Per
Med
CoE

HPC/Exascale
Centre of
Excellence in
Personalised
Medicine

PerMedCoE

A roadmap to scalability in Personalized Medicine

José Carbonell-Caballero

The PerMedCoE project has received funding from the European Union's Horizon 2020 research and innovation programme under the grant agreement Nº951773

Overview

Overview

HPC/Exascale Centre of Excellence for Personalised Medicine

BSC Barcelona Supercomputing Center
Centro Nacional de Supercomputación

EMBL-EBI

cnag
centre nacional d'anàlisi genòmica
centro nacional de análisis genómico

CSC ICT Solutions for Brilliant Minds

University of Ljubljana

CRG Centre for Genomic Regulation

uni.lu | LCSB

institut Curie

KTH VETENSKAP OCH KONST

MDC MAX DELBRÜCK CENTER FOR MOLECULAR MEDICINE IN THE HELMHOLTZ ASSOCIATION

HEIDELBERG UNIVERSITY HOSPITAL

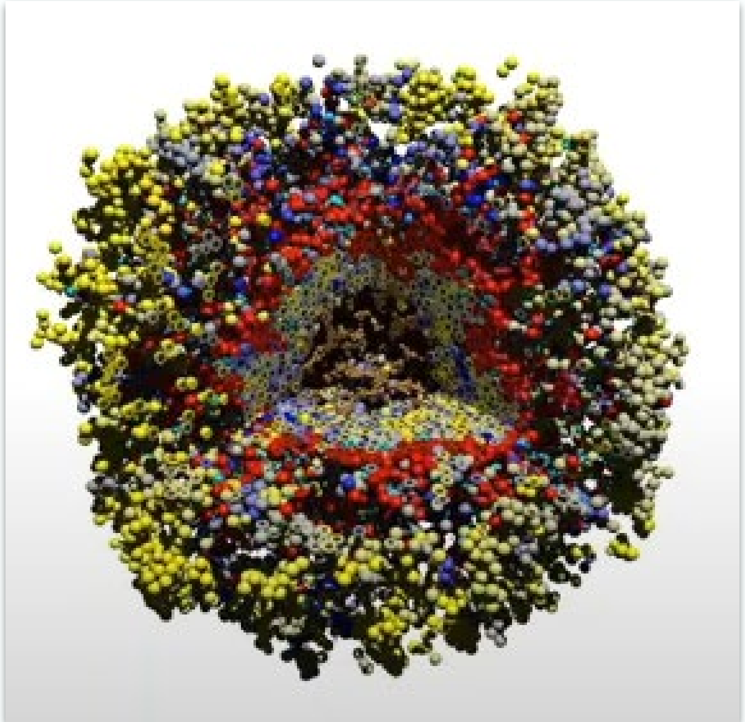
ELEM

Atos

PerMedCoE

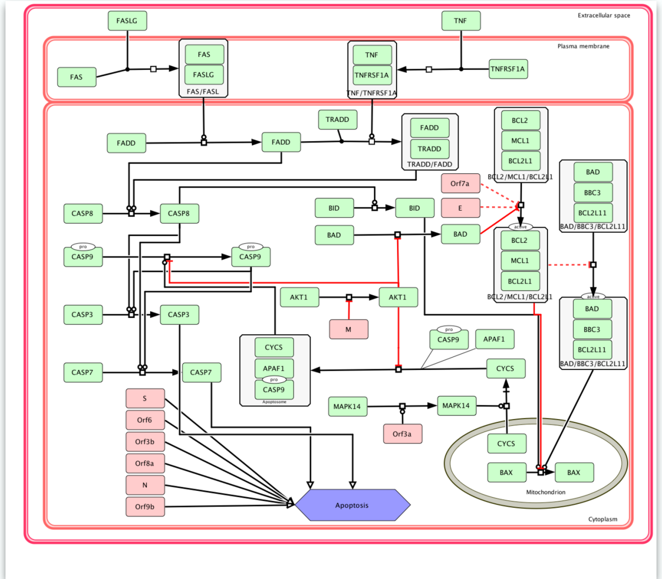
Overview

Cell level simulations



HPC

Molecular Pathways



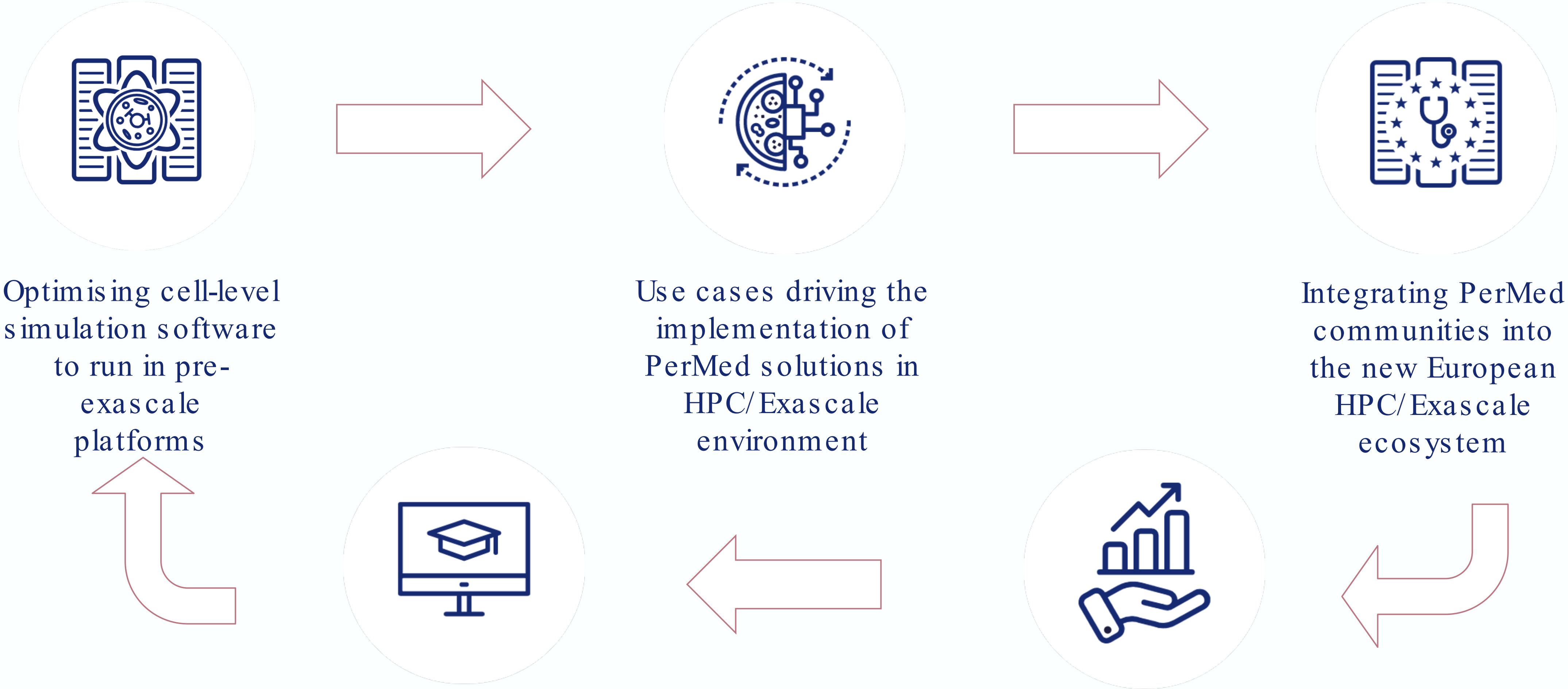
Overview

Motivation

- Simulation of cellular mechanistic models are essential for future paradigms
  (e.g. translation of omics data to medical relevant actions)
- The performance of current simulation software is still insufficient
  (e.g medical problems such as tumour evolution or patient-specific treatments)

- Sustainable roadmap to scale-up the essential computational biology tools
- Efficient and sustainable entry point to the HPC/Exascale-upgraded environments
- Translate omics analysis into actionable models of medical relevance.

Overview



Optimising cell-level simulation software to run in pre-exascale platforms

Use cases driving the implementation of PerMed solutions in HPC/Exascale environment

Integrating PerMed communities into the new European HPC/Exascale ecosystem

Building the basis for the sustainability of the PerMedCoE

Training biomedical professionals in the use of HPC/Exascale PerMed tools

Core tools

Core tools

PerMedCoE **optimises** key software for **cell-level simulations** and molecular **pathway modelling** to the new **HPC pre-exascale** platforms

PhysiCell

Agent-based modelling framework for multi-scale level simulations

COBRA

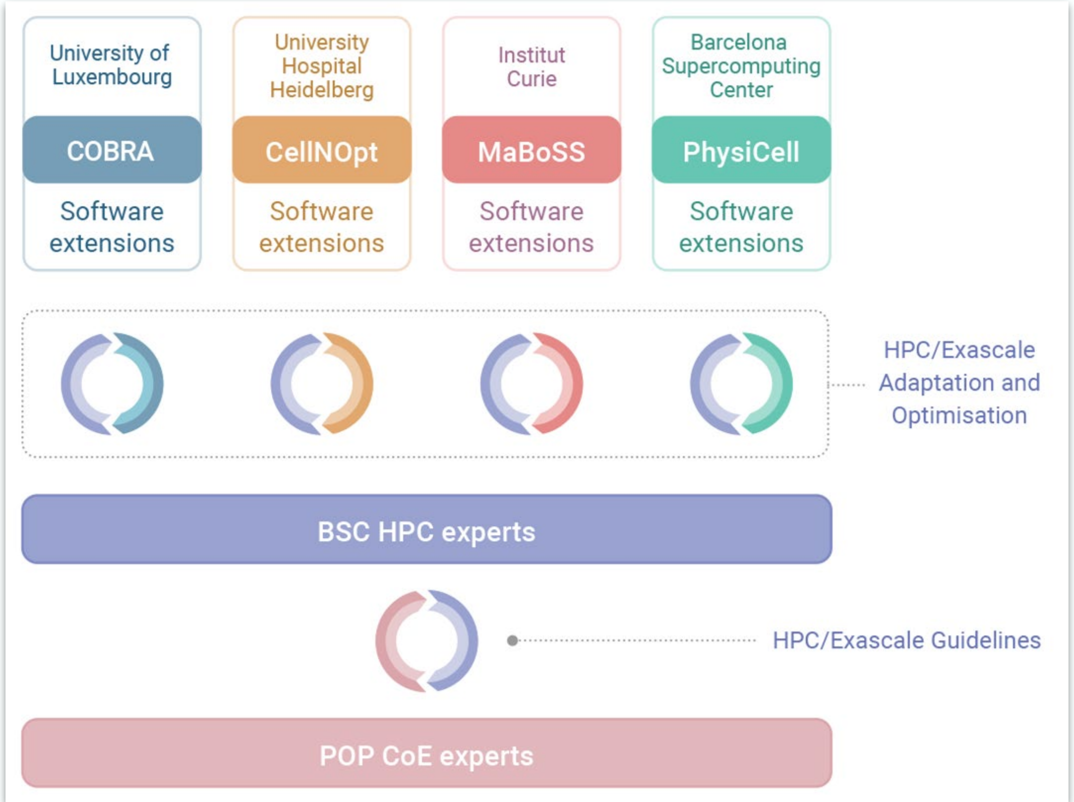
modelling of cellular metabolism at genome-scale

