

Slides, videos, links and more:

<https://github.com/physicell-training/ws2022>

# Session 4: Two complete modeling examples

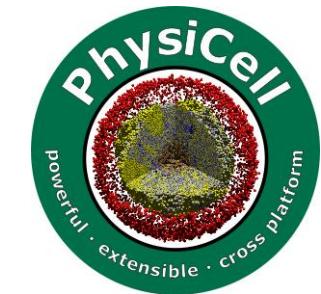


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 [@PhysiCell](https://twitter.com/PhysiCell)

## PhysiCell Project

July 25, 2022



# Session 4: Intermediate modeling workflow

- Goals:
  - Introduce the intermediate modeling workflow
    - ◆ Use PhysiCell model builder and implement models based on **template project**
  - Demonstrate implementation of the following:
    - ◆ Creating a simulation **domain**
    - ◆ Creating a **substrate**
      - » Neuman boundary conditions
      - » Dirichlet boundary conditions
    - ◆ Creating a **cell definition**
    - ◆ Constituting cell interactions and behaviors:
      - » Cell **secretion**
      - » Cell **uptake**
      - » Cell **birth** and **death**
      - » **Cell cycle models**
      - » **Motility** and **Chemotaxis**
      - » **Phagocytosis**
      - » Cell **mutation/transition**

# PhysiCell model builder

A graphical user interface (GUI) application to make it easier to create and edit a PhysiCell (XML) model.

## Config basics:

- Domain size, Simulation duration, Data output

## • Microenvironment:

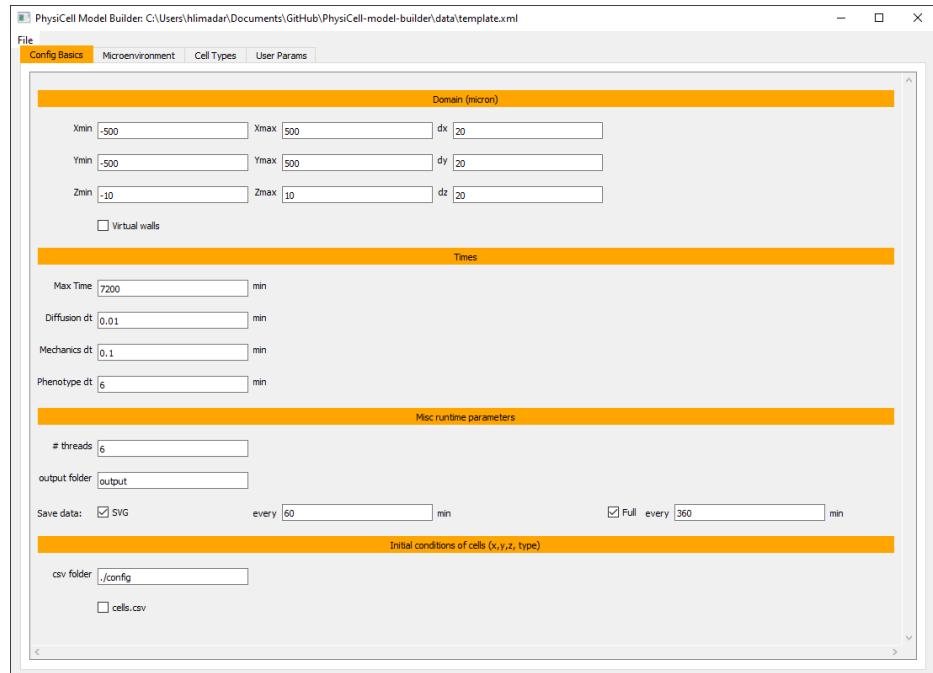
- Define diffusing substrates and boundary conditions

## • Cell types:

- Define cell types, including their base phenotypes (behaviors)

## • User params:

- Model-specific parameters



<https://github.com/PhysiCell-Tools/PhysiCell-model-builder>

# Example 1: Bacteria-immune model

# Goal: build a bacteria-immune model

- **Bacteria:**

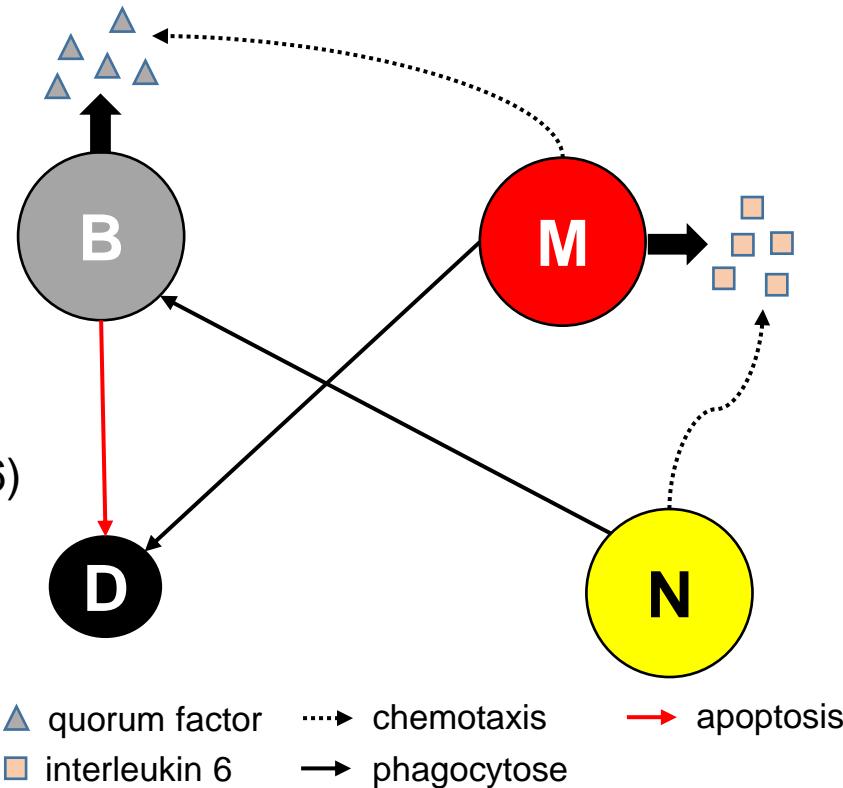
- Cycle, apoptosis, secrete quorum factor
- Random motility towards quorum factor

- **Macrophages:**

- Attracted to bacteria
- Phagocytose dead cells
- Secrete pro-inflammatory factor (e.g., IL-6)

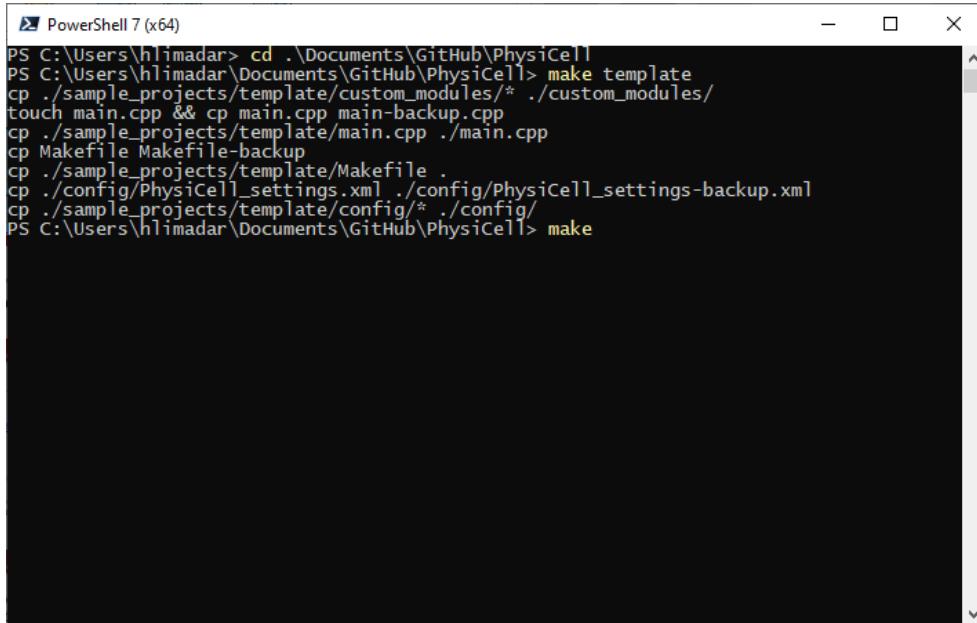
- **Neutrophils:**

- Attracted to pro-inflammatory factor
- Phagocytose live bacteria



# Start the template project

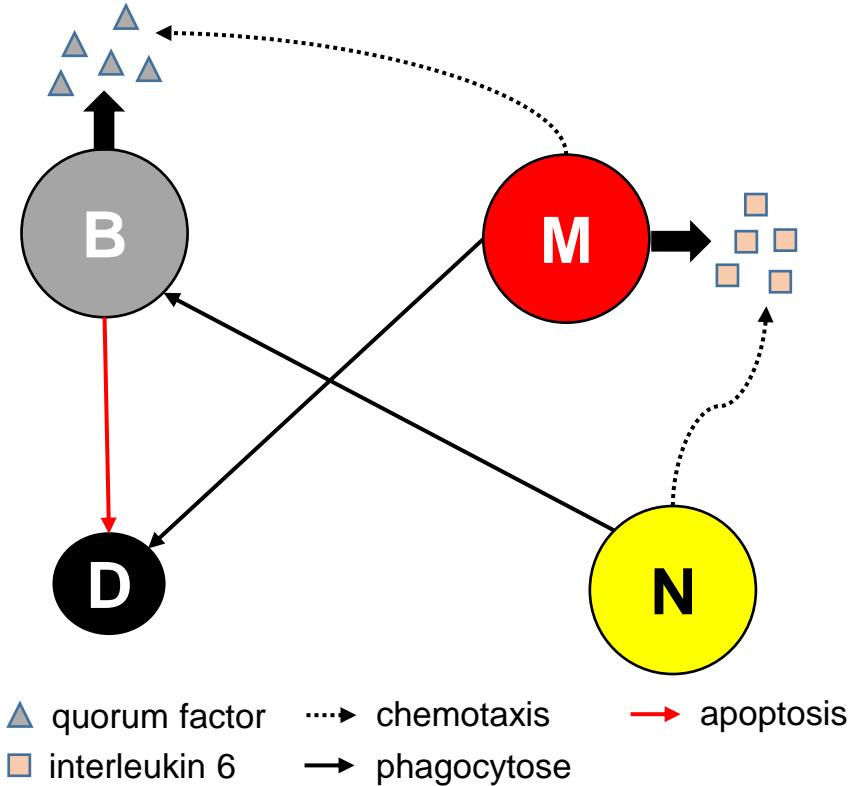
- Go to the terminal and open PhysiCell folder:
  - cd ..\Documents\GitHub\PhysiCell\
- Select the template project:
  - make template
- Compile the project:
  - make (-j 8)
- Open PhysiCell-model-builder in another terminal
  - python ..\PhysiCell-model-builder\bin\pmb.py



```
PS C:\Users\hlimadar> cd ..\Documents\GitHub\PhysiCell
PS C:\Users\hlimadar\Documents\GitHub\PhysiCell> make template
cp ./sample_projects/template/custom_modules/* ./custom_modules/
touch main.cpp && cp main.cpp main-backup.cpp
cp ./sample_projects/template/main.cpp ./main.cpp
cp Makefile Makefile-backup
cp ./sample_projects/template/Makefile .
cp ./config/PhysiCell_settings.xml ./config/PhysiCell_settings-backup.xml
cp ./sample_projects/template/config/* ./config/
PS C:\Users\hlimadar\Documents\GitHub\PhysiCell> make
```

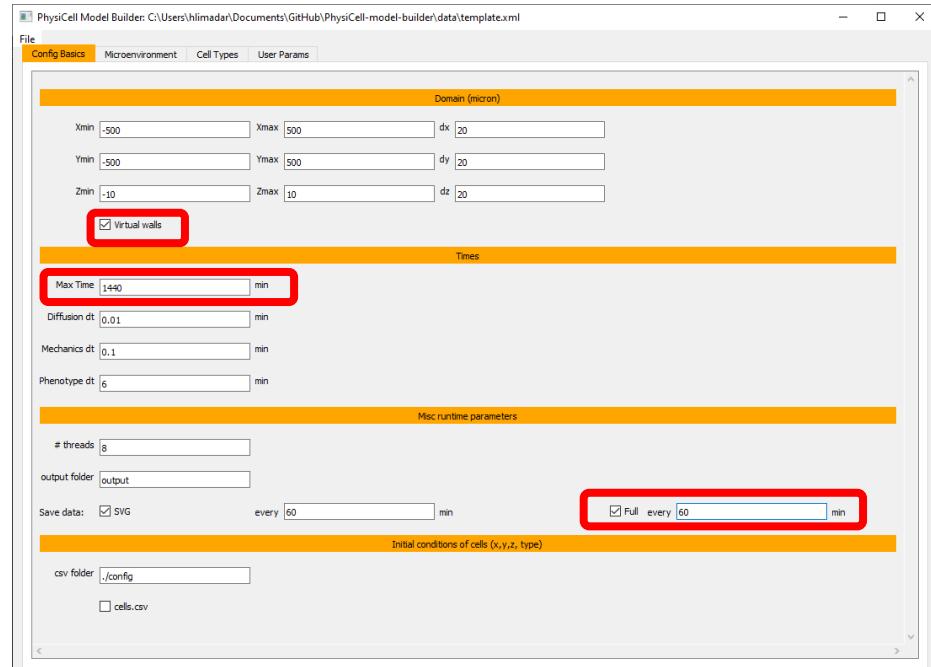
# Checklist

- Build iteratively:
  - Set the domain
  - Add diffusing substrates
  - Add bacteria and test
  - Add macrophages and test
  - Add neutrophils and test
- Testing hypotheses:
  - Change neutrophils chemotaxis and test



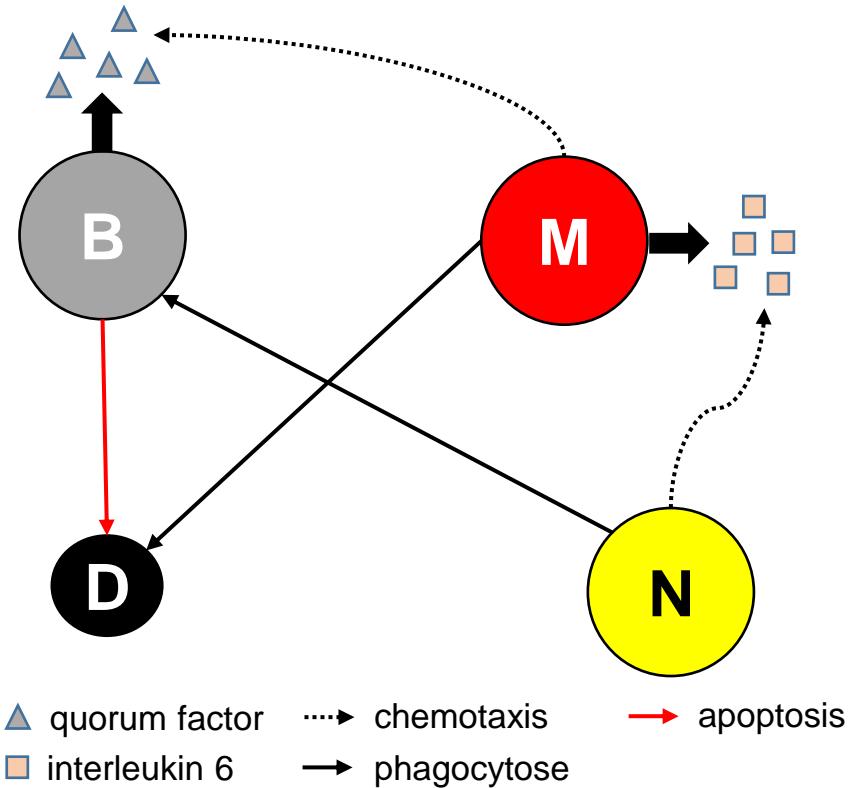
# Set up the domain

- Go to the **config basics** tab
- Choose domain settings (in  $\mu\text{m}$ )
  - leave  $Z_{\min} = -\frac{1}{2}\Delta z$  and  $Z_{\max} = \frac{1}{2}\Delta z$  for 2D models
  - Use “virtual walls” to apply a force to keep cells from leaving the domain
- Choose time settings (in min):
  - Set max simulation time to **1440** min (1 day)
- Choose save settings:
  - SVG: required for plotting cell positions
    - ◆ Save every 60 minutes (default setting)
  - Full: required for plotting diffusing substrates



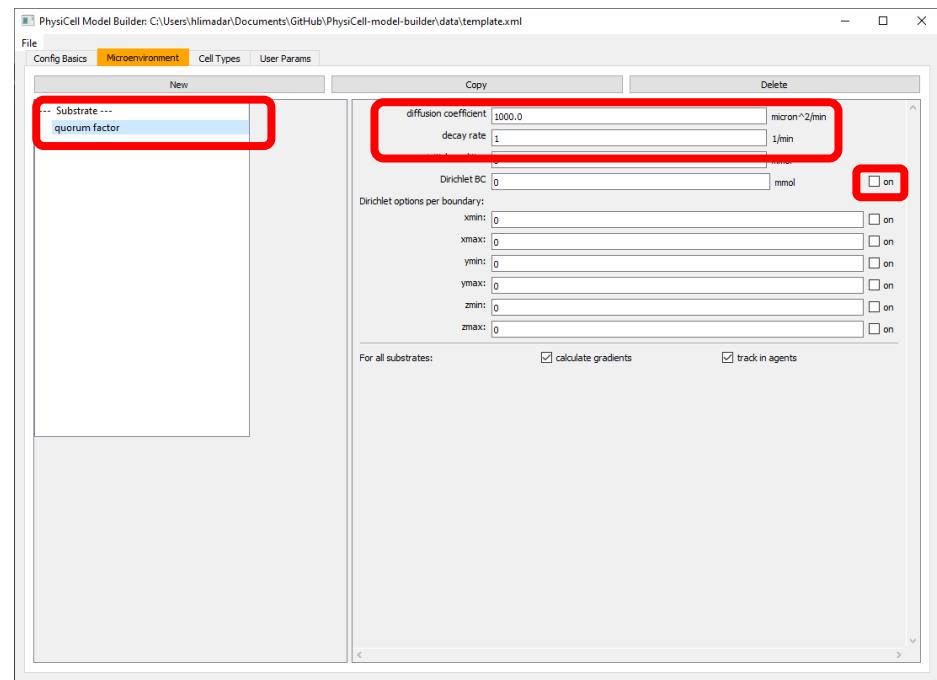
# Checklist

- Build iteratively:
  - ~~Set the domain~~
  - Add diffusing substrates
  - Add bacteria and test
  - Add macrophages and test
  - Add neutrophils and test
- Testing hypotheses:
  - Change neutrophils chemotaxis and test



