https://github.com/physicell-training/ws2021

# 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 5)
  - Full (Sessions 6-12)
- 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-projectsget a list of bunded projects

make [sample\_name] populate a sample project

make compile the project

make data-cleanup clean up date for another run

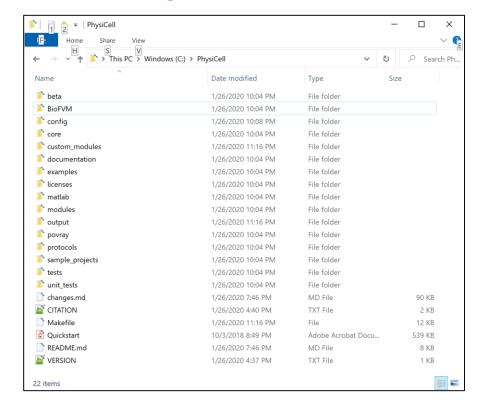
make reset
clear out the project to try another

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
  - Finding nearby cells
  - Ingesting cells
  - And more behaviors via phenotype (Sessions 3-4)

#### **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
  - custom data // custom scalar and vector data
  - functions // list of key cell functions

#### **Future refinement:**

Each cell should have a pointer to its Cell\_Definition

- (Sessions 3-4)
- (Session 6)
  - (Session 7)

#### **Cell state**

- Each Cell has an instance of Cell\_State called state:
  - std::vector<Cell\*> attached\_cells:

• Use this for your own custom storage of interacting cells for contact-based interactions

- std::vector<Cell\*> neighbors:
  - a vector of pointers to all (mechanically interacting) neighbor cells.
  - ♦ Automatically updated to include all cells with non-zero mechanical interactions
- std::vector<double> orientation:
  - ♦ Used during cell division: division plane passes through this vector.
  - ◆ A unit vector (length 1) directed from the cell's base to its apex
  - ◆ Cell division places daughter cells (randomly) perpendicular to this vector
  - ◆ In 2D, orientation = [0,0,1] so that daughter cells stay in plane
- double simple\_pressure:
  - ♦ 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

(Sessions 9-10)

(Sessions 9-10)

(Sessions 9-10)

#### Cell phenotype

- One of the most critical data elements in a PhysiCell Cell is phenotype
- Hierarchically organize key behavioral elements:
  - Phenotype (Sessions 3-4)
    - ◆ 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 11-12)
    - ♦ intracellular: a place for intracellular models (Sessions 11-12)

### 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

- 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
- <u>Best practice</u>: set up the **cell\_defaults** definition first. Copy this to create other cell types
- <u>Tip</u>: Refer back to the phenotype in your agent's cell definition as a reference parameter set (i.e., to get the initial parameter values)

More on this in Session 5.

# **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 5 today)
    - ◆ Build your own models based on the template project
    - ♦ All model setup in a GUI (no modification of C++)
  - Full (Introduced in Session 7 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 [-400,400] × [-400,400]
  - 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
  - cell\_definitions -- set baseline cell properties
  - initial\_conditions options to set initial cell positions via CSV
  - user\_parameters -- model-specific settings

### **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

#### **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

### **Edit settings: Save settings**

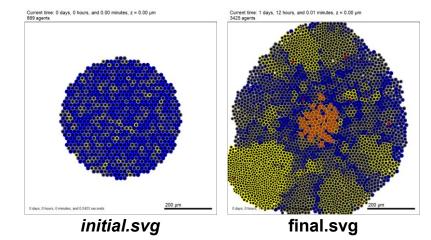
- Let's look at the overall block
  - Set max time to 1.5 days = 1.5 x 24 x 60 = 2160 minutes

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

#### 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)





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

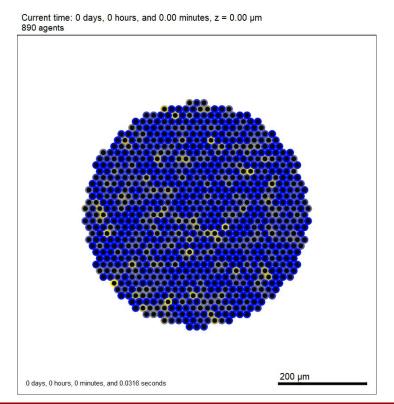
#### View results: GIF and movie

Make and animated GIF:

make gif (result: output/out.gif)

