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<https://github.com/physicell-training/ws2022>



Session 11: Simulating a TNF treatment with PhysiBoSS



Vincent Noël – Institut Curie

 @vincentnoel72

PhysiCell Project

July 27, 2022

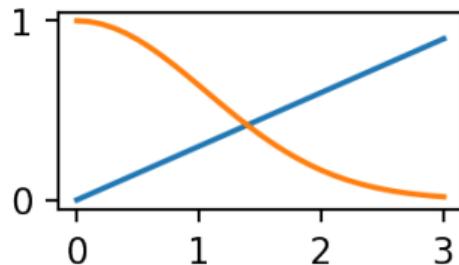


Outline

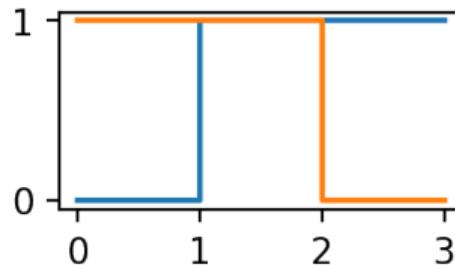
- › Boolean models
- › MaBoSS : Continuous time boolean modelling
- › PhysiBoSS
- › TNF model

Boolean models

Quantitative (ODEs)



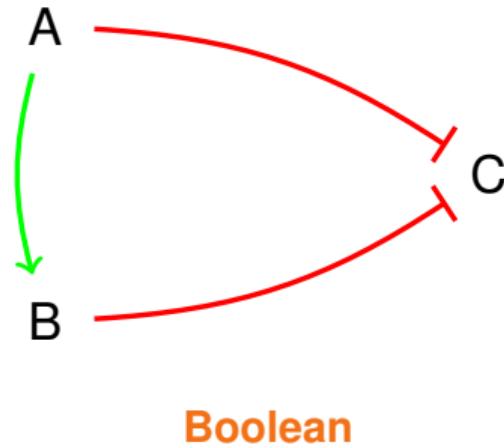
Qualitative (Boolean)



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

- › Values are 0/1 (false/true)
- › Sequences of events
- › Easy to write
- › Can simulate large models

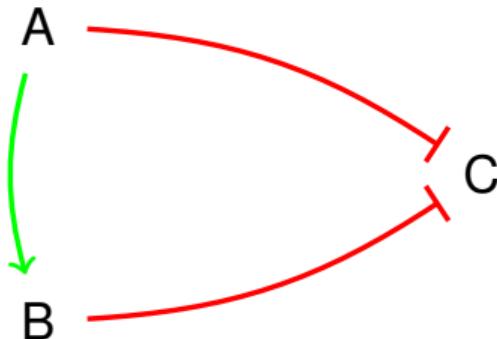
Boolean models



Formulas:

- › $A = \text{input}$
- › $B = A$
- › $C = !(A \text{ and } B)$

Boolean models



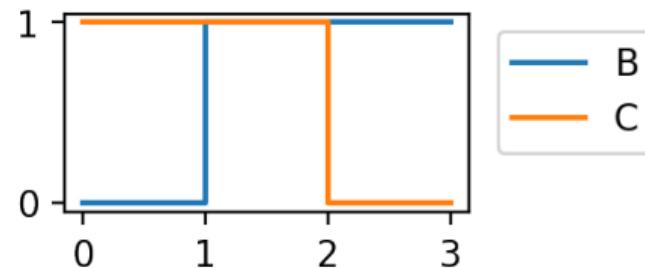
Boolean

Formulas:

- › $A = \text{input}$
- › $B = A$
- › $C = !(A \text{ and } B)$

Initial values:

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



Mathematical Modelling of Cell-Fate Decision in Response to Death Receptor Engagement

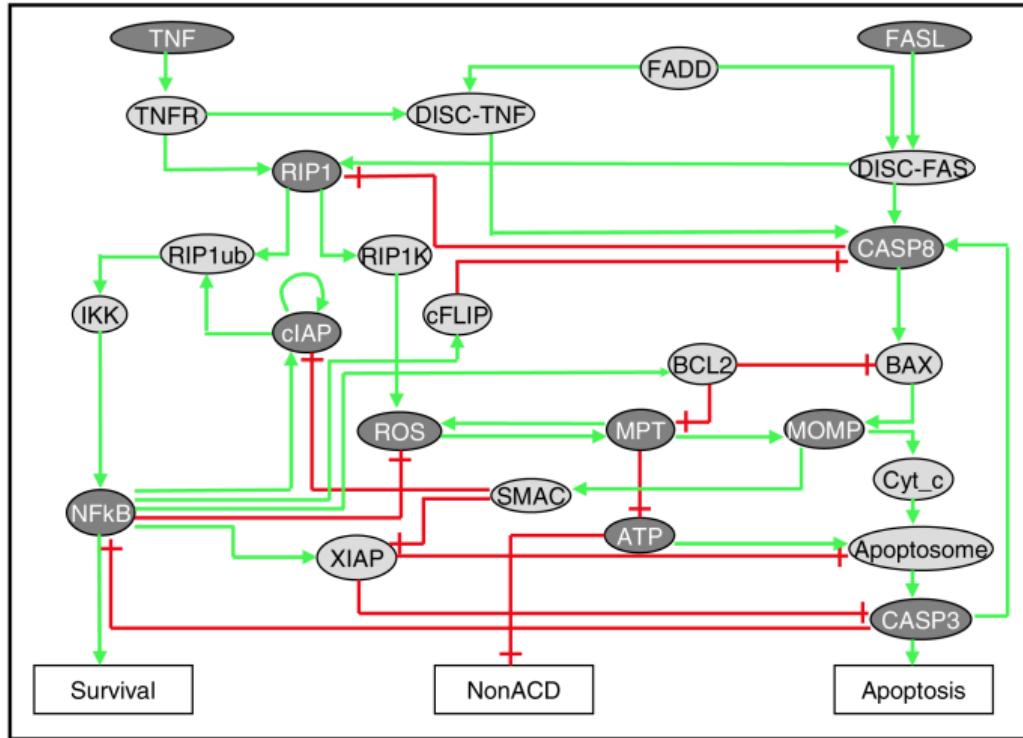
Laurence Calzone^{1,2,3*}, Laurent Tournier^{1,2,3}, Simon Fourquet^{1,2,3}, Denis Thieffry^{4,5}, Boris Zhivotovsky⁶, Emmanuel Barillot^{1,2,3†}, Andrei Zinovyev^{1,2,3‡}

1 Institut Curie, Paris, France, **2** Ecole des Mines ParisTech, Paris, France, **3** INSERM U900, Paris, France, **4** TAGC – INSERM U928 & Université de la Méditerranée, Marseille, France, **5** CONTRAINTES Project, INRIA Paris-Rocquencourt, France, **6** Karolinska Institutet, Stockholm, Sweden

Abstract

Cytokines such as TNF and FASL can trigger death or survival depending on cell lines and cellular conditions. The mechanistic details of how a cell chooses among these cell fates are still unclear. The understanding of these processes is important since they are altered in many diseases, including cancer and AIDS. Using a discrete modelling formalism, we present a mathematical model of cell fate decision recapitulating and integrating the most consistent facts extracted from the literature. This model provides a generic high-level view of the interplays between NFkB pro-survival pathway, RIP1-dependent necrosis, and the apoptosis pathway in response to death receptor-mediated signals. Wild type simulations demonstrate robust segregation of cellular responses to receptor engagement. Model simulations recapitulate documented phenotypes of protein knockdowns and enable the prediction of the effects of novel knockdowns. *In silico* experiments simulate the outcomes following ligand removal at different stages, and suggest experimental approaches to further validate and specialise the model for particular cell types. We also propose a reduced conceptual model implementing the logic of the decision process. This analysis gives specific predictions regarding cross-talks between the three pathways, as well as the transient role of RIP1 protein in necrosis, and confirms the phenotypes of novel perturbations. Our wild type and mutant simulations provide novel insights to restore apoptosis in defective cells. The model analysis expands our understanding of how cell fate decision is made. Moreover, our current model can be used to assess contradictory or controversial data from the literature. Ultimately, it constitutes a valuable reasoning tool to delineate novel experiments.

Boolean models



Boolean models

- › Fixed points
- › Depending on input values
- › Can be stochastic (update mode)
- › Possible phenotypes (cell fates)

	naïve	survival	apoptosis	necrosis
Survival	○○○○○○	●●●●●●	○○○○○○○○	○○○○○○○○
Apoptosis	○○○○○○	○○○○○○	●●●●●●●●	○○○○○○○○
NonACD	○○○○○○	○○○○○○	○○○○○○○○	●●●●●●●●
cFLIP	○○○○○○	●●●●●●	○○○○○○○○	○○○○○○○○
CASP3	○○○○○○	○○○○○○	●●●●●●●●	○○○○○○○○
Apoptosome	○○○○○○	○○○○○○	●●●●●●●●	○○○○○○○○
XIAP	○○○○○○	●●●●●●	○○○○○○○○	○○○○○○○○
Cyt_c	○○○○○○	○○○○○○	●●●●●●●●	●●●●●●●●
cIAP	○●○●●○●	●●●●●●	○○○○○○○○	○○○○○○○○
SMAC	○○○○○○	○○○○○○	●●●●●●●●	●●●●●●●●
MOMP	○○○○○○	○○○○○○	●●●●●●●●	●●●●●●●●
MPT	○○○○○○	○○○○○○	○○○○○○○○	●●●●●●●●
ATP	●●●●●●	●●●●●●	●●●●●●●●	○○○○○○○○
ROS	○○○○○○	○○○○○○	○○○○○○○○	●●●●●●●●
Bcl2	○○○○○○	●●●●●●	○○○○○○○○	○○○○○○○○
Bax	○○○○○○	○○○○○○	●●●●●●●●	○○○○●●●●
CASP8	○○○○○○	○○○○○○	●●●●●●●●	○○○○●●●●
NFkB	○○○○○○	●●●●●●	○○○○○○○○	○○○○○○○○
IKK	○○○○○○	●●●●●●	○○○○○○○○	○○○○○○○○
RIP1K	○○○○○○	●●●●●●	○○○○○○○○	○●○●○○○○
RIP1ub	○○○○○○	●●●●●●	○○○○○○○○	○○○○○○○○
RIP1	○○○○○○	●●●●●●	○○○○○○○○	○●○●○○○○
FADD	○○○○●●	○○○○●●	○○○●●●●●●	○○○●●●●●●
DISC-FAS	○○○○○○	○○●●●●	○○○○○●●●	○○○○●●●●
DISC-TNF	○○○○○○	○●●●●●	○○○●●●●●●	○○○●●●●●●
TNFR	○○○○○○	●●●●●●	○●○●○●●●	○●○●○●●●
TNF	○○○○○○	●●●●●●	○●○●○●●●	○●○●○●●●
FASL	○●●●○○	●●●●●●	○●○●○●●●	○●●●○●●●

Calzone et al, 2010

Boolean models

Name	Modified rules	Expected phenotypes	Qualitative results
Anti-oxidant	$\text{ROS}' = (\text{RIP1 OR MPT})$	Prediction.	Suppression of NF κ B anti-oxidant effect leads to no change in the decision process.
<i>APAF1</i> deletion	$\text{C3}' = 0$	<i>APAF1</i> ^{-/-} mouse thymocytes are not impaired in FAS-mediated apoptosis ([71]).	Apoptosis disappears and replaced by the naive state. Necrosis and survival are close to the wild type case situations.
<i>BAX</i> deletion	$\text{MOMP}' = \text{MPT}$	<i>BAX</i> deletion blocks FAS or TNF+CHX - induced apoptosis in some cell lines, such as HCT116 [72].	<i>BAX</i> deletion prevents apoptosis.
<i>BCL2</i> over-expression	$\text{MOMP}' = \text{MPT}$ $\text{MPT}' = 0$	FAS induces the activation of NF κ B pathway [29].	As expected, the survival and naive attractors are preserved while both death pathways are inhibited.
<i>CASP8</i> deletion	$\text{C8}' = 0$	<i>Caspase-8</i> deficient MEFs [41] or Jurkat cells [42] are resistant to FAS-mediated apoptotic cell death.	Apoptosis disappears. Compared to the wild type, a slight increase of necrosis is observed, while survival becomes the main cell fate.
constitutively activated <i>CASP8</i>	$\text{C8}' = 1$	Prediction.	Over-expression of caspase-8 leads to a loss of NF κ B activation.
<i>cFLIP</i> deletion	$\text{C8}' = \text{TNF OR FAS OR C3}$	<i>cFLIP</i> ^{-/-} MEFs are highly sensitive to FASL and TNF [73].	The increase of apoptosis is effectively observed in the <i>cFLIP</i> mutant; furthermore survival can no longer be sustained.
<i>cIAP</i> deletion	$\text{cIAP}' = 0$	NF κ B activation in response to TNF is blocked [53].	NF κ B activation is impaired, and only the apoptotic and necrotic attractors can be reached.
<i>FADD</i> deletion	$\text{C8}' = \text{C3 AND NOT NF}\kappa\text{B}$ $\text{RIP1}' = \text{NOT C8 AND TNF}$	<i>FADD</i> ^{-/-} mouse thymocytes are resistant to FAS mediated apoptosis [74]. <i>FADD</i> ^{-/-} MEFs are resistant to FASL and TNF [75]. In Jurkat cells treated with TNF+CHX, apoptosis is turned into necrosis [43].	FASL signalling is blocked and the 'naive' attractor is the only reachable one. In response to TNF, apoptosis disappears.
<i>NFκB</i> deletion	$\text{NF}\kappa\text{B}' = 0$	TNF induces both apoptosis and necrosis in $\text{NF-}\kappa\text{B p}65^{-/-}$ cells [76] or in $\text{IKK}\beta^{-/-}$ fibroblasts [35].	This mutant shows a strong increase of necrosis (to be related with concomitant apoptosis/necrosis).
constitutively active NF κ B	$\text{NF}\kappa\text{B}' = 1$	Prediction.	Both death pathways are shut down in this mutant.
<i>RIP1</i> deletion	$\text{RIP1}' = 0$	<i>RIPK1</i> ^{-/-} MEFs are hypersensitivity to TNF, no TNF-induced NF κ B activation, [77].	Both survival and necrosis states become unreachable. The effect of RIP1 silencing leads to a complete loss of the decision process (apoptosis becoming the only outcome).

