Introduction to MaBoSS and Continuous time Boolean modelling

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Computational Systems Biology for Complex Human Disease
from static to dynamic representations of disease mechanisms

April 2024

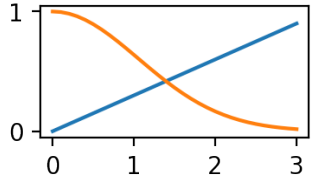
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La science pour la santé
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- MaBoSS : Continuous time boolean modelling
- Example on Cohen’s model of tumor invasion
- Example on Montagud’s model of prostate
- Using MaBoSS : WebMaBoSS
- Using MaBoSS : pyMaBoSS
- MaBoSS Ecosystem

MaBoSS : Continuous time boolean modelling

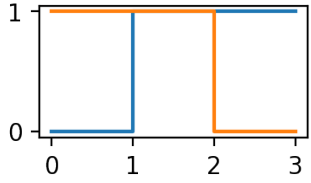
MaBoSS : Continuous time boolean modelling

Quantitative



- Values can be any quantity
- Continuous time
- Difficult to write
- Difficult to simulate large models

Qualitative



- 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 **Bo**olean **S**tochastic **S**imulator



https://maboss.curie.fr/

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

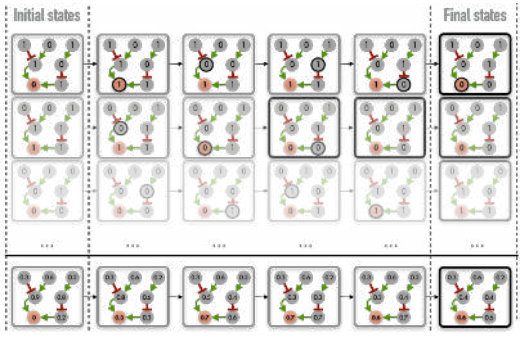
⇒ Fills the gap between ODE and Boolean modeling

MaBoSS : Continuous time boolean modelling

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

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

- These transitions are stochastic : multiple trajectories are possible

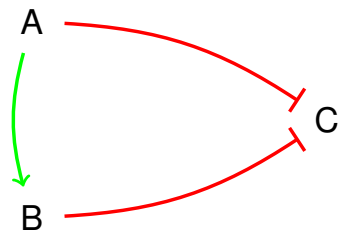


From a set of simulated trajectories, we compute mean trajectories:

$\Rightarrow$ We obtain probabilities per state over time

MaBoSS : Continuous time boolean modelling

› Toy example



Continuous time Boolean modelling

Formulas:

- $A.R_{up} = 1$
- $B.R_{up} = A\ ?\ 1 : 0$
- $C.R_{up} = (!A|!B)\ ?\ 1 : 0$
- $A.R_{down} = 0$
- $B.R_{down} = A\ ?\ 0 : 1$
- $C.R_{down} = (!A|!B)\ ?\ 0 : 1$

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

```
node A {
    rate_up = 1;
    rate_down = 0;
}

node B {
    logic = A;
    rate_up = @logic ? $act_B : 0;
    rate_down = 0;
}

node C {
    logic = !A | !B;
    rate_up = @logic ? $act_C : 0;
    rate_down = @logic ? 0 : $act_C;
}
```

MaBoSS : Continuous time boolean modelling

› Simulation settings : CFG file

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

```
A.istate = TRUE;
B.istate = FALSE;
C.istate = TRUE;

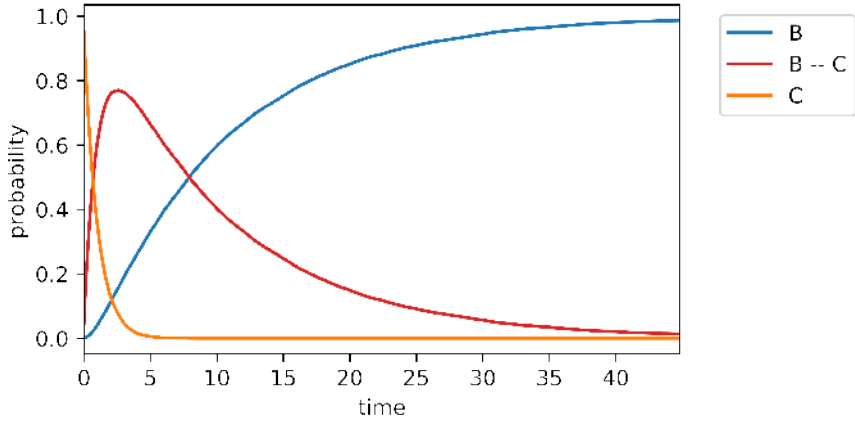
A.is_internal = TRUE;

$act_B = 1;
$act_C = 0.1;

max_time = 45;
sample_count = 10000;
use_physrandgen = 1;
thread_count = 1;
```

