



**Barcelona
Supercomputing
Center**
Centro Nacional de Supercomputación



EXCELENCIA
SEVERO
OCHOA

PhysiBoSS enables multiscale simulations of signalling pathways

Arnaud Montagud
Computational Biology group
Life Science Department

28 July 2021

PhysiCell Workshop 2021

A bit about myself



UNIVERSITAT
POLITÈCNICA
DE VALÈNCIA

« B.Sc. & M.Sc. Biology, Ph.D. Applied Maths



« Institut Curie

- Emmanuel Barillot – “Systems Biology of Cancer”
- Build Boolean models on gene interactions networks
- Goal: To have **actionable models of cancers**
 - **Stochastic simulations** of gene interaction networks
 - **Multiscale models** of cancers
 - Boolean models

« BSC



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- Alfonso Valencia – “Computational Biology”
- Develop simulation tools that can take advantage of HPC
 - Multiscale models of cancers
- Goal: To have **real-sized tumour simulations**
 - **Cellular heterogeneity**
 - Mutants and drugs
 - **Environment heterogeneity**
 - **Different cell types**
 - Immune therapy
 - **Cell evolution**
 - Resistance
 - Selection

Barcelona Supercomputing Center





MareNostrum 4

General Purpose

11.15 Pflops/s

3,456 nodes of
Intel Xeon v5
processors

14PB storage





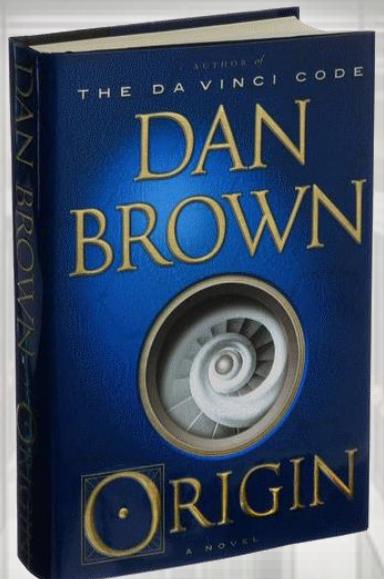
Emerging Technologies, for evaluation of 2020 Exascale systems

3 systems, each
of more than 0,5
Pflops/s
with ARMv8.
KNH,

Power9+NVIDIA,



But MareNostrum 4 inspires not only science...



Europe's Supercomputing infrastructure is distributed



24 members, including

5 Hosting Members (Switzerland, France, Germany, Italy and Spain)

524 scientific projects enabled

70 PFlops/s of peak performance on **7 world-class systems**

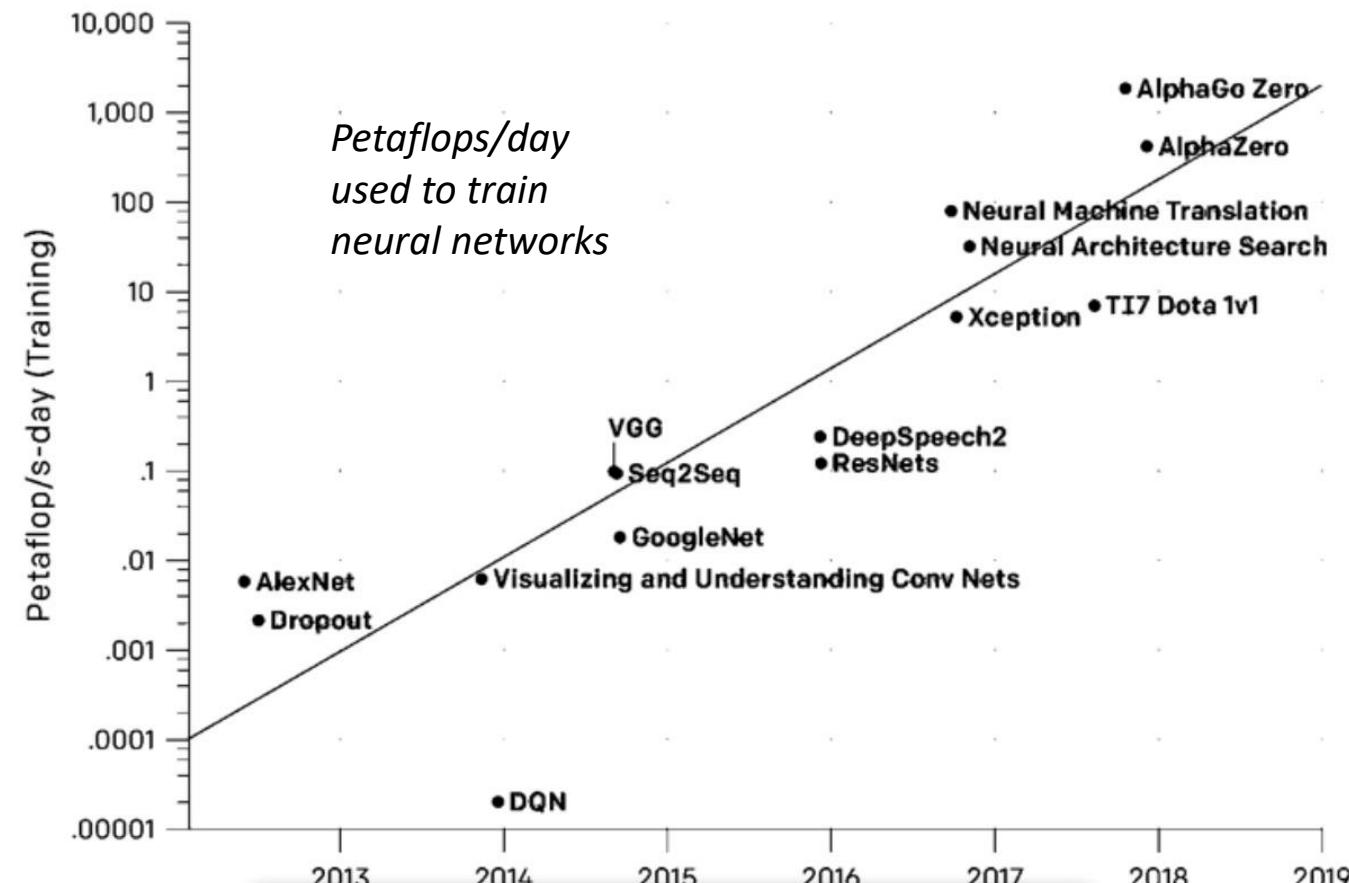
>10.000 people trained by **6 PRACE Advanced Training Centers** and others events

Access prace-ri.eu/hpc-access



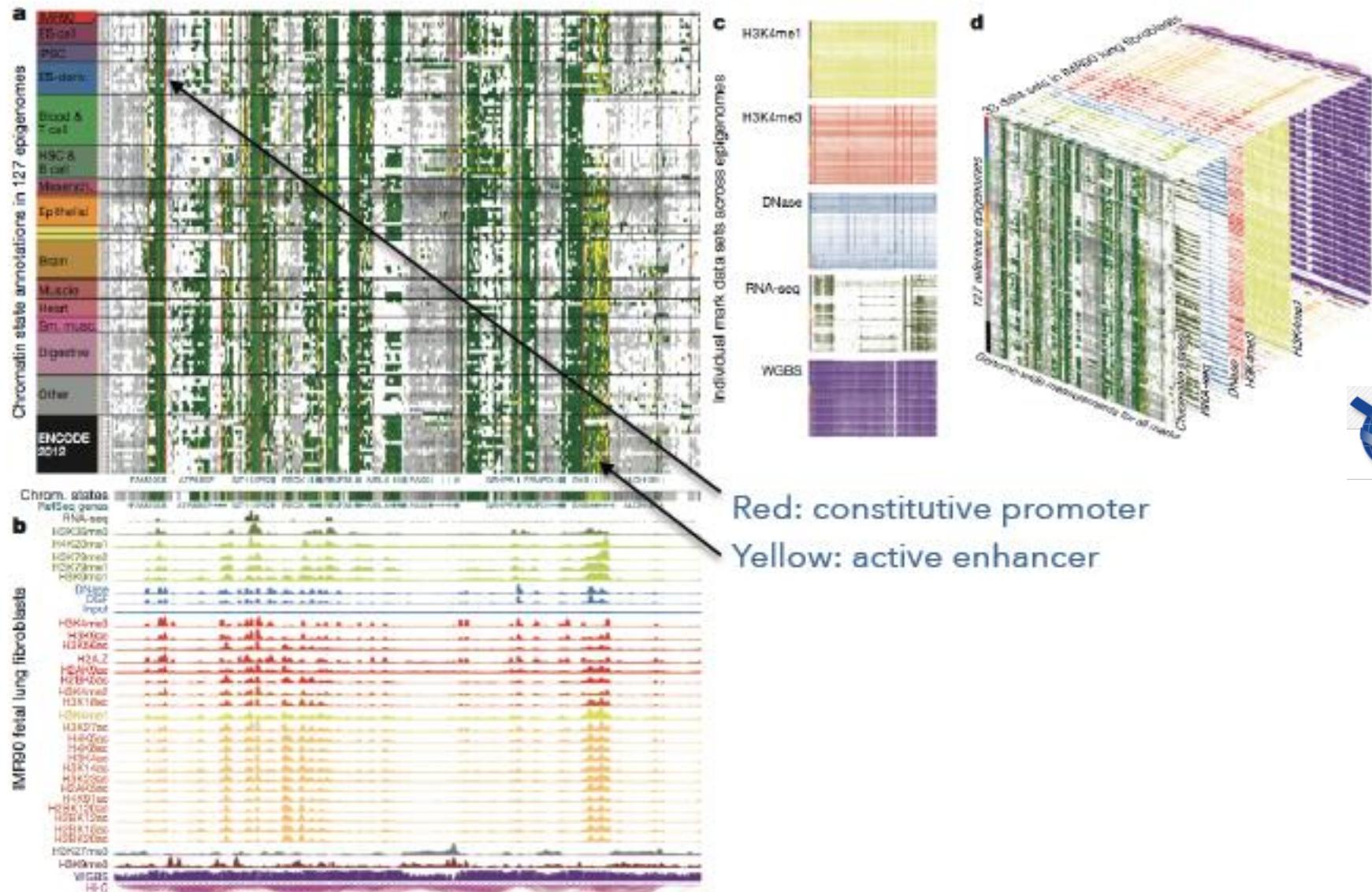
Advances in AI and HPC go hand by hand

Since GPUs were first used in AI (2012), **computing power** available to generate AI models has increased exponentially – and improvements in computing power has been key for **AI progress**.



Omics (r)evolution: 2000 – 2016?

Epigenomic information across tissues and marks



Single cell (r)evolution: 2016 -



Single-cell multi-omics



Machine learning



Personalized organoid disease
models

About 500 scientists, clinicians, patients, and stakeholders from 20 European countries and beyond have gathered in Berlin at the LifeTime Opening Conference. The pan-European initiative aims to revolutionize healthcare. It applies breakthrough technologies to the progression of human diseases and intends to find and implement new methods for personalized prevention, early diagnosis and treatment.



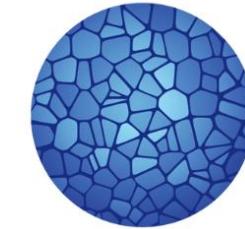
nature
REVIEWS
CANCER

Review Article | Published: 27 August 2019

Unravelling tumour heterogeneity by single-cell profiling of circulating tumour cells

Laura Keller & Klaus Pantel ✉

Nature Reviews Cancer (2019) | Download Citation ↓



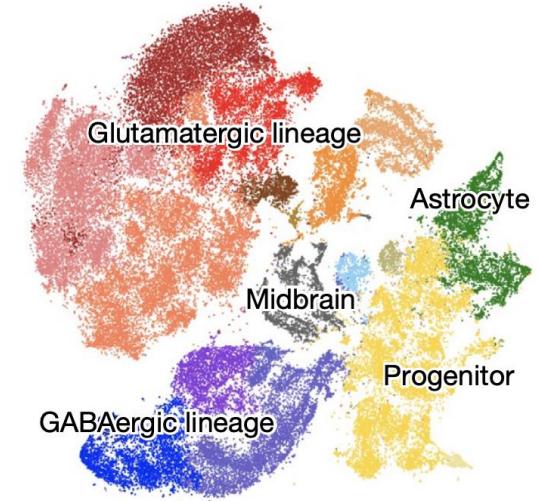
HUMAN
CELL
ATLAS

NATURE | www.nature.com/nature

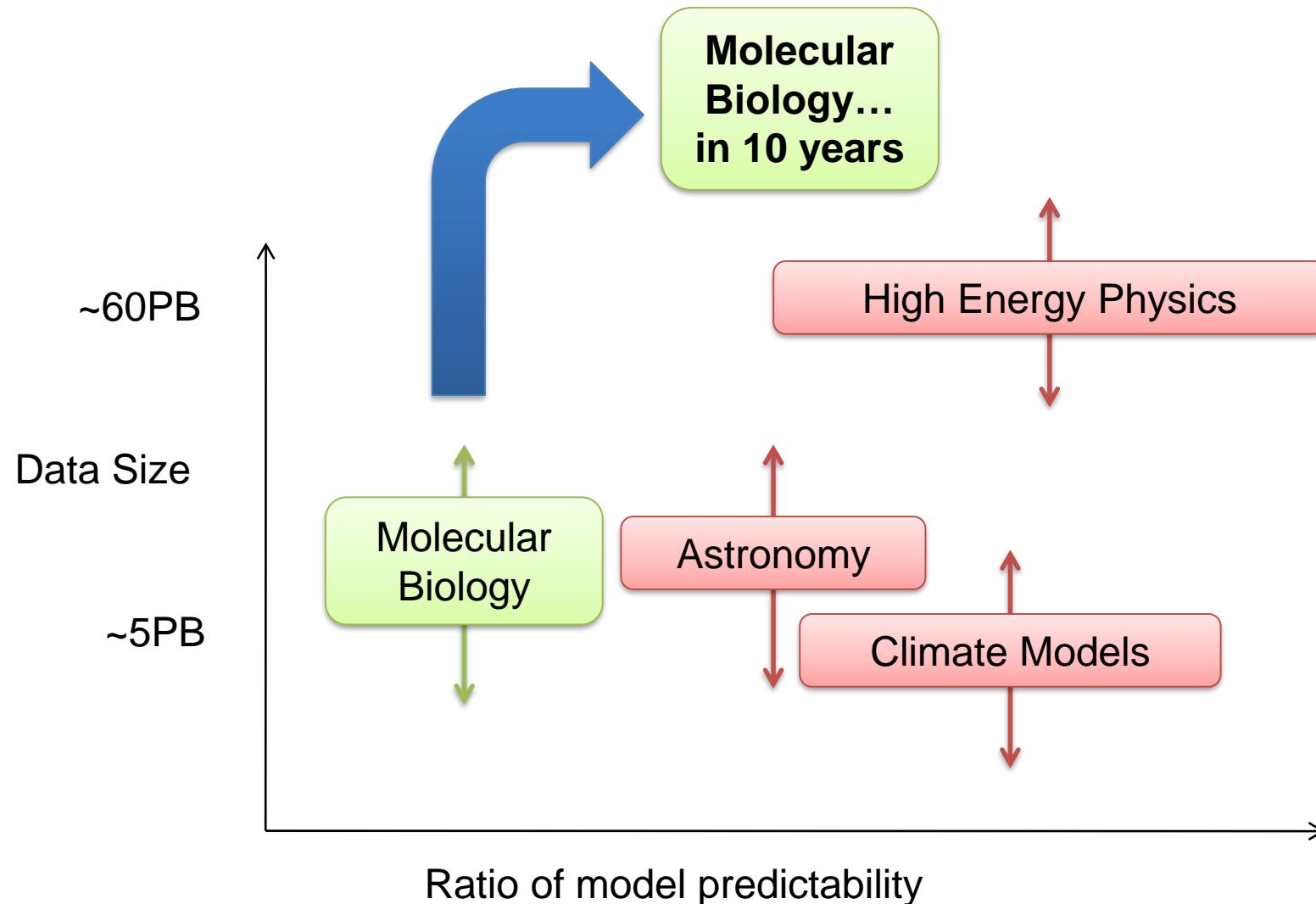
<https://doi.org/10.1038/s41586-019-1434-6>

Resolving medulloblastoma cellular architecture by single-cell genomics

Received: 13 September 2018; Accepted: 21 June 2019;
Published online: 24 July 2019



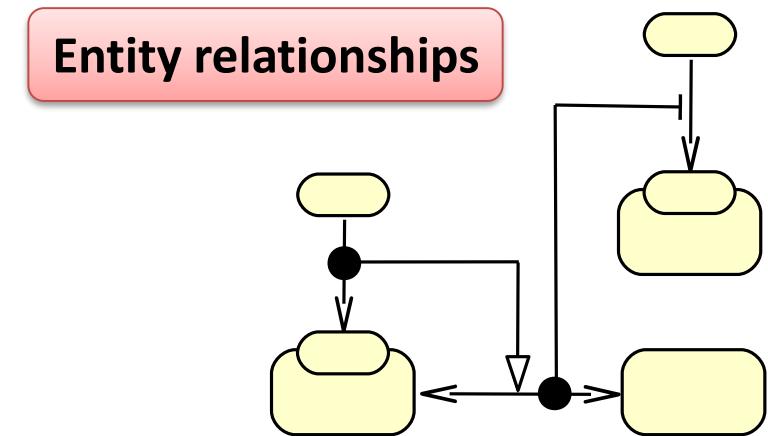
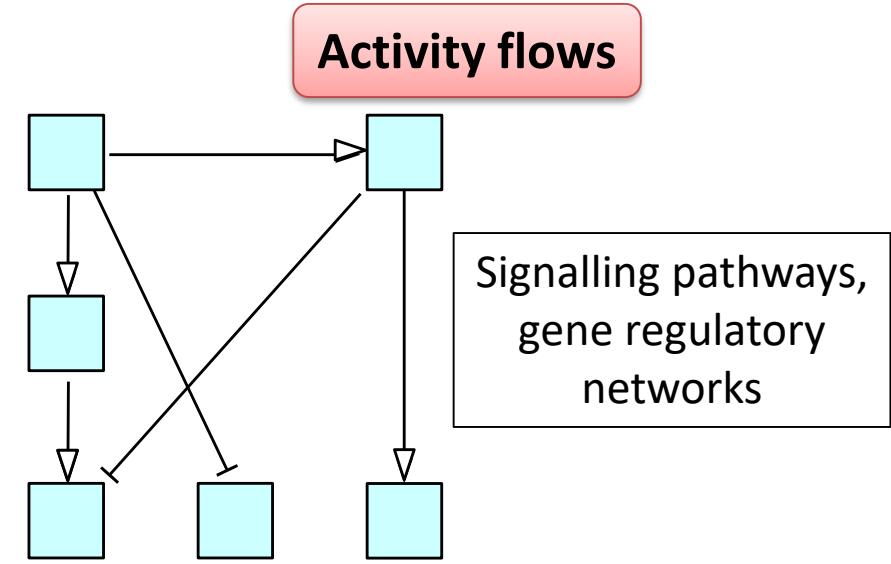
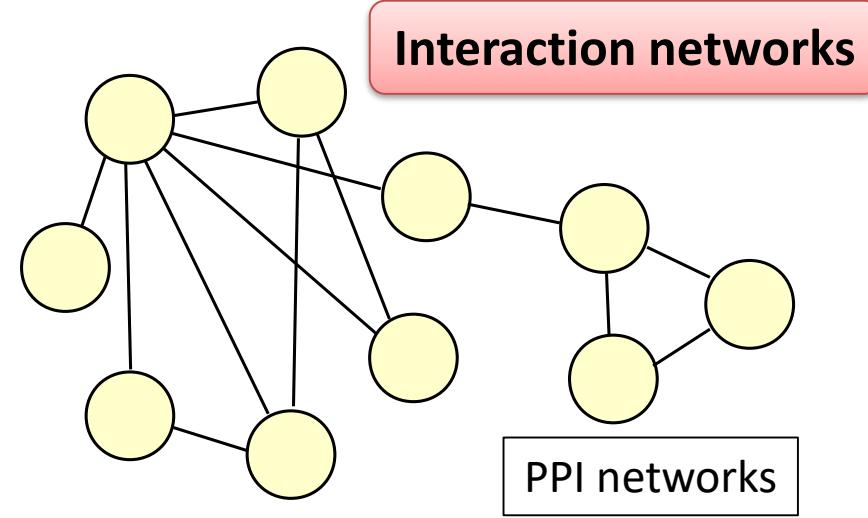
Molecular Biology means Big Data



From Ewan Birney, EBI

Data leads to Structure ...

Le Novere, Nat Rev Genet. 2015 Mar;16(3):146-58.



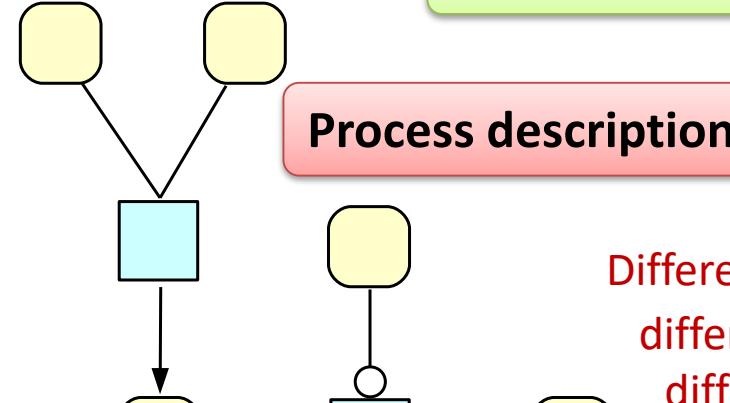
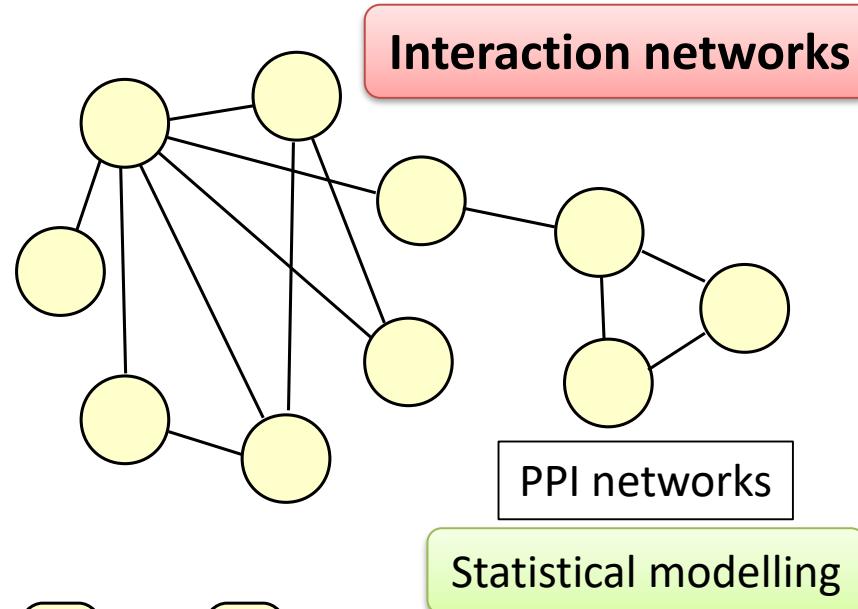
Metabolic networks, reaction networks

Molecular interactions, reaction networks

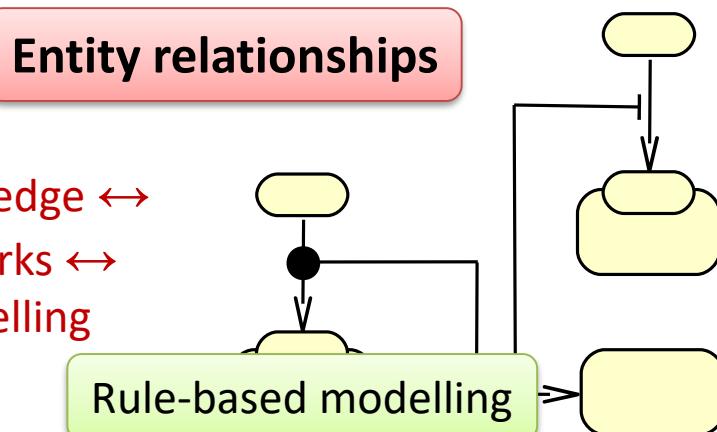
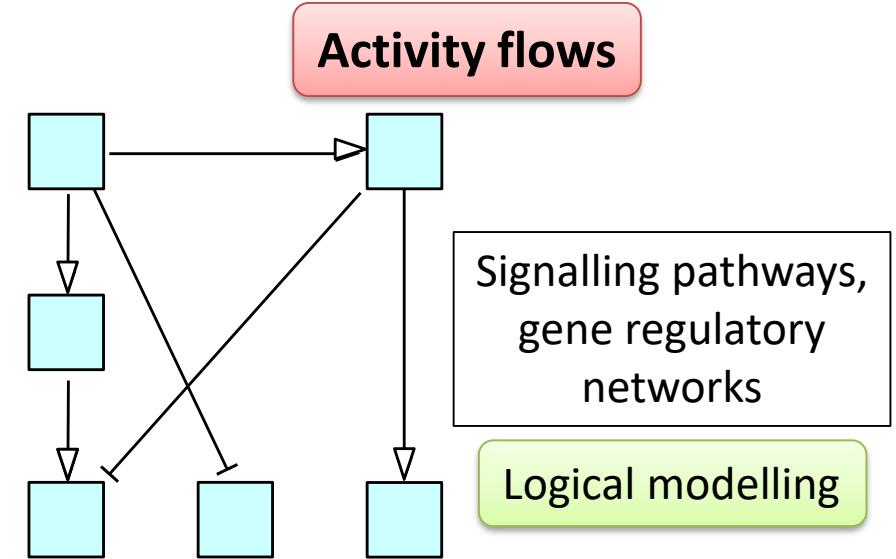
Slide from L. Calzone,
Institut Curie

Data leads to Structure ... and Structure leads to Modelling

Le Novere, Nat Rev Genet. 2015 Mar;16(3):146-58.