CellNOpt

modelling of signal transduction networks

MaBoSS

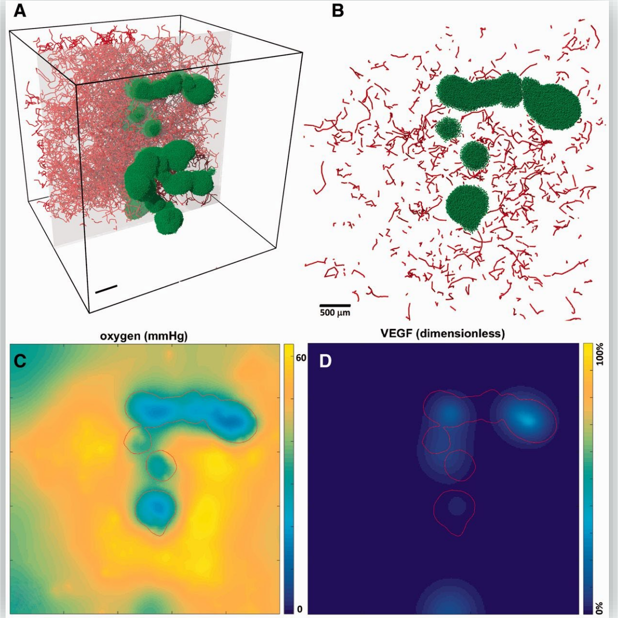
Stochastic simulations of Boolean models

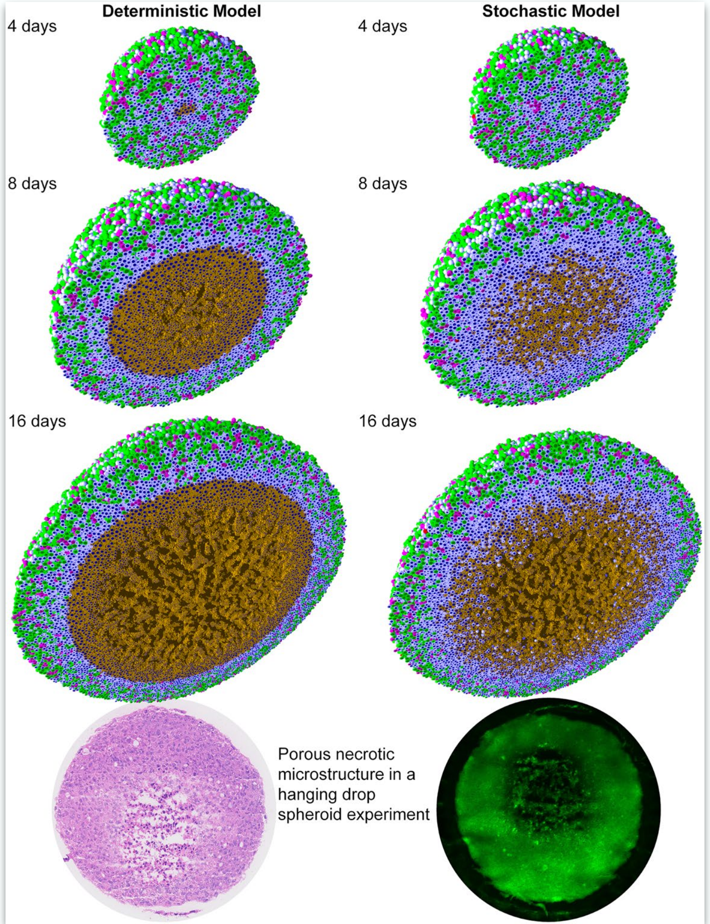


Core tools

PhysiCell

- Physics-based virtual microscope
- Implements agent-based programming
- Cell phenotype and cell-cell interactions
- Diffusion transport solver





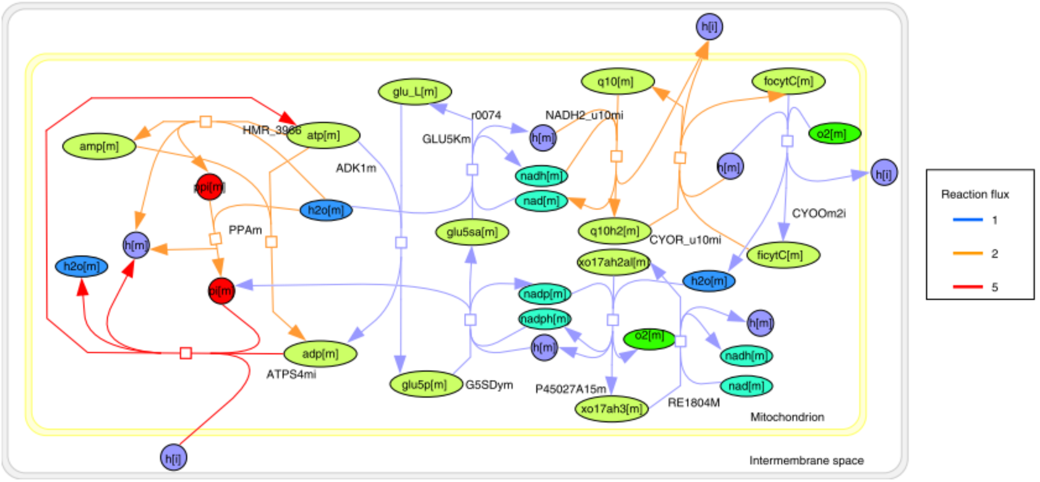
Porous necrotic microstructure in a hanging drop spheroid experiment

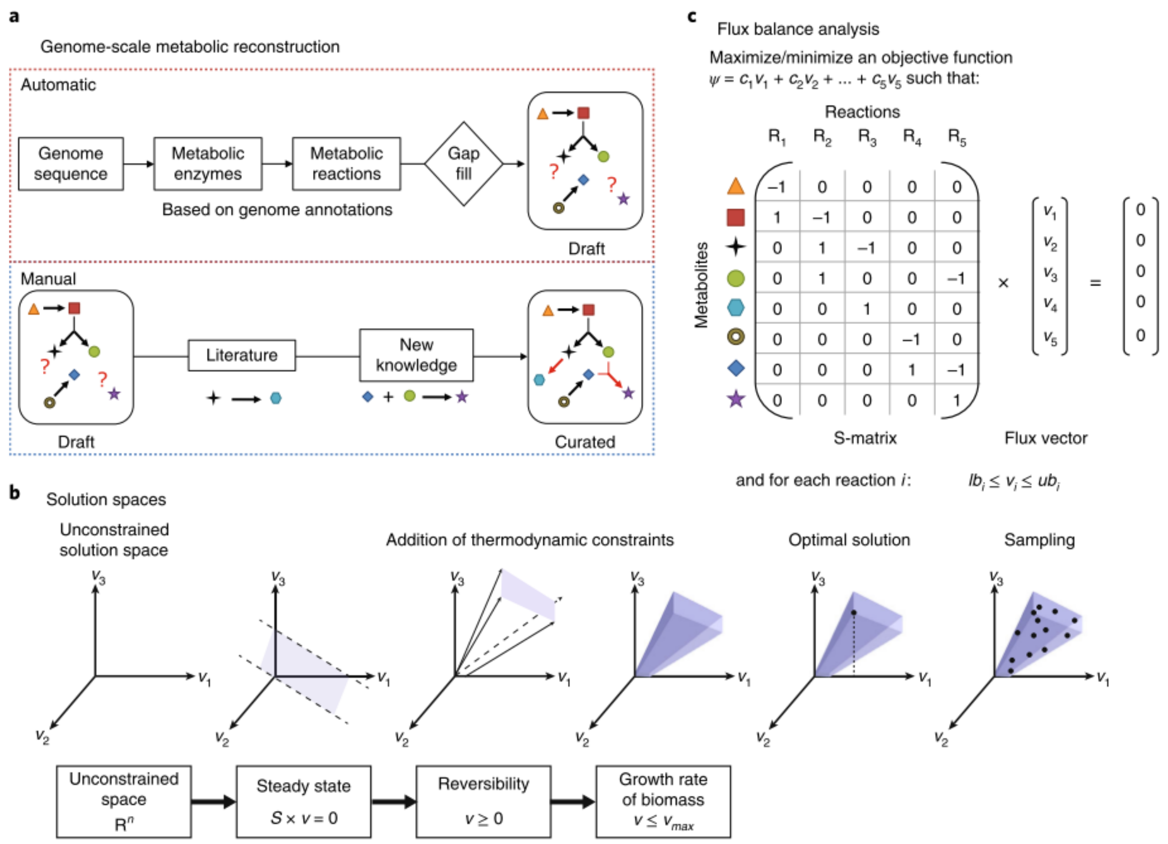
Ghaffarizadeh, A. et al (2018). https://doi.org/10.1371/journal.pcbi.1005991

Core tools

COBRA

(**CO**nstraints **B**ased **R**econstruction and **A**nalysis)



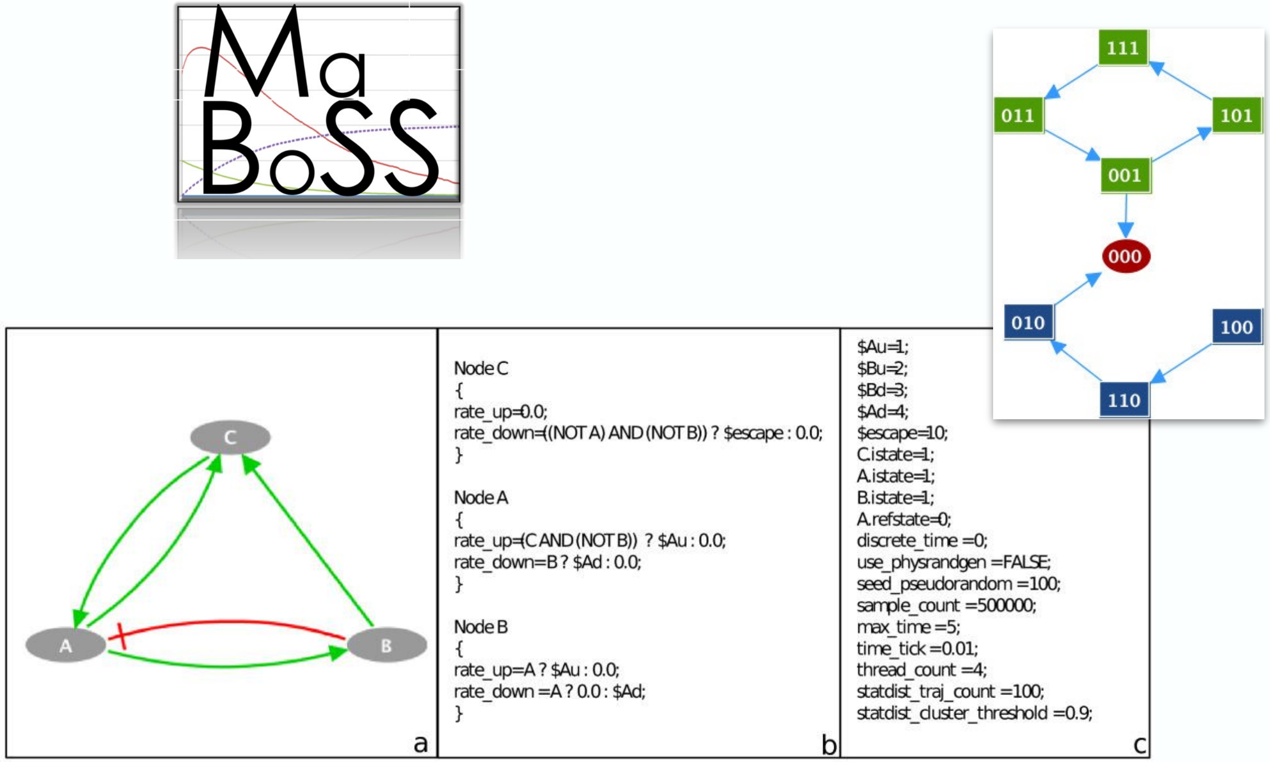


Heirendt, L., ...et al. (2019). *Nature Protocols, 14*(3), 639–702. https://doi.org/10.1038/s41596-018-0098-2

