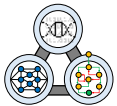
Toward a digital twin: Building multiscale models for Systems Biology

Vincent Noël[1]

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

Seminário de Pós-graduação em Modelagem Computacional - LNCC

November 11, 2024











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

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

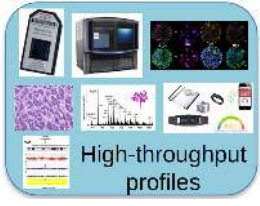
Computational Systems Biology of Cancer



Emmanuel Barillot

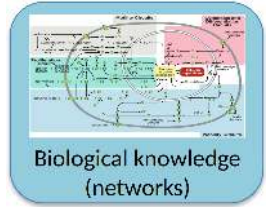


Laurence Calzone



Statistical analysis

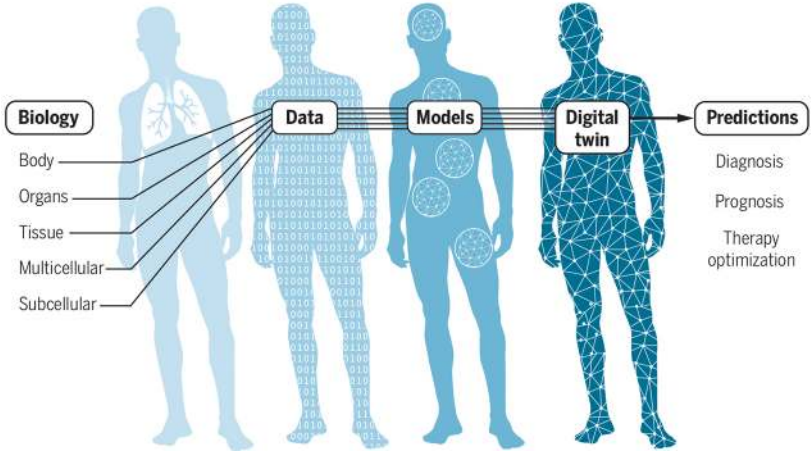




Mechanistic modeling

Mechanistic modeling of biological systems

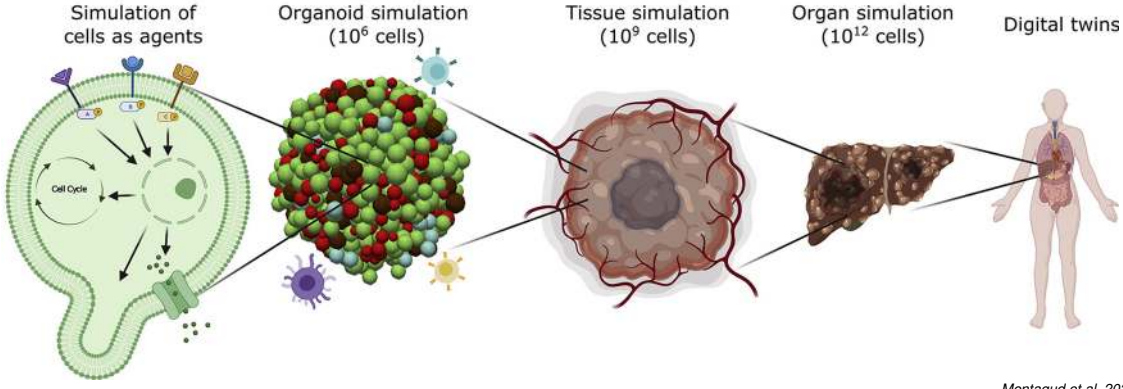
› Toward a Digital Twin



Lauberbacher et al, 2021

Mechanistic modeling of biological systems

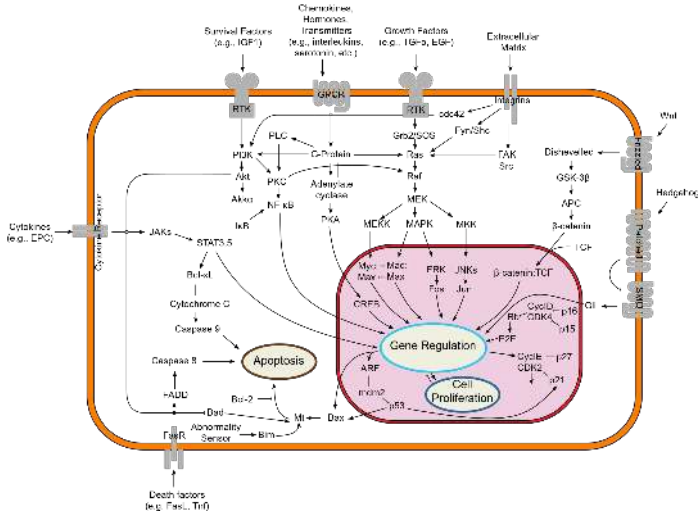
› A multiscale problem



Montagud et al, 2021

Mechanistic modeling of biological systems

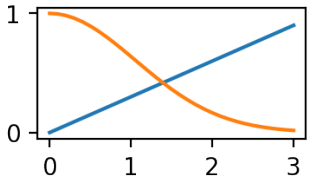
- Cell models
  - More studied
  - Signaling
  - Different frameworks



Mechanistic modeling of biological systems

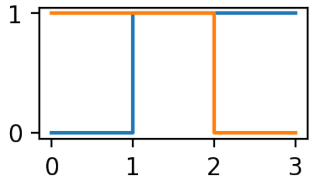
- Different frameworks

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


Gautier Stoll


Laurence Calzone

› Continuous time Boolean modeling



- Boolean
- Stochastic
- Physical time

Continuous time Markov process applied on a Boolean network state space

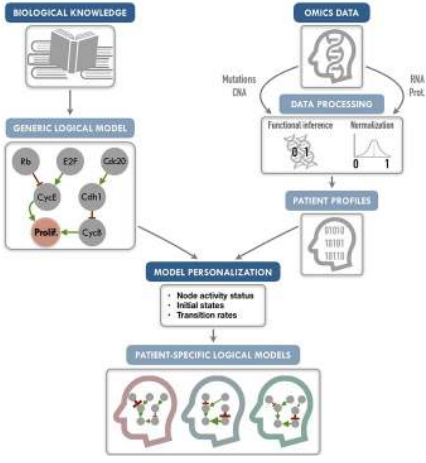
Transition rate :