Metabolic networks, reaction networks



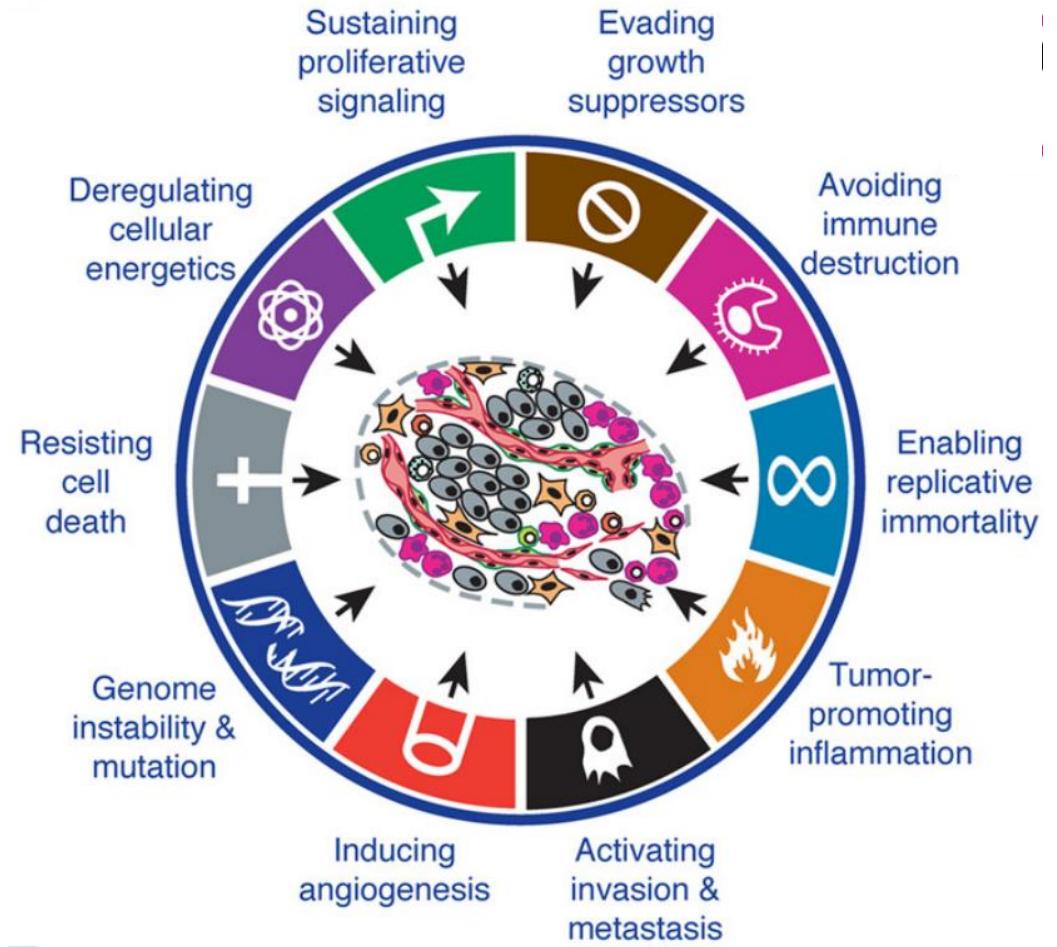
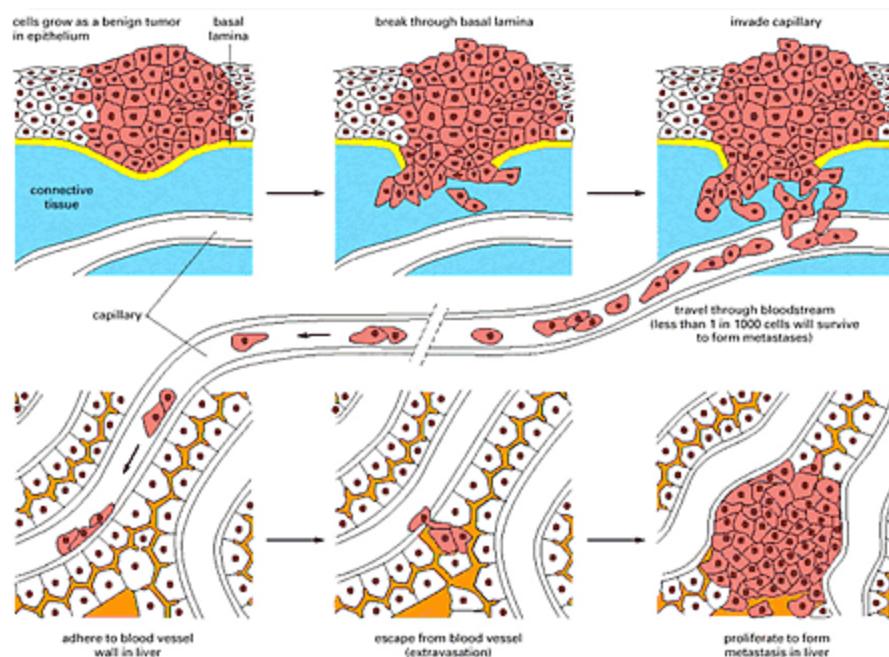
Slide from L. Calzone,
Institut Curie

Cancer: Many diseases in one concept

« Multistep process of abnormal cell growth

« Steps

- Benign tumour
- Basal lamina break
- Intravasation
- Extravasation
- Derived tumour → metastasis



Agent-based as multiscale modelling

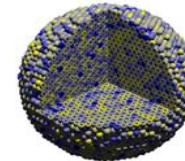


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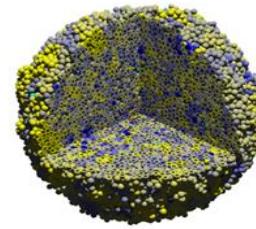
Multi-scale modeling framework: PhysiCell

An open source physics-based cell simulator for 3-D multicellular systems

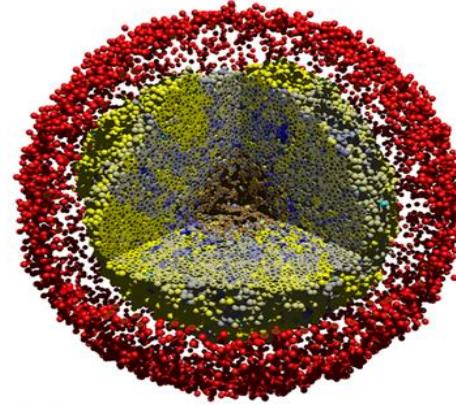
0 days
18,317 cells



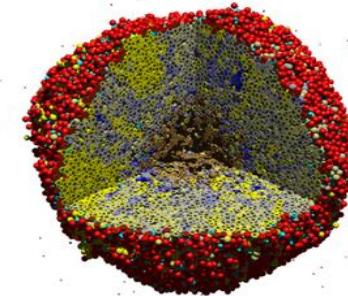
7 days
53,600 cells



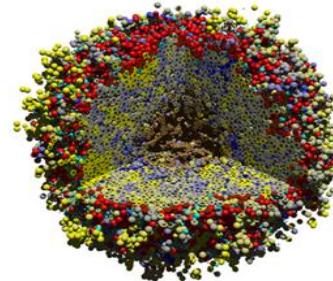
14 days + 3 min
111,479 cells



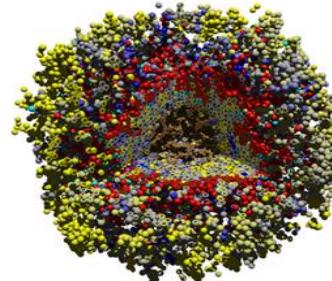
14 days + 6 hours
113,668 cells



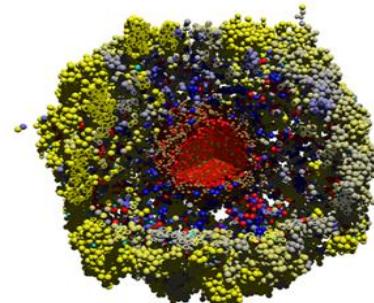
15 days
91,189 cells



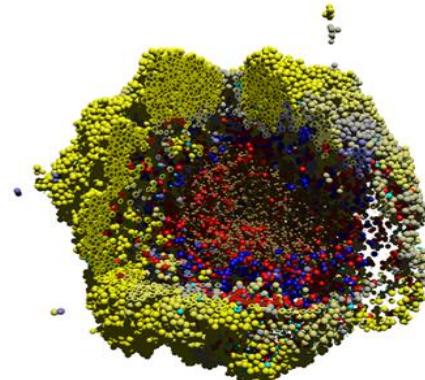
16 days
51,788 cells

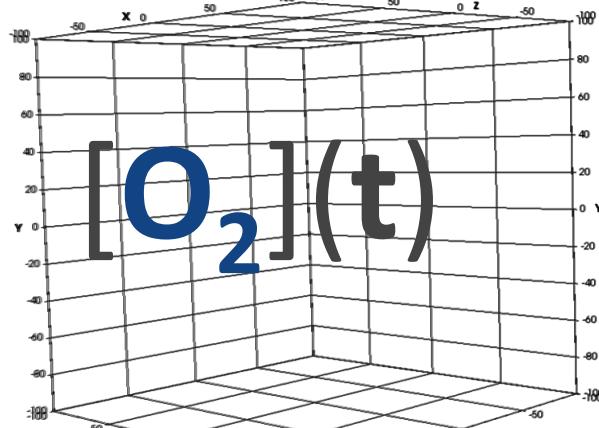


18 days
38,122 cells



21 days
66,978 cells





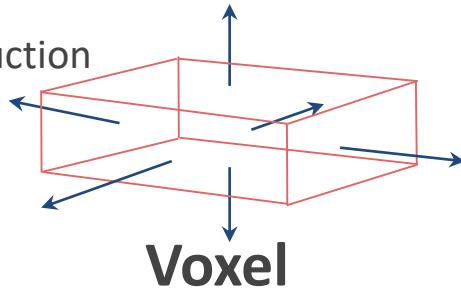
Reaction-Diffusion Equations

$$\frac{\partial \rho}{\partial t} = \underbrace{D \nabla^2 \rho}_{\text{diffusion}} - \underbrace{\lambda \rho}_{\text{decay}} + \underbrace{S(\rho^* - \rho)}_{\substack{\text{bulk source} \\ \text{sources and uptake by cells}}} - \underbrace{U \rho}_{\text{bulk uptake}}$$

$$+ \underbrace{\sum_{\text{cells } k} \delta(\mathbf{x} - \mathbf{x}_k) W_k [S_k(\rho_k^* - \rho) - U_k \rho]}_{\text{in } \Omega}$$

System of PDEs for each molecule:

- Diffusion term
- Decay
- Uptake/Production

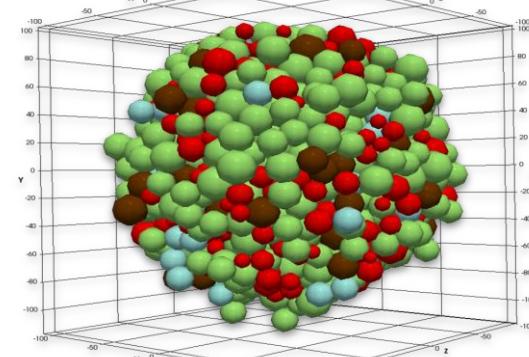
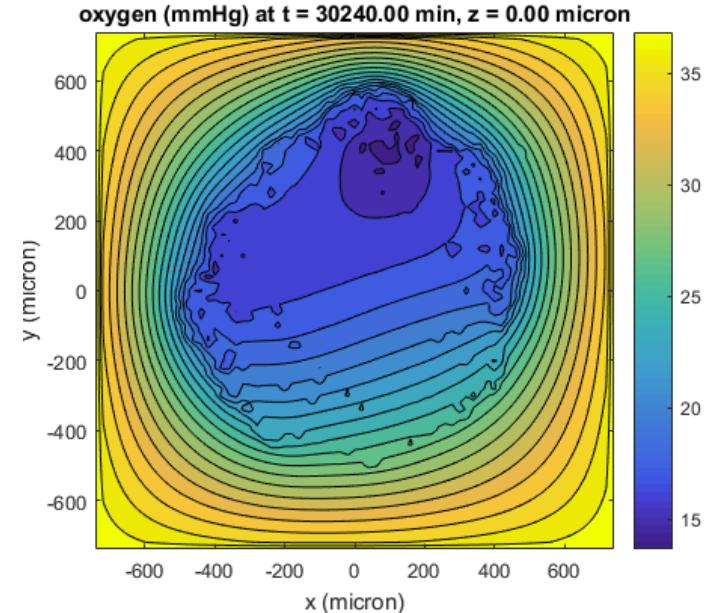


Surrounding physical environment

Surrogate for extra-cellular matrix

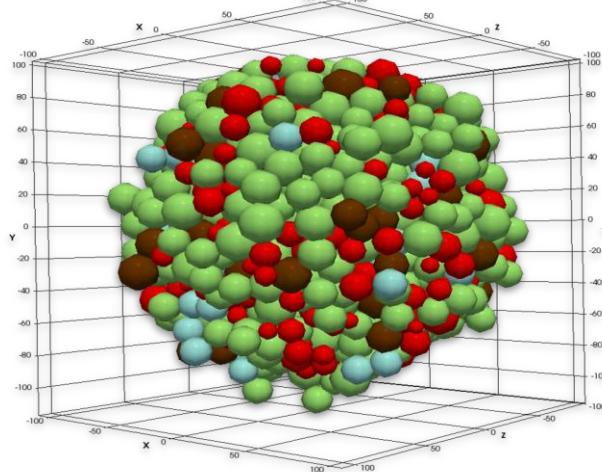
- Field with densities that can be produced & consumed
- Inert agents that can be moved

Gradient of chemical factors (O2)



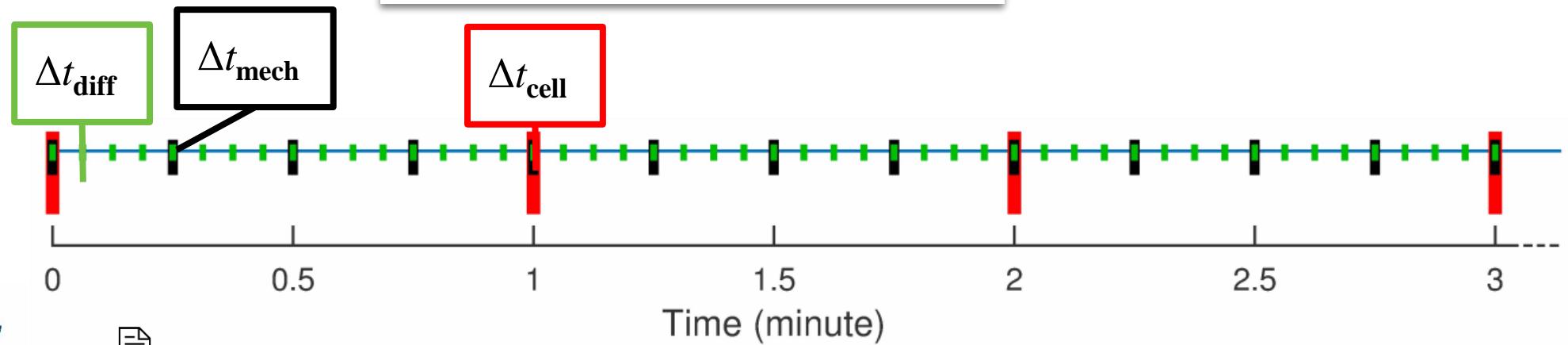
Slide from M. Ponce de L, BSC

Simulation workflow



Simulation's main loop

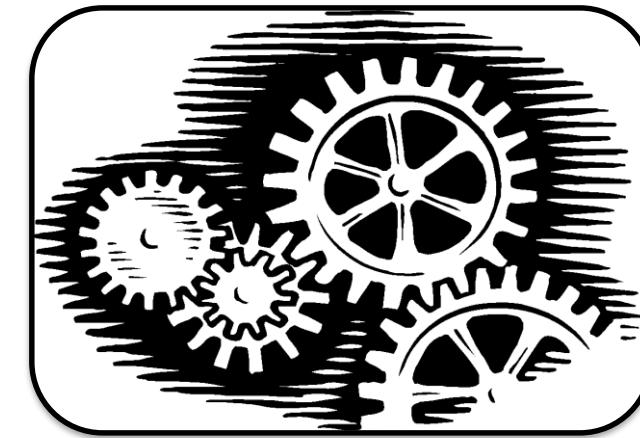
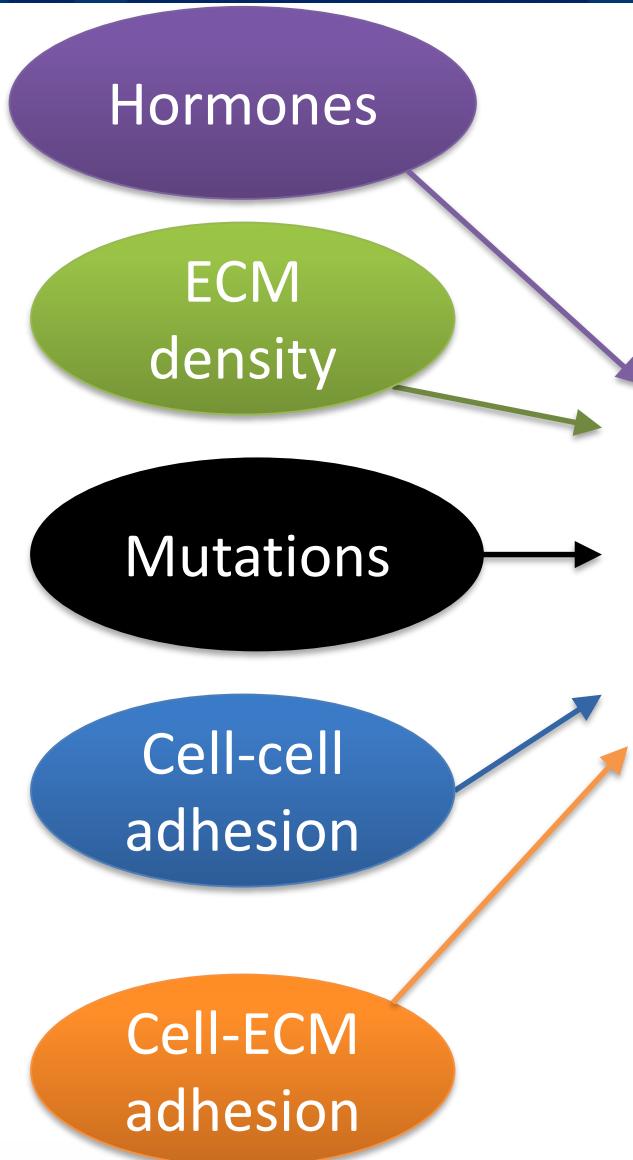
```
while t_current < tend  
    update_difussion()  
    if Δt % Δtmech == 0  
        update_cell_mechanics()  
    if Δt % Δtcell == 0  
        update_cell_processes()  
    Δt = 0  
    Δt += t_step  
    t_current += t_step
```



Time scales

- Δt_{diff} : (diffusion/transport): 0.01 min
- Δt_{mech} : (cell movement): 0.1 min
- Δt_{cell} : (cell processes): 6 min

Modifying agent-based to have genotype-to-phenotype modelling



Multi-scale modelling
Gene mutations
Signalling pathways
Cell - environment
ECM modification

	Cell-cell junctions	Tumor type
Amoeboid	-	Leukemia, lymphoma cell subsets (all tumors)
Mesenchymal	-	Stromal tumors, epithelial tumors after EMT
Amoeboid (multicellular)	?	All tumors developing amoeboid single-cell dissemination
Mesenchymal (multicellular)	(+)	Tumors with mesenchymal invasion; fibroblasts leading tumor cells
Cluster	++	Moderately differentiated epithelial tumors
Solid strand	++	Moderately differentiated epithelial tumors with subregions after EMT; basal and squamous cell carcinoma
Strand (with lumen)	++	Differentiated epithelial tumors; vascular neoplasia
Strand (protrusive)	++	Moderately differentiated epithelial tumors lacking EMT
Outward pushing tumor	++	All solid tumors

From Friedl and Alexander, Cell, 2011

Merging MaBoSS with PhysiCell: PhysiBoSS

Multi-scale ABM framework integrating physical dimension and cell signalling

PhysiCell (Macklin team at Indiana University)

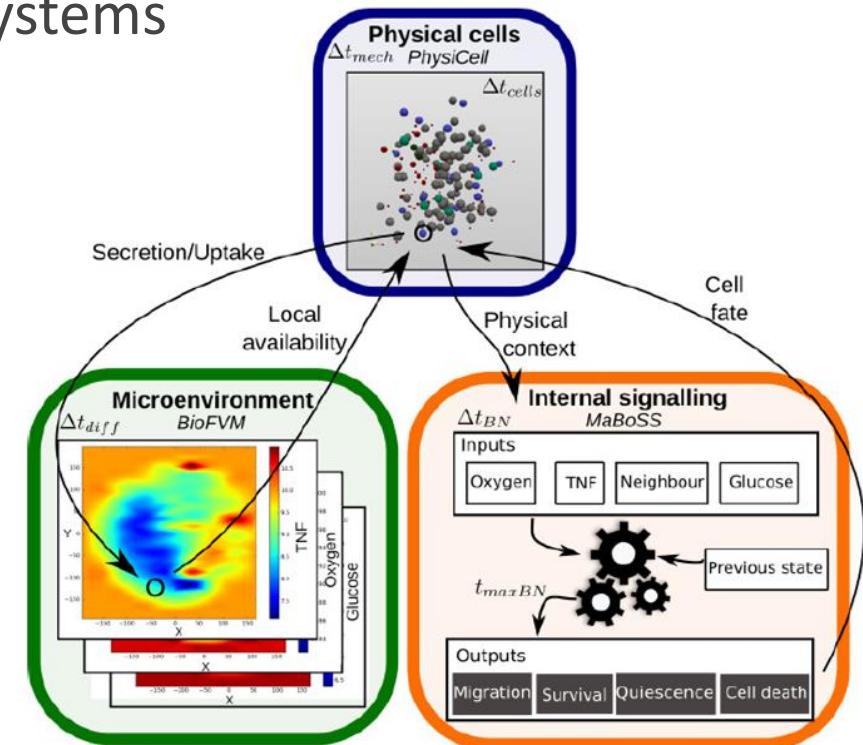
- Agent-based framework for simulating multicellular systems

MaBoSS (Barillot team at Institut Curie)

- Boolean model stochastic simulator for cell signalling

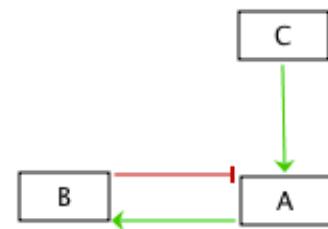
PhysiBoSS (Barillot team at Institut Curie)

- A PhysiCell extension to include cellular signalling
- This allows to perform combined studies of:
 - Environmental perturbation
 - Genetic perturbation