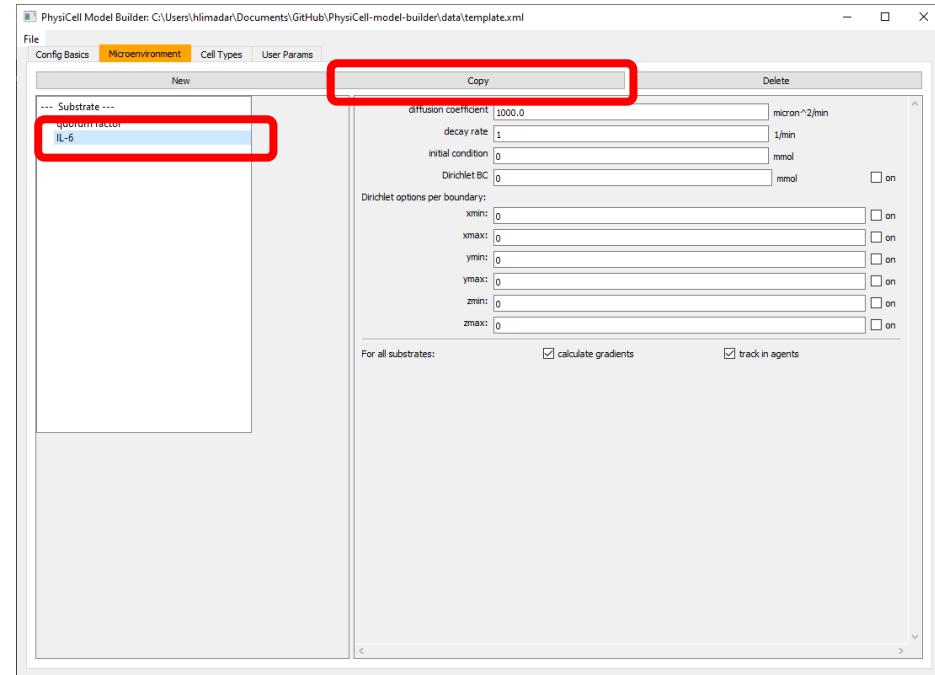
# Define substrates (1)

- Go to the **microenvironment** tab
- Double-click **substrate**
  - Rename to **quorum factor**
  - Set diffusion at  $1000 \mu\text{m}^2/\text{min}$
  - Set decay at  $1 \text{ min}^{-1}$ 
    - ◆ 100 mm diffusion length scale
  - **Disable** Dirichlet boundary conditions
  - Set initial condition to 0



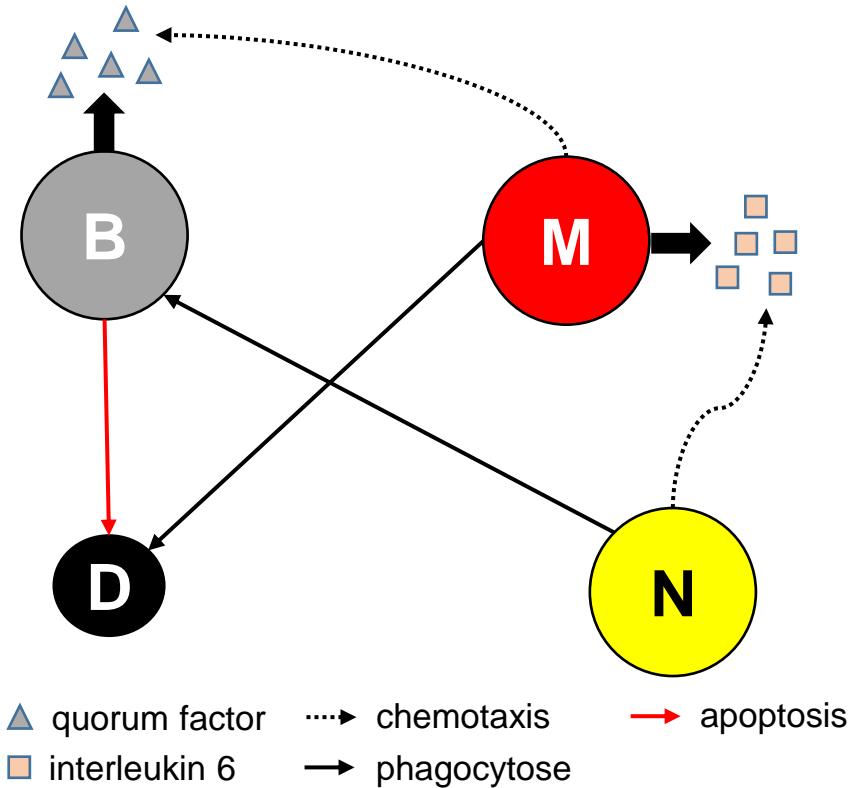
# Define substrates (2)

- Select quorum factor
- Click copy
- Rename to IL-6



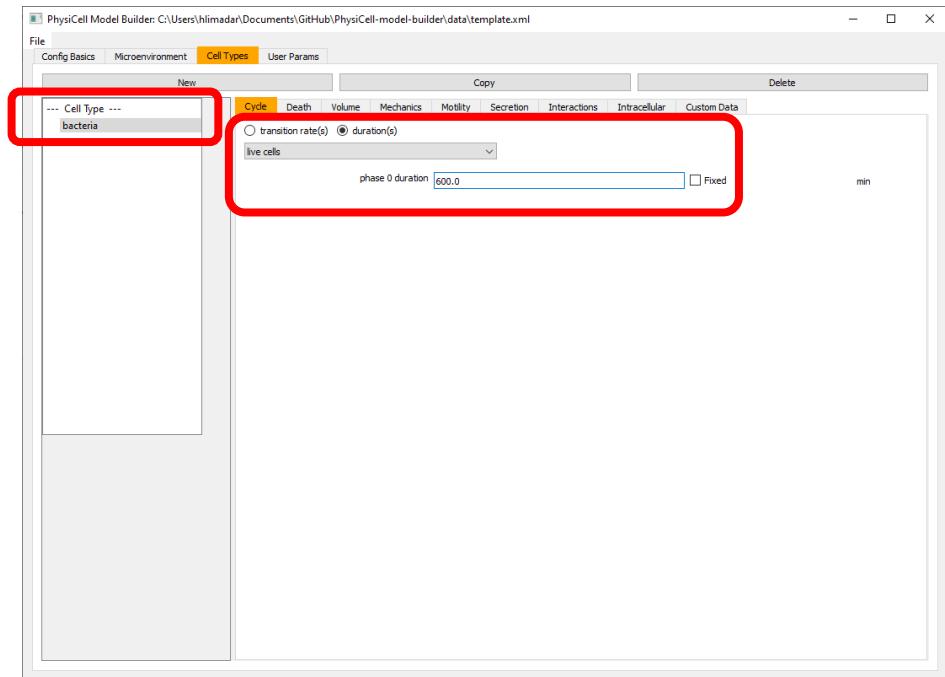
# Checklist

- Build iteratively:
  - Set the domain
  - Add diffusing substrates
  - Add bacteria and test
  - Add macrophages and test
  - Add neutrophils and test
- Testing hypotheses:
  - Change neutrophils chemotaxis and test



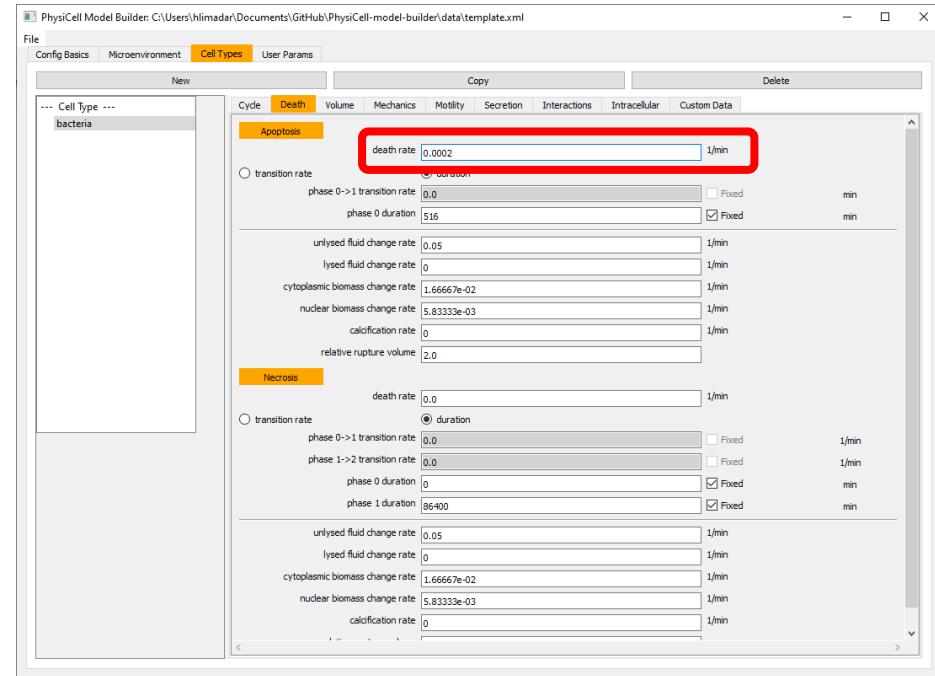
# Define bacteria (1)

- Go to the **cell types** tab
- Double-click on **default**
  - Rename to **bacteria**
- Let's set a moderate 10-hour cycle
  - Go to **Cycle**
    - ◆ Set the cycle model type to **live cells**
    - ◆ Set the cycle **duration** to **600 min**



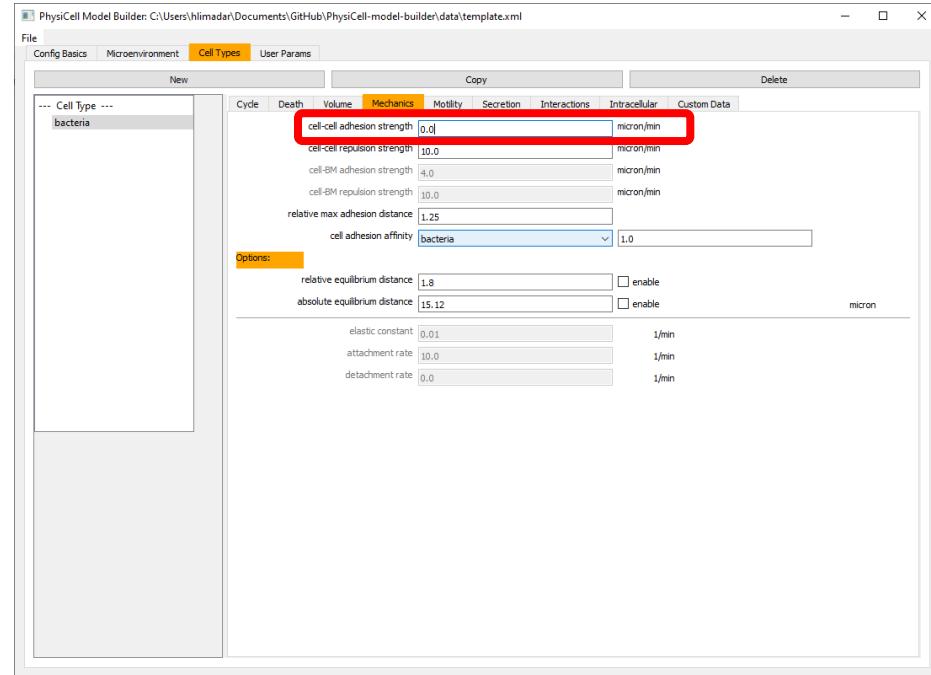
# Define bacteria (2)

- Let's set a low background death
  - Go to Death
  - ◆ Set the **apoptosis** rate to **0.0002**



# Define bacteria (3)

- Make them non-adhesive
  - Go to **Mechanics**
  - ◆ Set **cell-cell adhesion** to **0**

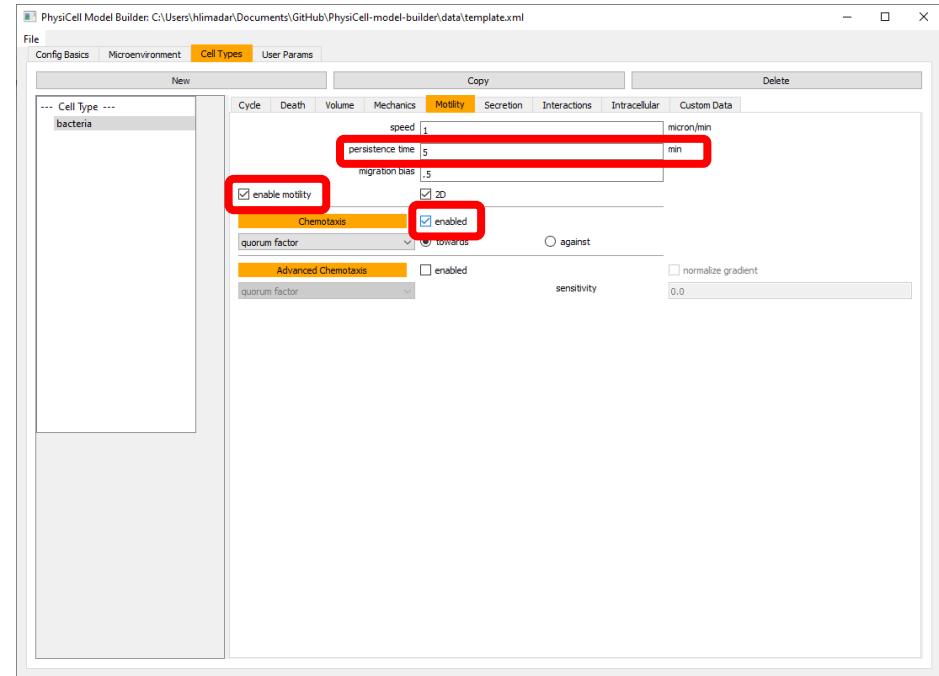


# Define bacteria (4)

- Make them chemotactic

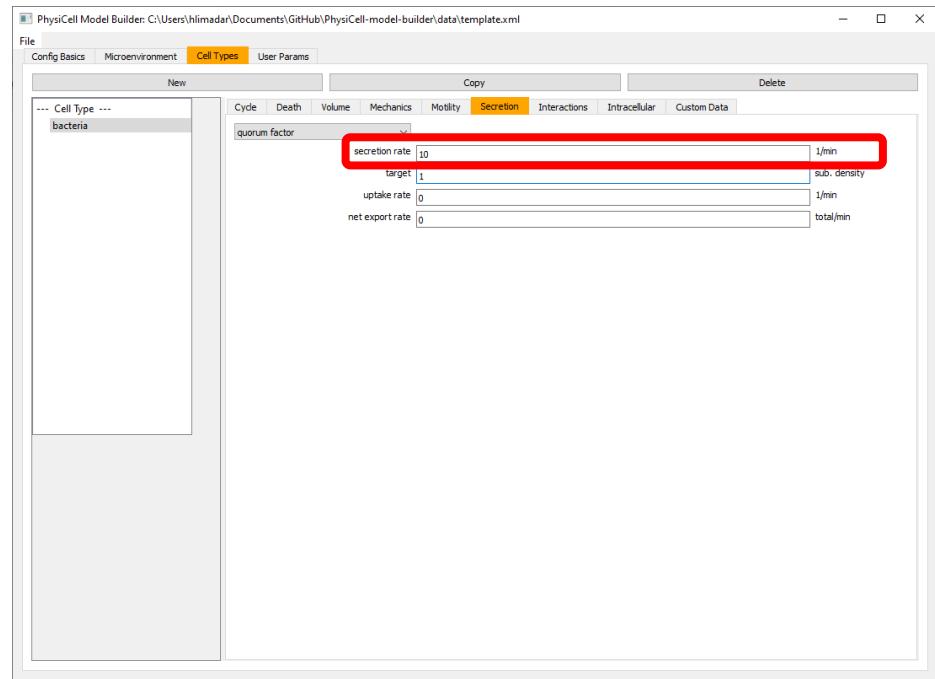
- Go to **Motility**

- ◆ Set **speed** to 1
- ◆ Set **persistence time** to 5
- ◆ Set **bias** to 0.5
- ◆ Check the box to enable motility
- ◆ Check the box to enable chemotaxis
- ◆ Select **quorum factor**



# Define bacteria (5)

- Make them secrete quorum factor
  - Go to **Secretion**
    - ◆ Choose **quorum factor** from the drop-down menu
    - ◆ Set **secretion rate** to 10
    - ◆ Set **target** to 1



# Test the model!

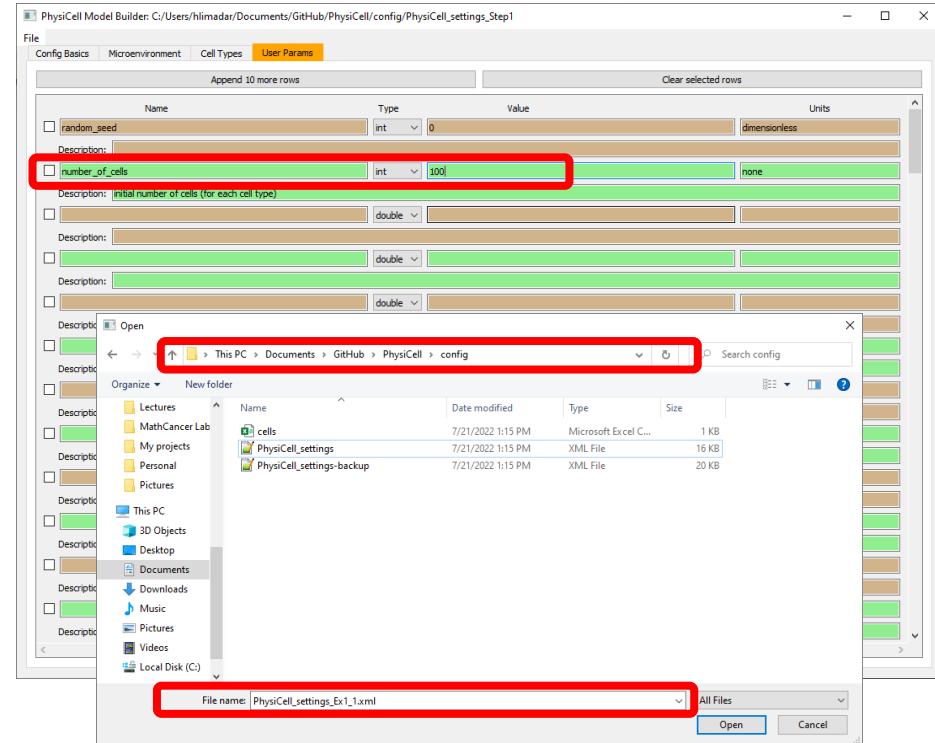
- Go to the **user params** tab
  - Set **number of cells** to 100
- Save as:  
PhysiCell\_settings\_Ex1\_1.xml
- run the model

