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

Session 8: Chemical Communication in PhysiCell

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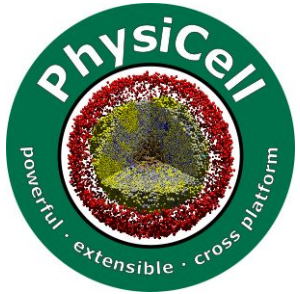


What we learned last session

- PhysiCell full modeling workflow
- Handy C++ Tidbits for Cell Agents
- Typical form / syntax of PhysiCell functions
- The customizable functions in Cell.functions
- How to assign new functions to a cell definition
- Sampling the microenvironment at Cell locations
- Controlling initial cell placement
- Custom coloring functions

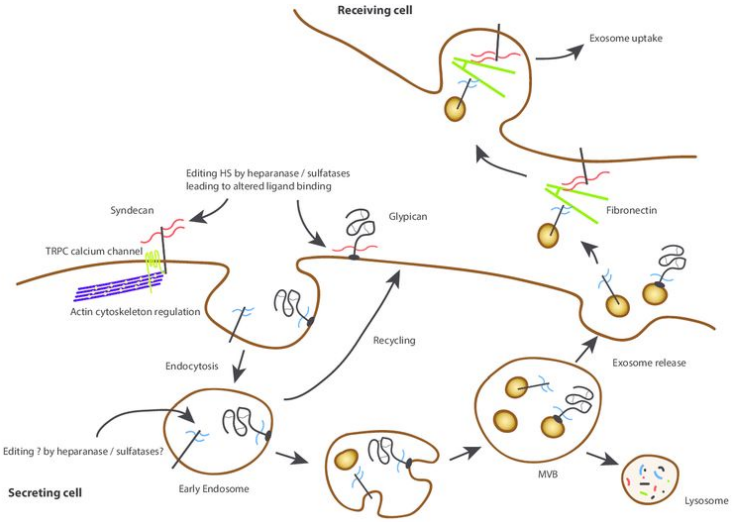
What we will learn in session 8

1. Secretion, uptake, export
   - How do we expect cells to communicate
   - How do we handle this process
     - ♦ Export/ Secretion/ Uptake definitions
2. Example: Quorum sensing (advanced)
   - Edit .cpp files to add custom functionality
   - Edit rates
   - Edit signal interactions

github repository

Chemical communication

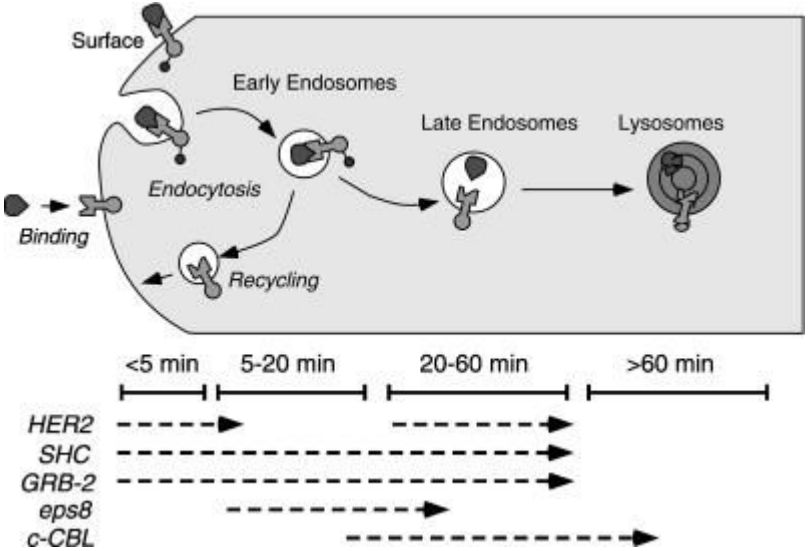
- Cells can communicate by secreting chemical factors:
  - Some stick to the extracellular matrix
    - ♦ Proteoglycans, Some forms of VEGF
    - ♦ Good for leaving “memory”
  - Many diffuse out into the surrounding tissue
    - ♦ IL6, VEGF, CXCL12, CXC/SDF1, Estrogen
    - ♦ Good for long distance communication
  - Some factors never leave the cell surface
    - ♦ Delta-like proteins (e.g., Dll4)
    - ♦ Adhesion molecules
    - ♦ Good for contact signals



Couchman, John & Multhaupt, Hinke & Sanderson, Ralph. (2016). Recent Insights into Cell Surface Heparan Sulphate Proteoglycans and Cancer. F1000Research. 5. 1541. 10.12688/f1000research.8543.1.

Chemical receptors

- Chemical signaling by receptors can be rate limited by **receptor trafficking**



Burke, P et al. "Regulation of epidermal growth factor receptor signaling by endocytosis and intracellular trafficking." Molecular biology of the cell vol. 12,6 (2001): 1897-910. doi:10.1091/mbc.12.6.1897

- If some steps are slower than others (e.g., slow recycling of receptors, or very stable receptor-ligand binding), then cells can use up all the receptors and lose response to further signal.

Indirect chemical communication

- Single-cell processes can deplete chemical resources
  - Consume resource during metabolism
  - Consume glucose in metabolism
  - Consume growth factors during cycling
- Gradients emerge due to non-homogeneous distribution of cells
- Amounts of chemical substrates has information on local conditions
- Substrate gradients have information on the nearby environment
- Thus, even when cells don't "intend" to communicate, they send information just by altering the chemical environment. This is an indirect communication

Export mathematics

Suppose each cell exports q at a constant rate E.

$$\frac{\partial q}{\partial t} = \nabla \cdot D\nabla q - \lambda q + \sum_i \delta(x - x_i)E$$

Now, define $Q(t) = \int_\Omega q\, dV$ to be the total q in the domain.

We can then find,

Q is proportional to the number of cells that secrete q.

Secretion mathematics

- You could also use regular secretion:

$$\frac{\partial q}{\partial t} = \nabla \cdot D\nabla q - \lambda q + \sum_i \delta(\mathbf{x} - \mathbf{x}_i) V_i \, S_i (q^* - q)$$

What will happen:

1. Cells will tend secrete until the nearby q density reaches q^*
2. q will have higher values near larger concentrations of cells
3. ∇q will point towards cells.

BUT:

1. $\int_\Omega q \, dV$ will ***not*** be proportional to the total cell count
2. Even a small population can drive q towards q^* for sufficiently large S_i

Uptake mathematics

Uptake is defined as,

$$\frac{\partial q}{\partial t} = \nabla \cdot D\nabla q - \lambda q - \sum_i \delta\left(\mathbf{x} - \mathbf{x}_i\right) V_i U_i q$$

We then expect uptake dependant on the rate constant U

Accessing internalized substrates

- By default, PhysiCell keeps track of the net amount of internalized substrates.
- Each environmental substrate has a corresponding internalized substrate with the same index.

```
phenotype.molecular.internalized_total_substrates[ index ]
```

- Cells can release their contents at death. Set this (on a per-substrate basis) via

```
phenotype.molecular.fraction_released_at_death[ index ]
```

- Similarly, if the cell is eaten, the attacking cell can acquire some or all of the contents

```
phenotype.molecular.fraction_transferred_when_ingested[ index ]
```

WARNING: If cells are secreting (or exporting), the internalized substrates can go to negative values unless you write code to internally generate this quantity. Use the "at death / when ingested" options with caution.

Biological example: Quorum sensing

Quorum sensing (Advanced)

- How can cells "see" or "count" how many cells are nearby?
- How can cells find nearby cells?
- How can cells build an army before attacking?

Quorum factors!

- Many cells (particularly bacteria) secrete a diffusible factor to help it communicate with others of its kind.
- Quorum factors communicate two key pieces of information:
  - They accumulate in regions of high cell density
  - The gradient points towards regions of higher cell density

Using what we know (1)

- Let's create a new project:
  - Diffusing substrate: resource
    - initial value: 0.25 (dimensionless)
    - D = 100000 μm^2/min
    - λ = 0.1 1/min
    - boundary value: 0.25 on $x_{\min}$,
    - zero flux on all other boundaries.
  - Cells of type "bacteria":
    - Uptake resource at rate chosen to get 100 micron length scale
    - They move by chemotaxis up resource gradients.
    - Place in a circle in the center
  - Cells of type "supplier":
    - Release resource at a high rate towards saturation value of 1
    - No birth or death
    - Can't be moved
    - Place randomly in the domain

Using what we know (2) (round 1)

- Let's start with one diffusing substrate:
  - resource (Dirichlet condition 1 mmHg)
- **Cell type "bacteria":**
  - **Proliferate proportional to resource**
  - **Die if resource is below a threshold**
- **Agent type "supplier":**
  - Don't proliferate or die.
  - Can't be moved
  - Release resource

Approach

- Change Dirichlet condition for resource in PhysiCell_settings.xml

- Add custom variables (to default definition):
  - R_necrosis, R_max_growth, necrosis_rate

- Create and use phenotype function for bacteria:
  - bacteria_phenotype

First, let's get a clean template project

- make data-cleanup
- make reset
- make template

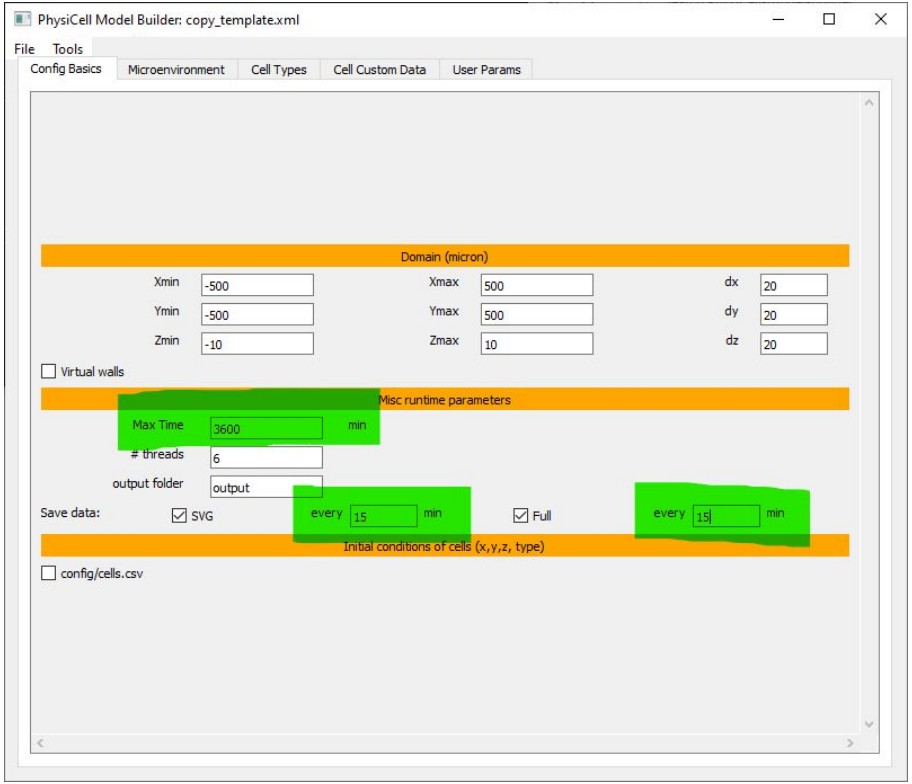
Simulation time and interval for outputs

From PhysiCell\config (anaconda)

python ..\..\PhysiCell-model-builder\bin\gui4xml.py

Set to 3600 minutes of simulation

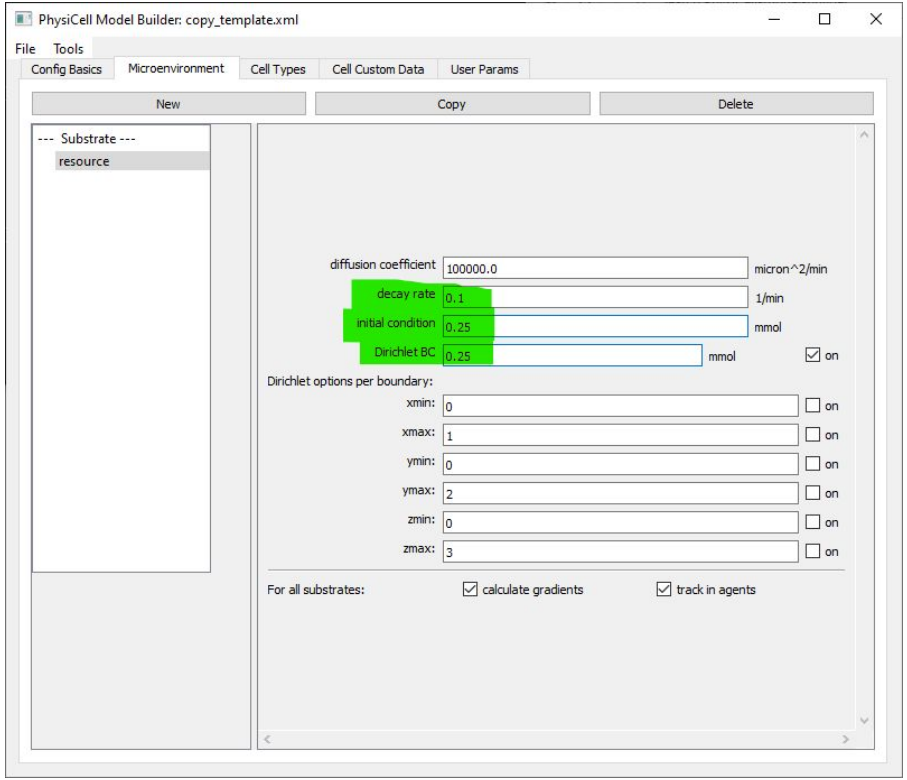
Output SVG files every 15 minutes



Changes to PhysiCell_settings.xml (1)

Set up the substrate

- Rename substrate to resource
- Change decay rate, initial condition, and boundary condition values.



