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Session 10: Examples of Contact Functions in PhysiCell

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PhysiCell Project

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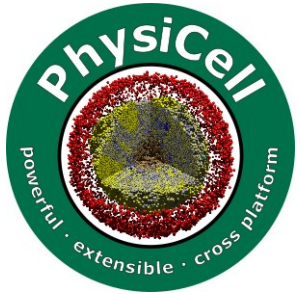


Goals

- Introduce cell contact functions
- Built-in spring adhesion functions
- Example: "worms"

Attaching cells

- PhysiCell allows you to manually connect (attach) cells for interactions:
  - `void Cell::attach_cell( Cell* pAddMe );`
    - This attaches **`pAddMe`** to the `Cell`.
    - It also attaches the `Cell` to `pAddMe`. (Attachments are tracked symmetrically.)
    - This operation checks to make sure they are not already attached.
    - The operation is thread-safe.
  - `void attach_cells( Cell* pCell_1, Cell* pCell_2 )`
    - This attaches `pCell_2` to `pCell_1`
    - This attaches `pCell_1` to `pCell_2`
    - This operation checks to make sure they are not already attached.
    - The operation is thread-safe.
- Each cell tracks a vector of attached cells in **`Cell.state.attached_cells.`**
  - Currently no functions in PhysiCell use this data structure.
  - You have complete freedom to manage and use it.
- `Cell.state.number_of_attached_cells()` gives the number of attached cells.

Detaching cells

- PhysiCell allows you to manually disconnect (deattach) cells for interactions:
  - `void Cell::detach_cell( Cell* pRemoveMe );`
    - This detaches **`pRemoveMe from`** the `Cell`.
    - It also detaches the `Cell` from `pRemoveMe`. (Attachments are tracked symmetrically.)
    - The operation is thread-safe.
  - `void detach_cells( Cell* pCell_1, Cell* pCell_2 )`
    - This detaches `pCell_2` from `pCell_1`
    - This detaches `pCell_1` from `pCell_2`
    - The operation is thread-safe.
  - `void Cell::remove_all_attached_cells( void )`
    - This runs `detach_cell()` on each attached Cell
- Cell division removes all attached cells
- Cell death removes all attached cells (at the end of death through the destructor `~Cell()`)

Example

- Suppose a cell is attempting to aggregate with similar cells
- We can have it search for nearby cells, and attach them if they are close.
- We can also have them detach if they sense a diffusible signal

```
void custom( Cell* pC , Phenotype& p , double dt )
{
   // test all nearby cells
   for( int k=0; k < pC->state.neighbors.size() ; k++ )
   {
      Cell* pThem = pC->state.neighbors[k];
      std::vector<double> displacement = pThem->position - pC->position;
      double distance = norm( displacement );

      // attach if (1) closer than sum of radii and (2) not attached to more than 6 cells.
      if( norm < pThem->phenotype.geometry.radius + p.geometry.radius &&
         pC->state.number_of_attached_cells() < 7 )
      { pC->attach_cell( pThem ); }
   }

   // scatter signal makes cells detach from everyone
   static int nS = microenvironment.find_density_index("signal");
   if( pC->nearest_density_vector()[nS] > 0.1 )
   { pC->remove_all_attached_cells(); }
   return;
}
```

Contact functions

- If Cell A and Cell B are attached, they can interact by contact functions
  - Contact functions are evaluated once per mechanics time step.
    - **Warning:** This is embedded in an OpenMP loop, so do consider thread safety!
  - The functions can act on both A and B.
  - Supposing A calls the function:
    - Writing to Cell A is thread-safe.
    - Writing to Cell B is not thread-safe. use `#pragma omp critical`

- Each cell has a contact function (default: NULL):
  - `Cell.functions.contact_function;`

- At each mechanics time step, each Cell does this:
  - For each `pCell` in `Cell.state.attached_cells():`
    - evaluate `contact_function( this , pCell );`

Contact functions: format

- Contact functions are a variation on the standard function syntax:
  - They need to reference both interacting cells:

```
some_contact_function( Cell* pA,Phenotype& phenotypeA, Cell* pB,Phenotype& phenotypeB, double dt );
```

  - Cell A (first argument) tends to call the function
    - pA is pointer to Cell A, with phenotype phenotypeA.
    - pB is pointer to Cell B, with phenotype phenotypeB.

- **Important note:** Often, A and B will have the same contact function:
  - Cell A will call contact_function(pCellA,phA, pCellB,phB, dt);
  - Cell B will call contact_function(pCellB,phB, pCellA,phA, dt);

  - Be aware of this to avoid "double counting" the interaction!

  - Also, take advantage of this for computational efficiency and thread safety:
    - Let the first call only write to cell A.
    - Let the second call only write to cell B.

A standard contact function: springs

- We wrote a standardized elastic adhesion (spring) function:

```
void standard_elastic_contact_function( Cell* pC1,Phenotype& p1, Cell* pC2,Phenotype& p2 , double dt )
```

- When Cell 1 evaluates the contact function, it adds an elastic interaction to the Cell 1 velocity:

$$\boldsymbol{v}_1 \mathrel{+}= E_1(\boldsymbol{x}_2 - \boldsymbol{x}_1)$$

  - Here, E_i is stored in `Cell.phenotype.mechanics.attachment_elastic_constant`.