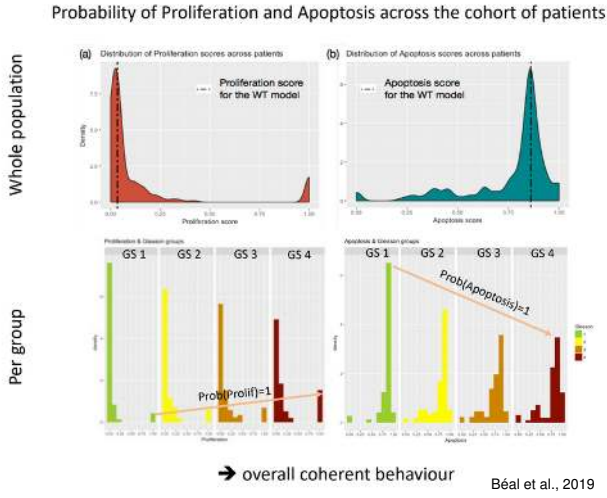
$$p(S \to S') = \begin{cases} R_i^{up}(S), & \text{if} S_i = 0 \\ R_i^{down}(S), & \text{if} S_i = 1 \end{cases}$$

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

Mechanistic modeling of biological systems

› Personalizing generic Boolean models with data

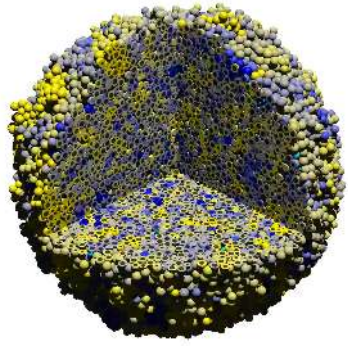




Béal et al., 2019

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

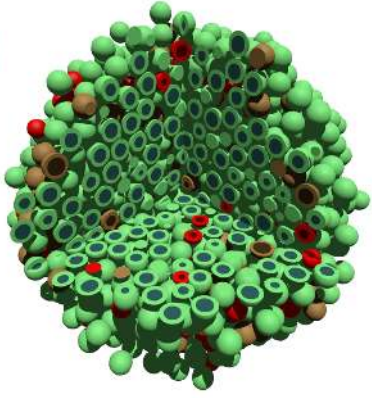
› PhysiCell : Agent-based modeling Framework



Paul Macklin



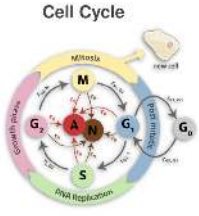
Randy Heiland



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

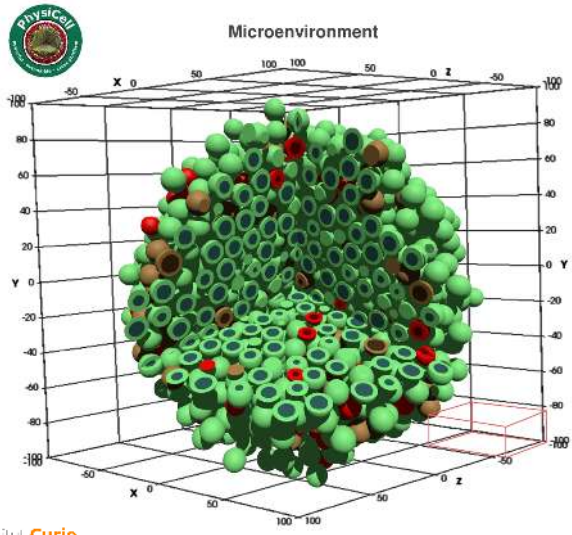
Cell agent properties

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



Mechanistic modeling of biological systems

› PhysiCell : Agent-based modeling Framework



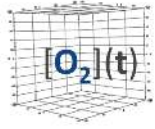
Diffusion equations

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

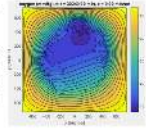
System of PDEs for each molecule:

- Diffusion term
- Decay
- Uptake/Production

PDEs are solved using BioFVM

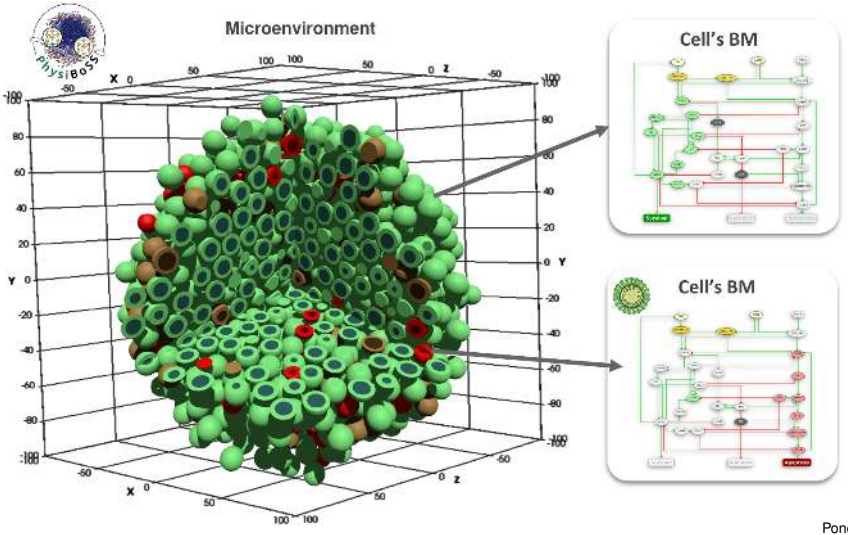






Mechanistic modeling of biological systems

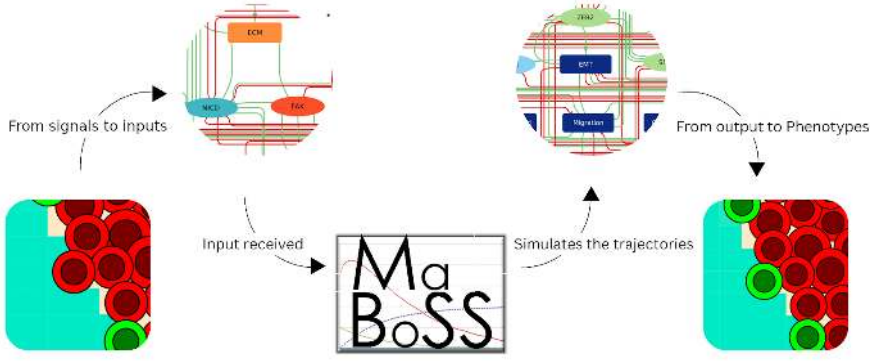
› PhysiCell + MaBoSS = PhysiBoSS



Ponce de Leon et al., 2022

Mechanistic modeling of biological systems

› PhysiCell + MaBoSS = PhysiBoSS



Ruscone et al., 2023

Building multiscale models with PhysiBoSS: a tutorial

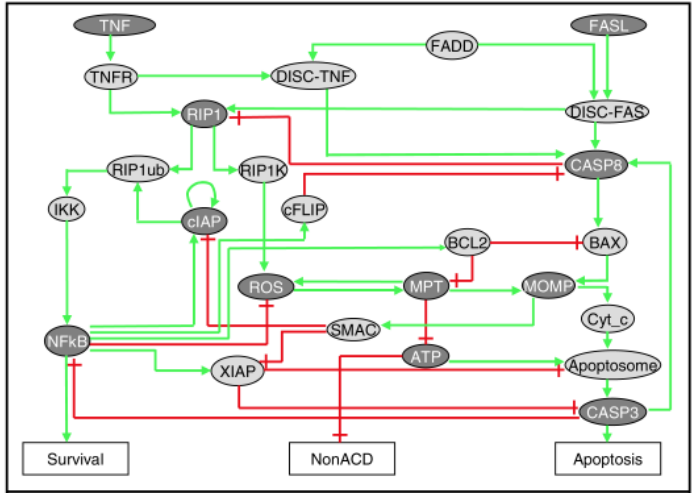
- Introduction
  - PhysiBoSS started from a fork of PhysiCell 1.1.0 (May 2017)
  - PhysiBoSS 2.0.0 was merged into PhysiCell 1.9.0 (July 2021) as an **add-on**
  - PhysiCell model building **simplified** a lot during the years : from pure C++ code, to XML definitions, and now using a GUI
  - PhysiBoSS 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

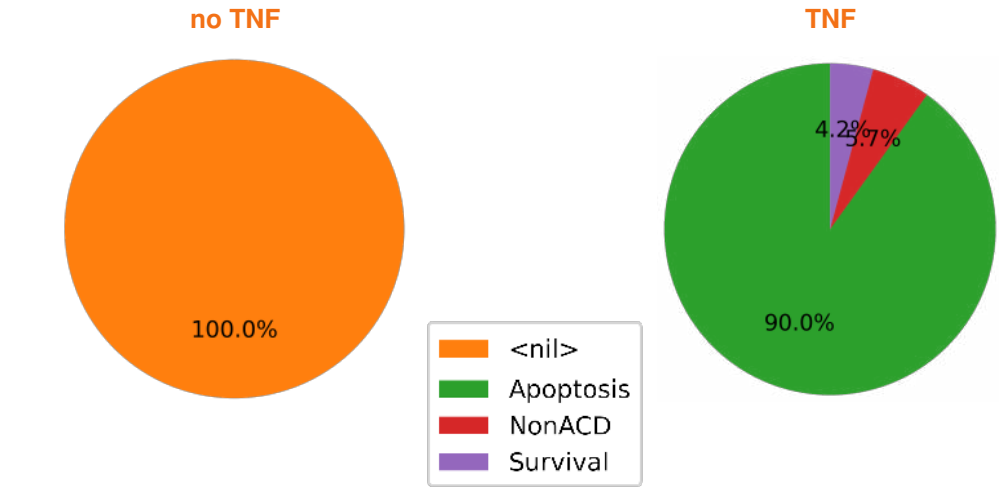
› Cell fate model: Boolean model



Calzone et al, 2010

Building multiscale models with PhysiBoSS: a tutorial

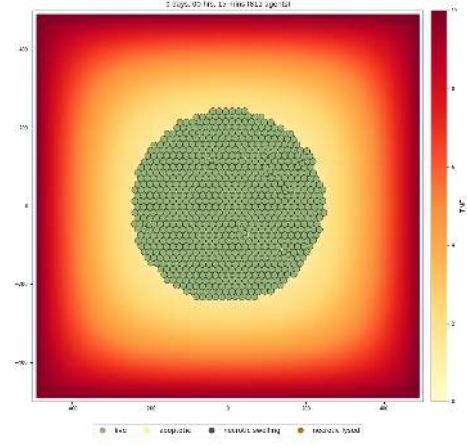
› Cell fate model: Boolean model



Building multiscale models with PhysiBoSS: a tutorial

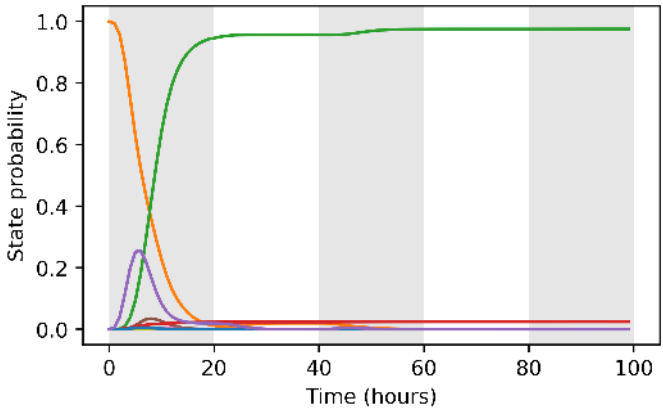
- Cell fate model: Multiscale model

  - 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



Building multiscale models with PhysiBoSS: a tutorial

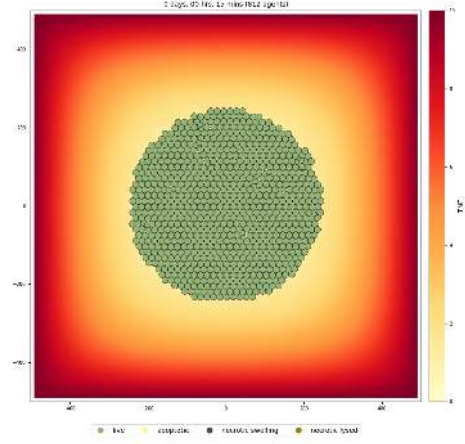
- Cell fate model: Pulsatile treatments

  - 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

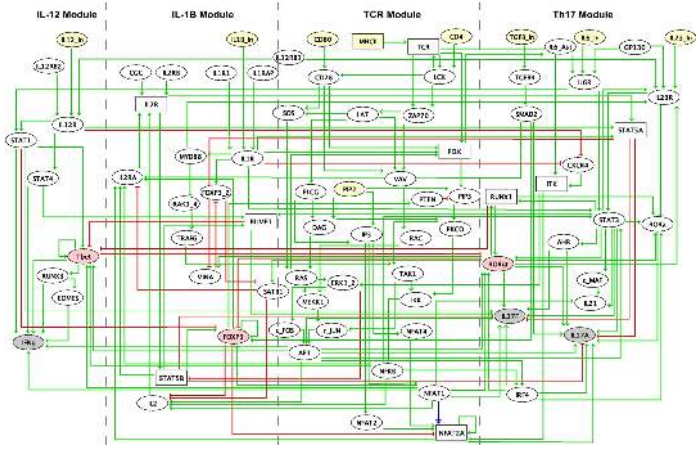


T-Cell differentiation model

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: Naive T-cells Boolean model

