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

Session 7: Functions in PhysiCell

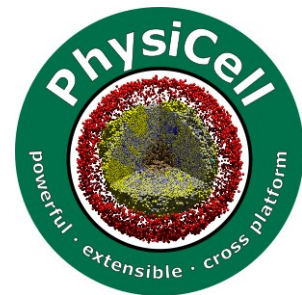


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 @MathCancer

PhysiCell Project

July 27, 2021



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Goals

- PhysiCell full modeling workflow
- Handy C++ Tidbits for Cell Agents
- Typical form / syntax / purpose of PhysiCell functions
- The customizable functions in Cell.functions
- How to assign new functions to a cell definition
- Sampling the microenvironment at Cell locations
- Example: Oxygen-based cell birth, death, and motility
- **Stretch goal:** Controlling initial cell placement
- **Stretch goal:** Custom coloring functions

Full modeling workflow

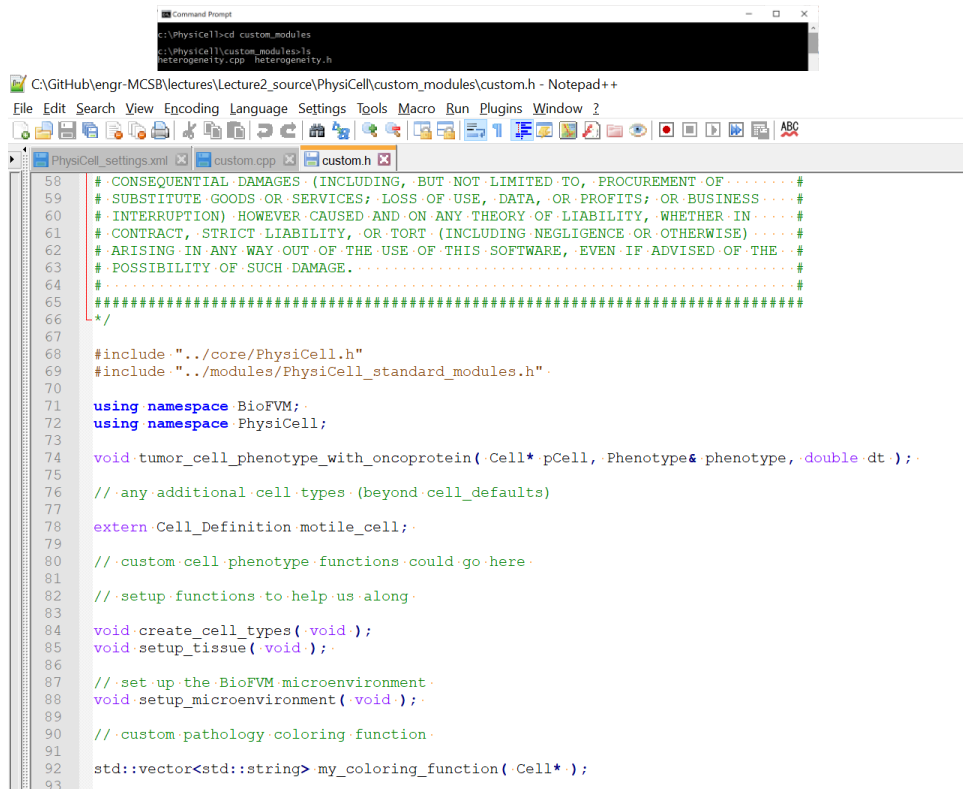
Suitable for creating a new PhysiCell model with custom C++ to drive dynamical phenotype changes

- 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

Project structure: custom modules

- Custom Modules

- Setup functions
- Cell definitions
- Custom functions
- any other modeling
- Custom coloring functions



The screenshot shows a Notepad++ window titled "C:\GitHub\engr-MCSB\lectures\Lecture2_source\PhysiCell\custom_modules\custom.h - Notepad++". The file content is as follows:

```
58  /* CONSEQUENTIAL DAMAGES (INCLUDING, BUT NOT LIMITED TO, PROCUREMENT OF .....#
59  /* SUBSTITUTE GOODS OR SERVICES; LOSS OF USE, DATA, OR PROFITS; OR BUSINESS .....#
60  /* INTERRUPTION) HOWEVER CAUSED AND ON ANY THEORY OF LIABILITY, WHETHER IN .....#
61  /* CONTRACT, STRICT LIABILITY, OR TORT (INCLUDING NEGLIGENCE OR OTHERWISE) .....#
62  /* ARISING IN ANY WAY OUT OF THE USE OF THIS SOFTWARE, EVEN IF ADVISED OF THE .....#
63  /* POSSIBILITY OF SUCH DAMAGE. ....#
64  /* .....#
65  /* .....#
66  */
67
68  #include "../core/PhysiCell.h"
69  #include "../modules/PhysiCell_standard_modules.h"
70
71  using namespace BioFVM;
72  using namespace PhysiCell;
73
74  void tumor_cell_phenotype_with_oncoprotein( Cell* pCell, Phenotype& phenotype, double dt );
75
76  // any additional cell types (beyond cell_defaults)
77
78  extern Cell_Definition motile_cell;
79
80  // custom cell phenotype functions could go here
81
82  // setup functions to help us along
83
84  void create_cell_types( void );
85  void setup_tissue( void );
86
87  // set up the BioFVM microenvironment
88  void setup_microenvironment( void );
89
90  // custom pathology coloring function
91
92  std::vector<std::string> my_coloring_function( Cell* );
93
```

Project structure: custom modules

- Custom Modules

- Any user-defined globals (at top)
- Setup functions

- ♦ `create_cell_types()`

- » Do all setup on all cell types
 - Adjust phenotype
 - Add / adjust custom data
 - Set functions