( Windows user )

```
.\project.exe .\config\PhysiCell_settings_Ex1_1.xml
```

( OSX user )

```
./project config/PhysiCell_settings_Ex1_1.xml
```



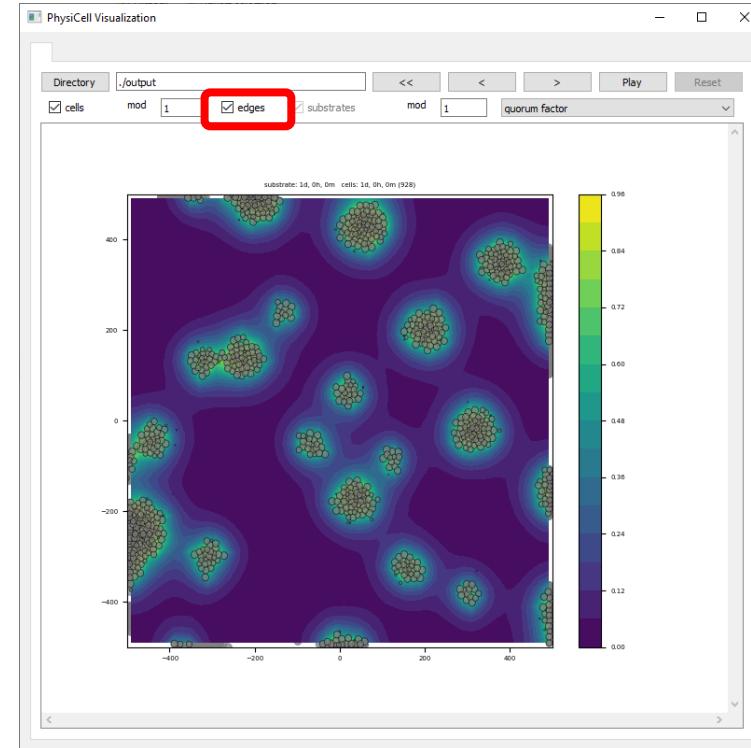
# View the results

- To see the results run:

```
python .\beta\plot_data.py (Windows)
```

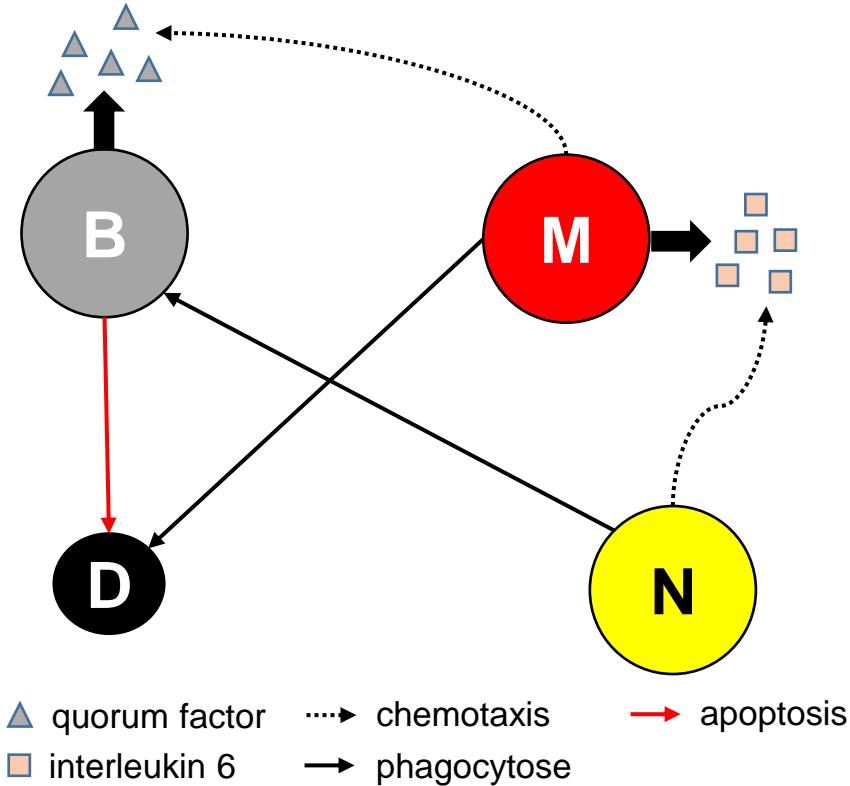
```
python beta/plot_data.py (Mac)
```

- Click **play** to automatically animate
- Click < or > to advance by 1 frame
- Click << to go to the start
- Check the edges to apply cell contours.
- Use the drop-down to change the substrate.



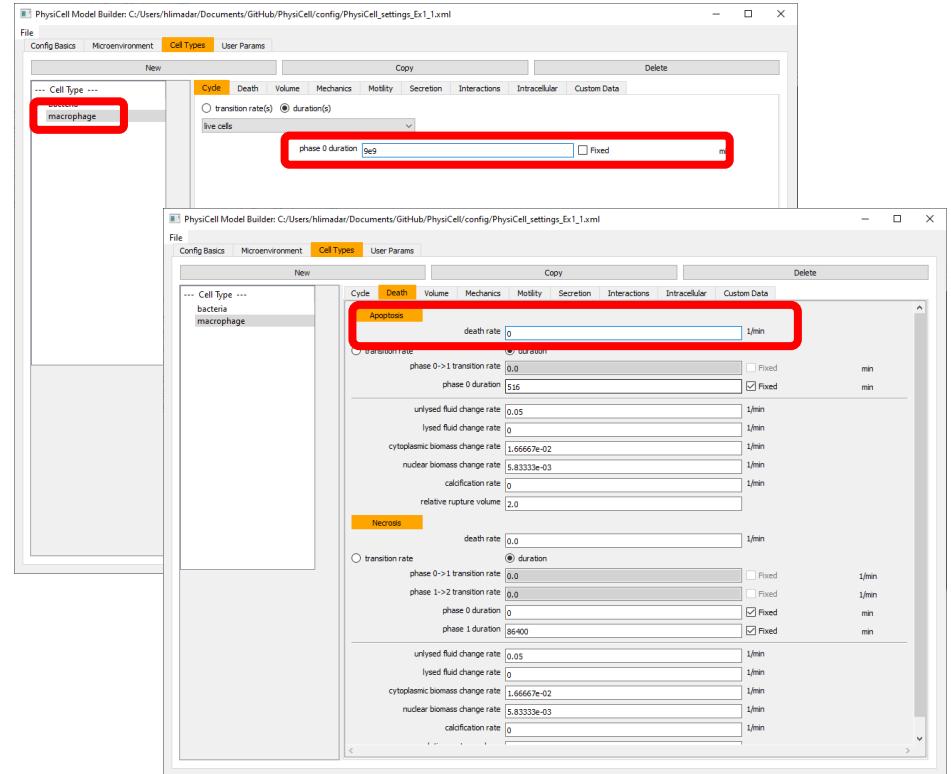
# Checklist

- Build iteratively:
  - Set the domain
  - Add diffusing substrates
  - Add bacteria and test
  - Add macrophages and test
  - Add neutrophils and test
- Testing hypotheses:
  - Change neutrophils chemotaxis and test



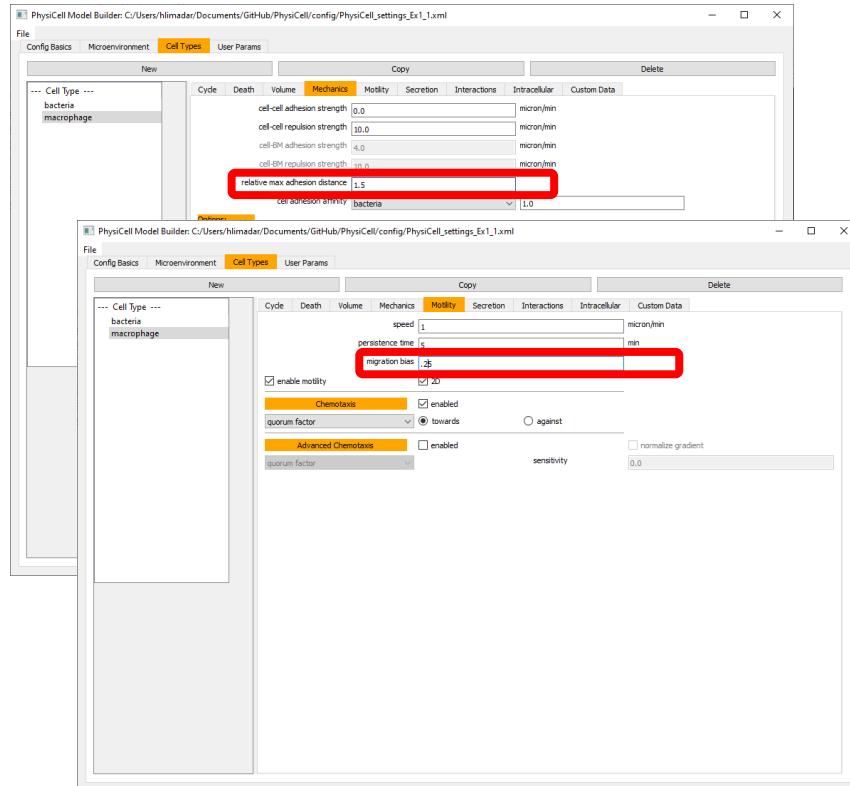
# Define macrophages (1)

- Go to the **cell types** tab
- Select **bacteria** and click **copy**
- Double-click the new type
  - Rename to **macrophage**
- Let's disable cycling and apoptosis
  - Go to **Cycle**
    - ◆ Set the cycle **duration** to **9e9 min**
  - Go to **Death**
    - ◆ Set the **apoptotic death rate** to **0**



# Define macrophages (2)

- Let's increase the range of mechanical interactions
  - Go to **Mechanics**
    - Set **relative max adhesion distance** to 1.5
      - (this is a multiple of cell radius)
- Let's enable chemotaxis towards quorum factor, but more random
  - Go to **Motility**
    - Set **migration bias** to 0.25

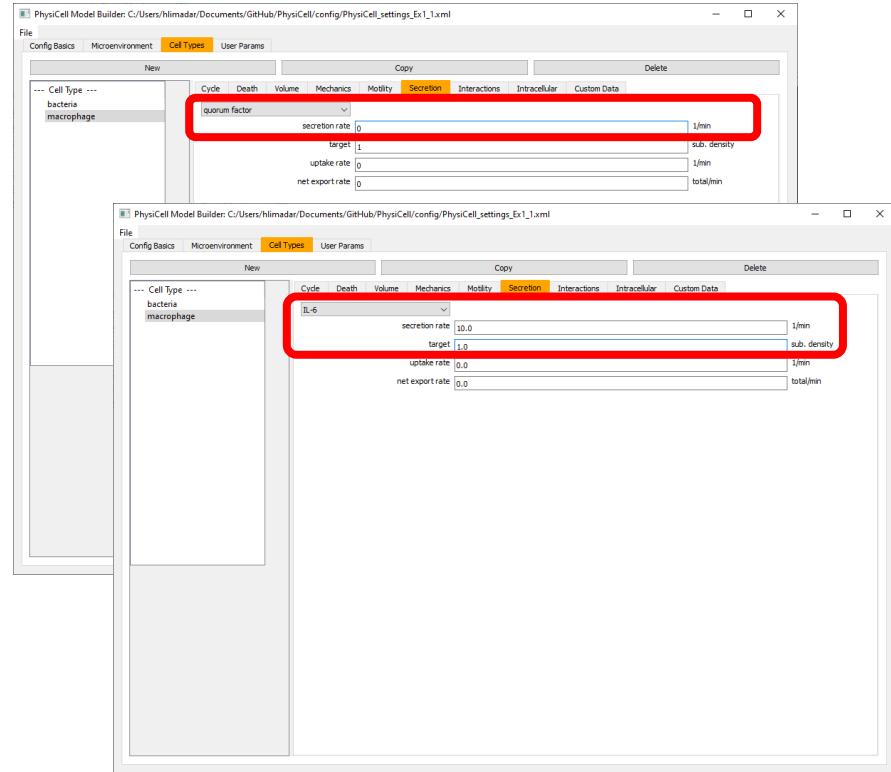


# Define macrophages (3)

- Let's secrete IL-6 and not quorum factor

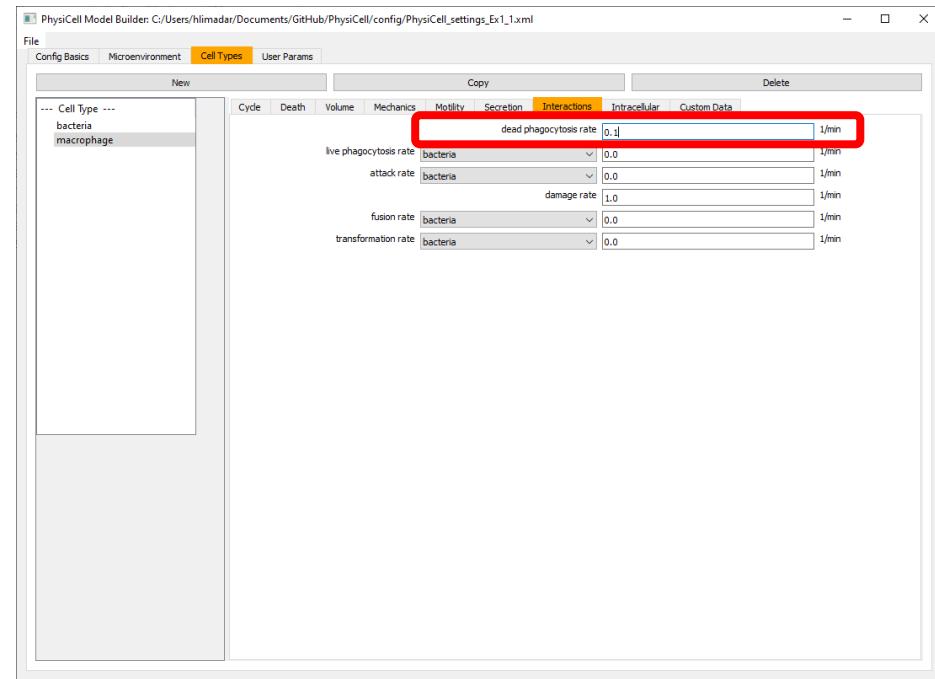
- Go to **Secretion**

- ◆ Choose **quorum factor** from the drop-down
  - » Set **secretion rate** to **0**
- ◆ Choose **IL-6** from the drop-down
  - » Set **secretion rate** to **10**
  - » Set **target** to **1**



# Define macrophages (4)

- Let's enable phagocytosis of dead cells
  - Go to **Interactions**
    - Set **dead phagocytosis rate** to 0.1



# Test the model!

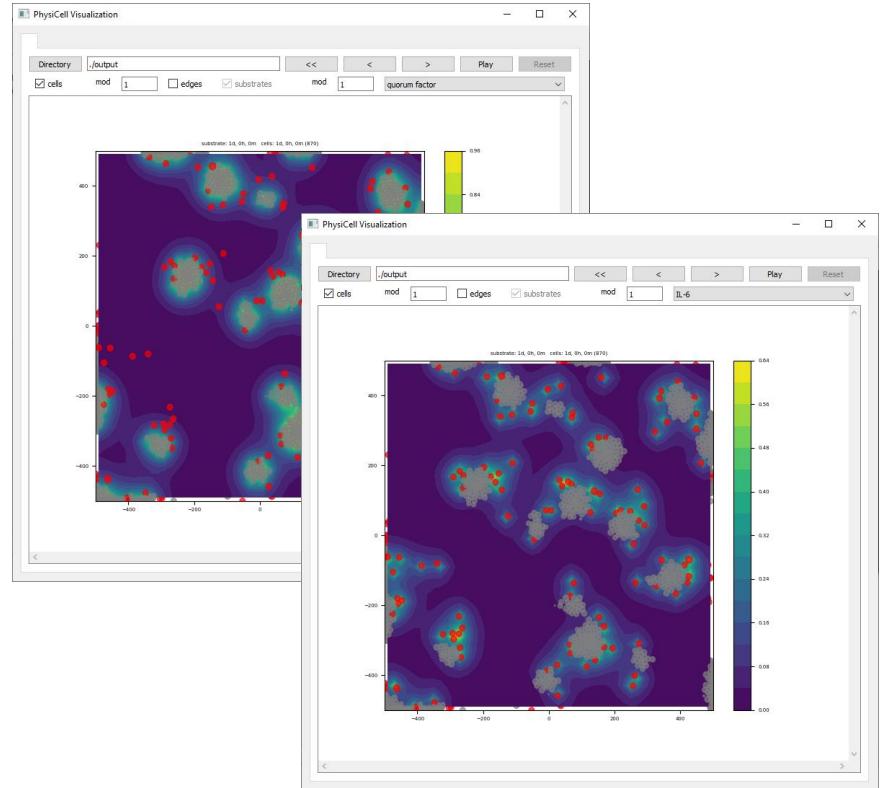
- Save as:  
PhysiCell\_settings\_Ex1\_2.xml

- Run the simulation

```
( Windows user )  
.\\project.exe  
.\\config\\PhysiCell_settings_Ex1_2.xml
```

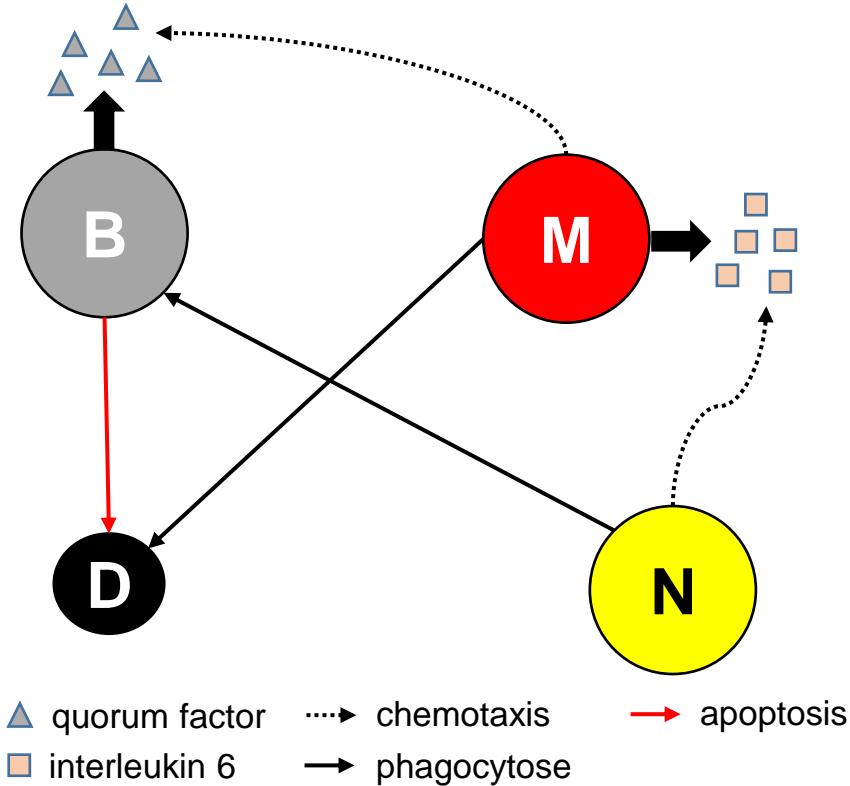
```
( OSX user )  
.\\project  
.\\config\\PhysiCell_settings_Ex1_2.xml
```

- Open **legend** file on output folder to see cell colors defined
  - grey: bacteria
  - red: macrophages



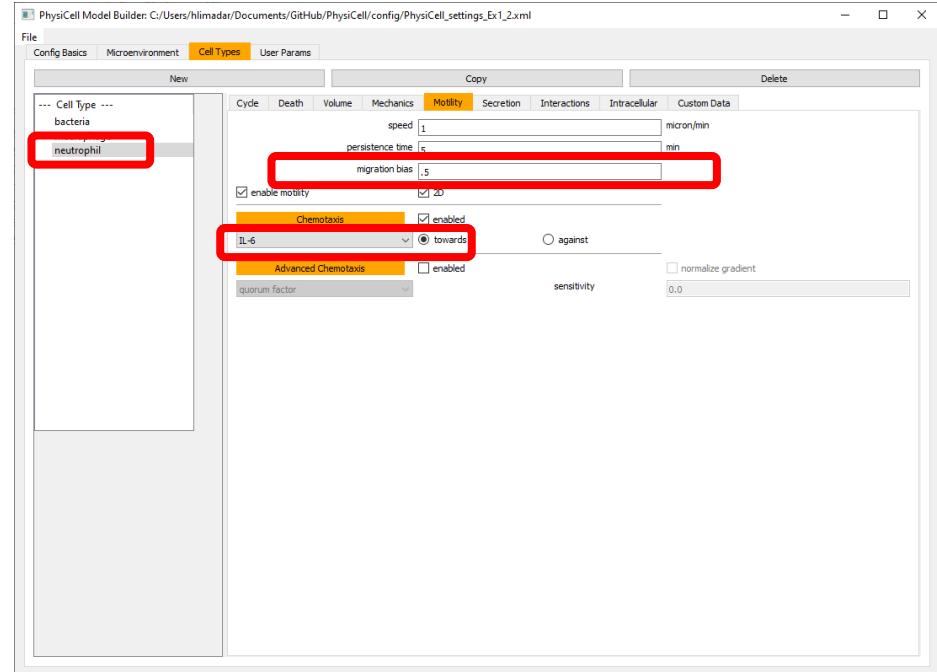
# Checklist

- Build iteratively:
  - Set the domain
  - Add diffusing substrates
  - Add bacteria and test
  - Add macrophages and test
  - Add neutrophils and test
- Testing hypotheses:
  - Change neutrophils chemotaxis and test