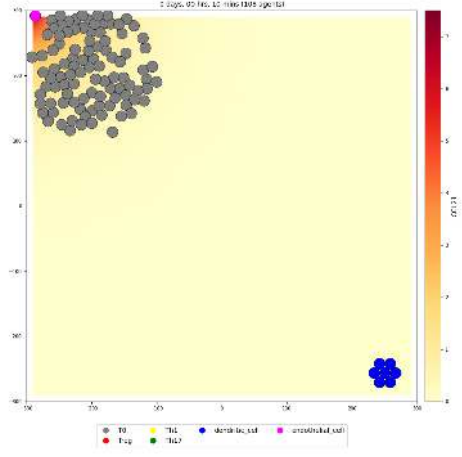


Corral-Jara et al, 2021

Building multiscale models with PhysiBoSS: a tutorial

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

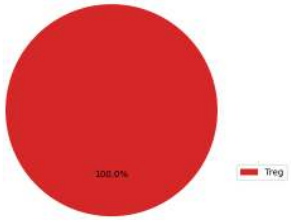
- › Multiple cell types : Endothelial, Dendritic, T0, Th1, Th17, Treg
- › Dendritic cells attracted to the gradient of CCL21 secreted by the endothelial cell
- › Goes back to a random walk once around the T-Cells
- › During contact with T-Cells, DCs trigger T0 differentiation into TH1, TH17, Treg

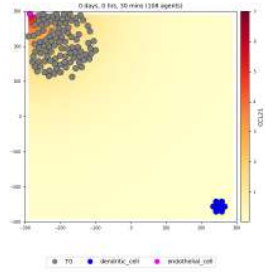


Building multiscale models with PhysiBoSS: a tutorial

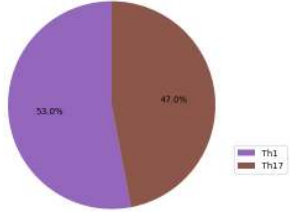
› T-Cell differentiation model: Mutants

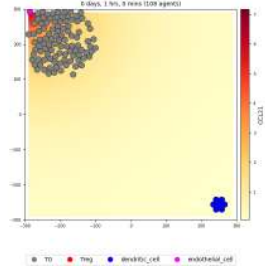
NFkB KO





FoxP3 KO

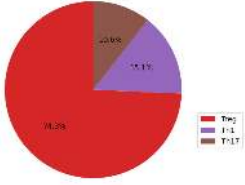


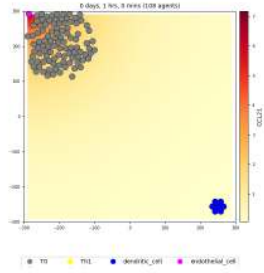


Building multiscale models with PhysiBoSS: a tutorial

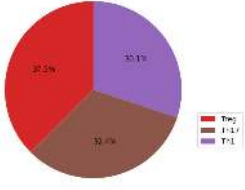
› T-Cell differentiation model: Partial inhibitions

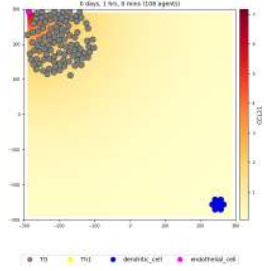
NFkB 90% inhibition





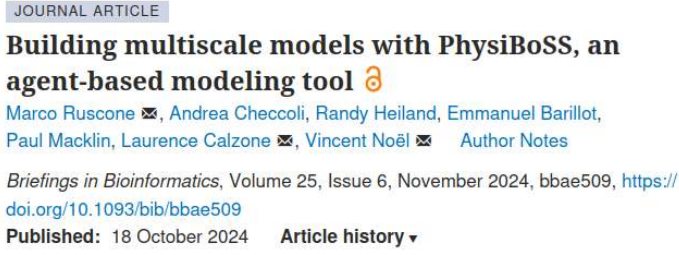
FoxP3 80% inhibition





Building multiscale models with PhysiBoSS: a tutorial

› Paper



JOURNAL ARTICLE

Building multiscale models with PhysiBoSS, an agent-based modeling tool

Marco Ruscone, Andrea Checcoli, Randy Heiland, Emmanuel Barillot, Paul Macklin, Laurence Calzone, Vincent Noël Author Notes

Briefings in Bioinformatics, Volume 25, Issue 6, November 2024, bbae509, https://doi.org/10.1093/bib/bbae509

Published: 18 October 2024 **Article history**

› Making multiscale modeling more accessible

› Available at Briefing in Bioinformatics

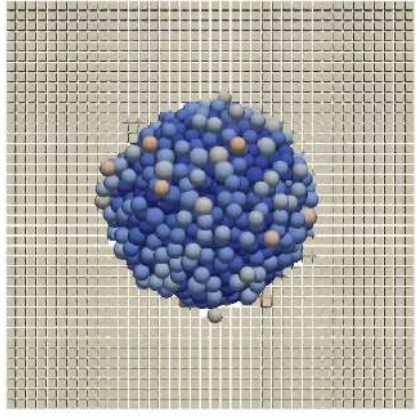
› https://github.com/PhysiBoSS/PhysiBoSS

