

Complex Systems Properties

Resultant Properties

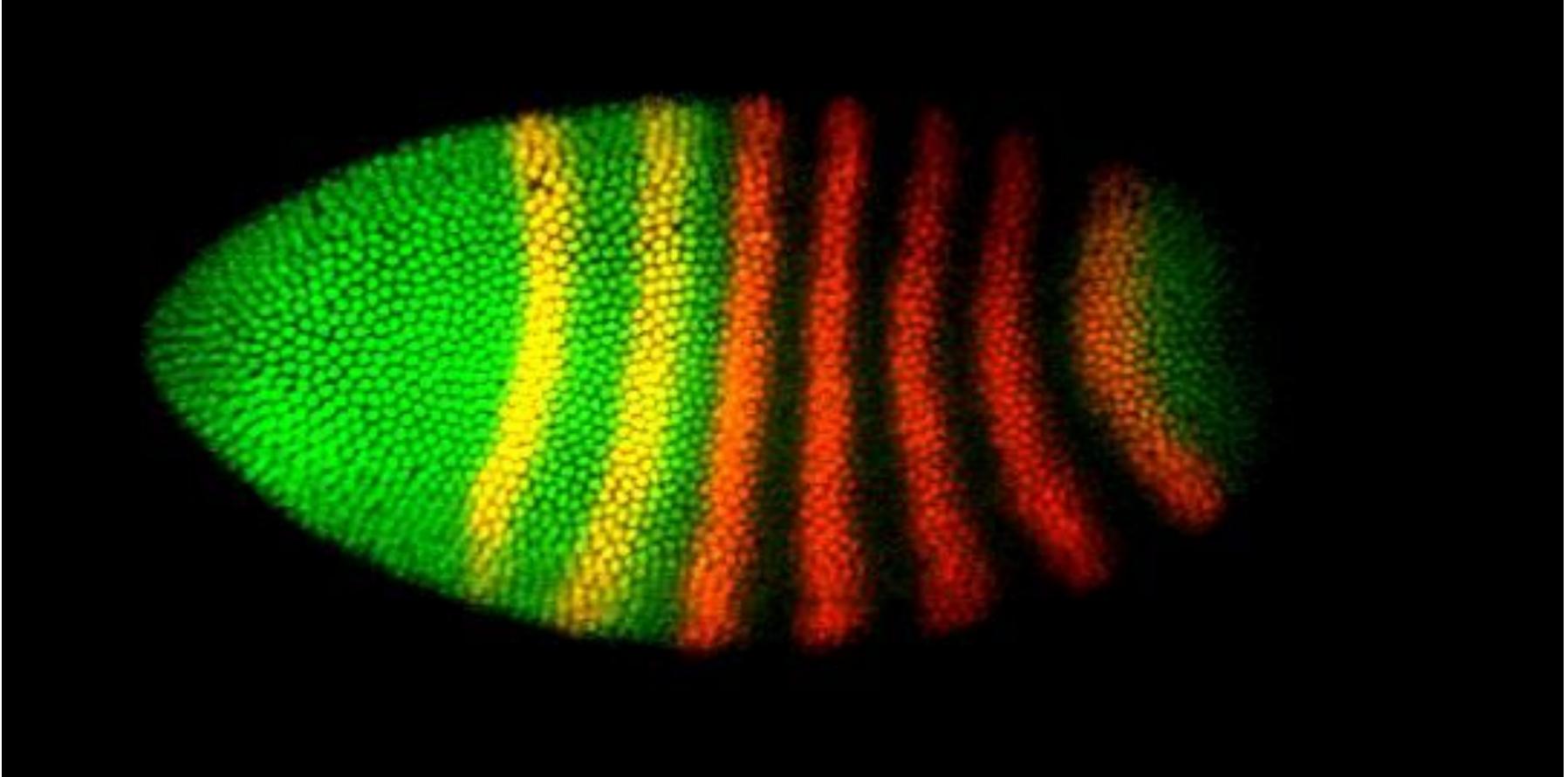
- Is either a sum or a difference of the co-operant forces.
- Are homogeneous and commensurable.
- Can be predicted from lower-level information.
- Examples: the mass, the charge, etc.

Emergent Properties

- Arise from the interactions of components.
- Not reducible to the properties of single components.
- The system is more than the sum of its parts
- Examples: Oscillations, Chaos, Fractal, Robustness, Evolvability



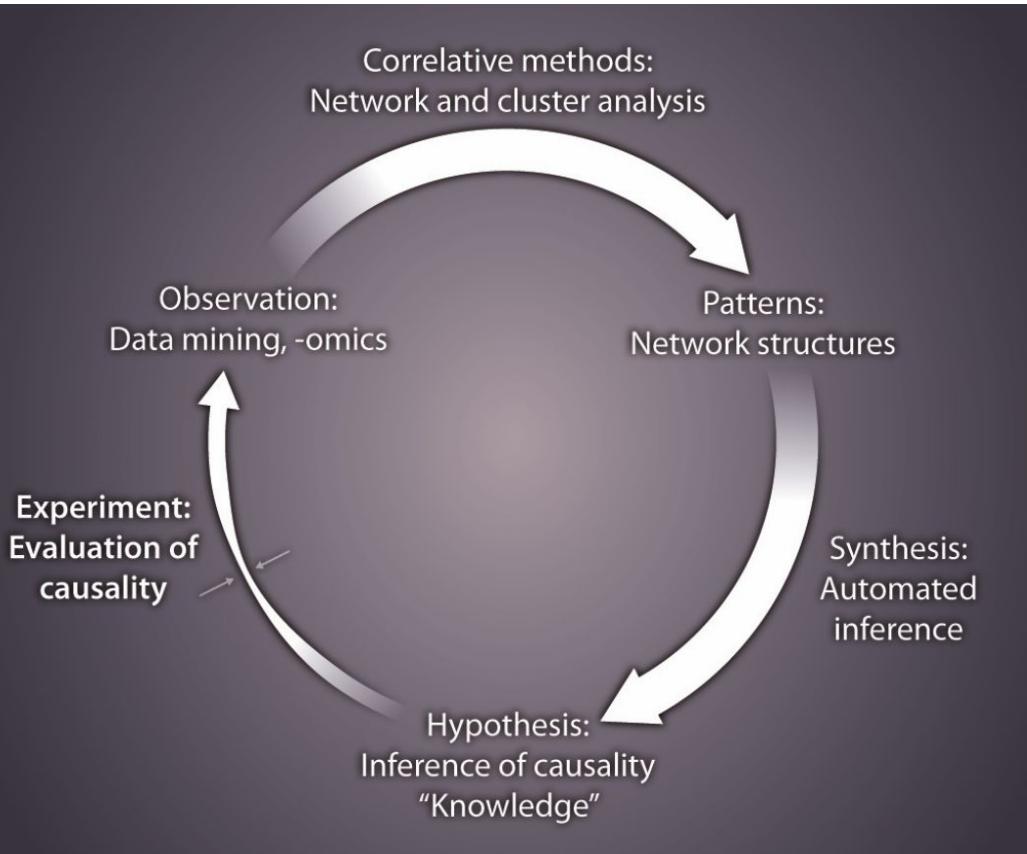
Emergent properties



Collective Behavior



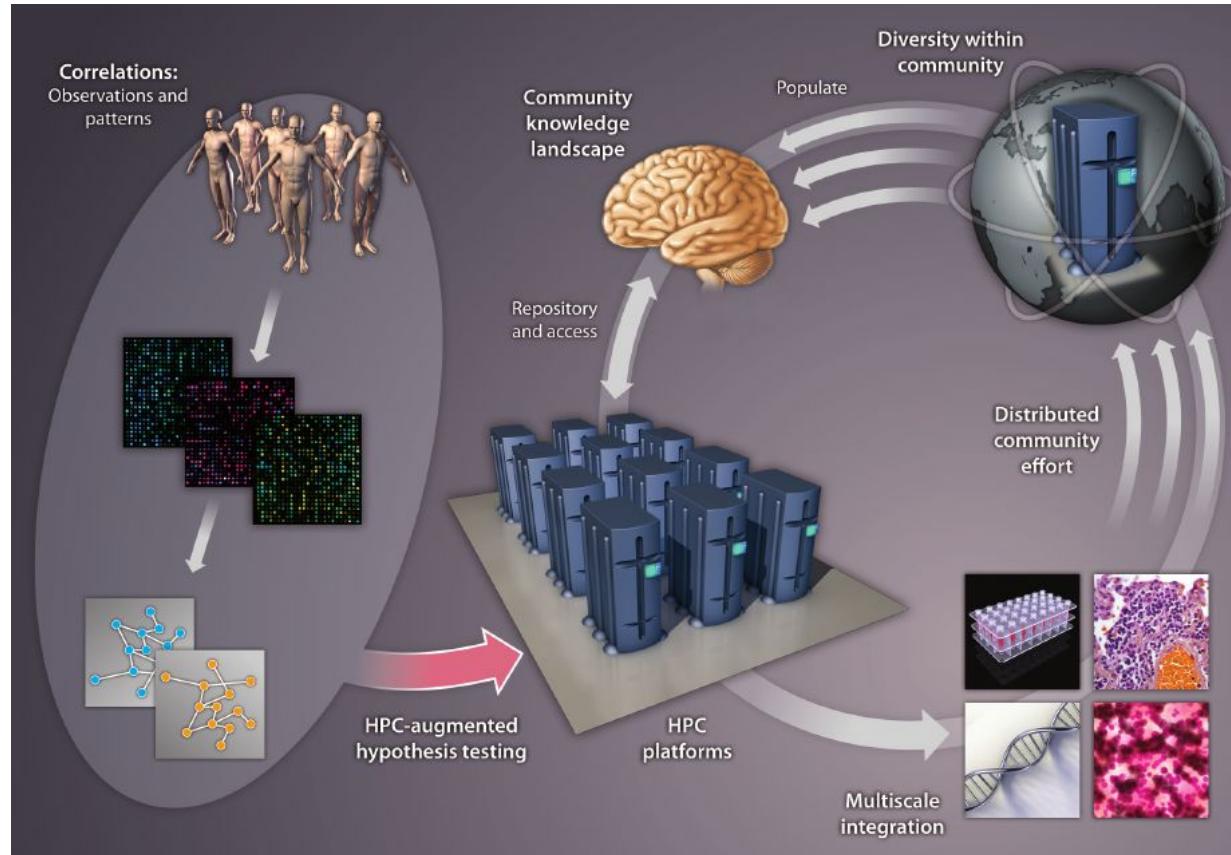
Current imbalance in the scientific process