Create the new cell definitions

Create a definition to bacteria (math)

- We want a diffusion distance of 10, and D = 100000 μm²/min. We need the uptake rate *U*:

$$100\ \mu m = L = \sqrt{\frac{D}{U}} = \sqrt{\frac{100000\ \mu m^2/\min}{U}}$$

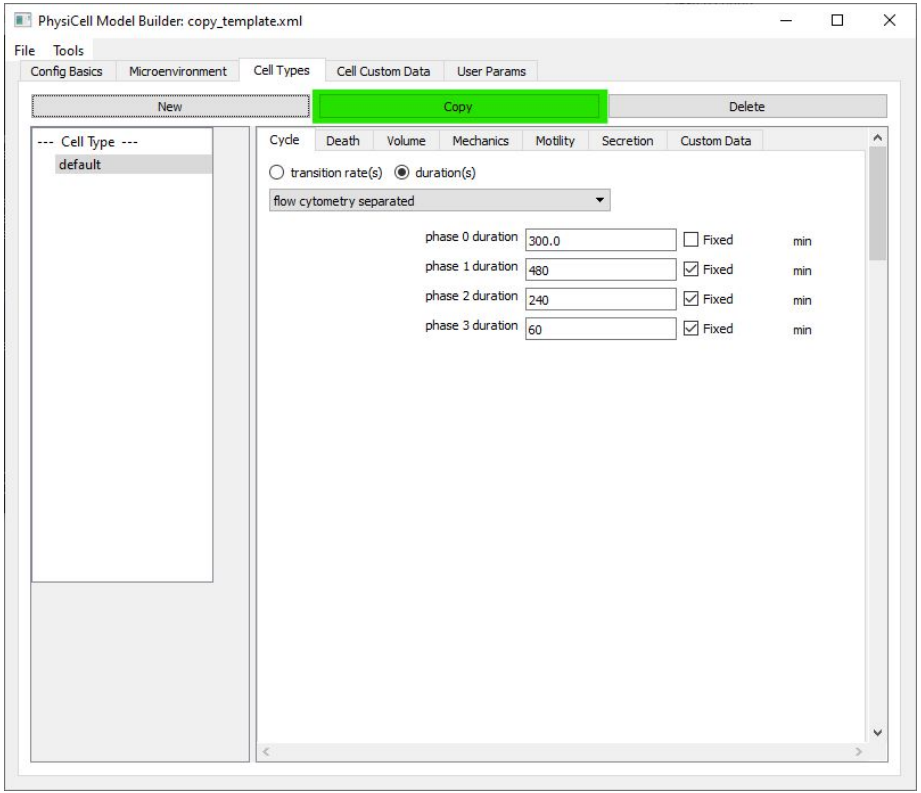
- Solving for *U*, we have:

$$U = \frac{D}{L^2} = \frac{100000\ \mu m^2/\min}{10000\ \mu m^2} = 10\ \min^{-1}$$

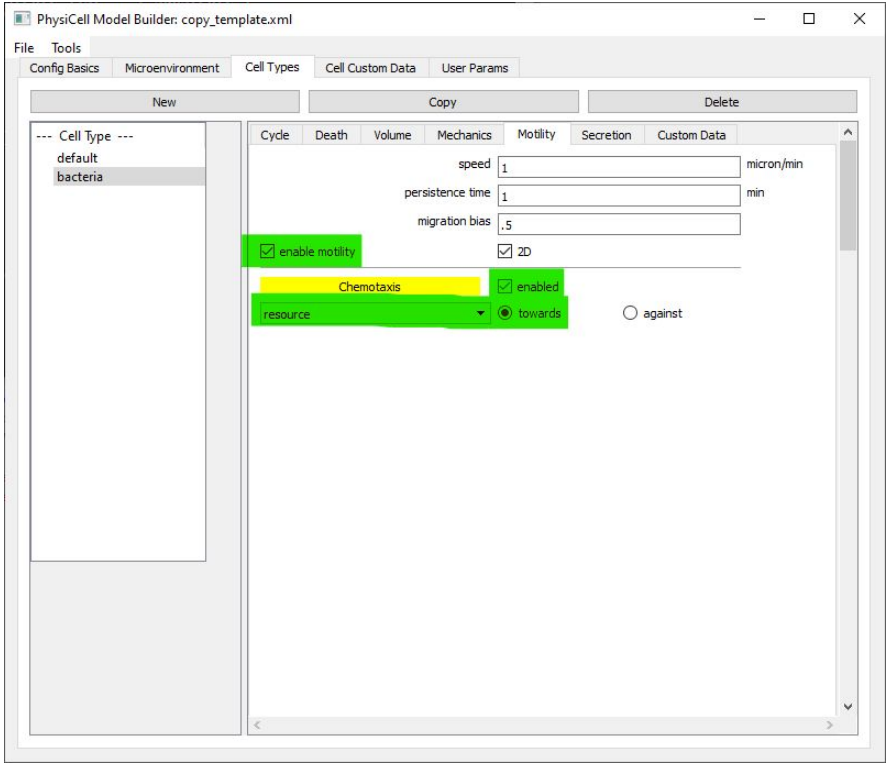
Changes to PhysiCell_settings.xml (2)

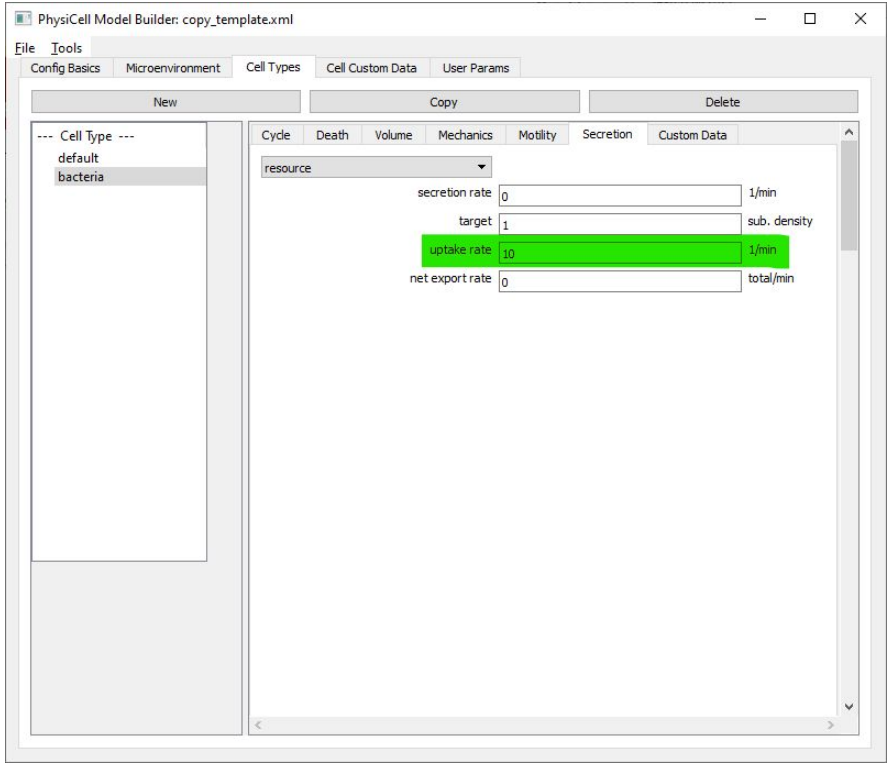
Create bacteria definition from default type

- Click on copy
- Activate chemotaxis on resource gradient direction
- Set the resource update rate



Changes to PhysiCell_settings.xml (3)

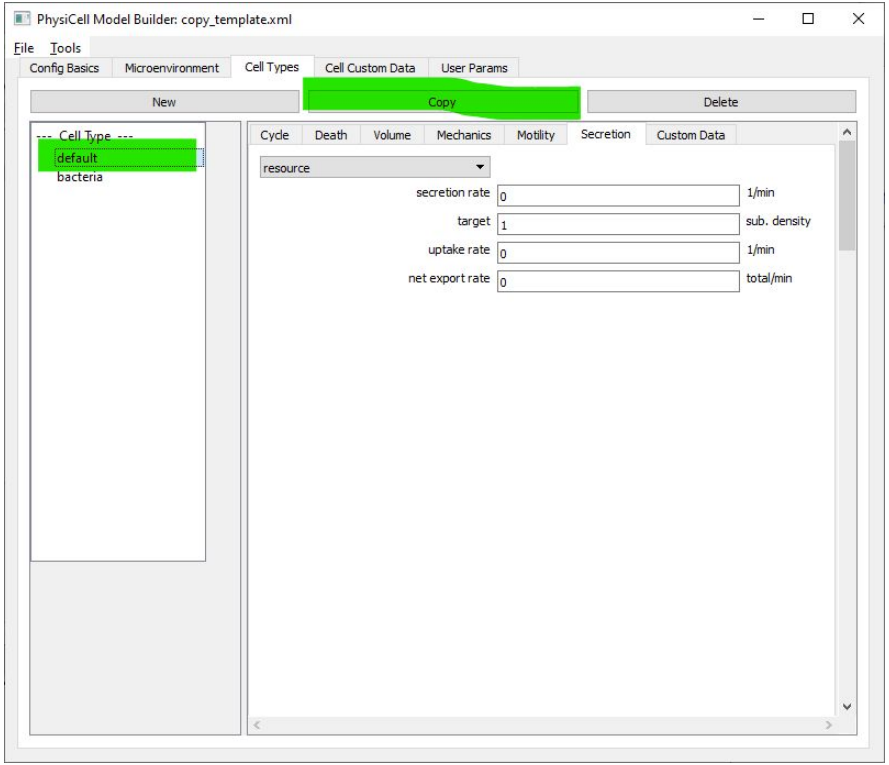




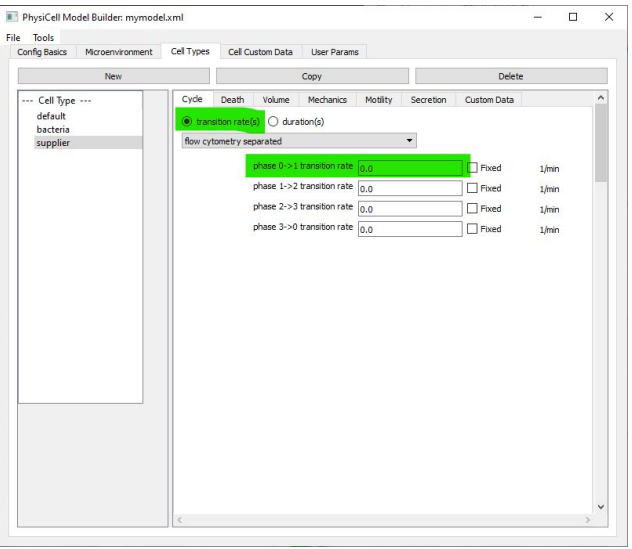
Changes to PhysiCell_settings.xml (4)

