Using MaBoSS for modeling heterogeneous cell behavior

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Outline

1. Population interpretation of probabilistic Boolean space
2. MaBoSS for probabilistic Boolean modelling
3. UpPMaBoSS.pl for dynamical and heterogeneous population modeling
4. Example with (TNF → cell fate) model

1. Population interpretation of probabilistic Boolean space

Boolean node state: 0 or 1 for node *i*.

Boolean network state: vector $\vec{S}$ of Boolean node state for a given network. For each node *i*, $S_i \in \{0,1\}$.

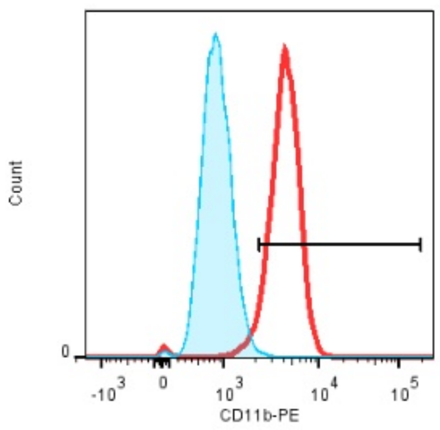
Network state space: set of possible Boolean network state, $\Sigma = \{\vec{S}\}$ for a given network.

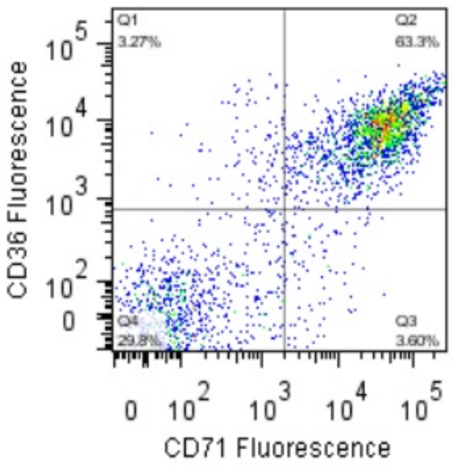
Probability space over network state space: give a probability for each network space.

$$P(\vec{S}) \in [0,1], \sum_{\vec{S} \in \Sigma} P(\vec{S}) = 1$$

1. Population interpretation of probabilistic Boolean space

Biological interpretation of network state probability: ratio of cells (among a population), that are in the given state (described by a Boolean network state). Can be used to confront theoretical prediction to cytometry data.





Missing:

- Global size of cell population
- Paracrine interaction, ie population dependant interaction

ALLCELLS

2. MaBoSS for probabilistic Boolean modelling

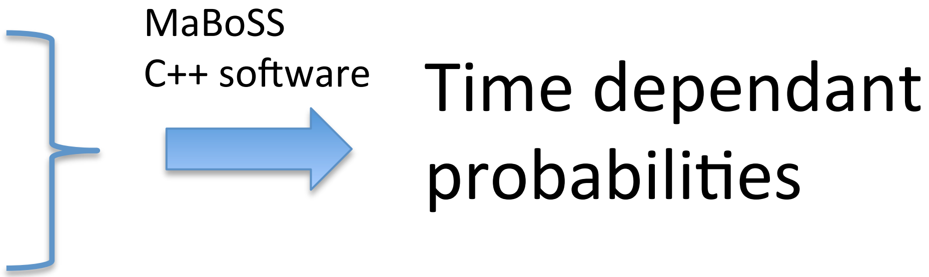
MaBoSS: $$P(\vec{S},t) \in [0,1], \sum_{\vec{S}\in\Sigma} P(\vec{S},t) = 1$$

time dependant probabilities (over network states)

within <u>Markov hypothesis</u>.

Inputs:

- Transition rates
- Initial conditions



MaBoSS
C++ software

Time dependant probabilities

Transition rate: $$\rho_{\vec{S}\to\vec{S}'} = \lim_{\Delta t\to 0} \frac{P[\vec{S}'(\Delta t) \mid \vec{S}(0)]}{\Delta t} \in [0,\infty[$$

2. MaBoSS for probabilistic Boolean modelling

Two files that define the model: a **bnd file** and a **cfg file**.

