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https://github.com/physicell-training/ws2023

Session 3: PhysiCell Signals, Behaviors, and Grammar

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PhysiCell Project

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Session Goals

- Learn about cells as signal processors
- Learn about signals in PhysiCell
- Learn about behaviors in PhysiCell
- Learn about PhysiCell's behavior grammar
- Prepare for rules-based modeling in PhysiCell

From single cells to cancer ecosystems

- **Single-cell behaviors:**
  - Growth
  - Division
  - Differentiation
  - Death
  - Consumption
  - Metabolism
  - Secretion
  - Signaling
  - Mutations
  - Motility
- **Cell-cell interactions:**
  - Adhesion
  - Mechanics
  - Predation
  - Contact communication
- **Physical constraints:**
  - Diffusion limits
  - Mechanical barriers

Multicellular cancer ecosystem

Multicellular systems biology seeks to *understand* these systems.
Multicellular systems engineering seeks to *control* them.

Source: Hanahan (2022)
DOI: 10.1158/2159-8290.CD-21-1059

Scientists use [models*] to detangle complex systems.

* animal, *in vitro*, engineered, mathematical, conceptual …

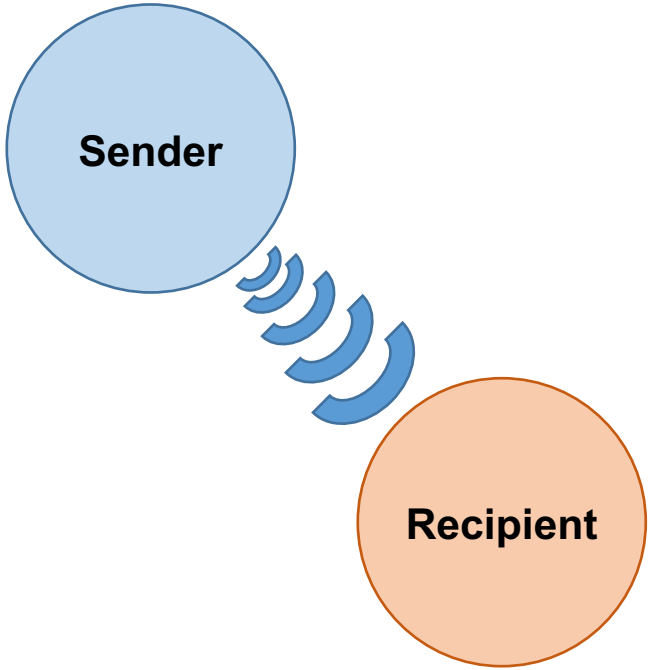
We use agent-based models as our virtual laboratory.

First, a conceptual model

Signal-Response as a Conceptual Framing

- Much of the complexity of this system can be decomposed into pairwise interactions between a ***sender*** and a ***recipient***

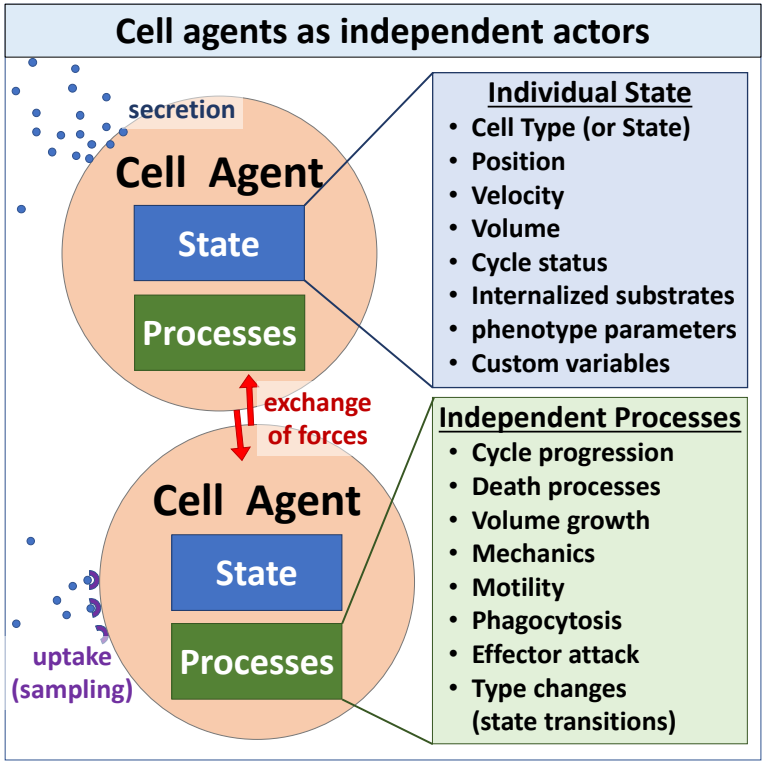
- A **signal** is a stimulus that can elicit a behavioral **response**:
  - A macrophage (**sender**) secretes IL-6 (**signal**) that drives chemotaxis (**response**) in a CD8 T cell (**recipient**)
  - An epithelial cell (**sender**) exerts pressure (**signal**) that decreases cycle entry (**response**) in another epithelial cell (**recipient**)



