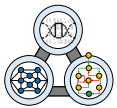
Toward a digital twin: Building multiscale models for Systems Biology

Vincent Noël[1]

[1]Computational Systems Biology of Cancer,
Institut Curie, INSERM U900, Mines ParisTech, PSL Research University, Paris

Sessões Collaborativas PROCC - Fiocruz

July 2024



institut Curie

Inserm
La science pour la santé
From science to health

MINES ParisTech

PSL
RESEARCH UNIVERSITY PARIS

Introduction

› About me



- 2004 - Bachelor degree in Computer Science
- 2008 - Master degree in Computational Biology
- 2012 - PhD in Applied Mathematics



- 2014 - Postdoc at Instituto Butantan in São Paulo



- 2018 - Postdoc at Institut Curie in Paris
- 2021 - Researcher at Institut Curie in Paris

Introduction

- Institut Curie



A hospital

- Largest French cancer center
- Largest European breast cancer center
- Over 2200 persons in two sites
- 50 000 patients per year

A research center

- Largest french cancer research center
- Over 1100 staff members
- 86 research teams
- Over 80 nationalities

Introduction

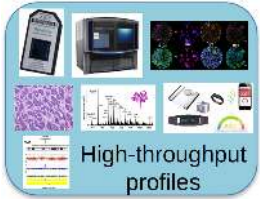
› Computational Systems Biology of Cancer



Emmanuel Barillot

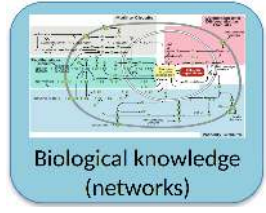


Laurence Calzone



Statistical analysis





Mechanistic modeling

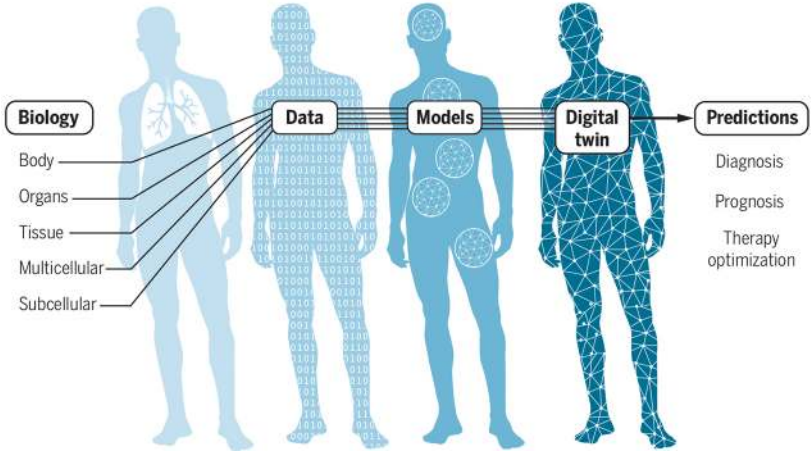
Outline

- Mechanistic modeling of biological systems
- Building multiscale models with PhysiBoSS: a tutorial
- Multiscale model of the different modes of cancer cell invasion
- Ongoing projects

Mechanistic modeling of biological systems

Mechanistic modeling of biological systems

› Toward a Digital Twin

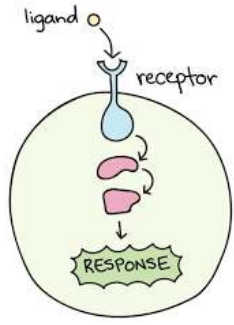


Lauberbacher et al, 2021

Mechanistic modeling of biological systems

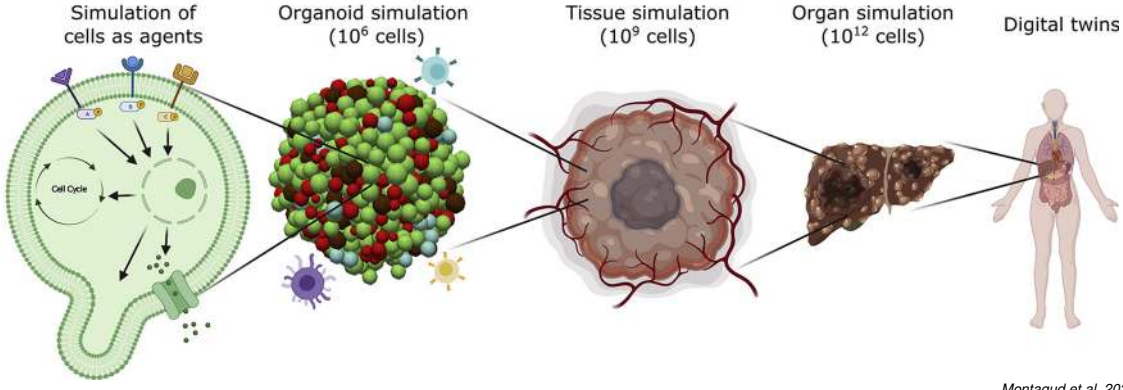
- Why mechanistic modeling ?

