

PerMedCoE Virtual Course:

Signalling pathways models and their integration into multiscale models
Introduction to MaBoSS

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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 N°951773

Program

- 9h - 9h10 : Presentation of the course
- 9h10 - 10h : Introduction to MaBoSS
- 10h - 10h15 : Break
- 10h15 - 11h15 : Hands on with WebMaBoSS
- 11h15 - 11h30 : Break
- 11h30 - 12h45 : Hands on with pyMaBoSS
- 12h45 - 13h : Concluding remarks

- Modelling Biological Systems
- MaBoSS : Continuous time boolean modelling
- Example on Cohen’s model of tumor invasion
- Using MaBoSS with WebMaBoSS
- Example on Montagud’s model of prostate
- Using MaBoSS with pyMaBoSS

Modelling Biological Systems

Modelling Biological Systems

Why ?

- Summarize what is known (published) about a process
- Understand which mechanisms are deregulated in diseases and why
- Identify possible intervention points to revert deregulations of normal phenotypes
- Anticipate the effect of drugs
- Optimize efficacy of treatments and minimize the side effects

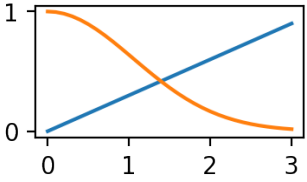
Example of questions

- What are the processes that are activated in high grade tumours in colon ?
- Should we treat all medulloblastoma patients with the same drug ?
- Can we understand the differentiation of immune cells ?
- Can the response of drug treatment for breast cancer patients be predicted ?

Modelling Biological Systems

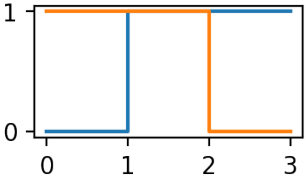
› Modelling Frameworks

Quantitative



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

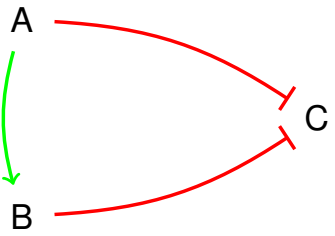
Qualitative



- Values are true/false
- Sequences of events
- Easy to write
- Can simulate large models

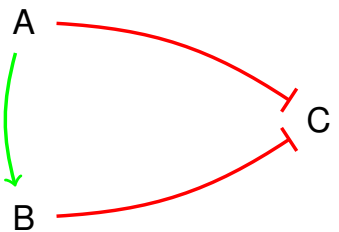
Modelling Biological Systems

› Example



Modelling Biological Systems

› Quantitative formalisms



Ordinary Differential Equations

Rates:

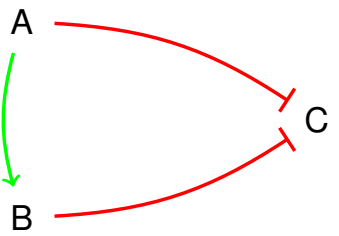
- $\frac{dA}{dt} = 0$
- $\frac{dB}{dt} = k_1.A$
- $\frac{dC}{dt} = -k_2.A.B.C$

Initial values:

- $A_0 = 1.0$
- $B_0 = 0.0$
- $C_0 = 1.0$

Modelling Biological Systems

› Quantitative formalisms



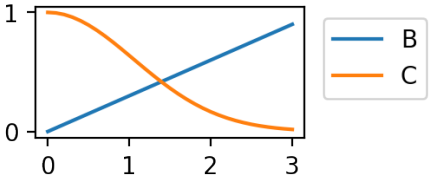
Ordinary Differential Equations

Rates:

- $\frac{dA}{dt} = 0$
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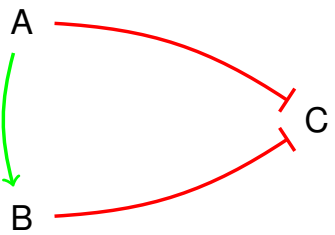
Initial values:

- $A_0 = 1.0$
- $B_0 = 0.0$
- $C_0 = 1.0$



Modelling Biological Systems

› Qualitative formalisms



Boolean

Formulas:

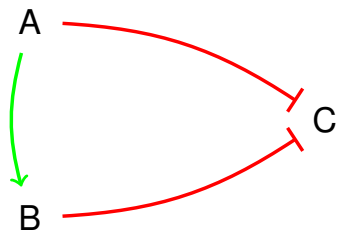
- A = 1
- B = A
- C = !A or !B

Initial values:

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

Modelling Biological Systems

› Qualitative formalisms



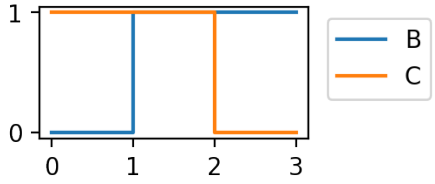
Boolean

Formulas:

- A = 1
- B = A
- C = !A or !B

Initial values:

- $A_0 = 1$
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- $C_0 = 1$



MaBoSS : Continuous time boolean modelling

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
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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.)

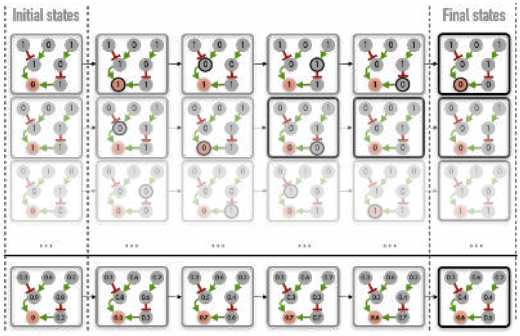
⇒ Fills the gap between ODE and Boolean modeling

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

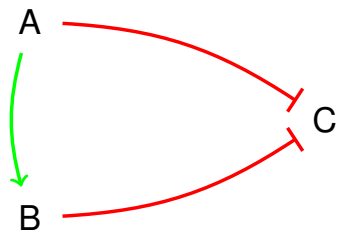


From a set of simulated trajectories, we compute mean trajectories:

⇒ 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;

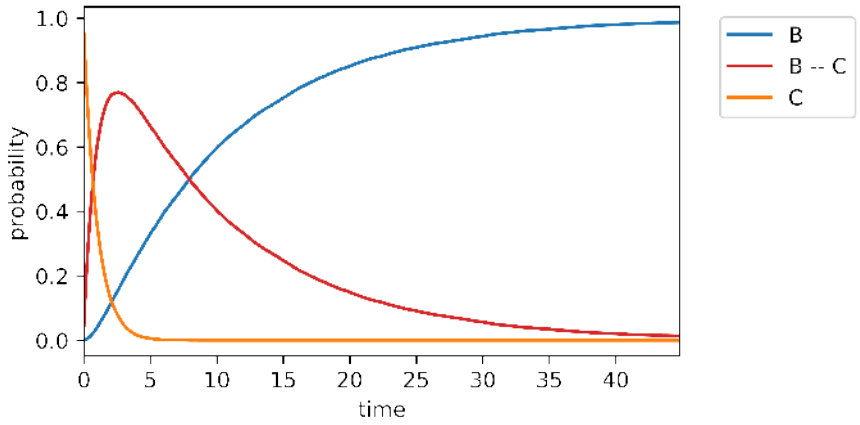
A.is_internal = TRUE;

$act_B = 1;
$act_C = 0.1;

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

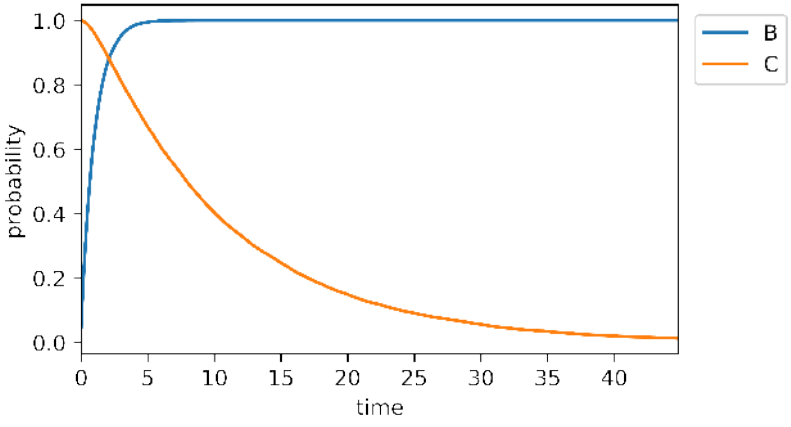
MaBoSS : Continuous time boolean modelling

› State probability trajectories



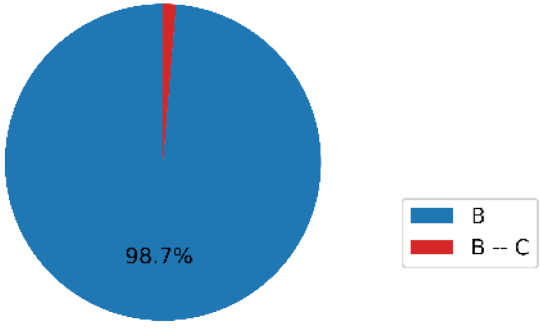
MaBoSS : Continuous time boolean modelling

