Slides, videos, links and more:
https://github.com/physicell-training/ws2022

Session 2: PhysiCell First Dive

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PhysiCell Project

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Goals

- Refresher: Sample and Template Projects
- Refresher: Project Structure
- Cells, Phenotype, and Cell Defintions
- Learn about general modeling workflow
  - ***Basic*** ***(Sessions 1, 2)***
  - Intermediate (Session 4)
  - Full (Sessions 6-end)
- Populate, build, and run a basic model (Basic Workflow)
- Load and visualize data in Python

Key Background

Refresher: Sample and Template Projects

- Sample projects are pre-built projects that are bundled with PhysiCell

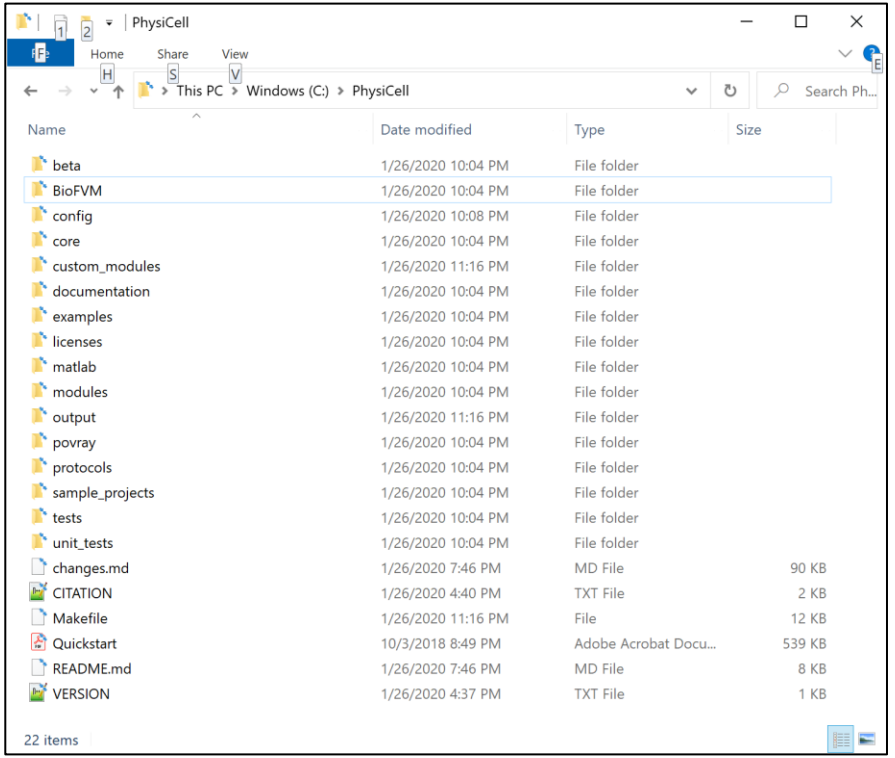
- **Key rules:**
  - make list-projects — get a list of bunded projects
  - make — compile the project
  - make data-cleanup — clean up date for another run
  - make reset — clear out the project to try another

- The **template** project is a good starting point for 2D and 3D projects.

Refresher: Project directory structure

- (key) directories:
  - **./ (root):** main source, Makefile, and executable go here
  - **./addons:** officially supported addons like PhysiBoSS and libRoadrunner
  - **./beta**: for beta-testing (don't use)
  - **./BioFVM:** diffusion solver
  - **./config:** configuration files
  - **./core:** PhysiCell core functions
  - **./custom_modules:** put custom code for your project here.
  - **./documentation:** user guide, etc.
  - **./examples:** deprecated
  - **./licenses:** yep
  - **./matlab:** scripts and functions to load data in matlab
  - **./modules:** standard add-ons for PhysiCell
  - **./output:** where data are stored (by default, but can be changed)
  - **./povray:** deprecated
  - **./protocols:** instructions mostly for maintainers (e.g., release protocols)
  - **./sample_projects:** where we add sample projects
  - **./tests:** for automated testing (WIP)
  - **./unit_tests:** for automated testing (WIP)

Most of your work will be in the red directories



Cells (1)

- Cells are the key entity in PhysiCell.

- Each cell keeps track of:
  - Type
  - ID
  - Position and velocity
  - State
  - Phenotype
    - Intracellular model and data are included here.
  - Custom data

Cells (2)

- Cells have built-in techniques for:
  - Division
  - Death
  - Changing type
  - Accessing / sampling the microenvironment
  - Secretion
  - Finding nearby cells
  - Mechanics
  - Ingesting, damaging, and fusing with other cells
  - And more behaviors via phenotype (Sessions 3 and 7)

Key cell information

- Each cell agent is a member of the `Cell` class.
- Some key data:
  - `std::string type_name` // human-readable name of cell type
  - `int type` // machine-readable unique integer identifier for cell type
  - `int ID` // cell agent's unique integer identifier. (different for each cell)
  - `std::vector<double> position` // the cell's current position (**never write this!**)
  - `std::vector<double> velocity` // the cell's current velocity
  - `cell_state` // things like size, pressure, and cells in contact
  - `phenotype` // behavioral properties / state (Session 3)
  - `custom_data` // custom scalar and vector data (Session 5)
  - `functions` // list of key cell functions (Session 6)