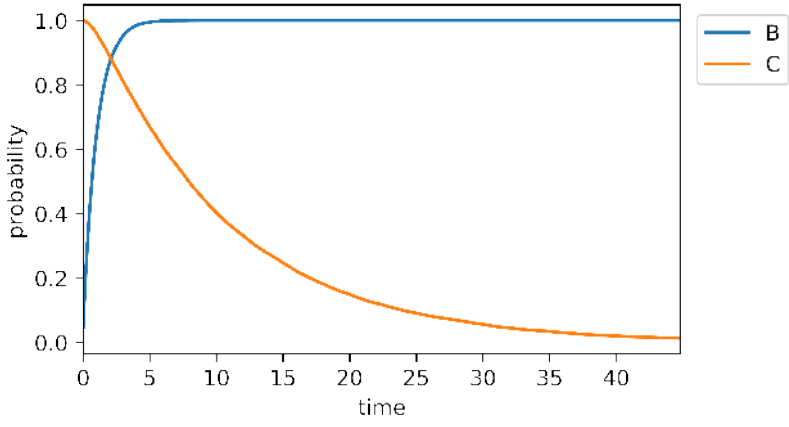
MaBoSS : Continuous time boolean modelling

› State probability trajectories



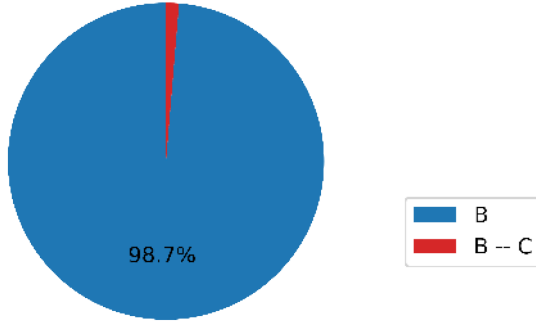
MaBoSS : Continuous time boolean modelling

› Node probability trajectories



MaBoSS : Continuous time boolean modelling

› Final ($\neq$ steady) state distribution



Example on Cohen’s model of tumor invasion

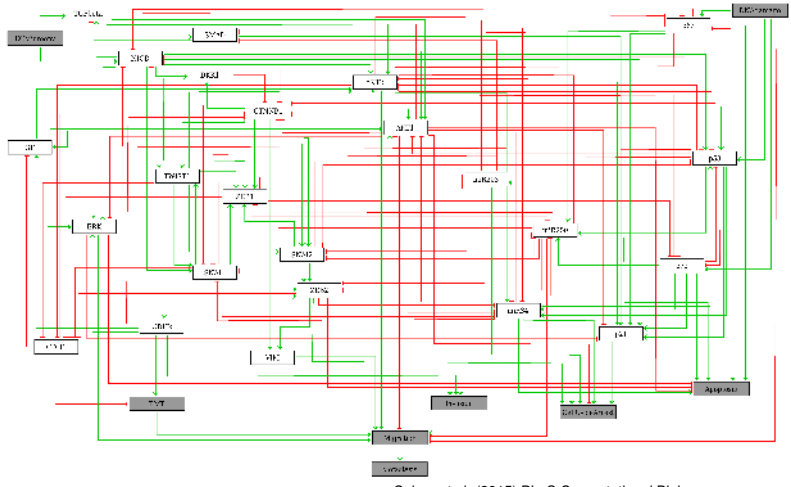
Example on Cohen's model of tumor invasion

Two input nodes:

- ECMicroenv
- DNADamage

Six output nodes:

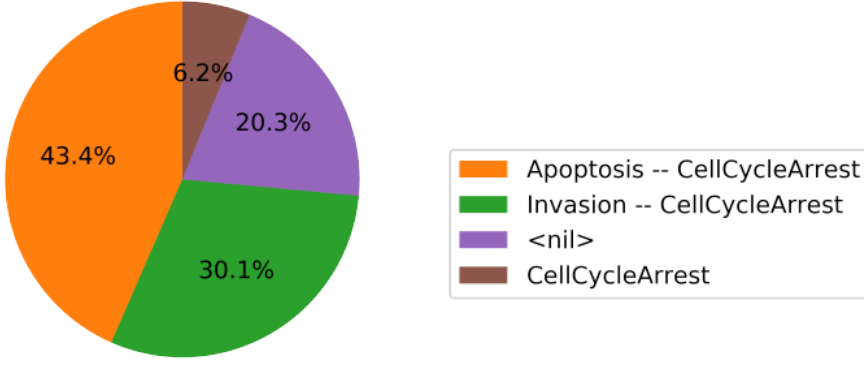
- EMT
- CellCycleArrest
- Apoptosis
- Invasion
- Migration
- Metastasis