  - Describe formally knowledge about a biological system
  - Predict the effect of therapeutical treatments
  - Explain complex/counter-intuitive results
  - Show limits of our knowledge about the system
  - Personalized medicine



Mechanistic modeling of biological systems

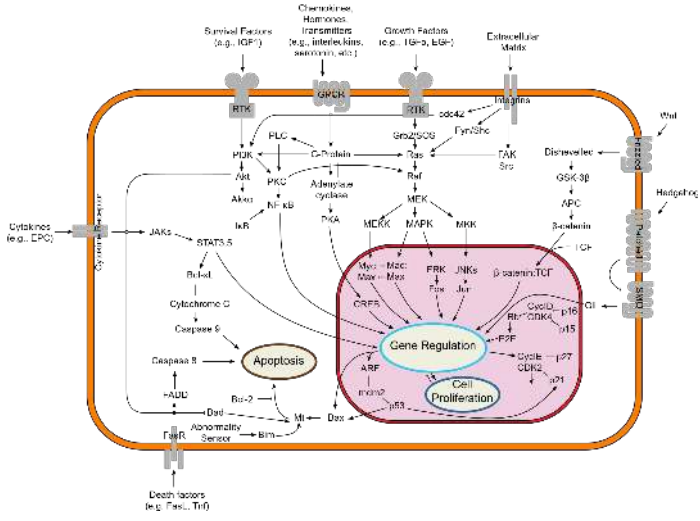
› A multiscale problem



Montagud et al, 2021

Mechanistic modeling of biological systems

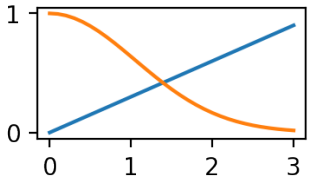
- Cell models
  - More studied
  - Signaling
  - Different frameworks



Mechanistic modeling of biological systems

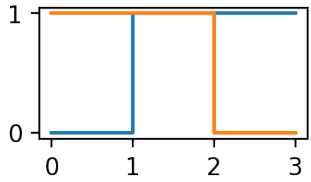
- Different frameworks

Quantitative (ODEs)



- Continuous values
- Continuous time
- Difficult to write
- Difficult to simulate large models

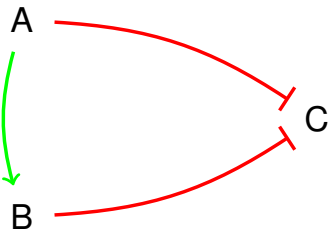
Qualitative (Boolean)



- Discrete values (true/false)
- Sequences of events
- Easy to write
- Can simulate large models

Mechanistic modeling of biological systems

- Boolean formalism



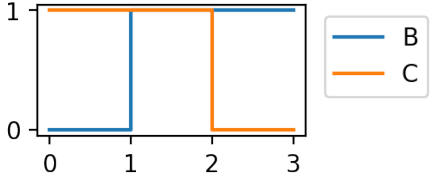
Simulation

Formulas

- A: A (input)
- B: A
- C: !A & !B

Initial values

- A_0: 1
- B_0: 0
- C_0: 1



Mechanistic modeling of biological systems



Gautier Stoll



Laurence Calzone

› Continuous time Boolean modeling



- Boolean
- Stochastic
- Physical time

Continuous time Markov process applied on a Boolean network state space

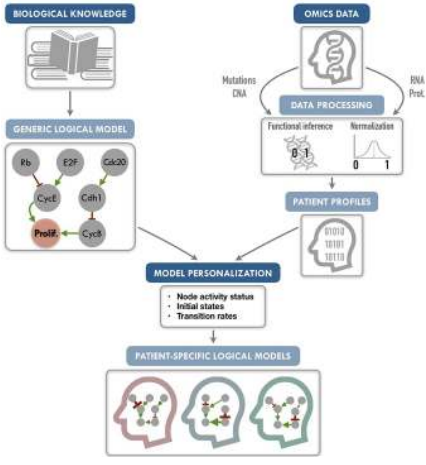
Transition rate :

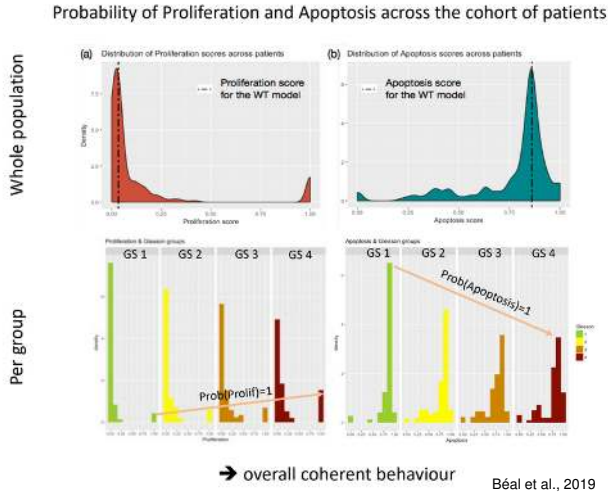
$$p(S \to S') = \begin{cases} R_i^{up}(S), & \text{if} S_i = 0 \\ R_i^{down}(S), & \text{if} S_i = 1 \end{cases}$$

$\Rightarrow$ We have a notion of time in our boolean simulation

Mechanistic modeling of biological systems

› Personalizing generic Boolean models with data

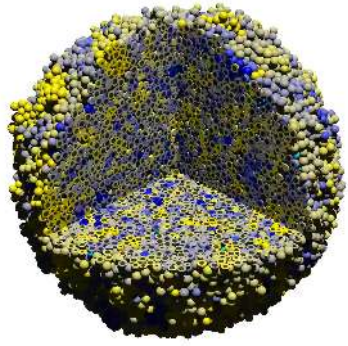




Béal et al., 2019

Mechanistic modeling of biological systems

- Organoid/Tissue models
  - Multi-cellular systems
  - Spatial information
  - Multiple cell types
  - Extra-cellular environment
  - Interactions



Ghaffarizadeh et al., 2018

Mechanistic modeling of biological systems

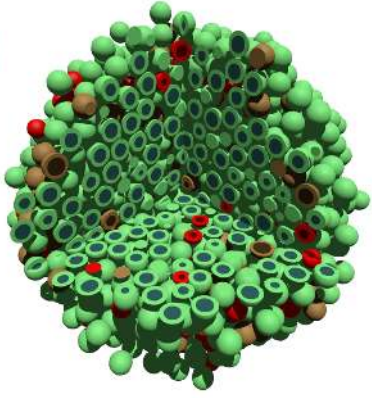
› PhysiCell : Agent-based modeling Framework



