Slides, videos, links and more:
https://github.com/physicell-training/ws2022

Session 3: Cell Phenotype

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PhysiCell Project

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Agenda:

- Background
- Time steps
- Diffusion in PhysiCell(Microenvironment)
- Cell Motility
- Cell Mechanics
- Cell Volume
- Cell interactions
- Cell Cycle
- Cell Death
- Cell Secretion and Uptake

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

Key parts of a PhysiCell model (2)

- **Cell agents (individual players)**:
  - Which cell type? (the cell agent is initialized based on a cell definition)
  - State variables:
    - position
    - mechanical pressure
    - interaction list (optional)
  - Phenotype **(the script)**
    - Cell cycle
    - Volume
    - Death
    - Motility
    - Mechanics
    - Substrate uptake & release
    - Cell interactions
  - Custom variables
  - Custom functions that act upon the phenotype, variables, and state **(script)**

A note about time steps

- PhysiCell is designed to account for the multiple time scales inherent to these problems, and has 3 time scales:
  - $\Delta t_{\text{diffusion}}$ diffusion, secretion, and uptake (default: 0.01 min)
  - $\Delta t_{\text{mechanics}}$ 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

Cell phenotype

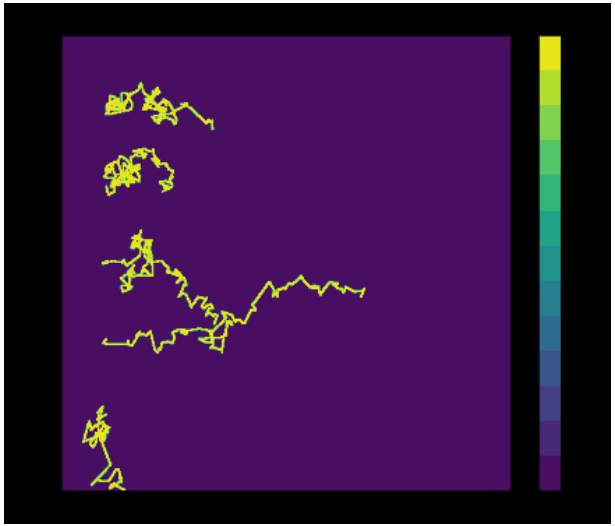
- One of the most critical data elements in a PhysiCell Cell is ***phenotype***
- Hierarchically organize key behavioral elements:
  - Phenotype
    - **cycle**: advancement through a cell cycle model
    - **death**: one or more types of cell death
    - **volume:** cell's volume regulation
    - **geometry:** 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
    - **molecular:** a place to store internalized substrates
    - **cell interactions:** contact interactions with neighboring cells

Documentation: User Guide, Sec. 10

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>
```

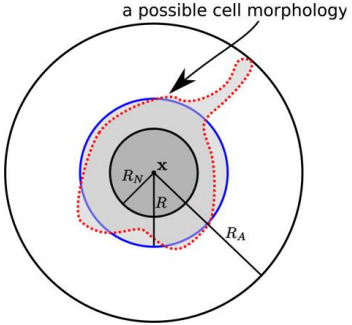
- If "enabled" is set to false, the cell will not be motile, regardless of what speed you give it above.
- If you set use_2D to true, then the cell restricts its motile motion to its current z-plane.
- chemotaxis allows you to use out-of-the-box chemotaxis:
  - set enabled to true to use this.
  - use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

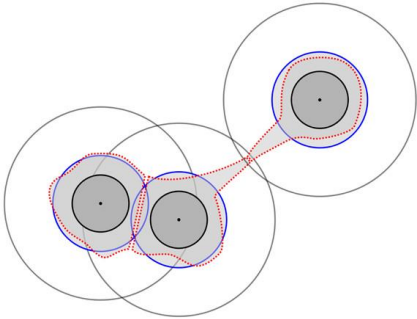
motility app demo

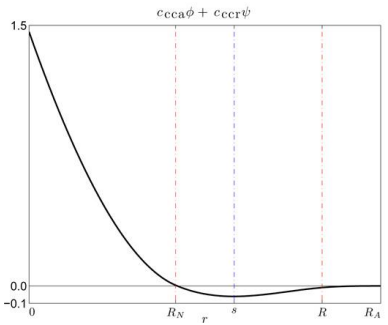
- https://nanohub.org/tools/trmotility/

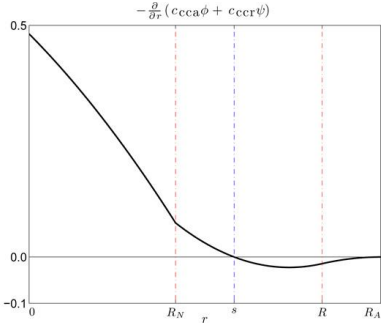
Phenotype: Mechanics

- **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.
- cell adhesion affinities for preferential adhesion. Default=1
- **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>
```

