Slides, videos, links and more:
https://github.com/physicell-training/ws2021

Session 5: A complete example (interactive)

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PhysiCell Project

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Goals

- Review the "intermediate" modeling workflow
- Build a model from start to finish
  - State the problem
  - Plan the model
  - Adapt the "template" project with Model Builder
  - Run and view results
- Explore the model (time permitting)
  - Change domain and cell placement
  - Contrast non-stochastic and stochastic proliferation rates

Intermediate modeling workflow

Suitable for creating a new PhysiCell model without writing custom C++ (no dynamical phenotype changes)

- Plan the model
- Populate and build the template project
- Edit configuration with Model Builder GUI
  - Edit domain
  - Edit microenvironment
  - Edit cell definitions
- Run
- View and evaluate results

Biological/Conceptual model

- Steps in Carcinogenesis Model
  - Diseased cells/tissue develops from healthy tissue
  - Let's think about starting with a non-cancerous ("wild-type") cell type:
    - Wild-type:
      - » Non-motile, slowly dividing adhesive cells
  - Progressively enable small changes in behavior forming 3 aberrant cell types:
    - Hyperplastic type:
      - » Increased proliferation
    - Cancerous type:
      - » Less adhesive, motile, fast dividing cells
    - Aggressive cancer type:
      - » Resource driven, very quickly dividing cells

Biological/Conceptual model

- Microenvironment
  - If we are going to have resource driven cells, we need to have a resource for the cells to seek
    - Consider a surrogate for nutrient for cancers: oxygen
- Domain
  - At this point in time, there are not obvious restrictions on the domain nor are we talking about a particular shape of tissue

Mathematical Model

- Need to translate the conceptual model into a quantitate or rules-based model
- Note - there are multiple layers of influence on cell behavior:
  - Gene mutations and/or changes in gene expression for examples
  - For this model, we simplify to the level of what might be observed by looking at cells only: growth rates, cell speed, etc
- By implementing this model, we can evaluate which behaviors of the simulated cells and cell populations match our expectations, and which don't

Mathematical Model

- Wild-type
  - low homeostatic proliferation rate/long cycle duration: 1440 min
  - High cell-cell adhesion: adhesion = 0.5
  - Non-motile: speed = 0
- Hyperplastic (overgrowing but not leaving)
  - Elevated proliferation rate/decrease cycle duration: 1080 min
  - High cell-cell adhesion: adhesion = 0.5
  - Non-motile: speed = 0
- Cancer
  - Elevated proliferation rate/decreased cycle duration: 900 min
  - High cell-cell adhesion: adhesion = 0.4
  - Motile: speed = 0.2 um/min
- Aggressive cancer
  - Elevated proliferation rate/decreasee cycle duration: 720 min
  - High cell-cell adhesion: adhesion = 0.4
  - Motile: speed = 0.2 um/min
  - Resource seeking – chemotactic with noticeable bias (0.25)

Note that in the interests of time – I have selected very short cycle times. This is so we get results quickly and have low run times – in the real world, the rates would be what was appropriate given modeling goals and available information

Mathematical Model

- Microenvironment
  - Model resource as oxygen, noting that other resources could be good surrogates
    - D = 100,000 um^2/min
    - Decay = 10 /min
      - Set by length scale
- Initial and boundary conditions
  - Chemical
    - Initial condition – 0 mmHg
    - Want to ensure gradient – set constant value BC at a reasonable value: BC = 38 mmHg
  - Cells
    - Many configurations of cells are reasonable for what is conceived of as mimicking almost an in vitro experiment
      - Random placement in domain of 2 cells per type
- Domain
  - 2-D
  - 500 um by 500 um

Questions?

Implementation Tools: PhysiCell and PhysiCell Model Builder

- We assume you have setup your system
  - Also, for some commands to run directly as written in the slides, the **PhysiCell** and **PhysiCell-model-builder** directories need to be at the same level/within the same directory
- Below are resources to obtain and install all necessary software for the rest of the tutorial:
  - Download PhysiCell 1.9.0 or later
    - http://PhysiCell.org/download
  - Download the PhysiCell model-builder GUI:
    - https://github.com/PhysiCell-Tools/PhysiCell-model-builder
  - Follow the setup tutorials
    - **QuickStart**: https://github.com/MathCancer/PhysiCell/blob/master/documentation/Quickstart.md
    - **MacOS**
      - Slides: https://github.com/physicell-training/ws2021/blob/main/pdfs/PhysiCell_ws2021_macOS_setup.pdf
      - Video: https://www.youtube.com/watch?v=mv_phTdanws
    - **Windows**
      - Slides: https://github.com/physicell-training/ws2021/blob/main/pdfs/PhysiCell_ws2021_Windows_setup.pdf
      - Video: https://www.youtube.com/watch?v=Jp3ZOMt761M

Implementation: Start Tools

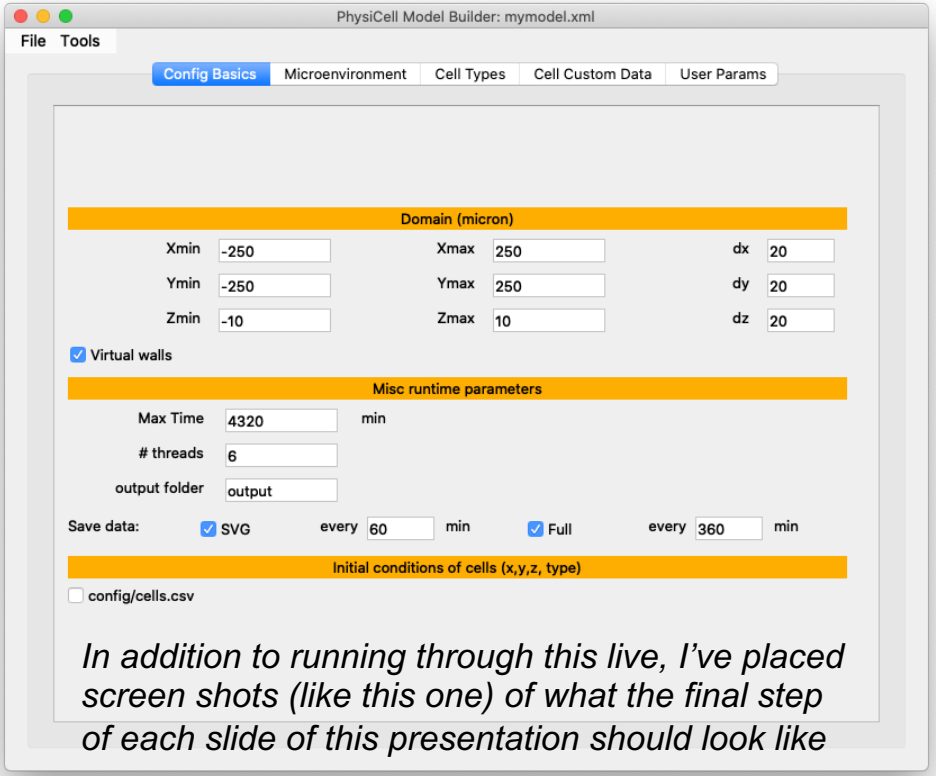
- Setup and build the template project
  - Open a terminal/shell and navigate to your **PhysiCell** directory
  - Enter the following
    - `make reset`
    - `make data-cleanup #Note this will remove everything in /output`
    - `make template`
    - `make`
- Open Model Builder GUI
  - Open a second terminal/shell and navigate to the **PhysiCell/config**
  - `python ../../PhysiCell-model-builder-1.1/bin/gui4xml.py` *

*This assumes 1) that the Model Builder and PhysiCell folders are within the same directory at the same level in the file tree. 2) You have downloaded Model Builder Release 1.1. *Modify this command as needed to start the Model Builder.*

