

Qualitative modelling of biological systems with MaBoSS

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PerMedCoE summer school
from pathway modelling tools to cell-level simulations

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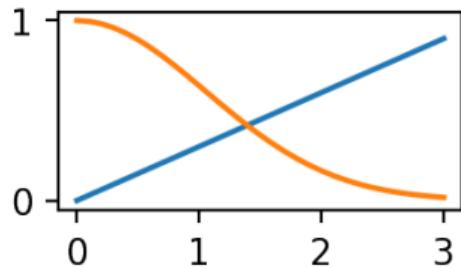
HPC/Exascale
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- › MaBoSS : Continuous time boolean modelling
- › Example on Cohen's model of tumor invasion
- › Example on Montagud's model of prostate
- › Using MaBoSS : WebMaBoSS
- › Using MaBoSS : pyMaBoSS
- › MaBoSS Ecosystem

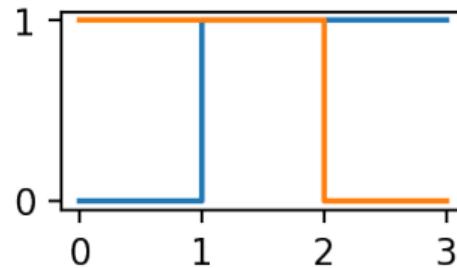
MaBoSS : Continuous time boolean modelling

MaBoSS : Continuous time boolean modelling

Quantitative



Qualitative



- › Values can be any quantity
- › Continuous time
- › Difficult to write
- › Difficult to simulate large models
- › Values are true/false
- › Sequences of events
- › Easy to write
- › Can simulate large models

MaBoSS : Continuous time boolean modelling

Methodology article | [Open Access](#) | Published: 29 August 2012

Continuous time boolean modeling for biological signaling: application of Gillespie algorithm

[Gautier Stoll](#)  , [Eric Viara](#), [Emmanuel Barillot](#) & [Laurence Calzone](#)

[BMC Systems Biology](#) 6, Article number: 116 (2012) | [Download Citation](#) 

6306 Accesses | 32 Citations | 1 Altmetric | [Metrics](#) 



Gautier Stoll



Eric Viara



Laurence Calzone



Emmanuel Barillot

MaBoSS : Continuous time boolean modelling

Markovian Boolean Stochastic Simulator



<https://maboss.curie.fr/>

- › Boolean
- › Stochastic
- › Physical time
- › Handle different time scale processes (transcription, phosphorylation, etc.)

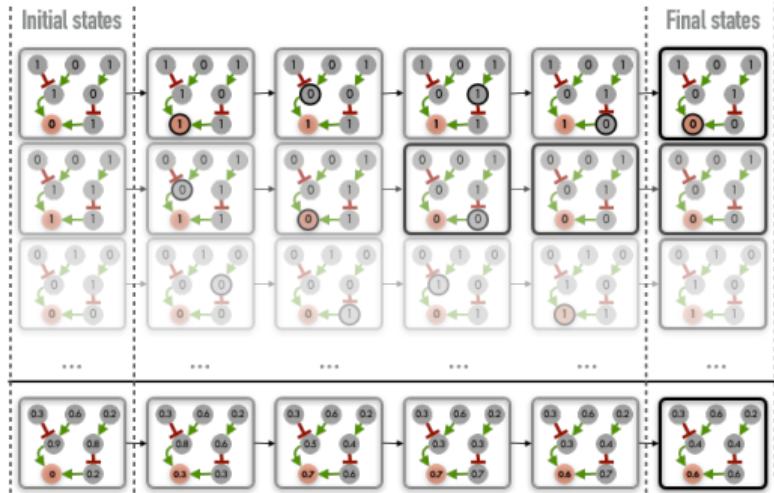
⇒ Fills the gap between ODE and Boolean modeling

MaBoSS : Continuous time boolean modelling

- › Simulate transitions from a boolean network state to another using a markov chain
- › Transition rate :

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

- › These transitions are stochastic : multiple trajectories are possible

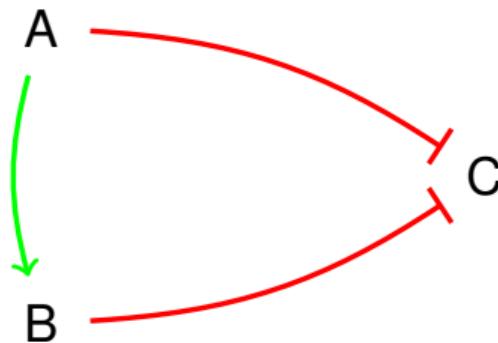


From a set of simulated trajectories, we compute mean trajectories:

⇒ We obtain probabilities per state over time

MaBoSS : Continuous time boolean modelling

- › Toy example



Continuous time Boolean modelling

Formulas:

- › $A.R_{up} = 1$
- › $B.R_{up} = A ? 1 : 0$
- › $C.R_{up} = (\neg A \mid \neg B) ? 1 : 0$
- › $A.R_{down} = 0$
- › $B.R_{down} = A ? 0 : 1$
- › $C.R_{down} = (\neg A \mid \neg B) ? 0 : 1$

Initial values:

- › $A_0 = 1$
- › $B_0 = 0$
- › $C_0 = 1$

MaBoSS : Continuous time boolean modelling

› Model definition : BND file

- › Definition of activation and inactivation rates
- › Allows complex cases : multiple rates for multiple states, ...
- › Possibility to use parameters defined in the simulation settings
- › Now allows other boolean model formats : SBML-qual, BNet

```
1 node A {  
2     rate_up = 1;  
3     rate_down = 0;  
4 }  
5  
6 node B {  
7     logic = A;  
8     rate_up = @logic ? $act_B : 0;  
9     rate_down = 0;  
10 }  
11  
12 node C {  
13     logic = !A | !B;  
14     rate_up = @logic ? $act_C : 0;  
15     rate_down = @logic ? 0 : $act_C;  
16 }
```

MaBoSS : Continuous time boolean modelling

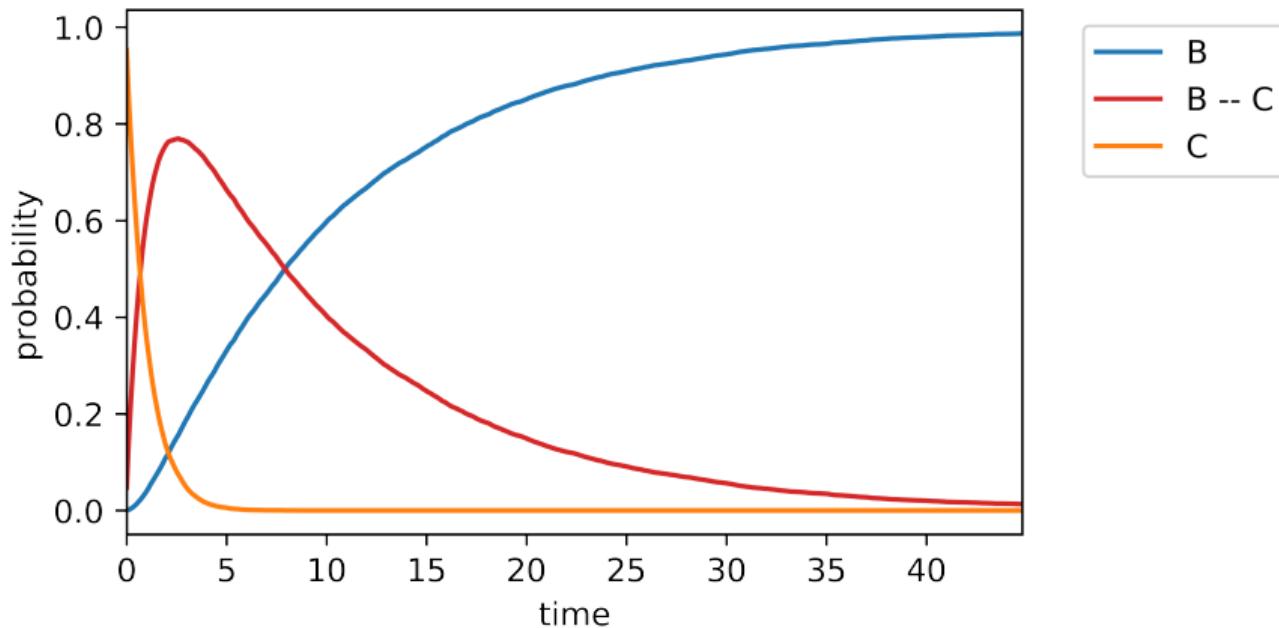
› Simulation settings : CFG file

- › Initial state of nodes (Fixed, Stochastic)
- › Internal/Output variables
- › Parameters
- › Settings

```
1 A.istate = TRUE;
2 B.istate = FALSE;
3 C.istate = TRUE;
4
5 A.is_internal = TRUE;
6
7 $act_B = 1;
8 $act_C = 0.1;
9
10 max_time = 45;
11 sample_count = 10000;
12 use_physrandgen = 1;
13 thread_count = 1;
```