- When Cell 2 evaluates the contact function, it adds an elastic interaction to the Cell 2 velocity:

$$\boldsymbol{v}_2 \mathrel{+}= E_2(\boldsymbol{x}_1 - \boldsymbol{x}_2)$$

- Notice that these are only equal and opposite when $E_1 = E_2$. We should probably fix that.

Example 1: forming a "worm"

- Let's see if we can make cells grow chains ("worms")
  - All cells secrete signal *S*
  - No birth or death
  - Cells with 0 attachments chemotax to ∇s
  - Cells test for contact within interaction distance
    - If two cells are within interaction distance, and if they both have fewer than *N*max attachments, then attach them.
  - All attached cells interact with an elastic spring-like adhesion
  - If a cell has 1 attachment:
    - Migration bias away from ∇s
    - Increase secretion of *s*
  - If a cell has more than 1 attachment
    - No migration
    - Decrease secretion of *s*

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)

- Domain and Microenvironment
  - [-500,500] x [-500,500], 1440 minutes max time.
  - signal with D = 100000, λ=10
  - default parameters, boundary and initial conditions to 0
  - Enable virtual wall

- Custom cell data (known once you have planned your cell functions)
  - max_attachments (max number of spring links per cell)

- Cell definitions
  - worm

Planning (2)

- worm phenotype
  - set cycling and apoptosis to zero
  - set secretion of signal to 10
  - set motility on, chemotaxis towards signal
    - ♦ speed = 1, migration bias = 1, persistence time 1 min

  - [-400,400] x [-400,400], 3000 minutes max time.
  - signal with D = 100000, λ=10
  - default parameters, boundary and initial conditions to 0
  - Enable virtual wall

Planning (3)

- Custom migration rule:
  - 2 or more links: migration speed 0
  - 1 link: -grad(s)
- Phenotype rule:
  - none
- Custom rule:
  - Look for cells to attach (if < Nmax)
  - Choose migration rules and secretion rate based on number of attachments
- Contact function:
  - Standard spring adhesion
- Coloring function:
  - no attachments: grey
  - 1 attachment: red
  - 2 attachments: blue
  - > 2 attachments: yellow
- create_cell_types()
  - Use the custom functions
- main.cpp
  - Use the custom coloring

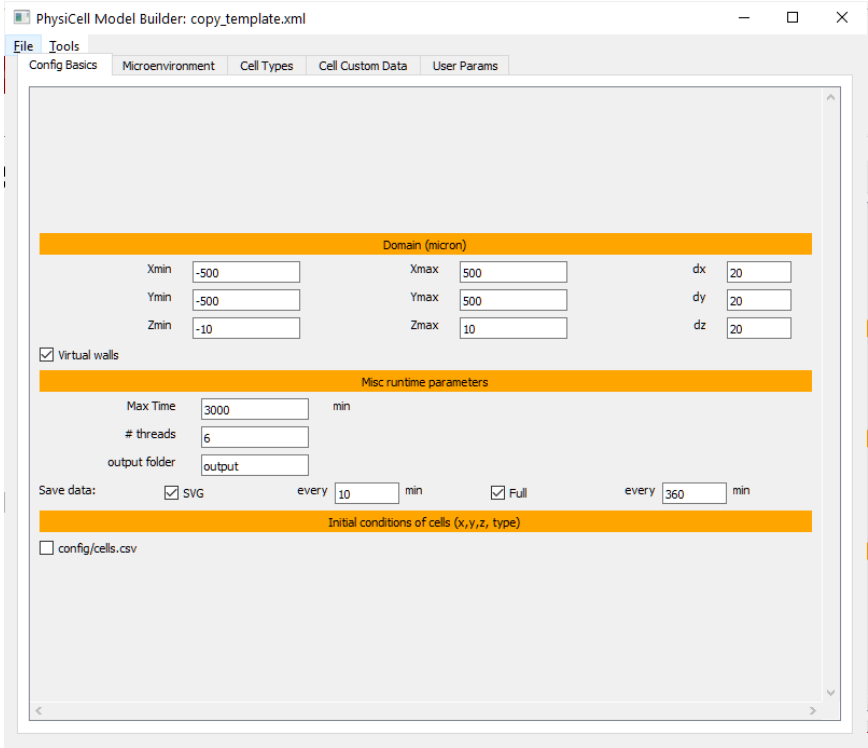
Start modeling!

