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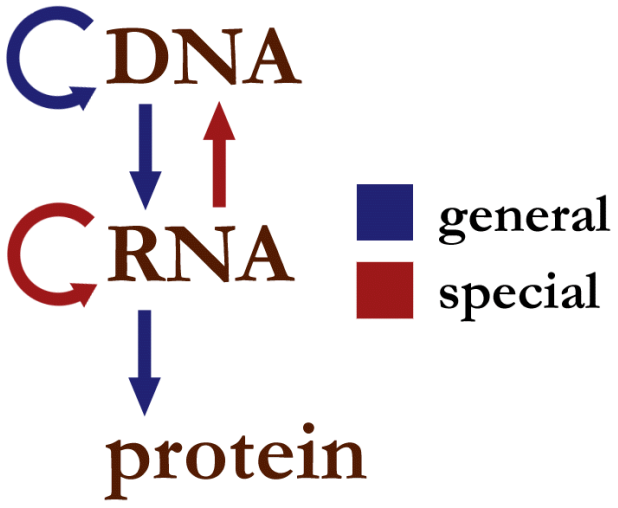
EXCELENCIA SEVERO OCHOA

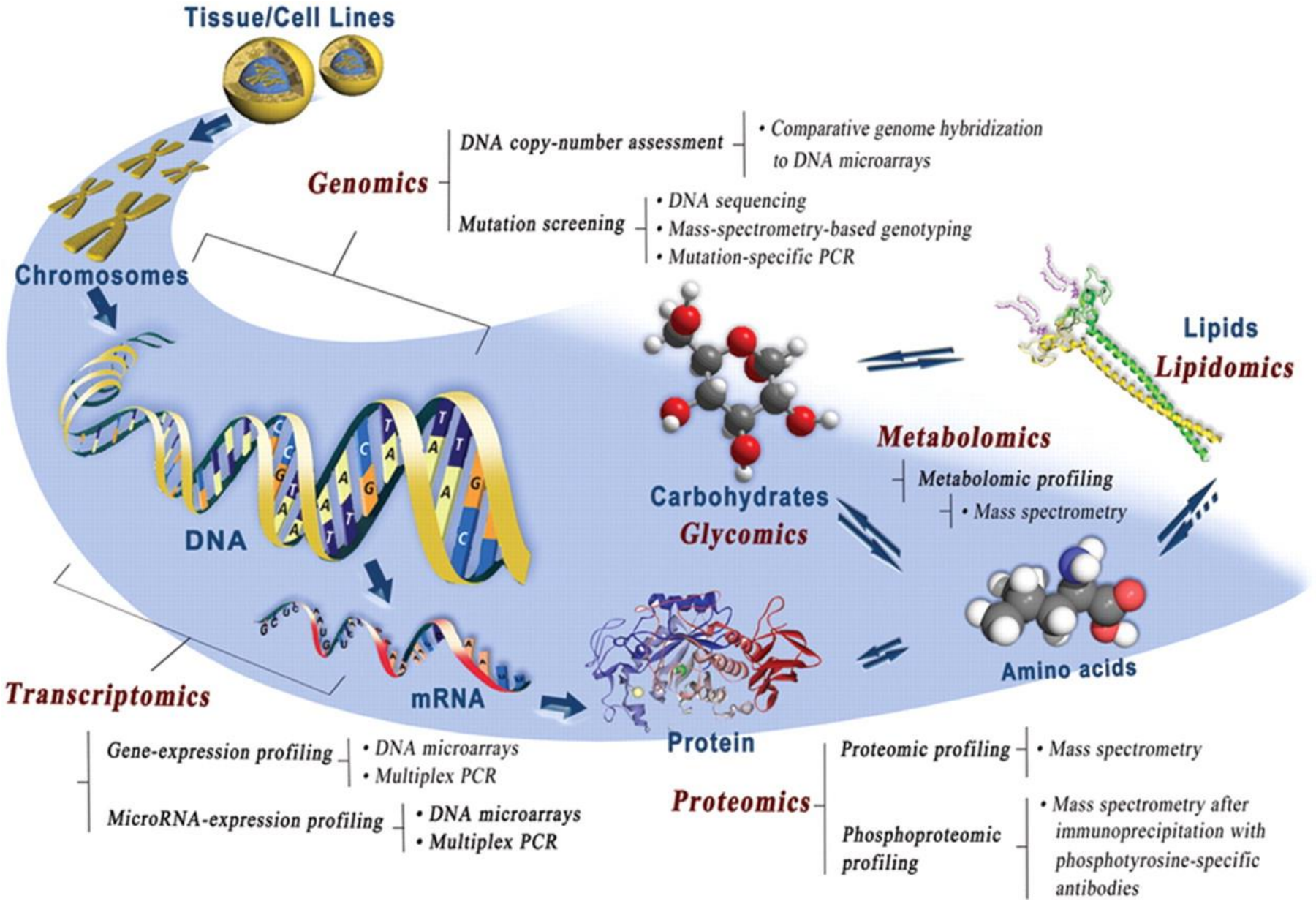
Personalised Medicine Centre of Excellence: how can HPC cell-level simulations help us fight against cancer and COVID

Arnau Montagud
Computational Biology group
Life Science Department

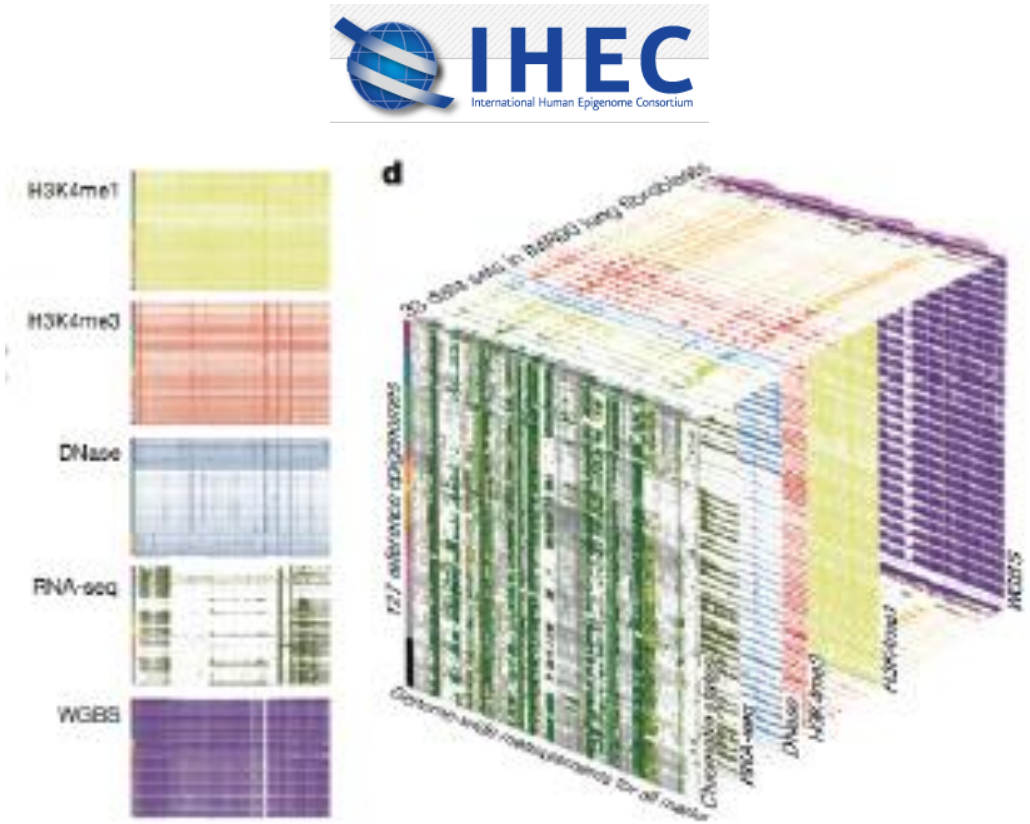
7 October 2019

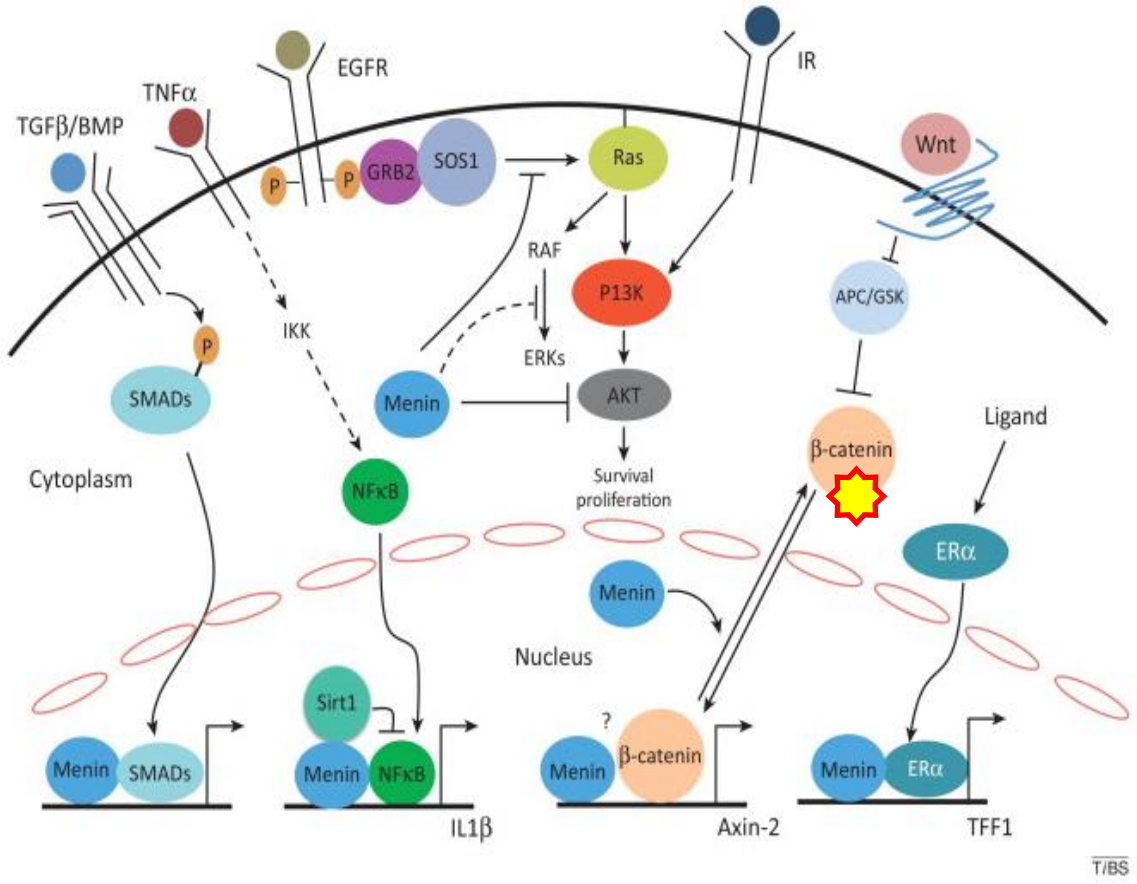
Central Dogma and the omics data





To infer mechanisms from omics data we need networks and models



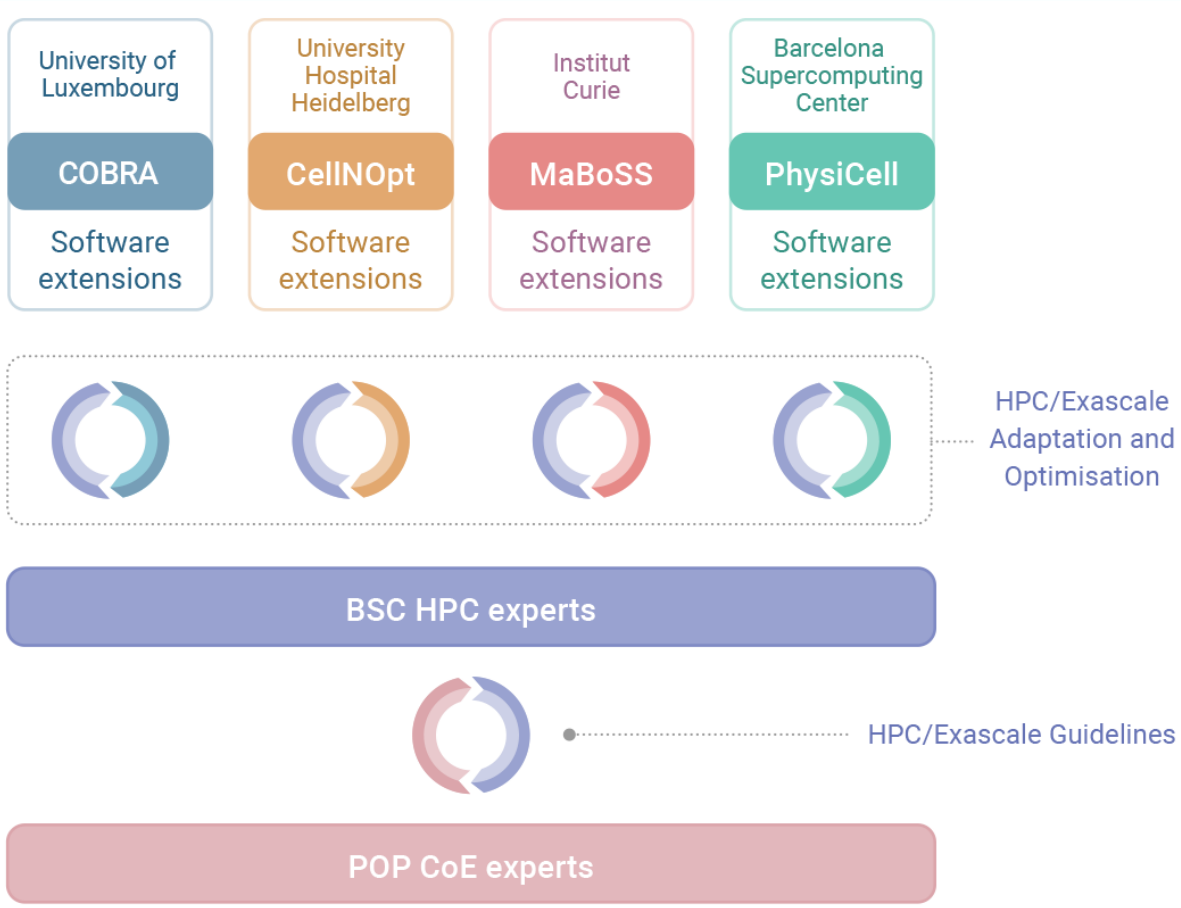


CORE APPLICATIONS

PerMedCoE optimises key software for cell-level simulations to the new preexascale platforms

The PerMedCoE four core applications are:

- **COBRA** for the simulation of cellular metabolism at genome-scale
- **CellNOpt** for modelling signal transduction networks
- **MaBoSS** for stochastic simulations of Boolean models
- **PhysiCell** an agent-based modelling framework for simulating cell-cell interactions

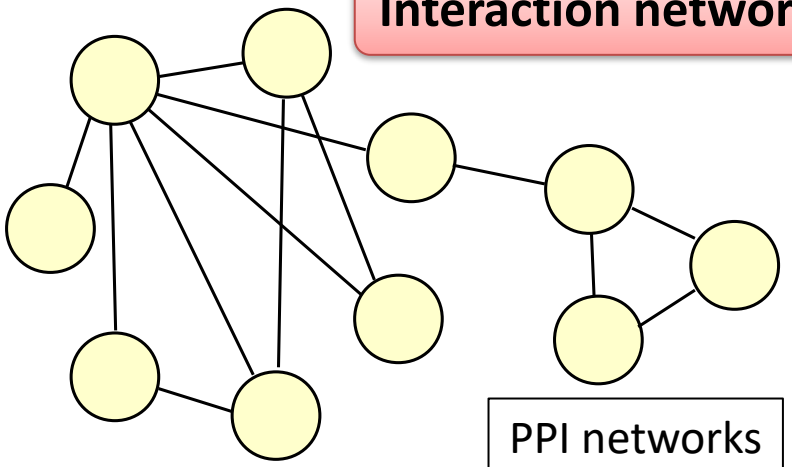


For more information, visit https://permedcoe.eu/core-applications/

Data leads to Structure … and Structure leads to Modelling

Le Novere, Nat Rev Genet. 2015 Mar;16(3):146-58.

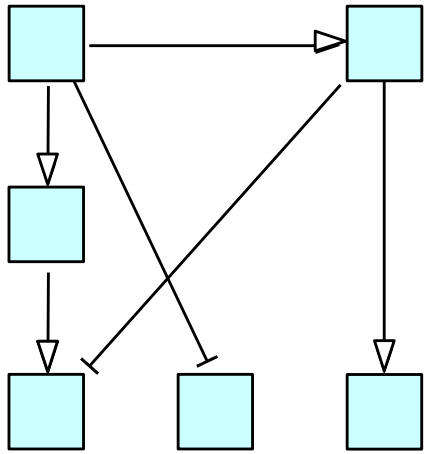
Interaction networks



PPI networks

Statistical modelling

Activity flows



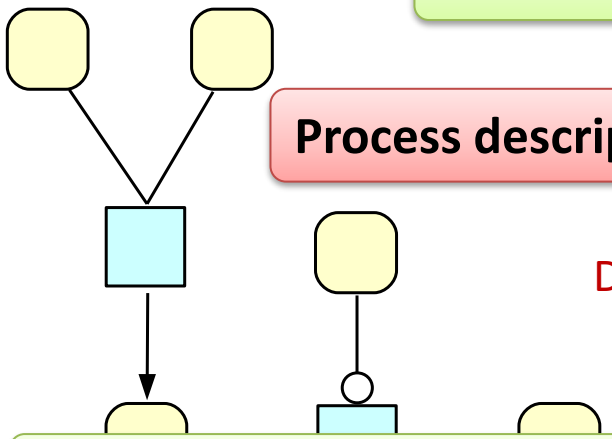
MaBoSS

CellNOpt

Signalling pathways, gene regulatory networks

Logical modelling

Process descriptions



PhysiCell

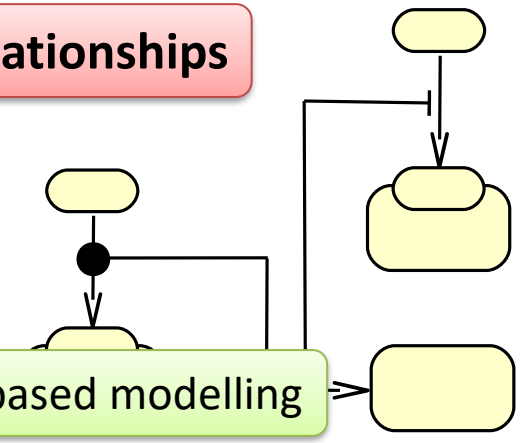
COBRA

Process modelling (FBA, ODEs, etc.)

Metabolic networks, reaction networks

Different biological knowledge ↔
different types of networks ↔
different types of modelling

Entity relationships



Rule-based modelling

Molecular interactions, reaction networks

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Slide from L. Calzone, Institut Curie

Metabolic modelling

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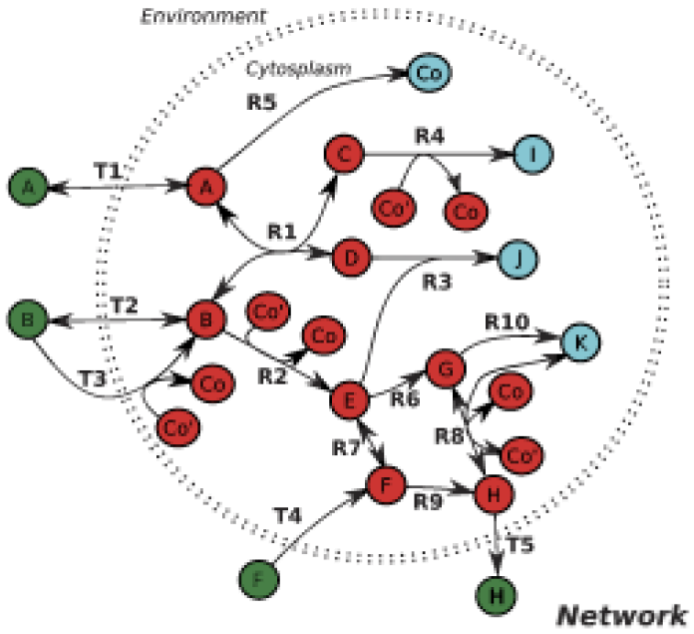
Omics data are used to build metabolic networks and metabolic models

- Network reconstruction
  - From the list of genes in the genome
- Flux balance analysis
  - Provides information on reactions' fluxes
  - Used to study cell growth and metabolite productivity
- Constraint-based metabolic model



Durot et al. *FEMS microb rev* 2009, **33**:164-90

$$\frac{dX_i}{dt} = S_{ij} \cdot v_j, \qquad \forall i \in M, \forall j \in N$$

		T1	T2	T3	T4	T5	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	Bio	Ass
Balanced	A	1	0	0	0	0	−1	0	0	0	−1	0	0	0	0	0	0	
	B	0	1	1	0	0	−1	−1	0	0	0	0	0	0	0	0	0	
	C	0	0	0	0	0	1	0	0	−1	0	0	0	0	0	0	0	
	D	0	0	0	0	0	1	0	−1	0	0	0	0	0	0	0	0	
	E	0	0	0	0	0	0	1	−1	0	0	−2	−1	0	0	0	0	
	F	0	0	0	1	0	0	0	0	0	0	0	1	0	−1	0	0	
	G	0	0	0	0	0	0	0	0	0	0	1	0	−1	0	−1	0	
	H	0	0	0	0	−1	0	0	0	0	0	0	0	1	0	0	0	
	I	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	−2	
	J	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	−2	
	K	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	−1	
	Co	0	0	1	0	0	0	1	0	1	2	0	0	−1	0	0	−1	
	Co'	0	0	−1	0	0	0	−1	0	−1	0	0	0	1	0	0	0	
Non balanced	Aext	−1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Bext	0	−1	−1	0	0	0	0	0	0	0	0	0	0	0	0	0	
	Fext	0	0	0	−1	0	0	0	0	0	0	0	0	0	0	0	0	
	Hext	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	
	Biomass	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	

Stoichiometric matrix

$$n > m$$

$$\sum_{i=1}^{M} \sum_{j=1}^{N} S_{ij} \cdot v_j = 0$$

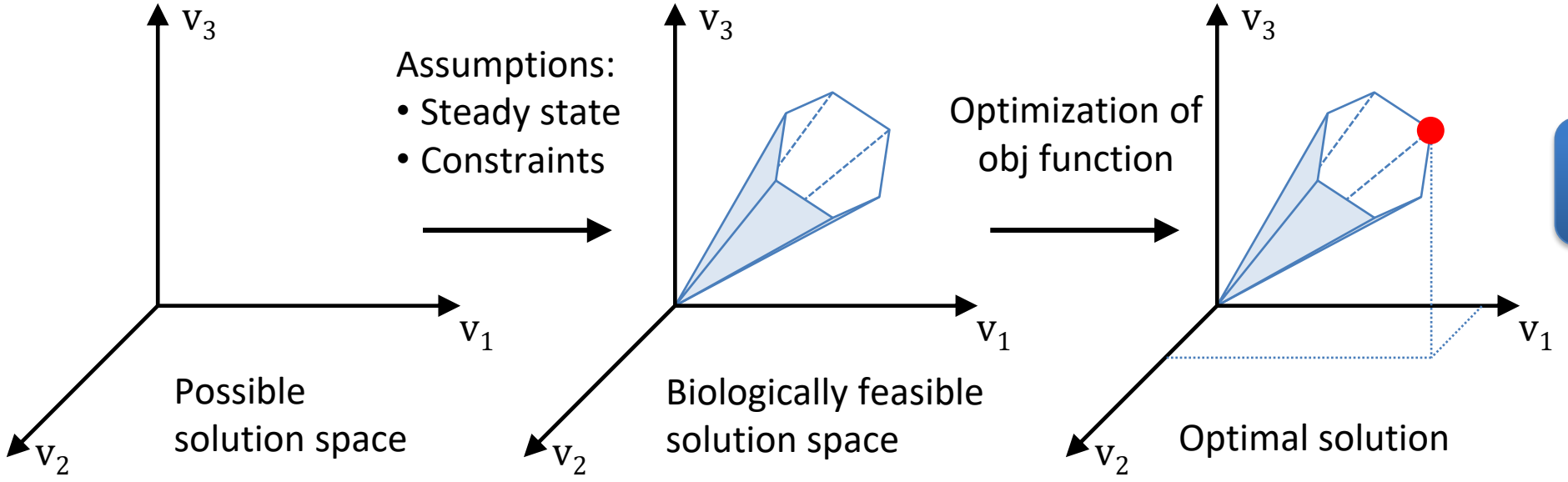
1. Consider steady state

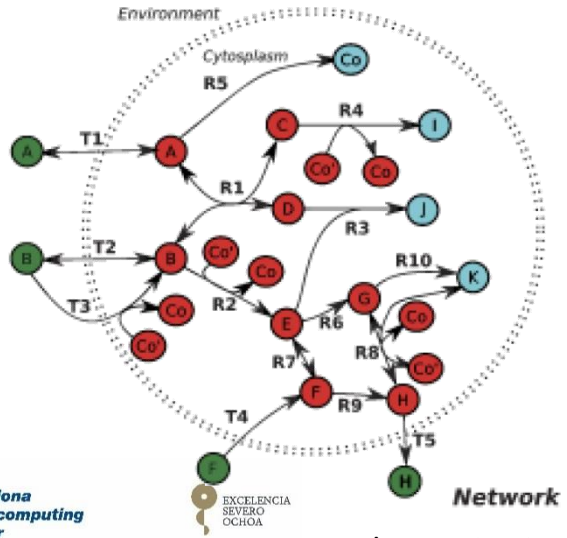
   Time (cell growth) >> Time (metabolic reactions)