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](#) 

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

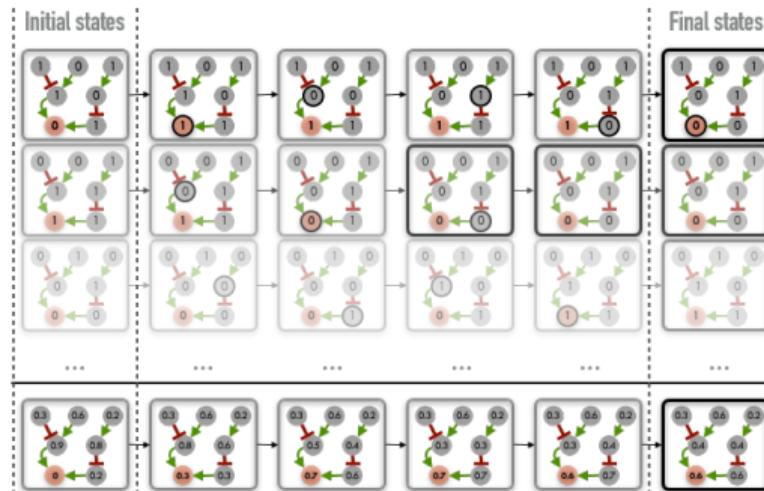
⇒ Fills the gap between ODE and Boolean modeling

