Slides, videos, links and more:
https://github.com/physicell-training/ws2021

Session 3: Phenotype & Diffusion

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Agenda:

- Introduction
- Diffusion in PhysiCell(Microenvironment)
- Cell Phenotype
  - Cell Motility
  - Cell Mechanics
  - Cell Volume

Key parts of a PhysiCell model (1)

- **Microenvironment (stage):**
  - diffusing substrates
    - diffusion coefficient
    - decay rate
    - boundary conditions
    - Defined in XML configuration file

- **Cell Definitions (types of players):**
  - name
  - default phenotype (more on next page)
  - defined in XML configuration file

A note about time steps

- PhysiCell is designed to account for the multiple time scales inherent to these problems, and has 3 time scales:
  - $\Delta t_{\mathrm{diffusion}}$ diffusion, secretion, and uptake (default: 0.01 min)
  - $\Delta t_{\mathrm{mechanics}}$ cell movement (default: 0.1 min)
  - Δt_{cell} phenotype and volume changes (default: 6 min)

- This allows some efficiency improvements: not all functions need to be evaluated at each time step.

- See the PhysiCell method paper. (Oddly, not in the User Guide (yet).)

Microenvironment

- Boundary Conditions
  - By default, Von Neuman boundaries
  - Dirichlet's conditions and fine tuning
  - Dirichlet's nodes

- Define all substrates in the environment
  - Diffusion rate constant
  - Decay Rate

XML config file Microenvironment

```xml
<microenvironment_setup>
    <variable name="oxygen" units="mmHg" ID="0">
        <physical_parameter_set>
            <diffusion_coefficient units="micron^2/min">100000.0</diffusion_coefficient>
            <decay_rate units="1/min">0.1</decay_rate>
        </physical_parameter_set>
        <initial_condition units="mmHg">38.0</initial_condition>
        <Dirichlet_boundary_condition units="mmHg" enabled="false">10.0</Dirichlet_boundary_condition>
      <Dirichlet_options>

      <boundary_value ID="xmin" enabled="true">10.0</boundary_value>
      <boundary_value ID="xmax" enabled="true">100.0</boundary_value>
      <boundary_value ID="ymin" enabled="false">100.0</boundary_value>
      <boundary_value ID="ymax" enabled="false">100.0</boundary_value>
      <boundary_value ID="zmin" enabled="false" hidden="true">100.0</boundary_value>
      <boundary_value ID="zmax" enabled="false" hidden="true">100.0</boundary_value>
 </Dirichlet_options>
```

Microenvironment App

- https://nanohub.org/resources/microenvnmtr

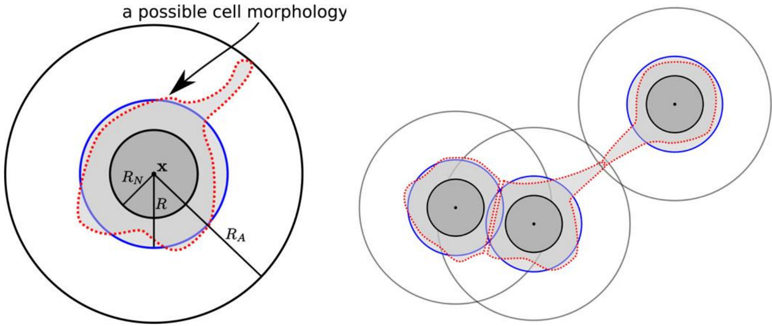
Cell phenotype

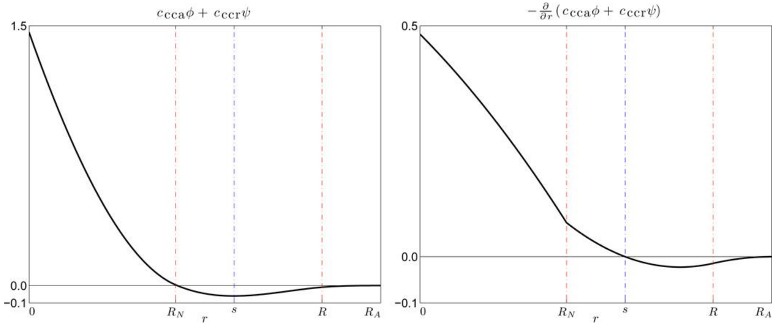
- One of the most critical data elements in a PhysiCell Cell is ***phenotype***
- Hierarchically organize key behavioral elements:
  - Phenotype
    - **cycle**: advancement through a cell cycle model
    - **death**: one or more types of cell death
    - **volume:** cell's volume regulation
    - **geometry:** cell's radius and surface area
    - **mechanics:** adhesion and resistance to deformation ("repulsion")
    - **motility:** active motion (other than "passive" mechanics)
    - **secretion:** both release and uptake of chemical substrates. Interfaces with BioFVM
    - **intracellular:** used for interacting with intracellular models. See Sessions 10-11.
    - **molecular:** a place to store internalized substrates

Documentation: User Guide, Sec. 10

Phenotype: Mechanics

- **Mechanics** keeps parameters for adhesion and "repulsion"
  - Key parameter: maximum adhesion distance
    - ♦ a multiple of the cell's radius
  - (as a multiple of the cell's radius)
- Default model uses potential functions, but this can be supplemented or replaced.