Paul Macklin



Randy Heiland

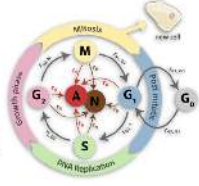


http://physicell.org
https://github.com/MathCancer/PhysiCell

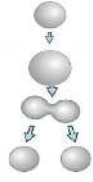
Cell agent properties

- Size (cell volume)
- Position (x, y, z)
- Phenotype
  - Cell cycle Model (G_0, *M, etc*)
  - Death Models
  - Rates
  - Custom Variables
  - Molecular models

Cell Cycle



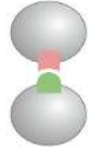
Growth



Migration

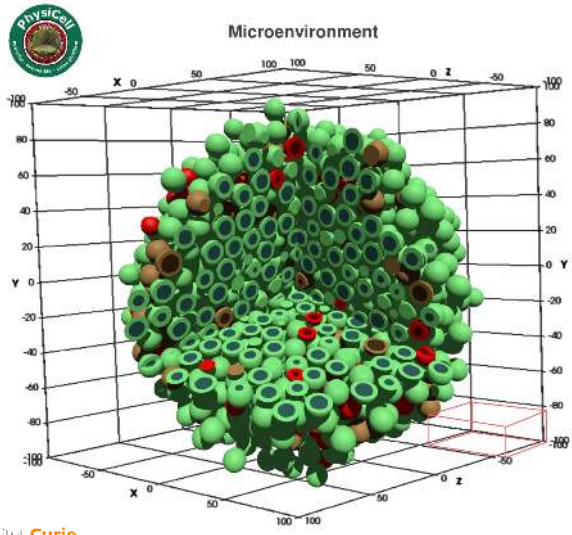


Cell-Cell interactions



Mechanistic modeling of biological systems

› PhysiCell : Agent-based modeling Framework



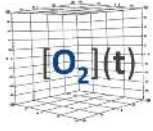
Diffusion equations

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

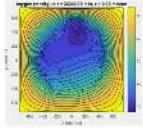
System of PDEs for each molecule:

- Diffusion term
- Decay
- Uptake/Production

PDEs are solved using BioFVM

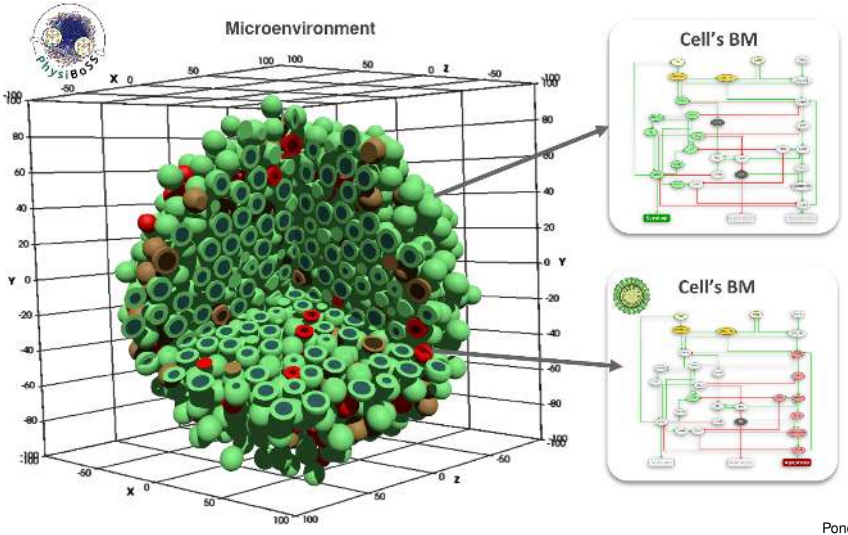






Mechanistic modeling of biological systems

› PhysiCell + MaBoSS = PhysiBoSS



Ponce de Leon et al., 2022

Mechanistic modeling of biological systems

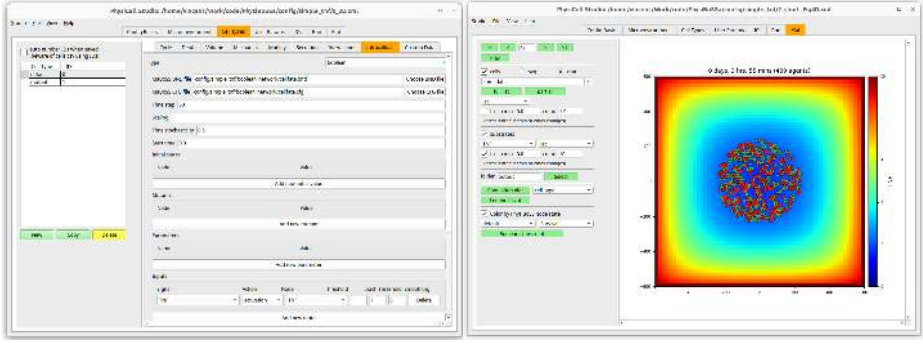
› PhysiCell Studio

Technical Release

PhysiCell Studio: a graphical tool to make agent-based modeling more accessible

Randy Heiland, Daniel Bergman, Blair Lyons, Grant Waldow, Julie Cass, Heber Lima da Rocha, Marco Ruscone, Vincent Noël, Paul Macklin*

DOI 10.46471/gigabyte.128 Views 85 Downloads 12



Mechanistic modeling of biological systems

› HPC/Exascale Centre of Excellence in Personalised Medicine



Alfonso Valencia

Goal

Develop a roadmap to scale-up essential simulation software to prepare the infrastructure of personalized medicine