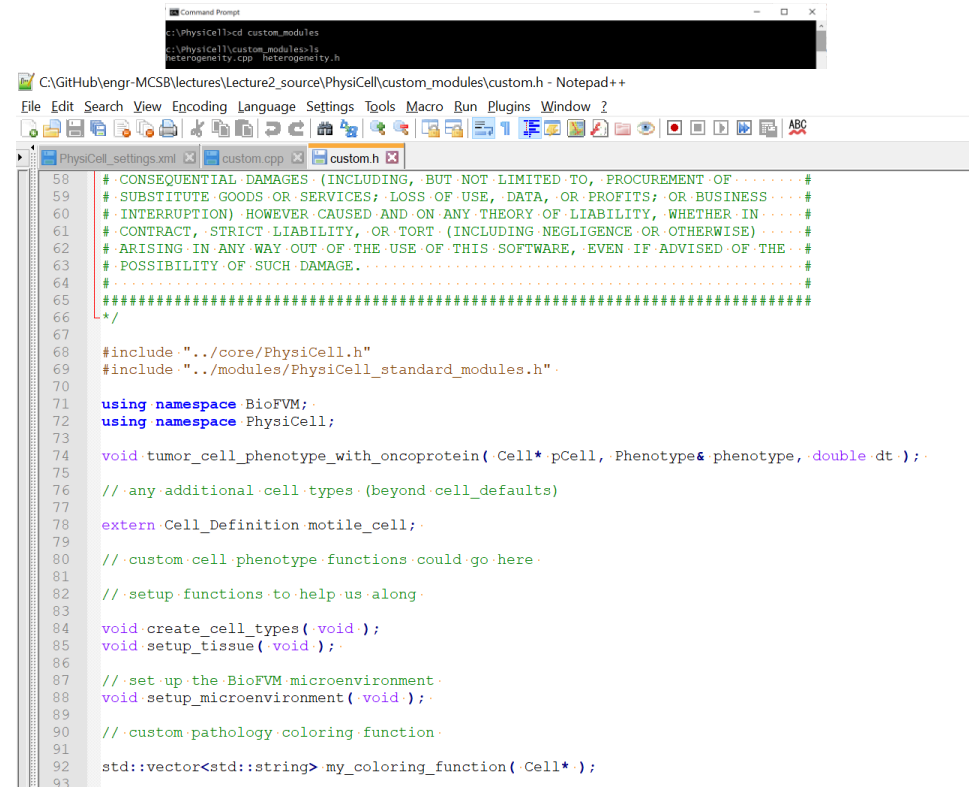
- ♦ `setup_tissue()`

- » Place initial cells in microenvironment
- » Modify each cell as needed

- Custom functions

- any other modeling

- Custom coloring functions



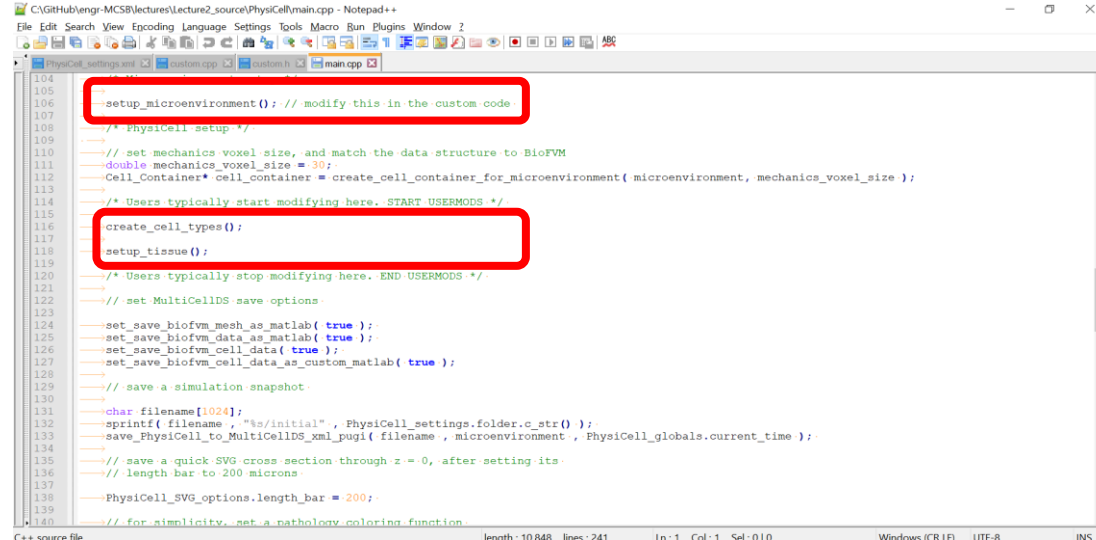
```
c:\PhysiCell>cd custom_modules
c:\PhysiCell\custom_modules>ls
heterogeneity.cpp  heterogeneity.h

C:\GitHub\engr-MCSB\lectures\Lecture2_source\PhysiCell\custom_modules\custom.h - Notepad++
File Edit Search View Encoding Language Settings Tools Macro Run Plugins Window ?
PhysiCell_settings.xml custom.cpp custom.h
58  /* CONSEQUENTIAL DAMAGES (INCLUDING, BUT NOT LIMITED TO, PROCUREMENT OF .....#
59  /* SUBSTITUTE GOODS OR SERVICES; LOSS OF USE, DATA, OR PROFITS; OR BUSINESS .....#
60  /* INTERRUPTION) HOWEVER CAUSED AND ON ANY THEORY OF LIABILITY, WHETHER IN .....#
61  /* CONTRACT, STRICT LIABILITY, OR TORT (INCLUDING NEGLIGENCE OR OTHERWISE) .....#
62  /* ARISING IN ANY WAY OUT OF THE USE OF THIS SOFTWARE, EVEN IF ADVISED OF THE .....#
63  /* POSSIBILITY OF SUCH DAMAGE. ....#
64  /* .....#
65  /* .....#
66  */
67
68 #include "../core/PhysiCell.h"
69 #include "../modules/PhysiCell_standard_modules.h"
70
71 using namespace BioFVM;
72 using namespace PhysiCell;
73
74 void tumor_cell_phenotype_with_oncoprotein( Cell* pCell, Phenotype& phenotype, double dt );
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78 extern Cell_Definition motile_cell;
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81
82 // setup functions to help us along
83
84 void create_cell_types( void );
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87 // set up the BioFVM microenvironment
88 void setup_microenvironment( void );
89
90 // custom pathology coloring function
91
92 std::vector<std::string> my_coloring_function( Cell* );
93
```

Project structure: main.cpp

- **main.cpp**

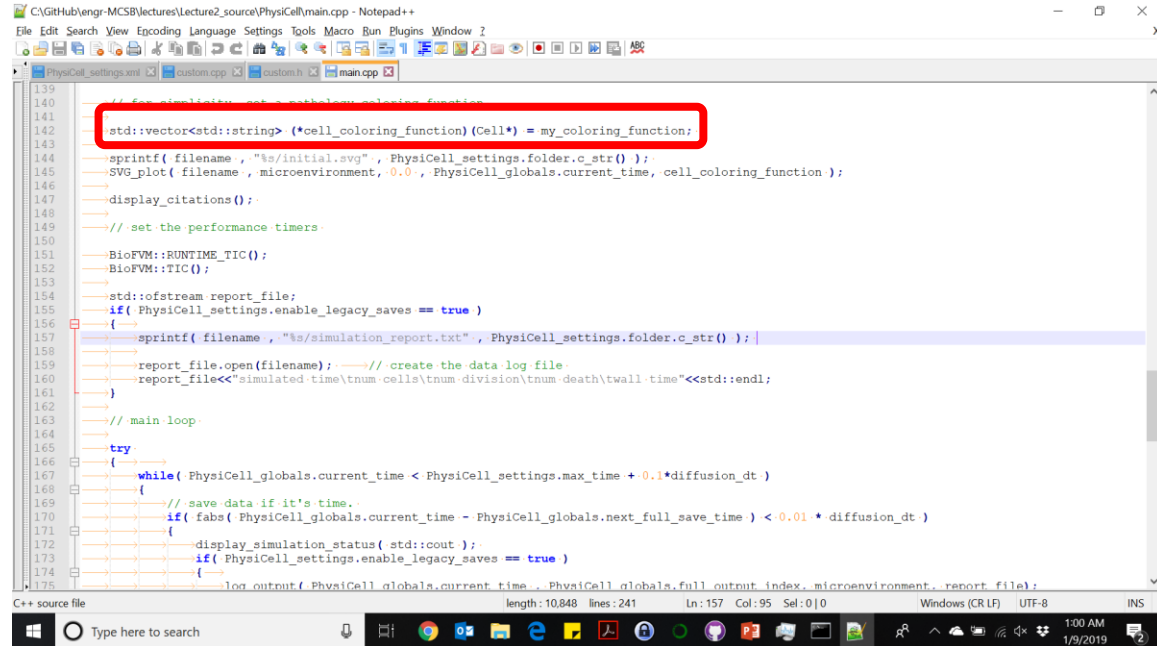
- (in the root directory)
- calls the setup functions



```
104
105 setup_microenvironment(); // modify this in the custom code
106
107 /* PhysiCell setup */
108
109
110 // set mechanics voxel size, and match the data structure to BioFVM
111 double mechanics_voxel_size = 30;
112 Cell_Container* Cell_container = create_cell_container_for_microenvironment( microenvironment, mechanics_voxel_size );
113
114 /* Users typically start modifying here. START USERMODS */
115
116 create_cell_types();
117 setup_tissue();
118
119 /* Users typically stop modifying here. END USERMODS */
120
121 // set MultiCellDS save options
122
123
124 set_save_biofvm_mesh_as_matlab( true );
125 set_save_biofvm_data_as_matlab( true );
126 set_save_biofvm_cell_data( true );
127 set_save_biofvm_cell_data_as_custom_matlab( true );
128
129 // save a simulation snapshot
130
131 char filename[1024];
132 sprintf( filename, "%s/initial", PhysiCell_settings.folder.c_str() );
133 save_PhysiCell_to_MultiCellDS_xml_pugi( filename, microenvironment, PhysiCell_globals.current_time );
134
135 // save a quick SVG cross section through z = 0, after setting its
136 // length bar to 200 microns
137
138 PhysiCell_SVG_options.length_bar = 200;
139
140 // for simplicity, set a pathology coloring function
```

Project structure: main.cpp (continued)