Primer to logical formalism

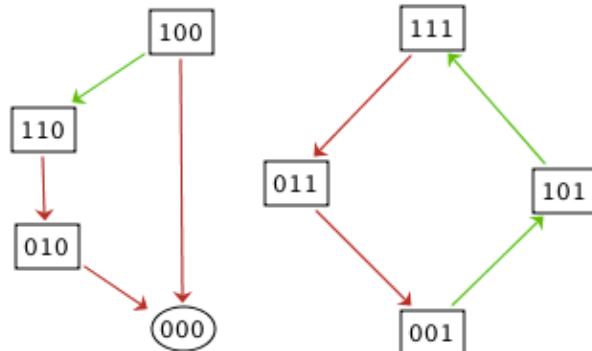
Regulatory graph



Logical rules

$$\begin{aligned}A &= !B \& C \\B &= A \\C &= \text{input}\end{aligned}$$

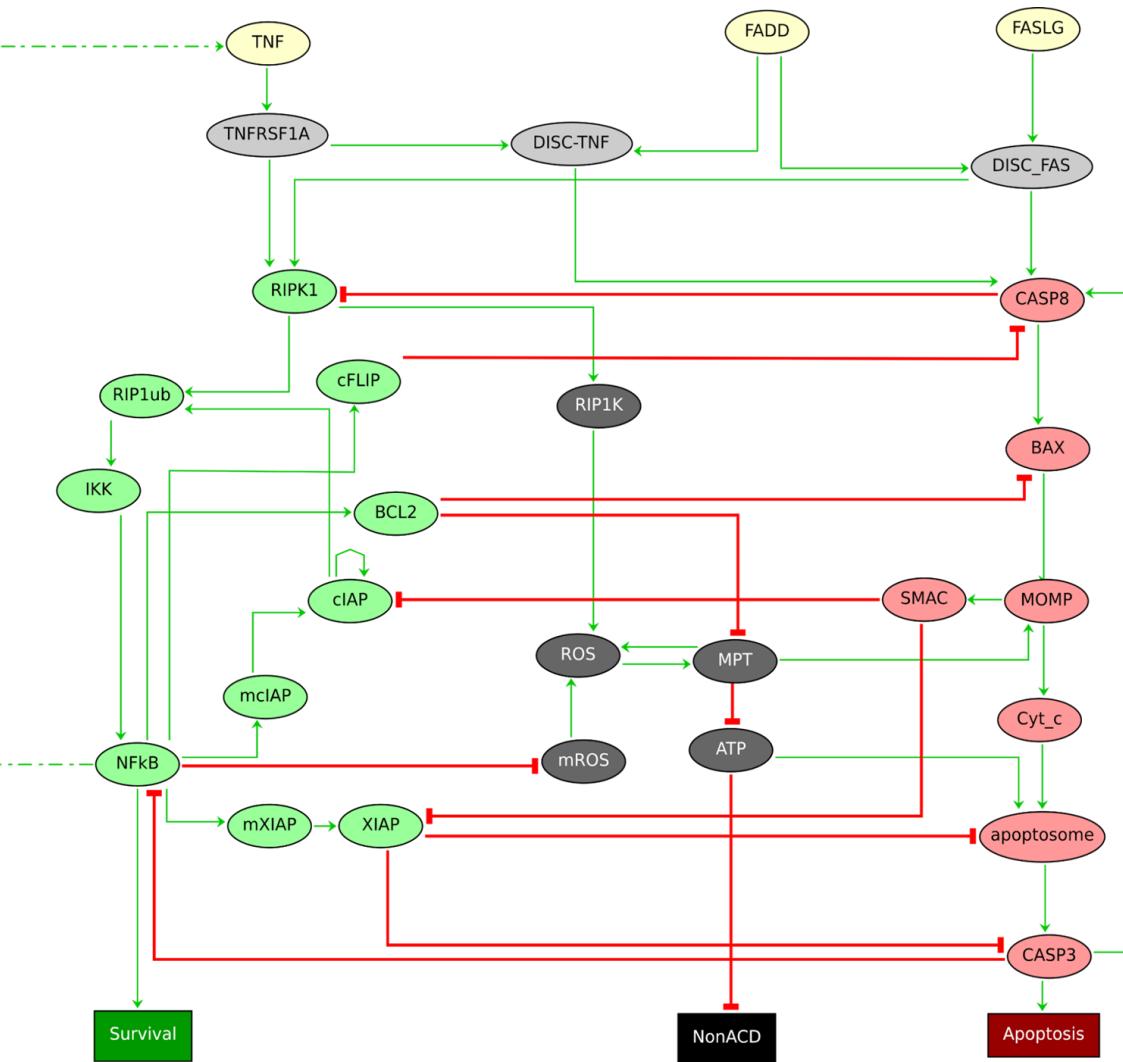
Solutions



- « Each variable can take **two states**: 0 or 1
- « **Boolean logic**:
 - Connectors: AND ($\&$), OR ($|$), NOT ($!$), XOR ($/$)
 - Logic depends on incoming arrows
- « Set of discrete variables as **abstractions of activity level** linked by logical rules as **signed interactions**
- « **Attractors** are subgraphs of the **state transition graph** with no outgoing arrows: can be stable states & cyclic attractors
- « Stable states = cell fates = phenotypes
- « Updating dynamics can be
 - synchronous: **all variables** that can be updated are updated
 - asynchronous: **only one variable** is updated at a time

Two examples of models: TNF response and cell fates and Metastasis model

A



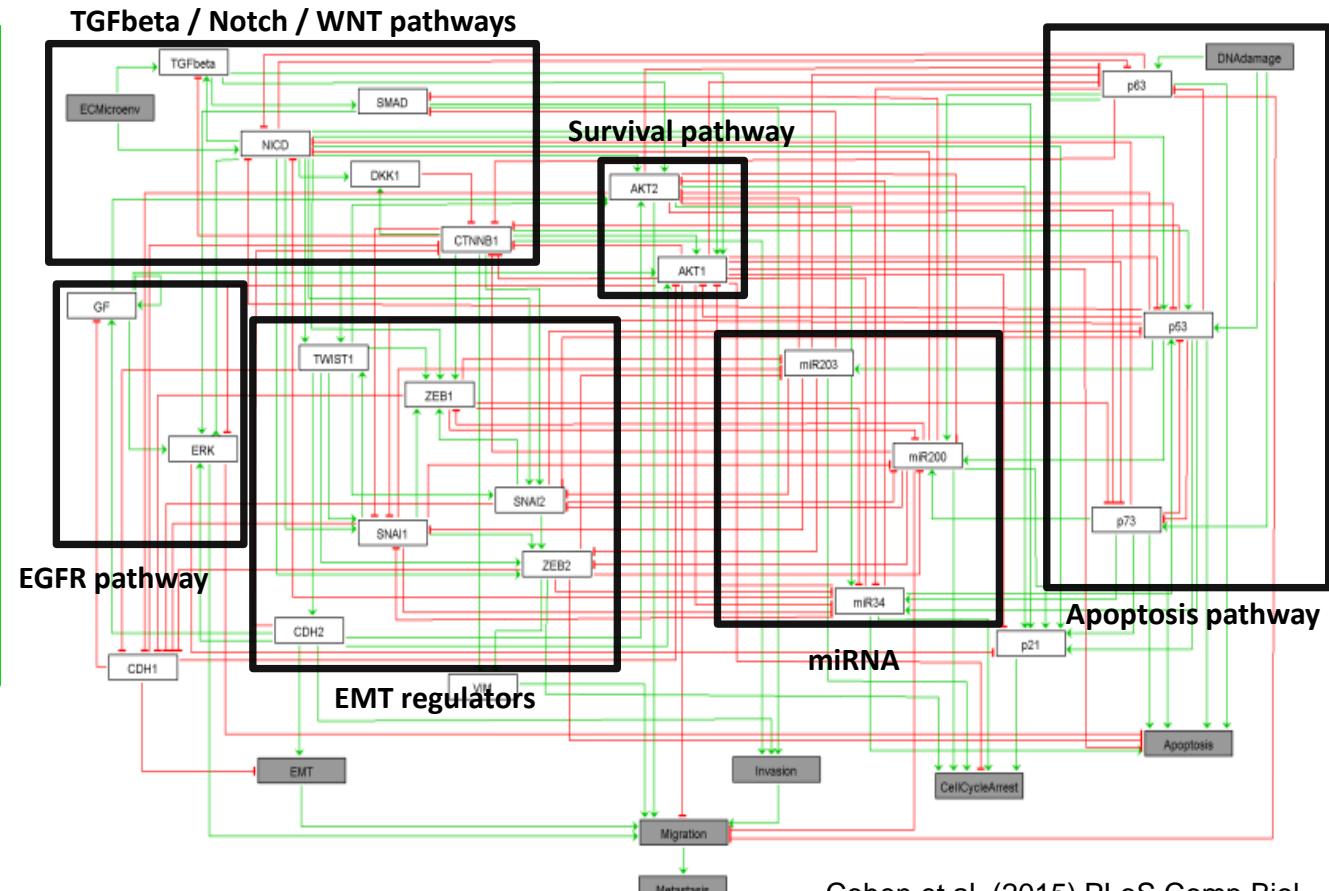
Letort et al., *Bioinformatics*, 2018, bty766

B

Convenient way to model regulatory and signalling networks

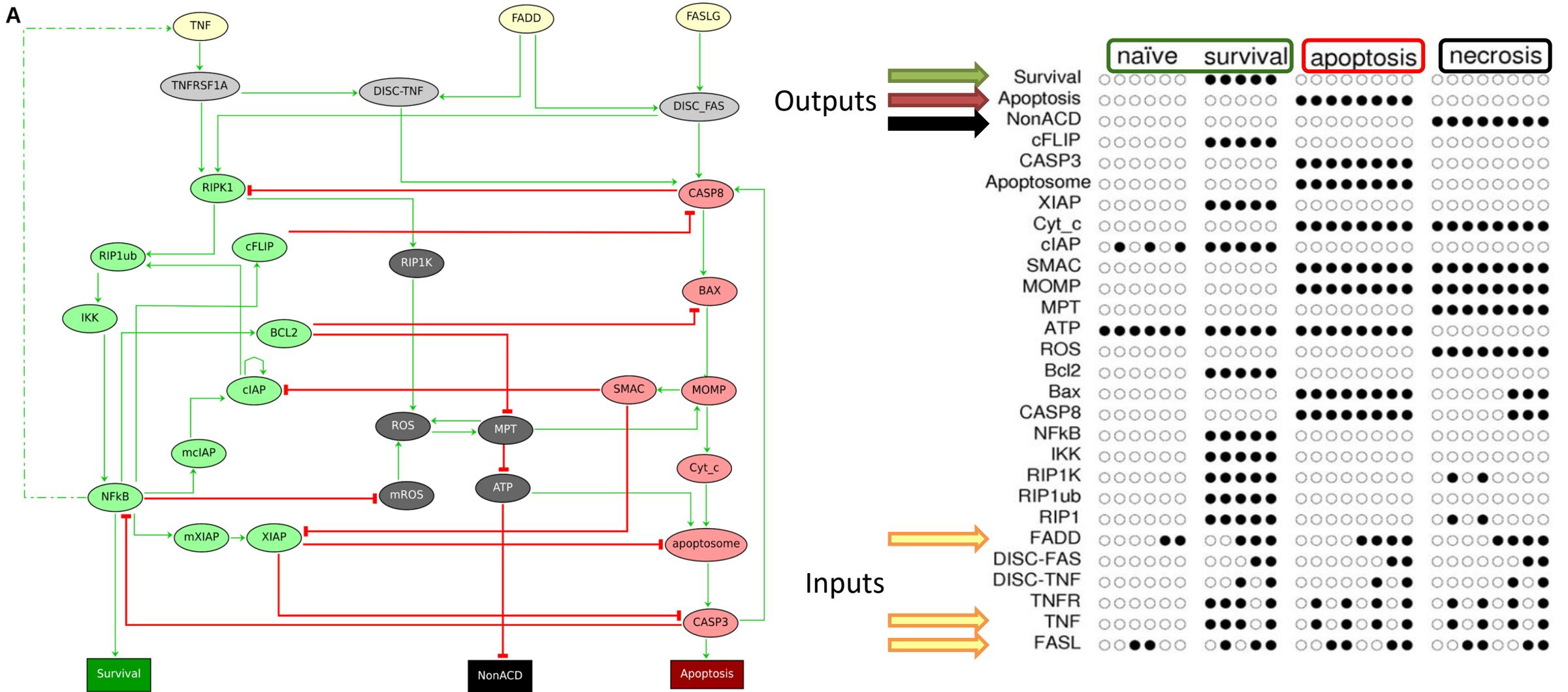
- Allows integration of literature & heterogeneous data
- Provides qualitative analysis

TGFbeta / Notch / WNT pathways



Cohen et al. (2015) PLoS Comp Biol

TNF response and cell fates



Analysing stable states probabilistically

« Continuous time Markov process on the Boolean transition state space

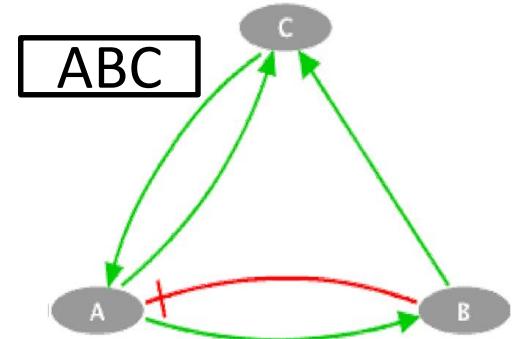
- Each Boolean state has an associated **probability**
- **Rate of change** associated to each transition
 - rate up and rate down
- Stochasticity, time, probabilities, ...

« Perturbations can be studied in a **probabilistic manner**

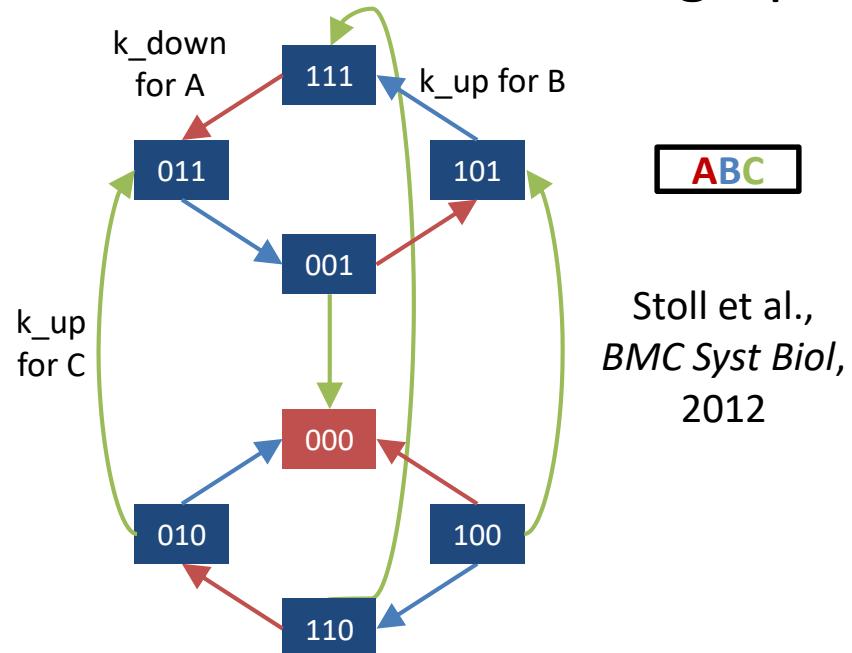
- Transient effects, such as knock downs
- **Dosage** experiments

« More information:

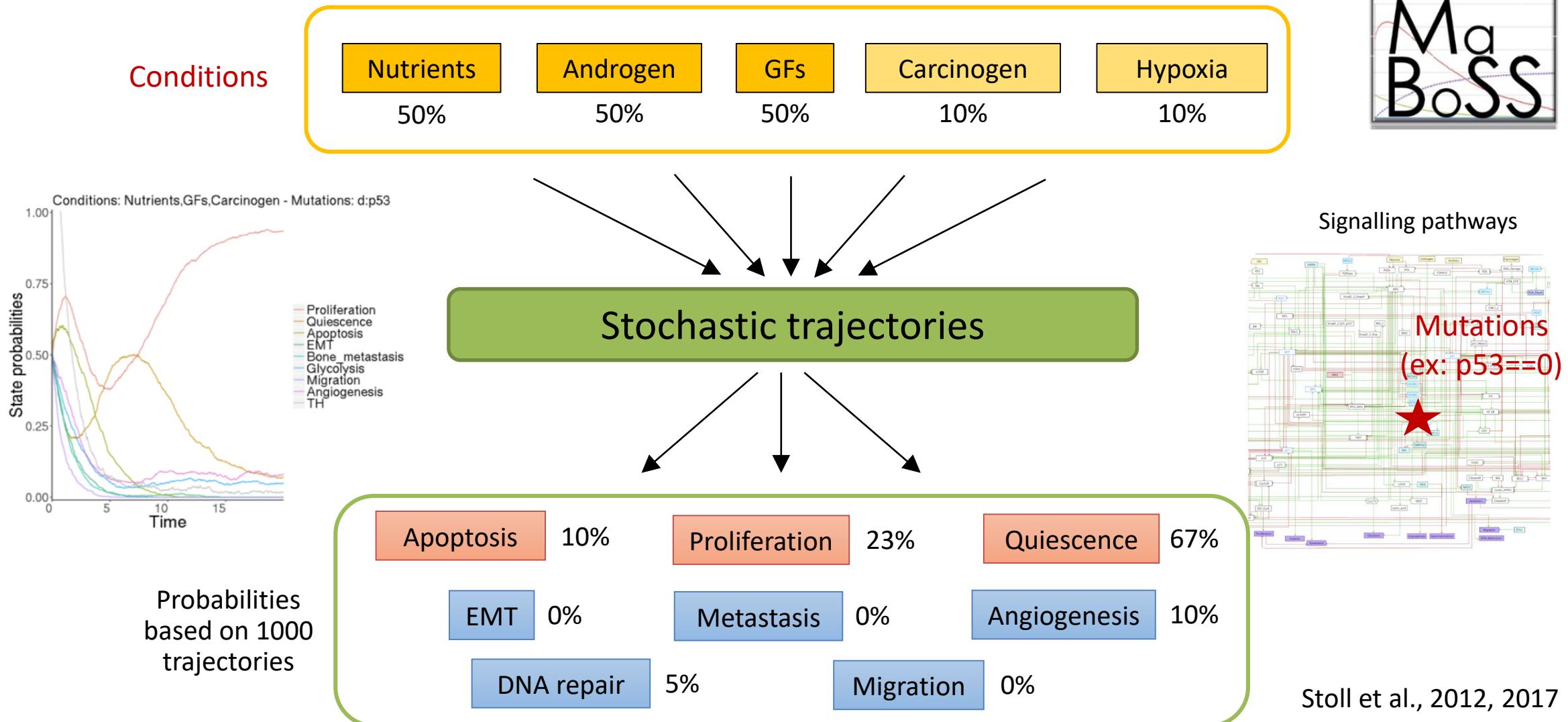
- Stoll et al., *BMC Syst Biol*, 2012, DOI: 10.1186/1752-0509-6-116
- Stoll et al., *Bioinformatics*, 2017, DOI: 10.1093/bioinformatics/btx123



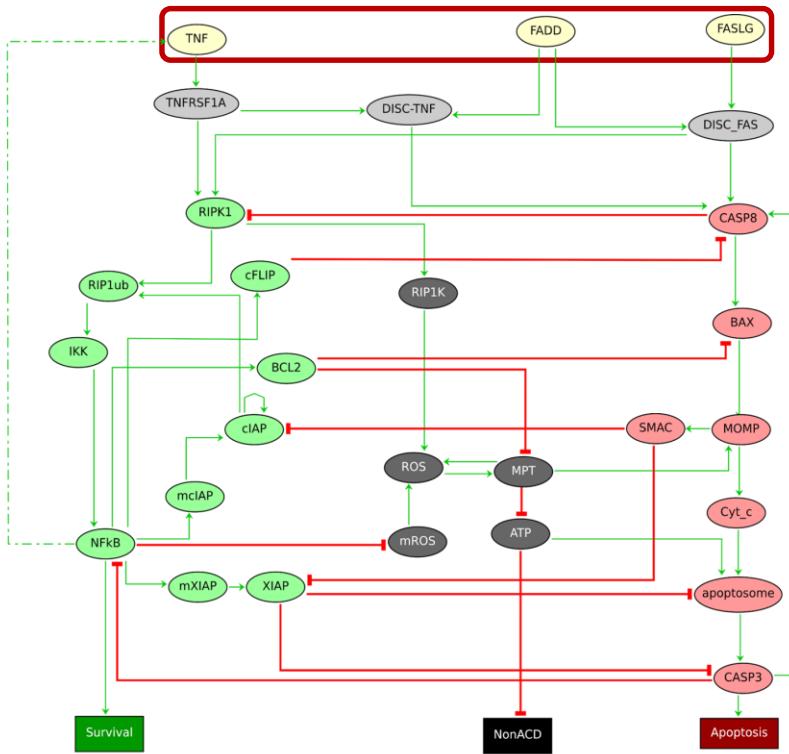
Boolean state transition graph



Stochastic simulations



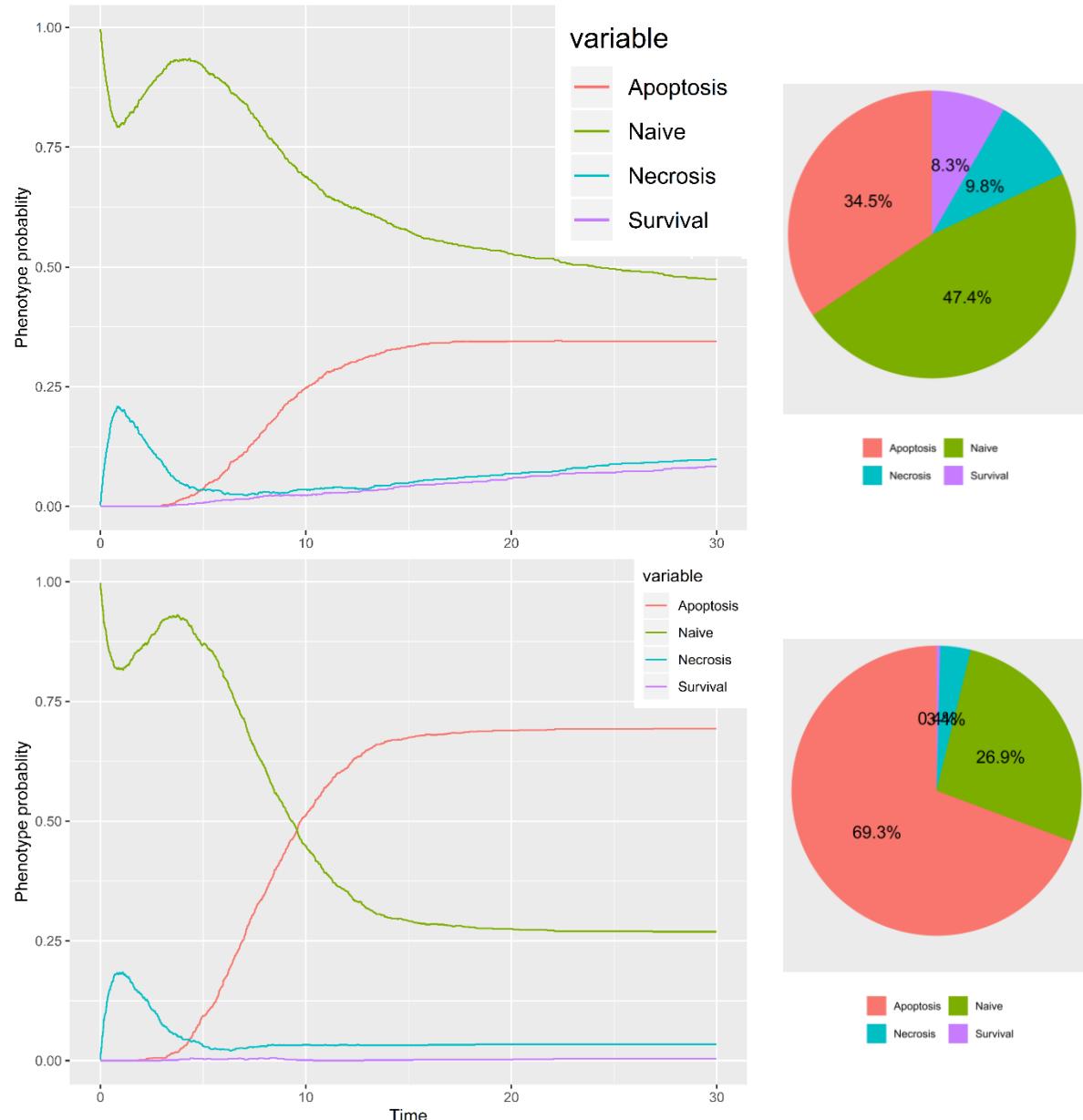
TNF response and cell fates' probabilities