Current Problem: out of sync

- HPC can be used to augment high-throughput causality representation and testing
- parallel testing of multiple candidate causal hypotheses.
- Bottleneck in in the scientific process at the point of causality evaluation

Bridging Correlation and Causality in the Petaflop Age



Modeling approaches in Systems Biology

Rule/Agent Based Modeling

- Agent-Based Models (multicellular systems):
 - Cellular Automata / Lattice-free Models
- Rule-Based Modelling (model checking)

Equation-Based Modeling (*)

- ODE/ODE (Biochemical Systems / Reaction-Diffusion)
- Stochastic processes (Gene Expression)
- Boolean Modeling (Regulatory networks)
- Constraint-Based Modeling (Genome-scale Metabolic models)

Hybrid / Multi-scale Modeling

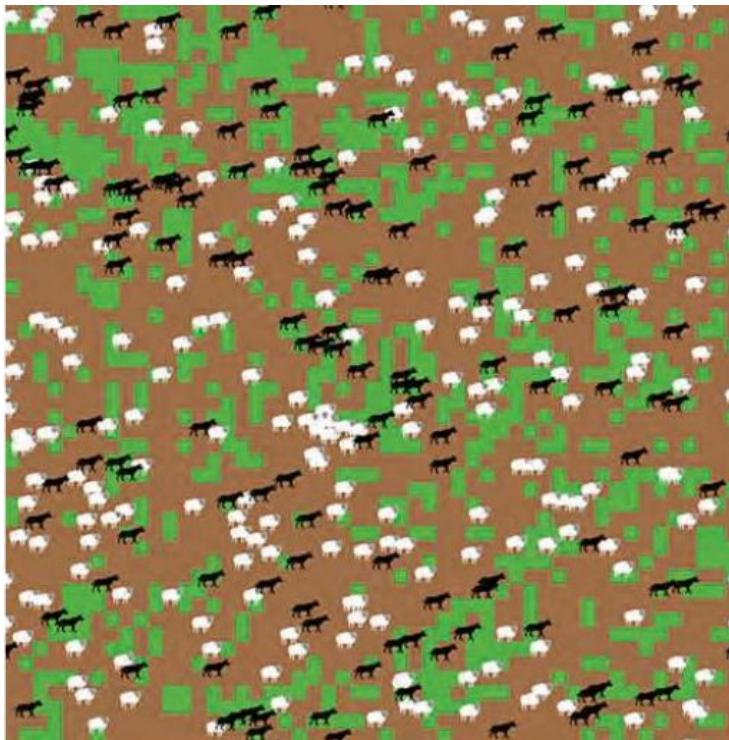
- Agent-Based Models + Internal Models

(*) ODEs/PDEs can also be used to coarse grained model population dynamics

Agent-Based Modeling

Example: Predator-Prey Interactions

Agent-based model



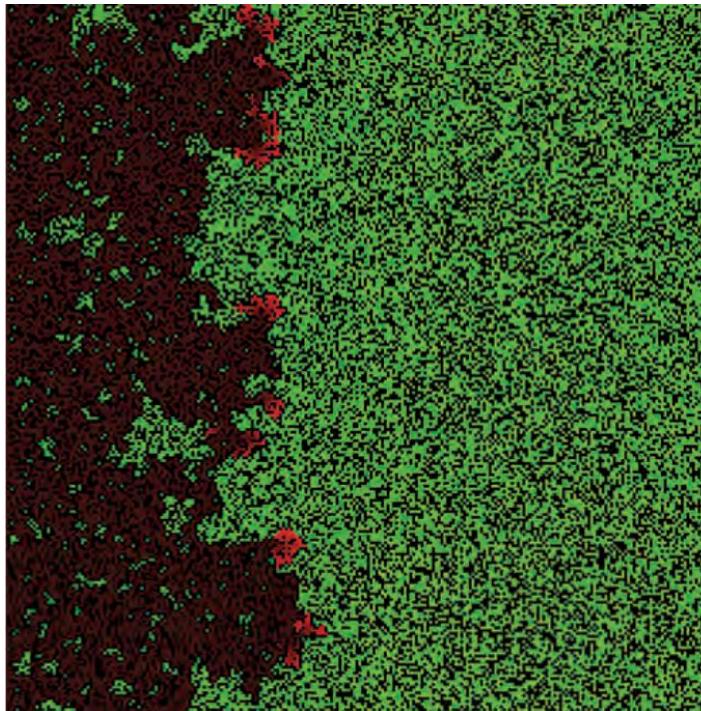
Equation-based model

$$\frac{d\text{Pred}}{dt} = K_1 * \text{Pred} * \text{Prey} - M * \text{Pred}$$

$$\frac{d\text{Prey}}{dt} = B * \text{Prey} - K_2 * \text{Pred} * \text{Prey}$$

Example: Forest Fires

Agent-based model



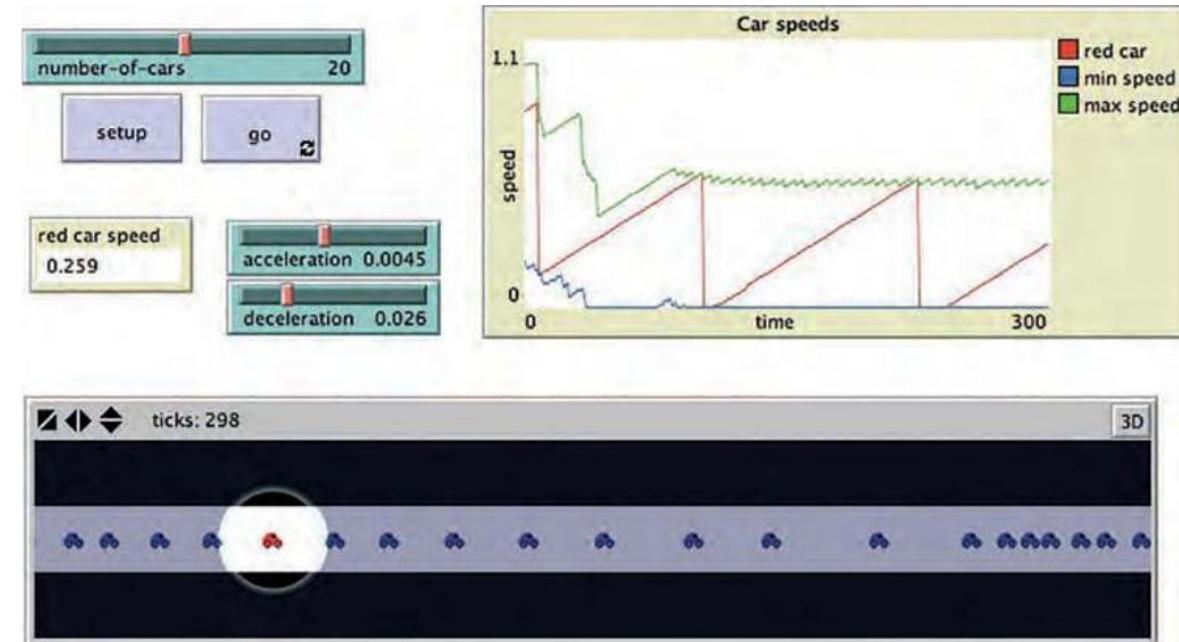
Equation-based model

$$\frac{dH(x,t)}{dt} = \theta \frac{d^2 H(x,t)}{dx^2}$$

$$\frac{dU_i}{dt} + U_j \frac{dU_i}{dx_j} = -\frac{1}{\rho} \frac{dP}{dx_i} + v \frac{d^2 U_i}{dx_j dx_j} - \frac{d}{dx_j} \overline{u_i^t u_j^t}$$



