PhysiBoSS, use of multiscale modeling tools in biomedical projects

Building multiscale models with PhysiBoSS

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Building Immune Digital Twins

May 24th, 2023









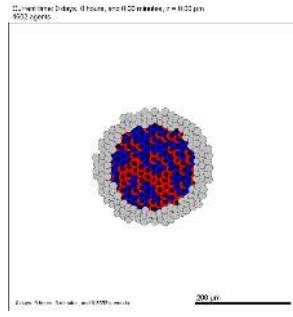


- Agent-based modeling
- PhysiBoSS
- Automatic Mapping
- PhysiCell Studio
- TNF model
- Cell cycle model
- Differentiation model

Agent-based modeling

We simulate multiple agents with simple defined behaviors. In our case we have cells that :

- Can proliferate/die
- Can grow/shrink
- Can move in space
- Can interact with other agents



⇒ Simple behavior for each agent, where complex phenomena can emerge in the system

Agent-based modeling

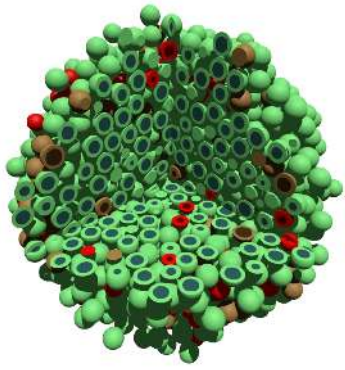
› PhysiCell



Paul Macklin



Randy Heiland



http://physicell.org
https://github.com/MathCancer/PhysiCell

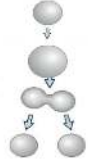
Cell agent properties

- Size (cell volume)
- Position (x, y, z)
- Phenotype
  - Cell cycle Model (G_0, *M, etc*)
  - Death Models
  - Rates
  - Custom Variables
  - Molecular models

Cell Cycle



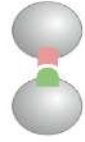
Growth



Migration

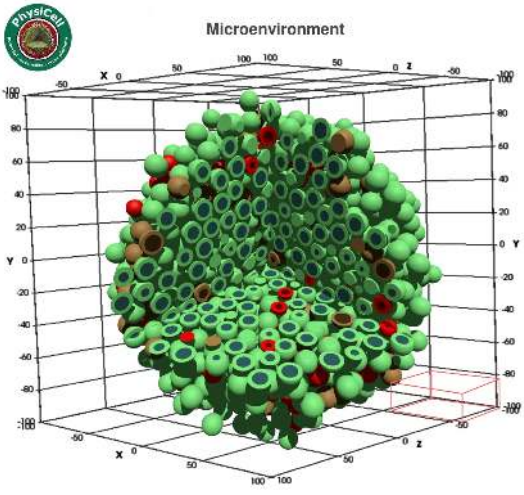


Cell-Cell interactions



Agent-based modeling

› PhysiCell



Diffusion equations

$$\frac{\partial \boldsymbol{\rho}}{\partial t} = \overbrace{\mathbf{D}\nabla^2\boldsymbol{\rho}}^{\text{diffusion}} - \overbrace{\boldsymbol{\lambda}\boldsymbol{\rho}}^{\text{decay}} + \overbrace{\mathbf{S}(\boldsymbol{\rho}^* - \boldsymbol{\rho})}^{\text{bulk source}} - \overbrace{\mathbf{U}\boldsymbol{\rho}}^{\text{bulk uptake}} + \overbrace{\sum_{\text{cells } k} \delta(\mathbf{x} - \mathbf{x}_k) W_k [\mathbf{S}_k(\boldsymbol{\rho}_k^* - \boldsymbol{\rho}) - \mathbf{U}_k \boldsymbol{\rho}]}^{\text{sources and uptake by cells}} \quad \text{in } \Omega$$

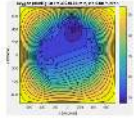
System of PDEs for each molecule:

- Diffusion term
- Decay
- Uptake/Production

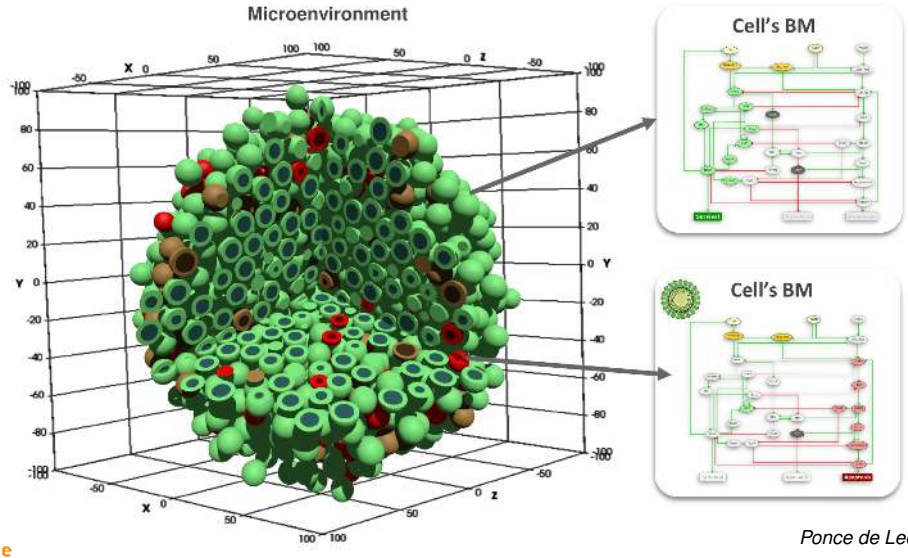
PDEs are solved using BioFVM







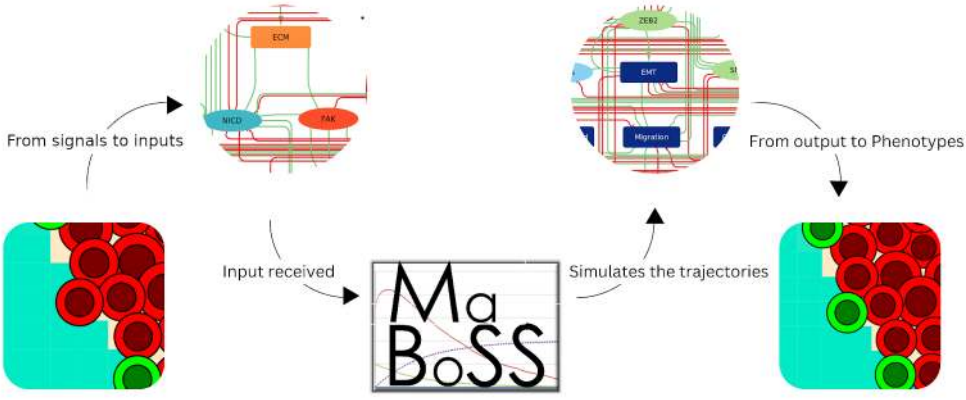
PhysiBoSS



Ponce de Leon et al., 2023

PhysiBoSS

› PhysiCell integration



Ruscone et al., 2023

PhysiBoSS

- PhysiCell integration

  - PhysiBoSS 1.0 was done using very large modifications of PhysiCell core C++ code

  - PhysiBoSS 2.0 was included in PhysiCell as an addon, allowing model integration via custom C++ code (but not core)

  - PhysiBoSS 2.2 now introduce automatic mapping, allowing definition of intracellular models without any C++ code, directly in PhysiCell's XML settings

PhysiBoSS

- PhysiCell XML settings

One file to describe a complete model

- Size of simulation box
- Simulation settings
- Output settings
- Substrates
- Cell types
- Initial conditions
- User parameters

```
<PhysiCell_settings version="devel-version">

    <domain>
        <x_min>-600</x_min>
        <x_max>600</x_max>
        <y_min>-600</y_min>
        <y_max>600</y_max>
        <z_min>-10</z_min>
        <z_max>10</z_max>
        <dx>20</dx>
        <dy>20</dy>
        <dz>20</dz>
        <use_2D>true</use_2D>
    </domain>

    <overall>
        <max_time units="min">1440</max_time>
        <time_units>min</time_units>
        <space_units>micron</space_units>
        <dt_diffusion units="min">0.5</dt_diffusion>
        <dt_mechanics units="min">1</dt_mechanics>
        <dt_phenotype units="min">6</dt_phenotype>
    </overall>

    <parallel>
        <omp_num_threads>6</omp_num_threads>
    </parallel>
```

PhysiBoSS

› PhysiCell XML settings

```
<cell_definitions>
    <cell_definition name="default" ID="0">
        <phenotype>
            <cycle code="5" name="live">
                <phase_transition_rates units="1/min">
                    <rate start_index="0" end_index="0" fixed_duration="false">0.00072</rate>
                </phase_transition_rates>
            </cycle>
            <death>
                <model code="100" name="apoptosis">
                    <death_rate units="1/min">5.31667e-05</death_rate>
                    <phase_transition_rates units="1/min">
                        <rate start_index="0" end_index="1" fixed_duration="false">0.020000</rate>
                    </phase_transition_rates>
                    <parameters>
                        <unlysed_fluid_change_rate units="1/min">0.05</unlysed_fluid_change_rate>
                        <lysed_fluid_change_rate units="1/min">0</lysed_fluid_change_rate>
                        <cytoplasmic_biomass_change_rate units="1/min">1.66667e-02</cytoplasmic_biomass_change_rate>
                        <nuclear_biomass_change_rate units="1/min">5.83333e-03</nuclear_biomass_change_rate>
                        <calcification_rate units="1/min">0</calcification_rate>
                        <relative_rupture_volume units="dimensionless">2.0</relative_rupture_volume>
                    </parameters>
                </model>
                <model code="101" name="necrosis">
```