Future refinement:

Each cell should have a pointer to its Cell_Definition

Cell state

- Each **Cell** has an instance of **Cell_State** called **state:**
  - std::vector<Cell*> attached_cells: (Sessions 7,15)
    - Use `attach_cell` and `detach_cell` to add or remove cells to this list
    - Cell-cell contact functions automatically evaluated for these cells
  - std::vector<Cell*> neighbors: (Sessions 7,15)
    - a vector of pointers to all (mechanically interacting) neighbor cells.
    - Automatically updated to include all cells within mechanical interaction distance
  - double simple_pressure: (Sessions 7,15)
    - a (normalized) measure of forces exerted by nearby adhered cells
    - in a 3-D, fully confluent (packed) tissue, 12 neighbors, and simple_pressure = 1
    - in a 2-D, fully confluent (packed) tissue, 6 neighbors, and simple_pressure = 0.5

Cell phenotype

- One of the most critical data elements in a PhysiCell Cell is ***phenotype***
- Hierarchically organize key behavioral elements:
  - Phenotype (Session 3,7)
    - **cycle**: advancement through a cell cycle model
    - **death**: one or more types of cell death
    - **volume:** cell's volume regulation
    - **geometry:** cell's radius and surface area
    - **mechanics:** adhesion and resistance to deformation ("repulsion")
    - **motility:** active motion (other than "passive" mechanics)
    - **secretion:** both release and uptake of chemical substrates. Interfaces with BioFVM
    - **molecular:** a place to store internalized substrates (Sessions 10-13)
    - **intracellular:** a place for intracellular models (Sessions 10-13)
    - **interactions:** cell-cell contact interactions & transformations (Sessions 7,15)

Phenotype-centric programming

- The core cell behaviors are implemented:
  - Cell cycling (with user-selectable models)
  - Cell death
  - Cell adhesion / repulsion
  - Cell motility
  - Cell secretion / uptake
  - Key cell interactions

- Modelers can focus on writing functions that control these behaviors.
- This is **phenotype-centric programming.**

Cell Definitions

- A **Cell Definition** is a convenient way to set the parameters and functions for a whole class of cells
  - Users can instantiate cells of a specific type using `create_cell( A_cell_defn )`
  - With no argument, new cells use the `cell_defaults` definition
    - For historical reasons, PhysiCell uses the first cell definition (with index 0) as its default

- Tip: Refer back to the phenotype in your agent's cell definition as a reference parameter set (i.e., to get the initial parameter values)
  - Use the "dictionaries" to get these reference values.

More on this in Sessions 4, 6.

Modeling Workflows

PhysiCell Modeling Workflows

- There are three typical modeling workflows in PhysiCell
  - **Basic** **(Introduced in Session 1 pre-workshop and 2 today)**
    - ♦ Build existing projects, change parameter values, and run
  - **Intermediate** **(Introduced in Session 4 today)**
    - ♦ Build your own models based on the template project
    - ♦ All model setup in a GUI (no modification of C++)
  - **Full** **(Introduced in Session 6 tomorrow)**
    - ♦ Enhance an intermediate model with custom C++ to implement cell hypotheses / rules

Basic modeling workflow

Basic modeling workflow

Suitable for running a built-in project with minor changes to parameters.

- Populate and build a project
- Edit settings
- Run
- View results

Choose, populate, and build a project

- Get list of sample projects:
  - `make list-projects`

- Populate the heterogeneity sample:
  - `make heterogeneity-sample`

- Compile the project
  - `make`

Edit settings

- Open the settings file:
  - **./config/PhysiCell_settings.xml**

- Let's change:
  - Change domain to [-500,500] × [-500,500]
  - Reduce max simulation time to 2160 minutes
  - Save full data ever 360 minutes
  - Set oncoprotein standard deviation to 3 (increase heterogeneity)
  - Set the max oncoprotein value to 10 (mean + 3 standard deviations)

Edit settings: XML

- Open ./config/PhysiCell_settings.xml
- Major sections:
  - **domain** -- how big of a region to simulate
  - **overall** -- how long to simulate, time step sizes
  - **parallel** -- OpenMP settings
  - **save** -- how often to save SVG images and full data
  - **microenvironment** -- settings on diffusing substrates
  - **user_parameters** -- model-specific settings
  - **cell_definitions** -- set baseline cell properties

Edit settings: Domain size

- Open `./config/PhysiCell-settings.xml`
- Let's set the domain size in the **domain** block
  - Switch to [-500,500] x [-500,500] x [-10,10] to speed it up

```
<PhysiCell_settings version="devel-version">
        <domain>
                <x_min>-500</x_min>
                <x_max>500</x_max>
                <y_min>-500</y_min>
                <y_max>500</y_max>
                <z_min>-10</z_min>
                <z_max>10</z_max>
                <dx>20</dx>
                <dy>20</dy>
                <dz>20</dz>
                <use_2D>true</use_2D>
        </domain>
```