- The 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: 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

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

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

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

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 seed 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

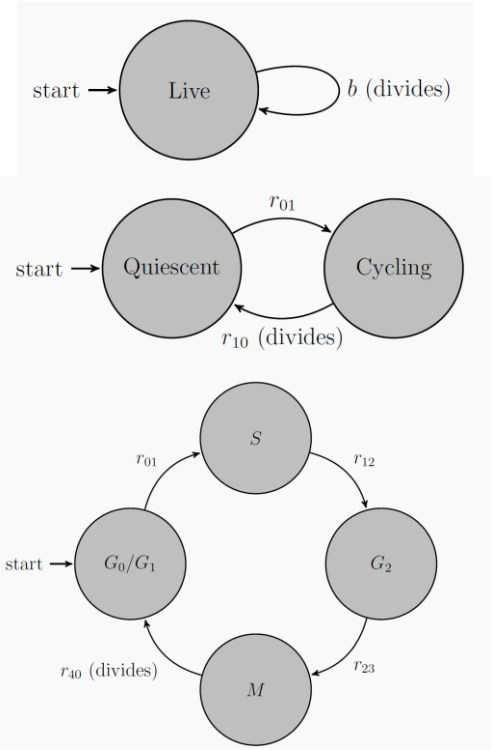
- https://nanohub.org/tools/volumetr

Cell interactions

- Phagocytosis
  - dead_phagocytosis_rate(scalar)
  - live_phagocytosis_rates(vector)
- cell attack that increases a tracked damage variable
  - attack_rates
  - damage_rate
- cell fusion
  - fusion_rates
- cell transformations
  - transformation_rates

Phenotype: Cycle

- Each agent's **phenotype** had a **cycle** with:
  - Cycle **model**
    - A directional graph: *nodes* are cycle **phases** $\{P_i\}$ and *edges* are **transition rates** $\{r_{ij}\}$
    - r_{ij} is the transition rate from phase P_i to phase P_j
    - One of the transitions must be marked as a *division transition*
    - Users can attach **arrest condition** functions to these transitions (e.g., size checks)
  - Cycle **data**
    - stores the cell's current transition rates



- **Documentation:** User Guide, Sec. 11.1

Phenotype: Cycle

Cell Cycles available in PhysiCell

- Live
- Ki-67 Basic
- Ki-67 Advanced
- Flow Cytometry
- Flow Cytometry Separated
- Cycling-Quiescent

Cell definition: cycle

```
      <cycle code="5" name="live">  <!-- pick a code to match PhysiCell_constants.h -->
        <!-- use phase_transition_rates OR phase_durations -->
        <phase_transition_rates units="1/min">
          <rate start_index="0" end_index="0" fixed_duration="false">0.002</rate>
        </phase_transition_rates>

        <!-- use phase_transition_rates OR phase_durations -->
<!--
        <phase_durations units="min">
          <duration index="0" fixed_duration="false">500.0</duration>
        </phase_durations>
-->
      </cycle>
```

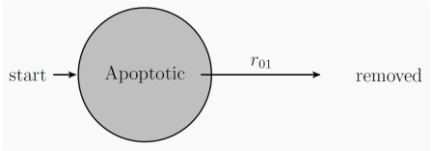
- For some problems, it's easier to work in terms of transition rates. Use the "phase_transition_rates" code for these.
  - In this example, the "live" cell cycle (with a single phase) transitions at a rate of 0.002 1/min.
- Sometimes, it's easier to work in terms of how long a cell spends in a phase. Use "phase_durations" for these.
  - In this example, the "live" cell cycle (with a single phase) lasts (on average) 500 minutes.

cycle app demo

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

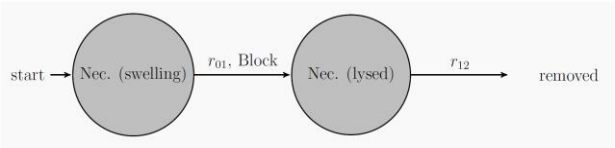
Phenotype: Death

- **Death** has one or more death models:
  - A specialized cycle model with a *removal* transition rate
  - Extra parameters to help govern cell volume
  - Each death model has an associate death rate
  - Also stores an easy Boolean ***dead*** to easily check if the cell is alive.