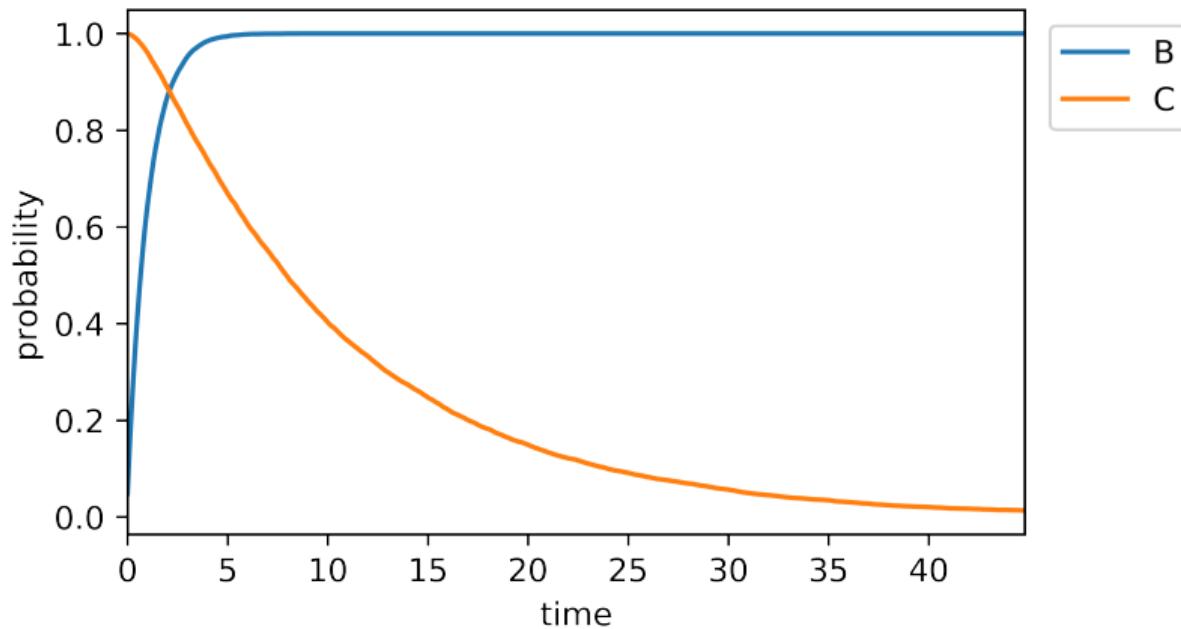
MaBoSS : Continuous time boolean modelling

- › State probability trajectories



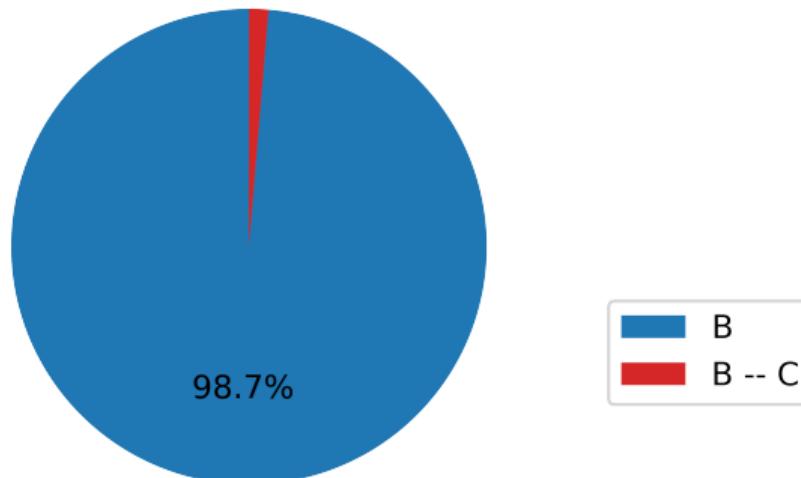
MaBoSS : Continuous time boolean modelling

- › Node probability trajectories



MaBoSS : Continuous time boolean modelling

- › Final (\neq steady) state distribution



Example on Cohen's model of tumor invasion

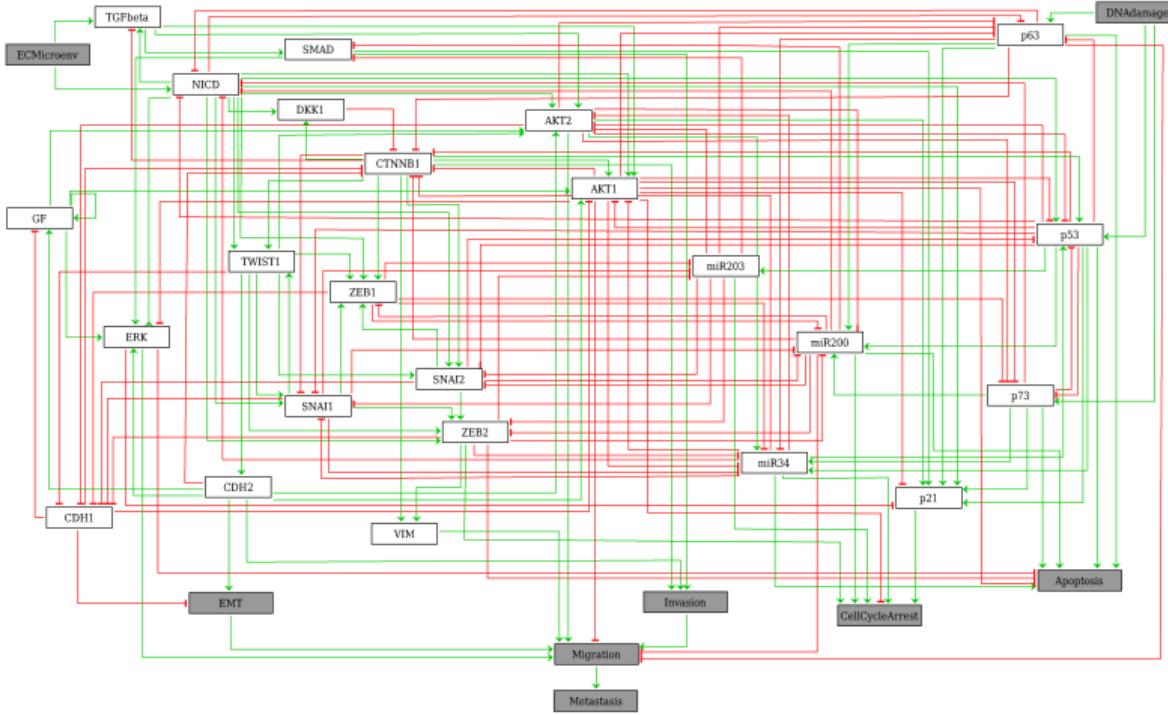
Example on Cohen's model of tumor invasion

Two input nodes:

- › ECMicroenv
- › DNADamage

Six output nodes:

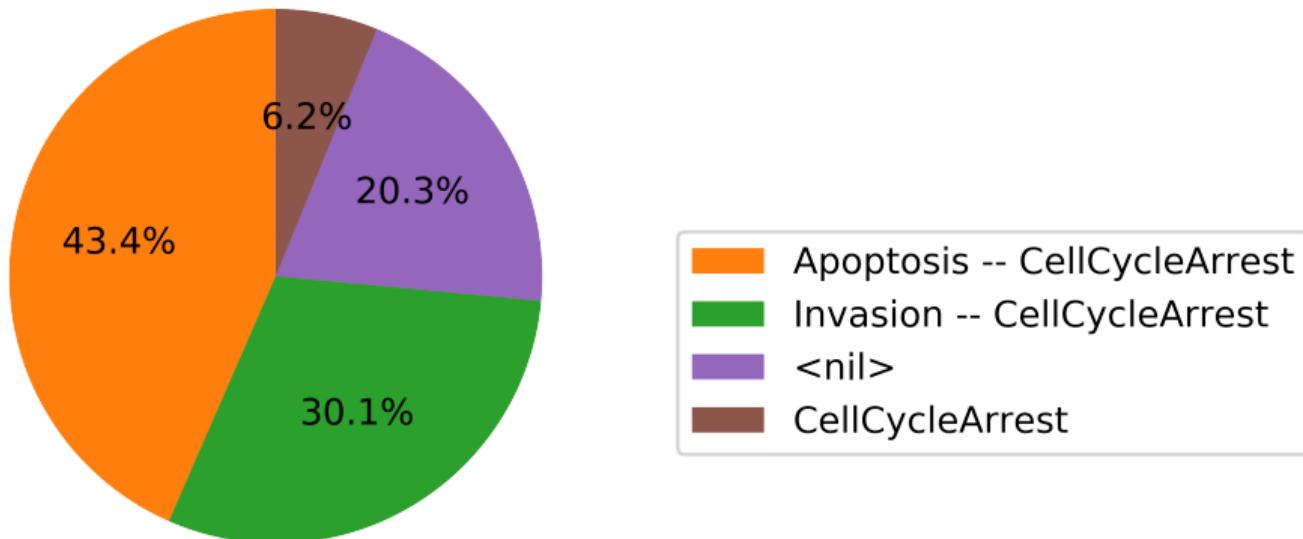
- › EMT
- › CellCycleArrest
- › Apoptosis
- › Invasion
- › Migration
- › Metastasis



