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Computational Biology Across Scales: From Pathway Modelling Tools to Cell-Level Simulations

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Academical Background

Master degree in Physics of Complex System for Biology

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- Dr. Laurence Calzone
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- Pr. Emmanuël Barillot

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Physics department, Turin

Institut Curie, Paris

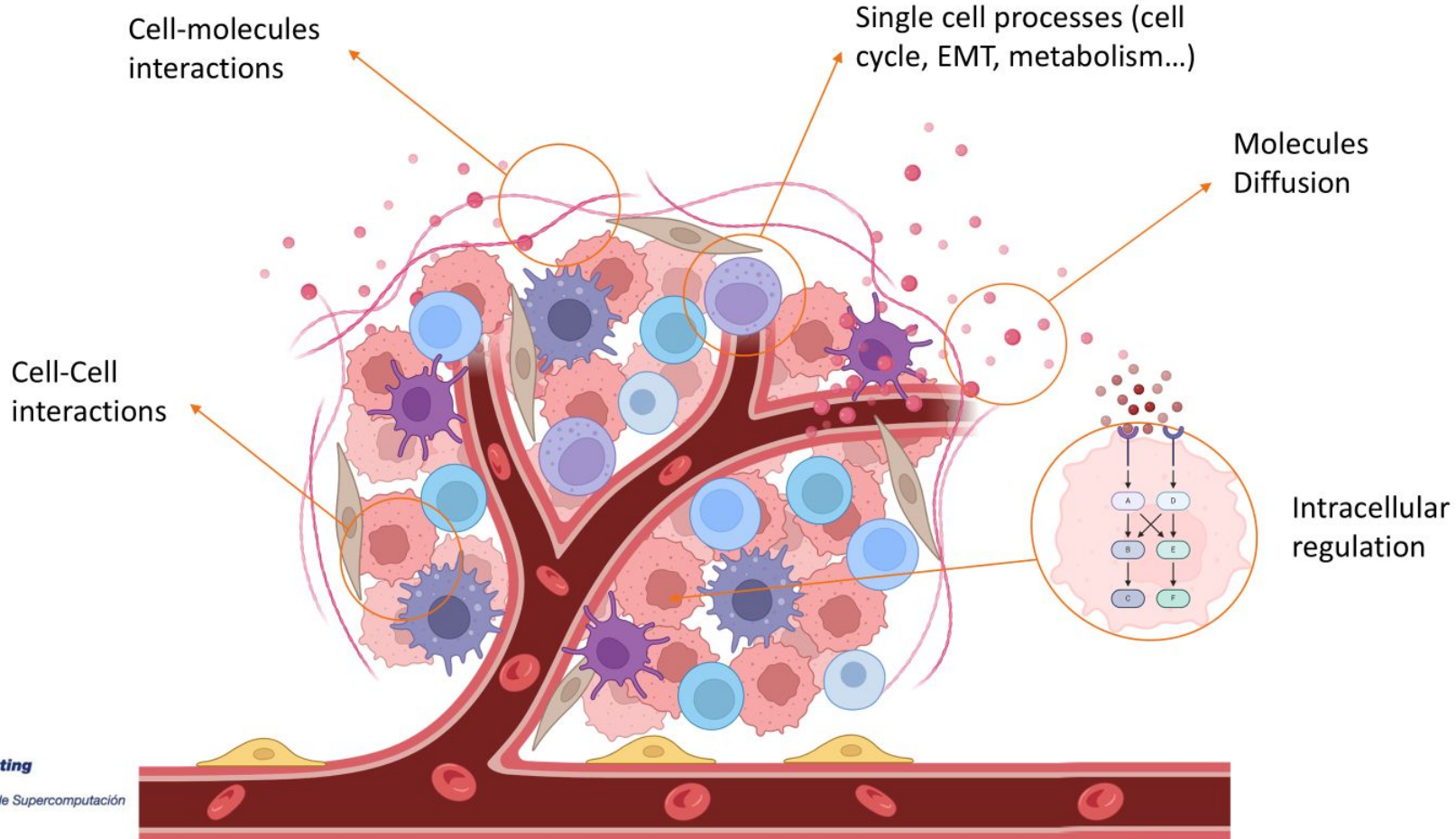
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BSC, Barcelona