Apoptosis

- PhysiCell has built-in apoptosis and necrosis death models



Necrosis

Documentation: User Guide, Sec. 11.2

Cell definition: death

```
<death>
     <model code="100" name="apoptosis">
          <death_rate units="1/min">0</death_rate>
          <!-- use phase_transition_rates OR phase_durations -->
          <phase_durations units="min">
               <duration index="0" fixed_duration="true">516</duration>
          </phase_durations>
          <parameters>
               <unlysed_fluid_change_rate units="1/min">0.05</unlysed_fluid_change_rate>
               <lysed_fluid_change_rate units="1/min">0</lysed_fluid_change_rate>
               <cytoplasmic_biomass_change_rate units="1/min">1.66667e-02</cytoplasmic_biomass_change_rate>
               <nuclear_biomass_change_rate units="1/min">5.83333e-03</nuclear_biomass_change_rate>
               <calcification_rate units="1/min">0</calcification_rate>
               <relative_rupture_volume units="dimensionless">2.0</relative_rupture_volume>
          </parameters>
     </model>
     <model code="101" name="necrosis">
          <death_rate units="1/min">0.0</death_rate>
          <!-- necrosis uses phase_duration[0] = 0 so that it always immediately
               tries to transition and instead checks volume against the rupture volume -->
          <phase_durations units="min">
               <duration index="0" fixed_duration="true">0</duration>
               <duration index="1" fixed_duration="true">86400</duration>
          </phase_durations>
          <parameters>
               <unlysed_fluid_change_rate units="1/min">0.05</unlysed_fluid_change_rate>
               <lysed_fluid_change_rate units="1/min">0</lysed_fluid_change_rate>
               <cytoplasmic_biomass_change_rate units="1/min">1.66667e-02</cytoplasmic_biomass_change_rate>
               <nuclear_biomass_change_rate units="1/min">5.83333e-03</nuclear_biomass_change_rate>
               <calcification_rate units="1/min">0</calcification_rate>
               <relative_rupture_volume units="dimensionless">2.0</relative_rupture_volume>
          </parameters>
     </model>
</death>
```

- Use death_rate to determine the rate of *starting* each mode of death.
- Use the phase_durations and parameters to control how cells progress through each death model.

death app demo

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

Phenotype: Secretion

- **Secretion** stores parameters for secretion, uptake, and generalized export of diffusing substrates

$$\frac{\partial \boldsymbol{\rho}}{\partial t} = \nabla \cdot (\boldsymbol{D} \nabla \boldsymbol{\rho}) - \boldsymbol{\lambda} \cdot \boldsymbol{\rho} + \sum_i \delta(\boldsymbol{x} - \boldsymbol{x}_i) V_i (\boldsymbol{S}_i \cdot (\boldsymbol{\rho}_i^* - \boldsymbol{\rho}) - \boldsymbol{U}_i \cdot \boldsymbol{\rho} + \boldsymbol{E}_i)$$

PhysiCell automatically tracks the mass of substrates removed from the tissue (added to cells) or added to tissue (removed from cells).

Documentation: User Guide Sec. 11.7

Important Parameters

- Differentiate between net export vs secretion rate
- Secretion rate is dependent upon Volume

Cell definition: Secretion

```
<secretion>
    <substrate name="chemical_A">
        <secretion_rate units="1/min">0</secretion_rate>
        <secretion_target units="substrate density">1</secretion_target>
        <uptake_rate units="1/min">0</uptake_rate>
        <net_export_rate units="total substrate/min">0</net_export_rate>
    </substrate>

    <substrate name="chemical_B">
        <secretion_rate units="1/min">0</secretion_rate>
        <secretion_target units="substrate density">1</secretion_target>
        <uptake_rate units="1/min">0</uptake_rate>
        <net_export_rate units="total substrate/min">0</net_export_rate>
    </substrate>

    <substrate name="chemical_C">
        <secretion_rate units="1/min">0</secretion_rate>
        <secretion_target units="substrate density">1</secretion_target>
        <uptake_rate units="1/min">0</uptake_rate>
        <net_export_rate units="total substrate/min">0</net_export_rate>
    </substrate>
</secretion>
```

secretion app demo

- https://nanohub.org/resources/32528

Coming up

- Example project Session 4
- Dictionary for Signals and Behaviors mapping session 5

- Reference to PhysiCell training Apps:

bioRxiv 2022.06.24.497566; doi: https://doi.org/10.1101/2022.06.24.497566

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