Implementation: Set up domain

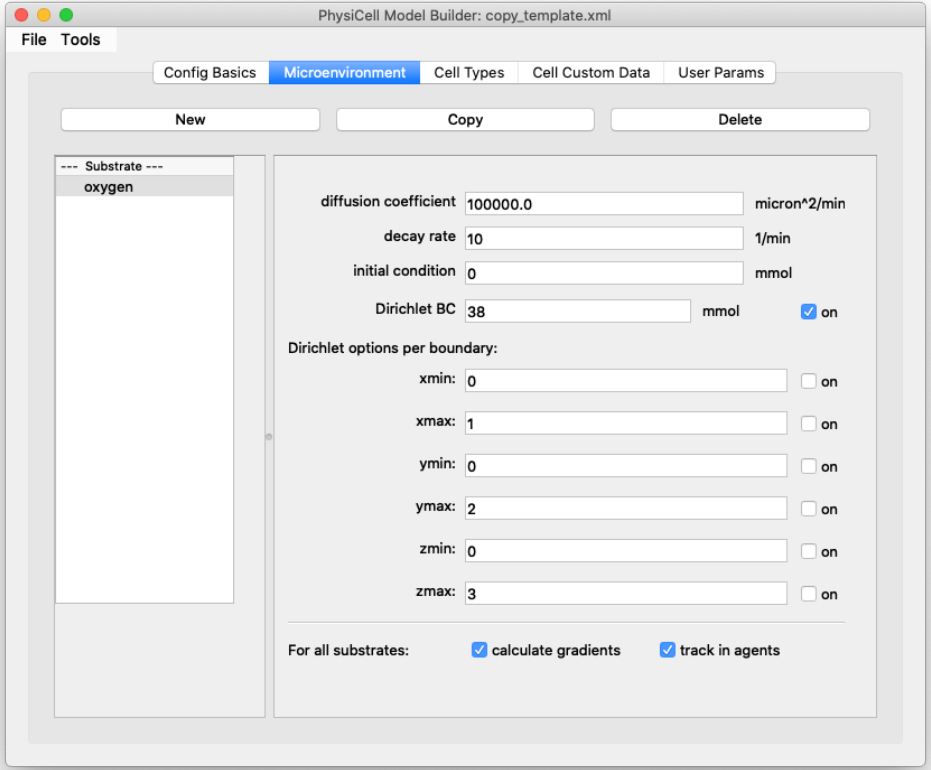
- Go to “Config Basics" tab*
  - Computational domain
  - Simulation time, output control, threading
  - Initial placement of cells
- Our domain
  - Square
  - Want long enough sim time that we see dynamics: 3 days
- Make your settings match those to the right:
  - Altered parameters/settings
    - Xmin: **-250**, Xmax: **250**, Ymin: **-250**, Ymax: **250**
      - » keep cells from leaving the domain
    - activate "virtual wall"
    - max time: **4320 min**

*Note these screen shots are from a Mac. Expect that each operating system may have a slightly different appearance.



Implementation: Set up microenvironment

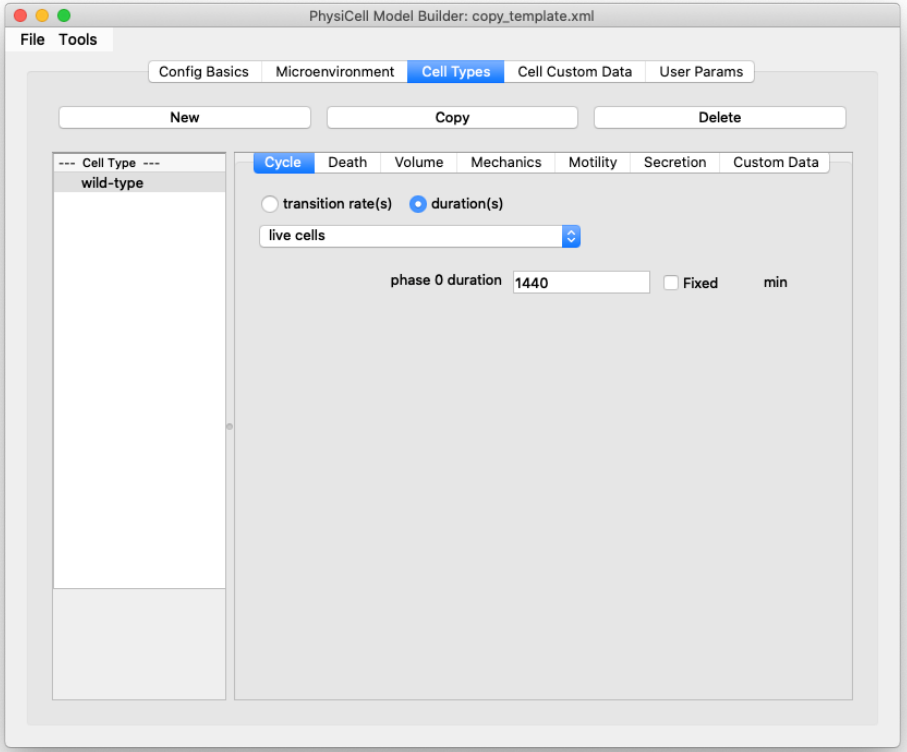
- Go to ”Microenvironment" tab
  - Used to create diffusing substrates/chemicals
  - Sets diffusion and decay rates
  - Sets initial and boundary conditions (on a boundary by boundary basis)
- Set up *oxygen*
  - Double-click "substrate"
    - Rename it oxygen (it has units of mmHg but we can’t change that here)
    - Set Dirichlet BC to 38 mmHg (and enable it!)
    - Other defaults are correct/appropriate



Questions?

Implementation: Set up cell types – wild-type

- Go to ”Cell Types" tab
  - Used to create cell types
  - Gives control over all aspects of cell phenotype
- Set up wild-type cell*
  - Double-click "default"
    - ♦ Rename it ”wild-type"
    - ♦ Click "cycle" subtab
      - » Choose “live cells” cycle model
      - » Set phase 0 duration to **1440** min (1 day cycle time)**
    - ♦ Click ”death" subtab
      - » Set “death rate” to **6.94e-07** (this is 0.1 % of the birth rate)
    - ♦ Click “Mechanics” subtab
      - » Set “cell-cell adhesion strength” to **0.5**
      - » Enable “relative equilibrium distance”



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**Remember that for this example we are setting very high rates to get quick results!!!

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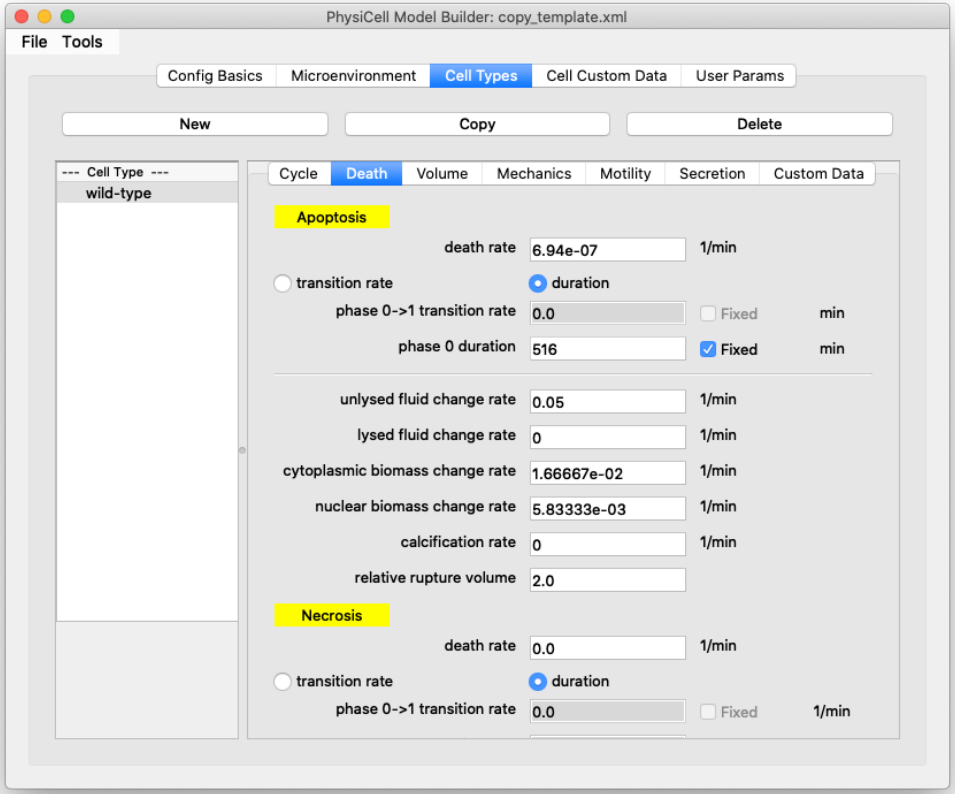