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



Béas et al, 2019

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

- ⇒ We obtain probabilities per state over time

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

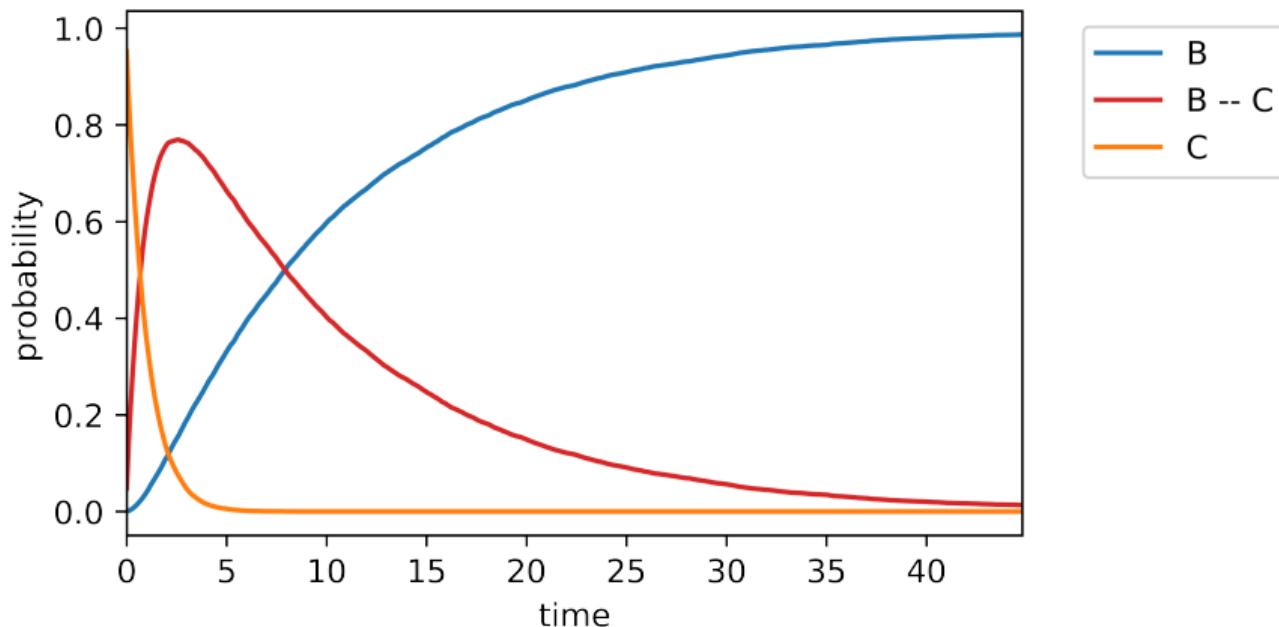
› Simulation settings : CFG file

- › 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;
```

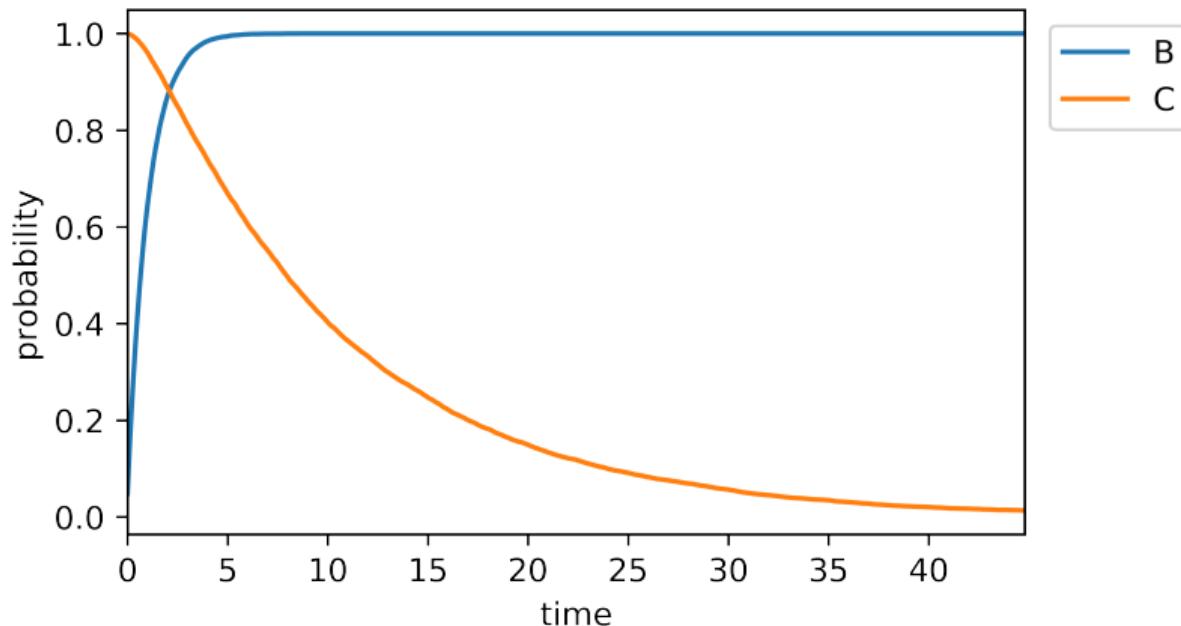
MaBoSS : Continuous time boolean modelling

- State probability trajectories



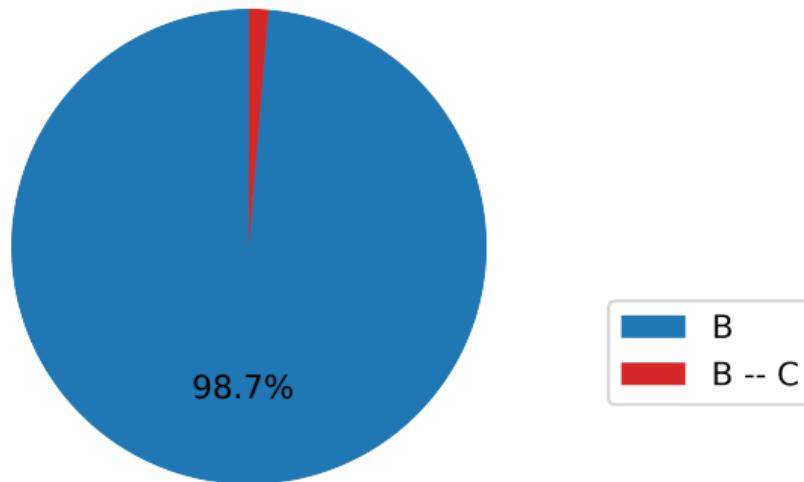
MaBoSS : Continuous time boolean modelling

- › Node probability trajectories



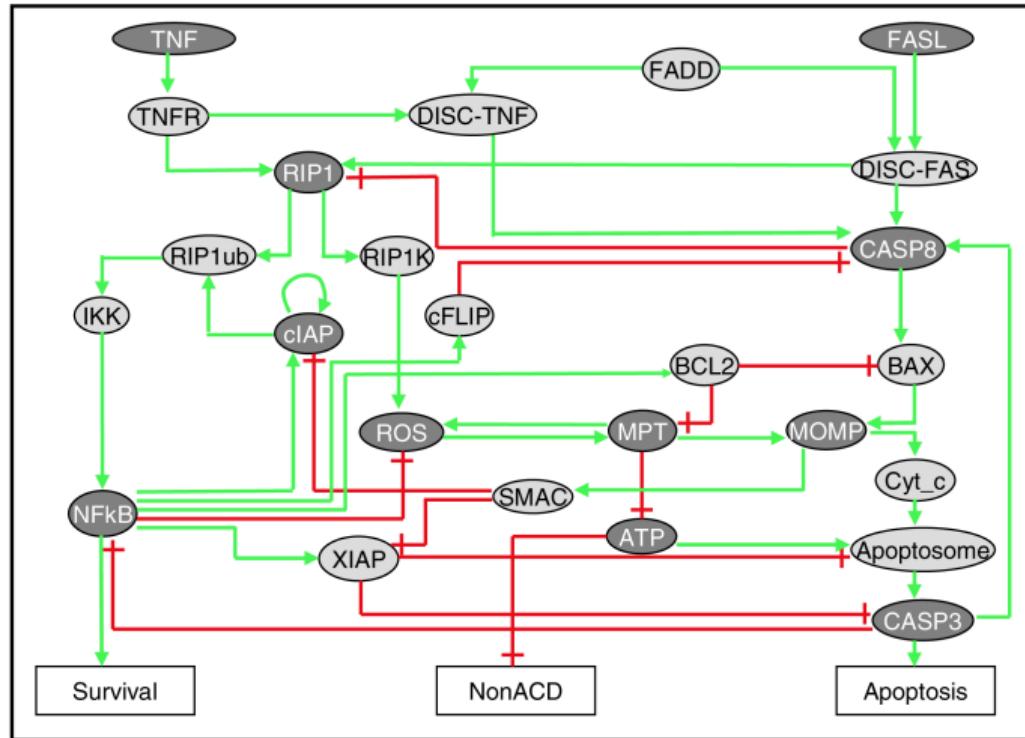
MaBoSS : Continuous time boolean modelling

- › Final (\neq steady) state distribution



MaBoSS : Continuous time boolean modelling

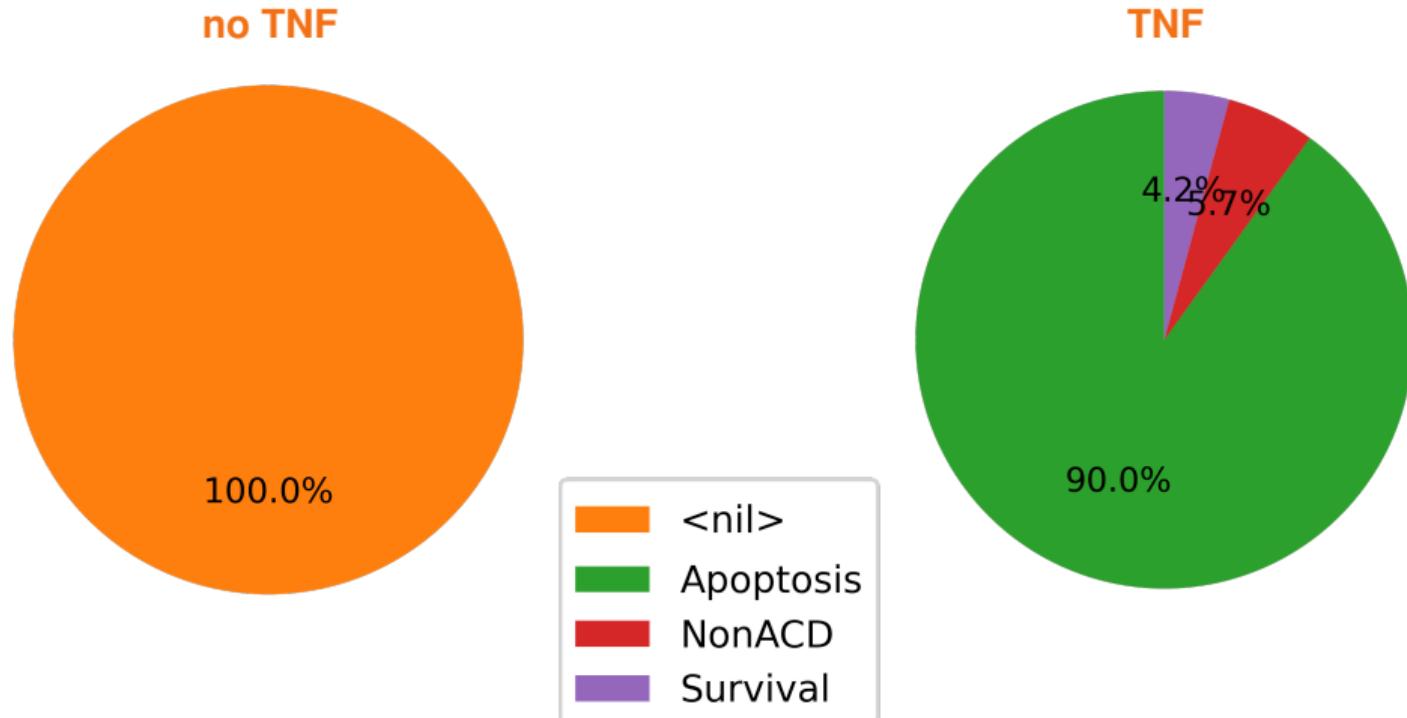
› Cell fate model



Calzone et al, 2010

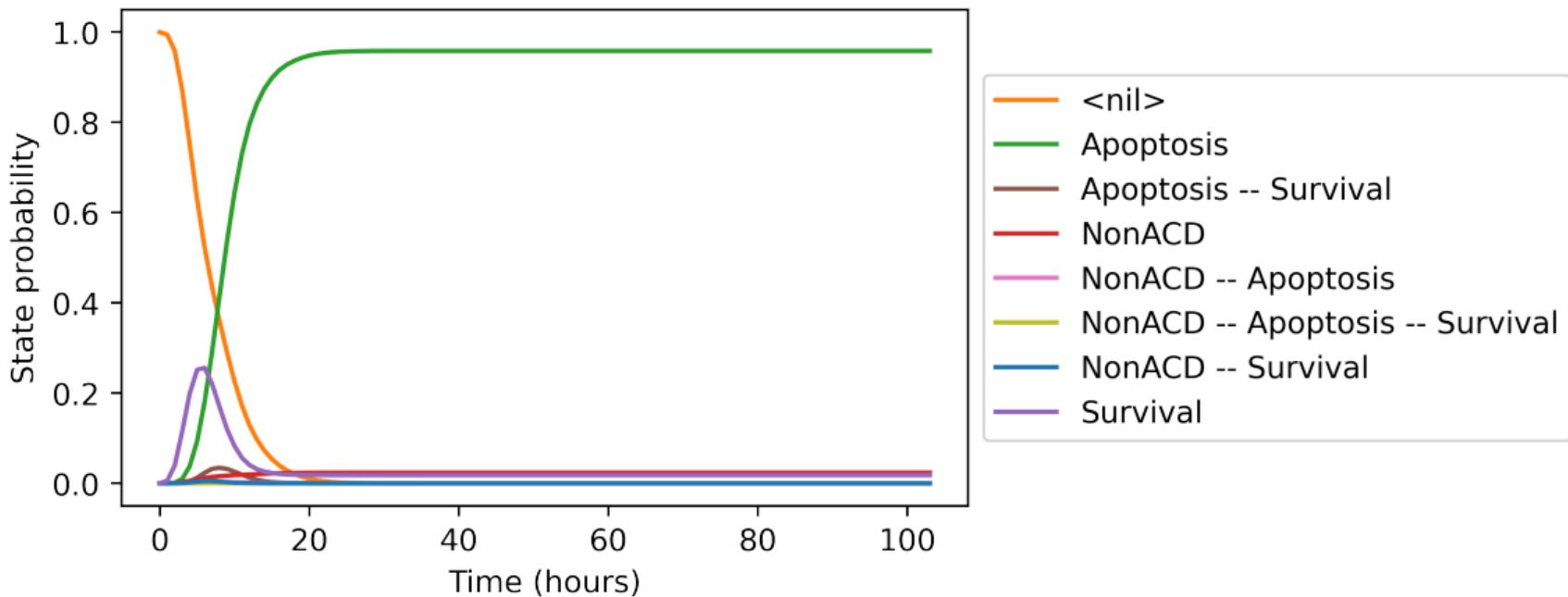
MaBoSS : Continuous time boolean modelling

› Cell fate model



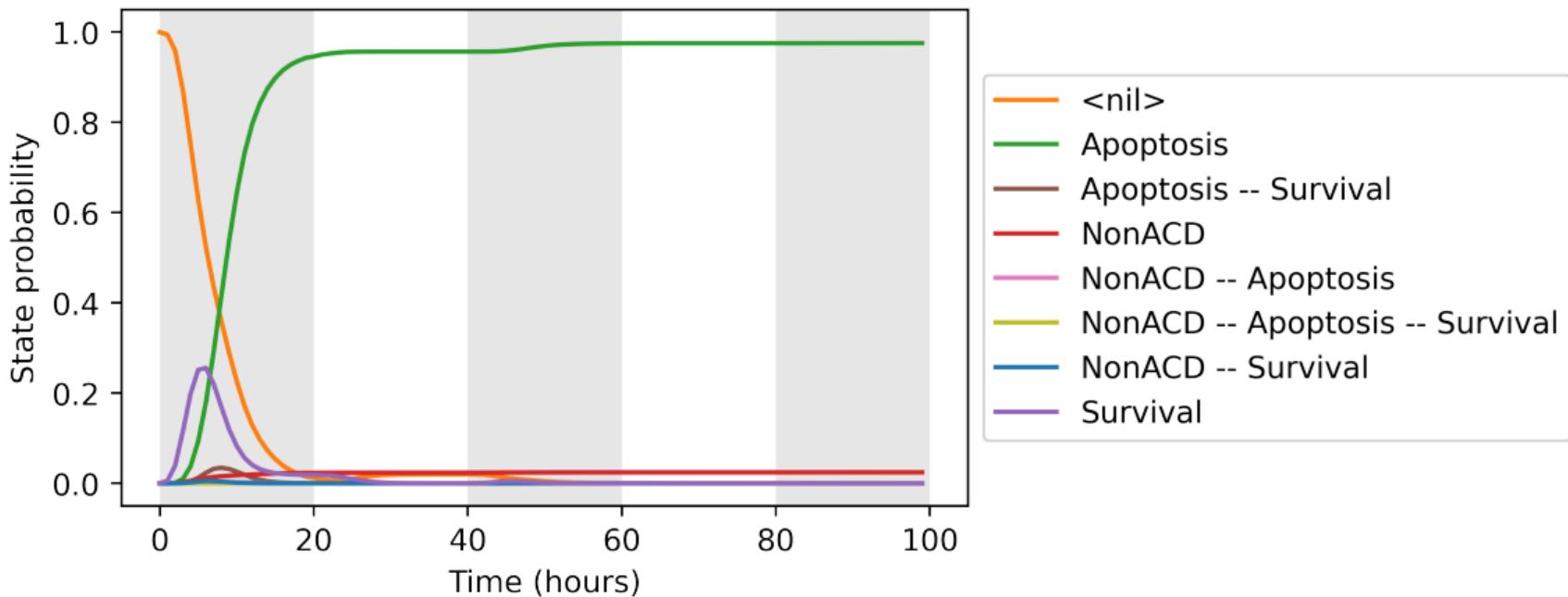
MaBoSS : Continuous time boolean modelling

› Cell fate model

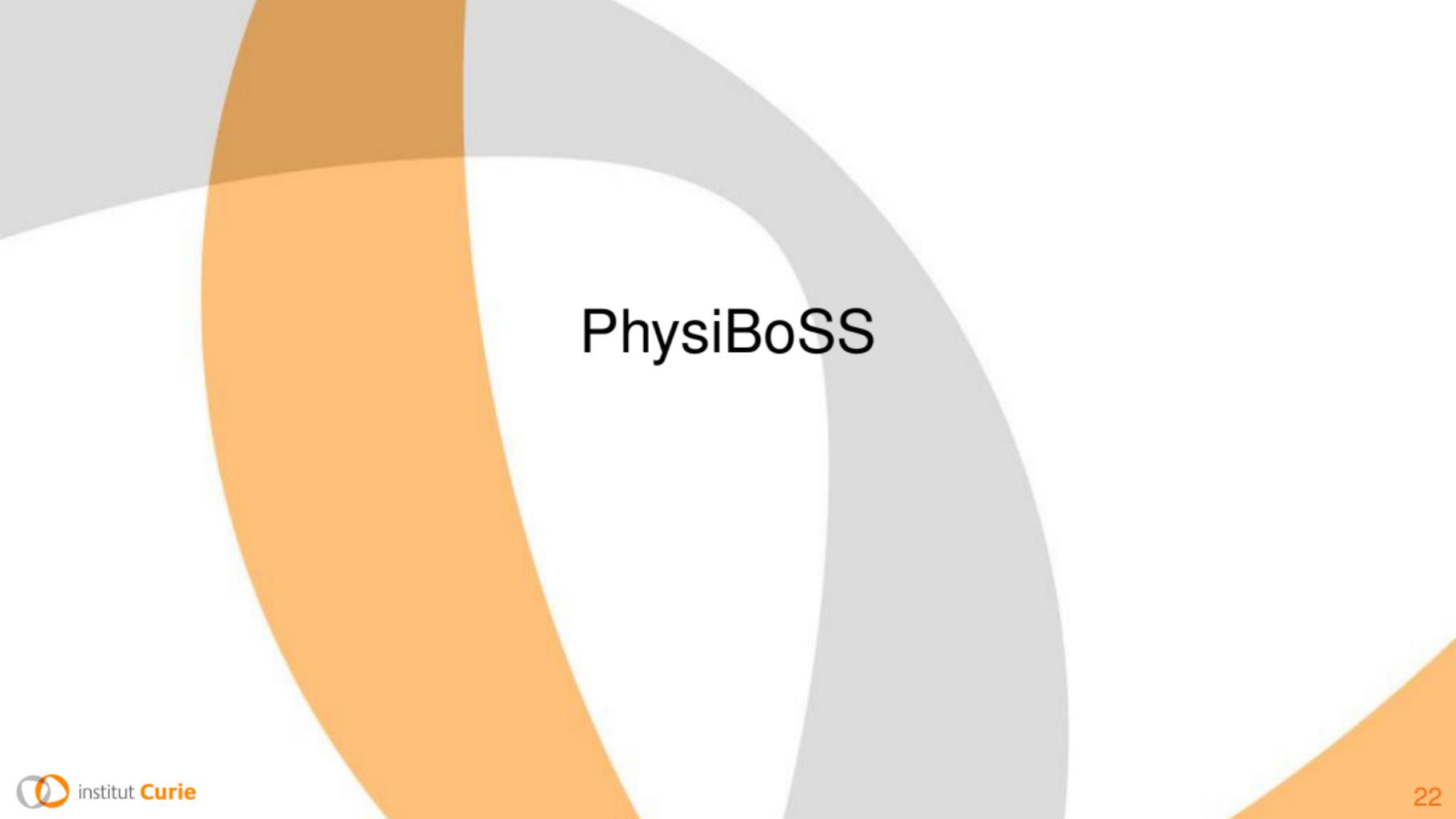


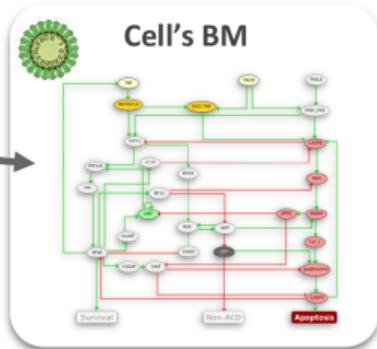
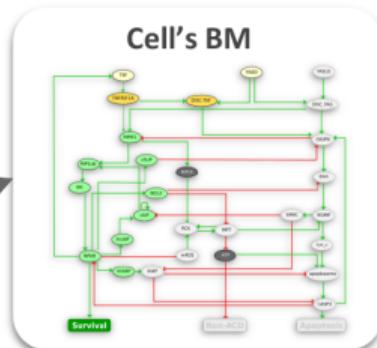
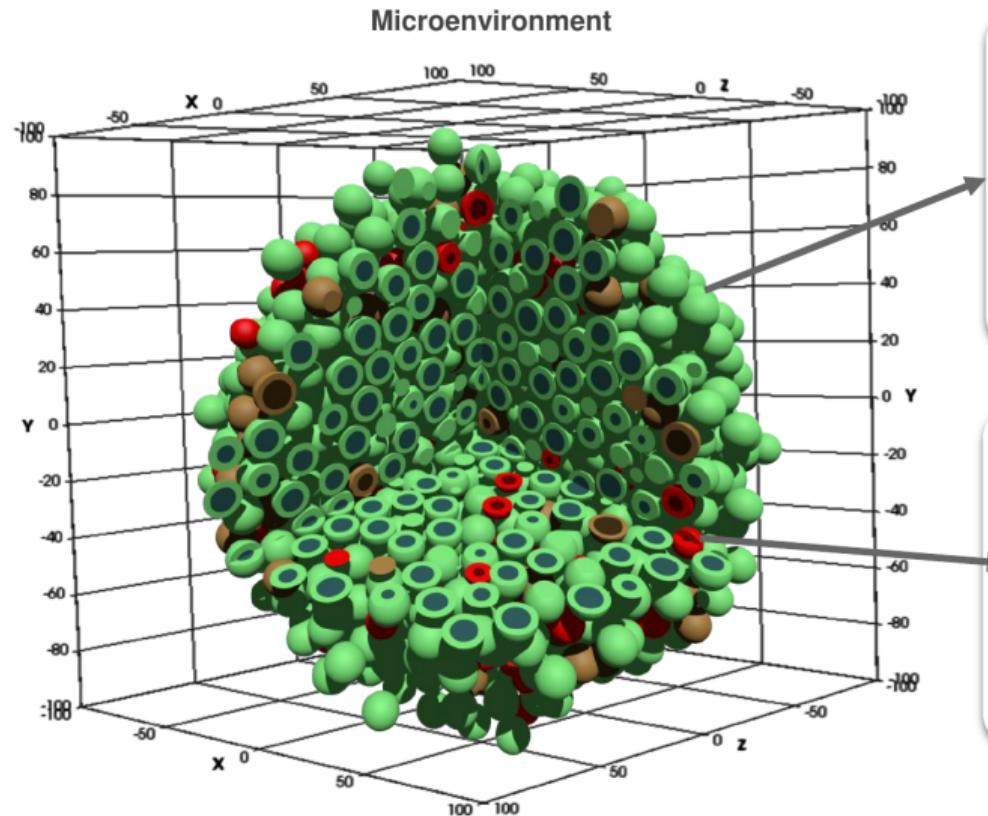
MaBoSS : Continuous time boolean modelling

› Cell fate model



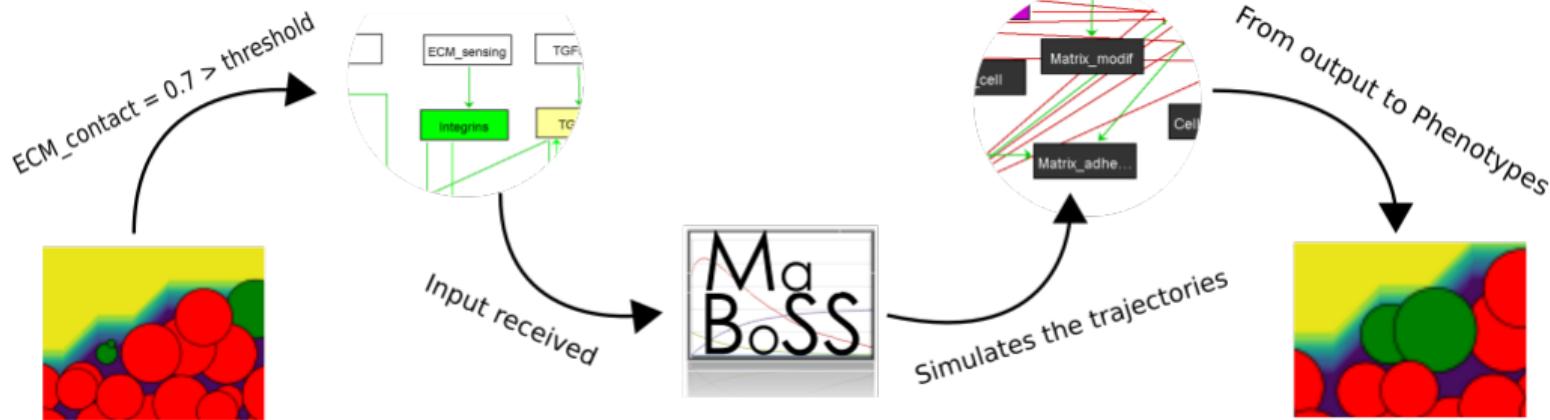
PhysiBoSS





Ponce de Leon et al, in preparation

PhysiBoSS



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

PhysiBoSS

- › Model definition (MaBoSS BND and CFG files)
- › Intracellular dt
- › Scaling, time stochasticity, ...
- › Initial values
- › Mapping
- › Parameter values