- **main.cpp**
 - set coloring function



```
C:\GitHub\engr-MCSB\Lectures\Lecture2_source\PhysiCell\main.cpp - Notepad++
File Edit Search View Encoding Language Settings Tools Macro Run Plugins Window ?

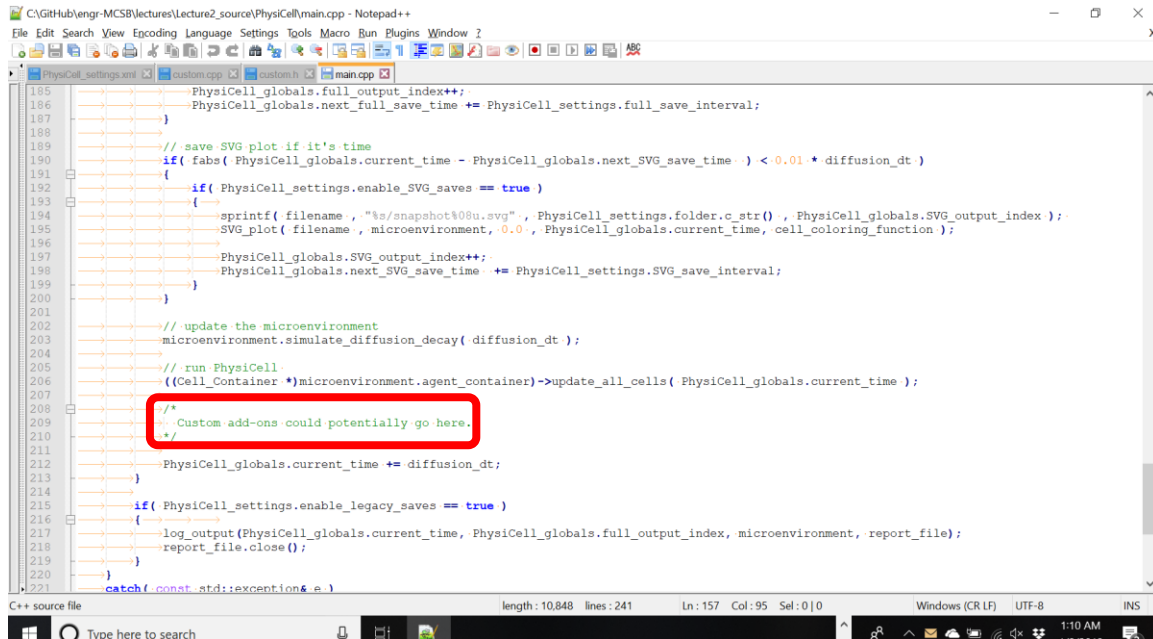
PhysiCell_settings.xml custom.cpp custom.h main.cpp
139 // for simplicity, set a pathless coloring function
140
141 std::vector<std::string> (*cell_coloring_function) (Cell*) = my_coloring_function;
142
143 printf( filename , "%s/initial.svg" , PhysiCell_settings.folder.c_str() );
144 SVG_plot( filename , microenvironment, 0.0 , PhysiCell_globals.current_time , cell_coloring_function );
145
146 display_citations();
147
148 // set the performance timers
149
150 BioFVM::RUNTIME_TIC();
151 BioFVM::TIC();
152
153 std::ofstream report_file;
154 if( PhysiCell_settings.enable_legacy_saves == true )
155 {
156     printf( filename , "%s/simulation_report.txt" , PhysiCell_settings.folder.c_str() );
157     report_file.open(filename); // create the data log file
158     report_file<<"simulated time\tnum. cells\tnum. division\tnum. death\twall time"<<std::endl;
159 }
160
161 // main loop
162
163 try
164 {
165     while( PhysiCell_globals.current_time < PhysiCell_settings.max_time + 0.1*diffusion_dt )
166     {
167         // save data if it's time
168         if( fabs( PhysiCell_globals.current_time - PhysiCell_globals.next_full_save_time ) < 0.01*diffusion_dt )
169         {
170             display_simulation_status( std::cout );
171             if( PhysiCell_settings.enable_legacy_saves == true )
172             {
173                 log_output( PhysiCell_globals.current_time , PhysiCell_globals.full_output_index , microenvironment , report_file );
174             }
175         }
176     }
177 }
```

Project structure: main.cpp (continued)

- **main.cpp**

- **main loop:**

- ♦ **This would be a good place to put extensions.**



```
C:\GitHub\enr-MCSB\lectures\Lecture2_source\PhysiCell\main.cpp - Notepad++
File Edit Search View Encoding Language Settings Tools Macro Run Plugins Window ?

PhysiCell_settings.xml custom.cpp custom.h main.cpp
185 PhysiCell_globals.full_output_index++;
186 PhysiCell_globals.next_full_save_time += PhysiCell_settings.full_save_interval;
187 }
188 // save SVG plot if it's time
189 if ( fabs( PhysiCell_globals.current_time - PhysiCell_globals.next_SVG_save_time ) < 0.01 * diffusion_dt )
190 {
191     if ( PhysiCell_settings.enable_SVG_saves == true )
192     {
193         sprintf( filename , "%s/snapshot%08u.svg" , PhysiCell_settings.folder.c_str() , PhysiCell_globals.SVG_output_index );
194         SVG_plot( filename , microenvironment , 0.0 , PhysiCell_globals.current_time , cell_coloring_function );
195         PhysiCell_globals.SVG_output_index++;
196         PhysiCell_globals.next_SVG_save_time += PhysiCell_settings.SVG_save_interval;
197     }
198 }
199 // update the microenvironment
200 microenvironment.simulate_diffusion_decay( diffusion_dt );
201 // run PhysiCell
202 {Cell_Container *}microenvironment.agent_container->update_all_cells( PhysiCell_globals.current_time );
203 /*
204  * Custom add-ons could potentially go here.
205  */
206 PhysiCell_globals.current_time += diffusion_dt;
207 }
208 if ( PhysiCell_settings.enable_legacy_saves == true )
209 {
210     log_output( PhysiCell_globals.current_time , PhysiCell_globals.full_output_index , microenvironment , report_file );
211     report_file.close();
212 }
213 }
214 catch( const std::exception& e )
```


Summary: Where things will go

- Declare custom functions in **./custom_modules/custom.h**
- Implement these functions in **./custom_modules/custom.cpp**
- Assign custom functions to cell definitions in custom.cpp in **create_cell_types()**;
- Declare any cell parameters needed for custom functions in the **custom_data** part of a cell definition in the XML configuration file
- Declare any parameters need to set up the simulation in the **user_parameters** part of the XML config file

Handy C++ Helpers (Part 1)



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Handy C++ Tidbits: Random Numbers

- `double UniformRandom(void);`
 - Get a uniformly distributed number in $U(0,1)$
- `double NormalRandom(double mean, double standard_deviation);`
 - Get a normally distributed number in $N(\text{mean}, \text{standard_deviation})$
- `std::vector<double> UniformOnUnitCircle(void);`
 - Get a uniformly random point on the Unit Circle
- `std::vector<double> UniformOnUnitSphere(void);`
 - Get a uniformly random point on (not in!) the unit sphere.
- `int choose_event(std::vector<double>& probabilities);`
 - Given a vector of probabilities $(p_0, p_1, \dots, p_{n-1})$, choose an integer in $[0, n-1]$ with the given probabilities.
 - The probabilities must sum to 1.

These use the STL 64-bit
Mersenne Twister in C++11.

Handy C++ Tidbits: Vectors

- `std::vector<double> normalize(std::vector<double>& v);`
 - Return a normalized vector. (Convention: return (0,0,0) for small vectors)
- `void normalize(std::vector<double>* v);`
 - Directly normalize the vector at v. (Convention: return (0,0,0) for small vectors)
- `double norm_squared(const std::vector<double>& v);`
 - Return a norm squared. (Handy and avoids an expensive square root.)
- `double norm(const std::vector<double>& v);`
 - Returns standard Euclidean (ℓ_2) norm.
- `double maxabs(const std::vector<double>& v);`
 - Returns the maximum absolute value in the vector. i.e., this is the ℓ_∞ norm.
- `void csv_to_vector(const char* buffer , std::vector<double>& vect);`
 - Starting with a character string, separates (by a comma delimiter), converts to doubles, and stores result in the vector.
- `char* vector_to_csv(const std::vector<double>& vect);`
 - Turns a vector into a comma-separated string. Should probably modernize these with `std::string`.

We have also defined expected
vector operations for
`std::vector<double>`:
+, -, *, /, +=, -=, *=, /=

Handy C++ tidbits: forced birth and death

- **Cell** methods for forcing cell birth and death

- `void flag_for_division(void);`

- ♦ Use this if you want to force the cell to divide at the next opportunity

- `void start_death(int death_model_index);`

- ♦ Use this to trigger a specific death model (at the next opportunity)

- `void lyse_cell(void);`

- ♦ Trigger **immediate death** that sets volume to 0, deactivates all functions, and detaches the cell from all other linked cells. Cell will be deleted at next `dt_cell` step.

- ♦ Safer than `flag_for_removal()`

Handy C++ tidbits: Boolean flags

- The **Cell** class has a few useful member data:
 - `bool is_out_of_domain;`
 - ♦ Set this to **true** if the cell is out of the domain.
 - ♦ I'm not 100% sure this is maintained up-to-date by the code. (It's on my to do list!)
 - `bool is_movable;`
 - ♦ This is ordinarily **true**, and allows the cell to be pushed by other cells.
 - ♦ Set this to **false** if you want the cell to exert forces on other cells, but don't want it to move (i.e., behave as a rigid barrier)

PhysiCell Cell Functions



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Functions in PhysiCell

- In PhysiCell, almost all cell functions have the following form:

```
void function( Cell* pCell, Phenotype& phenotype , double dt );
```

- pCell : pointer to a cell. Can be NULL
- phenotype: a cell phenotype. Usually pCell->phenotype.
- dt: how far the function / model should be advanced in time.
- These functions can access:
 - Cell **state** via pCell->state
 - Cell **custom** data via pCell->custom_data
 - Cell **functions** via pCell->functions
 - Cell **phenotype** via phenotype
 - nearby **microenvironment** via pCell->nearest_density_vector() and pCell->nearest_gradient_vector()

Functions in PhysiCell

- Almost all functions in PhysiCell have this form:

```
void my_function( Cell* pCell, Phenotype& phenotype, double dt );
```

All cells have the following key functions (in `pCell->functions`):

- `volume_update_function` (defaults to a built-in model)
- `update_migration_bias` (default NULL unless you enabled chemotaxis)
- `custom_cell_rule` (default NULL, evaluated at each mechanics time step)
- `update_phenotype` (default NULL, evaluated at each phenotype time step)
- `update_velocity` (defaults to a built-in model with potentials)
- `set_orientation` (automatically set as needed)
- `contact_function` (default NULL, evaluated at each mechanics time step)
 - We'll spend more time on this in Sessions 9-11

Purpose of the Functions

- **volume_update_function**
 - Dynamically grow / shrink cells towards "target" values
- **update_migration_bias**
 - Used whenever a cell chooses a new migration bias direction
- **custom_cell_rule**
 - A catch-all customization that's evaluated at each mechanics time step. (0.1 min)
 - Use this for rules that need frequent evaluation.
- **update_phenotype**
 - The general purpose rule to set phenotype parameters at each cell temp step. (6 min)
 - Generally where you spend the majority of your (implementation) time in a modeling project.
- **update_velocity**
 - Sets the cell velocity based on interaction potentials.
 - The custom rule and motility functions are automatically evaluated as well.
- **set_orientation**
 - Used during cell division to choose the division plane (a random plane through this vector).
 - We set this to (0,0,1) for 2-D simulations to ensure division in the xy-plane
- **contact_function**
 - A newer addition for cell-cell contact interactions such as adding/removing spring links. Evaluated at each mechanics step. More tomorrow.