› Node probability trajectories



MaBoSS : Continuous time boolean modelling

› Final ($\neq$ steady) state distribution



Example on Cohen’s model of tumor invasion

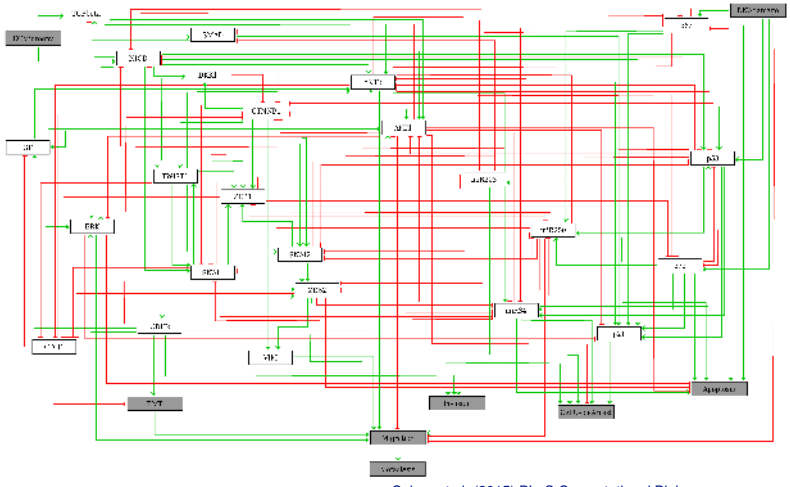
Example on Cohen's model of tumor invasion

Two input nodes:

- ECMicroenv
- DNADamage

Six output nodes:

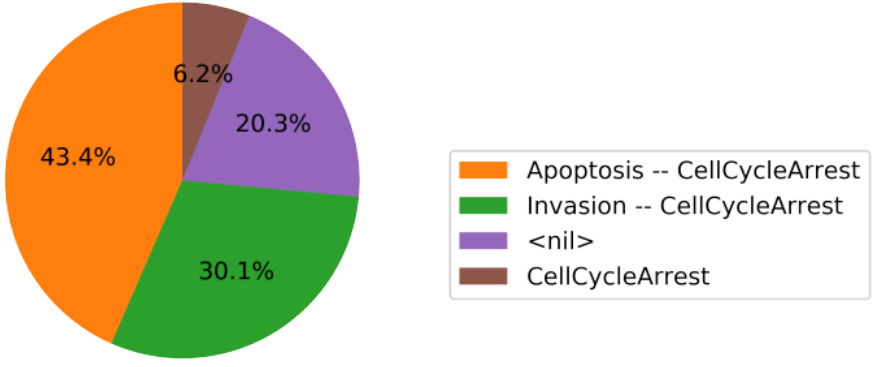
- EMT
- CellCycleArrest
- Apoptosis
- Invasion
- Migration
- Metastasis



Cohen et al. (2015) PLoS Computational Biology

Example on Cohen's model of tumor invasion

› Final state distribution

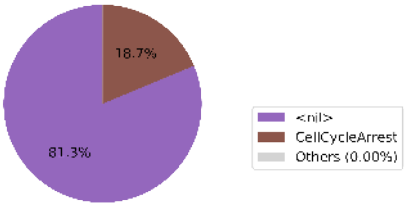


Example on Cohen's model of tumor invasion

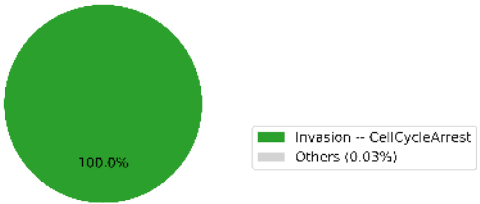
› Influence of Microenvironment

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

No Microenvironment



Microenvironment



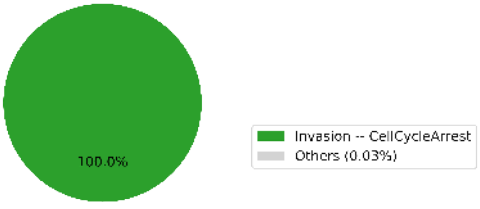
⇒ When we activate the microenvironment, we obtain an invasive phenotype

Example on Cohen's model of tumor invasion

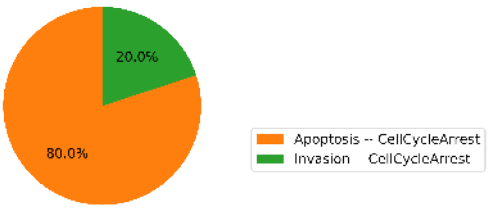
› Influence of DNA damage

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

Microenvironment



Microenvironment + DNA damage



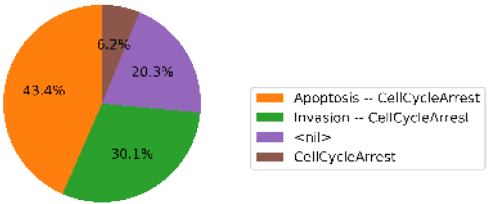
⇒ When we activate DNA damages, we are able to trigger apoptosis in 80% of the cells