1) Transition rate, define rate value (time^{-1}) and condition for activation and inhibition: logical operators (AND,OR, XOR, NOT) with real operators (+, -, *, /) and ternary conditional (? :).

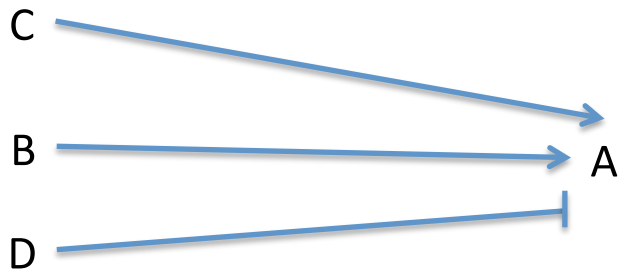
In **bnd file**:

```
Node A {
      rate_up  = (C AND B OR NOT D) ? 1.0 : 0.0;
      rate_down  = (C AND B OR NOT D) ? 0.0 : $Extern_variable; }
```

(condition ? value_if_cond_true : value_if_cond_false)

In **cfg file**:

```
$Extern_variable = 30;
```



2) Initial condition:

p[(A,B,C,D)=(0,0,0,0)]=0.7

p[(A,B,C,D)=(1,0,0,0)]=0.2

p[(A,B,C,D)=(1,1,1,1)]=0.1

In **cfg file**:

```
[A,B,C,D].istate = 0.7 [0,0,0,0] , 0.2 [1,0,0,0] , 0.1 [1,1,1,1];
```

3. UpPMaBoSS.pl for population modeling

The model is initially based on signalling pathways inside each cell, to which nodes representing cell death and cell division are added and inter-cell communications are specified.

Population dynamics using MaBoSS include:

1. Cell death,
2. Cell division,
3. Inter-cell communication (ligand → receptor for instance).

Possibility to model mutant effect on population dynamics for instance.

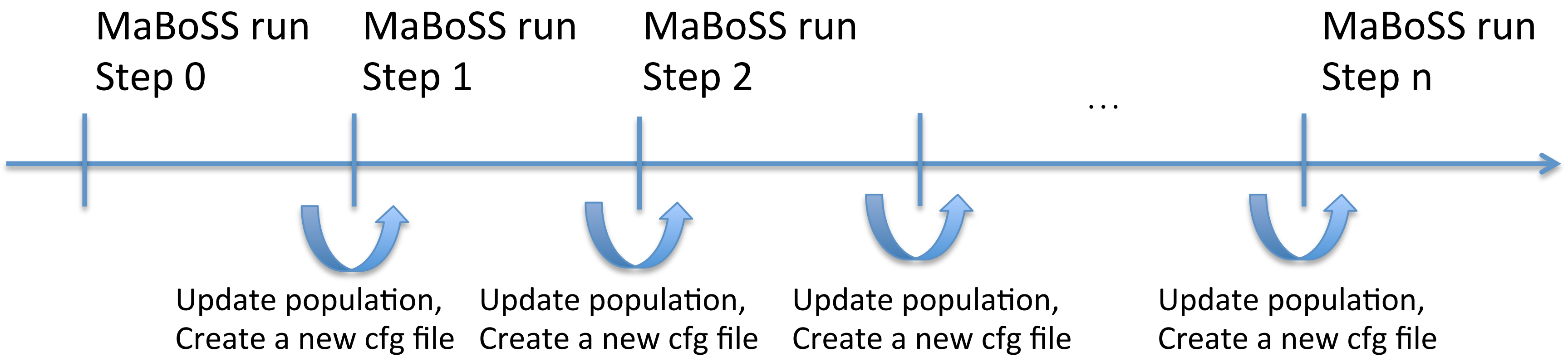
Outputs:

- size of cell population over time,
- probabilities of “network states” over time

UpPopMaBoSS.pl

Run MaBoSS several times (“steps”). For each MaBoSS run:

1. take the previous condition for “*Population update*”: cell death, cell division and inter-cell effects,
2. create a new **cfg file** for the following step with a new initial condition.



- New cfg file: take initial condition from final probability distribution of previous step, remove cell death state, double division state, update external variables that represent inter-cell interaction
- Total time = (max_time of a MaBoSS run) * (number of steps).