- 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

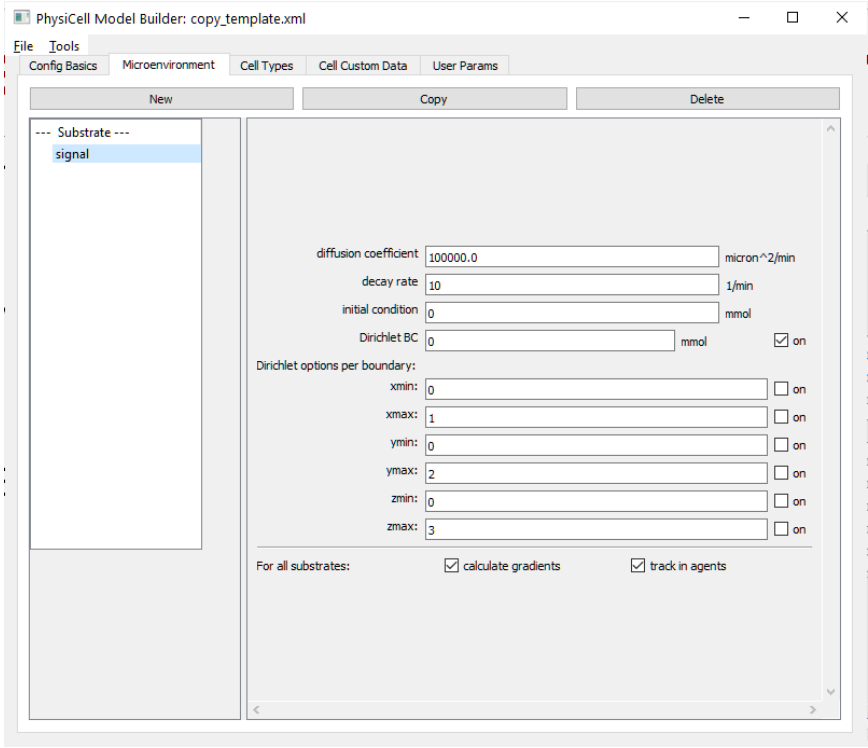
- Go to "config basics" tab
  - max time = 1440
- full output every 360 min
- SVG every 10 min
- activate "virtual wall"
  - keep cells from leaving the domain



Edit the model: microenvironment

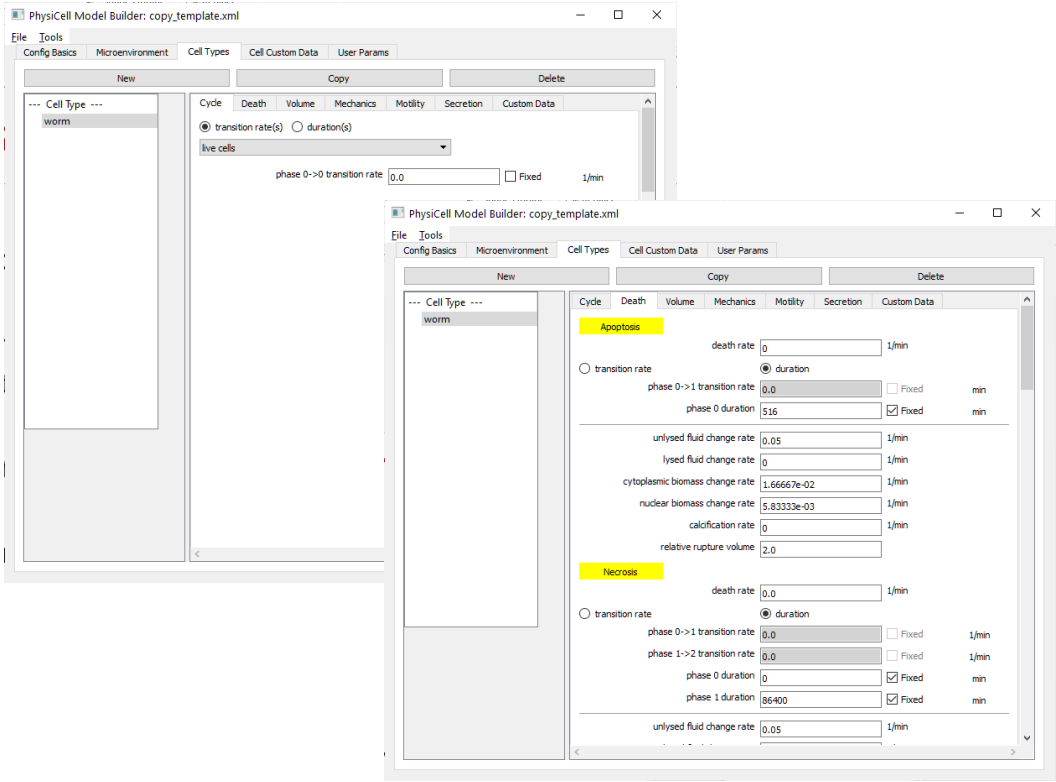
- Go to "microenvironment" tab

- double-click "substrate"
  - rename it signal
  - set Dirichlet BC to 0
  - enable the Dirichlet BC
  - set initial value to 0