Core tools

MaBoSS

- Stochastic modelling of boolean networks

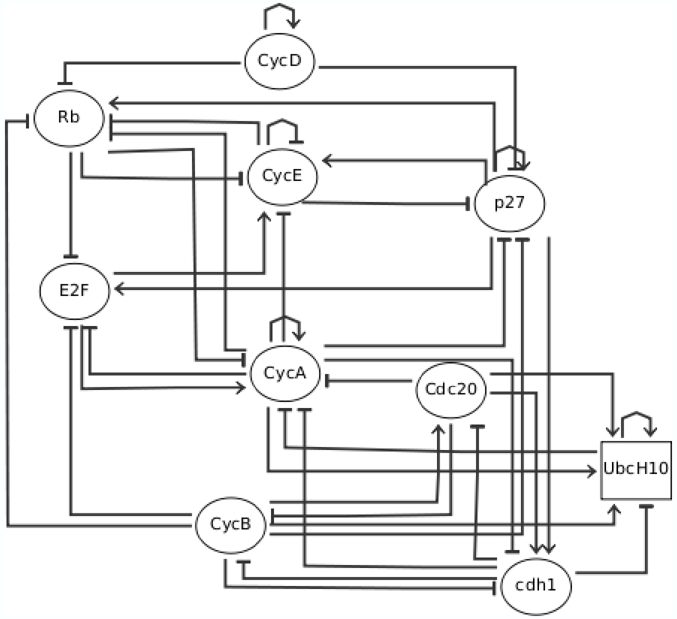


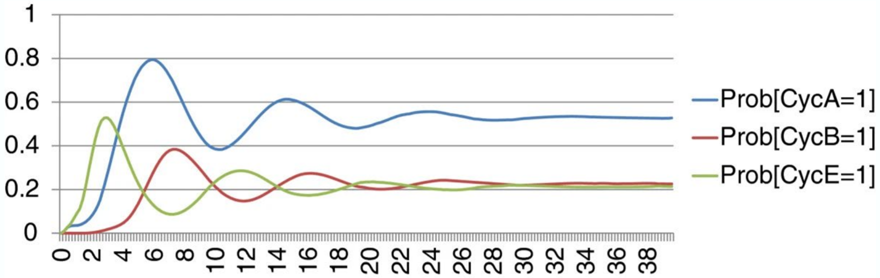
```
Node C
{
rate_up=0.0;
rate_down=((NOT A) AND (NOT B)) ? $escape : 0.0;
}

Node A
{
rate_up=(C AND (NOT B)) ? $Au : 0.0;
rate_down=B ? $Ad : 0.0;
}

Node B
{
rate_up=A ? $Au : 0.0;
rate_down =A ? 0.0 : $Ad;
}
```

```
$Au=1;
$Bu=2;
$Bd=3;
$Ad=4;
$escape=10;
C.istate=1;
A.istate=1;
B.istate=1;
A.refstate=0;
discrete_time =0;
use_physrandgen =FALSE;
seed_pseudorandom =100;
sample_count =500000;
max_time =5;
time_tick =0.01;
thread_count =4;
statdist_traj_count =100;
statdist_cluster_threshold =0.9;
```



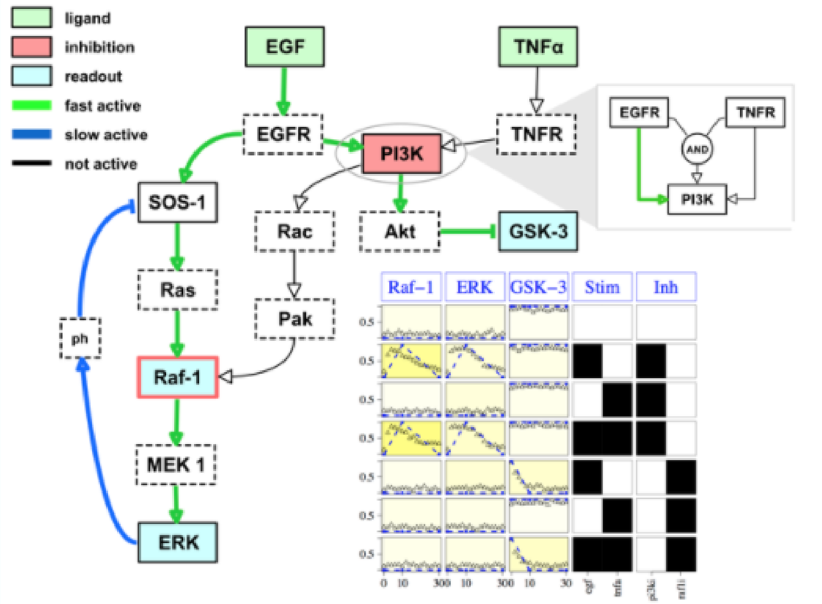


Stoll, G. et al (2017).Bioinformatics, 33(14), 2226–2228. https://doi.org/10.1093/bioinformatics/btx123

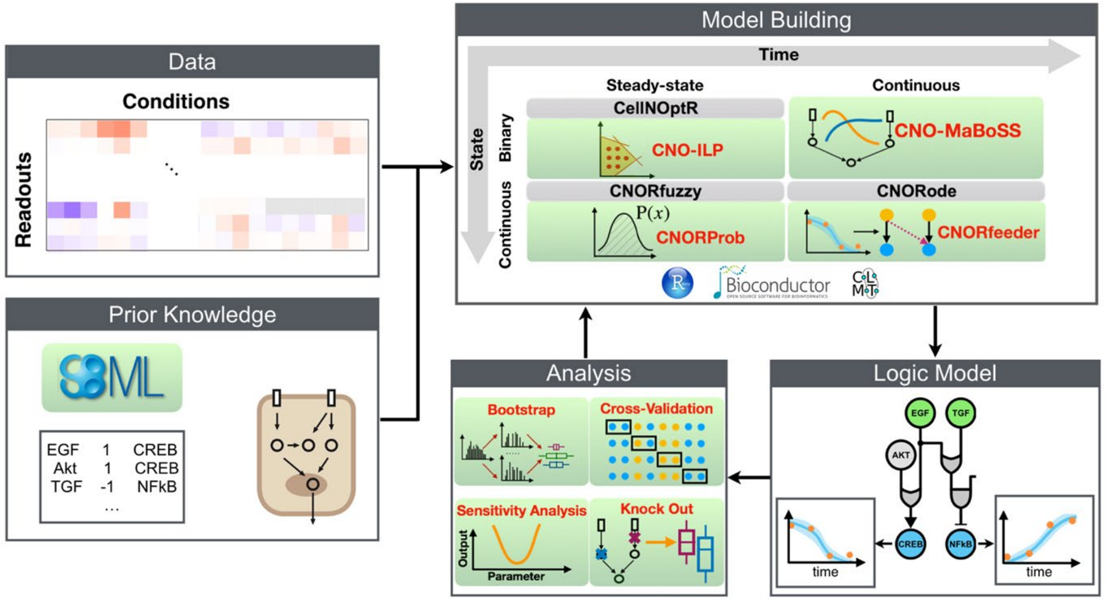
Core tools

CellNOpt

- Logic-based models of signal transduction



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



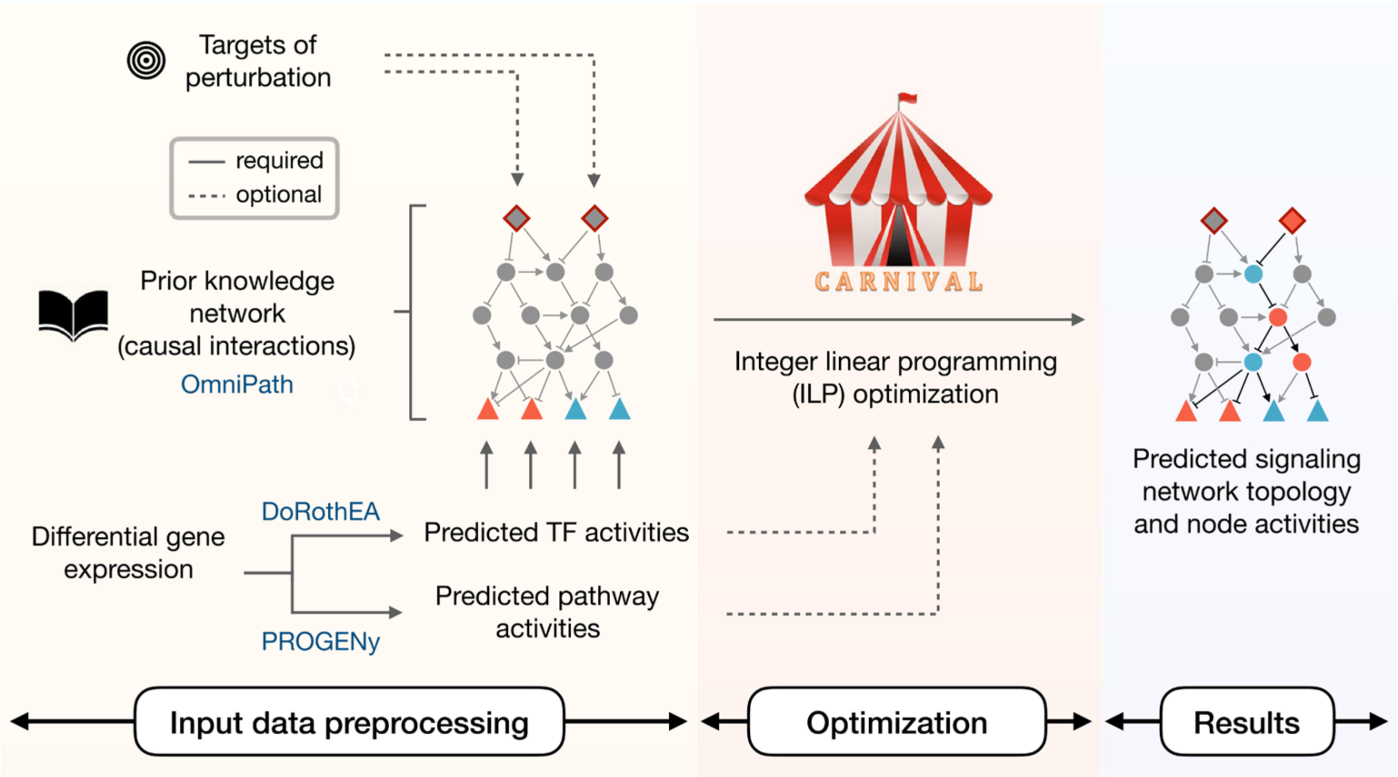
CellNOptR pipeline with packages and features (new implementations highlighted with green background). Perturbation data is combined prior knowledge of signalling and CellNOptR is used to contextualise the regulatory signalling interactions.