Multiscale model of the different modes of cancer cell invasion

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



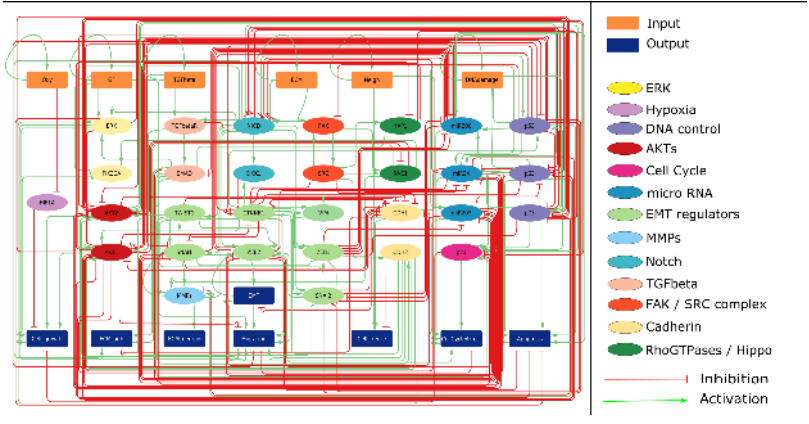
  - Studying the biophysical parameters favoring collective migration



Ruscone et al., 2023

Multiscale model of the different modes of cancer cell invasion

- Signalling network
  - 6 input nodes and 8 output nodes



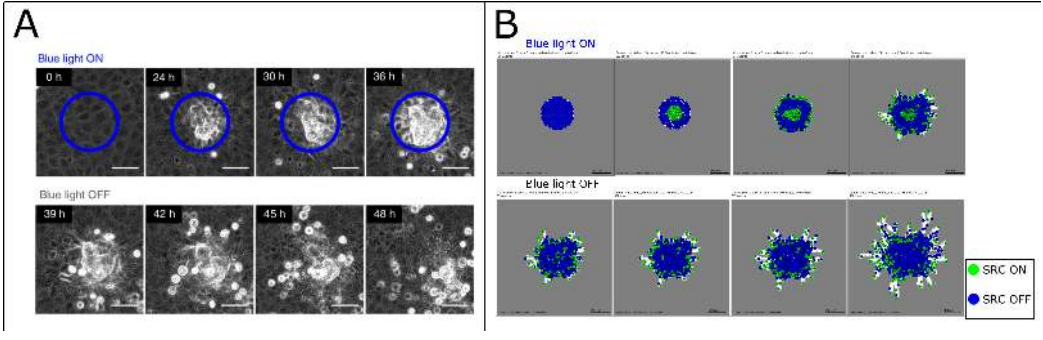
Ruscone et al., 2023

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

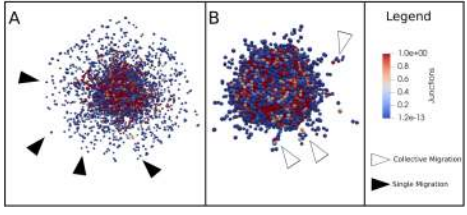


Ruscone et al., 2023

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

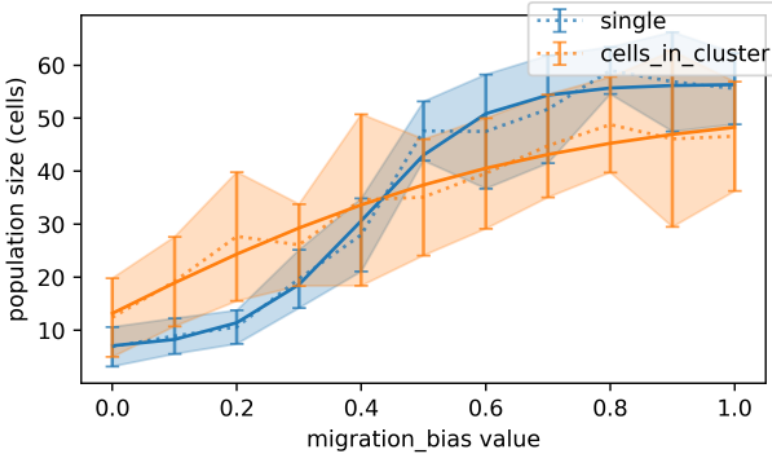


Cell-substrates interaction parameters		
ecm_adhesion_min	set the min adhesion between cells and ECM	1
ecm_adhesion_max	set the max adhesion between cells and ECM	2
cell_ecm_repulsion	set the value of ECM repulsion	15µm/min
Cell parameters		
max_interaction_factor	set the max distance of interaction	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)

HPC/Exascale Centre of Excellence in Personalised Medicine



Alfonso Valencia

Goal

Scale-up essential simulation software to prepare the infrastructure of personalized medicine

Results

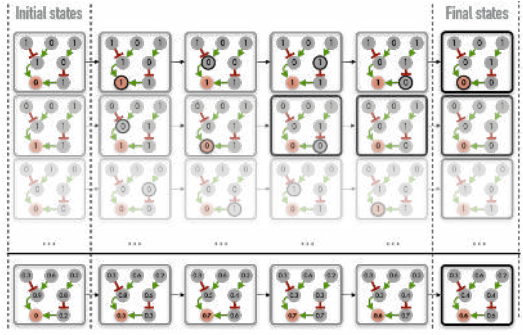
- HPC versions of MaBoSS, PhysiCell
- Example workflows of personalized medicine
- The tutorial and the cancer cell invasion model were produced within this project

Consortium of 12 partners from 7 EU Member States



- MaBoSS Simulation algorithm

- Simulate transitions from a boolean network state to another
- These transitions are stochastic : multiple trajectories are possible
- We simulate many trajectories until a defined max time