Cohen et al. (2015) PLoS Computational Biology

Example on Cohen's model of tumor invasion

- › Final state distribution

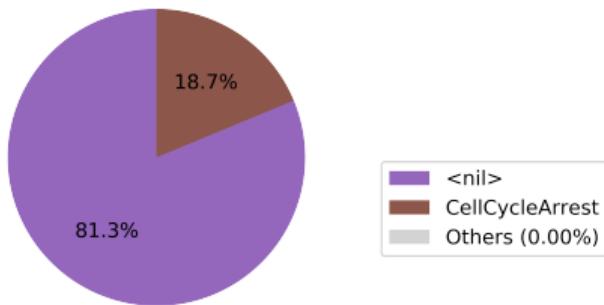


Example on Cohen's model of tumor invasion

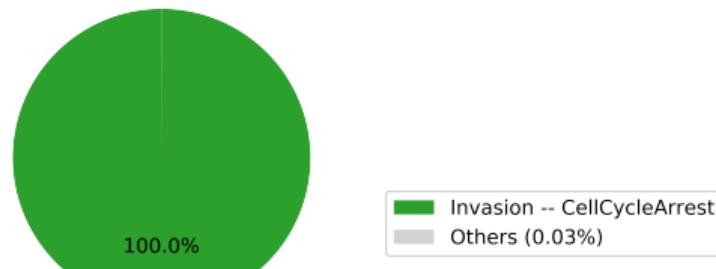
› Influence of Microenvironment

Here we simulate with different initial states : with or without the microenvironment (and without DNA damages)

No Microenvironment



Microenvironment



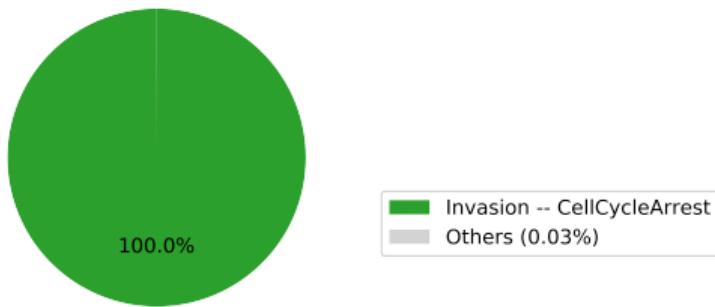
⇒ When we activate the microenvironment, we obtain an invasive phenotype

Example on Cohen's model of tumor invasion

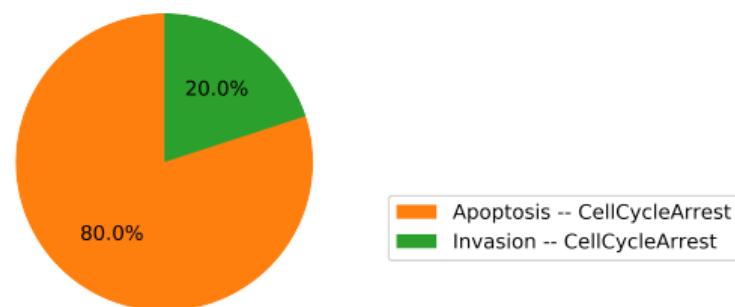
- Influence of DNA damage

Here again we modify the initial values : with and without DNA damages (with microenvironment)

Microenvironment



Microenvironment + DNA damage

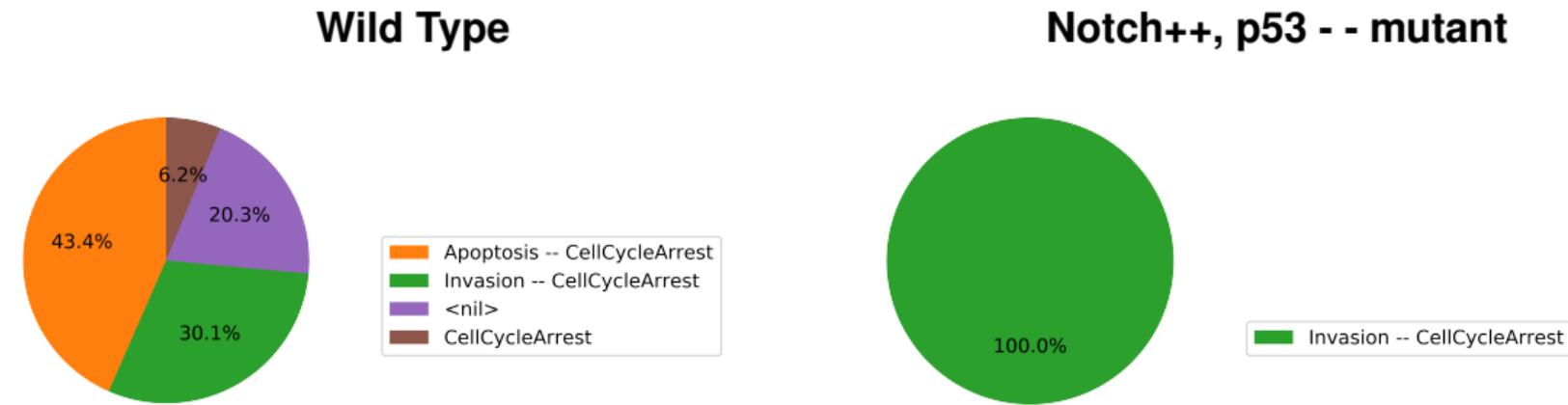


⇒ When we activate DNA damages, we are able to trigger apoptosis in 80% of the cells

Example on Cohen's model of tumor invasion

- › Notch++, p53- - mutant

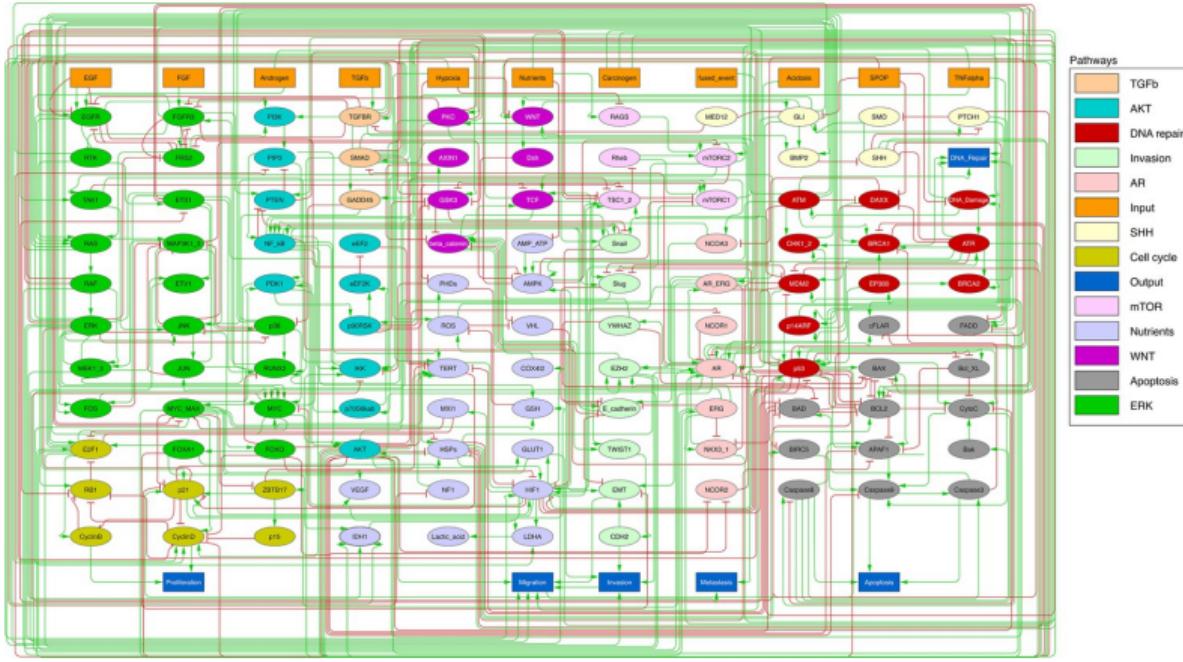
Here we modify the model to force the activity of Notch, and block the activity of p53