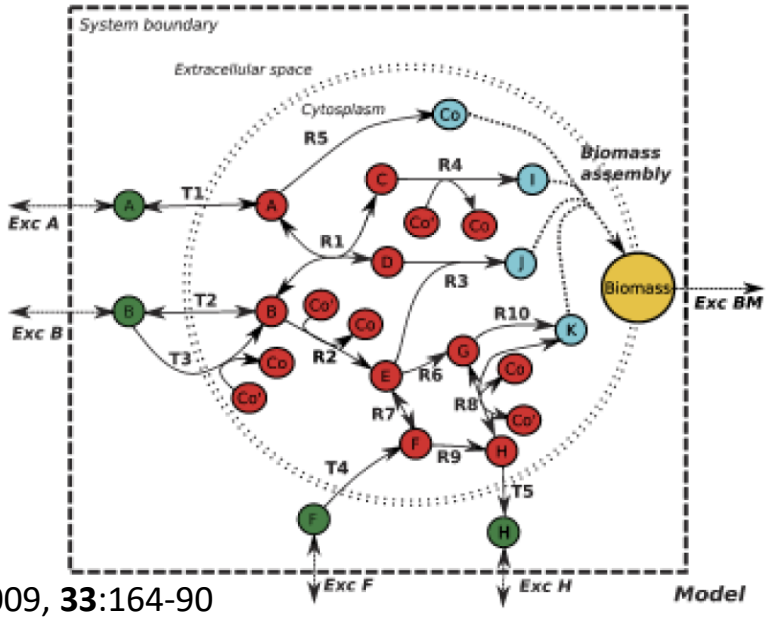
2. Impose constraints

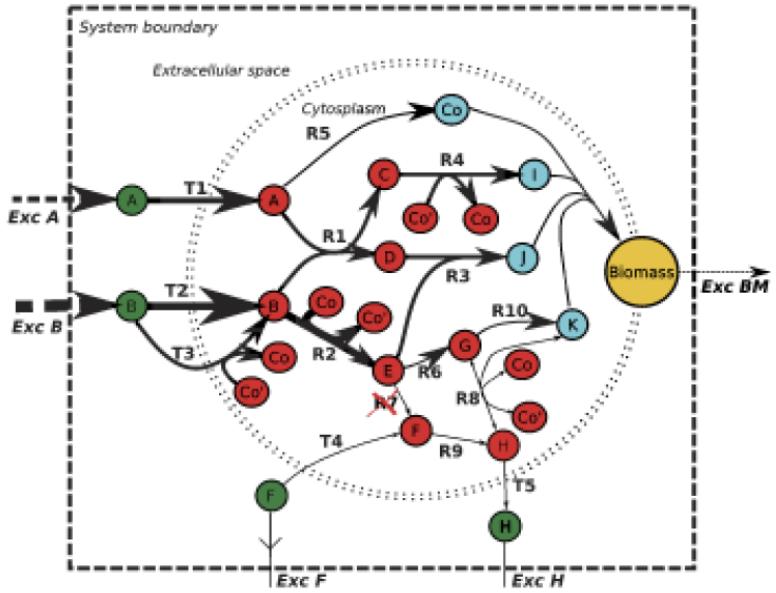
Stephanopoulos et al. (1998). San Diego: Academic Press

Flux Balance Analysis explained graphically









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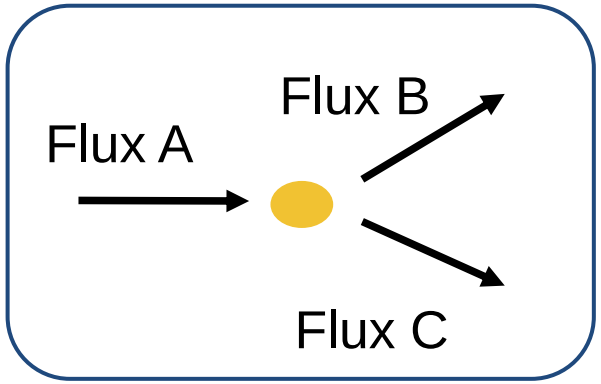
Durot et al. *FEMS microb rev* 2009, **33**:164-90

Alternatives to modelling cellular metabolism

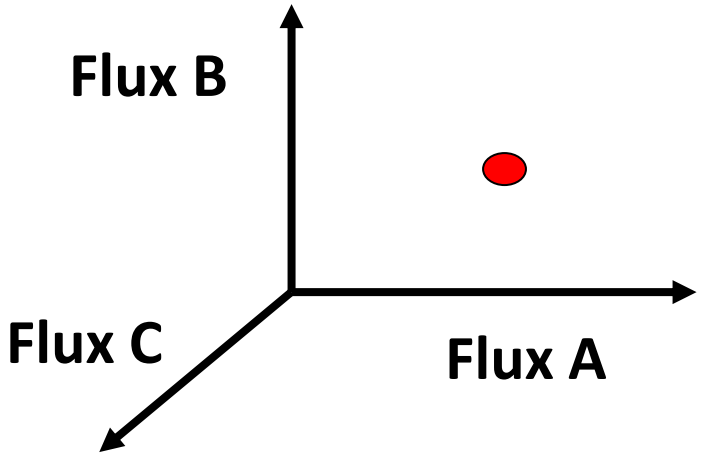
Kinetic modelling

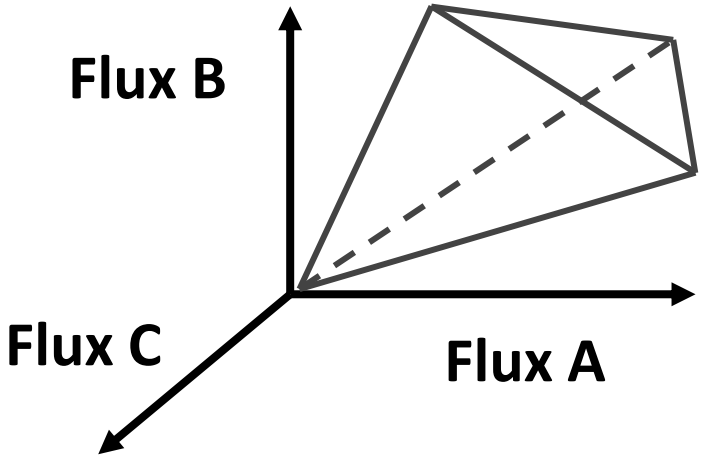
- Complete description
- Solution is a unique point



Constraint-based modelling

- Incomplete Information
- Solution space

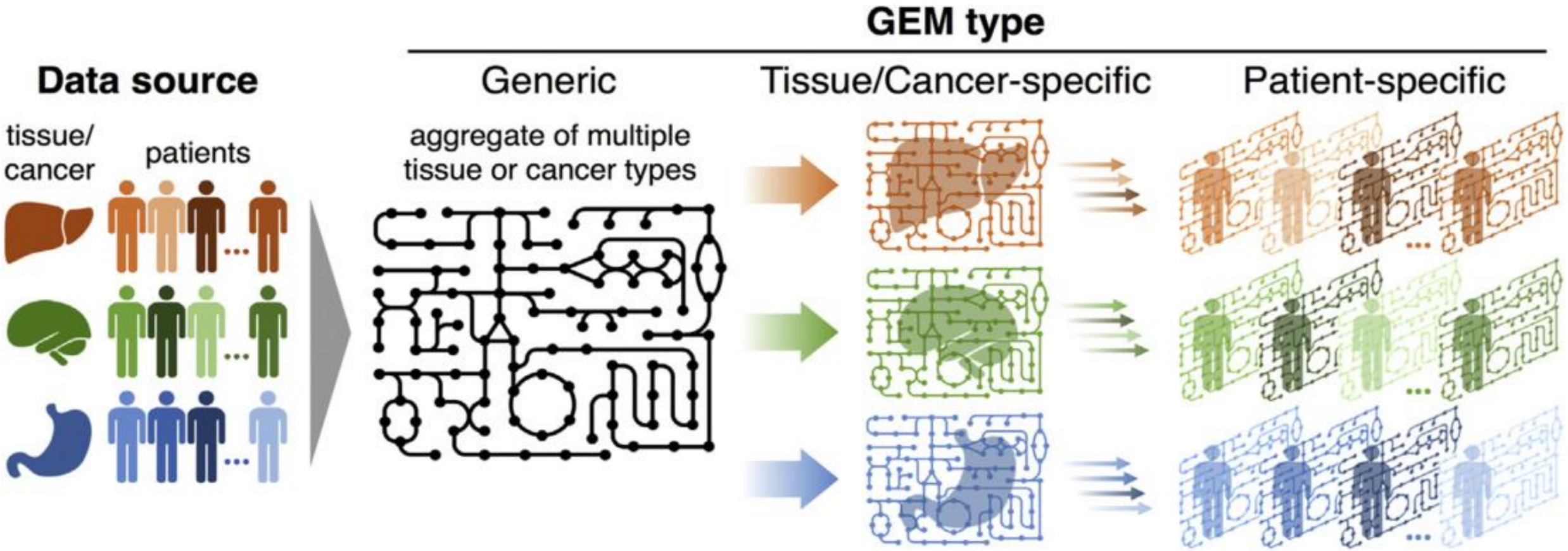




At genome-scale there are no detailed kinetic descriptions → many reactions have unknown mechanisms and parameters!

Slide from M. Ponce de L, BSC

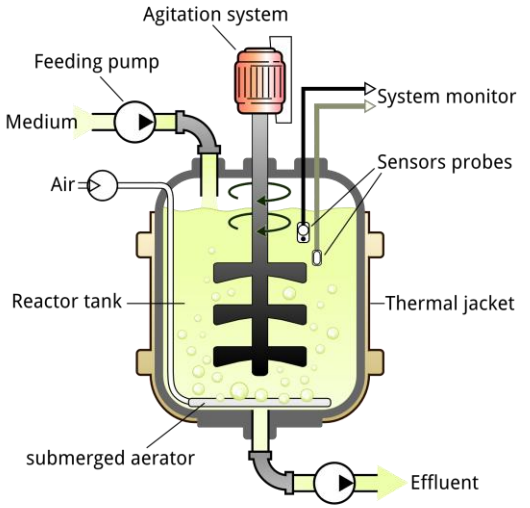
Context-specific metabolic modelling



Slide from M. Ponce de L, BSC

Constraint-based modelling applications in biomedicine

- Production of by-products
  - Antibiotics
  - Flavoured synthetic milk
- Data integration
- Cell maximal growth rate
- Single gene knockout
- Double gene knockout
  - Synthetic lethality
- Essential media components
  - Amino acids
  - Vitamins
- Biomarkers
- Combinatorial therapy
  - Diet restriction + drugs that target a given signalling pathway



If you want more information

https://opencobra.github.io/cobrapy/

- COnstraint-Based Reconstruction and Analysis
  - Matlab, Python, Julia
- Practical course "Constraint-based modelling: a primer on basics and examples"
  - https://github.com/ArnauMontagud/cobra_cbm_tutorial
  - Jupyter notebook
  - Adapted from Miguel de Ponce León

Logical modelling

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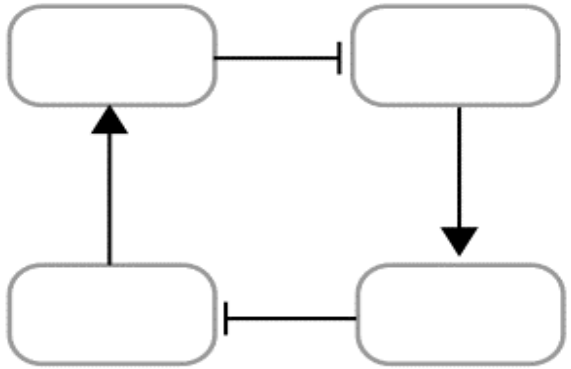
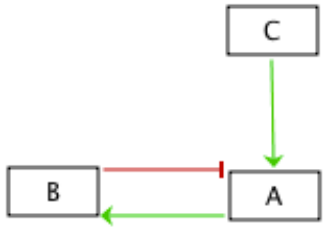
Logical formalism



- The questions are qualitative
- The data are discrete (mutations, copy number, etc.)
- Expression data are not absolute values
- No information over time
- No details about the precise biochemical reactions

Translation of an influence network into Boolean logic

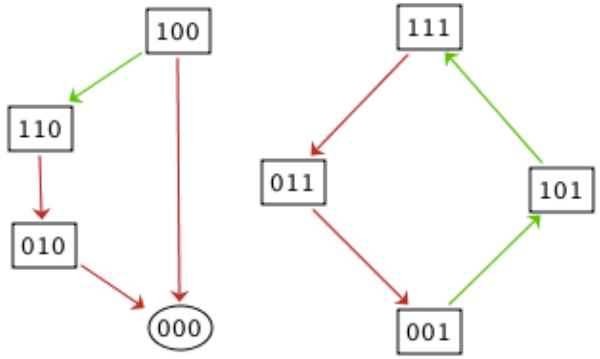
Regulatory graph



Logical rules

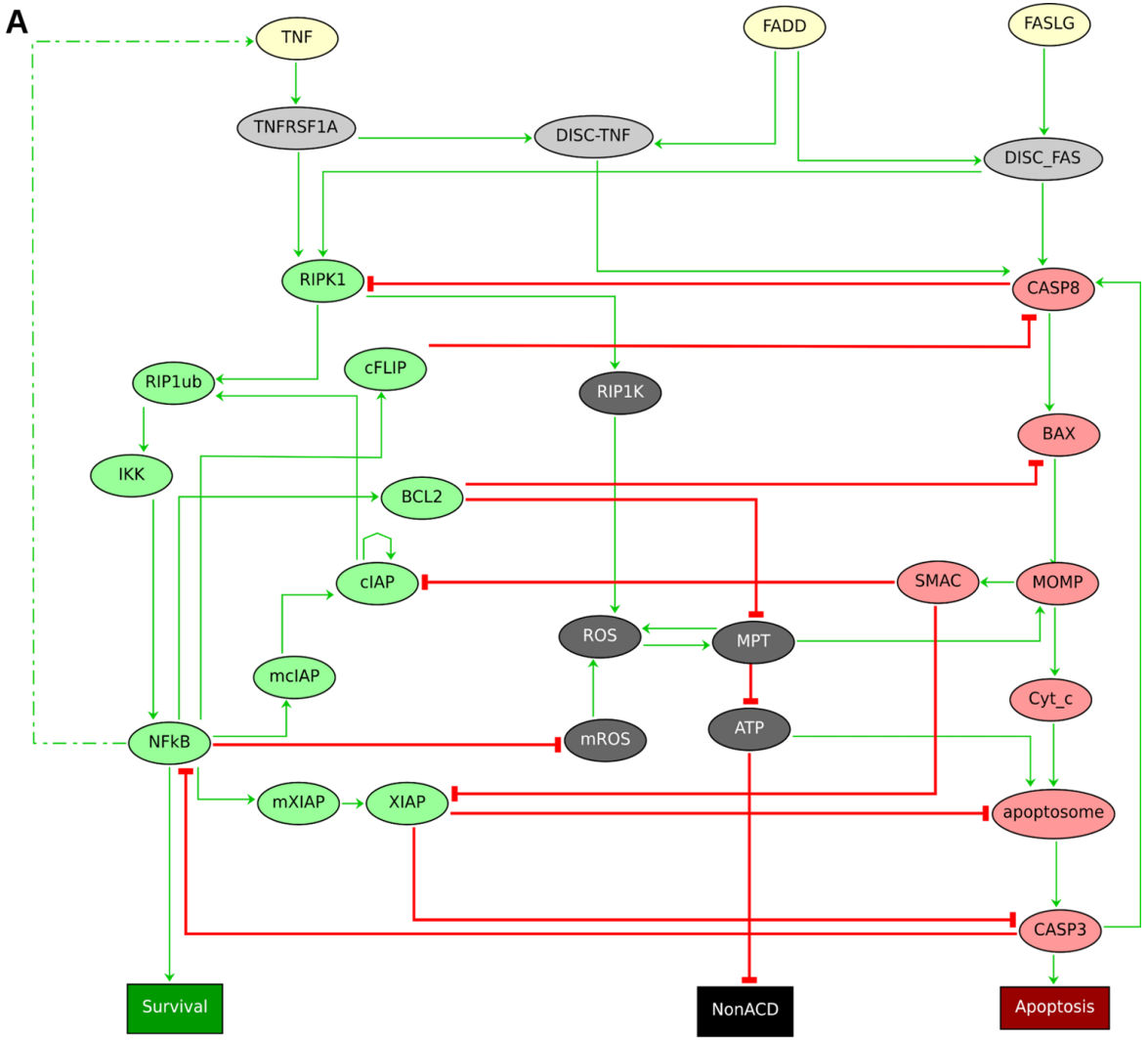
A = !B & C
B = A
C = input

Solutions



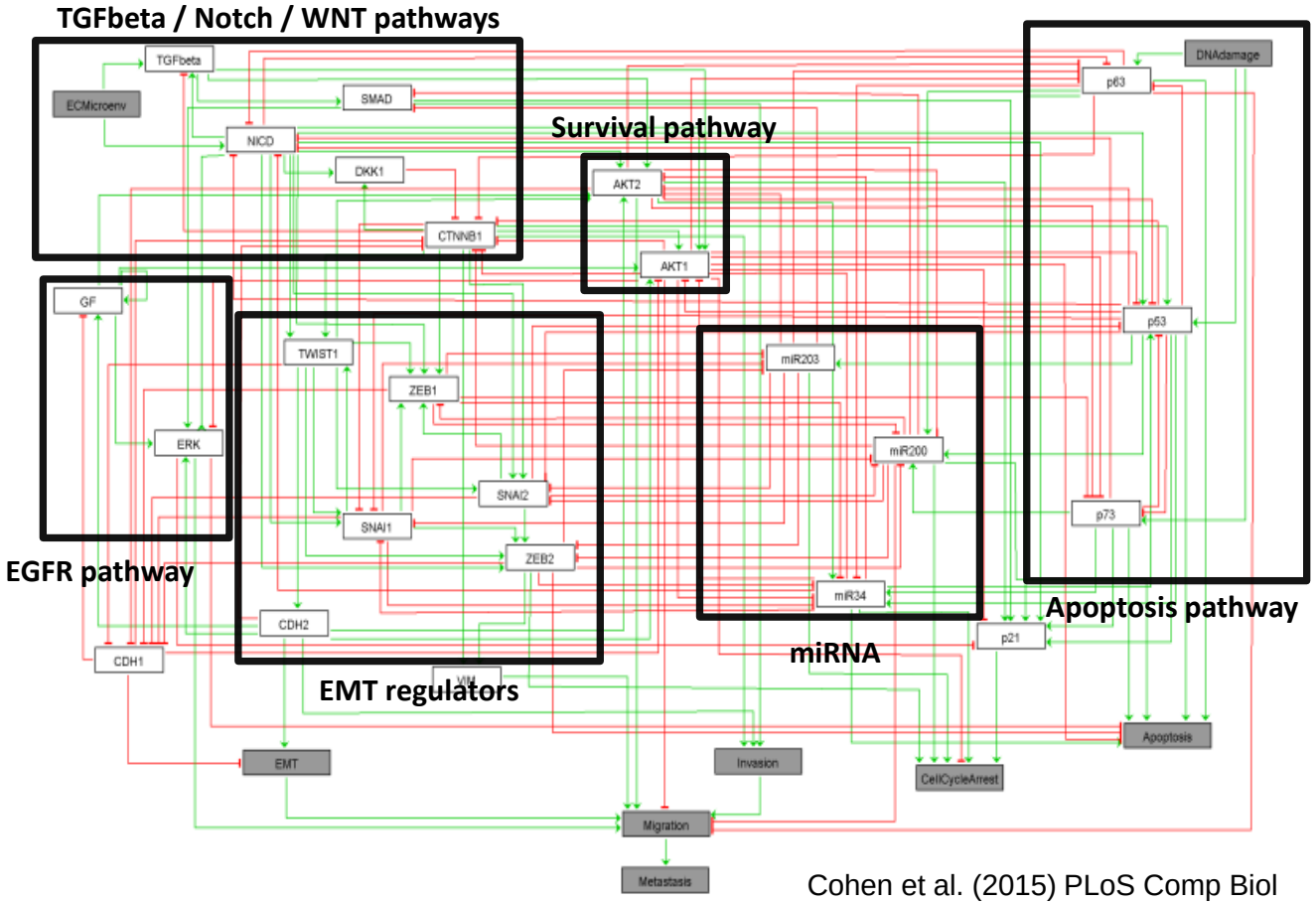
- Each variable can take two states: 0 or 1
- Boolean logic:
  - Connectors: AND (&), OR (|), NOT (!), XOR (/)
  - Logic depends on incoming arrows
- Set of discrete variables as abstractions of activity level linked by logical rules as signed interactions
- Attractors are subgraphs of the state transition graph with no outgoing arrows: can be stable states & cyclic attractors
- Stable states = cell fates = phenotypes
- Updating dynamics can be
  - synchronous: all variables that can be updated are updated
  - asynchronous: only one variable is updated at a time

Two examples of models: TNF response and cell fates and Metastasis model



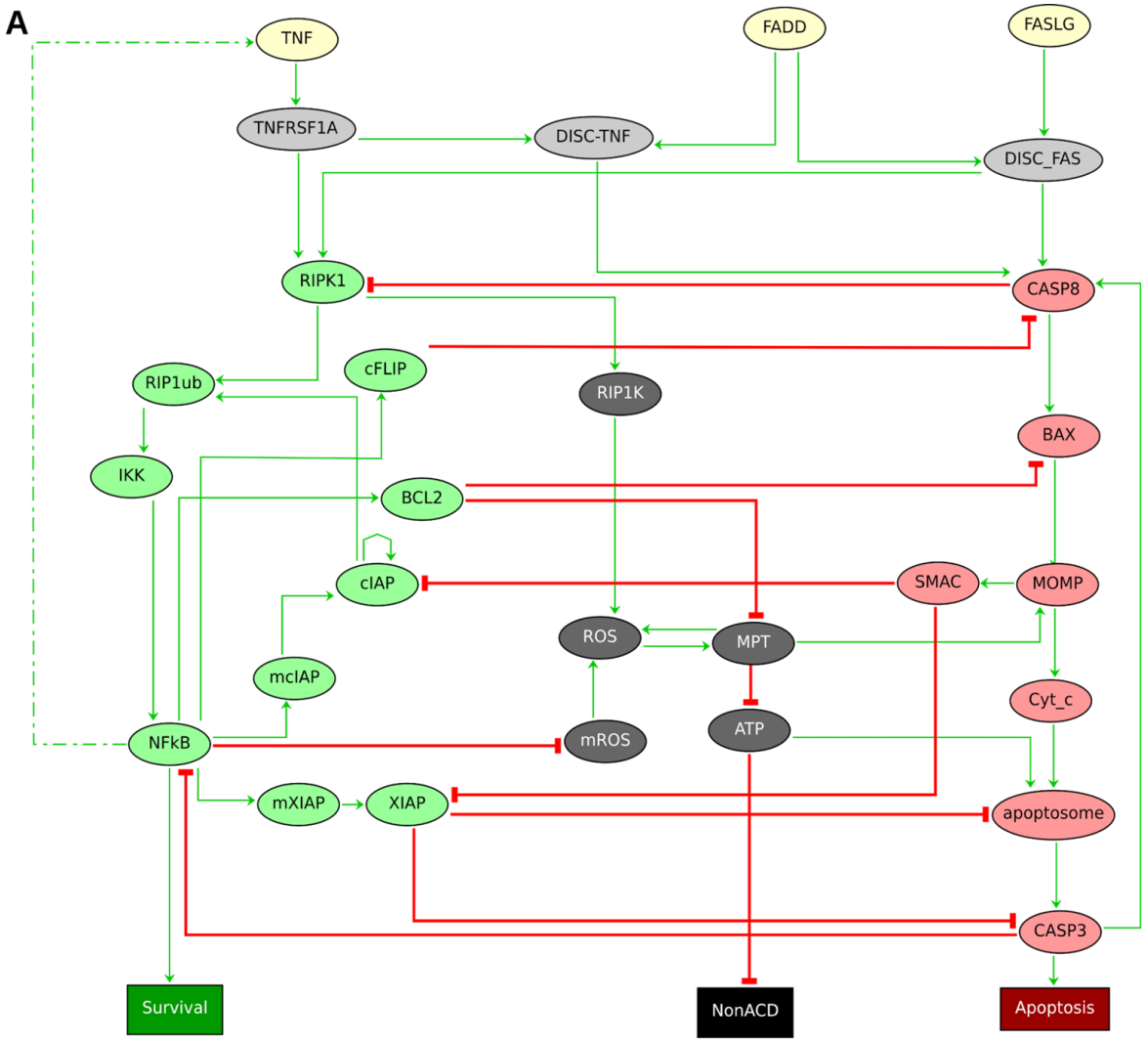
Letort et al., *Bioinformatics*, 2018, bty766

- Convenient way to model regulatory and signalling networks
  - Allows integration of literature & heterogeneous data
  - Provides qualitative analysis