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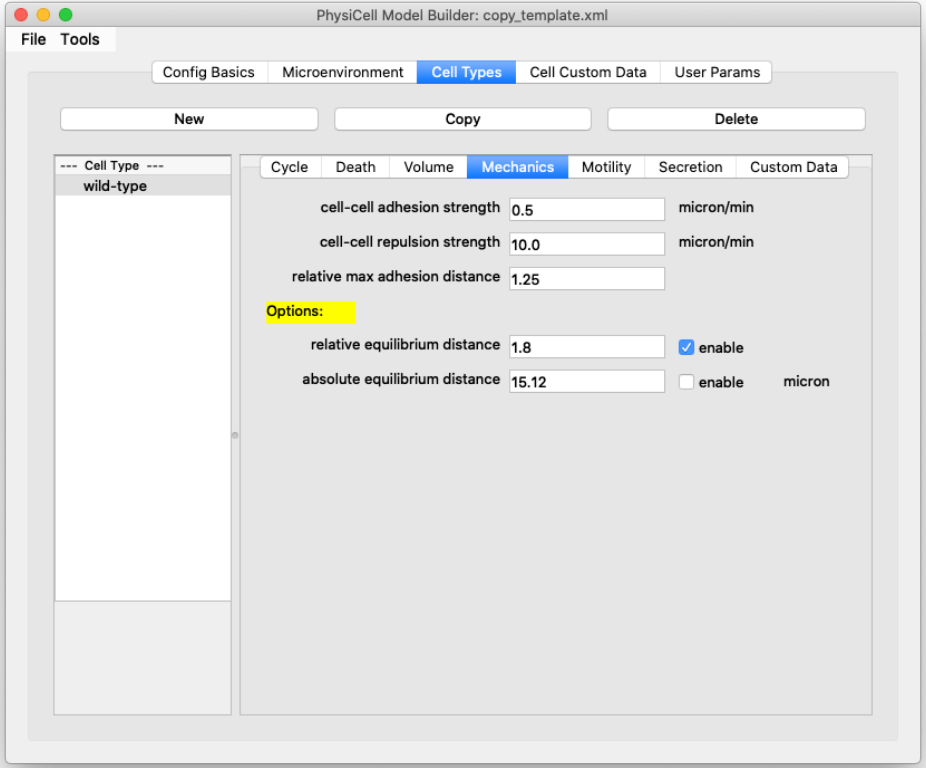

Questions?

Implementation: Set up cell types – hyperplastic

- From within the “Cell Types” tab
  - Click “Copy”
    - Creates a new cell type using parameters of the selected cell type
- Set up hyperplastic cell type
  - Double-click ”cell_def01"
    - Rename it “hyperplastic"
    - Click ”Cycle" subtab
      - » Set phase 0 duration to **1080** min
    - Click “Death" subtab
      - » Set “death rate” to **9.26e-7** (this is 0.1 % of the birth rate)
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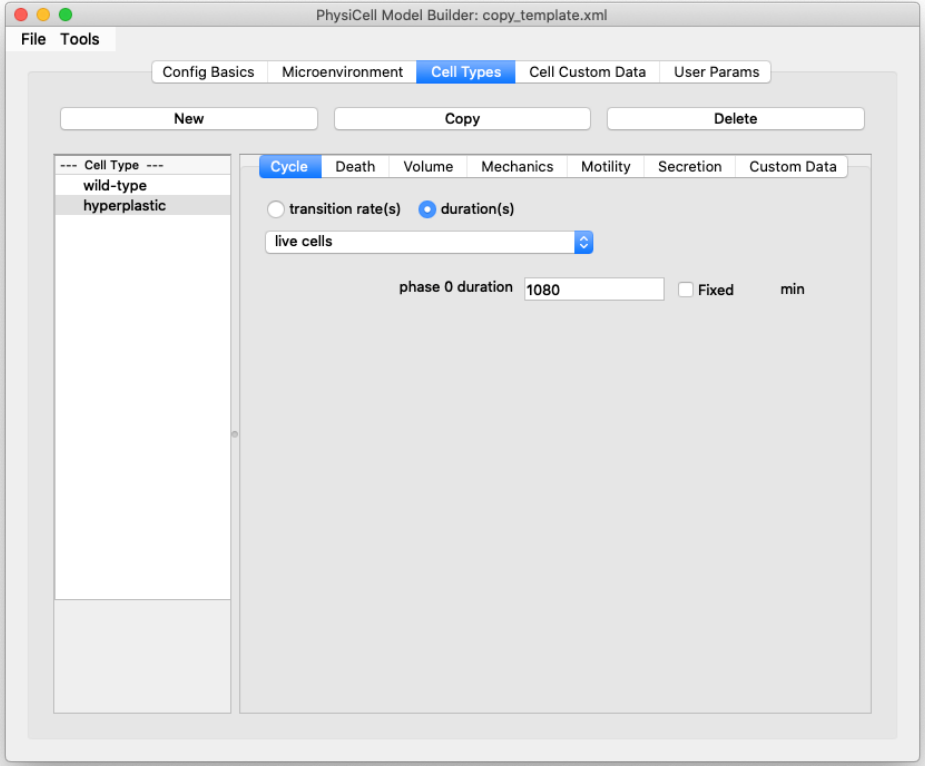

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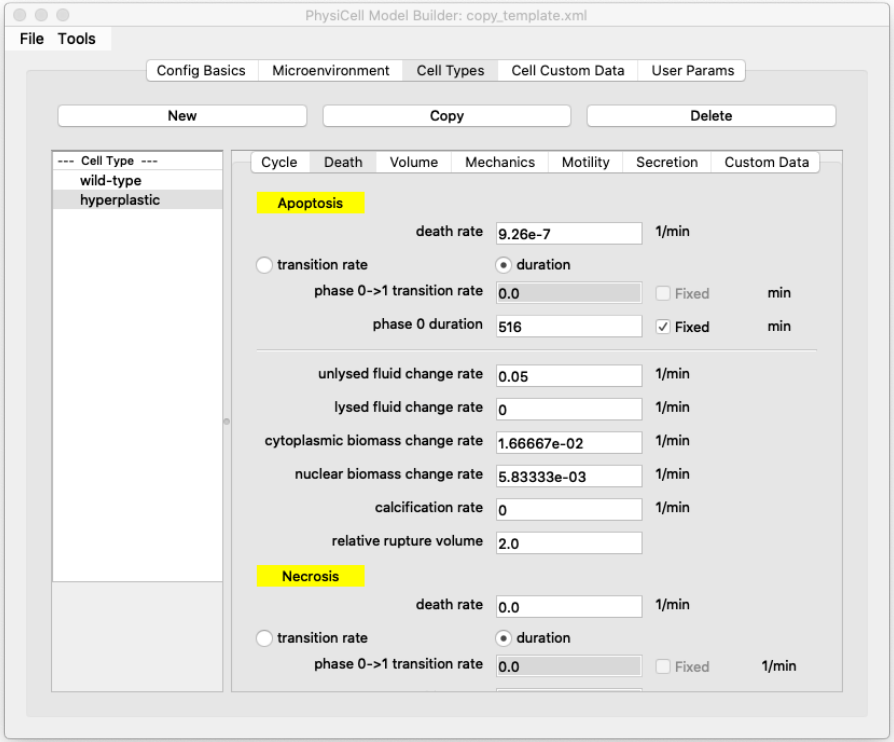