Example: Traffic Jams

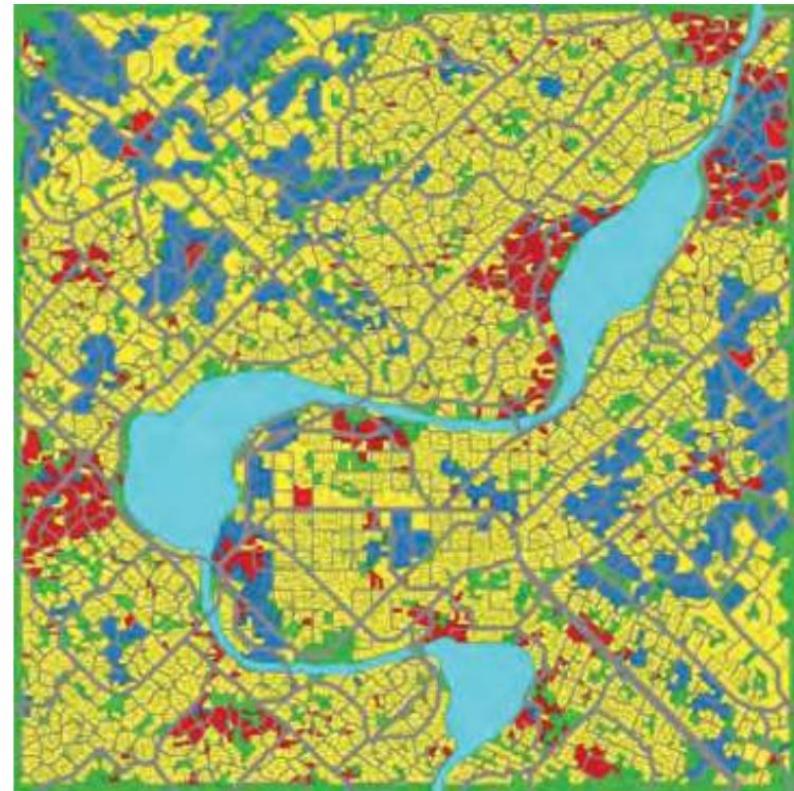


Example: Urban Modeling Applications

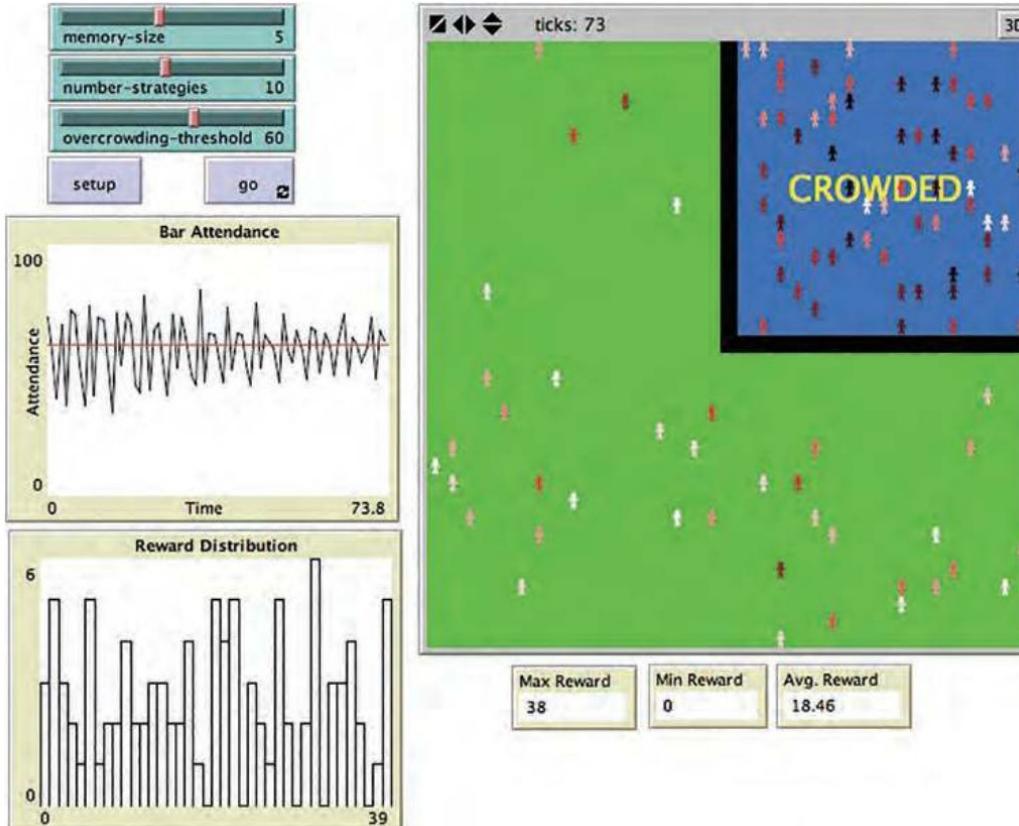
A



B



Example: Adaptive Systems (El Farol Model)



Should I stay or should I go

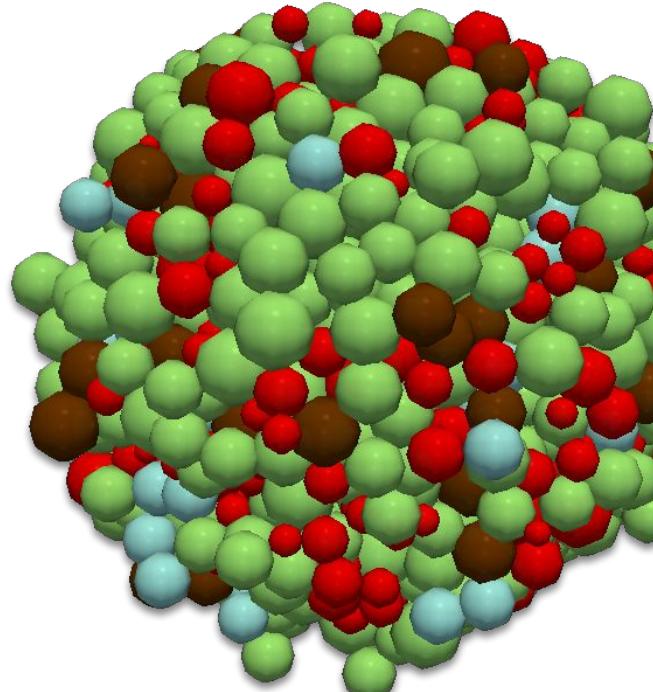
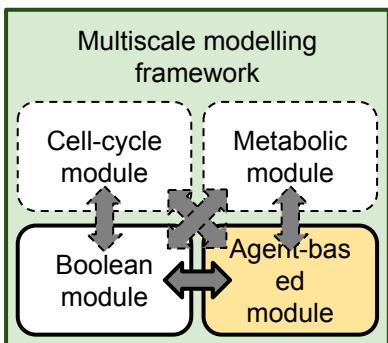
- Go to the bar / Stay Home
- Avoid crowded bar
- Repeated experiments

Decision Making Problem

- Agents adapt behaviour by updating rule based on previous experiences
- Different Strategies
- Reinforce Learning

Multi-scale Modeling Framework: PhysiCell

| Cell Cycle Phase |
|-----------------------|
| - Premitotic |
| - Postmitotic |
| - Ki67 negative |
| - Apoptotic |
| - Necrotic |
| - Necrotic (swelling) |
| - Necrotic (lysis) |



Cell agent properties

- Size (cell volume)
- Position (x, y, z)
- Signaling Network
- Cell internal state:
 - Phenotype
 - Cell cycle phase (G_0 , M , etc)
 - Gene expression profile
 - Other

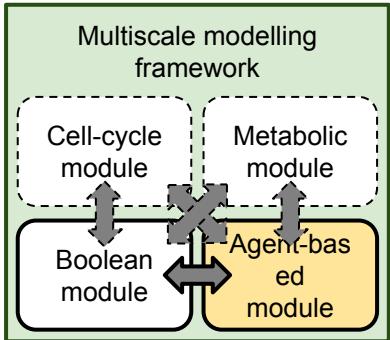
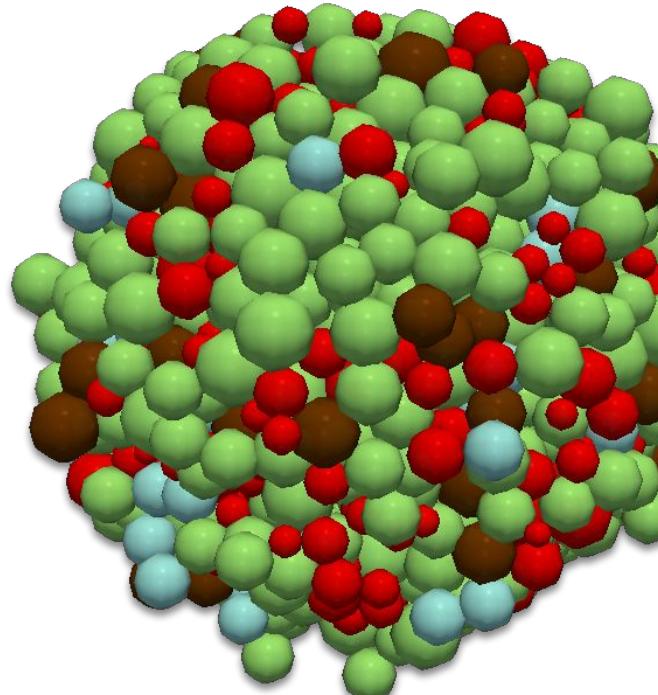


**Barcelona
Supercomputing
Center**

Centro Nacional de Supercomputación

Multi-scale Modeling Framework: PhysiCell

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Diffusion and mechanics are governed by differential equations