A short example

- In custom.h, declare your new function;

```
void my_phenotype_function( Cell* pCell, Phenotype& phenotype, double dt );
```

- In custom.cpp, write the code:

```
void my_phenotype_function( Cell* pCell, Phenotype& phenotype, double dt )
{
    // get a rate from cell's custom data
    double rate = pCell->custom_data["rate"];
    // change a cell's apoptosis rate
    phenotype.death.rates[0] = rate;
    return;
}
```

- Use the function

```
cell_defaults.functions.update_phenotype = my_phenotype_function;
```

- The best place to do this is in create_cell_types() in custom.cpp

Handy C++ Helpers (Part 2)



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Cell methods to access the microenvironment

- `int get_current_voxel index(void)`
 - Gives the index of the voxel that contains the agent's center.
 - More on this when we discuss diffusion
- `std::vector<double>& nearest_density_vector(void)`
 - a vector for all the substrate density values (stuff/volume) in the cell's voxel
 - allows the user to directly access (i.e., sample or modify) the vector of substrates at the cell's position
 - useful building functions that alter cell phenotype based on the microenvironment.
- `std::vector<double>& nearest_gradient(int substrate_index)`
 - for the substrate with index i , gives the gradient $\left[\frac{\partial}{\partial x}, \frac{\partial}{\partial y}, \frac{\partial}{\partial z} \right] \rho_i$ in the cell's voxel
 - useful for things like chemotaxis.
- `std::vector<gradient>& nearest_gradient_vector(void)`
 - gives a vector of **all** the gradients in the cell's voxel returns

More key functions

- `Cell_Definition* find_cell_definition(std::string)`
 - Get a pointer to a cell definition by searching for its name.
- `Cell_Definition* find_cell_definition(int)`
 - Get a pointer to a cell definition by searching for its integer type.
 - Since cells keep their `type_ID`, this can be quite handy for phenotype functions.
- `int Microenvironment::find_density_index(std::string)`
 - Search for the index in for a specific ucstrate
 - Useful for phenotype functions.
 - The default microenvironment in PhysiCell is named **microenvironment**.

Full Model Workflow: Example



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Scenario: Oxygen-dependent cells

- Let's illustrate these with an example:
 - tumor cells:
 - ♦ Cycle entry proportional to local pO_2
 - ♦ Necrosis probability increases below a pO_2 threshold
 - motile tumor cells:
 - ♦ Same as tumor cells, but:
 - » 1/10 cycling rate
 - » 1/10 apoptosis rate
 - » a more advanced chemotaxis up oxygen gradients
 - » migration slows as oxygen increases.

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

Planning (1)

- Microenvironment
 - [-400,400] x [-400,400], 2160 minutes max time.
 - Oxygen with default parameters, boundary and initial conditions to 38 mmHg
 - Enable virtual wall
- Custom cell data (known once you have planned your cell functions)
 - pO2_proliferation_saturation (max proliferation rate above this value)
 - pO2_proliferation_threshold (no proliferation below this value)
 - pO2_necrosis_threshold (necrosis starts at this value)
 - pO2_necrosis_saturation (necrosis at max value below this value)
 - max_necrosis_rate (max necrotic death rate for very low pO2)
 - pO2_half_max (for Hill function)
 - pO2_hill_power (for Hill function)
- Cell definitions
 - tumor
 - motile tumor

Planning (2)

- Tumor cell proliferation ($\sigma = \text{pO}_2$) with the simpler **live** cycle model.

$$r_{00} = \bar{r}_{00} \left(\frac{\sigma - \sigma_{\text{p_threshold}}}{\sigma_{\text{p_saturation}} - \sigma_{\text{p_threshold}}} \right)$$

- $\sigma_{\text{p_saturation}} = 38 \text{ mmHg (5\%)}$
- $\sigma_{\text{p_threshold}} = 5 \text{ mmHg (0.65\%)}$
- $\bar{r}_{00} = 0.00072 \text{ min}^{-1}$

- Tumor cell necrosis ($\sigma = \text{pO}_2$)

$$r_N = \bar{r}_N \left(\frac{\sigma_{\text{n_threshold}} - \sigma}{\sigma_{\text{n_threshold}} - \sigma_{\text{n_saturation}}} \right)$$

- $\sigma_{\text{n_threshold}} = 5 \text{ mmHg (0.65\%)}$
- $\sigma_{\text{n_saturation}} = 2.5 \text{ mmHg (0.32\%)}$
- $\bar{r}_N = 0.0028 \text{ min}^{-1}$

Planning (3)

- Tumor cell motility ($\sigma = \text{pO}_2$)
 - Let's use a basic Hill function to modulate speed and bias in (already) motile tumor cells
 - Assume as pO_2 increases, the "signal" is stronger for less random and faster migration.

$$\mathbf{d}_{\text{bias}} = \frac{\nabla \sigma}{|\nabla \sigma|}$$

$$\text{speed} = \bar{s} \left(1 - \frac{s}{1+s} \right), \quad \text{where } s = \left(\frac{\sigma}{\sigma_{\text{HM}}} \right)^{\text{hp}}$$

$$\text{bias} = \left(\frac{s}{1+s} \right)$$

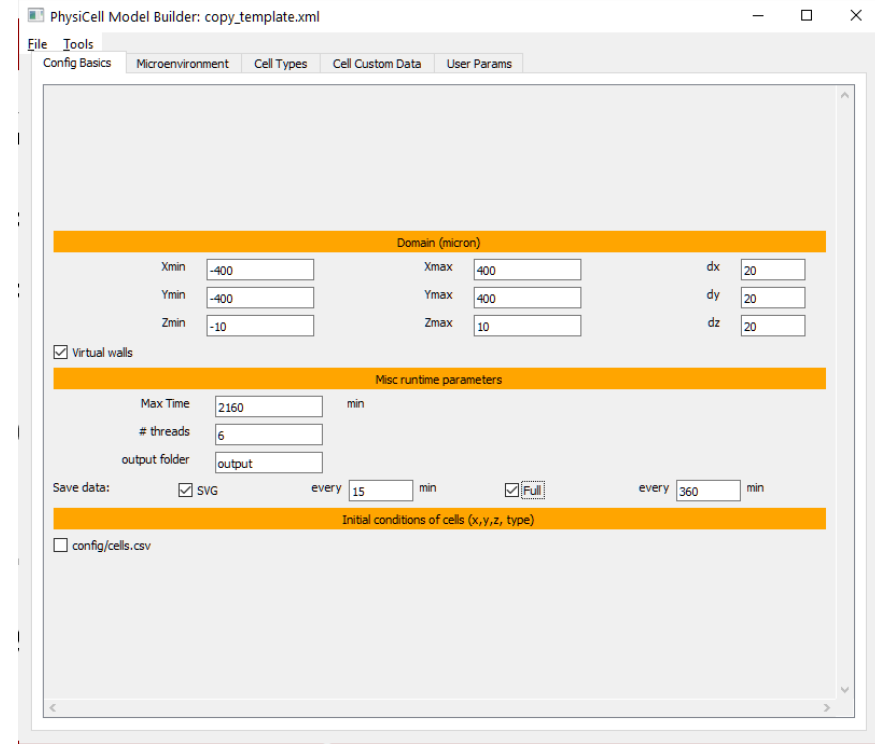
- $\bar{s} = 1 \mu\text{m}/\text{min}$
- $\sigma_{\text{HM}} = 4 \text{ mmHg (1\%)}$
- $\text{hp} = 2$
- set persistence time to 15 min

Start modeling!

