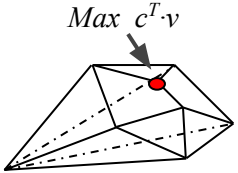
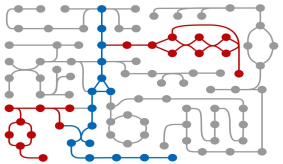
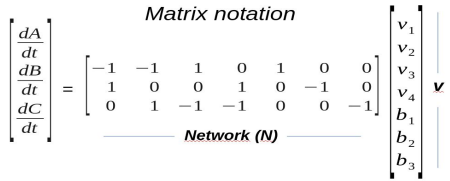
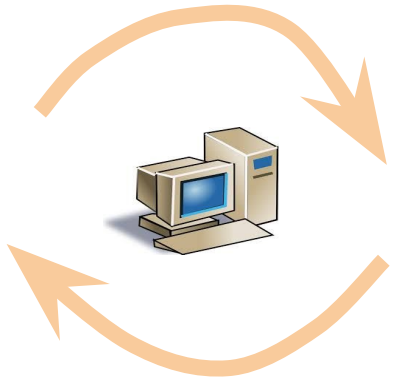
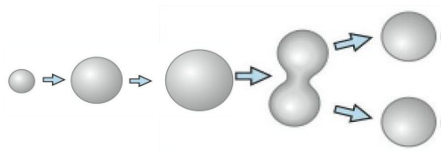
PhysiFBA: a PhysiCell extension to model cell metabolism

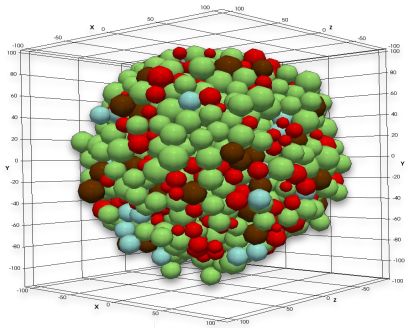


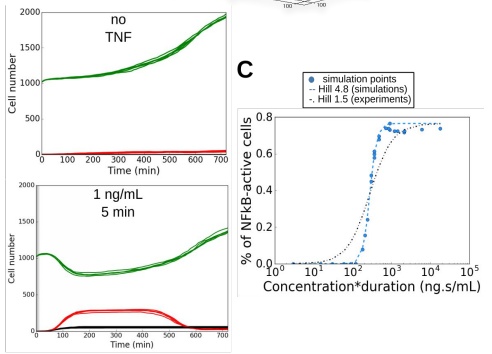












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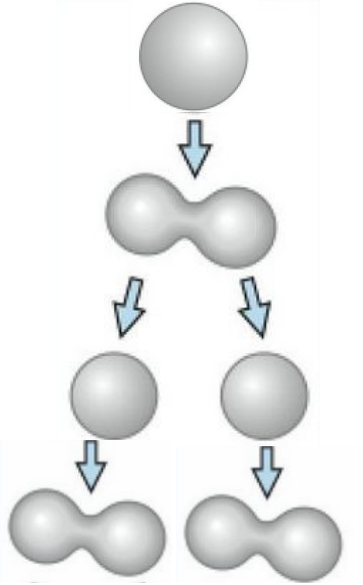
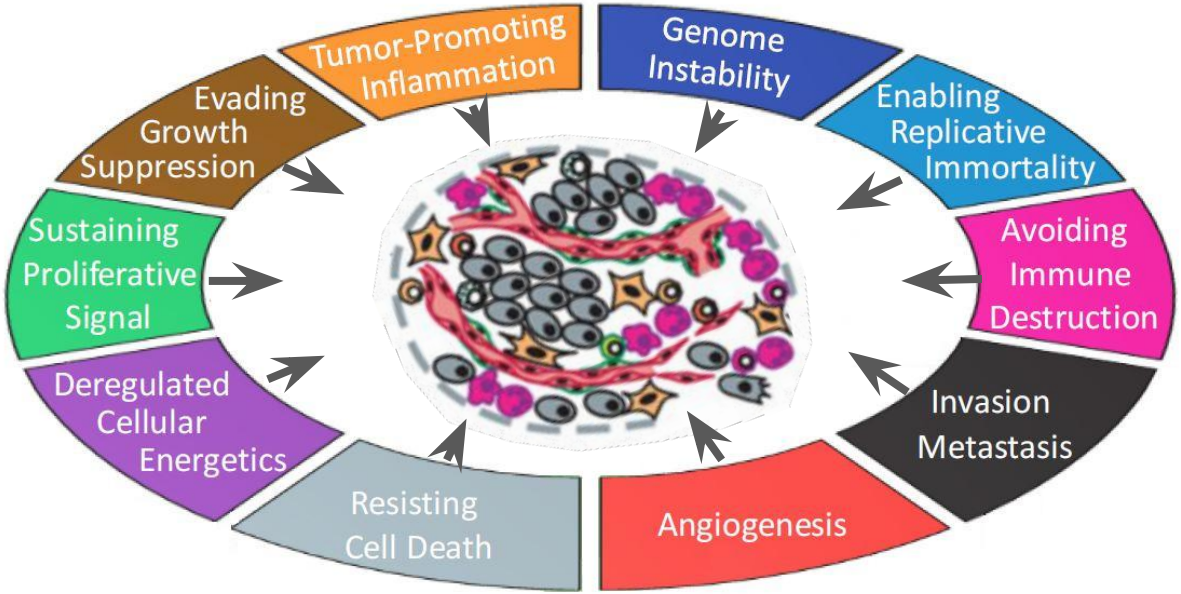
What is cancer?



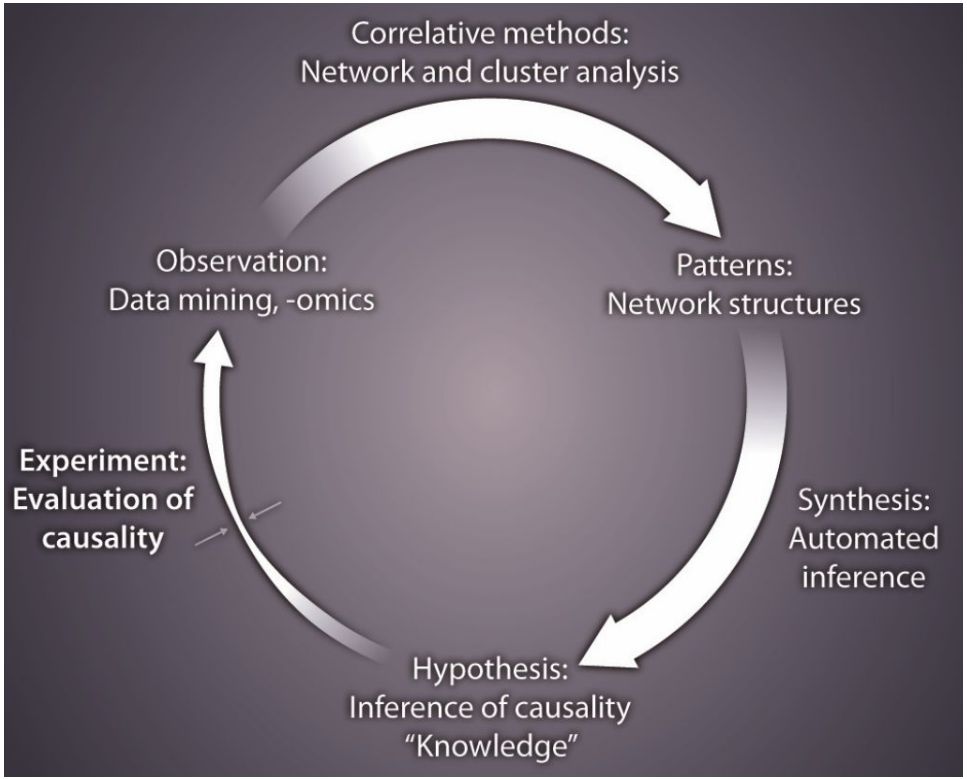
*"... Cancer is a group of diseases involving **abnormal cell growth** with the potential to invade or spread to other parts of the body…"*

Hallmarks



adapted from Hanahan & Weinberg. *Cell* **144,** 646–674 (2011).

Motivation: Current imbalance in the scientific process



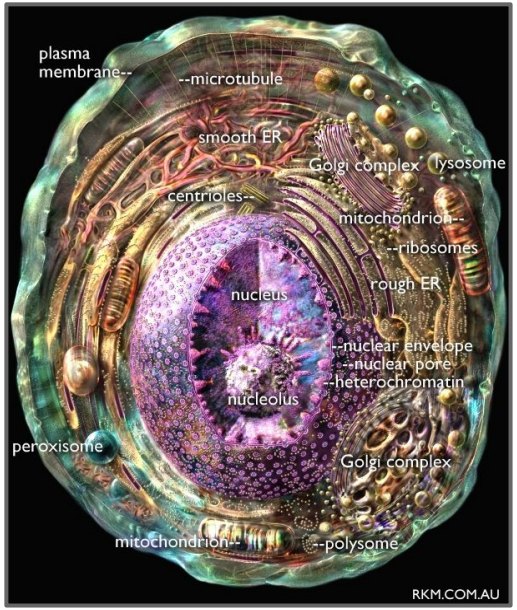
Current Problem: out of sync

- 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

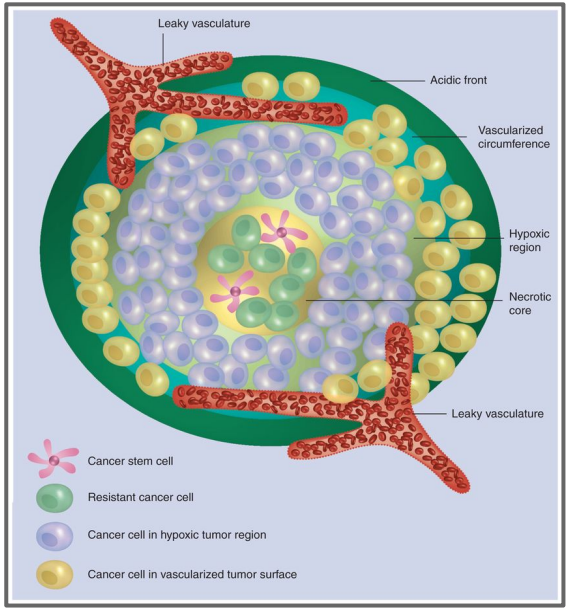
An,G. (2010). *Science Translational Medicine*

Computational Systems Biology of Cancer:

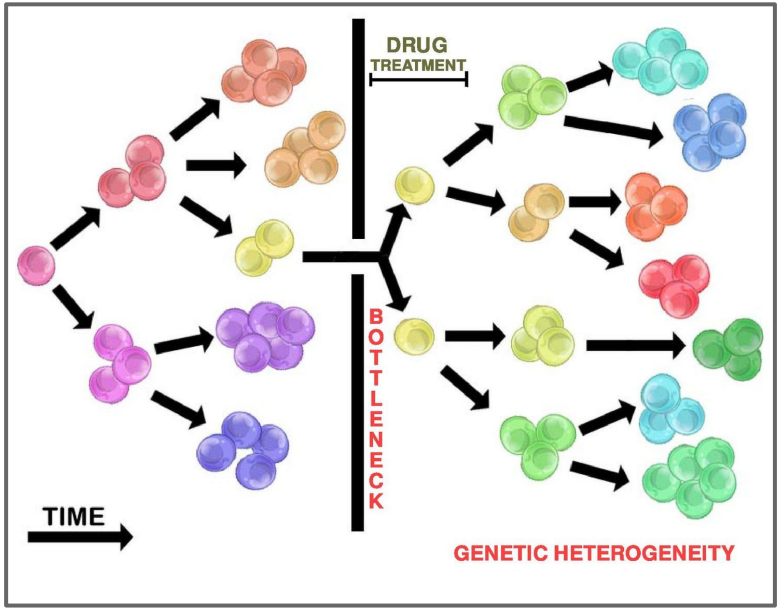
Modelling challenges



Cell complexity



Microenvironment complexity

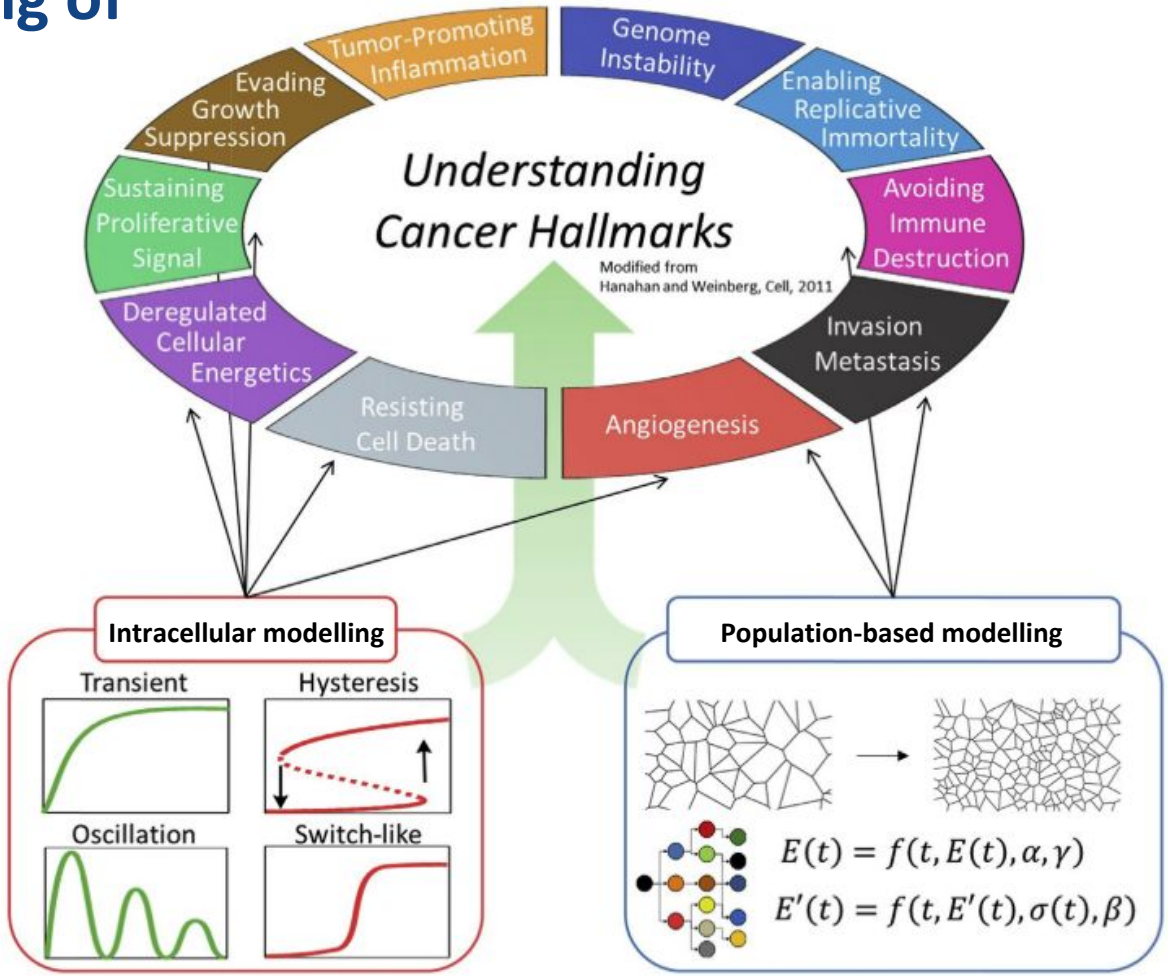


Evolutionary process (time complexity)