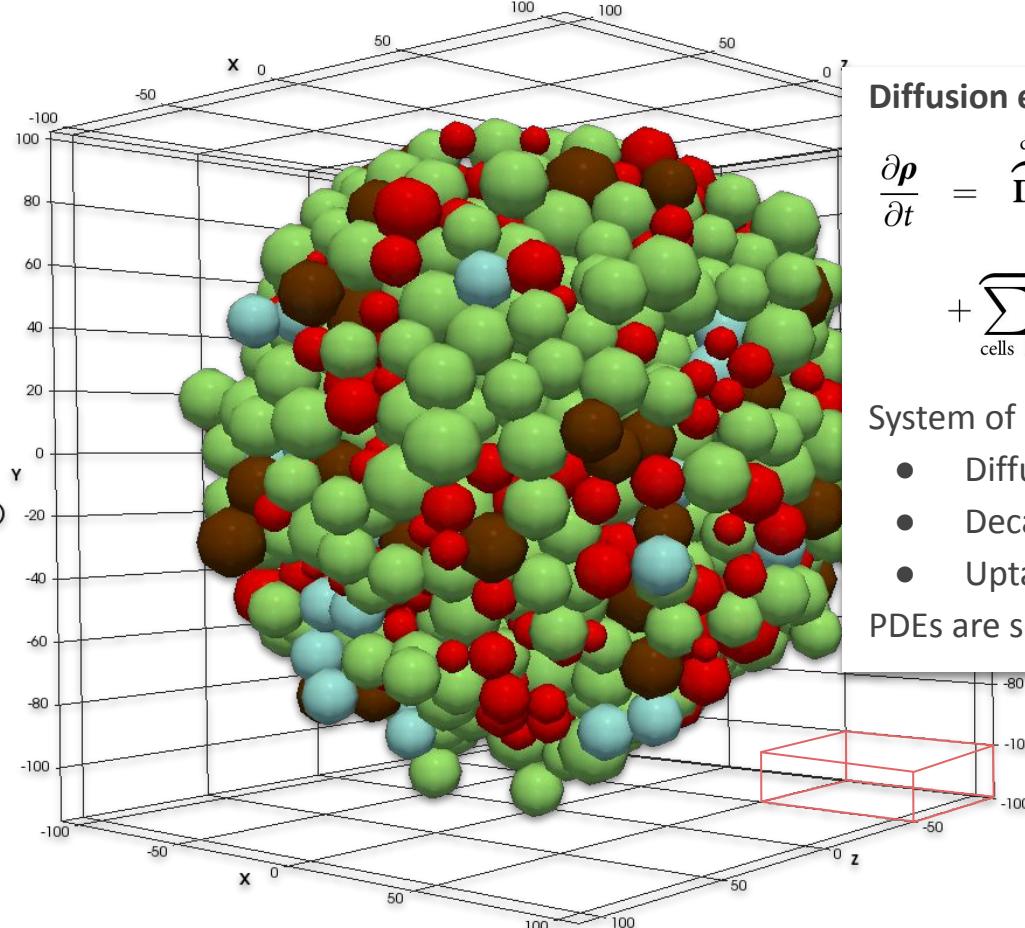
Diffusion equations

$$\frac{\partial \rho}{\partial t} = \overbrace{D \nabla^2 \rho}^{\text{diffusion}} - \overbrace{\lambda \rho}^{\text{decay}} + \overbrace{S(\rho^* - \rho)}^{\text{bulk source}} - \overbrace{\mathbf{U} \rho}^{\text{bulk uptake}} + \underbrace{\sum_{\text{cells } k} \delta(\mathbf{x} - \mathbf{x}_k) W_k [\mathbf{S}_k (\rho_k^* - \rho) - \mathbf{U}_k \rho]}_{\text{sources and uptake by cells}} \text{ in } \Omega$$

Mechanical equations

$$\mathbf{v}_i = \sum_{j \in \mathcal{N}(i)} \left(- \underbrace{\sqrt{c_{cca}^i c_{cca}^j} \nabla \phi_{1,R_{i,A}+R_{j,A}}(\mathbf{x}_i - \mathbf{x}_j)}_{\text{cell-cell adhesion}} - \underbrace{\sqrt{c_{ccr}^i c_{ccr}^j} \nabla \psi_{1,R_i+R_j}(\mathbf{x}_i - \mathbf{x}_j)}_{\text{cell-cell repulsion}} \right. \\ \left. - \underbrace{c_{cba}^i \nabla \phi_{1,R_{i,A}}(-d(\mathbf{x}_i) \mathbf{n}(\mathbf{x}_i))}_{\text{cell-BM adhesion}} - \underbrace{c_{cbr}^i \nabla \psi_{1,R_i}(-d(\mathbf{x}_i) \mathbf{n}(\mathbf{x}_j)) + \mathbf{v}_{i,\text{mot}}}_{\text{cell-BM repulsion}} \right).$$

The microenvironment



Diffusion equations

$$\frac{\partial \rho}{\partial t} = \overbrace{\mathbf{D} \nabla^2 \rho}^{\text{diffusion}} - \overbrace{\lambda \rho}^{\text{decay}} + \overbrace{\mathbf{S}(\rho^* - \rho)}^{\text{bulk source}} - \overbrace{\mathbf{U} \rho}^{\text{bulk uptake}}$$

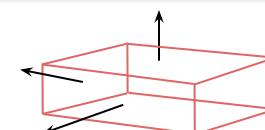
sources and uptake by cells

$$+ \underbrace{\sum_{\text{cells } k} \delta(\mathbf{x} - \mathbf{x}_k) W_k [\mathbf{S}_k (\rho_k^* - \rho) - \mathbf{U}_k \rho]}_{\text{in } \Omega}$$

System of PDEs for each molecule:

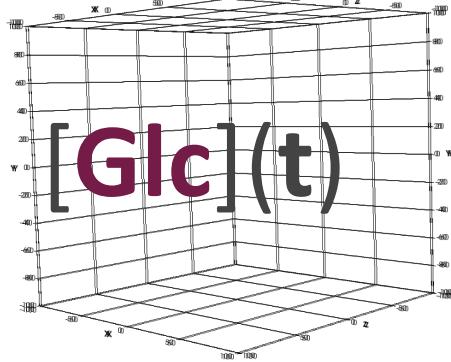
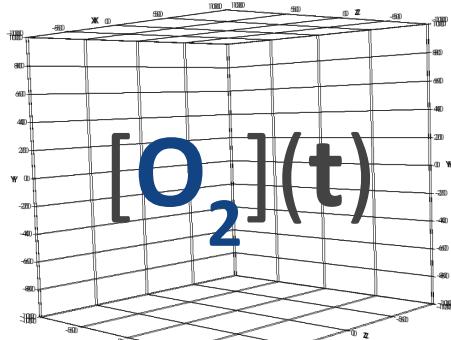
- Diffusion term
- Decay
- Uptake/Production

PDEs are solved time scale using BioFVM



Voxel

The microenvironment



Molecules density at time t are stored in **MultiCellIDS** format (XML) or CSV

Reaction-Diffusion Equations

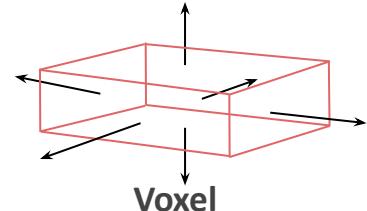
$$\frac{\partial \rho}{\partial t} = \underbrace{D \nabla^2 \rho}_{\text{diffusion}} - \underbrace{\lambda \rho}_{\text{decay}} + \underbrace{S(\rho^* - \rho)}_{\substack{\text{bulk source} \\ \text{sources and uptake by cells}}} - \underbrace{U \rho}_{\text{bulk uptake}}$$
$$+ \sum_{\text{cells } k} \delta(\mathbf{x} - \mathbf{x}_k) W_k [S_k(\rho_k^* - \rho) - U_k \rho] \text{ in } \Omega$$

System of PDEs for each molecule:

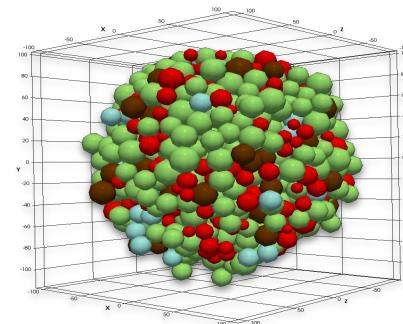
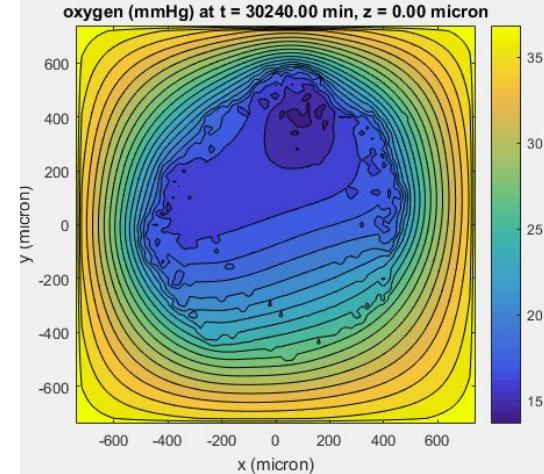
- Diffusion term
- Decay
- Uptake/Production