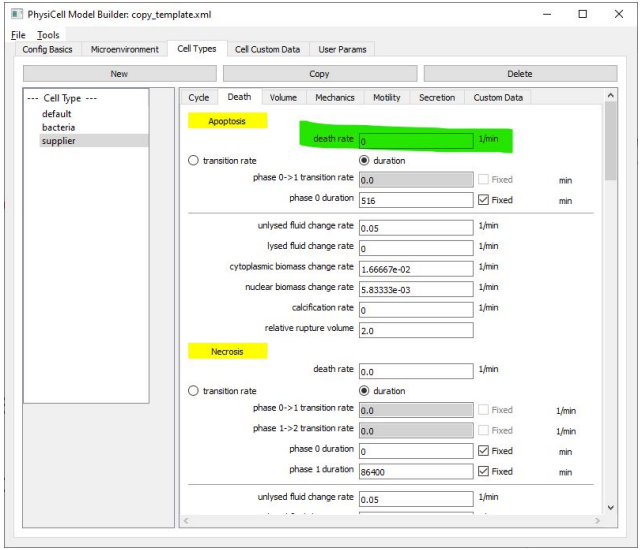
Create supplier definition from default type

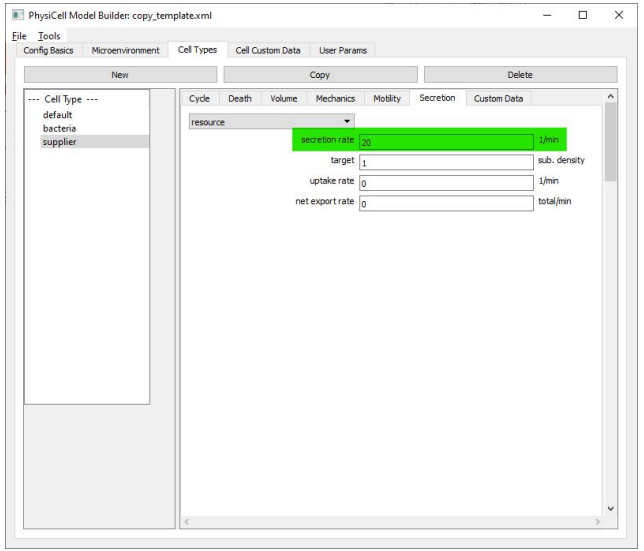
- Select default type and click on copy
- Set proliferation off
- Set dead off
- Set the resource secretion



Changes to PhysiCell_settings.xml (5)







Changes in custom.cpp

Change to 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* pBacteria = find_cell_definition( "bacteria" );
    pBacteria->functions.update_phenotype = bacteria_phenotype;

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

    build_cell_definitions_maps();
    display_cell_definitions( std::cout );

    return;
}
```

Modify cell placement

Changed to custom.cpp (setup_tissue)

```
void setup_tissue( void )
{
	double Xmin = microenvironment.mesh.bounding_box[0];
	double Ymin = microenvironment.mesh.bounding_box[1];
	double Zmin = microenvironment.mesh.bounding_box[2];

	double Xmax = microenvironment.mesh.bounding_box[3];
	double Ymax = microenvironment.mesh.bounding_box[4];
	double Zmax = microenvironment.mesh.bounding_box[5];

	if( default_microenvironment_options.simulate_2D == true )
	{
		Zmin = 0.0;
		Zmax = 0.0;
	}

	double Xrange = Xmax - Xmin;
	double Yrange = Ymax - Ymin;
	double Zrange = Zmax - Zmin;

	double center_x = 0.5*(Xmin+Xmax);
	double center_y = 0.5*(Ymin+Ymax);
	double center_z = 0.5*(Zmin+Zmax);

	// create some of each type of cell

	Cell* pC;

	// find cell definitions
	Cell_Definition* pBacteria = find_cell_definition( "bacteria" );

...
```

```
...

	// find cell definitions
	Cell_Definition* pBacteria = find_cell_definition( "bacteria" );

	Cell_Definition* pSupplier = find_cell_definition( "supplier" );

	for( int k=0; k<parameters.ints("number_of_bacteria"); k++ )
	{
		std::vector<double> position = {0,0,0};
		double r = NormalRandom(0,1) *
		parameters.doubles( "radius_bacteria_region" );
		double theta = 6.28318530718 * UniformRandom();

		position[0] = center_x + r*cos(theta);
		position[1] = center_y + r*sin(theta);
		position[2] = center_z;

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

	for( int k=0; k<parameters.ints("number_of_suppliers"); k++ )
	{
		std::vector<double> position = {0,0,0};
		position[0] = Xmin + UniformRandom()*Xrange;
		position[1] = Ymin + UniformRandom()*Yrange;
		position[2] = Zmin + UniformRandom()*Zrange;

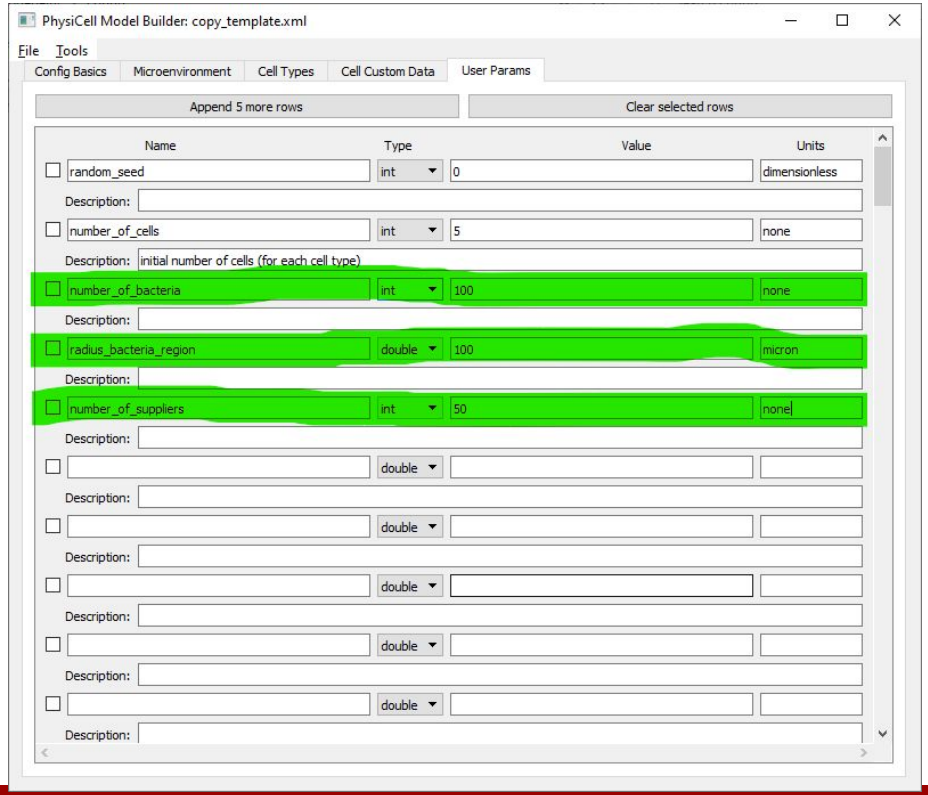
		pC = create_cell( *pSupplier );
		pC->assign_position( position );

		pC->is_movable = false;
	}

	return;
}
```

Changes to PhysiCell_settings.xml (6)

Define parameters on xml file



Bacteria phenotype (1)

```
// declare function in custom.h

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

// create it in custom.cpp

void bacteria_phenotype( Cell* pCell, Phenotype& phenotype , double dt )
{
	if( phenotype.death.dead == true )
	{
		pCell->functions.update_phenotype = NULL; // don't bother doing this function again!
		return;
	}

	// find my cell definition
	// don't use static if you plan to use this for more than one cell type
	static Cell_Definition* pCD = find_cell_definition( pCell->type_name );

	// find the index of resource
	static int nR = microenvironment.find_density_index( "resource" );

	// index of necrotic death model
	static int nNecrosis = 1; // PhysiCell_constants::necrosis_death_model;

	// sample microenvironment at cell position to get resource
	double R = pCell->nearest_density_vector()[nR];

	// check for necrotic death
	if( R < pCell->custom_data["R_necrosis"] )
	{ phenotype.death.rates[nNecrosis] = pCell->custom_data["necrosis_rate"]; }
	else
	{ phenotype.death.rates[nNecrosis] = 0.0; }

	// ...
```

Bacteria phenotype (2)

```
    // ...

    // set birth rate

    // set proliferation
    // first, set to the cell line rate
    phenotype.cycle.data.transition_rate(0,1) =
         pCD->phenotype.cycle.data.transition_rate(0,1);

    // scale with R
    double scaling_factor = (R - pCell->custom_data["R_necrosis"])
         / (pCell->custom_data["R_max_growth"] - pCell->custom_data["R_necrosis"]);
    if( scaling_factor > 1 )
    { scaling_factor = 1.0; }
    if( scaling_factor < 0 )
    { scaling_factor = 0.0; }

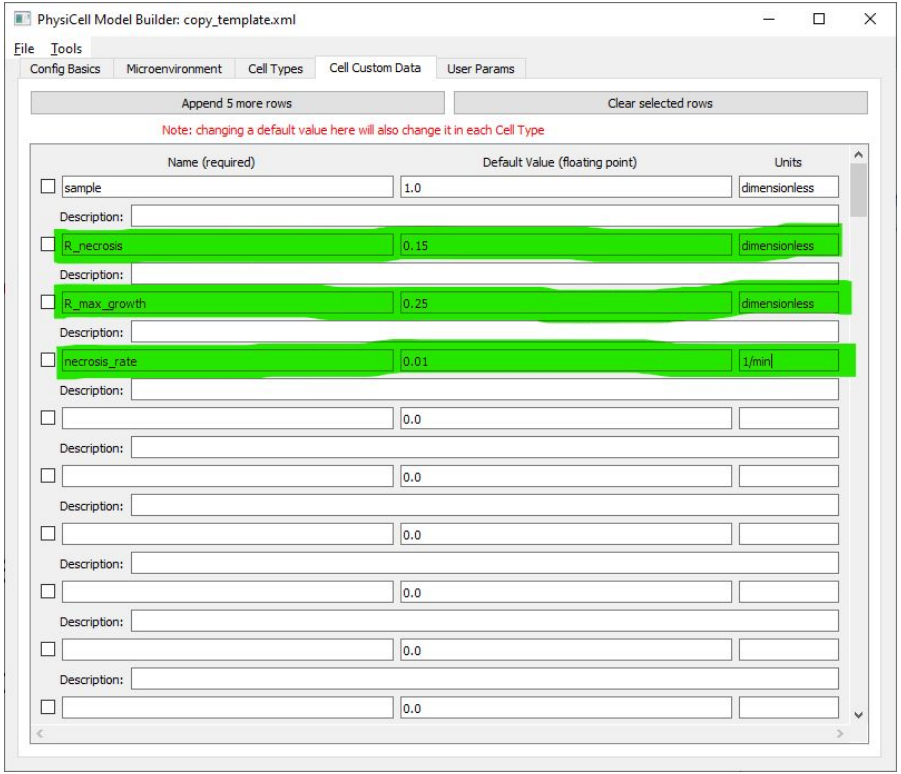
    // multiply by scaling factor
    phenotype.cycle.data.transition_rate(0,1) *= scaling_factor;

    return;
}
```

Changes to PhysiCell_settings.xml (7)

Update the default cell definition

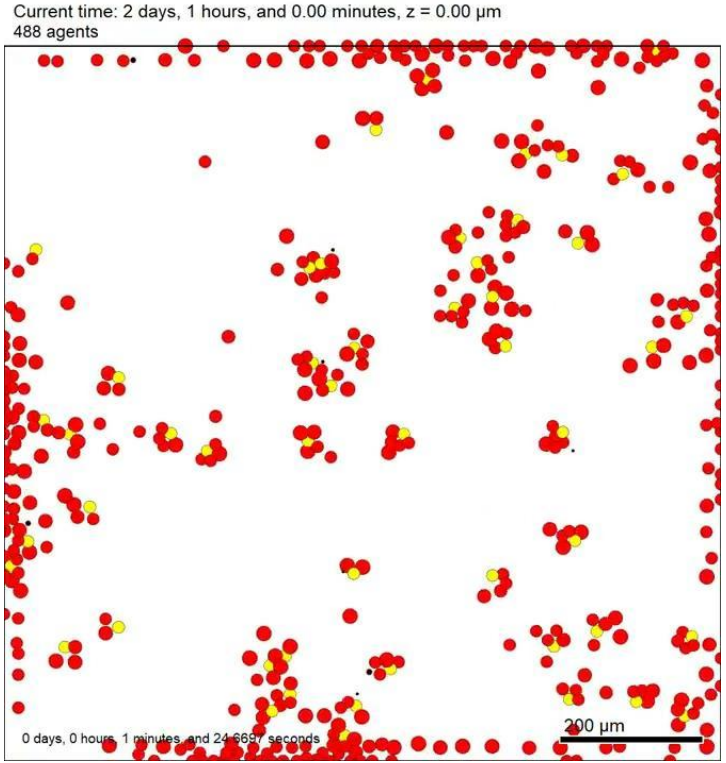
- Include to the custom data: R_necrosis, R_max growth, and necrosis_rate



Give it a try!