Results

› MPI and GPU versions of MaBoSS, PhysiCell

› Example workflows of personalized medicine

› The tutorial and the cancer cell invasion model were produced within this project

Consortium of 12 partners from 7 EU Member States



Mechanistic modeling of biological systems

- Take home message
  - MaBoSS (continuous time Boolean modeling) is a **simple** yet powerful tool for modeling **signaling**
  - PhysiBoSS allows the **integration** of intracellular models into agent-based simulations
  - **Multiscale models** describe intracellular signaling up to tissues
  - A step in the direction toward a **digital twin**‘

Building multiscale models with PhysiBoSS: a tutorial

Building multiscale models with PhysiBoSS: a tutorial

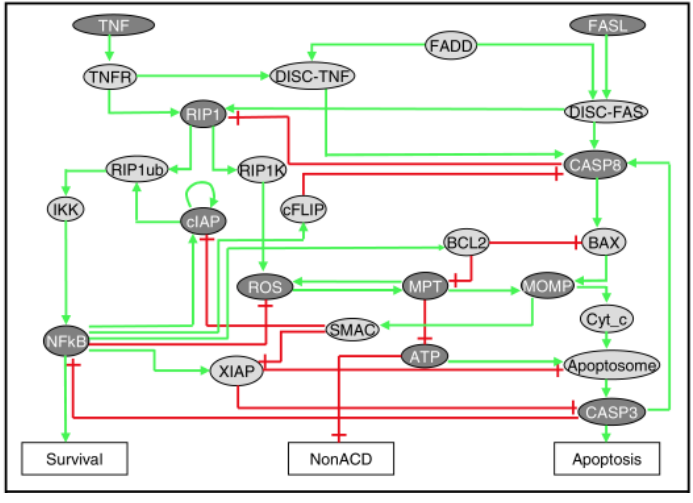
- Introduction
  - PhysiBoSS started from a fork of PhysiCell 1.1.0 (May 2017)
  - PhysiBoSS 2.0.0 was merged into PhysiCell 1.9.0 (July 2021) as an **add-on**
  - PhysiCell model building **simplified** a lot during the years : from pure C++ code, to XML definitions, and now using a GUI
  - PhysiBoSS followed along, with now an **automated mapping** between the agent-based model and the intracellular Boolean models
  - We are publishing a PhysiBoSS **tutorial**, showcasing the recent efforts by presenting 4 use cases

Cell fate model

Goal : Simulate the effect of the Tumor Necrosis Factor (TNF) on a population of cancer cells; rebuilding an existing model written only in C++

Building multiscale models with PhysiBoSS: a tutorial

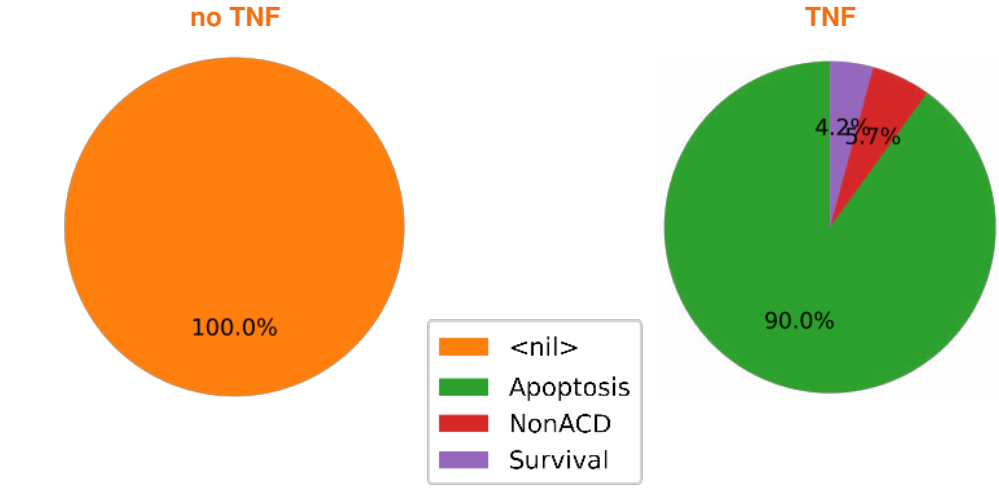
› Cell fate model: Boolean model



Calzone et al, 2010

Building multiscale models with PhysiBoSS: a tutorial

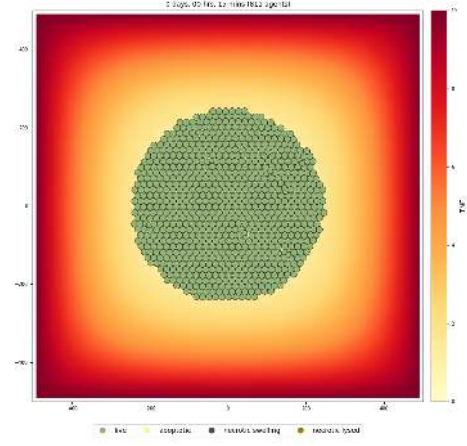
› Cell fate model: Boolean model



Building multiscale models with PhysiBoSS: a tutorial

› Cell fate model: Multiscale model

- › Simulating the Boolean model until steady state (≈ 24h)
- › TNF signal linked to TNF node
- › Apoptosis node linked to Apoptosis rate
- › Necrosis node linked to Necrosis rate
- › Resistant cells dominate quickly