```
<phenotype>
...
<intracellular type="maboss">
  <bnd_filename>./data/model_0.bnd</bnd_filename>
  <cfg_filename>./data/model.cfg</cfg_filename>
  <settings>
    <intracellular_dt>1</intracellular_dt>
    <time_stochasticity>0.1</time_stochasticity>
    <scaling>1.0</scaling>
    <parameters>
      <parameter intracellular_name="$time_scale">0.0</parameter>
    </parameters>
  </settings>
  <initial_values>
    <initial_value intracellular_name="A">1</initial_value>
    <initial_value intracellular_name="C">0</initial_value>
  </initial_values>
  <mapping>
    <input physicell_name="oxygen" intracellular_name="A">
      <settings>
        <action>inhibition</action>
        <threshold>10</threshold>
        <inact_threshold>10</inact_threshold>
      </settings>
    </input>
    <output physicell_name="apoptosis" intracellular_name="C">
      <settings>
        <action>activation</action>
        <value>5</value>
        <base_value>0</base_value>
        <smoothing>5</smoothing>
      </settings>
    </output>
  </mapping>
</intracellular>
...
</phenotype>
```

PhysiBoSS

Inputs : Signals to MaBoSS nodes

- › Oxygen inhibits the node A
- › The node A will be
 - › inactive when oxygen > 10
 - › active when oxygen < 10

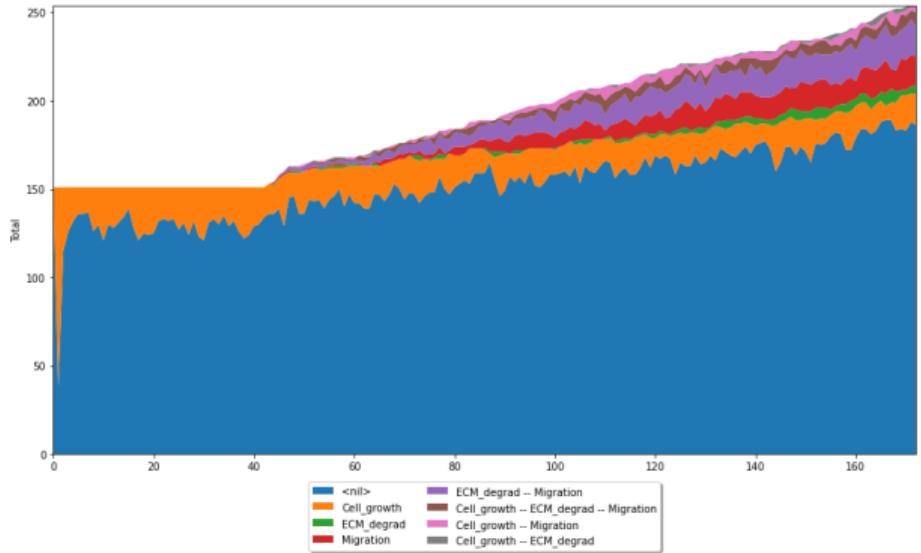
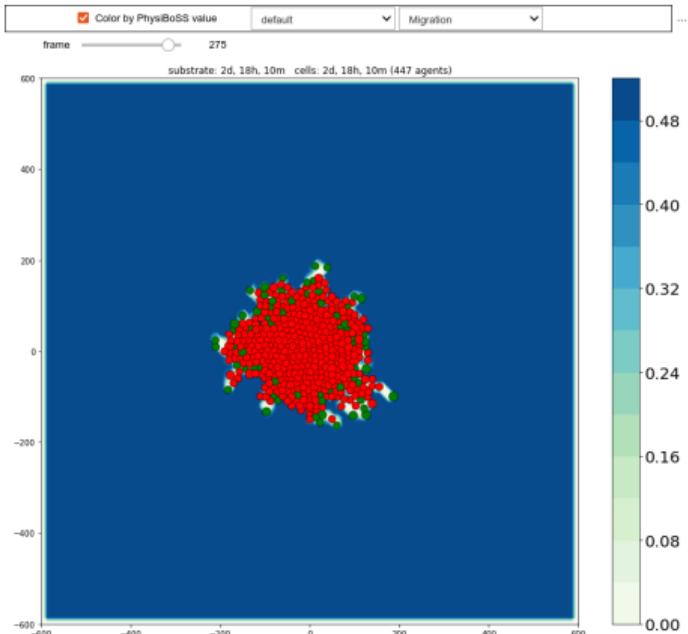
```
<input physicell_name="oxygen" intracellular_name="A">
  <settings>
    <action>inhibition</action>
    <threshold>10</threshold>
    <inact_threshold>10</inact_threshold>
  </settings>
</input>
```

Outputs : MaBoSS nodes to Behaviours

- › node C activates Apoptosis
- › The apoptosis rate will be set to :
 - › 5 if the node C is active
 - › 0 if the node C is inactive
- › The apoptosis rate will take 5 dt to reach 5

```
<output physicell_name="apoptosis" intracellular_name="C">
  <settings>
    <action>activation</action>
    <value>5</value>
    <base_value>0</base_value>
    <smoothing>5</smoothing>
  </settings>
</output>
```

PhysiBoSS



<https://github.com/sysbio-curie/PhysiCell-Jupyter-GUI>

Config Basics Microenvironment Cell Types User Params Run Plot Legend

New Copy Delete

--- Cell Type ---

- default**
- other
- another
- yet_another
- yet_yet_another
- last_one

Intracellular

Type: boolean

MaBoSS BND file: ./data/model_0.bnd | Choose BND file

MaBoSS CFG file: ./data/model.cfg | Choose CFG file

Time step: 1

Scaling: 1.0

Time stochasticity:

Initial states

Node	Value	Delete
A	1	Delete
C	0	Delete

Add new initial value

Mutants

Node	Value
------	-------

Add new mutant

Parameters

Name	Value
------	-------

Add new parameter

Inputs

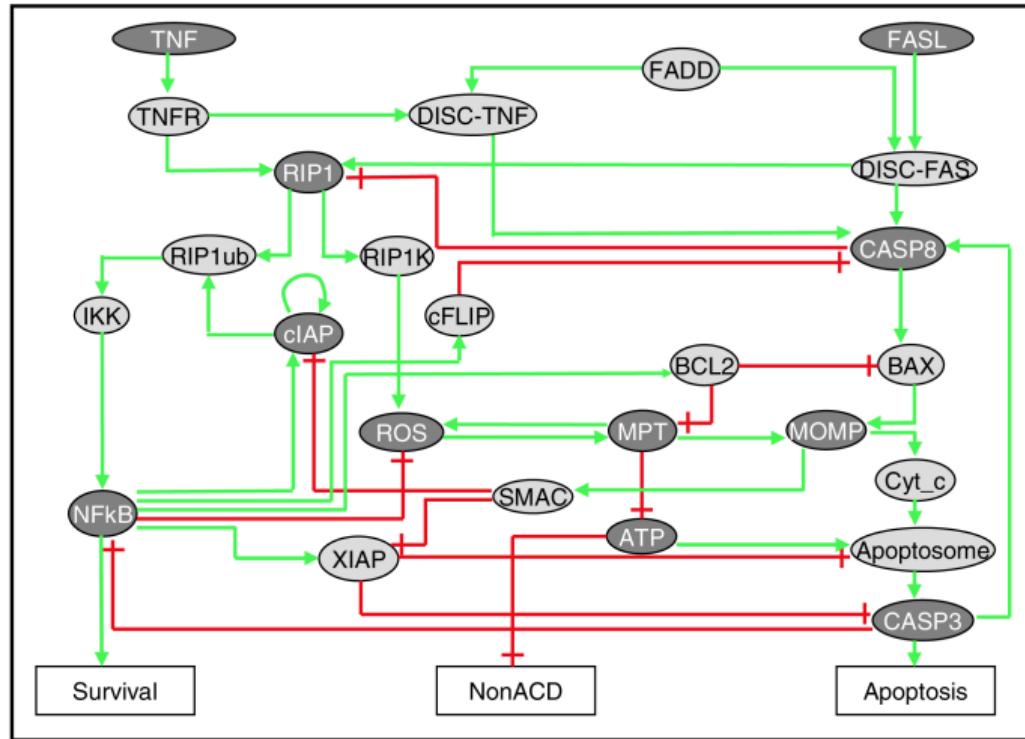
Signal	Action	Node	Threshold	Inact. Threshold	Smoothing
oxygen	inhibition	A	10	10	0

Add new input

Outputs

Signal	Action	Node	Value	Base_value	Smoothing
apoptosis	activation	C	5	0	5

Add new output



PhysiBoSS: a multi-scale agent-based modelling framework integrating physical dimension and cell signalling

Gaëlle Letort , Arnaud Montagud, Gautier Stoll, Randy Heiland, Emmanuel Barillot, Paul Macklin, Andrei Zinovyev, Laurence Calzone 

Bioinformatics, Volume 35, Issue 7, 01 April 2019, Pages 1188–1196, <https://doi.org/10.1093/bioinformatics/bty766>

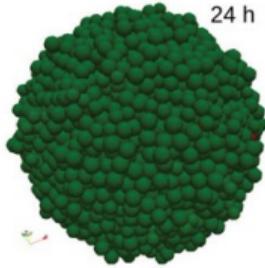
Published: 30 August 2018 **Article history ▾**



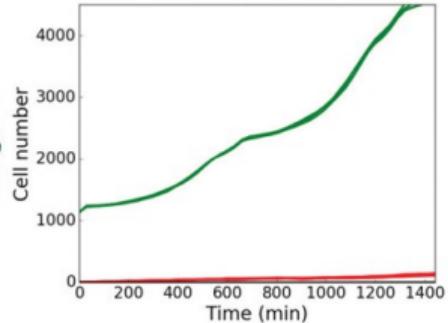
Gaëlle Letort

PhysiBoSS

A



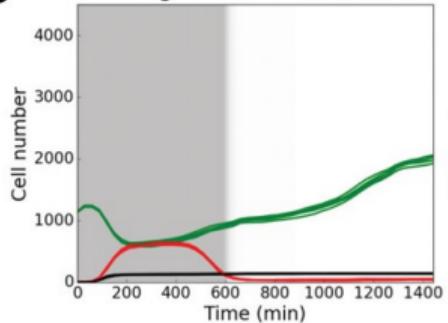
no TNF



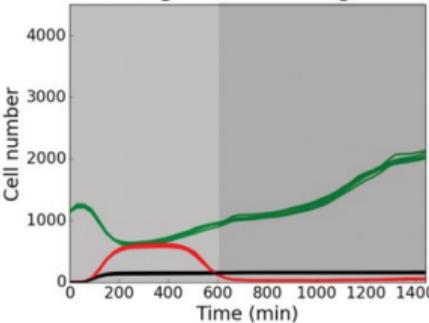
C

0.5 ng/mL

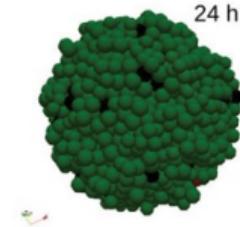
0



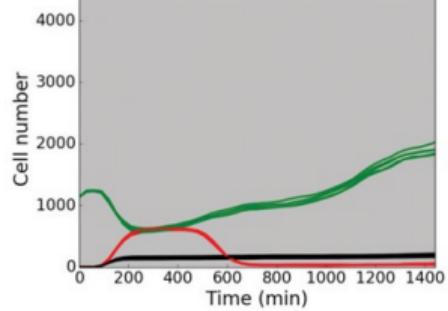
0.5 ng/mL
5 ng/mL



B

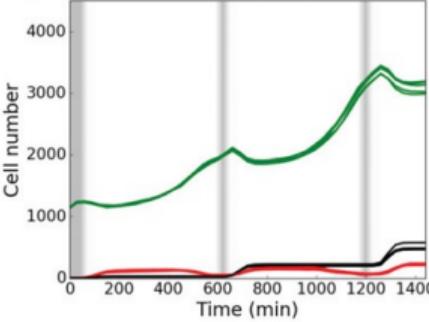
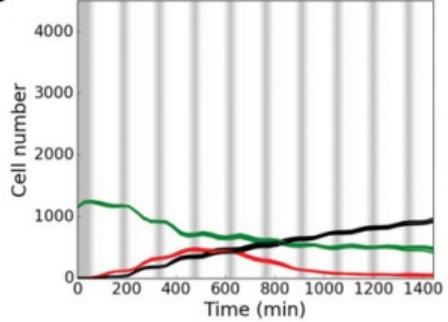


0.5 ng/mL



D

one pulse = 0.5 ng/mL, 10 min



Letort et al, 2019

ORIGINAL RESEARCH article

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Optimizing Dosage-Specific Treatments in a Multi-Scale Model of a Tumor Growth



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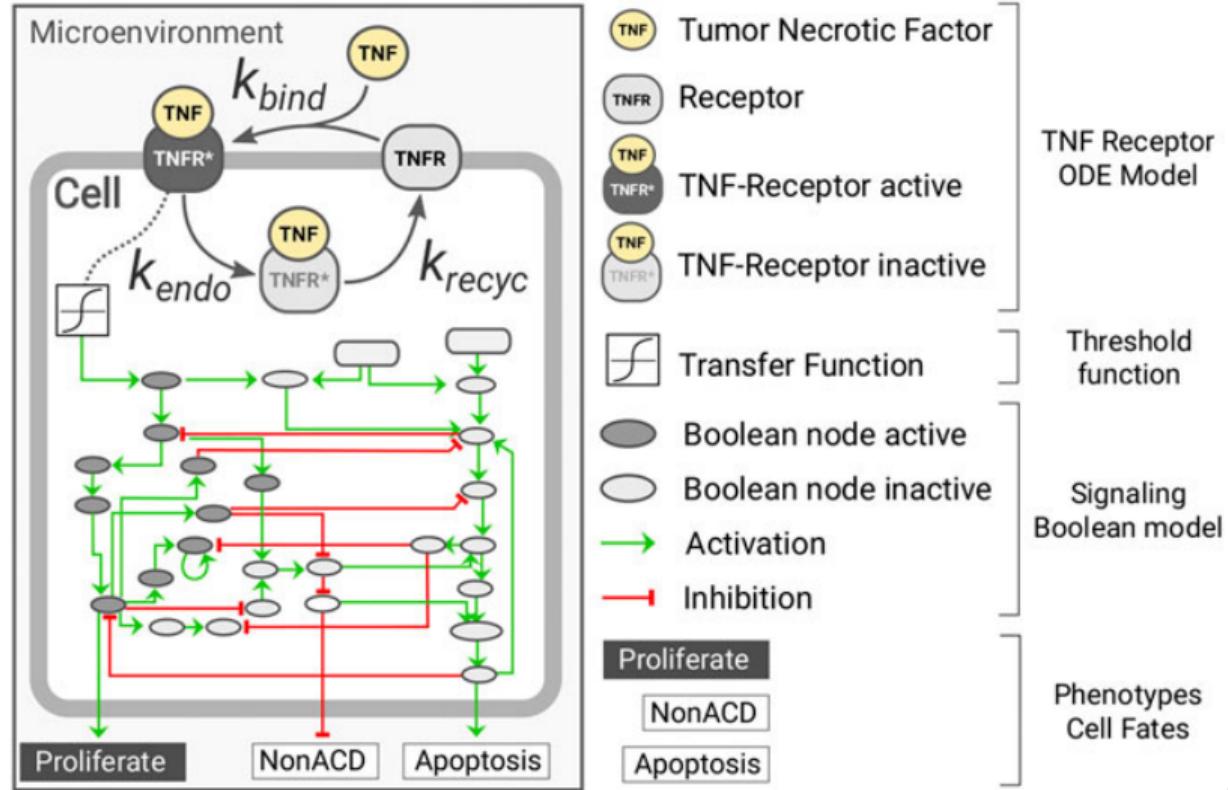
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Miguel Ponce de Leon

PhysiBoSS



Ponce de Leon et al., 2019

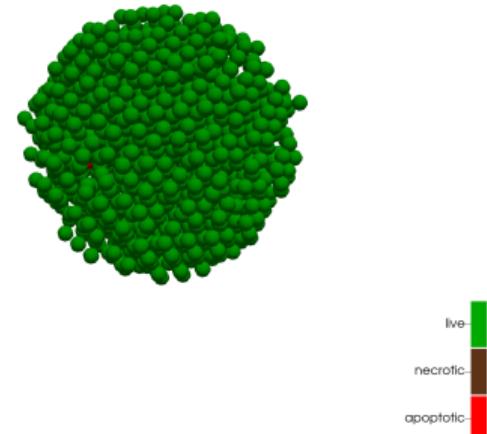
PhysiBoSS

Goals:

- › Develop a simple model of TNF treatment
- › Only boolean
- › Using PhysiBoSS 2.0

TNF model

- › PhysiCell model of spheroid
- › Simple model of tumor spheroid
- › Exponential growth
- › template, spheroid 3D, physiboss-cell-lines



TNF model

- › PhysiCell model of spheroid

From template

- › Latest version of main.cpp and custom.cpp
- › Building Signals and Behaviors dictionaries

custom.cpp

```
void create_cell_types( void )
{
    // set the random seed
    SeedRandom( parameters.ints("random_seed") );

    ...