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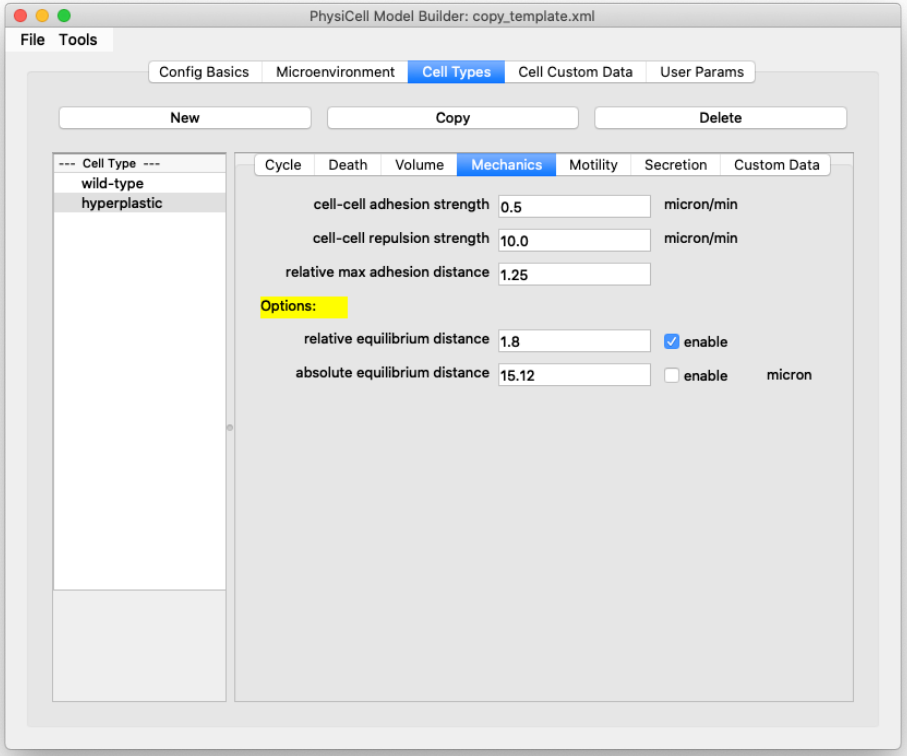
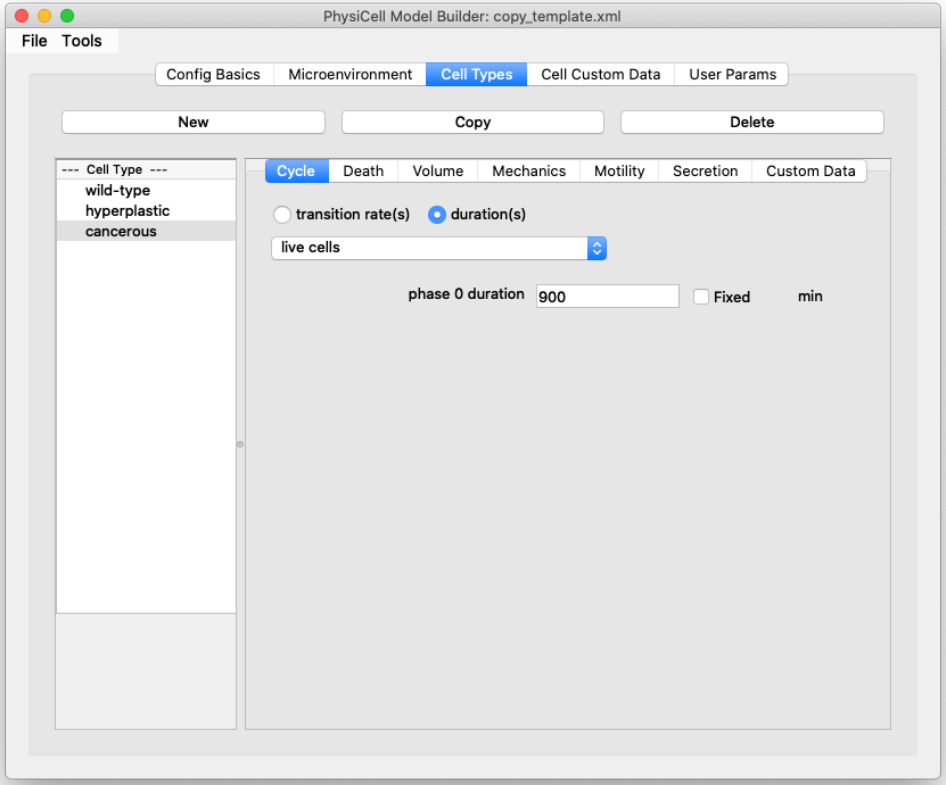


Implementation: Set up cell types – cancerous

- From within the “Cell Types” tab
  - Click “Copy” while “hyperplastic” cell type is selected
- Set up hyperplastic cell type
  - Double-click ”cell_def02"
    - ♦ Rename it “cancerous"
    - ♦ Click ”Cycle" subtab
      - » Set phase 0 duration to **900** min
    - ♦ Click “Death" subtab
      - » Set “death rate” to **1.111e-5** (this is 1.0 % of the birth rate)
    - ♦ Click “Mechanics” subtab
      - » Set “cell-cell adhesion strength” to **0.4**
    - ♦ Click “Motility” subtab
      - » Set “speed” to **0.2**
      - » Set “persistence time to **10**
      - » Click to “enable motility”



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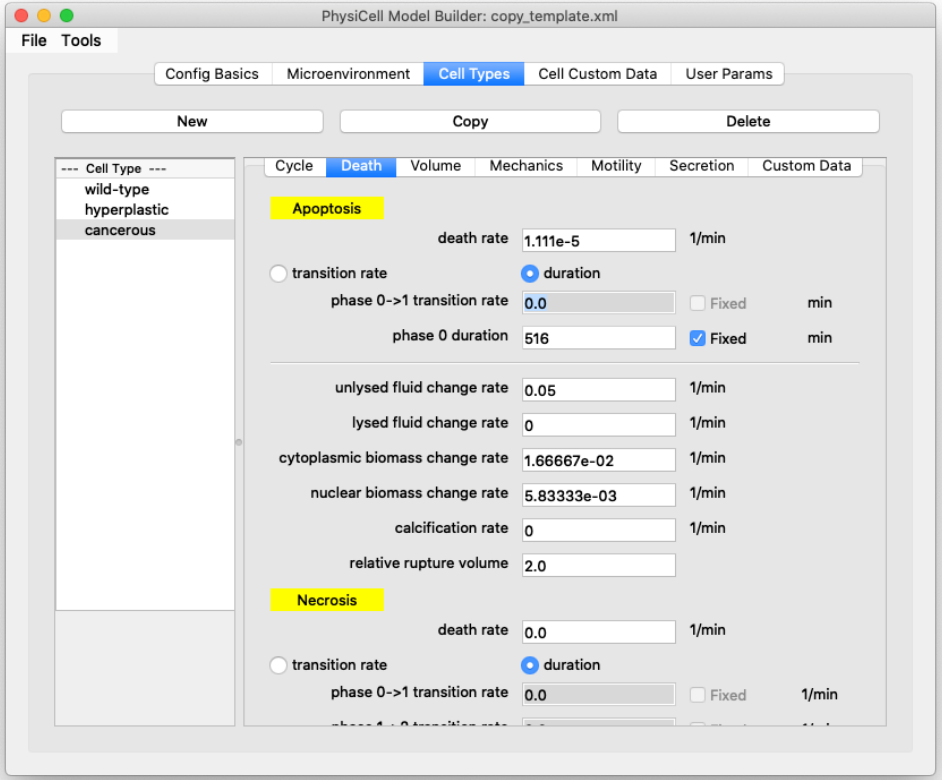

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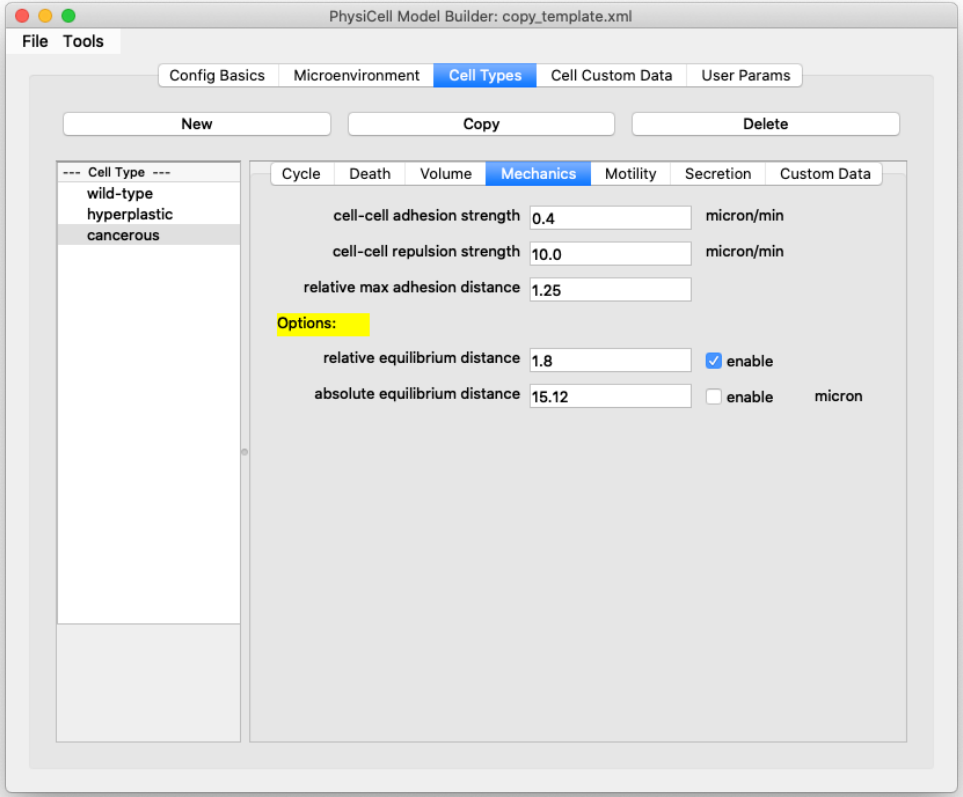