Edit settings: Save settings

- Let's look at the **overall** block
  - Set max time to 1.5 days = 1.5 x 24 x 60 = 2160 minutes

```
<overall>
        <max_time units="min">2160</max_time> <!-- 36 h * 60 min -->
        <time_units>min</time_units>
        <space_units>micron</space_units>
```

- Let's look at the **save** block
  - Set the full save interval to 6 hours = 360 minutes

```
<save>
        <folder>output</folder> <!-- use . for root -->
        <full_data>
                <interval units="min">360</interval>
                <enable>true</enable>
        </full_data>
```

Edit settings: User parameters

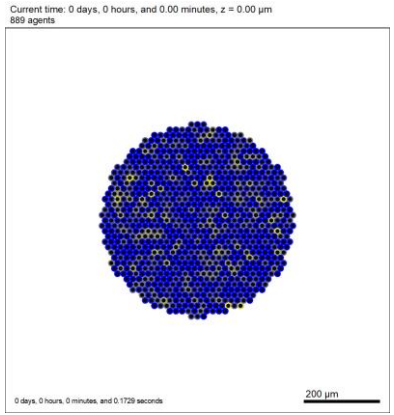
- Let's also look at the **user_parameters** block
  - Let's change the oncoprotein standard deviation (`oncoprotein_sd`) to 3 (more variation)
  - Let's change the max oncoprotein (`oncoprotein_max`) to mean + 3 sds = 1 + 9 = 10

```
<user_parameters>
  <tumor_radius type="double" units="micron">250.0</tumor_radius>
  <oncoprotein_mean type="double" units="dimensionless">
    1.0</oncoprotein_mean>
  <oncoprotein_sd type="double" units="dimensionless">3.0</oncoprotein_sd>
  <oncoprotein_min type="double" units="dimensionless">0.0</oncoprotein_min>
  <oncoprotein_max type="double" units="dimensionless">10</oncoprotein_max>
  <random_seed type="int" units="dimensionless">0</random_seed>
</user_parameters>
```

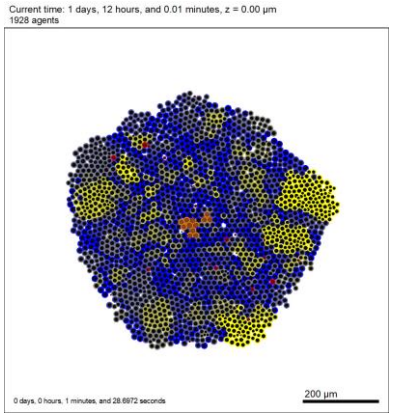
Run and View Results: Snapshots

- run:
  - **./heterogeneity** (MacOS or Linux)
  - **heterogeneity.exe** (Windows)

- Look in output:
  - Look at snapshot SVG files
  - Look at **legend.svg**
    - (Not much to see on this example)



initial.svg



final.svg

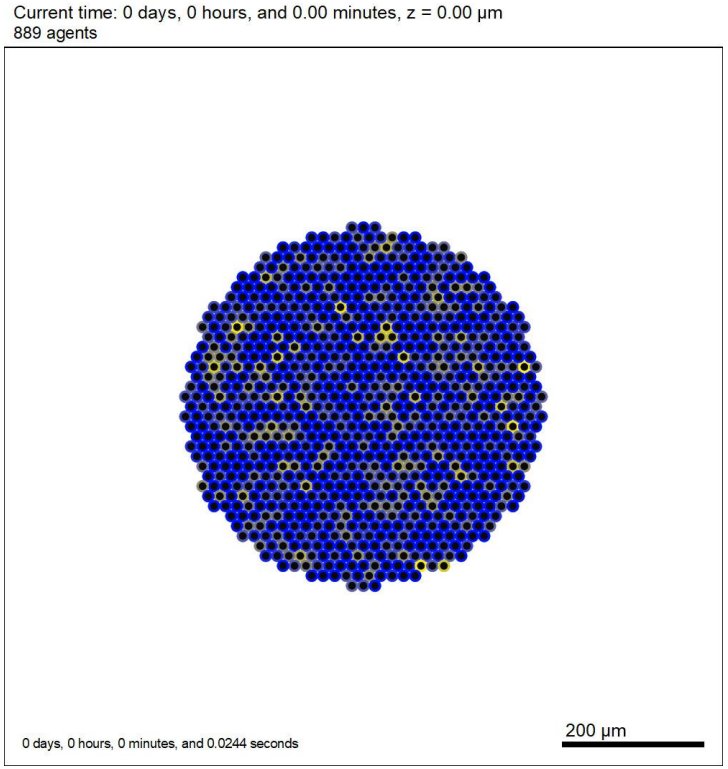
legend.svg

- Convert snapshots to JPEG:
  - `make jpeg` (results: output/snapshot00000000.jpg ...)