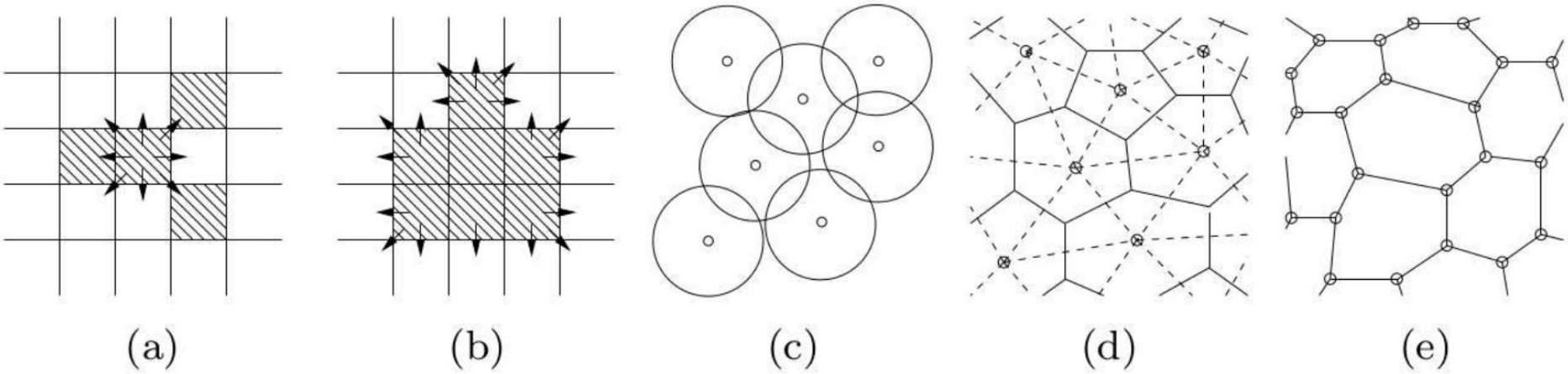
Computational Modelling of cancer

Complementary approaches used to model processes at different scales:

- **Intracellular scale:**
  - Cell Signalling
  - Gene regulation
  - Cell Metabolism
- **Population level**
  - Tumour growth
  - Invasion
  - Immune response
- **Hybrid Multi-Scale Models**
  - Intracell + Population



(*) Agent-Based Model for multicellular modelling



Cellular automaton | Cellular Potts | Overlapping spheres | Overlapping spheres | Vertex model

*"... An **agent-based model** (**ABM**) is a class of computational models for simulating the actions and interactions of autonomous agents (...) It combines elements of game theory, complex systems, emergence, ..., and evolutionary programming. Monte Carlo methods are used to introduce randomness..."* Source: https://en.wikipedia.org/wiki/Agent-based_model

(*) Modified from Osborne,J.M. *et al.* (2017). *PLOS Comp Bio.*

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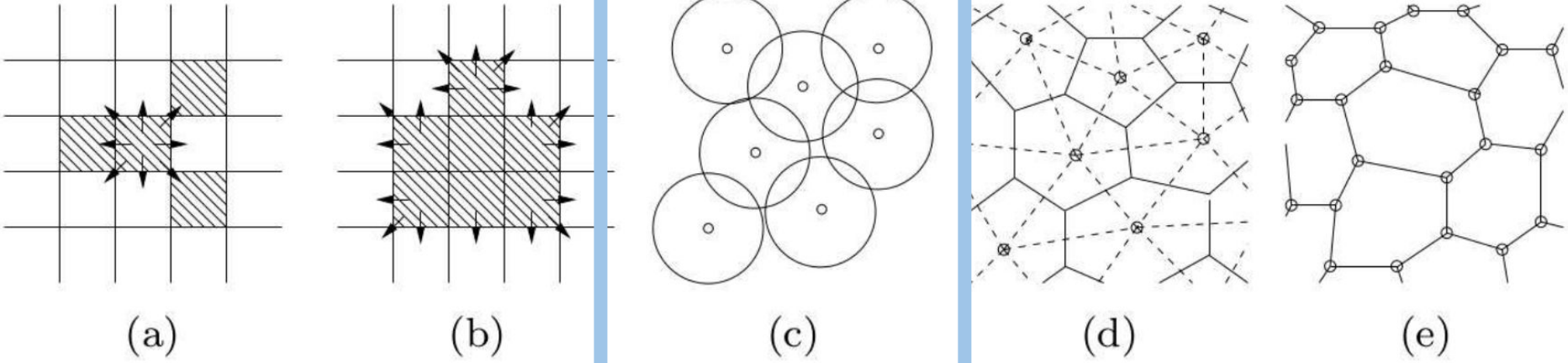
(*) Agent-Based Model for multicellular modelling

PhysiCell



Cellular automaton | Cellular Potts | Overlapping spheres | Overlapping spheres | Vertex model

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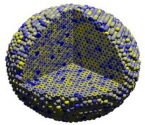
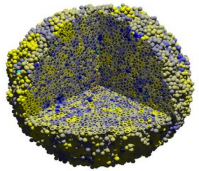
Multi-scale Modeling Framework: PhysiCell

An open source physics-based cell simulator for 3-D multicellular systems

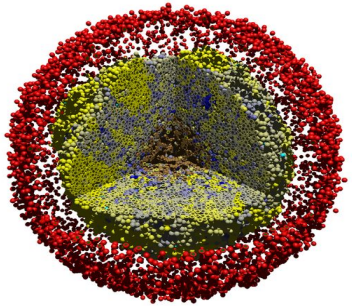
0 days
18,317 cells



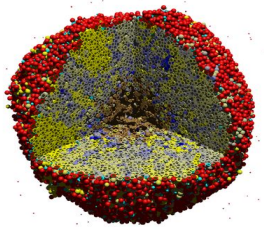
7 days
53,600 cells



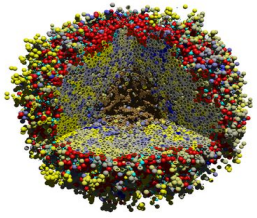
14 days + 3 min
111,479 cells



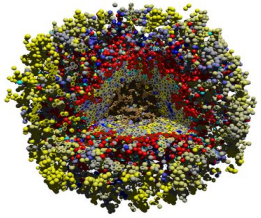
14 days + 6 hours
113,668 cells



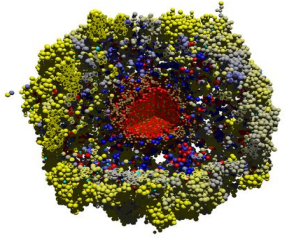
15 days
91,189 cells



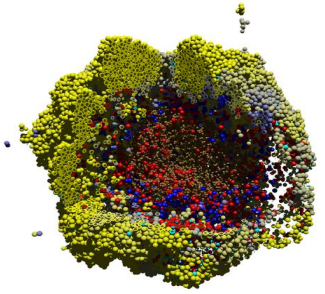
16 days
51,788 cells



18 days
38,122 cells

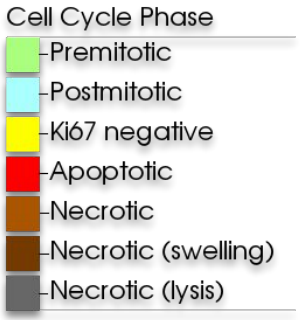


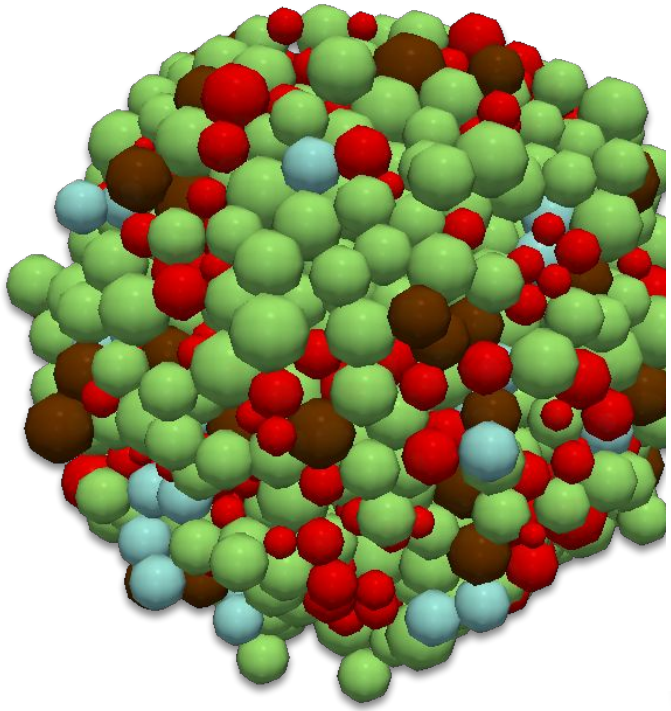
21 days
66,978 cells



Ghaffarizadeh, A. .... & **Macklin P.** (2018) *PLOS Comp Biol*.

The basic cell agent





Cell agent properties

- **Cell Volume**
  - nucleus
  - cytoplasm
- **Position** (x, y, z)
  - Neighborhood
  - Environment
- **Cell internal state**
  - Phenotype
  - Cell cycle phase (G_0, *M, etc*)
  - Growth rate

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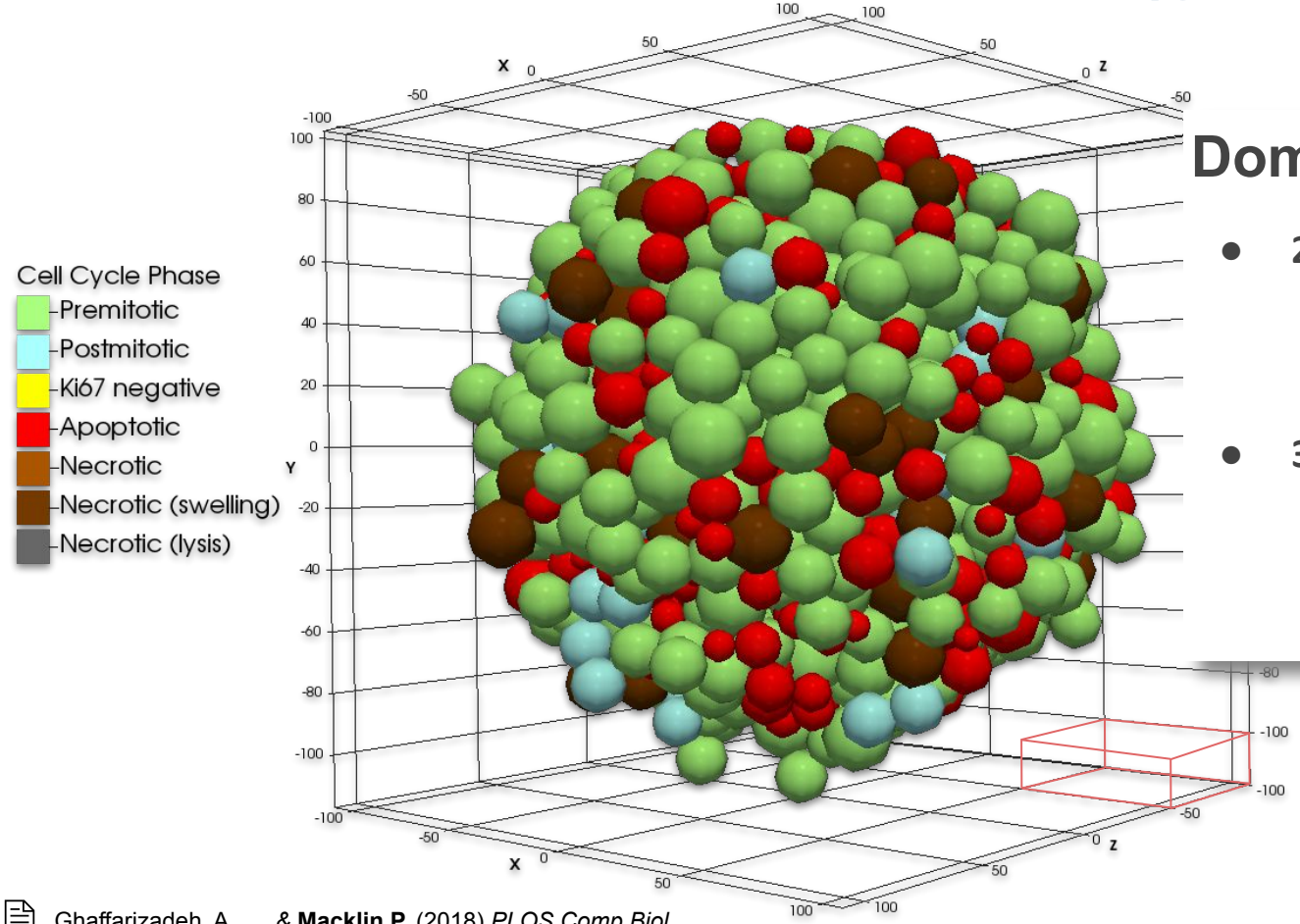
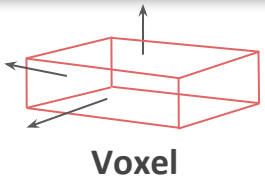
The simulation domain (grid/lattice)



Domain = Voxels' grid

- 2D-Monolayers
  - petri-dish
  - epitelia
  - bio-film
- 3D-Shapes
  - spheroid
  - ductal
  - more complex shapes