    /*
     * This initializes cell signal and response dictionaries
     */

    setup_signal_behavior_dictionaries();

    ...

    /*
     * This builds the map of cell definitions and summarizes the setup.
     */

    display_cell_definitions( std::cout );

    return;
}
```

TNF model

- PhysiCell model of spheroid

From spheroid 3D

- Cell definition

- Create sphere

- Controlled by user param

custom.cpp

```
void setup_tissue( void )
{
    // place a cluster of tumor cells at the center
    double cell_radius = cell_defaults.phenotype.geometry.radius;
    double cell_spacing = 0.95 * 2.0 * cell_radius;

    double tumor_radius = parameters.doubles( "tumor_radius" ); // 250.0;

    // Parameter<double> temp;

    int i = parameters.doubles.find_index( "tumor_radius" );

    Cell* pCell = NULL;

    std::vector<std::vector<double>> positions = create_cell_sphere_positions(cell_radius,tumor_radius);
    std::cout << "creating " << positions.size() << " closely-packed tumor cells ..." << std::endl;

    for( int i=0; i < positions.size(); i++ )
    {
        pCell = create_cell(); // tumor cell
        pCell->assign_position( positions[i] );
    }

    return;
}

std::vector<std::vector<double>> create_cell_sphere_positions(double cell_radius, double sphere_radius)
{
    std::vector<std::vector<double>> cells;
    int xc=0,yc=0,zc=0;
    double x_spacing= cell_radius*sqrt(3);
    double y_spacing= cell_radius*2;
    double z_spacing= cell_radius*sqrt(3);

    std::vector<double> tempPoint{3,0,0};
    // std::vector<double> cylinder_center(3,0.0);

    for(double z=-sphere_radius;z<sphere_radius;z+=z_spacing, zc++)
    {
        for(double x=-sphere_radius;x<sphere_radius;x+=x_spacing, xc++)
        {
            for(double y=-sphere_radius;y<sphere_radius;y+=y_spacing, yc++)
            {
                tempPoint[0]=x + (zc%2) * 0.5 * cell_radius;
                tempPoint[1]=y + (xc%2) * cell_radius;
                tempPoint[2]=z;

                if(sqrt(norm_squared(tempPoint))< sphere_radius)
                { cells.push_back(tempPoint); }
            }
        }
    }

    return cells;    You, now * Uncommitted changes
}
```

TNF model

- › PhysiCell model of spheroid

From PhysiBoSS cell lines

- › Makefile

Makefile

```
## MaBoSS configuration
# MaBoSS max nodes
ifndef MABOSS_MAX_NODES
MABOSS_MAX_NODES = 64
endif

# MaBoSS directory
MABOSS_DIR = addons/PhysiBoSS/MaBoSS-env-2.0/engine
CUR_DIR = $(shell pwd)
CUSTOM_DIR = sample_projects/Arnau_model/custom_modules

ifeq ($(OS), Windows_NT)
| LDL_FLAG = -ldl
endif

LIB := -L$(CUR_DIR)/$(MABOSS_DIR)/lib -lMaBoSS-static $(LDL_FLAG)
INC := -DADDON_PHYSIBOSS -I$(CUR_DIR)/$(MABOSS_DIR)/include -DMAXNODES=$(MABOSS_MAX_NODES)

# If max nodes > 64, change lib path
ifeq ($(shell expr $(MABOSS_MAX_NODES) '>' 64), 1)
LIB := -L$(CUR_DIR)/$(MABOSS_DIR)/lib -lMaBoSS_$(MABOSS_MAX_NODES)n-static $(LDL_FLAG)
endif
```

- › Export of intracellular data

main.cpp

```
char filename[1024];
sprintf( filename , "%s/initial" , PhysiCell_settings.folder.c_str() );
save_PhysiCell_to_MultiCellDS_v2( filename , microenvironment , PhysiCell_globals.current_time );

sprintf( filename , "%s/states_initial.csv" , PhysiCell_settings.folder.c_str());
MaBoSSIntracellular::save( filename, *PhysiCell::all_cells);
```

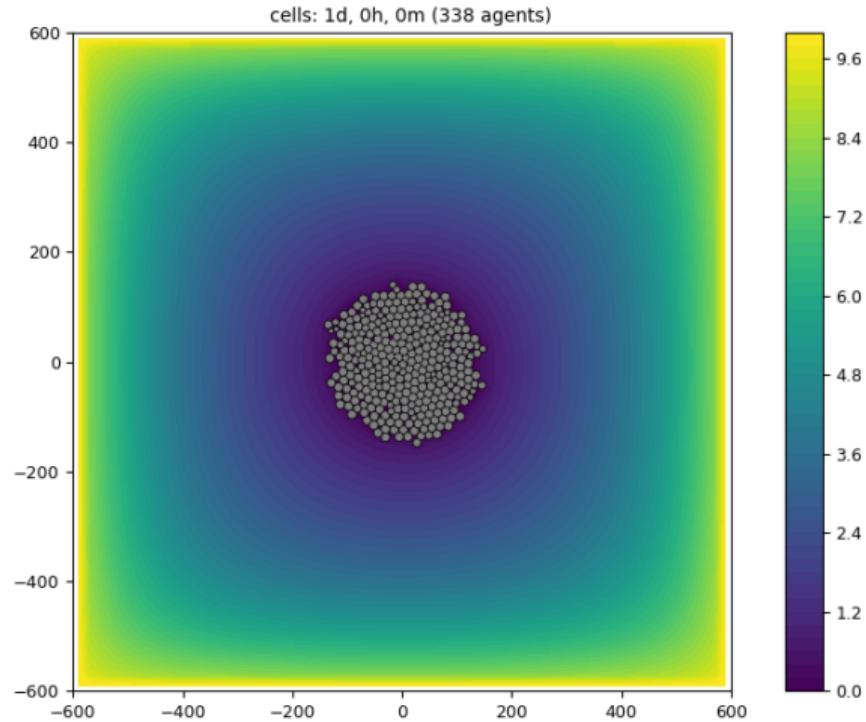
TNF model

› Adding TNF to the microenvironment

```
<microenvironment_setup>
    <variable ID="0" name="TNF" units="dimensionless">
        <physical_parameter_set>
            <diffusion_coefficient units="micron^2/min">1200.0</diffusion_coefficient>
            <decay_rate units="1/min">.0275</decay_rate>
        </physical_parameter_set>
        <initial_condition units="mmHg">0.0</initial_condition>
        <Dirichlet_boundary_condition enabled="True" units="mmHg">10.0</Dirichlet_boundary_condition>
        <Dirichlet_options>
            <boundary_value ID="xmin" enabled="True">10.0</boundary_value>
            <boundary_value ID="xmax" enabled="True">10.0</boundary_value>
            <boundary_value ID="ymin" enabled="True">10.0</boundary_value>
            <boundary_value ID="ymax" enabled="True">10.0</boundary_value>
            <boundary_value ID="zmin" enabled="True">10.0</boundary_value>
            <boundary_value ID="zmax" enabled="True">10.0</boundary_value>
        </Dirichlet_options>
    </variable>
```

TNF model

› Adding TNF to the microenvironment



TNF model

› Adding TNF to the microenvironment

```
int tnf_index = microenvironment.find_density_index("TNF");

if (PhysiCell_globals.current_time < 1000 && microenvironment.get_substrate_dirichlet_activation(tnf_index))
{
    microenvironment.set_substrate_dirichlet_activation(tnf_index, false);
}

if (parameters.bools("tnf_treatment")){
    if (PhysiCell_globals.current_time >= 1000 && PhysiCell_globals.current_time < 5320 && !microenvironment.get_substrate_dirichlet_activation(tnf_index))
    {
        std::cout << "TNF activation" << std::endl;
        microenvironment.set_substrate_dirichlet_activation(tnf_index, true);
    }
}
```

⇒ Activating TNF only after 1000min

TNF model

- › Adding the Boolean model

- › Boolean model

- › TNF concentration as input for TNF node

- › Apoptosis node triggers apoptosis

- › NonACD node triggers necrosis