```
make data-cleanup
make
.\project .\config\mymodel.xml


make jpeg
make movie
```



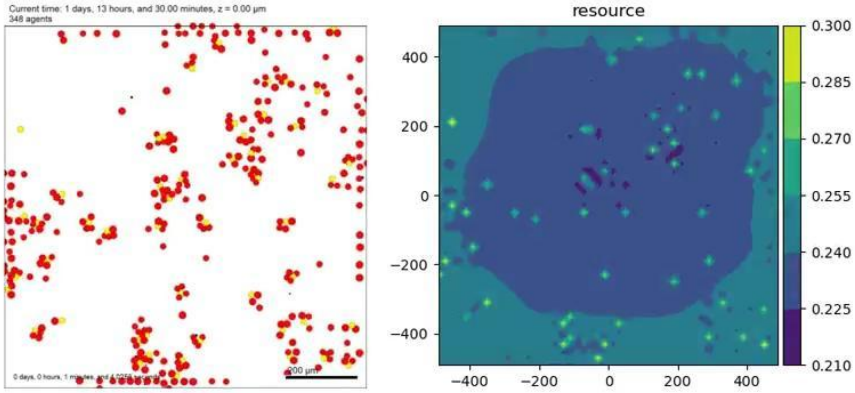
Link video

Optional visualization (advanced)

Load plot_CellSubs.py on \beta
\\ script to plot cells + substrates using pyMCDS.py

python beta\plot_CellSubs.py 0 240 1 output

Load Makefile on \PhysiCell
\\ generate movie cells + substrates
make movie2



Warning: It's necessary to run 'make jpeg' before that.

Link video

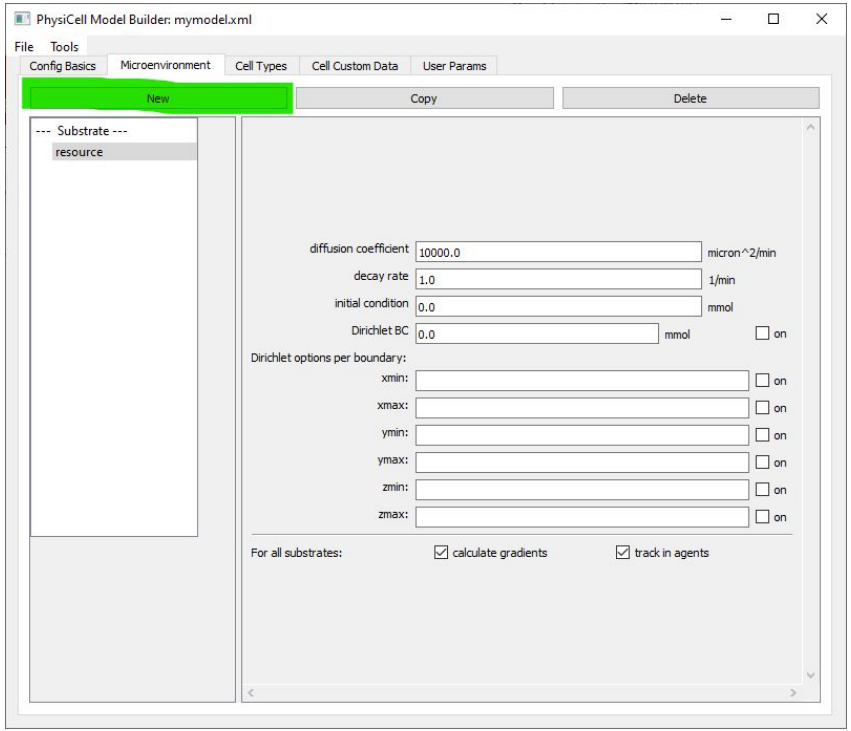
Using what we know (2) (round 2)

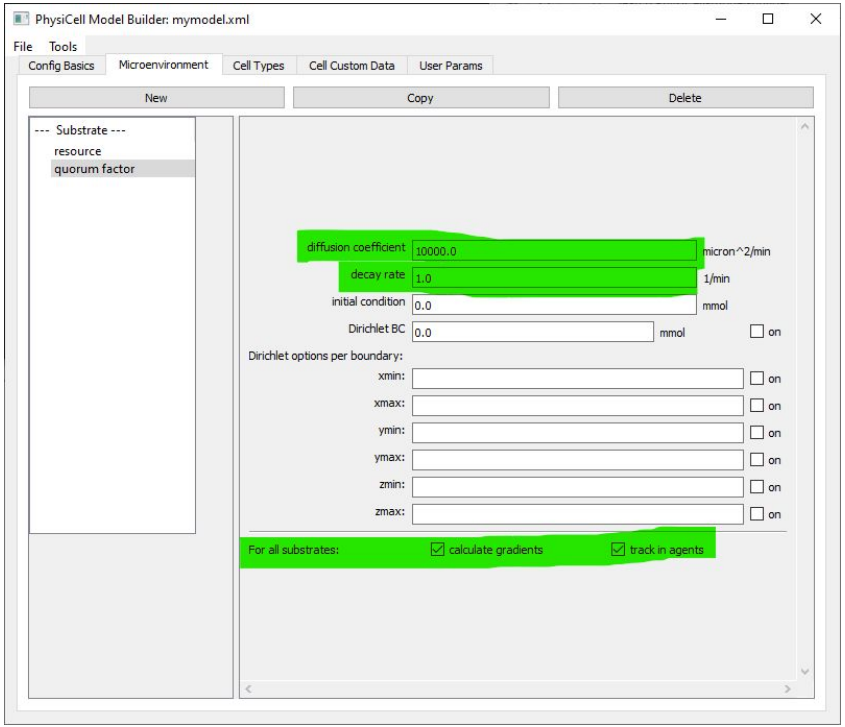
- Let's use two diffusing substrates:
  - resource (Dirichlet condition 1 mmHg)
  - **quorum factor (Neumann condition)**
- **Cell type "bacteria":**
  - Proliferate proportional to resource
  - Die if resource is below a threshold
  - **Secrete *q***
  - **Chemotax towards regions of high *q***
- **Agent type "supplier":**
  - Don't proliferate or die.
  - Can't be moved
  - Release resource

Approach

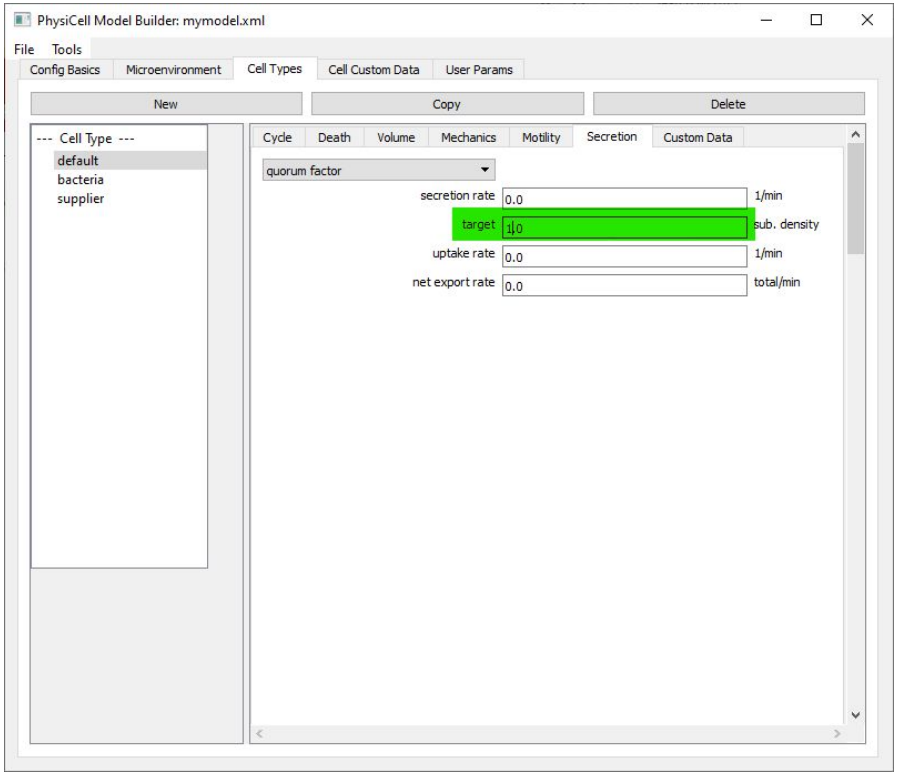
- In PhysiCell_settings.xml
  - Add "quorum factor" to microenvironment
    - Let's use a diffusion coefficient of 10000, decay rate of 1
    - Neumann conditions!
  - Add corresponding secretion / uptake to default cell definition
  - make sure bacteria export quorum factor
    - Let's use a rate of 1 for now.
  - change bacteria chemotaxis to quorum factor

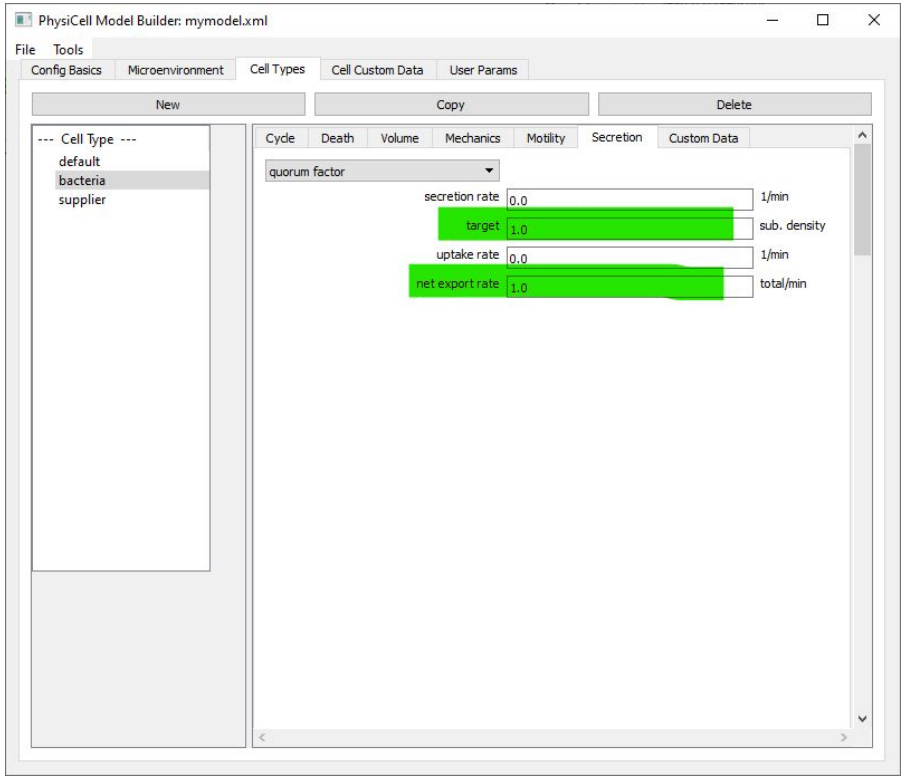
Changes to PhysiCell_settings.xml (1)



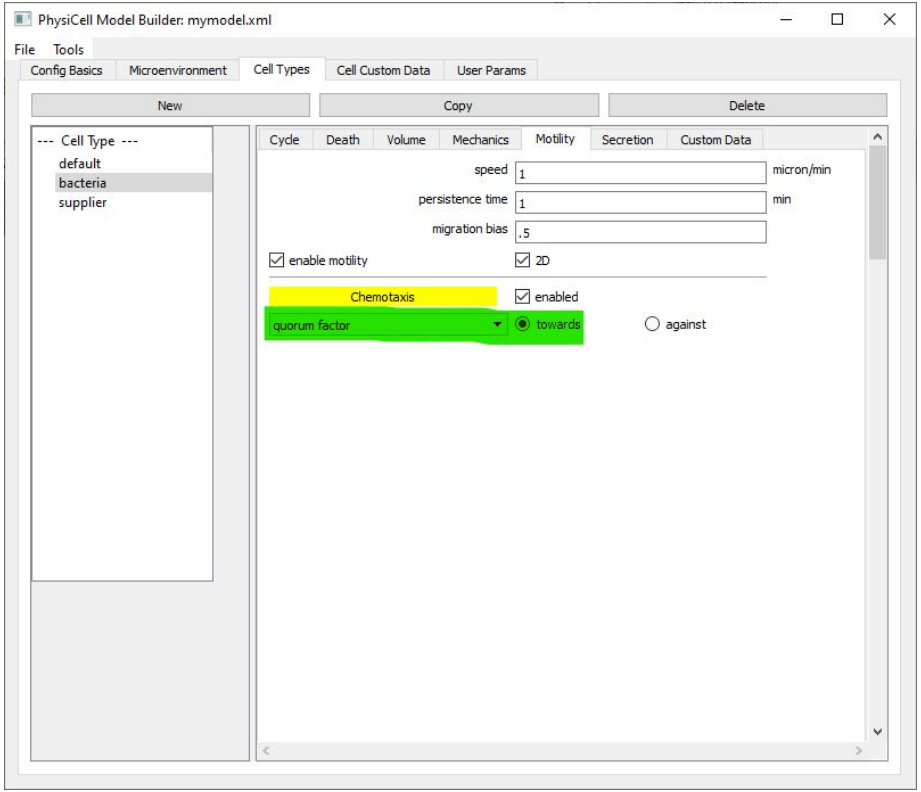


Changes to PhysiCell_settings.xml (2)





Changes to PhysiCell_settings.xml (3)



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```