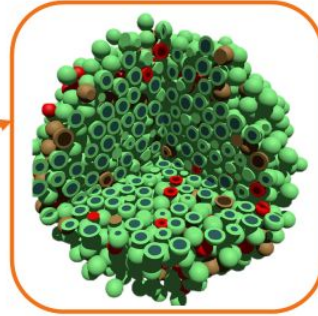
Outline

- Introduction
- Part 1 - Neko
 - Hands On - From static network to Boolean model (almost...)
- Part 2 - MaBoSS
 - Hands On - simulating the Boolean model
- Part 3 - PhysiCell/PhysiBoSS
 - Hands On - Simulating cells and their Boolean model

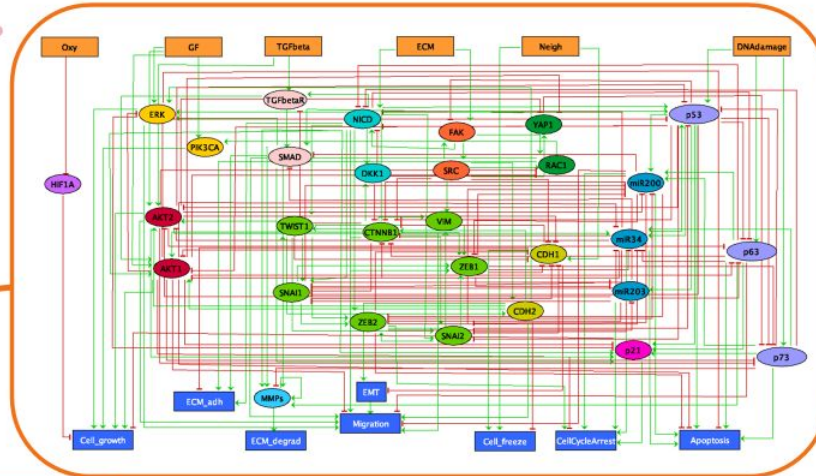
Multiscale processes in biology



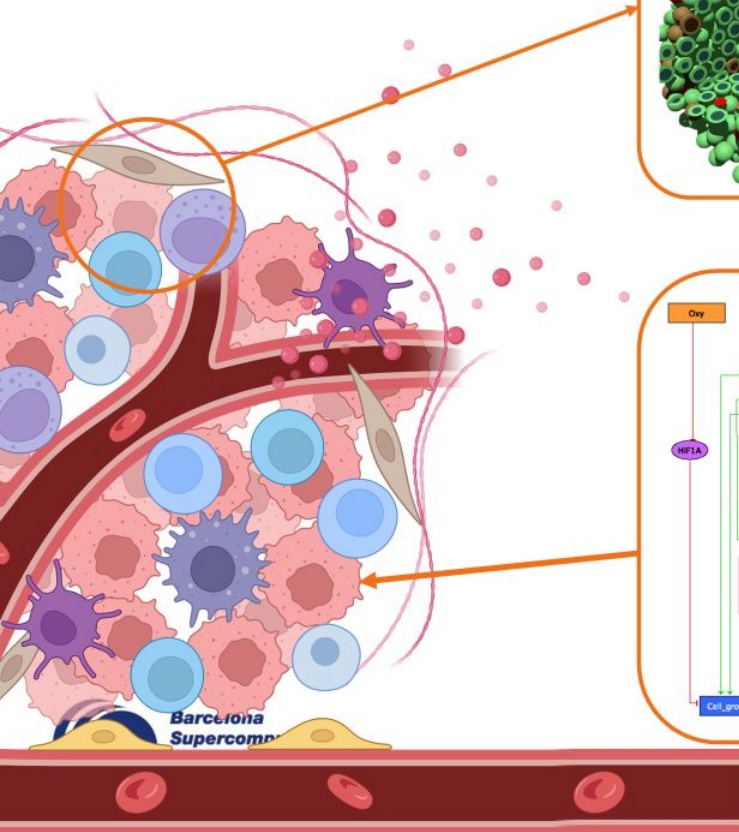
How to go multiscale



Simulating cells
physical properties
and molecules
diffusion with an
agent-based approach



Simulating
pathways activity
using an
**intracellular
model**: ODEs,
SDEs, Boolean...