⇒ The results shows that whatever the inputs, we obtain a invasive phenotype

Example on Montagud's model of prostate

Example on Montagud's model of prostate

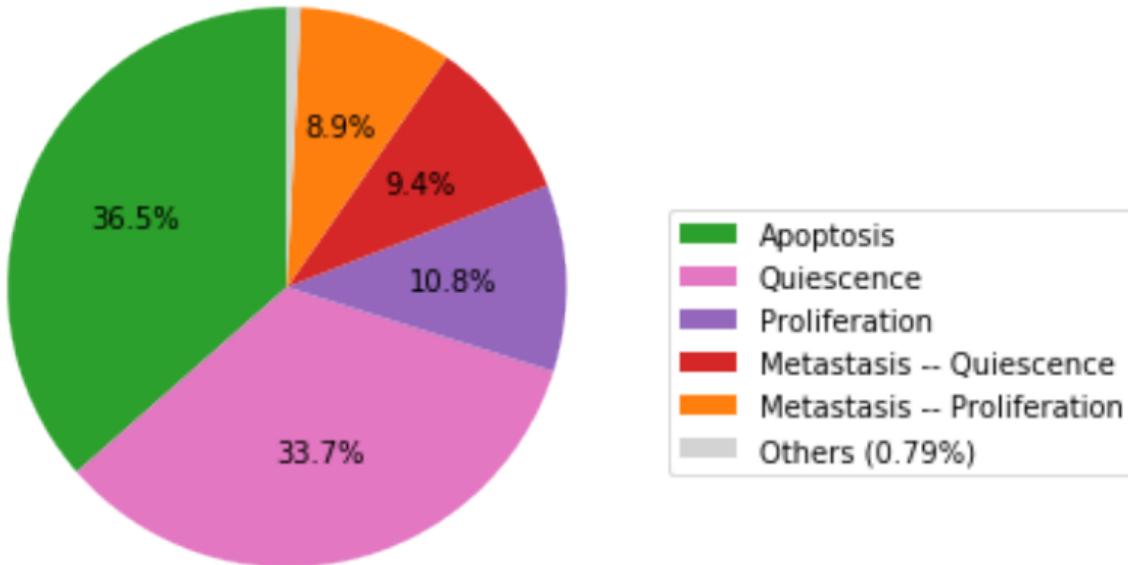


Montagud et al. (2022) eLife

The model can be considered as a model of healthy prostate cells when no mutants (or fused genes) are present. We refer to this model as the wild type model.

Example on Montagud's model of prostate

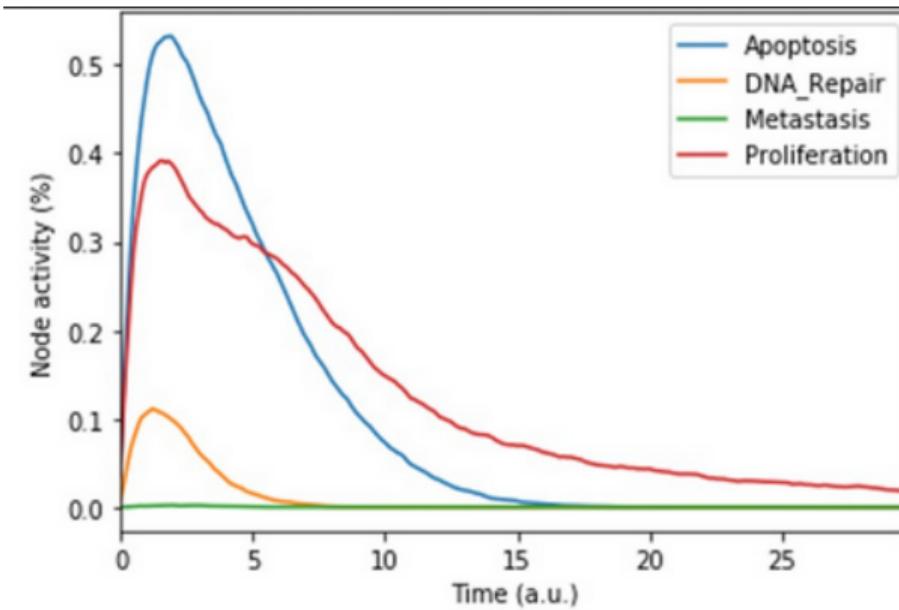
- › Any possible input value



This piechart show all possible behaviours of the model, and is based on simulation where all input combinations are tested.

Example on Montagud's model of prostate

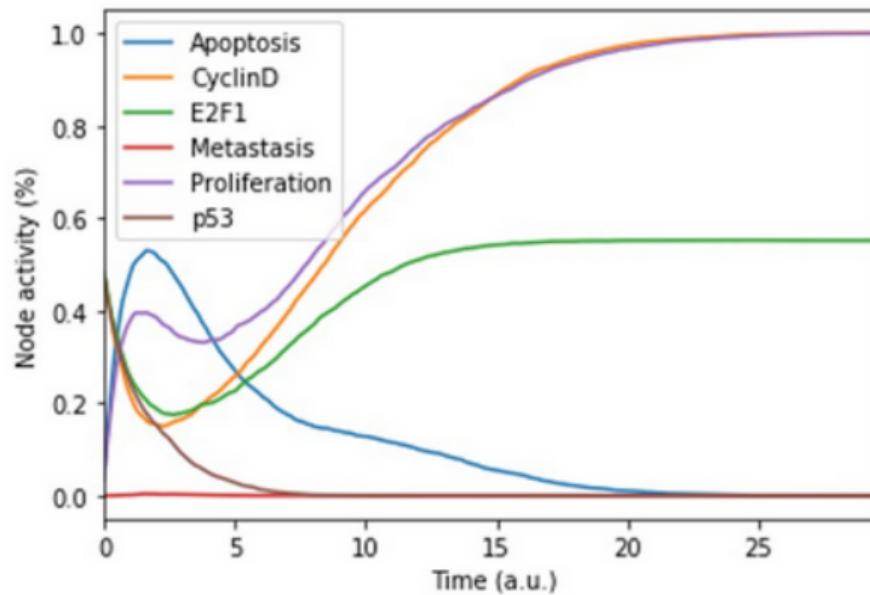
› Wild Type Phenotype



These healthy cells mostly exhibit quiescence (neither proliferation nor apoptosis) in the absence of any input.

Example on Montagud's model of prostate

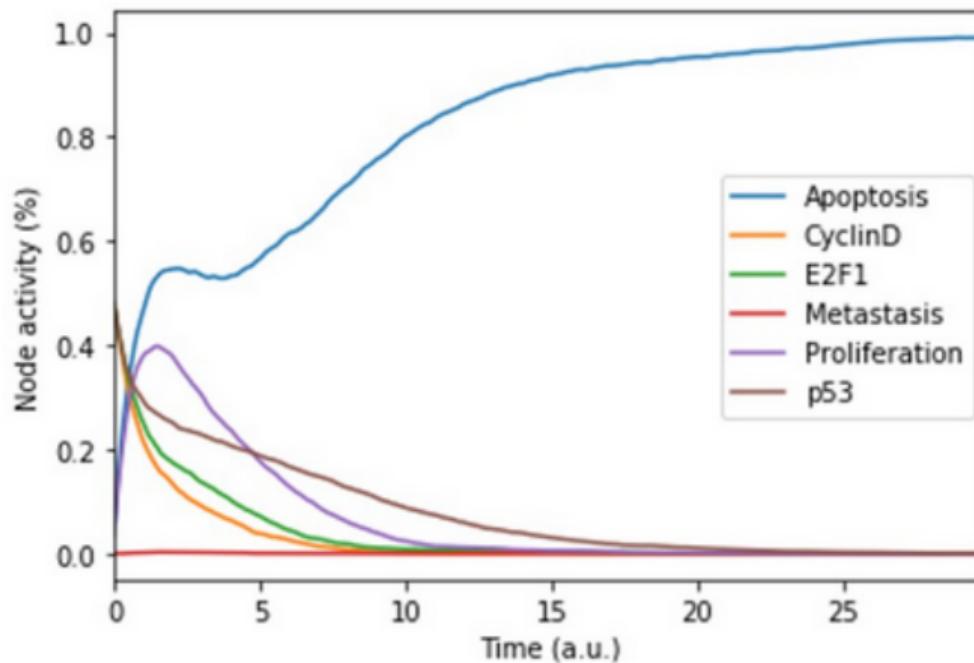
› Proliferative Phenotype



When Nutrients and growth factors (EGF or FGF) are present, Proliferation is activated.

Example on Montagud's model of prostate

› Apoptotic Phenotype



Cell death factors (such as Caspase 8 or 9) trigger Apoptosis in the absence of SPOP, while Hypoxia and Carcinogen facilitate apoptosis but are not necessary if cell death factors are present.