- populate and build the template project
 - `make template`
 - `make`
- Open Model Builder GUI
 - enter the `./PhysiCell/config` directory
 - `python ../../PhysiCell-model-builder/bin/gui4xml.py`

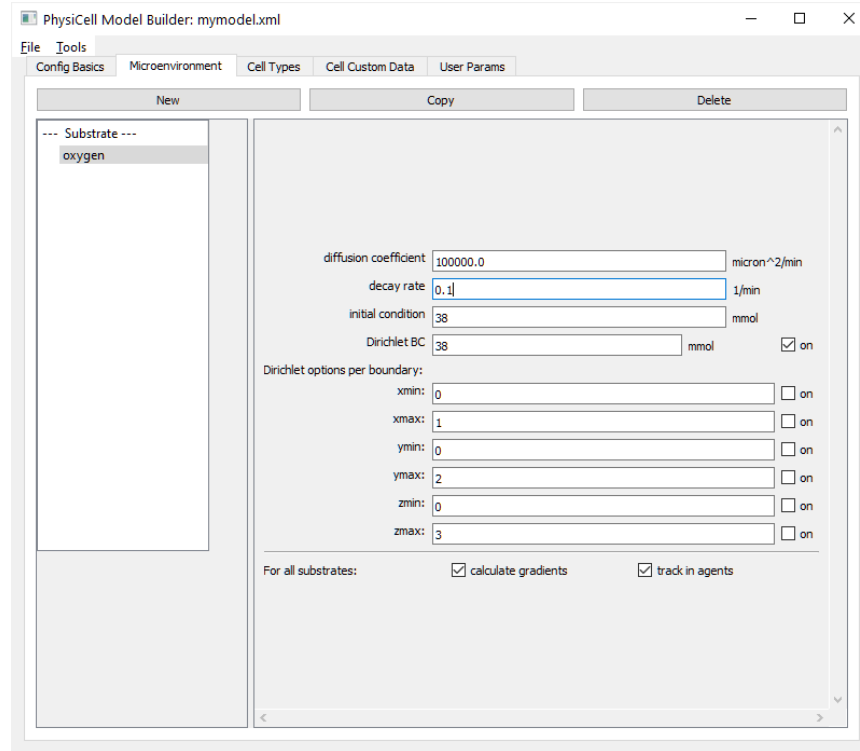
Edit the model: domain

- Go to "config basics" tab
- Xmin = -400, Xmax = 400
- Ymin = -400, Ymax = 400
- max time = 2160
- full output every 360 min
- SVG every 15 min
- activate "virtual wall"
 - keep cells from leaving the domain



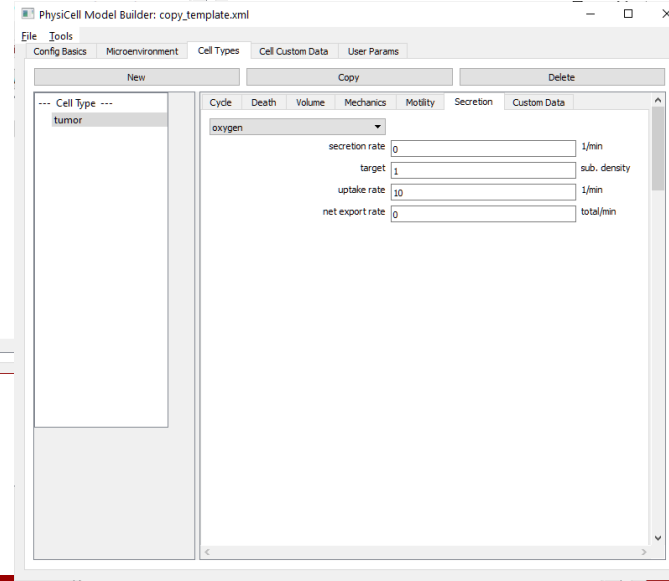
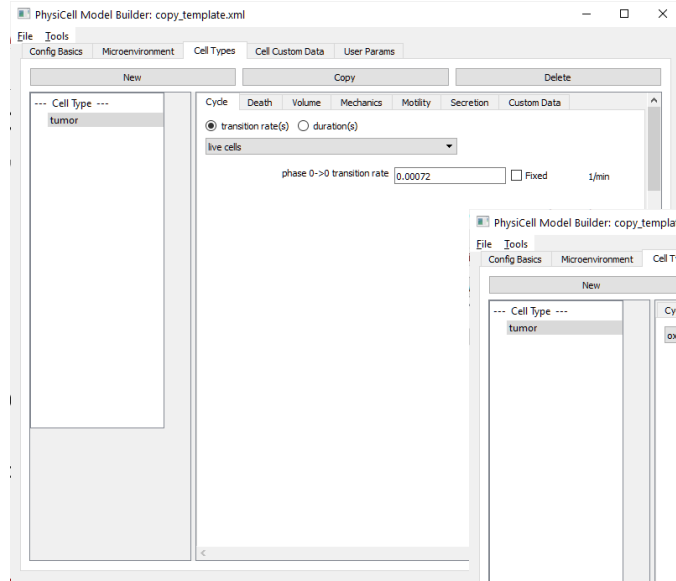
Edit the model: microenvironment

- Go to "microenvironment" tab
- double-click "substrate"
 - rename it oxygen, with units mmHg
 - reduce decay rate to 0.1
 - set Dirichlet BC to 38 (mmHg)
 - enable the Dirichlet BC
 - set initial value to 38 (mmHg)



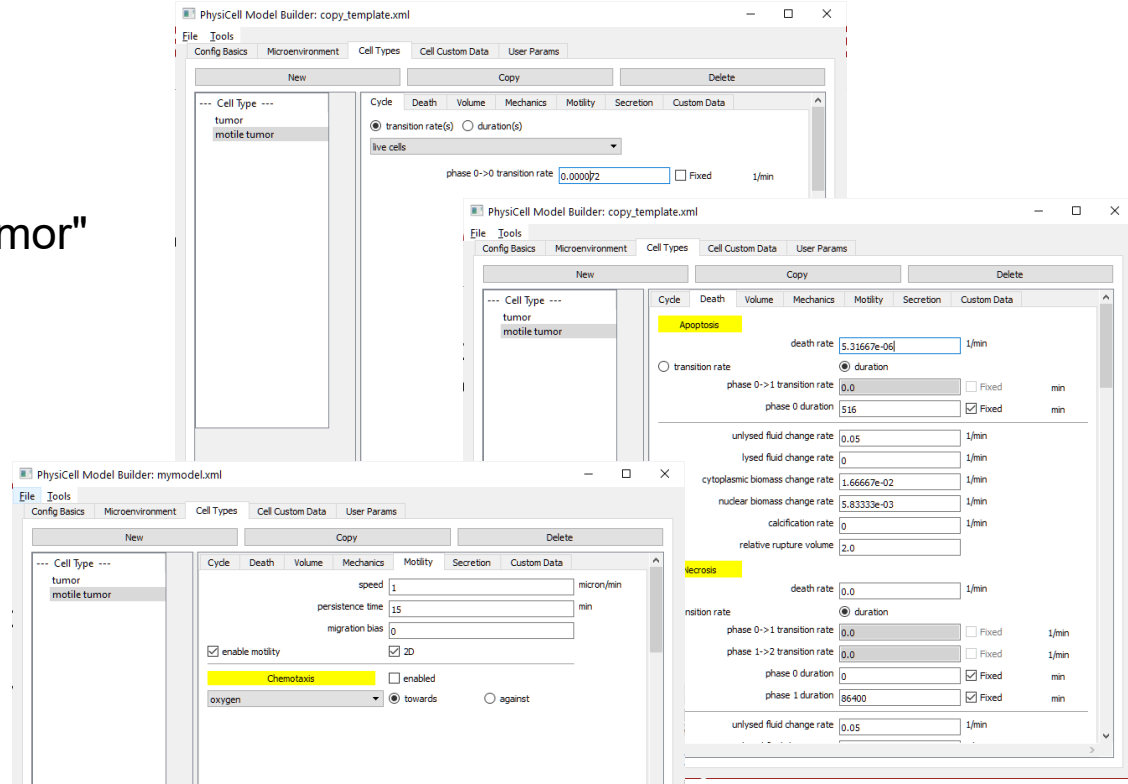
Edit the model: cell definitions (1)

- Go to "cell types" tab
- double-click "default"
 - rename it "tumor"
 - edit its phenotype:
 - ◆ click "cycle" subtab
 - » choose live cycle model
 - » select "transition rate(s)"
 - » set 0→0 transition to 0.00072
 - ◆ click "secretion" subtab
 - » Choose "oxygen" from dropdown
 - set uptake rate to 10



Edit the model: cell definitions (2)

- Go to "cell types" tab
- click "copy" to duplicate the tumor type
 - double click, rename to "motile tumor"
 - edit its phenotype:
 - click on "cycle"
 - set phase 00 transition to 0.000072
 - click on "death"
 - set apoptosis rate to 5.31667e-06
 - click on "motility"
 - set speed to 1
 - set persistence time to 15
 - set bias to 0 (we'll handle in-function later)
 - check to enable



Edit the model: custom cell data

- Go to "cell custom data" tab
 - add a new data called "pO2_proliferation_saturation"
 - Fill out the default value, units, and description
 - Check the box on left to make sure it's copied to all cell definitions
 - Add pO2_proliferation_threshold
 - Add pO2_necrosis_threshold
 - Add pO2_necrosis_saturation
 - Add max_necrosis_rate
 - Add pO2_half_max
 - Add pO2_hill_power