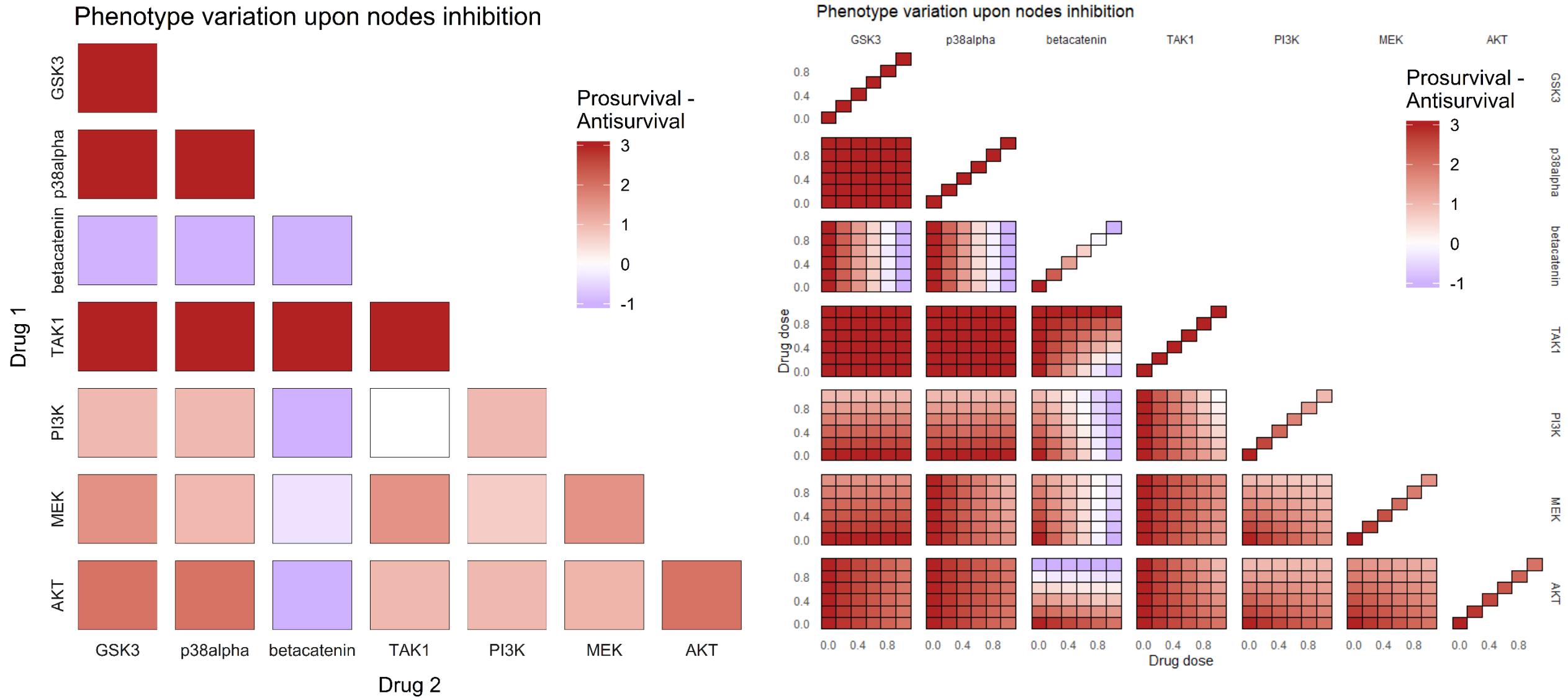
All inputs
random initial
conditions



FADD initial
condition = 1

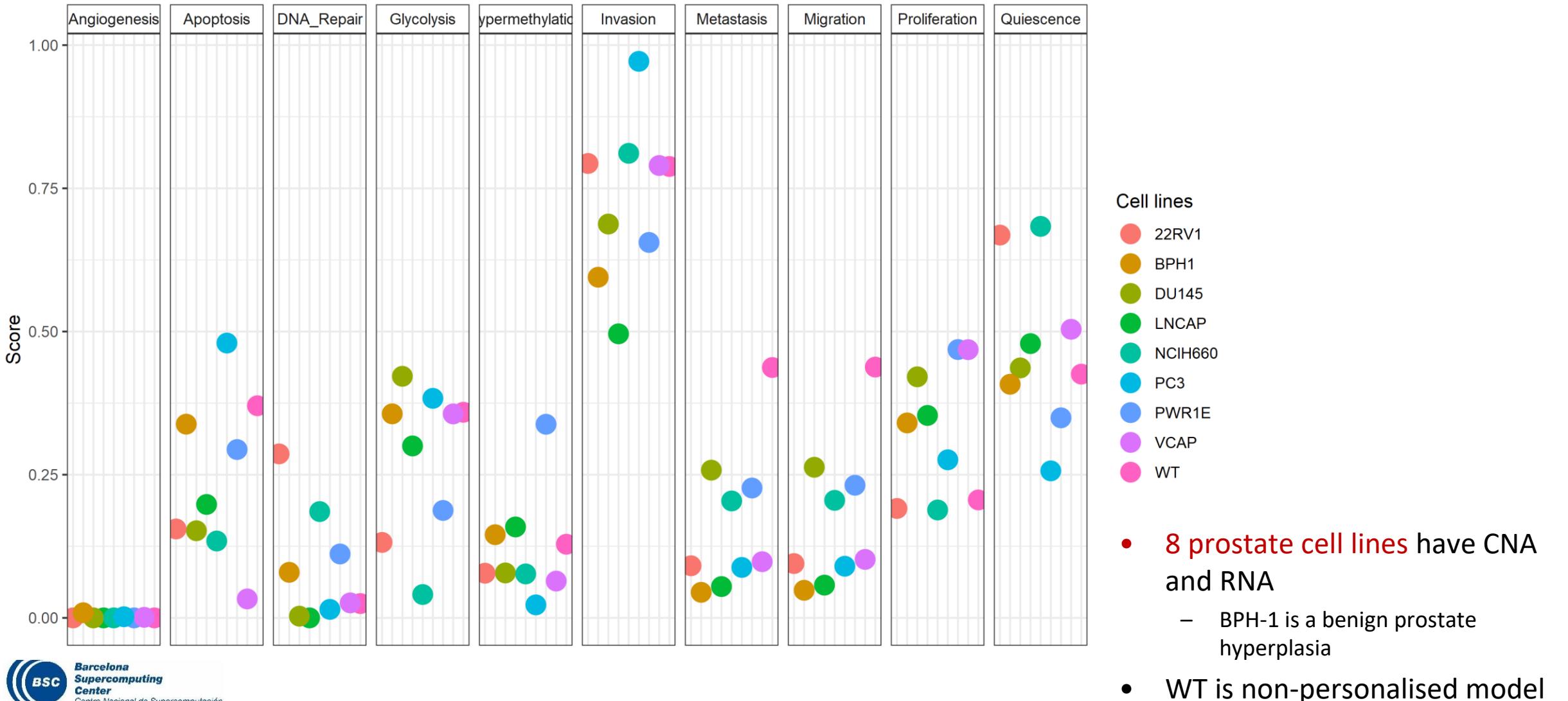


MaBoSS allows to explore drug dosages

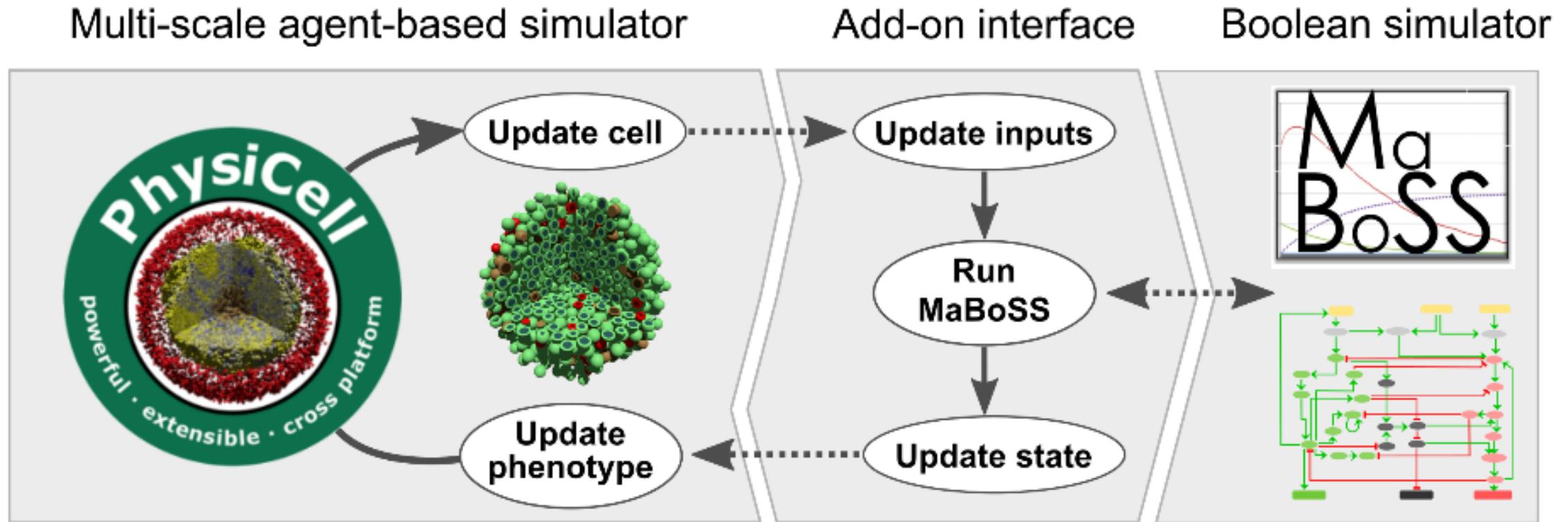


MaBoSS allows to have data-tailored Boolean models

Distribution of phenotypes scores across GDSC prostate cohort,
using Mutations as node states, RNA as transition rates
and random initial conditions



PhysiBoSS integrates the agents from PhysiCell and the signalling from MaBoSS



Letort et al., *Bioinformatics*, 2018, bty766
Ponce de Léon, Montagud, et al, in preparation

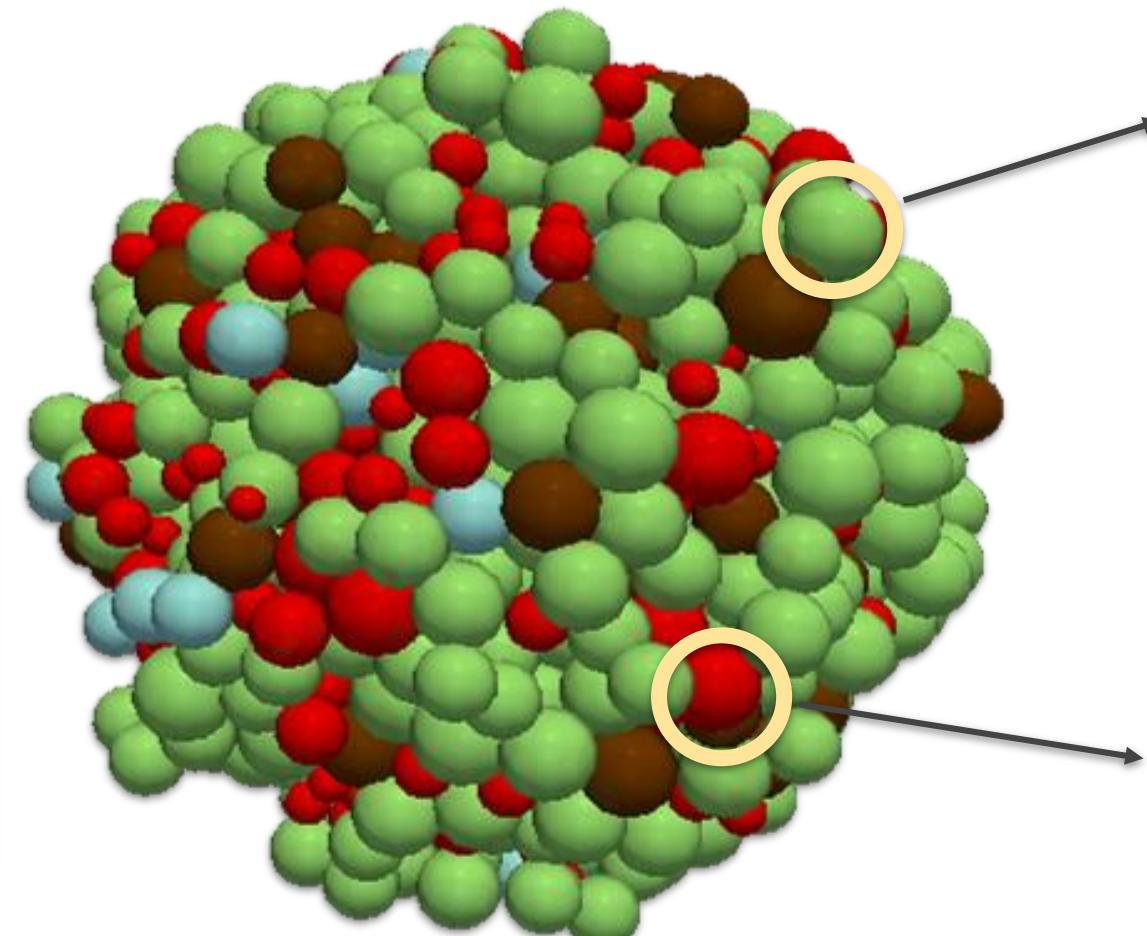
Different cells have different signalling states

Cell Cycle Phase

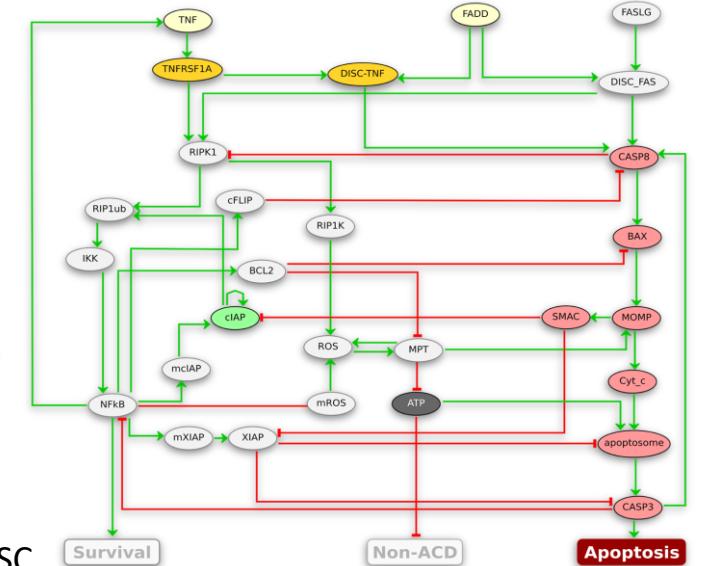
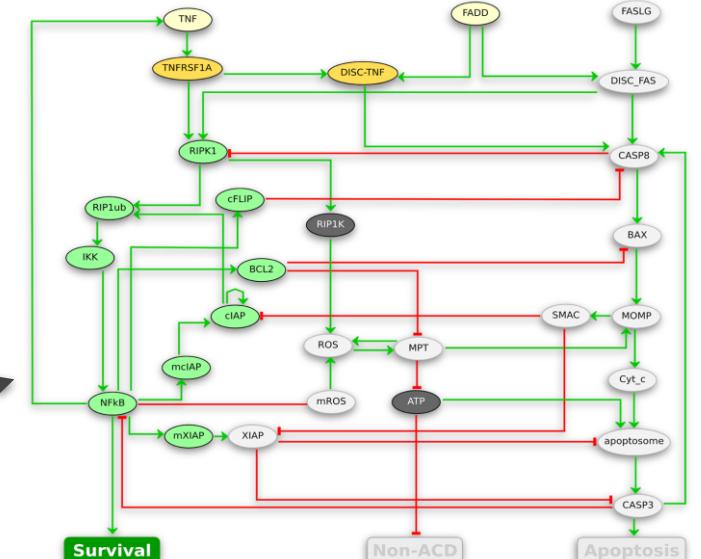
- Premitotic
- Postmitotic
- Ki67 negative
- Apoptotic
- Necrotic
- Necrotic (swelling)
- Necrotic (lysis)

Time scales

- $\Delta t_{\text{diff}} / \Delta t_{\text{mech}} / \Delta t_{\text{cell}}$
- $\Delta t_{\text{signaling}}$

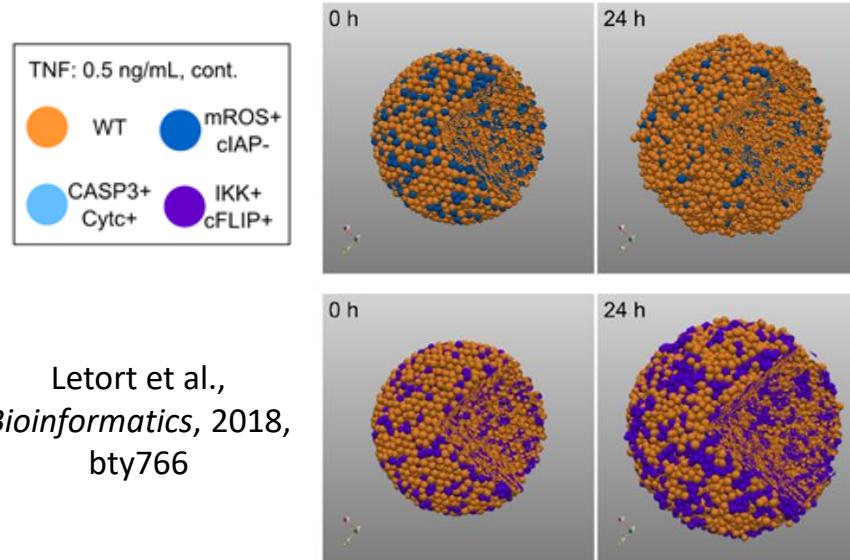


Slide from M. Ponce de León, BSC

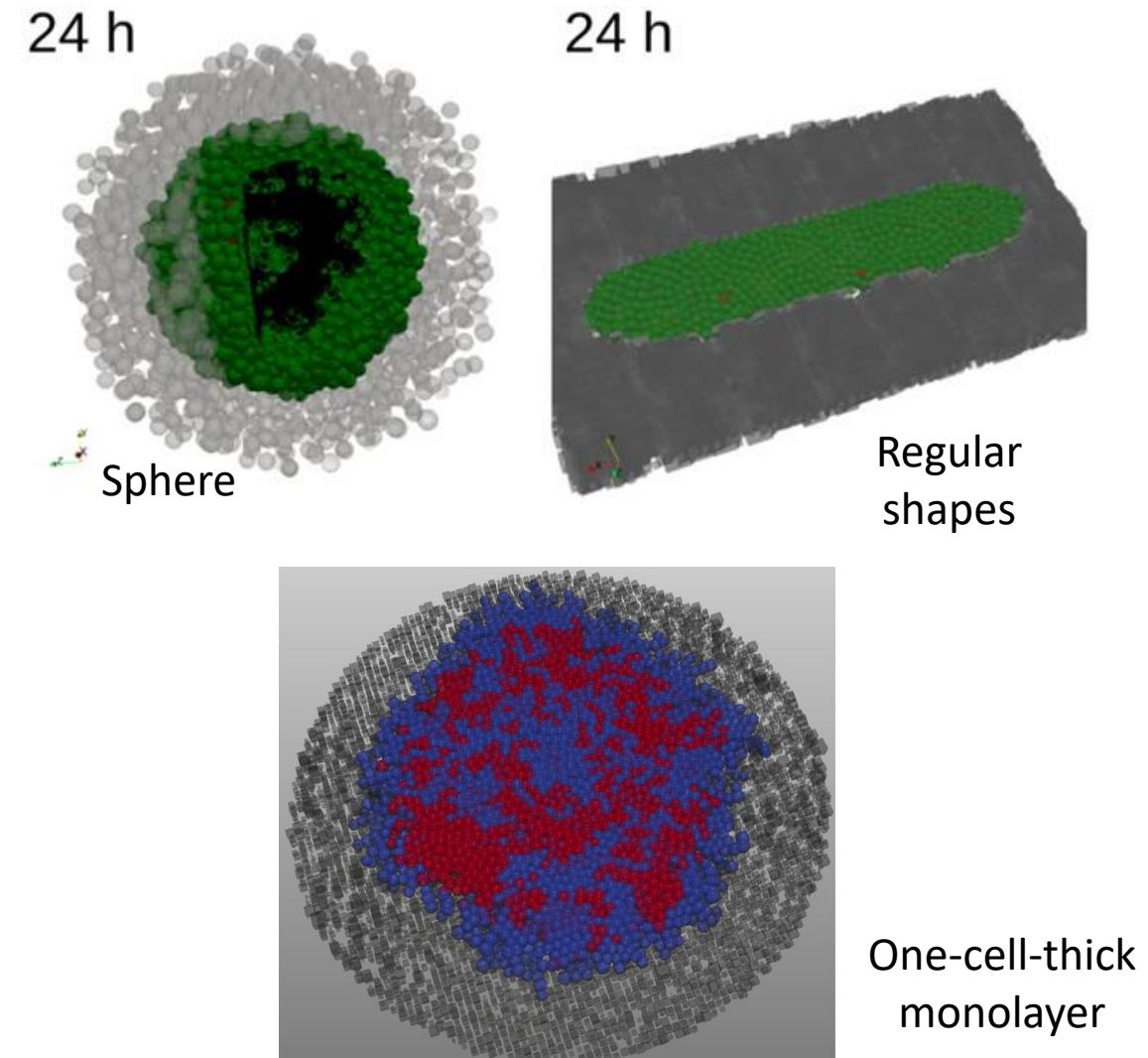


Agents can represent different cell strains

- With **different biology**
 - WT and mutants
 - Patient-specific networks
- With **different physical properties**
 - Cell-cell adhesion
 - Cell-matrix adhesion



Different tumour architectures

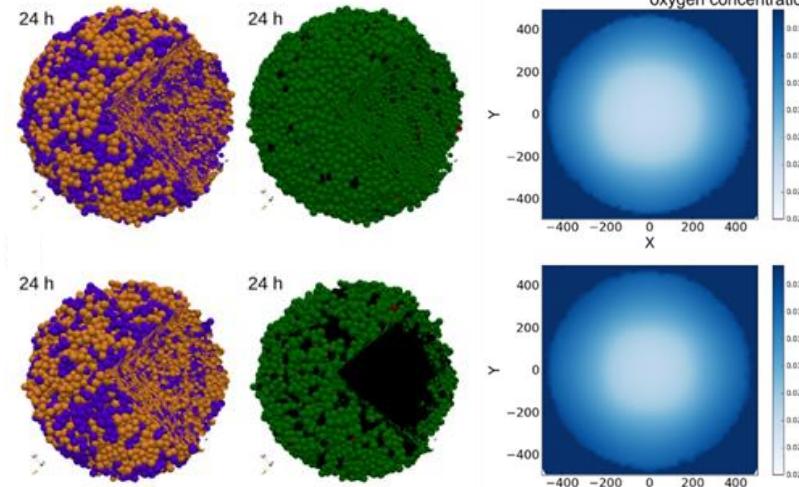


The framework allows for different environments

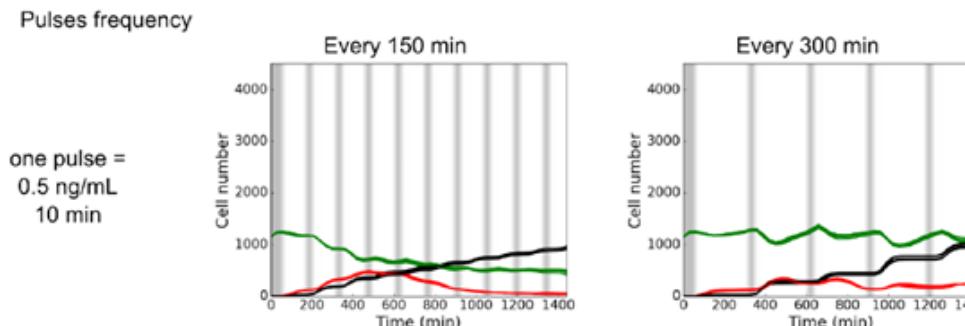
PhysiBoSS

« Dynamical environment with diffusible entities

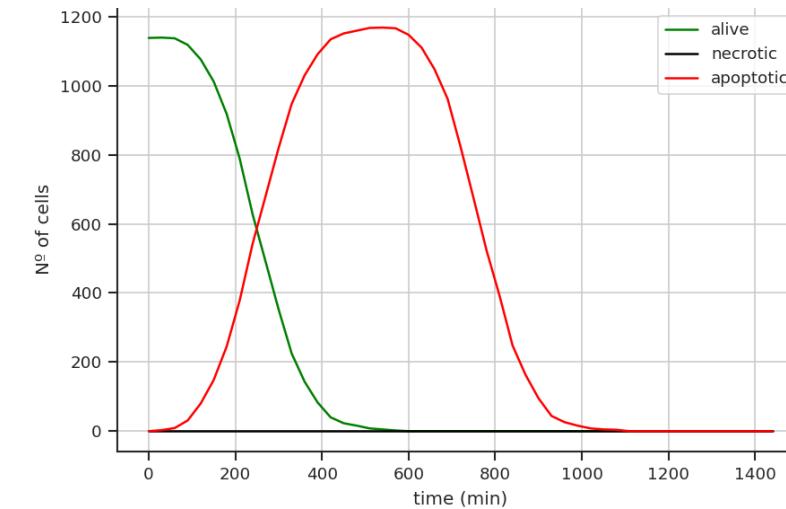
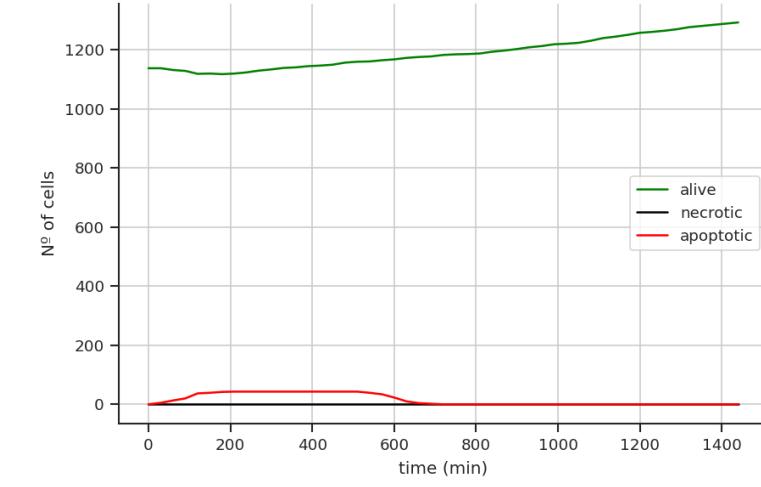
Oxygen
Glucose



