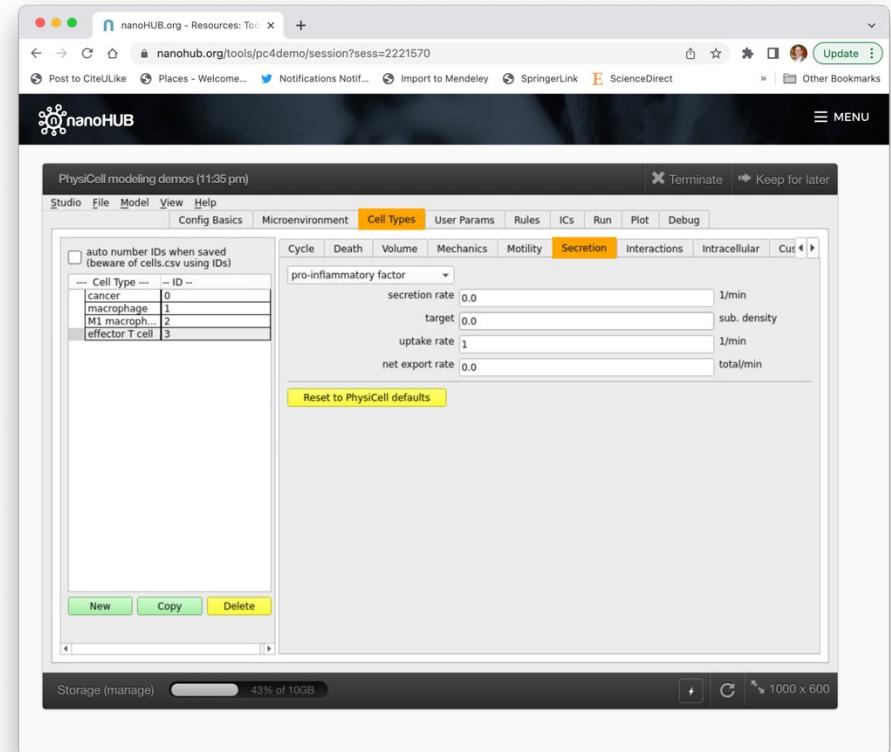


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Effector T cells: 2

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

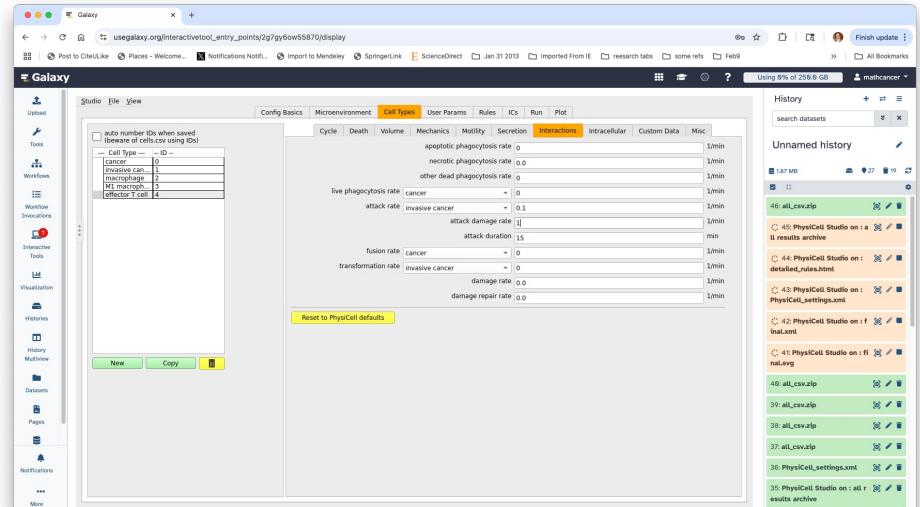


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Effector T cells: 3

- Change interactions
 - Go to **interactions**
 - Set **phagocytosis rates** to 0
 - Set **attack rate** for **cancer** to 0.1
 - Set **attack rate** for **invasive cancer** to 0.1
 - Leave **attack damage rate** at 1
 - Set **attack duration** to 15 min



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:	45
Hill power:	10
saturation value:	0.023
Applied to dead:	false
Click add the rule	

- Repeat for invasive cancer
- Make sure to click save!