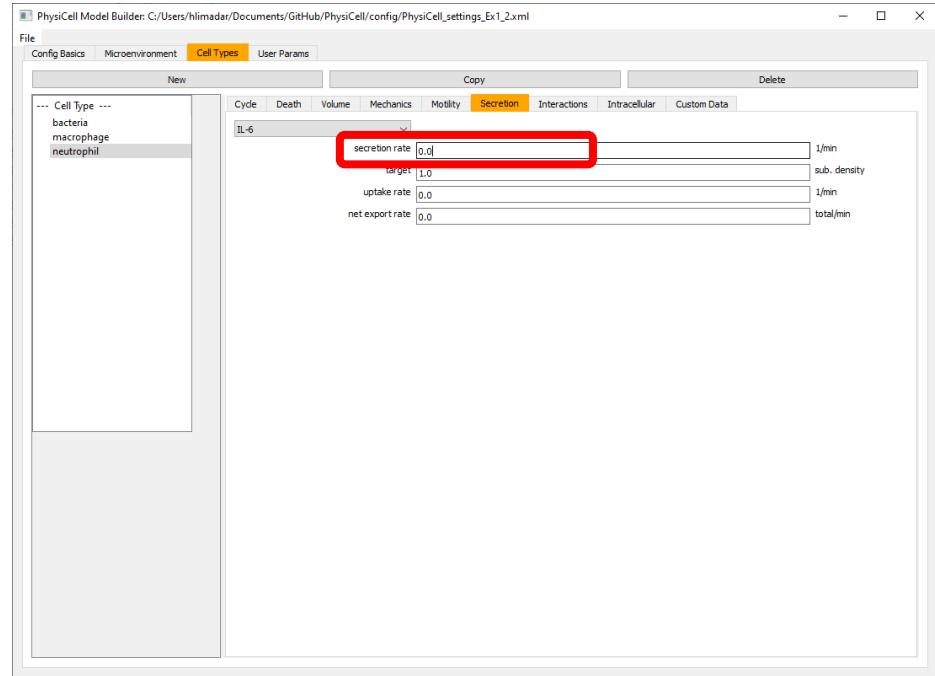
# Define neutrophils (1)

- Go to the **cell types** tab
- Select **macrophage**, click **copy**
- Double-click the new type
  - Rename to **neutrophil**
- Let's switch chemotaxis to IL-6
  - Go to **Motility**
    - ◆ Set **migration bias** to **0.5**
  - Go to **chemotaxis**
    - » Choose **IL-6** from the drop-down



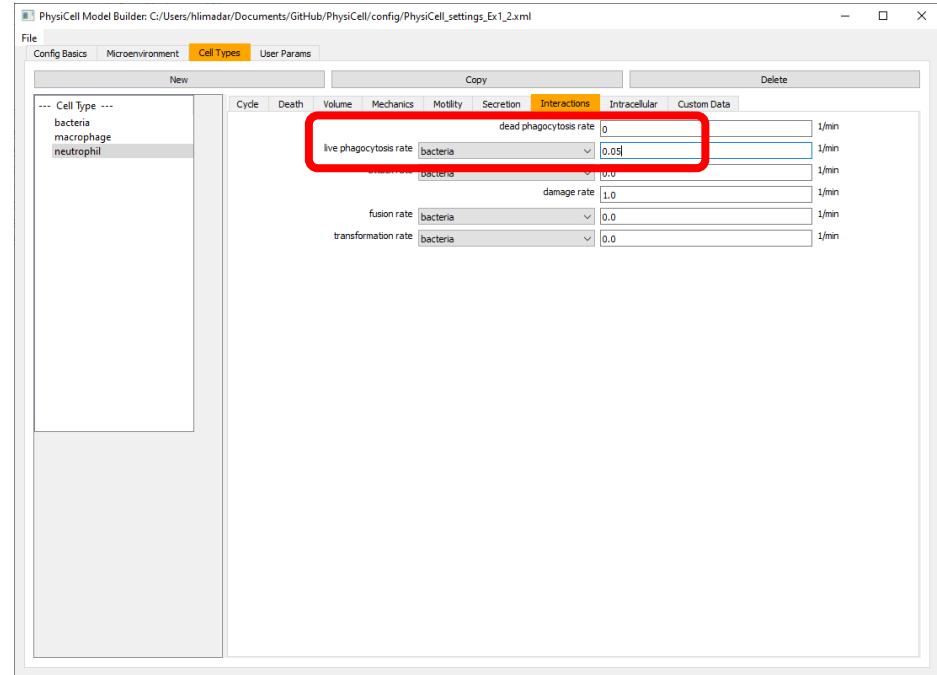
# Define neutrophils (2)

- Let's disable secretion
  - Go to **Secretion**
    - ◆ Choose **IL-6** from the drop-down
    - ◆ Set **secretion rate** to **0**



# Define neutrophils (3)

- Let's set up phagocytosis!
  - Go to **Interactions**
    - ◆ Set **dead cell phagocytosis** to **0**
    - ◆ Go to **live phagocytosis rate**
      - » Choose **bacteria** in the drop-down
      - » Set the rate to **0.05**



# Test the model!

- Save as: PhysiCell\_settings\_Ex1\_3.xml
- Run the simulation

( Windows user )

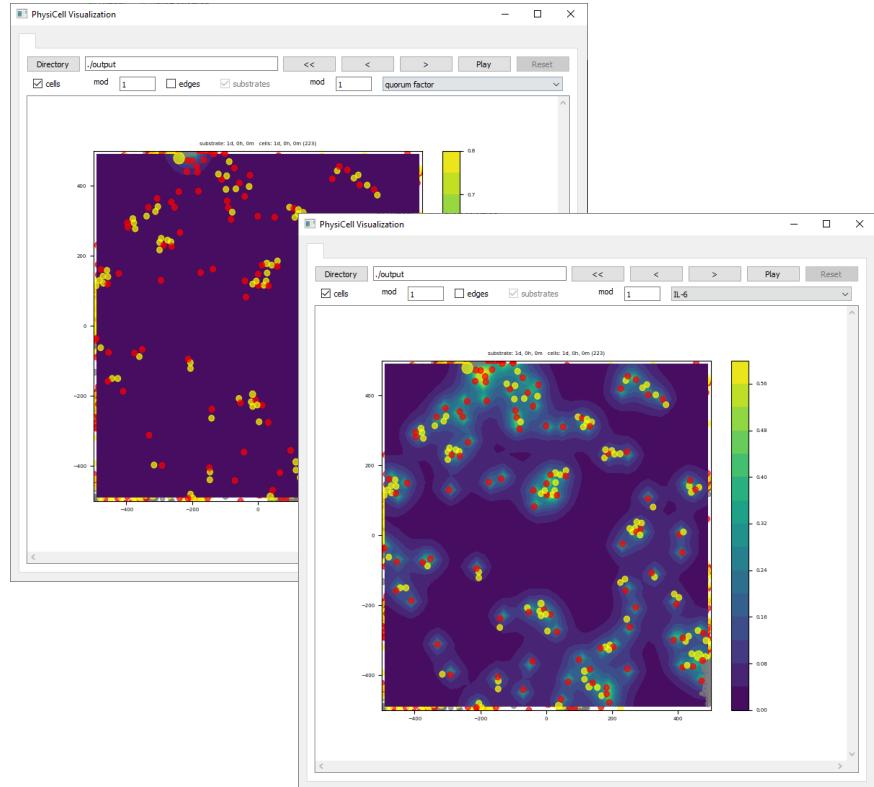
```
.\project.exe  
.\config\PhysiCell_settings_Ex1_3.xml
```

( OSX user )

```
.\project  
.\config\PhysiCell_settings_Ex1_3.xml
```

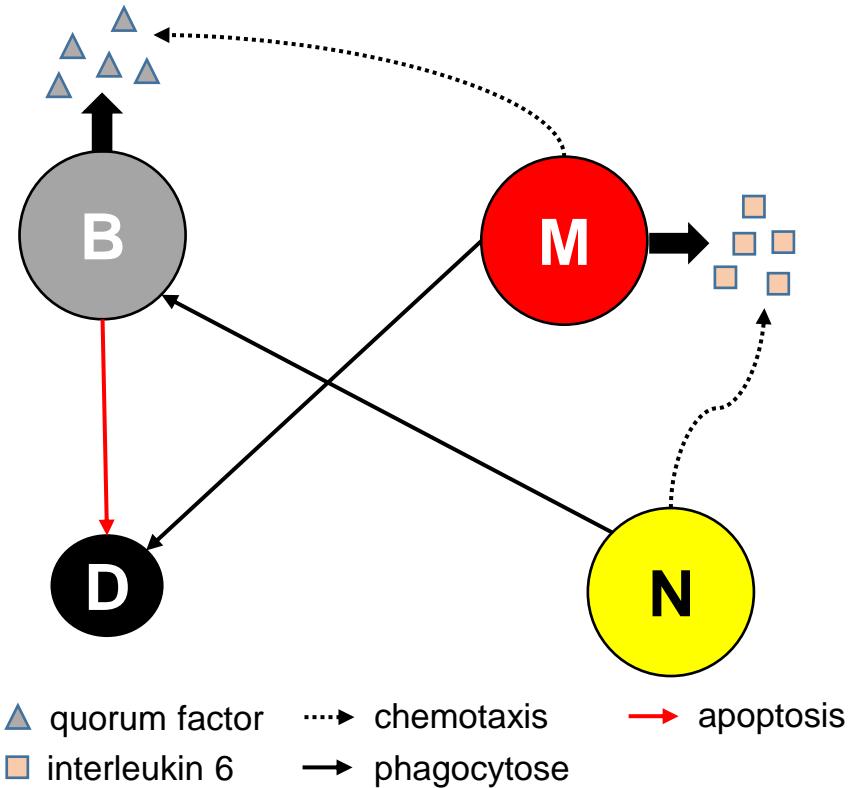
- Open **legend** file on output folder to see cell colors defined

- grey: bacteria
- red: macrophages
- yellow: neutrophils



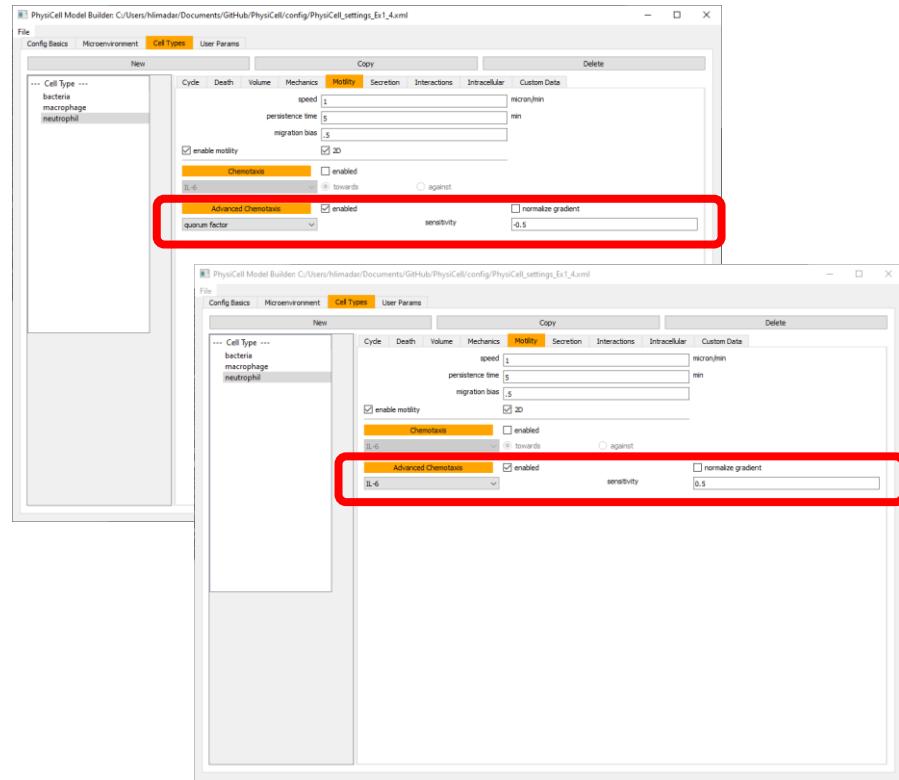
# Checklist

- Build iteratively:
  - Set the domain
  - Add diffusing substrates
  - Add bacteria and test
  - Add macrophages and test
  - Add neutrophils and test
- Testing hypotheses:
  - Change neutrophils chemotaxis and test



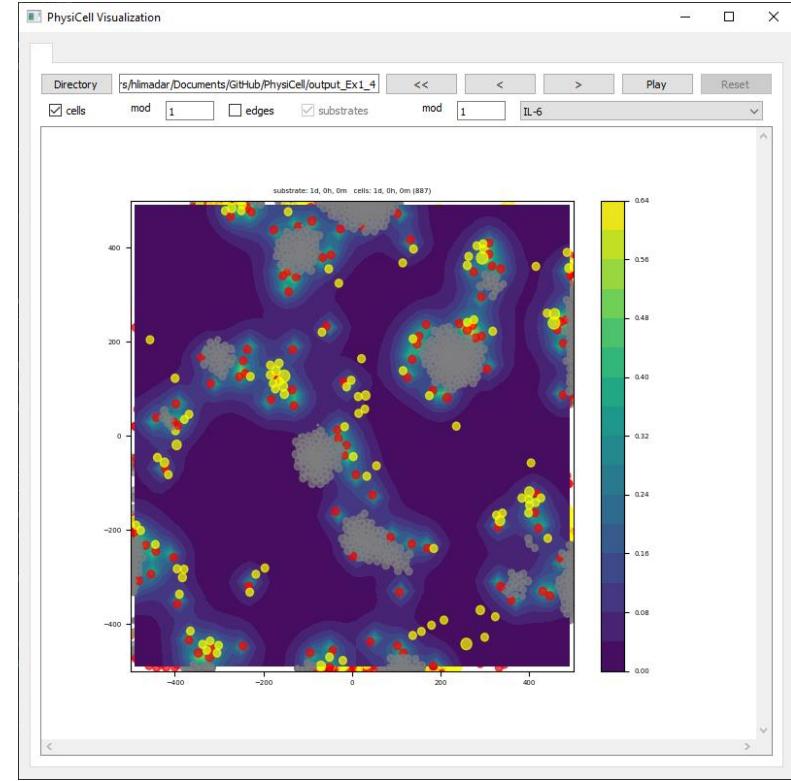
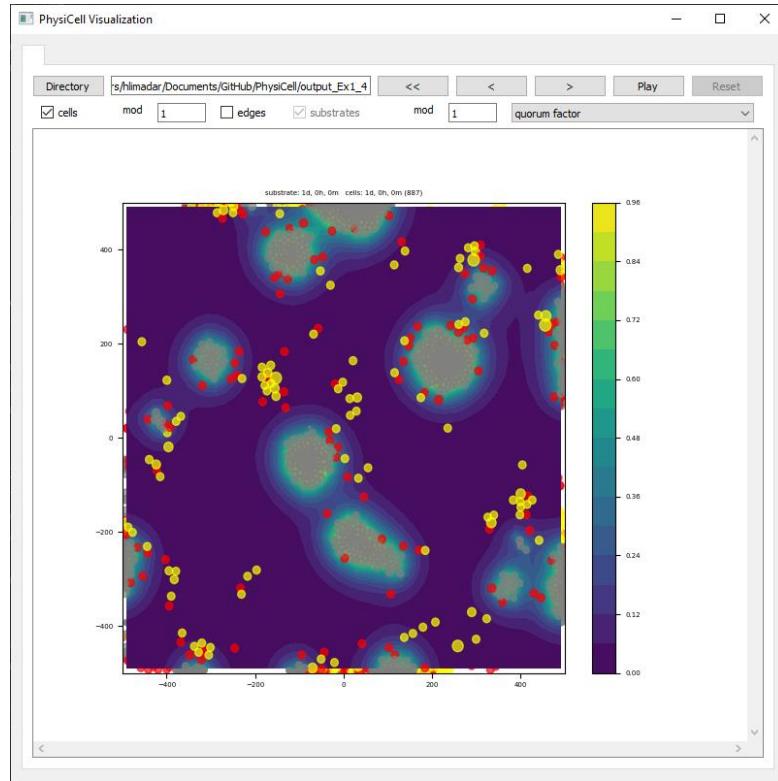
# Change neutrophil chemotaxis (1)

- Let's switch to advanced chemotaxis
  - Go to Motility
    - Check the box Advanced chemotaxis
    - Choose quorum factor from the drop-down and set -0.5
    - Choose IL-6 from the drop-down and set 0.5



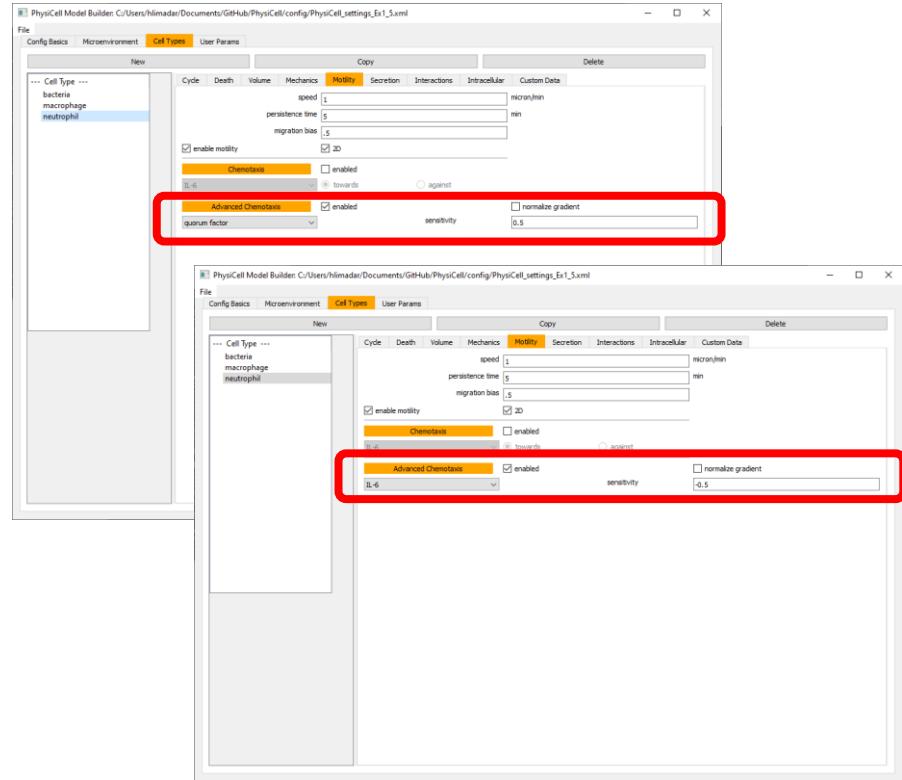
Save as: PhysiCell\_settings\_Ex1\_4.xml