Make an mp4 movie

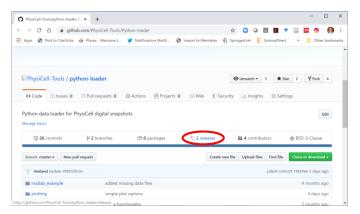
make movie (result: output/out.mp4)



# 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 on "releases" link
  - Click the green "clone or download" button
    - ♦ (For simplicity, I'm using "download ZIP" option)
- Copy the following Python file (end in .py) to the root of PhysiCell
  - pyMCDS



### Let's get started in ipython

**Jupyter Notebok Code Section 1** 

- Start ipython (interactive python)
  - ipython3 --pylab
- OR: download & start the Jupyter notebook
  - jupyter notebook Session2 heterogeneity.ipynb
- Import the python loader:
  - from pyMCDS import pyMCDS
- Import other useful things
  - import numpy as np
  - import matplotlib.pyplot as plt
- Let's see what is available
  - Type pyMCDS.
  - Hit "tab" to autocomplete
- Historical note:
  - MCDS = MultiCellDS, our multicellular data standard

```
IPython: C:Desktop/PhysiCell
C:\Users\PaulT\Desktop\PhysiCell> ipython
thon 3.7.3 (default, Apr 24 2019, 15:29:51) [MSC v.1915 64 bit (AMD64)]
   'copyright', 'credits' or 'license' for more information
Python 7.6.1 -- An enhanced Interactive Python, Type '?' for help.
  [1]: from pyMCDS import pyMCDS
       get 2D mesh()
                                   get concentrations()
       get cell df()
                                   get_concentrations_at()
                                                              get_mesh_spacing()
                                                                                          pvMCDS.pv
       get_cell_df_at()
                                   get_containing_voxel_ijk() get_substrate_names()
        get cell variables(
```

ect

Jupyter Notebok Code Section 2

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

```
mcds = pyMCDS('output0000000.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'])
```



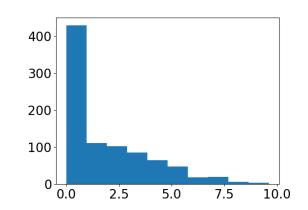
Jupyter Notebok Code Section 3

- 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)
```

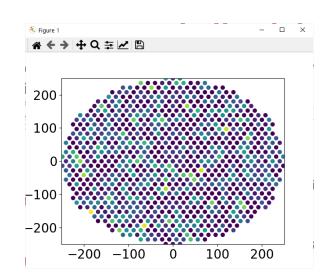


- Now, let's plot a histogram
  - plt.hist( mcds.data['discrete cells']['oncoprotein'] )

- 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

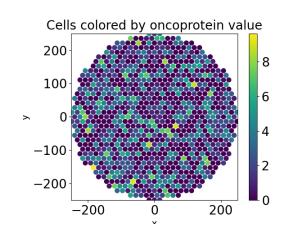
```
plt.colorbar()
```

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** 

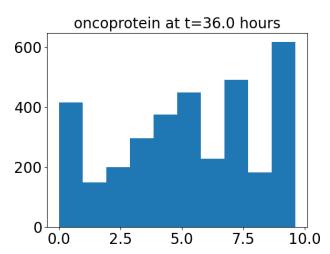




#### Let's load another time

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

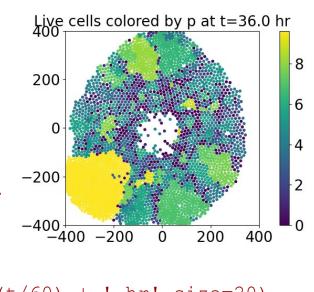
```
n_live = len( live ); print( n_live)
n_dead = len( dead ); print( n_dead );
```

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

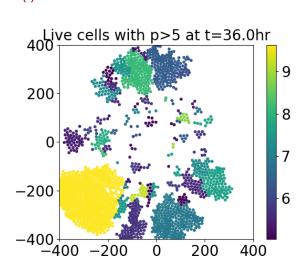
#### Let's do a fancier search

Jupyter Notebok Code Section 8a

• 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 ) 4
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.

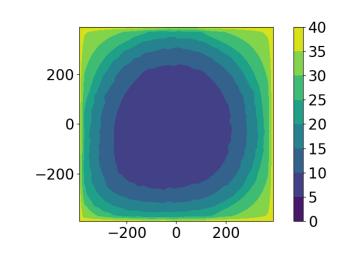


# Now let's plot the oxygen