Agent-based models are well-suited to this framing

Agent-based models: overview

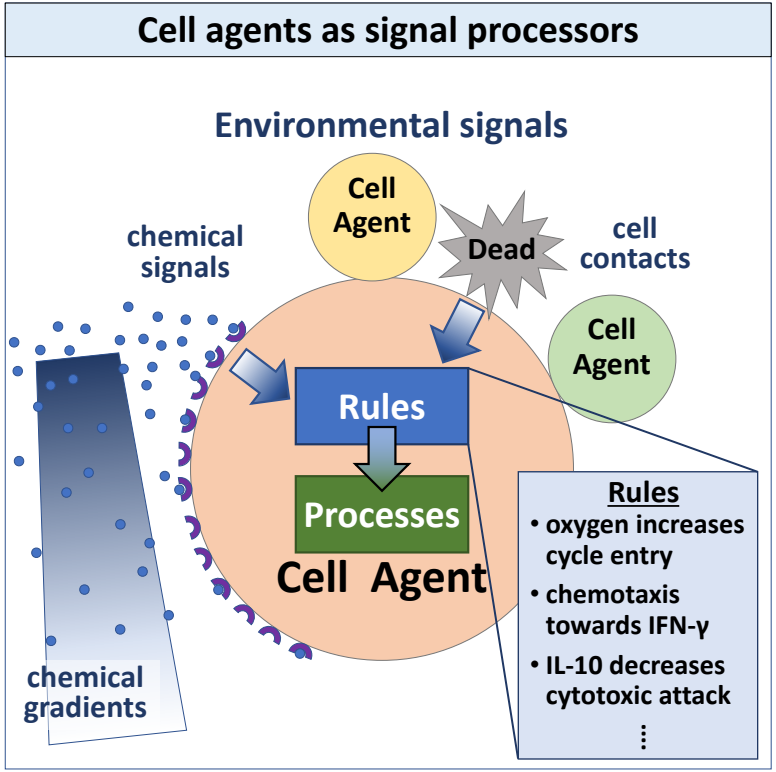
- Each cell is an **independent agent** with:
  - **Individual state**
    - Type
    - Position
    - Velocity
    - Phenotype parameters
    - Custom variables
  - **Independent processes**
    - Cycle and death processes
    - Volume growth
    - Mechanics and motility
    - Secretion and uptake / sampling
    - Phagocytosis, effector attack
    - State transitions (change of type)
    - Custom processes



Cell agents are signal processors

- Cells interact through chemical and physical **signals** (or stimuli)
  - Secreted chemical signals
  - Chemical gradients
  - Contact with a live or dead cell

    …
- Signals drive changes in **behavior**
  - Increased or decreased rates of cycling or death
  - Changes in motility, secretion, phagocytosis, …
- Signal-behavior relationships are **agent rules**

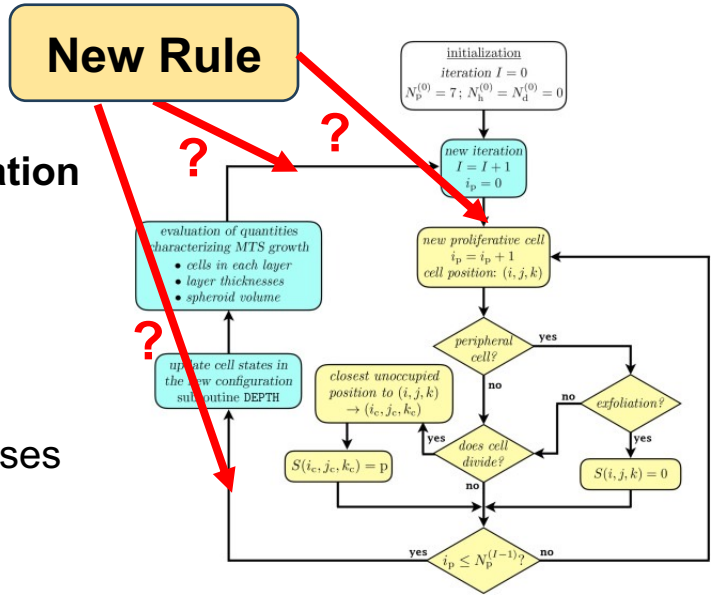


Cell rules:
A signal-response grammar

Problems with hand-written models

- Many models re-implement recurring elements
  - Does not leverage prior modeling
  - Increases likelihood of errors
  - Large coding effort **discourages multidisciplinary participation**
  - Variations in implementation add complexity to interpretation

- **Perhaps most importantly, as complexity grows:**
  - Harder to understand the full model
  - Harder to clearly communicate the current biological hypotheses
  - Harder to integrate new biological hypotheses
    - Placing new rules can break prior rules
    - Requires mathematical and software expertise
  - Harder for domain experts to participate in real time