Cohen et al. (2015) PLoS Computational Biology

Example on Cohen's model of tumor invasion

› Final state distribution

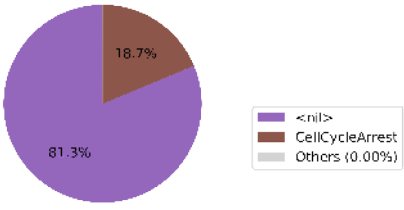


Example on Cohen's model of tumor invasion

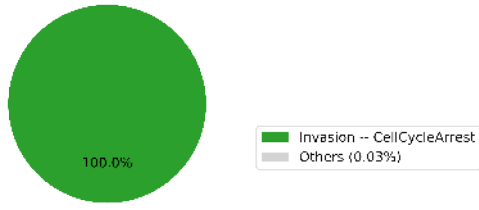
› Influence of Microenvironment

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

No Microenvironment



Microenvironment



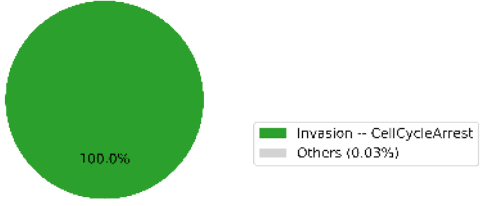
⇒ When we activate the microenvironment, we obtain an invasive phenotype

Example on Cohen's model of tumor invasion

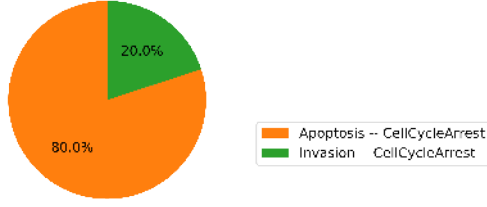
› Influence of DNA damage

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

Microenvironment



Microenvironment + DNA damage



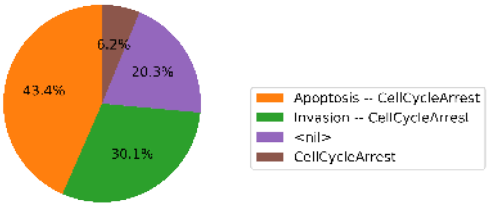
⇒ When we activate DNA damages, we are able to trigger apoptosis in 80% of the cells