Using MaBoSS : WebMaBoSS

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WebMaBoSS

A web tool for simulating Boolean models

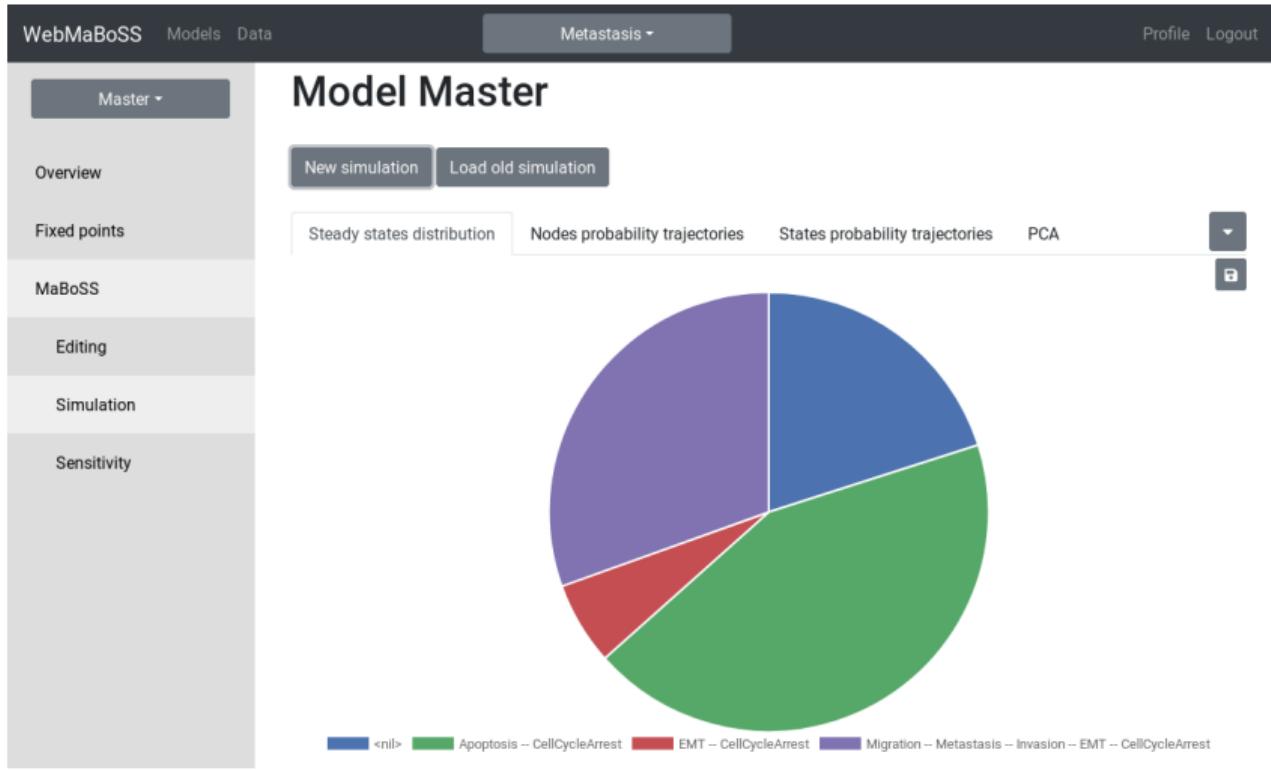
Click [here](#) to login if you already have an account, otherwise you can quickly create one [here](#). If you want to quickly test WebMaBoSS, you can have a look at our [demo project](#).

Model analysis	Compatibility	Public databases
WebMaBoSS allows simulations, and multiple outputs for results. It also allows sensitivity analysis by performing single and double mutations.	WebMaBoSS is able to import models in MaBoSS format (bnd, cfg files), BoolNet format, SBML-qual format, or in GINsim format. It also allows to export models in any of these three formats.	WebMaBoSS allows to browse models from CellCollective and BioModels, and import them.

WebMaBoSS was created and is maintained by the team [Computational System Biology of Cancer](#) at [Institut Curie](#). It is open-source and available on [GitHub](#), where you can also find instructions to run it locally and tutorials.

<https://maboss.curie.fr/webmaboss/>

Using MaBoSS : WebMaBoSS



Using MaBoSS : WebMaBoSS

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Import model

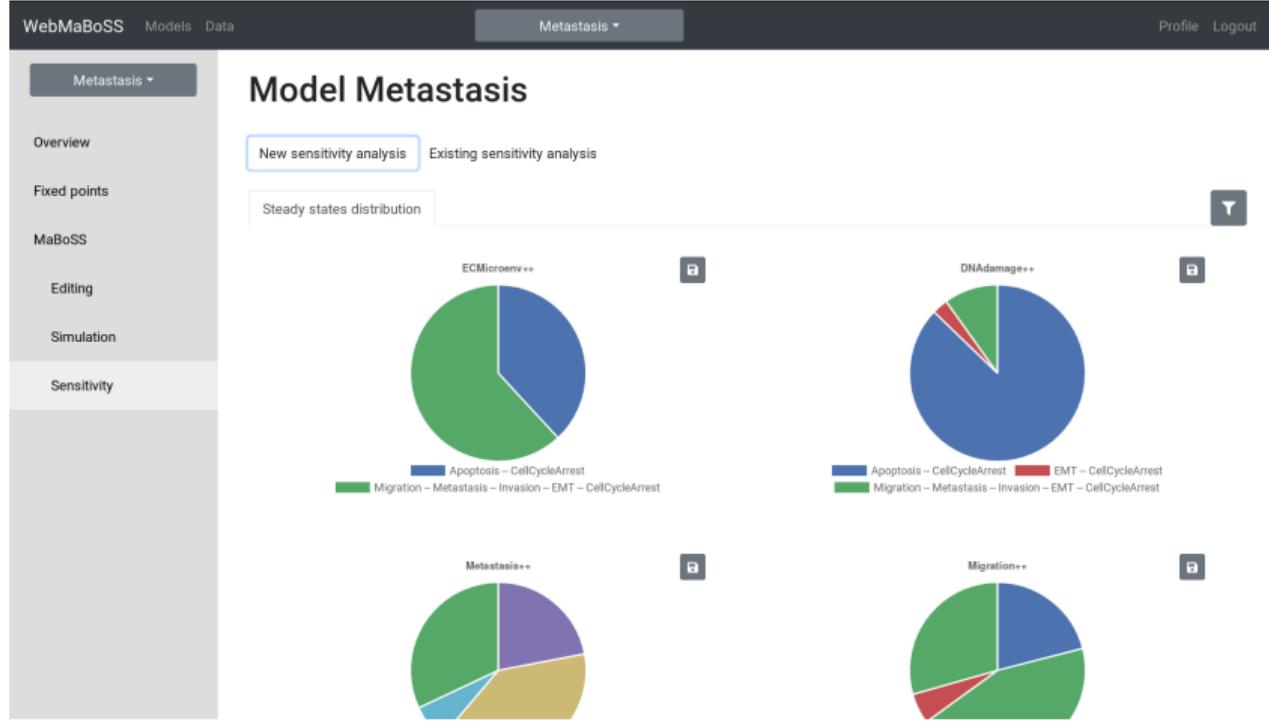
BioModels CellCollective

Name	Author
Traynard2016 - Mammalian cell cycle regulation - Logical Model	Pauline Traynard
Cacace2020 - Logical model of the regulatory network controlling...	Denis Thieffry
Howell2020- Compartmental Logical model of mitotic exit	Rowan Howell
Terfve2012 - Signalling in liver cancer - logical model	Vijayalakshmi Chelliah
Floc'hlay2020 - SeaUrchin_model_ginsim	Krishna Kumar Tiwari
Mbodj2016 - Mesoderm specification during Drosophila develop...	Denis Thieffry
Rodriguez-Jorge2019 - Boolean model of TCR signaling for CD4...	Denis Thieffry
Rodriguez-Jorge2019 - Boolean model of combined TCR and TL...	Denis Thieffry
Afenya2018 - peripheral blood dynamics in the disease state	Szeyi Ng

Use SBML names

Close

Using MaBoSS : WebMaBoSS



Using MaBoSS : pyMaBoSS

- › Initially developped by Nicolas Levy
- › Maintained by Aurelien Naldi, Loic Pauleve, me
<https://github.com/colomoto/pyMaBoSS>
- › Available on Pypi:
\$ pip install maboss
- › Available on Conda:
\$ conda install -c colomoto pymaboss