```
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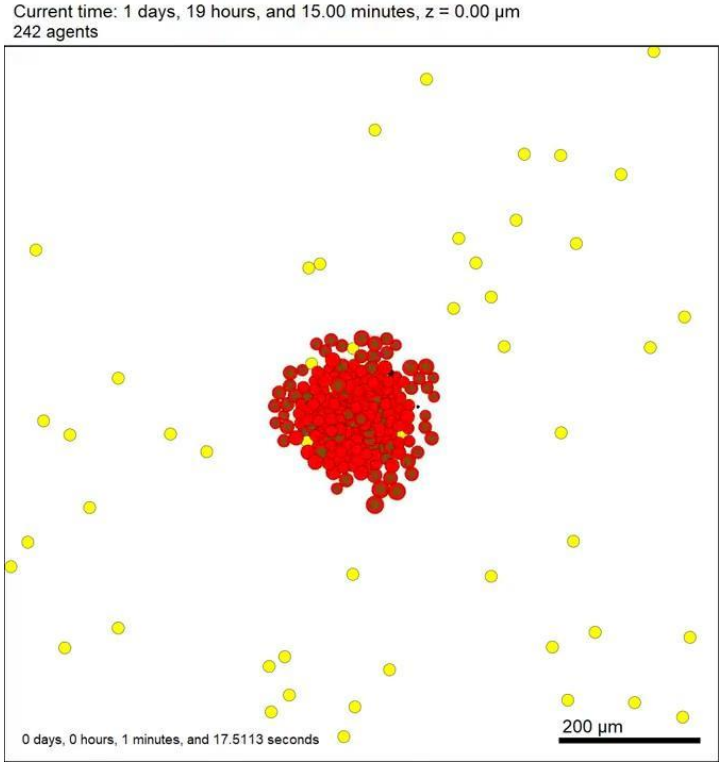
```



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Optional visualization (advanced)

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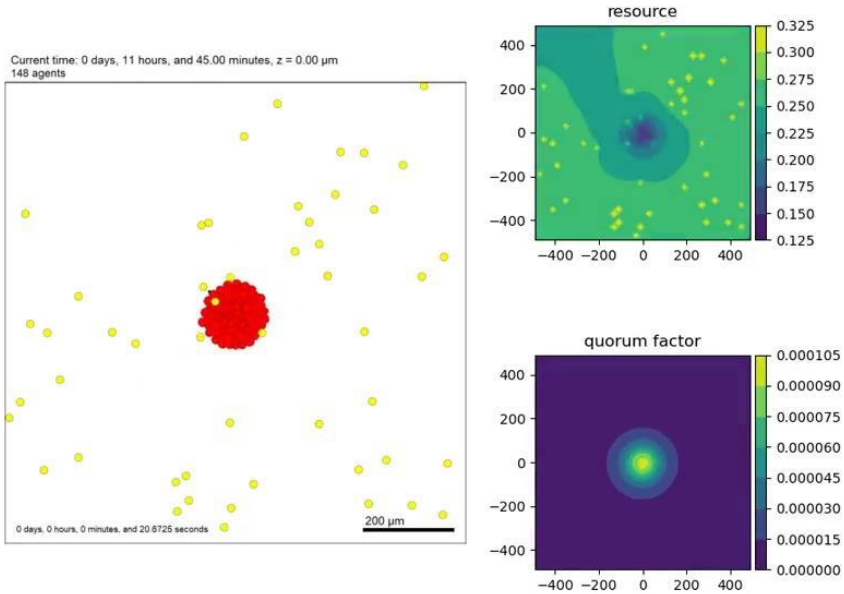


Link video

Using what we know (2) (round 3)

- Let's use two diffusing substrates:
  - resource (Dirichlet condition 1 mmHg)
  - quorum factor (Neumann condition)
- **Cell type "bacteria":**
  - Proliferate proportional to resource
  - Die if resource is below a threshold
  - Secrete q
  - Chemotax towards regions of high q
  - **Slow down motility when *q* is high**
- **Agent type "supplier":**
  - Don't proliferate or die.
  - Can't be moved
  - Release resource

Approach

- In PhysiCell_settings.xml
  - Add custom data to default cell definition
    - quorum_motility_slowdown (we'll default to 1e-4)

- In custom.cpp
  - In bacteria_phenotype()
    - scale phenotype.motility.speed by $\max\left(0,1-\frac{q}{q_{mot}}\right)$

Changes to bacteria phenotype (1)

```
void bacteria_phenotype( Cell* pCell, Phenotype& phenotype , double dt )
{
	if( phenotype.death.dead == true )
	{
		pCell->functions.update_phenotype = NULL; // don't bother doing this function again!
		return;
	}

	// find my cell definition
	// don't use static if you plan to use this for more than one cell type
	static Cell_Definition* pCD = find_cell_definition( pCell->type_name );

	// find the index of resource
	static int nR = microenvironment.find_density_index( "resource" );

	// find the index of quorum factor
	static int nQ = microenvironment.find_density_index( "quorum factor" );

	// index of necrotic death model
	static int nNecrosis = 1; // PhysiCell_constants::necrosis_death_model;

	// sample microenvironment at cell position to get resource
	double R = pCell->nearest_density_vector()[nR];
	double q = pCell->nearest_density_vector()[nQ];

	// ...
```

Changes to bacteria phenotype (2)

```
    // ...

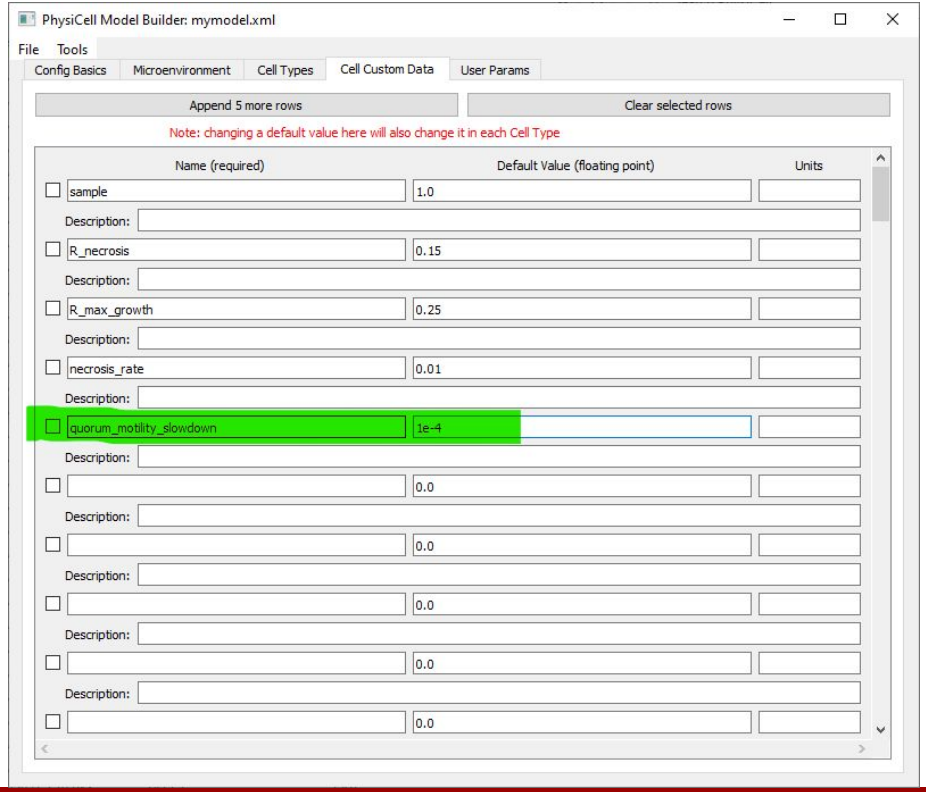
    // get the cell line's motile speed
    phenotype.motility.migration_speed = pCD->phenotype.motility.migration_speed;

    // get a scaling factor
    scaling_factor = 1.0 - q / pCell->custom_data["quorum_motility_slowdown"];
    if( scaling_factor < 0.0 )
    { scaling_factor = 0.0; }

    // scale migration speed
    phenotype.motility.migration_speed *= scaling_factor;

    return;
}
```

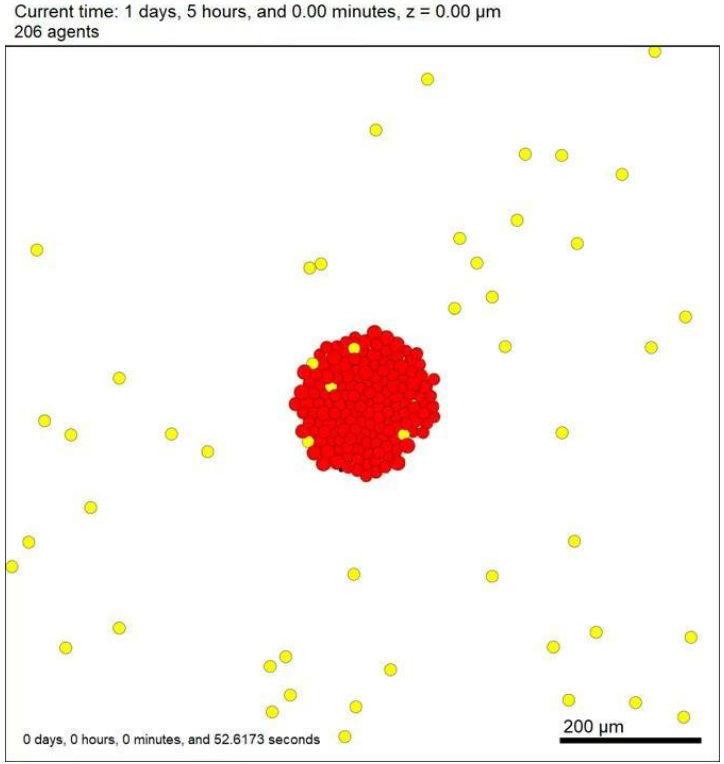
Changes to PhysiCell_settings.xml



Give it a try!