View results: GIF and movie

- Make and animated GIF:
  - **`make gif`** (result: output/out.gif)

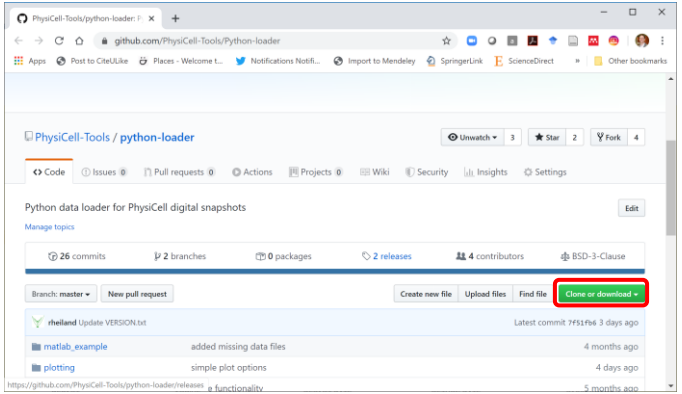
- Make an mp4 movie
  - **`make movie`** (result: output/out.mp4)



Loading data in Python

Let's get ready to load in Python

- We'll go to Python-loader and get the source:
  - https://github.com/PhysiCell-Tools/Python-loader



- Get the latest release:
  - Click the green "clone or download" button
    - I clone the repository to GitHub/Python-loader

- With a trick, you won't need to copy the python files to your project.

Let's get started

Jupyter Notebok Code Section 1

- Download the Jupyter notebook to the PhysiCell directory
  - link: [click here]
- Open Jupyter
- Navigate to your PhysiCell root directory, and open the notebook
- Trick to import the python loader from the GitHub repo:
  - `import sys`
  - `sys.path.insert(0, '../Python-loader/')`
  - `from pyMCDS import pyMCDS`

- Import other useful things
  - `import numpy as np`
  - `import matplotlib.pyplot as plt`

- Historical note:
  - MCDS = MultiCellDS, our multicellular data standard

Session 2 Jupyter notebook: (save to root of PhysiCell directory)
https://github.com/physicell-training/ws2022/raw/main/sessions/session_02/code/Session2_heterogeneity.ipynb

Let's load a single time

Jupyter Notebok Code Section 2

- Syntax: result = pyMCDS(filename , directory):

```
mcds = pyMCDS('output00000000.xml', 'output')
```

- Let's get some basic info on the snapshot:

```
print( mcds.get_time() )  # what simulation time is saved here?
print( mcds.get_cell_variables() ) # what data are saved in the cells?
print( mcds.get_substrate_names() )  # what diffusing substrates?
```

- mcds.data is a dict. Let's see what's available:

```
mcds.data.keys()
```

```
Out[41]: dict_keys(['metadata', 'mesh', 'continuum_variables', 'discrete_cells'])
```

Let's access cell data

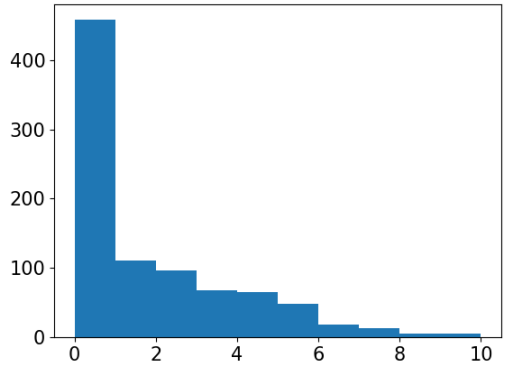
Jupyter Notebok Code Section 3

- First, let's find out the mean value of the oncoprotein
  - np.mean(mcds.data['discrete_cells']['oncoprotein'])

```
Out[61]: 1.8305931655741
```

- Let's make sure matplotlib doesn't use small fonts

```
import matplotlib
matplotlib.rc('xtick', labelsize=20)
matplotlib.rc('ytick', labelsize=20)
```



- Now, let's plot a histogram
  - `plt.hist( mcds.data['discrete_cells']['oncoprotein'] )`

Let's plot the cells

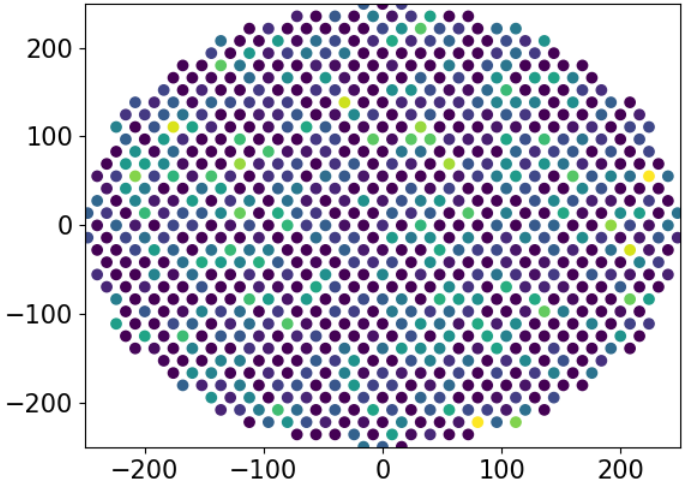
Jupyter Notebok Code Section 4

- We'll do a scatter plot of the cells, and color by oncoprotein.
- First, let's grab the data to make our typing easier

```
cx = mcds.data['discrete_cells']['position_x']
cy = mcds.data['discrete_cells']['position_y']
op = mcds.data['discrete_cells']['oncoprotein']
```

- Now, a scatter plot.
  - Note: these are not plotting by the ***physical*** cell size

```
plt.scatter(cx,cy,c=op)
```



- If there are some cells out of range, fix the axes:

```
plt.axis([-250,250,-250,250])
```

- This plot is pretty ugly. let's improve it.