PDEs are solved time scale using

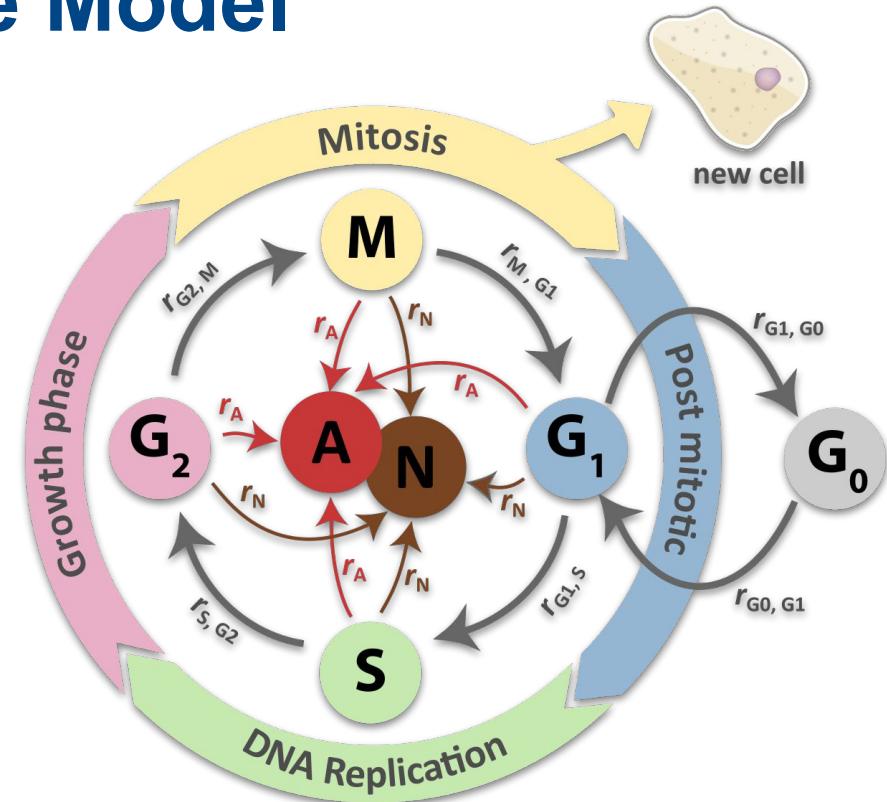
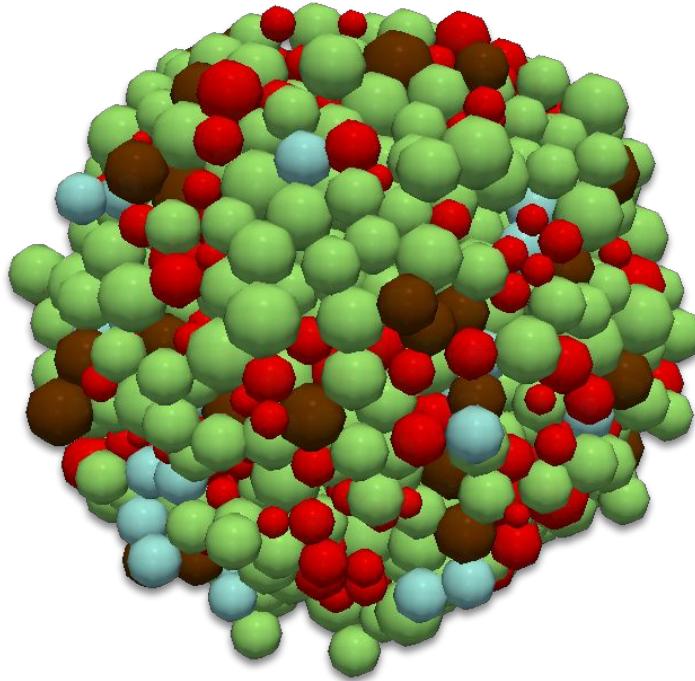
BioFVM



Gradients in chemical factors (O_2)



Cell Cycle Model

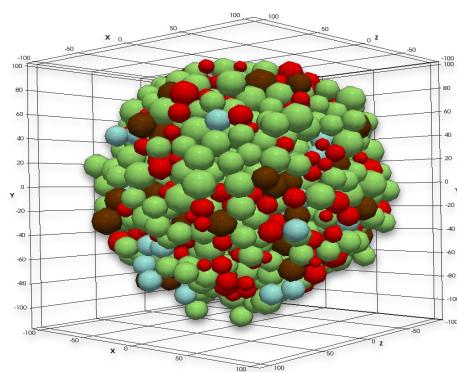


Prob(transition from X_i to X_j | not arrested) $\approx r_{ij} \Delta t$.

Stochastic transition rates (experimental)

$r_{G2,M}, r_{M,G1}, r_{G2,S}, \dots, r_A, r_N$

Multi-scale Modeling Framework: PhysiCell

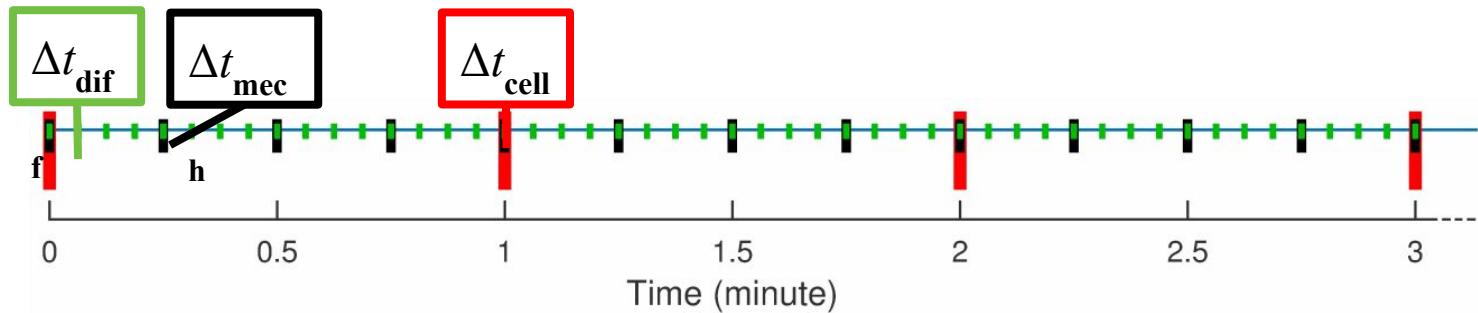


Simulation's Main Loop

```
while t_current < tend
    update_difussion()
    if Δt % Δtmech == 0
        update_cell_mechanics()
    if Δt % Δtcell == 0
        update_cell_processes()
    Δt = 0
    Δt += t_step
    t_current += t_step
```

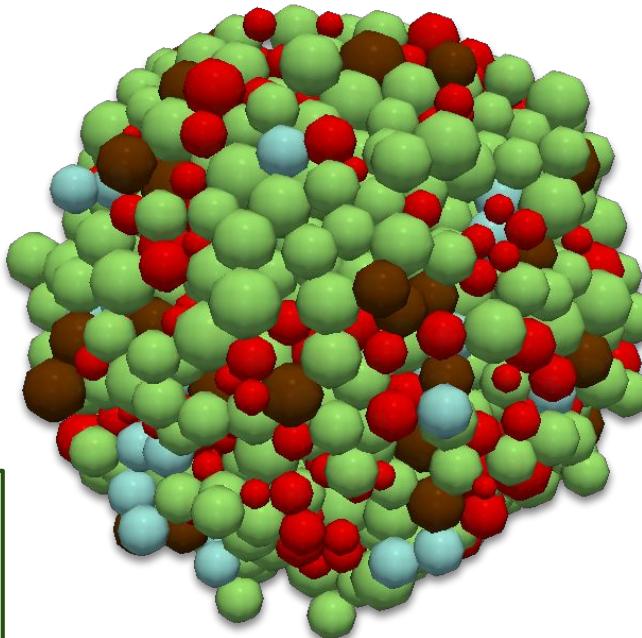
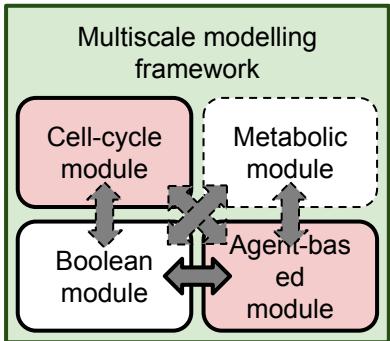
Time scales

- Δt_{diff} : (diffusion/transport): 0.01 min
- Δt_{mech} : (cell movement): 0.1 min
- Δt_{cell} : (cell processes): 6 min



Multi-scale Modeling Framework: PhysiCell

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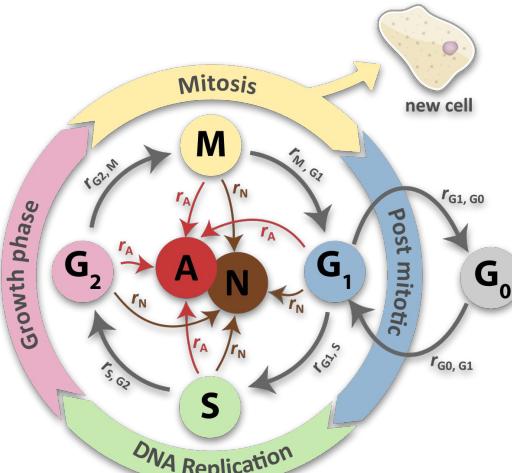