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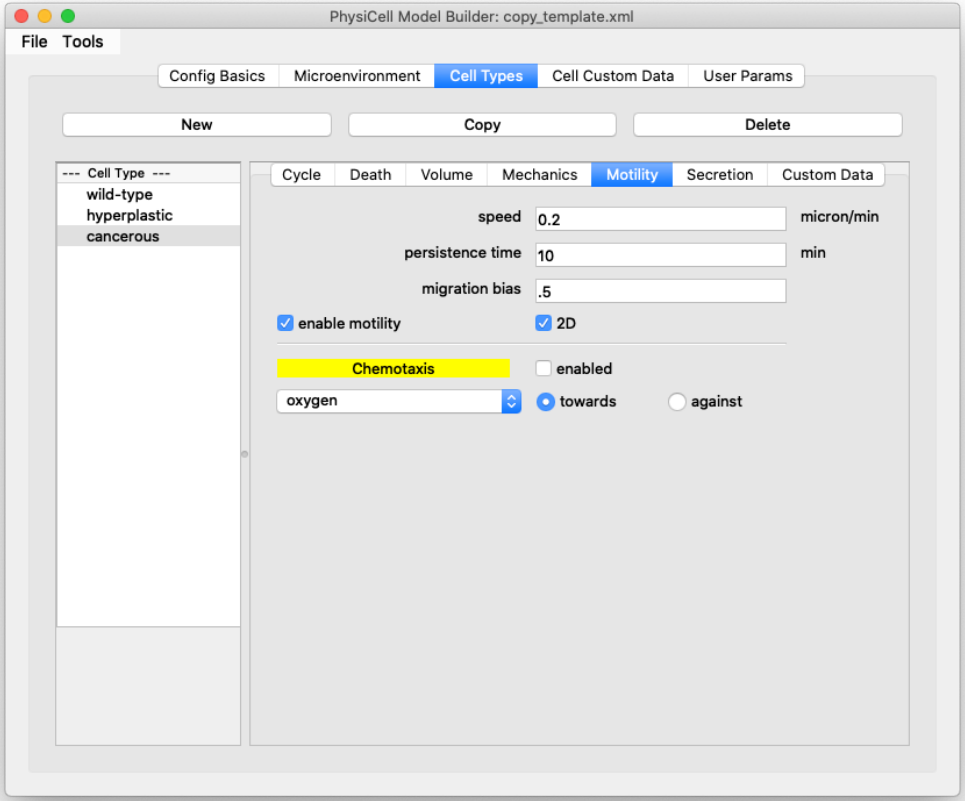
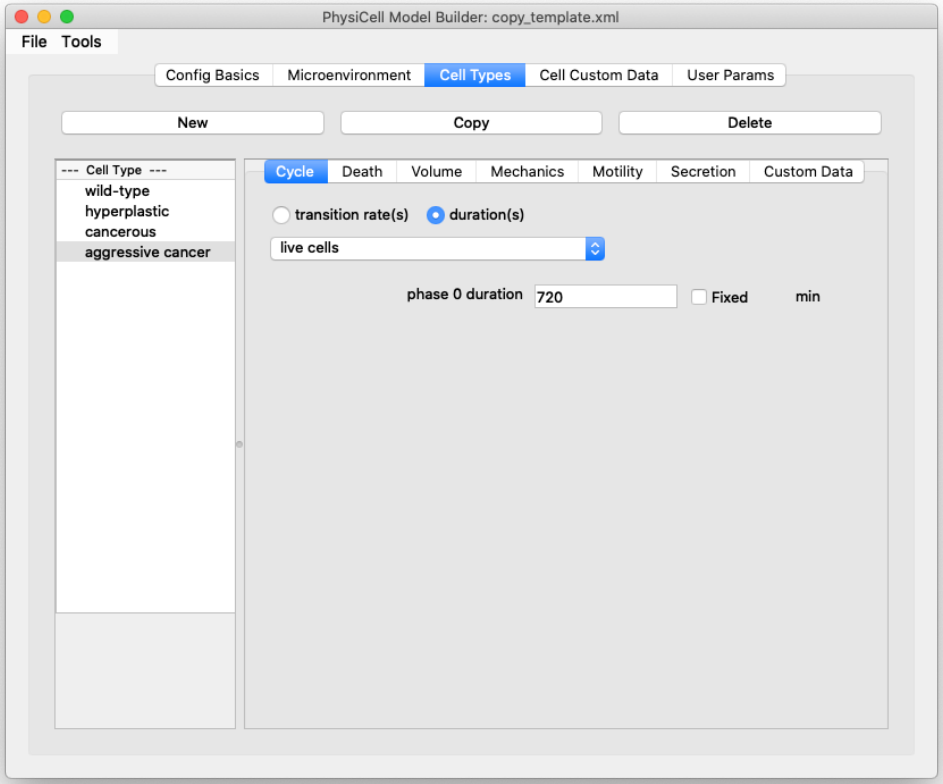


Implementation: Set up cell types – aggressive cancer

- From within the “Cell Types” tab
  - Click “Copy” while “cancerous” cell type is selected
- Set up aggressive cancer cell type
  - Double-click ”cell_def03"
    - ♦ Rename it “aggressive cancer"
    - ♦ Click ”Cycle" subtab
      - » Set phase 0 duration to **720** min (1/2 a day)
    - ♦ Click “Death" subtab
      - » Set “death rate” to **5.555e-5** (this is 4.0 % of the birth rate)
    - ♦ “Mechanics” → No change
    - ♦ Click “Motility” subtab
      - » Set “migration bias” to **0.25**
      - » Click “enabled” to enable chemotaxis



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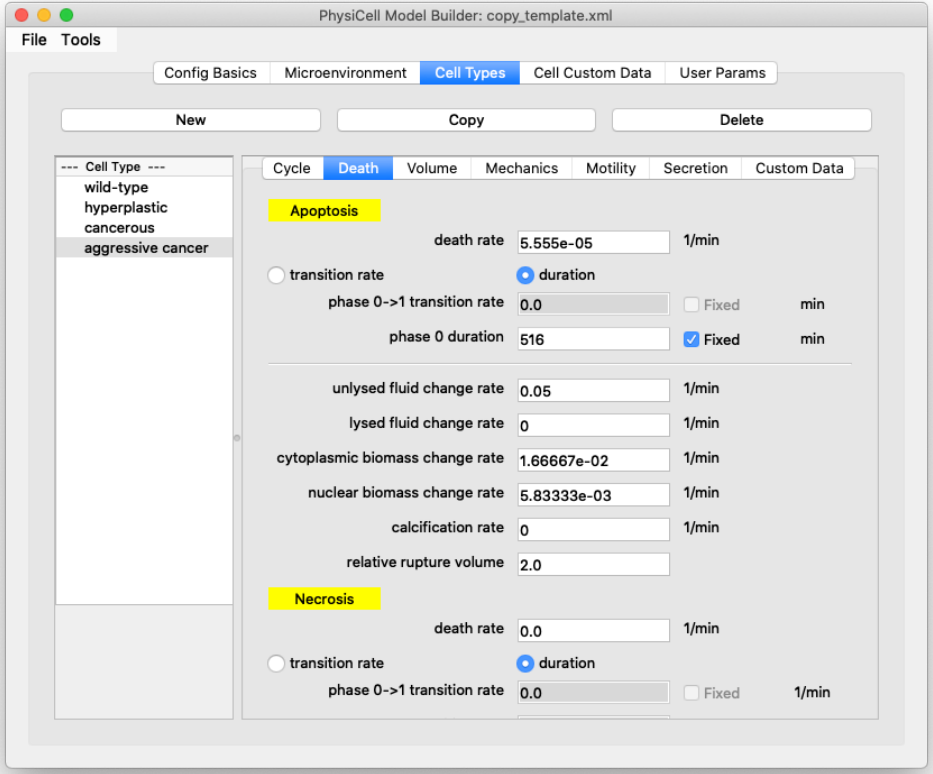