Example on Cohen's model of tumor invasion

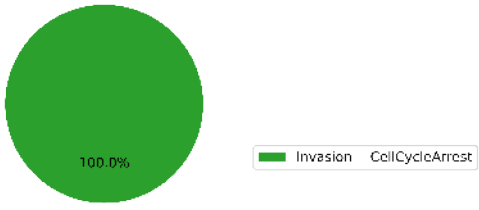
› Notch++, p53- - mutant

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

Wild Type



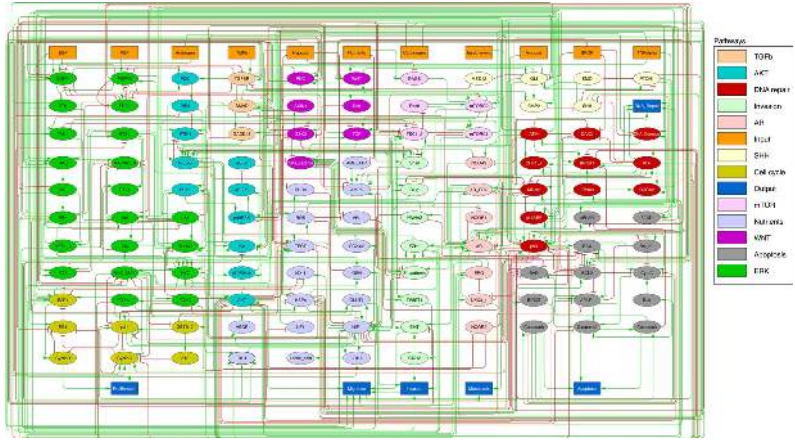
Notch++, p53 - - mutant



⇒ 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

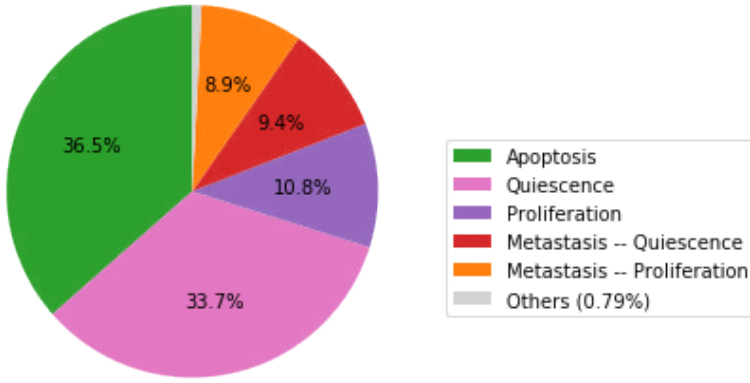


Montagud et al. (2022) eLife

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

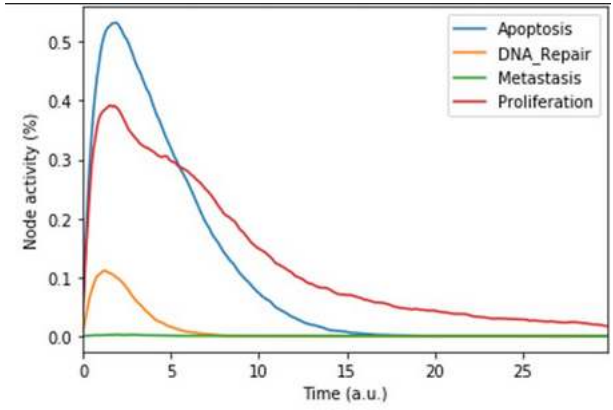
- Any possible input value



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

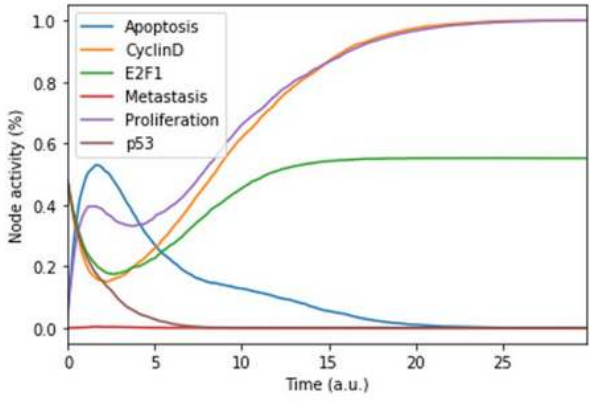