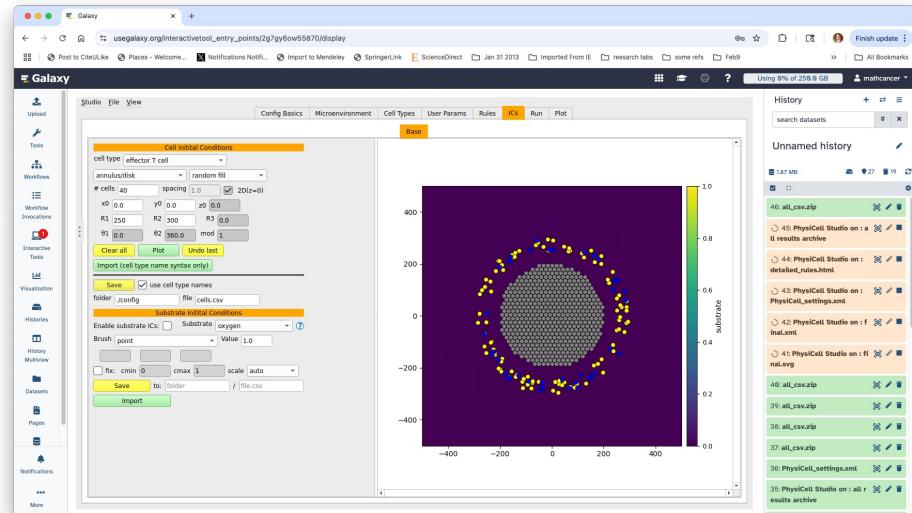
The screenshot shows the PhysiCell Studio interface with the 'Rules' tab selected. A new rule is being added for 'invasive cancer' responding to 'damage' with 'apoptosis' behavior. The rule table lists existing rules for various cell types and signals. The 'Import' button is highlighted.

CellType	Signal	Direction	Behavior	Saturation value	Half-max	Hill power	Apply to dead	
4	invasive cancer	oxygen	increases	transform to cancer	0.01	7.5	5	<input type="checkbox"/>
5	cancer	drug	increases	apoptosis	5e-3	0.5	4	<input type="checkbox"/>
6	cancer	dead	increases	debris secretion	1	0.5	10	<input checked="" type="checkbox"/>
7	invasive cancer	dead	increases	debris secretion	1	0.5	10	<input checked="" type="checkbox"/>
8	macrophage	z1 with dead cell	increases	transform to M1 macrophage	0.1	0.5	10	<input type="checkbox"/>
9	Cancer	damage	increases	apoptosis	0.023	45	10	<input type="checkbox"/>
10	invasive cancer	damage	increases	apoptosis	0.023	45	10	<input type="checkbox"/>
11								<input type="checkbox"/>
12								<input type="checkbox"/>
13								<input type="checkbox"/>