Example on Cohen's model of tumor invasion

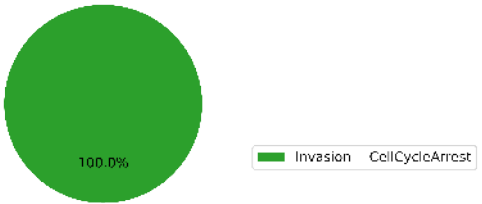
› Notch++, p53- - mutant

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

Wild Type



Notch++, p53 - - mutant

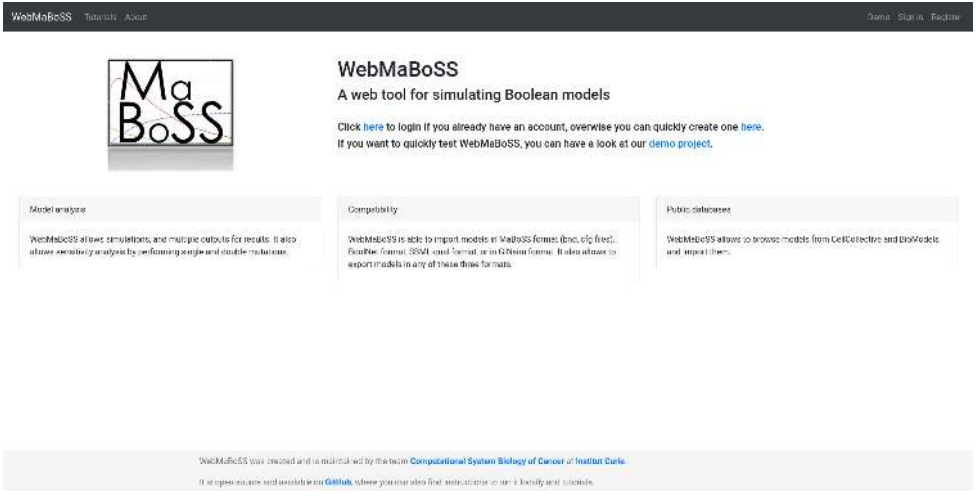


⇒ The results shows that whatever the inputs, we obtain a invasive phenotype

Using MaBoSS with WebMaBoSS

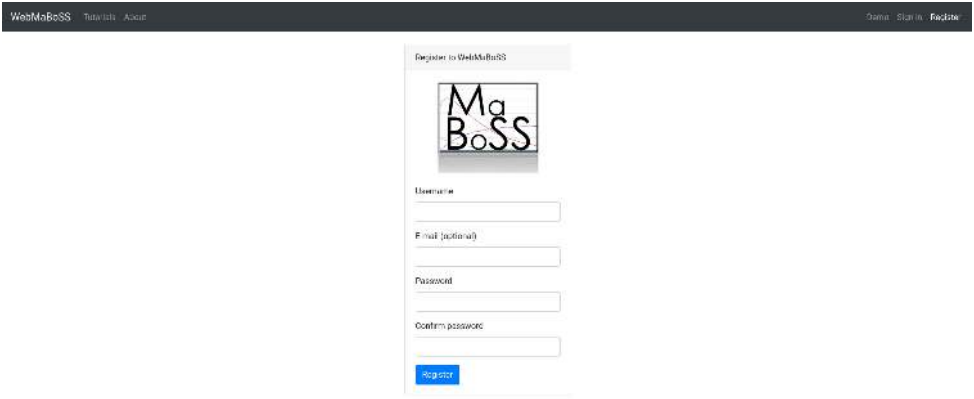
Using MaBoSS with WebMaBoSS

› Home



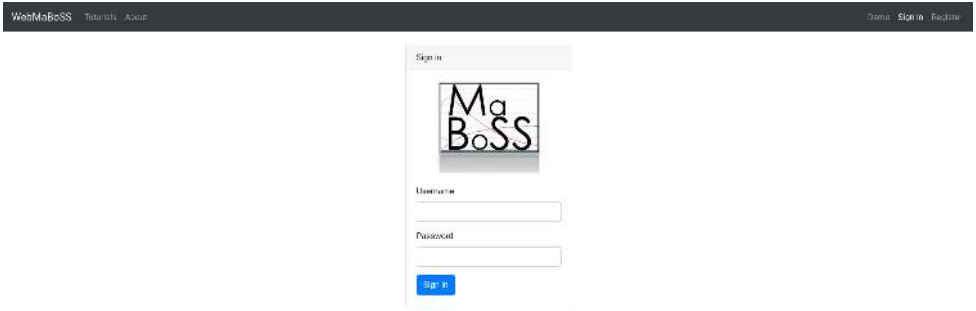
Using MaBoSS with WebMaBoSS

› Create an account



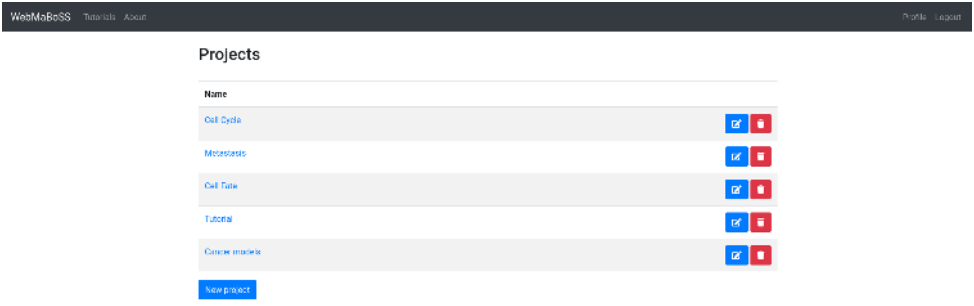
Using MaBoSS with WebMaBoSS

› Logging in



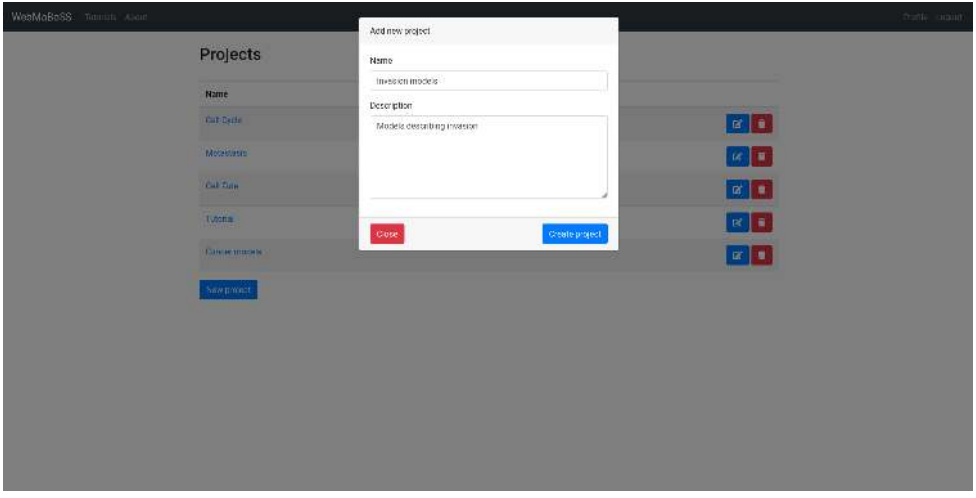
Using MaBoSS with WebMaBoSS

› List of projects



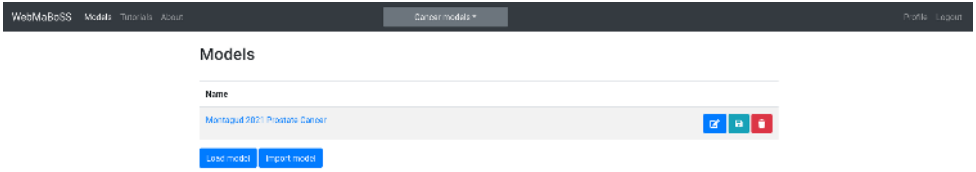
Using MaBoSS with WebMaBoSS

› Creating a project



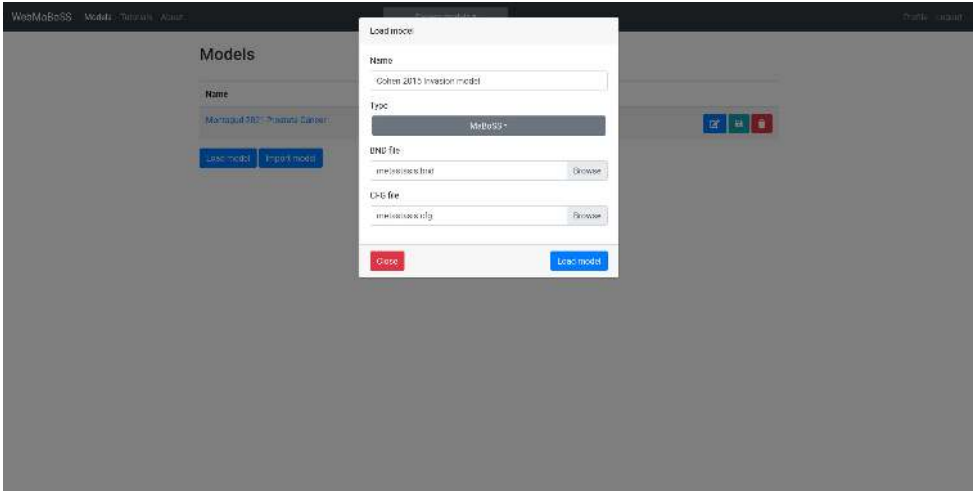
Using MaBoSS with WebMaBoSS

› List of models