› Wild Type Phenotype



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

Example on Montagud's model of prostate

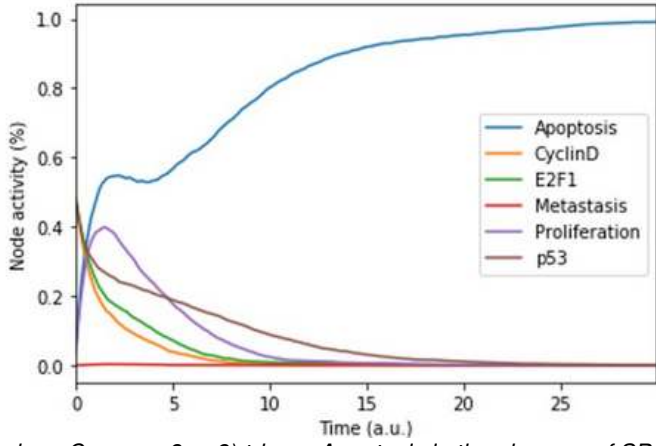
› Proliferative Phenotype



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

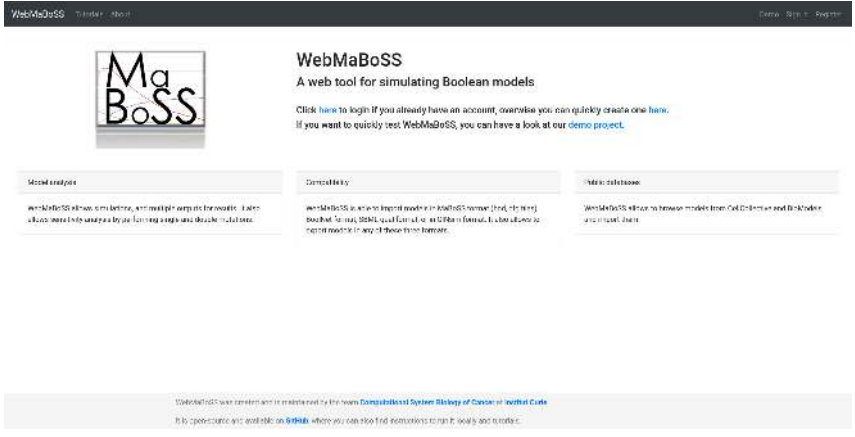
Example on Montagud's model of prostate

› Apoptotic Phenotype



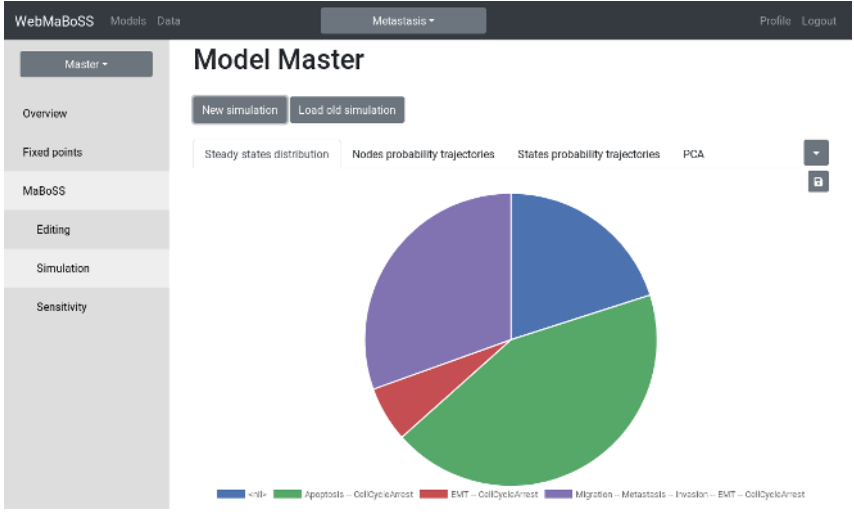
Cell death factors (such as Caspase 8 or 9) trigger Apoptosis in the absence of SPOP, while Hypoxia and Carcinogen facilitate apoptosis but are not necessary if cell death factors are present.

