Construção de Modelos Multiescala para Biologia de Sistemas

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Webinários em Física Biológica - Sociedade Brasileira de Física

March 2026

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



- 2025 - Visiting researcher at HCFMUSP, São Paulo

Institut Curie



A hospital

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

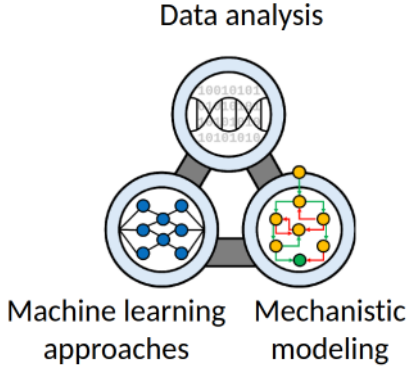
A research center

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

Computational Systems Biology of Cancer



Emmanuel Barillot

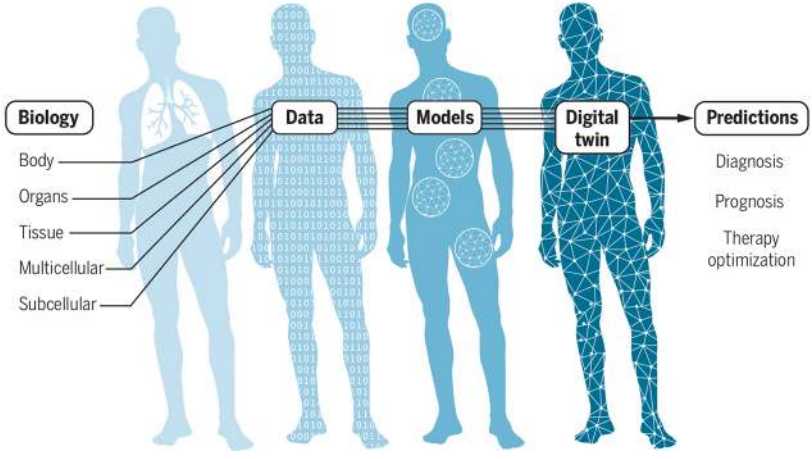




Laurence Calzone

Mechanistic modeling of biological systems

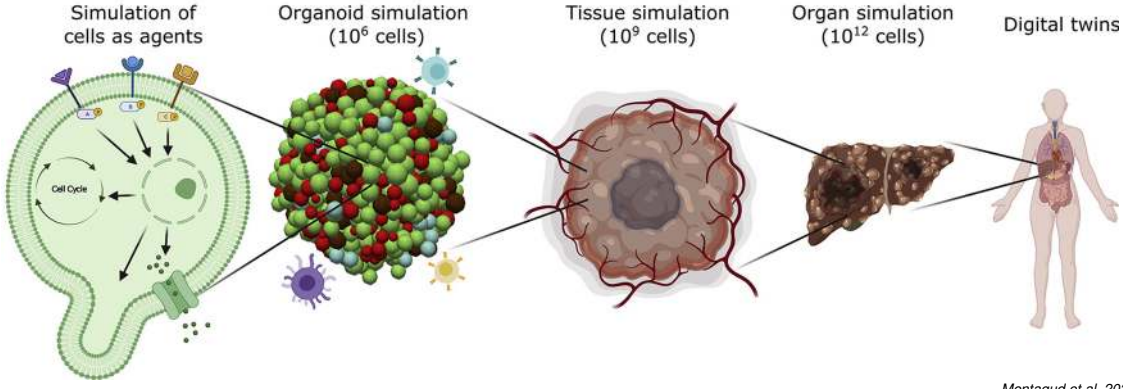
› Toward a Digital Twin



Lauberbacher et al, 2021

Mechanistic modeling of biological systems

› A multiscale problem

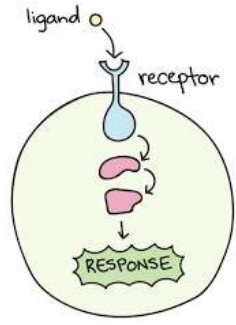


Montagud et al, 2021

Mechanistic modeling of biological systems

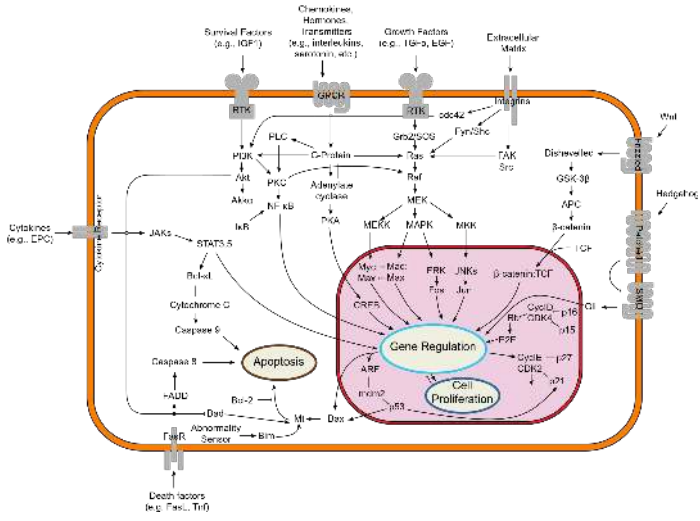
› Why mechanistic modeling ?

- 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



Cell models

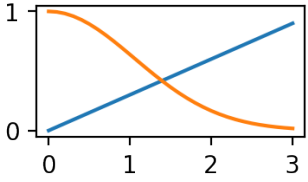
- More studied
- Signaling
- Different frameworks



Cell models

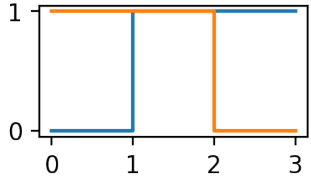
- Different frameworks

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

Cell models


Gautier Stoll


Laurence Calzone

› Continuous time Boolean modeling



- Boolean
- Stochastic
- Physical time

Continuous time Markov process applied on a Boolean network state space

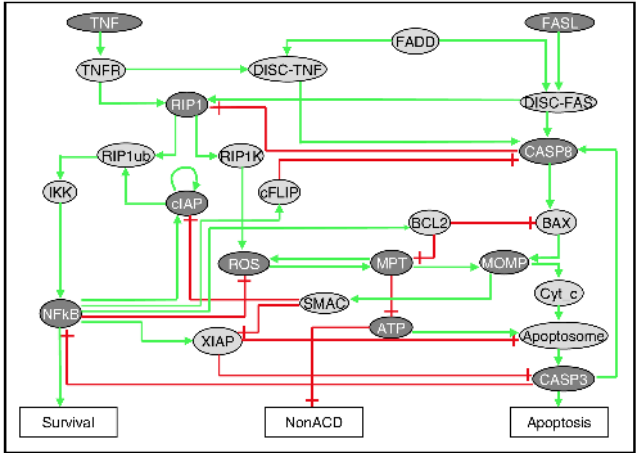
Transition rate :