```
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
                                                                Live cells colored by p at t=36.0 hr
plt.clf()
                                                                                            35
mcds.get substrate names();
                                                                200
                                                                                           30
o2 = mcds.get concentrations( 'oxygen');
                                                                                           -25
X,Y = mcds.qet 2D mesh();
                                                                                           -20
plt.contourf(X, Y, o2[:,:,0], cmap='spring');
                                                                                           -15
plt.colorbar()
                                                               -200
                                                                                           10
plt.scatter( cx[live], cy[live], c=op[live], s=circle size);
                                                               -400
plt.axis('image')
                                                                  -400 - 200
                                                                                 200
plt.axis([-400,400,-400,400])
plt.title('Live cells colored by p at t='+str(t/60) + 'hr', size=20)
                                                                               Jupyter Notebok
# let's plot dead cells as white and transparent
                                                                                Code Section 10
plt.scatter( cx[dead], cy[dead], c='w', s=circle size, alpha=0.5 );
```

### 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

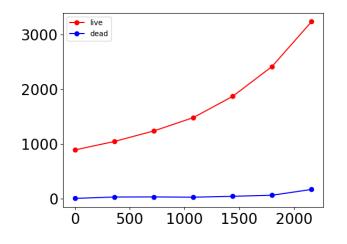
```
last index = 6;
live count = np.zeros( last index+1 );
dead count = np.zeros( last index+1 );
mean p = np.zeros( last index+1 );
std p = np.zeros( last index+1 );
times = np.zeros( last index+1 );
for n in range( 0, last index+1 ):
     filename='output'+"%08i"%n+'.xml'
     mcds=pyMCDS(filename, '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()</pre>
     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])
```



#### 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' } )
poly=np.polyfit( times, np.log(live count), 1)
print( poly[0] )
# growth rate is 0th element
# in units of 1/min
# 0.0005928392815655603
plt.clf()
plt.plot(times, mean p);
# mean increases rapidly
# due to selection processes
```

Jupyter Notebok Code Section 12



500

1000

1500

2000

#### 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">45</interval>
     <enable>true</enable>
  </svg>
  <legacy data>
     <enable>false</enable>
  </legacy data>
</save>
```

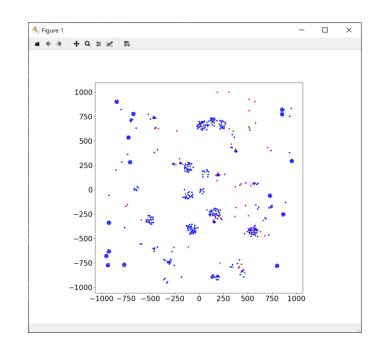
#### Let's load the last time

```
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']
```

#### Let's plot each type a different color

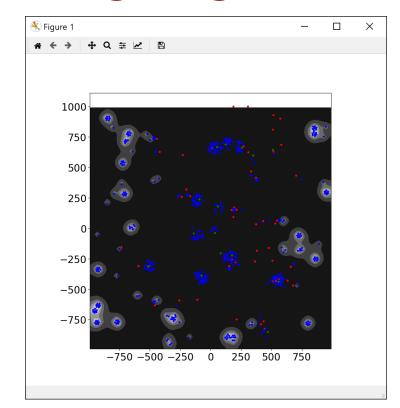
```
circle_size=20

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');
```



#### 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='q',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');
```



#### 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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- Breast Cancer Research Foundation
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- National Cancer Institute (U01CA232137)
- National Science Foundation (1720625)

#### **Training Materials:**

Administrative supplement to NCI U01CA232137 (Year 2)