Intercellular communication:
Pulses of TNF



« Different combinations of drugs

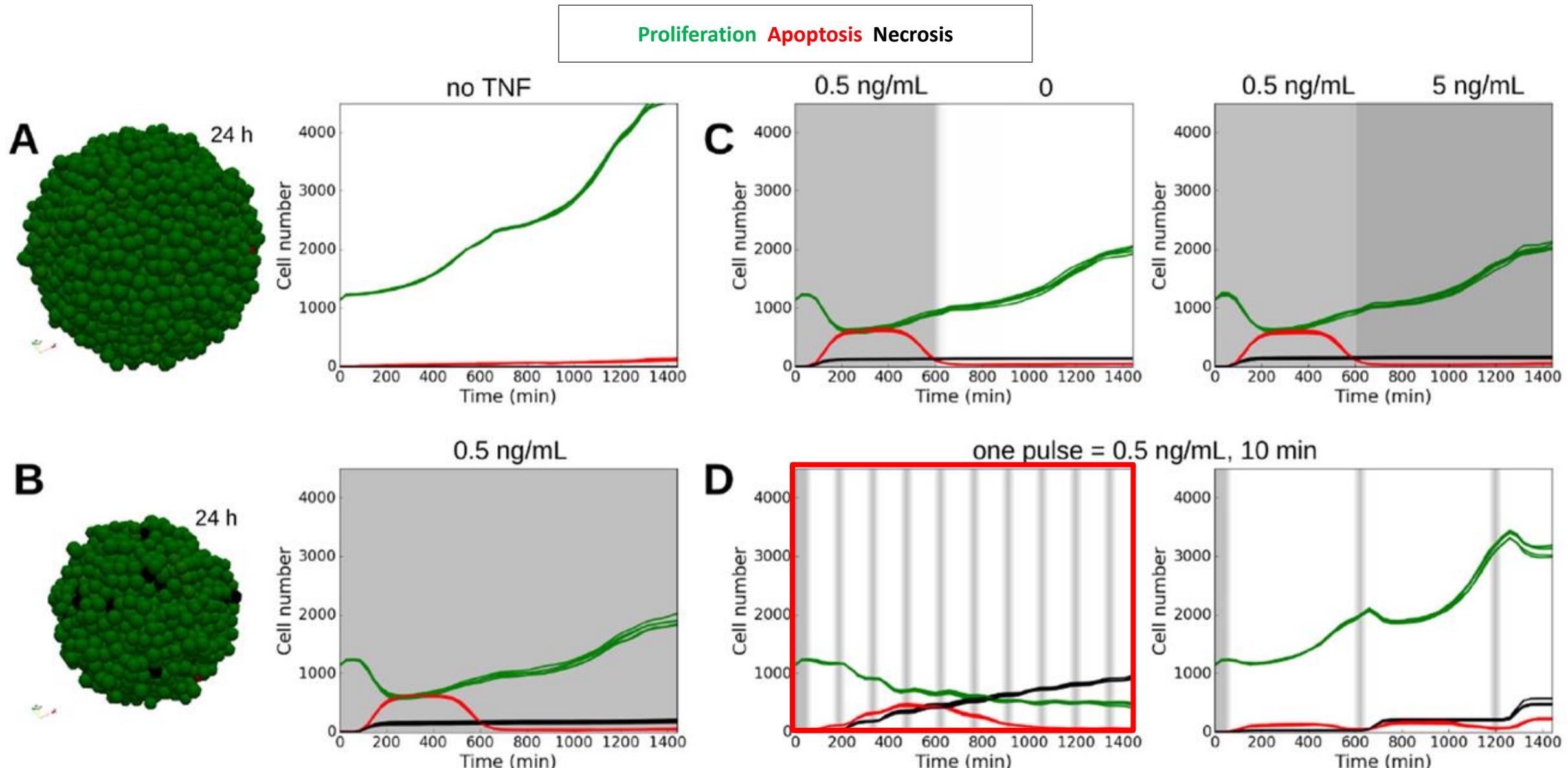


AKTi

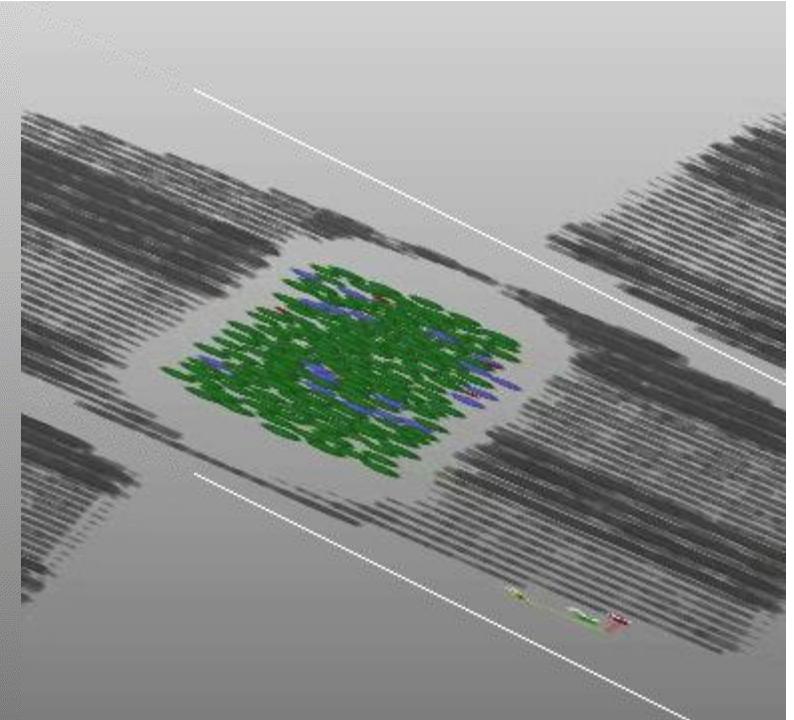
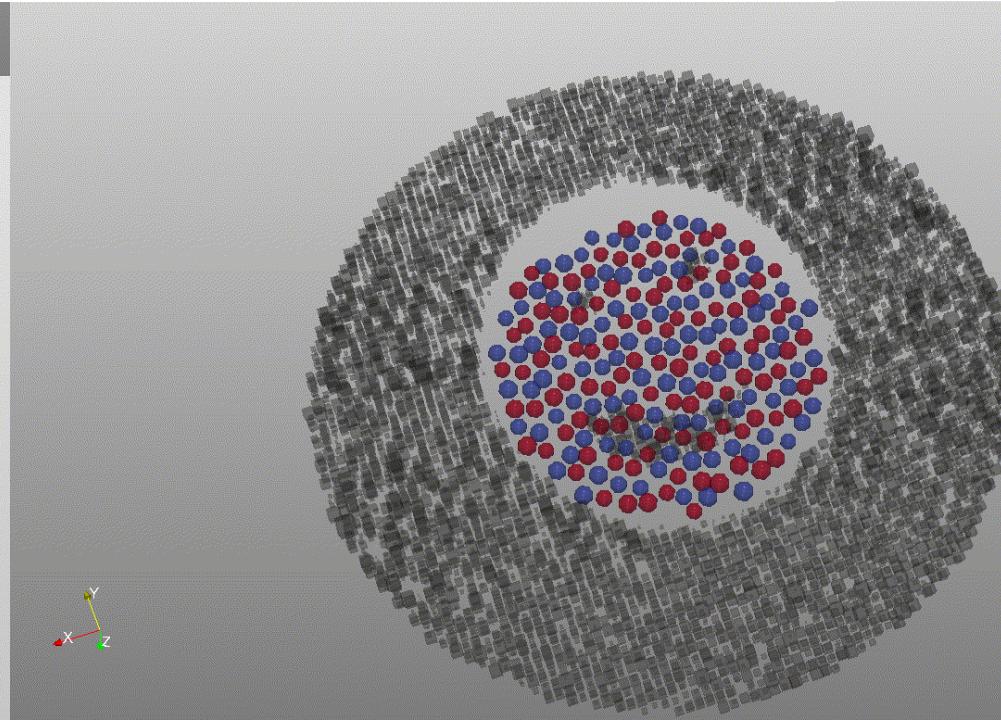
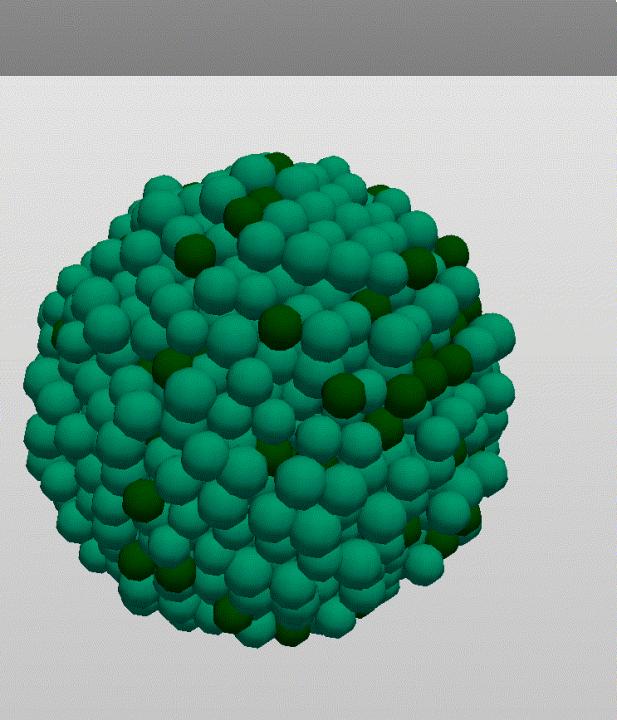
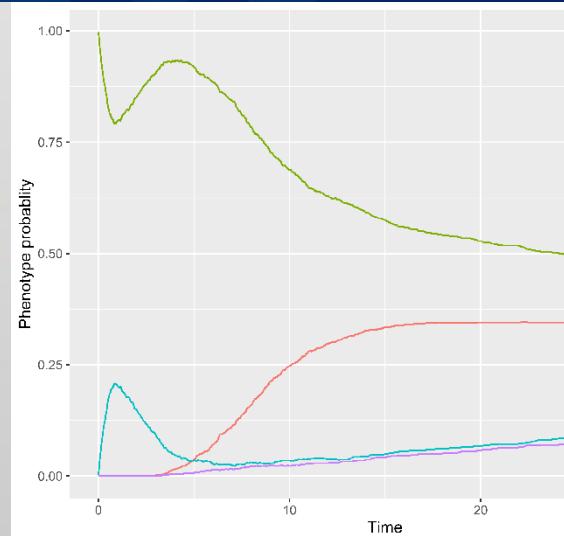
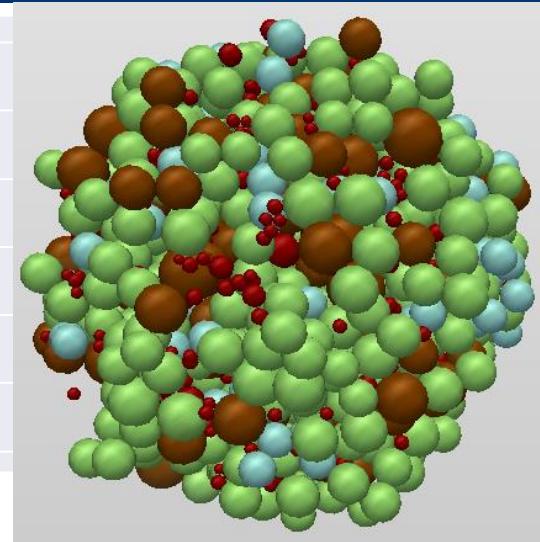
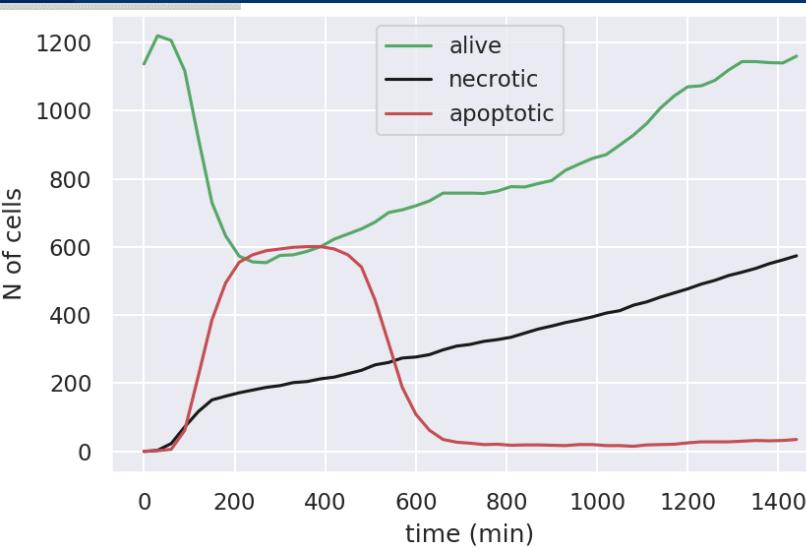
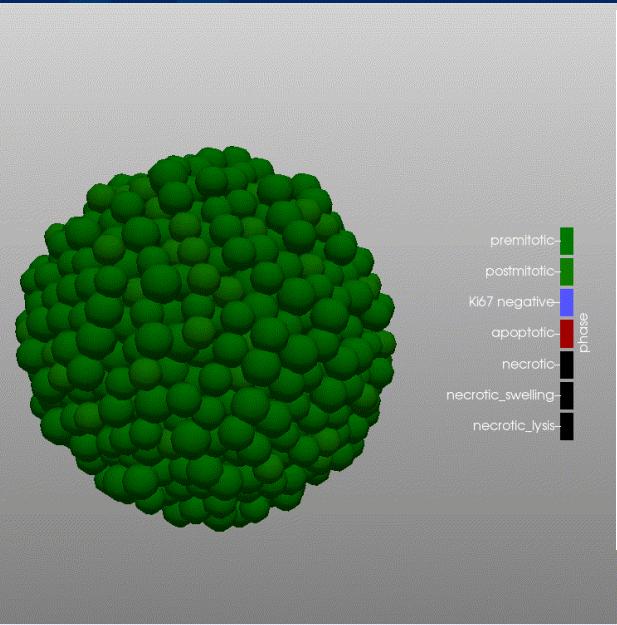
AKTi +
BCATi

The framework allows for finding optimal drug regimes

PhysiBoSS



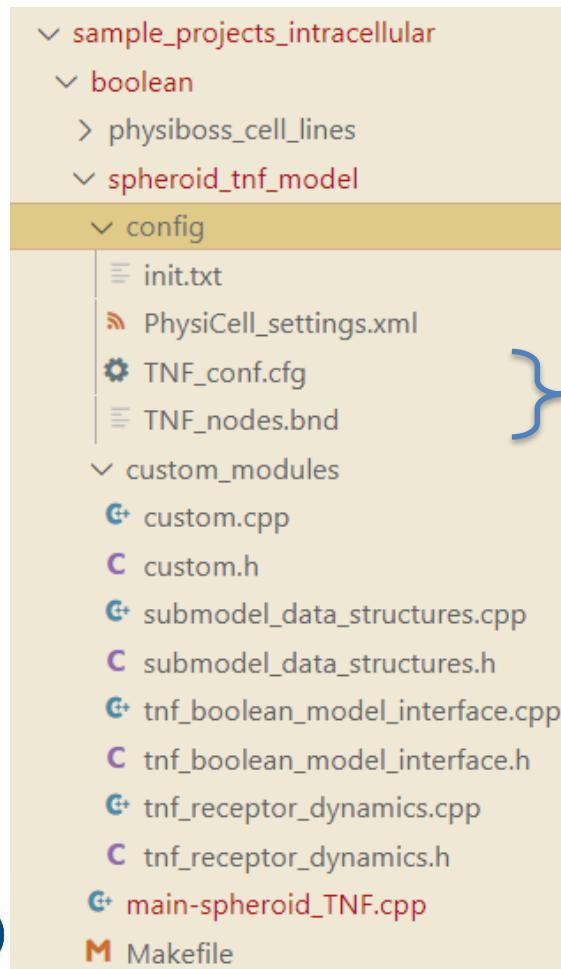
Examples of use of PhysiBoSS



Let's see some code !

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

- /sample_projects_intracellular/boolean/
physiboss_cell_lines



PhysiCell configuration

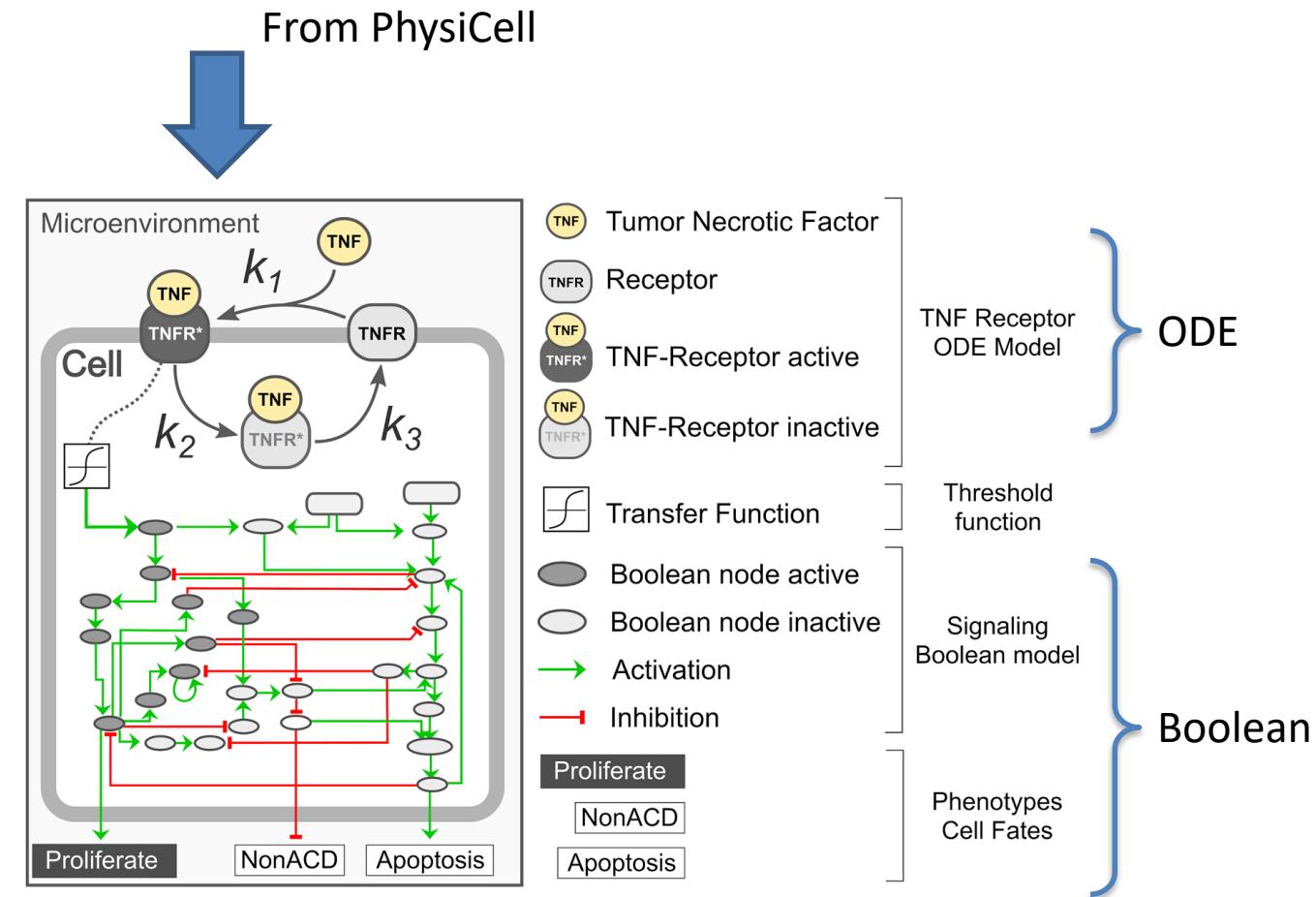
Boolean model

Structural functions

Submodel definitions

PhysiCell ↔ MaBoSS interface

ODE dynamics



<https://arxiv.org/abs/2103.14132>

tnf_boolean_model_interface file

```
sample_projects_intracellular > boolean > spheroid_tnf_model > custom_modules > C tnf_boolean_model_interface.h > ..  
21  
22 #include "../core/PhysiCell.h"  
23 #include "../modules/PhysiCell_standard_modules.h"  
24  
25 using namespace BioFVM;  
26 using namespace PhysiCell;  
27  
28 #include "./submodel_data_structures.h"  
29  
30 void tnf_boolean_model_interface_setup();  
31  
32 void update_boolean_model_inputs( Cell* pCell, Phenotype& phenotype, double dt );  
33  
34 void update_cell_from_boolean_model( Cell* pCell, Phenotype& phenotype, double dt );  
35  
36 void tnf_bm_interface_main( Cell* pCell, Phenotype& phenotype, double dt );
```

```
> custom_modules > C tnf_boolean_model_interface.cpp > update_cell_from_boolean_model(Cell *, Phenotype &, double)  
123  
124 void tnf_bm_interface_main( Cell* pCell, Phenotype& phenotype,  
125 double dt )  
126 {  
127     if( phenotype.death.dead == true )  
128     {  
129         pCell->functions.update_phenotype = NULL;  
130         return;  
131     }  
132  
133     if ( pCell->phenotype.intracellular->need_update() )  
134     {  
135         // First we update the Boolean Model inputs  
136         update_boolean_model_inputs(pCell, phenotype, dt );  
137  
138         // Run maboss to update the boolean state of the cell  
139         pCell->phenotype.intracellular->update();  
140  
141         // update the cell fate based on the boolean outputs  
142         update_cell_from_boolean_model(pCell, phenotype, dt );  
143  
144         // Get track of some boolean node values for debugging  
145         update_monitor_variables(pCell);  
146     }  
147  
148 }  
149  
return;
```

update_cell_from_boolean_model function

```
> custom_modules > tnf_boolean_model_interface.cpp > update_cell_from_boolean_model(Cell *, Phenotype &, double
55
56
57
58
59
60
61
62
63
64
65
66 void update_cell_from_boolean_model(Cell* pCell, Phenotype&
phenotype, double dt)
67 {
68     static int nTNF_external = microenvironment.find_density_index
("tnf");
69     static int nTNF_export_rate = pCell->custom_data.
find_variable_index("TFN_net_production_rate");
70
71     static int apoptosis_model_index = phenotype.death.
find_death_model_index("Apoptosis");
72     static int necrosis_model_index = phenotype.death.
find_death_model_index("Necrosis");
73
74 // Getting the state of the boolean model readouts (Readout
can be in the XML)
75     bool apoptosis = pCell->phenotype.
intracellular->get_boolean_variable_value("Apoptosis");
76     bool nonACD = pCell->phenotype.
intracellular->get_boolean_variable_value("NonACD");
77     bool survival = pCell->phenotype.
intracellular->get_boolean_variable_value("Survival");
78     bool NFkB = pCell->phenotype.
intracellular->get_boolean_variable_value("NFkB");
79
80     if (apoptosis)
81     {
82         pCell->start_death(apoptosis_model_index);
83         return;
84     }
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107 }
```

```
> custom_modules > tnf_boolean_model_interface.cpp > update_cell_from_boolean_model(Cell *, Phenotype &, double
79
80     if ( apoptosis )
81     {
82         pCell->start_death(apoptosis_model_index);
83         return;
84     }
85
86     if ( nonACD )
87     {
88         pCell->start_death(necrosis_model_index);
89         return;
90     }
91
92     if ( survival && pCell->phenotype.cycle.current_phase_index()
== PhysiCell_constants::Ki67_negative )
93     {
94         pCell->phenotype.cycle.advance_cycle(pCell, phenotype, dt)
95     }
96
97     // If NFkB node is active produce some TNF
98     if ( NFkB )
99     {
100         phenotype.secretion.net_export_rates[nTNF_external] =
pCell->custom_data[nTNF_export_rate];
101     } else
102     {
103         phenotype.secretion.net_export_rates[nTNF_external] = 0;
104     }
105
106     return;
107 }
```