```
make data-cleanup
make
.\project .\config\mymodel.xml


make jpeg
make movie
```



Link video

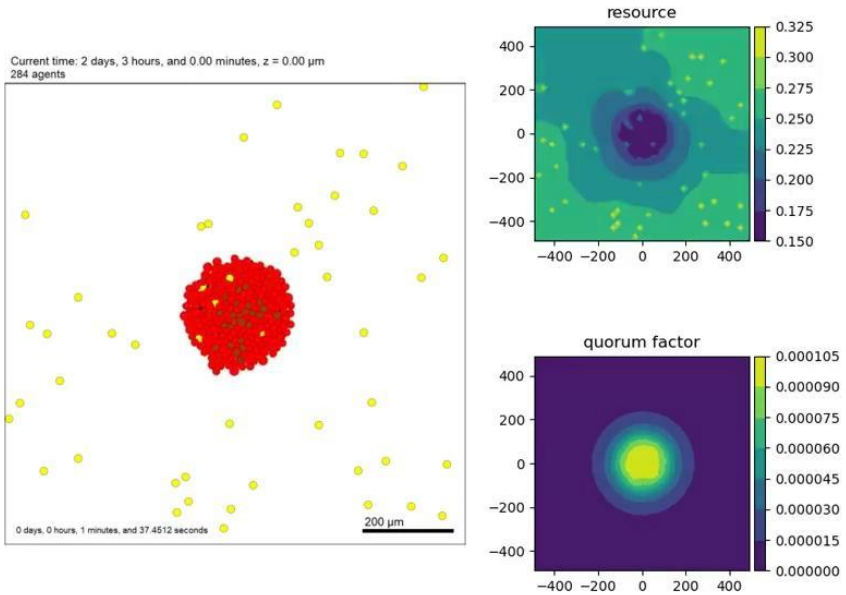
Optional visualization (advanced)

Load plot_CellSubs.py on \beta
\\ script to plot cells + substrates using pyMCDS.py

python beta\plot_CellSubs.py 0 240 1 output

Load Makefile on \PhysiCell
\\ generate movie cells + substrates
make movie2

Warning: It's necessary to run 'make jpeg' before that.



Link video

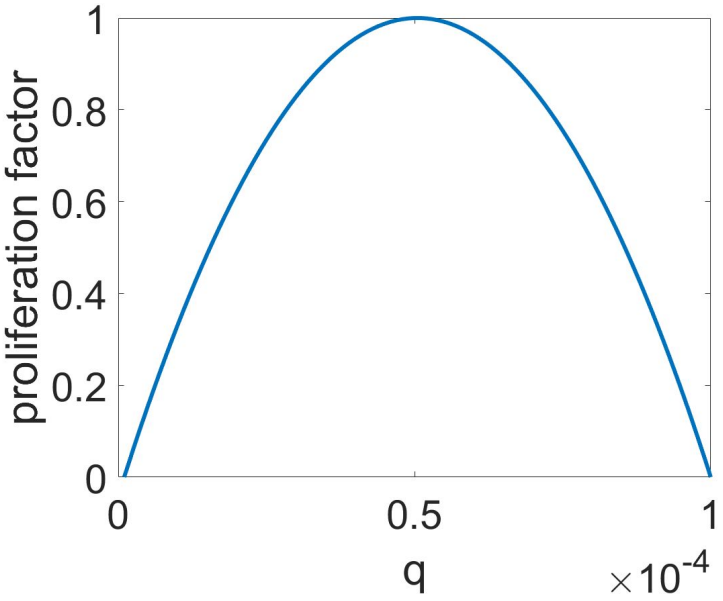
Using what we know (2) (round 4)

- Let's use two diffusing substrates:
  - resource (Dirichlet condition 0.25)
  - Quorum factor (Neumann condition)
- **Cell type "bacteria":**
  - Proliferate proportional to resource
  - **Low proliferation when *q* is low (too far from colony) or *q* is too high (overcrowding)**
  - Die if resource is below a threshold
  - Secrete *q*
  - Chemotax towards regions of high *q*
  - Slow down motility when *q* is high
- **Agent type "supplier":**
  - Don't proliferate or die.
  - Can't be moved
  - Release resource

Approach

- In PhysiCell_settings.xml
  - Add custom data to default cell definition
    - quorum_low_proliferation (default this to 1e-6)
    - quorum_high_proliferation(default this to 1e-4)

- In custom.cpp
  - In bacteria_phenotype()
    - proliferation is zero if q < qL or if q > qH
    - scale proliferation by $\frac{4}{(q_H - q_L)^2}(q - q_L)(q_H - q)$



Changes to bacteria_phenotype()

```
// ...
// scale with R
double scaling_factor = (R - pCell->custom_data["R_necrosis"])
     / (pCell->custom_data["R_max_growth"] - pCell->custom_data["R_necrosis"]);
if( scaling_factor > 1 )
{ scaling_factor = 1.0; }
if( scaling_factor < 0 )
{ scaling_factor = 0.0; }

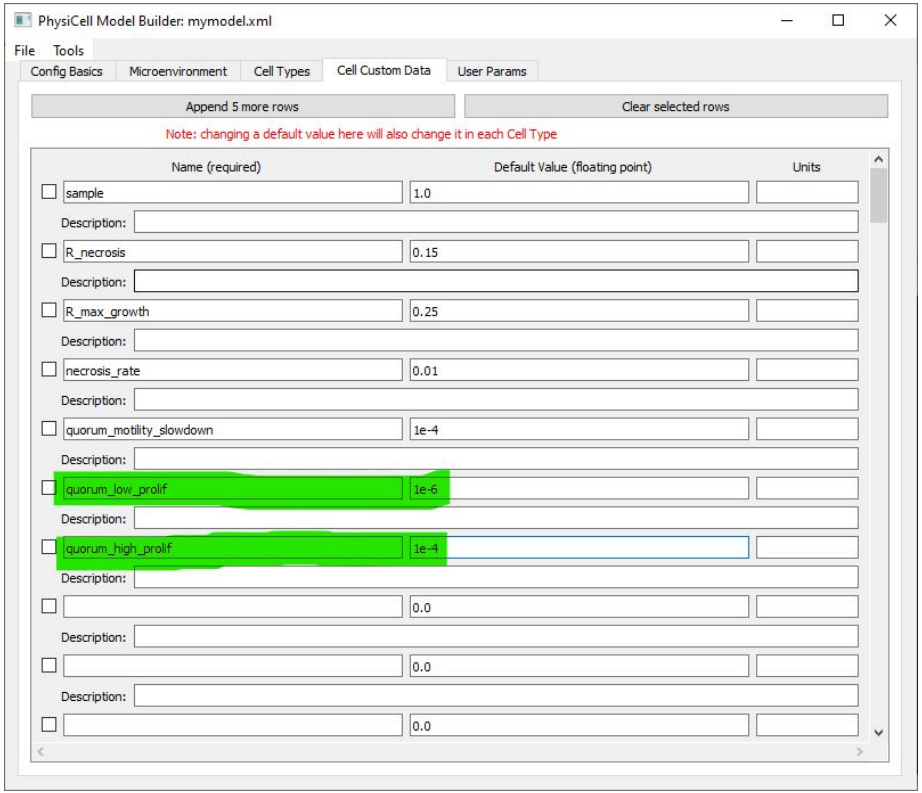
// scale with quorum factor
double Qlow = pCell->custom_data["quorum_low_prolif"];
double Qhigh = pCell->custom_data["quorum_high_prolif"];
double constant = 4.0 / pow( Qhigh - Qlow , 2.0 );

// no proliferation if Q is low or high
if( q < Qlow || q > Qhigh )
{ scaling_factor = 0.0; }

scaling_factor *= ( constant*(q-Qlow)*(Qhigh-q) );

// multiply by scaling factor
phenotype.cycle.data.transition_rate(0,1) *= scaling_factor;
```

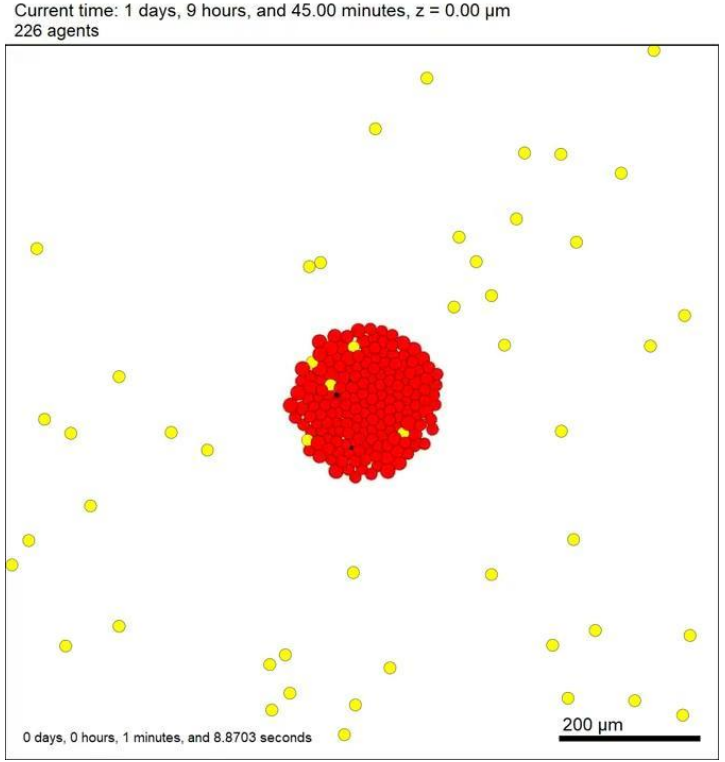
Changes to PhysiCell_settings.xml



Give it a try!

```
make data-cleanup
make
.\project .\config\mymodel.xml
```

```
make jpeg
make movie
```



Link video

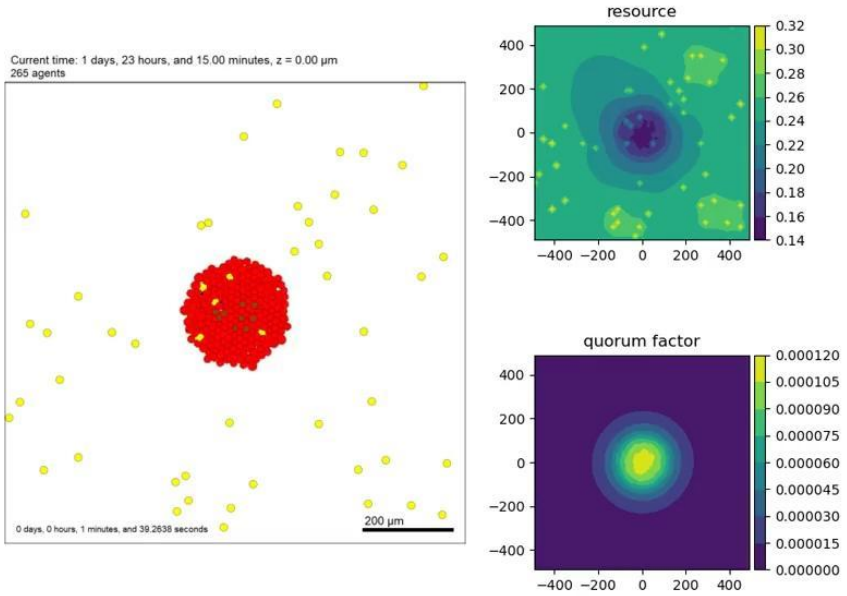
Optional visualization (advanced)

Load plot_CellSubs.py on \beta
\\ script to plot cells + substrates using pyMCDS.py

python beta\plot_CellSubs.py 0 240 1 output

Load Makefile on \PhysiCell
\\ generate movie cells + substrates
make movie2

Warning: It's necessary to run 'make jpeg' before that.



Link video

Using what we know (2) (round 5)

- Let's use two diffusing substrates:
  - resource (Dirichlet condition 1)
  - quorum factor (Neumann condition)
- **Cell type "bacteria":**
  - Proliferate proportional to resource
  - Low proliferation when q is low (too far from colony) or q is too high (overcrowding)
  - Die if resource is below a threshold
  - Secrete *q*
  - Chemotax towards regions of high *q*
  - Slow down motility when q is high
  - **Increase migration bias as *q* increases (random wandering when far from colonies)**
- **Agent type "supplier":**
  - Don't proliferate or die.
  - Can't be moved
  - Release resource

Approach

- In custom.cpp
  - In bacteria_phenotype()
    - ♦ scale motility bias by $\frac{q}{q_m}$

Changes to bacteria_phenotype()