Terfve, C. et al (2012). BMC Systems Biology, 6. https://doi.org/10.1186/1752-0509-6-133

Core tools

CARNIVAL

(**CA**usal **R**easoning for **N**etwork identification using **I**nteger **VAL**ue programming)



Targets of perturbation

— required
---- optional

Prior knowledge network (causal interactions)
OmniPath

Differential gene expression
DoRothEA
PROGENy
Predicted TF activities
Predicted pathway activities

CARNIVAL
Integer linear programming (ILP) optimization

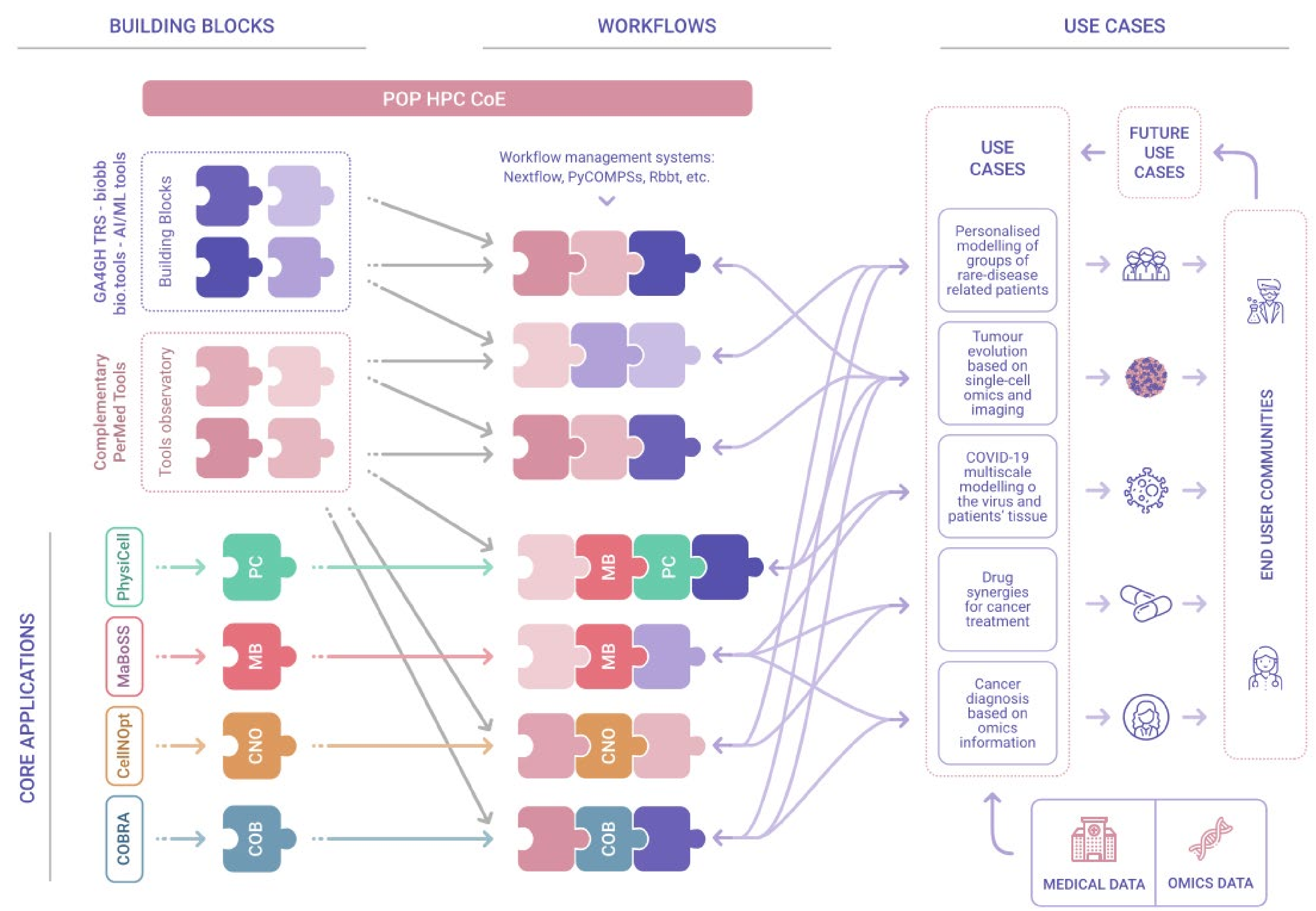
Predicted signaling network topology and node activities

Input data preprocessing
Optimization
Results

Liu, A., et al (2019). Npj Systems Biology and Applications, 5(1), 1–10. https://doi.org/10.1038/s41540-019-0118-z

Building blocks and Workflows

Building blocks and Workflows



Building blocks and Workflows

Containers

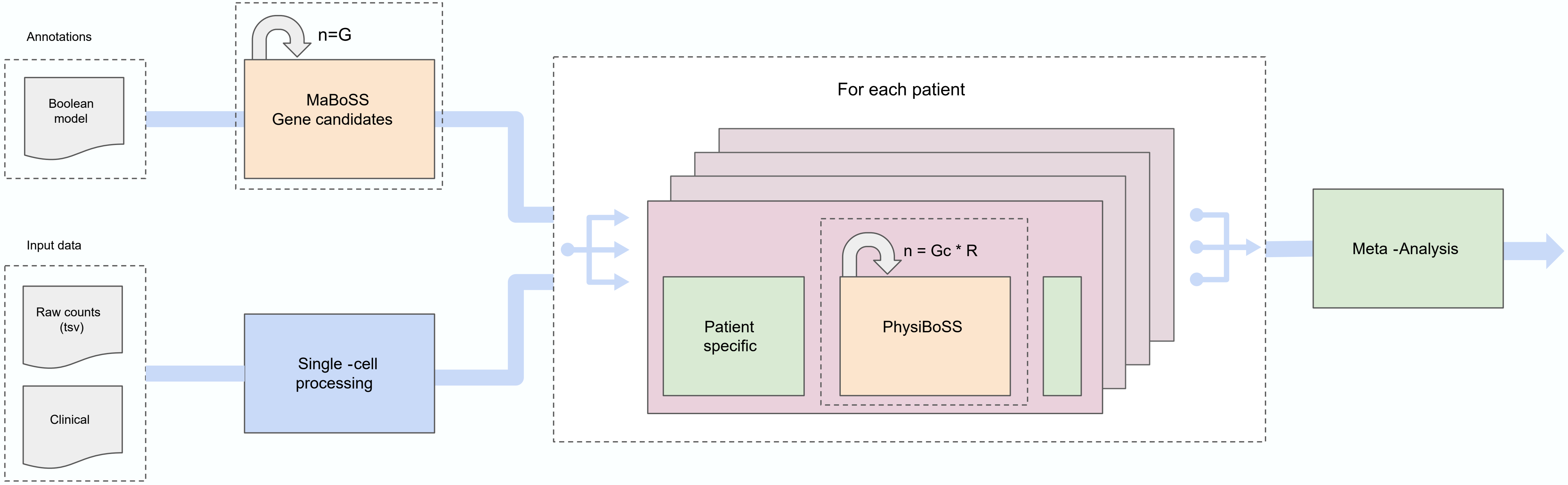
docker

Workflow managers

COMPSs

nextflow

Building blocks and Workflows



Annotations

Boolean model

n=G

MaBoSS
Gene candidates

Input data

Raw counts (tsv)