Using MaBoSS : WebMaBoSS

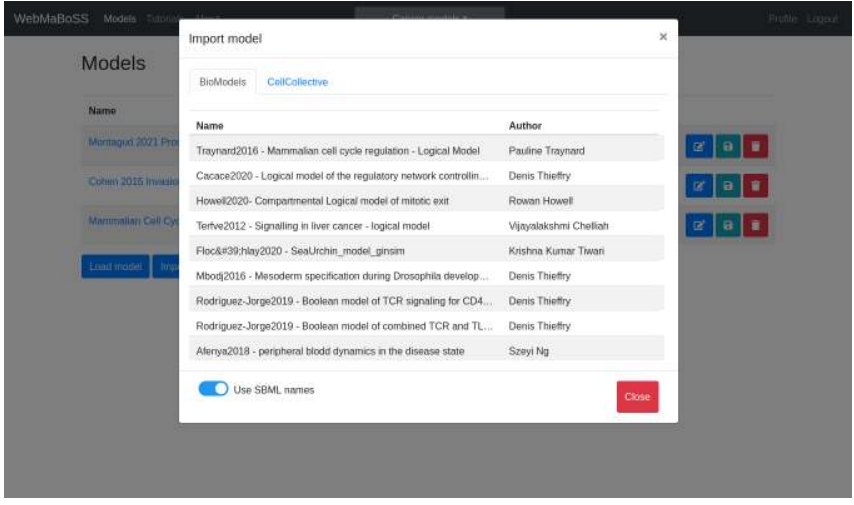


https://maboss.curie.fr/webmaboss/

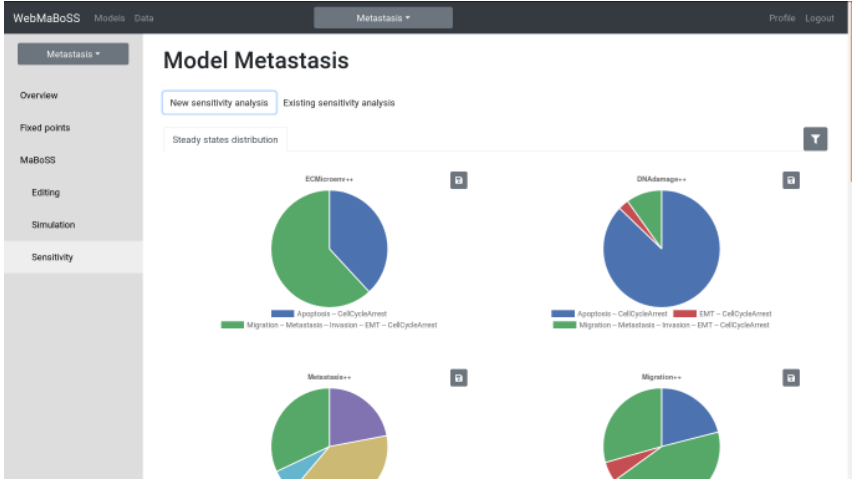
Using MaBoSS : WebMaBoSS



Using MaBoSS : WebMaBoSS



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

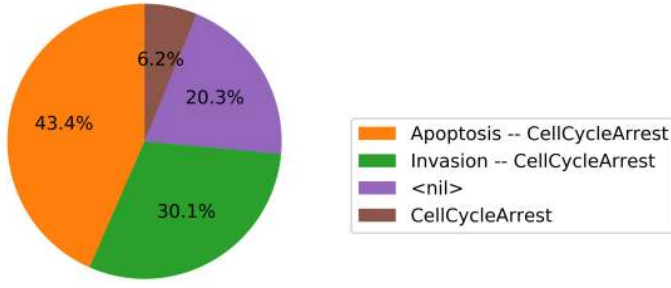

Aurelien Naldi


Loïc Paulevé


Vincent Noël

Using MaBoSS : pyMaBoSS

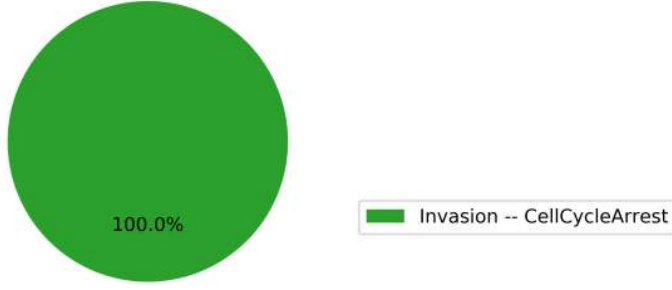
```
import maboss
model = maboss.load("metastasis.bnd", "metastasis.cfg")
res = model.run()
res.plot_piechart()
```



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

Using MaBoSS : pyMaBoSS

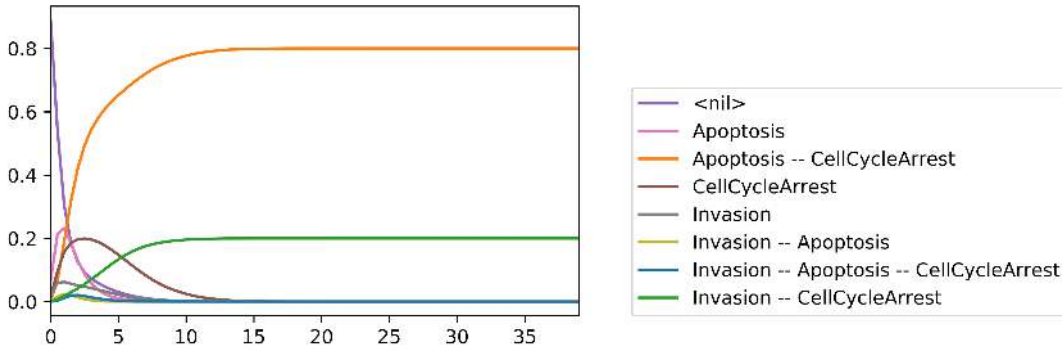
```
model_mutant = model.copy()
model_mutant.mutate('NICD','ON')
model_mutant.mutate('p53','OFF')
res_mutant = model_mutant.run()
res_mutant.plot_piechart()
```