Building multiscale models with PhysiBoSS: a tutorial

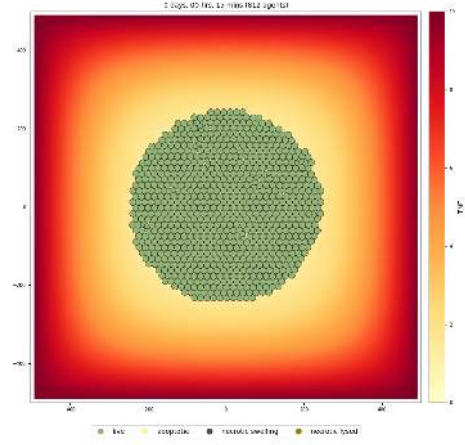
- Cell fate model: Pulsatile treatments

  - Resistance to TNF treatment can be "forgotten"

  - Removing and reintroducing TNF periodically

  - We are able to control the size of the resistant population

  - With the right timings, we can get rid of the tumor



- Cell fate model: Perspectives

  - Simple model representing a drug effect on a tumor

  - Replacing thousands of lines of C++ with 4 mapping rules

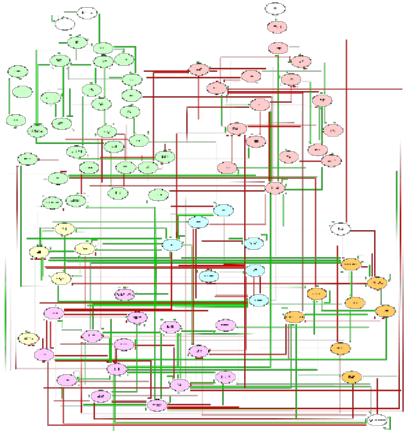
  - Cell fate model can be improved with a more complex one, with more signals

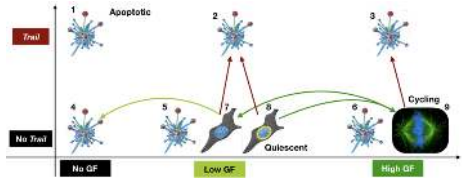
Cell cycle model

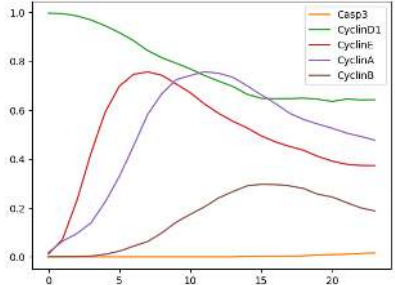
Goal : Replace PhysiCell simple cell cycle by a more complex mechanistic one, based on signaling

Building multiscale models with PhysiBoSS: a tutorial

› Cell cycle model: Boolean model







Sizek et al. 2019

Building multiscale models with PhysiBoSS: a tutorial

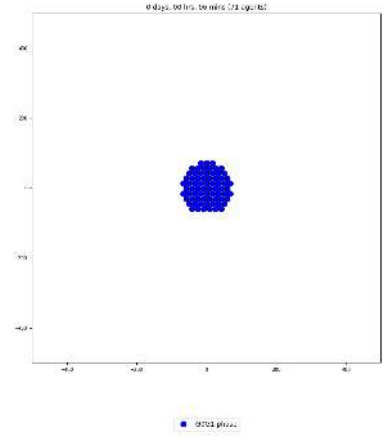
- Cell cycle model: Reproducing PhysiCell's cell cycle model

  - Short Boolean simulations to capture transient effects

  - Mapping each entry node to the exit rate of the previous phase

  - We can use a scaling parameter to set the duration of the cell cycle

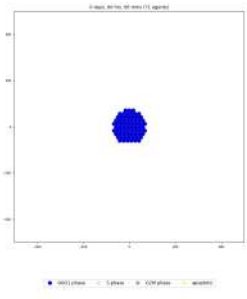
  - We can adjust MaBoSS model rates to adjust relative phases durations



Building multiscale models with PhysiBoSS: a tutorial

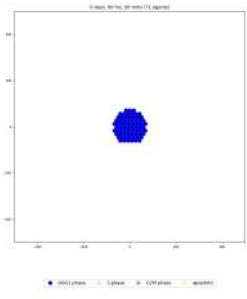
› Cell cycle model: Mutants analysis

Plk1- -



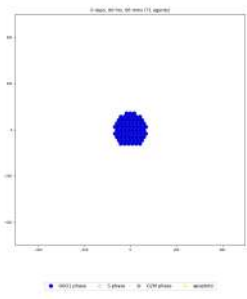
⇒ Cycle arrest in G2

FoxO3- -



⇒ Mitotic catastrophe

p110++



⇒ No Apoptosis

- Cell cycle model: Perspectives

  - A more realistic cell cycle model, reproducing known mutants

  - Many possible improvements in the Boolean model

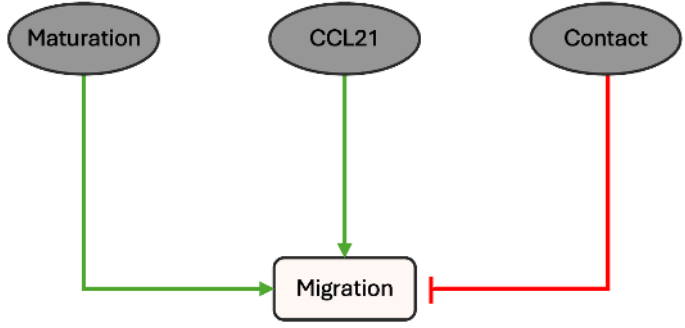
  - Could be used together with model personalization

T-Cell differentiation model

Goal : Simple model describing the migration of mature dendritic cells to the lymph node, and their role in the differentiation of naive T cells