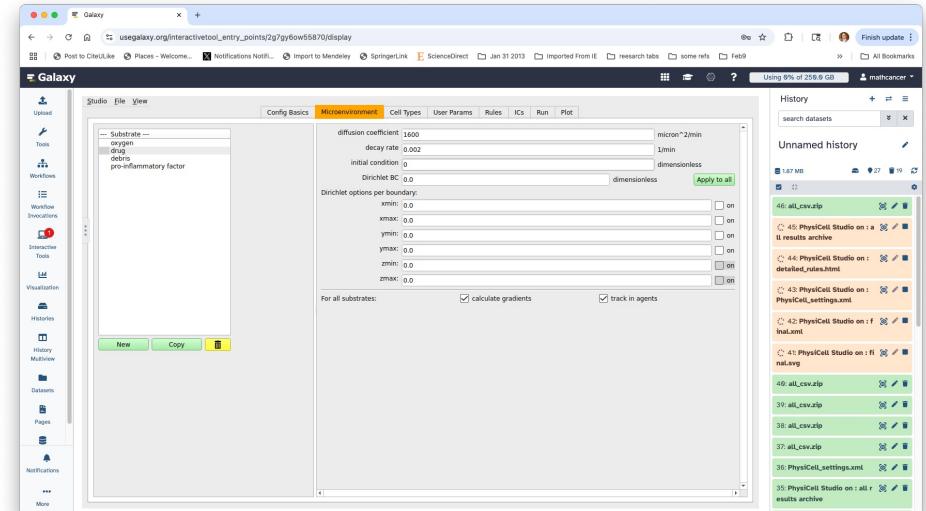
Effector T cells: 5

- Lastly, add cells!
 - Go to **ICs**
 - Choose **effector T cell**
 - Annulus/Circle, **random fill**, 40 cells
 - Min radius 250
 - max radius 300
 - plot, save



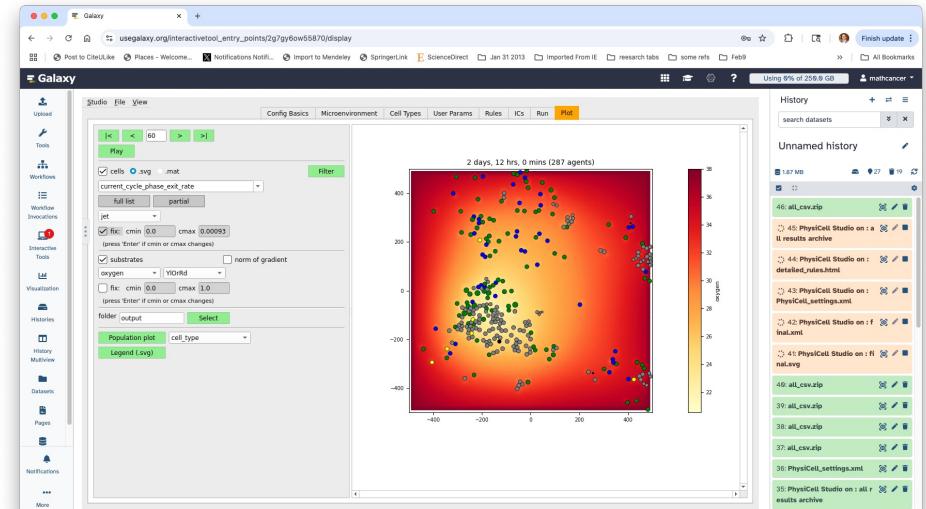
Remove drug

- Go to the **microenvironment** tab
- Select **drug**
- Set the **drug** initial condition to **0**



Run and Visualize

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- **Observe**
 - They attack and kill off cancer cells!
- Try these variations:
 - Add a *little* drug at $t = 0$



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Some suggested explorations

- **Using chemotherapy to trigger immune response**

- Try increasing the initial value of drug
- Try setting drug as a Dirichlet boundary condition

- **Timed release of therapy from "vessels"**

- Add "vessel" agents
- Make them increase secretion at T1, and decrease secretion at T2

- **Weird drug side effects**

- Add rules to "off-target" immune cells

- **Necrosis**

- Make high necrosis in absence of O₂
- Add rule that O₂ decreases necrosis

- **Adding an anti-inflammatory (M2) macrophage population**

- Add a similar M2 that releases anti-inflammatory factor
- Add a transition M1 to M2 in low O₂. And a low background M1 → M2 transition rate
- Add a rule that anti-inflammatory factor reduces attack rate in T cells

- **Fibrosis**

- CAFs drawn to pro-inflammatory factor
- CAFs release ECM
- Low-to-medium ECM increases migration speed in tumor cells, increases EMT, reduces MET
- High-to-medium ECM blocks migration speed in tumor and immune cells (and macrophages) → "wall them in"
- Alternate formulation: ECM *agents*. ECM release = asymmetric division by CAF agents.



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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**
 - **Elana Fertig** : Co-leadership, immune model development, CoGAPS and spatial transcriptomics
 - **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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 - Jeremy Goecks (Moffitt)
 - Junhao Qiu (Moffitt)
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