Nicolas Levy



Aurelien Naldi



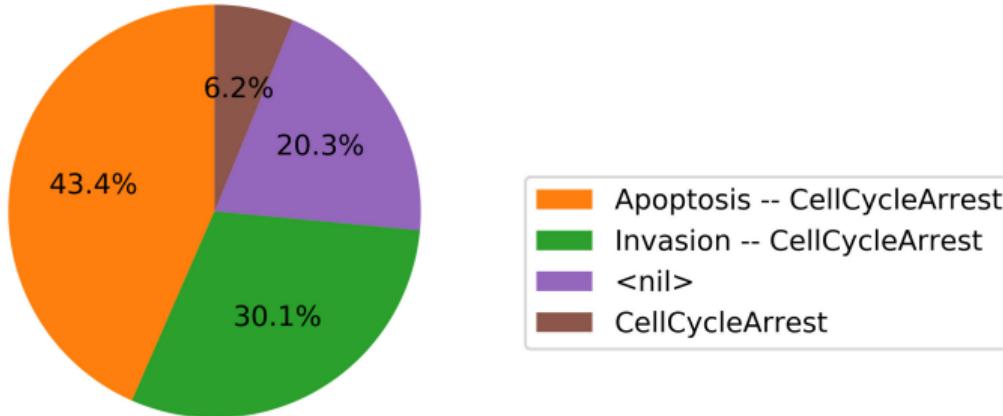
Loïc Paulev 



Vincent No l

Using MaBoSS : pyMaBoSS

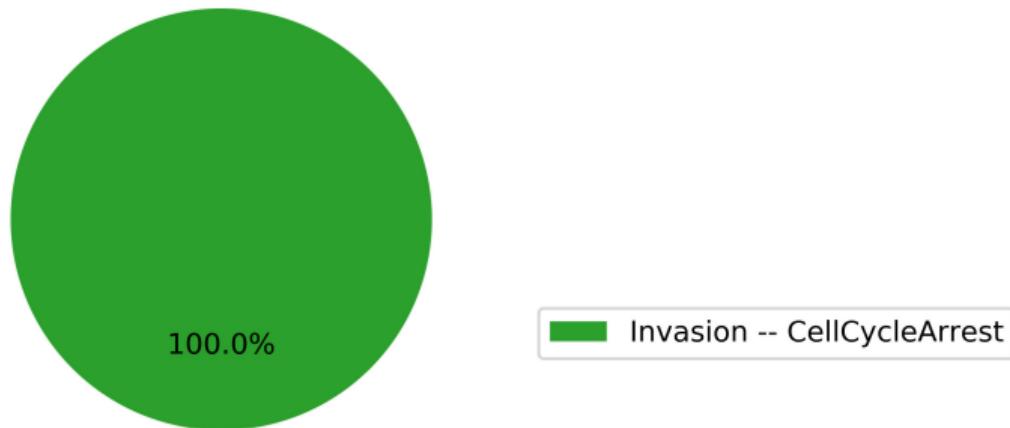
```
import maboss  
model = maboss.load("metastasis.bnd", "metastasis.cfg")  
res = model.run()  
res.plot_piechart()
```



- › A few lines of code to simulate the model and plot the steady states distribution

Using MaBoSS : pyMaBoSS

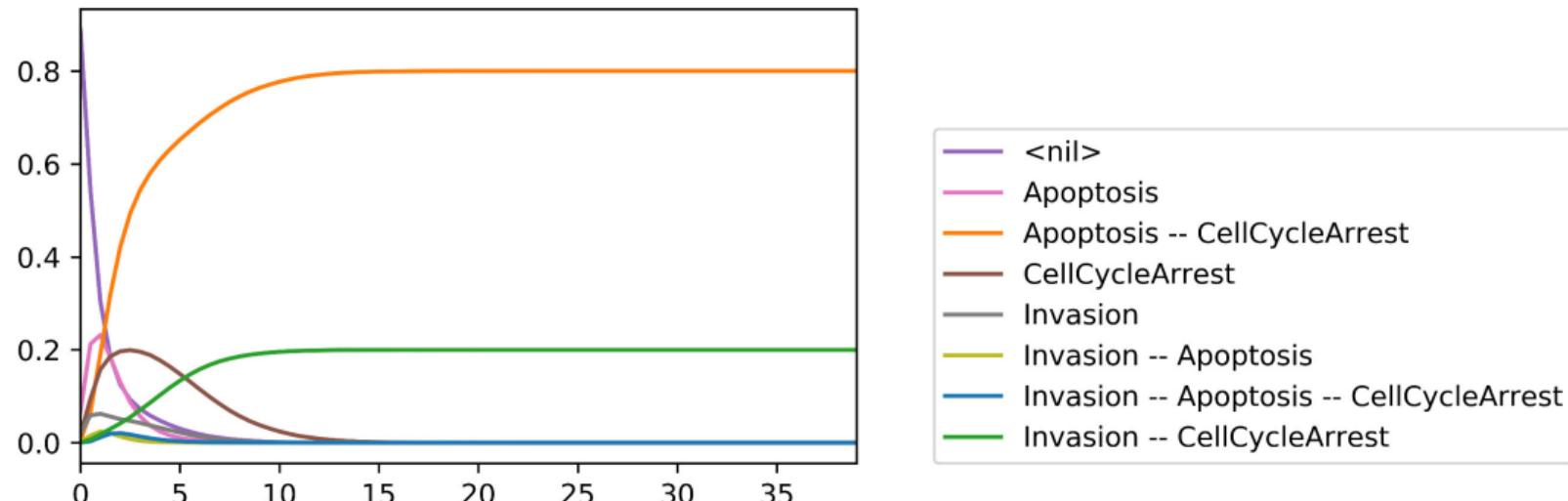
```
model_mutant = model.copy()
model_mutant.mutate('NICD','ON')
model_mutant.mutate('p53','OFF')
res_mutant = model_mutant.run()
res_mutant.plot_piechart()
```



- › Performing mutant simulations

Using MaBoSS : pyMaBoSS

```
res.plot_trajectory()
```



- › Visualizing state probability trajectories

Using MaBoSS : pyMaBoSS

```
res.get_nodes_probtraj()
```

	Apoptosis	CellCycleArrest	EMT	Invasion	Metastasis	Migration
0.0	0.009598	0.000902	0.000000	0.005312	0.000000	0.000000
0.2	0.050760	0.011256	0.000233	0.028856	0.000000	0.000000
0.4	0.106823	0.037696	0.001628	0.063692	0.000000	0.000000
0.6	0.165967	0.085195	0.004456	0.099778	0.000000	0.000000
0.8	0.221066	0.138753	0.010313	0.125779	0.000000	0.000000
1.0	0.265365	0.195669	0.018824	0.145638	0.000000	0.000098
1.2	0.300923	0.255950	0.030564	0.158304	0.000000	0.000100
1.4	0.330531	0.313228	0.045127	0.169356	0.000006	0.000188

- › Getting the results as Panda dataframes

Using MaBoSS : pyMaBoSS



PROTOCOLS
published: 06 July 2018
doi: 10.3389/fphys.2018.00787



Prediction of Mutations to Control Pathways Enabling Tumor Cell Invasion with the CoLoMoTo Interactive Notebook (Tutorial)

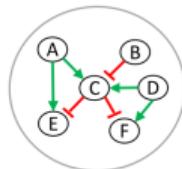
Nicolas Levy^{1,2}, Aurélien Naldi³, Céline Hernandez³, Gautier Stoll^{4,5,6,7,8}, Denis Thieffry³, Andrei Zinovyev^{9,10,11,12}, Laurence Calzone^{9,10,11} and Loïc Paulevé^{1*}

- › Python Notebook with Logical Modelling tools
- › Reproducible research

MaBoSS Ecosystem

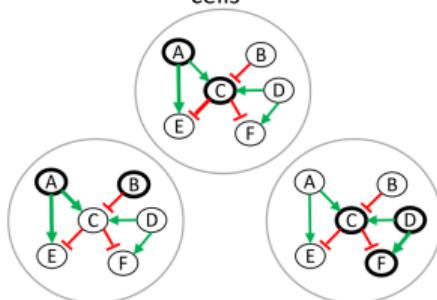
MaBoSS Ecosystem

MaBoSS
Model of an individual cell



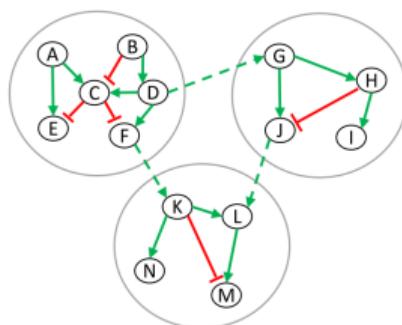
EnsembleMaBoSS

Ensembles of models of non interacting cells



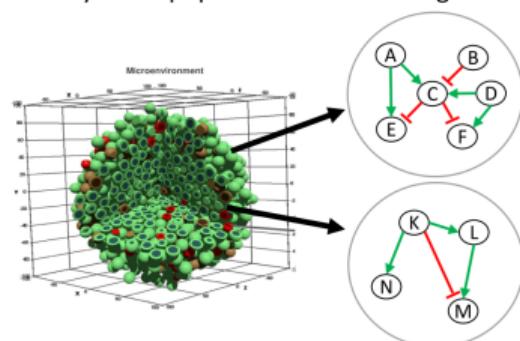
UPMaBoSS

Model of dynamic populations of interacting cells



PhysiBoSS

Model of spatial organization of dynamic population of interacting cells



MaBoSS Ecosystem

- › EnsembleMaBoSS

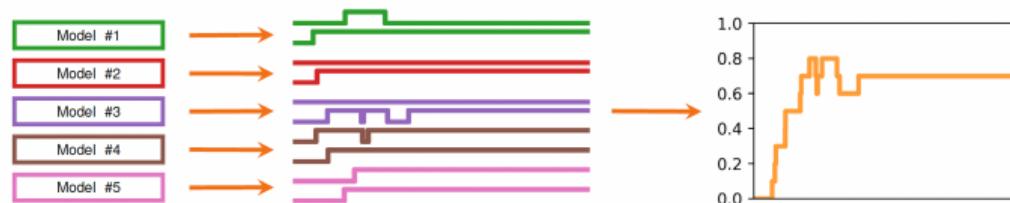
Problem: Sometimes we can't decide which boolean formula is the right one

The principle: Define constraints and use Answer-Set-Programming to produce models that satisfy them

BoNesis (Chevalier et al.)