```
    // get the cell line's motile speed
    phenotype.motility.migration_speed = pCD->phenotype.motility.migration_speed;
    // get a scaling factor
    scaling_factor = 1.0 - 1 / pCell->custom_data["quorum_motility_slowdown"];
    if( scaling_factor < 0.0 )
    { scaling_factor = 0.0; }
    // scale migration speed
    phenotype.motility.migration_speed *= scaling_factor;

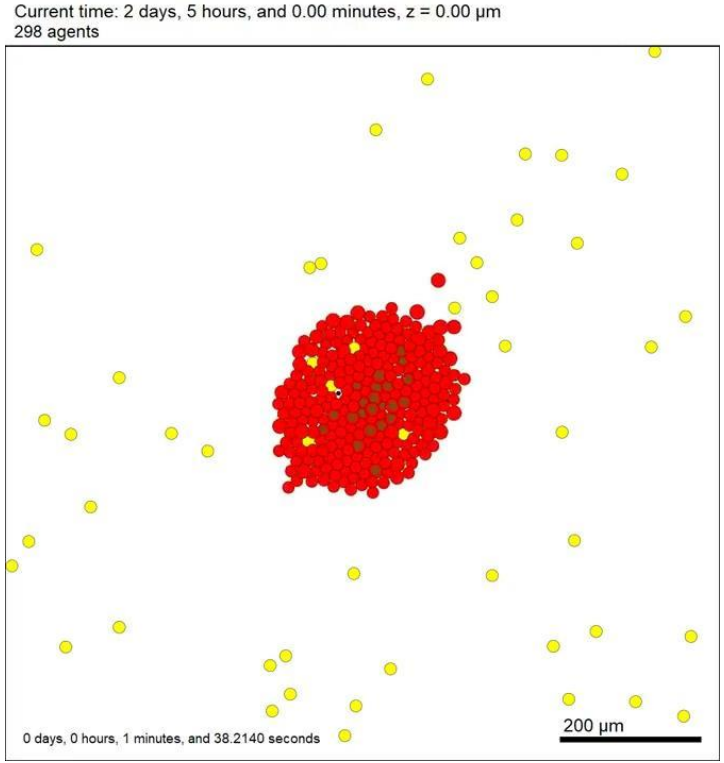
    // scale migration bias by the quorum factor
    scaling_factor = q / pCell->custom_data["quorum_motility_slowdown"];
    if( scaling_factor > 1.0 )
    { scaling_factor = 1.0; }
    phenotype.motility.migration_bias = pCD->phenotype.motility.migration_bias;
    phenotype.motility.migration_bias *= scaling_factor;

    return;
}
```

Give it a try!

```
make data-cleanup
make
.\project .\config\mymodel_4.xml


make jpeg
make movie
```



Link video

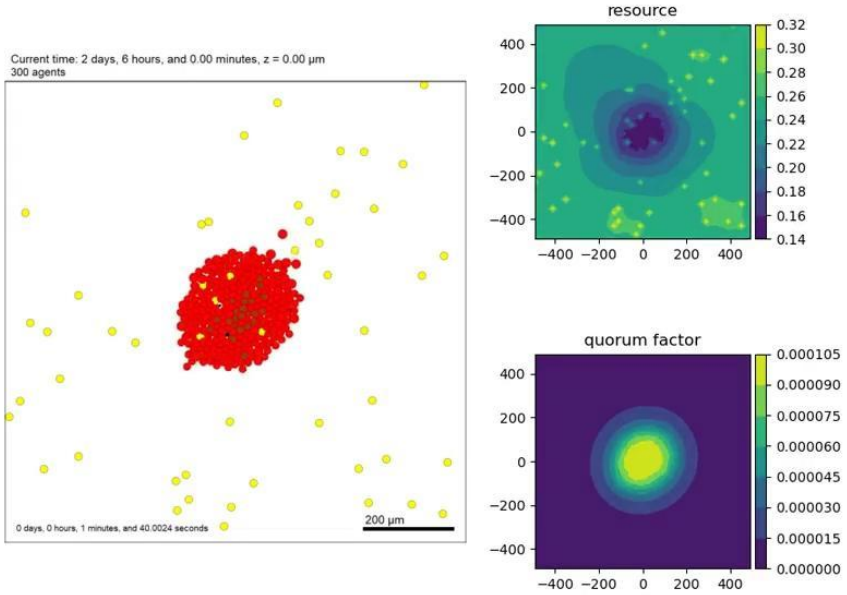
Optional visualization (advanced)

Load plot_CellSubs.py on \beta
\\ script to plot cells + substrates using pyMCDS.py

python beta\plot_CellSubs.py 0 240 1 output

Load Makefile on \PhysiCell
\\ generate movie cells + substrates
make movie2

Warning: It's necessary to run 'make jpeg' before that.



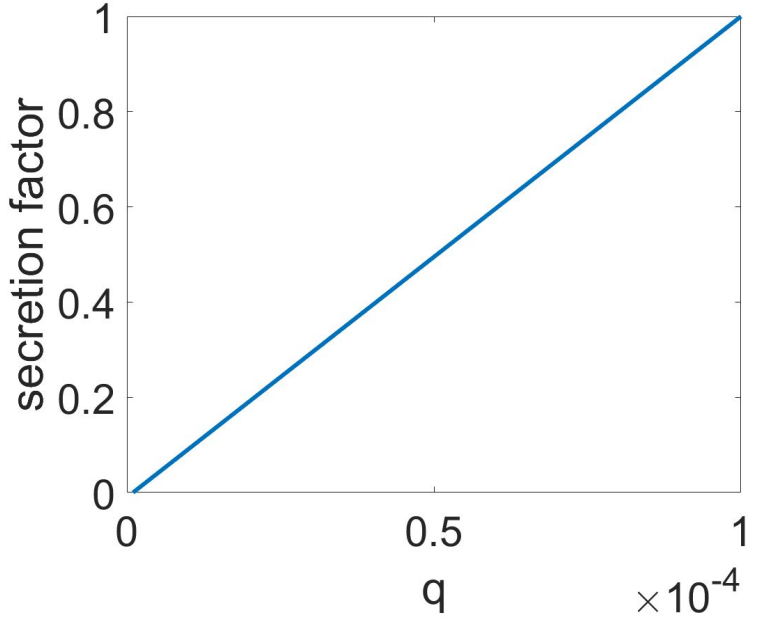
Link video

Using what we know (2) (round 6)

- Let's use two diffusing substrates:
  - resource (Dirichlet condition 1)
  - quorum factor (Neumann condition)
- **Cell type "bacteria":**
  - Proliferate proportional to resource
  - Low proliferation when q is low (too far from colony) or q is too high (overcrowding)
  - Die if resource is below a threshold
  - Secrete *q*
  - Chemotax towards regions of high *q*
  - Slow down motility when q is high
  - Increase migration bias as q increases (random wandering when far from colonies)
- **Agent type "supplier":**
  - Don't proliferate or die.
  - Can't be moved
  - Release resource
  - **resource release increases when *q* is high (dynamic response to "needs" of nearby colony)**

Approach

- In PhysiCell_settings.xml
  - Create new custom cell data:
    - max_R_release_rate, min_R_release_rate
    - q_max_R_release , q_min_R_release
- In custom.cpp / custom.h
  - Create supplier_phenotype()
  - Linear R release rate: $r_{low} + (r_{hi} - r_{low}) \frac{q - q_{low}}{q_{hi} - q_{low}}$
  - Make sure supplier use this function



Use the function (create_cell_types())

```
    // ...

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

    Cell_Definition* pBacteria = find_cell_definition( "bacteria" );
    pBacteria->functions.update_phenotype = bacteria_phenotype;

    Cell_Definition* pSupplier = find_cell_definition( "supplier" );
    pSupplier->functions.update_phenotype = supplier_phenotype;

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

    build_cell_definitions_maps();
    display_cell_definitions( std::cout );

    return;
}
```

Supplier phenotype

```
void supplier_phenotype( Cell* pCell, Phenotype& phenotype , double dt )
{
	// find my cell definition
	// don't use static if you plan to use this for more than one cell type
	static Cell_Definition* pCD = find_cell_definition( pCell->type_name );

	// find the index of resource
	static int nR = microenvironment.find_density_index( "resource" );

	// find the index of quorum factor
	static int nQ = microenvironment.find_density_index( "quorum factor" );

	// sample microenvironment at cell position to get resource and quorum factor
	double q = pCell->nearest_density_vector()[nQ];

	double Qlow  = pCell->custom_data["quorum_low_R_release"];
	double Qhigh = pCell->custom_data["quorum_high_R_release"];
	double Rlow  = pCell->custom_data["low_R_release"];
	double Rhigh = pCell->custom_data["high_R_release"];

	if( q < Qlow )
	{ phenotype.secretion.secretion_rates[nR] = Rlow; return; }

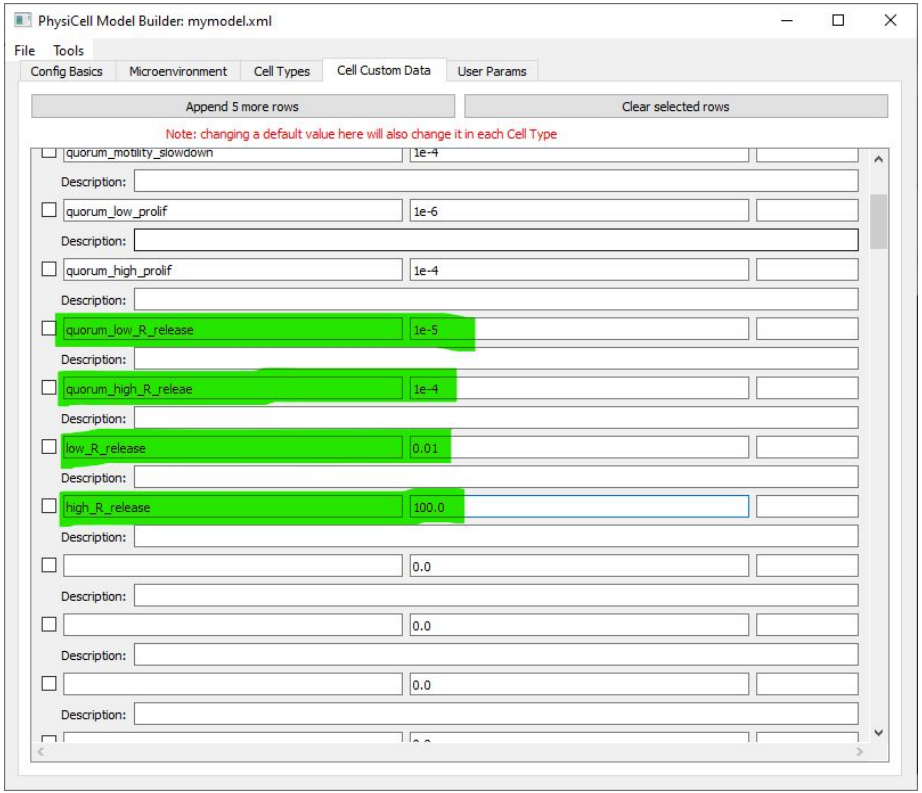
	if( q > Qhigh )
	{ phenotype.secretion.secretion_rates[nR] = Rhigh; return; }

	double scaling_factor = (q-Qlow)/(Qhigh-Qlow);
	phenotype.secretion.secretion_rates[nR] = Rlow + (Rhigh-Rlow)*scaling_factor;