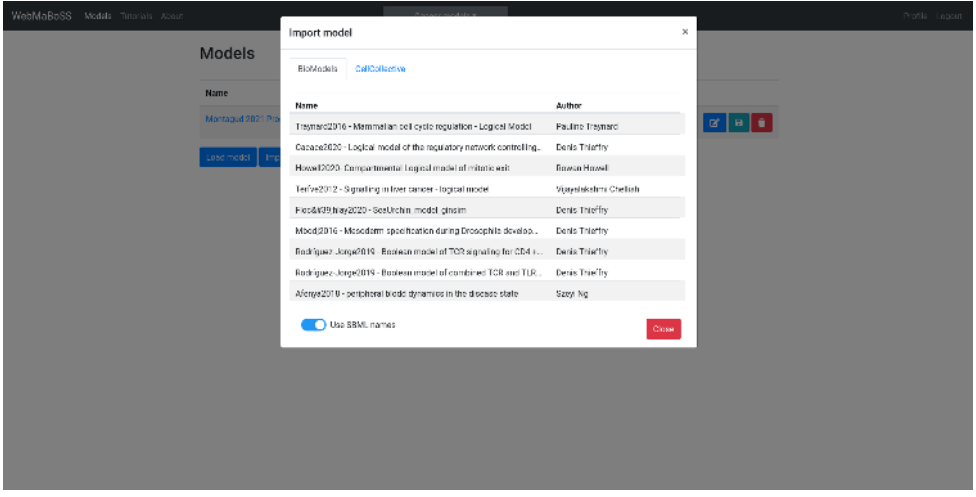
Using MaBoSS with WebMaBoSS

› Loading a model



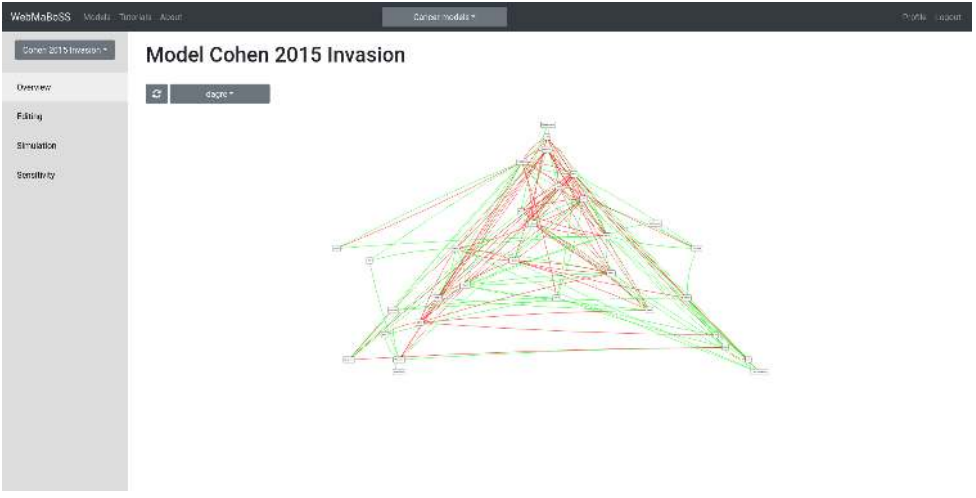
Using MaBoSS with WebMaBoSS

› Importing a model



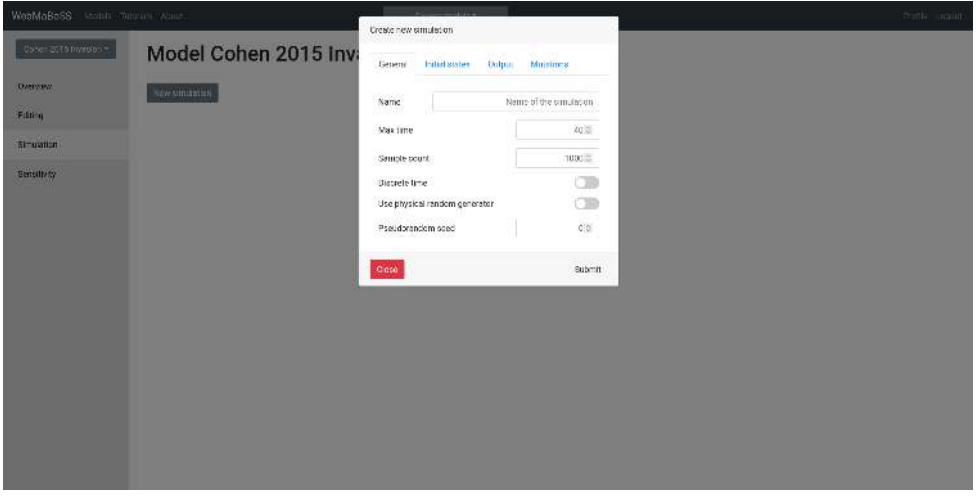
Using MaBoSS with WebMaBoSS

› Model interaction graph



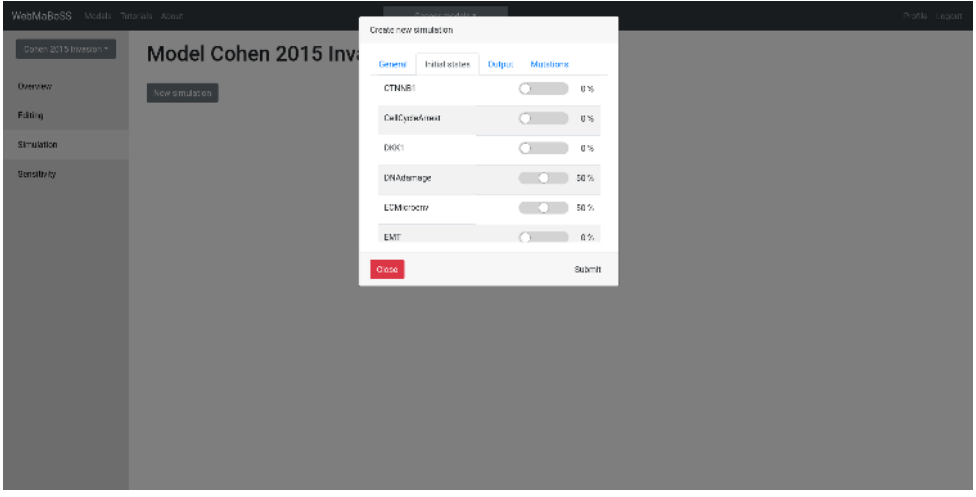
Using MaBoSS with WebMaBoSS

› Creating a new simulation : General settings



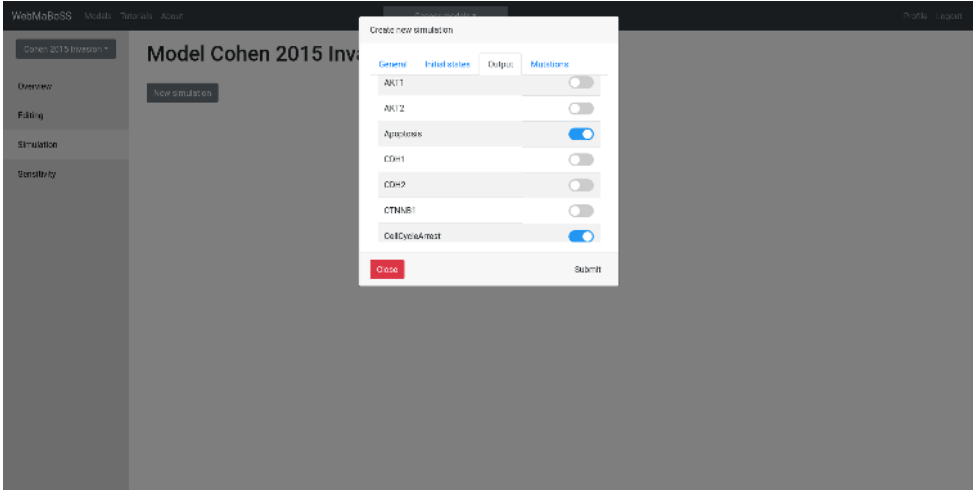
Using MaBoSS with WebMaBoSS

› Creating a new simulation : Initial states



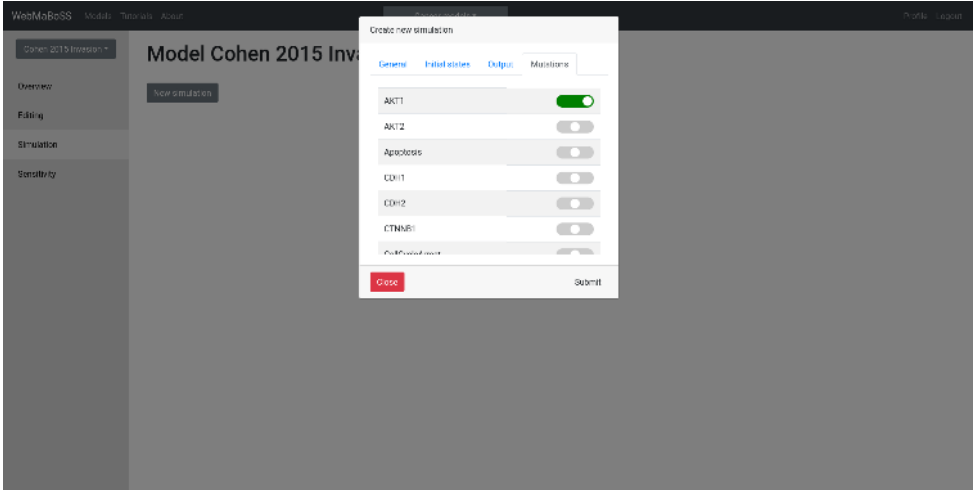
Using MaBoSS with WebMaBoSS

› Creating a new simulation : Output nodes



Using MaBoSS with WebMaBoSS

› Creating a new simulation : Mutants



Using MaBoSS with WebMaBoSS

› Simulation results : Final states



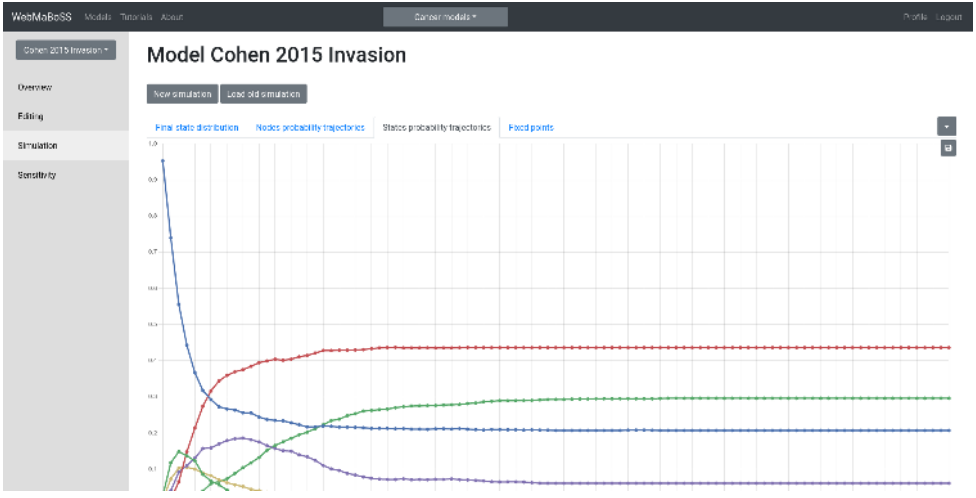
Using MaBoSS with WebMaBoSS

› Simulation results : Node trajectories