Where do we start?

The recipe for a good multiscale model:

A Cell Cycle model!

1. A good **biological question** → what do you want/need to simulate?

2. A nice **intracellular model** → to simulate pathways activity

**Cyclins activity and
Apoptotic switch!**

3. An **agent-based** modeling framework → to simulate cell's physical properties and phenotypes

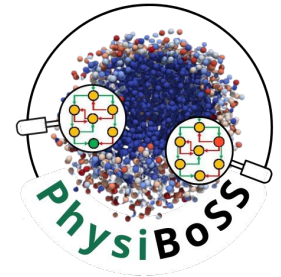
**Modeling a cell population
growing and try different
mutants condition!**

From a static network to multiscale



**Explore new
scenarios**

- 01 Create Static Network
- 02 Convert to Boolean Model
- 03 Validate Simulation
- 04 Integrate with PhysiBoSS
- 05 Start In Silico Experiments



Before we start

1. Make sure to have anaconda and git!
2. Clone the following repo:
https://github.com/marcorusc/HandsOn_PRI_Me.git
3. Once cloned, from the cloned folder, create the environment with conda using:
conda create --name hands_on --file hands_on-env.txt

Conda mini-cheatsheet:

1. Get Anaconda distribution here:
<https://www.anaconda.com/download>
2. Activate environment:
conda activate <env_name>
3. List packages in the env:
conda list
4. You can install packages in your env by pip or conda:
pip install <package_name>
conda install <package_name>

Part 1 - Introducing NeKo



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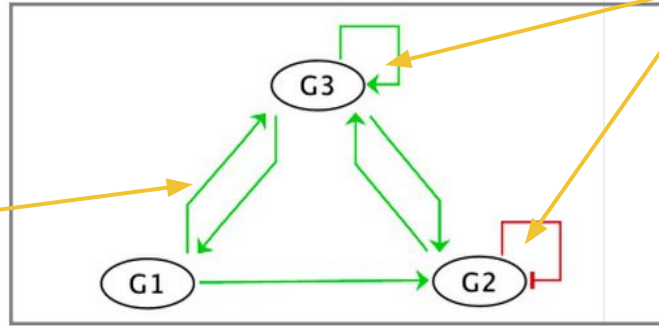
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What is a Boolean model?