# Test the model!



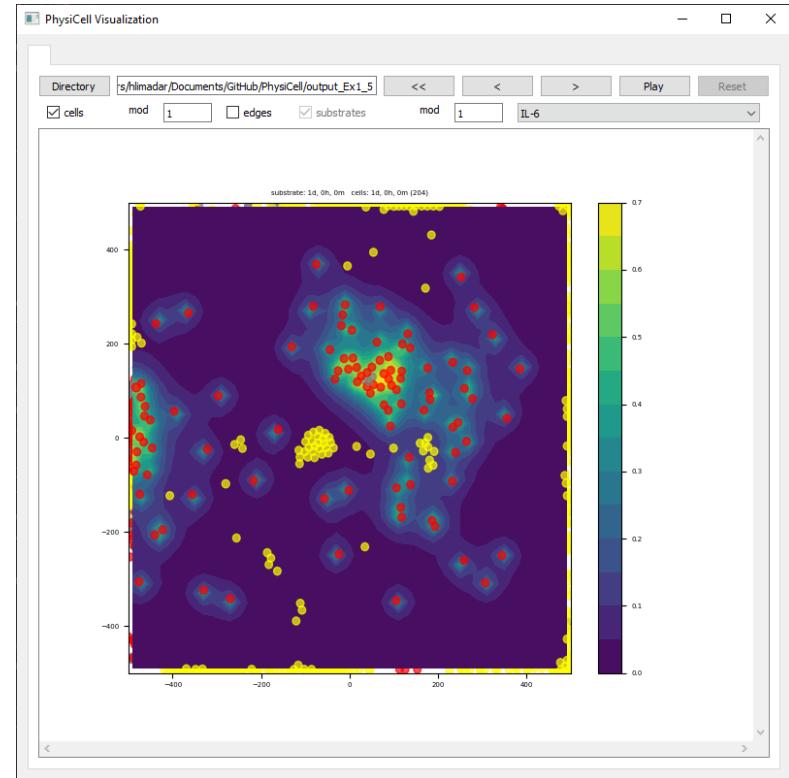
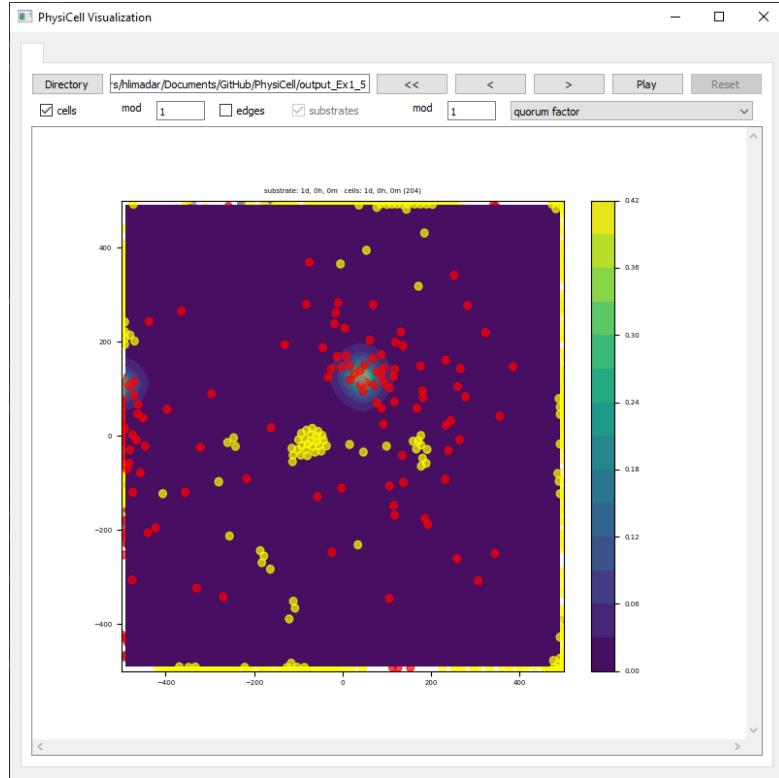
# Change neutrophil chemotaxis (1)

- Let's switch to advanced chemotaxis
  - Go to Motility
    - Check the box Advanced chemotaxis
      - Choose quorum factor from the drop-down and set 0.5
      - Choose IL-6 from the drop-down and set -0.5



Save as: PhysiCell\_settings\_Ex1\_5.xml

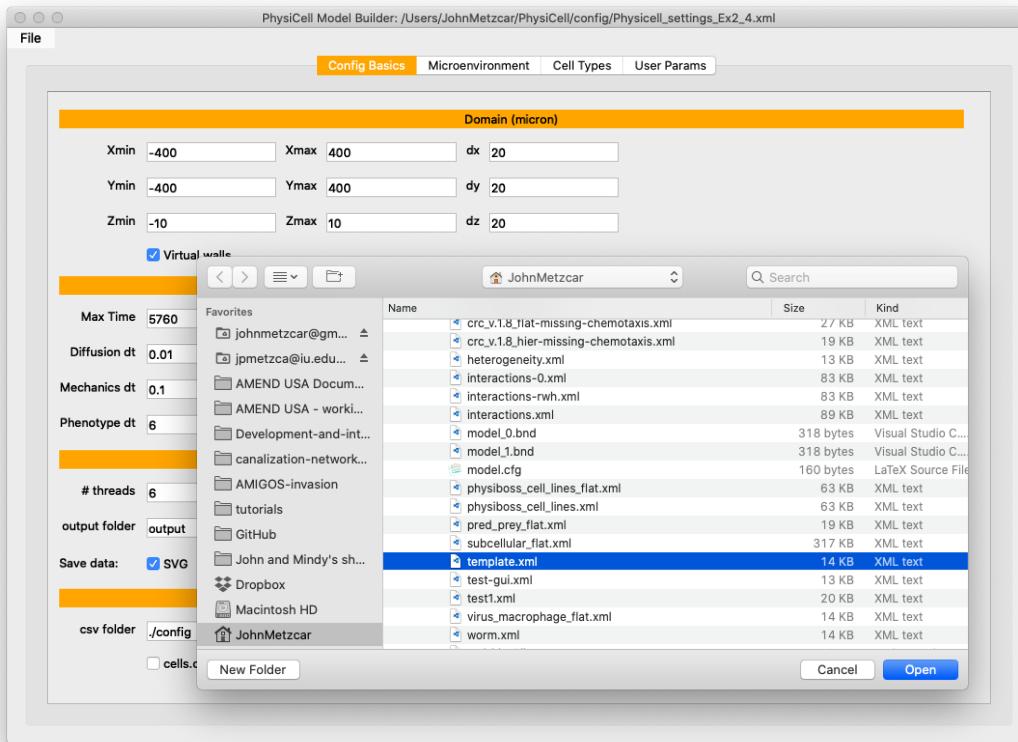
# Test the model!



# Example 2: Tumor-immune model

# Resetting for Example 2

- In model builder:
  - Go to the **File → Open**
  - Navigate to **PhysiCell-model-builder/data**
  - Select **template.xml**
- In Terminal:
  - From within the PhysiCell folder enter **make data-cleanup** #Note this will remove everything in /output
- Ready to go!!



# Goal: Build a simple tumor-immune model

- Tumor:

- Wild Type tumor cells:

- ◆ Proliferate and apoptose at a constant rate
    - ◆ Secrete a tumor factor
    - ◆ Randomly mutate

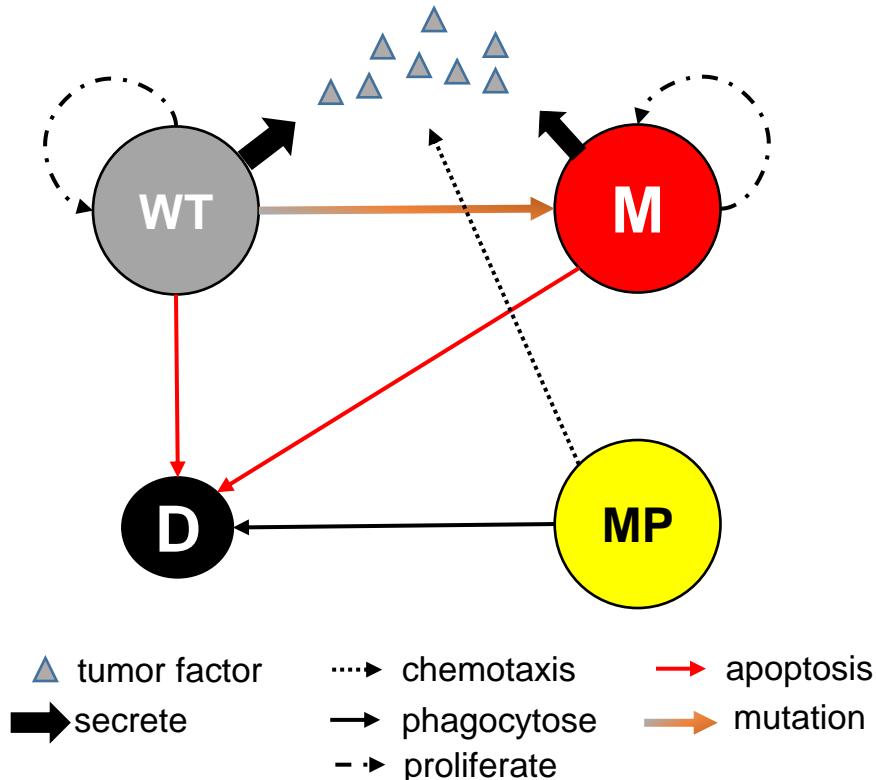
- Mutant tumor cells:

- ◆ Random migration, slower proliferation
    - ◆ Less secretion of tumor factor

- Immune:

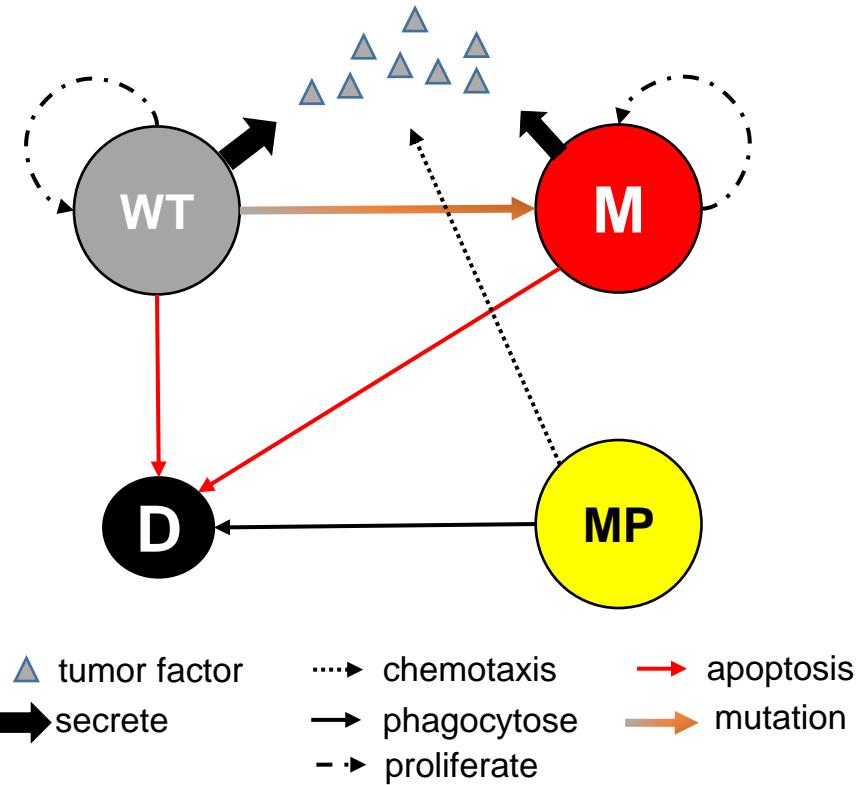
- Macrophages

- ◆ Attracted to tumor factor
    - ◆ Phagocytose (consume) dead cells



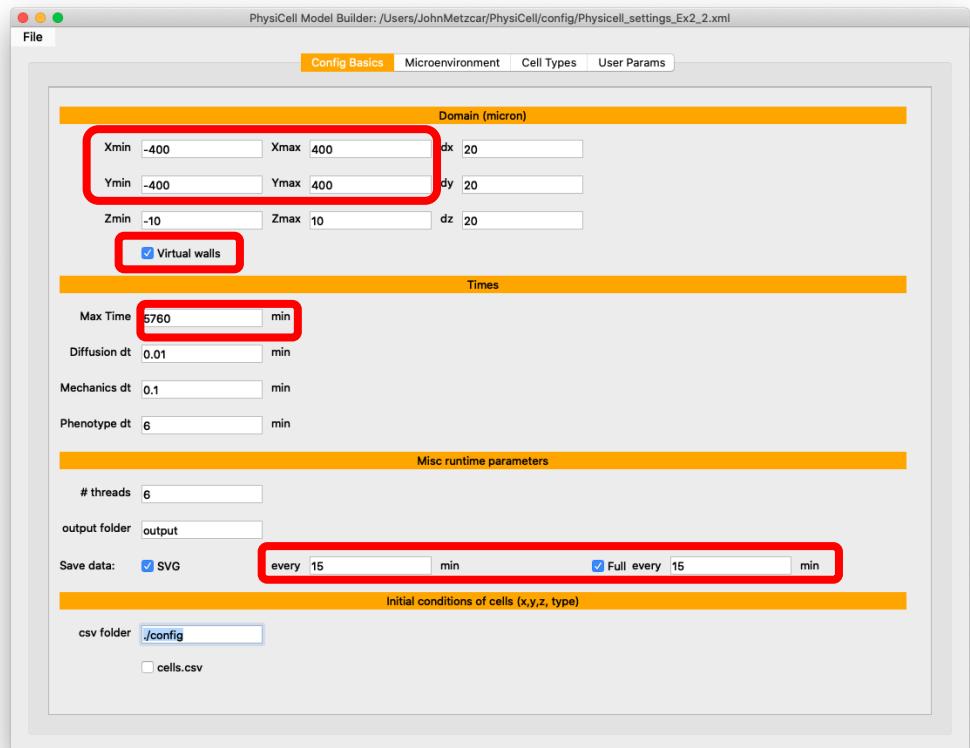
# Checklist

- Build iteratively:
  - Set the domain
  - Add diffusing substrates
  - Add WT tumor cells and test
  - Add mutant tumor cells and test
  - Add transition from WT to mutant cells
  - Add macrophages and test



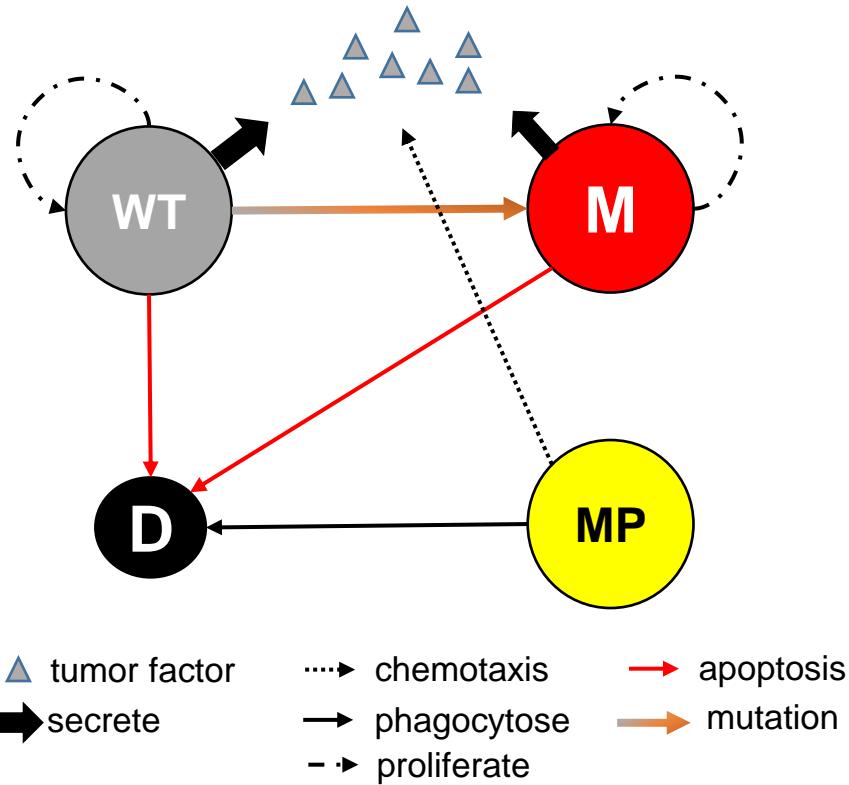
# Set up the domain

- Go to the **config basics** tab
- Choose domain settings (in  $\mu m$ )
  - leave  $Z_{min} = -\frac{1}{2}\Delta z$  and  $Z_{max} = \frac{1}{2}\Delta z$  for 2D models
  - Use “virtual walls” to apply a force to keep cells from leaving the domain
  - Use a [-400,400] by [-400,400] domain
    - ◆ Set Xmin and Ymin to -400
    - ◆ Set Xmax and Ymax to 400
- Choose time settings (in min):
  - Max time is the simulation end time – set to 5760 minutes
- Choose save settings:
  - SVG: required for plotting cell positions – set to 15 minutes
  - Full: required for plotting diffusing substrates – set to 15 minutes
- Save as: PhysiCell\_settings\_Ex2\_1.xml



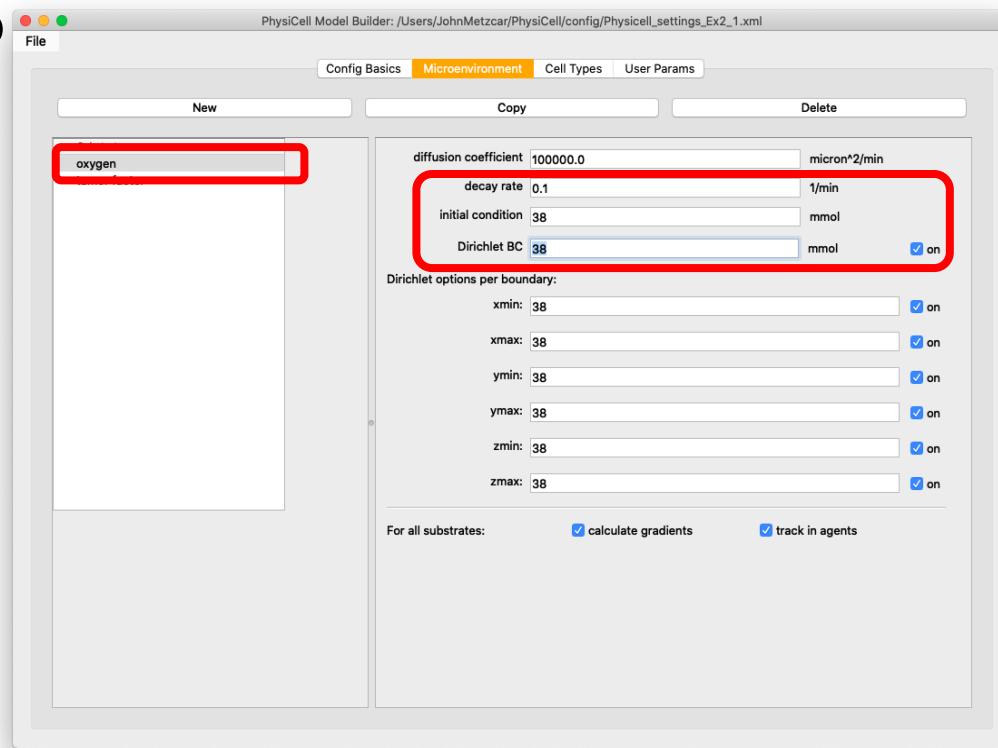
# Checklist

- Build iteratively:
  - Set the domain
  - Add diffusing substrates
  - Add WT tumor cells and test
  - Add mutant tumor cells and test
  - Add transition from WT to mutant cells
  - Add macrophages and test