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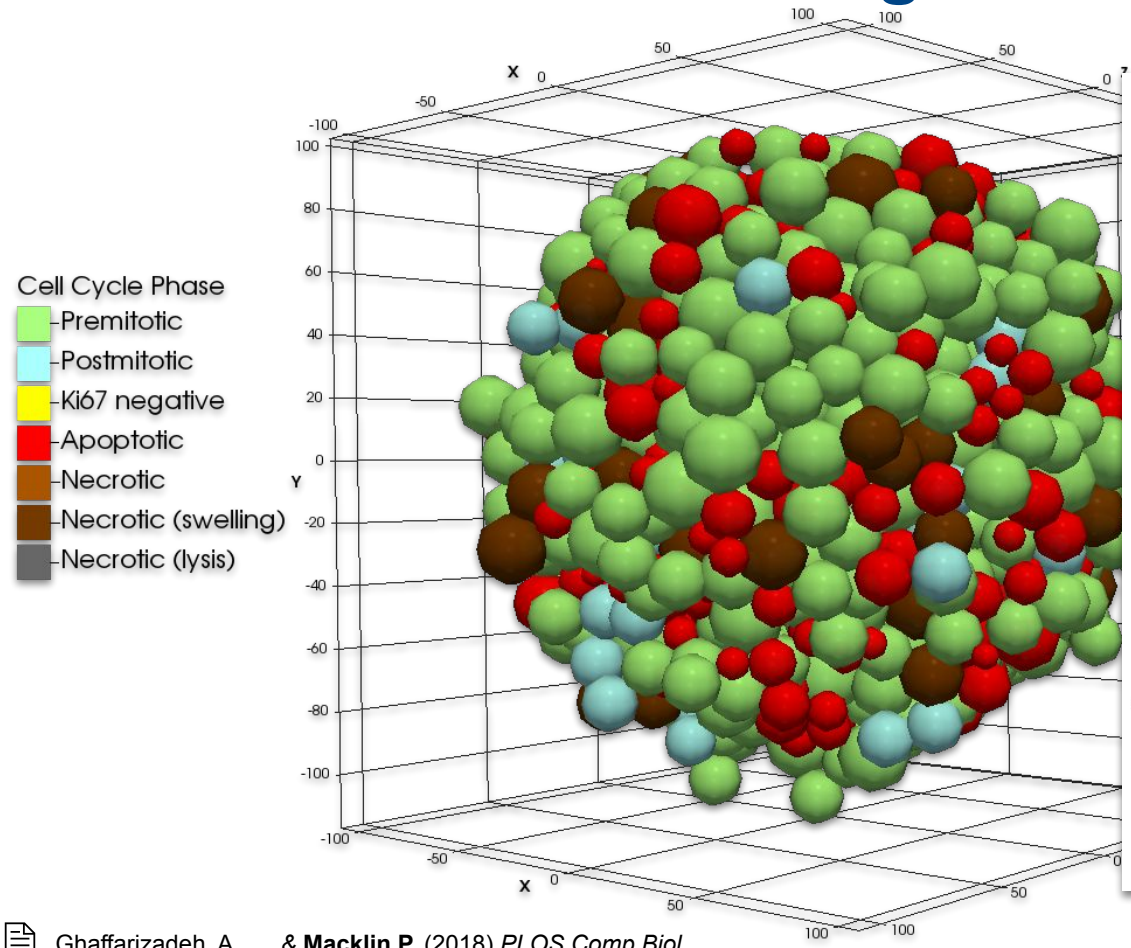
Multi-scale Modeling Framework: PhysiCell



Diffusion and mechanics are governed by differential equations

Diffusion equations

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

$$+ \overbrace{\sum_{\text{cells } k} \delta(\mathbf{x} - \mathbf{x}_k) W_k [\mathbf{S}_k(\boldsymbol{\rho}_k^* - \boldsymbol{\rho}) - \mathbf{U}_k \boldsymbol{\rho}]}^{\text{sources and uptake by cells}} \text{ in } \Omega$$

Mechanical equations

$$\mathbf{v}_i = \sum_{j \in \mathcal{N}(i)} \left(\overbrace{- \sqrt{c^i_{\text{cca}} c^j_{\text{cca}}} \nabla \phi_{1, R_{i,A} + R_{j,A}} (\mathbf{x}_i - \mathbf{x}_j)}^{\text{cell-cell adhesion}} \overbrace{- \sqrt{c^i_{\text{ccr}} c^j_{\text{ccr}}} \nabla \psi_{1, R_i + R_j} (\mathbf{x}_i - \mathbf{x}_j)}^{\text{cell-cell repulsion}} \right).$$

$$\overbrace{- c^i_{\text{cba}} \nabla \phi_{1, R_{i,A}} (-d(\mathbf{x}_i)\mathbf{n}(\mathbf{x}_j))}^{\text{cell-BM adhesion}} \overbrace{- c^i_{\text{cbr}} \nabla \psi_{1, R_i} (-d(\mathbf{x}_i)\mathbf{n}(\mathbf{x}_j))}^{\text{cell-BM repulsion}} + \mathbf{v}_{i,\text{mot}}$$

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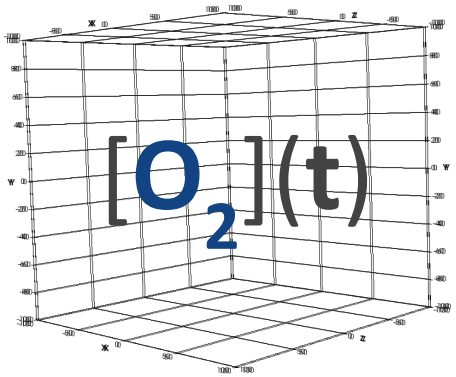
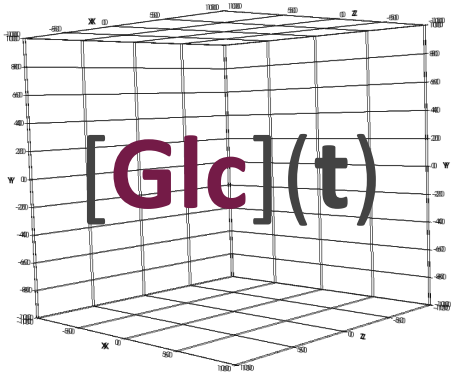
The microenvironment





Molecules density (concentrations) at time ***t*** are stored in MultiCellDS format (XML), Matlab (.m) or CSV

Reaction-Diffusion Equations

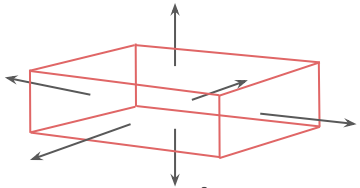
$$\frac{\partial \boldsymbol{\rho}}{\partial t} = \overbrace{\mathbf{D}\nabla^2\boldsymbol{\rho}}^{\text{diffusion}} - \overbrace{\boldsymbol{\lambda}\boldsymbol{\rho}}^{\text{decay}} + \overbrace{\mathbf{S}(\boldsymbol{\rho}^* - \boldsymbol{\rho})}^{\text{bulk source}} - \overbrace{\mathbf{U}\boldsymbol{\rho}}^{\text{bulk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

$$+ \overbrace{\sum_{\text{cells } k} \delta(\mathbf{x} - \mathbf{x}_k) W_k [\mathbf{S}_k(\boldsymbol{\rho}_k^* - \boldsymbol{\rho}) - \mathbf{U}_k\boldsymbol{\rho}]}^{\text{sources and uptake by cells}} \text{ in } \Omega$$

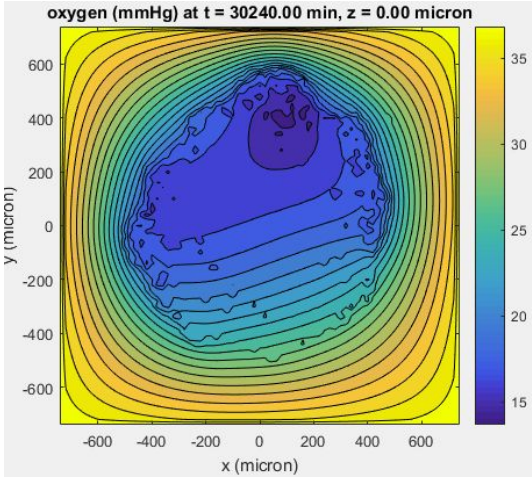
System of PDEs for each molecule density:

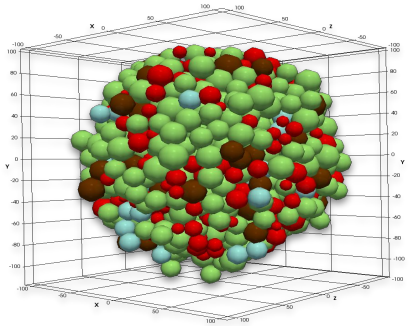
- Diffusion term
- Decay
- Uptake/Production

PDEs are solved time scale using **BioFVM**

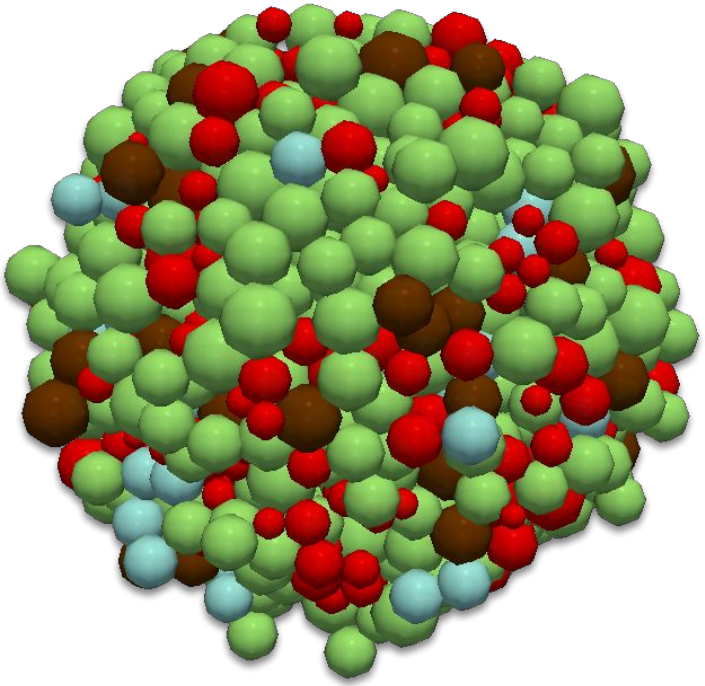


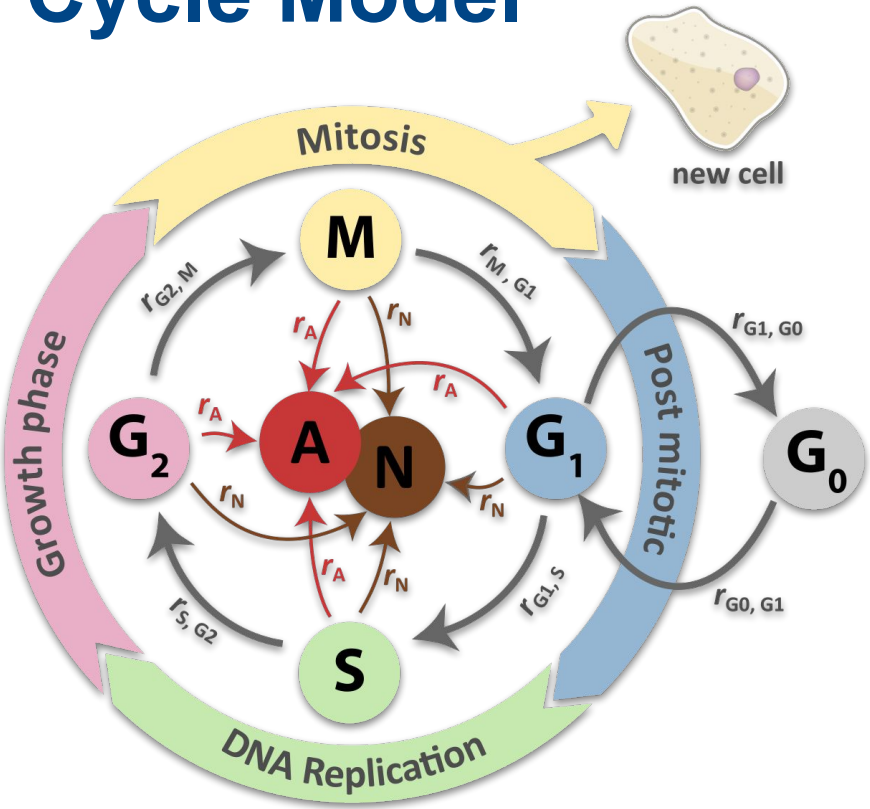
Gradients in chemical factors (O2)