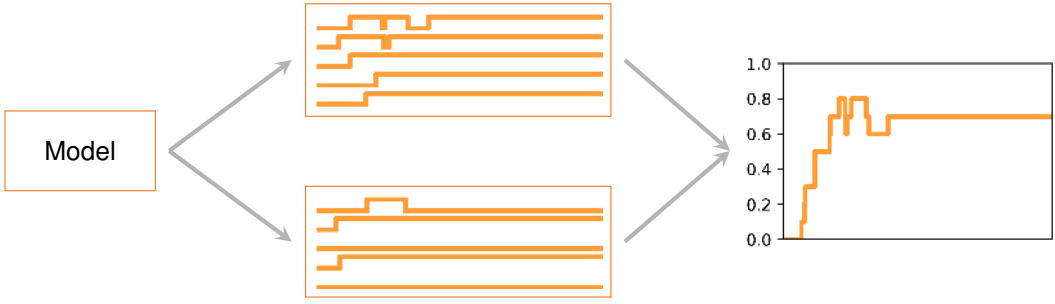
Béal, 2020

⇒ From a set of simulated trajectories, we compute distributions

HPC/Exascale Centre of Excellence in Personalised Medicine

› Improvements to MaBoSS threads implementation

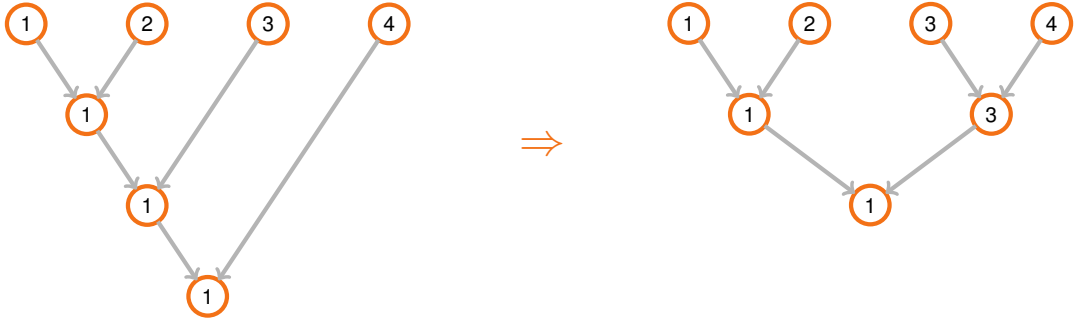
Modern processors are multi-cores (Laptop $\sim$ 8 cores, HPC $\sim$ 32 cores)



$\Rightarrow$ We can distribute the simulations on multiple cores

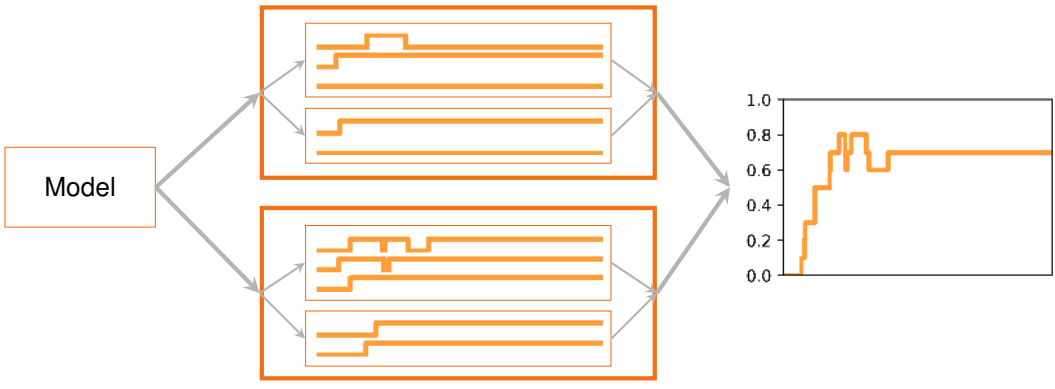
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- Improvements to MaBoSS threads implementation
  - From linear to logarithmic complexity



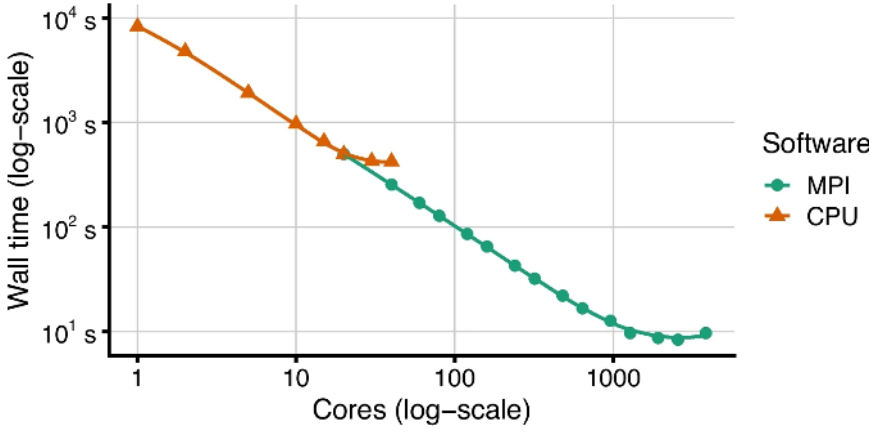
› MaBoSS MPI Implementation

Clusters have a lot of connected machines



⇒ We can distribute the simulations on multiple cores and further on multiple machines

- MaBoSS MPI Implementation

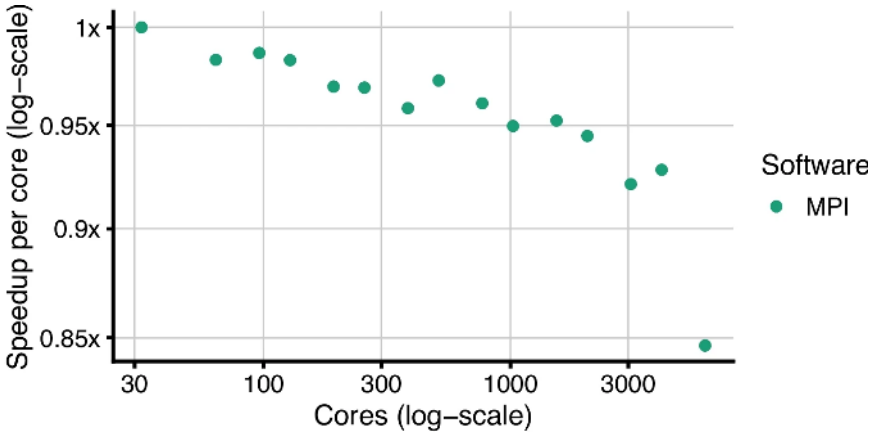


Šmelko et al., 2024

- Test on Sizek et al. model of cell cycle (≈100 nodes)