PhysiCell Model Builder: mymodel.xml

File Tools

Config Basics Microenvironment Cell Types Cell Custom Data User Params

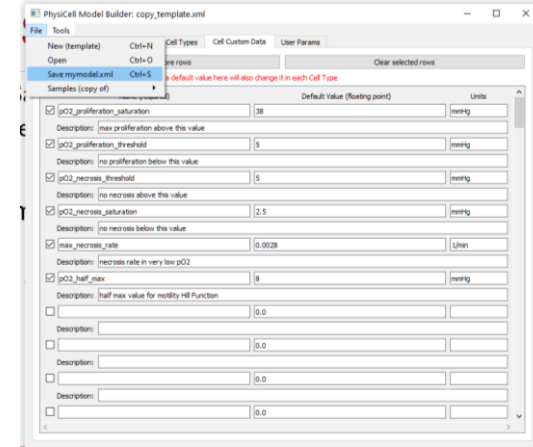
Append 5 more rows Clear selected rows

Note: changing a default value here will also change it in each Cell Type

	Name (required)	Default Value (floating point)	Units
<input checked="" type="checkbox"/>	pO2_proliferation_saturation	38	mmHg
	Description: max proliferation above this value		
<input checked="" type="checkbox"/>	pO2_proliferation_threshold	5	mmHg
	Description: no proliferation below this value		
<input checked="" type="checkbox"/>	pO2_necrosis_threshold	5	mmHg
	Description: no necrosis above this value		
<input checked="" type="checkbox"/>	pO2_necrosis_saturation	2.5	mmHg
	Description: no necrosis below this value		
<input checked="" type="checkbox"/>	max_necrosis_rate	0.0028	1/min
	Description: necrosis rate in very low pO2		
<input checked="" type="checkbox"/>	pO2_half_max	4	mmHg
	Description: half max value for motility Hill Function		
<input checked="" type="checkbox"/>	pO2_hill_power	2	dimensionless
	Description: hill power		
<input type="checkbox"/>		0.0	
	Description:		
<input type="checkbox"/>		0.0	
	Description:		
<input type="checkbox"/>		0.0	
	Description:		

Save to the project

- Go to "File", then "Save mymodel.xml"
 - This saves to wherever we ran PhysiCell Model Builder
- If needed, copy mymodel.xml to `./PhysiCell/config/`
- Since we ran inside the config directory, it's already there!



Unzip [Session7_checkpoint1.zip](#)
in `./PhysiCell` to get this code.

Declare custom functions

- In `./custom_modules/custom.h`, declare:

```
void tumor_phenotype( Cell* pC, Phenotype& p, double dt);
```

```
void motile_tumor_phenotype( Cell* pC, Phenotype& p, double dt);
```

```
void motility_rule( Cell* pC, Phenotype& p, double dt );
```

Custom phenotype rule (1)

```
void tumor_phenotype( Cell* pC, Phenotype& p, double dt)
{
    // find my cell definition
    // find index of O2 in the microenvironment
    // find index of necrosis death model

    // sample O2

    // set birth rate
    // get base rate from cell definition
    // set multiplier to 1.0
    // sample pO2. if pO2 < pO2_proliferation_saturation:
    //     multiplier = (pO2 - pO2_proliferation_threshold)
    //     / (pO2_proliferation_saturation - pO2_proliferation_threshold)
    // if pO2 < pO2_proliferation_threshold, set multiplier = 0.0
    // transition rate = base_rate * multiplier

    // set necrosis rate
    // multiplier = 0.0
    // if pO2 < pO2_necrosis_threshold
    //     multiplier = (pO2_necrosis_threshold - pO2)
    //     / (pO2_necrosis_threshold - pO2_necrosis_saturation)
    // if pO2 < pO2_necrosis_saturation
    //     multiplier = 1
    // necrosis rate = max_necrosis_rate * multiplier

    // if dead, set secretion / uptake rates to zero

    // trick: if dead, overwrite with NULL function pointer.
}
```

Custom phenotype rule (2)

```
void tumor_phenotype( Cell* pC, Phenotype& p, double dt)
{
    // find my cell definition
    Cell_Definition* pCD = find_cell_definition( pC->type );

    // find index of O2 in the microenvironment
    static int nO2 = microenvironment.find_density_index( "oxygen" );

    // find index of necrosis death model
    static int nNecro = p.death.find_death_model_index( "Necrosis" );

    // sample O2
    double pO2 = pC->nearest_density_vector()[nO2];

    // set birth rate
    // get base rate from cell definition
    double base_rate = pCD->phenotype.cycle.data.transition_rate(0,0);
    // set multiplier to 1.0
    double multiplier = 1.0;
```

Custom phenotype rule (3)

```
// sample pO2. if pO2 < pO2_proliferation_saturation:
if( pO2 < pC->custom_data["pO2_proliferation_saturation"] )
{
    // multiplier = (pO2 -pO2_proliferation_threshold)
    //      /(pO2_proliferation_saturation-pO2_proliferation_threshold)

    multiplier = (pO2 - pC->custom_data["pO2_proliferation_threshold"] )
        /( pC->custom_data["pO2_proliferation_saturation"]
            -pC->custom_data["pO2_proliferation_threshold"] );
}

// if pO2 < pO2_proliferation_threshold, set multiplier = 0.0
if( pO2 < pC->custom_data["pO2_proliferation_threshold"] )
{ multiplier = 0.0; }

// transition rate = base_rate * multiplier
p.cycle.data.transition_rate(0,0) = base_rate * multiplier;
```



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Custom phenotype rule (4)

```
// set necrosis rate
// multiplier = 0.0
multiplier = 0.0;

// if pO2 < pO2_necrosis_threshold
if( pO2 < pC->custom_data["pO2_necrosis_threshold"] )
{
    // multiplier = (pO2_necrosis_threshold - pO2)
    //      / (pO2_necrosis_threshold - pO2_necrosis_saturation)

    multiplier = (pC->custom_data["pO2_necrosis_threshold"] - pO2 )
        / ( pC->custom_data["pO2_necrosis_threshold"]
            - pC->custom_data["pO2_necrosis_saturation"] );
}

// if pO2 < pO2_necrosis_saturation
// multiplier = 1
if( pO2 < pC->custom_data["pO2_necrosis_saturation"] )
{ multiplier = 1.0; }

// necrosis rate = max_necrosis_rate * multiplier
p.death.rates[nNecro] = pC->custom_data["max_necrosis_rate"] * multiplier;
```


Custom phenotype rule (5)

```
// if dead, set secretion / uptake rates to zero
// trick: if dead, overwrite with NULL function pointer.
if( p.death.dead == true )
{
    p.secretion.set_all_secretion_to_zero();
    p.secretion.set_all_uptake_to_zero();
    pC->functions.update_phenotype = NULL;
}

return;
}

void motile_tumor_phenotype( Cell* pC, Phenotype& p, double dt)
{ return; }
```

Unzip [Session7_checkpoint2.zip](#)
in ./PhysiCell to get this code.

Custom motility rule (1)

```
void motility_rule( Cell* pC, Phenotype& p, double dt )
{
    // find my cell definition
    // find index of O2 in the microenvironment

    // sample pO2
    // sample pO2 gradient

    // check against pO2_half_max; set motility false and exit if needed

    // set migration bias direction to grad(pO2)
    // normalize

    // set the Hill multiplier
    //  $s = (pO2/pO2\_half\_max)^{pO2\_hill\_power}$ 
    //  $hill = s / (1+s)$ ;

    // set speed
    //  $speed = base\_speed * (1-hill)$ 

    // migration bias
    //  $bias = hill$ 

    // trick: if dead, overwrite with NULL function pointer.
}
```



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Custom motility rule (2)

```
void motility_rule( Cell* pC, Phenotype& p, double dt )
{
    // find my cell definition
    Cell_Definition* pCD = find_cell_definition( pC->type );

    // find index of O2 in the microenvironment
    static int nO2 = microenvironment.find_density_index( "oxygen" );

    // sample pO2
    double pO2 = pC->nearest_density_vector()[nO2];

    // sample pO2 gradient
    // set migration bias direction to grad(pO2)
    p.motility.migration_bias_direction = pC->nearest_gradient(nO2);

    // normalize
    normalize( &(p.motility.migration_bias_direction) );
}
```

Custom motility rule (3)

```
// set the Hill multiplier
// s = (pO2/pO2_half_max)^pO2_hill_power
// hill = s / ( 1+s );
double temp = pow( pO2 / pC->custom_data["pO2_half_max"] , pC->custom_data["pO2_hill_power"] );
double hill = temp / (1.0 + temp );

// set speed
// speed = base_speed * hill
p.motility.migration_speed = pCD->phenotype.motility.migration_speed * (1-hill);

// migration bias
// bias = multiplier
p.motility.migration_bias = hill;

// trick: if dead, overwrite with NULL function pointer.
if( p.death.dead == true )
{ pC->functions.update_migration_bias = NULL; }
}
```

Assign the functions

```
// in create_cell_types():

/*
    Put any modifications to individual cell definitions here.

    This is a good place to set custom functions.
*/

cell_defaults.functions.update_phenotype = phenotype_function;
cell_defaults.functions.custom_cell_rule = custom_function;
cell_defaults.functions.contact_function = contact_function;

Cell_Definition* pCD = find_cell_definition( "tumor" );
pCD->functions.update_phenotype = tumor_phenotype;

pCD = find_cell_definition( "motile tumor" );
pCD->functions.update_phenotype = motile_tumor_phenotype;
pCD->functions.update_migration_bias = motility_rule;

/*
    This builds the map of cell definitions and summarizes the setup.
*/

// ...
```

Let's modify the setup

- Let's start with 200 of each cell type. Open `./config/mymodel.xml`:
- Scroll down to **user_parameters**

```
<user_parameters>
  <random_seed type="int" units="dimensionless"
    description="">0</random_seed>
  <number_of_cells type="int" units="none"
    description="initial number of cells
    (for each cell type)">200</number_of_cells>
</user_parameters>
```

Unzip [Session7_checkpoint3.zip](#)
in `./PhysiCell` to get this code.