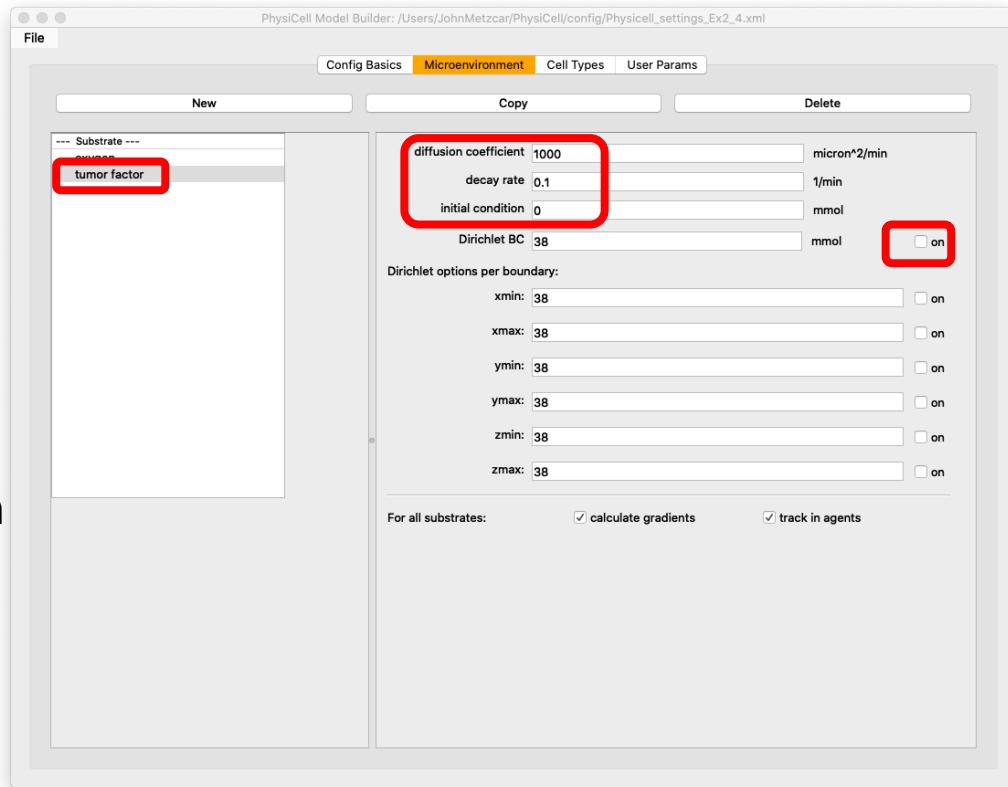
# Define substrates (1)

- Go to the **microenvironment** tab
- Double-click **substrate**
  - Rename to **oxygen**
  - Keep diffusion at  $100,000 \mu\text{m}^2/\text{min}$
  - Set decay at  $0.1 \text{ min}^{-1}$ 
    - ◆ 1 mm diffusion length scale
  - (1 mm length scale)
  - Set Dirichlet boundary conditions to 38 mmHg (5% O<sub>2</sub>: physioxic conditions)
  - Set initial condition to 38 mmHg



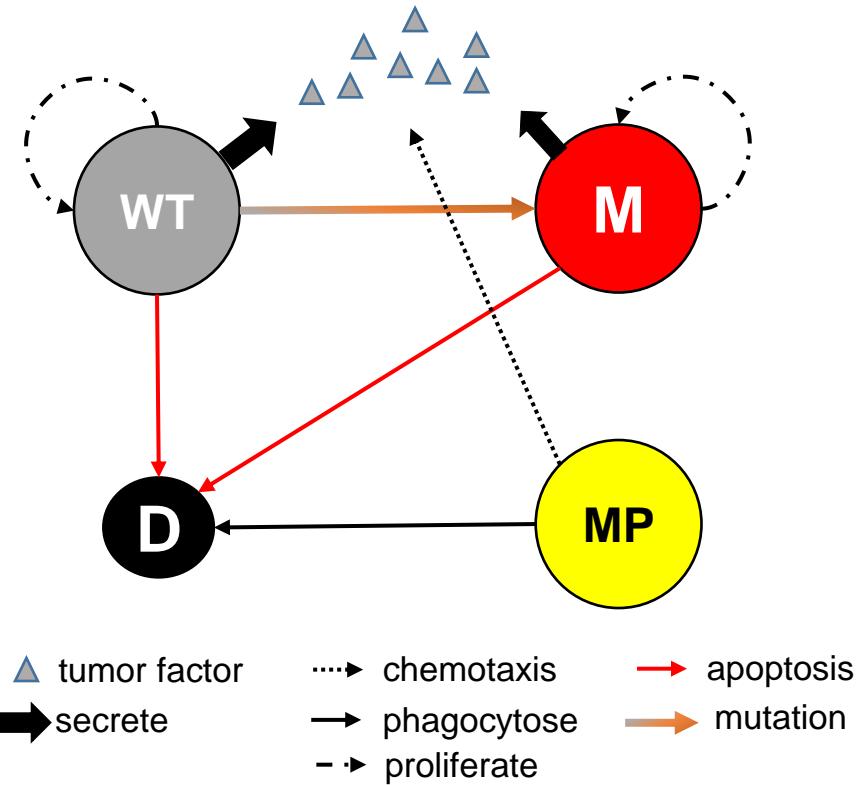
# Define substrates (2)

- Make sure **oxygen** is selected
- Click **copy**
- Rename to **tumor factor**
  - Set diffusion at  $1000 \mu\text{m}^2/\text{min}$
  - Set decay at  $0.1 \text{ min}^{-1}$ 
    - ◆  $100 \mu\text{m}$  diffusion length scale
  - Disable Dirichlet boundary condition
  - Set initial condition to 0



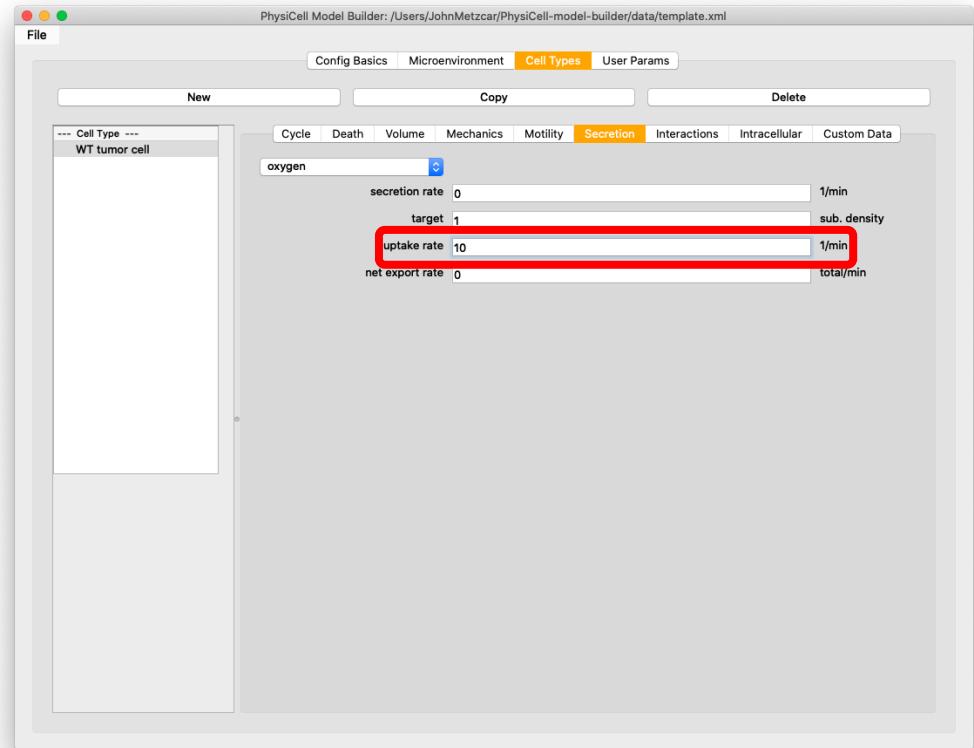
# Checklist

- Build iteratively:
  - Set the domain
  - Add diffusing substrates
  - Add WT tumor cells and test
  - Add mutant tumor cells and test
  - Add transition from WT to mutant cells
  - Add macrophages and test



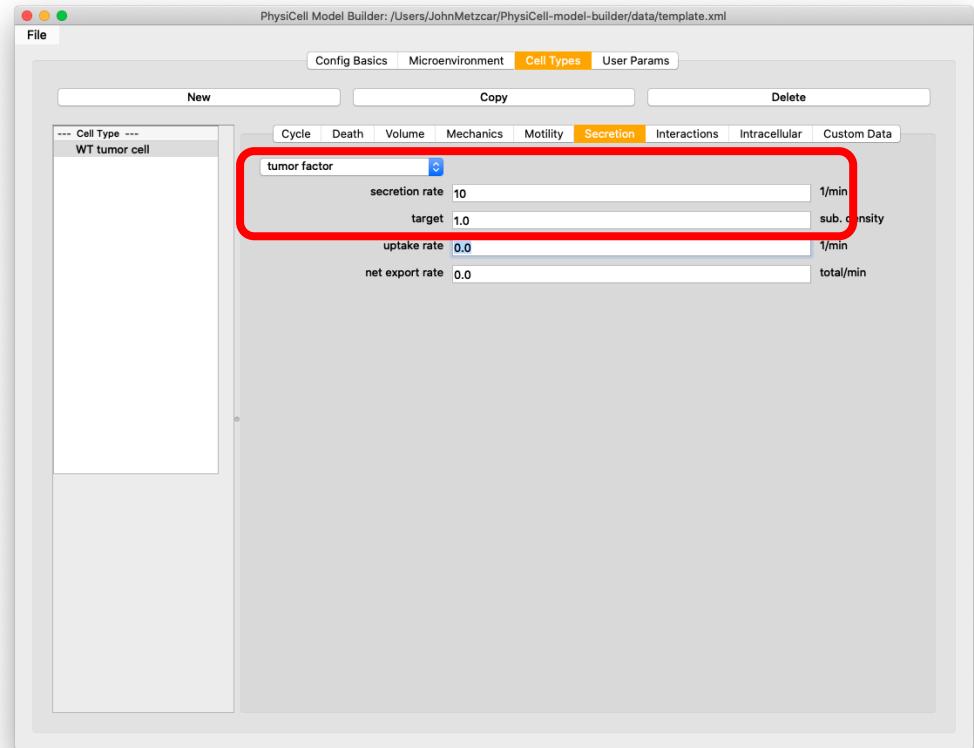
# Define WT tumor cells

- Go to the **cell types** tab
- Double-click on **default**
  - Rename to **WT tumor cell**
- Go to **Secretion**
  - Choose **oxygen** from drop-down
    - ◆ Set uptake rate to 10
      - » 100  $\mu\text{m}$  length scale in packed tissue
    - Choose **tumor factor** from drop-down
      - ◆ Set secretion rate to 10
      - ◆ Set target to 1



# Define WT tumor cells

- Go to the **cell types** tab
- Double-click on **default**
  - Rename to **WT tumor cell**
- Go to **Secretion**
  - Choose **oxygen** from drop-down
    - ◆ Set uptake rate to 10
      - » 100  $\mu\text{m}$  length scale in packed tissue
    - Choose **tumor factor** from drop-down
      - ◆ Set secretion rate to 10
      - ◆ Set target to 1



# Test the model!

- Go to the **user params** tab
  - Set **number of cells** to 25

- Save as:

PhysiCell\_settings\_Ex2\_1.xml (if not done already)

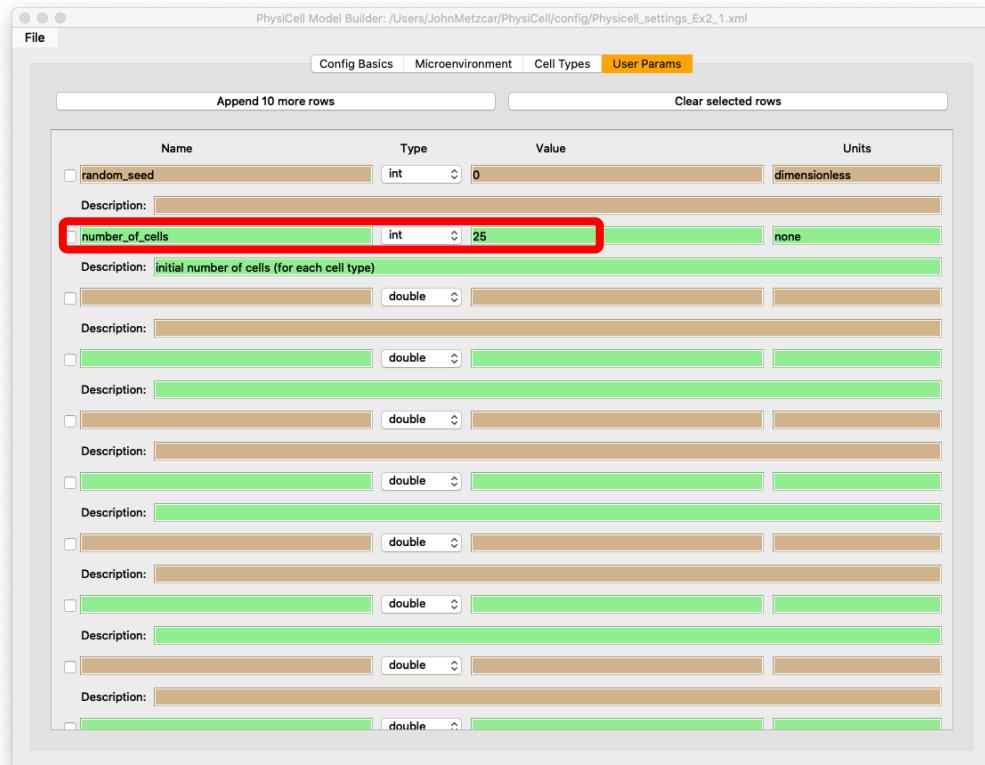
- run the model

( Windows user )

```
.\project.exe .\config\PhysiCell_settings_Ex2_1.xml
```

( OSX user )

- ./project config/PhysiCell\_settings\_Ex2\_1.xml



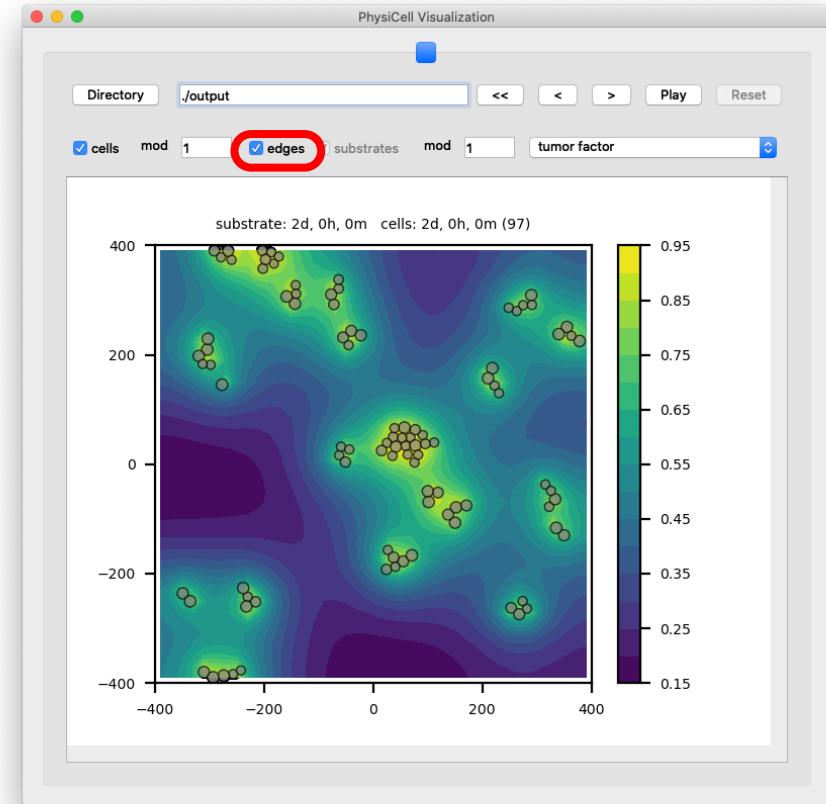
# View the results

- To see the results run:

```
python .\beta\plot_data.py (Windows)
```

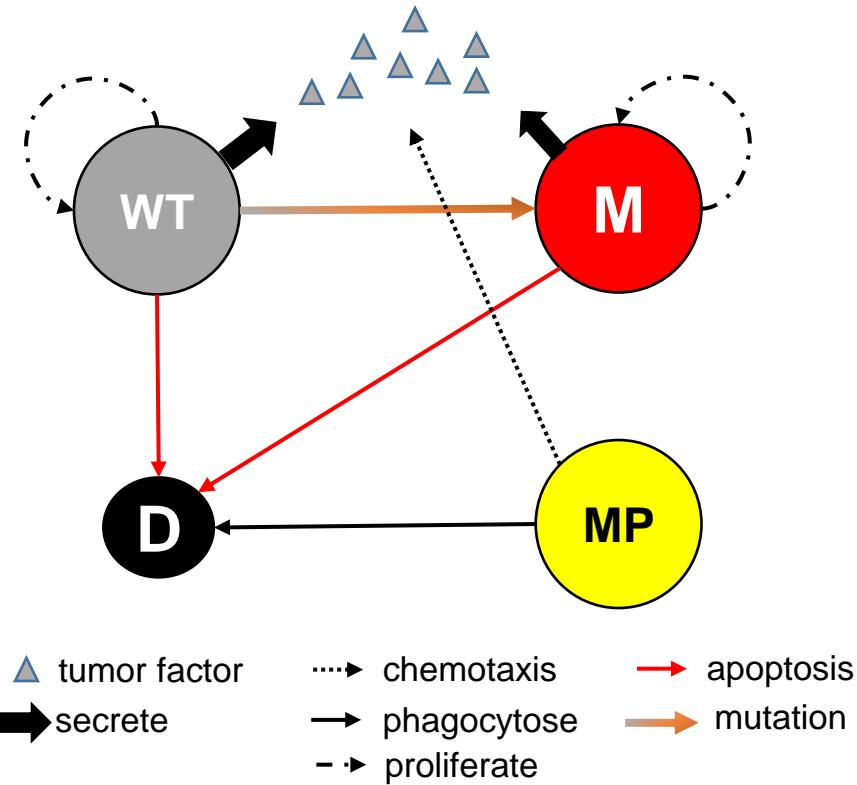
```
python beta/plot_data.py (Mac)
```

- Click **play** to automatically animate
- Click < or > to advance by 1 frame
- Click << to go to the start
- Check the edges to apply cell contours.
- Use the drop-down to change the substrate.