Cohen et al. (2015) PLoS Comp Biol

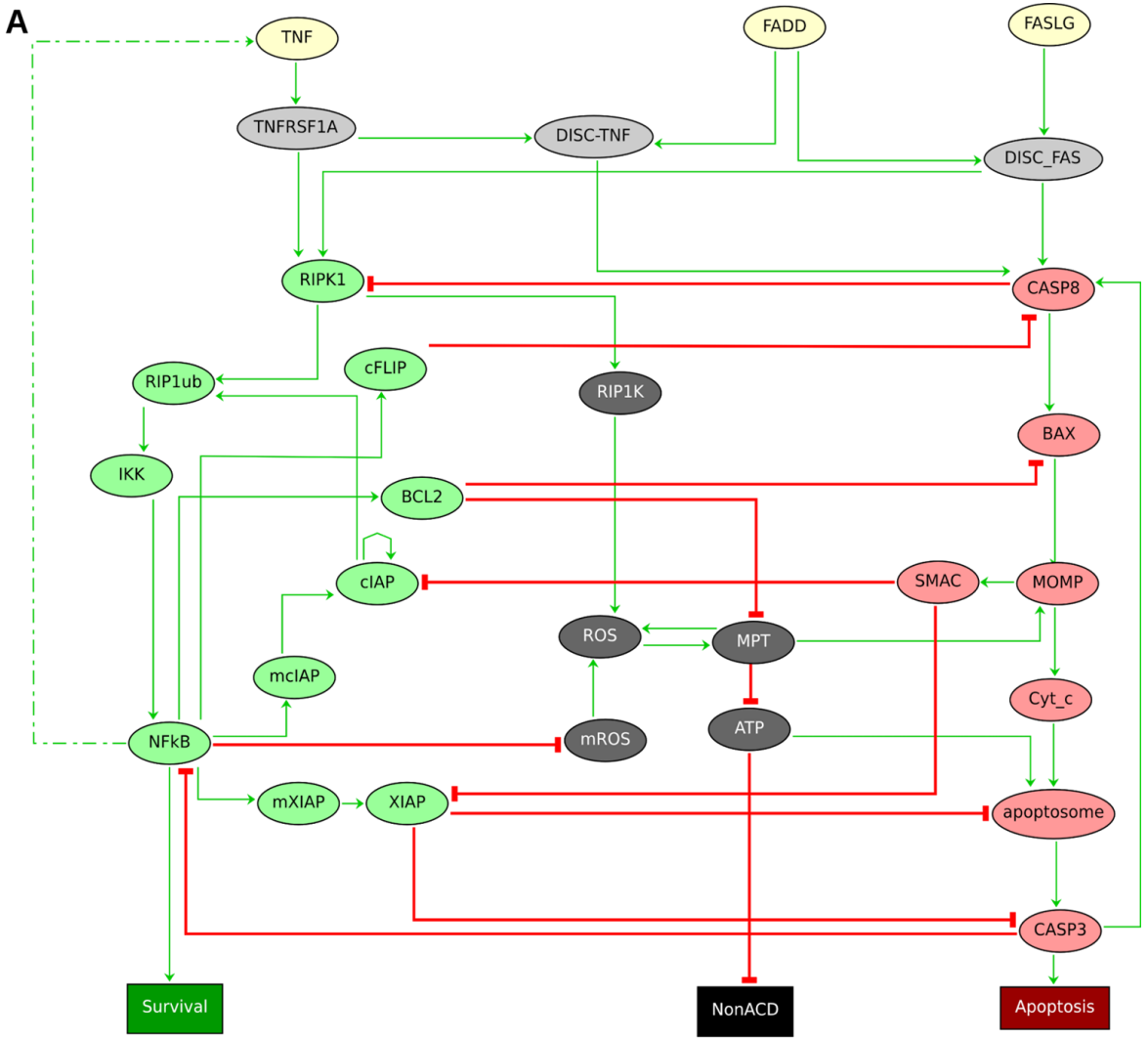
What insights can we get from the mathematical model



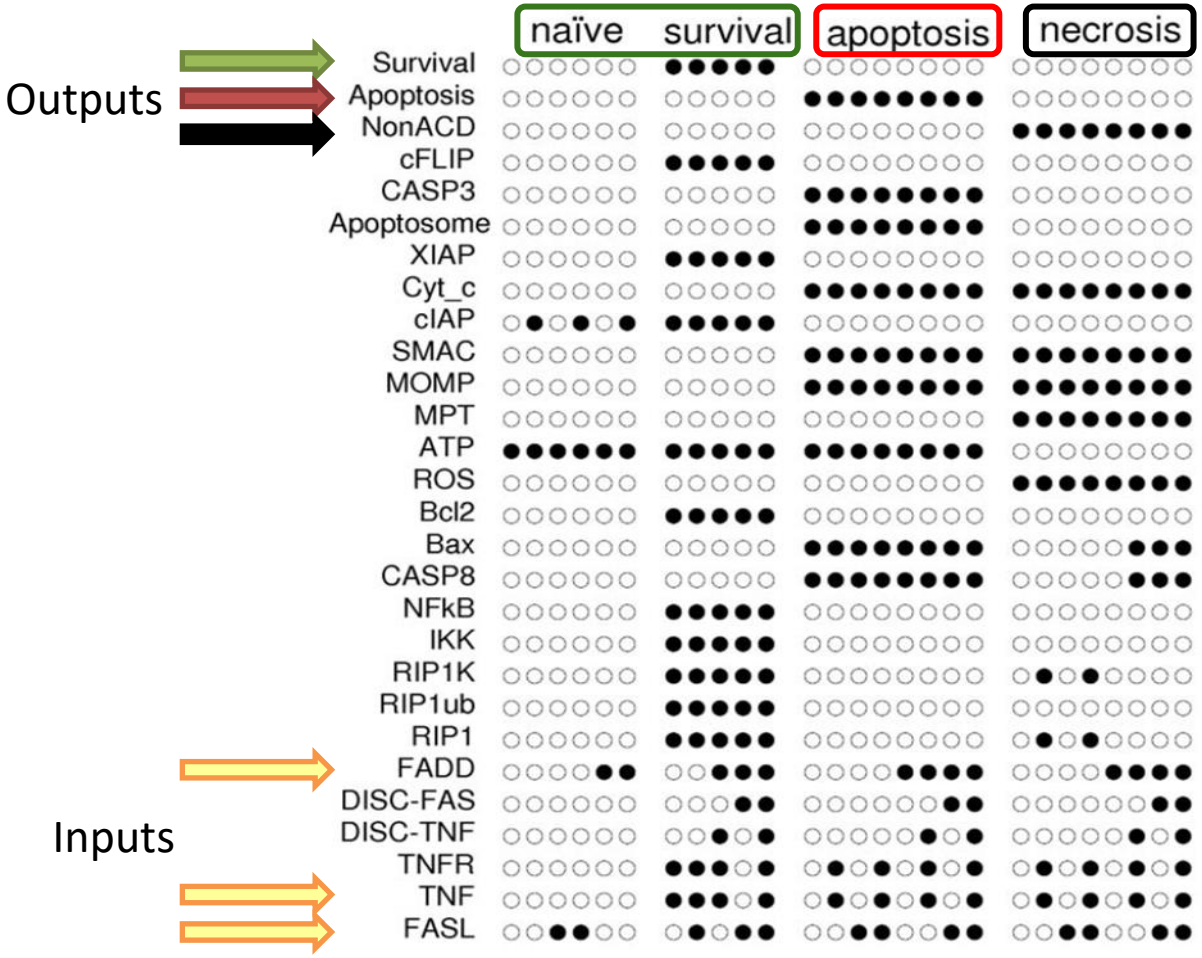
Letort et al., *Bioinformatics*, 2018, bty766

- What are the solutions of the model that can be interpreted biologically?
- What are the important nodes of the network?
- How robust/sensitive is the model?
- Can we predict genetic interactions (epistasis, synthetic lethality) from the model?
  - Knock outs & overexpression
- Can we simplify/reduce the model to highlight the most important processes?

TNF response and cell fates



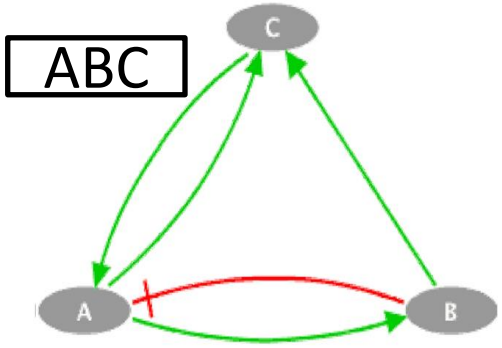
Letort et al., *Bioinformatics*, 2018, bty766



Calzone et al., *PLoS Comput Biol*, 2010, 6(3): e1000702

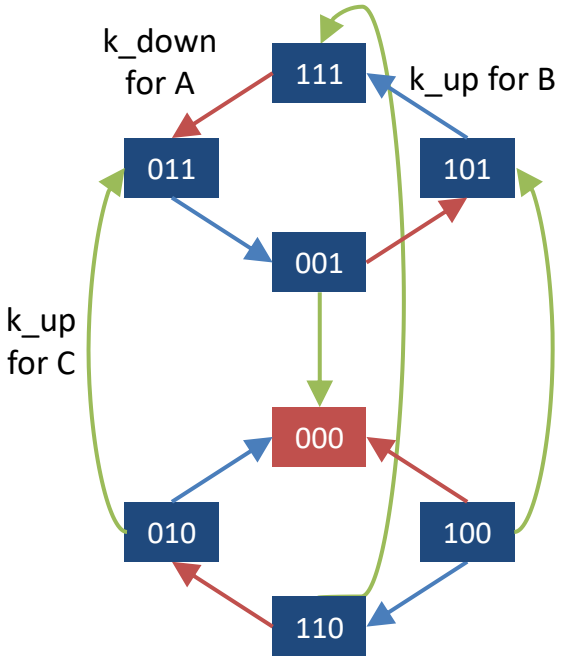
Analysing stable states probabilistically

- Continuous time Markov process on the Boolean transition state space
  - Each Boolean state has an associated probability
  - Rate of change associated to each transition
    - rate up and rate down
  - Stochasticity, time, probabilities, …



- Perturbations can be studied in a probabilistic manner
  - Transient effects, such as knock downs
  - Dosage experiments

Boolean state transition graph



Stoll et al., *BMC Syst Biol*, 2012

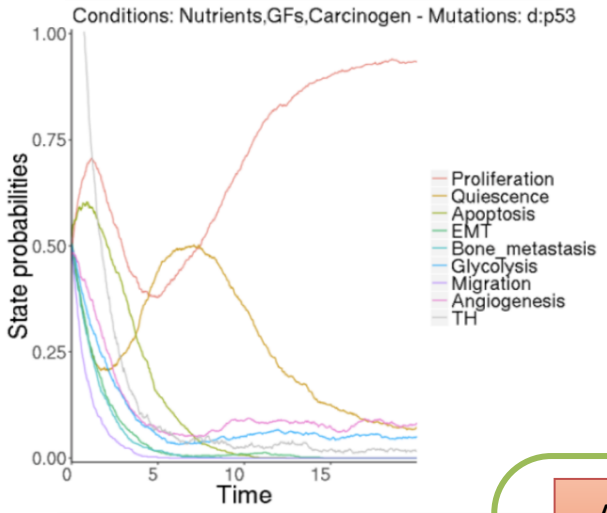
- More information:
  - Stoll et al., *BMC Syst Biol*, 2012, DOI: 10.1186/1752-0509-6-116
  - Stoll et al., *Bioinformatics*, 2017, DOI: 10.1093/bioinformatics/btx123

Stochastic simulations

MaBoSS

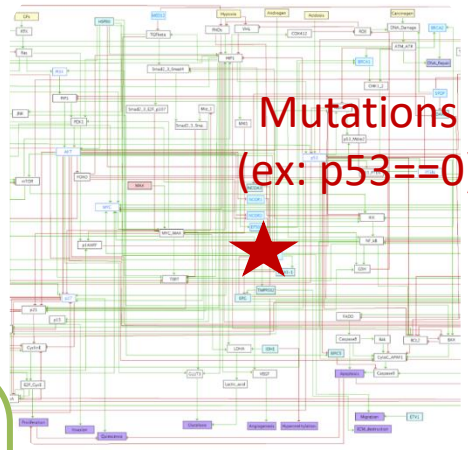
Conditions

Nutrients	Androgen	GFs	Carcinogen	Hypoxia
50%	50%	50%	10%	10%



Stochastic trajectories

Signalling pathways



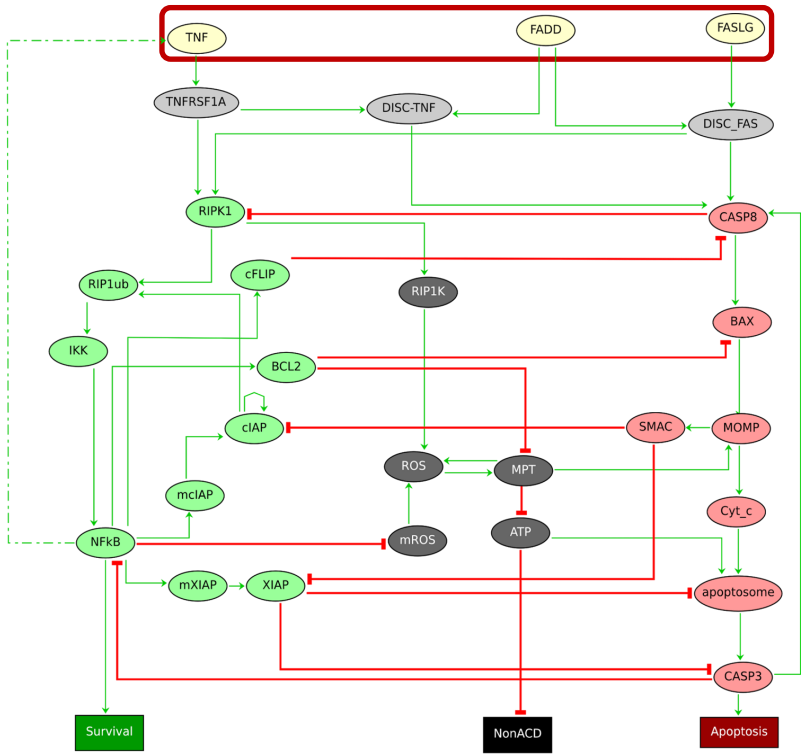
Probabilities based on 1000 trajectories

Apoptosis	10%	Proliferation	23%	Quiescence	67%
EMT	0%	Metastasis	0%	Angiogenesis	10%
DNA repair	5%	Migration	0%		

Stoll et al., 2012, 2017

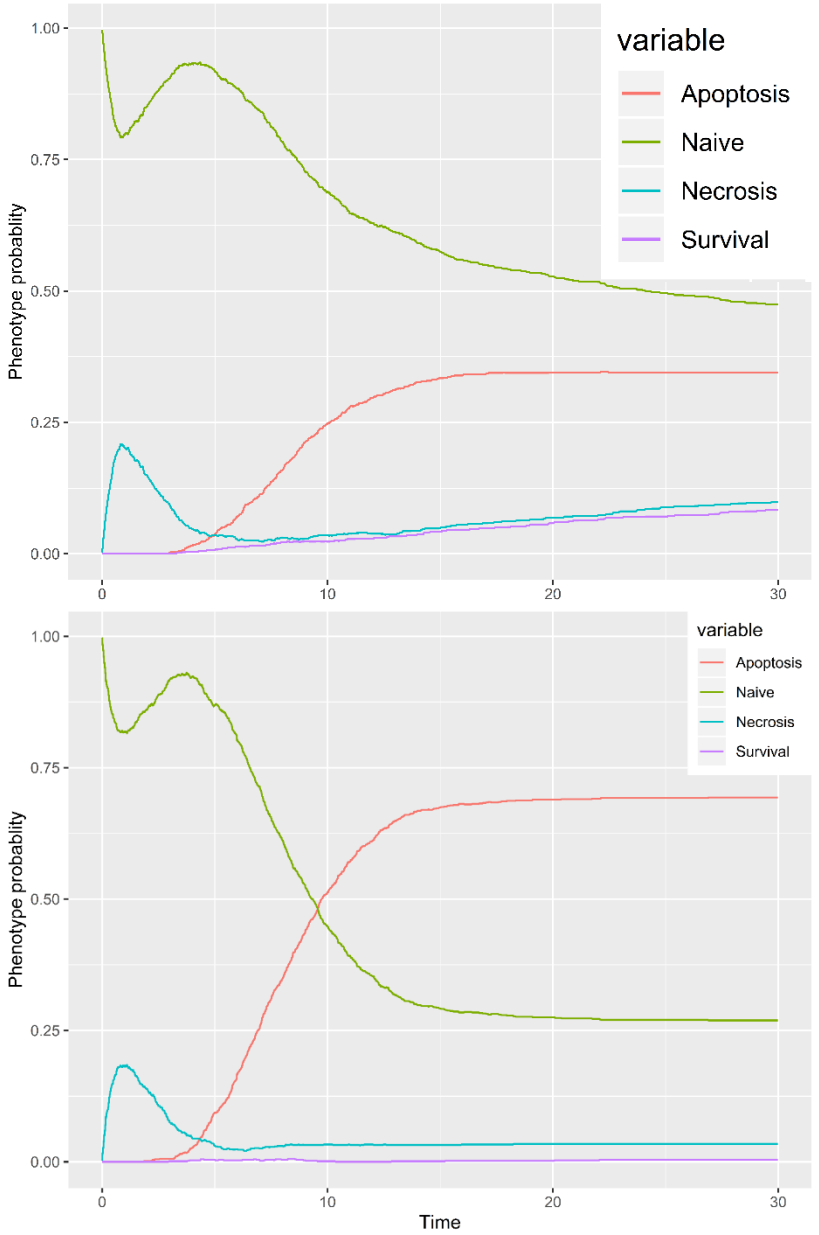
TNF response and cell fates' probabilities

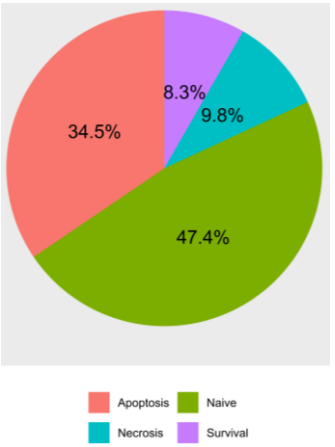
MaBoSS

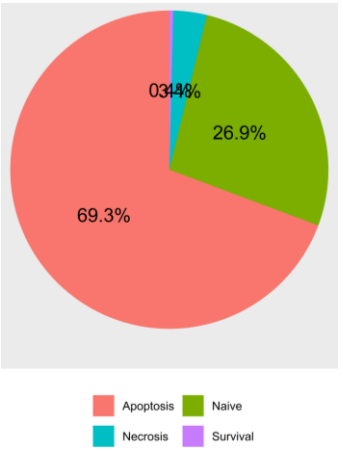


All inputs random initial conditions

FADD initial condition = 1







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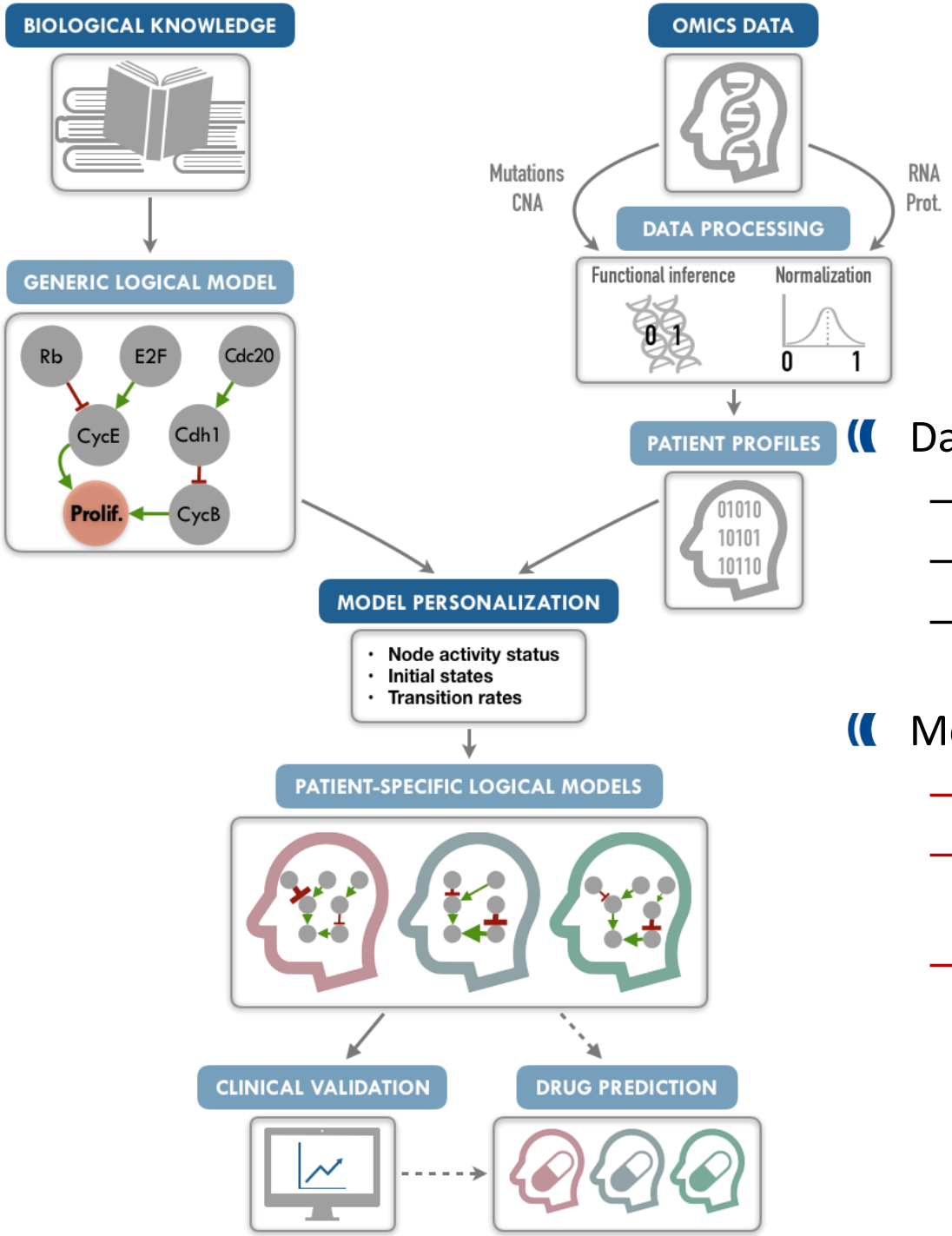
Modelling patient-specific Boolean networks

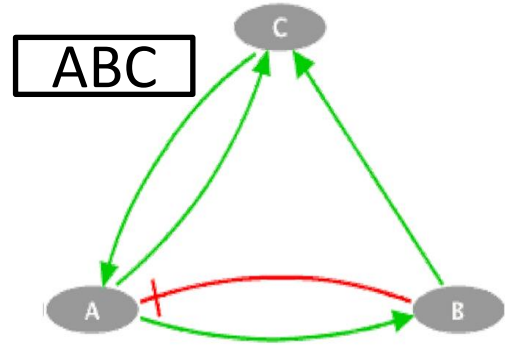
MaBoSS



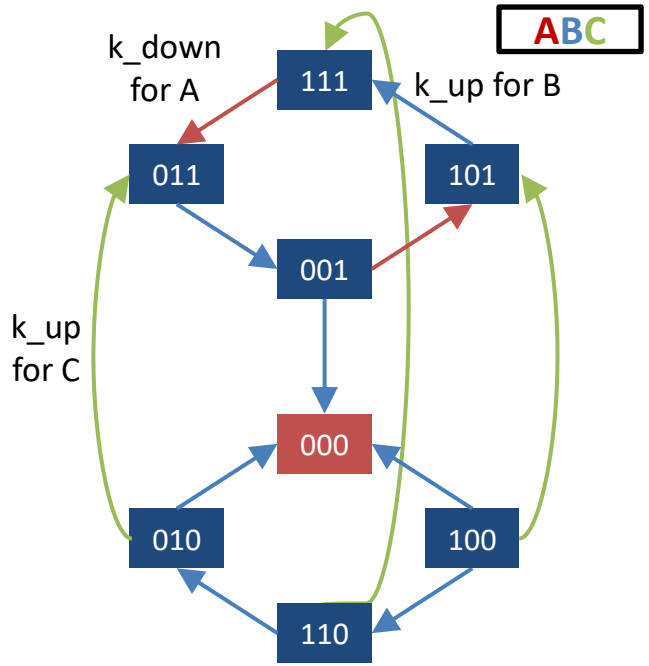
Béal et al., *Frontiers in Physiology*, 2019

- Data types:
  - Copy Number Alterations
  - Mutations
  - Expression: RNA and/or proteins

- Modelling framework's variables:
  - Node states = mutants
  - Initial conditions = growth media conditions or experimental setup
  - Transitions rates = Gene's ability to activate or deactivate