Clinical

Single -cell processing

For each patient

Patient specific

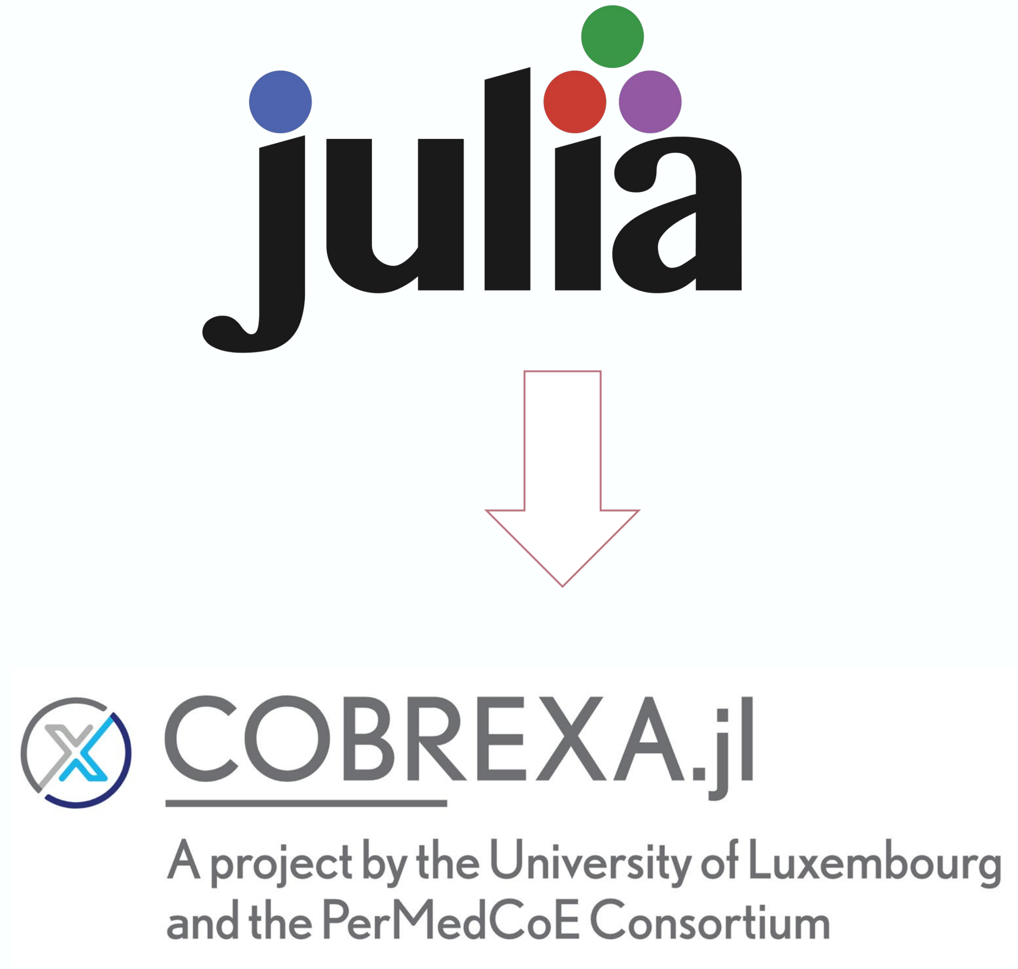
n = Gc * R

PhysiBoSS

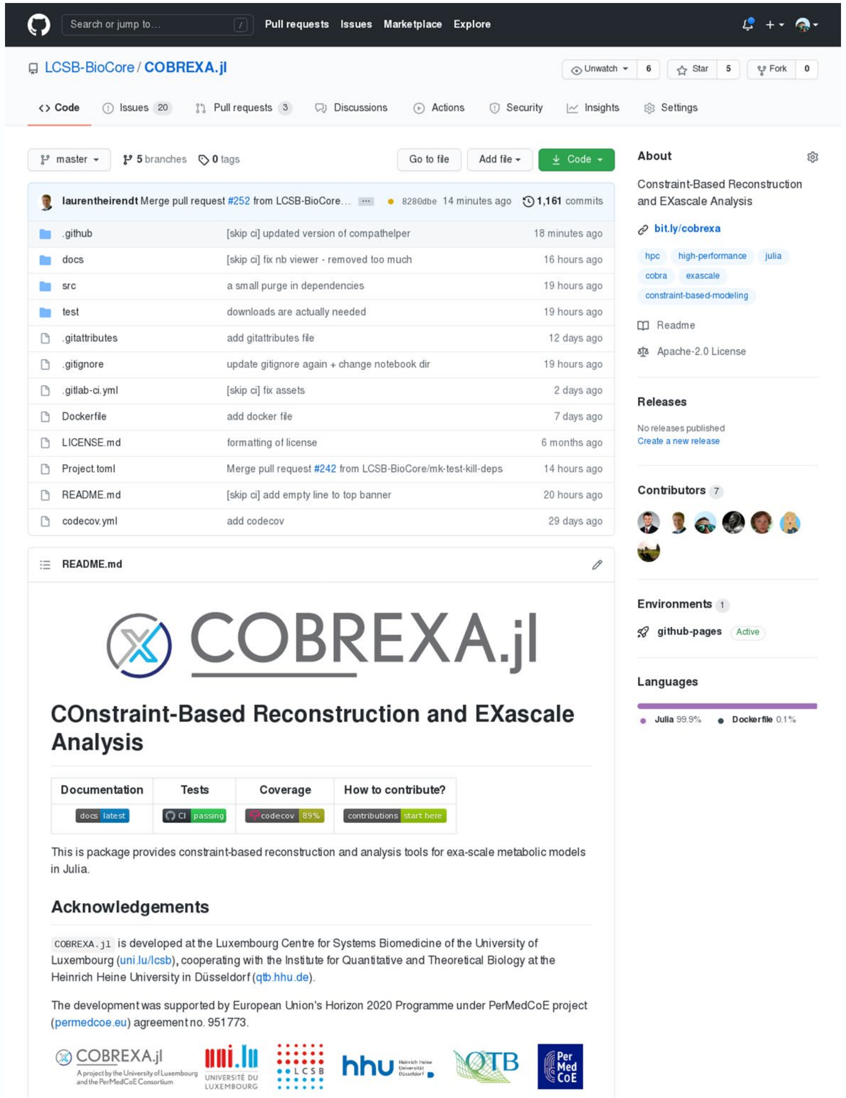
Meta -Analysis

Refactoring strategies

Refactoring strategies



A project by the University of Luxembourg and the PerMedCoE Consortium



LCSB-BioCore / **COBREXA.jl**

5 branches **0** tags

laurentheirendt Merge pull request #252 from LCSB-BioCore… 8280dbe 14 minutes ago **1,161** commits

.github	[skip ci] updated version of compathelper	18 minutes ago
docs	[skip ci] fix nb viewer - removed too much	16 hours ago
src	a small purge in dependencies	19 hours ago
test	downloads are actually needed	19 hours ago
.gitattributes	add gitattributes file	12 days ago
.gitignore	update gitignore again + change notebook dir	19 hours ago
.gitlab-ci.yml	[skip ci] fix assets	2 days ago
Dockerfile	add docker file	7 days ago
LICENSE.md	formatting of license	6 months ago
Project.toml	Merge pull request #242 from LCSB-BioCore/mk-test-kill-deps	14 hours ago
README.md	[skip ci] add empty line to top banner	20 hours ago
codecov.yml	add codecov	29 days ago

About

Constraint-Based Reconstruction and EXascale Analysis

bit.ly/cobrexa

Readme

Apache-2.0 License

Releases

No releases published
Create a new release

Contributors 7

Environments 1

github-pages Active

Languages

Julia 99.9% Dockerfile 0.1%

README.md

COnstraint-Based Reconstruction and EXascale Analysis

Documentation	Tests	Coverage	How to contribute?
docs latest	CI passing	codecov 89%	contributions start here

This is package provides constraint-based reconstruction and analysis tools for exa-scale metabolic models in Julia.

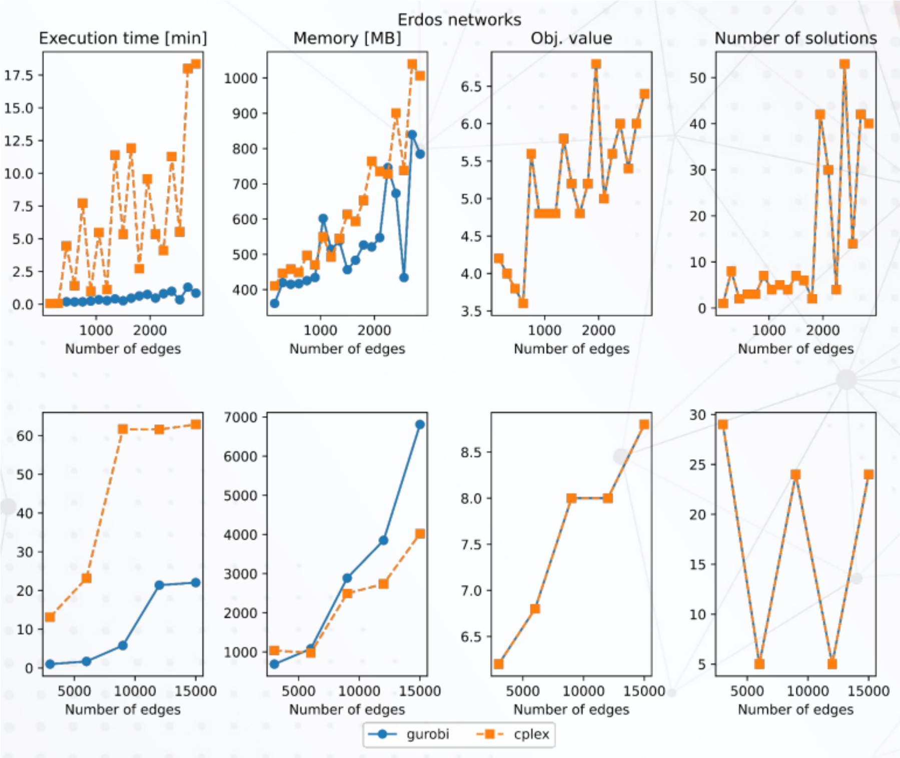
Acknowledgements

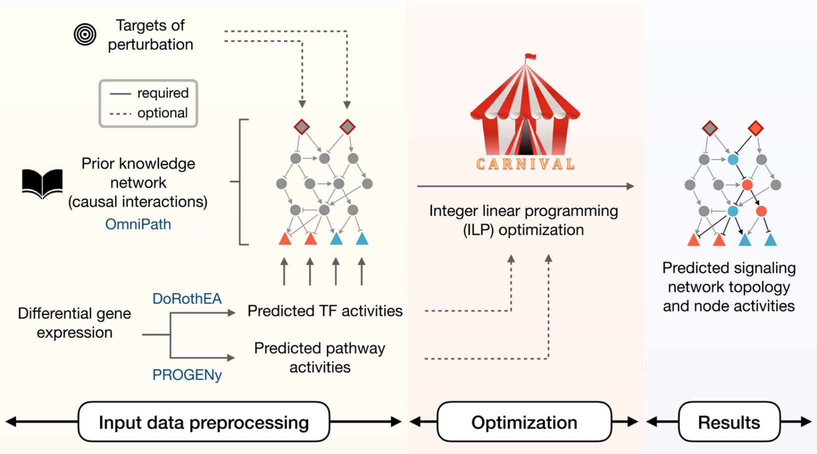
`COBREXA.jl` is developed at the Luxembourg Centre for Systems Biomedicine of the University of Luxembourg (uni.lu/lcsb), cooperating with the Institute for Quantitative and Theoretical Biology at the Heinrich Heine University in Düsseldorf (qtb.hhu.de).

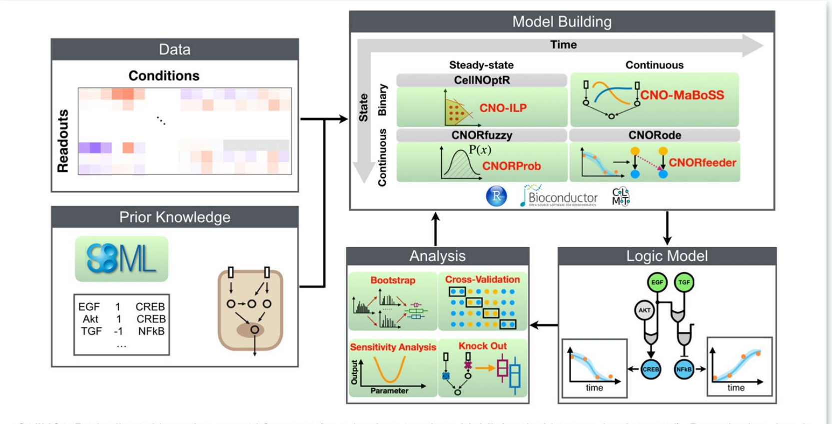
The development was supported by European Union's Horizon 2020 Programme under PerMedCoE project (permedcoe.eu) agreement no. 951773.

Refactoring strategies

- Benchmarking ILP solvers





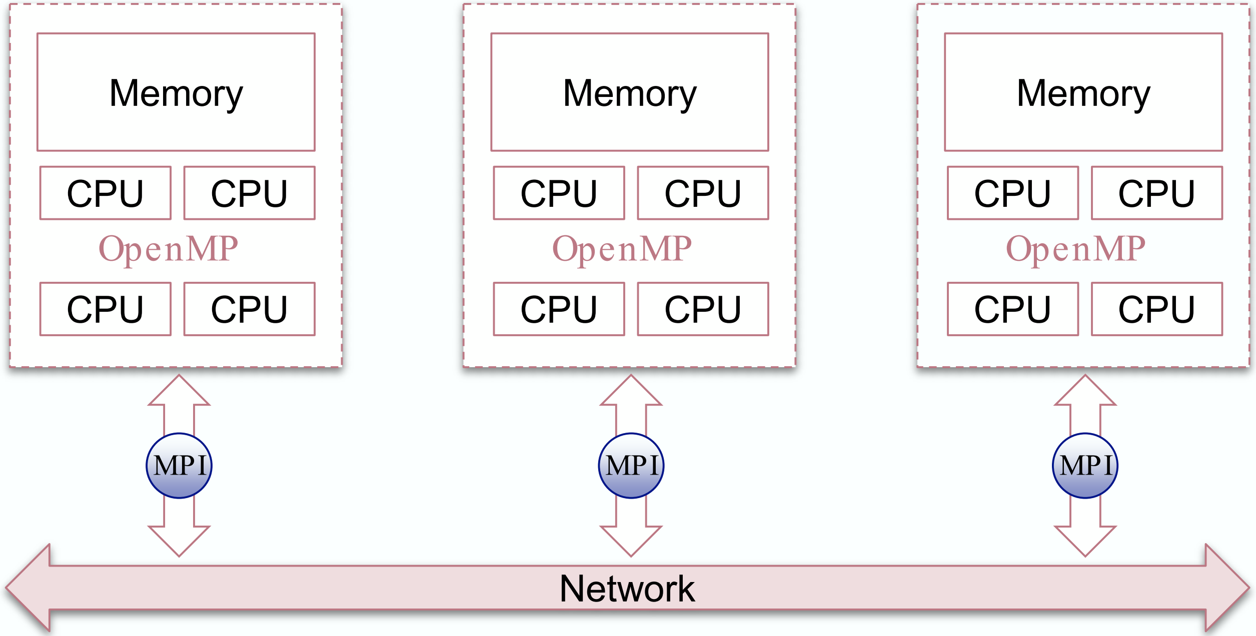


CellNOptR pipeline with packages and features (new implementations highlighted with green background). Perturbation data is combined prior knowledge of signalling and CellNOptR is used to contextualise the regulatory signalling interactions.