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

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

Cell models

› Example: Cell fate upon Tumor Necrosis Factor (TNF) treatment




```
node IKK {
  logic = RIP1ub;
  rate_up = @logic ? 1 : 0;
  rate_down = @logic ? 0 : 1;
}

node CASP3 {
  logic = apoptosome AND (NOT XIAP);
  rate_up = @logic ? 1 : 0;
  rate_down = @logic ? 0 : 1;
}

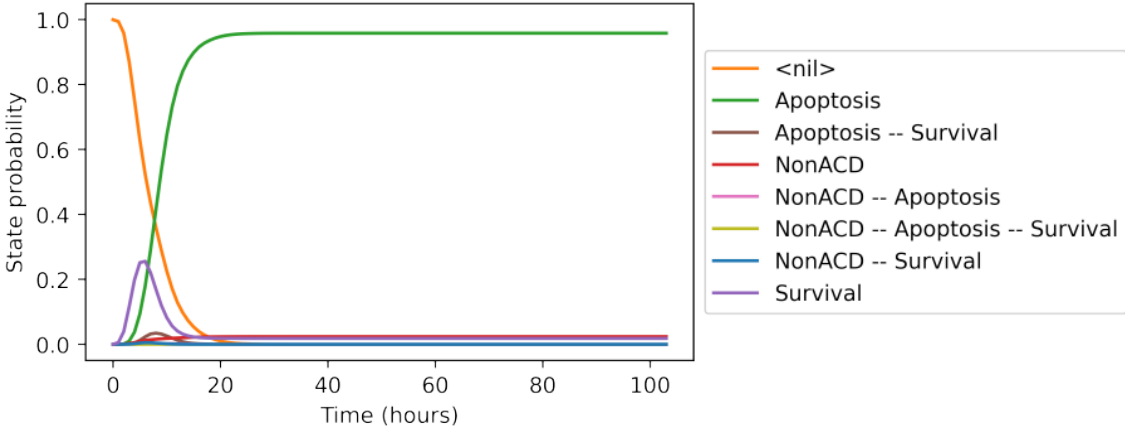
node NFkB {
  logic = IKK AND (NOT CASP3);
  rate_up = @logic ? 1 : 0;
  rate_down = @logic ? 0 : 1;
}

node cFLIP {
  logic = NFkB;
  rate_up = (@logic) ? $TransRate : 0;
  rate_down = (@logic ? 0 : 1);
}
```