Outputs

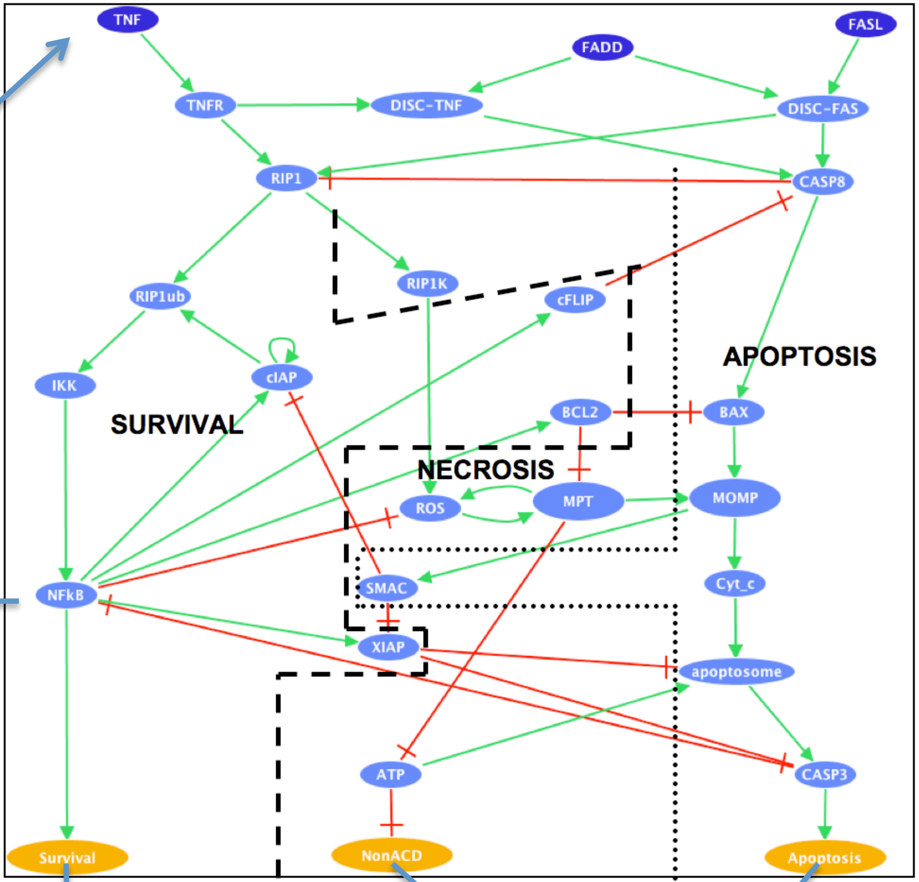
1) MaBoSS output csv files (probabilities over network states over time).
2) Final probability distribution over network state for each step/MaBoSS run.
3) Population ratio for each step/MaBoSS run.

The “population ratio” is a number that represents the relative size of the cell population compared to the initial population size. Therefore:

- Population ratio = 1 → Stable size
- Population ratio > 1 → Growing population
- Population ratio < 1 → Decreasing population

Example with TNF → cell fate

Use published cell fate model (GINsim/MaBoSS), available on the web page



Production of TNF induced by NFkB

Cell Division / Proliferation

Cell Death

In the **bnd file**:

- add a node for cell death, a node for cell division
- modify the TNF node, in order that its activation is controlled by an external variable ($TNF_induc).

```
node TNF
{ rate_up = $TNF_induc;
  rate_down = $Degr_TNF;}
```

TNF can be induced by setting the initial condition or controlling the external variable $TNF_induc

```
node Proliferation
{ rate_up = Survival ? $DivRate : 0.0;
  rate_down = 0.0;}
```

Survival induces cell division, and thus proliferation

```
node Death
{ rate_up = (NonACD | Apoptosis) ? 1 : 0.0;
  rate_down = 0.0; }
```

Cell death is induced by either Apoptosis or NonACD (non-apoptotic cell death)

In the initial **cfg file** (used for step 0):