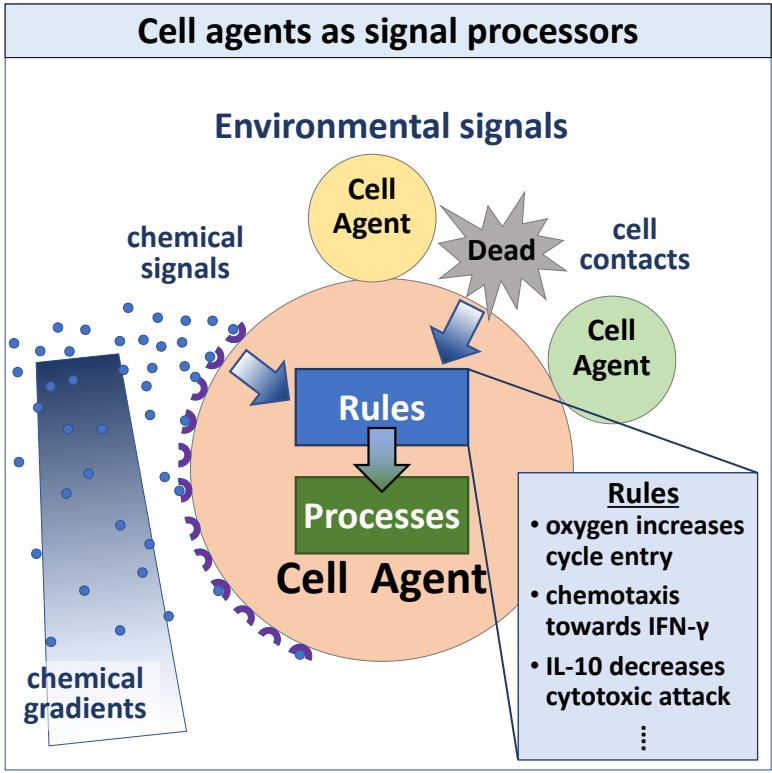
DOI: 10.1016/j.ejmp.2020.07.026

Goal: Create a modeling grammar

- **Goal:** Create a formal language for cell rules that:
  - Can be written in human-readable "plain English"
    - Facilitates tools for easy model construction
    - ***This could turn model building into knowledge mapping.***
  - Can readily be "translated" to a standard mathematical form
    - PhysiCell can parse the rules into mathematics without hand-coding
    - More reusable, maintainable model
  - Can easily integrate new knowledge with prior knowledge
  - Can combine data-driven and knowledge-driven workflows

Key elements for a computable model grammar

- A "dictionary" of standard cell process (behavior) models
- A "dictionary" of signals (stimuli) that modulate behaviors
- A grammar (a language) to connect signals to behavioral responses
- Automatically map grammar statements onto mathematics and code



Reference Cell Behavior Models

A dictionary of behaviors

- Based on years of modeling, we created a "dictionary" of standardized behaviors ***and well-defined reference models***

- **Cycling**
  - Exit rates from each cycle phase
- **Death**
  - Apoptotic and necrotic death rates
- **Transport**
  - Secretion, uptake, and export rates
- **Migration and chemotaxis**
  - Migration speed, bias, persistence time
  - Chemotactic sensitivities (to each diffusible factor)
- **Mechanics and Adhesion**
  - Adhesion and repulsion potential coefficients
  - Adhesion affinities (to each cell type)
  - Elastic adhesion constant, maximum number of adhesions
  - Rate of forming and breaking elastic adhesions
- **Transformation**
  - Rate of transforming (to each cell type)
- **Fusion**
  - Rate of fusing (combining with) each cell type
- **Phagocytosis (or ingestion / predation)**
  - Rate of ingesting dead cells
  - Rate of ingesting live cells (one rate for each type)
- **Effector Attack**
  - Rate of attacking live cells (one for each type), Immunogenicity (one for each cell type
  - Rate of causing damage during attack
- **Custom symbols**

- Each **symbol** can be **uniquely matched to a mathematical parameter** in a reference process model

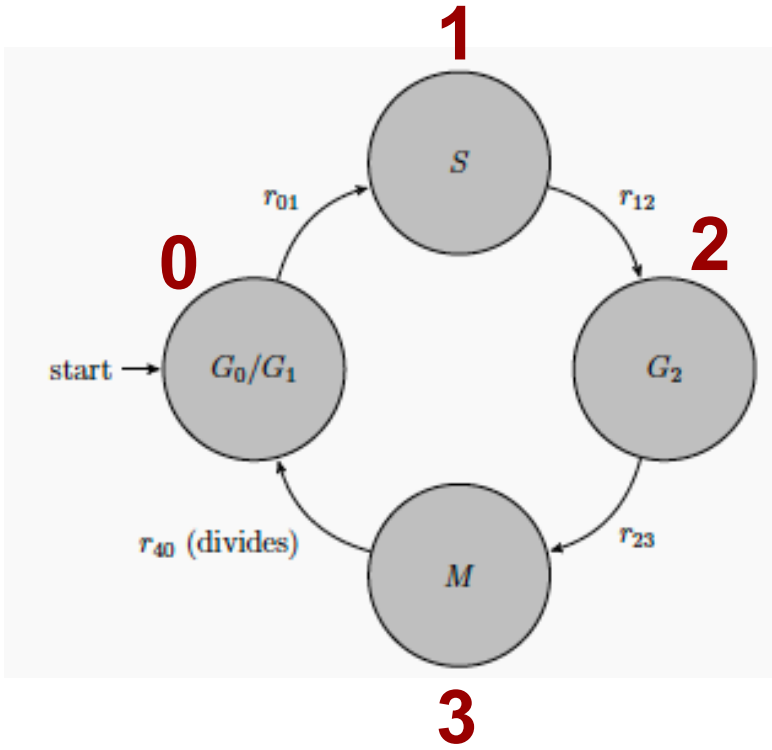
Reference cell behavior models: Cycling

- Transition between cycle phases
- Divide into two cells at end of last phase
  - Random placement, preserving center of volume

- Key parameters:
  - cycle entry (rate of moving from phase 0 to 1)
  - exit rates r_i (transition from phase *i* to phase *i*+1)

- Mathematics:
  - In any time period $[t, t + \Delta t]$, the probability of exiting phase i is:

$$P(\text{exit phase } i) = r_{i,i+1}\Delta t.$$



Reference behavior models: Death

- **Apoptosis** (prototypical non-inflammatory death)
  - Gradually shrink, get removed
  - Key parameter: apoptotic death rate (rate of starting apoptosis)
    - **Note:** This is the rate of a cell *becoming* apoptotic! Non-zero time scale (hours) to complete.