Refactoring strategies

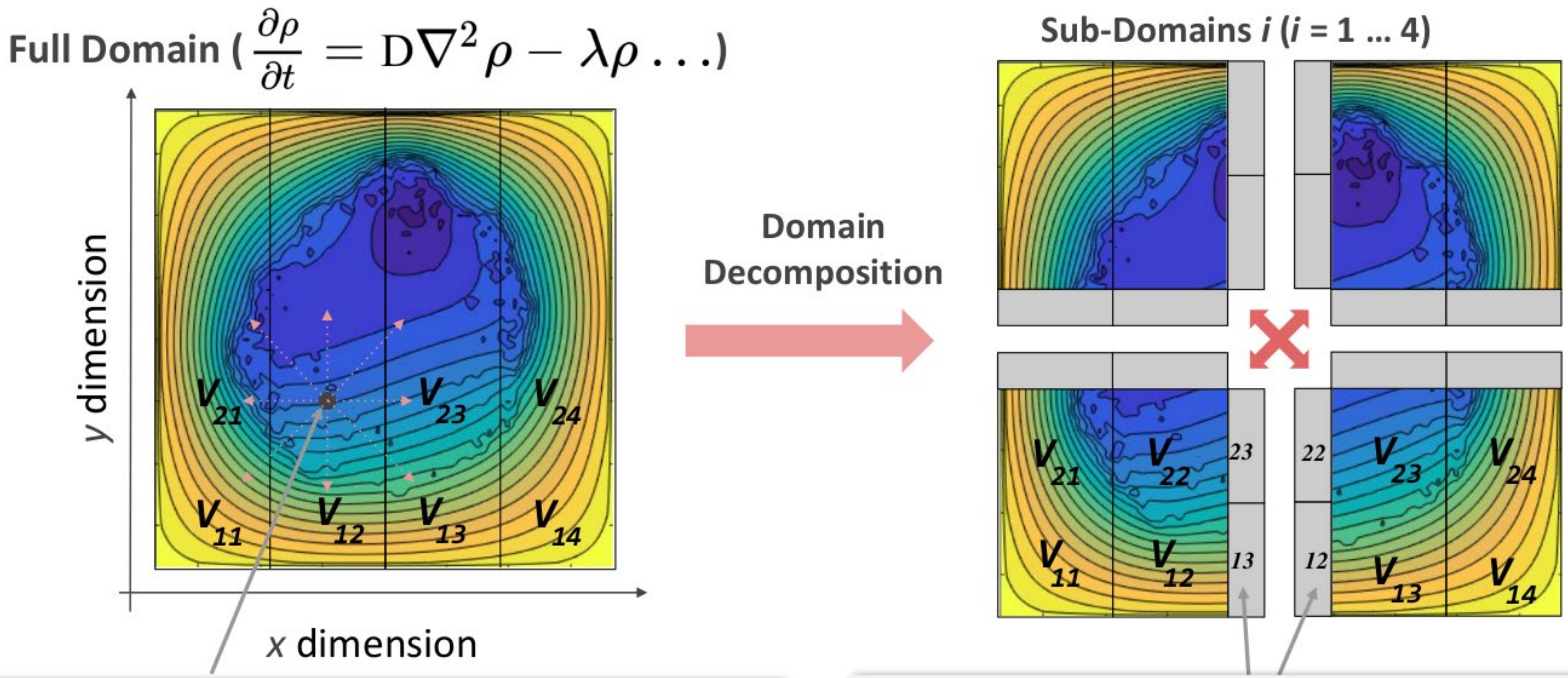
MPI (Message Passing Interface)

- Distributed computing
- Combined with parallel computing (OpenMP)
- Combine the resources of different nodes as a single larger machine



Refactoring strategies

PhysiCell-MPI



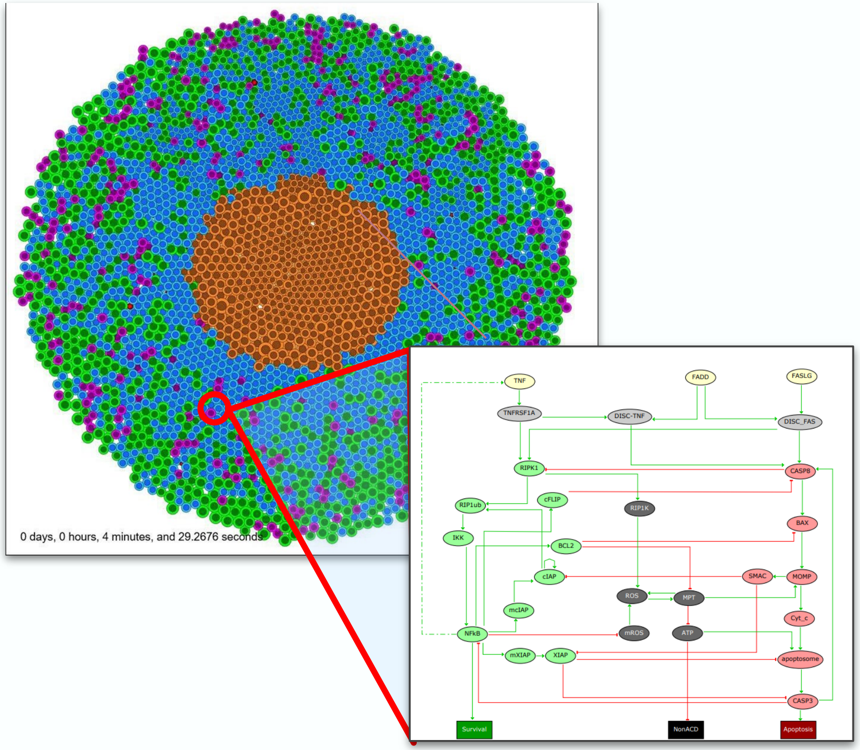
Individual Voxel: stores the values of each molecule concentration. Connected to other voxels through Moore neighborhood (PDE solver)

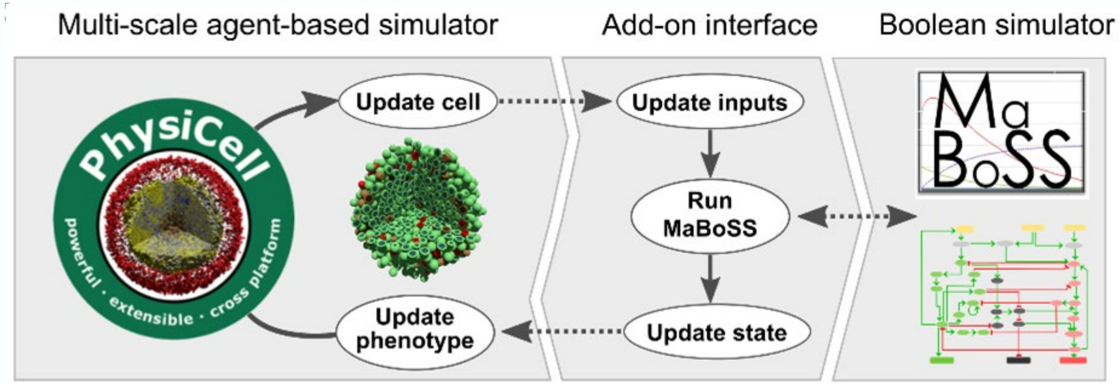
Ghost (Halo) Cells: needed to update boundary voxels in a transparent way. Needed to exchange information between neighbour voxels

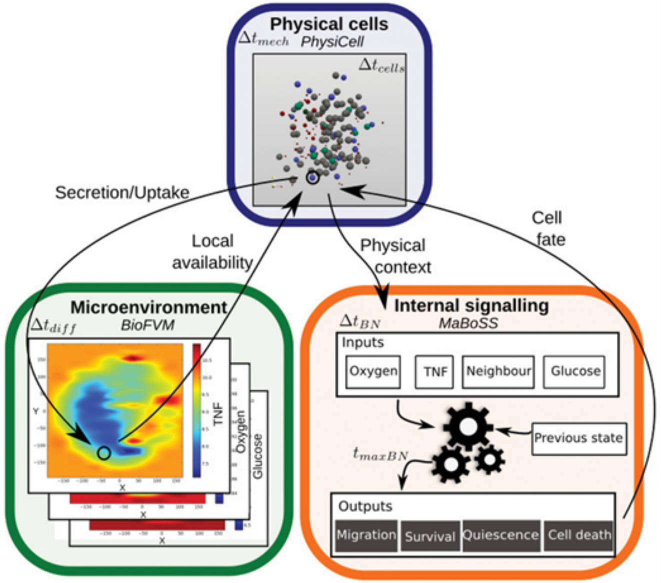
Refactoring strategies

PhysiBoss (PhysiCell + MaBoSS)