```
<intracellular type="maboss">
  <bnd_filename>config/boolean_network/CellFateModel.bnd</bnd_filename>
  <cfg_filename>config/boolean_network/CellFateModel.cfg</cfg_filename>
  <settings>
    <intracellular_dt>1440.0</intracellular_dt>
    <time_stochasticity>0.0</time_stochasticity>
    <scaling>60.0</scaling>
  </settings>
  <mapping>
    <input intracellular_name="TNF" physicell_name="TNF">
      <settings>
        <action>activation</action>
        <threshold>0.01</threshold>
        <smoothing>0</smoothing>
      </settings>
    </input>
    <output intracellular_name="Apoptosis" physicell_name="apoptosis">
      <settings>
        <action>activation</action>
        <value>1000000</value>
        <base_value>0</base_value>
        <smoothing>0</smoothing>
      </settings>
    </output>
    <output intracellular_name="NonACD" physicell_name="necrosis">
      <settings>
        <action>activation</action>
        <value>1000000</value>
        <base_value>0</base_value>
        <smoothing>0</smoothing>
      </settings>
    </output>
  </mapping>
</intracellular>
```

TNF model

- › Choosing intracellular_dt

Short intracellular dt

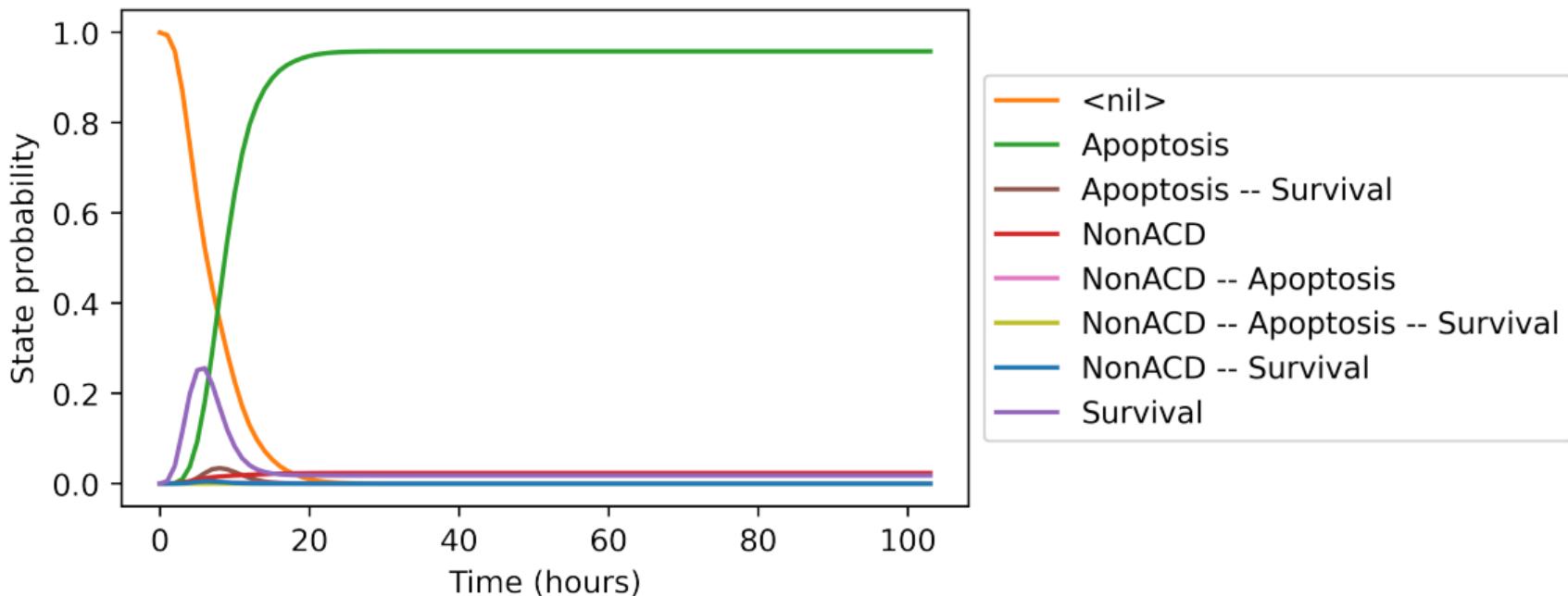
- › Integrate transient activation of some nodes
- › Needs a well curated model

Long intracellular dt

- › Wait for steady state of the model
- › Doesn't integrate possible issues with transient effects

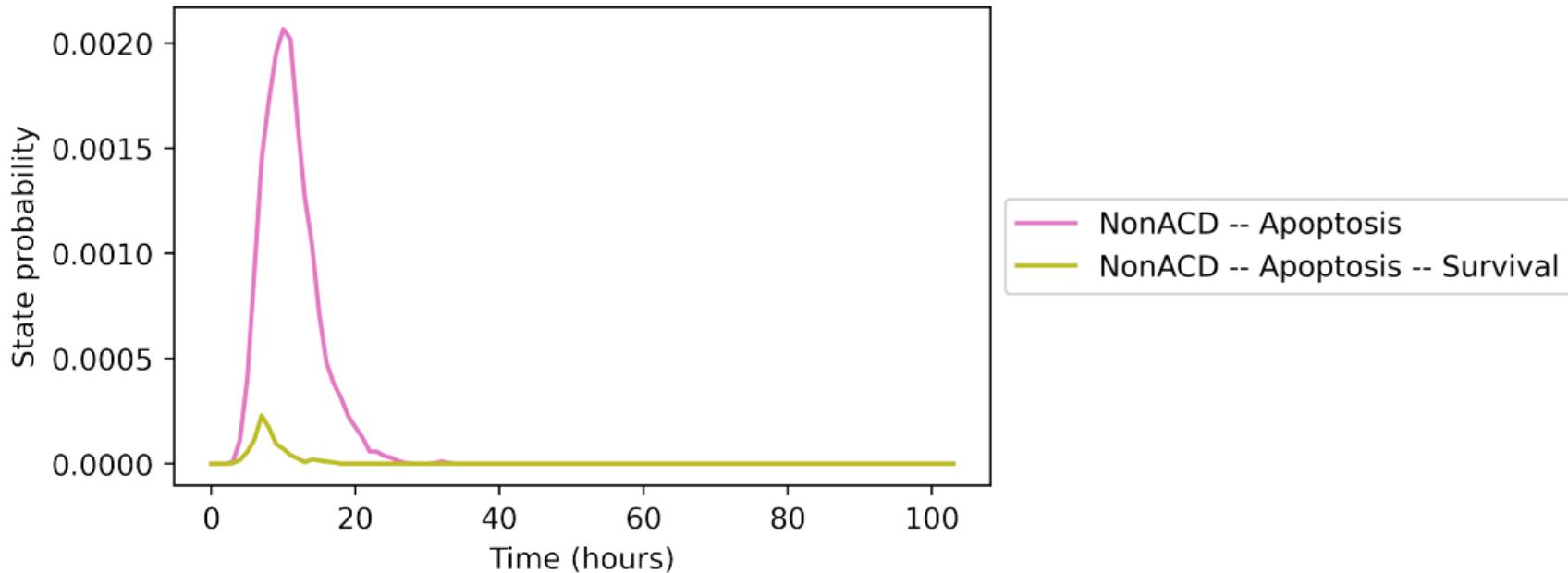
TNF model

- › Choosing intracellular_dt



TNF model

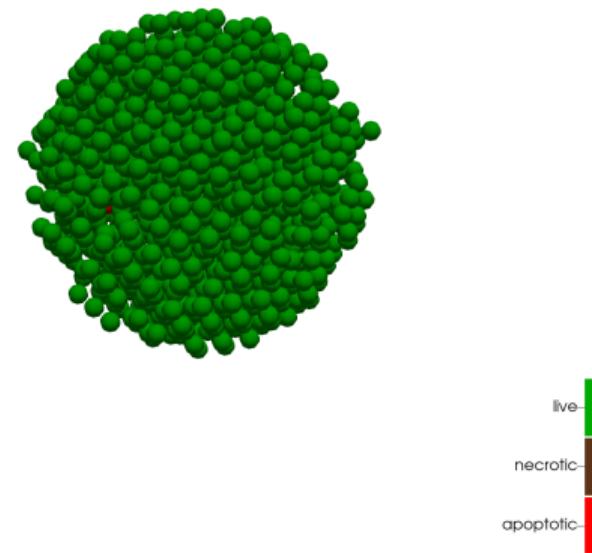
- Choosing intracellular_dt



⇒ To avoid NonACD – Apoptosis, we choose 24h

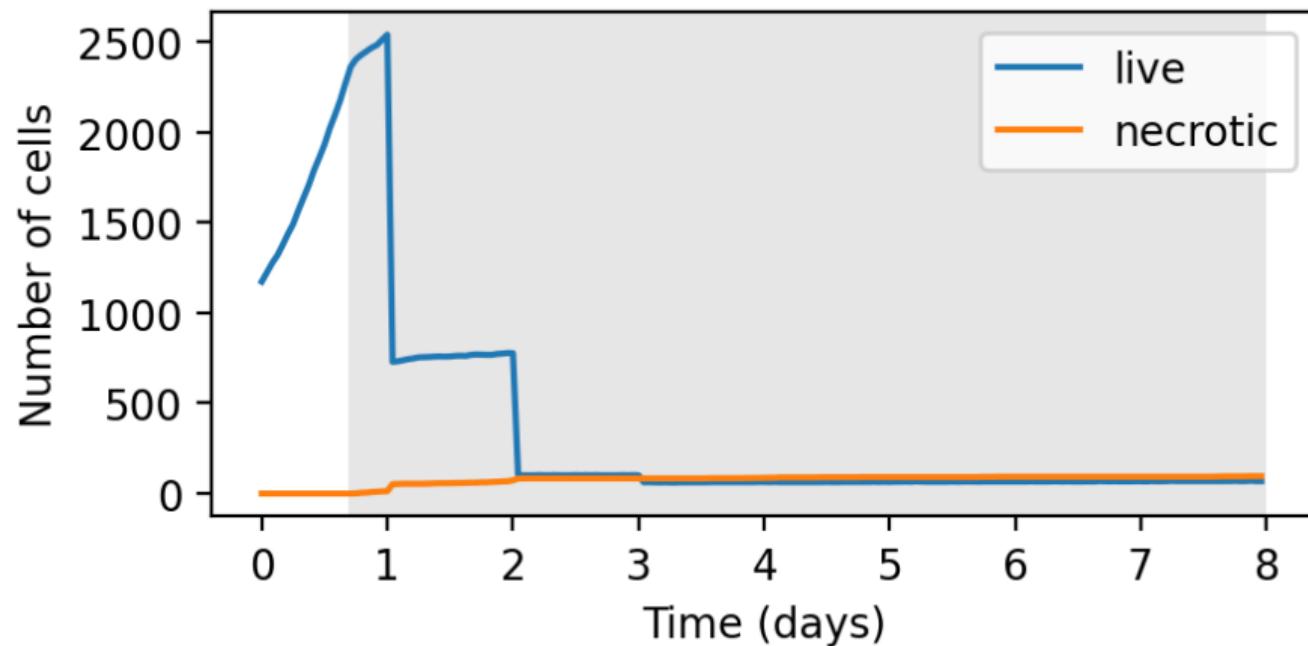
TNF model

› Results with constant TNF



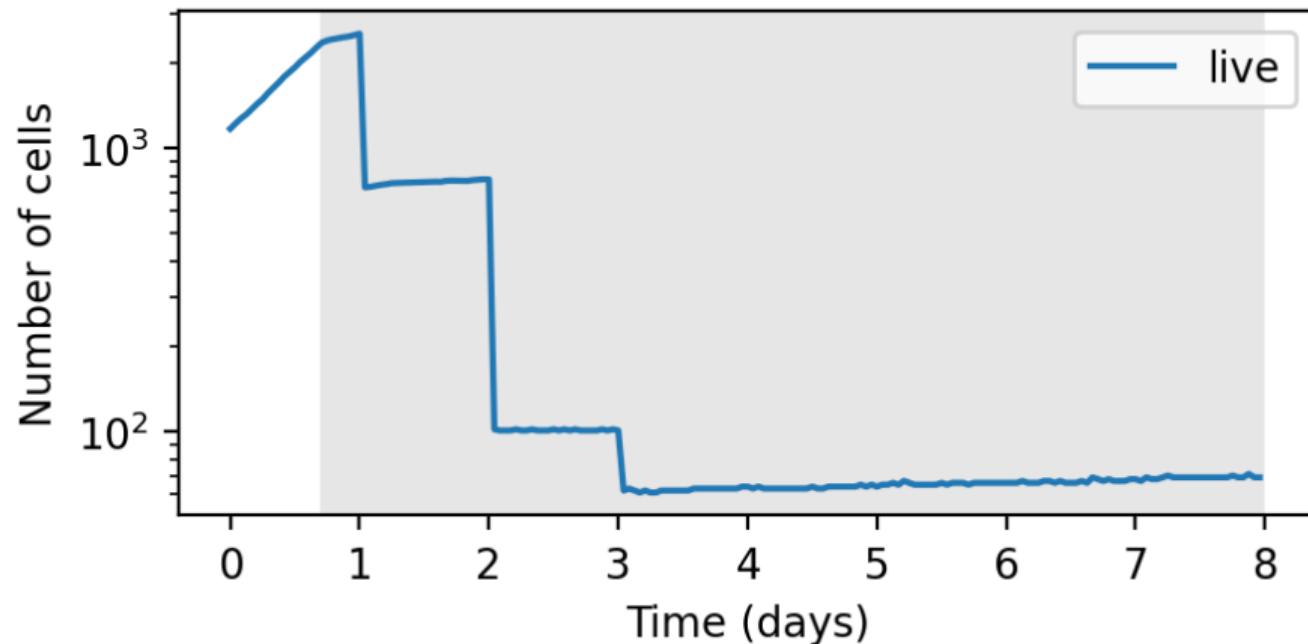
TNF model

› Results with constant TNF



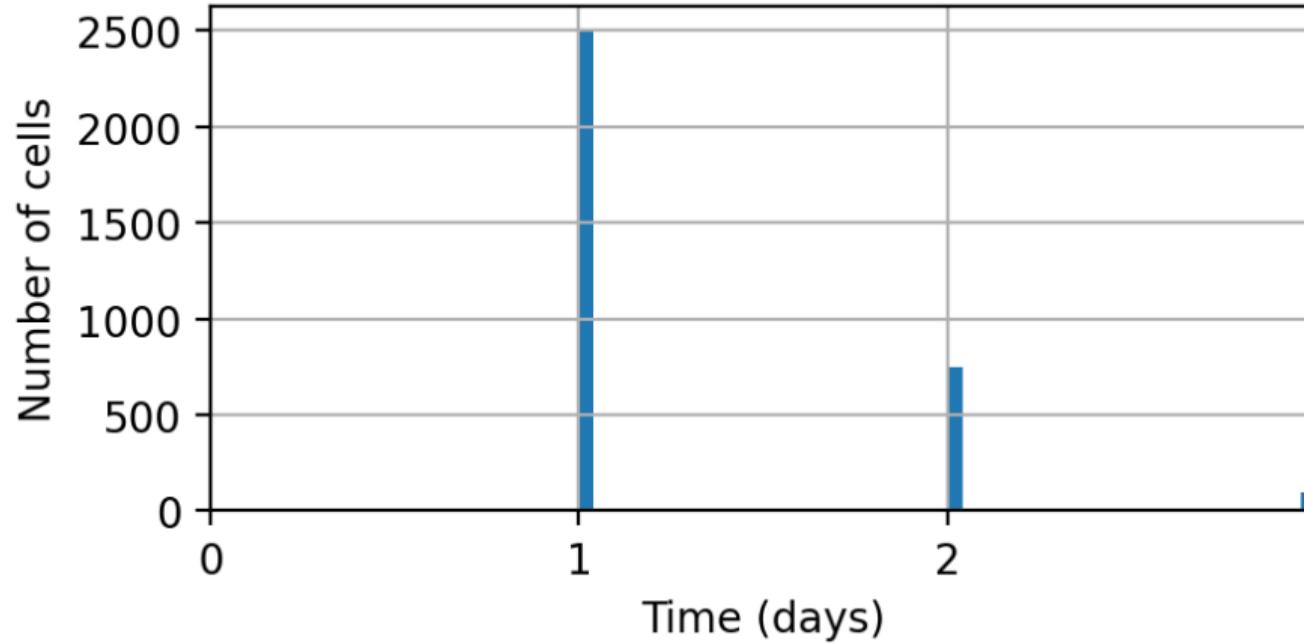
TNF model

› Results with constant TNF



TNF model

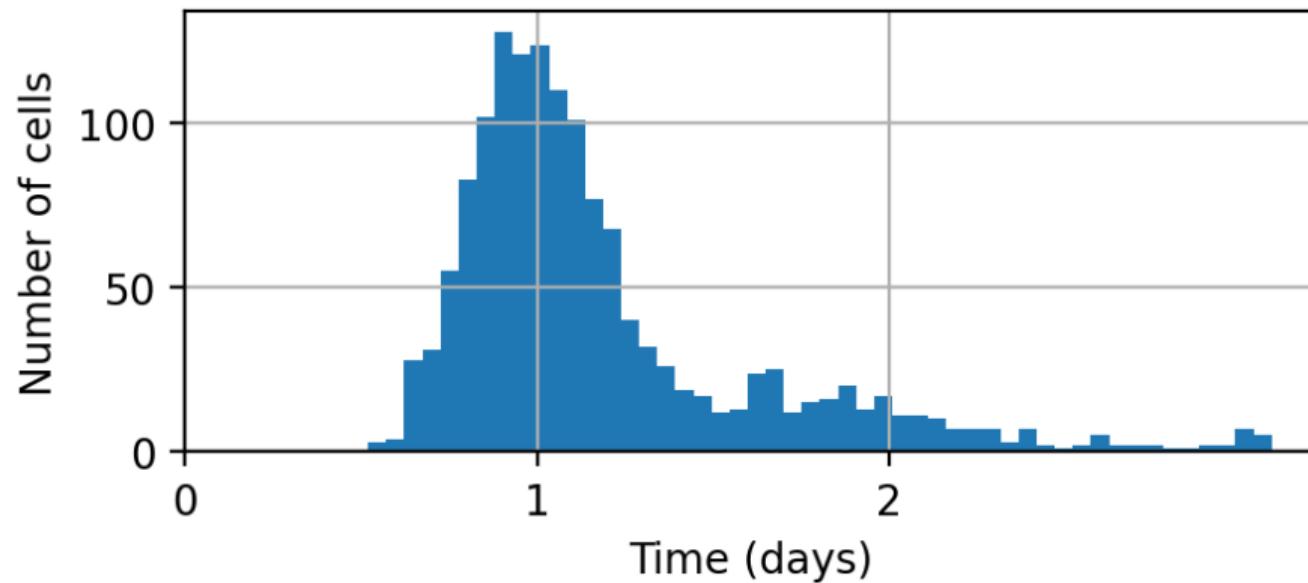
- › Time stochasticity



- › `time_stochasticity = 0.0`

TNF model

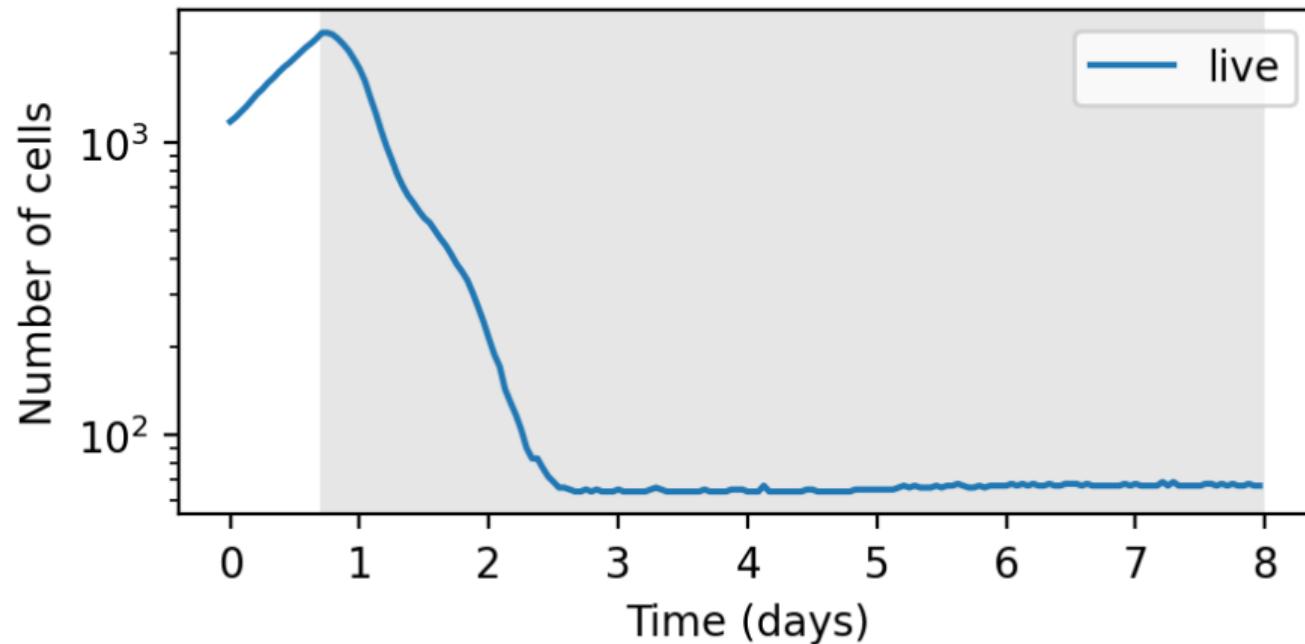
- › Time stochasticity



- › `time_stochasticity = 0.2`

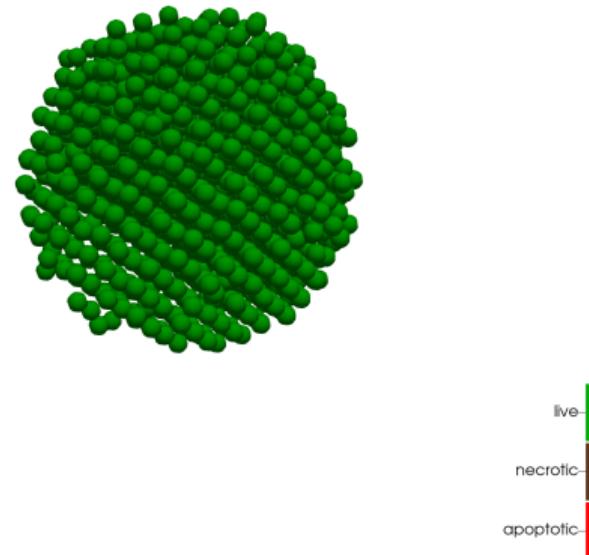
TNF model

- › Time stochasticity



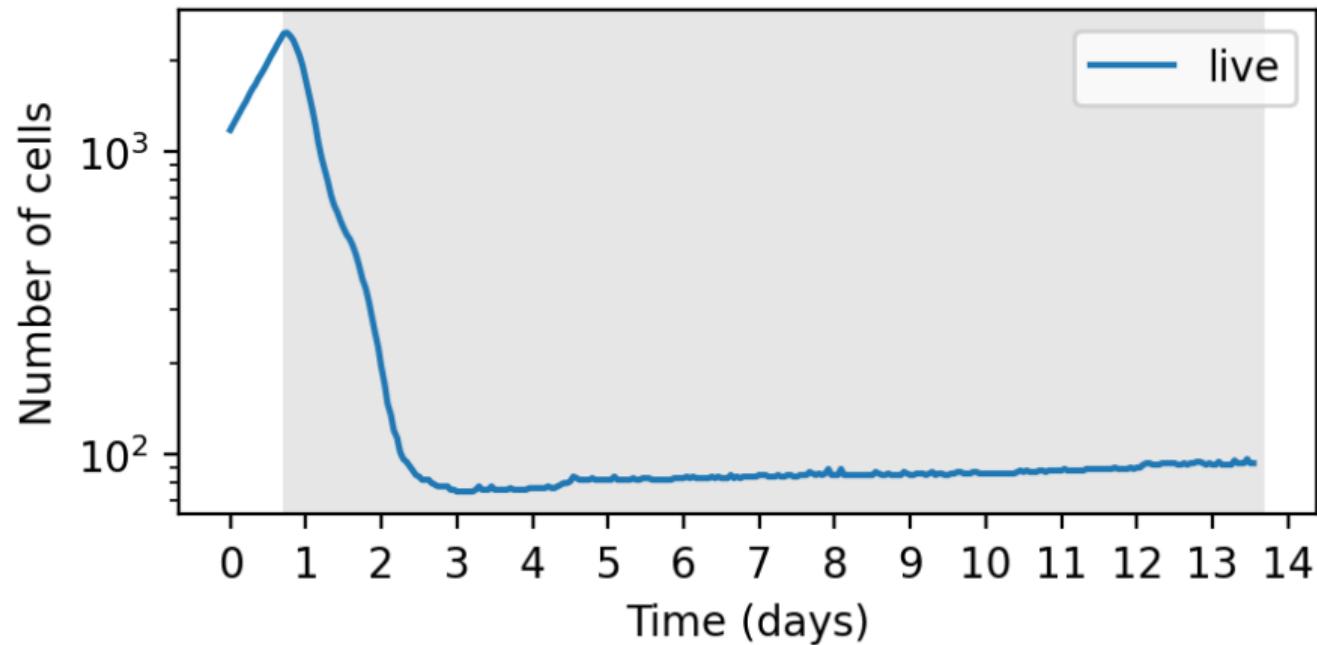
TNF model

- › Time stochasticity



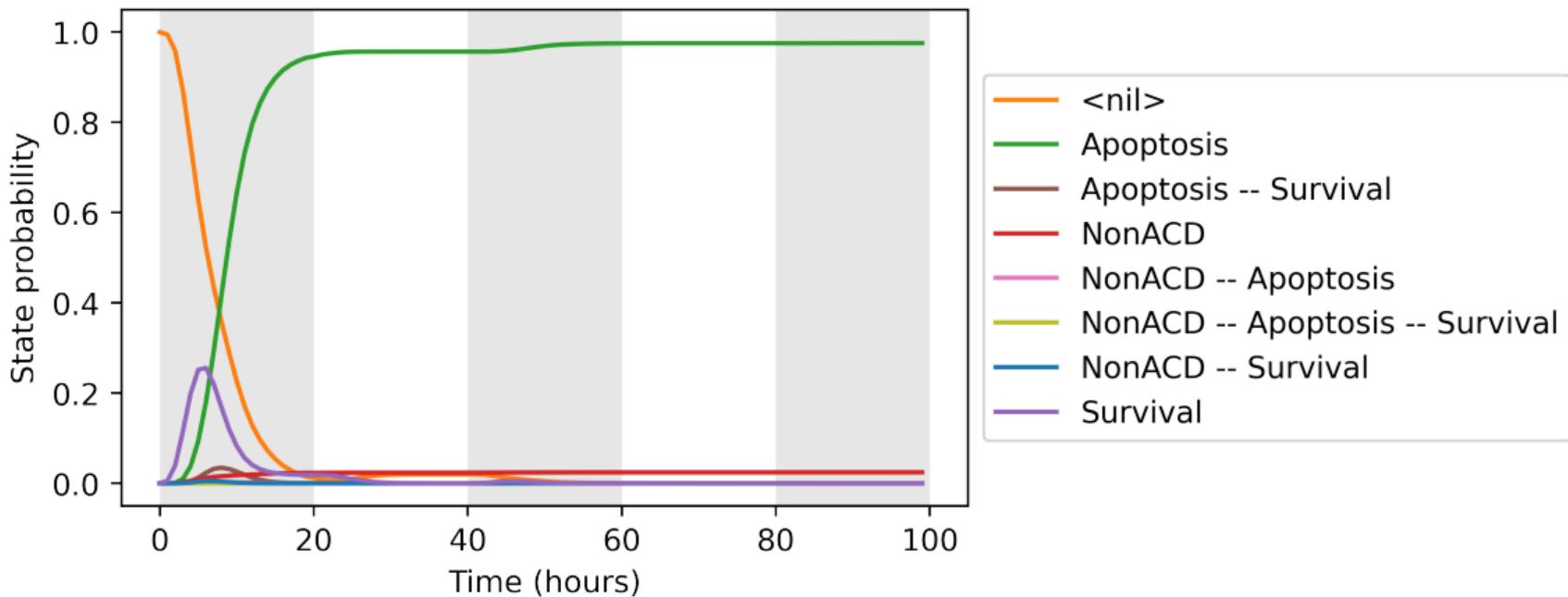
TNF model

- › Creating pulses of TNF



TNF model

- › Creating pulses of TNF



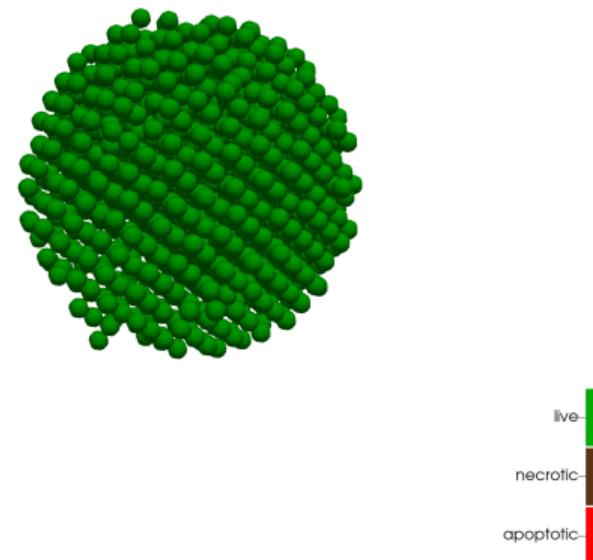
TNF model

› Creating pulses of TNF