$$P(\text{cell becomes apoptotic}) = d_A \Delta t$$

- **Necrosis** (prototypical inflammatory death)
  - First swell, burst, then shrink
  - Key parameter: necrotic death rate
    - **Note:** This is the rate of a cell *becoming* necrotic! Non-zero time scale (days) to complete.

$$P(\text{cell becomes necrotic}) = d_N \Delta t$$

Reference behavior models: Transport

- cells can secrete, uptake (consume), and export diffusible substrates

- Key parameters:
  - secretion rates
  - secretion targets
  - uptake rates,
  - net export rates

$$\frac{\partial \rho}{\partial t} = D\nabla^2\rho - \lambda\rho + \sum_{\text{cells } i}\left(\delta(\boldsymbol{x}-\boldsymbol{x}_i)V_i\left[\overbrace{S_i\left(\rho_i^* - \rho\right)}^{\text{secretion}} - \overbrace{U_i\rho}^{\text{uptake}}\right] + \delta(\boldsymbol{x}-\boldsymbol{x}_i)\overbrace{E_i}^{\text{export}}\right)$$

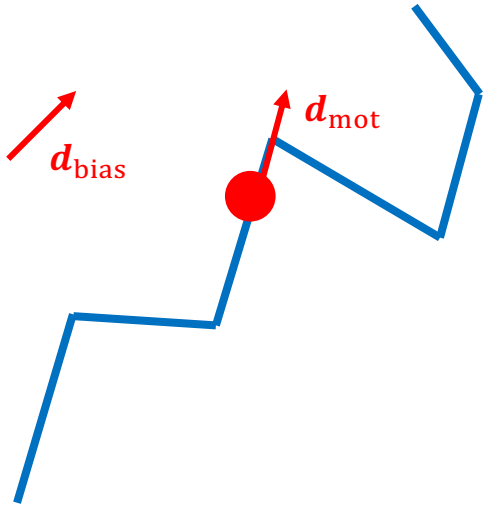
Reference behavior models: Migration

- migration is a biased random walk:
  - Move some time along a bias direction, then resample, move again
  - **motility direction**:

$$\boldsymbol{d}_{\text{mot}} = \frac{b\,\boldsymbol{d}_{\text{bias}} + (1-b)\boldsymbol{\xi}}{\|b\,\boldsymbol{d}_{\text{bias}} + (1-b)\boldsymbol{\xi}\|}$$

  - **migration velocity (contributed to cell velocity):**

$$\boldsymbol{v}_{\text{mot}} = s\,\boldsymbol{d}_{\text{mot}}.$$



- Key parameters:
  - migration speed (linear speed)
  - persistence time (mean time between direction changes)
  - bias (directedness)

Reference behavior models: Chemotaxis

- **chemotaxis (advanced)**
  - bias direction is a weighted sum of chemical gradients

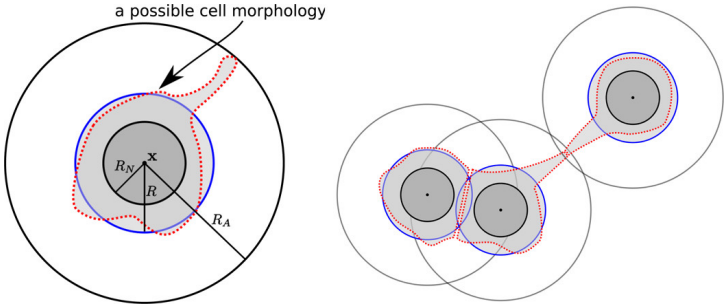
$$\boldsymbol{d}_{\text{bias}} = \omega_0 \nabla c_0 + \cdots + \omega_m \nabla c_m,$$

  - Key parameters:
    - weights (-1 to 1) of each chemical gradient
    - **Note:** "basic" chemotaxis just sets most weights to 0.

Reference behavior models: Cell Adhesion

- **cell-cell adhesion (basic)**
  - Use potential functions for an attractive force

$$\sqrt{A_{ij}\,\alpha_i \cdot A_{ji}\alpha_j}\left(1-\frac{\|\boldsymbol{x}_j-\boldsymbol{x}_i\|}{R_{A,i}R_i+R_{A,j}R_j}\right)^{n+1}\frac{(\boldsymbol{x}_j-\boldsymbol{x}_i)}{\|\boldsymbol{x}_j-\boldsymbol{x}_i\|},$$



  - Key parameters:
    - adhesive affinity (affinity of type *i* to type *j*)
    - adhesion strength
    - max adhesion distance (relative to cell radius)

Reference behavior models: Cell Adhesion

- **cell-cell adhesion (elastic / advanced)**
  - form and break elastic spring links to contacting cells
    - Cell *i* can stochastically form adhesive links to cell *j:*

$$P(i \text{ links to } j \text{ in } [t, t+\Delta t]) = r_{A,ij}\Delta t = r_{A,i}\, A_{ij}\Delta t$$

    - Cell *i* can stochastically break adhesive links

$$P(i \text{ detaches from } j \text{ in } [t, t+\Delta t]) = u_{D,i}\, \Delta t$$

    - Strength of adhesive link *i* to *j*:

$$\sqrt{A_{ij}\, \epsilon_i \cdot A_{ji}\epsilon_j} \cdot (\boldsymbol{x}_j - \boldsymbol{x}_i),$$

  - Key parameters:
    - adhesive affinity
    - elastic constant
    - attachment rate
    - detachment rate
    - maximum number of adhesions