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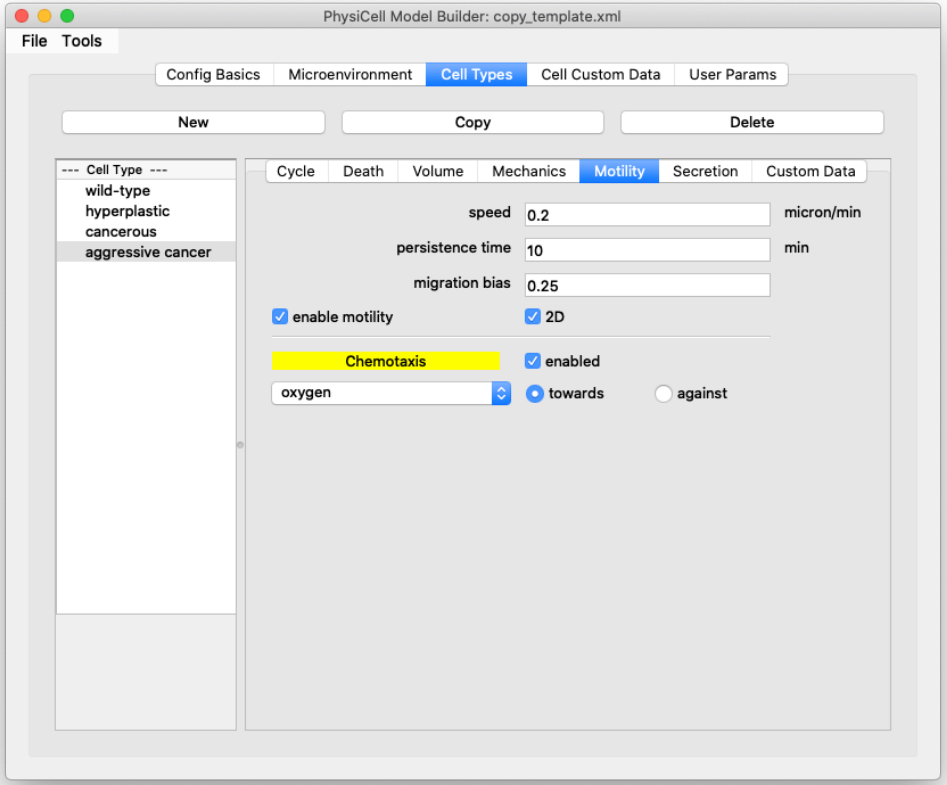
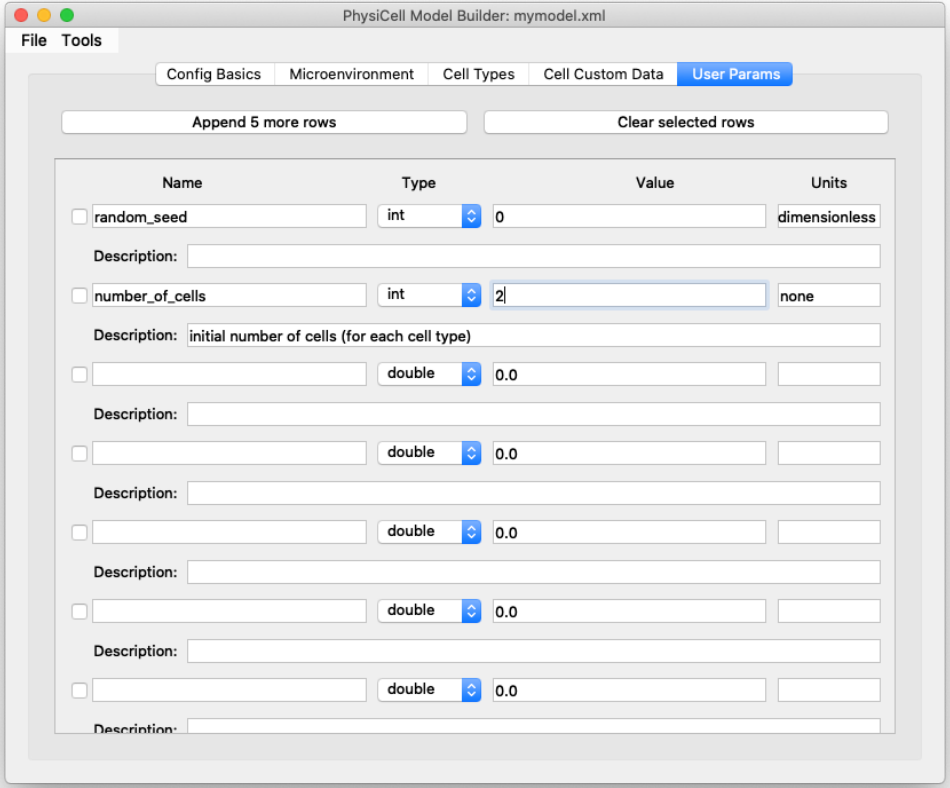


Implementation: User Parameters

- Click on the tab “User Params”
  - Set the variable “number_of_cells” to 2

- Set up is done!!!!!!



Questions?

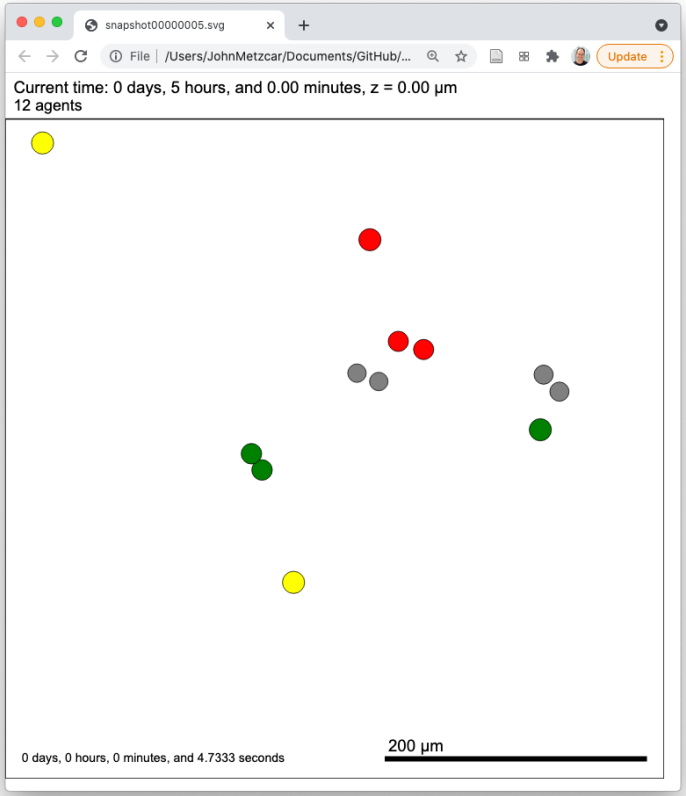
Save and run

- Go to "File", then "Save mymodel.xml"
  - This saves the file into the directory where the Model Builder is running
  - We assume started PhysiCell/config
- Run the model with this new config file
  - `./project ./config/mymodel.xml` (Linux and MacOS)
  - `project.exe ./config/mymodel.xml` (Windows)

- Alternative: overwrite ./config/PhysiCell_settings.xml with mymodel.xml

View Results

- Visualize an individual SVG file
  - Double clicking on file (or using cmd+o on Mac/ctrl+o) will open in browser or default program
  - Sometimes just the file preview may be adequate
- To view dynamics, make an animated gif
  - Within an active PhysiCell terminal run:
    - ♦ **`make gif`**
      - » Executing this command will take longer with more and bigger files and will vary from system to system
      - » For this example, expect 10-15 seconds
- Expected behavior:
  - Gray wild-type cells stay together and grow slowly
  - Red hyperplastic cells grow noticeably faster than wild-type
  - red stromal cells are recruited to tumor center