Cell state and decisions depend on embedded boolean models



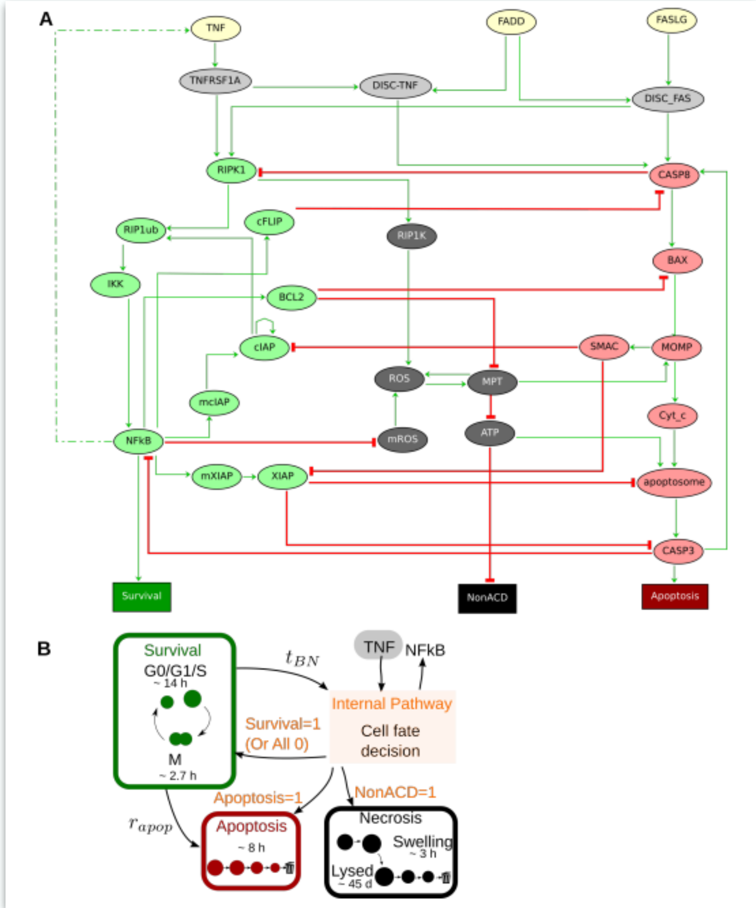




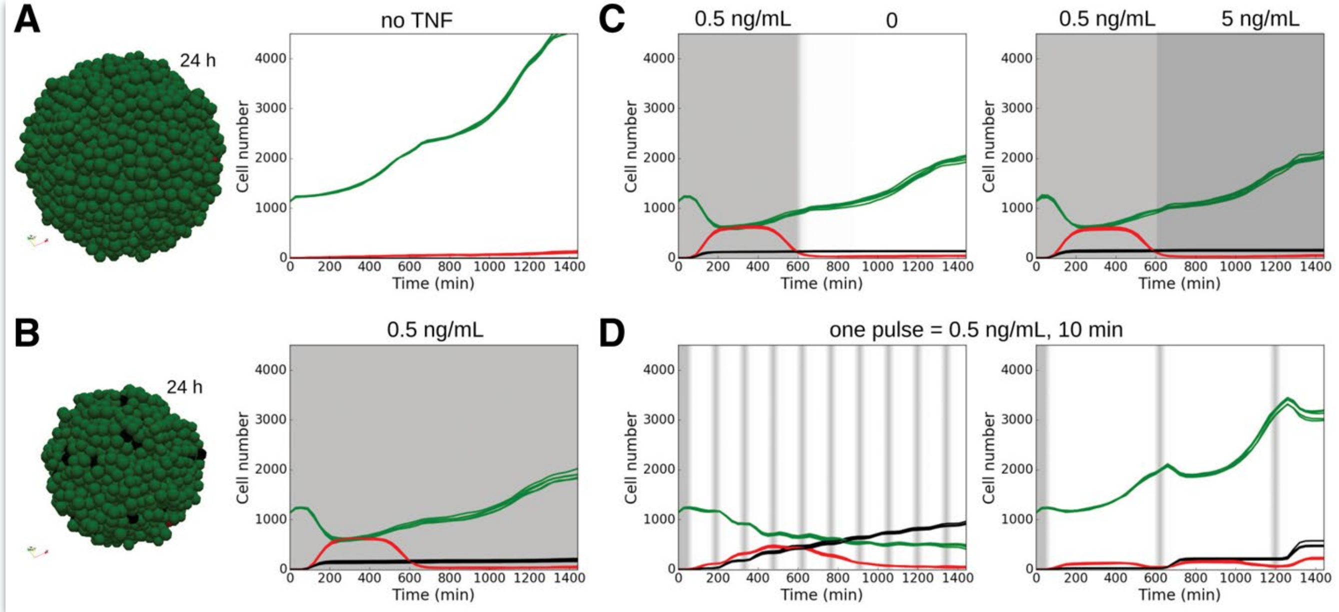
Letort, G., Montagud, A. et al (2019). Bioinformatics, 35(7), 1188–1196. https://doi.org/10.1093/bioinformatics/bty766

Refactoring strategies

In silico modelling of drugs/treatments dynamics



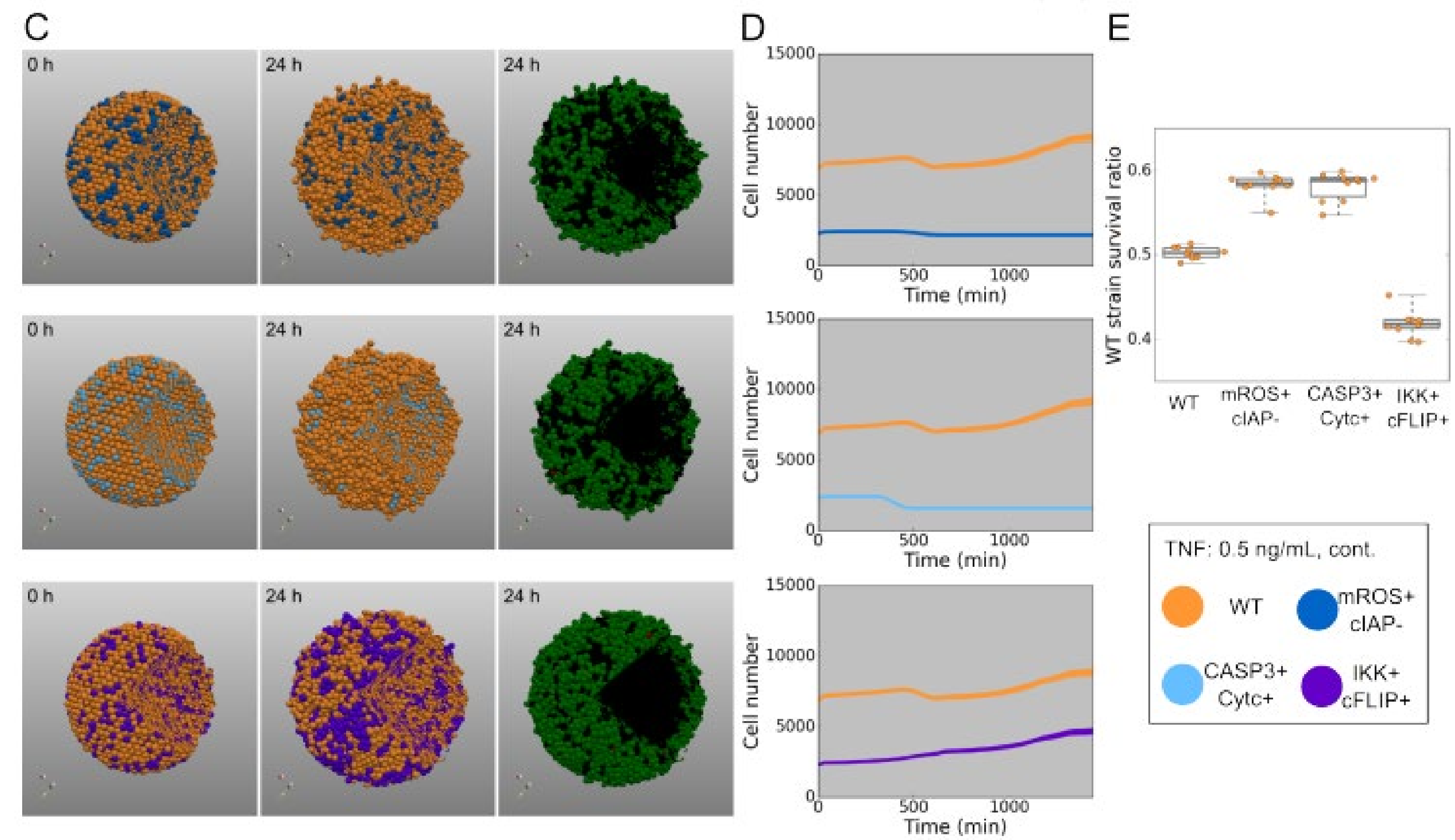
TNF treatment



Letort, G., Montagud, A. et al (2019). Bioinformatics, 35(7), 1188–1196. https://doi.org/10.1093/bioinformatics/bty766

Refactoring strategies

Simulate heterogeneous cell populations



Use Cases

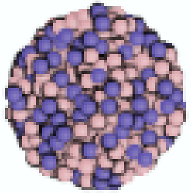
Use Cases

Different realistic biomedical scenarios to focus on personalized models

Cancer Diagnosis Based on Omics Information

Drug Synergies for Cancer Treatment

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



Tumour Evolution Based on Single-Cell Omics and Imaging

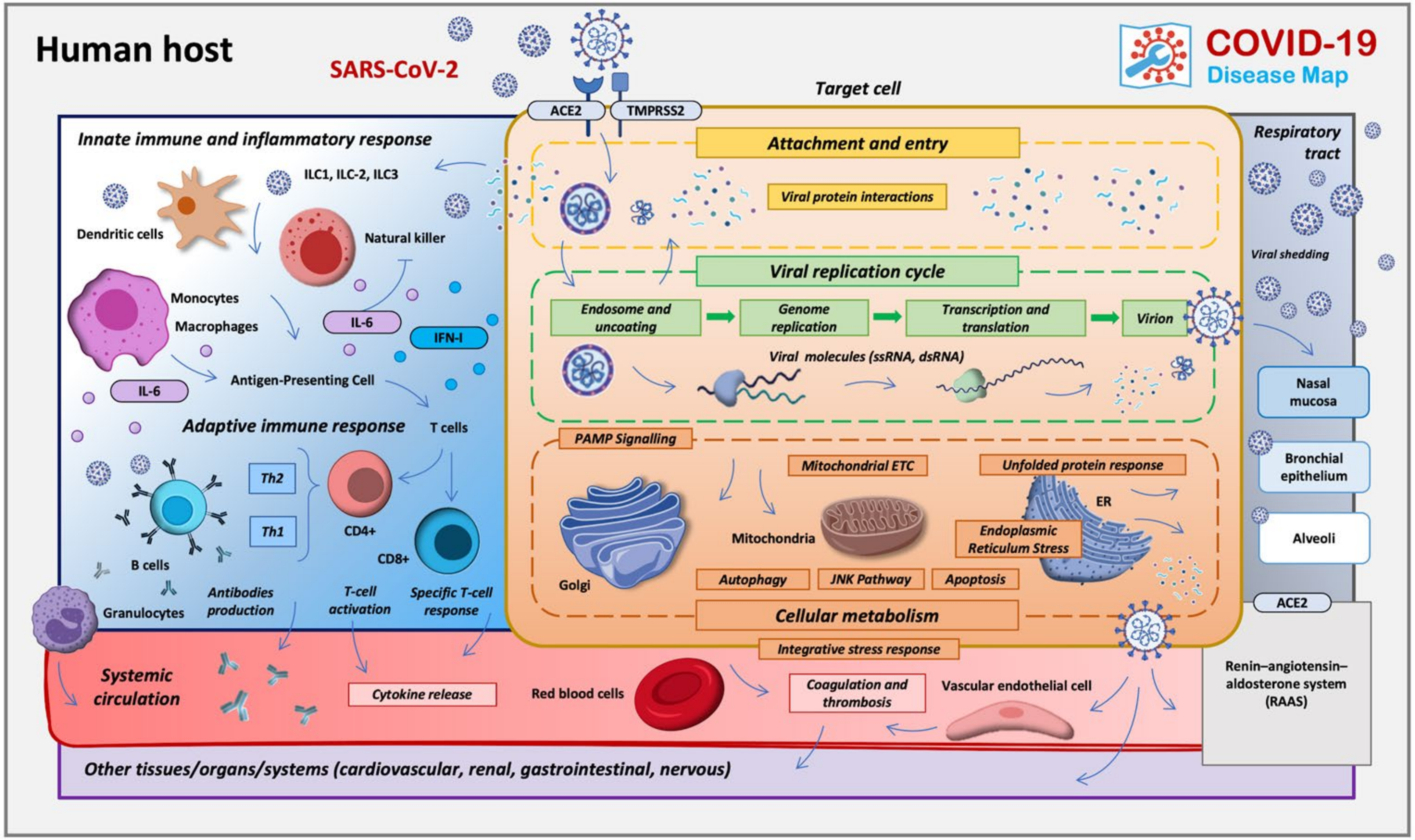
Personalised Modelling of Groups of Rare-Disease Related Patients