A simpler alternative to ODEs and SDEs

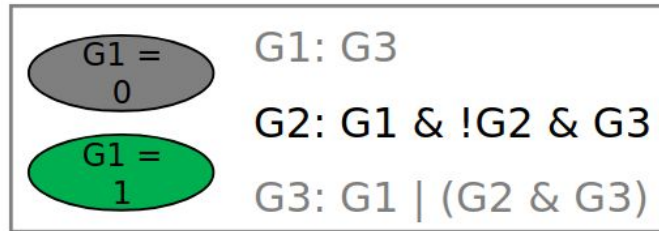
Interactions

Network

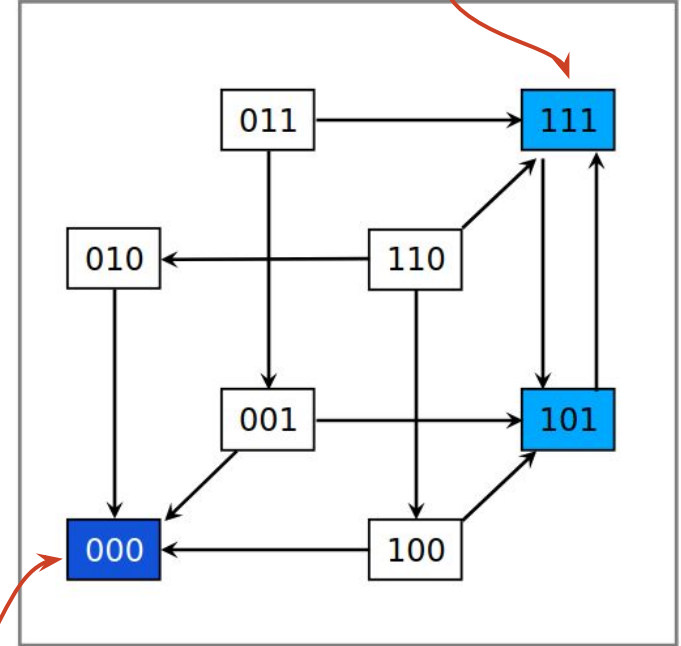


Genes/Proteins

Dynamics



Cyclic attractor



Attractor

How do we build a Boolean model?

Two approaches:

1. Data

2. No Data



Carnival, Signaling profiler, Augusta...



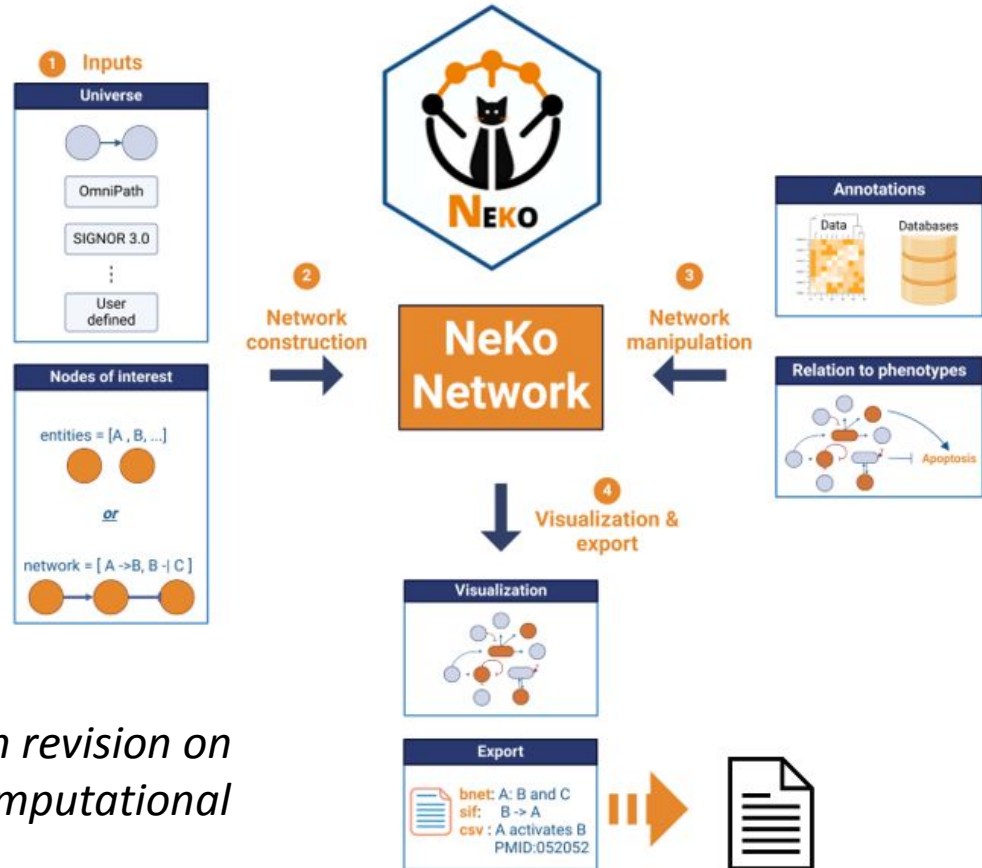
1. Reading LOTS of publications
2. Exploring many databases AND reading LOTS of publication

It can take up to 6 months (or even more...)



Introducing NeKo

An extensible and adaptable python package to create static networks and Boolean models from prior-knowledge



NeKo, what do you need?