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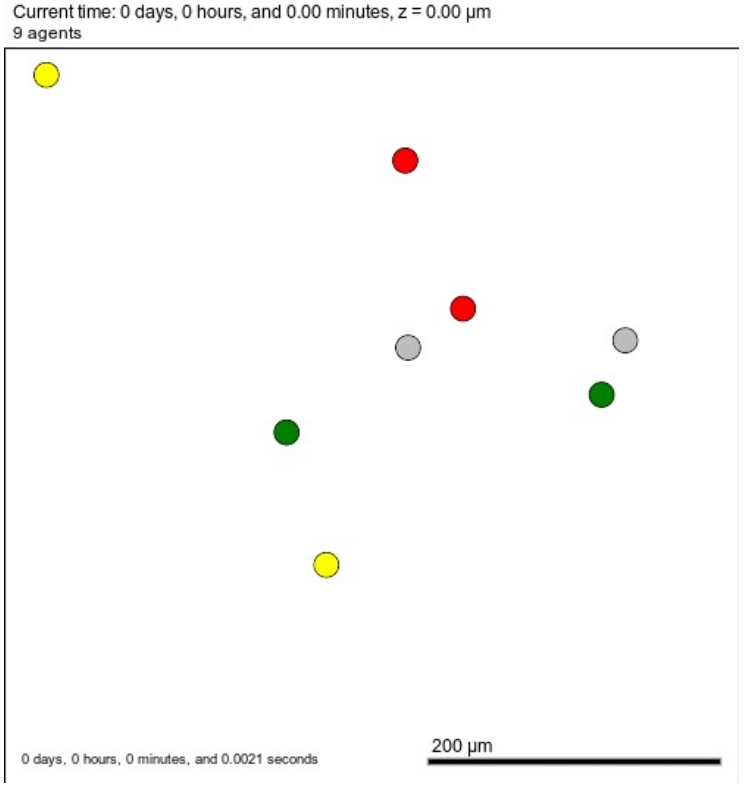
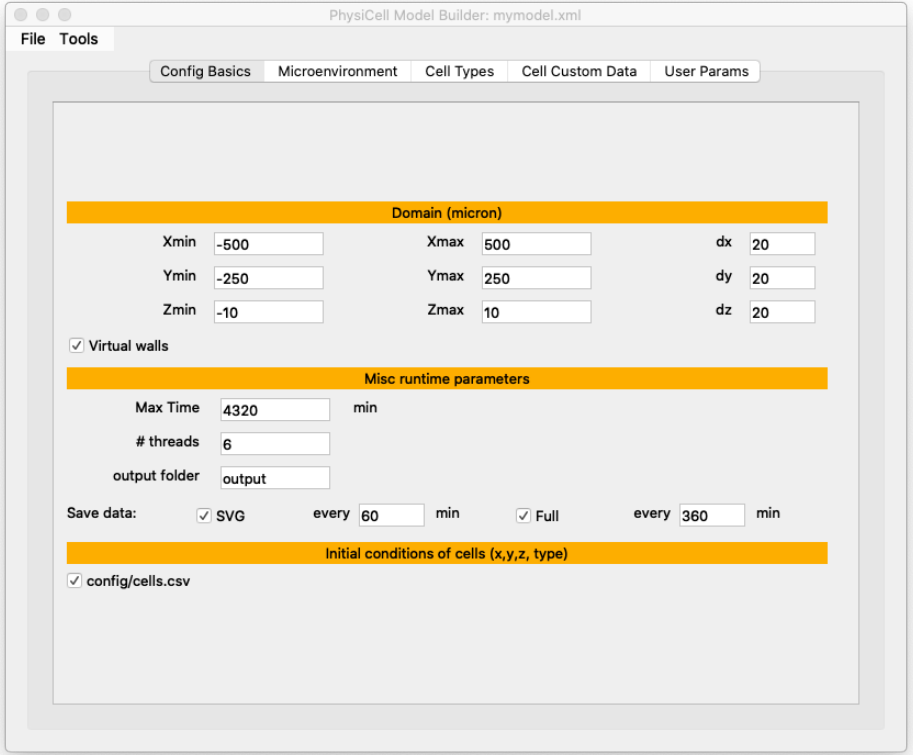
  - Yellow cancerous cells move randomly and grow quickly
  - Green aggressive cancer cells move to boundary and grow fastest



Questions?

Model variation: Domain and cell position

- From within the “Config Basics” tab
  - Change Xmin to **-500** and Xmas to **500**
  - Check “config/cells.csv”
- From within the “User Params” tab
  - Change “number_of_cells” to **0**
- Save within the File menu



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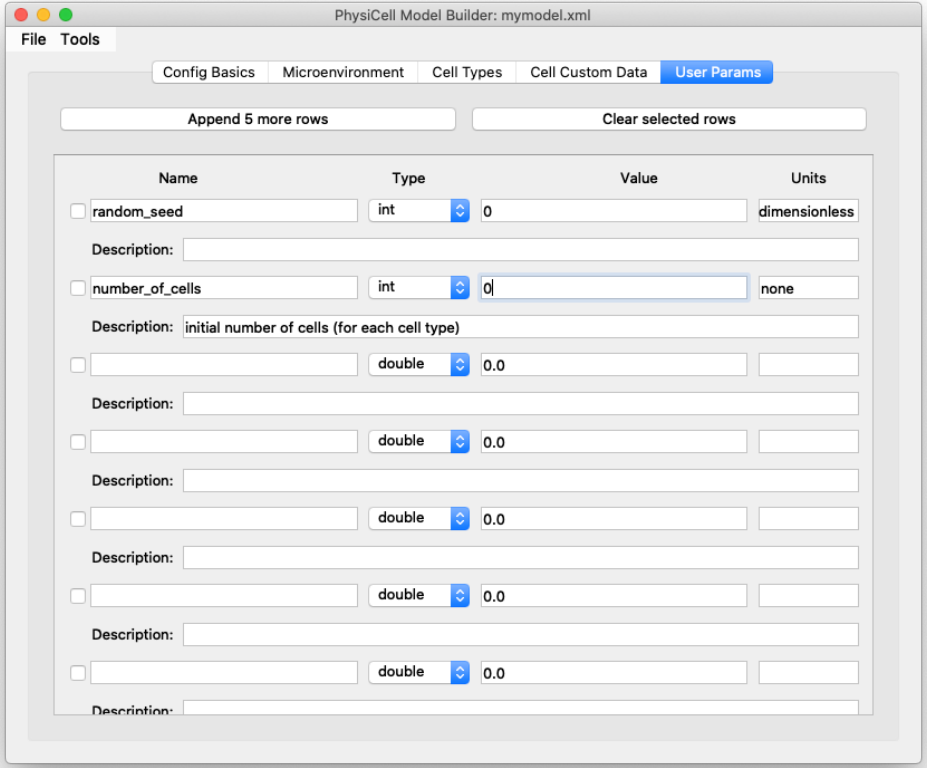
  - Change “number_of_cells” to **0**
- Save within the File menu



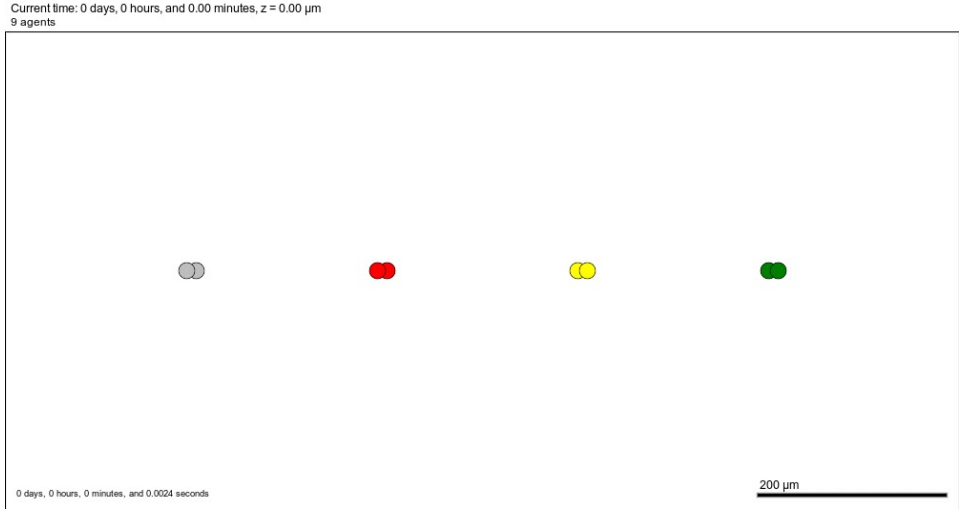
Model variation: Domain and cell position