- set cell division ($DivRate) (cell death rate is 1 hour in the bnd file)
- define an external variable that control the strength of TNF production by NFkB ($ProdTNF_NFkB)
- set carefully the max_time (tricky)
- set the initial condition for step 0

```
[TNF].istate = 1 [1] , 0 [0];
$ProdTNF_NFkB = 1;
$TransRate = 1/24;
$DivRate = 1/24;
$Degr_TNF = 1/6;
$TNF_induc = 0;
max_time = 3;
```

Treat cells with TNF → initial state is 1

Production of TNF by NFkB is switched on

Mean transcription time = 24 hours
Mean Division time = 24 hours
Mean TNF degradation time = 6 hours

TNF is only induced by initial condition (not by NFkB initially)

Time for population update = 3 hours (tricky to set up)

In the **upp file**:

- Define the cell death node, the division node, the number of steps.
- Define how the external variable that control TNF is updated (according to NFkB status).

Node for cell death

Node for cell division

External variable $TNF_induc is updated according to state probabilities at the end of each MaBoSS run

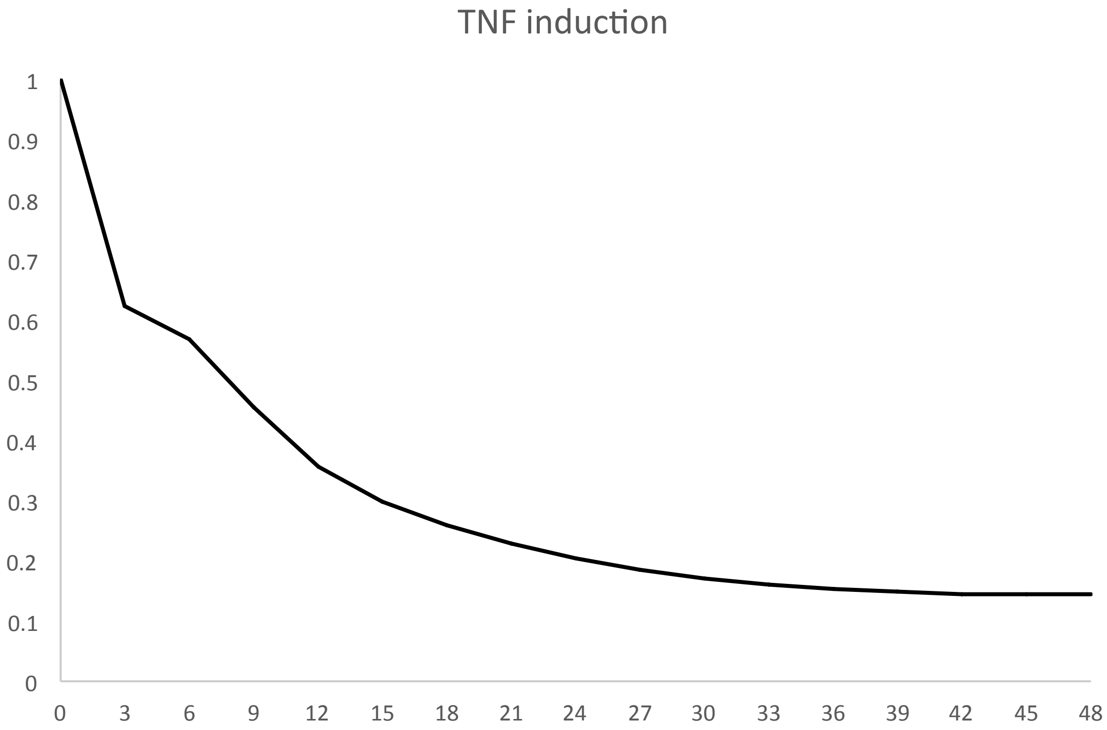
```
death = CellDeath;
division = Proliferation;

$TNF_induc u= $ProdTNF_NFkB*p[(NFkB,Death) = (1,0)];

# u= means update of the external variable

# NB: more than one variable can be defined as such
# (here representative of the microenvironment)

# $ProdTNF_NFkB corresponds to the strength of the feedback
# that way it is easier to cancel the feedback when put to 0

# 16 steps are chosen to account for 48 hours because max_time = 3

steps = 16;

MaBoSS = ./MaBoSS
```