Calzone et al, 2010

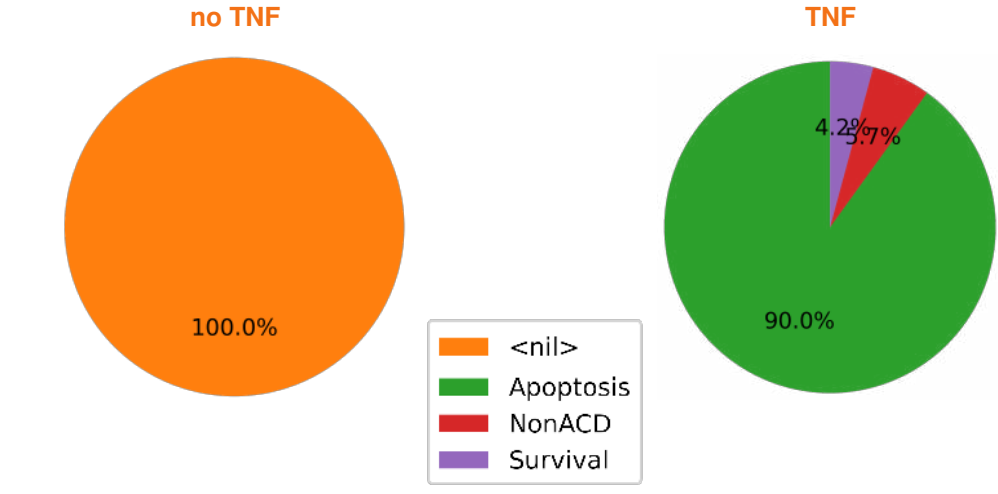
Cell models

› Example: Cell fate upon Tumor Necrosis Factor (TNF) treatment



Cell models

› Example: Cell fate upon Tumor Necrosis Factor (TNF) treatment

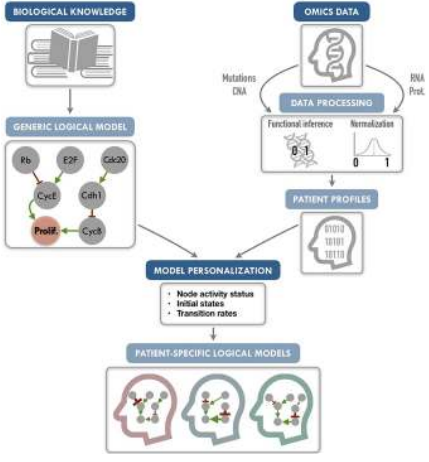


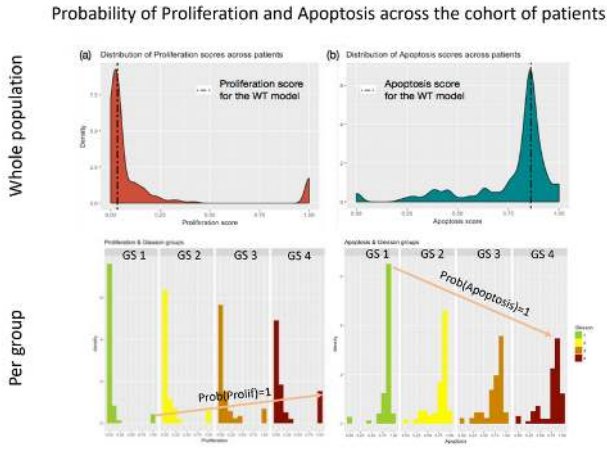
Cell models

› Personalizing generic Boolean models with data



Jonas Béal



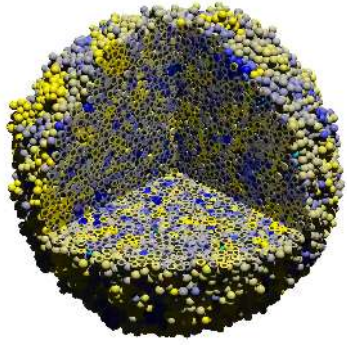


➔ overall coherent behaviour

Béal et al., 2019

Multicellular models

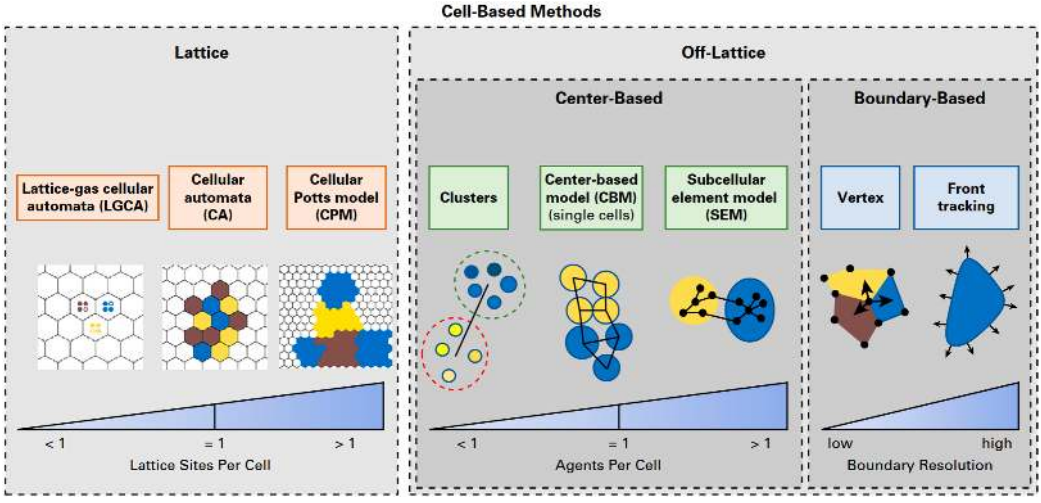
- Multi-cellular systems
- Spatial information
- Multiple cell types
- Extra-cellular environment
- Interactions



Ghaffarizadeh et al., 2018

Multicellular models

› Agent-based modeling frameworks



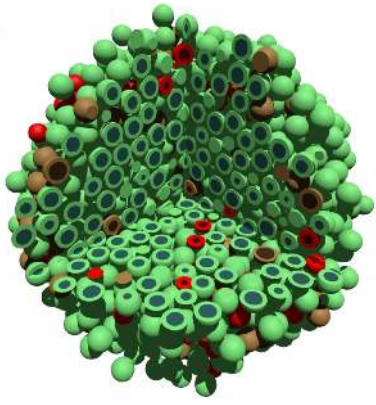
Metzcar et al., 2019

Multicellular models

› PhysiCell


Paul Macklin


Randy Heiland



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

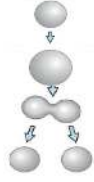
Cell agent properties

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

Cell Cycle



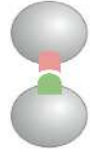
Growth



Migration



Cell-Cell interactions

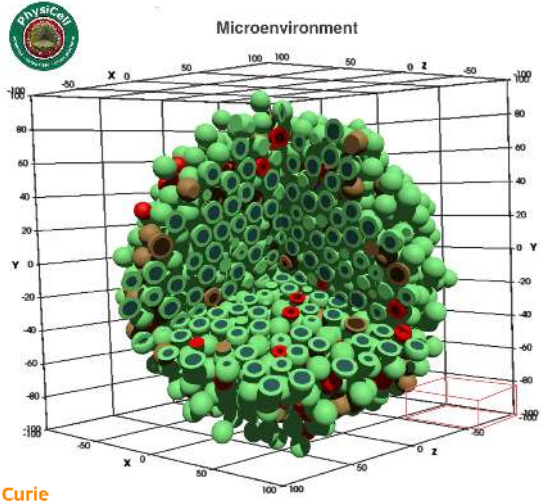


Multicellular models

› PhysiCell


Paul Macklin


Randy Heiland



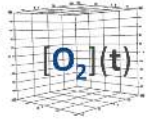
Diffusion equations

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

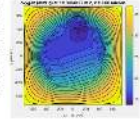
System of PDEs for each molecule:

- Diffusion term
- Decay
- Uptake/Production

PDEs are solved using BioFVM

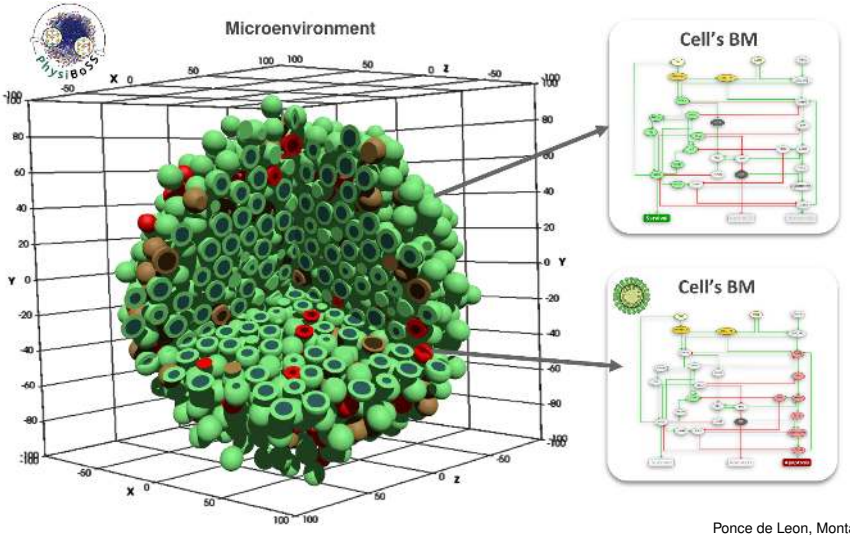






Multicellular models

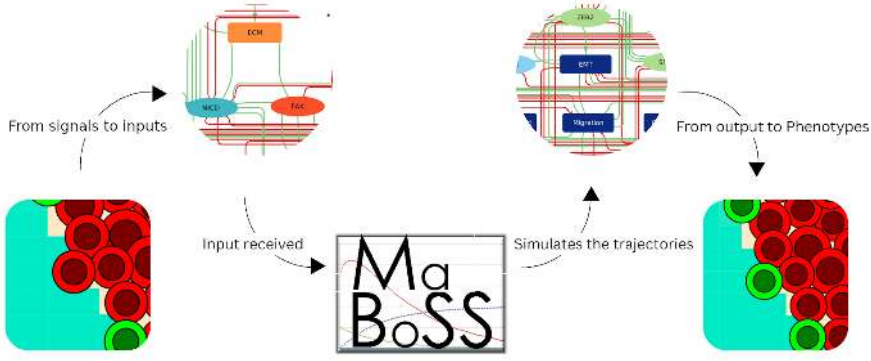
› PhysiCell + MaBoSS = PhysiBoSS



Ponce de Leon, Montagud, Noël et al., 2022

Multicellular models

› PhysiCell + MaBoSS = PhysiBoSS



Ruscone et al., 2023

Building multiscale models with PhysiBoSS: a tutorial



Marco Ruscone

› Introduction

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[4,5,6,7], Randy Heiland[8], Emmanuel Barillot[1,2,3], Paul Macklin[8], Andrei Zinovyev[1,2,3] and Laurence Calzone[1,2,3,*]



ARTICLE OPEN

PhysiBoSS 2.0: a sustainable integration of stochastic Boolean and agent-based modelling frameworks