› Performing mutant simulations

Using MaBoSS : pyMaBoSS

```
res.plot_trajectory()
```



› Visualizing state probability trajectories

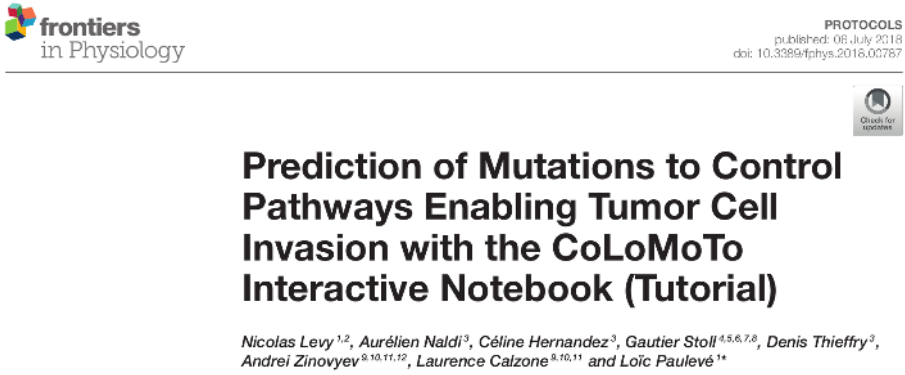
Using MaBoSS : pyMaBoSS

```
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



frontiers in Physiology

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

Check for updates

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

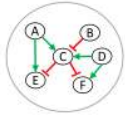
Nicolas Levy[1,2], *Aurélien Naldi*[3], *Céline Hernandez*[3], *Gautier Stoll*[4,5,6,7,8], *Denis Thieffry*[3], *Andrei Zinovyev*[9,10,11,12], *Laurence Calzone*[9,10,11] *and Loïc Paulevé*[1*]

- Python Notebook with Logical Modelling tools
- Reproducible research

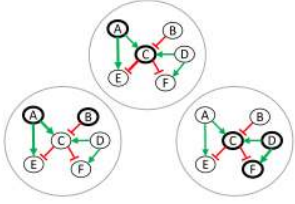
MaBoSS Ecosystem

MaBoSS Ecosystem

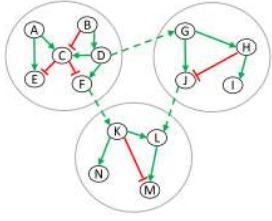
MaBoSS
Model of an individual cell



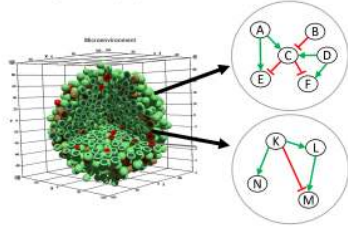
EnsembleMaBoSS
Ensembles of models of non interacting cells



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.)

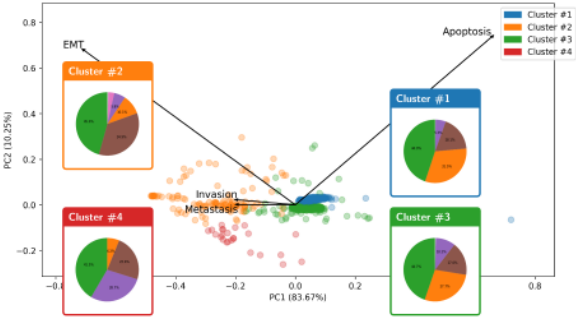
- › Start from an interaction graph (network without rules)
- › Logical rules are based in incoming interactions
- › Models must satisfy some biological properties (stable states)
- › Stable states must be reachable from set of initial conditions

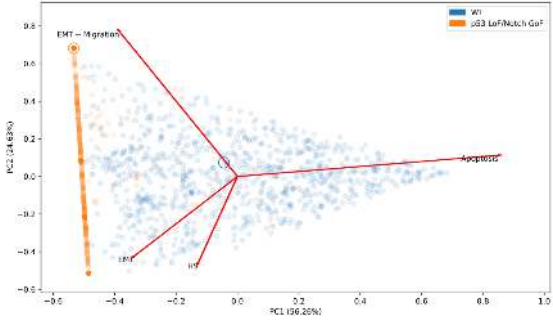
EnsembleMaBoSS Models created by BoNesis can be run with MaBoSS



MaBoSS Ecosystem

› EnsembleMaBoSS





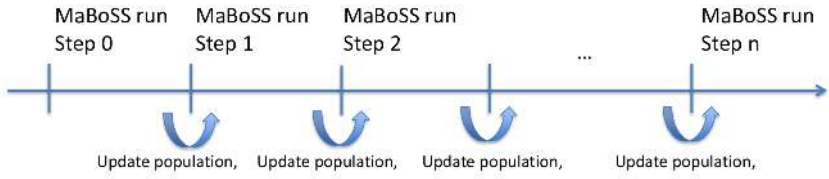
⇒ Select a subset of models based on their steady state distribution