Reference behavior models: Resistance to deformation

- **resistance to deformation and overlap**
  - Use potential function as a "repulsive" force

$$-\sqrt{\beta_i \cdot \beta_j}\left(1-\frac{\|x_j - x_i\|}{R_i + R_j}\right)^{n+1}\frac{(x_j - x_i)}{\|x_j - x_i\|},$$

  - Key parameters:
    - repulsive strength

Reference behavior models: Transformation

- **transformation (type change)**
  - Transition from type *i* to type *j*
    - Differentiation, Transdifferentiation, mutation, …

$$P(i \text{ transforms to cell of type } j \text{ in } [t, t+\Delta t]) = r_{T,ij}\,\Delta t.$$

  - Key parameters:
    - transition rates

Reference behavior models: Fusion

- **fusion**
  - cells *i* and *j* combine volumes, re-center position, add their number of nuclei
  - Key parameter:
    - fusion rates (type *i* to type *j*)

Reference behavior models: Phagocytosis

- **phagocytosis**
  - Cell *i* consumes cell *j* (and acquire volume)
  - Key parameters:
    - rate of phagocytosing dead cells,
    - rates of phagocytosing live cell types

Reference behavior models: Effector attack

- **effector attack**
  - Cell *i* attacks (damages) cell *j*
    - rate of attacking is a function of:
      - » attack rate of *i* on *j*
      - » immunogenicity of *j* to *i*

$$P(i \text{ attacks } j \text{ in } [t, t+\Delta t]) = \overbrace{r_{A,ij}}^{\substack{\text{rate of } i \\ \text{attacking } j}} \cdot \overbrace{g_{ji}}^{\substack{\text{immunogenicity} \\ \text{of } j \text{ to } i}} \Delta t$$

    - the attack increases damage of *j* based on its damage rate
    - **Note:** Requires an additional hypothesis to cause death in cell *j*
  - Key parameters:
    - attack rates
    - immunogenicities
    - damage rate

Behavior Dictionary

- With standardized forms, behaviors are fully controlled by well-defined parameters
- A full dictionary of available behaviors is auto-generated based on the types of cells and diffusible substrates
- This allows for a controlled vocabulary (an ontology)

Behavior name	Biophysical meaning	Parameter
{substrate X} secretion	secretion rate of (extracellular) chemical factor X	S
{substrate X} secretion target	extracellular target concentration for secreted factor X	ρ^*
{substrate X} uptake	uptake rate of chemical factor X	U
{substrate X} export	net export rate of chemical factor X	E
cycle entry	rate of entering the cell cycle	r_{01}
exit from cycle phase {n}	transition rate between the n^{th} and $n+1^{th}$ cycle phases	$r_{n,n+1}$
apoptosis	rate of beginning apoptotic cell death	d_A
necrosis	rate of beginning necrotic cell death	d_N
migration speed	the cell's (locomotive) migration speed	s
migration bias	the cell's bias to migrate along a selected bias direction	b
migration persistence time	mean time traveled before choosing a new migration direction	$T_{\text{persistence}}$
chemotactic response to {X}	the cell's relative chemotactic affinity for diffusible factor X	c_j
cell-cell adhesion	the strength of cell-cell adhesion	α_{cca}
cell-cell adhesion elastic constant	strength of elastic cell-cell adhesions	ϵ
adhesive affinity to {cell type X}	…	…
relative maximum adhesion distance		
cell-cell repulsion		
cell-BM adhesion		
cell-BM repulsion		
phagocytose dead cell		
phagocytose {cell type X}		
attack {cell type X}		
fuse to {cell type X}		
transform to {cell type X}		
custom:{X}		

Accessing behaviors

- A simple API allows us to access the human-interpretable behaviors

```
set_single_behavior( pCell , behavior_name , behavior_value )
```

•Examples:

```
set_single_behavior( pCell , ”cycle entry” , 0.001);
set_single_behavior( pCell , ”phagocytose dead cell” , 0.01);
set_single_behavior( pCell , ”secrete TGB-beta” , 10);
```

- We can also access reference values (from a cell definition)

```
get_single_base_behavior( pCell , behavior_name );
```

- We can set/get vectors of parameters with a similar API.

Signal Dictionary

- Based on the cell types and diffusible substrates in a simulation, we can auto-generate dictionaries of available signals
- With standardized access, it's much easier to write cell rules
- This allows for a controlled vocabulary (an ontology)

Signal name	Biophysical meaning
{substrate X}	extracellular concentration of chemical factor X
intracellular {substrate X}	intracellular concentration of chemical factor X
{substrate X} gradient	slope of the extracellular concentration field of factor X
pressure	mechanical pressure (from other cells in close proximity)
volume	the cell's current total volume
contact with {cell type X}	number of cells of type X that are in physical contact
contact with live cell	number of live cells that are in physical contact
contact with dead cell	number of dead cells that are in physical contact
contact with basement membrane	1 if in contact with basement membrane. 0 otherwise.
damage	amount of damage (of any type)
dead	1 if the cell is dead (or dying). 0 otherwise.
total attack time	total amount of time the cell has been attacked.
time	current simulation time
custom:{X}	use a custom variable or symbol *X* to drive cell behavior

Accessing signals

- A simple API allows us to access the human-interpretable behaviors

```
get_single_signal( pCell , signal_name )
```

- Examples:

```
get_single_signal( pCell , "oxygen" );
get_single_signal( pCell , "pressure" );
get_single_signal( pCell , "contact with melanocyte" );
```

- We can set/get vectors of parameters with a similar API.