Miguel Ponce-de-Leon[1,2], Arnau Montagud[1,2], Vincent Noël[2,3,4], Annika Meert[1], Gerard Pradas[1], Emmanuel Barillot[2,3,4], Laurence Calzone[2,3,4] and Alfonso Valencia[5,6,7]

› Progressively, we were able to simplify the usage of PhysiBoSS

› We reached the point were there was no need to code (C++)

› We decided to write a more didactic tutorial to PhysiBoSS

Multicellular models

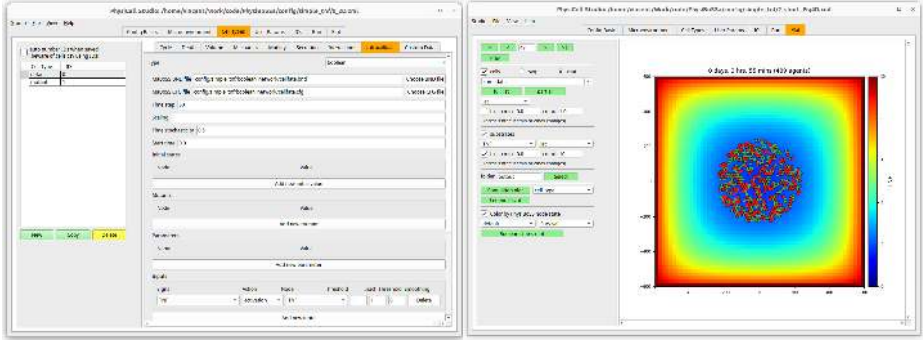
› PhysiCell Studio

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

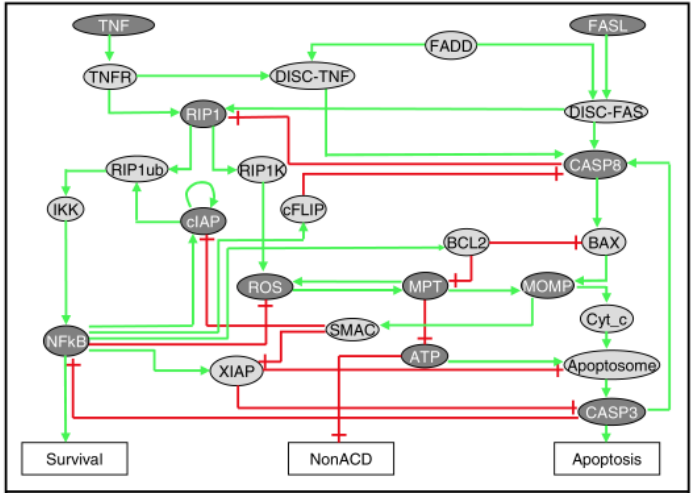


Cell fate model

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

Multicellular models

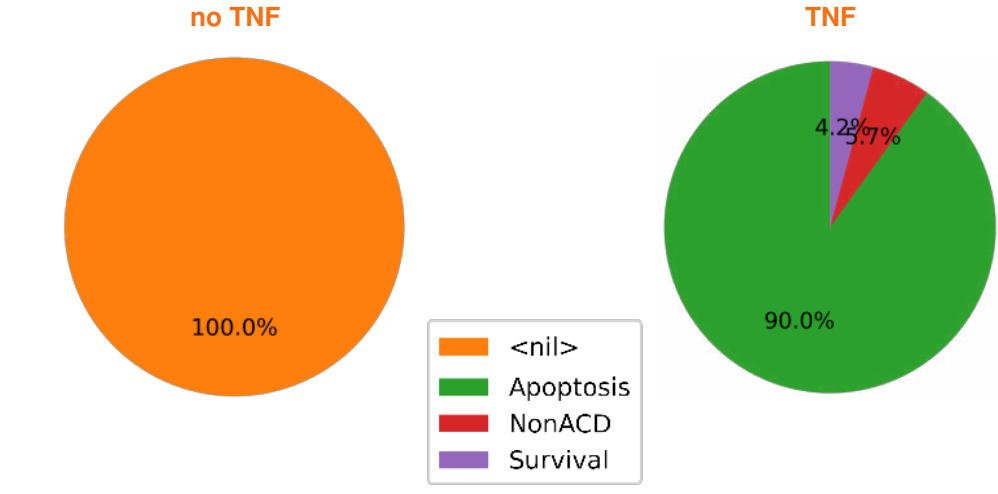
› Cell fate model: Boolean model



Calzone et al, 2010

Multicellular models

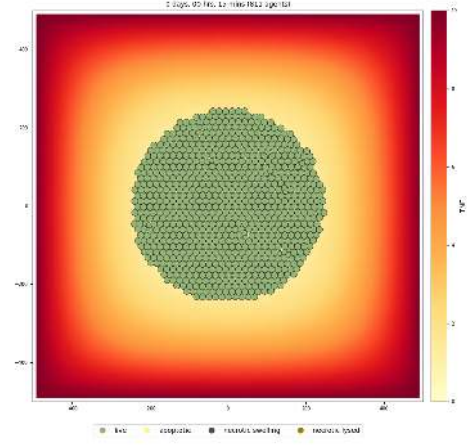
› Cell fate model: Boolean model



Multicellular models

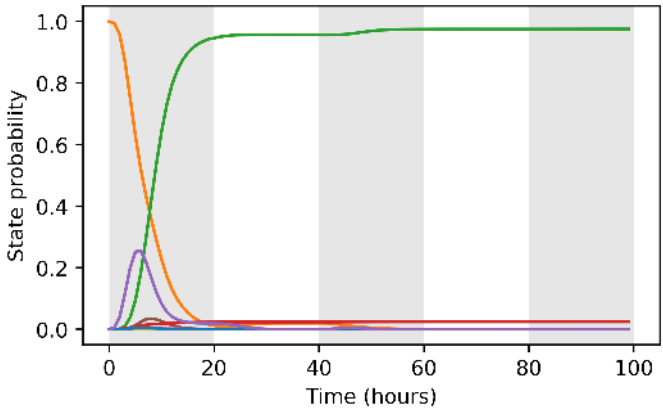
- Cell fate model: Multiscale model

  - 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



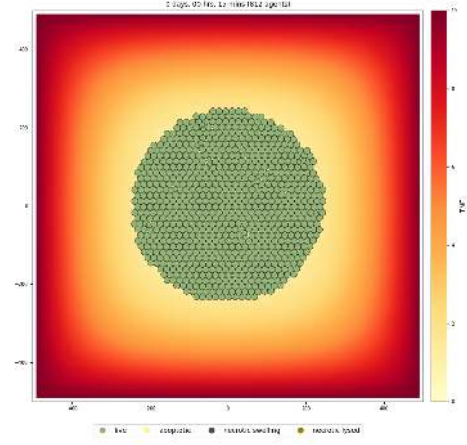
Multicellular models

› Cell fate model: Pulsatile treatments



Multicellular models

- 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

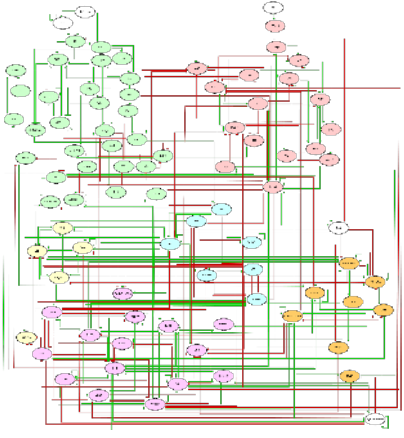


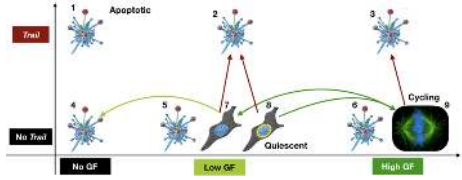
Cell cycle model

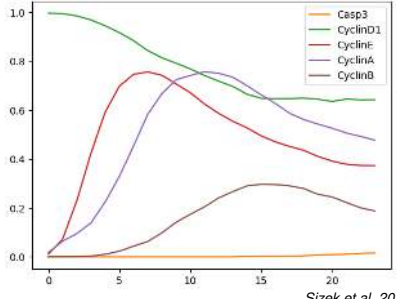
Goal : Replace PhysiCell simple cell cycle by a more complex mechanistic one, based on signaling