(*) Standard Cell Cycle Model



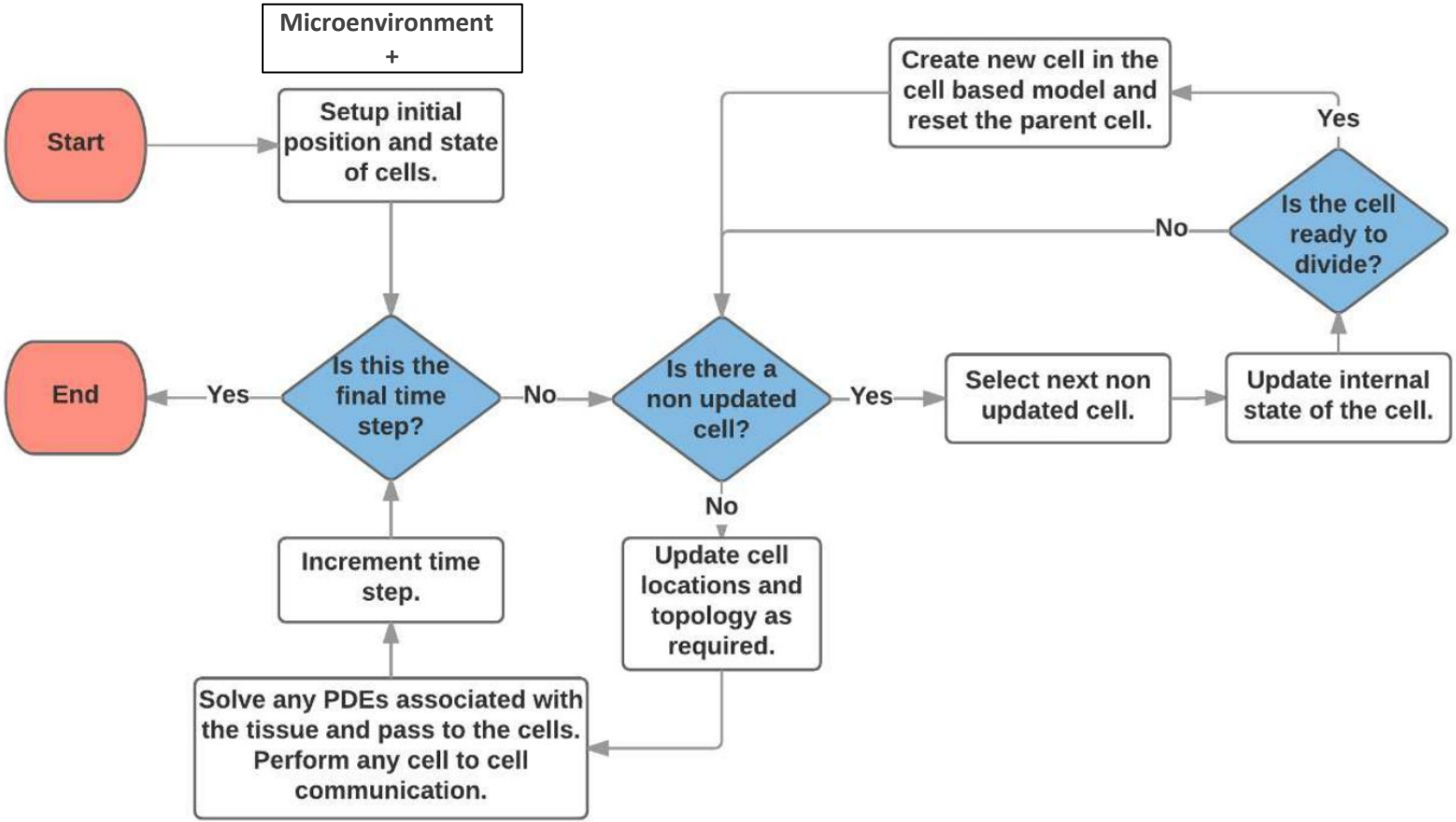


$$\text{Prob}(\text{transition from } X_i \text{ to } X_j | \text{not arrested}) \approx r_{ij}\Delta t.$$

Stochastic transition rates (experimental)

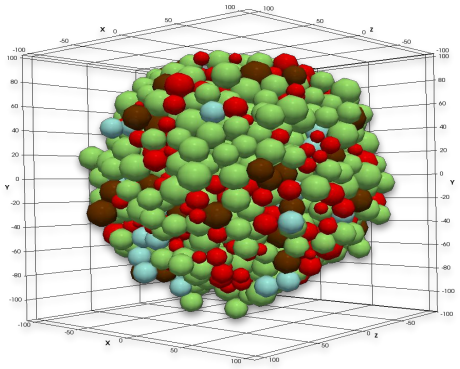
$r_{G2,M}$, $r_{M,G1}$, $r_{G2,S}$, … , r_A, r_N