```
if (parameters.bools("pulse_tnf")){  
    if (PhysiCell_globals.current_time >= 5320 && PhysiCell_globals.current_time < 8200 && microenvironment.get_substrate_dirichlet_activation(tnf_index))  
    {  
        std::cout << "TNF in activation" << std::endl;  
        microenvironment.set_substrate_dirichlet_activation(tnf_index, false);  
    }  
  
    if (PhysiCell_globals.current_time >= 8200 && PhysiCell_globals.current_time < 12520 && !microenvironment.get_substrate_dirichlet_activation(tnf_index))  
    {  
        std::cout << "TNF activation" << std::endl;  
        microenvironment.set_substrate_dirichlet_activation(tnf_index, true);  
    }  
  
    if (PhysiCell_globals.current_time >= 12520 && PhysiCell_globals.current_time < 15400 && microenvironment.get_substrate_dirichlet_activation(tnf_index))  
    {  
        std::cout << "TNF inactivation" << std::endl;  
        microenvironment.set_substrate_dirichlet_activation(tnf_index, false);  
    }  
  
    if (PhysiCell_globals.current_time >= 15400 && PhysiCell_globals.current_time < 19720 && !microenvironment.get_substrate_dirichlet_activation(tnf_index))  
    {  
        std::cout << "TNF activation" << std::endl;  
        microenvironment.set_substrate_dirichlet_activation(tnf_index, true);  
    }  
  
    if (PhysiCell_globals.current_time >= 19720 && microenvironment.get_substrate_dirichlet_activation(tnf_index))  
    {  
        std::cout << "TNF inactivation" << std::endl;  
        microenvironment.set_substrate_dirichlet_activation(tnf_index, false);  
    }  
}
```

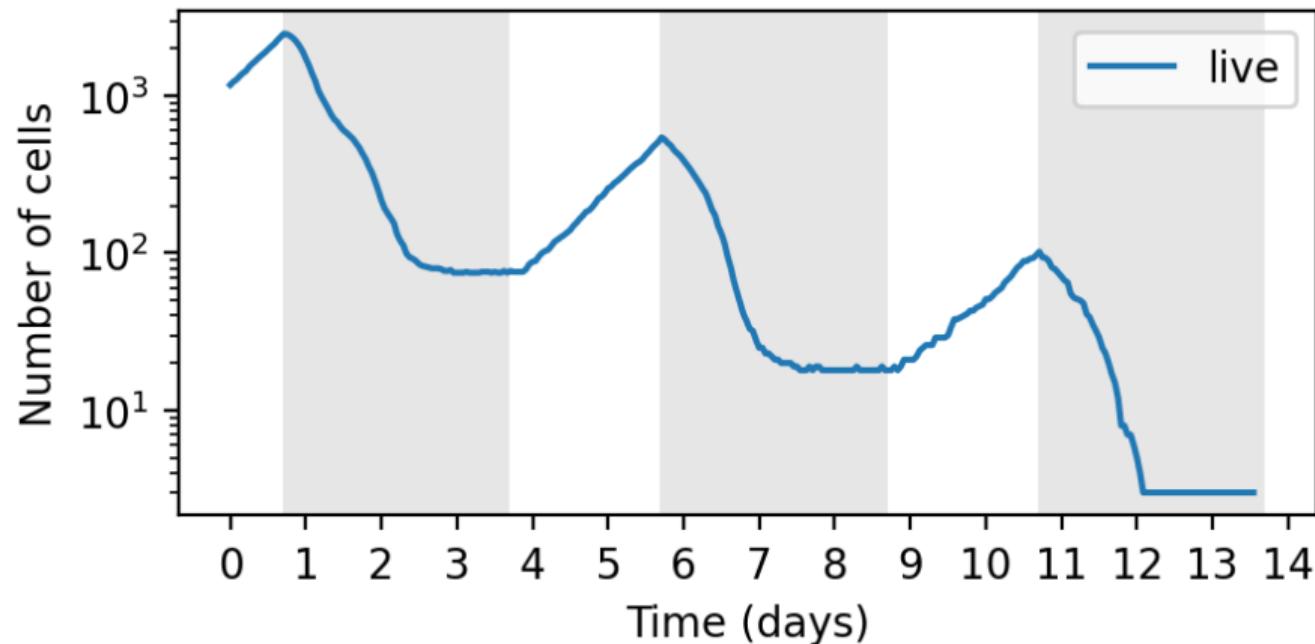
TNF model

- › Creating pulses of TNF



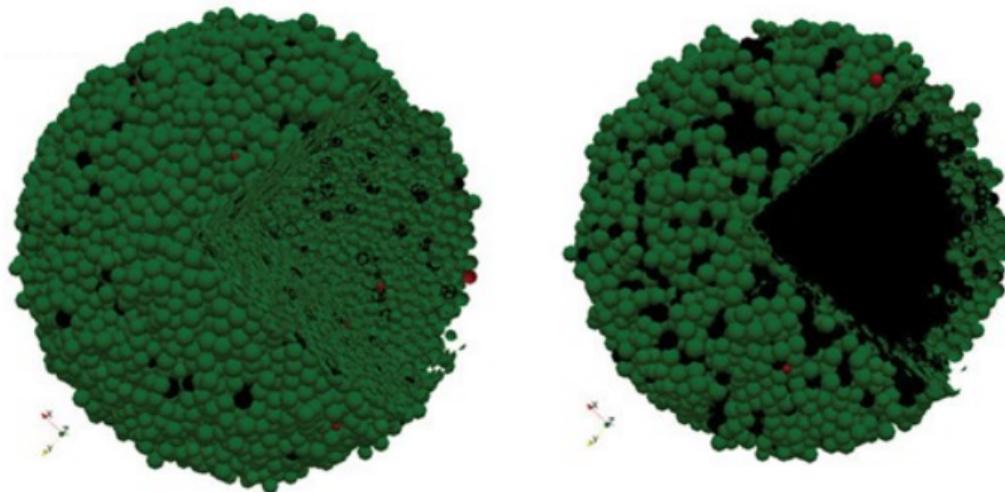
TNF model

- › Creating pulses of TNF



TNF model

- Adding tumor necrotic core



TNF model

› Adding tumor necrotic core

BND file

```
node OXYGEN
{
    rate_up = 0.0;
    rate_down = 0.0;
}

node NonACD
{
    logic = !OXYGEN | !ATP;
    rate_up = @logic ? 1.0 : 0.0;
    rate_down = @logic ? 0.0 : 1.0;
}

node Apoptosis
{
    logic = OXYGEN & CASP3;
    rate_up = @logic ? 1.0 : 0.0;
    rate_down = @logic ? 0.0 : 1.0;
}

node Survival
{
    logic = OXYGEN & NFkB;
    rate_up = @logic ? 1.0 : 0.0;
    rate_down = @logic ? 0.0 : 1.0;
```

CFG file

```
Cyt_c.istate = FALSE ;
XIAP.istate = FALSE ;
apoptosome.istate = FALSE ;
CASP3.istate = FALSE ;
cFLIP.istate = FALSE ;
OXYGEN.istate = TRUE;
NonACD.istate = FALSE ;
Apoptosis.istate = FALSE ;
Survival.istate = FALSE ;
```

TNF model

› Adding tumor necrotic core