Multicellular models

› Cell cycle model: Boolean model







Sizek et al, 2019

Multicellular models

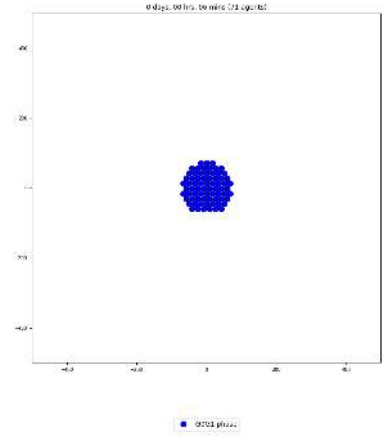
- Cell cycle model: Reproducing PhysiCell's cell cycle model

  - 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

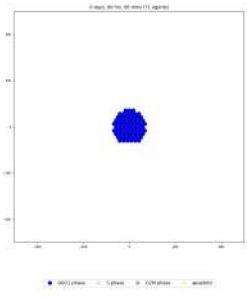
  - We can adjust MaBoSS model rates to adjust relative phases durations



Multicellular models

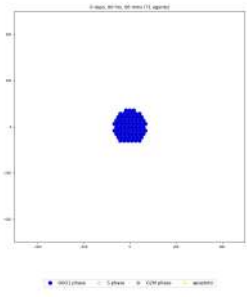
› Cell cycle model: Mutants analysis

Plk1- -



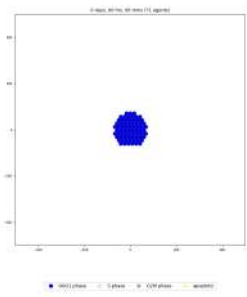
⇒ Cycle arrest in G2

FoxO3- -



⇒ Mitotic catastrophe

p110++



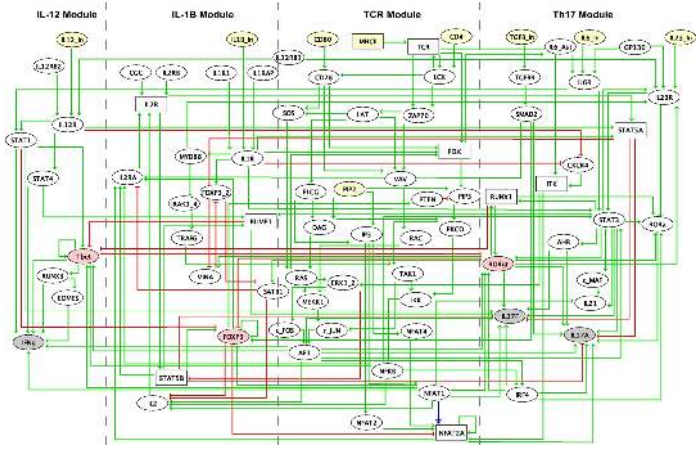
⇒ No Apoptosis

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

Multicellular models

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



Corral-Jara et al, 2021

Multicellular models

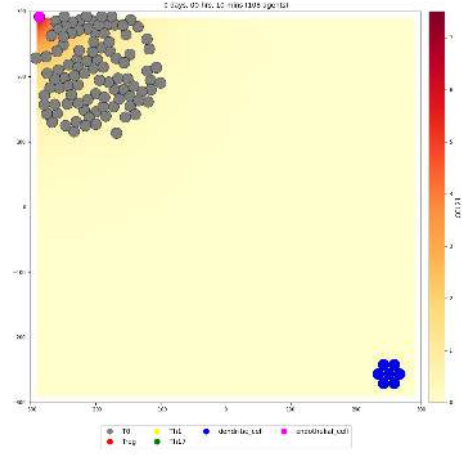
- T-Cell differentiation model: Naive T-cells Boolean model

  - 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

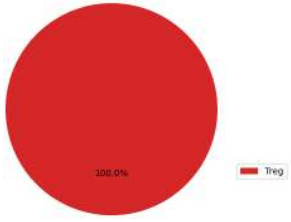
  - During contact with T-Cells, DCs trigger T0 differentiation into TH1, TH17, Treg

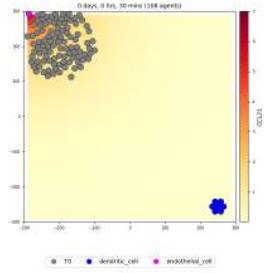


Multicellular models

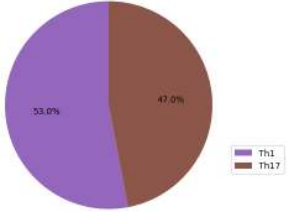
› T-Cell differentiation model: Mutants

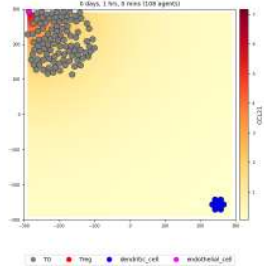
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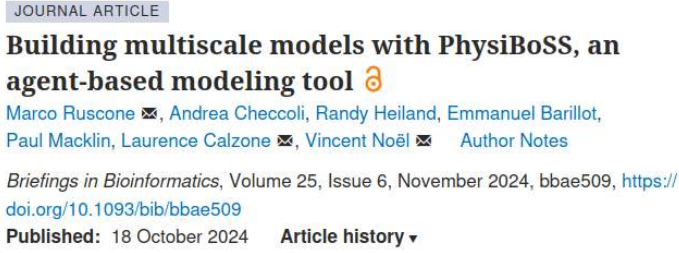
FoxP3 KO