Simulation workflow



(*) Modified from Osborne,J.M. *et al.* (2017). *PLOS Comp Bio.*

Simulation workflow

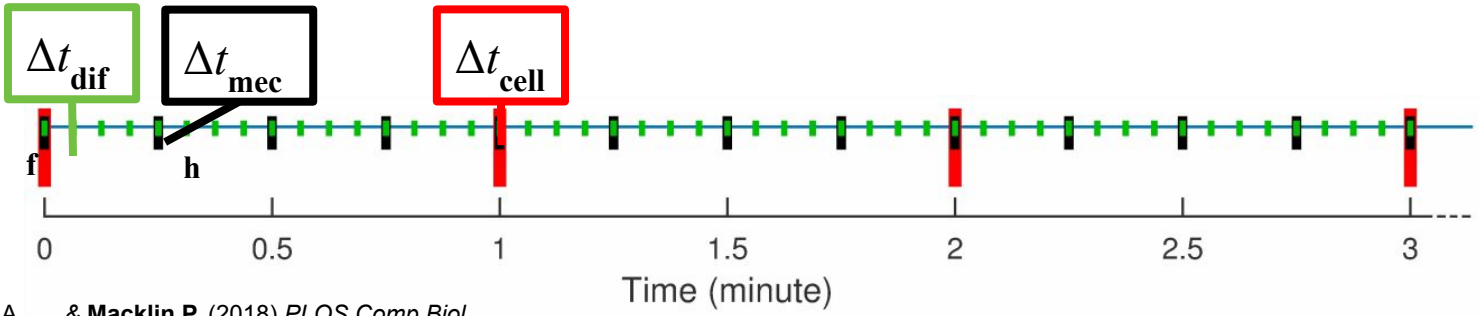


Simulation's Main Loop

```
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



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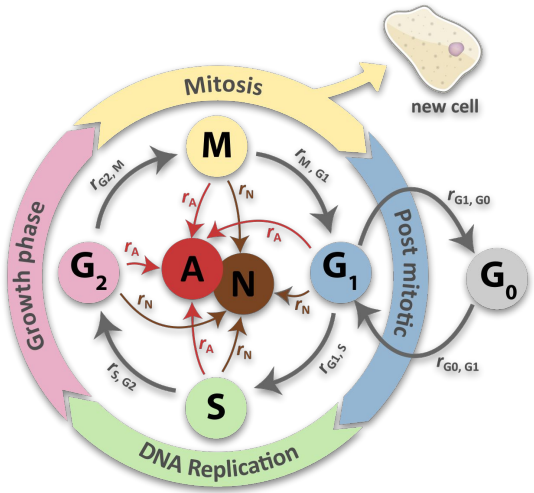
Modeling cell cycle transitions (rule-based)

Transition rates are governed by user defined rules



Stochastic transition rates

$r_{G2,M}$, $r_{M,G1}$, … , r_A, r_N

Entering cell cycle rate

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

Necrosis rate

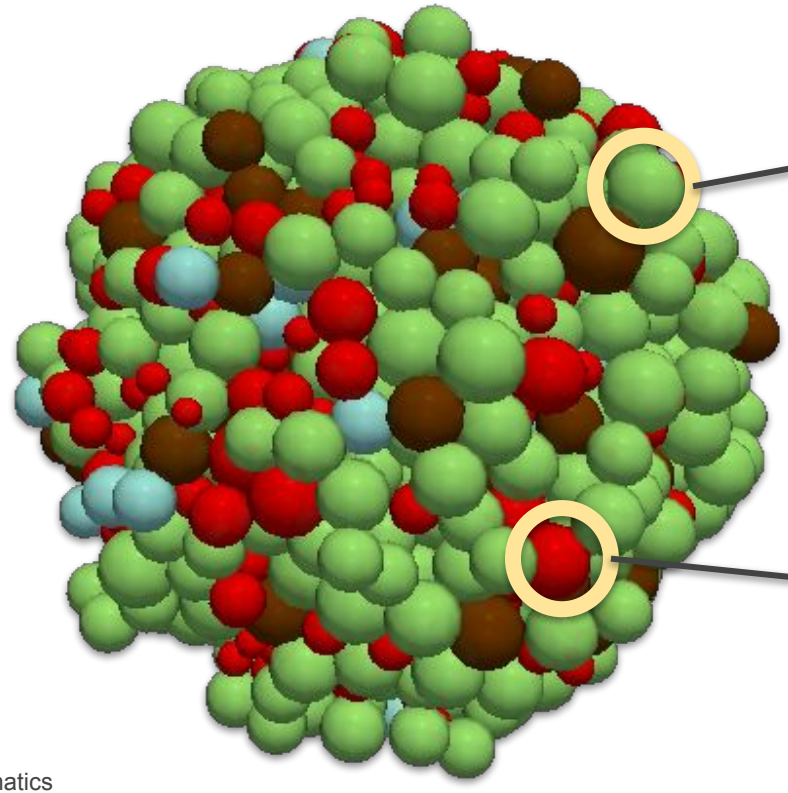
$$r_N(\mathrm{pO}_2) = \begin{cases} 0 & \text{if } O_{2,thr} < O_2 \\ r_{\mathrm{N,\,Max}} \left(\dfrac{pO_{2,thr} - pO_2}{pO_{2,thr} - pO_{2,crit}} \right) & \text{if } O_{2,crit} < O_2 \le O_{2,thr} \\ r_{\mathrm{N,\,Max}} & \text{if } O_2 \le O_{2,crit} \end{cases}$$

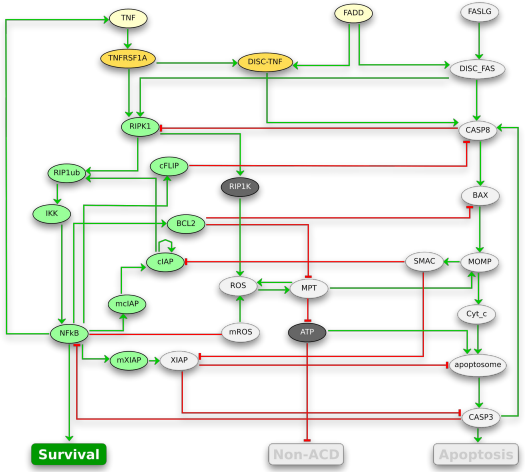
$$\mathrm{Prob}(S_i(t + \Delta t) = D_i) = 1 - \exp(-r_i \Delta t) \approx r_i \Delta t.$$

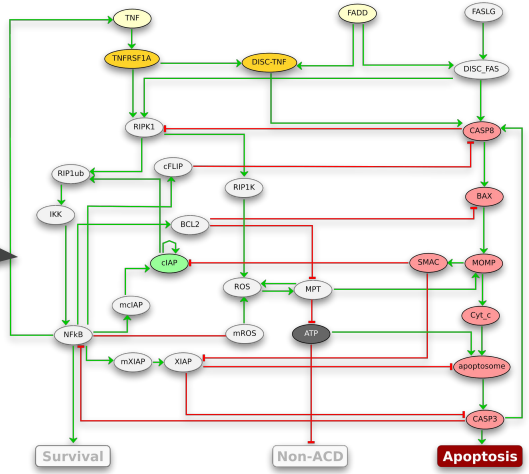
Modeling cell signaling: PhysiBoSS

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

Different cell signaling states

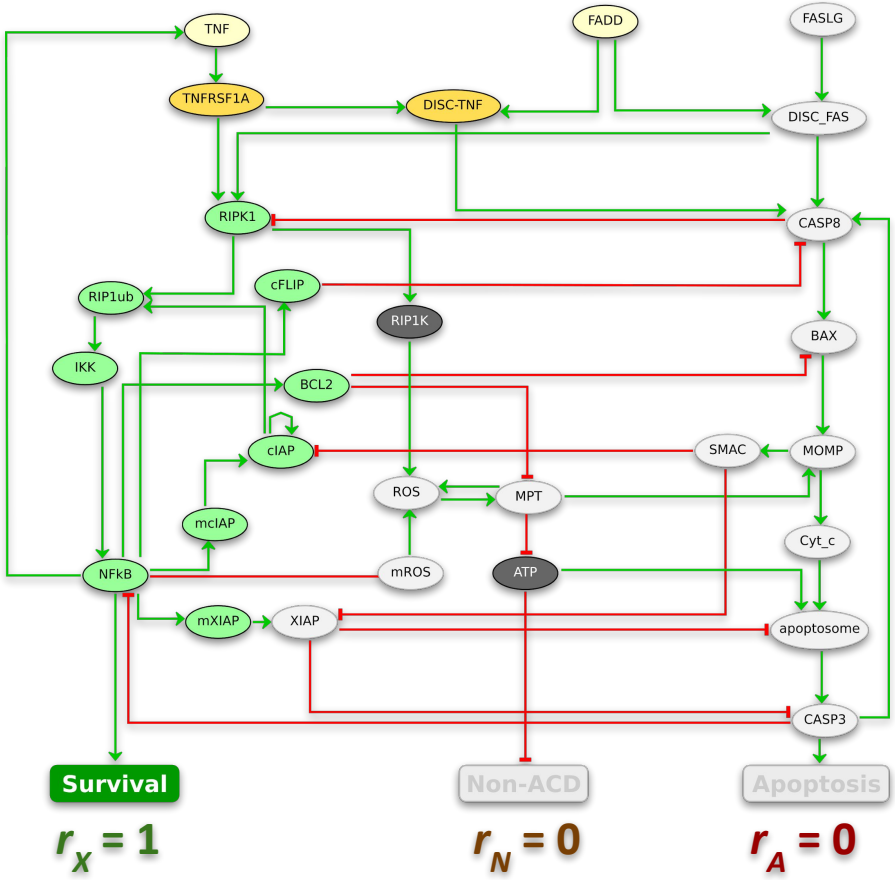


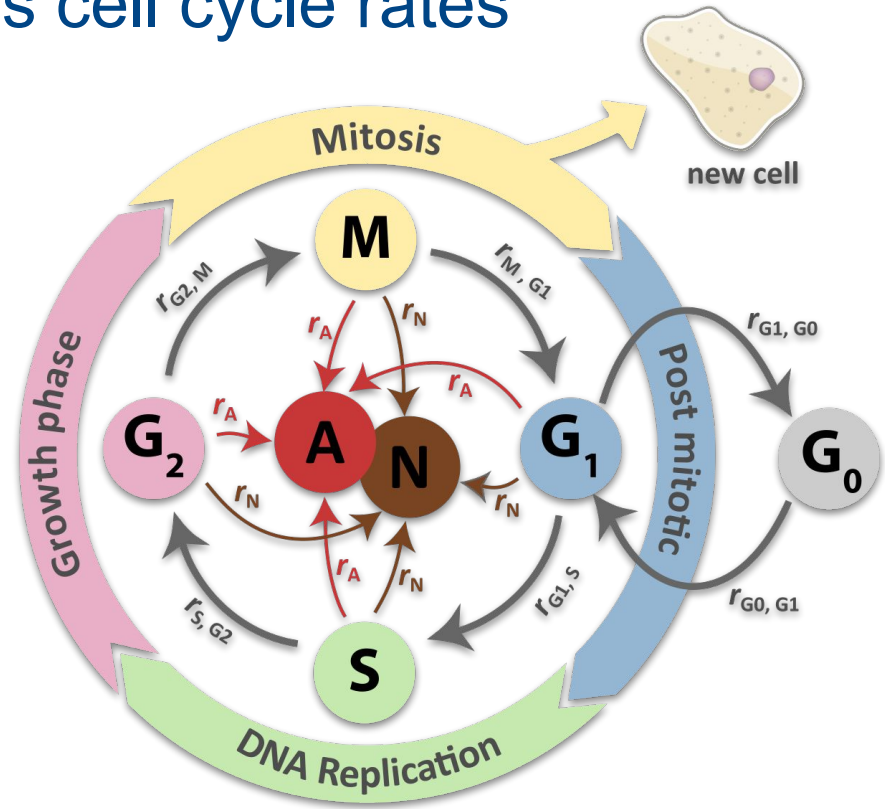




Letort, Montagud *et al.*, 2018. Bioinformatics

Signalling → updates cell cycle rates

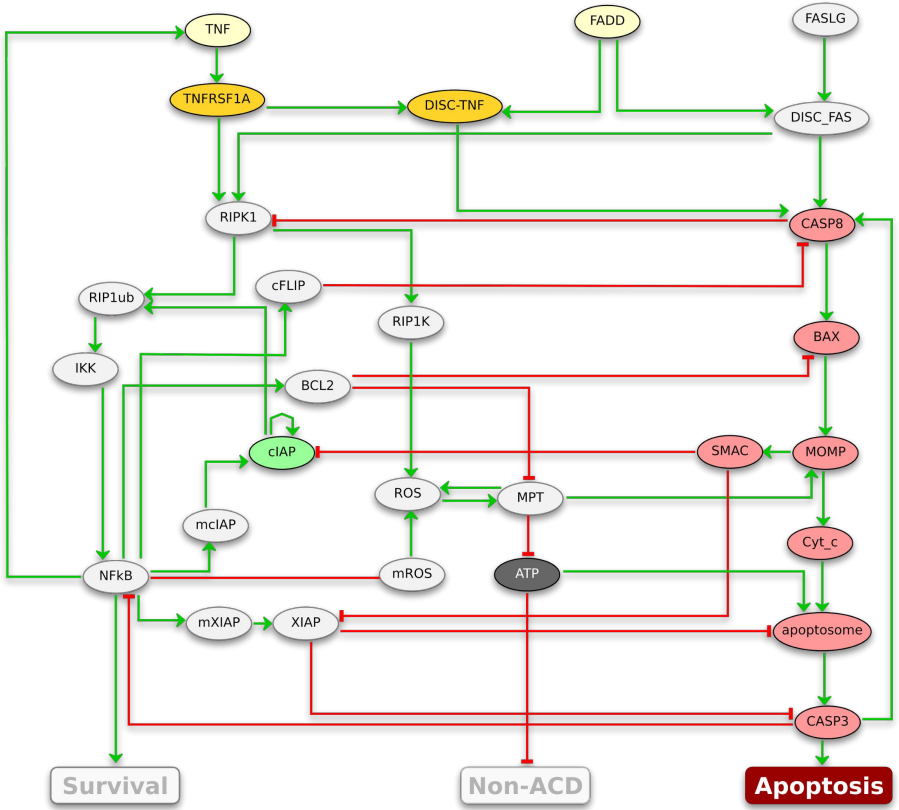


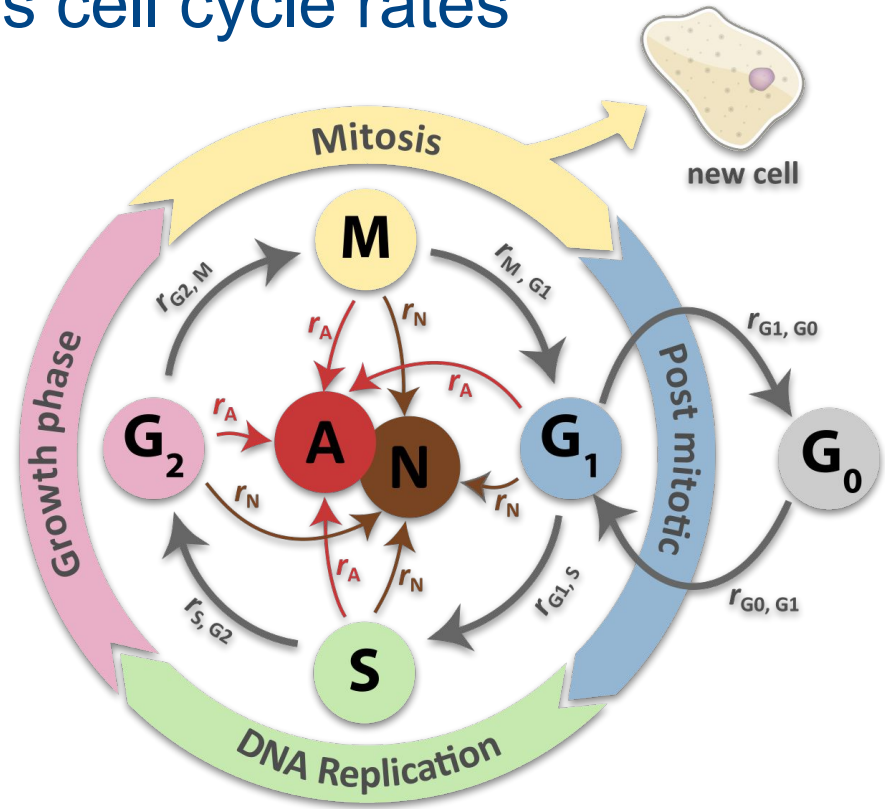


Stochastic transition rates (experimental)

$r_{G2,M}$, $r_{M,G1}$, $r_{G2,S}$, ... , r_A, r_N

Signalling → updates cell cycle rates





Stochastic transition rates (experimental)

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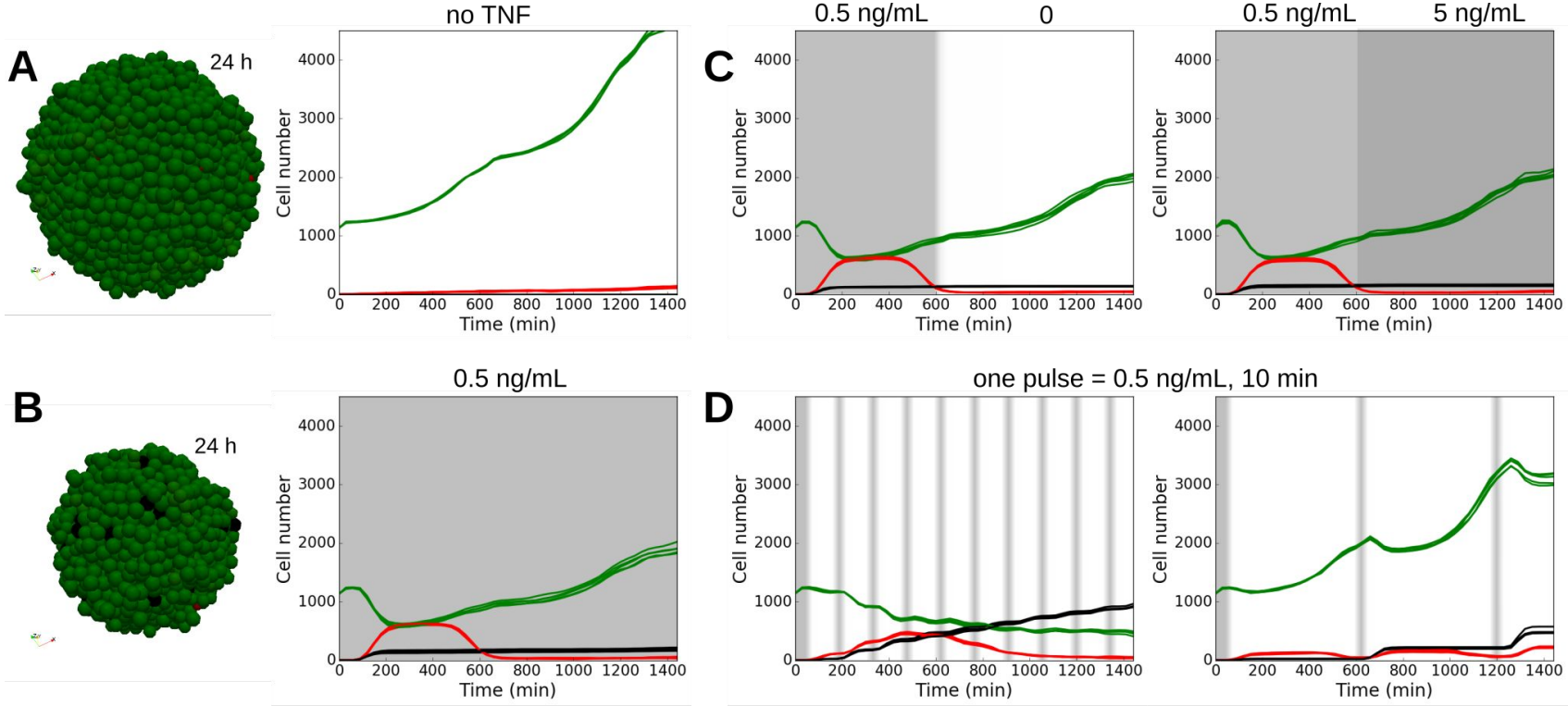
Environment heterogeneity: TNF pulse studies

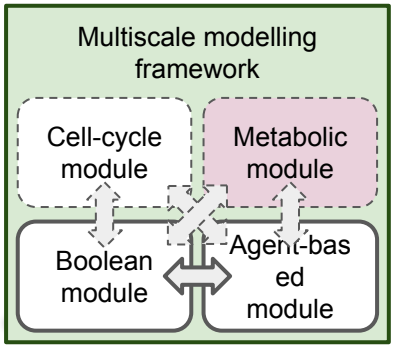
Proliferation Apoptosis Necrosis

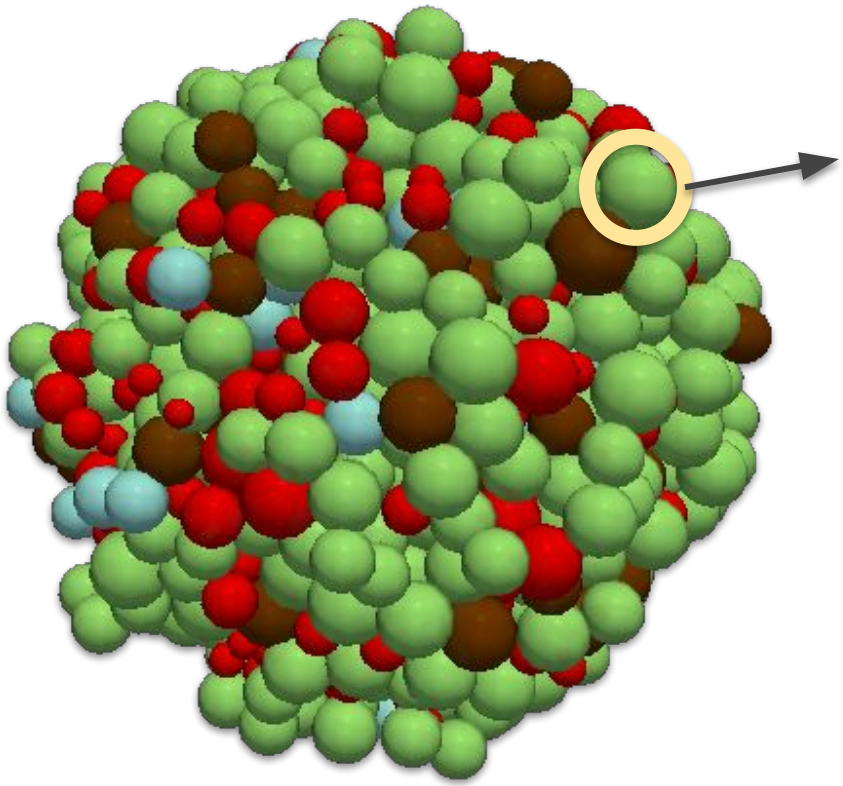


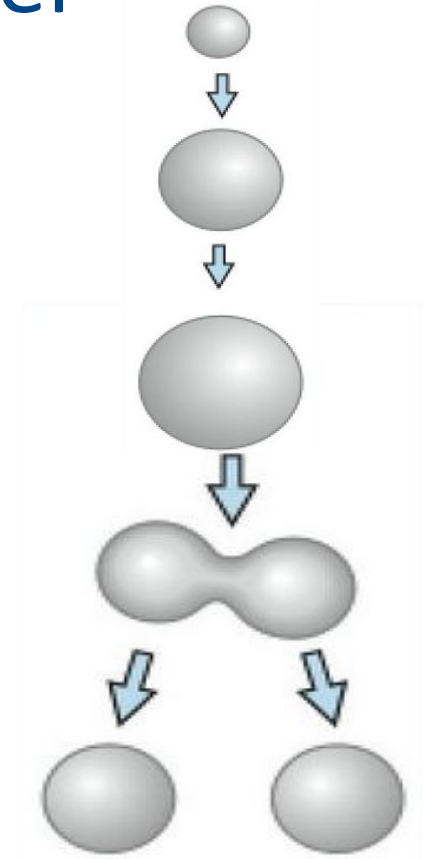
Letort, Montagud *et al.*, 2018. Bioinformatics

The cell growth model

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