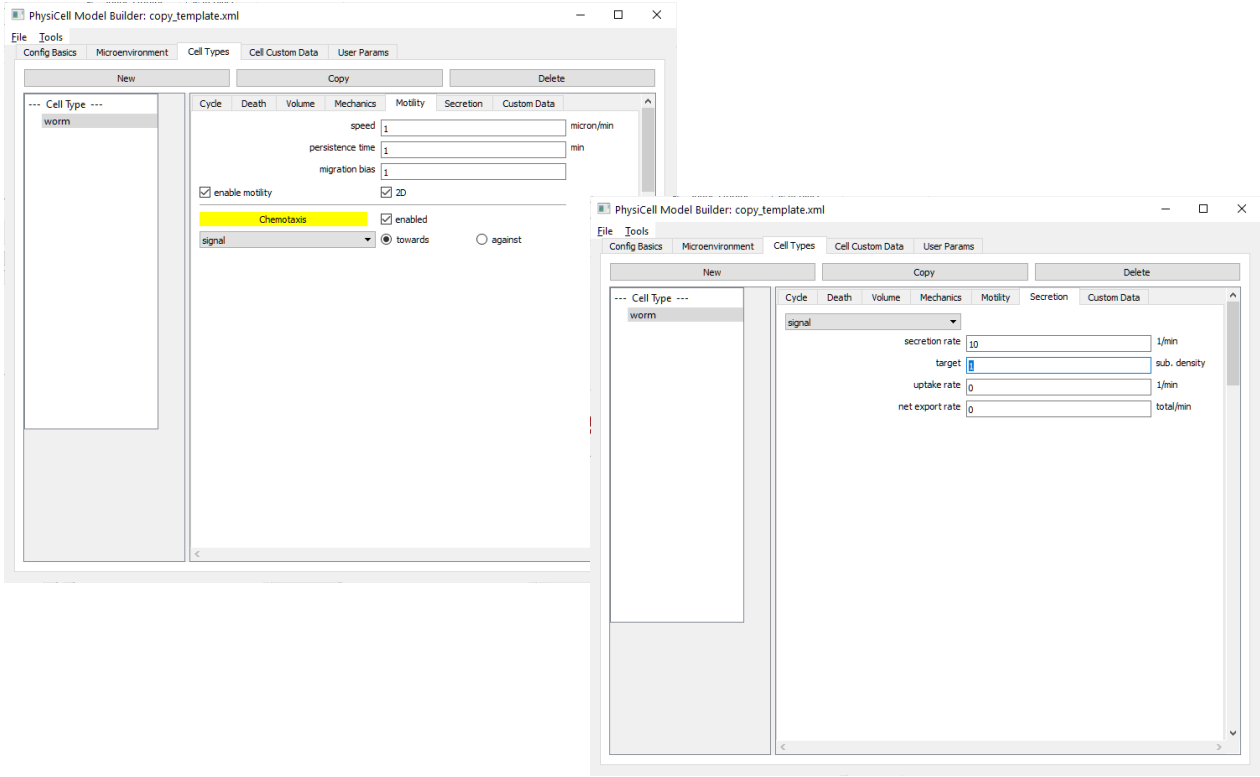
Edit the model: cell definitions (1)

- Go to "cell types" tab
- double-click "default"
  - rename it "worm"
  - edit its phenotype:
    - ♦ click "cycle" subtab
      - » choose live cycle model
      - » select "transition rate(s)"
      - » set 0→0 transition to 0
    - ♦ click "death" subtab
      - » set apoptosis to 0



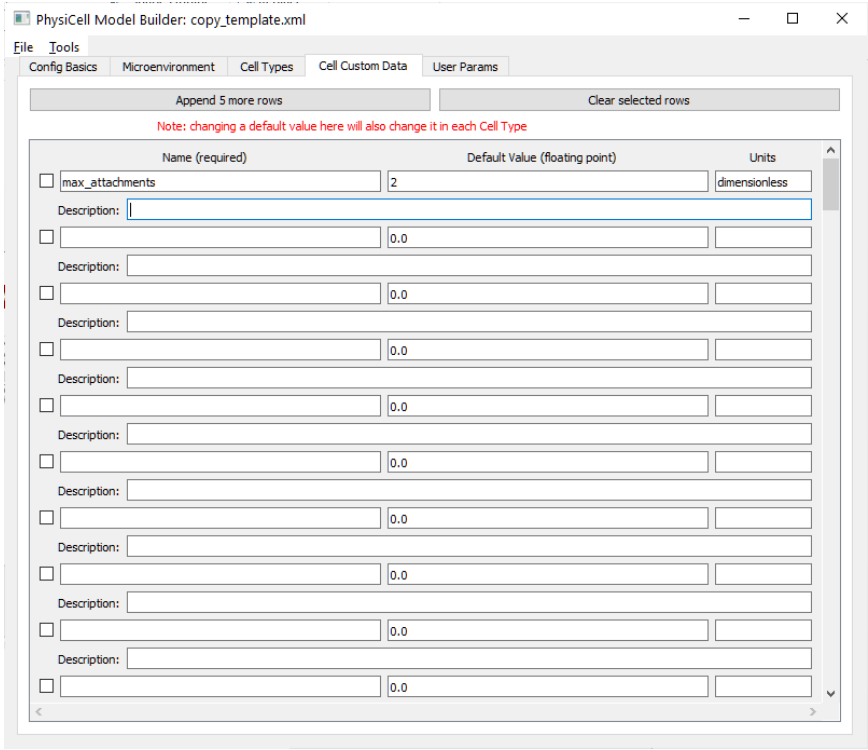
Edit the model: cell definitions (2)