Cell agent properties

- Size (cell volume)
- Position (x, y, z)
- Signaling Network
- Cell internal state:
 - Phenotype
 - **Cell cycle phase (G_0 , M , etc)**
 - Gene expression profile
 - Other

Modeling cell cycle: Stochastic (rule-based)

Transition rates are governed
by user defined rules



Stochastic transition rates

$$r_{G2,M}, r_{M,G1}, \dots, r_A,$$

$$r_N$$

Entering cell cycle rate

$$r_{Q1} = \frac{1}{\bar{T}_Q} \max \left\{ \left(\frac{pO_2 - pO_{2,\text{hypoxia}}}{\bar{pO}_2 - pO_{2,\text{hypoxia}}} \right), 0 \right\},$$

Necrosis rate

$$r_N(pO_2) = \begin{cases} 0 & \text{if } O_{2,thr} < O_2 \\ r_{N, \text{Max}} \left(\frac{pO_{2,thr} - pO_2}{pO_{2,thr} - pO_{2,crit}} \right) & \text{if } O_{2,crit} < O_2 \leq O_{2,thr} \\ r_{N, \text{Max}} & \text{if } O_2 \leq O_{2,crit} \end{cases}$$

$$\text{Prob}(S_i(t + \Delta t) = D_i) = 1 - \exp(-r_i \Delta t) \approx r_i \Delta t.$$

Multi-scale modeling: Linking subcellular and population dynamics

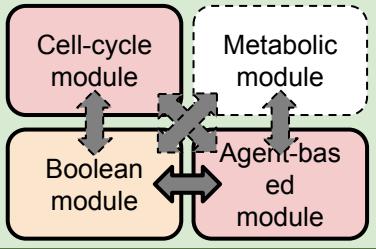
Wiring the agents with a signal transduction network

Modeling cell signaling: PhysiBoSS

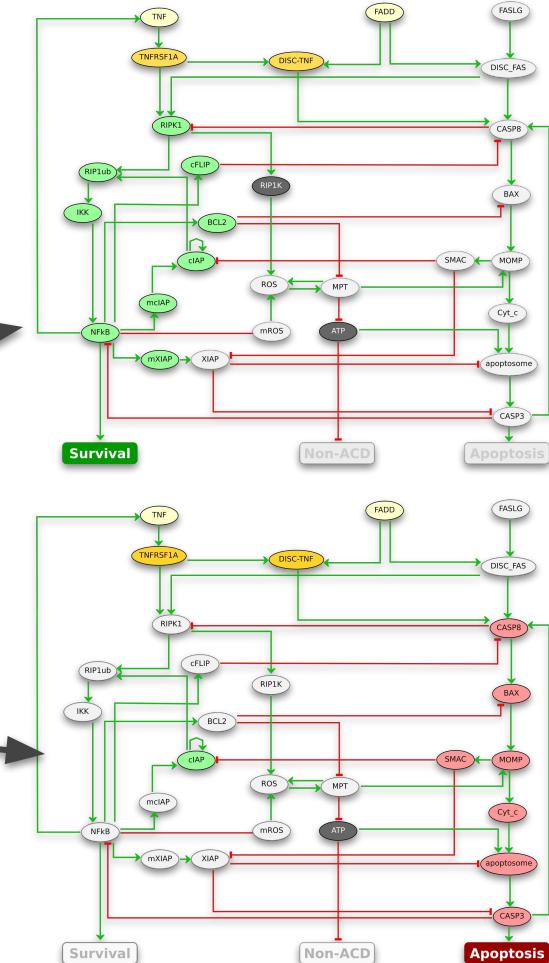
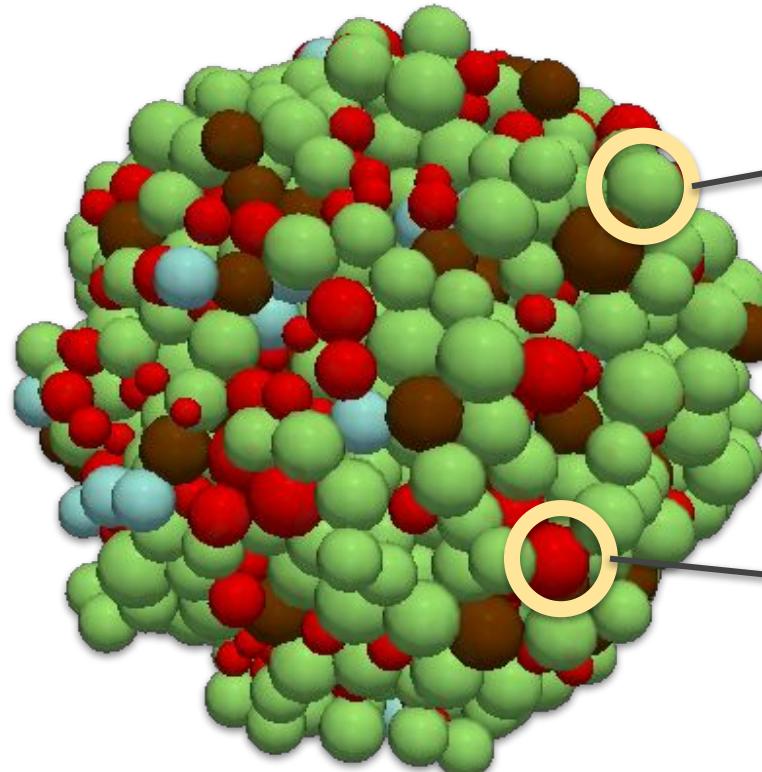
Cell Cycle Phase

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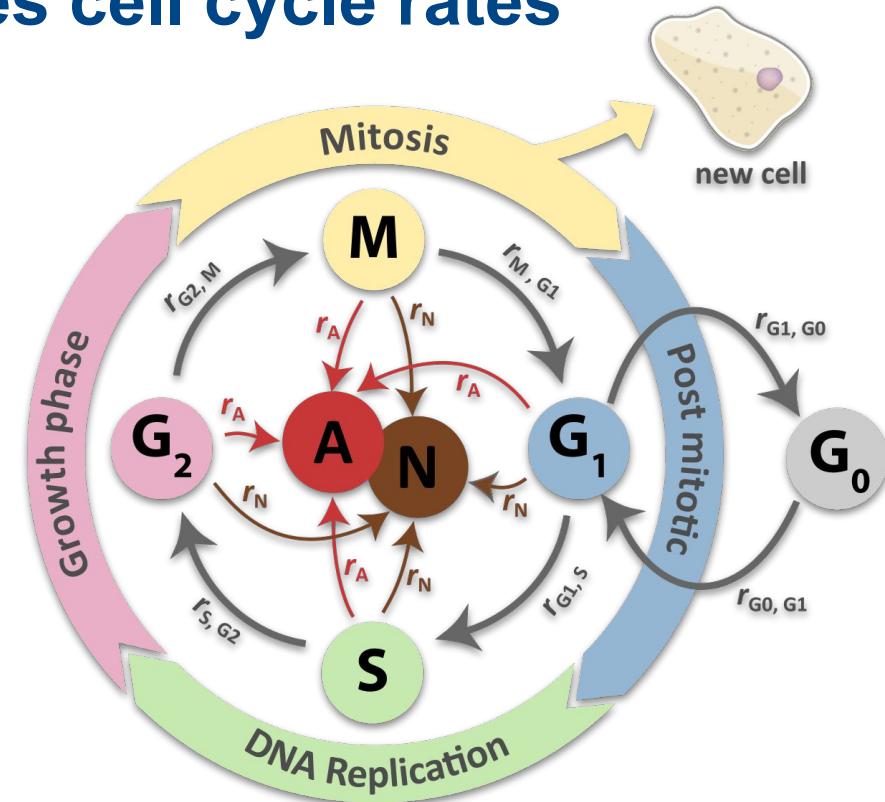
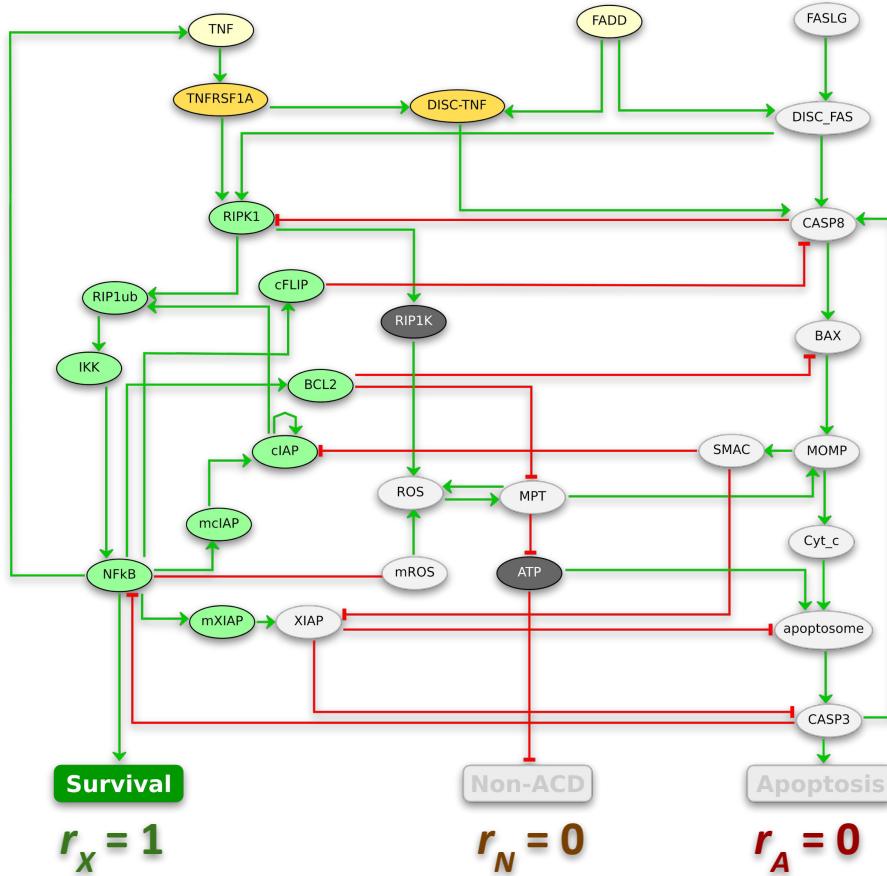
Multiscale modelling framework