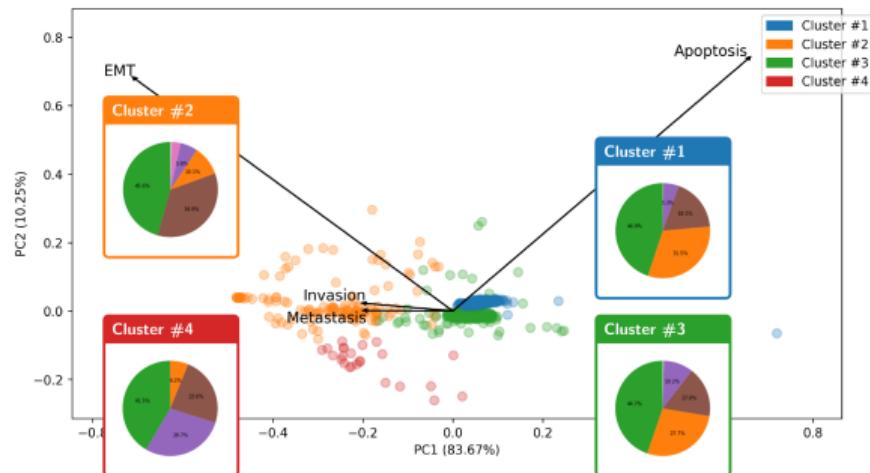
- › Start from an interaction graph (network without rules)
- › Logical rules are based in incoming interactions
- › Models must satisfy some biological properties (stable states)
- › Stable states must be reachable from set of initial conditions

EnsembleMaBoSS Models created by BoNesis can be run with MaBoSS

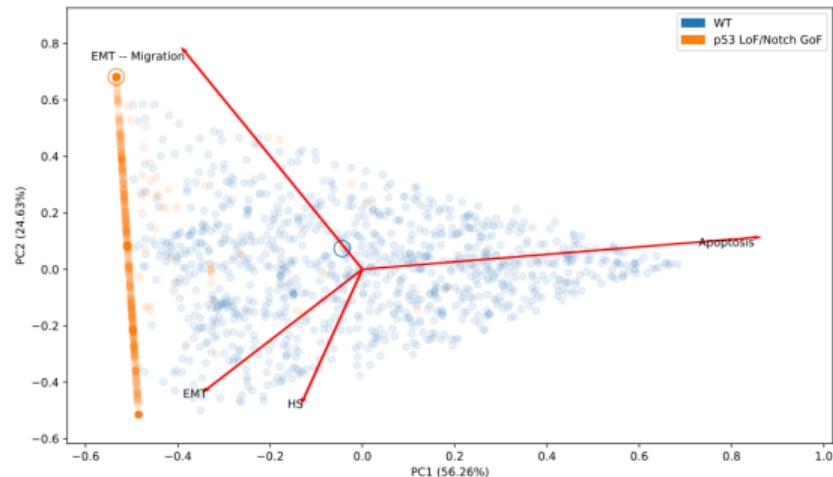


MaBoSS Ecosystem

› EnsembleMaBoSS



⇒ Select a subset of models based on their steady state distribution

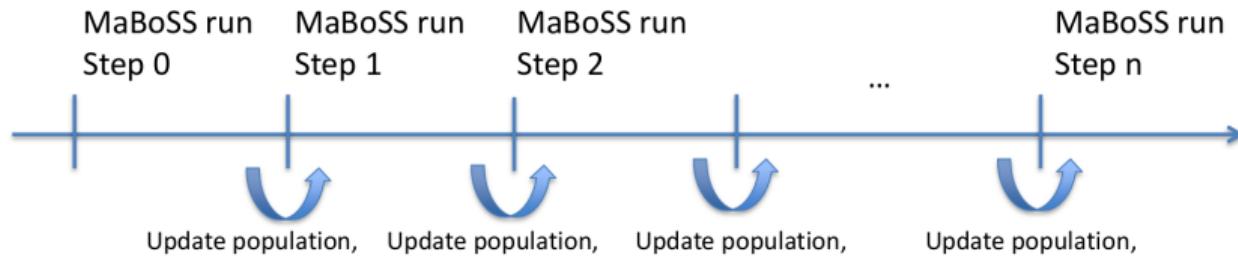


⇒ Analyse the composition of the ensemble before/after a treatment

MaBoSS Ecosystem

› UPMaBoSS : Population models

- › We start from an existing MaBoSS model
- › We add model nodes for division and death
- › We add inter-cellular communication
- › Chaining MaBoSS simulations, updating population and communication between each



MaBoSS Ecosystem

› UPMaBoSS : Population models

Cell division



$p(\text{divide}) \times 2$



$$\text{population} = \text{population} * (1 + p(\text{divide}))$$

Rescale (sum=1)

Cell death



$p(\text{dead}) = 0$



$$\text{population} = \text{population} * (1 - p(\text{dead}))$$

Intercellular communication

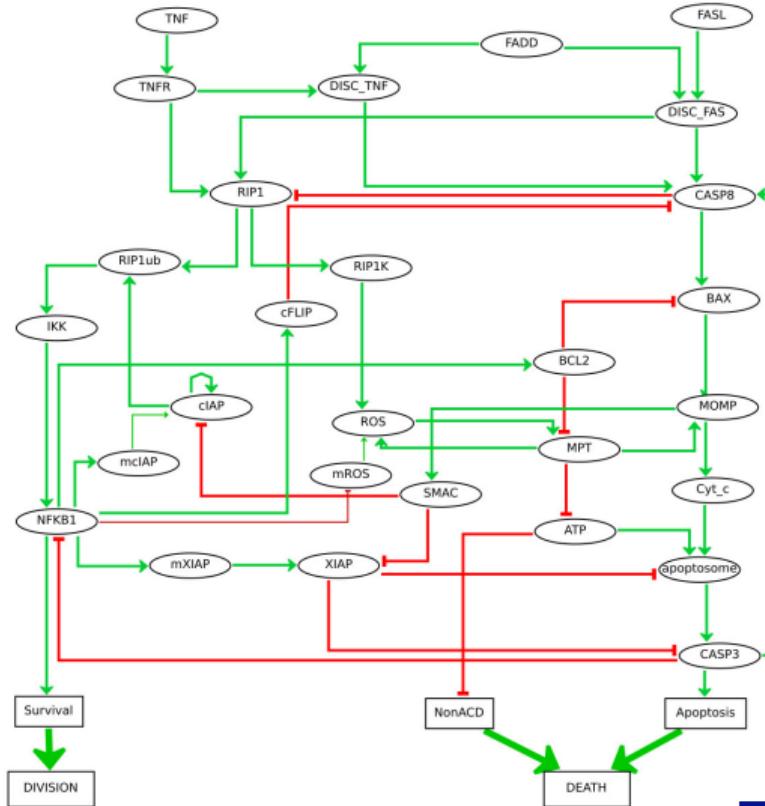
Update the environmental condition of other cells

MaBoSS Ecosystem

- › UPMaBoSS : Population models

We map the cell fates to population updates :

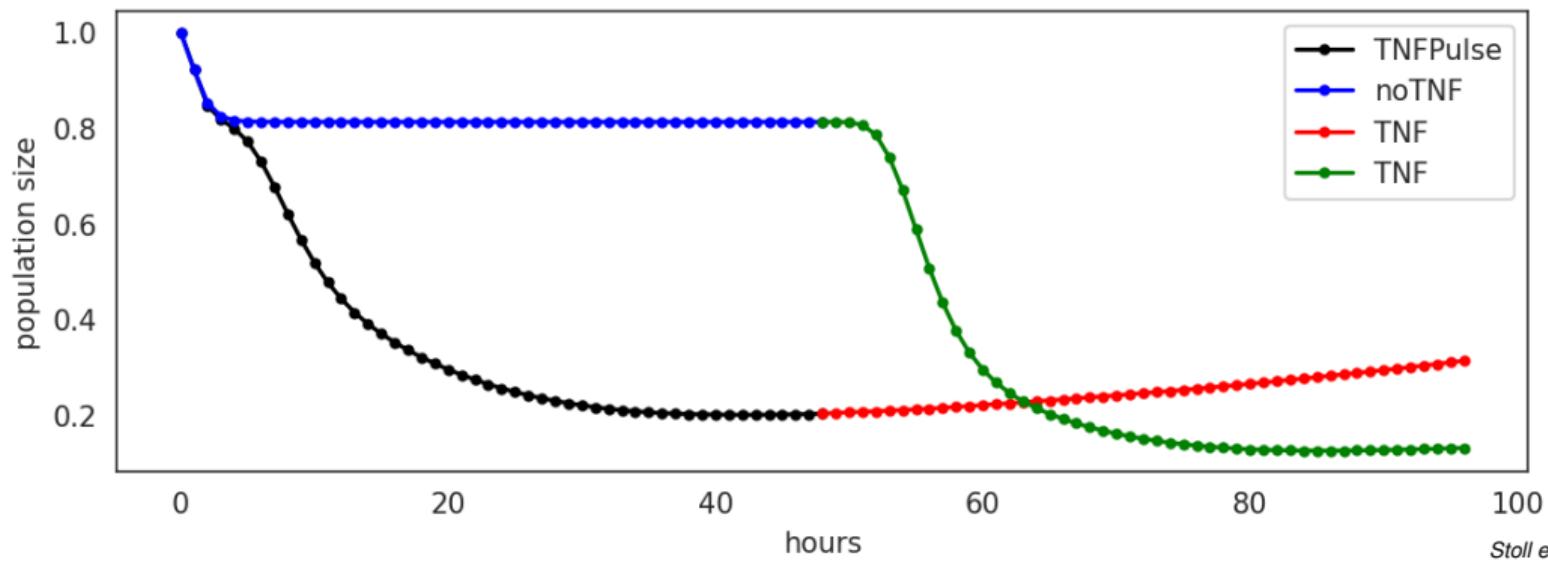
- › Survival node : Cell division
- › Apoptosis and NonACD : Cell death