Update operator

Number of steps → total time = 16*3 hours

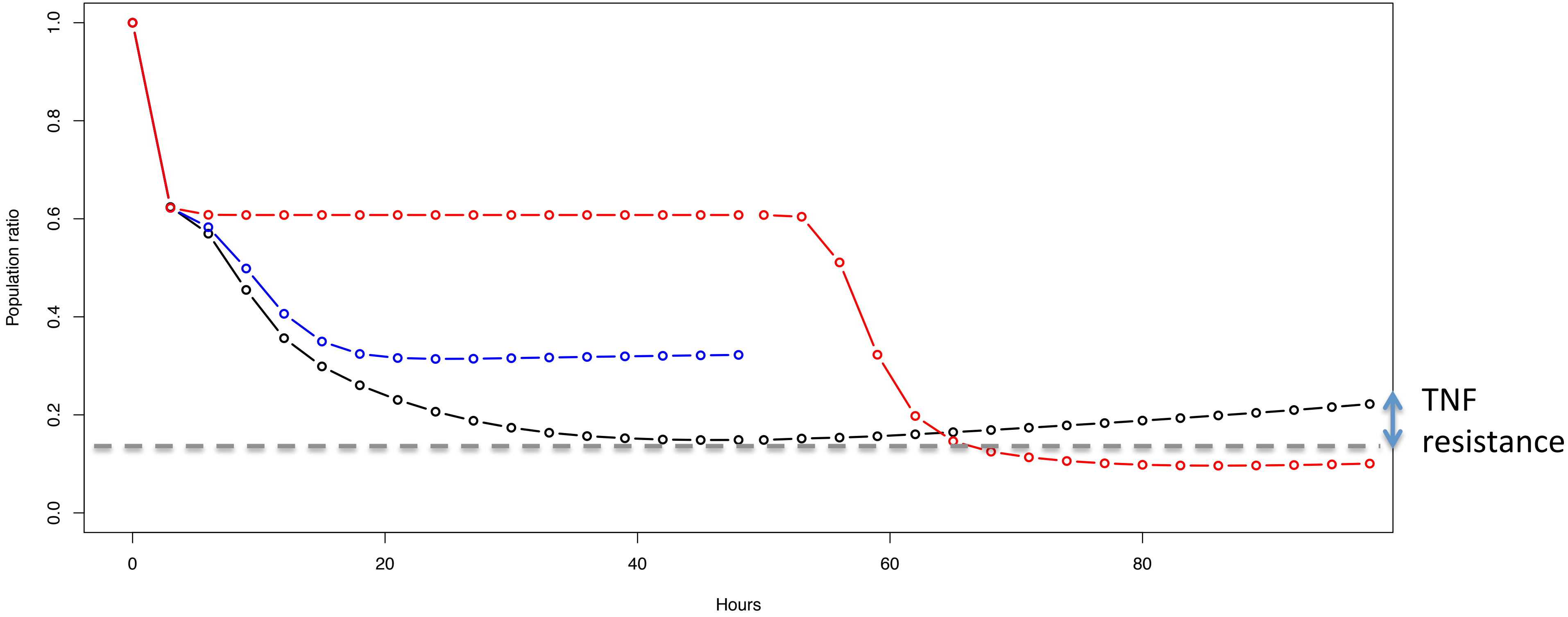
MaBoSS executable name

Population ratio of TNF induction model



```
$ProdTNF_NFkB = 1;
$TNF_induc = 0;
[TNF].istate = 1 [1] , 0 [0];
```