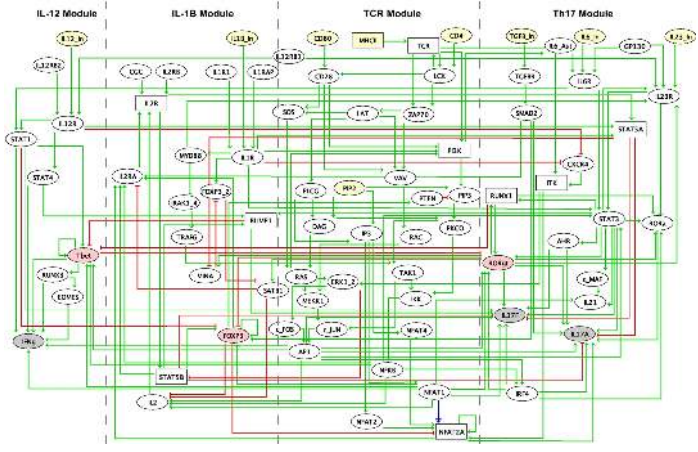
Building multiscale models with PhysiBoSS: a tutorial

› T-Cell differentiation model: Dendritic cells Boolean model



Building multiscale models with PhysiBoSS: a tutorial

› T-Cell differentiation model: Naive T-cells Boolean model

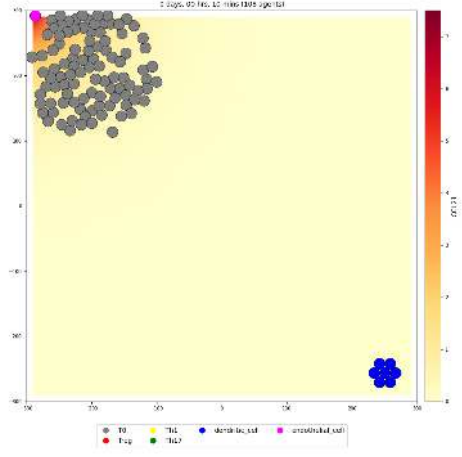


Corral-Jara et al, 2021

Building multiscale models with PhysiBoSS: a tutorial

› T-Cell differentiation model: Naive T-cells Boolean model

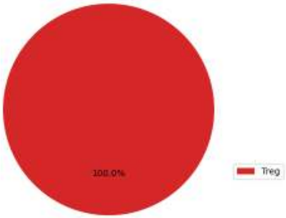
- › Multiple cell types : Endothelial, Dendritic, T0, Th1, Th17, Treg
- › Dendritic cells attracted to the gradient of CCL21 secreted by the endothelial cell
- › Goes back to a random walk once around the T-Cells
- › During contact with T-Cells, DCs trigger T0 differentiation into TH1, TH17, Treg

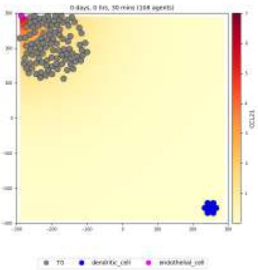


Building multiscale models with PhysiBoSS: a tutorial

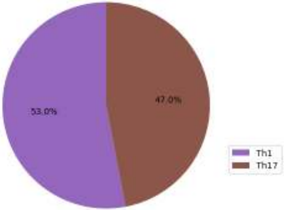
› T-Cell differentiation model: Mutants

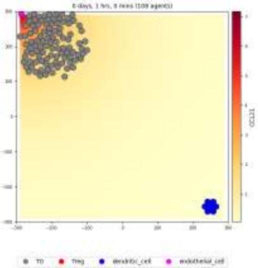
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FoxP3 KO

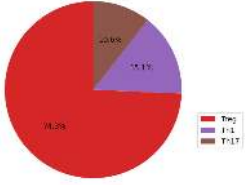


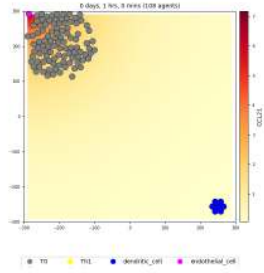


Building multiscale models with PhysiBoSS: a tutorial

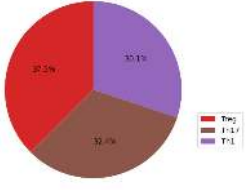
› T-Cell differentiation model: Partial inhibitions

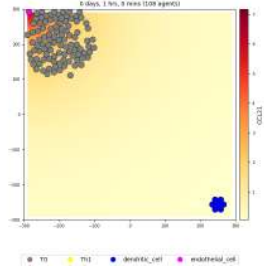
NFkB 90% inhibition





FoxP3 80% inhibition





Building multiscale models with PhysiBoSS: a tutorial

- T-Cell differentiation model: Perspectives
  - Simple model of immune cells interactions
  - Immune system is a perfect candidate for multiscale modeling
  - Needs better cell-type specific Boolean models
  - Projects ongoing about cancer and immune system interactions (Car-T, TLSs)

Building multiscale models with PhysiBoSS: a tutorial

› Preprint



› Making multiscale modeling more accessible

› Under review at Briefing in Bioinformatics

› https://github.com/PhysiBoSS/PhysiBoSS

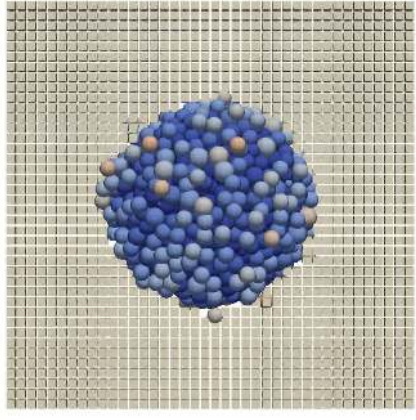
Building multiscale models with PhysiBoSS: a tutorial

Multiscale model of the different modes of cancer cell invasion

- Goal
  - Modeling of the initial stage of metastasis
  - Different migration modes :
    - Single
    - Collective