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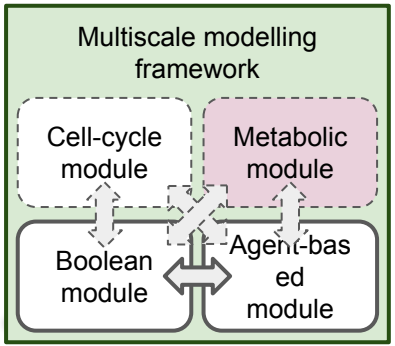
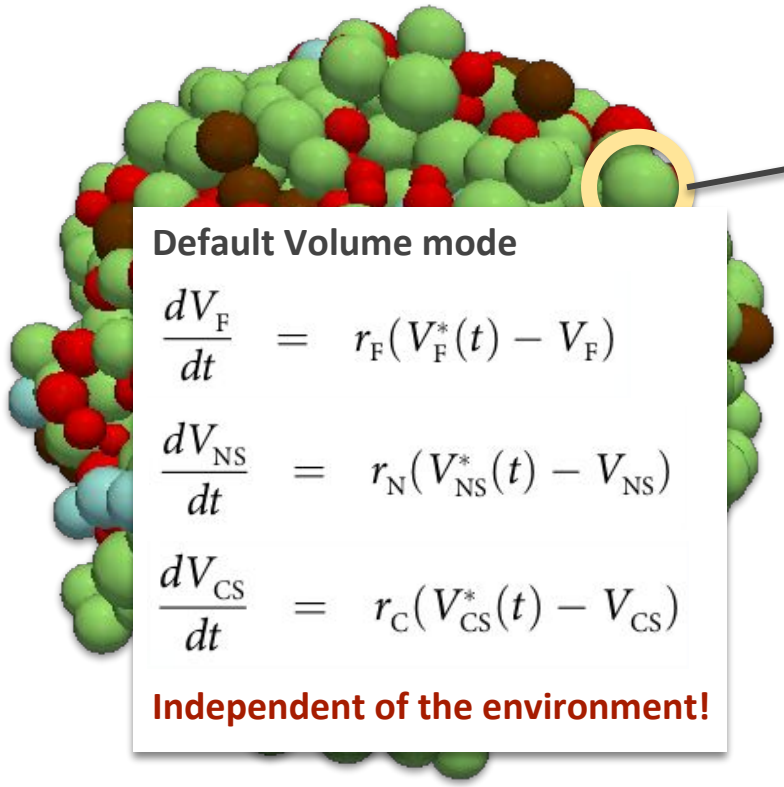




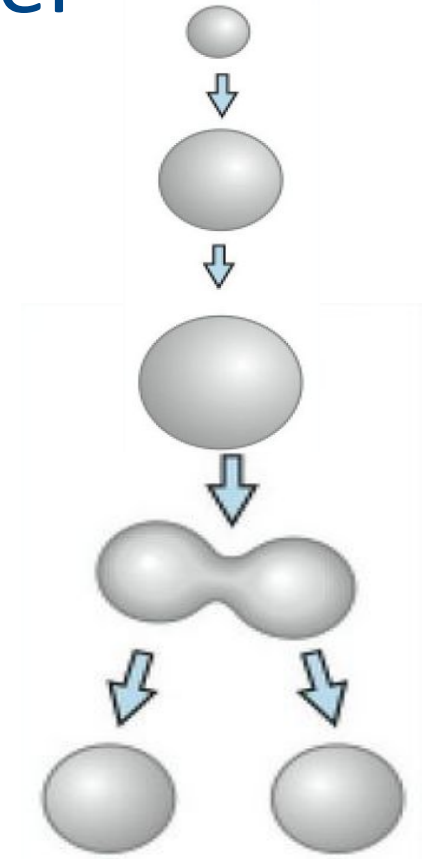
Default Volume mode

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

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

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

Independent of the environment!



What is a cell made of?

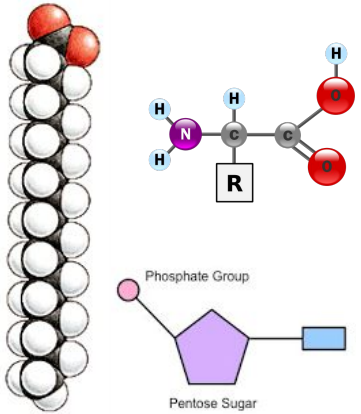
Level (scale) of description

Chemistry

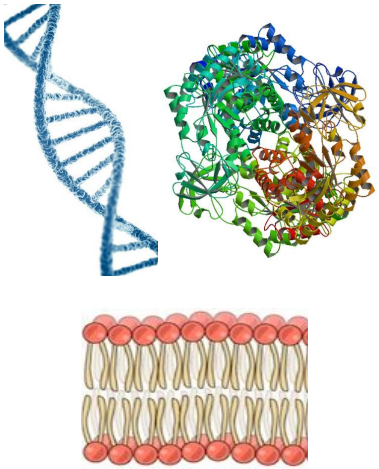
H_2O C

N P

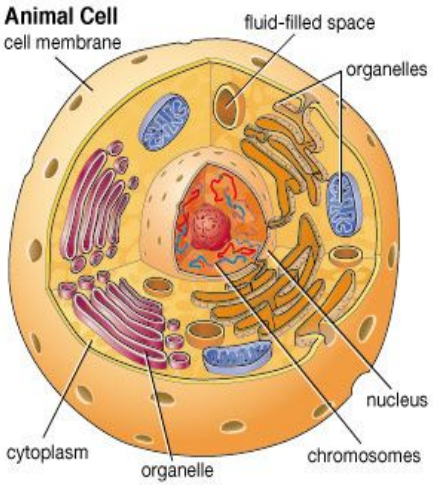
Building blocks



Macromolecules



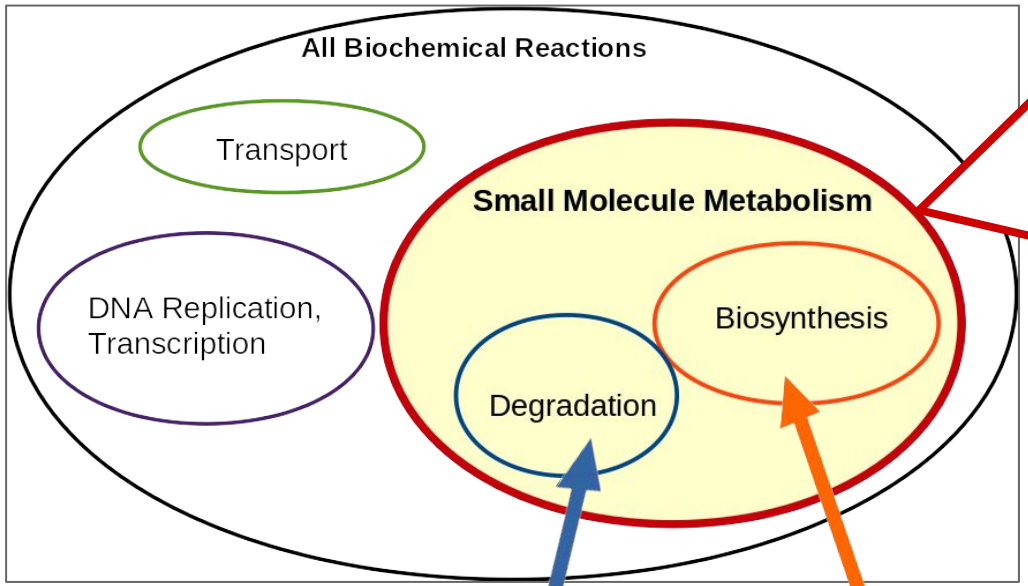
Cell

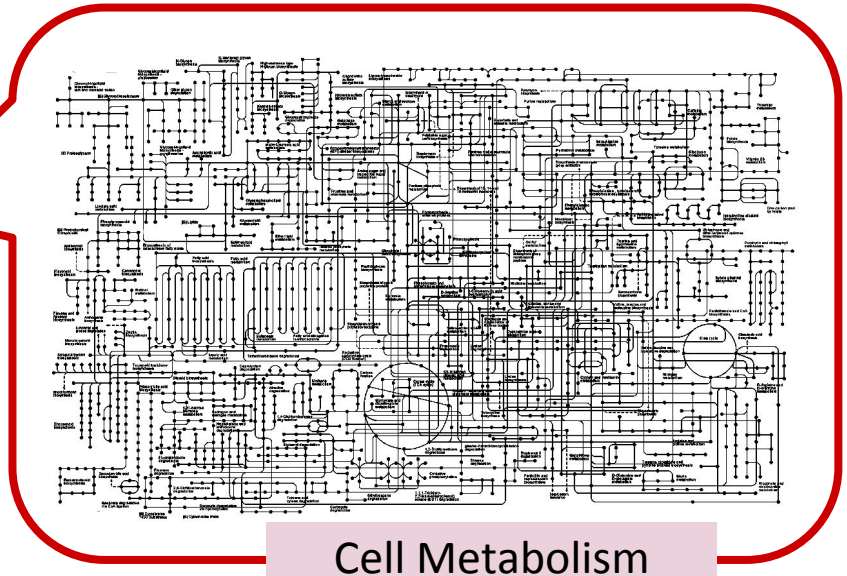


Cell's molecular factory: metabolism → What is metabolism?

Metabolism: the molecular factory of the cell

*Is the **network** of biochemical reactions and transport processes that occur within a cell and allow **cell maintenance and growth***





Cell Metabolism

- Generation of **energy (catabolism)** and **building block (anabolism)**
- Include the enzymatic reaction that act over small molecules

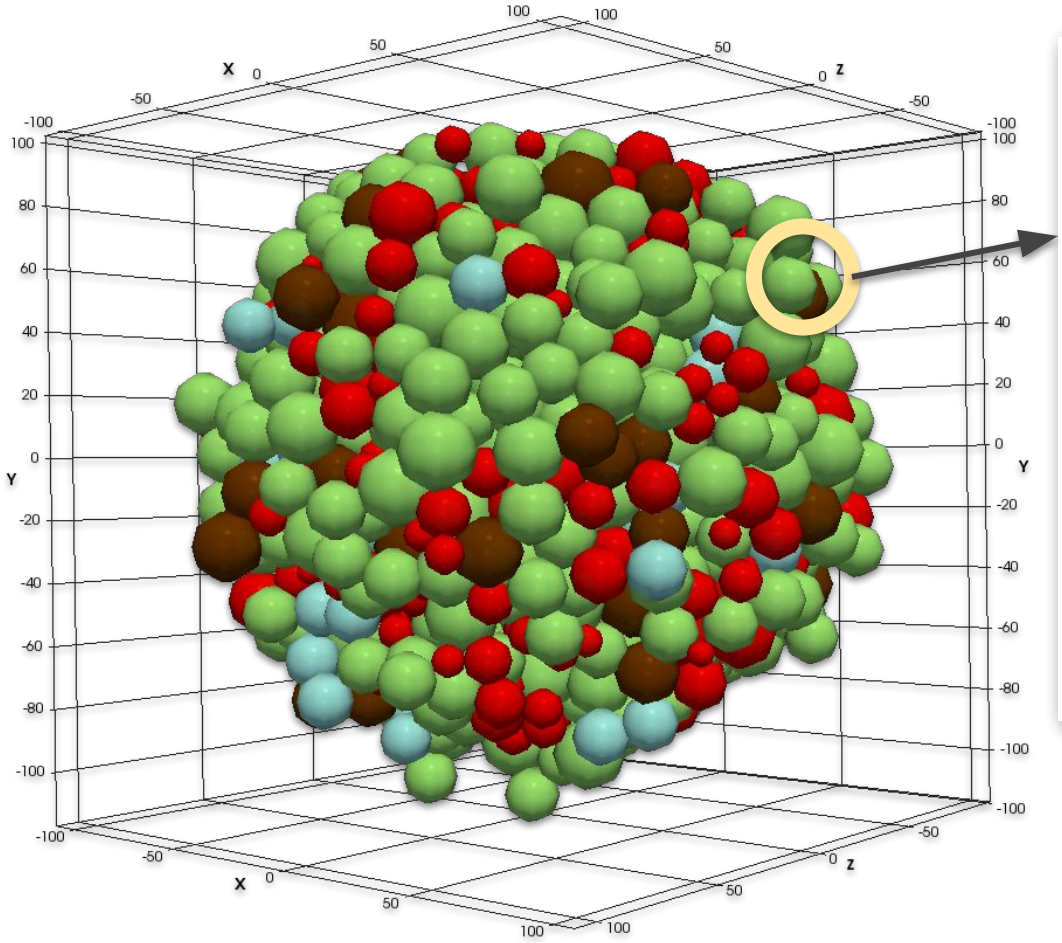
Metabolic modeling goes multicelluar!

Connecting a metabolic model to the agent and the environment

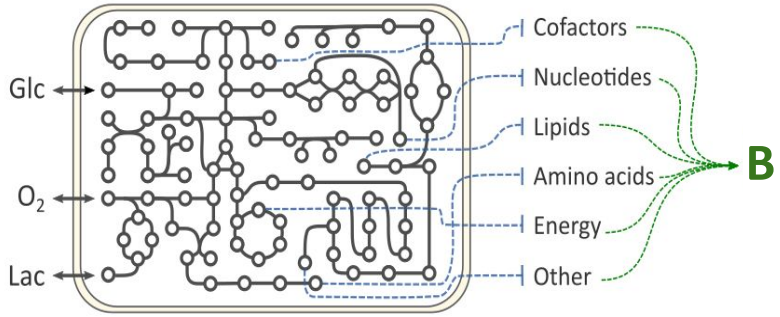
Barcelona Supercomputing Center
Centro Nacional de Supercomputación

SO Mobility Fellowship

Connecting Metabolism to PhysiCell



Genome-Scale Metabolic Model



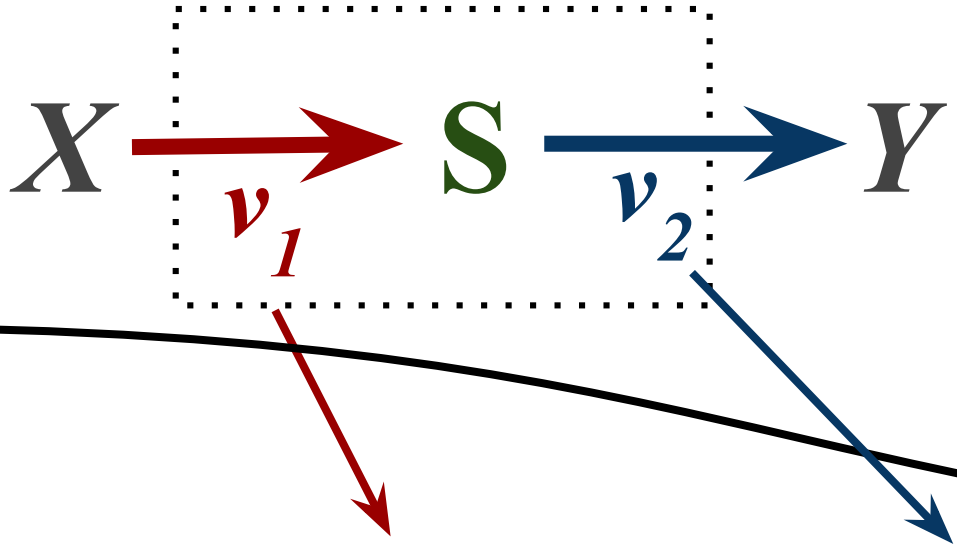
Constrinat-Based Modelling → metabolic phenotype

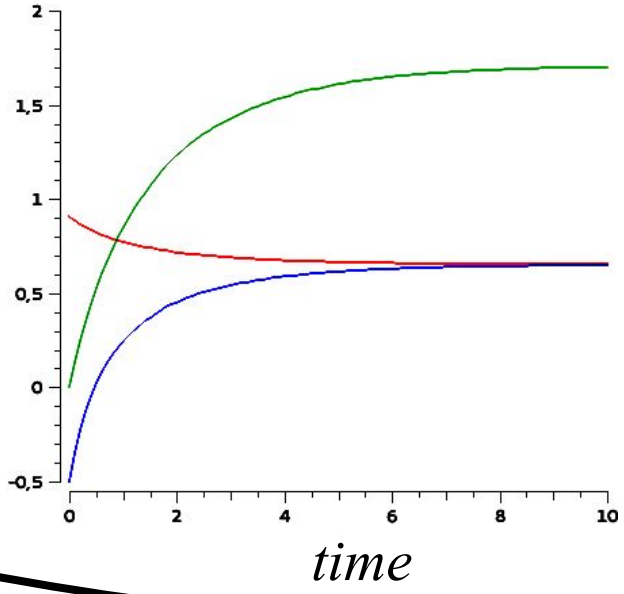
- Import fluxes
- Excretion fluxes
- Growth rate μ

Modeling cellular metabolism

- Rule-Based Modeling (PhysiCell default)
- Kinetic Modeling (ODEs)
- Constraint-based modeling (Linear Programming)

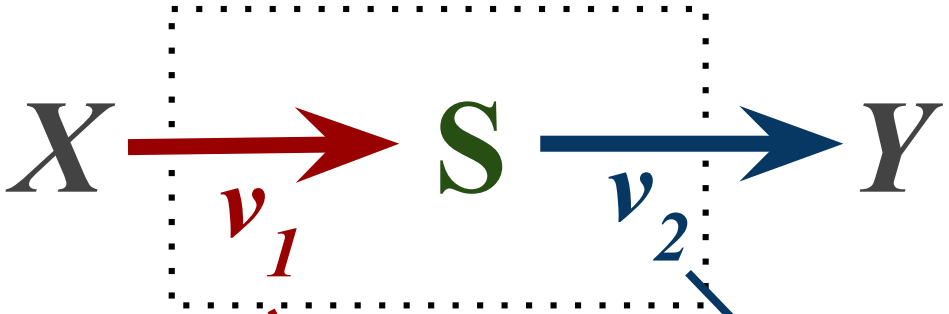
Kinetic description

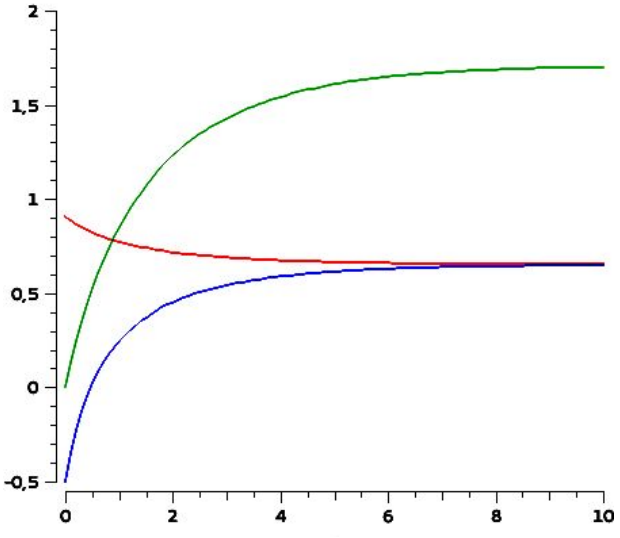