Multicellular models

› 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

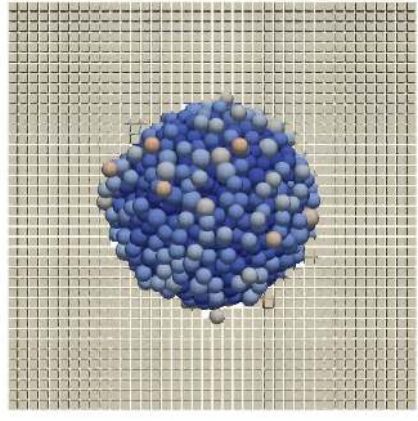


Marco Ruscone

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



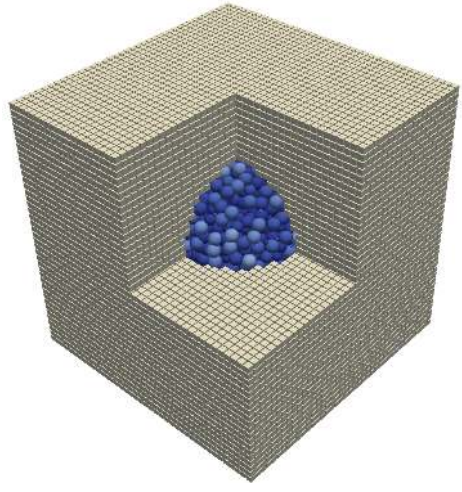
  - Studying the biophysical parameters favoring collective migration



Ruscone et al., 2023

Multiscale model of the different modes of cancer cell invasion

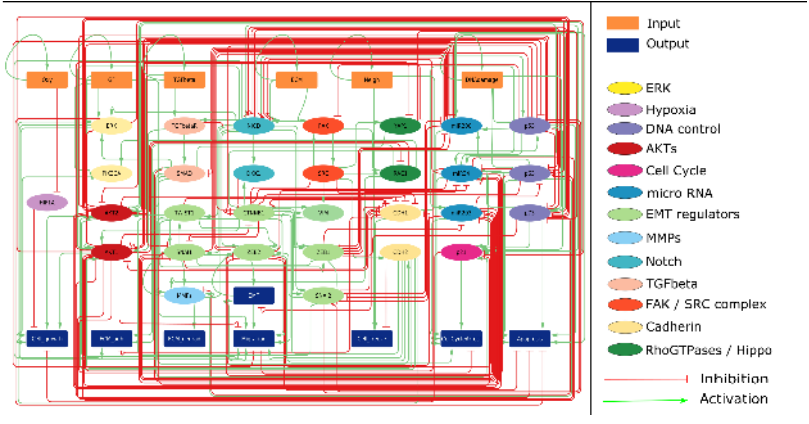
- Extracellular Matrix
  - A substrate of the microenvironment
  - A barrier for the cells
  - Cell-ECM contact triggers signalling
  - Cells produce metaloprotease to degrade ECM



Ruscone et al., 2023

Multiscale model of the different modes of cancer cell invasion

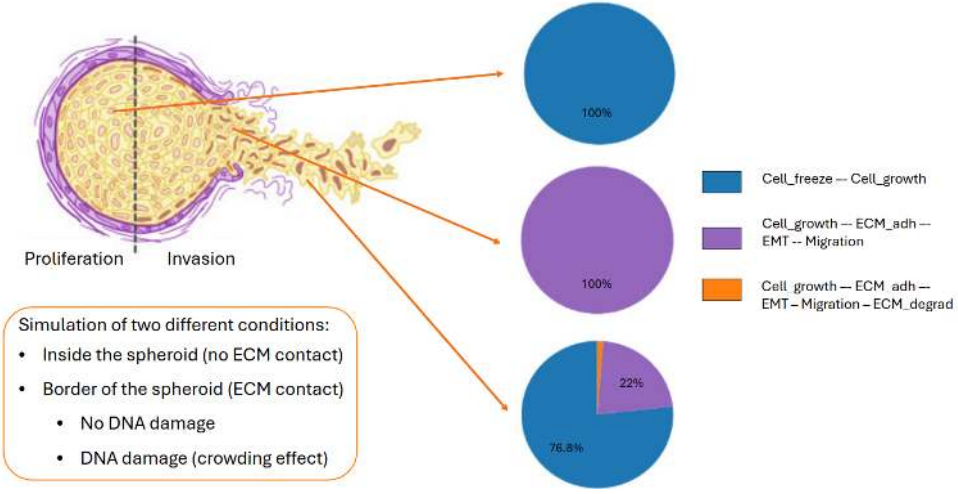
- Signalling network
  - 6 input nodes and 8 output nodes



Ruscone et al., 2023

Multiscale model of the different modes of cancer cell invasion

› Signalling network



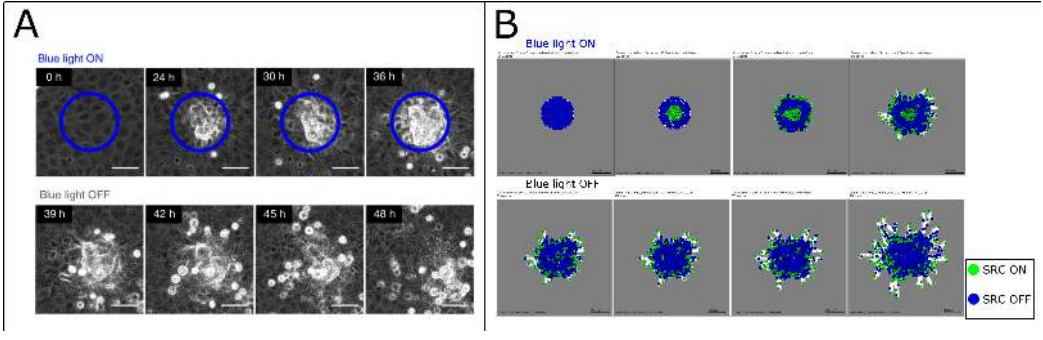
Ruscone et al., 2024

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

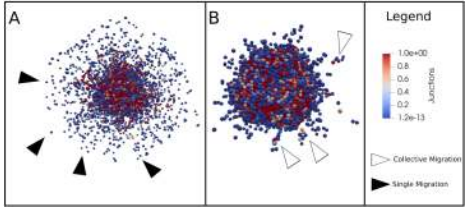


Ruscone et al., 2023

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

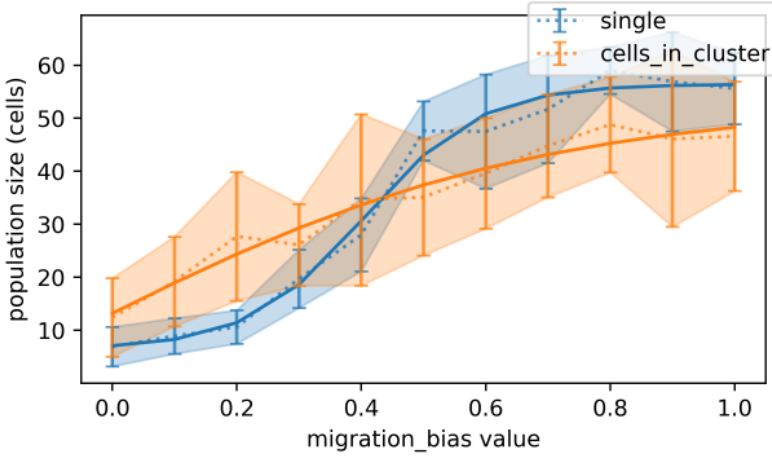


Cell-substrates interaction parameters		
ecm_adhesion_min	set the min adhesion between cells and ECM	1
ecm_adhesion_max	set the max adhesion between cells and ECM	2
cell_ecm_repulsion	set the value of ECM repulsion	15µm/min
Cell parameters		
max_interaction_factor	set the max distance of interaction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