Hypothesis statements with the grammar

- For [cell type T], [S] increases / decreases [B] [optional arguments]
  - **Cell type T** is as cell type defined in the simulation model
  - **S** is a signal in our signal dictionary
  - **B** is a behavioral parameter in our behavior dictionary
- **Examples:**
  - For M0 macrophages, necrotic cell debris increases transformation to M1 macrophages
  - For malignant epithelial cells, doxorubicin increases apoptosis

Mathematical mapping

Response functions

- If signal *S* increases / decreases behavior *B*
  - Use a monotonically increasing response function $0 \le R(s) \le 1$ to vary the behavioral parameter *p* from its value p_0 towards its maximal response value p_{M}

$$p(s) = p_0 + (p_{\mathrm{M}} - \mathrm{p}_0)R(s) = \big(1 - R(s)\big) \cdot p_0 + R(s) \cdot p_M$$

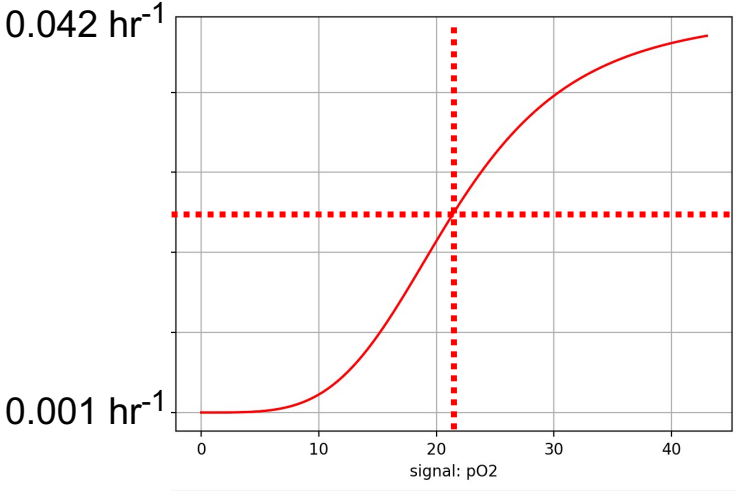
  - We generally use **Hill response functions:**

$$R(s) = \frac{s^h}{s_{\mathrm{half}}^h + s^h} = \frac{\left(\frac{s}{s_{\mathrm{half}}}\right)^h}{1 + \left(\frac{s}{s_{\mathrm{half}}}\right)^h} \text{ if } s \ge 0, \qquad \text{and } H(s) = 0 \text{ if } s < 0.$$

Sample rule

- **Oxygen increases cycle entry** from 0.001 hr^{-1} towards 0.042 hr^{-1} with a Hill response function, with half-max 21.5 mmHg and Hill power 4.

$$r_{01} = 0.001 + (0.042 - 0.001)\frac{(pO_2)^4}{21.5^4 + (pO_2)^4}$$



Integrating many hypotheses

- **Multivariate Hill response functions**
  - Can integrate multiple signals with independent half-maxes and Hill powers
  - Reduce back down to original Hill function if all but one input is zero

- **Total up response:**

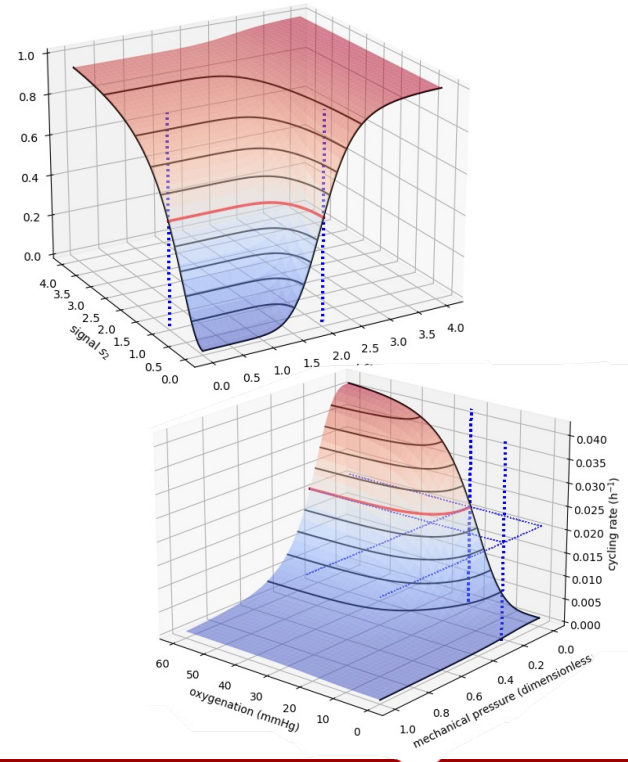
$$U = H_M(\boldsymbol{u}; \boldsymbol{u}_{\text{half}}, \boldsymbol{p}) = \frac{\left(\frac{u_1}{u_1^*}\right)^{p_1} + \left(\frac{u_2}{u_2^*}\right)^{p_2} + \cdots + \left(\frac{u_m}{u_m^*}\right)^{p_m}}{1 + \left(\frac{u_1}{u_1^*}\right)^{p_1} + \left(\frac{u_2}{u_2^*}\right)^{p_2} + \cdots + \left(\frac{u_m}{u_m^*}\right)^{p_m}}$$