- 1) A research focus, ex: cell invasion, metabolism, cell cycle...
- 2) A set of genes of interest (**SEEDS**)
- 3) One or more databases to interrogate: Omnipath, Signor, Huri, Kegg, Wikipathway....



Universe

NeKo_network(**SEEDS**, *Universe*)

Pandas Dataframe:
Source, Target, Effect

*~10.000 / 100.000
interactions*



Choose one or more **STRATEGIES**

We are going to discuss
them during the hands on

NeKo Hands On

- Installation (if not done)
- Opening Jupyter Notebook and importing NeKo
- Create our first Network object
- Populate the Network
- Visualize the Network
- Changing database
- Exporting the Network

How to install

1. Make sure to have your environment activated
2. `pip install nekomata` (the name `neko` was already taken...)
3. install dependencies if necessary (it should not)
4. If issues check: <https://github.com/sysbio-curie/Neko> or ask me!

Hands on:

- Navigate in the folder NeKo with: *cd NeKo* (on Linux)
- Open a Jupyter Notebook: *jupyter notebook*
- **Hands On!**

Question: Can we create a working Boolean model using just NeKo?

Part 2 - Introducing MaBoSS

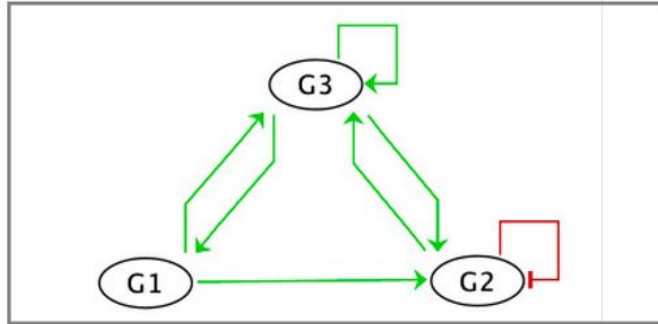


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Refresh: Boolean model

Network

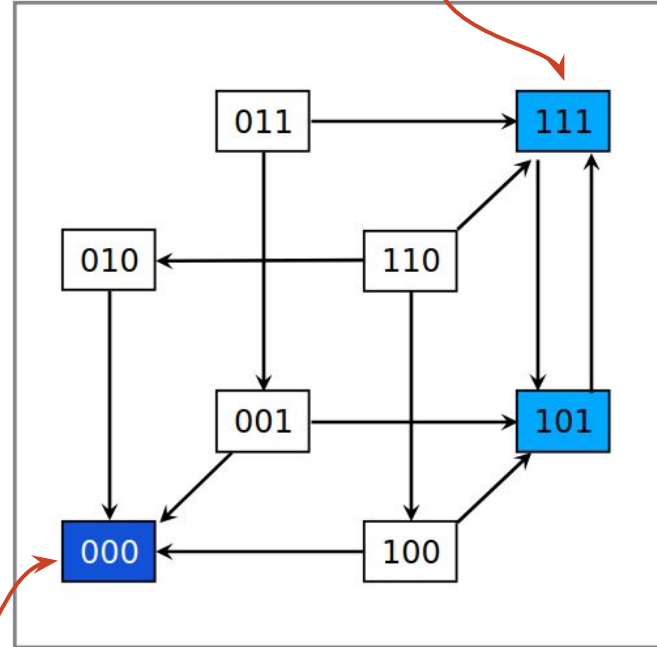


Dynamics



Attractor

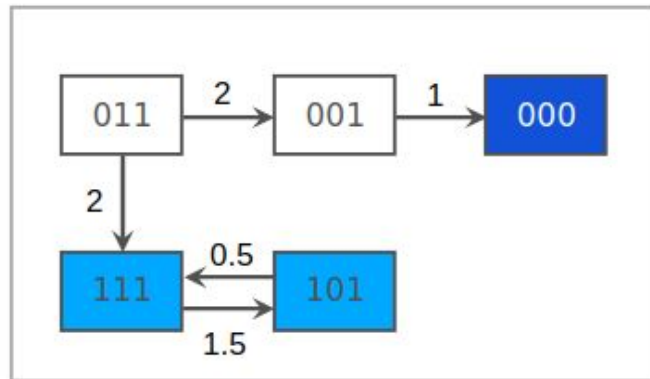
Cyclic
attractor



Markovian Boolean Stochastic Simulator

- C++ software with Python binding
- Simulates continuous time Markov process on BN
- Stochastic transition between nodes state through logical equation
- Leverages the Gillespie algorithm