- Go to "cell types" tab
- double-click "worm"
  - edit its phenotype:
    - ♦ click "motility" tab
      - » speed = 1
      - » persistence time = 1
      - » migration bias = `1
      - » check "enabled"
      - » chemotaxis "enabled"
        - ○ towards signal
    - ♦ click "secretion" tab
      - » choose "signal"



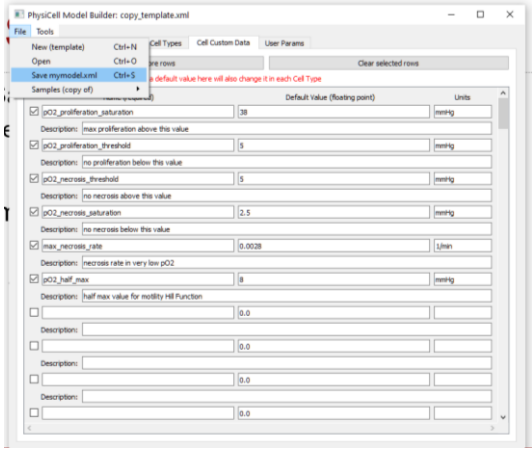
Edit the model: cell definitions (3)

- Go to "custom cell data" tab
- rename to "max_attachments"
  - set value to 2



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 Session10_checkpoint1.zip in ./PhysiCell to get this code.

Declare custom functions

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

```
void stretch_migration_direction(
      Cell* pCell, Phenotype& phenotype, double dt );
void middle_migration_direction(
      Cell* pCell, Phenotype& phenotype, double dt );
void custom_worm_function( Cell*, Phenotype&, double );
void worm_contact_function( Cell* pMe, Phenotype& phenoMe,
      Cell* pThem, Phenotype &phenoThem, double dt );

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

Migration rules

```
// These functions are used by PhysiCell to choose a migration direction whenever
// a cell makes a turn.

void stretch_migration_direction( Cell* pCell, Phenotype& phenotype, double dt )
{
  phenotype.motility.chemotaxis_direction = -1;

  phenotype.motility.migration_speed = 0.2;
  phenotype.motility.migration_bias = 0.5;
  phenotype.motility.persistence_time = 10;

  return chemotaxis_function( pCell,phenotype,dt);
}

void middle_migration_direction( Cell* pCell, Phenotype& phenotype, double dt )
{
  phenotype.motility.migration_speed = 0; // 0.1;
  return;
}
```

Custom rule (1)

```
void custom_worm_function( Cell* pCell, Phenotype& phenotype , double dt )
{
   // look for cells to form attachments
   int number_of_attachments = pCell->state.number_of_attached_cells();
   std::vector<Cell*> nearby = pCell->nearby_interacting_cells();

   int n = 0;
   while( number_of_attachments < (int) pCell->custom_data["max_attachments"] &&
      n < nearby.size() )
   {
      if( nearby[n] != pCell &&
           nearby[n]->state.number_of_attached_cells() <
           nearby[n]->custom_data["max_attachments"] )
      {
         attach_cells( nearby[n] , pCell );
         number_of_attachments++;
      }
      n++;
   }
```

Custom rule (2)

```
  // if no attachments, use chemotaxis
  if( number_of_attachments == 0 )
  { pCell->functions.update_migration_bias = chemotaxis_function; }

  // if 1 attachment, use stretch
  if( number_of_attachments == 1 )
  {
     pCell->functions.update_migration_bias = stretch_migration_direction;
     phenotype.secretion.secretion_rates[0] = 100;
  }

  // if 2 or more attachments, use middle
  if( number_of_attachments > 1 )
  {
     pCell->functions.update_migration_bias = middle_migration_direction;
     phenotype.secretion.secretion_rates[0] = 1;
  }

  return;
}
```

Contact function

```
// PhysiCell has a built-in contact function for elastic spring-like attachmetns

void worm_contact_function( Cell* pMe, Phenotype& phenoMe,
  Cell* pOther, Phenotype& phenoOther, double dt )
{ return standard_elastic_contact_function(pMe,phenoMe,pOther,phenoOther,dt); }
```

Set the cell to use these

```
void create_cell_types( void )
{
   // set the random seed
   SeedRandom( parameters.ints("random_seed") );

// etc etc etc etc etc

   /*
      This parses the cell definitions in the XML config file.
   */

   initialize_cell_definitions_from_pugixml();

   /*
      Put any modifications to individual cell definitions here.