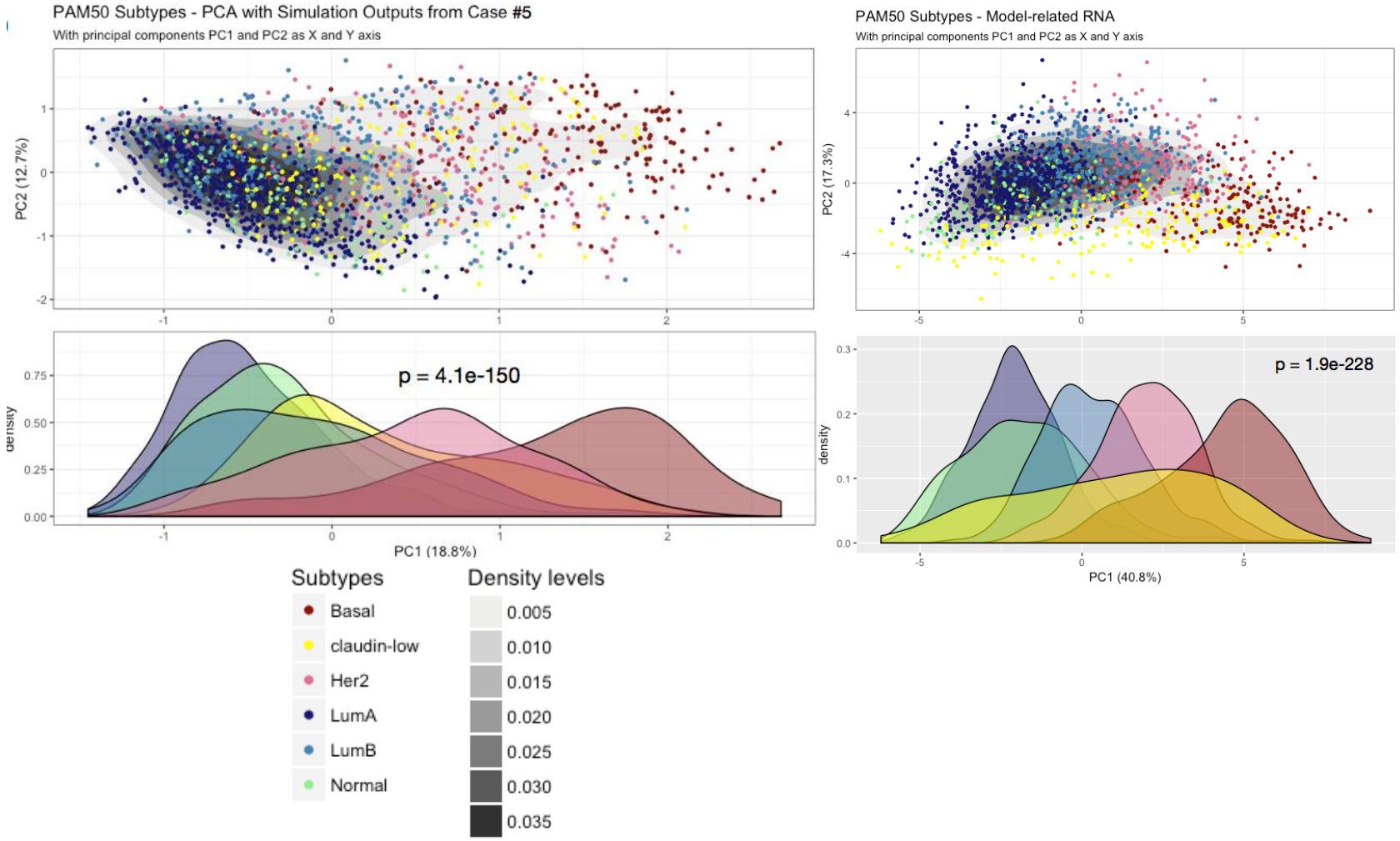
Boolean state transition graph

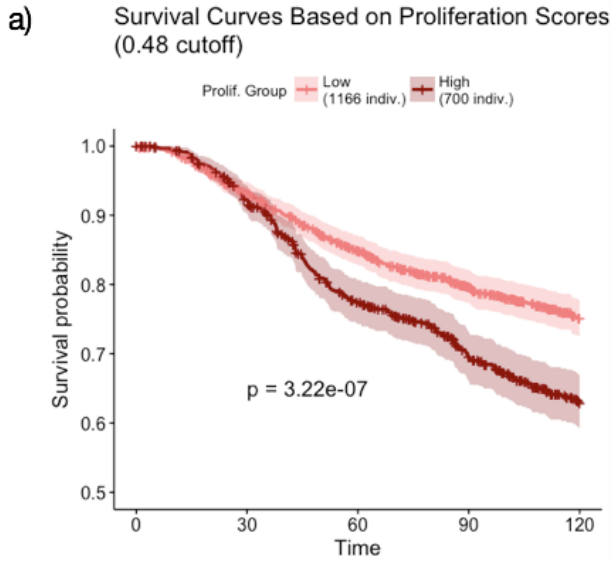


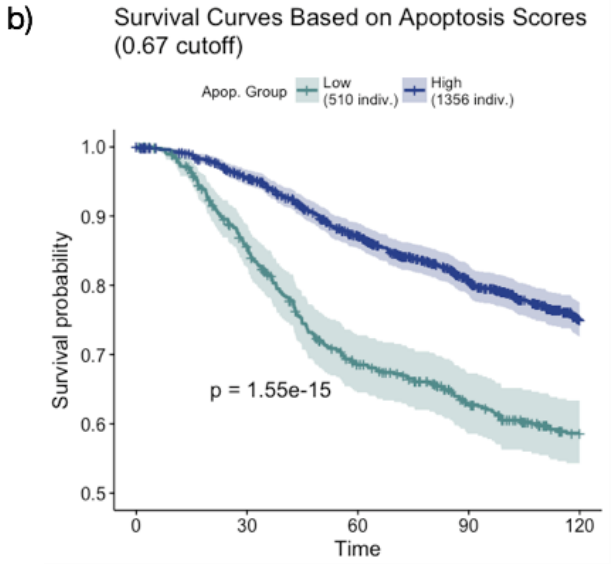
Stoll et al.,
BMC Syst Biol, 2012

Phenotypes correlate with clinical data: METABRIC models vs PAM50 and survival data

MaBoSS







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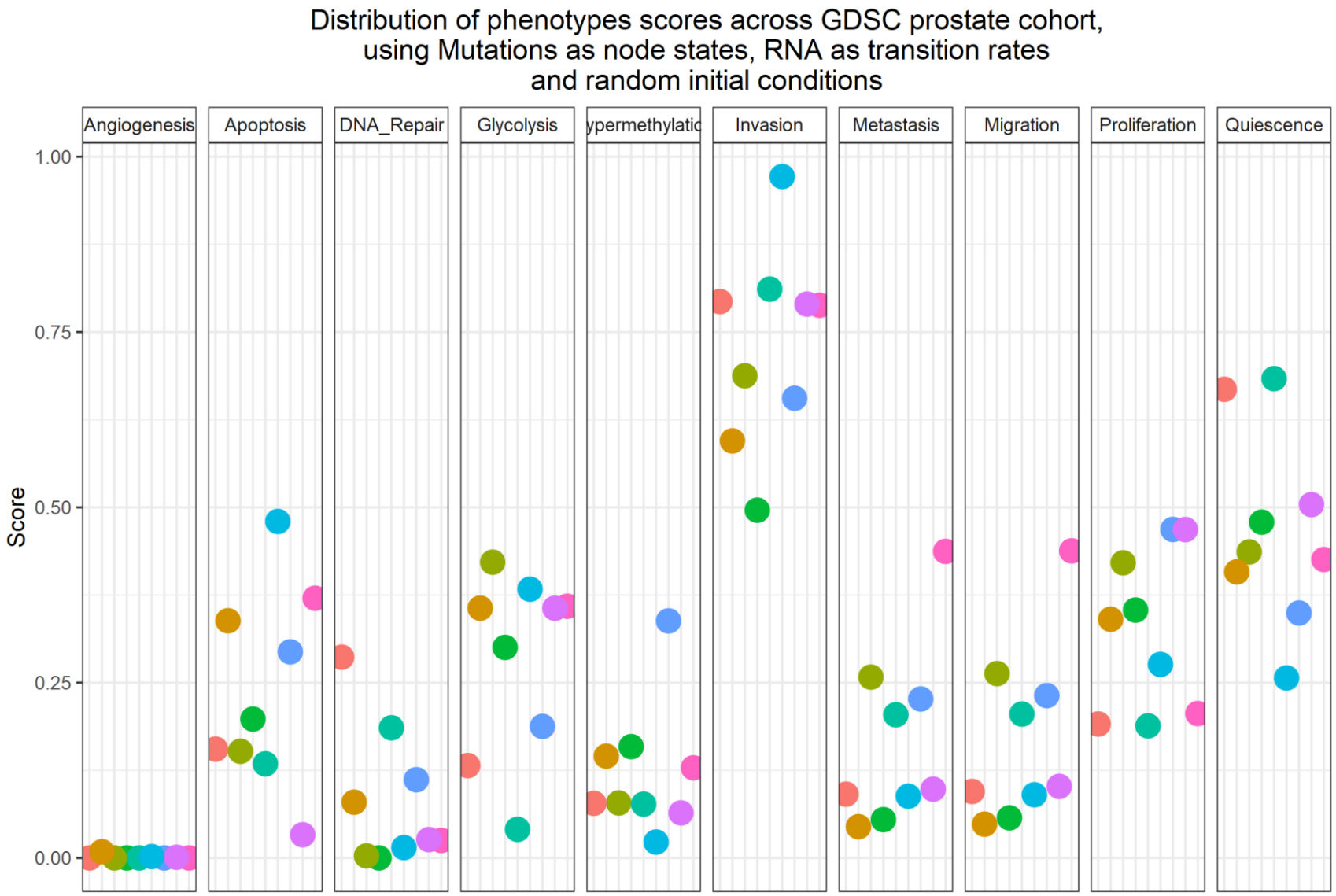
Cell-line-specific Boolean models



- 8 prostate cell lines have CNA and RNA
  - BPH-1 is a benign prostate hyperplasia
- WT is non-personalised model

If you want more information

Logical modelling pipeline

- Extensive and comprehensive studies can be done with a validated model and tools on the field
- Experimentally friendly hypotheses can come out of these studies
- Available at GitHub

https://github.com/sysbio-curie/Logical_modelling_pipeline

OXFORD

Briefings in Bioinformatics, 2017, 1–12

doi: 10.1093/bib/bbx163
Paper

Conceptual and computational framework for logical modelling of biological networks deregulated in diseases

Arnau Montagud, Pauline Traynard, Loredana Martignetti, Eric Bonnet, Emmanuel Barillot, Andrei Zinovyev and Laurence Calzone

Flexible pipeline of methods

- Generates data-tailored models
  - Cell lines
  - Patients
- Correlates with clinical data
  - Highly dependent on available clinical data
- Available at GitHub

https://github.com/sysbio-curie/PROFILE

Personalization of Logical Models With Multi-Omics Data Allows Clinical Stratification of Patients

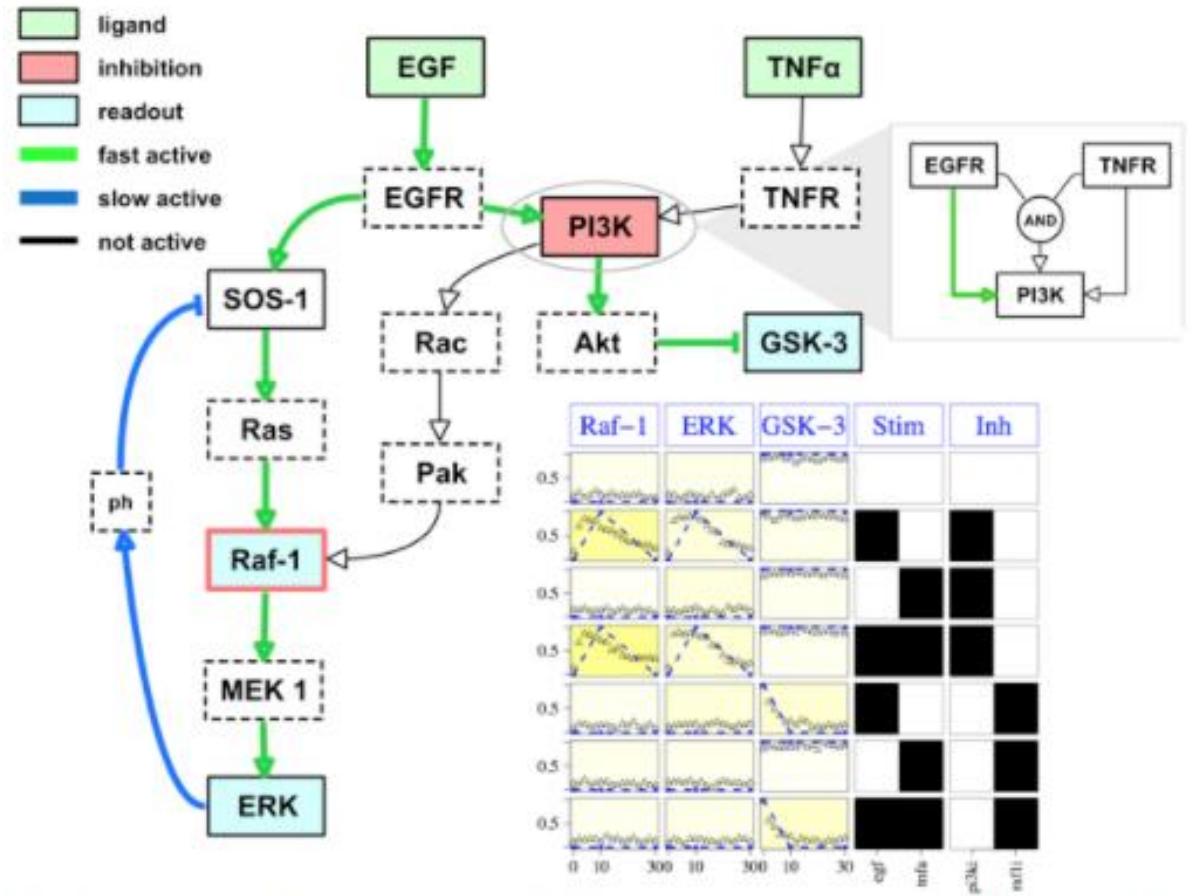
Jonas Béal, Arnau Montagud, Pauline Traynard, Emmanuel Barillot and Laurence Calzone**

Institut Curie, PSL Research University, Mines Paris Tech, Inserm, U900, Paris, France

If you want more information – CellNOpt

- **CellNOpt**
- Identification of signaling models based on perturbation data and prior knowledge

- https://saezlab.github.io/CellNOptR/
- https://github.com/saezlab/cellnopt



An illustration of how we use our logic modeling method CellNOpt to better understand deregulation of signal transduction in disease. Left: simple pathway model; right: experimental data and match between model simulations and data.

Agent-based as multiscale modelling

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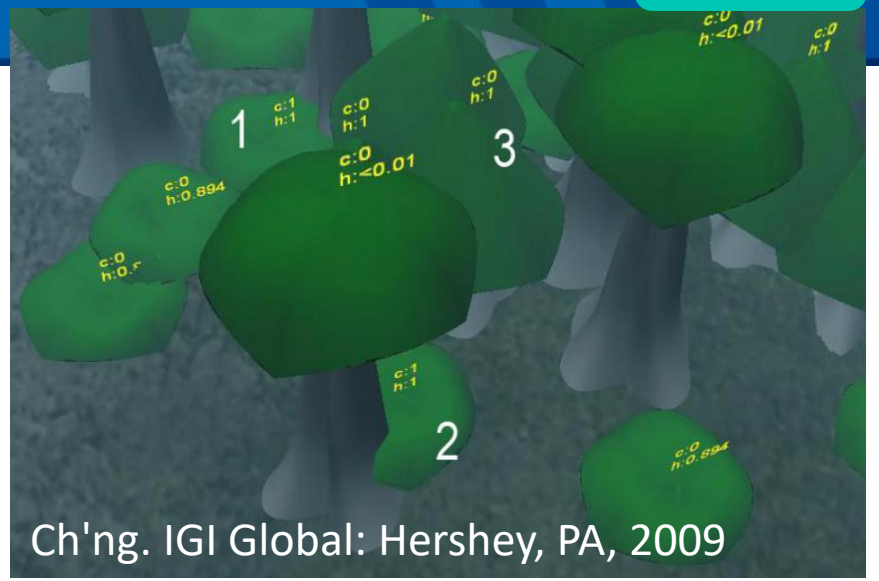
Agent-based modelling

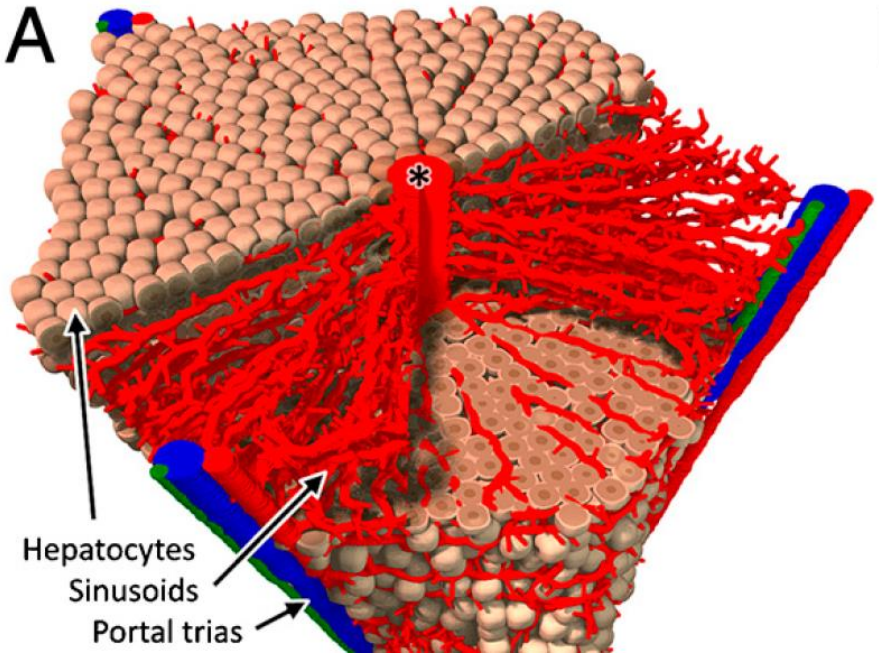
PhysiCell

- Agent-based models are composed of:

1. numerous agents;
2. decision-making heuristics;
3. an interaction topology; and
4. a description of the environment.



- Examples:
  - Ecology
  - Environmental Science
  - Artificial Intelligence
  - Tissue Biology



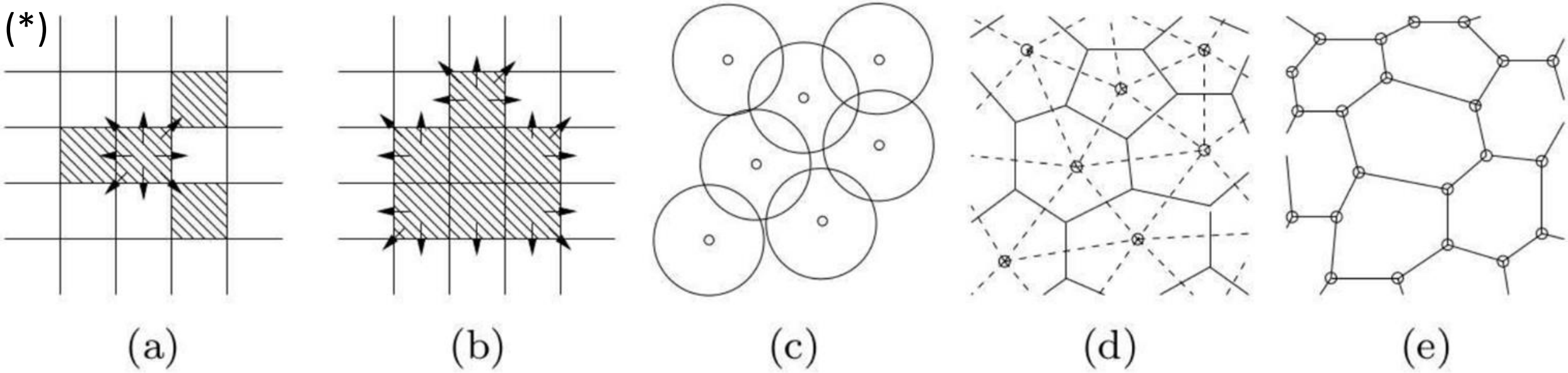
Hoehme et al, PNAS, 2010

PhysiCell

Agent-based model for multicellular modelling

Different ABM approaches for multicellular modelling

(*)



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

*"... An **agent-based model** is a class of computational models for simulating the actions and interactions of autonomous agents (...)*
It combines elements of game theory, complex systems, emergence, (...). Monte Carlo methods are used to introduce randomness..." (**)

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

(**) Source: https://en.wikipedia.org/wiki/Agent-based_model

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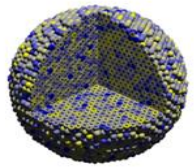
PhysiCell

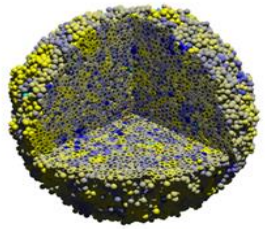
Multi-scale modeling framework: PhysiCell

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

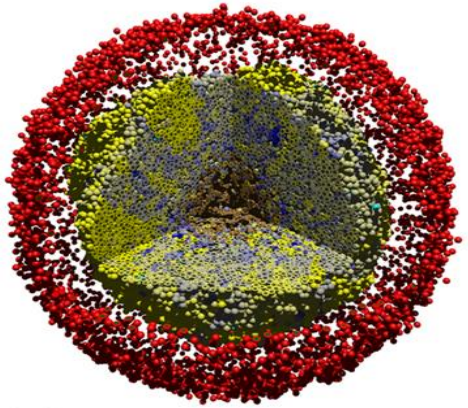
0 days
18,317 cells



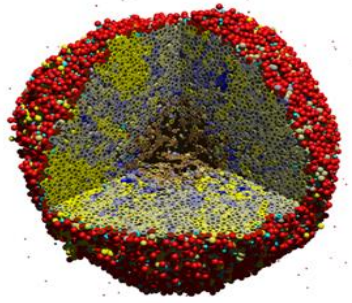
7 days
53,600 cells



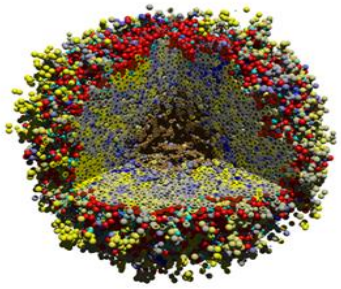
14 days + 3 min
111,479 cells



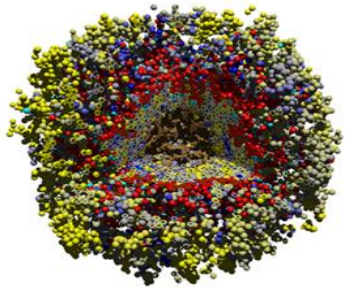
14 days + 6 hours
113,668 cells



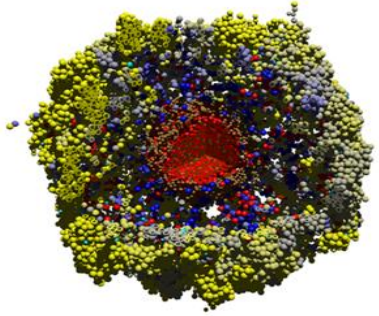
15 days
91,189 cells



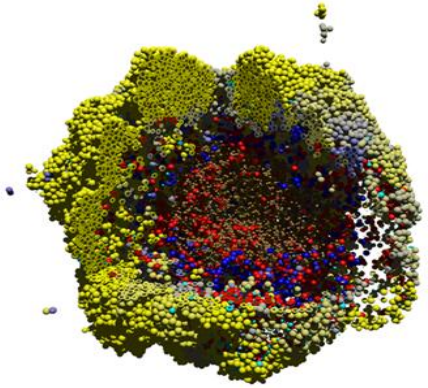
16 days
51,788 cells



18 days
38,122 cells



21 days
66,978 cells



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EXCELENCIA SEVERO OCHOA

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

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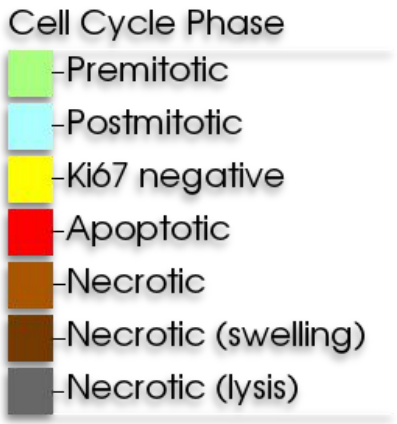
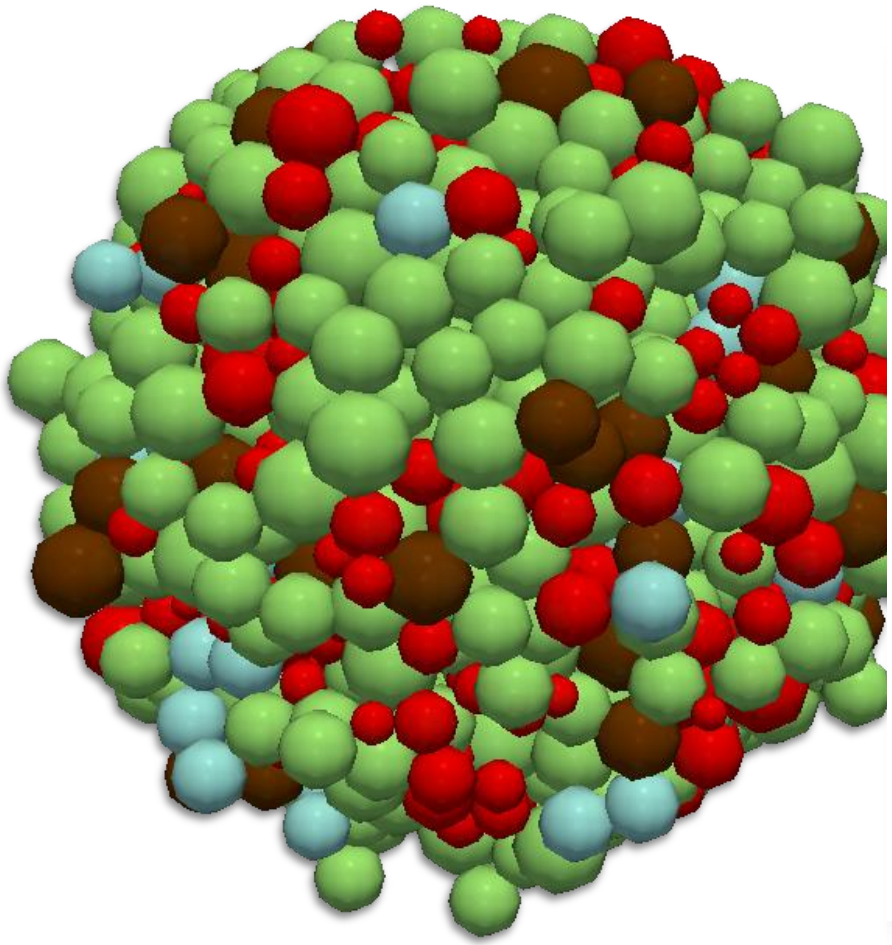
The basic cell agent has properties