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Rebuild and run the project

- Open the XML config file and set max simulation time to 3600 minutes
- rebuild:
 - `make`
- run:
 - `./project ./config/mymodel.xml` (linux, MacOS)
 - `project ./config/mymodel.xml` (Windows)



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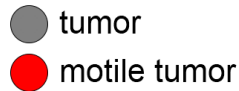
PhysiCell.org

 **@PhysiCell**

View results!

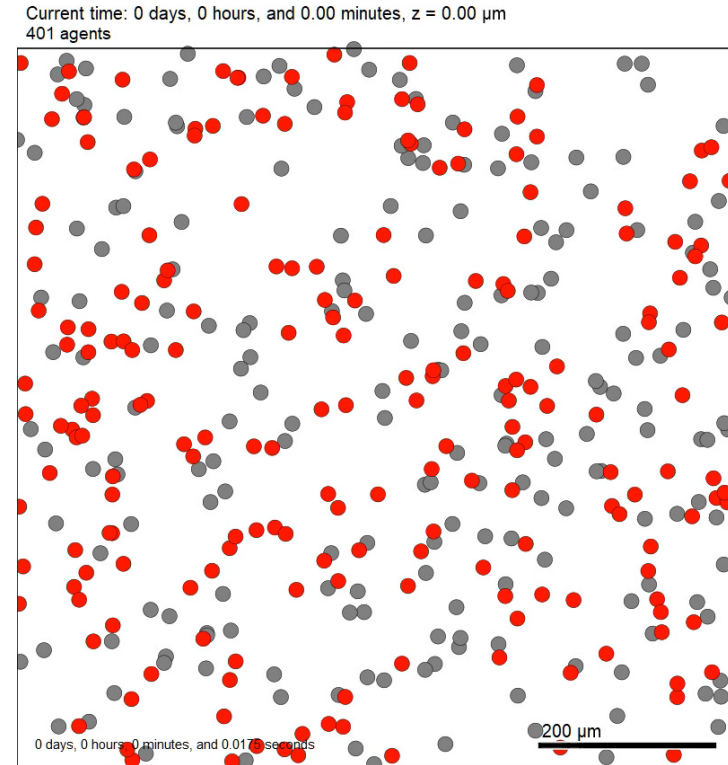
- make animated GIF

- **make gif**



- Expected behavior:

- gray tumor cells proliferate
 - ◆ fastest near higher pO₂ on boundary
 - gray cells proliferate faster than red
 - red motile tumor cells migrate towards outer boundary
 - red migration slows down as they near boundary



Handy C++ Helpers (Part 3)



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Handy C++ tidbits: creating cells

- Functions to help (properly) create and place new cells
 - `Cell* create_cell(void);`
 - ♦ Create a new **Cell** using the default cell definition (cell_defaults: has ID 0)
 - ♦ Returns a pointer to the cell, allowing you to further access and modify it
 - `Cell* create_cell(Cell_Definition& cd);`
 - ♦ Create a new **Cell** using supplied cell definition
 - ♦ Returns a pointer to the cell, allowing you to further access and modify it
 - `bool assign_position(std::vector<double> new_position);`
 - ♦ Use this if you want to manually set the cell's position.
 - ♦ Fully compatible with BioFVM and its data structures
 - ♦ Useful for initialization

Example: Creating a new (default) cell

```
// declare a cell pointer
Cell* pCell = NULL;

// create a cell
pCell = create_cell();

// assign its position
std::vector<double> position = {0,0,0};
pCell->assign_position( position );

// set any other state variables or properties
pCell->phenotype.motility.is_motile = false;
pCell->custom_data[ "damage" ] = 0.0;
```

Example: Creating and placing a new (custom) cell

```
// declare a cell pointer
Cell* pCell = NULL;

// find the cell definition for fibroblasts
Cell_Definition* pCD = find_cell_definition( "fibroblast" );

// create a cell (of type *pCD)
pCell = create_cell( *pCD );

// choose a random point on the circle of radius 3 centered at (4,-2,0)
std::vector<double> position = UniformOnUnitCircle();
position *= 3.0; position += {4,-2,0};
pCell->assign_position( position );
```

Handy C++ tidbits: accessing all cells

- **all_cells** is a pointer to a vector of all cell agents.

- Here's the syntax to use it to traverse all cell agents:

```
for( int i=0 ; i < (*all_cells).size() ; i++ )
{
    Cell* pCell = (*all_cells)[i];
    std::cout << "cell " << i << " at " << pCell
        << " is type " << pCell->type
        << " and death status is " << pCell->phenotype.death.dead
        << std::endl;
}
```

Full Model Workflow: Example 2



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Scenario: Oxygen-dependent cells v2

- Let's illustrate these with an example:
 - tumor cells:
 - ♦ Cycle entry proportional to local pO_2
 - ♦ Necrosis probability increases below a pO_2 threshold
 - motile tumor cells:
 - ♦ Same as tumor cells, but:
 - » 1/10 cycling rate
 - » 1/10 apoptosis rate
 - » a more advanced chemotaxis up oxygen gradients
 - » stop migrating above a threshold value
- **Specify how many of each cell type, and place them closer to origin**

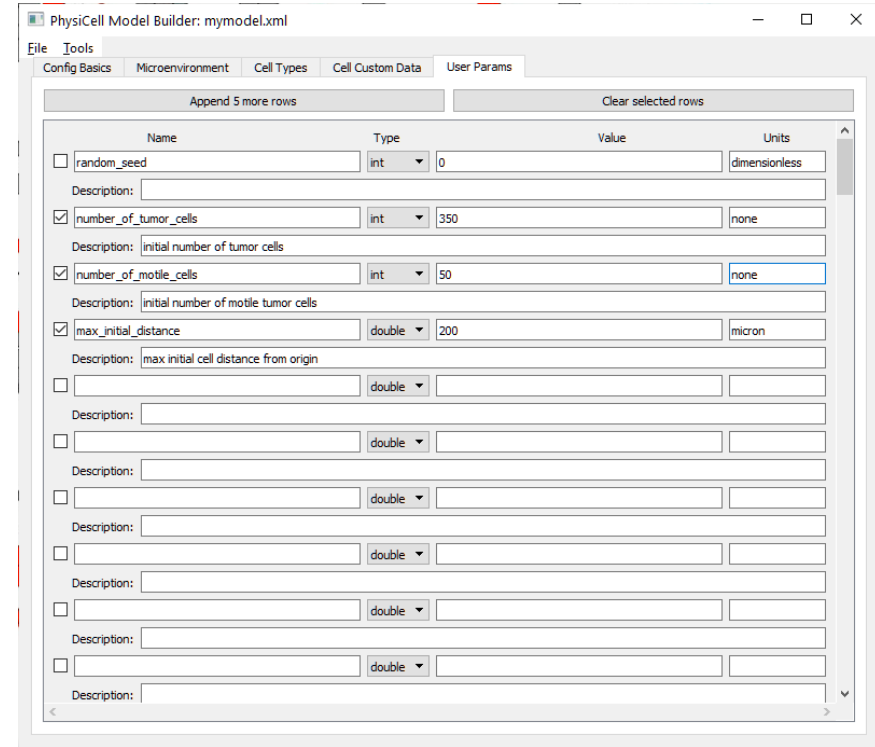
Full modeling workflow

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

Add new user parameters

- Go to "user parameters" in Model Builder
 - rename "number_of_cells" to "number_of_tumor_cells"
 - ♦ Set its value to 750
 - ♦ Change its description to "initial number of tumor cells"
 - add another parameter called "number_of_motile_cells"
 - ♦ set its type to int
 - ♦ set its value to 50
 - ♦ set units and description
 - add another parameter called "max_initial_distance"
 - ♦ keep its type as double
 - ♦ set its value and units to 250 micron
 - ♦ set description to "max initial cell distance from origin"
- Resave mymodel.xml



Edit setup_tissue (1)