Adapted from Stoll et al

MaBoSS Ecosystem

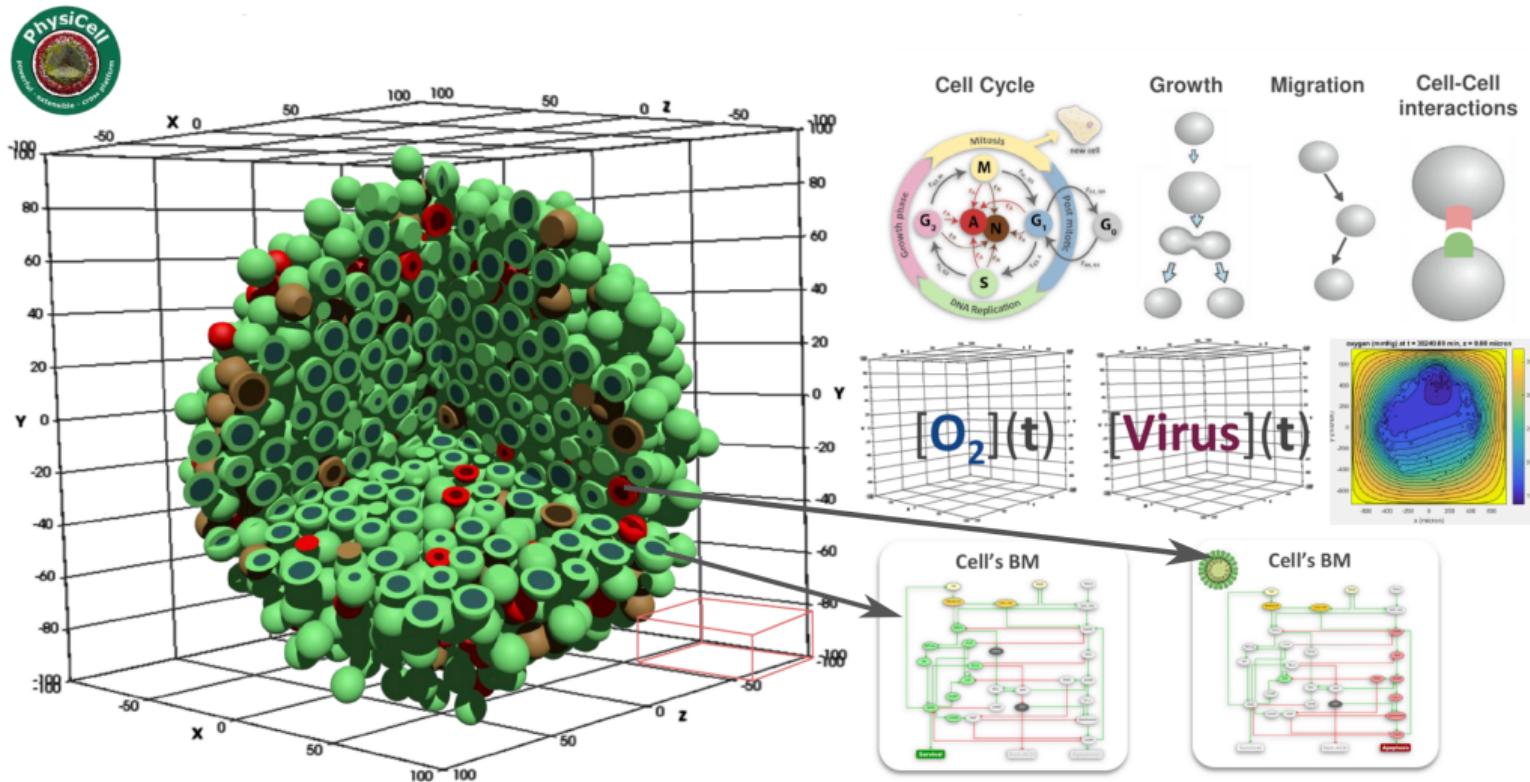
- › UPMaBoSS : Population models



- › Study the resistance to TNF treatment

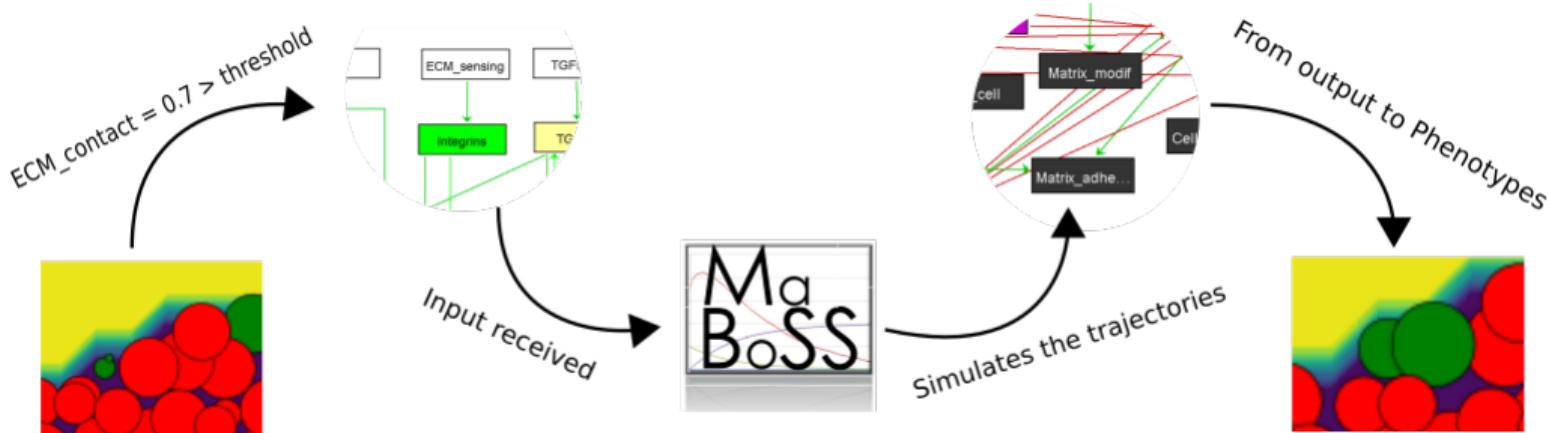
MaBoSS Ecosystem

› PhysiBoSS : Agent-based models



MaBoSS Ecosystem

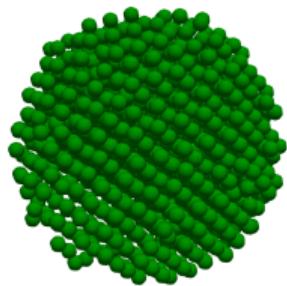
- › PhysiBoSS : Agent-based models



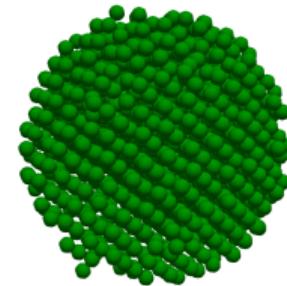
- › We take signals as inputs, and modify behaviors according to outputs
- › Each cell runs one single (stochastic) simulation every *intracellular_dt*

MaBoSS Ecosystem

- › PhysiBoSS : Agent-based models



Sustained TNF treatment



Pulses of TNF treatment

Acknowledgments



MaBoSS early team



Gautier Stoll



Eric Viara



Laurence Calzone



Emmanuel Barillot

MaBoSS ecosystem team



Aurelien Naldi



Denis Thieffry



Loïc Paulevé



Nicolas Levy



Stéphanie
Chevalier



Arnaud
Montagud



Vincent Noël



Gaëlle Letort



Mihaly Koltai



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