	return;
}
```

Add `void supplier_phenotype( Cell* pCell, Phenotype& phenotype , double dt )` to custom.h

Changes in PhysiCell_settings.xml

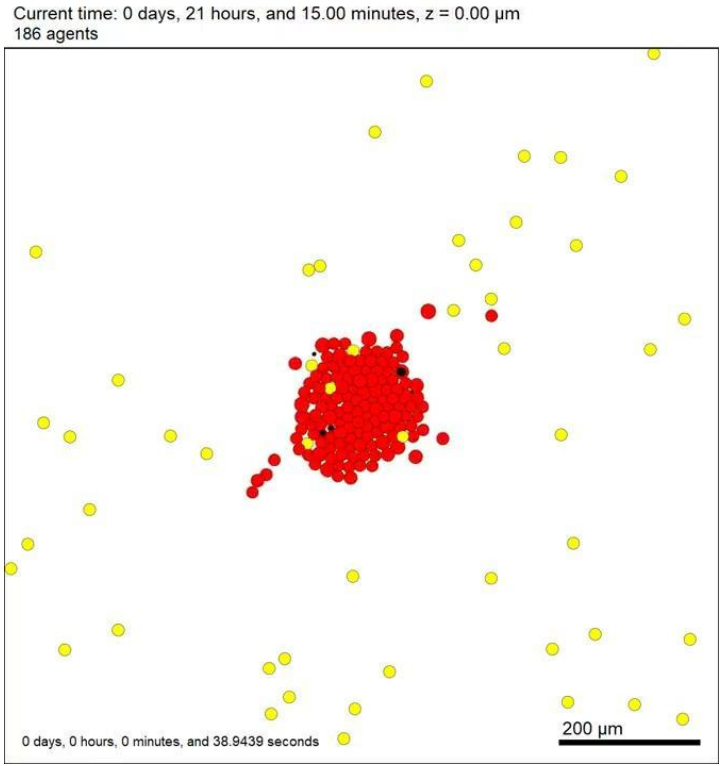


Give it a try!

```
cp ..\PhysiCell-model-builder\mymodel.xml
.\config\mymodel_6.xml
```

```
make data-cleanup
make
.\project .\config\mymodel_6.xml
```

```
make jpeg
make movie
```



Link video

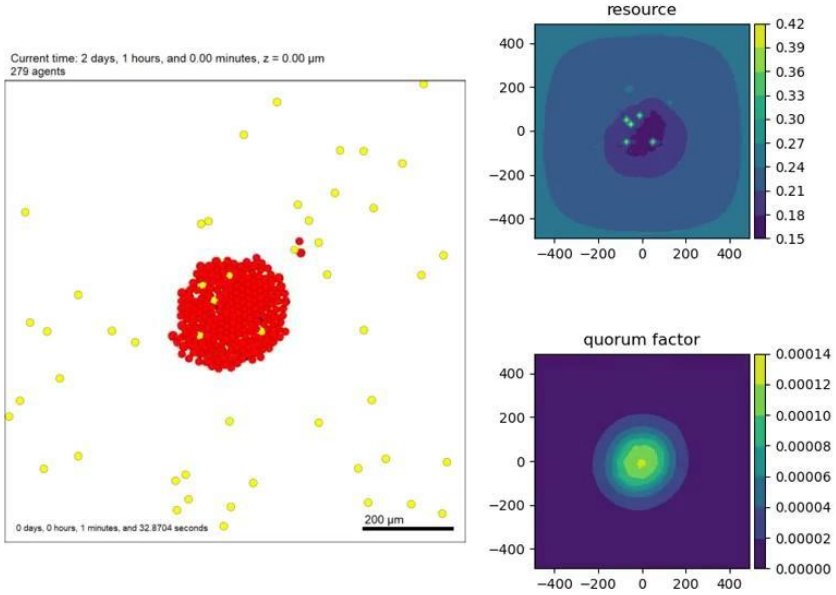
Optional visualization (advanced)

Load plot_CellSubs.py on \beta
\\ script to plot cells + substrates using pyMCDS.py

python beta\plot_CellSubs.py 0 240 1 output

Load Makefile on \PhysiCell
\\ generate movie cells + substrates
make movie2

Warning: It's necessary to run 'make jpeg' before that.



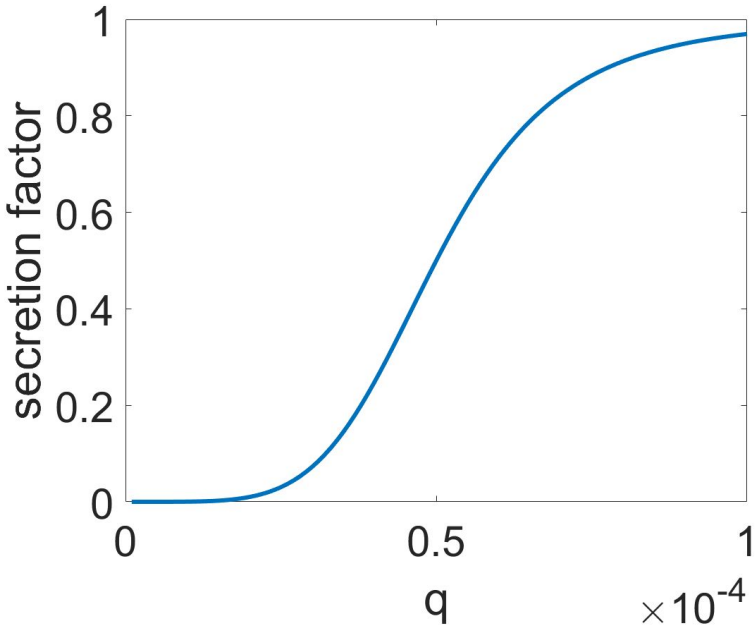
Link video

Mathematics: Hill Functions

$$H(q) = \frac{q^n}{h^n + q^n}$$

Hill power

half-max



Changes to custom.cpp

```
     if( q < Qlow )
     { phenotype.secretion.secretion_rates[nR] =
Rlow; return; }

     if( q > Qhigh )
     { phenotype.secretion.secretion_rates[nR] =
Rhigh; return; }
     double h = Qlow/2
     double scaling_factor =
pow(q,5)/(pow(h,5)+pow(q,5));
     phenotype.secretion.secretion_rates[nR] =
Rlow + (Rhigh-Rlow)*scaling_factor;

     return;
}
```

3-Types model (Intermediate homework [optional])

- In physics, the ***3-body problem*** shows how 3 objects with very simple interactions (gravitation) can demonstrate chaotic behavior.
- **Let's build a similar system for biology!**

- **3 cell types** (**A**,**B**,**C**) each secrete their own chemical factor
  - ***visualization***: assume each cell fluoresces proportionally to its signal

- Each cell type can:
  - **divide** and **die** in response to resource (R), A, B, C, and pressure
  - **move** in response to A, B, C, and R
  - **secrete** (or not secrete) in response to A, B, C, and R

- ***What can happen in this general system?***

Try this model yourself!

https://nanohub.org/tools/pc3types

Mathematics: Hill Functions

- Let's define a ***Hill function*** $H(s)$:

Hill power

$$H(s) = \frac{s^n}{s^n + h^n}$$

half-max

- Let's write:

$$U = \text{sum of promoter signals}$$
$$D = \text{sum of inhibitor signals}$$

- We can use these signals to control a parameter p via a Hill function:

$$p = \left[p_0 + \overbrace{(p_{\max} - p_0)H(U)}^{p \to p_{\max} \text{ as } U \to \infty}\right] \left[\overbrace{1 - H(D)}^{p \to 0 \text{ as } D \to \infty}\right]$$

Exercise: tumor competition

- Let's look at 2 tumor sub-clones:

- Population A:
  - Regular proliferation and death

- Population B:
  - Increased proliferation
  - Cost: more sensitive to resource depletion

Build the model

- Cell Type A:
  - Use default parameters

- Cell Type B:
  - double B_base_cycle to 0.00144
  - double B_max_cycle to 0.0144
  - increase B_necrosis_threshold to 0.6

- set to no Type C cells
  - number_of_C = 0

Run the model

- How do pink (Type A) and green (Type B) cells compete in high-resource regions?

- How do pink (Type A) and green (Type B) cells compete in low-resource regions?

Exercise: tumor co-option of stromal cells

- Let's look at two interacting cell populations:
  - Tumor cells attract stromal cells and "convince" them to secrete a growth factor.

- Population A (tumor):
  - Secretes signal A
  - Signal B **promotes** proliferation
  - No proliferation without signal B

- Population B (stromal):
  - No proliferation without signal A
  - Chemotaxis towards Signal A (and stops in regions of high signal A)
  - Signal A **promotes** secretion of Signal B

Build the model (1)

- Cell Type A:
  - Cycling
    - A_base_cycle = 0 (no proliferation without signal B)
    - A_max_cycle = 0.00072 (slow the kinetics down a bit)
    - A_cycle_B = promote (signal B enables proliferation)
    -
- Cell Type B:
  - Cycling
    - B_base_cycle = 0
    - B_max_cycle = 0.000072 (less proliferation than tumor cells)
    - B_cycle_A (signal A promotes proliferation)
  - Secretion
    - B_base_secretion = 0 (no secretion without signal A)
    - B_signal_A = promote (signal A stimulates secretion)
  - Motility
    - B_speed_base = 0.5 (increase the base speed a bit)
    - B_speed_A = inhibit (slow down when you reach the tumor)

Build the model (2)

- Now, switch to the cell types tab, and select Type B
- Let's turn on chemotaxis

- Cell Type B:
  - phenotype:motility
    - enabled = on (turn on motility)
    - chemotaxis:
      - enabled = on (use chemotaxis to guide migration)
      - substrate = signal A (chemotaxis towards tumor cells)
      - direction = 1 (move up the gradient towards stronger signal A)

Run the model

- Set 25 initial type A cells, and 1 initial type B cell. 0 Type C cells.
  - Where do green (type B) cells end up?
  - Where do you see the most pink cells (Type A)?
- Increase to 5 initial type B cells.
  - Where do green (type B) cells end up?
  - Where do you see the most pink cells (Type A)?
- Increase B_cycle_max to 0.00018. What happens?
- Set 0 initial Type B cells. What happens?

Exercise: a population with a quorum factor

- Cells can use ***quorum factors*** to find each other and sense population size.

- Population A (bacteria):
  - Secretes signal A
  - Signal A **promotes** proliferation
  - Movement towards signal A (help for aggregation)
  - Signal A **inhibits** migration (they stop moving when they find their home)

Build the model

- Cell Type A:
  - Cycling
    - A_base_cycle = 0.0 (no proliferation without signal B)
    - A_max_cycle = 0.0072 (fast birth once aggregated)
    - A_cycle_A = promote (signal B enables proliferation)
  - secretion
    - A_signal_A = promote
  - motility
    - A_base_speed = 1
    - A_max_speed = 1
    - A_speed_A = inhibit
- Turn on chemotaxis towards signal A as before in the "cell types" tab

Run the model

- Set 25 initial type A cells, and 0 Type B cells. 0 Type C cells.
  - What happens?
- Set 5 initial type A cells, and 0 Type B cells. 0 Type C cells.
  - What happens?
- Set 1 initial type A cells, and 0 Type B cells. 0 Type C cells.
  - What happens?

Exercise: add attackers

- Cells can use ***quorum factors*** to find each other and sense population size.

- Population A (bacteria):
  - Secretes signal A
  - Signal A **promotes** proliferation
  - Signal B **promotes** death (it's a poison)
  - Movement towards signal A (help for aggregation)
  - Signal A **inhibits** migration (they stop moving when they find their home)

- Population B (attackers):
  - Migration towards signal A
  - No proliferation or death
  - Signal A **promotes** secretion of signal B
  - Signal A **inhibits** migration (they stop moving when they find their target)

Build the model

- Cell Type A:
  - death
    - A_death_B = promote (Type B signal kills it)
    - A_max_death 0.005 (B signal increases death)

- Cell Type B:
  - Cycling
    - B_base_cycle = 0.0
    - B_max_cycle = 0
  - death
    - B_base_death = 0
    - B_max_death = 0
  - secretion
    - B_signal_A = promote
  - motility
    - B_base_speed = 1
    - B_max_speed = 1
    - B_speed_A = inhibit
- Turn on chemotaxis towards signal A as before in the "cell types" tab

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