- In `./custom_modules/custom.cpp` find `setup_tissue`
- Comment out the current placement code:

```
/*  
for( int k=0; k < cell_definitions_by_index.size() ; k++ )  
{  
    Cell_Definition* pCD = cell_definitions_by_index[k];  
    std::cout << "Placing cells of type " << pCD->name << " ... " << std::endl;  
    for( int n = 0 ; n < parameters.ints("number_of_cells") ; n++ )  
    {  
        std::vector<double> position = {0,0,0};  
        position[0] = Xmin + UniformRandom()*Xrange;  
        position[1] = Ymin + UniformRandom()*Yrange;  
        position[2] = Zmin + UniformRandom()*Zrange;  
  
        pC = create_cell( *pCD );  
        pC->assign_position( position );  
    }  
}  
*/
```



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Edit setup_tissue (2)

```
        pC->assign_position( position );
    }
}

*/

// place tumor cells
double max_distance = parameters.doubles("max_initial_distance");

Cell_Definition* pCD = find_cell_definition( "tumor" );
std::cout << "Placing cells of type " << pCD->name << " ... " << std::endl;
for( int k=0 ; k < parameters.ints( "number_of_tumor_cells" ); k++ )
{
    std::vector<double> position = {0,0,0};
    double r = sqrt(UniformRandom())* max_distance;
    double theta = UniformRandom() * 6.2831853;
    position[0] = r*cos(theta);
    position[1] = r*sin(theta);

    pC = create_cell( *pCD );
    pC->assign_position( position );
}
```

Edit setup_tissue (3)

```
// place motile tumor cells
pCD = find_cell_definition( "motile tumor" );

std::cout << "Placing cells of type " << pCD->name << " ... " << std::endl;
for( int k=0 ; k < parameters.ints( "number_of_motile_cells" ); k++ )
{
    std::vector<double> position = {0,0,0};
    double r = sqrt(UniformRandom()) * max_distance;
    double theta = UniformRandom() * 6.2831853;
    position[0] = r*cos(theta);
    position[1] = r*sin(theta);

    pC = create_cell( *pCD );
    pC->assign_position( position );
}

std::cout << std::endl;

// load cells from your CSV file (if enabled)
load_cells_from_pugixml();

return;
}
```

Unzip [Session7_checkpoint4.zip](#)
in ./PhysiCell to get this code.

Rebuild and run the project

- Open the XML config file and set max simulation time to 3600 minutes
- rebuild:
 - `make`
- run:
 - `./project ./config/mymodel.xml` (linux, MacOS)
 - `project ./config/mymodel.xml` (Windows)



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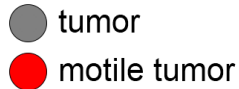
PhysiCell.org

 @PhysiCell

View results!

- make movie

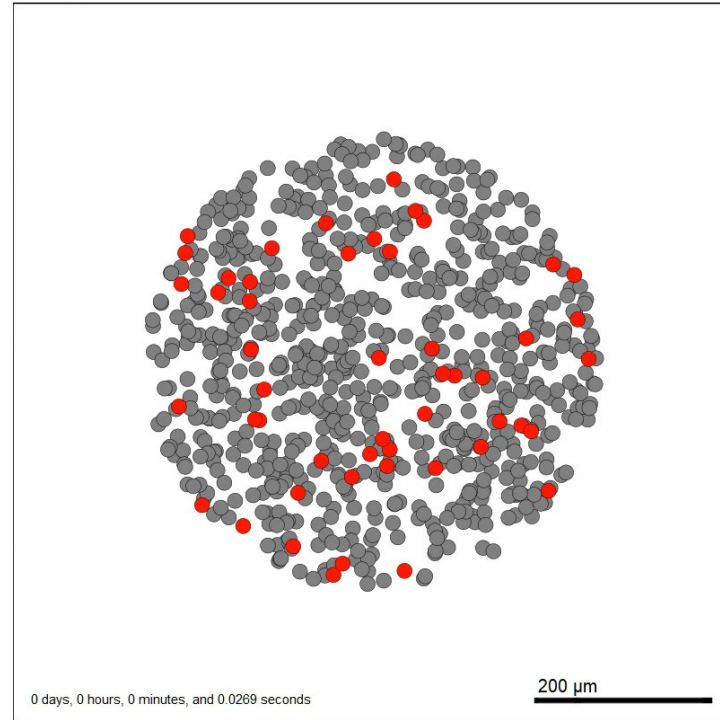
- make jpeg && make movie



- Expected behavior:

- gray tumor cells proliferate
 - ♦ fastest near higher pO₂ on boundary
 - gray cells proliferate faster than red
 - red motile tumor cells migrate towards outer boundary
 - red migration slows down as they near boundary

Current time: 0 days, 0 hours, and 0.00 minutes, z = 0.00 μ m
801 agents



Full Model Workflow: Example 3



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Scenario: Oxygen-dependent cells v3

- Let's illustrate these with an example:
 - tumor cells:
 - ♦ Cycle entry proportional to local pO₂
 - ♦ Necrosis probability increases below a pO₂ threshold
 - motile tumor cells:
 - ♦ Same as tumor cells, but:
 - » 1/10 cycling rate
 - » 1/10 apoptosis rate
 - » a more advanced chemotaxis up oxygen gradients
 - » stop migrating above a threshold value
 - Specify how many of each cell type, and place them closer to origin
 - Dial initial and boundary pO₂ down to 15 mmHg
 - **Color non-motile tumor cells based on current cycling rate**

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

Custom coloring functions for SVGs (1)

Declare the function in the custom header file

```
std::vector<std::string> my_coloring_function( Cell* );
```

Create it in the custom cpp file

```
std::vector<std::string> my_coloring_function( Cell* pCell )
{
    // color 0: cytoplasm fill
    // color 1: outer outline
    // color 2: nuclear fill
    // color 3: nuclear outline

    // start black
    std::vector< std::string > = {"black", "black", "black", "black" };
    // make the cytoplasm red if it's not dead
    if( pCell->phenotype.death.dead == false )
    { output[0] = "red"; }
    return output;
}
```

Let's make our shade from blue (zero prolifer rate) to yellow (max prolifer rate)

Coloring function (1)

```
// declare new coloring in custom.h

std::vector<std::string> custom_coloring_function( Cell* );

// start work in custom.cpp

std::vector<std::string> custom_coloring_function( Cell* pC )
{
    // start with paint-by-numbers
    std::vector<std::string> output = paint_by_number_cell_coloring(pC);

    // get tumor cell def
    static Cell_Definition* pTC = find_cell_definition( "tumor" );

    // return if not live tumor cell
    if( pC->phenotype.death.dead || pC->type != pTC->type )
    { return output; }
```

Coloring function (2)

```
// get relative birth rate
double s = pC->phenotype.cycle.data.transition_rate(0,0) /
    pTC->phenotype.cycle.data.transition_rate(0,0);

// make color
int color = (int) round( 255.0 * s );
char szColor [1024];

// blue to yellow
sprintf( szColor, "rgb(%u,%u,%u)",color,color,255-color );

// modify output
output[0] = szColor;
output[2] = szColor;
output[3] = szColor;

return output;
}
```

Tell PhysiCell to use your coloring function

In main.cpp

```
std::vector<std::string> (*cell_coloring_function) (Cell*) =  
    custom_coloring_function;
```

Colors follow the W3C standards for SVG files. Names, RGB values, etc.

<https://www.w3.org/TR/SVG11/types.html#ColorKeywords>

User Guide: Section 14.2

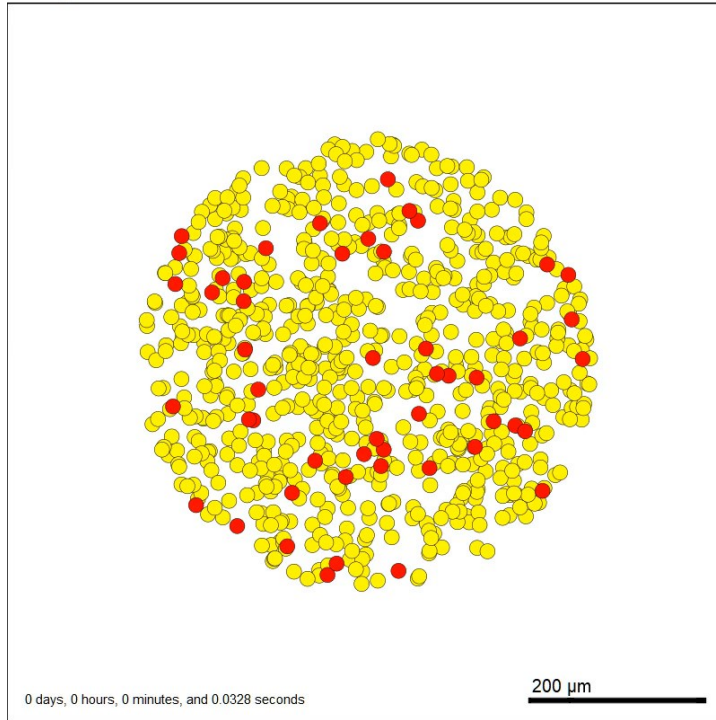
Unzip [Session7_checkpoint5.zip](#)
in ./PhysiCell to get this code.

Run and View results!

- `make && ./project ./config/mymodel.xml`
- `make movie`
 - `make jpeg && make movie`

● tumor
● motile tumor

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



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

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