PhysiMeSS

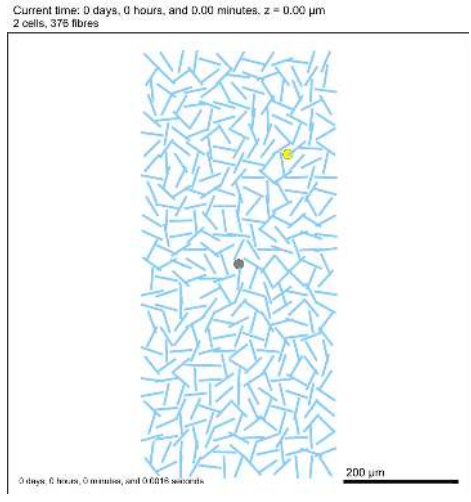
PhysiMeSS


Marco Ruscone


Cicely McNamara


Robin Shuttleworth

- Going closer to Physics: Fibres as agents
- Rigid sticks (2D) or cylinders (3D)
- Acts as an obstacle to cells
- Cells can degrade fibres
- Fibres can form crosslinks



PhysiMeSS

› Fibre orientation


Marco Ruscone

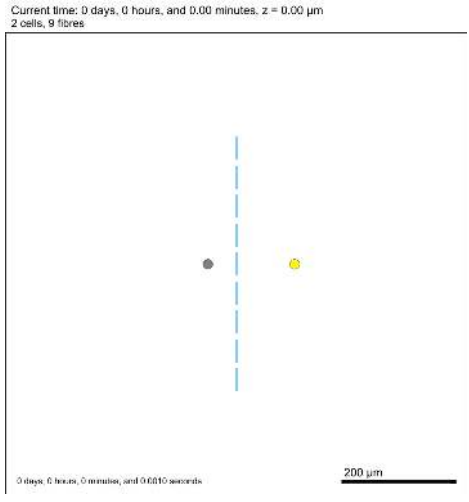

Cicely McNamara


Robin Shuttleworth

› Cells can modify fibre orientation

› This can depends on number of crosslinks

› To really propagate this, we need fibre-fibre mechanics



PhysiMeSS

- Custom degradation

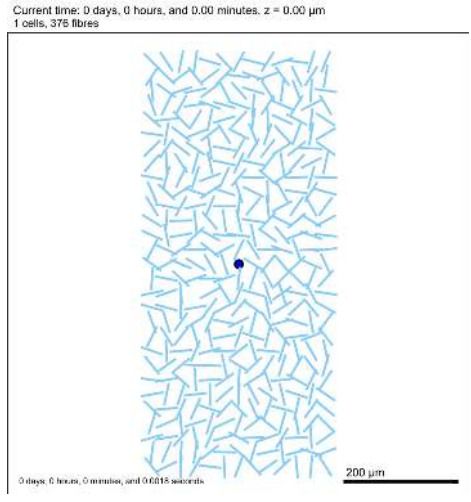

Marco Ruscone


Cicely McNamara


Robin Shuttleworth

- Reproducing tumor growth within ECM

- Pressure-dependent degradation



PhysiMeSS

› Perspectives


Ambre Jaeger


Marco Ruscone


Cicely McNamara


Robin Shuttleworth

(GIGA)byte

TECHNICAL RELEASE

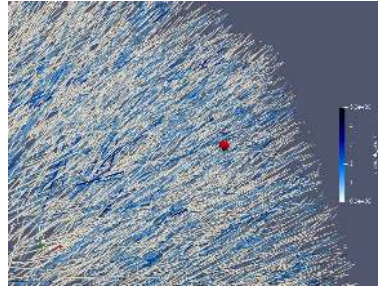
PhysiMeSS - a new physiCell addon for extracellular matrix modelling

Vincent Noël[1,2,3,*], Marco Ruscone[1,2,3,4], Robyn Shuttleworth[5] and Cicely K. Macnamara[6,*]