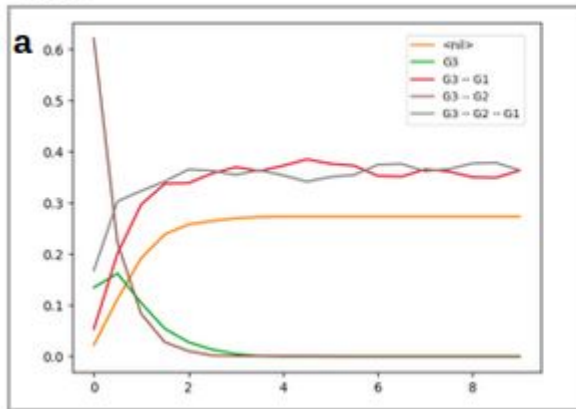
```
Node TWIST1
logic = (
  rate_up =
  rate_down
)
```



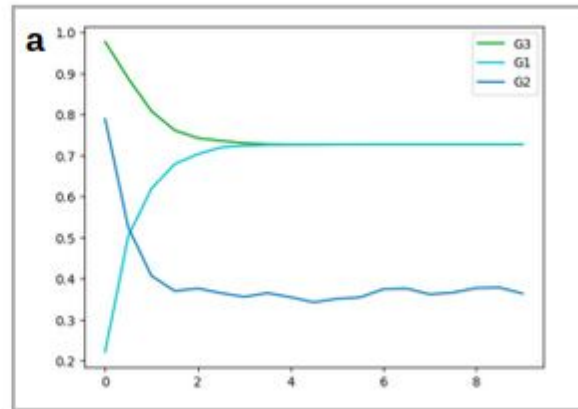
(NICD) | HIF1A;

1.0 : 0.0;

A
State



Node



MaBoSS, what do you need?

- A .bnd file containing your network model
- A .cfg file containing your network configuration (can be modified using Python)
- Possible model repositories to try: <https://www.cellcollective.org/>, <https://www.ebi.ac.uk/biomodels/>, http://ginsim.org/models_repository
- There is also an online version of MaBoSS → WebMaBoSS ! <https://webmaboss.vincent-noel.fr/>

MaBoSS Hands On

- Installation (if not done)
- Opening Jupyter Notebook and importing MaBoSS
- Loading our first MaBoSS model
- Simulate the model
- Visualize the results
- Try some mutations

How to install

1. Make sure to have your environment activated
2. *conda install -c colomoto maboss*
3. You can always use WebMaBoSS if it does not work on local:
<https://webmaboss.vincent-noel.fr/>

Hands On:

- Navigate in the folder MaBoSS with: *cd MaBoSS* (on Linux)
- Open a Jupyter Notebook: *jupyter notebook*
- **Hands On!**

Don't miss the seminar by Dr. Laurence Calzone (Institut Curie, Paris) on March !

Part 2 - Introducing the PhysiCell ecosystem



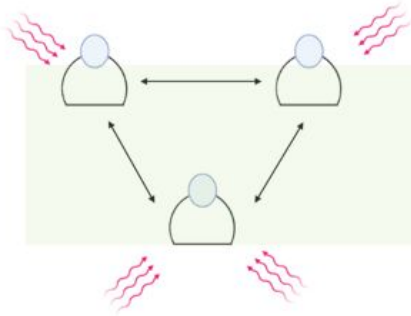
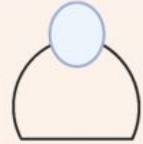
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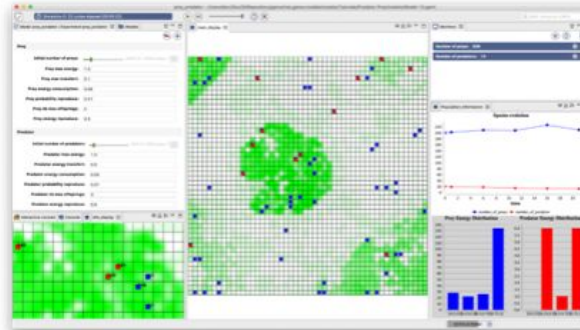
Multi Agent-based Systems