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

   Cell_Definition* pCD = find_cell_definition("worm");

   pCD->functions.update_phenotype = NULL;
   pCD->functions.custom_cell_rule = custom_worm_function;
   pCD->functions.contact_function = worm_contact_function;

   pCD->phenotype.mechanics.attachment_elastic_constant = 0.03;
```

Coloring function

```
std::vector<std::string> worm_coloring_function( Cell* pCell )
{
  if( pCell->state.number_of_attached_cells() == 0 )
  { return { "grey", "black", "grey", "grey"}; }

  if( pCell->state.number_of_attached_cells() == 1 )
  { return { "red", "black", "red", "red"}; }

  if( pCell->state.number_of_attached_cells() == 2 )
  { return { "blue", "black", "blue", "blue"}; }

  return { "yellow", "black", "yellow", "yellow" };
}
```

Use the coloring function in main.cpp

```
// ...

// for simplicity, set a pathology coloring function

std::vector<std::string> (*cell_coloring_function)(Cell*) =
   worm_coloring_function; // my_coloring_function;


// ...
```

Unzip Session10_checkpoint2.zip in ./PhysiCell to get this code.

Rebuild and run the project

- Open the XML config file and set:
  - number of cells to 500
  - max time to 720 min

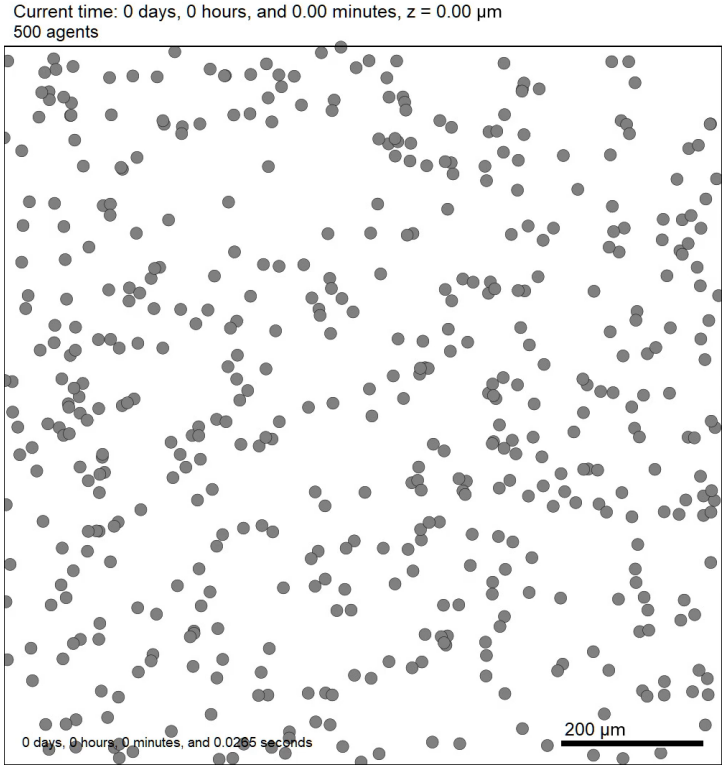
- rebuild:
  - `make`

- run:
  - `./project ./config/mymodel.xml` (linux, MacOS)
  - `project ./config/mymodel.xml` (Windows)

View results!

- make movie
  - `make jpeg && make movie`

- Expected behavior:
  - grays (0 attachments) move towards others
  - many cells get attached
    - red: one attachment
    - blue: two attachments
  - "worms" get stretched
    - red cells migrate away from others to stretch worms



Example 2: give the worm a head

- We'll use diffusion of a signaling factor along the worms help them work out heads and tails:
  - Each agent has stochastic level of "Head" protein
  - If a cell has > 1 attached cell, then diffuse Head across connections:

$$\frac{dH_i}{dt} = \sum_j r_{\text{transfer}}\left(H_j - H_i\right)$$

(and $\frac{dH_j}{dt} = -r_{\text{transfer}}\left(H_j - H_i\right)$)

  - If the cell has one attachment, don't overwrite Head value. Use initial value.
  - If a cell has 1 attachment, it is at the "head" if $H_{\text{self}} > H_{\text{attached}}$

Cell migration

- head cells:
  - strong avoidance chemotaxis
  - They guide the worm

- tail cells:
  - they don't actively migrate. they are dragged.

- middle cells:
  - they sample "head" signal to determine gradient
  - they follow the upstream cell

Approach

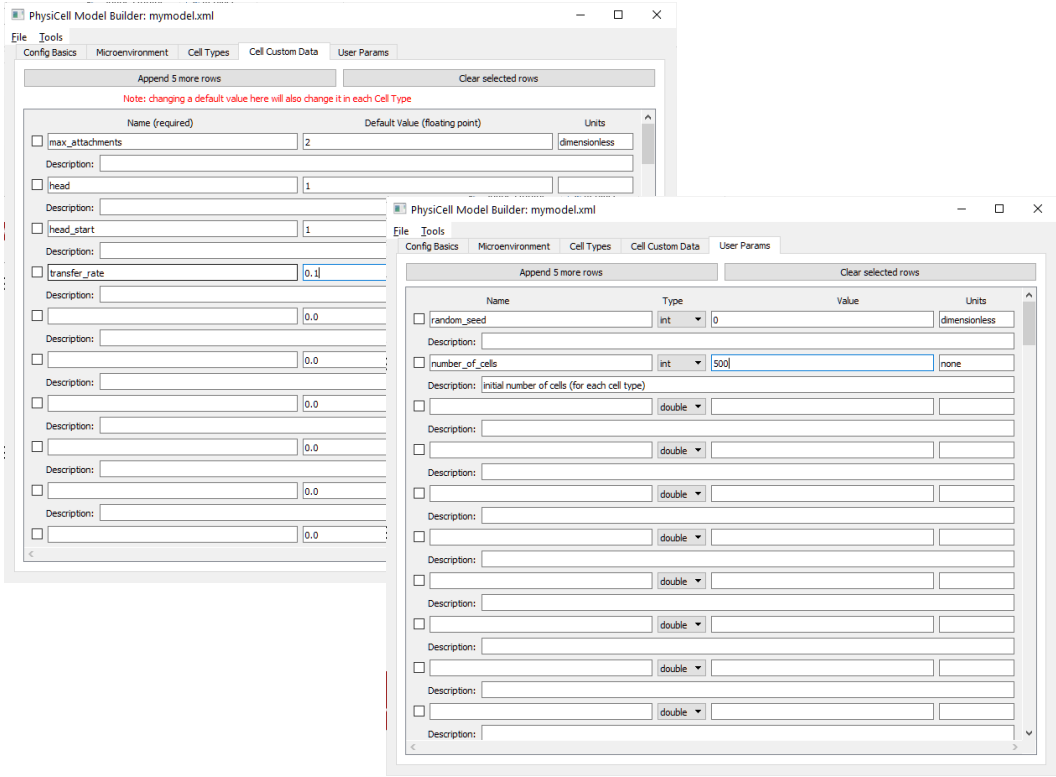
- Update setup_tissue:
  - Each cell gets random value of Head

- Update the contact function:
  - If more than one attachment:
    - ♦ check each attachment
      - » If Head_me > Head_other, diffuse some head protein into neighbor
      - » If Head_me <= Head_other, don't (This avoids double-counting the diffusion!)

- Update the custom rule:
  - Set motility function accordingly based on sensed position

Edit the model

- Go to "custom cell data" tab
  - Add
    - head (initial value 1)
    - head_start (initial value 1)
    - transfer_rate (initial value 0.1)
- Go to "user parameters" tab
  - Set initial cell count to 500



Edit setup_tissue()