Improving the plot scatter plot

- Let's replot with bigger dots

```
plt.clf()
plt.scatter( cx , cy, c=op, s=30 )
```

- Make sure aspect ratio is right:

```
plt.axis( 'image' )
plt.axis( [-250,250,-250,250] )
```

- Now, let's add a colorbar

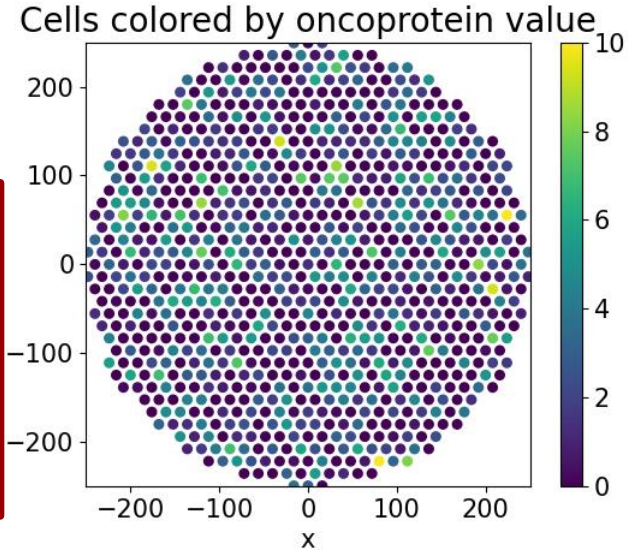
```
plt.colorbar()
```

- Now, let's add labels

```
plt.title( 'Cells colored by oncoprotein value' , size=20)
plt.xlabel( 'x' , size=15 )
plt.ylabel( 'y', size=15 )
```

The right value will vary based on your screen resolution, zoom, and window size.

This will take some experimentation!

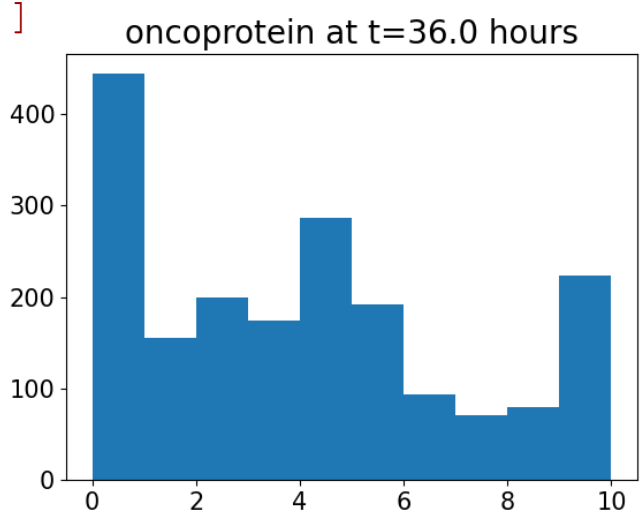


Jupyter Notebok Code Section 5

Let's load another time

Jupyter Notebok Code Section 6

```
mcds = pyMCDS('output00000006.xml', 'output')
t=mcds.get_time()
cx = mcds.data['discrete_cells']['position_x']
cy = mcds.data['discrete_cells']['position_y']
op = mcds.data['discrete_cells']['oncoprotein']
plt.clf()
plt.hist( op )
plt.title( 'oncoprotein at t=' + \
str(t/60) + ' hours' , size=20)
```



Let's find live and dead cells

- Each cycle model has a unique code
  - Codes ≥ 100 denote death cycles

- Let's get the cycle code of each cell, and convert to integers

```
cycle = mcds.data['discrete_cells']['cycle_model']
cycle = cycle.astype( int )
```

- Let's find the live cells

```
live = np.argwhere( cycle < 100 ).flatten()
dead = np.argwhere( cycle >= 100 ).flatten()
```