Different cell signaling states



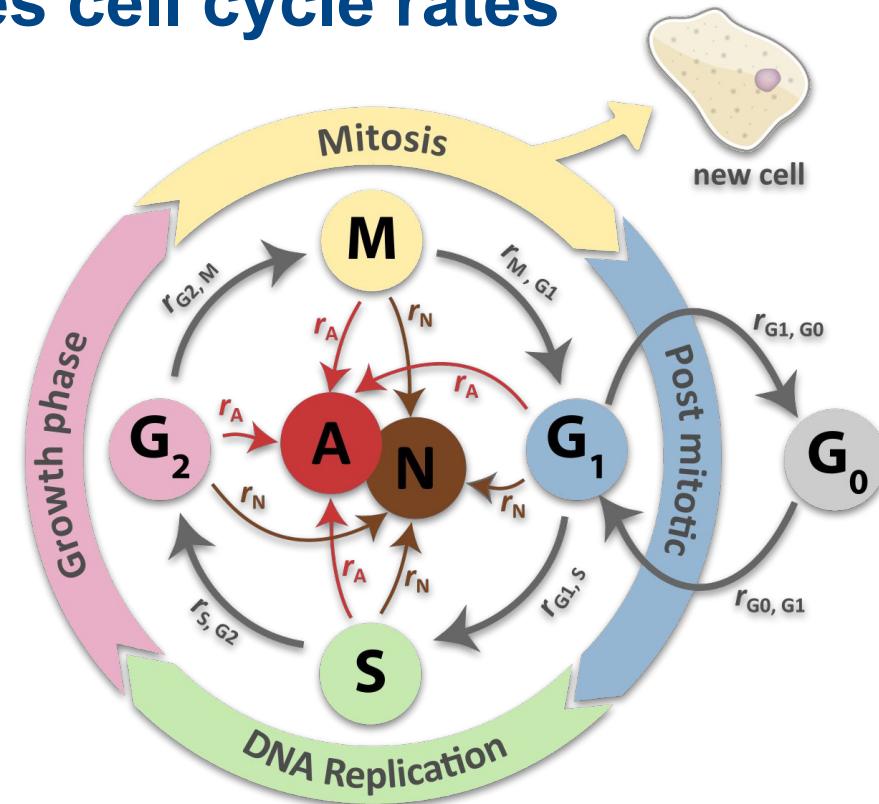
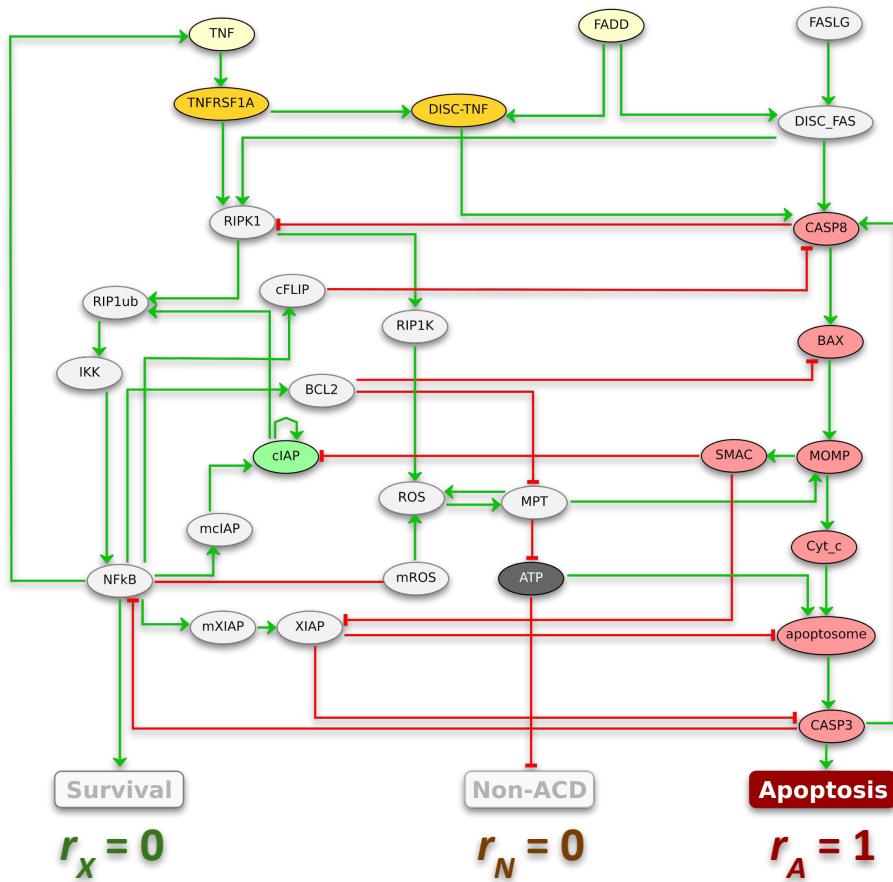
Signalling → updates cell cycle rates



Stochastic transition rates (experimental)

$$r_{G2,M}, r_{M,G1}, r_{G2,S}, \dots, r_A, \\ r_N$$

Signalling → updates cell cycle rates



Stochastic transition rates (experimental)

$$r_{G2,M}, r_{M,G1}, r_{G2,S}, \dots, r_A, r_N$$

Multi-scale modeling: Linking subcellular and population dynamics

Connecting cell metabolism to the agents and the environment

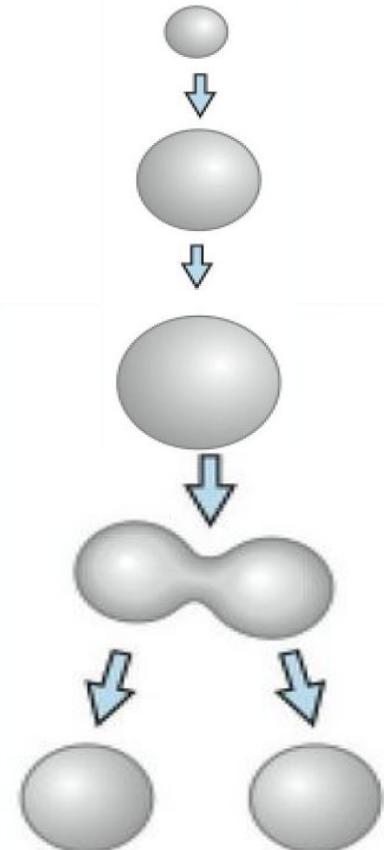
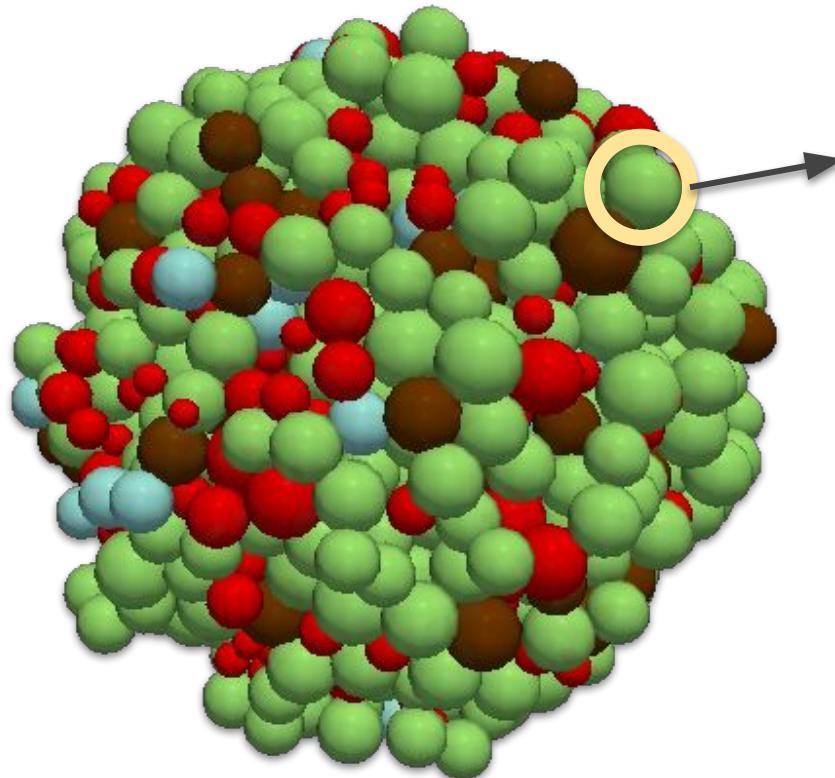
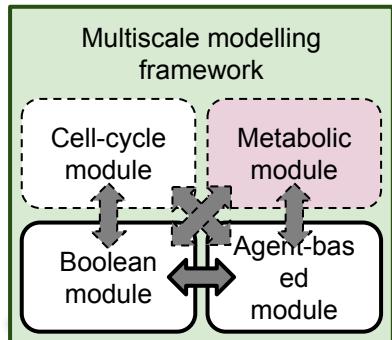
Modeling cellular metabolism