$$\frac{d([S])}{dt} = \left(\frac{\frac{Vf_{(V1)} \cdot [X]}{Kms_{(V1)}} - \frac{Vr_{(V1)} \cdot [S]}{Kmp_{(V1)}}}{1 + \frac{[X]}{Kms_{(V1)}} + \frac{[S]}{Kmp_{(V1)}}} \right) + \left(\frac{\frac{Vf_{(V2)} \cdot [S]}{Kms_{(V2)}} - \frac{Vr_{(V2)} \cdot [Y]}{Kmp_{(V2)}}}{1 + \frac{[S]}{Kms_{(V2)}} + \frac{[Y]}{Kmp_{(V2)}}} \right)$$

Kinetic description

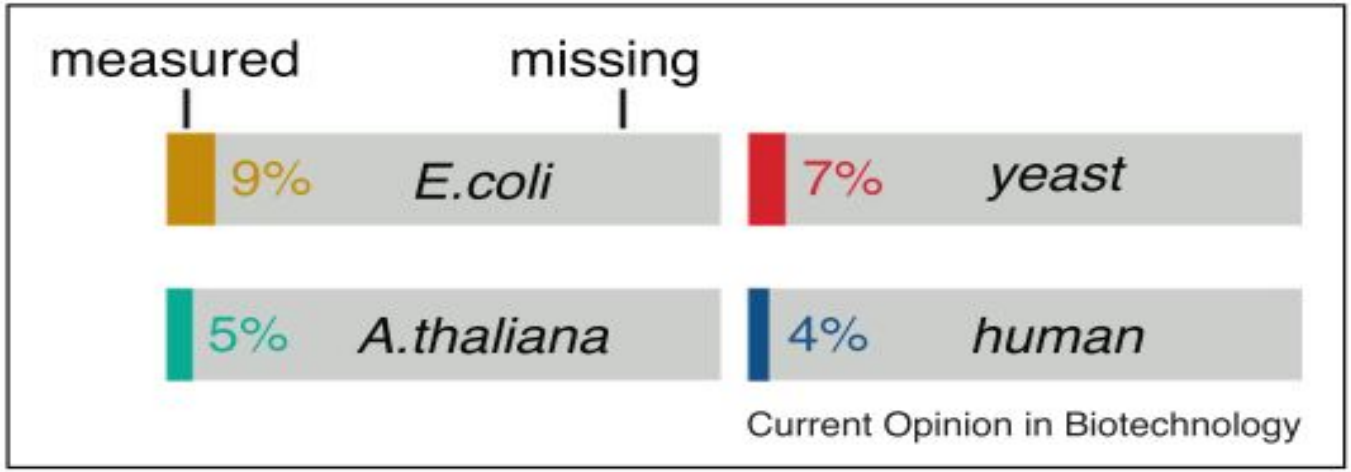




Many parameters!

$$\frac{d([S])}{dt} = \left(\frac{\frac{Vf_{(V1)} \cdot [X]}{Kms_{(V1)}} - \frac{Vr_{(V1)} \cdot [S]}{Kmp_{(V1)}}}{1 + \frac{[X]}{Kms_{(V1)}} + \frac{[S]}{Kmp_{(V1)}}} \right) + \left(\frac{\frac{Vf_{(V2)} \cdot [S]}{Kms_{(V2)}} - \frac{Vr_{(V2)} \cdot [Y]}{Kmp_{(V2)}}}{1 + \frac{[S]}{Kms_{(V2)}} + \frac{[Y]}{Kmp_{(V2)}}} \right)$$

Kinetic constants: the state of the art



Nº of reactions from GEMs:

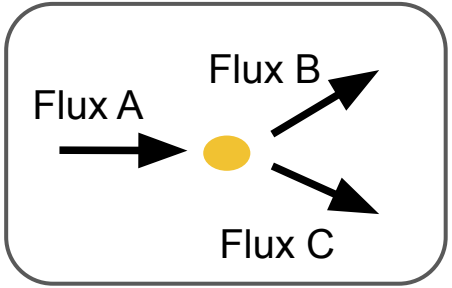
- *E. coli* (*i*JO1266): 2251
- Budding yeast (*i*ND750): 1149
- Arabidopsis (--): 1363
- Human (Recon1): 7785

Davidi, Dan and Ron Milo. 2017. Curr. Op Biotech

Modeling cellular metabolism

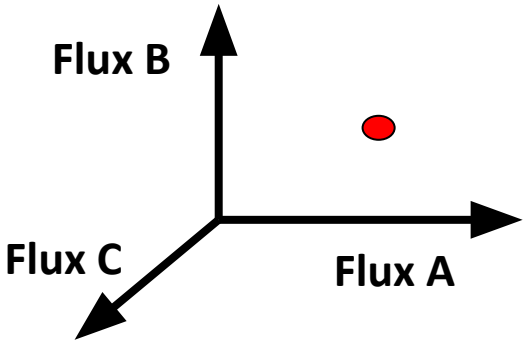
Teoría (kinetic modeling)

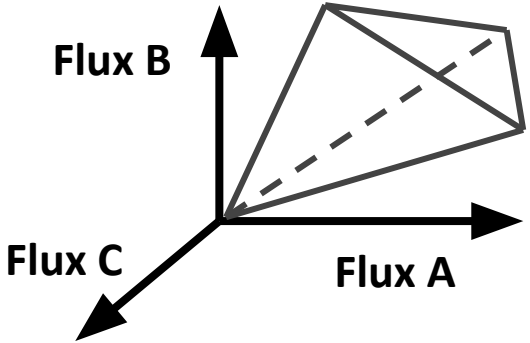
- Complete description (all)
- Solution is a unique point



Constraint-based modeling

- Incomplete Information
- Solution space

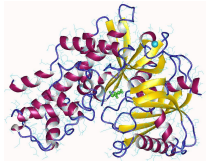




At genome-scale there are no detailed kinetic descriptions → many reaction (unknown mechanisms and thousands of parameters)!

Constraint-Based Modeling

Glucose + ATP



Glucose-6-P + ADP

Glucokinase (single reaction)

Glucokinase

Glucose	-1	
ATP	-1	
G-6-P	+1	
ADP	+1	

$\rightarrow N$

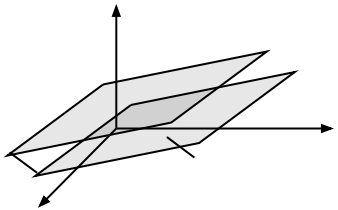
Stoichiometric matrix N (metabolic network)

The Constraints

"... All cellular activity is constrained by mass transfer ..."

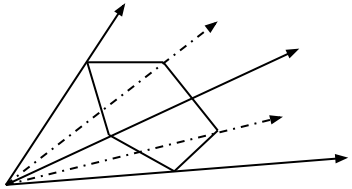
Mass Balance

$N \cdot v = 0$



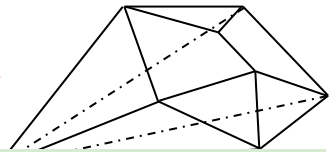
Thermodynamics

$v_i > 0$



Enzyme Capacities

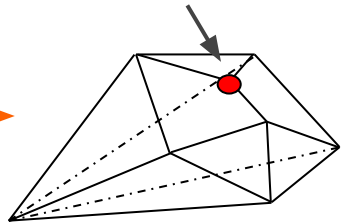
$v_i < v_{max}$



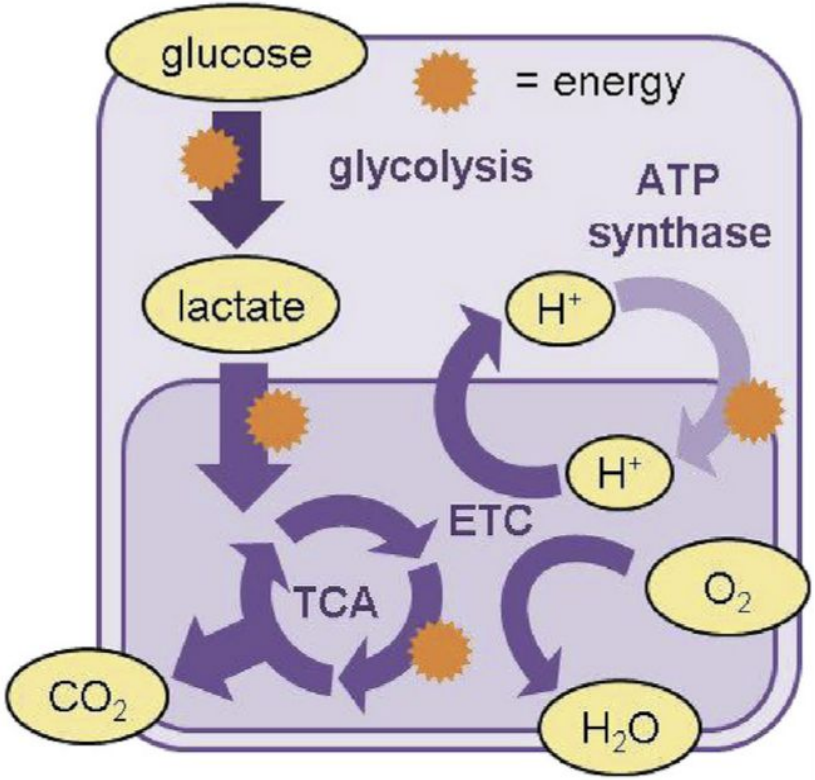
Flux Space

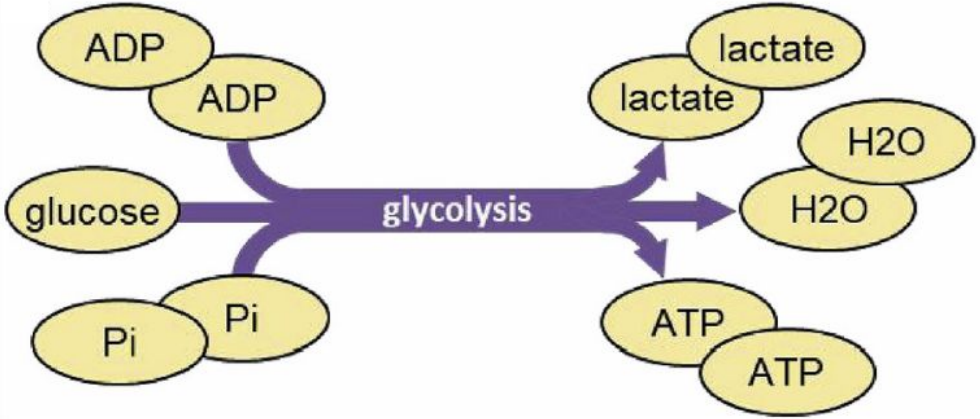
Cell Objective

$Max \;\; c^T \cdot v$