update_monitor_variables and update_boolean_model_inputs functions

```
custom_modules > tnf_boolean_model_interface.cpp > update_cell_from_boolean_model(Cell *, Phenotype &, double)
109
110 void update_monitor_variables(Cell* pCell)
111 {
112     static int index_tnf_node = pCell->custom_data.
113         find_variable_index("tnf_node");
114     static int index_fadd_node = pCell->custom_data.
115         find_variable_index("fadd_node");
116     static int index_nfk_b_node = pCell->custom_data.
117         find_variable_index("nfbk_node");
118
119     pCell->custom_data[index_nfk_b_node] = pCell->phenotype.
120         intracellular->get_boolean_variable_value( "NFKB" );
121     pCell->custom_data[index_tnf_node] = pCell->phenotype.
122         intracellular->get_boolean_variable_value("TNF");
123     pCell->custom_data[index_fadd_node] = pCell->phenotype.
124         intracellular->get_boolean_variable_value("FADD");
125
126     return;
127 }
```

```
> spheroid_tnf_model > custom_modules > tnf_boolean_model_interface.cpp > tnf_boolean_model_interface_setup()
44
45 void update_boolean_model_inputs( Cell* pCell, Phenotype&
46 phenotype, double dt )
47 {
48     if( pCell->phenotype.death.dead == true )
49     { return; }
50
51     static int nR_EB = pCell->custom_data.find_variable_index(
52         "bound_external_TNFR" );
53
54     static int nTNF_threshold = pCell->custom_data.
55         find_variable_index( "TNFR_activation_threshold" );
56
57     // This is the step transfer function used to update the state
58     // of boolean model inputs
59     // using the state of the receptor dynamics model. The
60     // continuos value thresholded is
61     // the total TNF-receptor complex (doi:10.1016/j.cellsig.2010.
62     // 08.016)
63     if ( pCell->custom_data[nR_EB] > pCell->custom_data
64 [nTNF_threshold] )
65     { pCell->phenotype.intracellular->set_boolean_variable_value
66 ("TNF", 1); }
67     else
68     { pCell->phenotype.intracellular->set_boolean_variable_value
69 ("TNF", 0); }
70
71     return;
72 }
```

custom file

sample_projects_intracellular > boolean > spheroid_tnf_model > custom_modules > **C** custom.h > ...

```
79 struct init_record
80 {
81     float x;
82     float y;
83     float z;
84     float radius;
85     int phase;
86     double elapsed_time;
87 };
88
89 //setup functions to help us along
90 void create_cell_types( void );
91 void setup_tissue( void );
92
93 //set up the BioFVM microenvironment
94 void setup_microenvironment( void );
95
96 //custom pathology coloring function
97 std::vector<std::string> my_coloring_function( Cell* );
98
99 //custom cell phenotype function to update cell fate based on the
100 //BM and the
101 //tnf receptor model dynamics
102 void tumor_cell_phenotype_with_signaling( Cell* pCell, Phenotype&
103     phenotype, double dt );
104
105 //function to keep updated some cell custom variables
106 void update_monitor_variables( Cell* pCell );
107
108 //helper function to read init files
109 std::vector<init_record> read_init_file(std::string filename, char
110     delimiter, bool header);
```

sample_projects_intracellular > boolean > spheroid_tnf_model > custom_modules > **C** custom.h > ...

```
108
109 //helper function that calculates sphere volume
110 inline float sphere_volume_from_radius(float radius) {return 4/3 * 
111     PhysiCell_constants::pi * std::pow(radius, 3);}
112
113 //helper function to inject density surrounding a spheroid
114 void inject_density_sphere(int density_index, double
115     concentration, double membrane_lenght);
116
117 //helper function to remove a density
118 void remove_density( int density_index );
119
120 //function to create a message
121 //std::string cells_message_builder(std::vector<Cell*> all_cells,
122 //double timepoint);
123
124 double total_live_cell_count();
125
126 double total_dead_cell_count();
127
128 |
```

Intracellular class in core/PhysiCell_phenotype file

core > C PhysiCell_phenotype.h > {} PhysiCell > Intracellular

```
549 class Intracellular
550 {
551     private:
552     public:
553         std::string intracellular_type; //specified in XML
554         <intracellular type="...": "maboss", "sbml", ...
555         //bool enabled;
556
557         //===== specific to SBML =====
558         //std::string sbml_filename;
559
560         //===== generic =====
561         //This function parse the xml cell definition
562         virtual void initialize_intracellular_from_pugixml
563             (pugi::xml_node& node) = 0;
564
565         //This function initialize the model, needs to be called on
566         //each cell once created
567         virtual void start() = 0;
568
569         //This function checks if it's time to update the model
570         virtual bool need_update() = 0;
571
572         //This function update the model for the time_step defined in
573         //the xml definition
574         virtual void update() = 0;
575
576         //Get value for model parameter
577         virtual double get_parameter_value(std::string name) = 0;
578
579         //Set value for model parameter
580         virtual void set_parameter_value(std::string name, double value)
```

core > C PhysiCell_phenotype.h > {} PhysiCell

```
576     // Set value for model parameter
577     virtual void set_parameter_value(std::string name, double value)
578         = 0;
579
580     virtual std::string get_state() = 0;
581
582     virtual Intracellular* clone() = 0;
583
584
585     //===== specific to "maboss" =====
586     virtual bool has_variable(std::string name) = 0;
587     virtual bool get_boolean_variable_value(std::string name) = 0;
588     virtual void set_boolean_variable_value(std::string name, bool
589         value) = 0;
590
591     //virtual bool get_double_variable_value(std::string name) = 0;
592     //virtual void set_double_variable_value(std::string name, bool
593         value) = 0;
594     virtual void print_current_nodes() = 0;
595
596
597     //===== specific to "roadrunner" =====
598     virtual int update_phenotype_parameters(PhysiCell::Phenotype&
599         phenotype) = 0;
600     virtual int validate_PhysiCell_tokens(PhysiCell::Phenotype&
601         phenotype) = 0;
602     virtual int validate_SBML_species() = 0;
603     virtual int create_custom_data_for_SBML(PhysiCell::Phenotype&
604         phenotype) = 0;
605 }
```

PhysiCell_settings.xml file

sample_projects_intracellular > boolean > spheroid_tnf_model > config > PhysiCell_settings.xml

```
154 <cell_definitions>
155   <cell_definition name="default" ID="0">
156     <phenotype>
157       <cycle code="5" name="live_cells_cycle_model">
158         <transition_rates units="1/min">
159           <!-- Cycle duration -->
160           <rate start_index="0" end_index="0"
161             fixed_duration="false">0.0075</rate>
162         </transition_rates>
163       </cycle>
164
165     <death>
166       <model code="100" name="apoptosis"> ...
167       </model>
168
169       <model code="101" name="necrosis"> ...
170       </model>
171     </death>
172
173     <secretion>
174       <substrate name="oxygen"> ...
175       </substrate>
176       <substrate name="tnf"> ...
177       </substrate>
178     </secretion>
179     <molecular />
180
181     <intracellular type="maboss">
182       <bnd_filename>./config/TNF_nodes.bnd</bnd_filename>
183       <cfg_filename>./config/TNF_conf.cfg</cfg_filename>
184       <time_step>10</time_step>
185     </intracellular>
186   </phenotype>
```



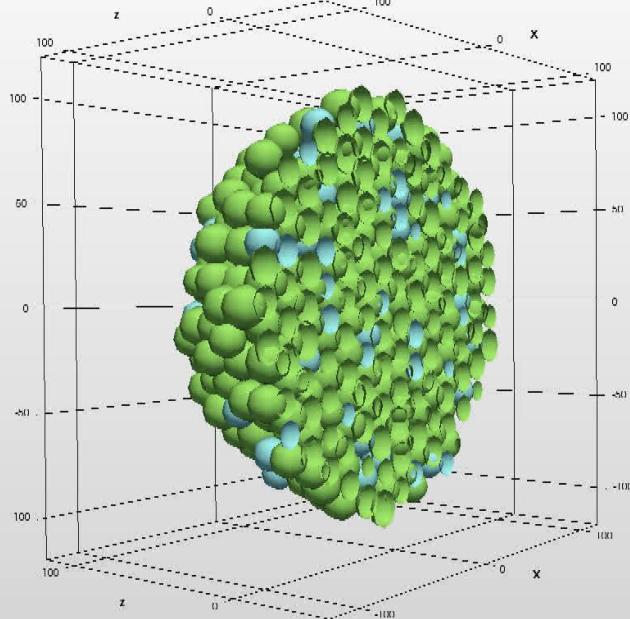
⌚ Intracellular key allows to

- Load & read model
- Set model values
 - Obtain mutants
 - Personalise models

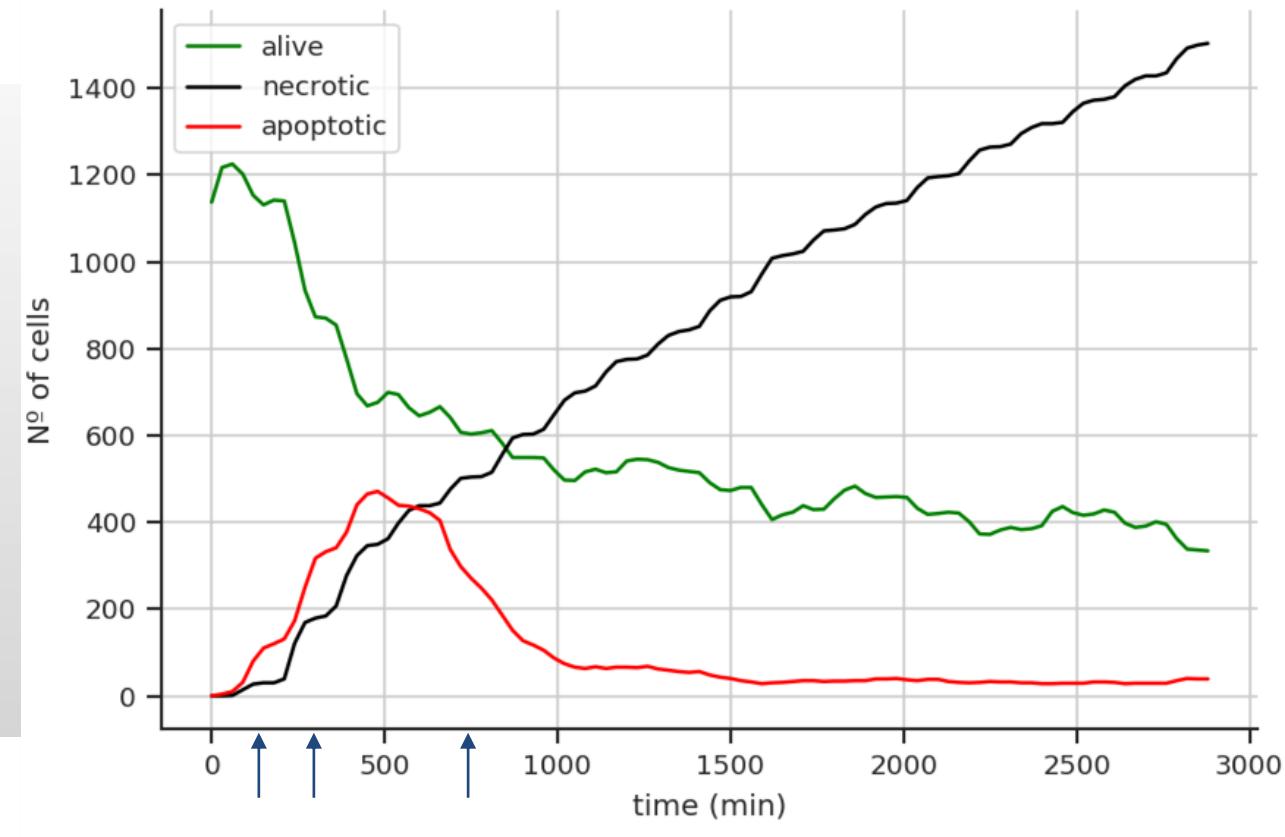
PhysiBoSS experiment: TNF pulse studies

Cell Cycle Phase

- [Green] Premitotic
- [Cyan] Postmitotic
- [Yellow] Ki67 negative
- [Red] Apoptotic
- [Brown] Necrotic
- [Dark Brown] Necrotic (swelling)
- [Grey] Necrotic (lysis)



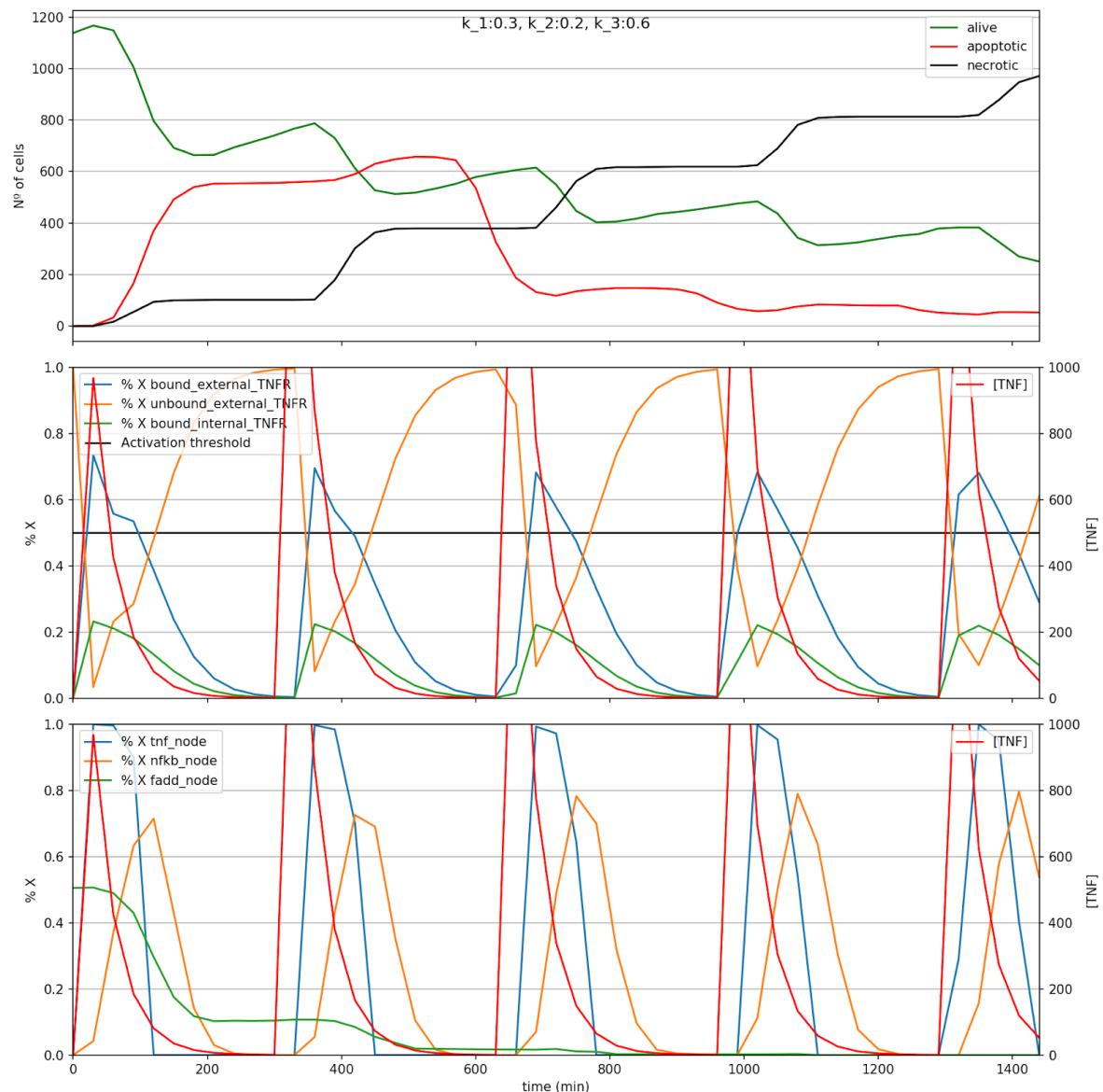
~48 h simulation time, 30 min wall time
~2500 cells



TNF pulses every 150 min

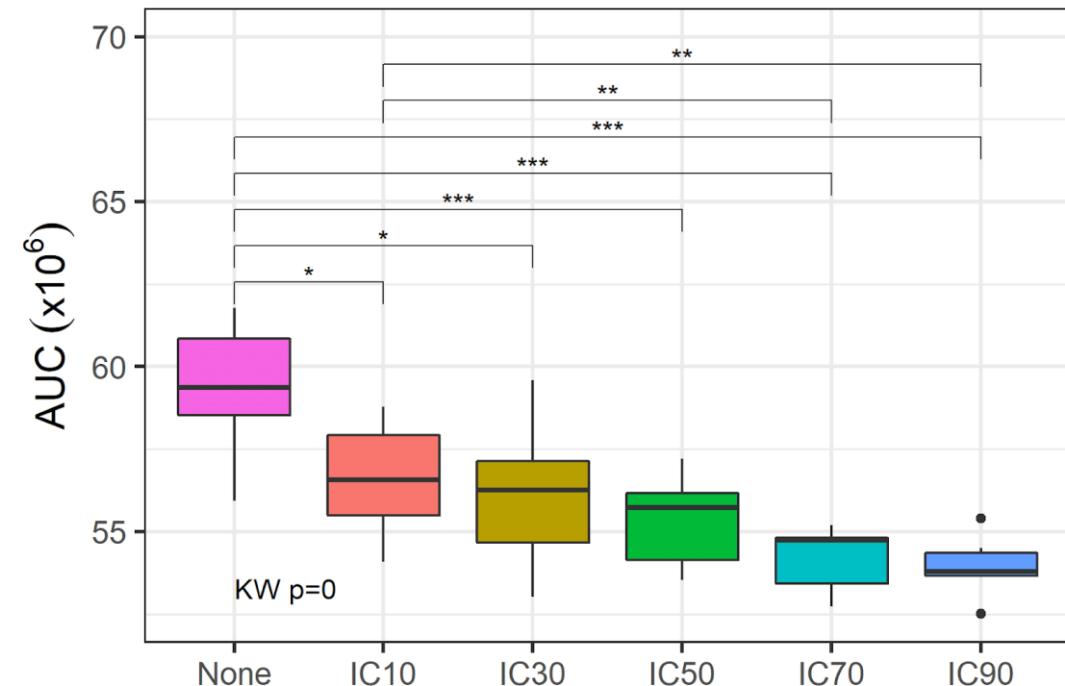
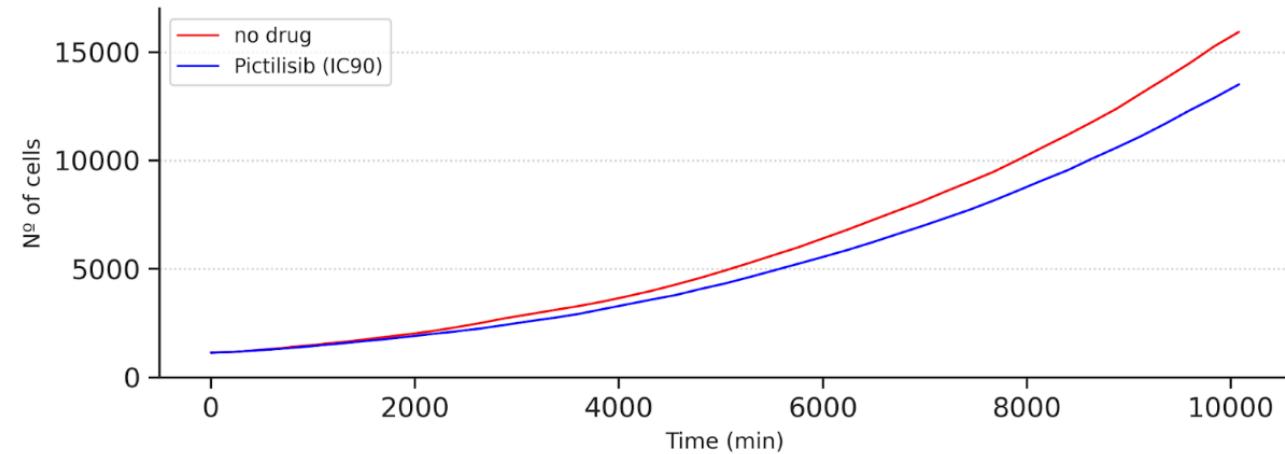
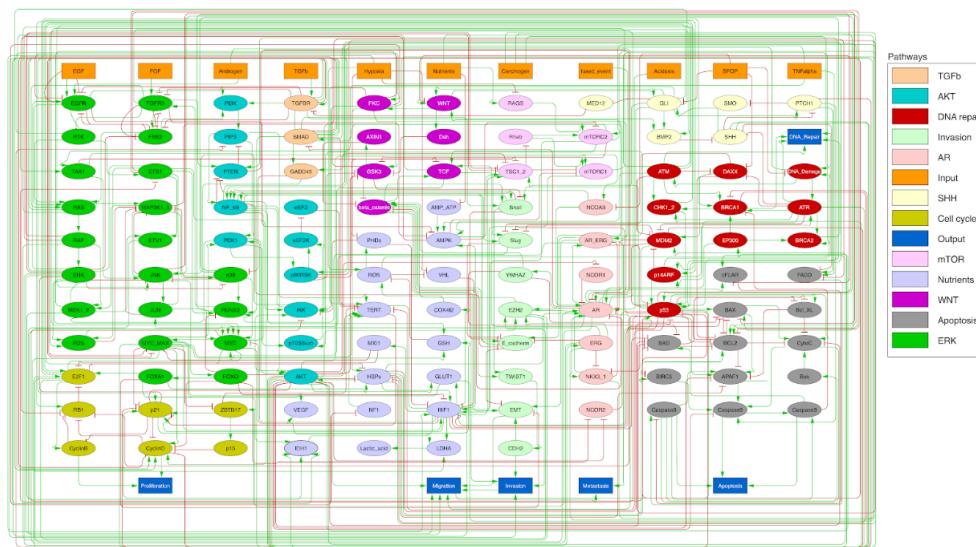
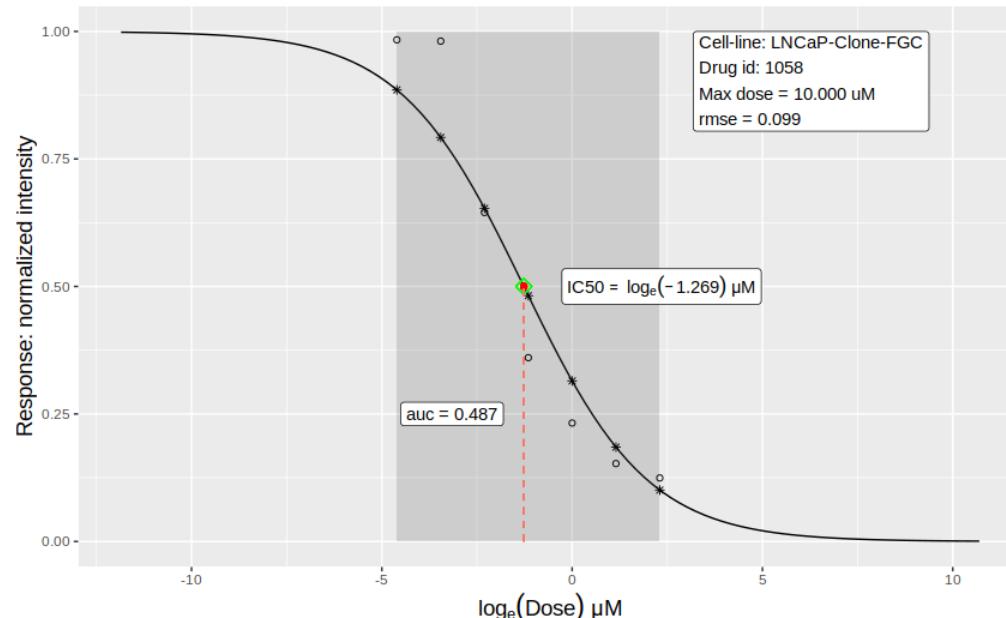
Setting custom data is VERY useful if you want to plot variables

```
sample_projects_intracellular > boolean > spheroid_tnf_model > config > PhysiCell_settings.xml  
218 </phenotype>  
219 <custom_data>  
220    <!-- Time steps for maboss update-->  
221    <next_physiboss_run units="dimensionless">10.</  
     next_physiboss_run>  
222  
223    <!-- Molecular model internal variables-->  
224    <TNFR_binding_rate type="double" units="1/min" description="TNF  
     receptor binding rate">0.243</TNFR_binding_rate>  
225    <TNFR_endocytosis_rate type="double" units="1/min"  
     description="TNF receptor-TNF endocytosis rate">0.128</  
     TNFR_endocytosis_rate>  
226    <TNFR_recycling_rate type="double" units="1/min"  
     description="TNF receptor recycling">0.293</TNFR_recycling_rate>  
227    <TNFR_activation_threshold type="double" units=""  
     description="TNFR threshold to update booleano model input">0.  
     5</TNFR_activation_threshold>  
228    <TNFR_receptors_per_cell type="double" units="dimensionless"  
     description="number of TNFR receptors per cell">1.0</  
     TNFR_receptors_per_cell>  
229    <TFN_net_production_rate type="double" units="TNF/cell/min"  
     description="The total TNF produced by the cell when NFkB is  
     active">0</TFN_net_production_rate> <!-- 0.5 ng/mL -->  
230  
231    <!-- Auxiliary variables used to monitorize simulation-->  
232    <tnf_node units="dimensionless">0</tnf_node>  
233    <fadd_node units="dimensionless">0</fadd_node>  
234    <nfk_b_node units="dimensionless">0</nfk_b_node>  
235    <external_tnf units="TNF/um^3">0</external_tnf>  
236  
237    </custom_data>  
238 </cell_definition>  
239 </cell_definitions>
```