Cell agent properties

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

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

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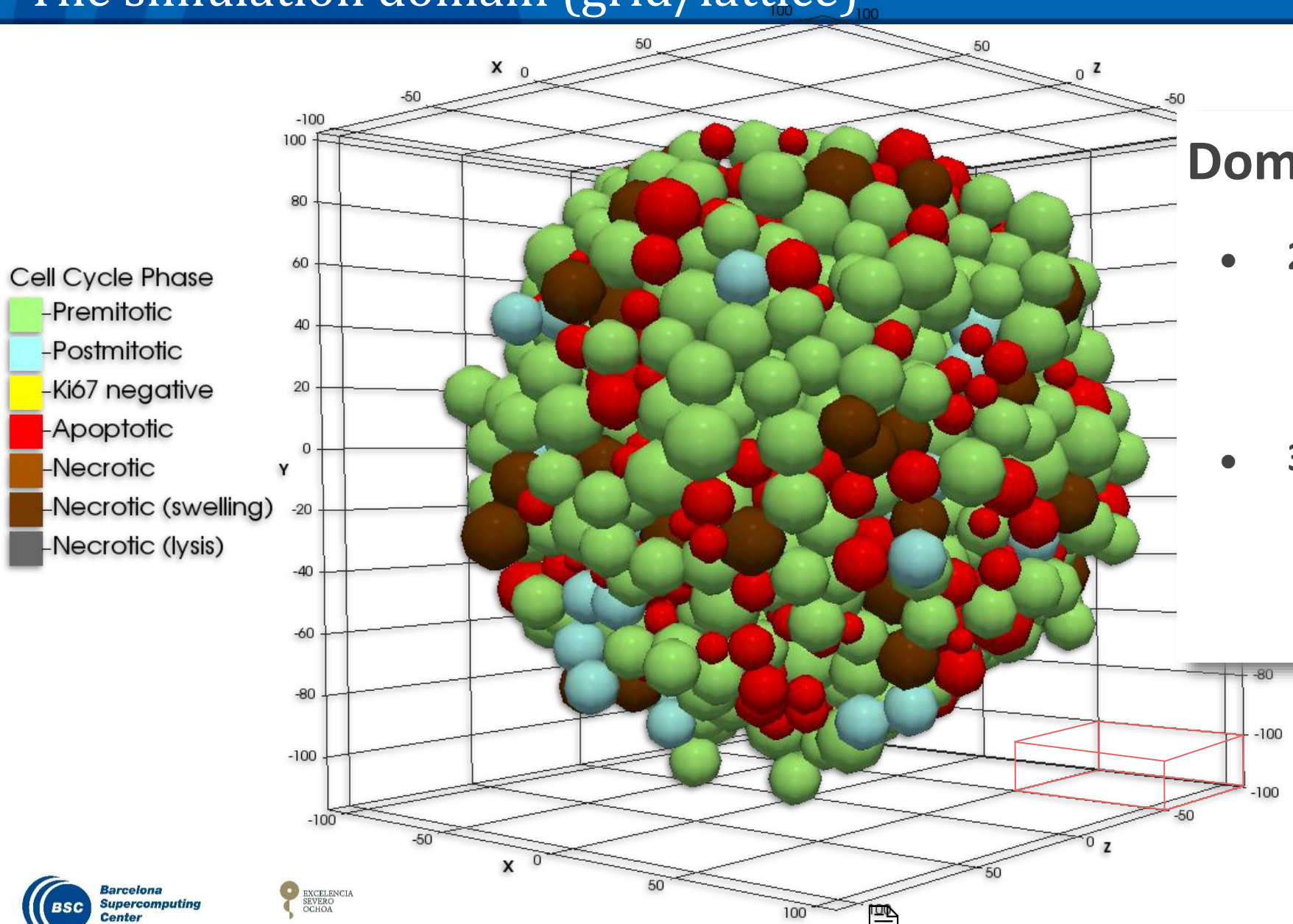
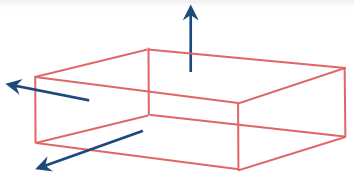
The simulation domain (grid/lattice)

PhysiCell



Domain = Voxels' grid

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



Voxel

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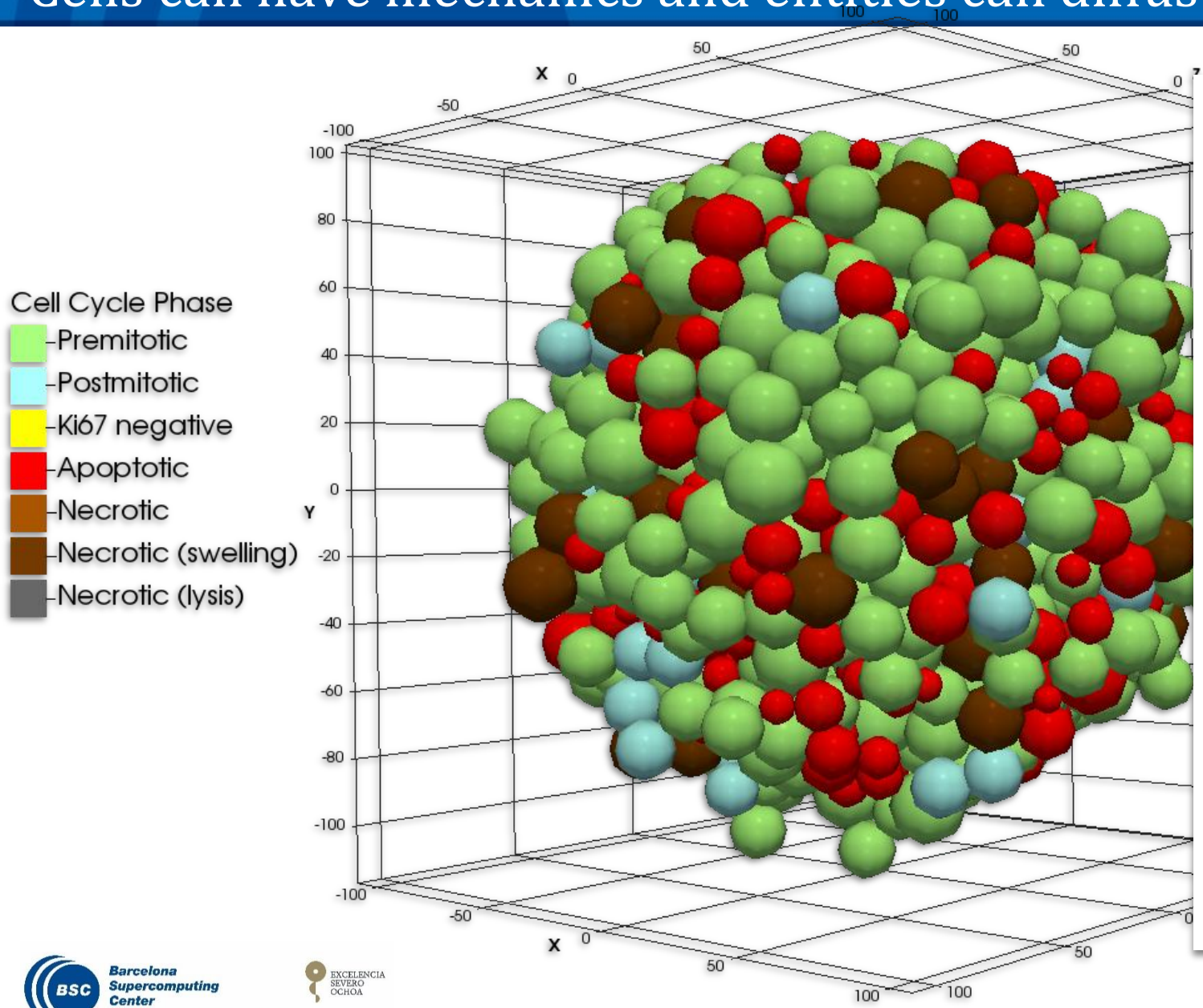
Cells can have mechanics and entities can diffuse

PhysiCell

PhysiCell



Diffusion and mechanics are directed by differential equations

Mechanical equations

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

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

Diffusion equations

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

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

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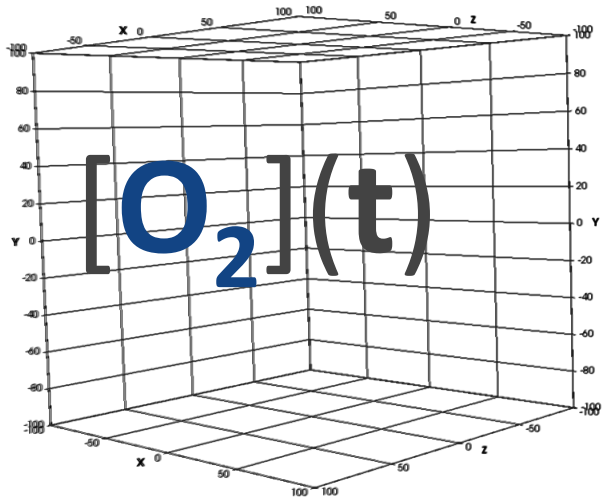
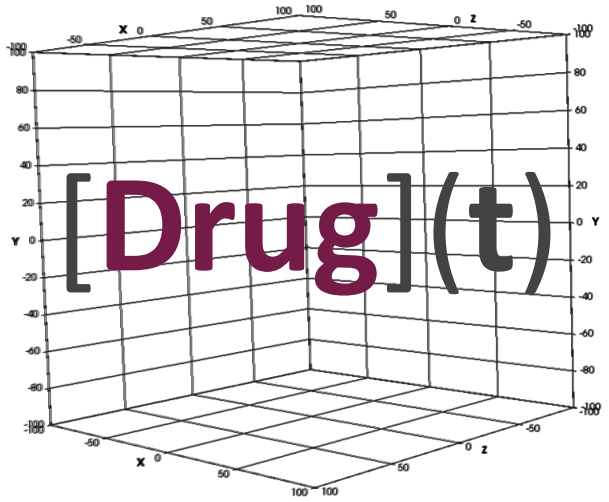
Environment can be dynamic and reactive

PhysiCell

PhysiCell





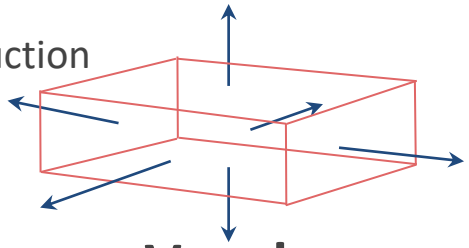
Reaction-Diffusion Equations

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

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

System of PDEs for each molecule:

- Diffusion term
- Decay
- Uptake/Production



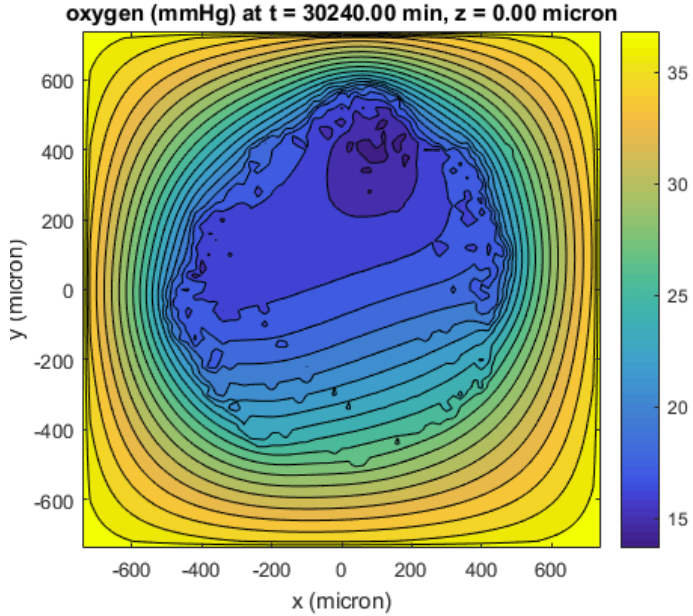
Voxel

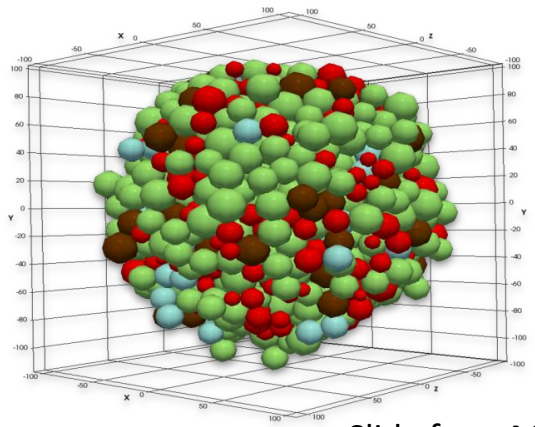
Surrounding physical environment

Surrogate for extra-celular matrix

- Field with densitities that can be produced & consumed
- Inert agents that can be moved

Gradient of chemical factors (O2)





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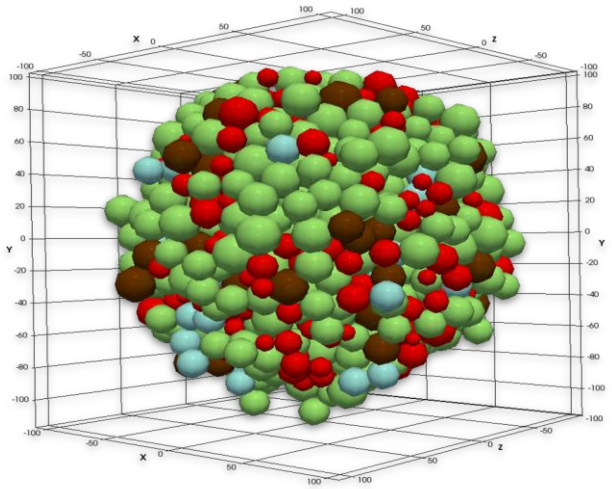
Simulation workflow