Documentation: User Guide 11.5

Cell definition: mechanics

```
<mechanics>
   <cell_cell_adhesion_strength units="micron/min">0.4</cell_cell_adhesion_strength>
   <cell_cell_repulsion_strength units="micron/min">10.0</cell_cell_repulsion_strength>
   <relative_maximum_adhesion_distance units="dimensionless">1.25</relative_maximum_adhesion_distance>

   <options>
      <set_relative_equilibrium_distance enabled="false"
            units="dimensionless">1.8</set_relative_equilibrium_distance>
      <set_absolute_equilibrium_distance enabled="false"
            units="micron">15.12</set_absolute_equilibrium_distance>
   </options>
</mechanics>
```

- **Options** give you some easy ways to *override* the cell-cell adhesion strength to accomplish other calibration goals:
  - **set_relative_equilibrium_distance** lets you choose the equilibrium cell-cell spacing, as a multiple of the cell radius. It will automatically choose a cell_cell_adhesion_strength to meet your selected equilibrium spacing.
    - 2.0 would have an equilibrium spacing of 2 cell radii (radius of cell 1 + radius of cell 2). Don't exceed this!
    - 1.8 or 1.9 is more typical.
  - **set_absolute_equilibrium_distance** allows you to choose this equilibrium distance in absolute (dimensional) units. This may or may not make sense as the cell changes size!

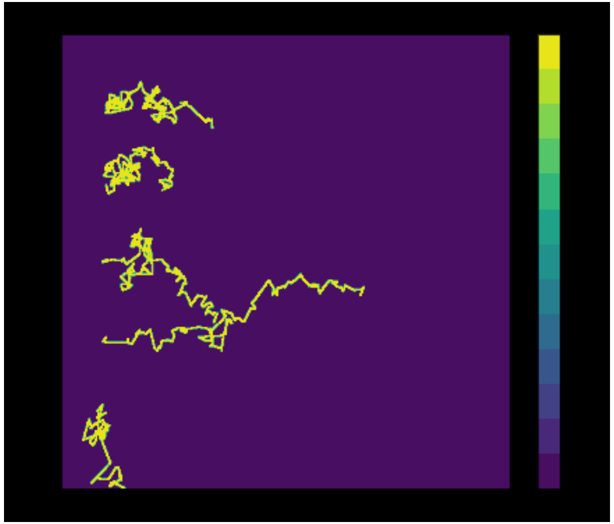
mechanics app demo

- https://nanohub.org/tools/trmechanics/

Phenotype: Motility

$$\mathbf{v}_{\text{mot}} \sim s(b\mathbf{d}_{\text{bias}} + (1-s)\mathbf{d}_{\text{rand}})$$

- **Motility** controls biased random migration
  - Migration speed s
  - Bias direction $\mathbf{d}_{\text{bias}}$
  - Migration bias $0 \leq b \leq 1$
    - If $b = 1$, deterministic motion
    - If $b = 0$, purely Brownian motion
  - Persistence time T_{per}



Cell definition: motility

```
<motility>
    <speed units="micron/min">1</speed>
    <persistence_time units="min">1</persistence_time>
    <migration_bias units="dimensionless">.5</migration_bias>

    <options>
        <enabled>false</enabled>
        <use_2D>true</use_2D>
        <chemotaxis>
            <enabled>false</enabled>
            <substrate>substrate</substrate>
            <direction>1</direction>
        </chemotaxis>
    </options>
</motility>
```

- If "enabled" is set to false, the cell will not be motile, regardless of what speed you give it above.
- If you set use_2D to true, then the cell restricts its motile motion to its current z-plane.
- chemotaxis allows you to use out-of-the-box chemotaxis:
  - set enabled to true to use this.
  - use "substrate" to choose which chemical factor it follows.
  - use direction = 1 to go up the gradient, and -1 to go against the gradient
  - **Important!!! If the "substrate" does not match something defined in the microenvironment above, the initialization will fail.**

motility app demo

- https://nanohub.org/tools/trmotility/

Phenotype: Volume

- **volume** records the cell's sub-volumes:
  - nuclear and cytoplasmic
  - solid vs. fluid
  - calcified fraction
  - key parameters
- a very simple **default model** to regulate volume based on ODEs
  - Change the parameters, target values based on environment and cell state

$$\frac{dV_F}{dt} = r_F\left(V_F^* - V_F\right)$$

$$\frac{dV_{NS}}{dt} = r_N\left(V_{NS}^* - V_{NS}\right)$$

$$\frac{dV_{CS}}{dt} = r_C\left(V_{CS}^* - V_{CS}\right)$$

Documentation: User Guide 11.3

Cell definition: Phenotype: Volume

```
<volume>
   <total units="micron^3">2494</total>
   <fluid_fraction units="dimensionless">0.75</fluid_fraction>
   <nuclear units="micron^3">540</nuclear>

   <fluid_change_rate units="1/min">0.05</fluid_change_rate>
   <cytoplasmic_biomass_change_rate units="1/min">0.0045</cytoplasmic_biomass_change_rate>
   <nuclear_biomass_change_rate units="1/min">0.0055</nuclear_biomass_change_rate>

   <calcified_fraction units="dimensionless">0</calcified_fraction>
   <calcification_rate units="1/min">0</calcification_rate>


   <relative_rupture_volume units="dimensionless">2.0</relative_rupture_volume>
</volume>
```

- This gives both the steady-state "target" volume of the cell type and the initial volume for any cells you place in the simulation.
- Use the change rates to control how quickly cells move towards their target volume.
- The relative rupture volume is mostly useful to death models.
- Distinguish between State variables vs Target Parameters

Phenotype: Volume app demo

- https://nanohub.org/tools/volumetr

Next Session

- Cell Phenotype Continued
  - Cell Cycle
  - Cell Death
  - Cell Secretion and Uptake

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