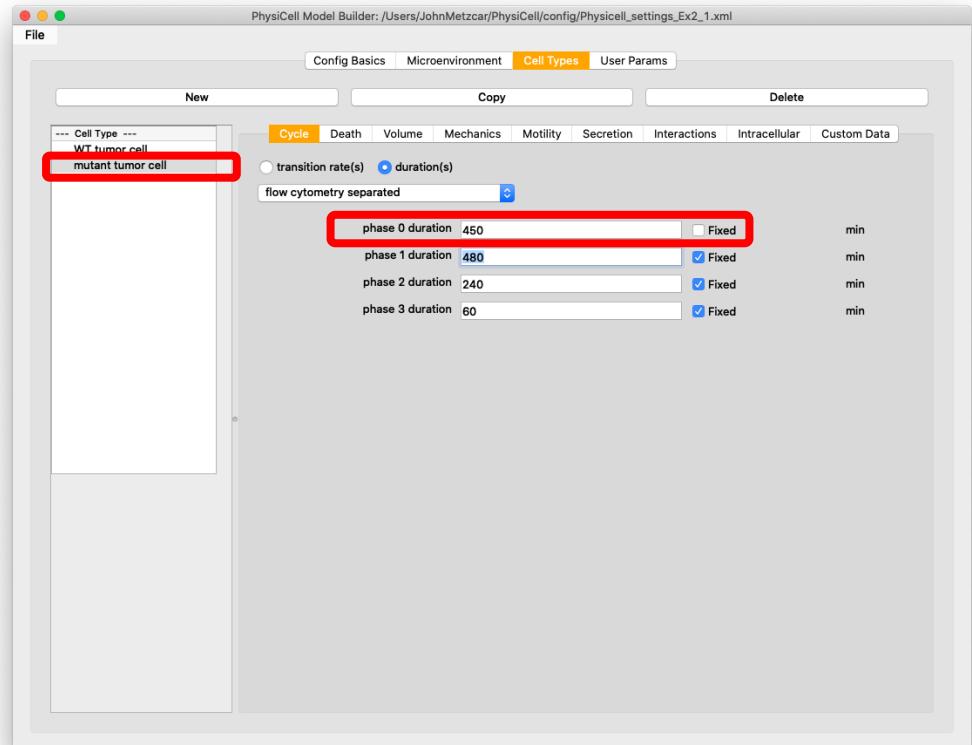
# Checklist

- Build iteratively:
  - Set the domain
  - Add diffusing substrates
  - Add WT tumor cells and test
  - Add mutant tumor cells and test
  - Add transition from WT to mutant cells
  - Add macrophages and test



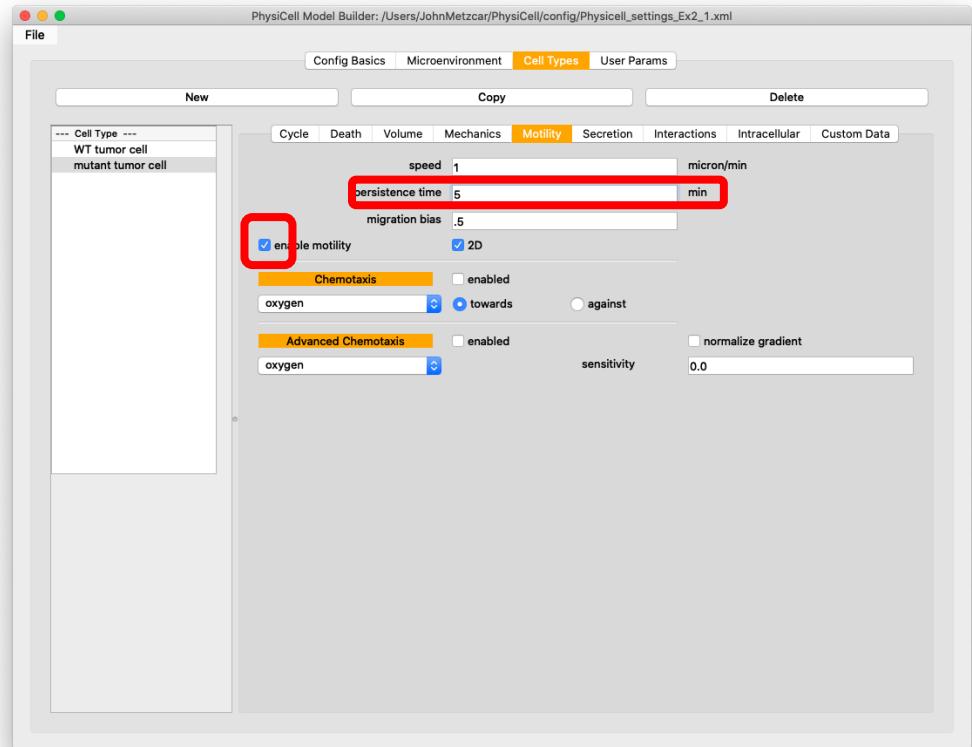
# Define mutant tumor cells (1)

- Go to the **cell types** tab
- Click on **WT tumor cell**
- Copy the cell type
  - Rename it to **mutant tumor cell**
- Reduce cycling
  - Click on the **cycle** tab
  - Increase time in G0/G1 to **450** min.



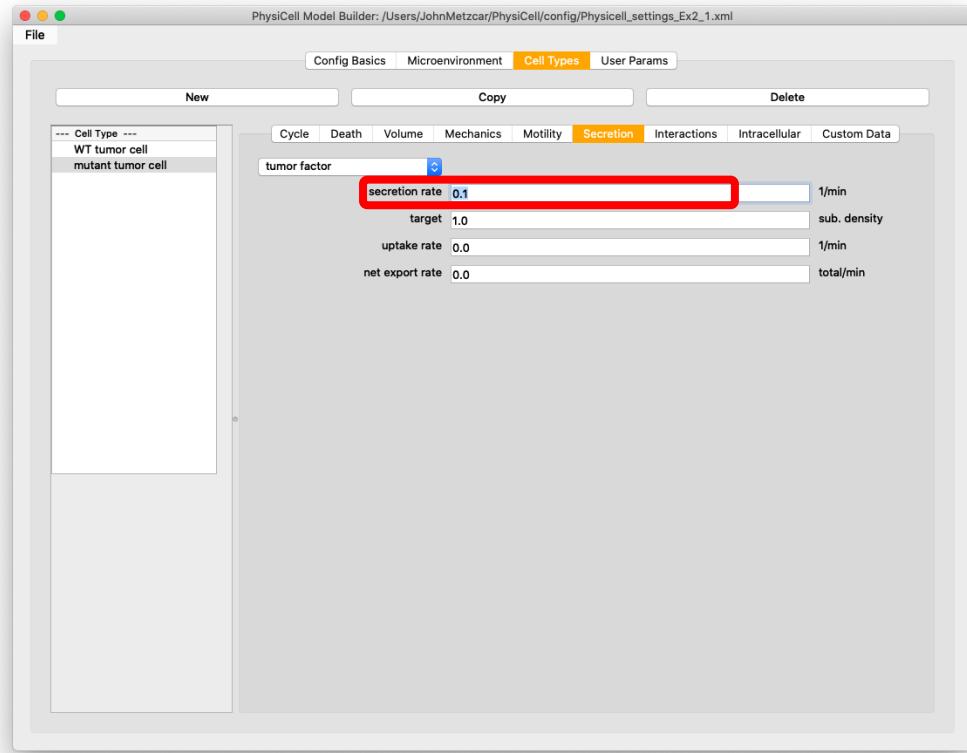
# Define mutant tumor cells (2)

- Turn on random motility
  - Click on the **motility** tab
  - Leave mean speed at **1  $\mu\text{m}/\text{min}$**
  - Set persistence time to **5 min**
  - Leave bias at 0.5
    - ◆ (doesn't affect this result)
  - Make sure to click the checkbox to enable motility!



# Define mutant tumor cells (3)

- Reduce tumor factor secretion
  - Click on the **secretion** tab
  - Choose **tumor factor** from the drop-down menu
  - Set the value to **0.1**



# Test the model!

- Save as:

PhysiCell\_settings\_Ex2\_2.xml

- Run the model

( Windows user )

```
\project.exe .\config\PhysiCell_settings_Ex2_2.xml
```

( OSX user )

```
./project config/PhysiCell_settings_Ex2_2.xml
```

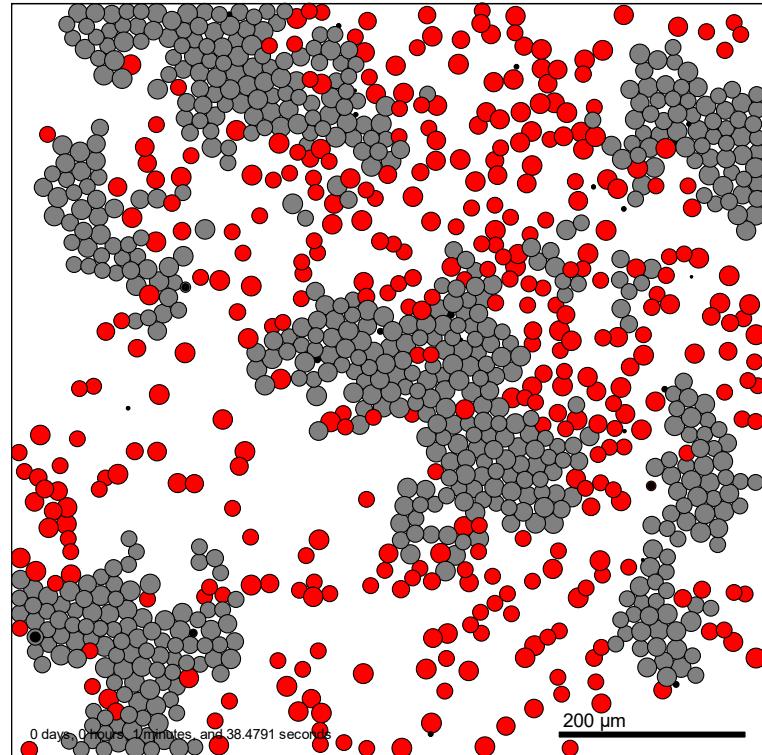
- Visualize the results via the **output** folder or PhysiCell Visualization (see previous slides)

- Grey: WT tumor cells
- Red: mutant tumor cells
- See the **legend** tab to verify colors

- Notice:

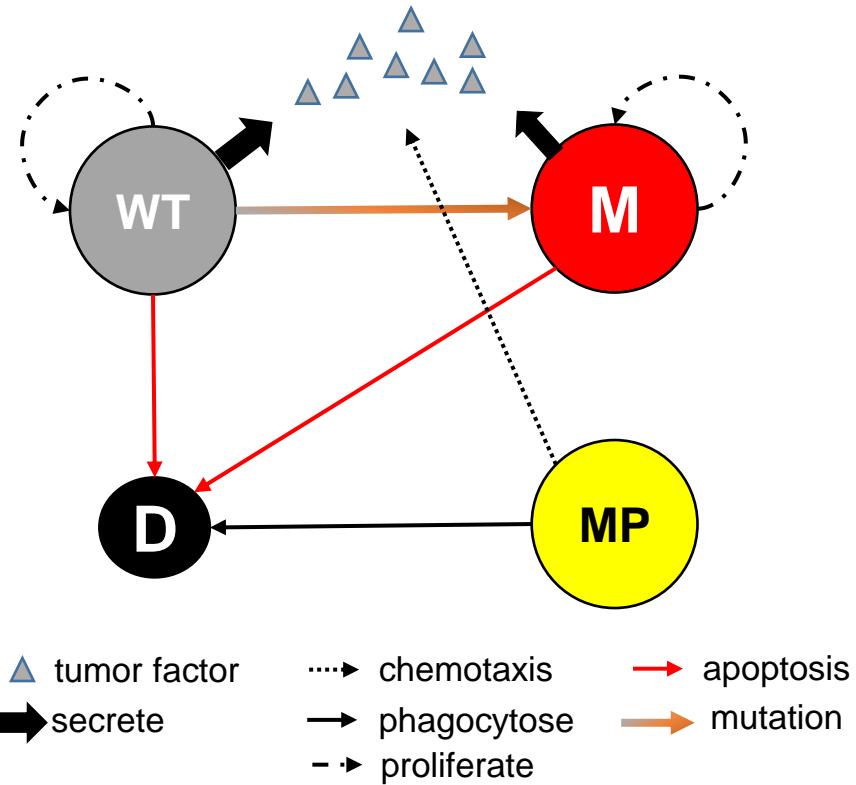
- Red cells are motile
- Red cells proliferate more slowly
- Grey cells dominate population at day 4

Current time: 4 days, 0 hours, and 0.00 minutes, z = 0.00 µm  
1025 agents



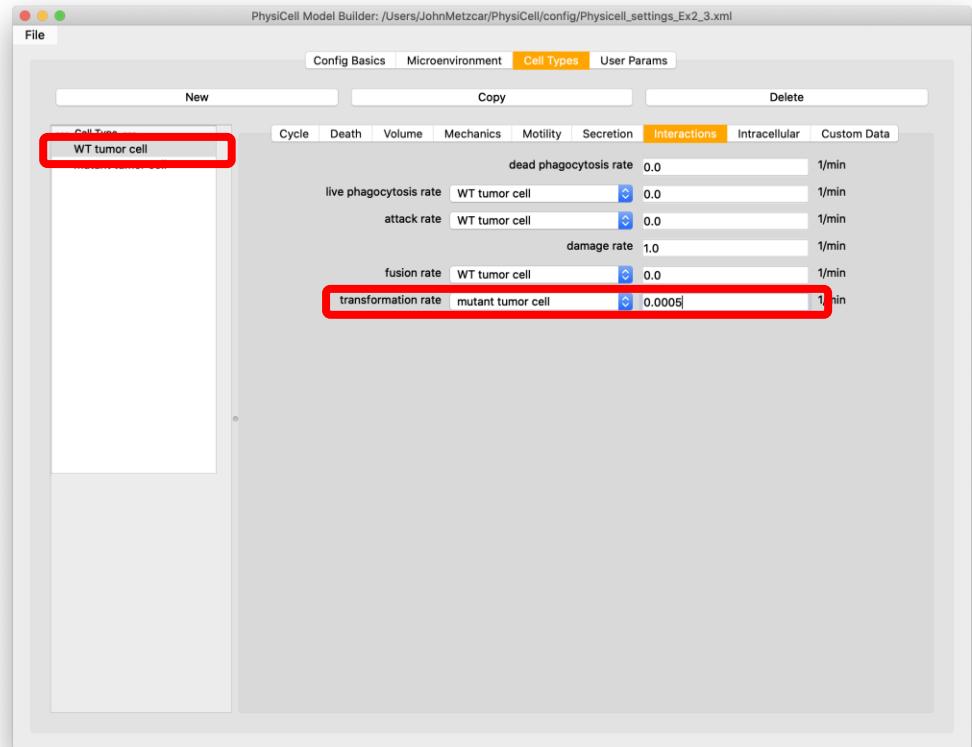
# Checklist

- Build iteratively:
  - Set the domain
  - Add diffusing substrates
  - Add WT tumor cells and test
  - Add mutant tumor cells and test
  - Add transition from WT to mutant cells
  - Add macrophages and test



# Enable mutations

- Select the **WT tumor cell** type
- Go to the **interactions** tab
- Go to **transformation rate**
- Choose **mutant tumor cell** from the drop-down
- Set the rate to **0.0005**



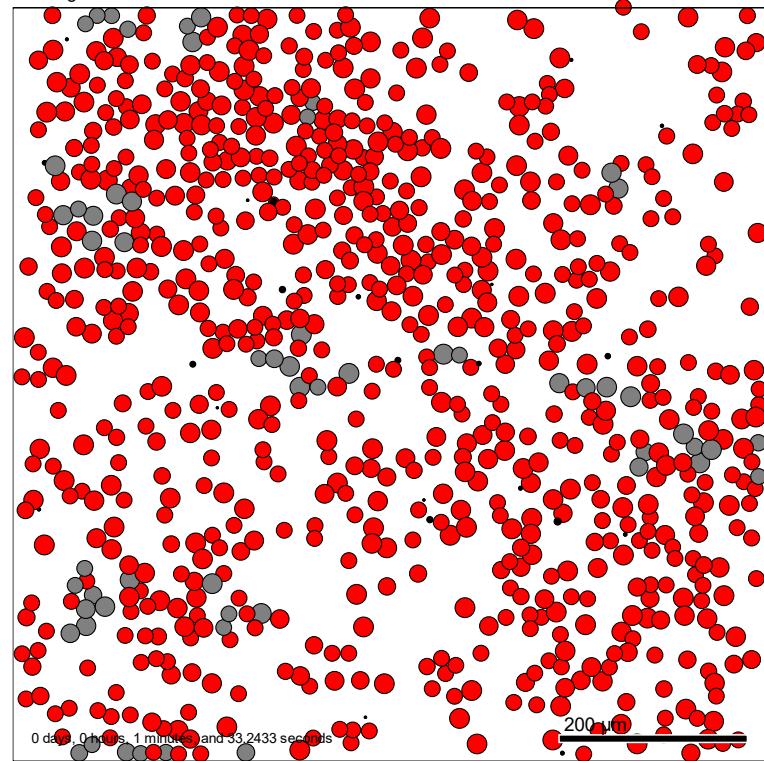
# Test the model!

- Save as:  
PhysiCell\_settings\_Ex2\_3.xml
- Run the model

```
( Windows user )  
\project.exe ./config/PhysiCell_settings_Ex2_3.xml  
  
( OSX user )  
../project config/PhysiCell_settings_Ex2_3.xml
```

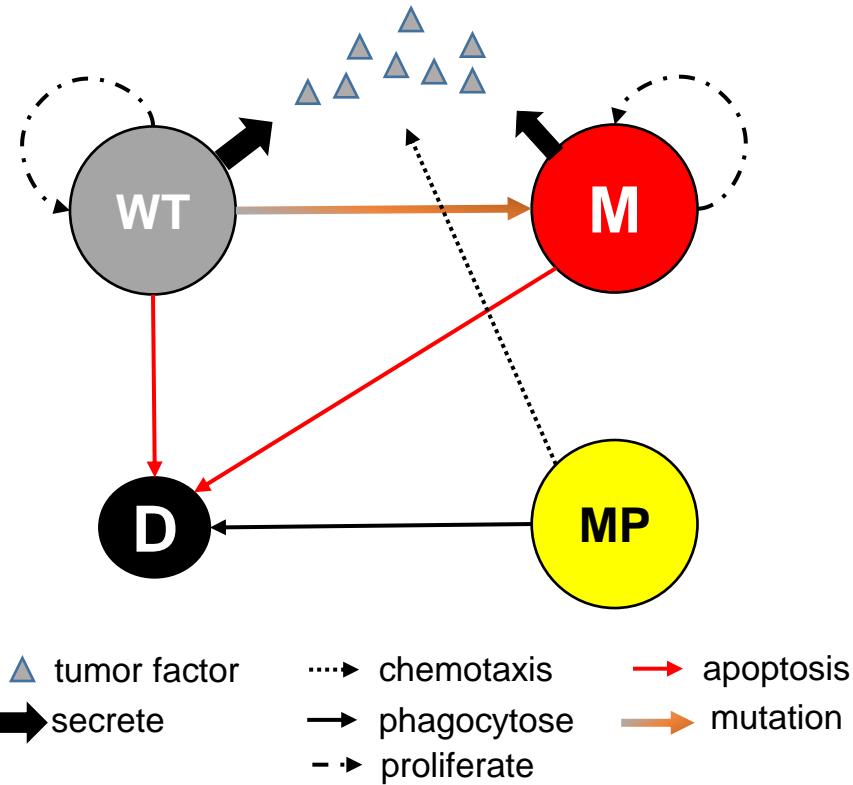
- Visualize the results via the **output** folder or PhysiCell Visualization (see previous slides)
  - Grey: WT tumor cells
  - Red: mutant tumor cells
  - See **legend.svg** to verify colors
- Notice:
  - Red cells are motile
  - Red cells proliferate more slowly
  - Grey cells turn to red cells
  - Red cells dominate the population at Day 4

Current time: 4 days, 0 hours, and 0.00 minutes, z = 0.00  $\mu\text{m}$   
831 agents