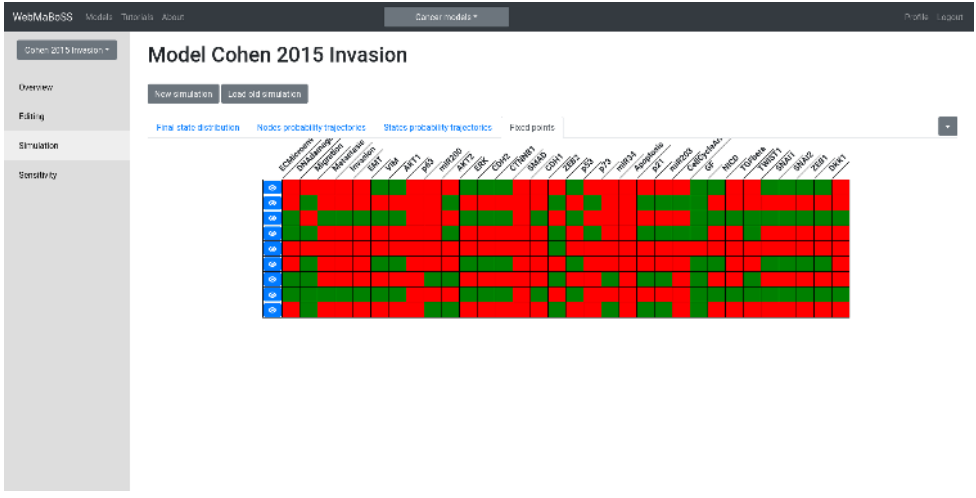
Using MaBoSS with WebMaBoSS

› Simulation results : State trajectories



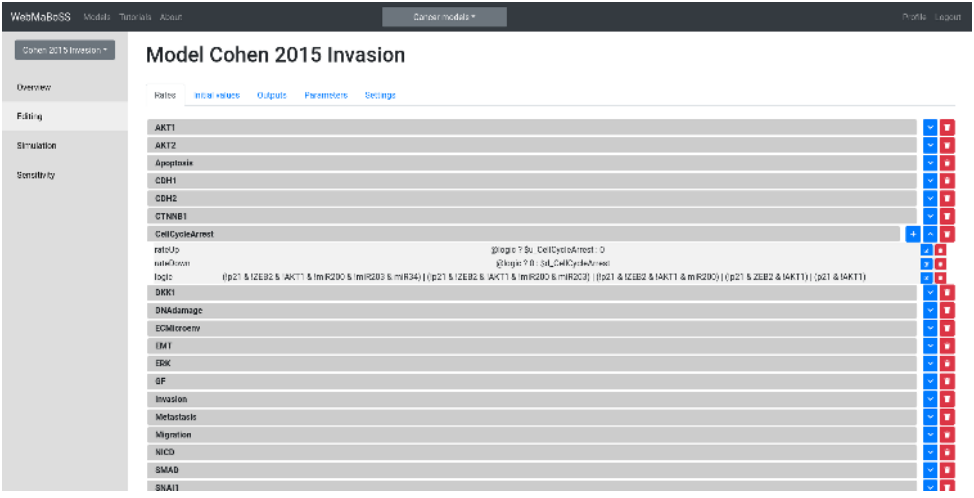
Using MaBoSS with WebMaBoSS

› Simulation results : Fixed points



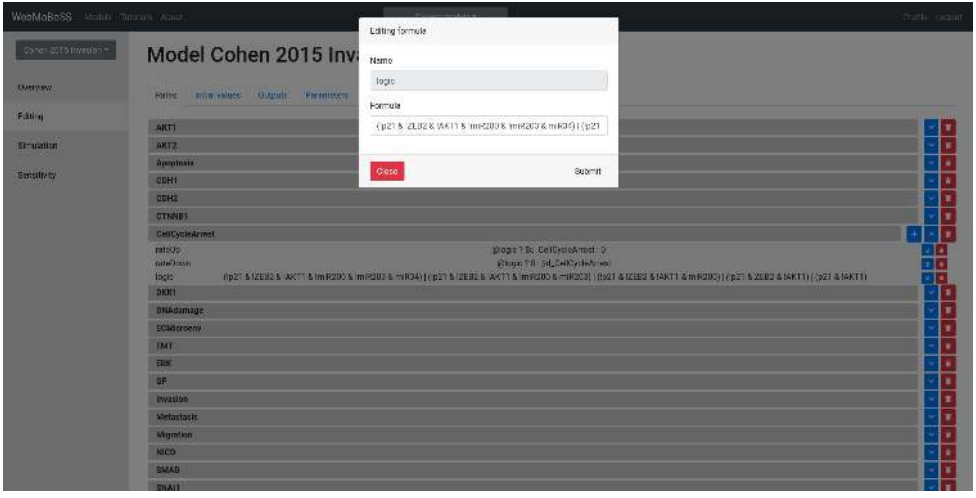
Using MaBoSS with WebMaBoSS

› Model editing : (in)activation rules



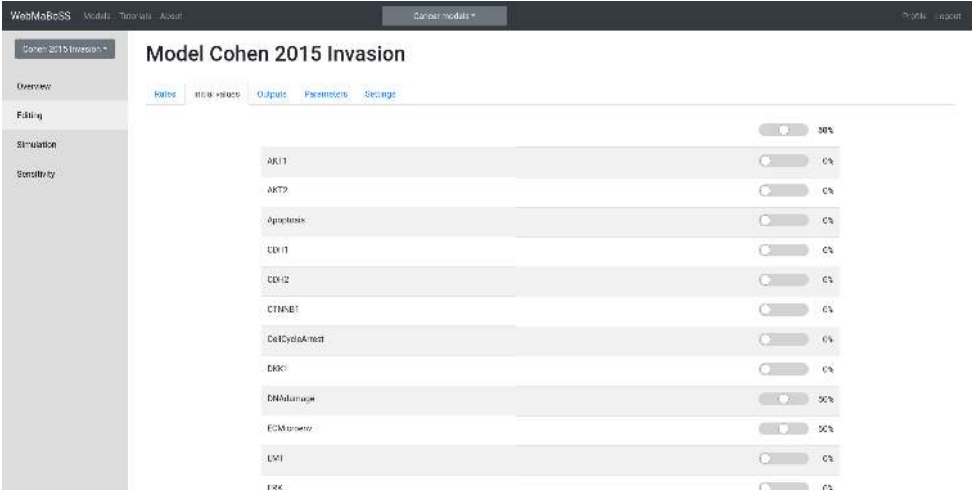
Using MaBoSS with WebMaBoSS

› Model editing : (in)activation rules



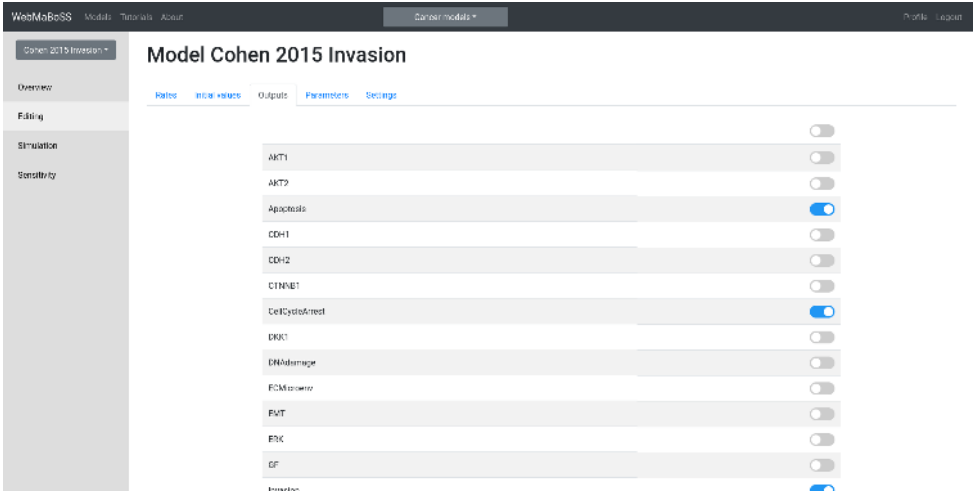
Using MaBoSS with WebMaBoSS

› Model editing : Initial states



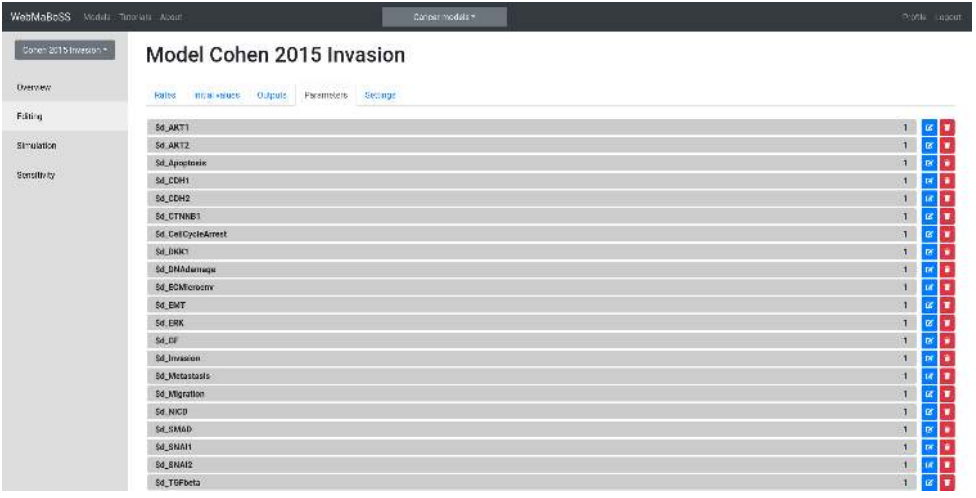
Using MaBoSS with WebMaBoSS

› Model editing : Output nodes



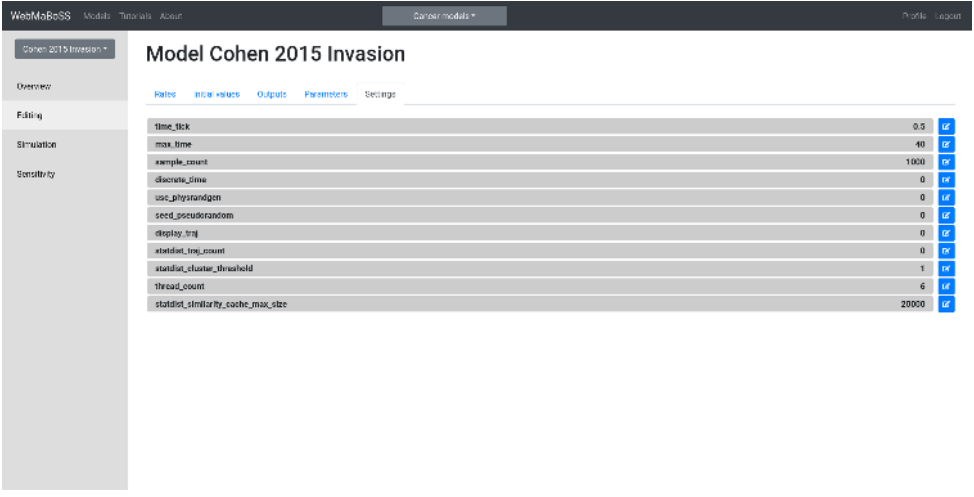
Using MaBoSS with WebMaBoSS

› Model editing : Parameters



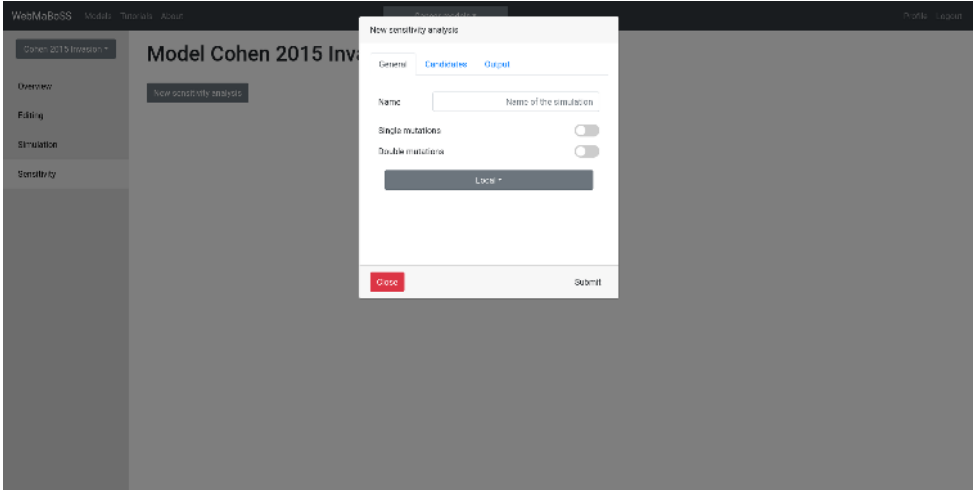
Using MaBoSS with WebMaBoSS

› Model editing : Settings