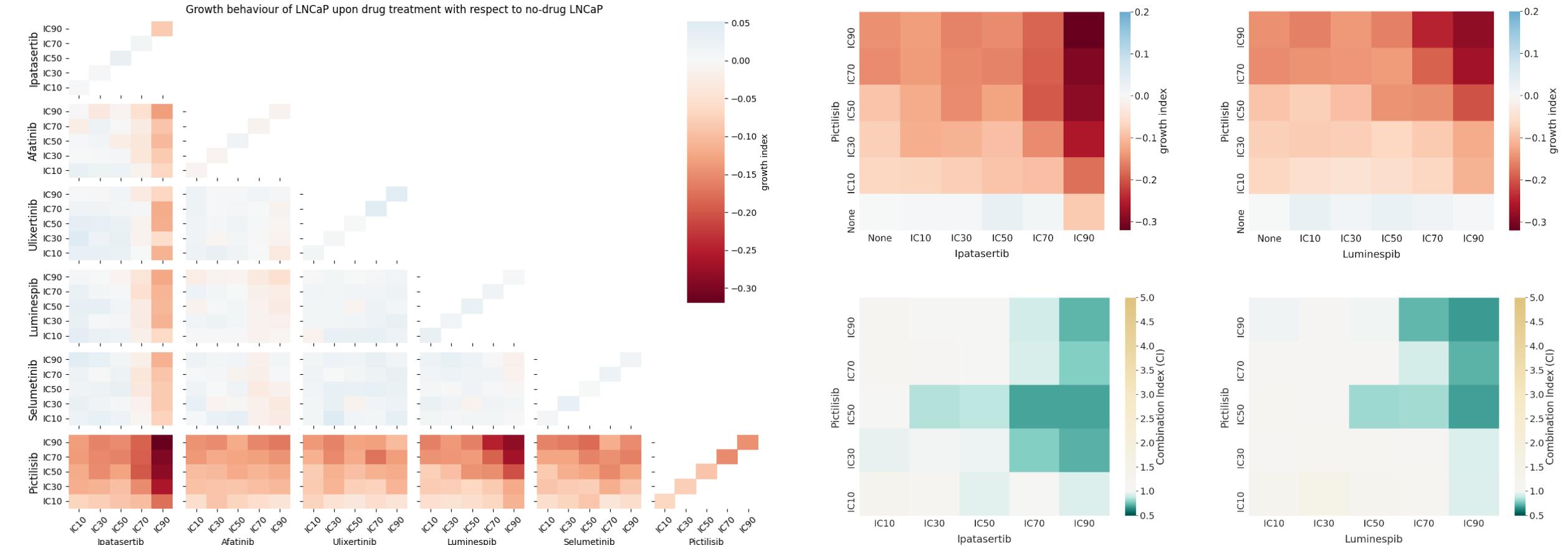


Drug synergy studies in a prostate cell line

Dose response: cell line 907788 ; drug 1058_10 .

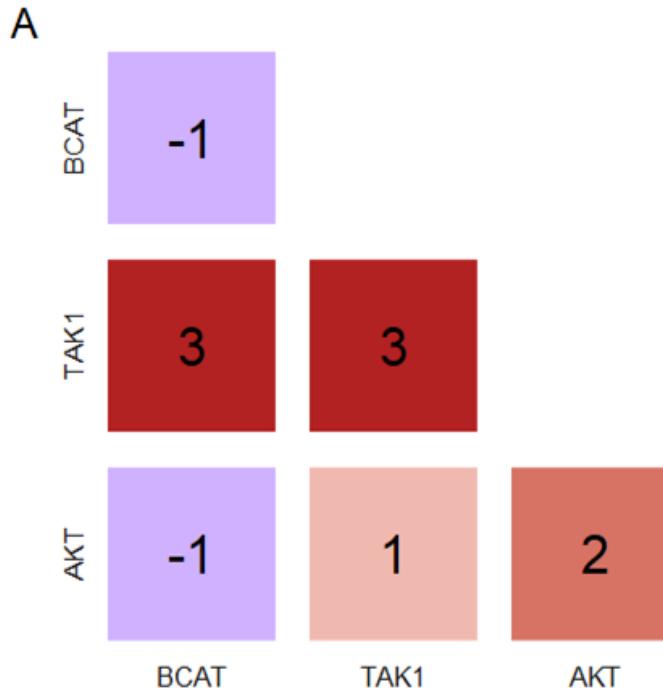


Drugs in PhysiBoSS: drug synergy studies in LNCaP

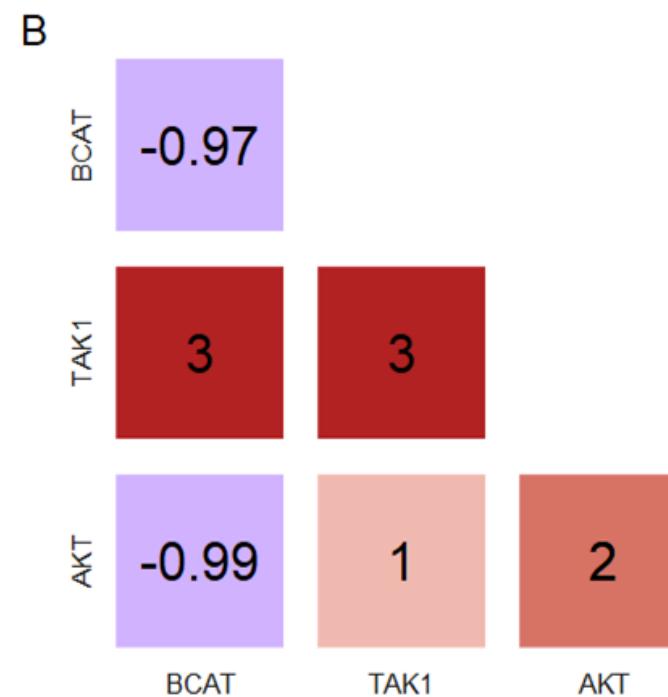


$$\text{Growth index} = \log_2 \frac{\text{AUC}(\text{with drug})}{\text{AUC}(\text{without drug})}$$

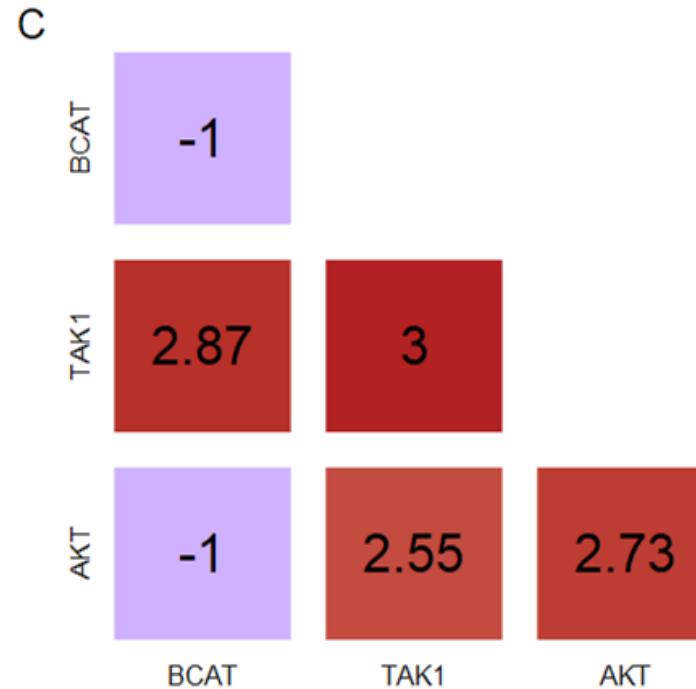
Drug synergy studies in a gastric cell line



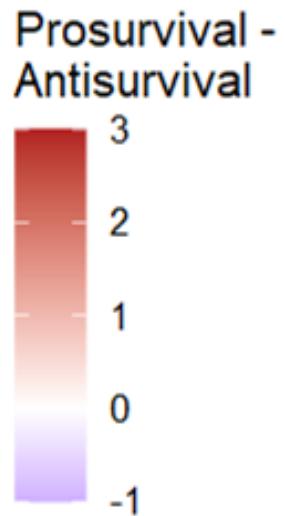
Original paper
Multivalued Boolean



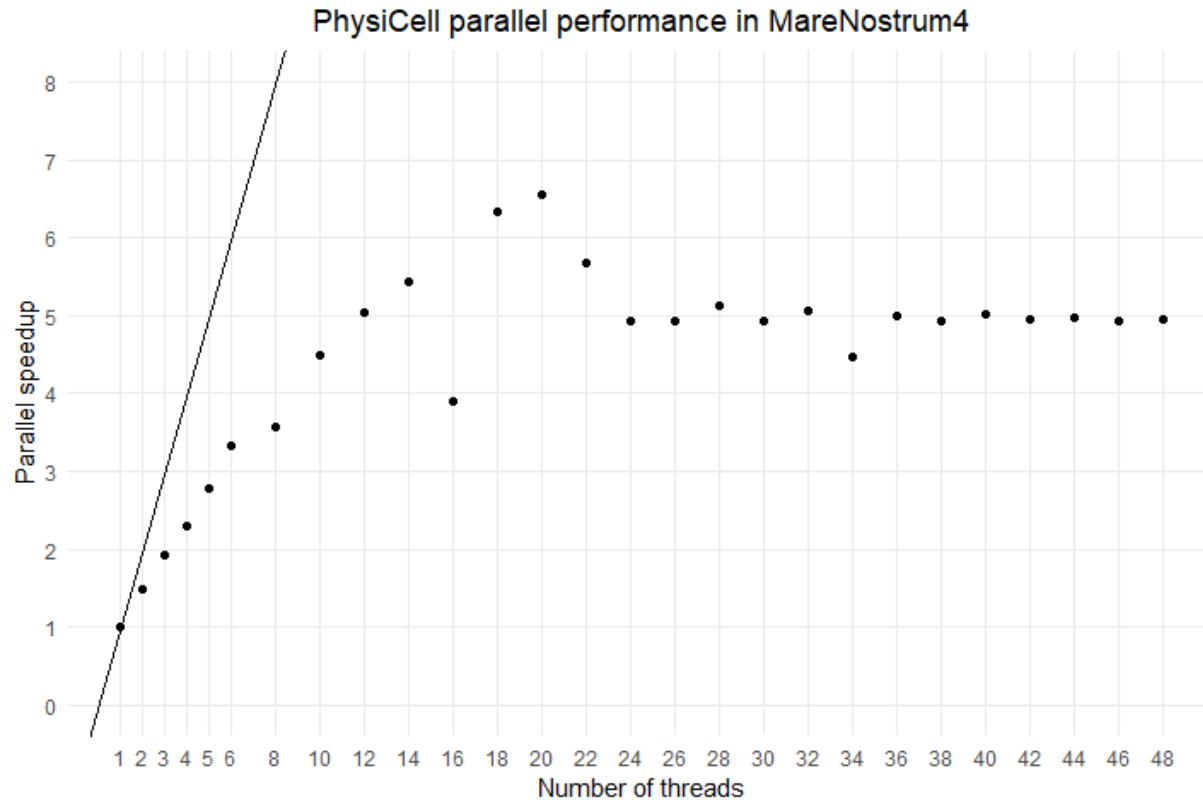
MaBoSS
Stochastic Boolean



PhysiBoSS
Stochastic Boolean +
agents + environment

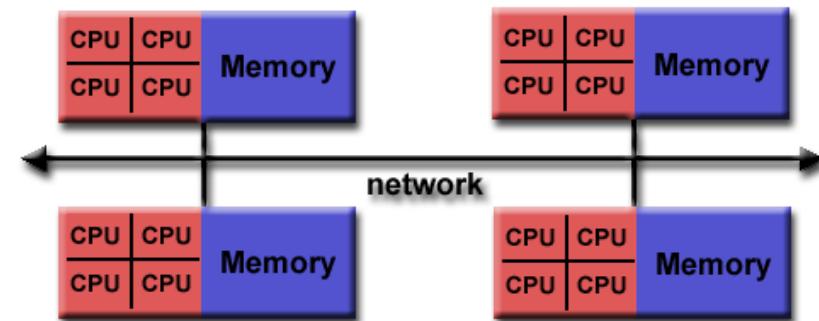


Multi-scale modelling can be parallelised and distributed



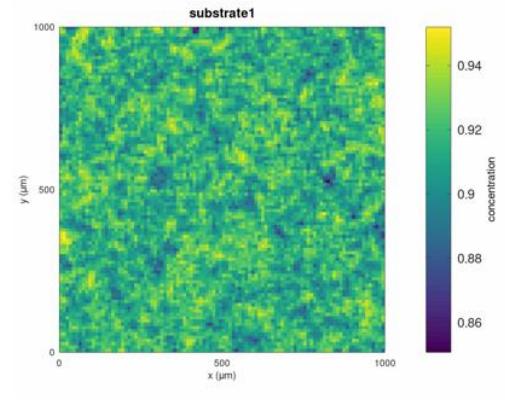
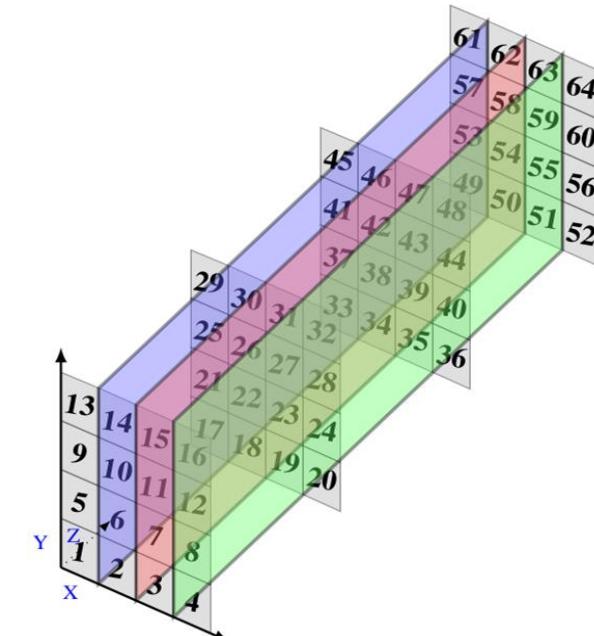
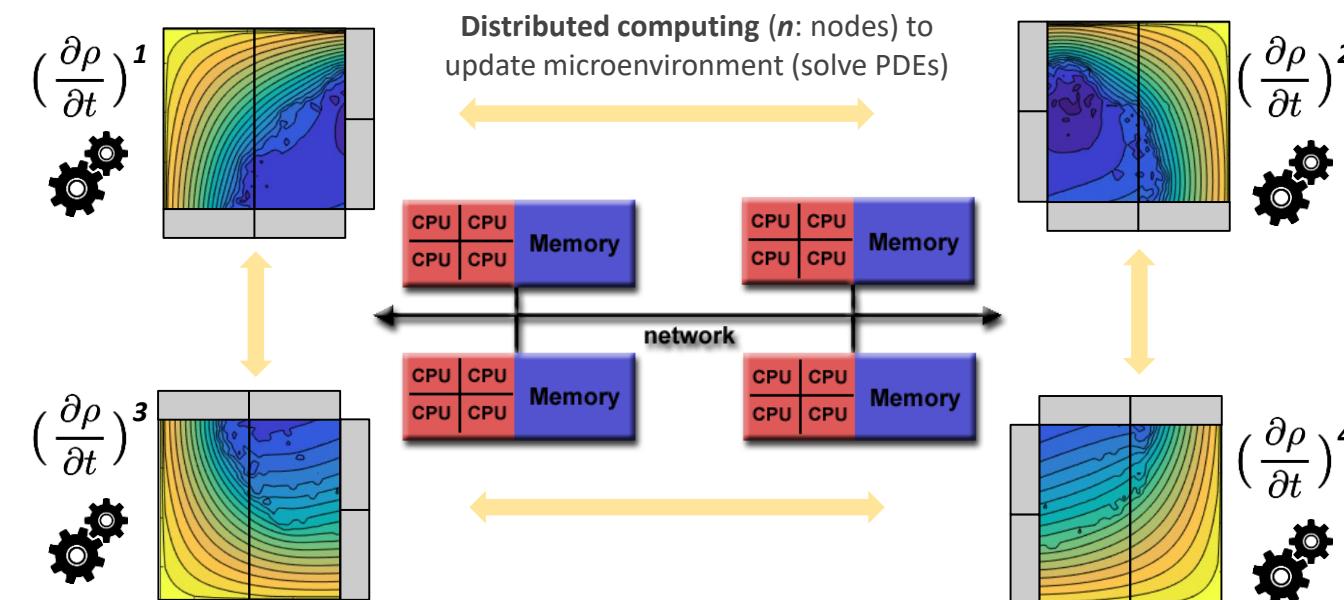
Collaboration with Gaurav Saxena from
High-Level Support Team at BSC

- « PhysiCell supports only **shared memory parallelization** using OpenMP
- « We are implementing **distributed-memory** with MPI to parallelise generic core kernels using
 - simulation initialization
 - domain partitioning
 - agents' generation
- « Preliminary results of **PhysiCell-MPI**
 - **Expand the scope** of the simulations by several orders of magnitude
 - **Enable** the simulation of **complex behaviours**

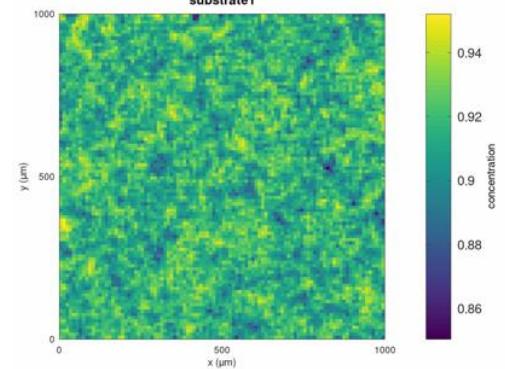


Ongoing work: Parallelising simulations with PhysiCell-MPI

Collaboration with Gaurav Saxena from High-Level Support Team at BSC



(a) OpenMP (48 threads)



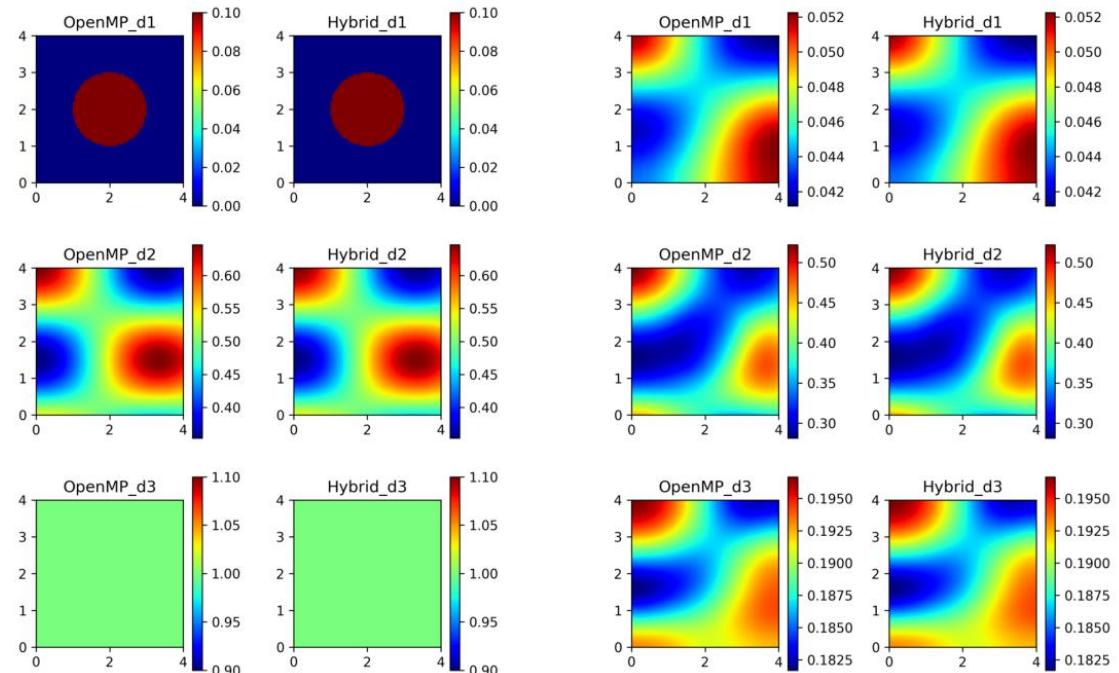
(b) Hybrid($n=1$)

BioFVM-X and PhysiCell-X allow for bigger, more complex simulations

« BioFVM-X vs BioFVM

- Pure OpenMP BioFVM sim with 400 substrates on a domain of 1500^3
 - Out of memory !
- Hybrid sim with 400 and 800 substrates on a domain of 1500^3 in 2 nodes
 - Works !

« Currently testing PhysiCell-X



(a) Initial densities at $z=2.025$

(b) Final densities at $z=2.025$

Table 1. Time (in seconds) of execution for the pure OpenMP and the Hybrid version for a problem of size $7680 \times 7680 \times 7680$ (≈ 0.5 billion voxels). The pure OpenMP version terminates while throwing Out Of Memory error.