Agent-oriented Programming

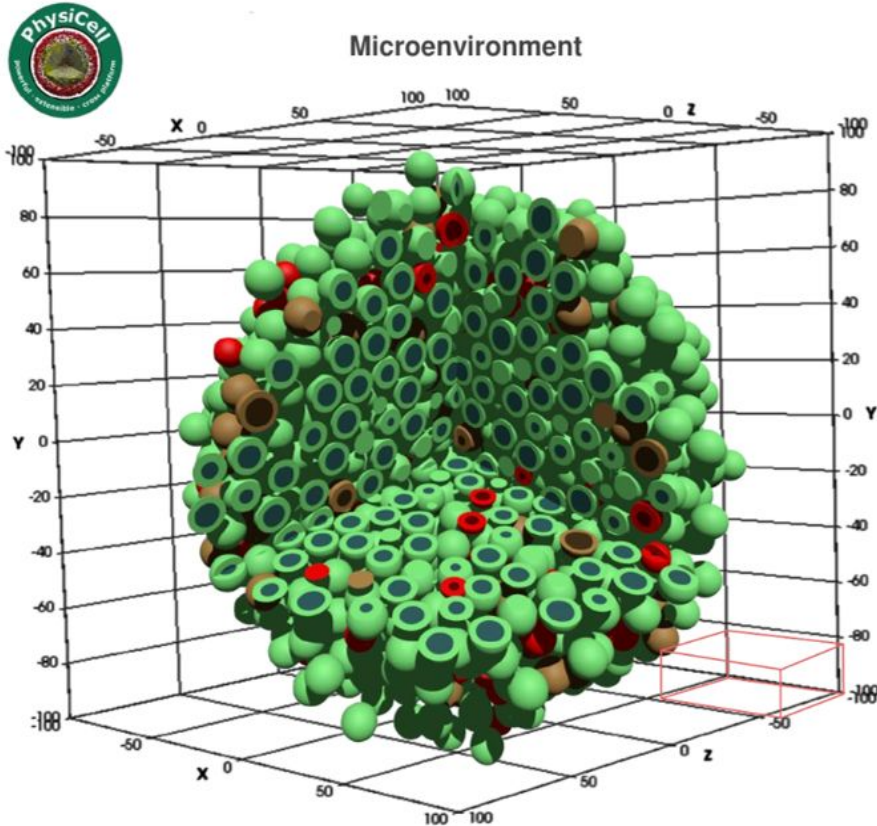
- **Autonomous:** makes independent decisions without any human intervention
- **Social:** communication with other agents
- **Reactive:** perceives the environment and can modify its surrounding