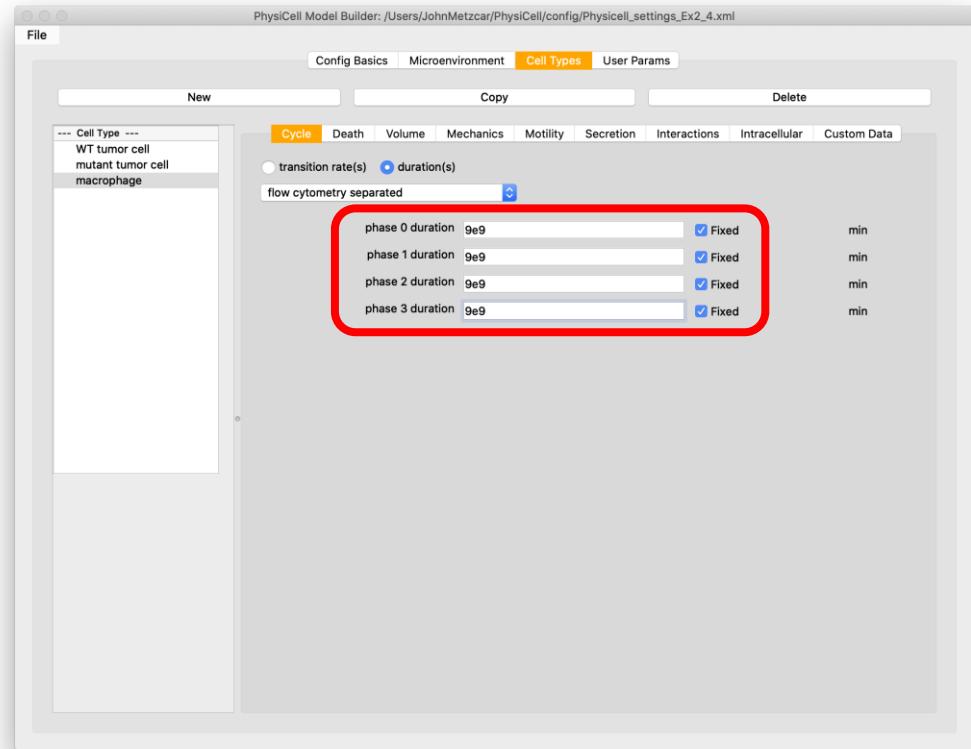
# Checklist

- Build iteratively:
  - Set the domain
  - Add diffusing substrates
  - Add WT tumor cells and test
  - Add mutant tumor cells and test
  - Add transition from WT to mutant cells
  - Add macrophages and test



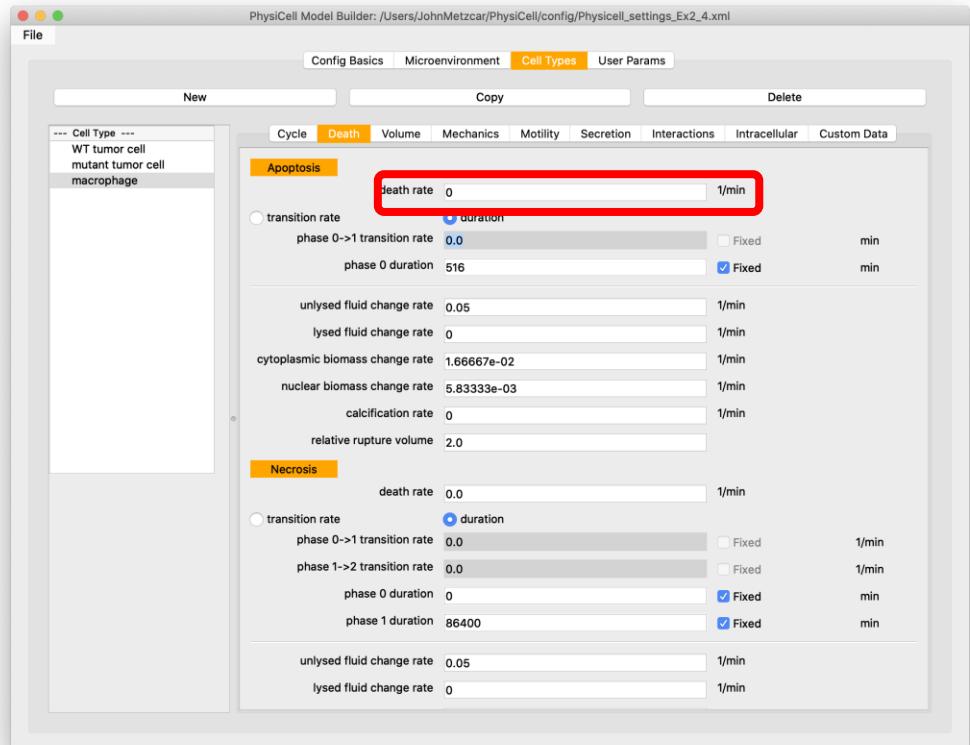
# Define macrophages (1)

- Go to the **cell types** tab
- Click on **mutant tumor cell**
- Copy the cell type
  - Rename it to **macrophage**
- Disable cycling
  - Click on the **cycle** tab
  - Increase time in G0/G1 to **9e9** min with **fixed duration**



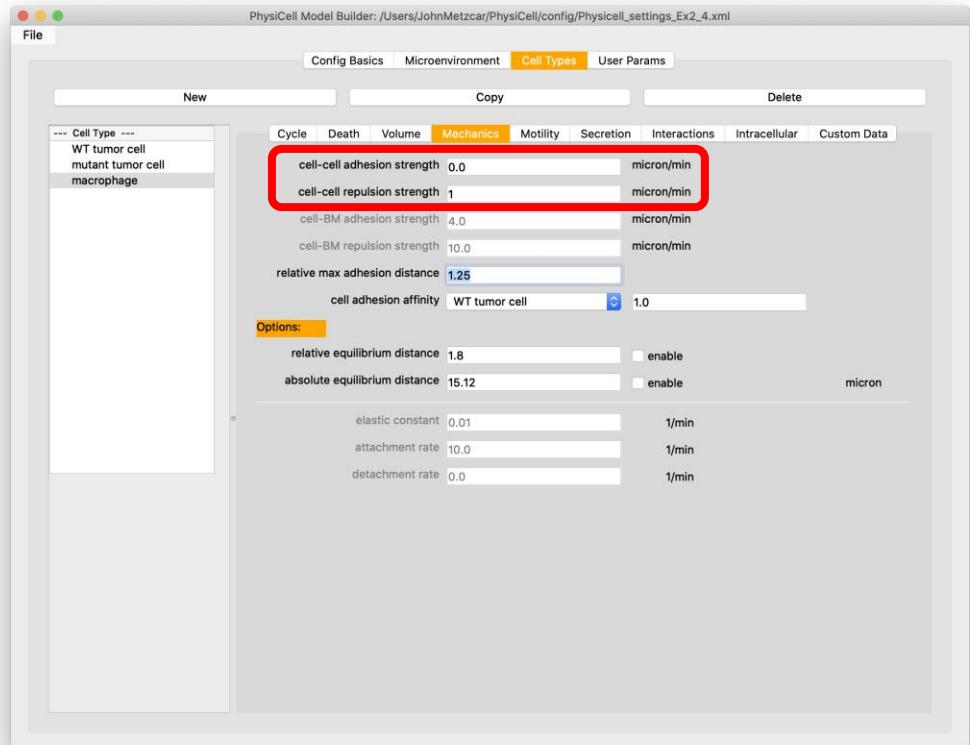
# Define macrophages (2)

- Disable apoptotic death
  - Click on the **death** tab
  - Go to the section on **apoptosis**
  - Set the **death rate** to **0**



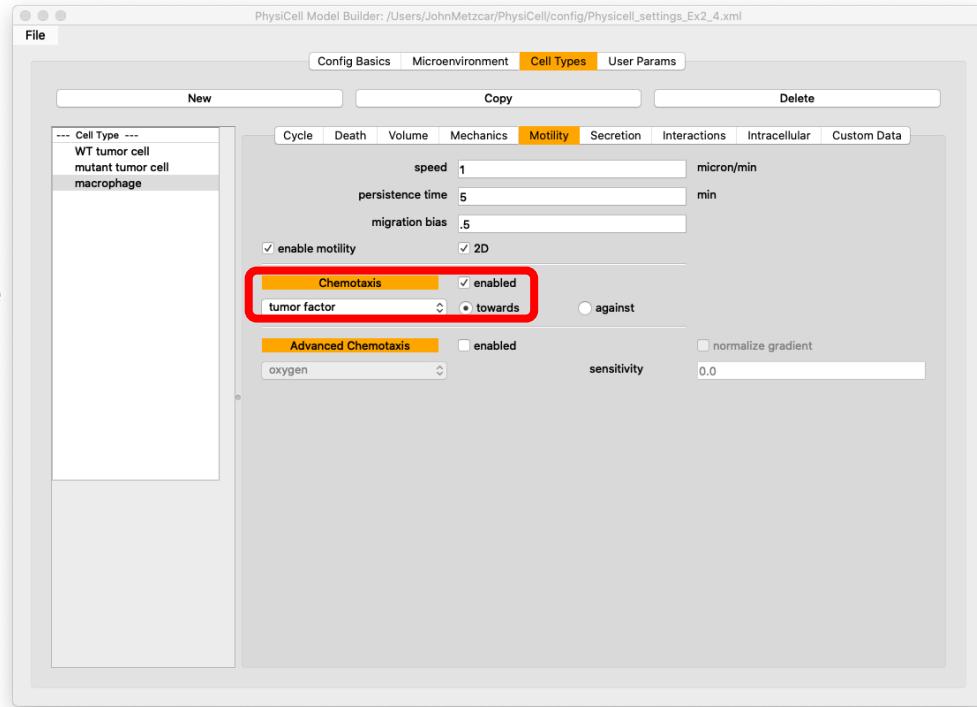
# Define macrophages (3)

- Disable adhesion
  - Click on the **mechanics** tab
  - Set **cell-cell adhesion** to **0**
- Make the cells more deformable (allow more overlap)
  - Click on the **mechanics** tab
  - Set **cell-cell repulsion** to **1**



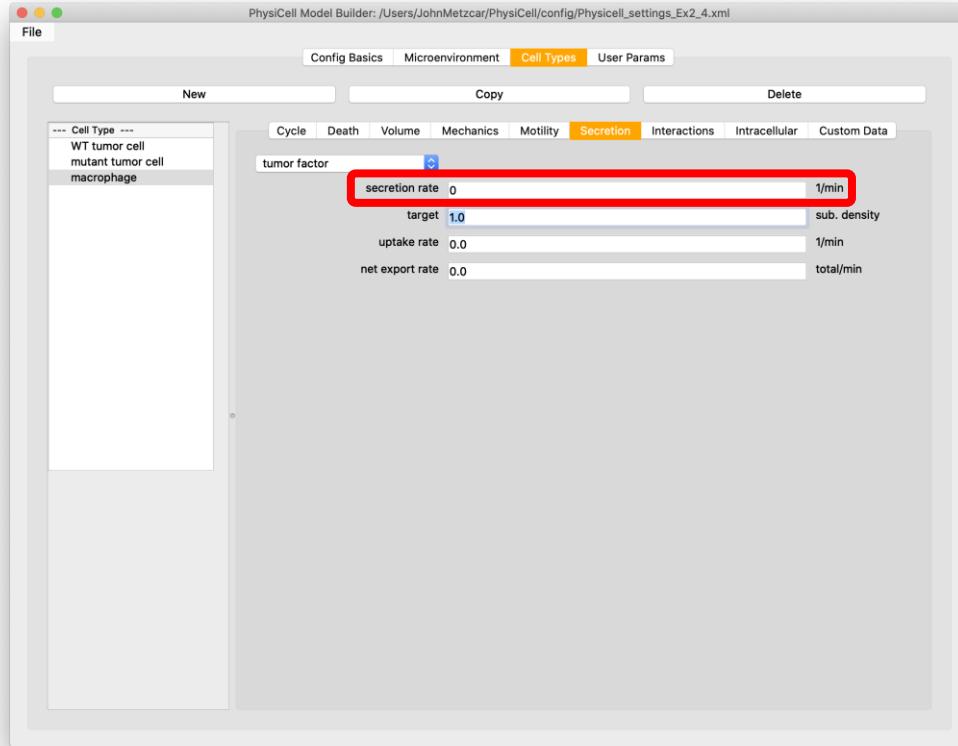
# Define macrophages (4)

- Turn on chemotaxis up both debris and tumor factor
  - Click on **motility**
  - Set **migration bias** at **0.5**
  - Make sure motility is enabled with the checkbox
  - Go to **chemotaxis**
  - Choose **tumor factor** in the drop-down
  - Make sure you click the checkbox to enable chemotaxis



# Define macrophages (5)

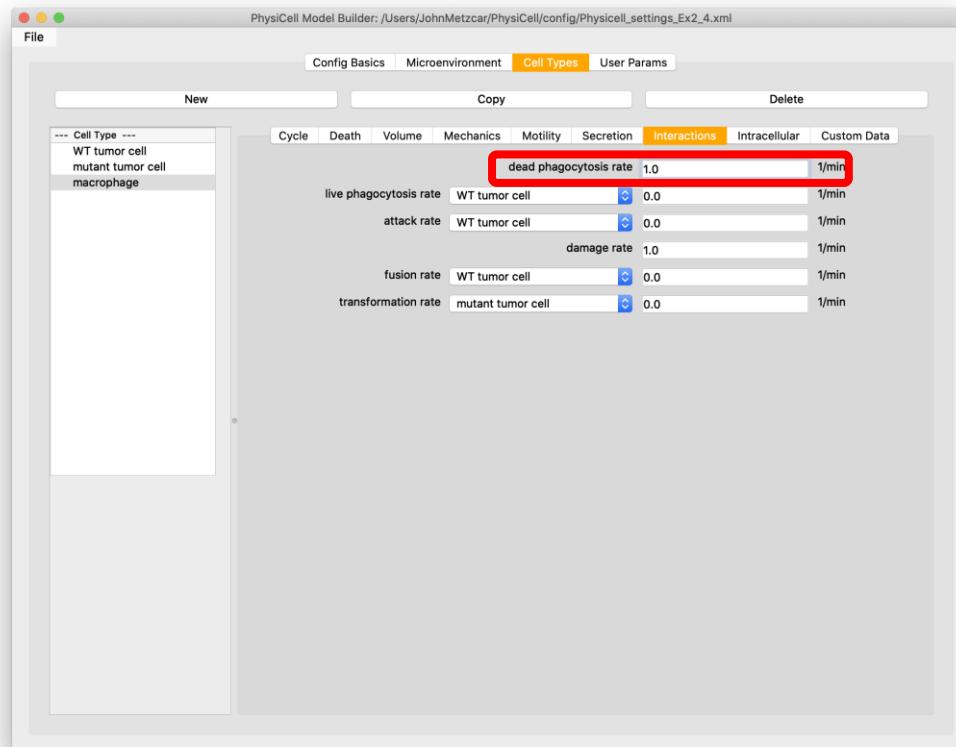
- Turn OFF secretion
  - Click on **Secretion**
  - Select **tumor factor**
  - Set **secretion rate** to 0.0



# Define macrophages (6)

- Enable phagocytosis of dead cells
  - Click on **interactions**
  - Set the **dead phagocytosis rate** to 1

**Note:** If the dead cell phagocytosis rate is  $r$ , then the mean time the macrophage spends in contact with a dead cell before phagocytosing it is  $\frac{1}{r}$ .



# Test the model!

- Save as:

PhysiCell\_settings\_Ex2\_4.xml

- Run the model

( Windows user )

```
\project.exe .\config\PhysiCell_settings_Ex2_4.xml
```

( OSX user )

```
./project config/PhysiCell_settings_Ex2_4.xml
```

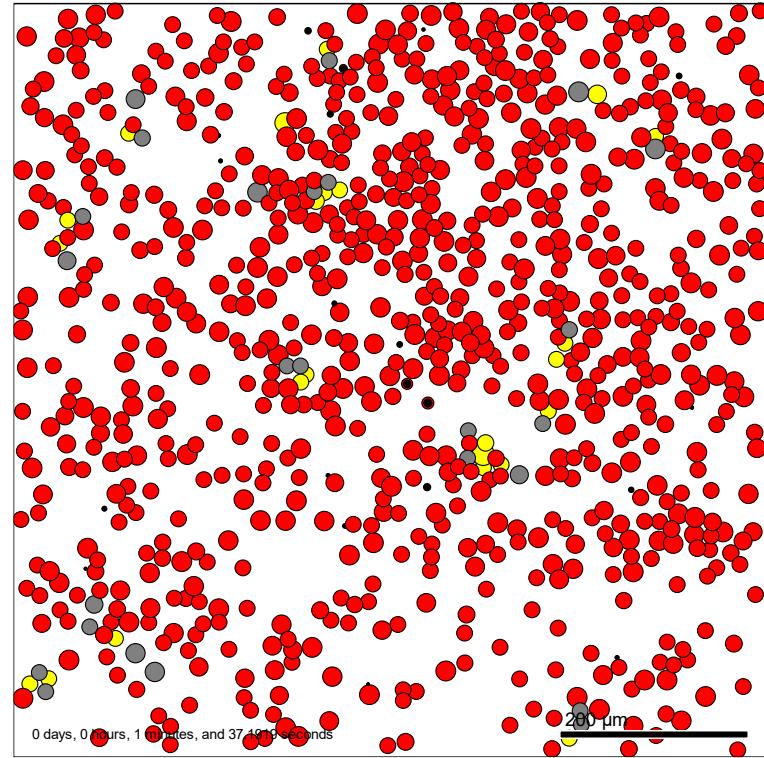
- Visualize the results via the **output** folder or PhysiCell Visualization (see previous slides)

- Grey: WT tumor cells
- Red: mutant tumor cells
- Yellow: macrophages
- See **legend.svg** to verify colors

- Notice:

- Yellow cells will co-localize with tumor cells, with a preference for grey.

Current time: 4 days, 0 hours, and 0.00 minutes, z = 0.00  $\mu\text{m}$   
858 agents



# Session 4: Intermediate modeling workflow

- Goals:
  - Introduce the intermediate modeling workflow → **Both Examples 1 and 2**
    - ◆ Use PhysiCell model builder and implement models based on **template project**
  - Demonstrate implementation of the following:
    - ◆ Creating a simulation **domain**
    - ◆ Creating a **substrate**
      - » Neuman boundary conditions
      - » Dirichlet boundary conditions
    - ◆ Creating a **cell definition**
    - ◆ Constituting cell interactions and behaviors:
      - » Cell **secretion**
      - » Cell **uptake**
      - » Cell **birth** and **death**
      - » **Cell cycle models**
      - » **Motility** and **Chemotaxis**
      - » **Phagocytosis**
      - » Cell **mutation/transition**

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  - ◆ Creating a ~~substrate~~
    - » Neuman boundary conditions → **Example 1**
    - » Dirichlet boundary conditions → **Example 2**
  - ◆ Creating a ~~cell definition~~
    - ◆ Constituting cell interactions and behaviors:
      - » Cell secretion → **Examples 1 and 2**
      - » Cell birth and death → **Examples 1 and 2**
      - » Phagocytosis → **Examples 1 and 2**
      - » Cell cycle models → **Examples 1 (live and dead) and 2 (flow cytometry separated)**
      - » Motility and Chemotaxis → **Examples 1 (advanced chemotaxis) and 2 (regular chemotaxis and random motility)**
      - » Cell mutation/transition → **Example 2**
      - » Cell uptake → **Example 2**

# Funding Acknowledgements



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- National Science Foundation (1720625, 1818187)

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- NIH Common Fund (3OT2OD026671-01S4)