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

Session 4: Phenotype & Diffusion

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Agenda:

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

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
  - 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).)

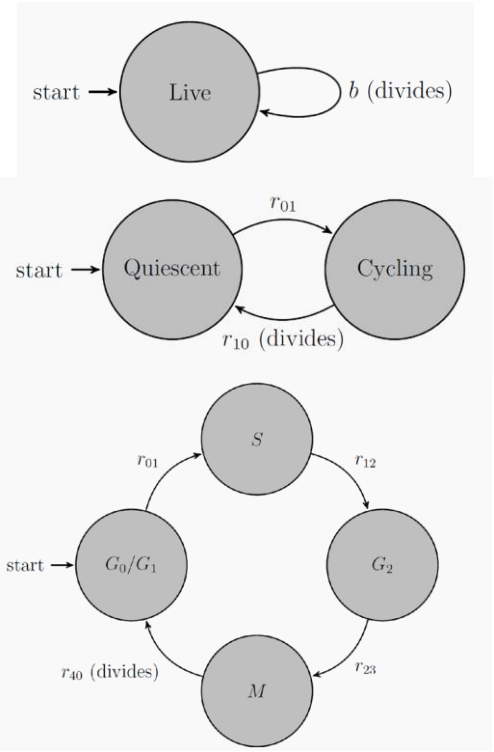
Cell phenotype

- 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: 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

- As a default, cells are phase changes stochastically. (you can change)

$$\text{Prob}(\text{transition from } X_i \text{ to } X_j | \text{not arrested}) \approx r_{ij}\Delta t.$$

- Example
  - Phase Transition rate = 0.016666 1/min
  - Phase Duration rate = 60 min

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>
```

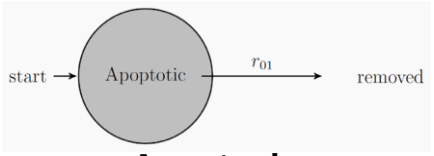
- For some problems, it's easier to work in terms of transition rates. Use the "phase_transition_rates" code for these.
  - In this example, the "live" cell cycle (with a single phase) transitions at a rate of 0.002 1/min.
- Sometimes, it's easier to work in terms of how long a cell spends in a phase.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

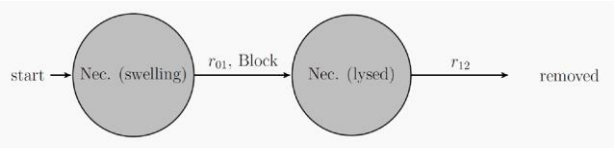
Phenotype: Death

- **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.

Phenotype: Death

- Apoptosis:

$$\text{Prob}(\mathcal{S}_i(t+\Delta t) = D_i) \quad = \quad 1 - \exp(-r_i \Delta t) \approx r_i \Delta t.$$

- Necrosis:

$$r_{Q1} \quad = \quad \frac{1}{T_Q} \max\left\{ \left(\frac{\text{pO}_2 - \text{pO}_{2,\text{hypoxia}}}{\text{pO}_2 - \text{pO}_{2,\text{hypoxia}}} \right), 0 \right\},$$

death app demo

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

Phenotype: Secretion

$$\frac{\partial \boldsymbol{\rho}}{\partial t} = \mathbf{D} \circ \nabla^2 \boldsymbol{\rho} - \boldsymbol{\lambda} \circ \boldsymbol{\rho} + \sum_i \delta(\mathbf{x} - \mathbf{x}_i) \left[V_i \mathbf{S}_i \circ (\boldsymbol{\rho}_i^* - \boldsymbol{\rho}) - V_i \mathbf{U}_i \circ \boldsymbol{\rho} + \mathbf{E}_i \right],$$

Symbol	Meaning	Dimensions
$\boldsymbol{\rho}$	vector of substrate densities (or concentrations)	substance/volume
$\mathbf{D}$	vector of diffusion coefficients	length^2/time
$\boldsymbol{\lambda}$	vector of decay rates	1/time
V_i	volume of cell i	volume
$\mathbf{x}_i$	cell i's position (center)	length
$\mathbf{S}_i$	vector of cell i's secretion rates	1/time
$\boldsymbol{\rho}_i^*$	vector of cell i's secretion saturations	substance/volume
$\mathbf{U}_i$	vector of cell i's uptake rates	1/time
$\mathbf{E}_i$	vector of cell i's net export rates	substance/time

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/trsecretion

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