PhysiCell

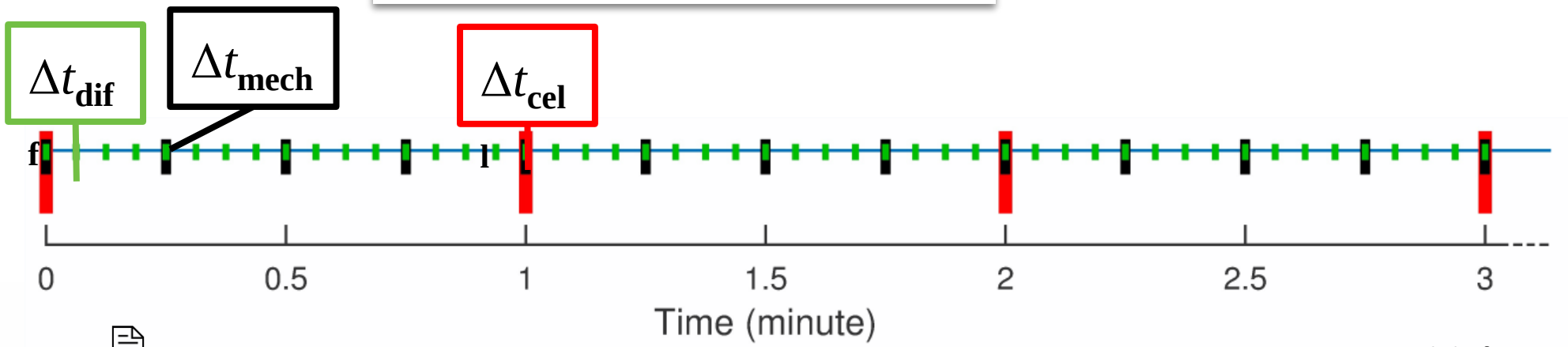


Simulation's main loop

```
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



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

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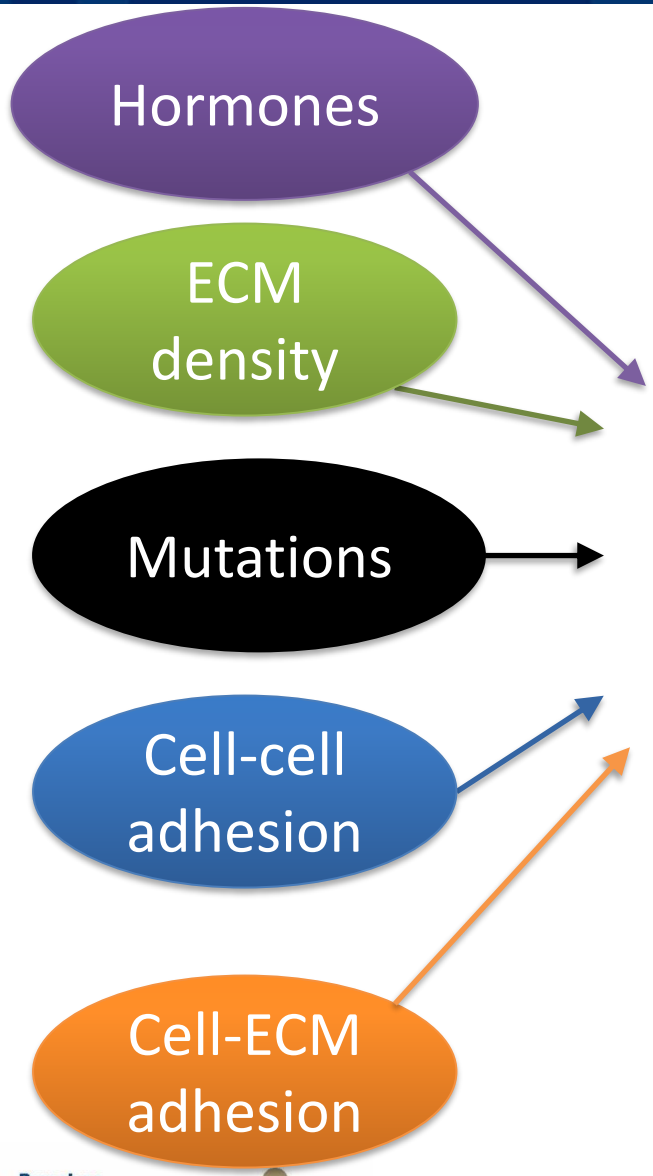
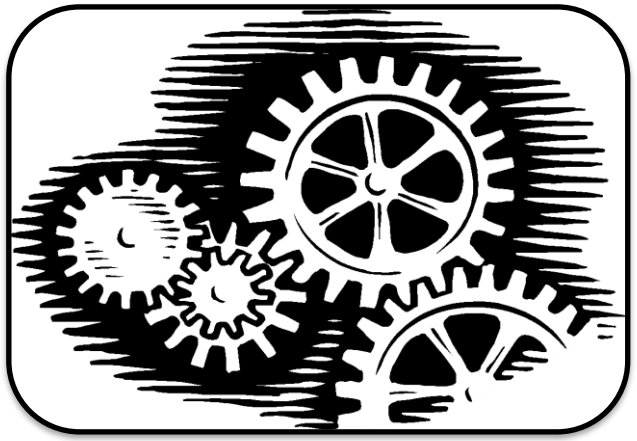
Modifying agent-based to have genotype-to-phenotype modelling

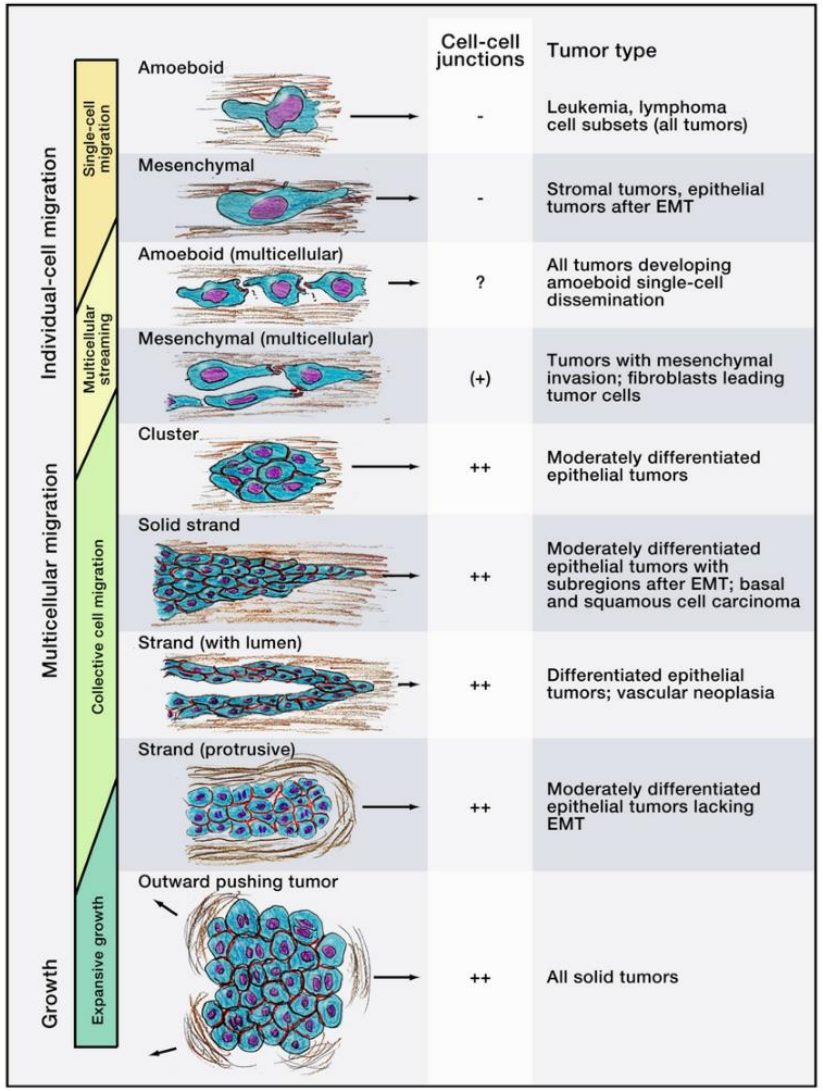
PhysiCell





Multi-scale modelling

Gene mutations
Signalling pathways
Cell - environment
ECM modification



From Friedl and Alexander, Cell, 2011

Merging MaBoSS with PhysiCell: PhysiBoSS

Multi-scale ABM framework integrating physical dimension and cell signalling

MaBoSS (Barillot team at Institut Curie)

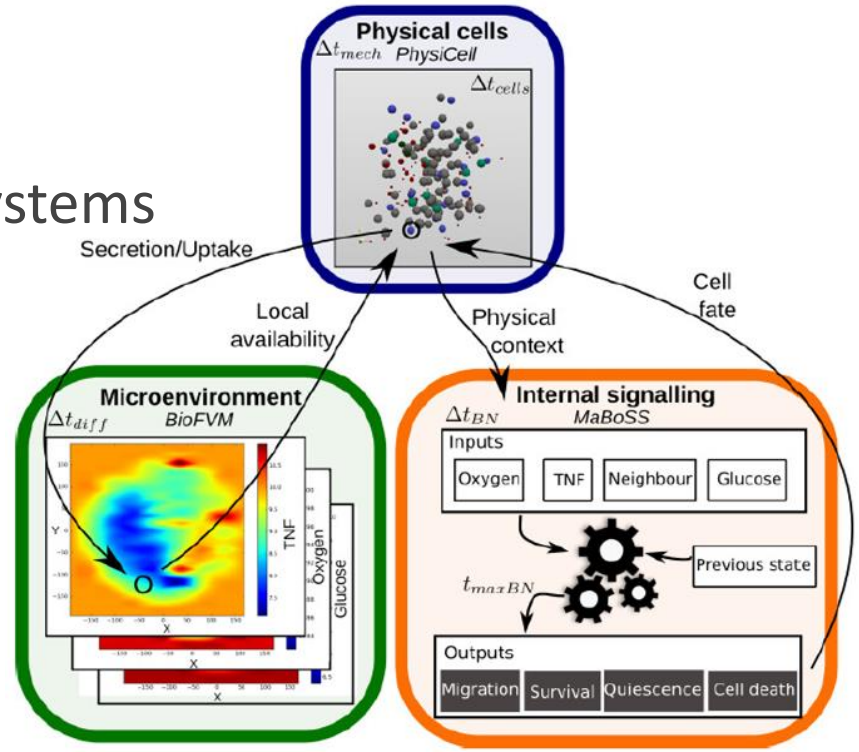
- Boolean model stochastic simulator for cell signalling

PhysiCell (Macklin team at Indiana University)

- Agent-based framework for simulating multicellular systems

PhysiBoSS (Barillot team at Institut Curie)

- A PhysiCell extension to include cellular signalling
- This allows to perform combined studies of:
  - Environmental perturbation
  - Genetic perturbation



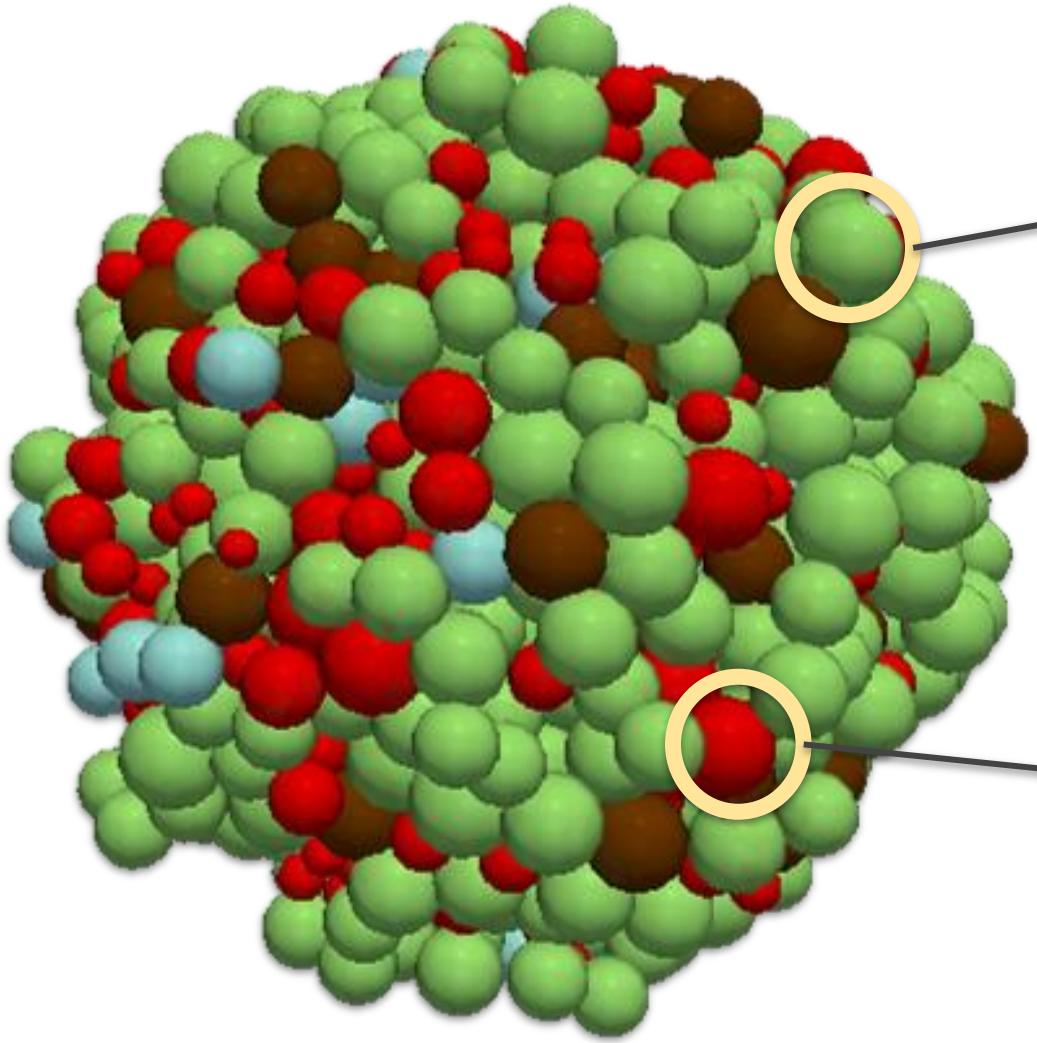
Letort, **Montagud** *et al.*, 2018. Bioinformatics

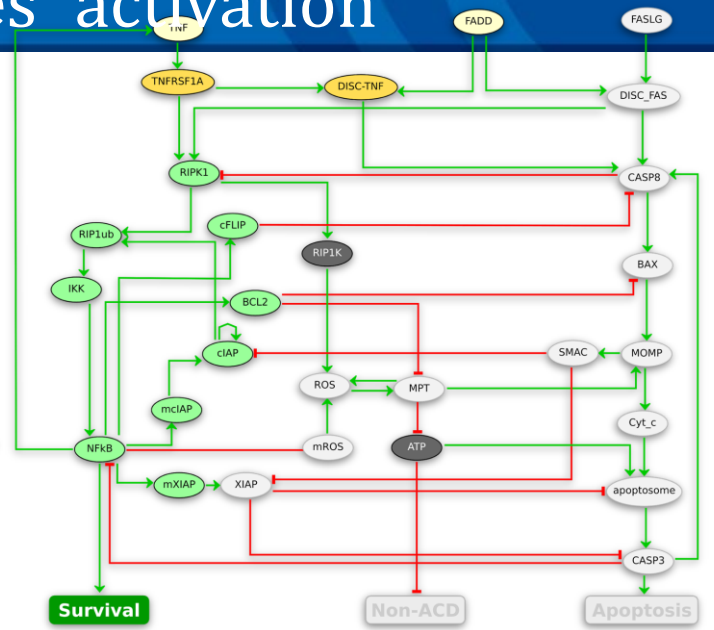
Cells have different phenotypes depending on their genes´ activation

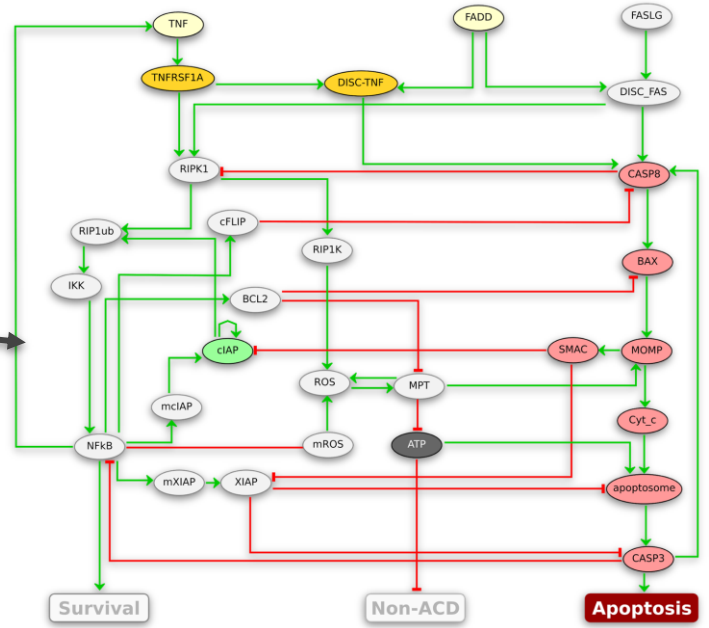
PhysiCell

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

Different cell signaling states





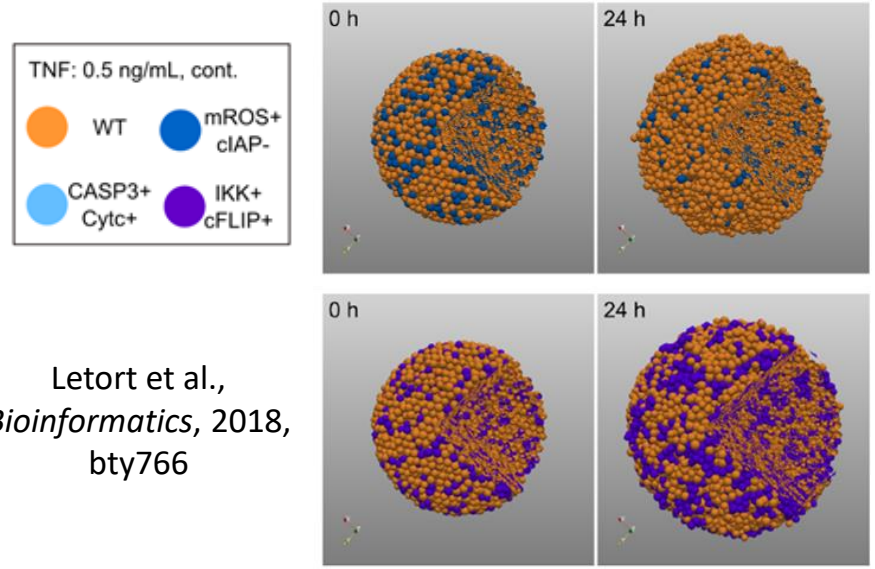


Time scales

- Δt_{diff} / Δt_{mech}/ Δt_{cell}
- $\Delta t_{signaling}$

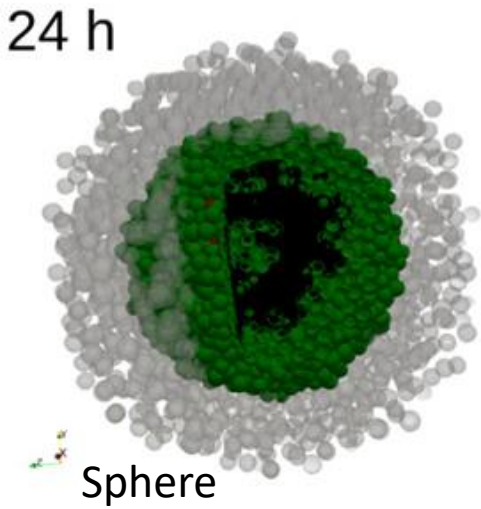
The framework allows for genetic and environmental heterogeneities

- Agents can represent different cell strains
  - With different biology
    - WT and mutants
    - Patient-specific networks
  - With different physical properties
    - Cell-cell adhesion
    - Cell-matrix adhesion

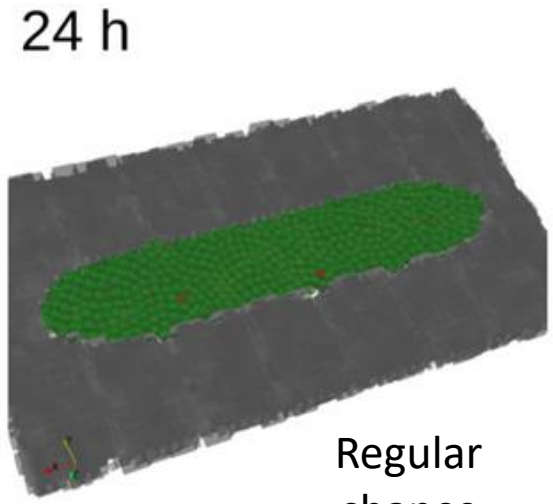


Letort et al., *Bioinformatics*, 2018, bty766

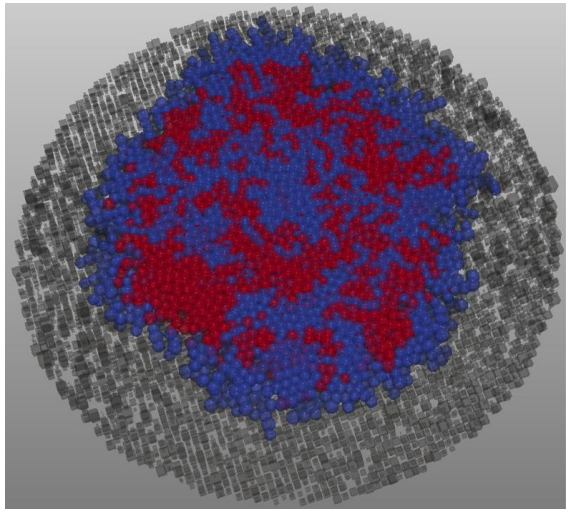
- Different tumour architectures



Sphere



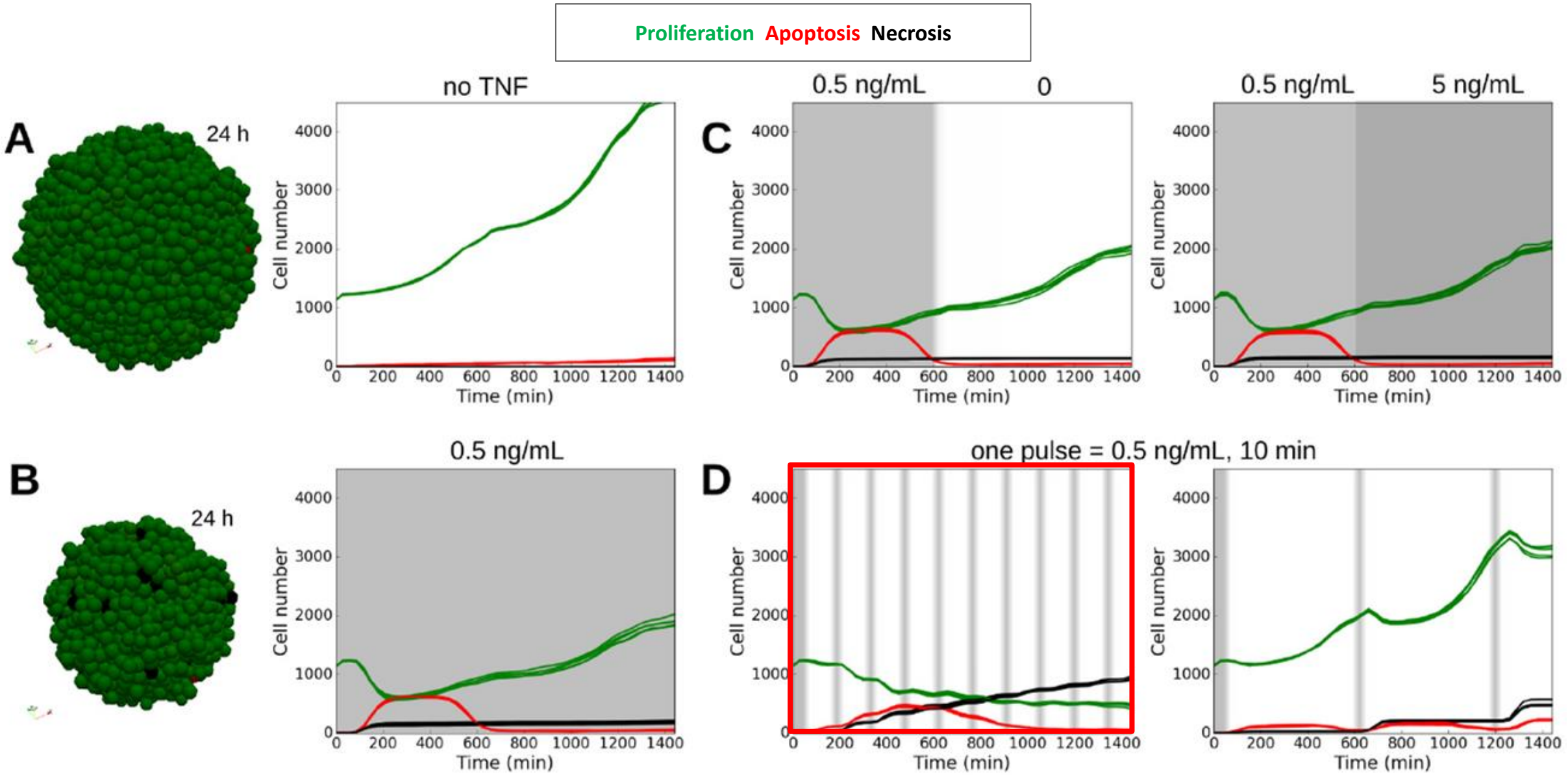
Regular shapes



One-cell-thick monolayer

The framework allows for finding optimal drug regimes

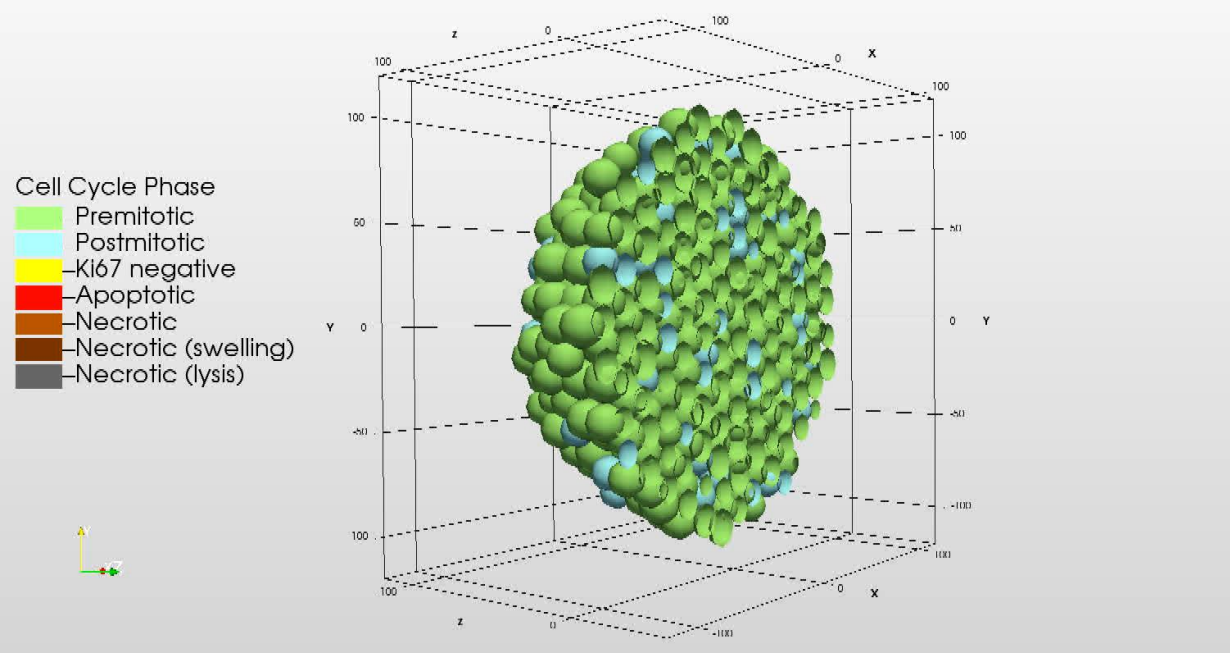
PhysiBoSS

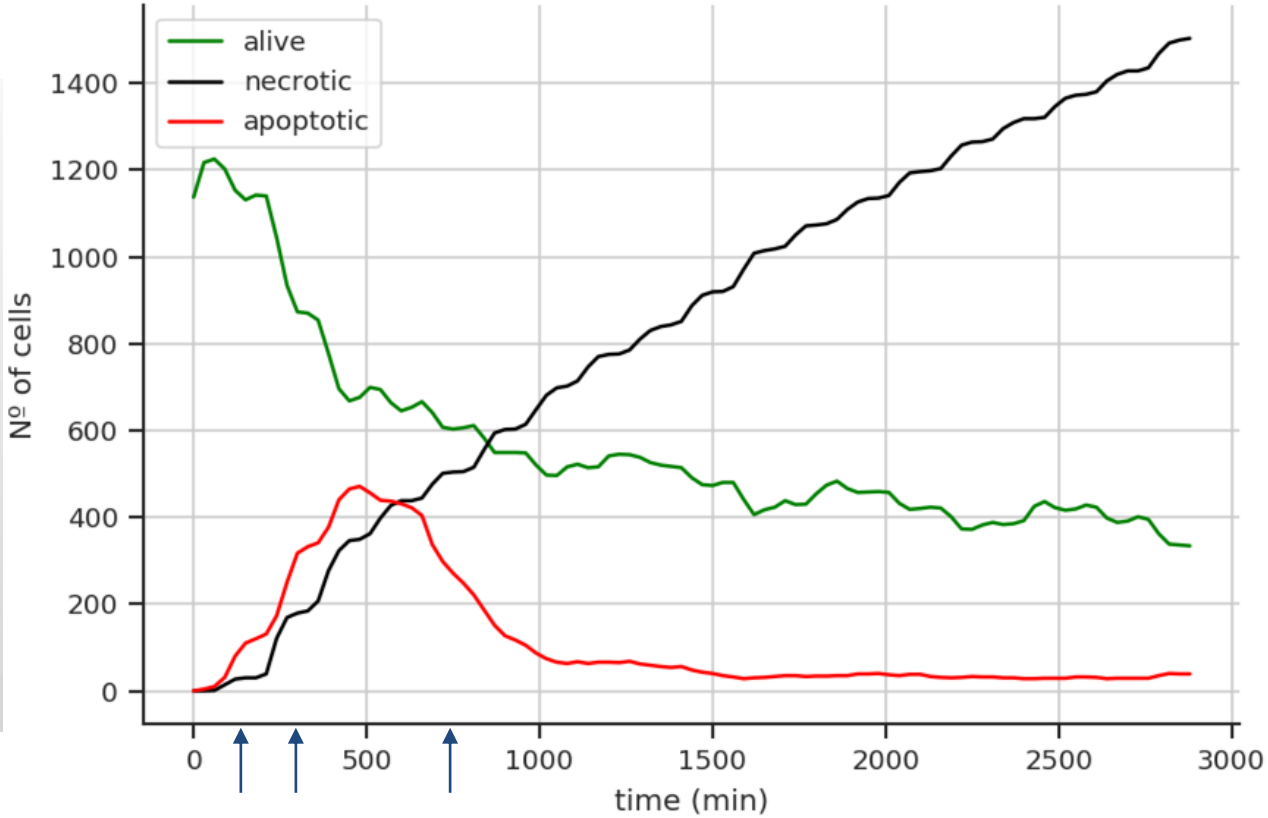


Letort et al., *Bioinformatics*, 2018, bty766

PhysiBoSS experiment: TNF pulse studies

PhysiBoSS





~48 h simulation time, 30 min wall time
~2500 cells

TNF pulses every 150 min

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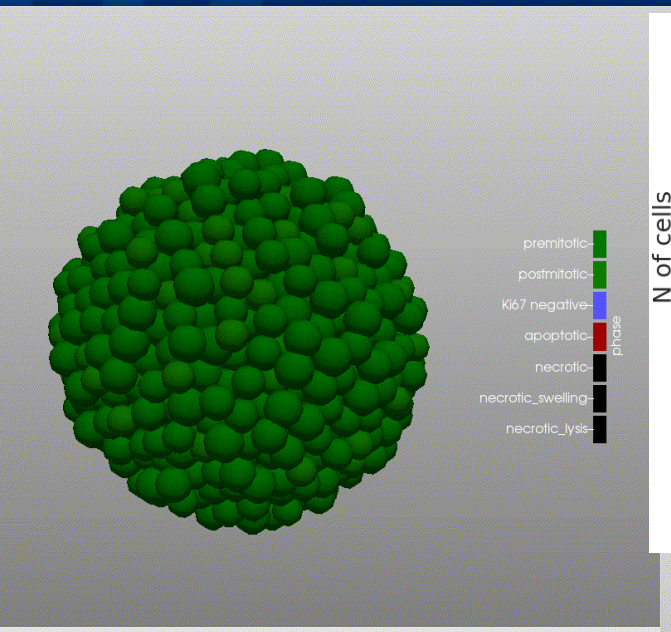
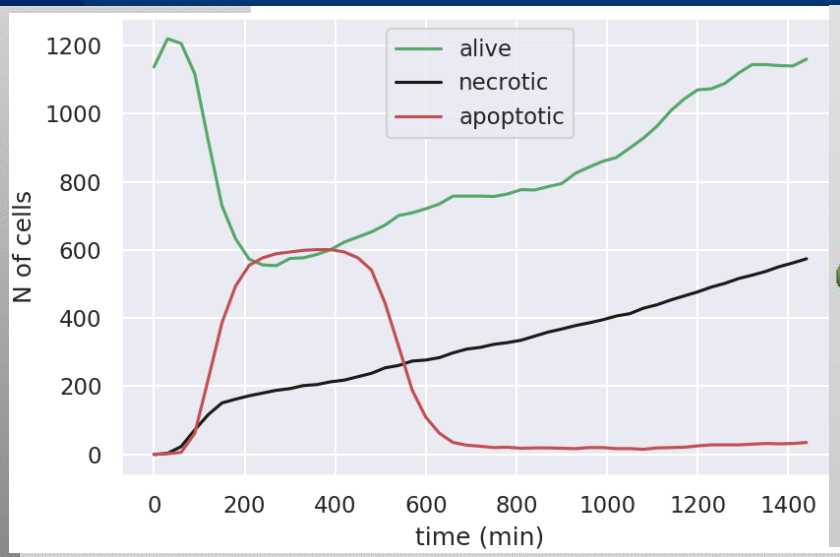
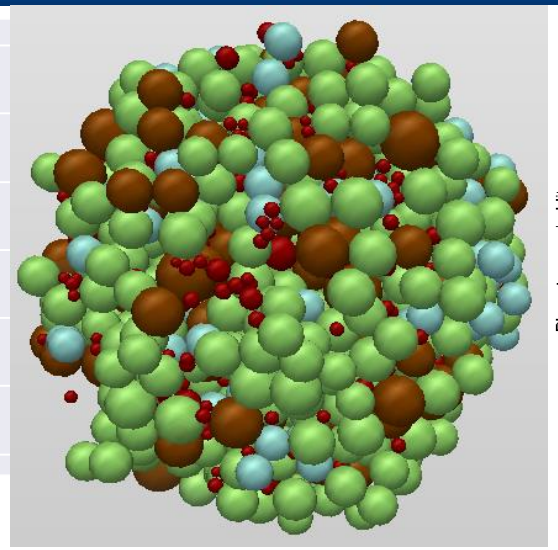
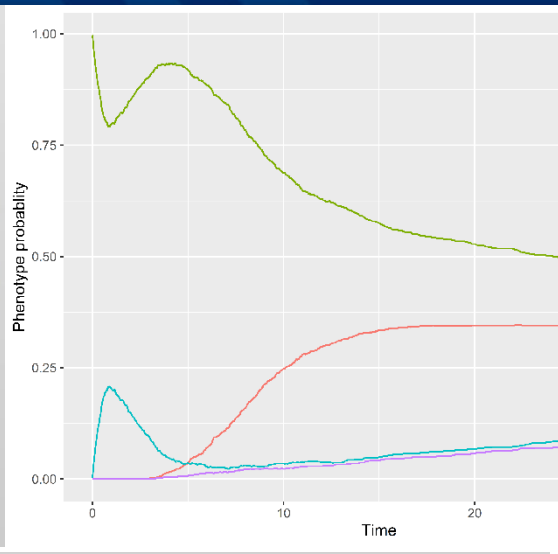
Slide from M. Ponce de L, BSC

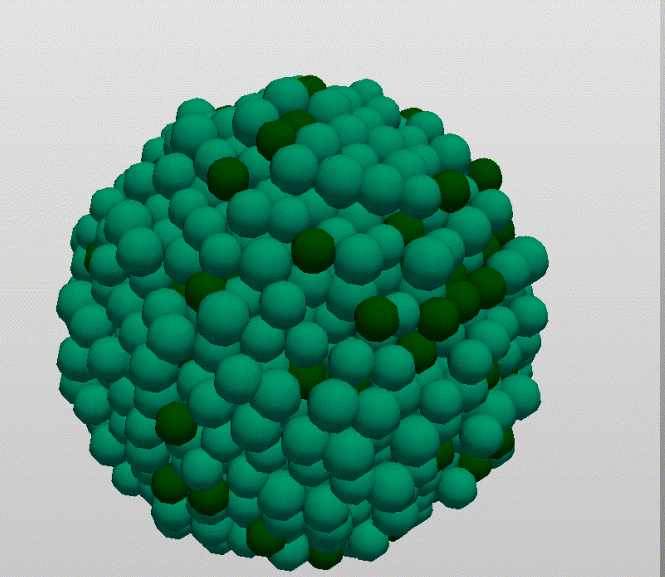
Examples of use of PhysiBoSS