Jupyter Notebok Code Section 7

Let's work with these

Jupyter Notebok Code Section 8

- Live and dead cell counts

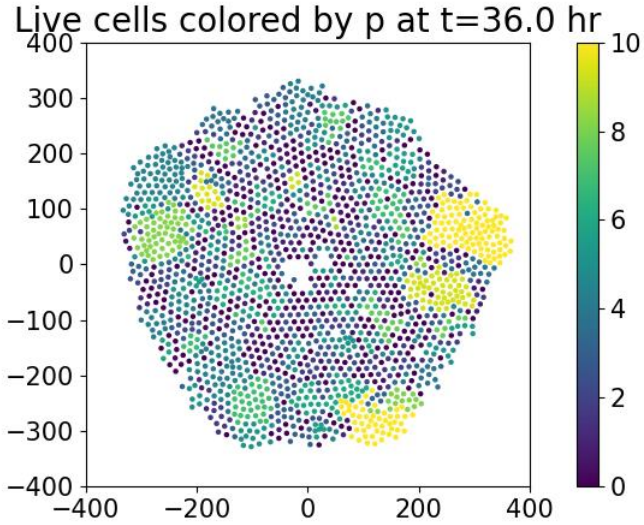
```
n_live = len( live ); print( n_live)
n_dead = len( dead ); print( n_dead );
```

- Mean oncoprotein in live cells only

```
np.mean( op[live] )
```

- Let's scatter plot of only live cells

```
plt.clf()
plt.scatter( cx[live],cy[live],c=op[live],s=10);
plt.colorbar()
plt.axis('image')
plt.axis([-400,400,-400,400])
plt.title( 'Live cells colored by p at t=' +str(t/60) + ' hr',size=20)
```

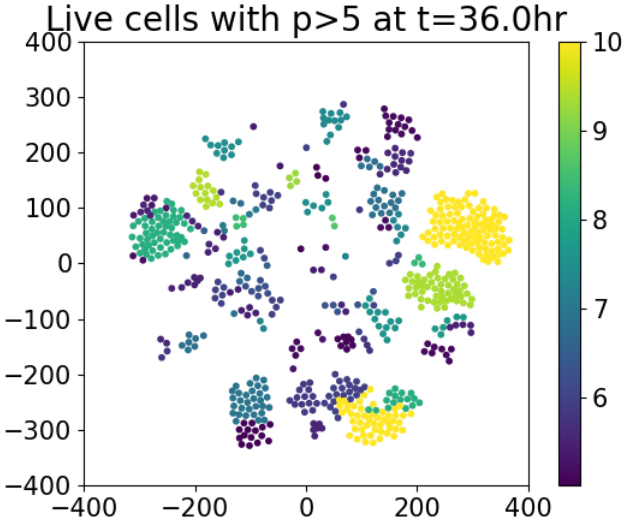


More data loading

Let's do a fancier search

- Only plot live cells with $p > 5$:

```
ind = np.argwhere( (cycle<100) & (op>5) ) .flatten()
plt.clf()
plt.scatter( cx[ind], cy[ind], c=op[ind], s=10 )
plt.title( 'Live cells with p>5 at t='\
+str(t/60) + 'hr', size=20)
plt.axis('image')
plt.axis([-400,400,-400,400])
plt.colorbar()
```

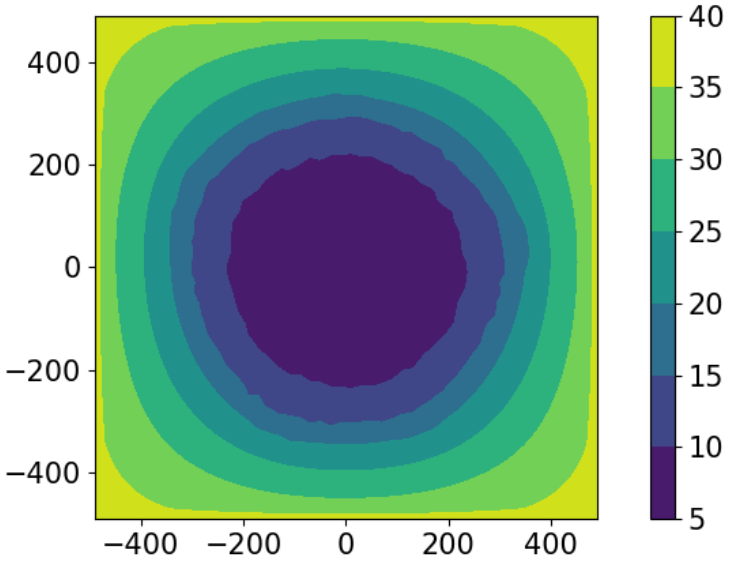


- **Note:** The best circle size (s=10) will vary based on your desktop resolution, zoom and window size. You will need to experiment.

Now let's plot the oxygen

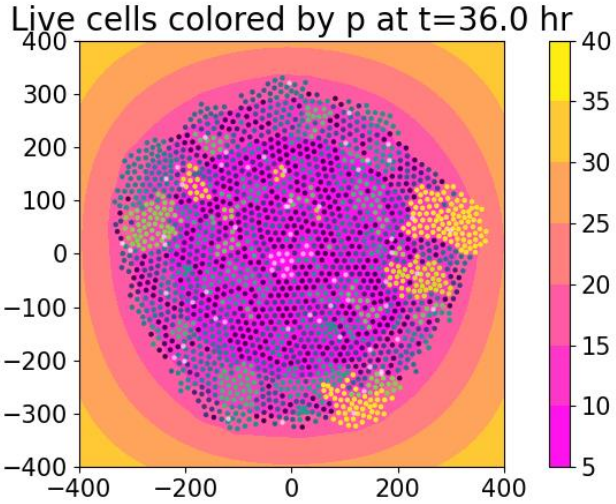
Jupyter Notebok Code Section 9

```
plt.clf()
mcds.get_substrate_names();

o2 = mcds.get_concentrations( 'oxygen' );
X,Y = mcds.get_2D_mesh();

plt.clf()
plt.contourf(X,Y,o2[:,:,0]);
plt.colorbar()
plt.axis('image')
```