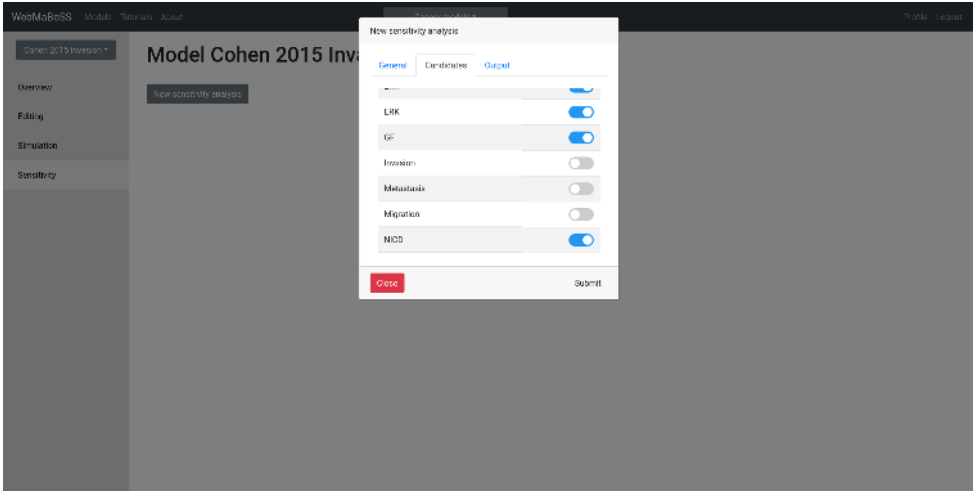
Using MaBoSS with WebMaBoSS

› Sensitivity analysis : General settings



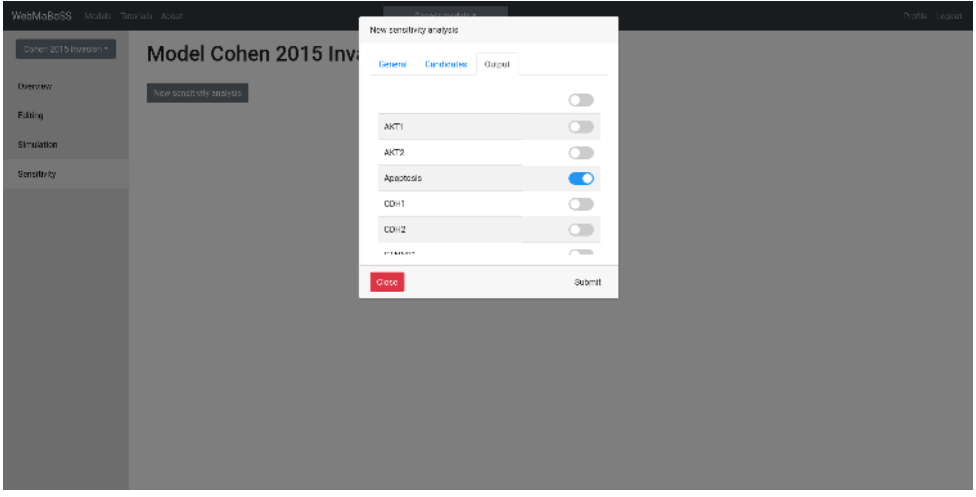
Using MaBoSS with WebMaBoSS

› Sensitivity analysis : Mutant candidates



Using MaBoSS with WebMaBoSS

› Sensitivity analysis : Output nodes



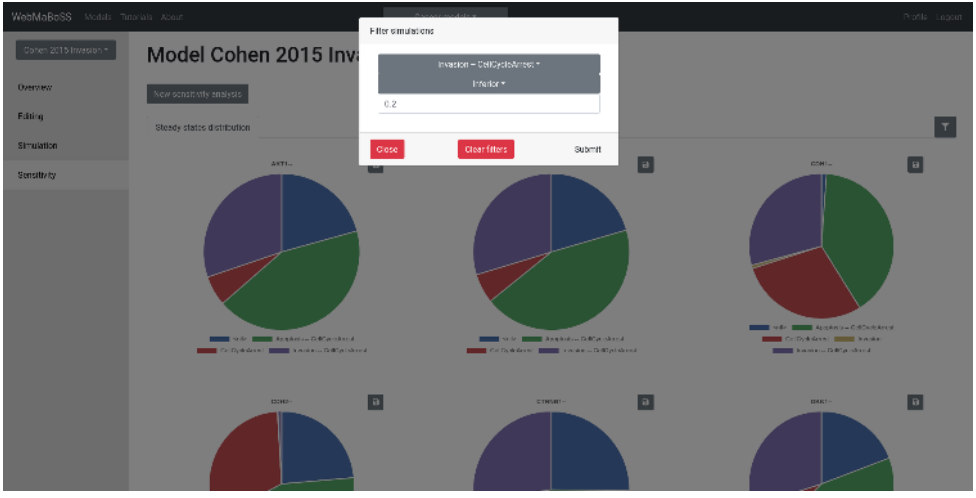
Using MaBoSS with WebMaBoSS

› Sensitivity analysis : Results



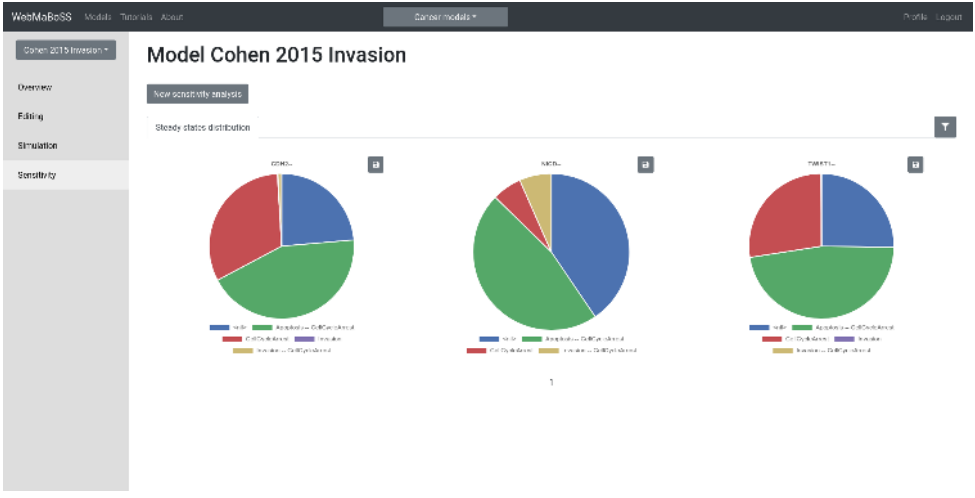
Using MaBoSS with WebMaBoSS

› Sensitivity analysis : Filtering results



Using MaBoSS with WebMaBoSS

› Sensitivity analysis : Filtered results



Using MaBoSS with WebMaBoSS

- Hands on

  - Create a new project

  - Load Cohen's model (bnd and cfg available in google drive)

  - Perform default simulation, report CellCycleArrest state final percentage

  - Perform simulation with ECMicroenv and DNADamage on, report Apoptosis node final percentage