- **Total down response:**

$$D = H_M(\boldsymbol{d}; \boldsymbol{d}_{\text{half}}, \boldsymbol{q}) = \frac{\left(\frac{d_1}{d_1^*}\right)^{q_1} + \left(\frac{d_2}{d_2^*}\right)^{q_2} + \cdots + \left(\frac{d_n}{d_n^*}\right)^{q_n}}{1 + \left(\frac{d_1}{d_1^*}\right)^{q_1} + \left(\frac{d_2}{d_2^*}\right)^{q_2} + \cdots + \left(\frac{d_n}{d_n^*}\right)^{q_n}}.$$

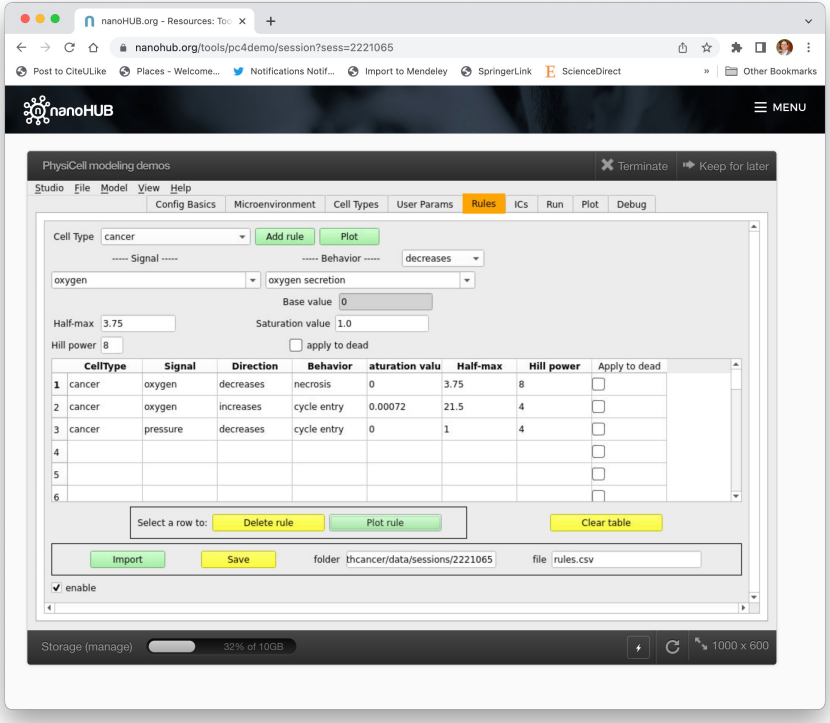
- **Integrated response:**

$$p(\boldsymbol{u}, \boldsymbol{d}) = (1 - D) \cdot [(1 - U) \cdot p_0 + U \cdot p_M\ ] + D \cdot p_m$$



Graphical model editing

- With a clear model representation, it's also easy to write tools to graphically edit and run models
  - Key to getting multidisciplinary researchers involved!
  - Immediate link between hypothesis statement and visualization
- See **Session 2**.
  - We'll use *PhysiCell Studio* extensively throughout our workshop.



Automated model annotation

- We auto-generate formatted HTML tables as we parse the rules
  - (We can generate LaTeX, DOCX, etc. too …)
- Thus, the underlying hypotheses are summarized for inclusion in the methods section for later papers.

Cell Hypothesis Rules (detailed)

In tumor cells:

- oxygen increases cycle entry from 0 towards 0.00072 with a Hill response, with half-max 21.5 and Hill power 4.
- pressure decreases cycle entry from 0 towards 0 with a Hill response, with half-max 1 and Hill power 4.
- oxygen decreases necrosis from 0.0028 towards 0 with a Hill response, with half-max 3.75 and Hill power 8.
- damage increases apoptosis from 7.2e-05 towards 0.072 with a Hill response, with half-max 180 and Hill power 2.
- dead increases debris secretion from 0 towards 0.017 with a Hill response, with half-max 0.1 and Hill power 10. Rule applies to dead cells.
- IFN-gamma decreases migration speed from 0.5 towards 0 with a Hill response, with half-max 0.25 and Hill power 2.

In M0 macrophage cells:

- contact with dead cell increases transform to M1 macrophage from 0 towards 0.05 with a Hill response, with half-max 0.1 and Hill power 10.
- contact with dead cell decreases migration speed from 1 towards 0.1 with a Hill response, with half-max 0.1 and Hill power 4.
- dead increases debris secretion from 0 towards 0.017 with a Hill response, with half-max 0.1 and Hill power 10. Rule applies to dead cells.

In M1 macrophage cells:

- contact with dead cell decreases migration speed from 1 towards 0.1 with a Hill response, with half-max 0.1 and Hill power 4.
- oxygen decreases transform to M2 macrophage from 0.01 towards 0 with a Hill response, with half-max 5 and Hill power 4.
- IFN-gamma increases cycle entry from 7.2e-05 towards 0.00036 with a Hill response, with half-max 0.25 and Hill power 2.
- IFN-gamma increases phagocytose dead cell from 0.01 towards 0.05 with a Hill response, with half-max 0.25 and Hill power 2.
- dead increases debris secretion from 0 towards 0.017 with a Hill response, with half-max 0.1 and Hill power 10. Rule applies to dead cells.

In M2 macrophage cells:

- contact with dead cell decreases migration speed from 1 towards 0.1 with a Hill response, with half-max 0.1 and Hill power 4.
- IFN-gamma decreases cycle entry from 7.2e-05 towards 0 with a Hill response, with half-max 0.25 and Hill power 2.
- IFN-gamma increases phagocytose dead cell from 0.01 towards 0.05 with a Hill response, with half-max 0.25 and Hill power 2.
- dead increases debris secretion from 0 towards 0.017 with a Hill response, with half-max 0.1 and Hill power 10. Rule applies to dead cells.