```
   // create some of each type of cell

   Cell* pC;

   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 );

         pC->custom_data["head"] = UniformRandom();
         pC->custom_data["head_start"] = pC->custom_data["head"];
      }
   }
   std::cout << std::endl;

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

   return;
}
```

Update function declarations in custom.h

```
void custom_worm_function( Cell*, Phenotype&, double );
void worm_contact_function( Cell* pMe, Phenotype& phenoMe,
  Cell* pThem, Phenotype &phenoThem, double dt );

std::vector<std::string> worm_coloring_function( Cell* pCell );

void head_migration_direction( Cell* pCell, Phenotype& phenotype, double dt );
void tail_migration_direction( Cell* pCell, Phenotype& phenotype, double dt );
void middle_migration_direction( Cell* pCell, Phenotype& phenotype , double dt );
```

edit contact function

```
void worm_contact_function( Cell* pMe, Phenotype& phenoMe,
   Cell* pOther, Phenotype& phenoOther, double dt )
{
   standard_elastic_contact_function(pMe,phenoMe,pOther,phenoOther,dt);

   if( pMe->state.number_of_attached_cells() > 1 )
   {
      double head_me = pMe->custom_data["head"];
      double head_other = pOther->custom_data["head"];

      // make the trnasfer
      if( head_me > head_other )
      {
         double amount_to_transfer = dt * pMe->custom_data["transfer_rate"]
            * (head_me - head_other );
         pMe->custom_data["head"] -= amount_to_transfer;
         #pragma omp critical
         { pOther->custom_data["head"] += amount_to_transfer; }
      }
   }

}
```

edit custom function (1)

```
void custom_worm_function( Cell* pCell, Phenotype& phenotype , double dt )
{
   // bookkeeping

   static int nSignal = microenvironment.find_density_index("signal");

   // look for cells to form attachments, if 0 attachments
   int number_of_attachments = pCell->state.number_of_attached_cells();
   std::vector<Cell*> nearby = pCell->nearby_interacting_cells();

   if( number_of_attachments == 0 )
   {
      int n = 0;
      while( number_of_attachments < (int) pCell->custom_data["max_attachments"] && n < nearby.size() )
      {
         if( nearby[n]->state.number_of_attached_cells() < nearby[n]->custom_data["max_attachments"] )
         {
            attach_cells( nearby[n] , pCell );
            number_of_attachments++;
         }
         n++;
      }
   }

   // if no attachments, use chemotaxis
   if( number_of_attachments == 0 )
   { pCell->functions.update_migration_bias = chemotaxis_function; }
```

edit custom function (2)