Now let's plot the oxygen with cells

```
circle_size = 10

plt.clf()
mcds.get_substrate_names();

o2 = mcds.get_concentrations( 'oxygen' );
X,Y = mcds.get_2D_mesh();
plt.contourf(X,Y,o2[:,:,0],cmap='spring');
plt.colorbar()

plt.scatter( cx[live],cy[live],c=op[live],s=circle_size);
plt.axis('image')
plt.axis([-400,400,-400,400])
plt.title( 'Live cells colored by p at t=' +str(t/60) + ' hr', size=20)

# let's plot dead cells as white and transparent
plt.scatter( cx[dead],cy[dead],c='w',s=circle_size, alpha=0.5 );
```



Jupyter Notebok Code Section 10

Now, let's do some time series analysis

- Let's get live and dead cell counts, mean *p* (in live cells). We need to loop overall simulation times

```
last_index = 6;
live_count = np.zeros( last_index+1 );
dead_count = np.zeros( last_index+1 );
mean_p = np.zeros( last_index+1 );
std_p = np.zeros( last_index+1 );
times = np.zeros( last_index+1 );
for n in range( 0,last_index+1 ):
     filename='output'+"%08i"%n+'.xml'
     mcds=pyMCDS(filename,'output')
     times[n]= mcds.get_time()
     cycle=mcds.data['discrete_cells']['cycle_model']
     p = mcds.data['discrete_cells']['oncoprotein']
     live = np.argwhere(cycle<100).flatten()
     dead = np.argwhere(cycle>=100).flatten()
     live_count[n] = len(live)
     dead_count[n] = len(dead)
     mean_p[n] = np.mean( p[live] )
     std_p[n] = np.std( p[live] )
```

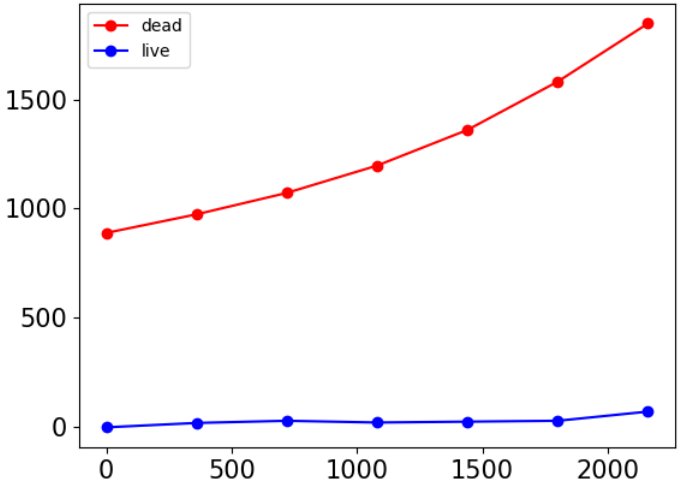
Jupyter Notebok Code Section 11

Let's plot and get growth rates

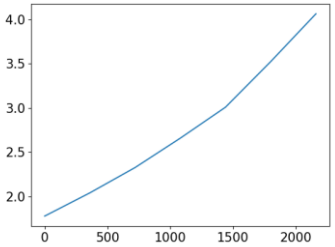
```
plt.clf()
plt.plot( times, live_count , 'r-o' )
plt.plot( times, dead_count , 'b-o' );
plt.legend( {'live', 'dead' } )
```

Jupyter Notebok Code Section 12

```
poly=np.polyfit( times,np.log(live_count),1)
print( poly[0] )
# growth rate is 0th element
# in units of 1/min
# 0.0003373436446715521
```




```
plt.clf()
plt.plot(times,mean_p);
# mean increases rapidly
# due to selection processes
```



Cleanup

- Clear out data (to prepare for another run)
  - **make data-cleanup** (clears all out of /output)

- Reset to a clean slate (e.g., to start another project)
  - **make reset** (depopulates custom files, restores Makefile)

Let's work on data with multiple types

- Let's go and run the biorobots sample

```
make data-cleanup
make reset
make biorobots-sample
make
```

- Edit the config file:
  - run to 720 min
  - save full data ever 240 min
  - save SVGs every 30 min

```
./biorobots
```

```
<save>
   <folder>output</folder> <!-- use . for root -->

   <full_data>
      <interval units="min">240</interval>
      <enable>true</enable>
   </full_data>

   <SVG>
      <interval units="min">30</interval>
      <enable>true</enable>
   </SVG>

   <legacy_data>
      <enable>false</enable>
   </legacy_data>
</save>
```