```
<variable name="oxygen" units="mmHg" ID="1">
  <physical_parameter_set>
    <diffusion_coefficient units="micron^2/min">1000.00</diffusion_coefficient>
    <decay_rate units="1/min">.00001</decay_rate>
  </physical_parameter_set>
  <initial_condition units="mmHg">10.0</initial_condition>
  <Dirichlet_boundary_condition units="mmHg" enabled="true">38.0</Dirichlet_boundary_condition>
  <Dirichlet_options>
    <boundary_value ID="xmin" enabled="True">38.0</boundary_value>
    <boundary_value ID="xmax" enabled="True">38.0</boundary_value>
    <boundary_value ID="ymin" enabled="True">38.0</boundary_value>
    <boundary_value ID="ymax" enabled="True">38.0</boundary_value>
    <boundary_value ID="zmin" enabled="True">38.0</boundary_value>
    <boundary_value ID="zmax" enabled="True">38.0</boundary_value>
  </Dirichlet_options>
</variable>
```

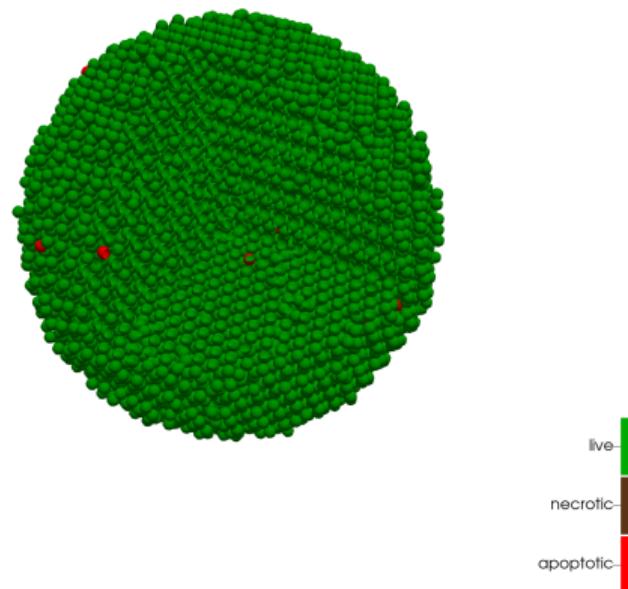
TNF model

› Adding tumor necrotic core

```
<mapping>
    <input intracellular_name="TNF" physicell_name="TNF">
        <settings>
            <action>activation</action>
            <threshold>0.01</threshold>
            <smoothing>0</smoothing>
        </settings>
    </input>
    <input intracellular_name="OXYGEN" physicell_name="oxygen">
        <settings>
            <action>activation</action>
            <threshold>0.05</threshold>
            <smoothing>0</smoothing>
        </settings>
    </input>
```

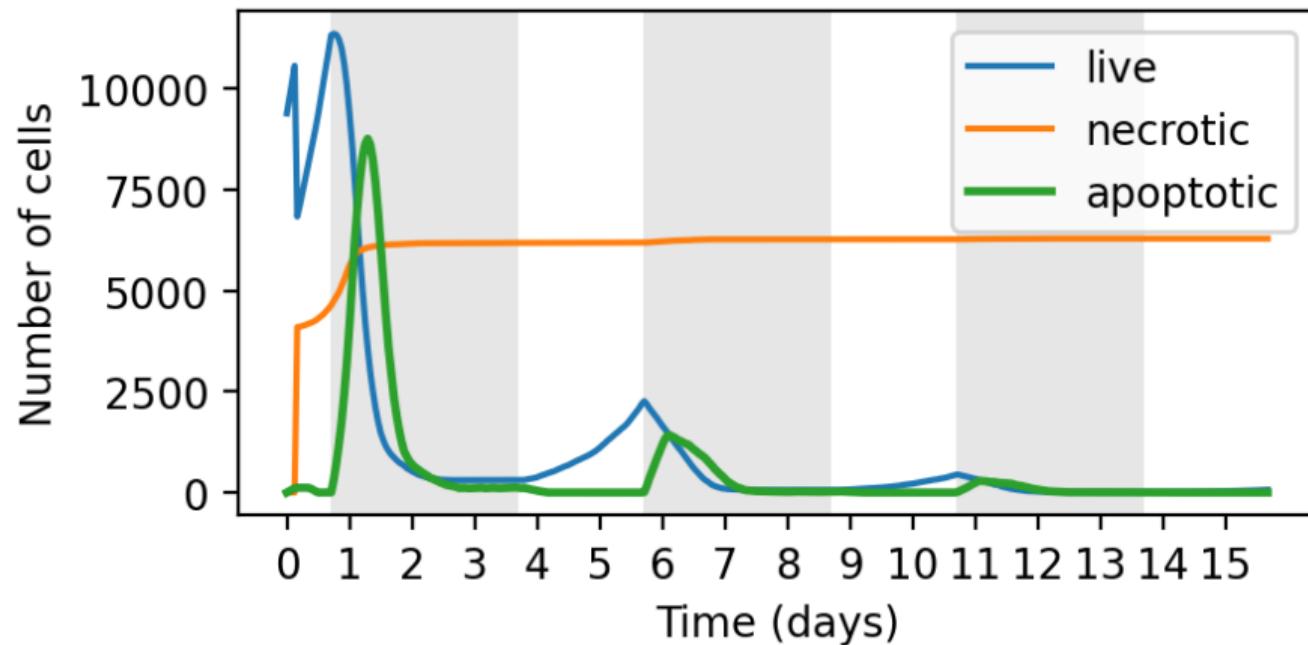
TNF model

- Adding tumor necrotic core



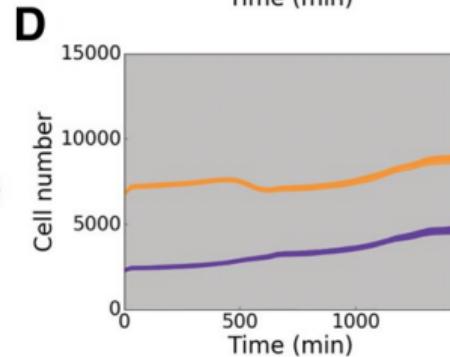
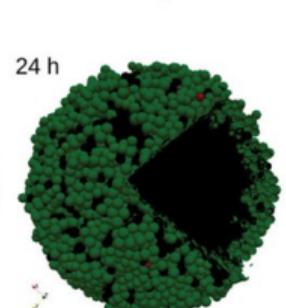
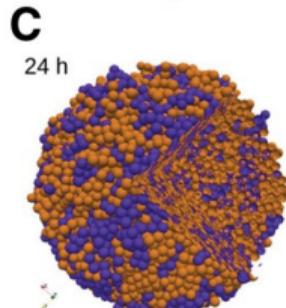
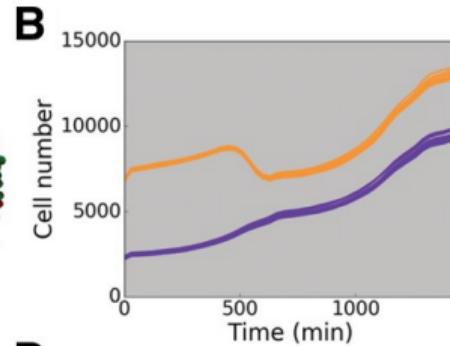
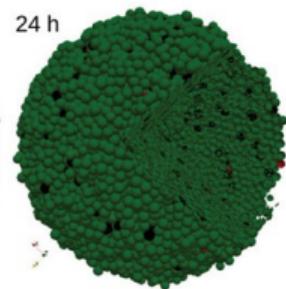
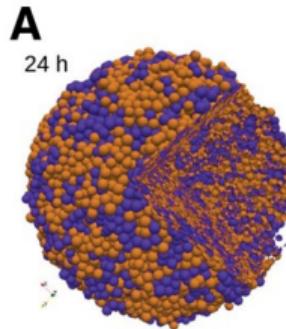
TNF model

- Adding tumor necrotic core



TNF model

- › Add IKK/cFLIP mutant population



TNF model

- › Add IKK/cFLIP mutant population

- › New cell definition

- › Copy from default

- › Add mutations to the intracellular model

```
<intracellular type="maboss">
  <bnd_filename>config/boolean_network/CellFateModel_with_oxygen.bnd</bnd_filename>
  <cfg_filename>config/boolean_network/CellFateModel_with_oxygen.cfg</cfg_filename>
  <settings>
    <intracellular_dt>1440.0</intracellular_dt>
    <time_stochasticity>0.2</time_stochasticity>
    <scaling>60.0</scaling>
    <mutations>
      <mutation intracellular_name="IKK">1.0</mutation>
      <mutation intracellular_name="cFLIP">1.0</mutation>
    </mutations>
  </settings>
  <mapping>
    <input intracellular_name="TNF" physicell_name="TNF">
      <settings>
        <action>activation</action>
        <threshold>0.01</threshold>
        <smoothing>0</smoothing>
      </settings>
    </input>
    <input intracellular_name="OXYGEN" physicell_name="oxygen">
      <settings>
        <action>activation</action>
        <threshold>0.05</threshold>
        <smoothing>0</smoothing>
      </settings>
    </input>
    <output intracellular_name="Apoptosis" physicell_name="apoptosis">
      <settings>
        <action>activation</action>
        <value>1000000</value>
        <base_value>0</base_value>
        <smoothing>0</smoothing>
      </settings>
    </output>
    <output intracellular_name="NonACD" physicell_name="necrosis">
      <settings>
        <action>activation</action>
        <value>1000000</value>
        <base_value>0</base_value>
        <smoothing>0</smoothing>
      </settings>
    </output>
  </mapping>
```

TNF model

› Add IKK/cFLIP mutant population

```
void setup_tissue( void )
{
    // place a cluster of tumor cells at the center
    double cell_radius = cell_defaults.phenotype.geometry.radius;
    double cell_spacing = 0.95 * 2.0 * cell_radius;

    double tumor_radius = parameters.doubles( "tumor_radius" ); // 250.0;

    // Parameter<double> temp;

    int i = parameters.doubles.find_index( "tumor_radius" );

    Cell* pCell = NULL;

    std::vector<std::vector<double>> positions = create_cell_sphere_positions(cell_radius,tumor_radius);
    std::cout << "creating " << positions.size() << " closely-packed tumor cells ... " << std::endl;

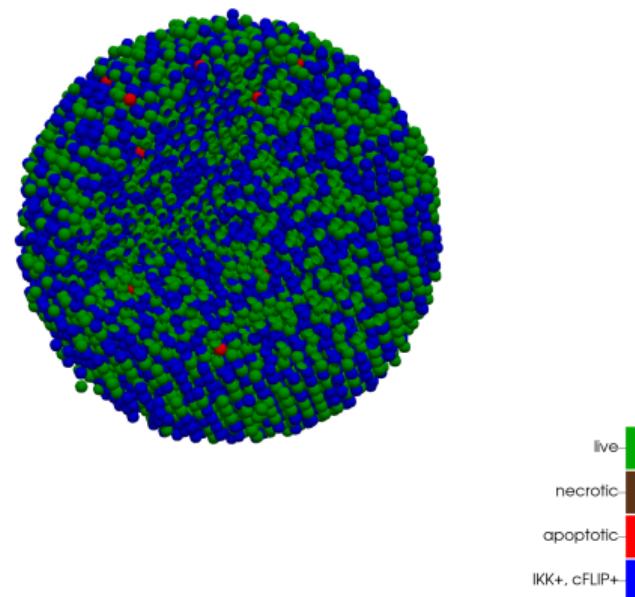
    for( int i=0; i < positions.size(); i++ )
    {
        pCell = create_cell(get_cell_definition(
            [PhysiCell::UniformRandom()*100] > parameters.doubles("percentage_mutants") ? "default":"mutant"
        ));

        pCell->assign_position( positions[i] );
    }
}

return;
}
```

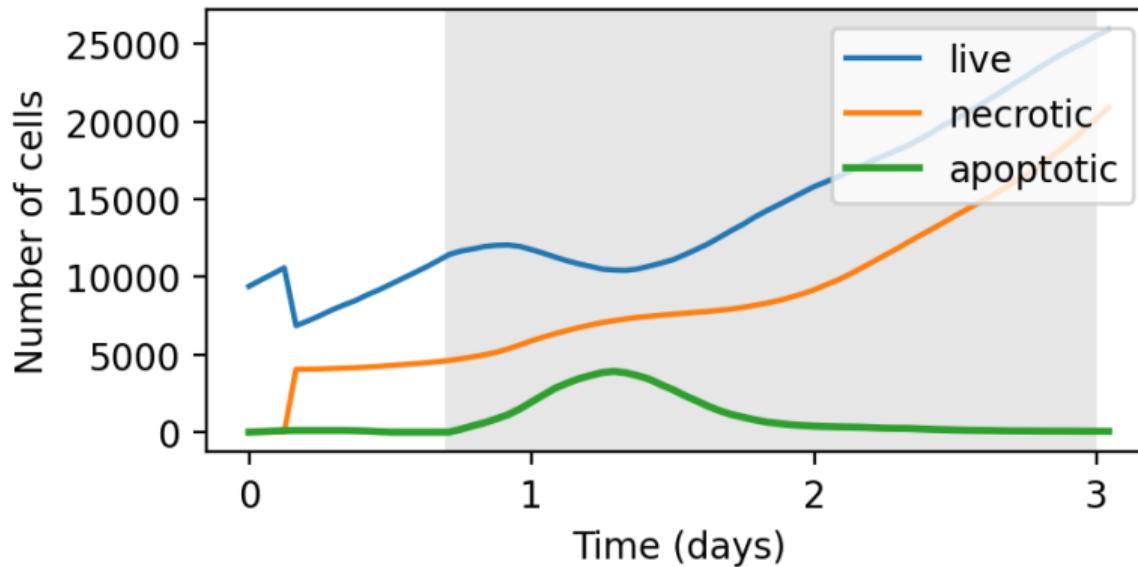
TNF model

- › Add IKK/cFLIP mutant population



TNF model

- › Add IKK/cFLIP mutant population



Conclusion

- › A small example showing what PhysiBoSS can do
- › Parametrization is not easy
- › New bugfixes and things learned while preparing it
- › This model will be included into PhysiCell's next version !

<https://github.com/PhysiBoSS/PhysiBoSS>
development branch, sample project **simple-spheroid-tnf**

Conclusion

- › PhysiBoSS started as a fork of PhysiCell, even before it was published
- › 5 years later, PhysiBoSS is now tightly included into PhysiCell ecosystem
- › Writing models is getting easier !
- › Feel free to send me questions/issues/suggestions

<https://github.com/PhysiBoSS/PhysiBoSS>

vincent.noel@curie.fr

Acknowledgments



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Laurence Calzone



Emmanuel Barillot



Marco
Ruscone



Andrei
Zinovyev



Arnau
Montagud



Miguel Ponce
de Leon



Gerard
Pradas



INDIANA UNIVERSITY



Randy
Heiland



Paul
Macklin



Furkan
Kurtoglu



Gaëlle
Letort



HPC/Exascale
Centre of
Excellence in
Personalised
Medicine

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- Jayne Koskinas Ted Giovanis Foundation for Health and Policy
- National Cancer Institute (U01CA232137)
- National Science Foundation (1720625, 1818187)

PhysiBoSS Development:

- European Union (PrECISE project: H2020-PHC-668858, INFORE: H2020-ICT-825070, PerMedCoE: H2020-ICT-951773)
- ITMO Cancer (Chemotaxis, INVADE)

Training Materials:

- Administrative supplement to NCI U01CA232137 (Year 2)

Other Funding:

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