Capture non-intuitive collective behaviors from simple agent-agent interactions



Introducing PhysiCell



Diffusion equations

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

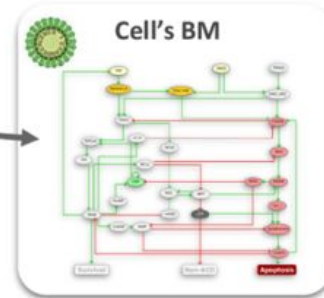
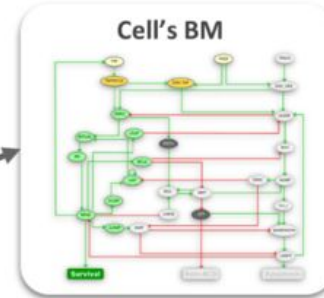
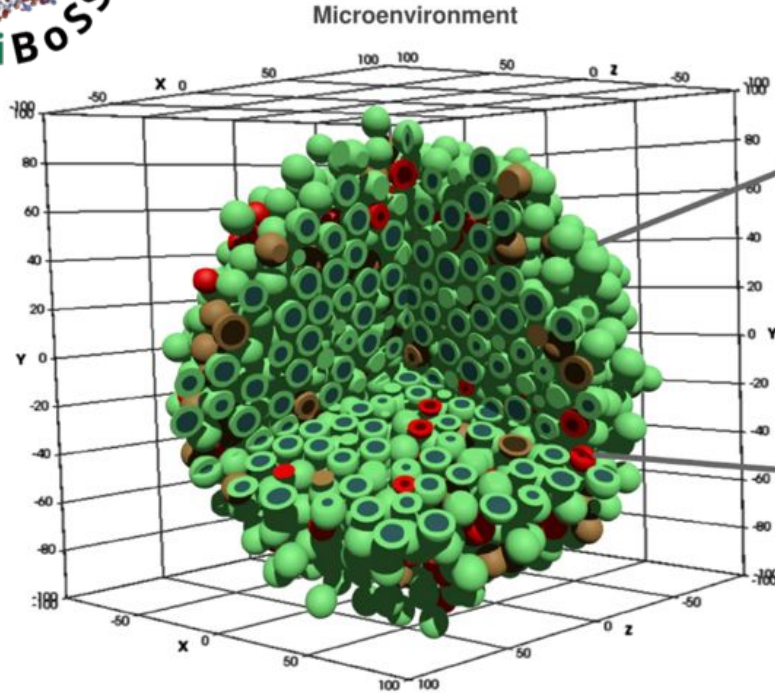
System of PDEs for each molecule:

- Diffusion term
- Decay
- Uptake/Production

PDEs are solved using BioFVM



Introducing PhysiBoSS



**Markovian Boolean
Stochastic Simulator**

$$\rho_{(S \rightarrow S')} = R_i^{\text{up}}(S) \text{ if } S_i = 0$$

$$\rho_{(S \rightarrow S')} = R_i^{\text{down}}(S) \text{ if } S_i = 1$$

PhysiBoSS, what do you need?

- A .bnd file containing your network model
- A .cfg file containing your network configuration (can be modified using Python)
- The official GUI of PhysiCell → PhysiCell Studio installed (next slide)
- Nothing else! PhysiCell provides us with a list of possible **signals** and **behaviors**!

PhysiBoSS Hands On

- Installation (if not done)
- Opening the PhysiCell GUI
- Creating a simple model of cell growth controlled by a Boolean model
- Simulate the model
- Visualize the results
- Try some mutations

How to install

1. Clone PhysiCell on your machine:
git clone <https://github.com/MathCancer/PhysiCell.git>
2. Clone the PhysiCell-Studio on your machine in a separate folder:
git clone <https://github.com/PhysiCell-Tools/PhysiCell-Studio.git>
3. Navigate in your PhysiCell folder and compile the template project:
cd ~/your/path/to/PhysiCell
make template_BM
make -j
4. Now open the studio from the PhysiCell folder:
python ~/path/to/PhysiCell-Studio/bin/studio.py -e project -c config/PhysiCell_settings.xml



Hands On:

- Interesting Boolean models can be found in the **MaBoSS** folder of the **Hands On material** → Sizek **Cell Cycle model** and Corral **Differentiation model**
- Ready-to-use config file for PhysiCell are available in the **PhysiCell** folder of the **Hands On material** → Cell Cycle model mutations, Corral Differentiation model mutations
- **Hands On!**

References

- Ruscone, Marco, Eirini Tsirovouli, Andrea Checcoli, Denes Turei, Emmanuel Barillot, Julio Saez-Rodriguez, Loredana Martignetti, Åsmund Flobak, and Laurence Calzone. “**NeKo: A Tool for Automatic Network Construction from Prior Knowledge.**” bioRxiv, October 15, 2024. <https://doi.org/10.1101/2024.10.14.618311>.
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Gaëlle Letort



INDIANA UNIVERSITY



Paul Macklin



Randy Heiland



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Thank you for your participation!

Questions?

Marco Ruscone, PhD