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- MaBoSS MPI Implementation



Šmelko et al., 2024

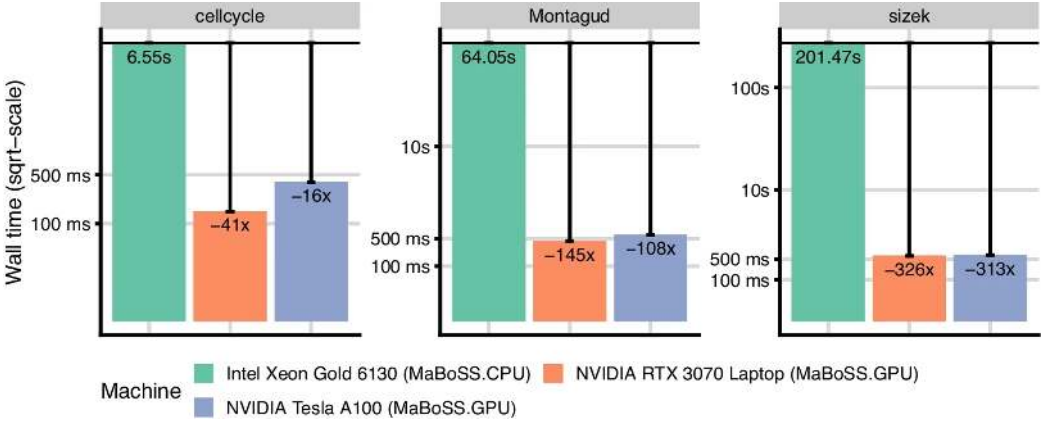
- Test on a 1000 nodes synthetic model

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Adam Šmelko

- MaBoSS GPU implementation



- Test on biological models

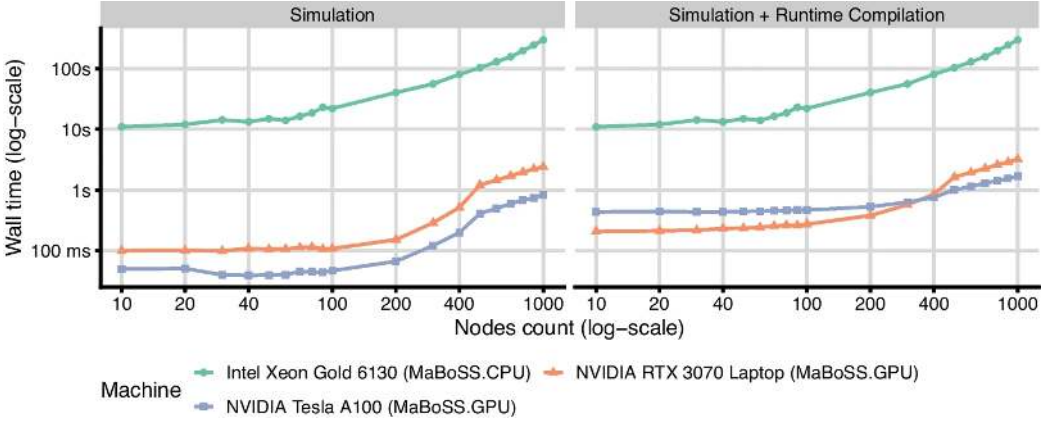
Šmelko et al., 2024

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Adam Šmelko

- MaBoSS GPU implementation



- Test on synthetic models

Šmelko et al., 2024

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Adam Šmelko

› MaBoSS for HPC environments paper

Software | Open access | Published: 24 May 2024

Maboss for HPC environments: implementations of the continuous time Boolean model simulator for large CPU clusters and GPU accelerators

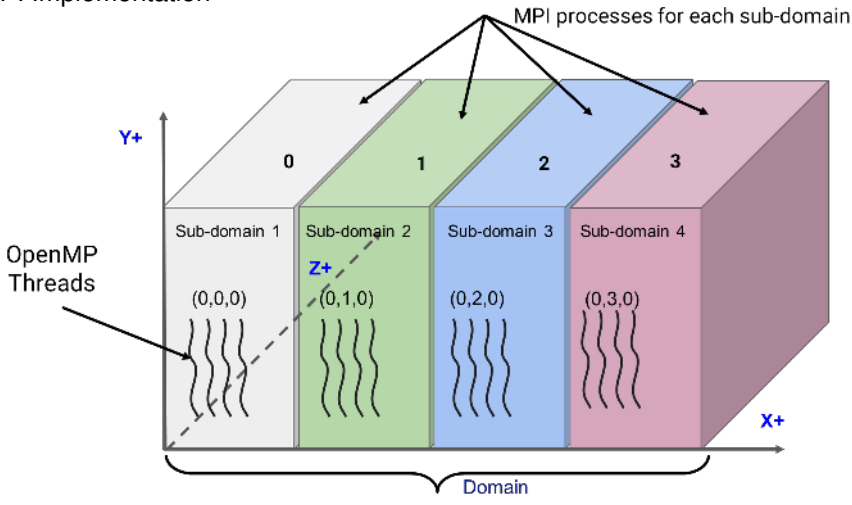
Adam Šmelko, Miroslav Kratochvíl, Emmanuel Barillot & Vincent Noël

BMC Bioinformatics **25**, Article number: 199 (2024) | Cite this article

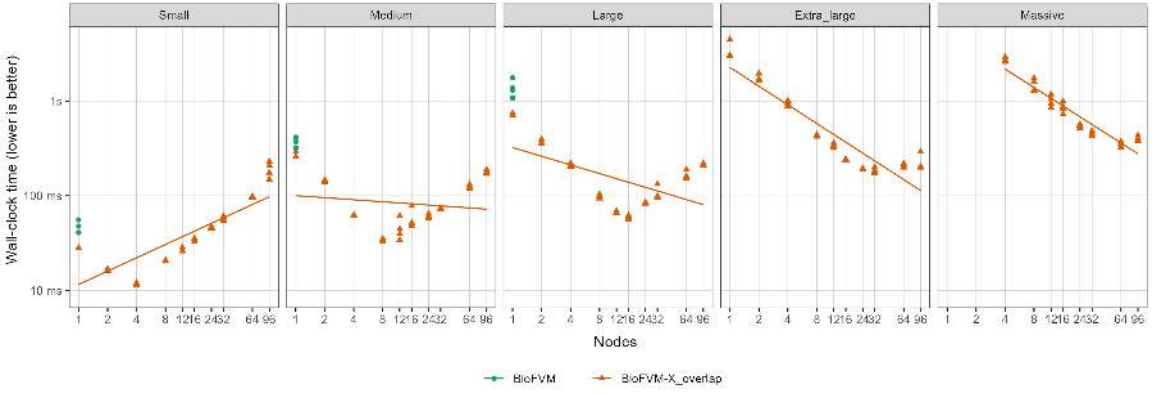
753 Accesses | Metrics

- Runtime model compilation for MPI implementation
- Extending the GPU implementation to MaBoSS ecosystem
- Packaging the GPU implementation (Python extension ?)