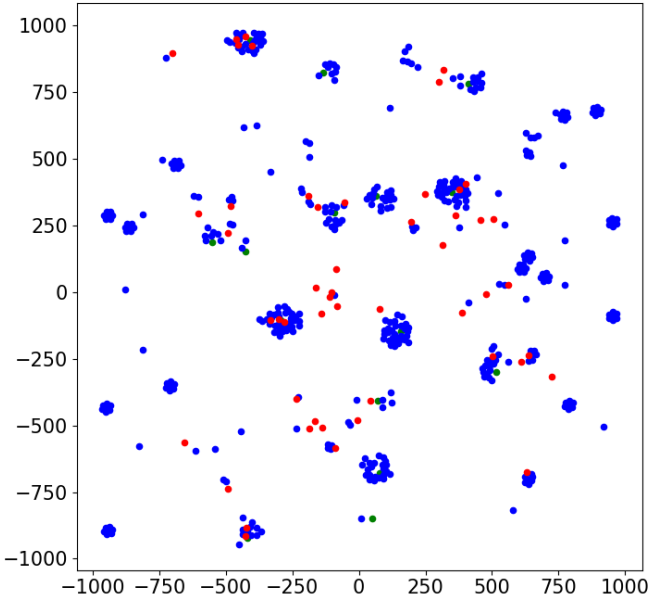
Let's load the last time

```
n = 3
filename='output'+"%08i"%n+'.xml'
mcds=pyMCDS(filename,'output')
t = mcds.get_time()
cell_type=mcds.data['discrete_cells']['cell_type']
cell_type=cell_type.astype(int)

ind1 = np.argwhere(cell_type==1).flatten(); # director
ind2 = np.argwhere(cell_type==2).flatten(); # cargo
ind3 = np.argwhere(cell_type==3).flatten(); # worker

cx = mcds.data['discrete_cells']['position_x']
cy = mcds.data['discrete_cells']['position_y']
```

Jupyter Notebok
Code Section 13

Let's plot each type a different color

```
circle_size=20

plt.clf()
plt.figure(figsize=(15,15))
plt.scatter(cx[ind1],cy[ind1],c='g',s=circle_size)
plt.scatter(cx[ind2],cy[ind2],c='b',s=circle_size)
plt.scatter(cx[ind3],cy[ind3],c='r',s=circle_size)
plt.axis('square');
```

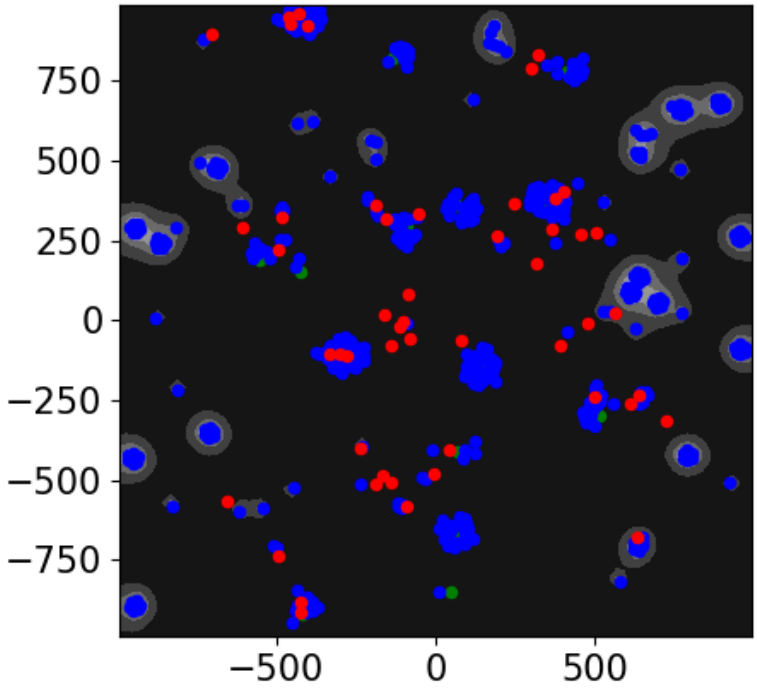


Jupyter Notebok Code Section 14

Overlay on top of the cargo signal

```
mcds.get_substrate_names();

cs = mcds.get_concentrations( 'cargo signal' );
X,Y = mcds.get_2D_mesh();

plt.clf()
plt.figure(figsize=(15,15))
plt.contourf(X,Y,cs[:,:,0],cmap='gray');

plt.scatter(cx[ind1],cy[ind1],c='g',s=circle_size)
plt.scatter(cx[ind2],cy[ind2],c='b',s=circle_size)
plt.scatter(cx[ind3],cy[ind3],c='r',s=circle_size)
plt.axis('image');
```

Jupyter Notebok
Code Section 15



Cleanup

- Clear out data (to prepare for another run)
  - **make data-cleanup** (clears all out of /output)

- Reset to a clean slate (e.g., to start another project)
  - **make reset** (depopulates custom files, restores Makefile)

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 results

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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