  - Perform simulation with NICD++, p53– mutant, report number of fixed points

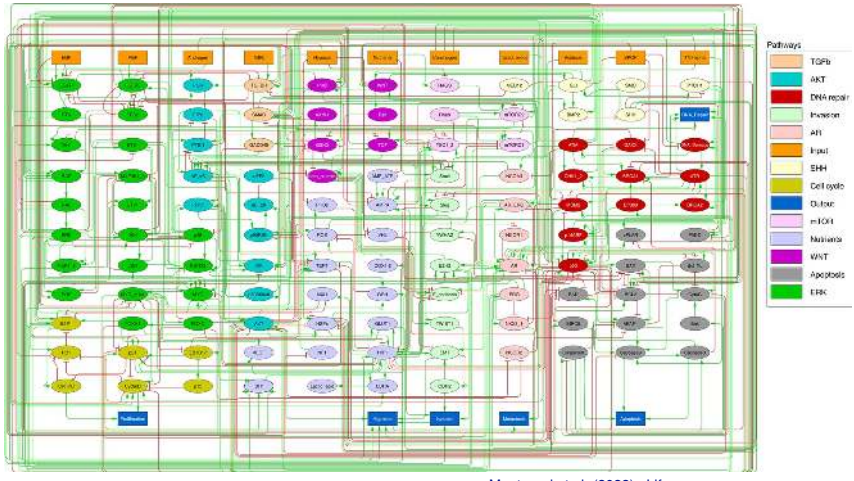
Using MaBoSS with WebMaBoSS

› Hands on

- Perform sensitivity analysis on single mutants, testing only inhibitions
- Filter mutants where state Invasion – CellCycleArrest is less than 20%
- Report mutants found with such phenotypes

Example on Montagud's model of prostate

Example on Montagud's model of prostate

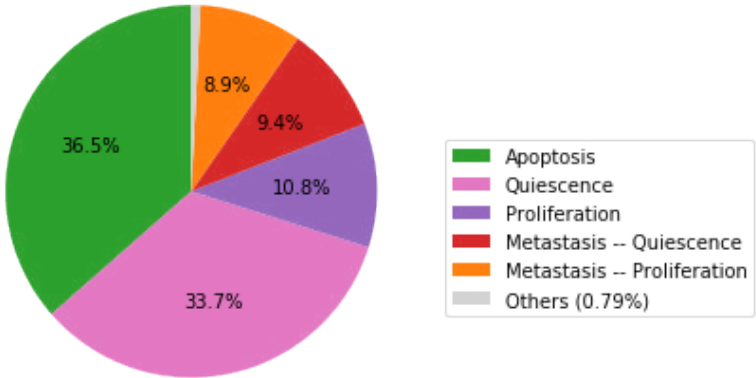


Montagud et al. (2022) eLife

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

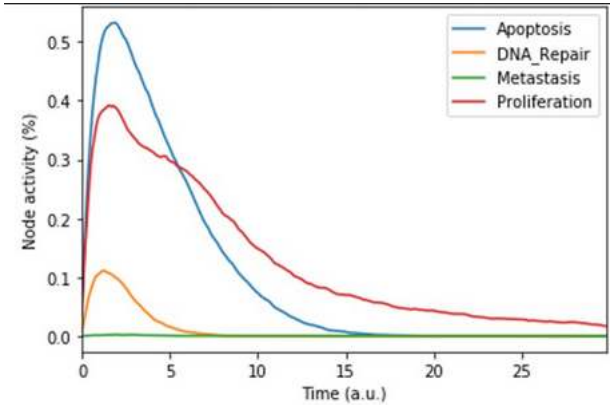
› Any possible input value



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

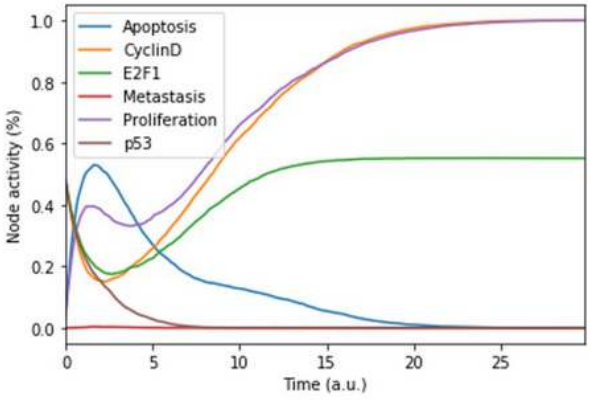
› Wild Type Phenotype



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

Example on Montagud's model of prostate

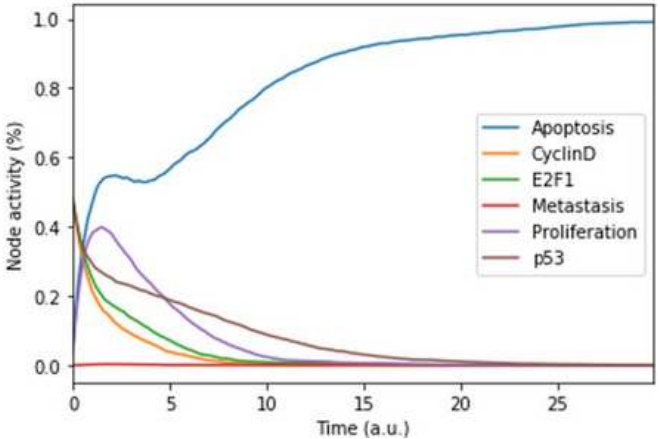
› Proliferative Phenotype



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

Example on Montagud's model of prostate

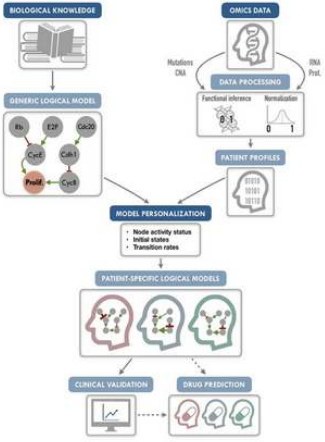
› Apoptotic Phenotype



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.

Example on Montagud's model of prostate

› PROFILE : Model personalization

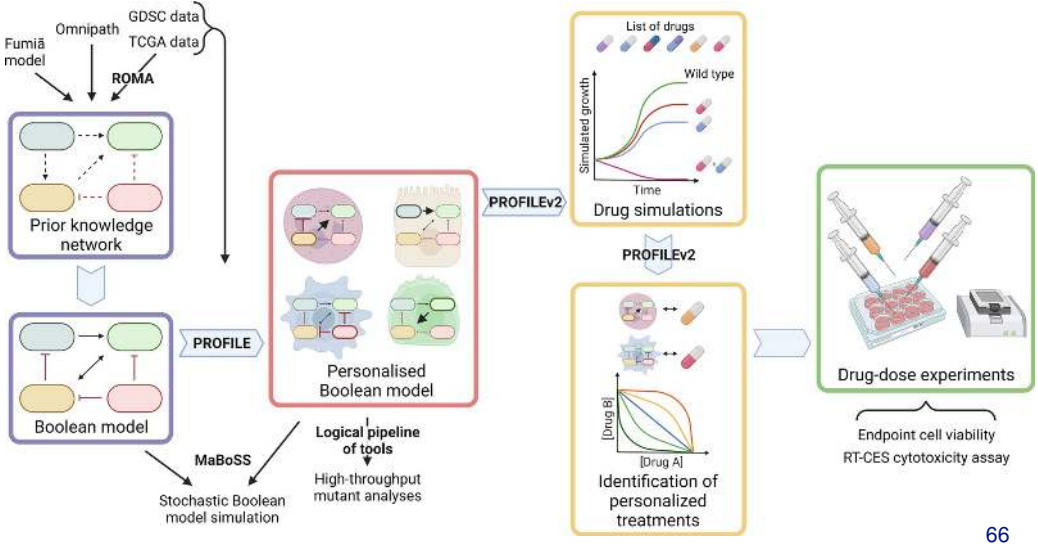




PROFILE: https://github.com/sysbio-curie/PROFILE

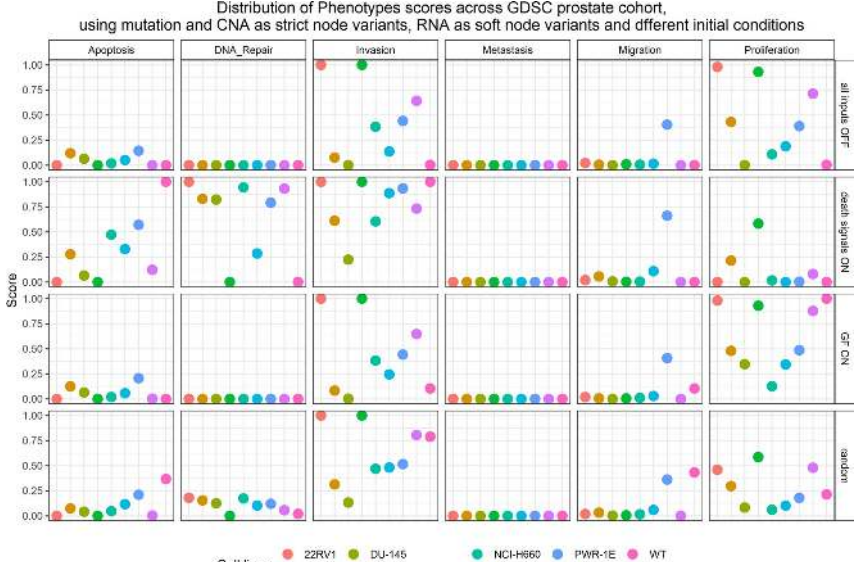
Example on Montagud's model of prostate

› PROFILEv2 pipeline



Example on Montagud's model of prostate

› PROFILEv2 with multiple cell lines



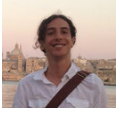
Using MaBoSS with pyMaBoSS

- 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 with pyMaBoSS

› Loading a model

```
In [1]: import maboss
        model = maboss.load("metastasis.bnd", "metastasis.cfg")
```

```
In [ ]: sbml_model = maboss.loadSBML("Cohen.sbml", "metastasis.cfg")
```