- PhysiCell MPI Implementation



- PhysiCell MPI Implementation



- Make sense for very large simulation setups

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Adam Šmelko

› PhysiCell 2.0 alpha

	100x100 voxels, 900 agents, 600m simul. time	300x300 voxels, 14300 agents, 600m simul. time	100x100x100 voxels, 14300 agents, 60m simul. time	200x200x200 voxels, 88700 agents, 60m simul. time
i7-8650U laptop CPU (4 HT cores)	4.5s (12.7s)	38.3s (256.3s)	18.6s (246.3s)	-
2 sockets Intel Xeon Platinum 8160 CPU (2x24 cores)	18.7s (14.4s)	27.4s (116.9s)	6.8s (156.6s)	36.8s (1231.6s)

› New implementation in modern C++, correctly using vectorisation

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- Perspectives



  - Adam Šmelko just started a post-doc at Barcelona Supercomputing Center
  - Goal is to start a new, more modular implementation of PhysiCell
  - GPU support for diffusion + agent mechanics
  - Improved MPI support (dynamic slicing, communication optimization)

Ongoing projects

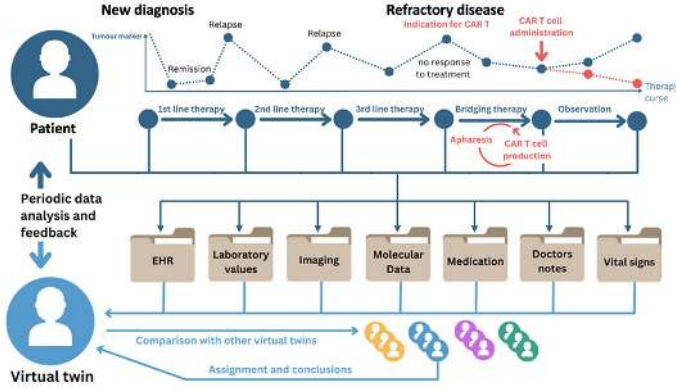
› Certainty

CERTAINTY
A cellular immunotherapy virtual twin for personalised cancer treatment


Maximilian Merz


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



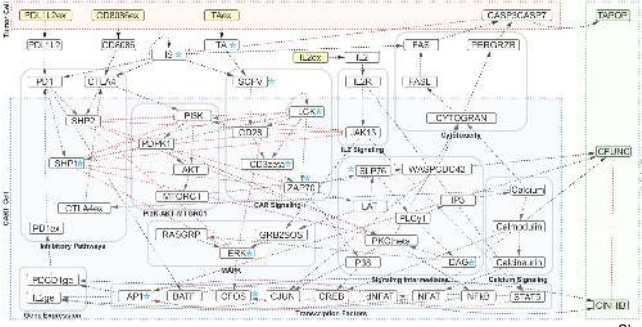
Sophia Orozco Ruiz



Gautier Stoll

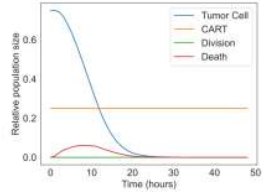


Laurence Calzone

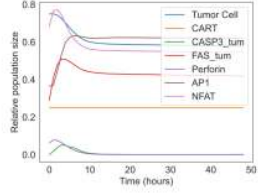


Shah et al., 2023

Follow treatment over time for WT case



Follow treatment for patients with CD28 altered



› Initial work on Boolean intracellular models and personalization

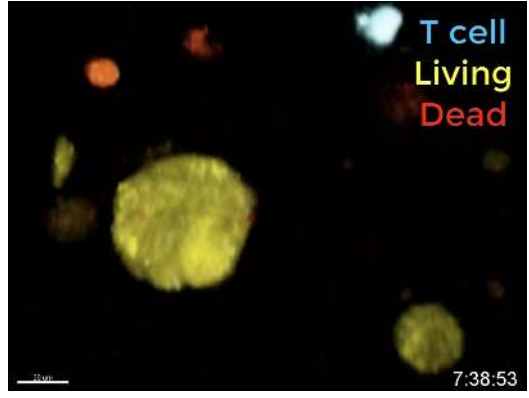
Ongoing projects

› Certainty


Jürgen Kuball


Zsolt Sebestyén

- Integration of these models in a PhysiBoSS multiscale model
- Based on 3D live imaging of tumor organoids
- Development of new methods for multiscale model personalization
- Model simulations to find optimal treatment



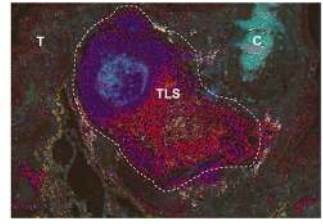
Ongoing projects

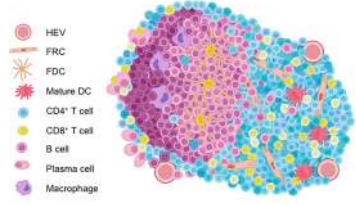
- Multiscale modeling of Tertiary Lymphoid Structures
  - A predictor for favorable responses to immune checkpoint blockade
  - A complex spatial organization of immune cells
  - Creating a permissive milieu for TLS assembly and maturation could pave the way to combinatorial therapies
  - Multiscale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

A.C.Camargo Cancer Center



Tiago Medina





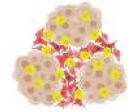
Domblides et al., 2021

Ongoing projects

- Modeling of CAF-mediated T-cell Exclusion in Human Lung Tumors
  - Develop mechanistic understanding of T-cell exclusion
  - Create new methods for spatial transcriptomics Xenium datasets
  - Automatically build personalizing multiscale model
  - Student starting in January

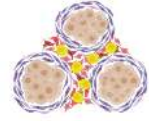


Helene Salmon



FAP⁺ CAF

T cell–permissive CAF



FAP⁺αSMA⁺ CAF

T cell–excluding CAF

Take-home message

- Multiscale models are important for describing complex **multi-cellular** systems, with **spatial** properties
- Intracellular models are key to personalize signaling and test treatments
- We are developing new methods for **multiscale model personalization**
- We are interested in optimization methods for these multiscale models (surrogate models)
- I moved to **São Paulo**, and I am looking for **students** and **collaborations** to build personalized multiscale models

Aknowledgments



Marco Ruscone



Sophia Orozco Ruiz



Laurence Calzone



Gaëlle Letort



Emmanuel Barillot



Gautier Stoll



Andrea Checcoli



Guido Kroemer



Randy Heiland



Paul Macklin



Arnau Montagud



Miguel Ponce de Leon



Alfonso Valencia



Kristin Reiche



Maximilian Merz



Adam Šmelko



Jurgen Kuball



Zsolt Sebestyen



Helene Salmon



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