```
   // if 1 attachment, do some logic
   if( number_of_attachments == 1 )
   {
      // constant expression in end cells
      pCell->custom_data["head"] = pCell->custom_data["head_start"];

      // am I the head?
      bool head = false;
      if( pCell->custom_data["head"] > pCell->state.attached_cells[0]->custom_data["head"] )
      { head = true; }

      if( head )
      { pCell->functions.update_migration_bias = head_migration_direction; }
      else
      { pCell->functions.update_migration_bias = tail_migration_direction; }
      phenotype.secretion.secretion_rates[nSignal] = 100;
   }

   // if 2 or more attachments, use middle
   if( number_of_attachments > 1 )
   {
      pCell->functions.update_migration_bias = middle_migration_direction;
      phenotype.secretion.secretion_rates[nSignal] = 1;
   }

   return;
}
```

migration bias functions

```
void head_migration_direction( Cell* pCell, Phenotype& phenotype, double dt )
{
   phenotype.motility.chemotaxis_direction = -1;
   phenotype.motility.migration_speed = 0.75;
   phenotype.motility.migration_bias = 0.5;
   phenotype.motility.persistence_time = 60;

   return chemotaxis_function( pCell,phenotype,dt);
}

void tail_migration_direction( Cell* pCell, Phenotype& phenotype, double dt )
{
   phenotype.motility.chemotaxis_direction = -1;
   phenotype.motility.migration_speed = 0;
   phenotype.motility.migration_bias = 0.5;
   phenotype.motility.persistence_time = 100;

   return chemotaxis_function( pCell,phenotype,dt);
}


void middle_migration_direction( Cell* pCell, Phenotype& phenotype , double dt )
{
   // get velocity from "Upstream"
   Cell* pUpstream = pCell->state.attached_cells[0];

   if( pCell->state.attached_cells[1]->custom_data["head"] >
      pCell->state.attached_cells[0]->custom_data["head"] )
   { pUpstream = pCell->state.attached_cells[1]; }
}
```

edit coloring

```
// only head cell is red

std::vector<std::string> worm_coloring_function( Cell* pCell )
{
  if( pCell->state.number_of_attached_cells() == 0 )
  { return { "grey", "black", "grey", "grey"}; }

  if( pCell->state.number_of_attached_cells() == 1 &&
    pCell->custom_data["head"] > pCell->state.attached_cells[0]->custom_data["head"] )
  { return { "red", "black", "red", "red"}; }

  if( pCell->state.number_of_attached_cells() == 2 )
  { return { "blue", "black", "blue", "blue"}; }

  return { "yellow", "black", "yellow", "yellow" };
}
```

Rebuild and run the project

- Open the XML config file and set:
  - number of cells to 500
  - max time to 1440 min

- rebuild:
  - `make`

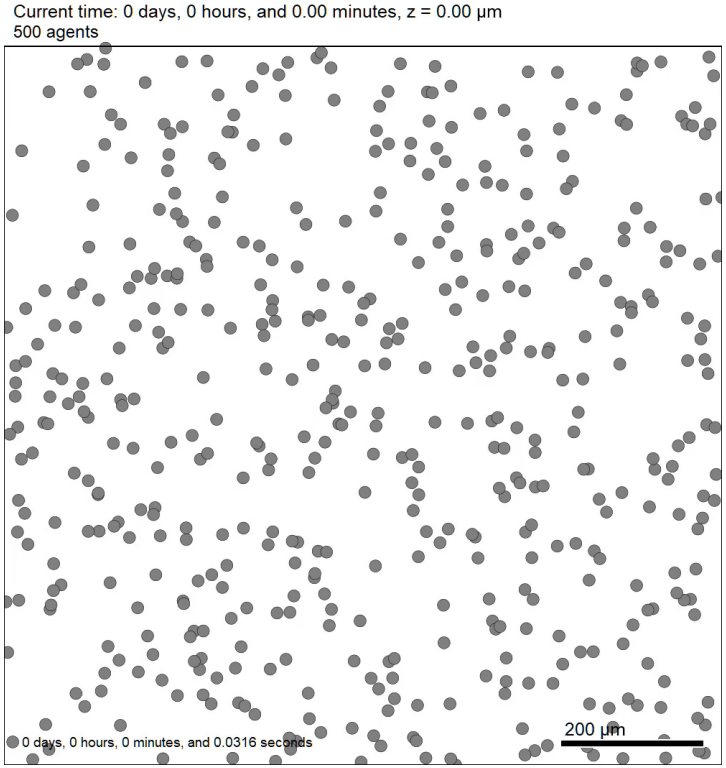
Unzip Session10_checkpoint3.zip in ./PhysiCell to get this code.

- run:
  - `./project ./config/mymodel.xml` (linux, MacOS)
  - `project ./config/mymodel.xml` (Windows)

View results!

- make movie
  - `make jpeg && make movie`

- Expected behavior:
  - grays (0 attachments) move towards others
  - many cells get attached
    - blue: one attachment
    - red: two attachments, head
    - yellow: two attachments, tail
  - "worms" get stretched
    - red cells migrate away from others to stretch worms
    - red ells lead the worm



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