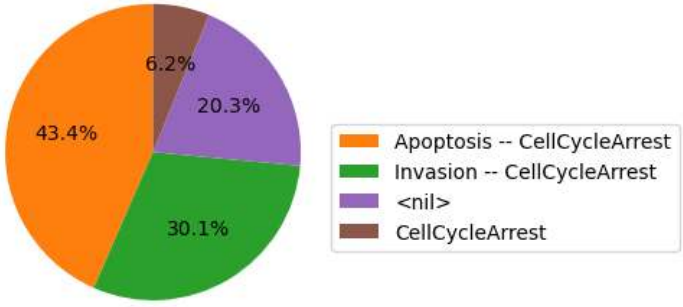
```
In [ ]: bnet_model = maboss.loadBNet("Cohen.bnet", "metastasis.cfg")
```

› MaBoSS is directly compatible with SBML, BNet, and MaBoSS proprietary format for network representation

Using MaBoSS with pyMaBoSS

› Running a simulation

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

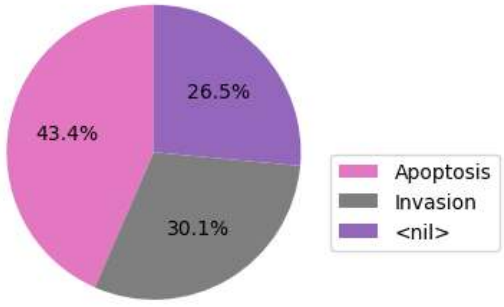


› A few lines of code to simulate the model and plot the final states distribution

Using MaBoSS with pyMaBoSS

› Changing output nodes

```
model.network.set_output(["Apoptosis", "Invasion"])
res = model.run()
res.plot_piechart()
```

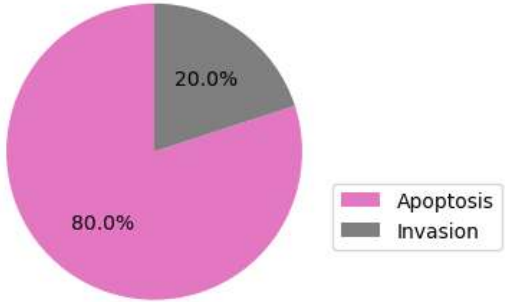


› Controlling which node is included in the results (Ex: remove CellCycleArrest)

Using MaBoSS with pyMaBoSS

› Changing initial states

```
model.network.set_istate("ECMicroenv", [0, 1])
model.network.set_istate("DNAdamage", [0, 1])
res = model.run()
res.plot_piechart()
```

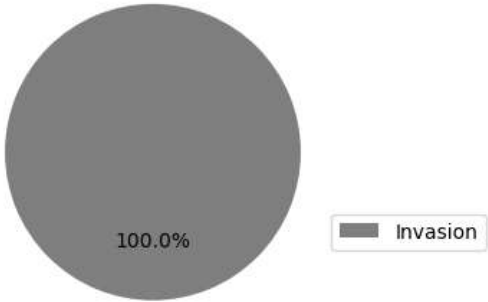


› Simulating with specific initial values

Using MaBoSS with pyMaBoSS

› Simulating mutations

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

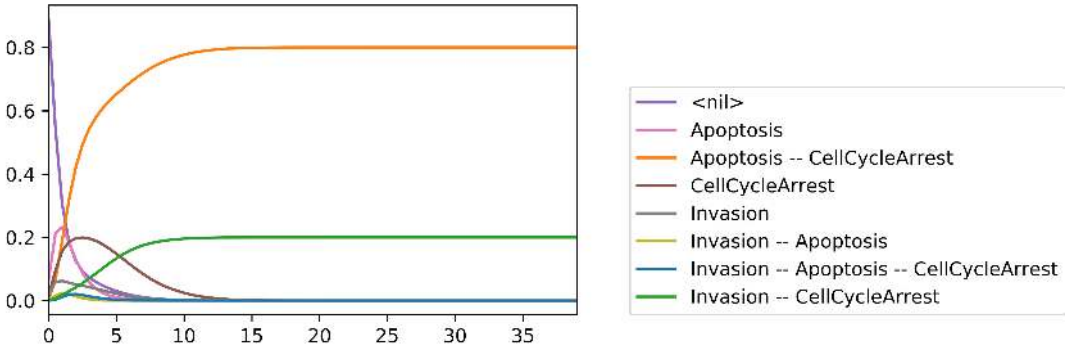


› Performing mutant simulations

Using MaBoSS with pyMaBoSS

› Results : State probability distribution trajectories

```
res.plot_trajectory()
```

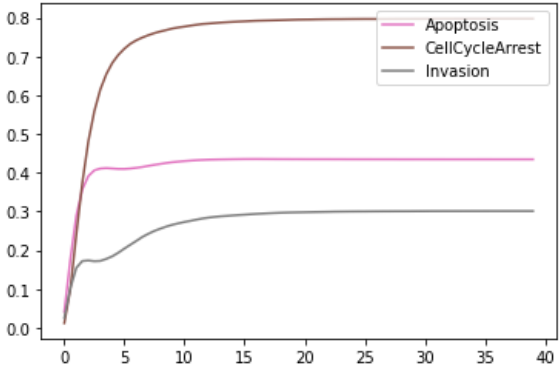


› Visualizing state probability trajectories

Using MaBoSS with pyMaBoSS

› Results : Nodes probability trajectories

```
res.plot_node_trajectory()
```



› Visualizing state probability trajectories

Using MaBoSS with pyMaBoSS

› Results : State probability distribution trajectories values

```
res.get_states_probtraj()
```

	<nil>	Apoptosis	Apoptosis -- CellCycleArrest	CellCycleArrest	Invasion	Invasion -- Apoptosis	Invasion -- Apoptosis -- CellCycleArrest	C
0.0	0.927211	0.036734	0.002495	0.008816	0.023224	0.001194	0.000086	
0.5	0.682001	0.124939	0.035559	0.056035	0.081564	0.012353	0.002428	
1.0	0.485872	0.146506	0.109373	0.103834	0.104372	0.022607	0.010071	
...	...	...	...	...	...	...	...	
38.0	0.202716	0.000000	0.434370	0.061990	0.000004	0.000000	0.000000	
38.5	0.202714	0.000000	0.434370	0.061996	0.000000	0.000000	0.000000	
39.0	0.202719	0.000000	0.434370	0.061991	0.000000	0.000000	0.000000	

› Visualizing state probability trajectories

Using MaBoSS with pyMaBoSS

› Results : Nodes probability trajectories values

```
res.get_nodes_probtraj()
```

	Apoptosis	CellCycleArrest	Invasion
0.0	0.040509	0.011637	0.024744
0.5	0.175279	0.099143	0.101466
1.0	0.288557	0.240643	0.154415
...	...	...	...
38.0	0.434370	0.797280	0.300924
38.5	0.434370	0.797286	0.300920
39.0	0.434370	0.797281	0.300920

› Getting the node probability trajectories as Panda dataframes

Using MaBoSS with pyMaBoSS

› Results : Last state probability distributions

```
res.get_last_states_probtraj()
```

	<nil>	Apoptosis -- CellCycleArrest	CellCycleArrest	Invasion -- CellCycleArrest
39.0000	0.202719	0.43437	0.061991	0.30092

```
res.get_last_nodes_probtraj()
```

	Apoptosis	CellCycleArrest	Invasion
39.0000	0.43437	0.797281	0.30092

› Getting the last state probability distribution as Panda dataframes

Using MaBoSS with pyMaBoSS

- Hands on

  - Load Montagud's model
  - Simulate and plot default model
  - Simulate and plot model with all initial values at zero
  - Simulate proliferative conditions
  - Simulate proliferative conditions with MYC_MAX inhibition

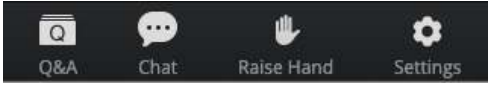
Using MaBoSS with pyMaBoSS

› Hands on

- Simulate a batch in inhibitions
- Filter inhibition with zero proliferation and report which ones
- Simulate default conditions for all personalized models, and build a dataframe which all the final states. Report min/max apoptosis
- Simulate proliferative conditions with MYC_MAX inhibition for all personalized models, build dataframe with all the final states
- Filter patients with less than 10% of Proliferation and report them

Questions ?

- Write your questions using the Q&A button





Thanks !

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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

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