TNF resistance from population ratio over time

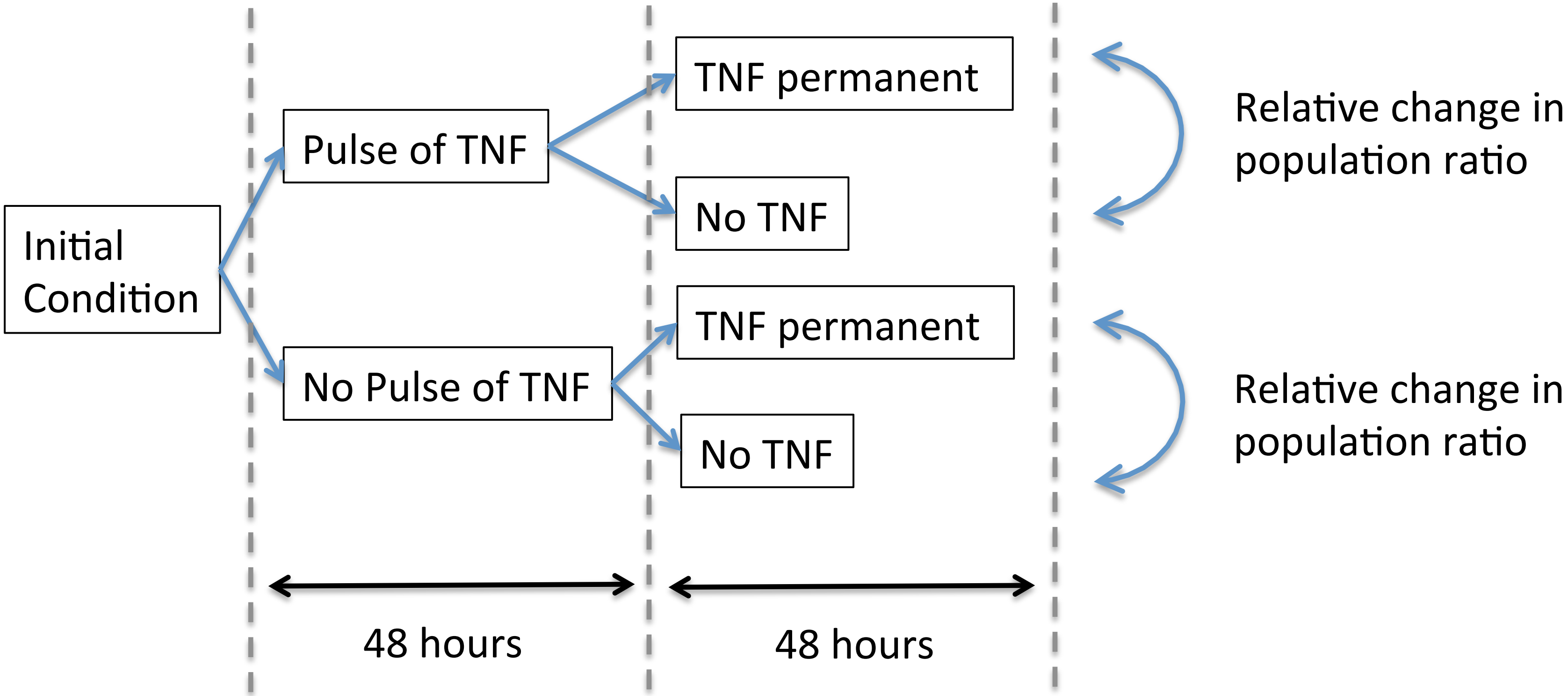


No TNF / then TNF permanent induction
$ProdTNF_NFkB = 1;
$Degr_TNF = 1/6;
$TNF_induc = 0; (at 0 hours)
$TNF_induc = 20; (at 48 hours)
[TNF].istate = 0 [1] , 1 [0]; (at 0 hours)
[TNF].istate = 1 [1] , 0 [0]; (at 48 hours)