- Rule-Based Modeling (*ad-hoc*)
- Kinetic Modeling (ODEs)
- Constraint-based modeling (Linear Optimization)

The cell growth model

Cell Cycle Phase

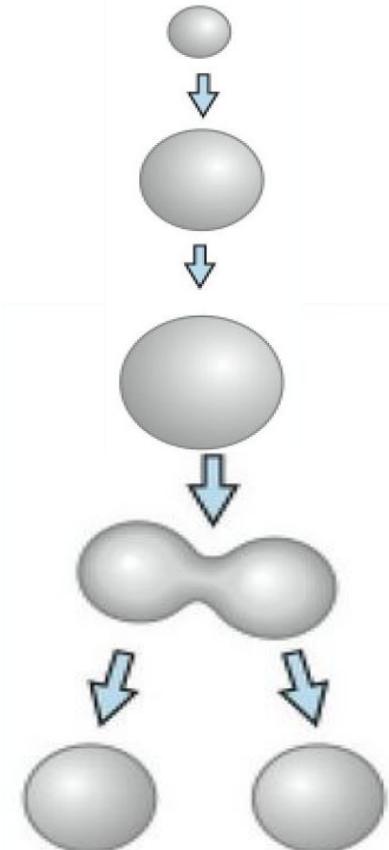
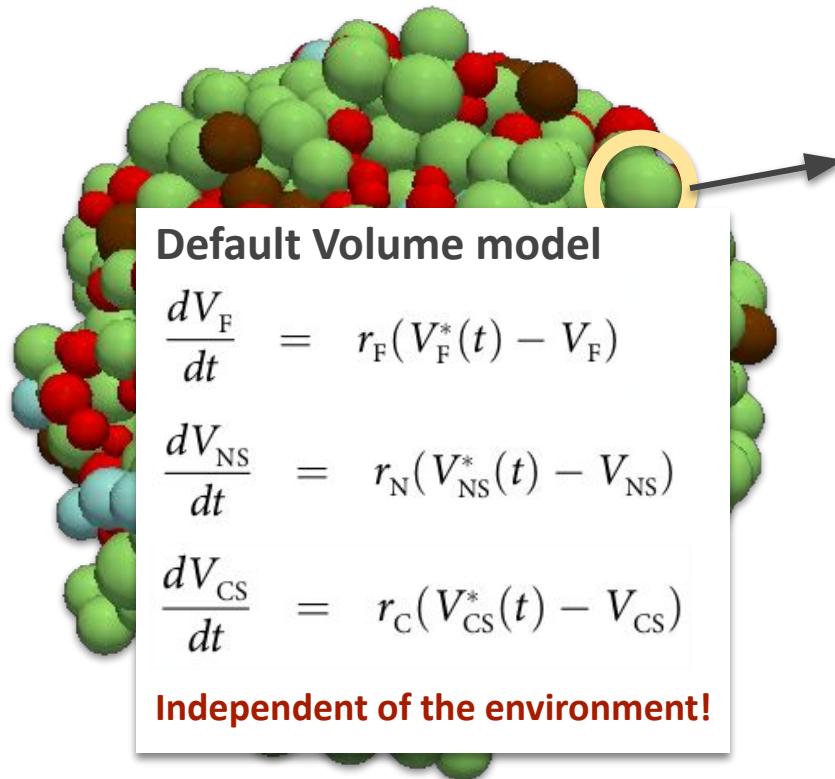
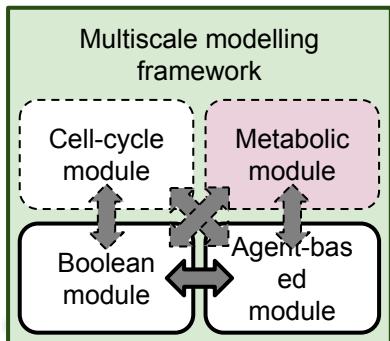
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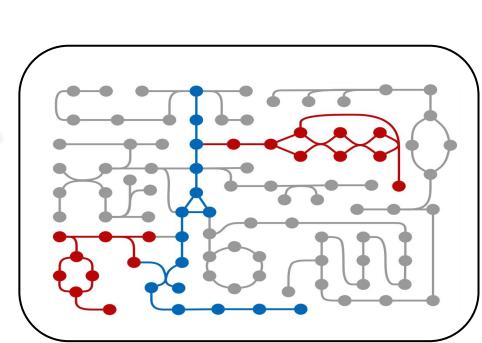
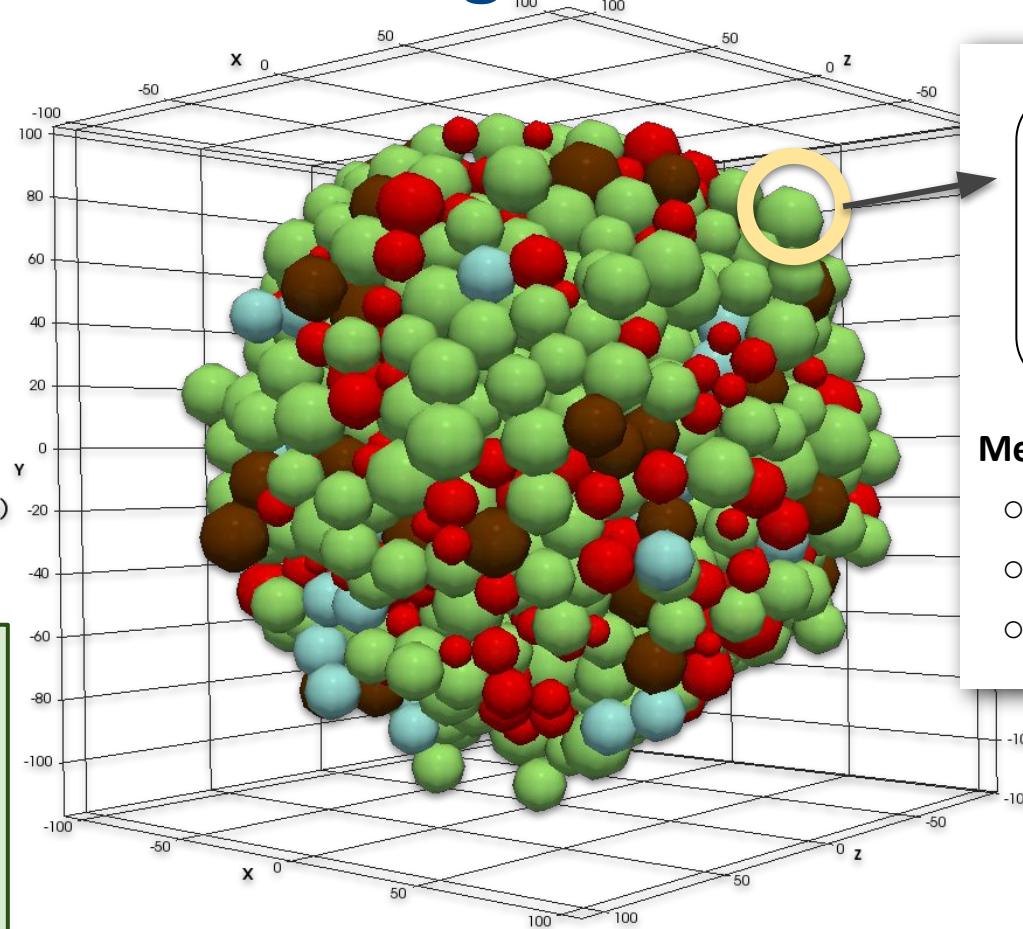
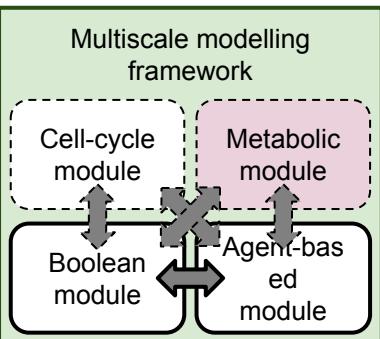
Cell Cycle Phase

- [Green] - Premitotic
- [Light Blue] - Postmitotic
- [Yellow] - Ki67 negative
- [Red] - Apoptotic
- [Brown] - Necrotic
- [Dark Brown] - Necrotic (swelling)
- [Grey] - Necrotic (lysis)



The cell growth model

| Cell Cycle Phase | |
|------------------|---------------------|
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| ■ | Necrotic (swelling) |
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Metabolic phenotype

- Import fluxes (sources)
- Excretion fluxes (sinks)
- Growth rate μ (if prolif.)