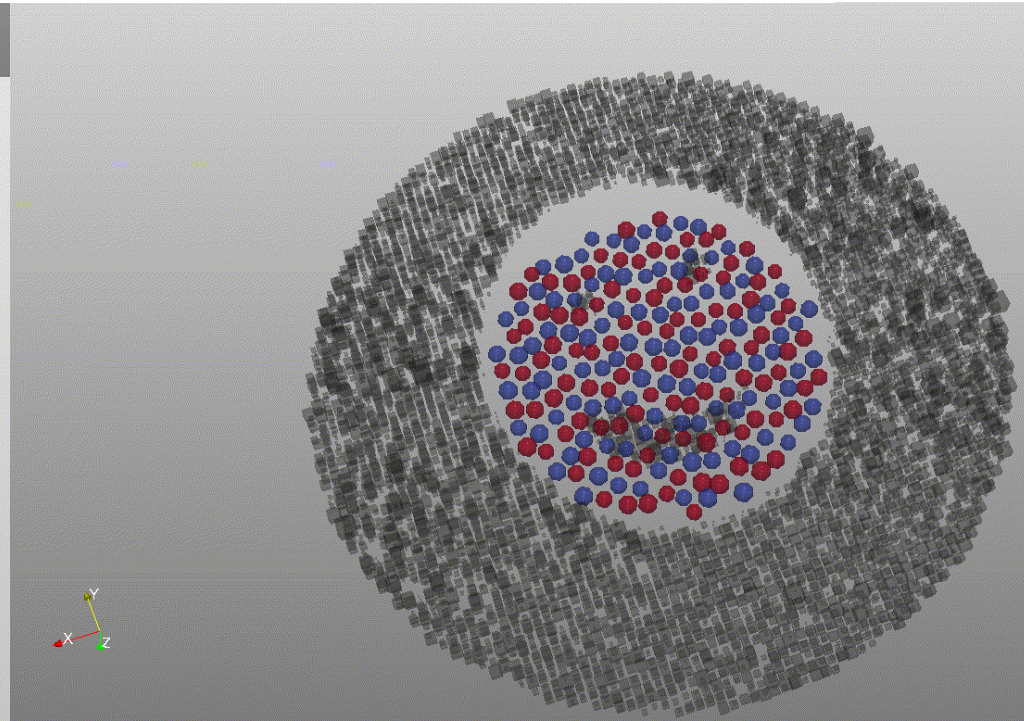


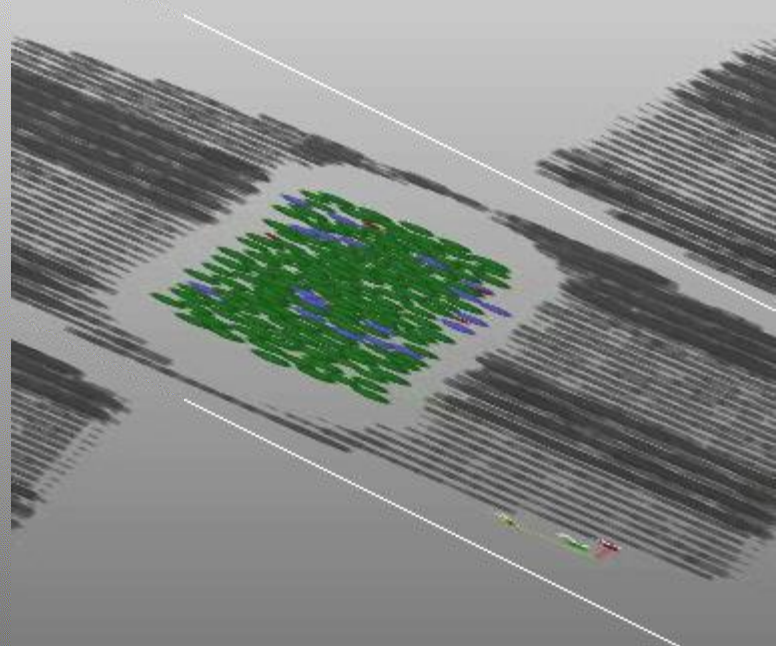






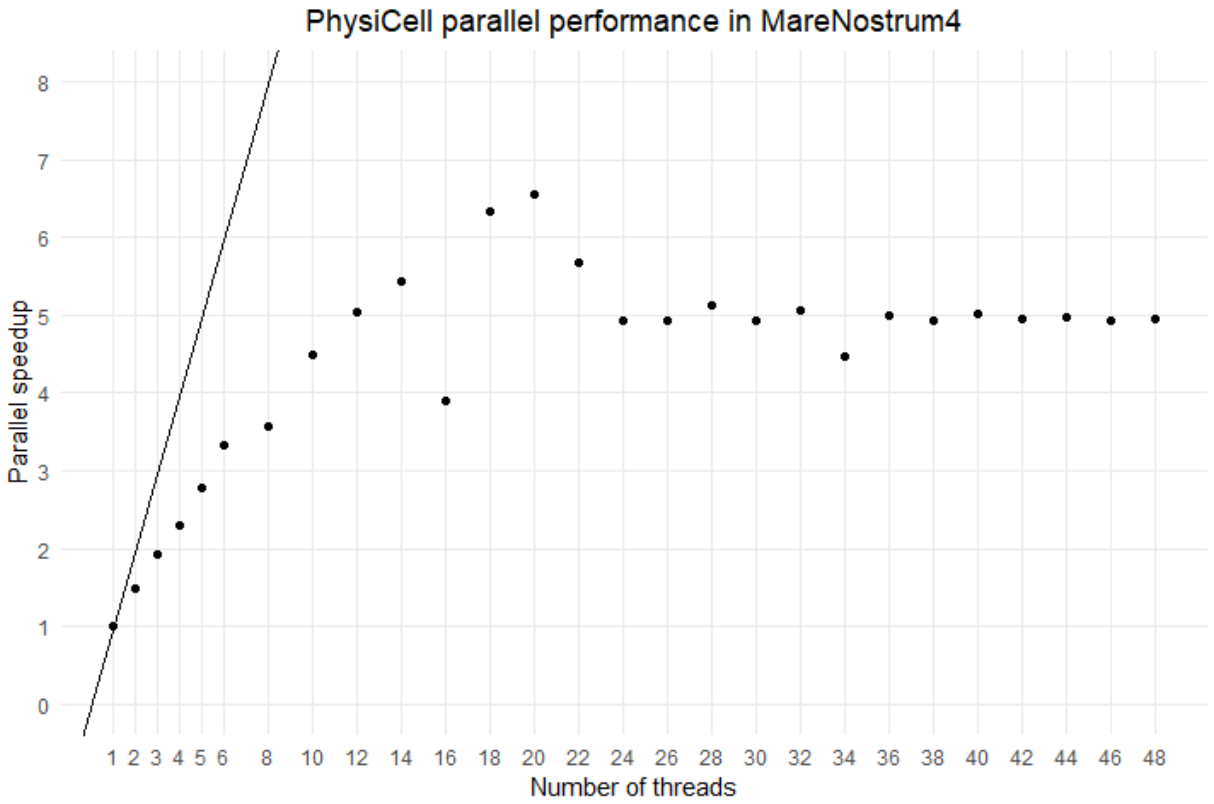






Ongoing work: Migrating PhysiBoSS to use MPI

- Currently:
  - Intra-node shared memory
  - OpenMP is possible: 1 node
  - max 48 cores in MN4
  - 1B cells in several simulations

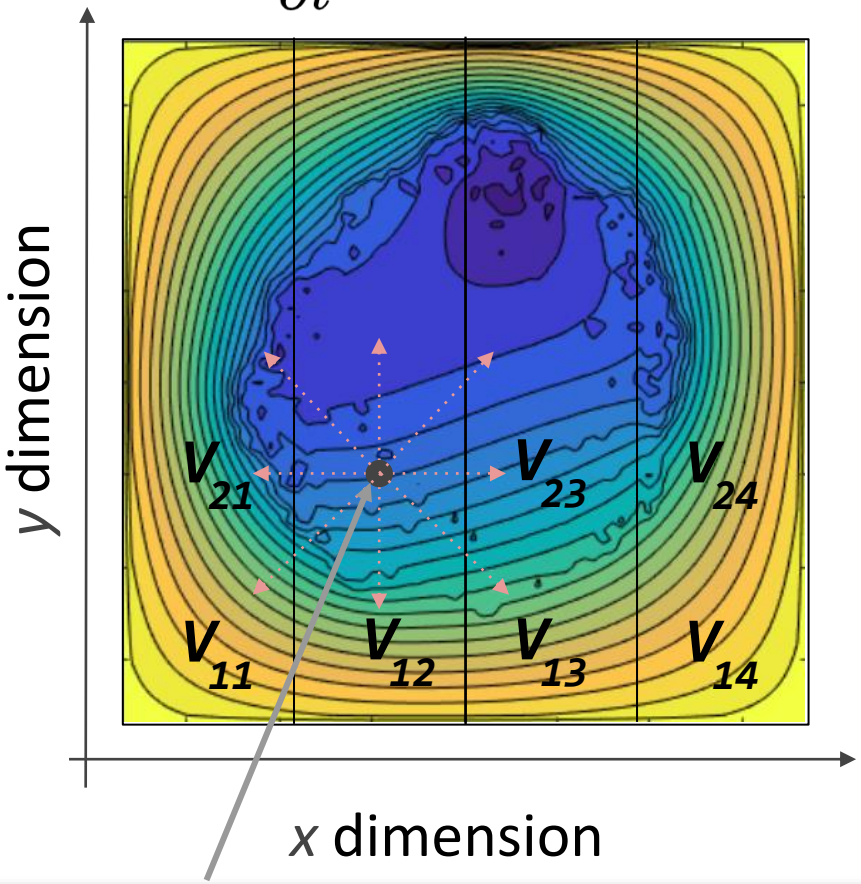


- Ideal:
  - Inter-node shared memory
  - Combine OpenMP + MPI
  - 1B cells in one single simulation

- Lead by Gaurav Saxena, BSC
- Goals:
  - Expand the scope of the simulations by several orders of magnitude
  - Enable the simulation of complex behaviours

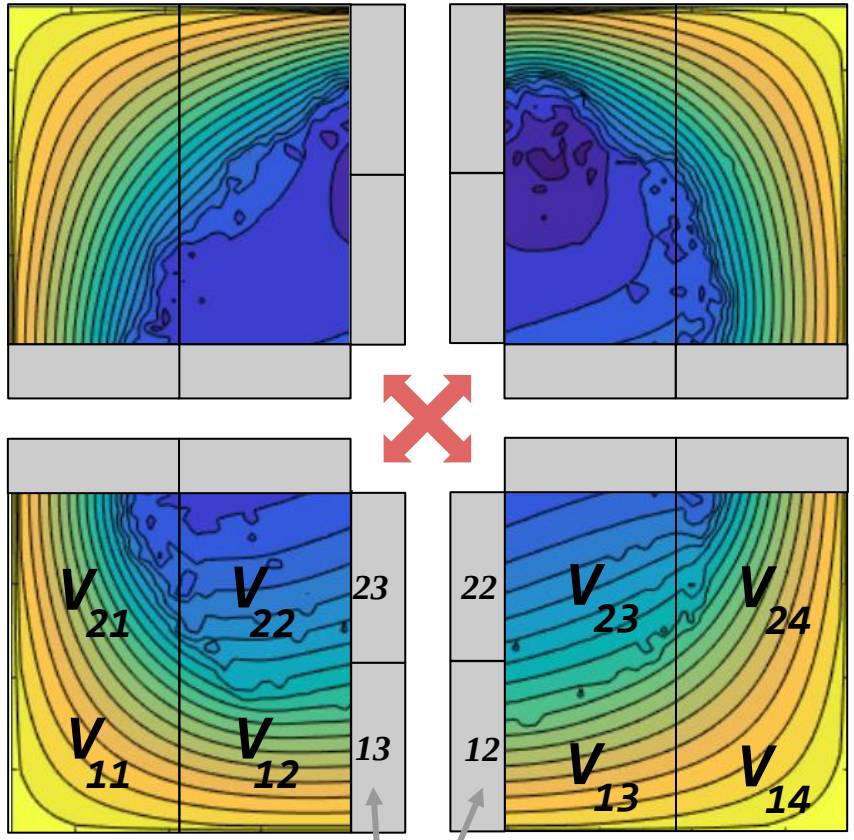
Domain decomposition: 2D example

Full Domain ($\frac{\partial \rho}{\partial t} = \mathrm{D}\nabla^2\rho - \lambda\rho \ldots$ **)**



Domain Decomposition

Sub-Domains *i* (*i* = 1 … 4)

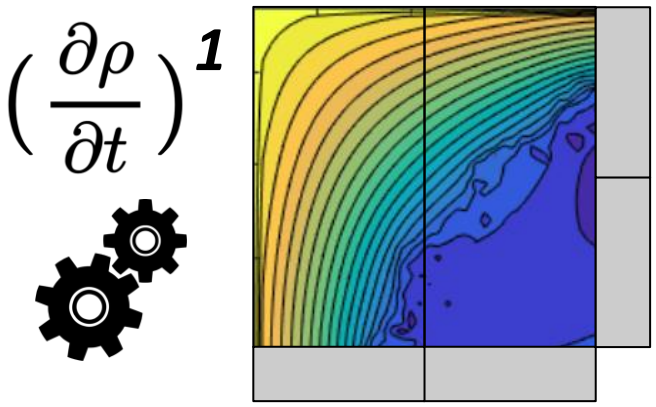


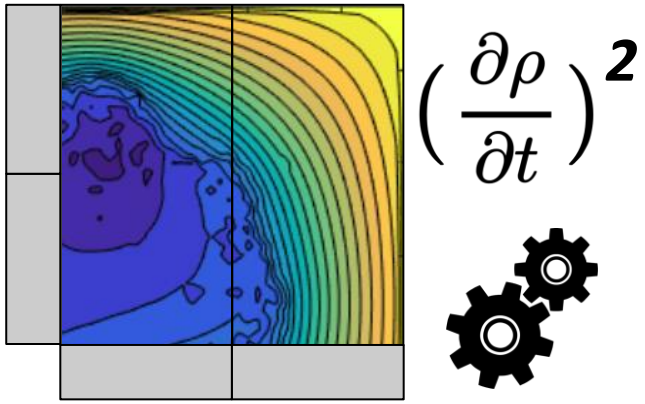
Individual Voxel: stores the values of each molecule concentration. Connected to other voxels through Moore neighborhood (PDE solver)

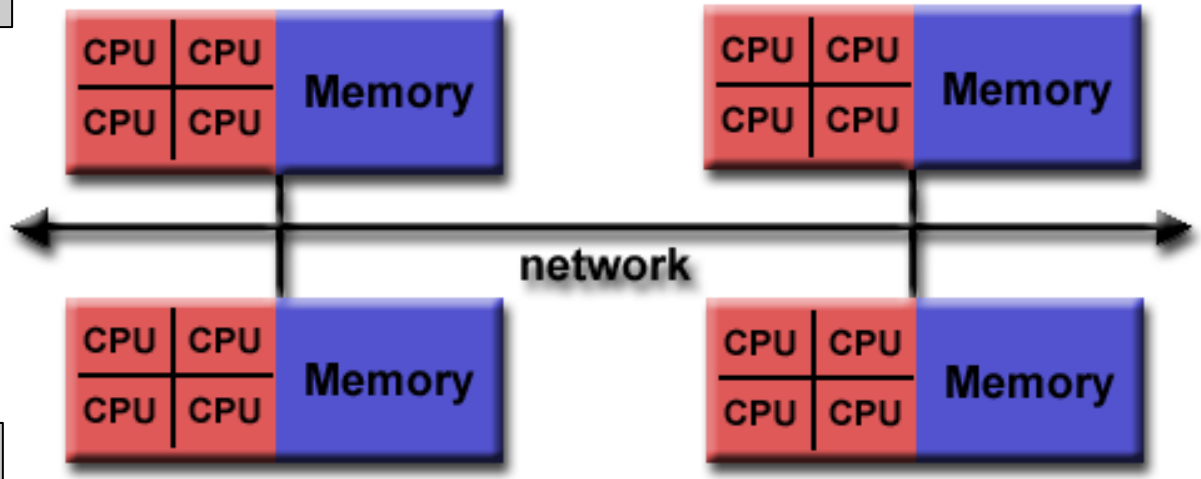
Ghost (Halo) Cells: needed to update boundary voxels in a transparent way. Needed to exchange information between neighbour voxels

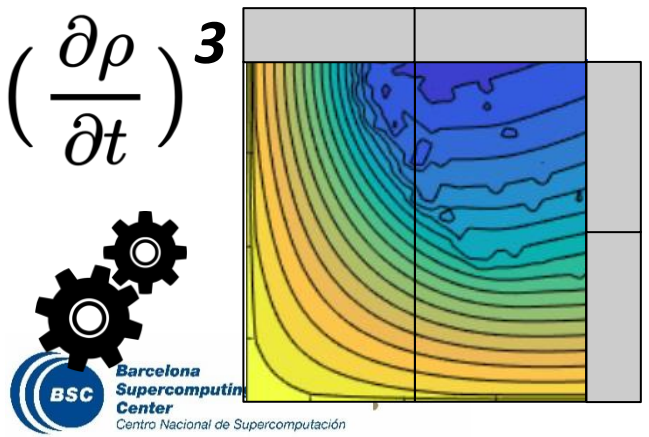
Domain decomposition: 2D example

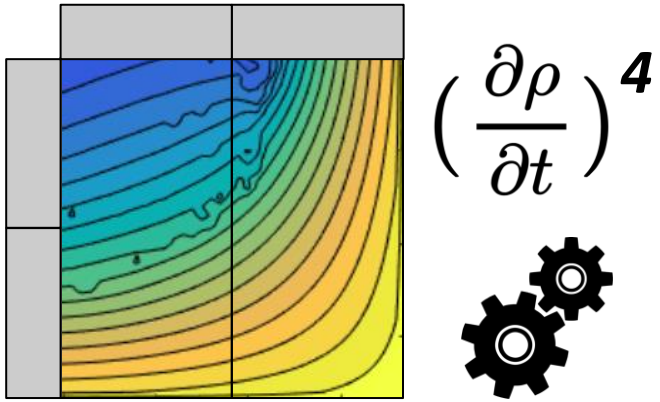
Distributed computing (***n***: nodes) to update microenvironment (solve PDEs)











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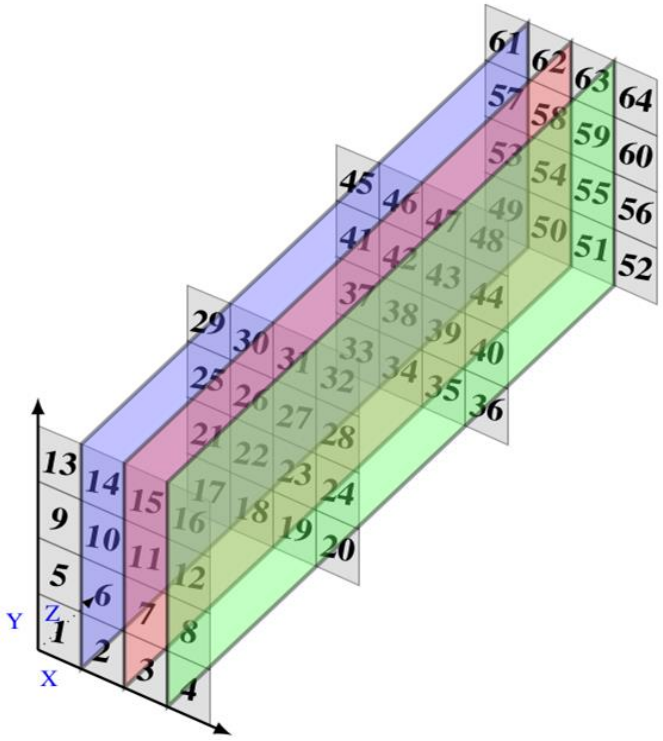
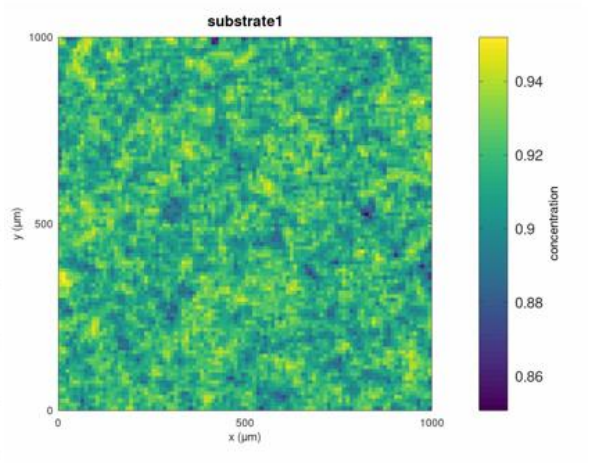
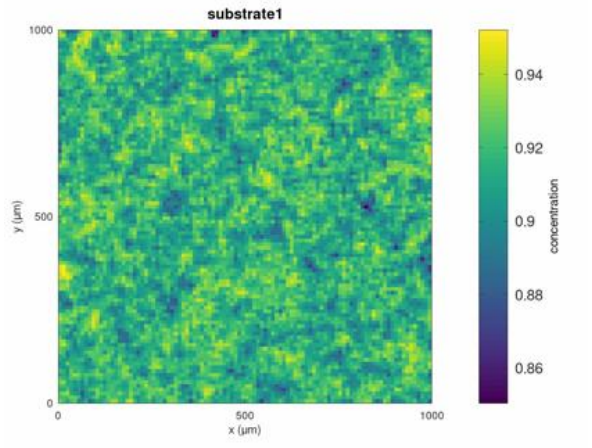
Ongoing work: Migrating PhysiBoSS to use MPI

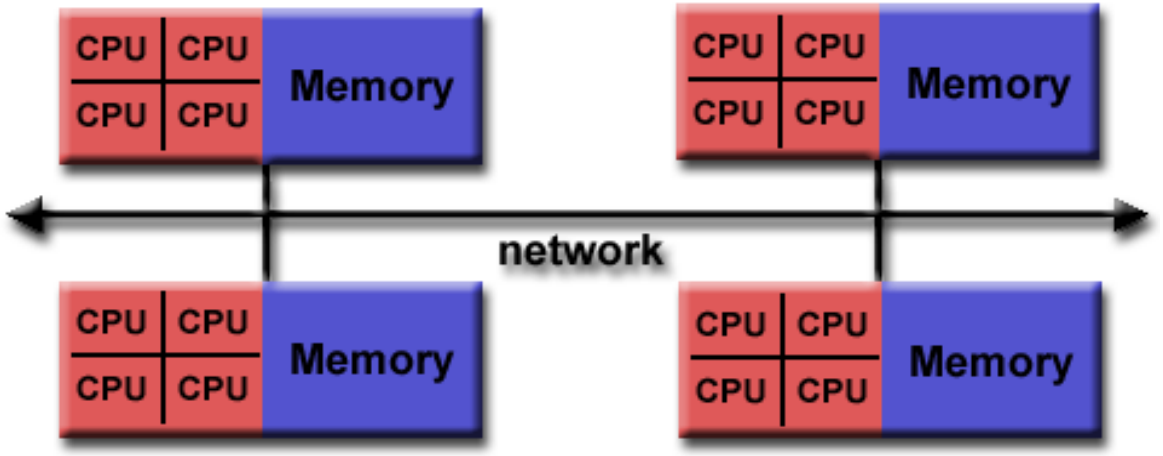




(a) OpenMP (48 threads)



(b) Hybrid(n=1)

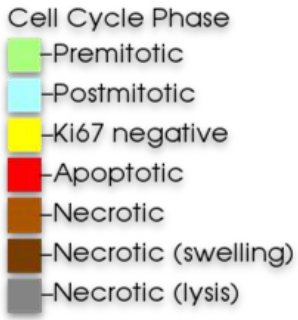


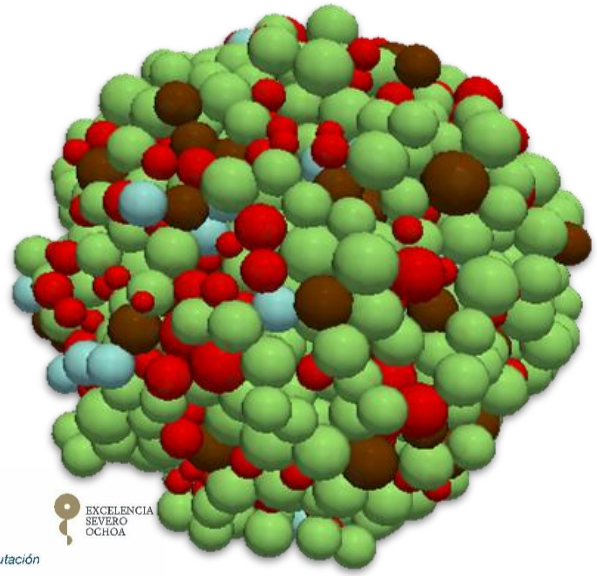
- Collaboration with Gaurav Saxena & David Vicente, HLST, BSC
  - Refactoring parts of the code to implement MPI
  - Environmental data has to be shared among different nodes

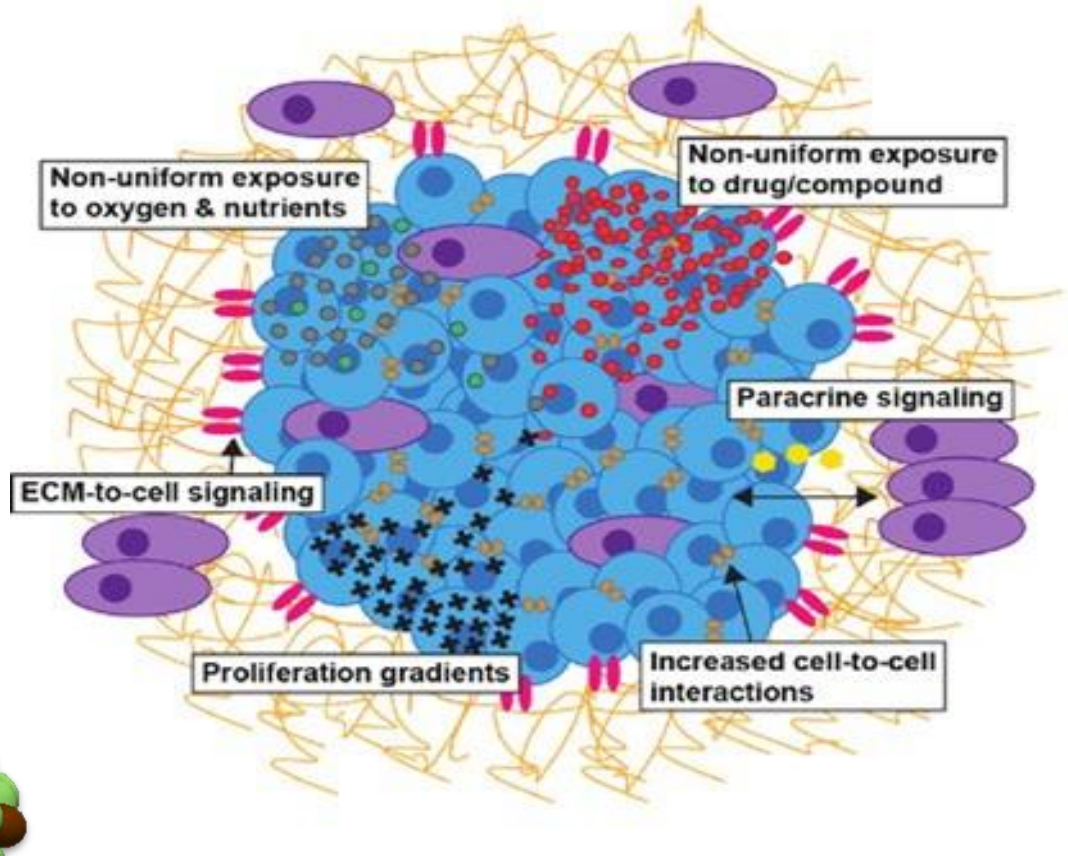
PhysiCell

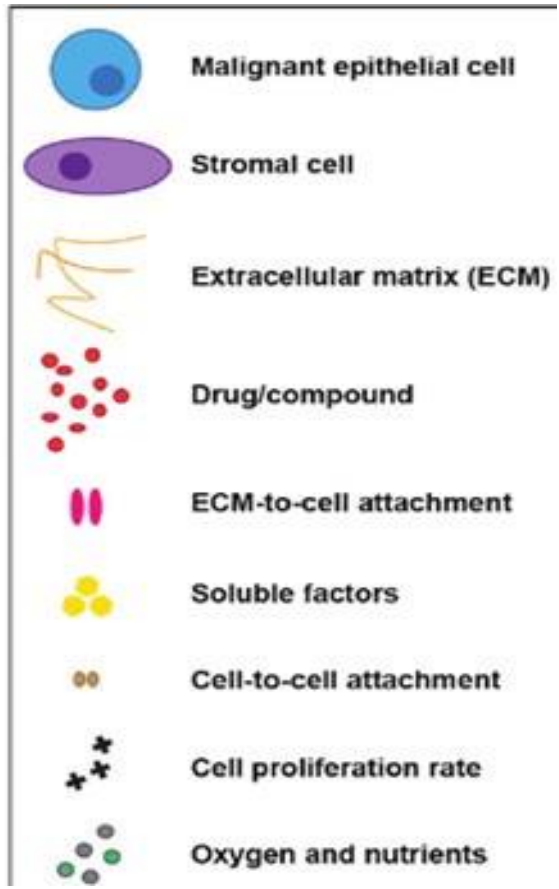
Ongoing: to have different kind of cells in the microenvironment

- Cells could be:
  - Stromal cells
  - Immune cells
  - Cancer-associated cells
- We want to model cancer-immune system interaction

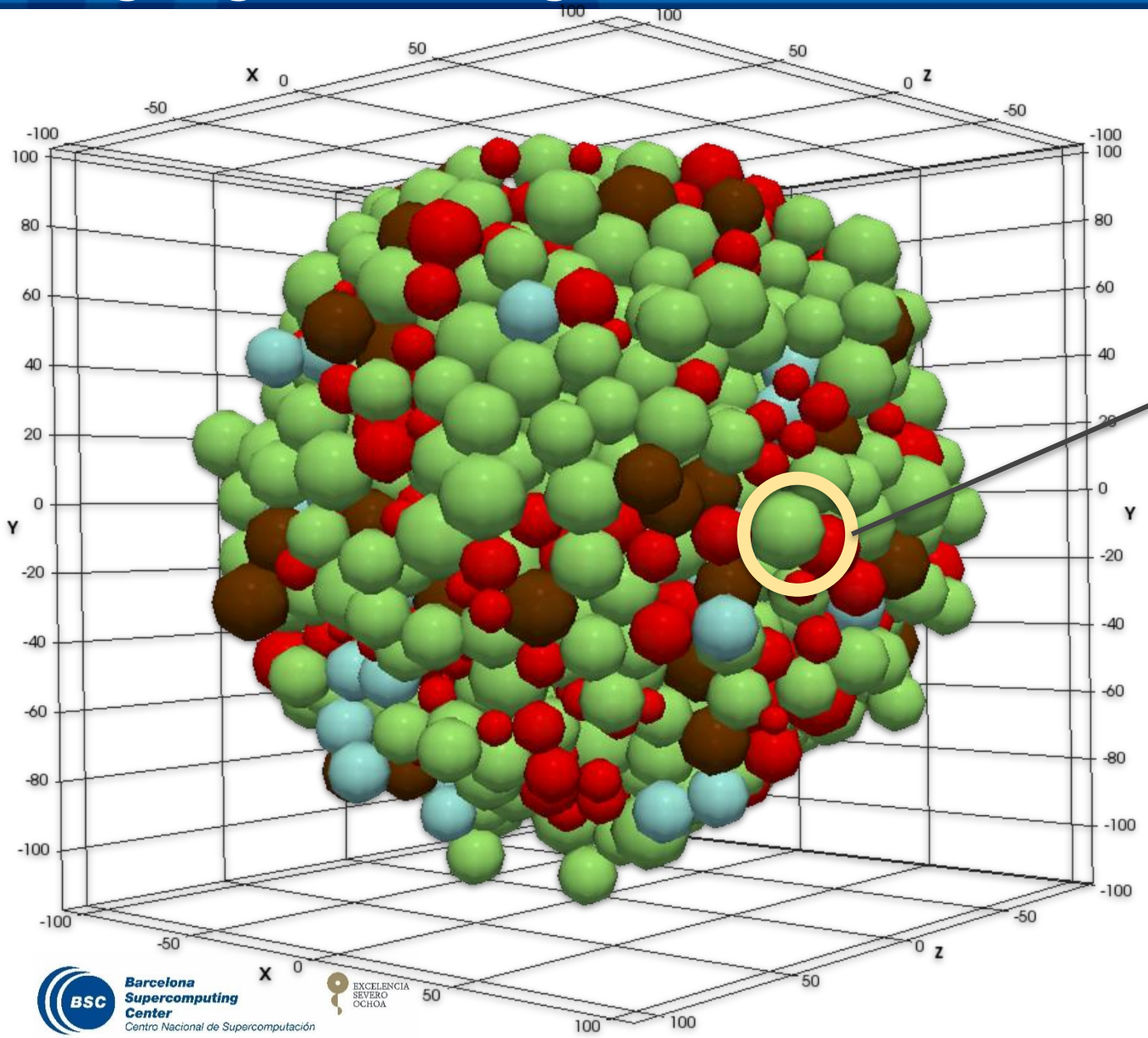




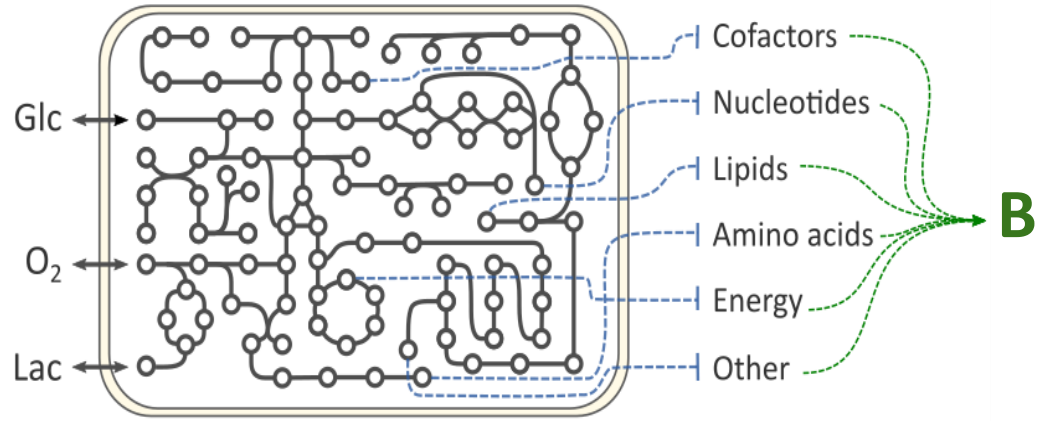




Ongoing: Connecting metabolic models to PhysiCell



Genome-Scale Metabolic Model



Constrinat-Based Modelling → metabolic phenotype

- Import fluxes
- Excretion fluxes
- Growth rate μ

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If you want more information

- Open source code for multi-scale modelling
  - Available at GitHub
- Uses agent-based modelling for physical phenomena
- PhysiBoSS uses Boolean modelling for biological phenomena
  - Adapted from MaBoSS