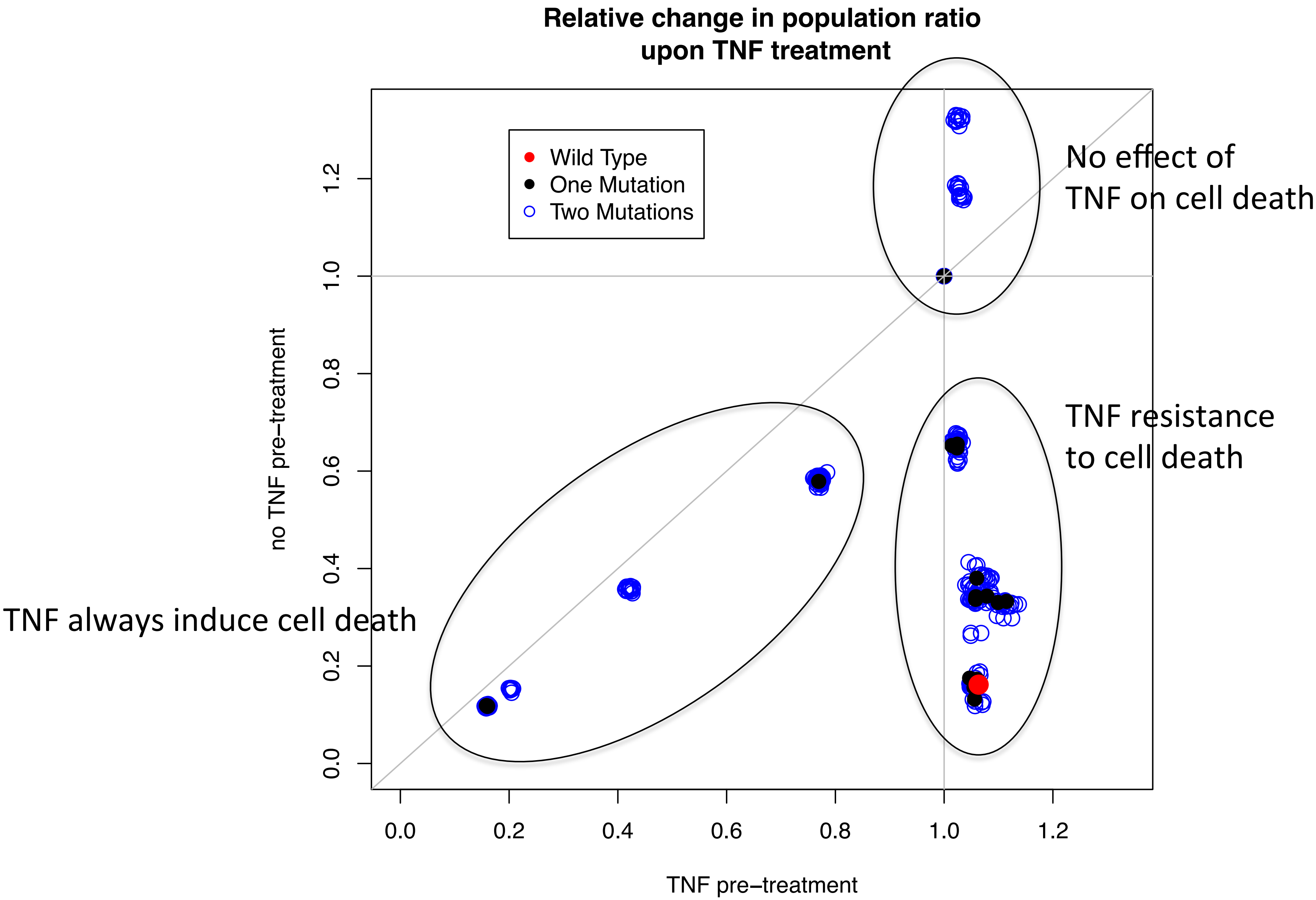
TNF (pulse) then TNF permanent induction
$ProdTNF_NFkB = 1;
$Degr_TNF = 1/6;
$TNF_induc = 0; (at 0 hours)
$TNF_induc = 20; (at 48 hours)
[TNF].istate = 1 [1] , 0 [0]; (at 0 hours)
[TNF].istate = 1 [1] , 0 [0]; (at 49 hours)

TNF (pulse)
No TNF feedback from NFkB
$ProdTNF_NFkB = 0;
$Degr_TNF = 1/6;
$TNF_induc = 0;
[TNF].istate = 1 [1] , 0 [0];

In silico “Experimental” protocol



Simulation for every single and double mutations



No effect of
TNF on cell death

TNF resistance
to cell death

TNF always induce cell death

Perspective

- Study time step dependance
- Apply UpPMaBoSS.pl to C. Hernandez model of T-cell differentiation
- Apply UpPMaBoSS.pl to Immungenic Cell Death
- Asynchronous population update?

Acknoledgements

- D. Thieffry and C. Hernandez
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