Constraint-Based Modeling: example



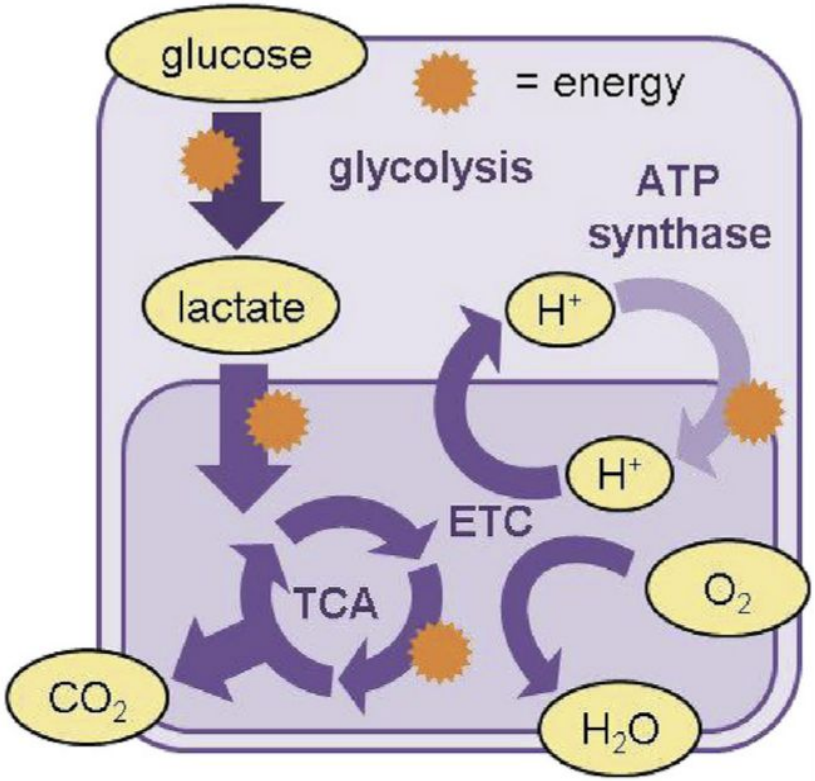


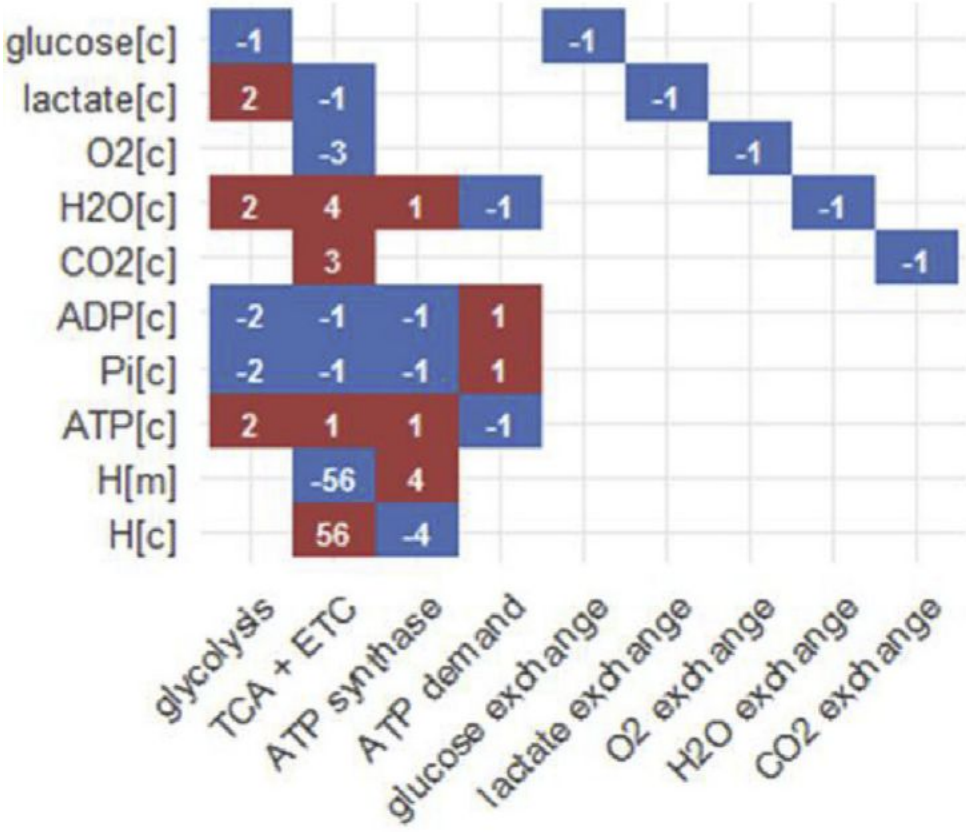
Metabolite	Abbreviation	Coefficient
Adenosine diphosphate	ADP	-2
Phosphate	Pi	-2
Glucose	Glucose	-1
Lactate	Lactate	2
Water	H20	2
Adenosine triphosphate	ATP	2

Rawls *et al.*, 2019

(Rawls *et al.*, 2019)

Constraint-Based Modeling: example





Rawls *et al.*, 2019

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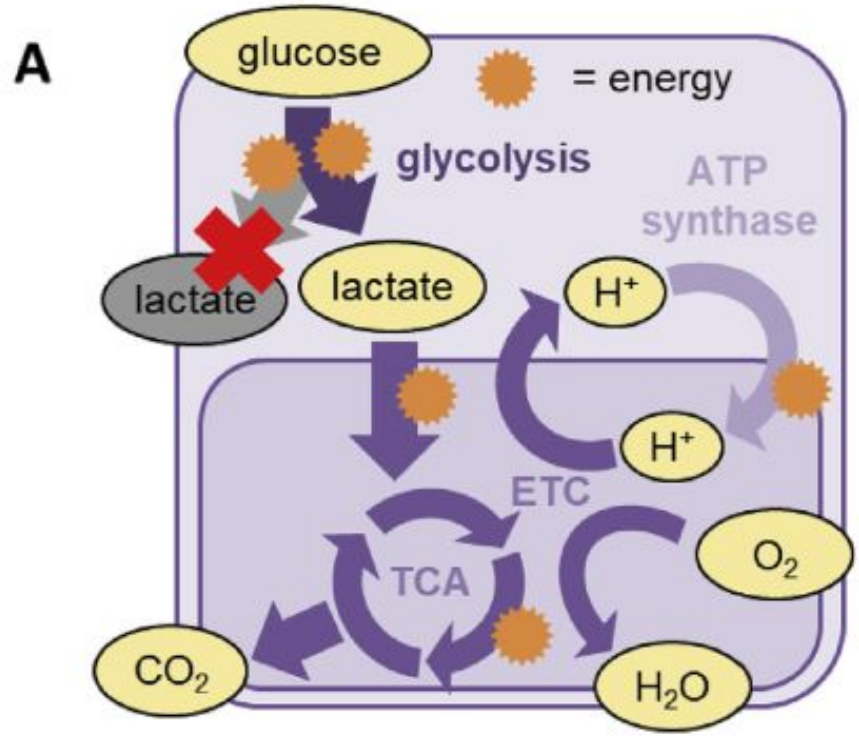
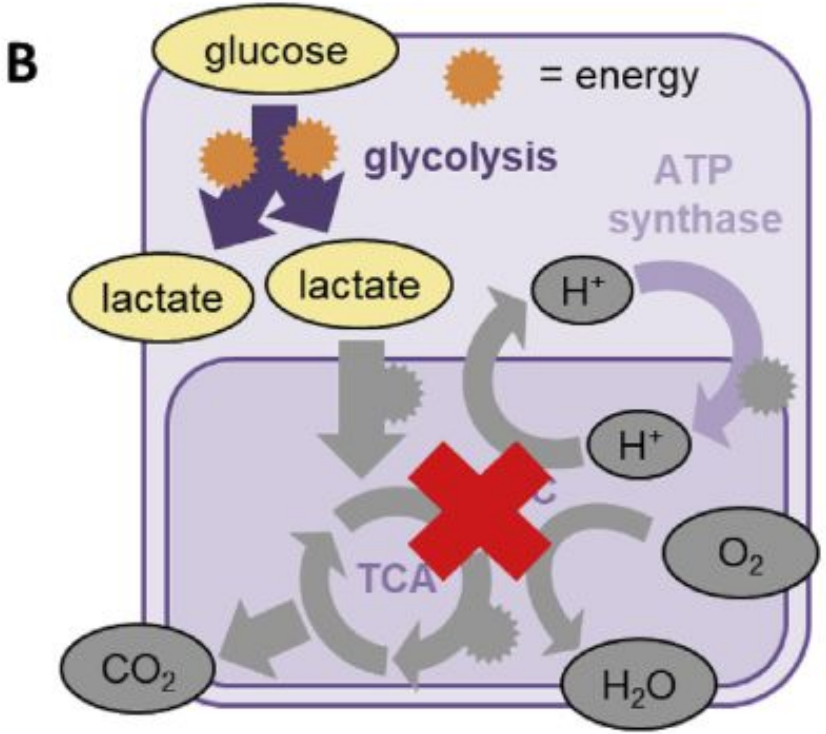


Aerobic condition
ATP rate = 32/Glc/t



Anaerobic condition
ATP rate = 2/Glc/t

Rawls *et al.*, 2019

Extending the growth model to consider metabolism

Connecting metabolic variables to the agent and the environment

Metabolic model

- Stoichiometric matrix
- Context (GPRs + expression)
- Biomass equation

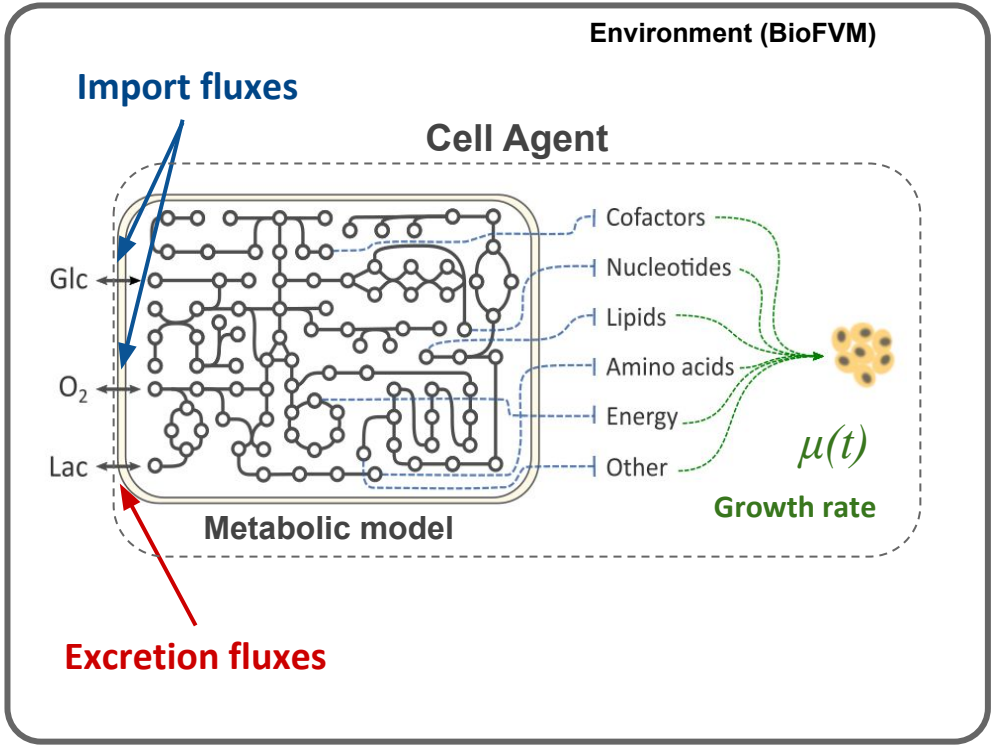
Simulation

- Dynamic Flux Balance Analysis

Metabolic phenotype

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

Interface with the ABM



Integrating cell metabolism: modeling considerations

1. Find bounds for the exchange fluxes

$$l = \frac{v_{max} \cdot [C_{i,j}]}{K_M + [C_{i,j}]}$$

2. Set bounds and solve dFBA

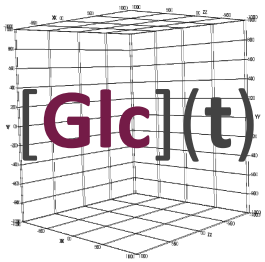
$$\begin{aligned} &\text{Maximize} && c^T v \\ &\text{Subject to} && S \cdot v = 0 \\ & && l \le v \le u \end{aligned}$$

$$\boldsymbol{\mu} := \boldsymbol{v}_{biomass}$$

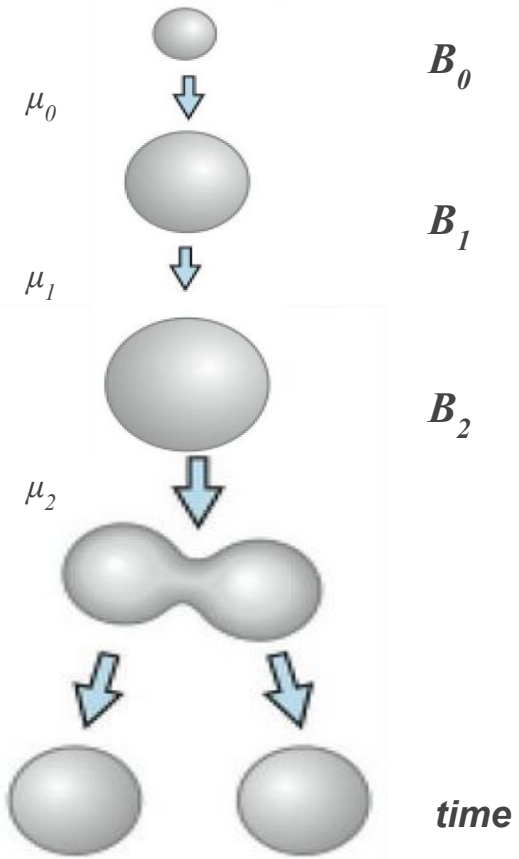
$$v_i \quad \forall i \in J_{Exchanges}$$

3. Update ABM

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



$$B_{t+1} = B_t \cdot v_{biomass} + B_t$$



PhysiFBA: architecture

Systems Biology Markup Language

Metabolic model parser

Optimization Library

Pluggable Metabolic Module

PhysiCell physics-based cell simulator

Ponce-de-León *et* al. (in preparation)

Special Thanks To

EXCELENCIA SEVERO OCHOA

Computational Biology Group (BSC)
- Arnau Montagud
- Davide Cirillo

Centre de la Regulación Genómica (CRG)
- Michelle Monti

Indiana University
- Paul Macklin
- Randy Heiland
- John Metzcar

INFORE Team