› Needs a good biological example

› new 3D implementation by Marco and Ambre at BSC

› Still lack fibre-fibre interactions



Ongoing projects

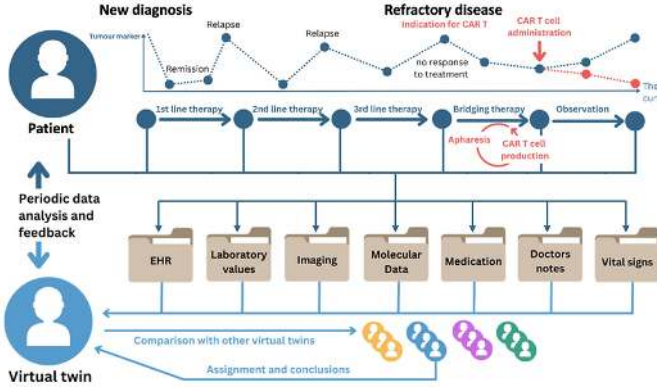
› Certainty

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



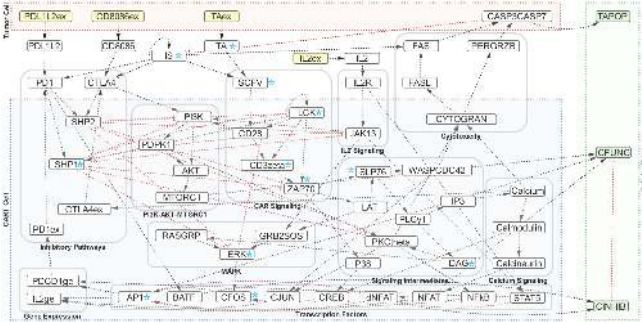
Funded by the European Union

Ongoing projects

› Certainty



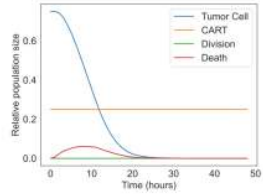
Sophia Orozco Ruiz



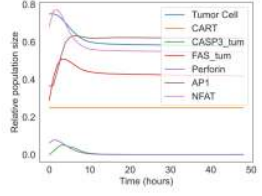
Shah et al., 2023

› Initial work on Boolean intracellular models and personalization

Follow treatment over time for WT case



Follow treatment for patients with CD28 altered

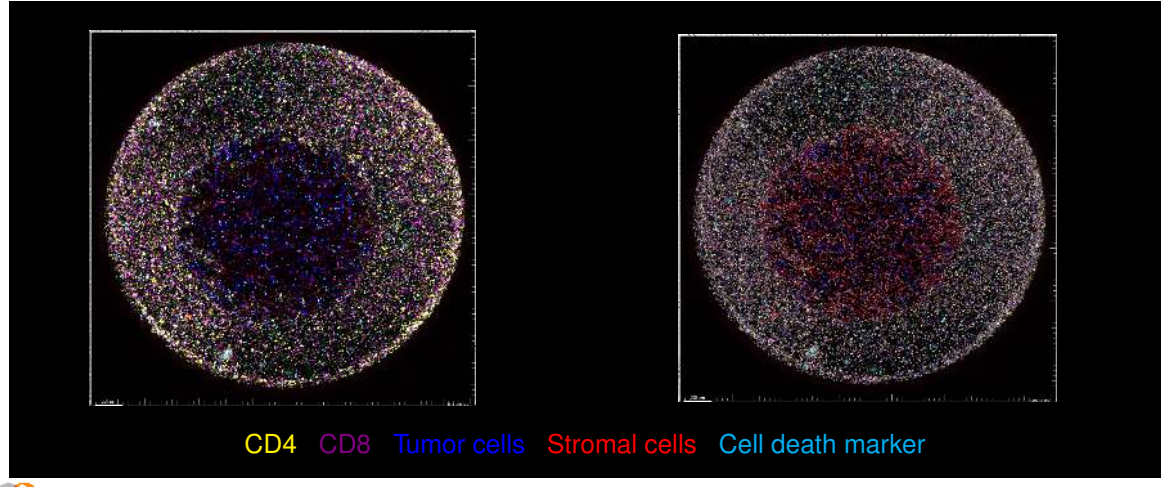


Ongoing projects

- Certainty


Yiteng Dang


Zsolt Sebestyen

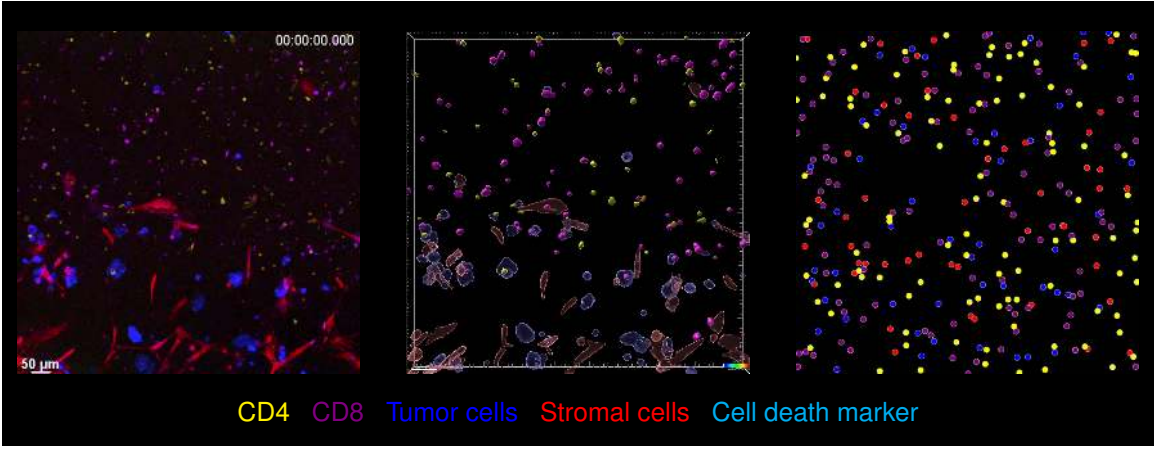


Ongoing projects

› Certainty


Yiteng Dang


Zsolt Sebestyen



Ongoing projects

- Modeling of CAF-mediated T-cell Exclusion in Human Lung Tumors

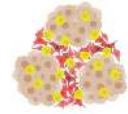


Agathe Sobkowicz



Helene Salmon

- Develop mechanistic understanding of T-cell exclusion
- Create new methods for spatial transcriptomics datasets
- Automatically initialized personalized multiscale model
- Propose exclusion mitigation interventions



FAP⁺ CAF

T cell–permissive CAF



FAP⁺αSMA⁺ CAF

T cell–excluding CAF

Ongoing projects

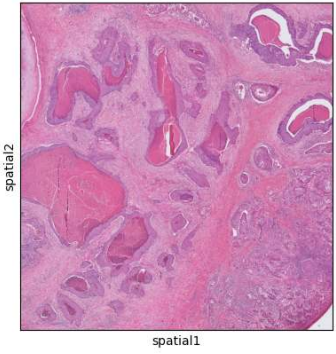
› Modeling of CAF-mediated T-cell Exclusion in Human Lung Tumors

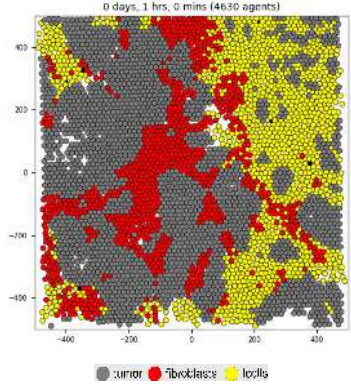


Agathe Sobkowicz



Helene Salmon





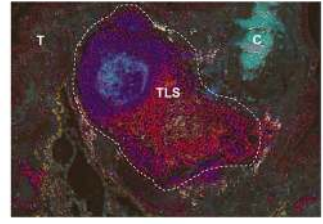
⇒ Initializing simulation with cell position, cell type, and cell state

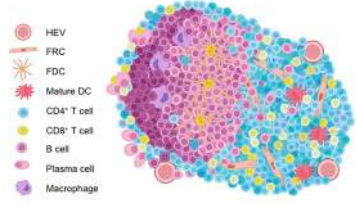
Ongoing projects



Tiago Medina

- 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





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 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

institutCurie

BSC Barcelona Supercomputing Center Centro Nacional de Supercomputación

INDIANA UNIVERSITY

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

CERTAINTY — A cellular immune therapy virtual twin for personalised cancer treatment

FRANCE — PROGRAMME DE RECHERCHE



Marco Ruscone



Sophia Orozco Ruiz



Laurence Calzone



Gaëlle Letort



Emmanuel Barillot



Gautier Stoll



Jonas Béal



Randy Heiland



Paul Macklin



Cicely McNamara



Robin Shuttleworth



Ambre Jaeger



Kristin Reiche



Maximilian Merz



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Jurgen Kuball



Zsolt Sebestyen



Agathe Sobkowicz



Helene Salmon



Tiago Medina

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