https://github.com/MathCancer/PhysiCell

http://physicell.org/tutorials/

RESEARCH ARTICLE

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

Ahmadreza Ghaffarizadeh[1], Randy Heiland[2], Samuel H. Friedman[1,3], Shannon M. Mumenthaler[1], Paul Macklin[1,2]*

1 Lawrence J. Ellison Institute for Transformative Medicine, University of Southern California, Los Angeles, California, United States of America, **2** Intelligent Systems Engineering, Indiana University, Bloomington, Indiana, United States of America, **3** Opto-Knowledge Systems, Inc., Torrance, California, United States of America

* macklinp@iu.edu

https://github.com/bsc-life/PhysiBoSSv2

Systems biology

PhysiBoSS: a multi-scale agent based modelling framework integrating physical dimension and cell signalling

Gaelle Letort[1,2,3]*, Arnau Montagud[1,2,3], Gautier Stoll[4], Randy Heiland[5], Emmanuel Barillot[1,2,3], Paul Macklin[5], Andrei Zinovyev[1,2,3] and Laurence Calzone[1,2,3,]*

USE CASES

PerMedCoE works on five use cases to drive the development of cell-level simulations

Cancer Diagnosis Based on Omics Information

Drug Synergies for Cancer Treatment

COVID-19 Multiscale Modelling of the Virus and Patients' Tissue

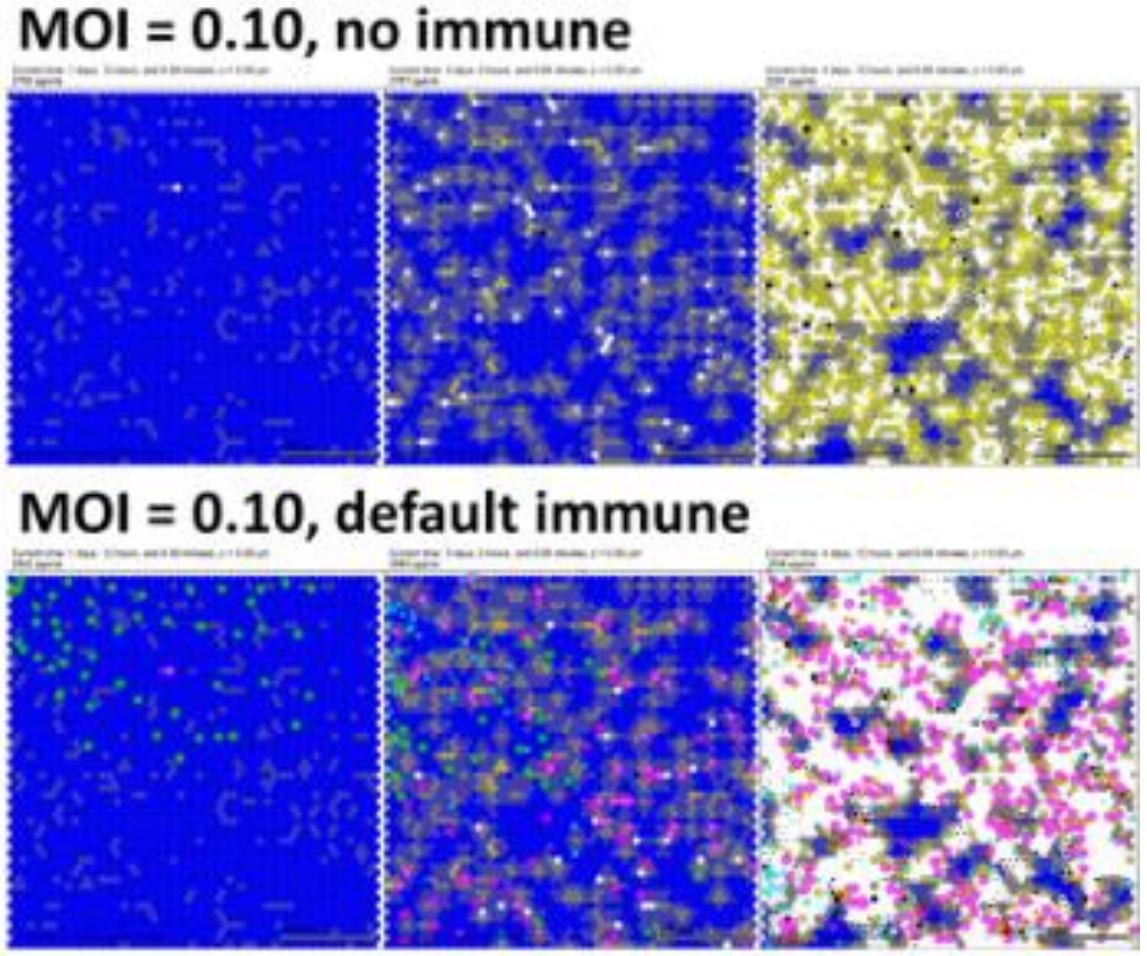
Tumour Evolution Based on Single-Cell Omids and Imaging

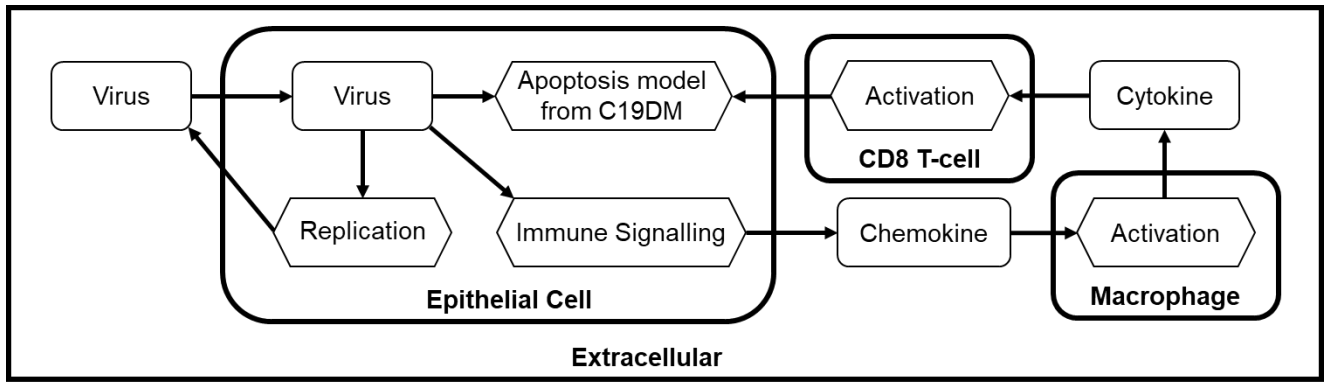
Personalised Modelling of Groups of Rare-Disease Related Patients

Multiscale modelling for COVID-19 infection

- Our work builds upon the PhysiCell for COVID initiative, a multiscale model of SARS-CoV-2 dynamics in lung tissue that can integrate
  - virus infection
  - epithelial host cell demise
  - different immune cells' response
- We incorporate PhysiBoSS so we can integrate Boolean models
  - offers mechanistic insights of SARS-CoV-2 infection and dissemination among human host cells

MOI: multiplicity of infection

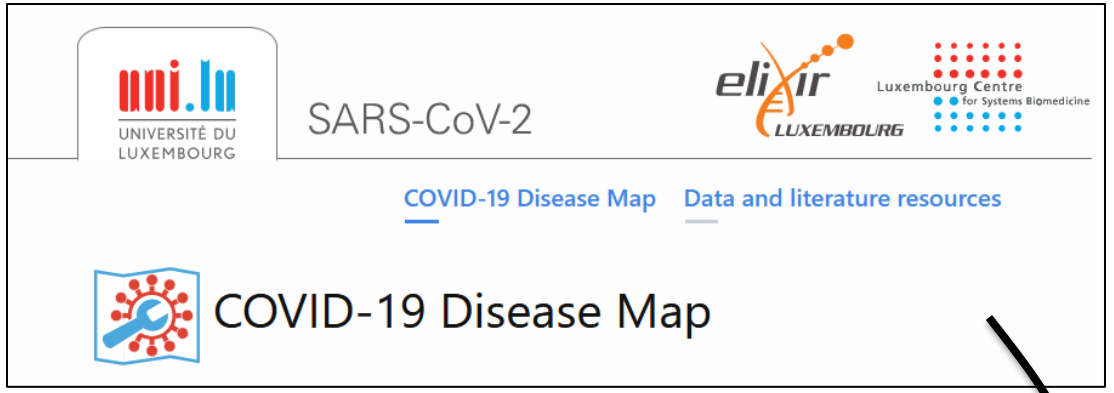




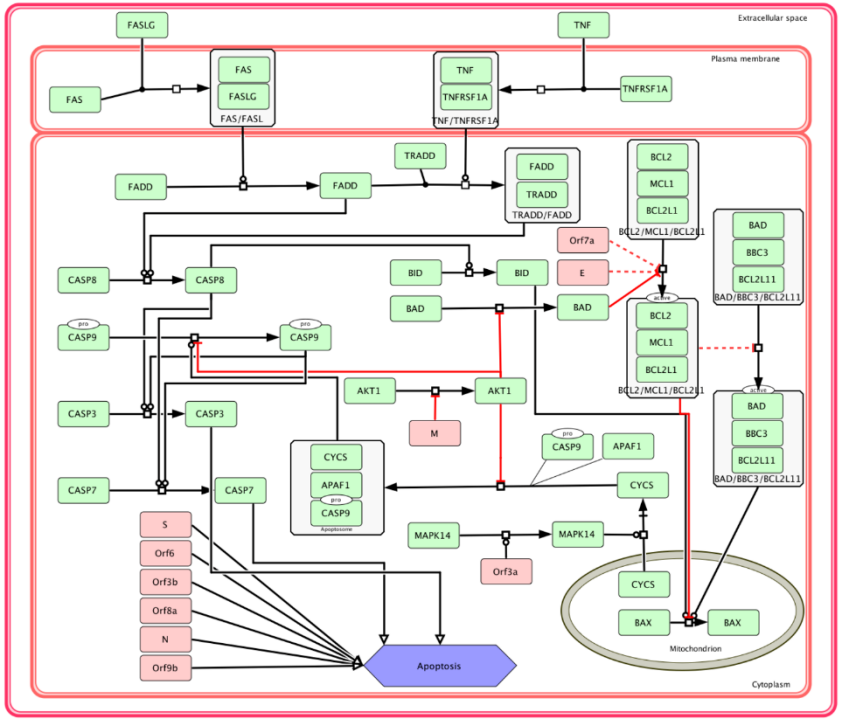
PhysiBoSS-COVID can integrate cell-specific Boolean models

- We incorporate cell- and pathway-specific Boolean models to detail the interactions of virus and human cells.
- These models come from the COVID-19 Disease Map initiative
  - Integrates and formalises mechanistic knowledge of COVID-19 infection
  - Map to model converted by CaSQ
- These Boolean models can then be simulated using MaBoSS allowing for the study of the cells' mechanisms and their perturbations

https://covid.pages.uni.lu/



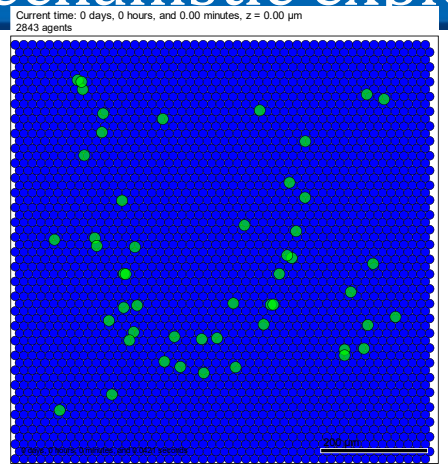
CaSQ



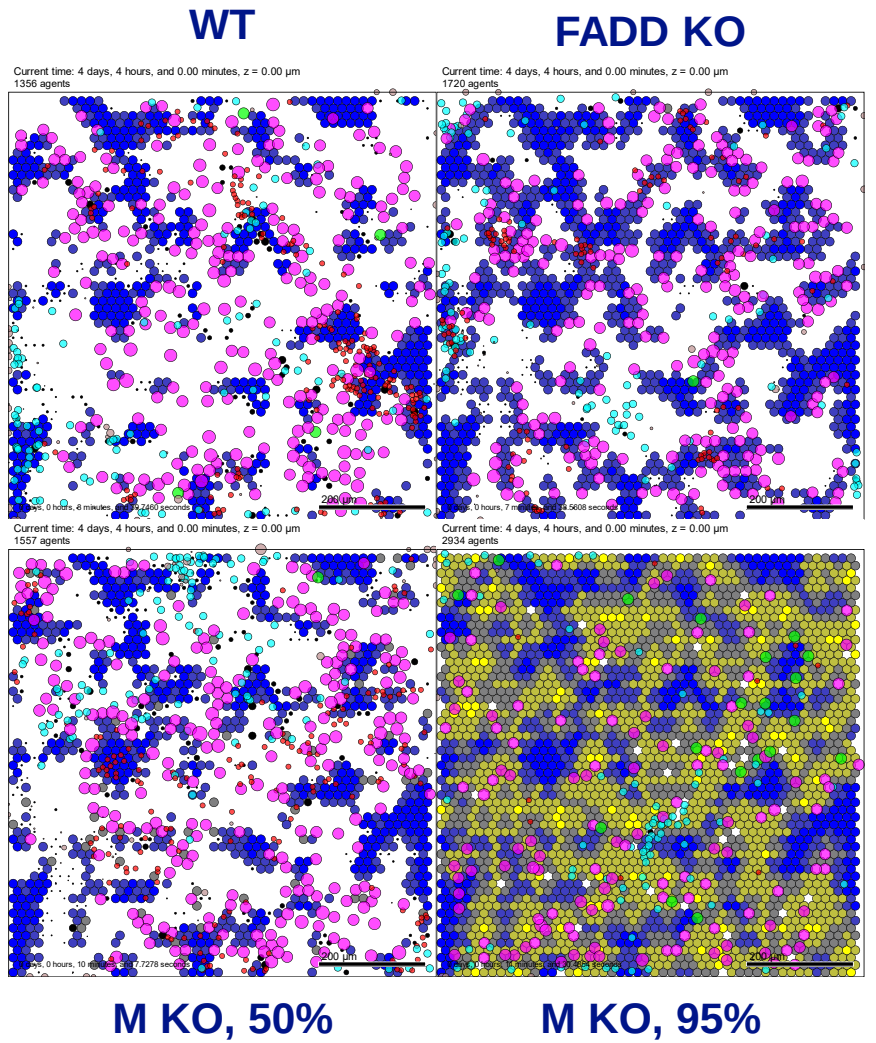
PhysiBoSS allows for the mechanistic exploration of COVID-19 infection

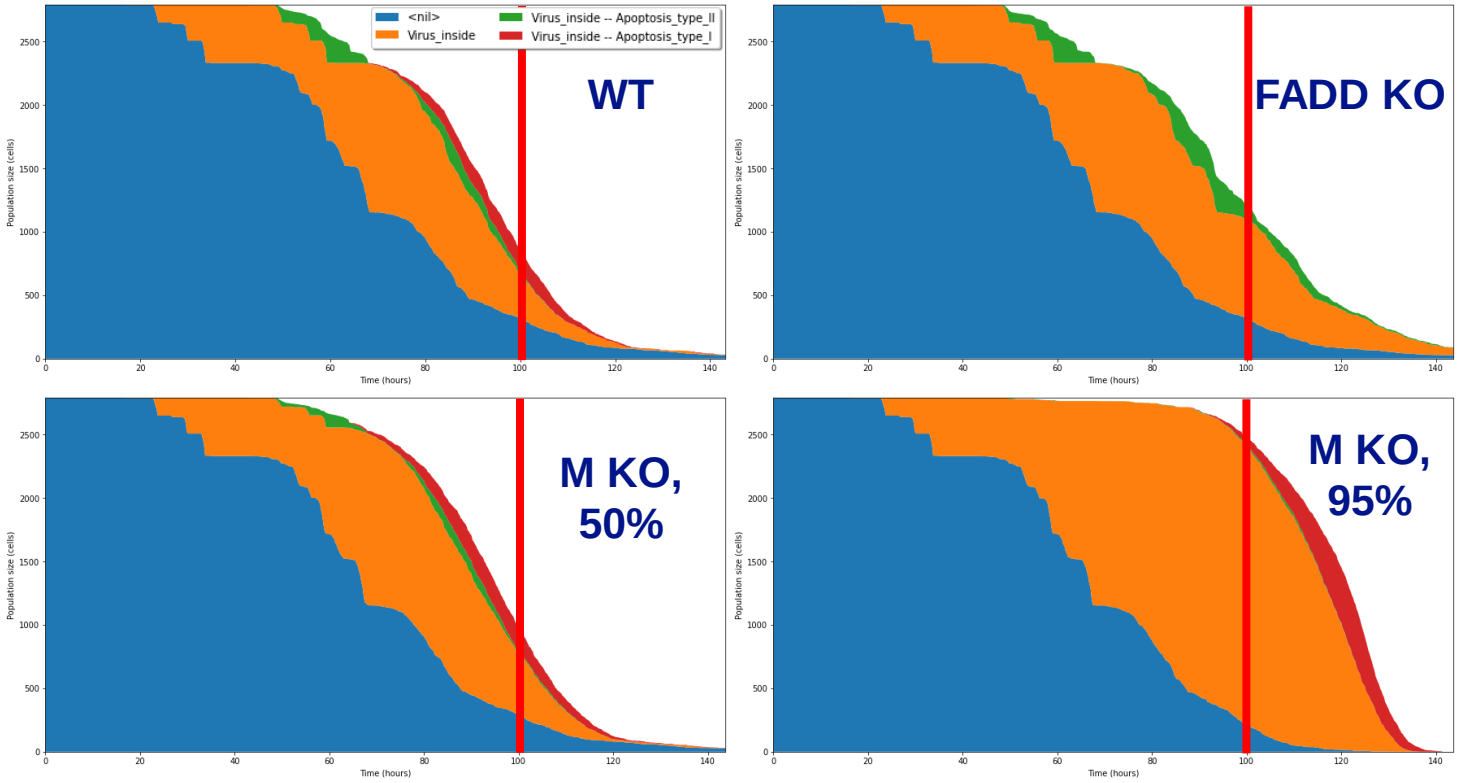
- With PhysiBoSS we can now inspect
  - mutants that affect epithelial cells' apoptosis
  - heterogeneous cell populations

t=0



t=100 hours





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