- Open “cells.csv” from PhysiCell/config
  - Enter the values to the right into “cells.csv” and save
- *Alternatively*, load the supplied “cells.csv” into PhysiCell/config
- Rerun:
  - `./project ./config/mymodel.xml` (Linux and MacOS)
  - `project.exe ./config/mymodel.xml` (Windows)

	A	B	C	D
1	-300	0	0	0
2	-310	0	0	0
3	-100	0	0	1
4	-110	0	0	1
5	100	0	0	2
6	110	0	0	2
7	300	0	0	3
8	310	0	0	3

Model variation: Domain and cell position

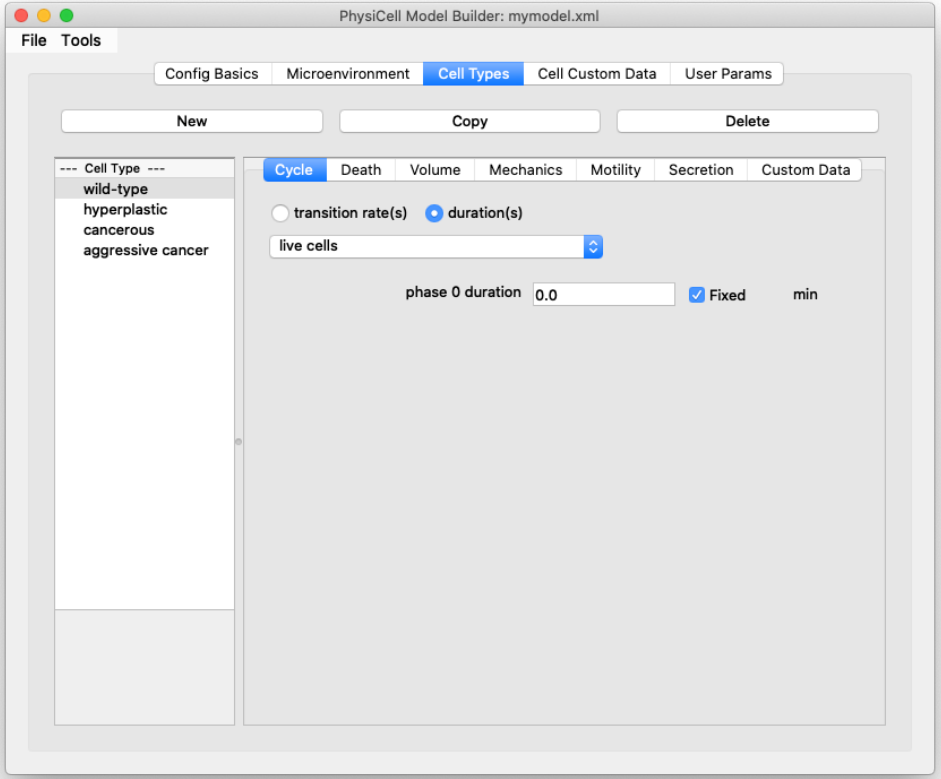
- To view dynamics, make an animated gif
  - Within an active PhysiCell terminal run:
    - **`make gif`**
- Expected behavior:
  - Same as previous
    - Spreading cells out reduces influence of one population on another → behaviors may be more comparable



Questions?

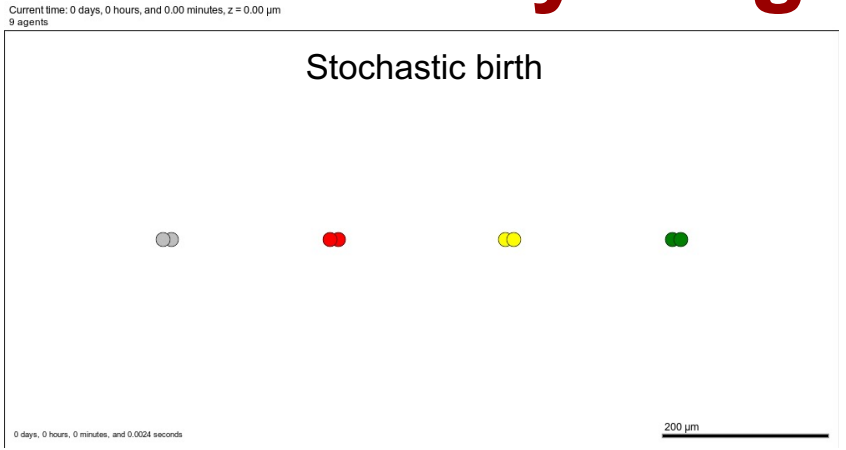
Model variation: Non-stochastic cycling

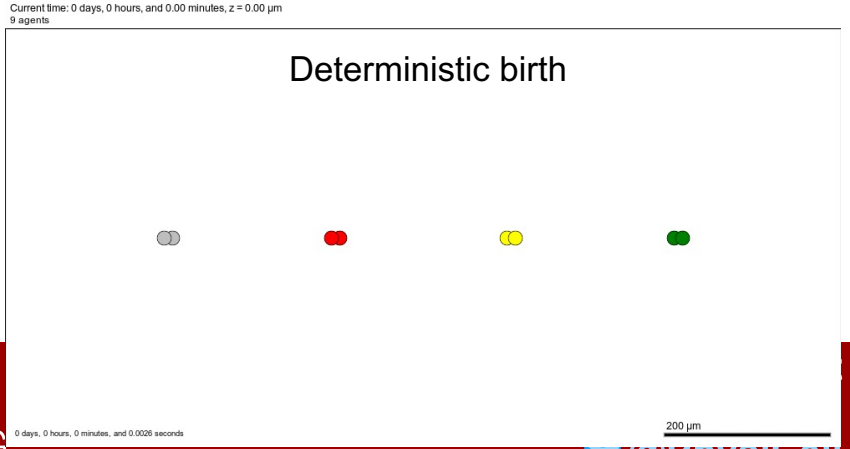
- From within the “Cell Types” tab
  - Click on “wild-type” cell
  - Click “Cycle" subtab
    - Check “Fixed” to give the cell cycle a fixed, non-stochastic length
  - Repeat for each cell type (hyperplastic, cancerous, aggeressive cancer)
- Save within the File menu
- Rerun:
  - `./project ./config/mymodel.xml` (Linux and MacOS)
  - `project.exe ./config/mymodel.xml` (Windows)



Model variation: Non-stochastic cycling

- To view dynamics, make an animated gif
  - Within an active PhysiCell terminal run:
    - **`make gif`**
- Expected behavior:
  - Same previous
    - Gray wild-type cells stay together and grow slowly
    - Red hyperplastic cells grow noticeably faster than wild-type
    - Yellow cancerous cells move randomly and grow quickly
    - Green aggressive cancer cells move to boundary and grow fastest
  - Cells divide as groups – like on a clock (especially apparent in Red and Gray)





Review of goals

- Review the "intermediate" modeling workflow (see below!)
- Build a model from start to finish
  - State the problem – “Steps” in Carcinogenesis Model
  - Plan the model – set up each cell’s proliferation rates, the microenvironment, and domain
  - Adapt the "template" project with Model Builder – set up domain, microenvironment, and 4 cell types
  - Run and view results
- Explore the model
  - Changed domain size and shape and pre-placed cells to highlight individual populations
  - Explored differences of stochastic versus non-stochastic birth

Looking Forward: Full modeling workflow

Suitable for creating a new PhysiCell model with custom C++ to drive dynamical phenotype changes

- Plan the model
- Populate a project
- Edit configuration Model Builder GUI
  - Edit domain
  - Edit microenvironment
  - Edit cell definitions
  - **Add custom variables**
  - **Add custom parameters**
- **Edit custom modules:**
  - **Declare functions in custom.h**
  - **Implement functions in custom.cpp**
  - **Assign functions to cell definitions**
- **Edit initial cell placement**
- **Edit cell coloring function**
- Build
- Run
- View results

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