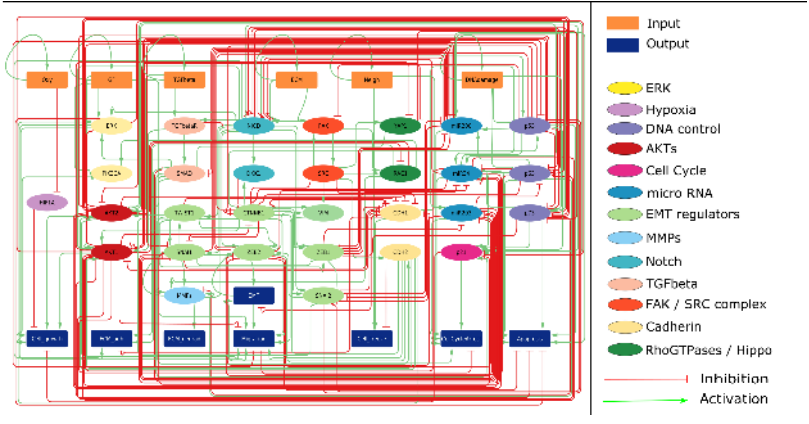
  - Studying the biophysical parameters favoring collective migration



Ruscone et al., 2023

Multiscale model of the different modes of cancer cell invasion

- Signalling network
  - 7 input nodes and 7 output nodes



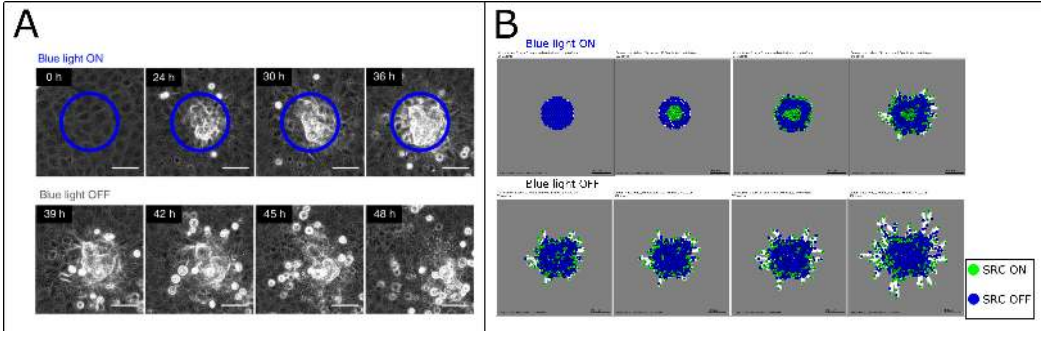
Ruscone et al., 2023

Multiscale model of the different modes of cancer cell invasion

› Reproducing opto-genetics experiment

Local light-activation of the Src oncoprotein in an epithelial monolayer promotes collective extrusion

Sarah Moitrier, Nastassia Pricoupenko, Adèle Kerjouan, Christiane Oddou, Olivier Destaing, Aude Battistella, Pascal Silberzan & Isabelle Bonnet

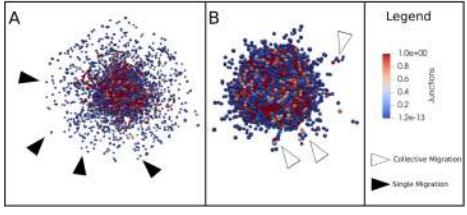


Ruscone et al., 2023

Multiscale model of the different modes of cancer cell invasion

› Parameter sensitivity

- The model includes more than 25 parameters
- The different modes of invasion depends on the parameter values

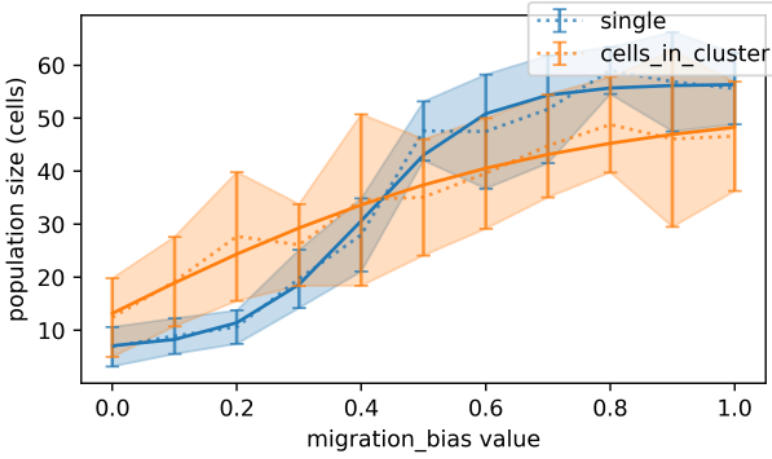


Cell-substrates interaction parameters		
ecm_adhesion_min	set the min adhesion between cells and ECM	1
ecm_adhesion_max	set the max adhesion between cells and ECM	2
cell_ecm_repulsion	set the value of ECM repulsion	15µm/min
Cell parameters		
max_interaction_factor	set the max distance of interaction	1.3µm
homotypic_adhesion_min	set the min adhesion between cells of the same type	0.4
homotypic_adhesion_max	set the max adhesion between cells of the same type	0.8
Threshold parameters		
contact_ECM_threshold	change the threshold needed to trigger ECM interaction	0.(
contact_TGFβ_threshold	change the threshold needed to trigger TGFβ interaction	0.02
contact_cell_cell_threshold	change the threshold needed to trigger Neigh node	0.3
epith_cell_junctions_attach_threshold	change the threshold needed to attach cells in cluster with cell junction	0.05
mes_cell_junctions_detach_threshold	change the threshold needed to detach cells in cluster with cell junction	0.03
Motility parameters		
migration_bias	change value of migration bias for cells with migration node active	0.85
migration_speed	change value of migration speed for cells with migration node active	0.5µm/min
motility_amplitude_min	change the min value of motility amplitude	0.1
motility_amplitude_max	change the max value of motility amplitude	0.8