In naive T cell cells:

- IL-10 decreases transform to CD8 T cell from 0.001 towards 0 with a Hill response, with half-max 0.25 and Hill power 2.
- IFN-gamma increases transform to CD8 T cell from 0.001 towards 0.01 with a Hill response, with half-max 0.25 and Hill power 2.
- dead increases debris secretion from 0 towards 0.017 with a Hill response, with half-max 0.1 and Hill power 10. Rule applies to dead cells.

In CD8 T cell cells:

- IFN-gamma increases cycle entry from 7.2e-05 towards 0.00093 with a Hill response, with half-max 0.25 and Hill power 2.
- IL-10 decreases attack tumor from 0.01 towards 0 with a Hill response, with half-max 0.25 and Hill power 2.
- IL-10 decreases migration speed from 1 towards 0.1 with a Hill response, with half-max 0.25 and Hill power 2.
- contact with tumor decreases migration speed from 1 towards 0.1 with a Hill response, with half-max 0.1 and Hill power 2.
- IL-10 increases transform to exhausted T cell from 0 towards 0.005 with a Hill response, with half-max 0.25 and Hill power 4.
- dead increases debris secretion from 0 towards 0.017 with a Hill response, with half-max 0.1 and Hill power 10. Rule applies to dead cells.

In exhausted T cell cells:

- dead increases debris secretion from 0 towards 0.017 with a Hill response, with half-max 0.1 and Hill power 10. Rule applies to dead cells.

Example: tumor-immune

In tumor cells:
- oxygen increases cycle entry
- pressure decreases cycle entry
- oxygen decreases necrosis
- damage increases apoptosis
- dead increases debris secretion
- IFN-gamma decreases migration speed

In M0 macrophages:
- contact with dead cell increases transform to M1 macrophage
- contact with dead cell decreases migration speed
- dead increases debris secretion

In M1 macrophages:
- contact with dead cell decreases migration speed
- oxygen decreases transform to M2 macrophage
- IFN-gamma increases cycle entry
- IFN-gamma increases phagocytose dead cell
- dead increases debris secretion

In M2 macrophages:
- contact with dead cell decreases migration speed
- IFN-gamma decreases cycle entry
- IFN-gamma increases phagocytose dead cell
- dead increases debris secretion

In naive T cells:
- IL-10 decreases transform to CD8 T cell
- IFN-gamma increases transform to CD8 T cell
- increases debris secretion
- dead

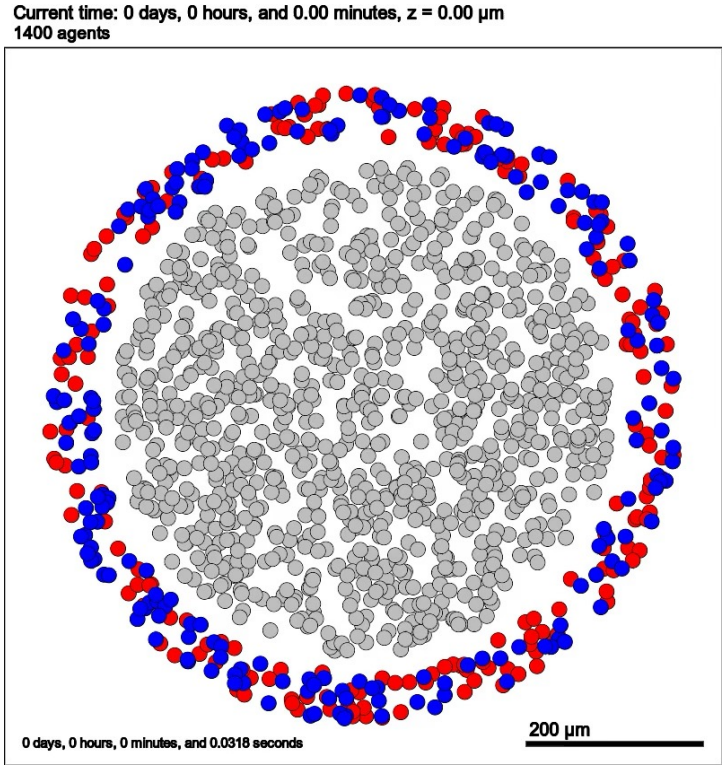
In CD8 T cells:
- IFN-gamma increases cycle entry
- IL-10 decreases attack tumor
- IL-10 decreases migration speed
- contact with tumor decreases migration speed
- IL-10 increases transform to exhausted T cell
- dead increases debris secretion

In exhausted T cells:
- dead increases debris secretion

Joint work with OHSU:
- Lisa Coussens
- Joe Gray
- Laura Heiser
- Young Hwan-Chang

Sample result

- tumor
- M0 macrophage
- M1 macrophage
- M2 macrophage
- naive T cell
- CD8 T cell
- exhausted T cell



Joint work with OHSU:

- Lisa Coussens
- Joe Gray
- Laura Heiser
- Young Hwan-Chang

Future directions

- Standardized models for symmetric and asymmetric division
- Standardized models for processes
  - (long range interactions via protrusions)
- More sophisticated response functions
- AND (or product), and low symbols
  - (oxygen and glucose) increases cycle entry
  - low oxygen increases necrosis ..

Next session

- Introduce PhysiCell Studio (and PhysiCell Cloud)
  - Build, run, and explore complex models *without coding*

- Iteratively build a tumor-immune model
  - Proliferation and oxygen uptake
  - Mechanofeedback
  - Oxygen-based birth and hypoxia-based necrosis

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