Use cases

UC5: COVID-19

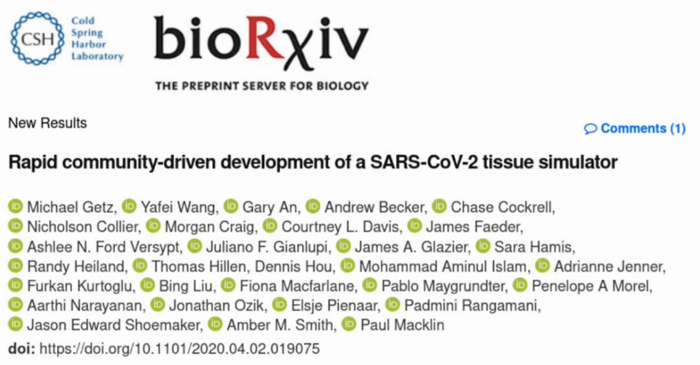
systems
medicine
disease
maps

COVID-19 Disease Map



Use cases

UC5: COVID-19



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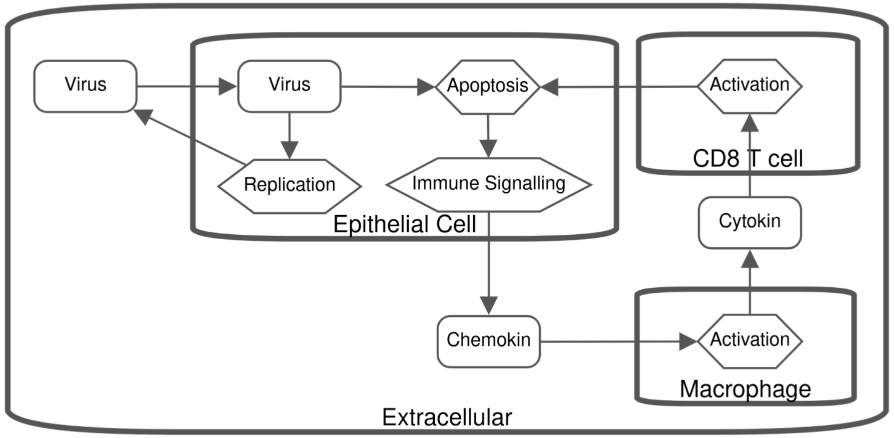
New Results

Comments (1)

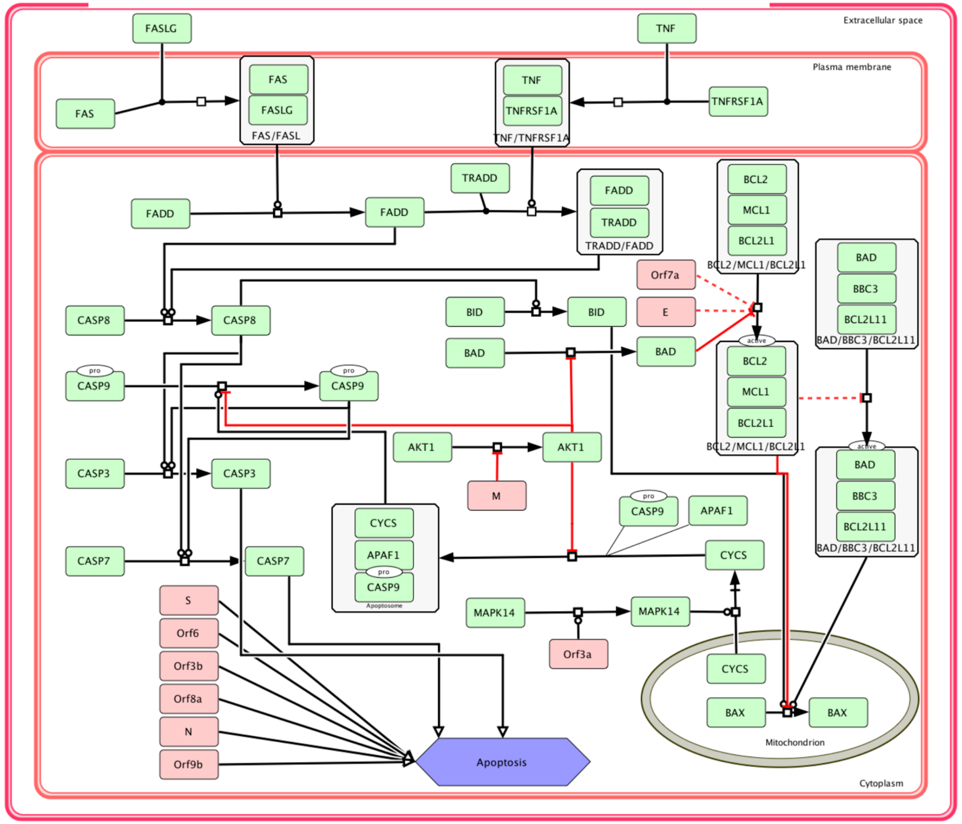
Rapid community-driven development of a SARS-CoV-2 tissue simulator

Michael Getz, Yafei Wang, Gary An, Andrew Becker, Chase Cockrell, Nicholson Collier, Morgan Craig, Courtney L. Davis, James Faeder, Ashlee N. Ford Versypt, Juliano F. Gianlupi, James A. Glazier, Sara Hamis, Randy Heiland, Thomas Hillen, Dennis Hou, Mohammad Aminul Islam, Adrianne Jenner, Furkan Kurtoglu, Bing Liu, Fiona Macfarlane, Pablo Maygrundter, Penelope A Morel, Aarthi Narayanan, Jonathan Ozik, Elsje Pienaar, Padmini Rangamani, Jason Edward Shoemaker, Amber M. Smith, Paul Macklin

doi: https://doi.org/10.1101/2020.04.02.019075

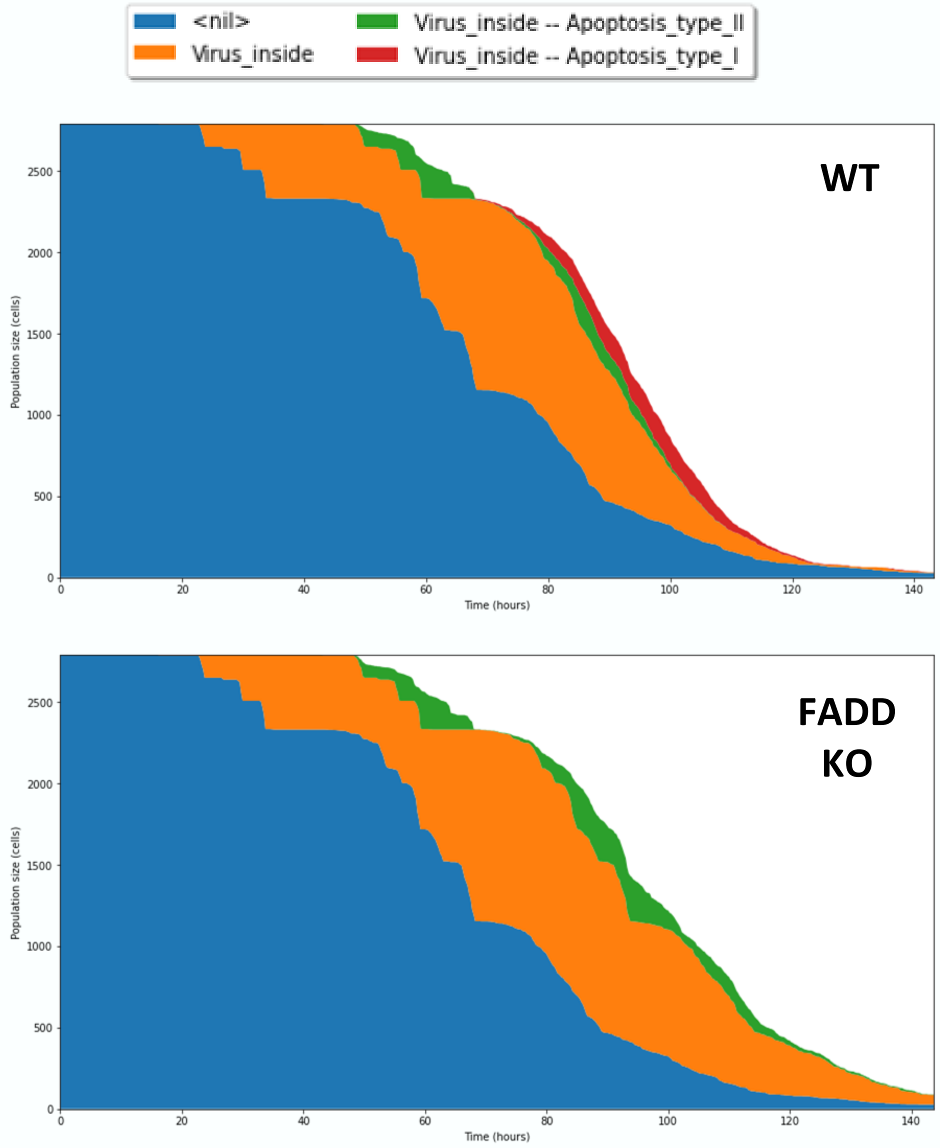


COVID-19 Disease Map

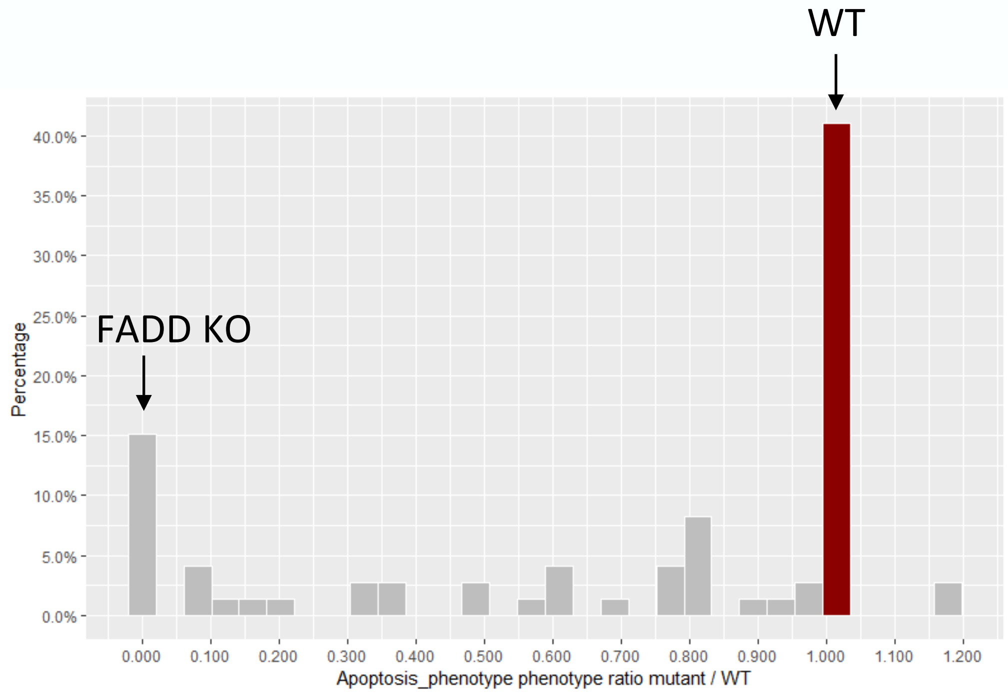


- Virus as a substrate
- Epithelial cells as tissue
- Immune system cells interactions
- Boolean model inside epithelial cells

Use cases



- Mutants that affect epithelial cells' apoptosis
- Heterogeneous cell populations



Arnau Montagud (BSC)
Vincent Nöel (IC)

THANK YOU

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The PerMedCoE project has received funding from the European Union's Horizon 2020 research and innovation programme under the grant agreement Nº951773