7680x7680x7680	OpenMP	Hyb(n=4)	Hyb(n=8)
Build μ -environment	-	141.98	67.81
Gaussian Profile	-	0.916	0.448
Initial File Write	-	2.56	4.1
Agent generation	-	0.1060	0.0023
Source/Sink/Diffusion	-	1109.69	1210.41
Final File Write	-	4.83	3.32
Total Time	-	1260	1286.1

<https://permedcoe.eu/>



HPC/Exascale
Centre of
Excellence in
Personalised
Medicine

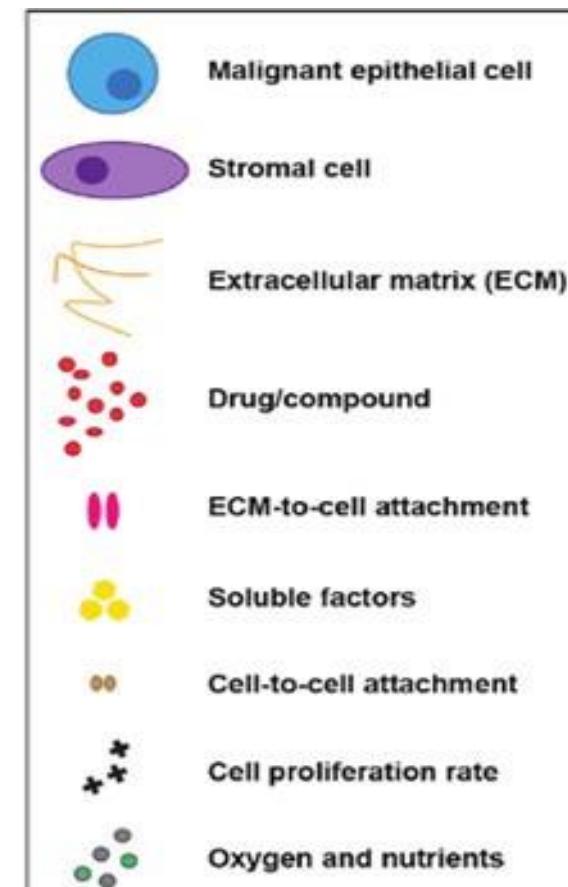
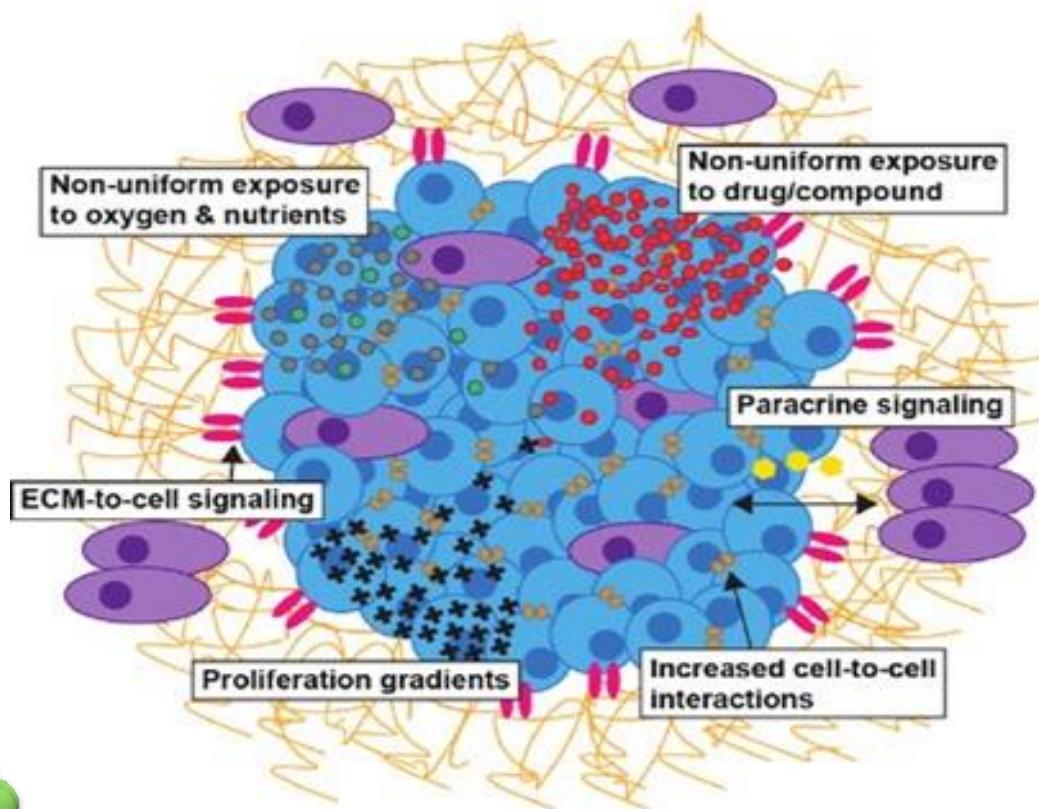
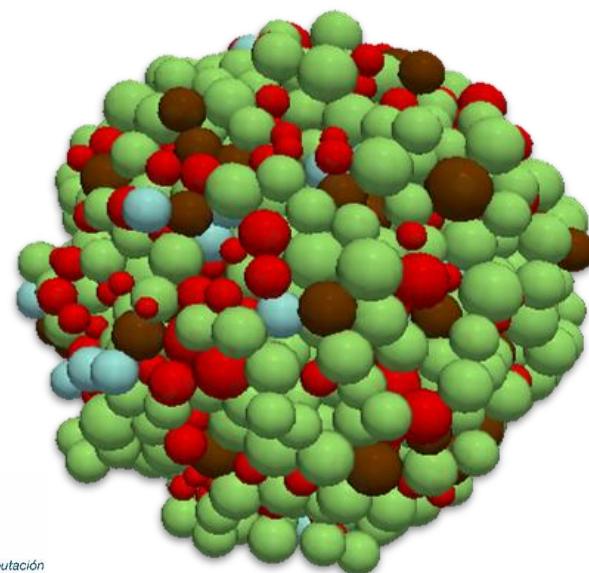
Ongoing: to have different kind of cells in the microenvironment

« Cells could be:

- Stromal cells
- Immune cells
- Cancer-associated cells

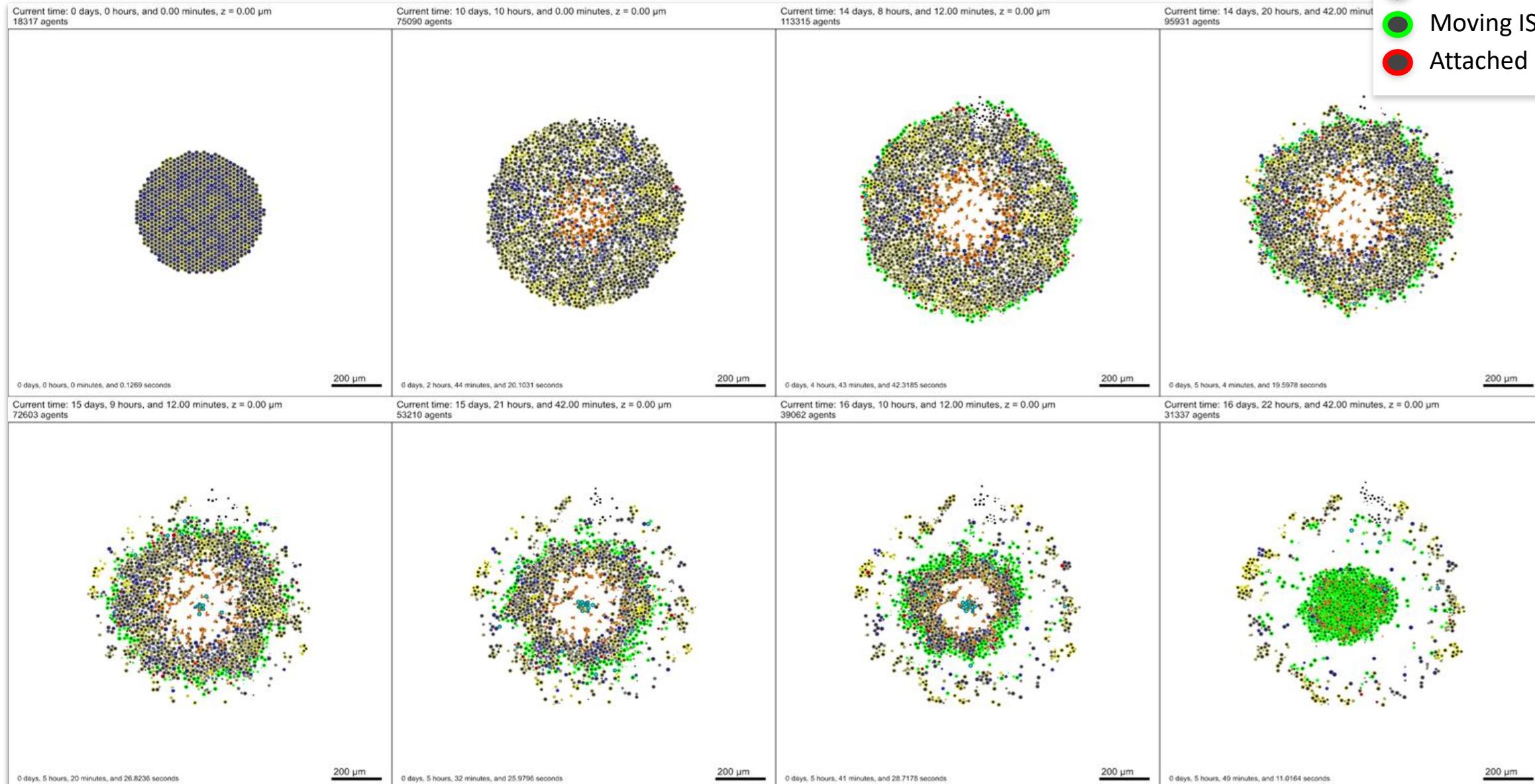
« We want to model cancer-immune system interaction

Cell Cycle Phase
– Premitotic
– Postmitotic
– Ki67 negative
– Apoptotic
– Necrotic
– Necrotic (swelling)
– Necrotic (lysis)



- Growing TC
- Quiescent TC
- Necrotic TM
- Moving ISC
- Attached ISC

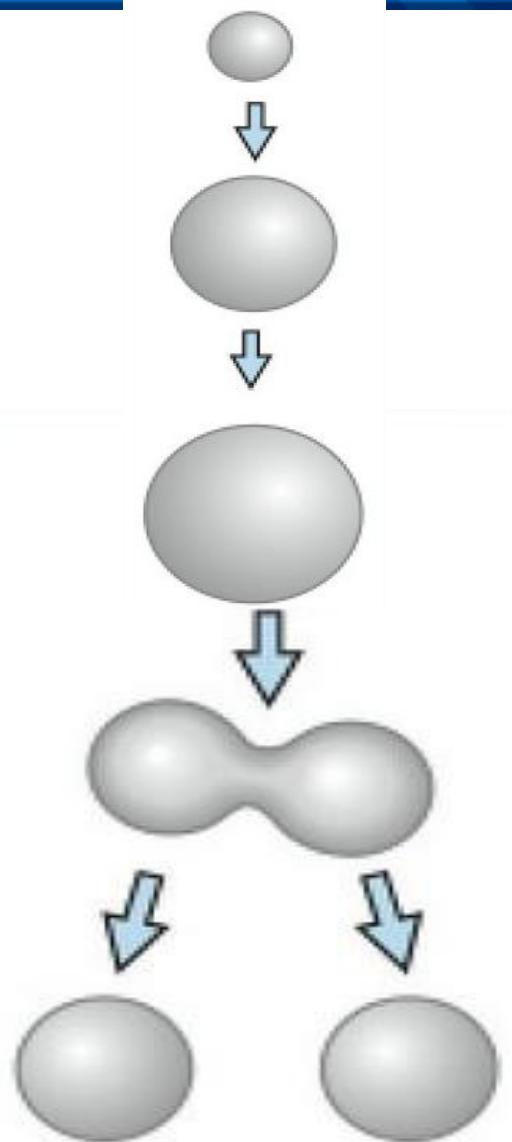
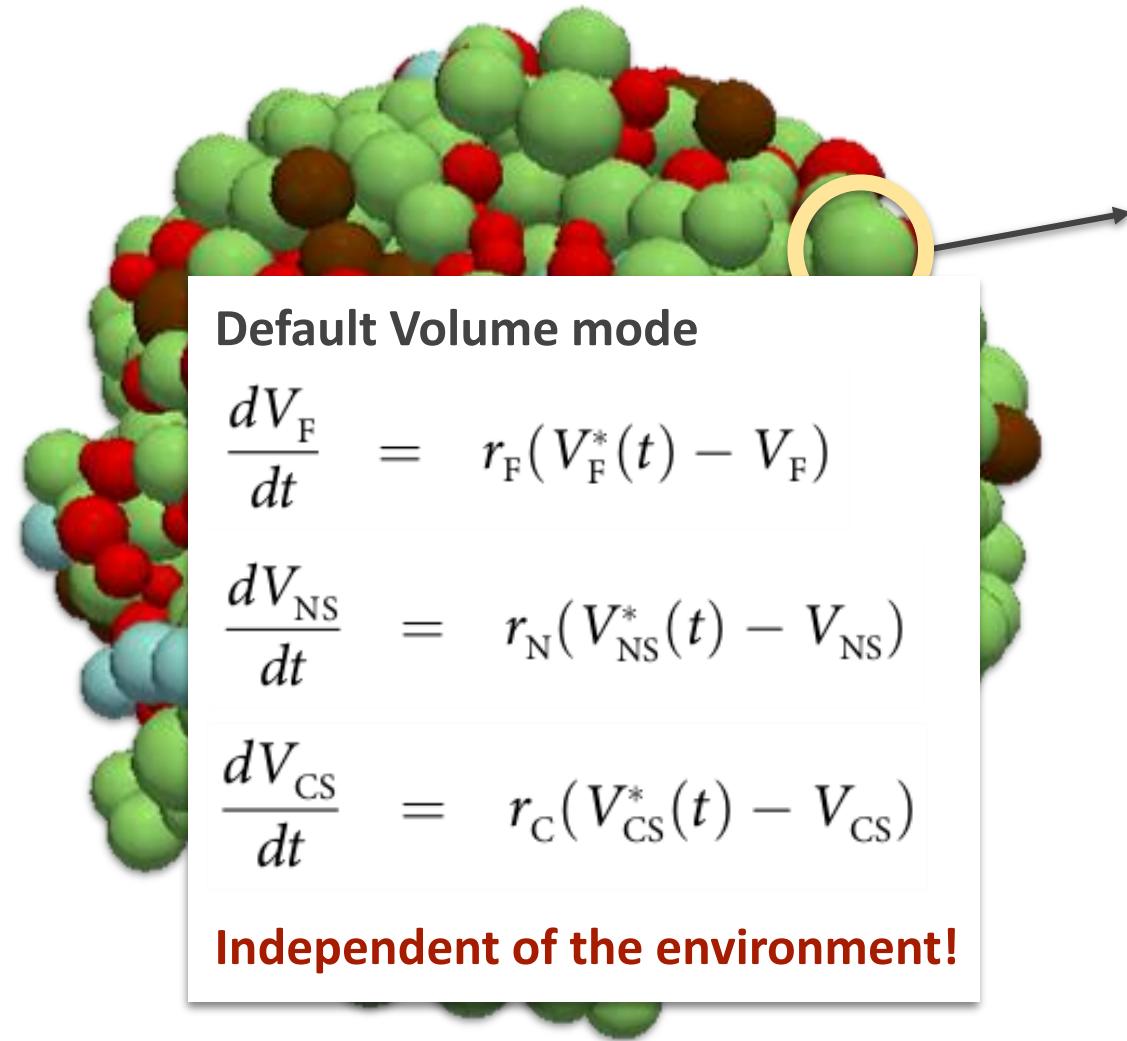
Ongoing : to have different kind of cells in the microenvironment



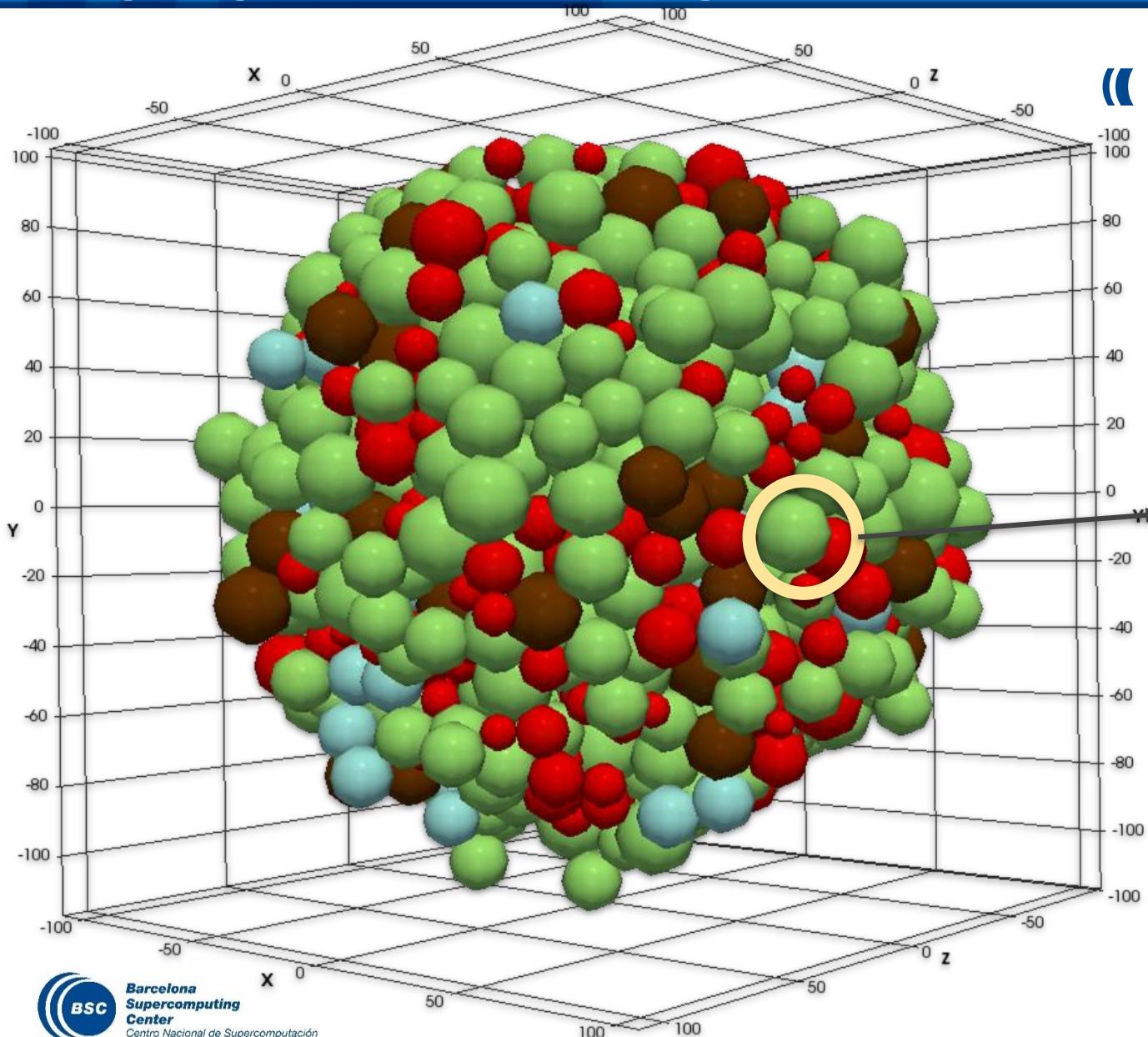
Ongoing work: Connecting metabolic models to PhysiCell

Cell Cycle Phase

- Premitotic
- Postmitotic
- Ki67 negative
- Apoptotic
- Necrotic
- Necrotic (swelling)
- Necrotic (lysis)

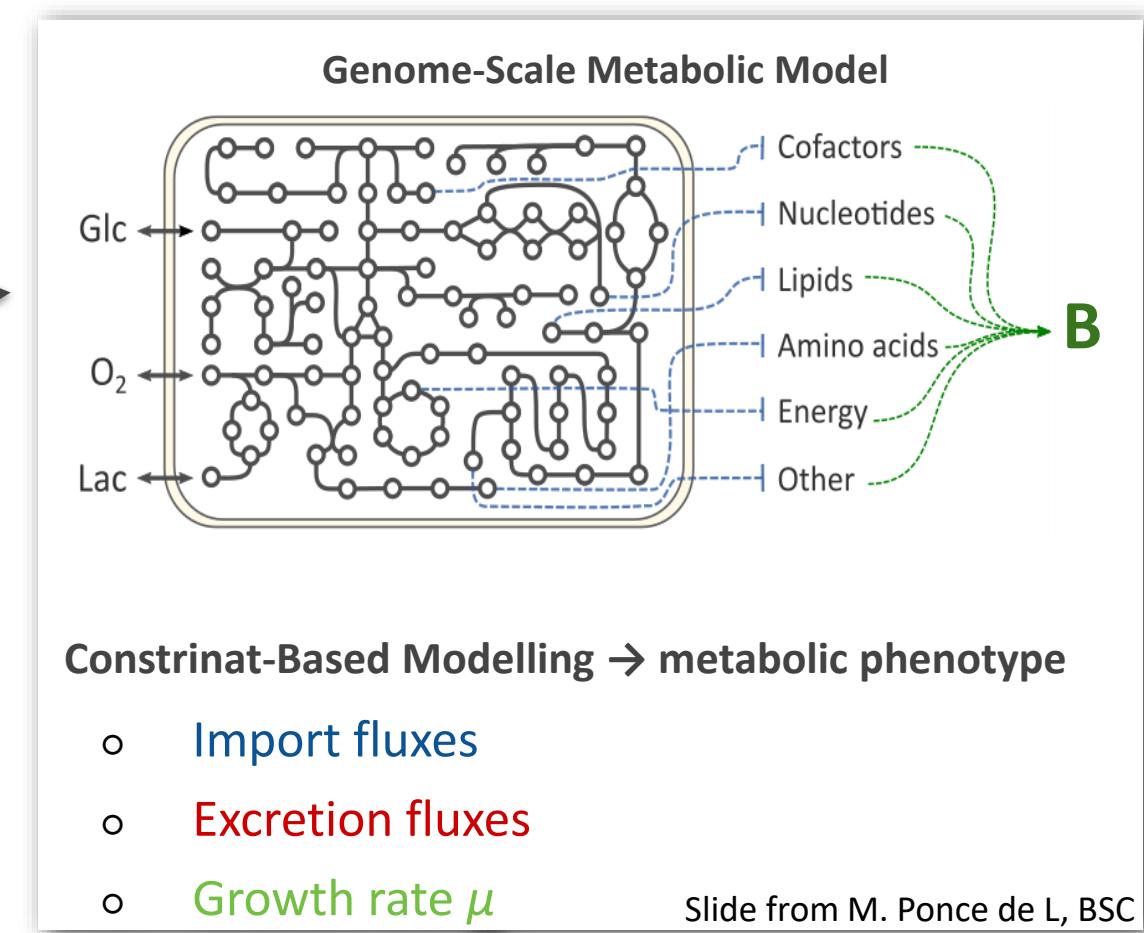


Ongoing work: Connecting metabolic models to PhysiCell



Collaboration with Paul Macklin, Indiana University

- Miguel Ponce de León did a short stay



Extending the growth model to consider metabolism

Connecting metabolic variables to the agent and the environment

Metabolic model

- o Stoichiometric matrix
- o Context (GPRs + expression)
- o Biomass equation

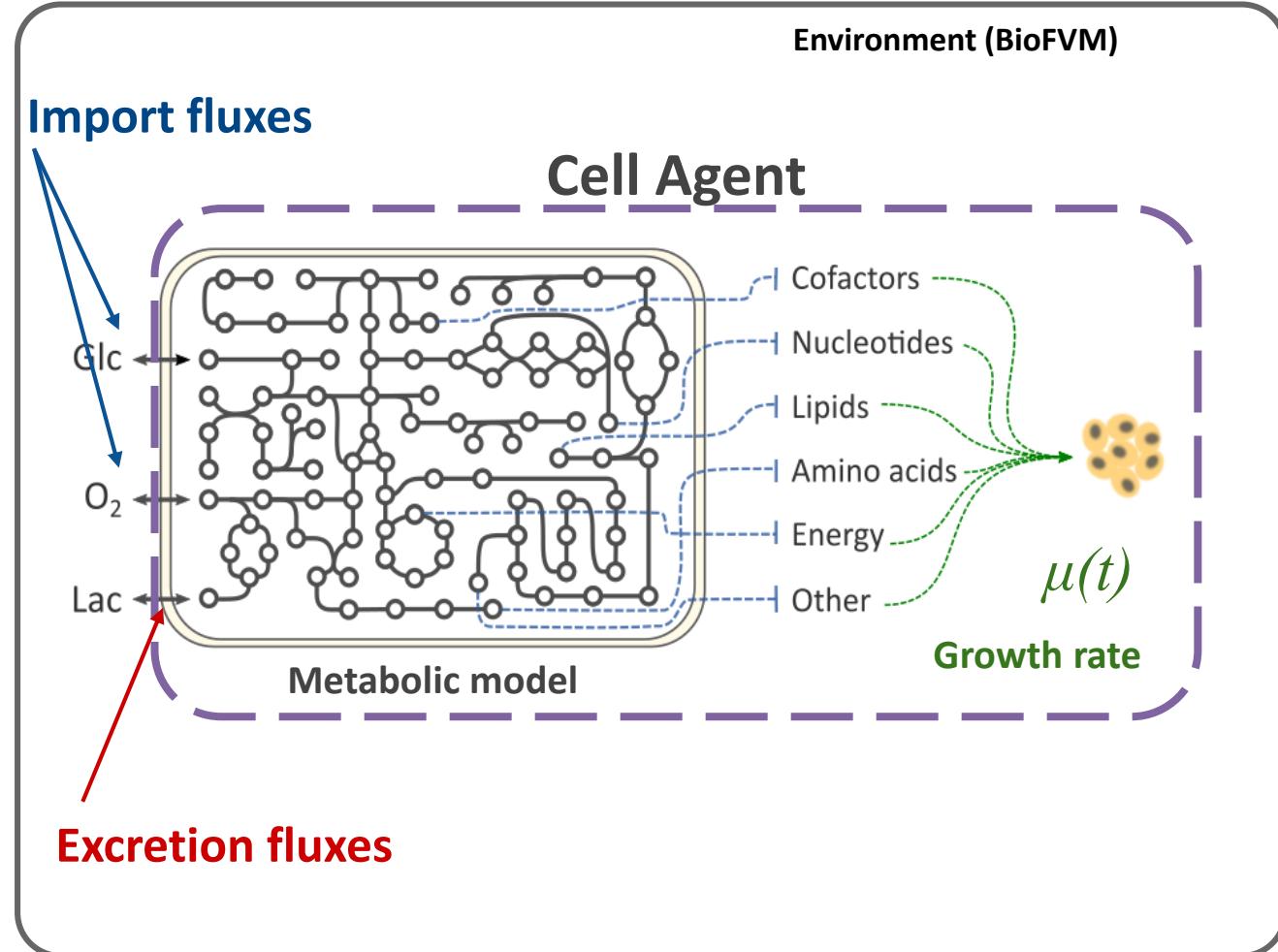
Simulation

- o Dynamic Flux Balance Analysis

Metabolic phenotype

- o **Import fluxes** (sources)
- o **Excretion fluxes** (sinks)
- o **Growth rate μ** (if prolif.)

Interface
with
the ABM



Acknowledgments



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Projects

PerMedCoE, EU ref. 951773
INFORE, EU ref. 825070
iPC, EU ref. 826121