Ruscone et al., 2023

Multiscale model of the different modes of cancer cell invasion

› Parameter sensitivity : migration bias



Multiscale model of the different modes of cancer cell invasion

› Perspectives



JOURNAL ARTICLE

Multiscale model of the different modes of cancer cell invasion

Marco Ruscone, Arnau Montagud, Philippe Chavrier, Olivier Destaing, Isabelle Bonnet, Andrei Zinovyev, Emmanuel Barillot, Vincent Noël, Laurence Calzone

Bioinformatics, Volume 39, Issue 6, June 2023, btad374, https://doi.org/10.1093/bioinformatics/btad374

Published: 08 June 2023 **Article history**

› The model can reproduce the early steps of invasion.

› An updated version is included in the tutorial paper

› Still room for a lot of improvements (and validation)

Ongoing projects

› Certainty

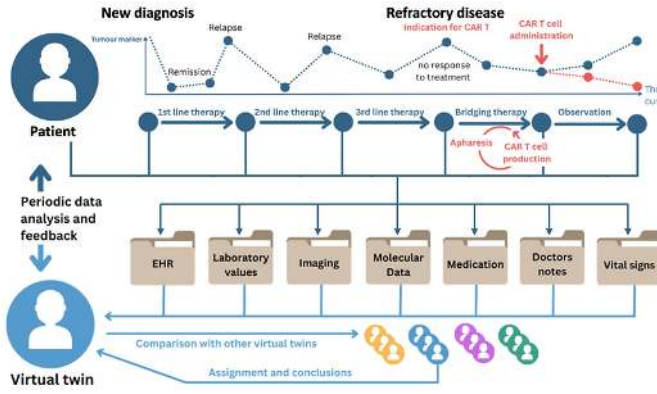
CERTAINTY
A cellular immunotherapy virtual twin for personalised cancer treatment

Fraunhofer IZI



Kristin Reiche

- Build virtual twins for CAR-T therapies in Multiple Myeloma
- Propose treatments that are tailored to each individual
- Use both statistical (ML) and mechanical model



Funded by the European Union

Ongoing projects

› Certainty



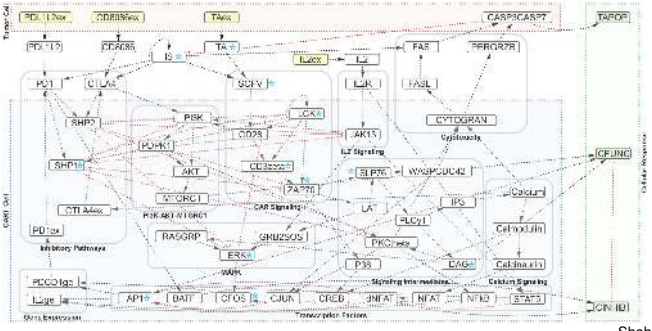
Sophia Orozco Ruiz



Gautier Stoll

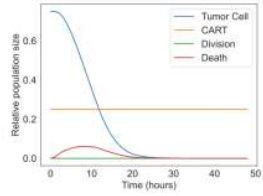


Laurence Calzone

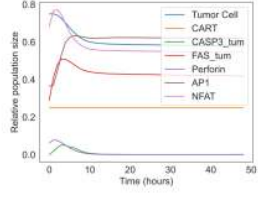


Shah et al., 2023

Follow treatment over time for WT case



Follow treatment for patients with CD28 altered



› Initial work on Boolean intracellular models and personalization

› Integration of these models in a PhysiBoSS multiscale model

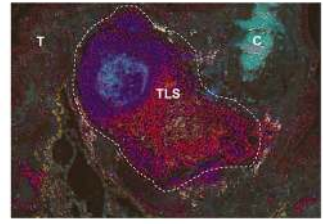
Ongoing projects

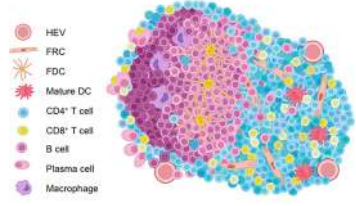
- Multiscale modeling of Tertiary Lymphoid Structures
  - A predictor for favorable responses to immune checkpoint blockade
  - A complex spatial organization of immune cells
  - Creating a permissive milieu for TLS assembly and maturation could pave the way to combinatorial therapies
  - Multiscale framework such as PhysiBoSS are a perfect fit
  - Looking for a student !

A.C.Camargo Cancer Center



Tiago Medina





Domblides et al., 2021

Take-home message

- Multiscale models are important for describing complex **multi-cellular** systems, with **spatial** properties
- Intracellular models are key to personalize signaling
- PhysiBoSS is getting **simpler**
- Tutorial **available** on GitHub $\Longrightarrow$
- More work needs to be done on multiscale personalization



- I'm **moving to São Paulo**, and I am looking for **students** and **collaborations** !

Aknowledgments

Computational Systems Biology of Cancer

institutCurie

Per Med CoE — HPC/Exascale Centre of Excellence in Personalised Medicine

Barcelona Supercomputing Center — Centro Nacional de Supercomputación

INDIANA UNIVERSITY

A.C.Camargo Cancer Center

CERTAINTY — A cellular immunotherapy virtual twin for personalised cancer treatment



Marco Ruscone



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Arnau Montagud



Miguel Ponce de Leon



Gerard Pradas



Alfonso Valencia



Tiago Medina



Gautier Stoll



Andrea Checcoli



Randy Heiland



Paul Macklin



Kristin Reiche

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