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

MaBoSS Ecosystem

› UPMaBoSS : Population models

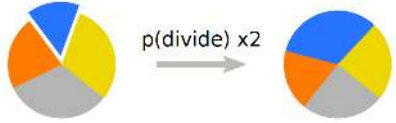
- We start from an existing MaBoSS model
- We add model nodes for division and death
- We add inter-cellular communication
- Chaining MaBoSS simulations, updating population and communication between each



MaBoSS Ecosystem

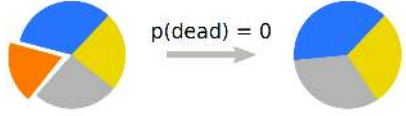
› UPMaBoSS : Population models

Cell division



$$population = population * (1 + p(divide))$$

Cell death



$$population = population * (1 - p(dead))$$

Intercellular communication

Update the environmental condition of other cells

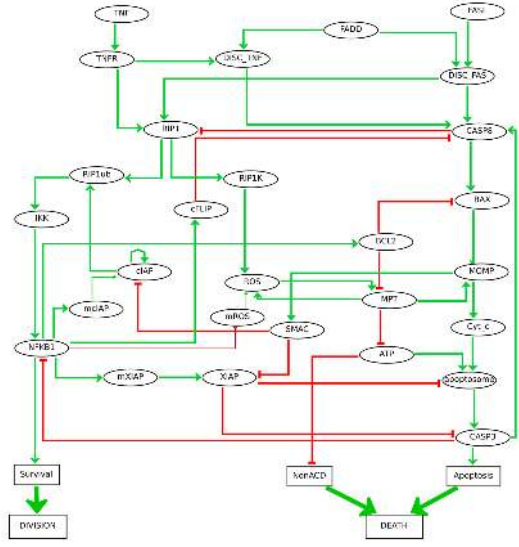
MaBoSS Ecosystem

› UPMaBoSS : Population models

We map the cell fates to population updates :

› Survival node : Cell division

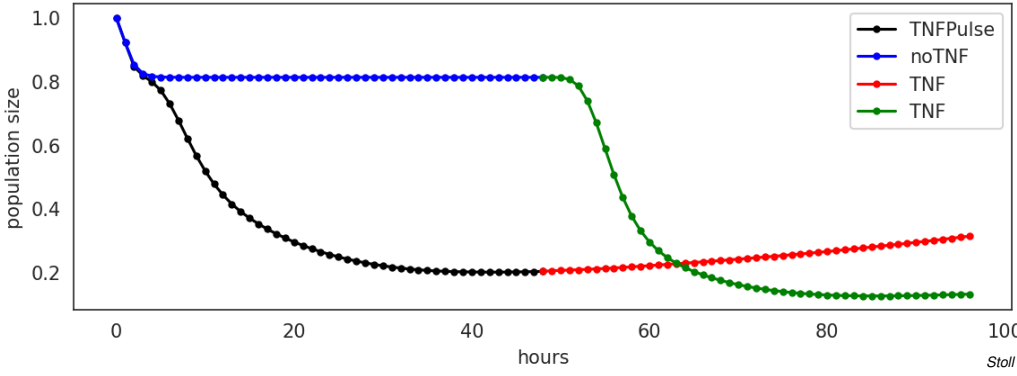
› Apoptosis and NonACD : Cell death



Adapted from Stoll et al., 2022

MaBoSS Ecosystem

› UPMaBoSS : Population models

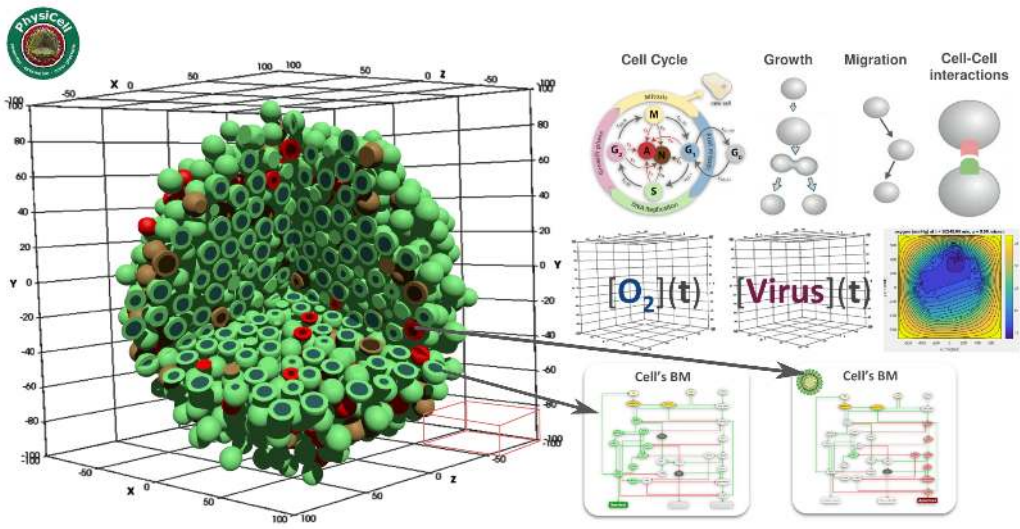


Stoll et al., 2022

› Study the resistance to TNF treatment

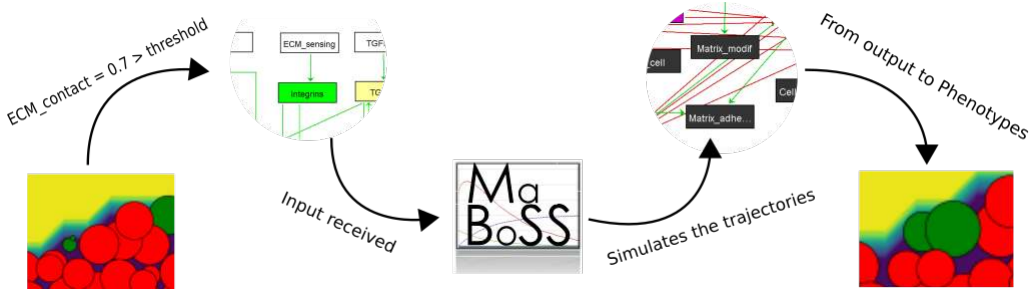
MaBoSS Ecosystem

› PhysiBoSS : Agent-based models



MaBoSS Ecosystem

› PhysiBoSS : Agent-based models

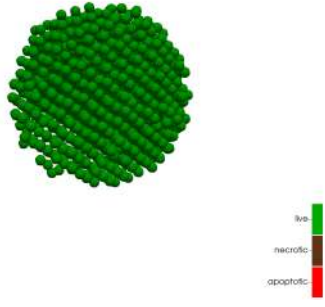


› We take signals as inputs, and modify behaviors according to outputs

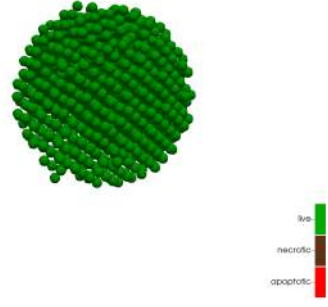
› Each cell runs one single (stochastic) simulation every *intracellular_dt*

MaBoSS Ecosystem

› PhysiBoSS : Agent-based models



Sustained TNF treatment



Pulses of TNF treatment

Aknowledgments

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