PhysiBoSS

- PhysiBoSS XML settings
  - MaBoSS BND amd CFG files
  - Update period
  - Scaling
  - Inheritance
  - Parameters
  - Mutations
  - Initial values
  - Mapping

```
<phenotype>
    ...
    <intracellular type="maboss">
        <bnd_filename>./config/model_0.bnd</bnd_filename>
        <cfg_filename>./config/model.cfg</cfg_filename>
        <initial_values>
            <initial_value intracellular_name="A">1</initial_value>
            <initial_value intracellular_name="C">0</initial_value>
        </initial_values>
        <settings>
            <intracellular_dt>1</intracellular_dt>
            <time_stochasticity>0.0</time_stochasticity>
            <scaling>1.0</scaling>
            <start_time>0.0</start_time>
            <inheritance global="False" />
            <mutations>
                <mutation intracellular_name="C">0</mutation>
            </mutations>
        </settings>
        <mapping/>
    </intracellular>
</phenotype>
```

Automatic Mapping

Automatic Mapping

- PhysiCell's signals and behaviors

Signals

- oxygen (extra/intracellular, gradient)
- pressure
- volume
- contact with cell (type, live/dead)
- damage
- dead
- total attack time
- time
- custom:somedata
- apoptotic

Behaviors

- oxygen (secretion, uptake, ...)
- cycle entry
- exit from cycle phase
- apoptosis
- necrosis
- migration (speed, bias, persistence)
- chemotactic response to oxygen
- cell-cell adhesion
- cell-cell repulsion
- custom:someotherdata

Automatic Mapping

- Inputs and outputs

Input Mapping : *PhysiCell signal → MaBoSS input node*

- Activation or Inhibition
- Continuous to Boolean : thresholds
- Smooth/Sharp transition

```
<input physicell_name="TNF" intracellular_name="TNF">
    <settings>
        <action>activation</action>
        <threshold>1</threshold>
        <smoothing>0</smoothing>
    </settings>
</input>
```

Output Mapping : *MaBoSS output node → PhysiCell Behavior*

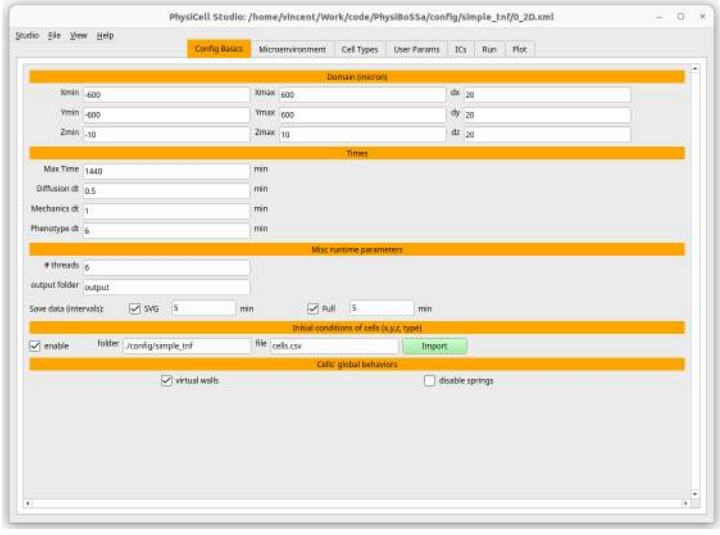
- Activation or Inhibition
- Boolean to Continuous : levels
- Smooth/Sharp transition

```
<output physicell_name="apoptosis" intracellular_name="Apoptosis">
    <settings>
        <action>activation</action>
        <value>1000000</value>
        <base_value>0</base_value>
    </settings>
</output>
```

PhysiCell Studio

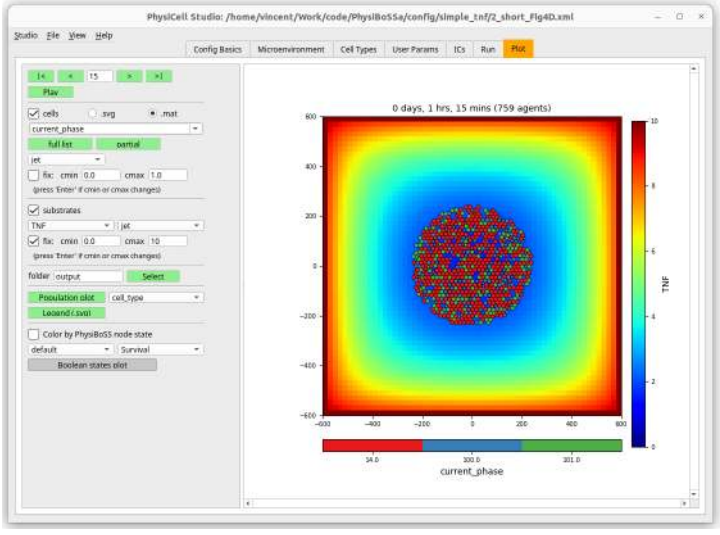
PhysiCell Studio

› Edit basic configuration



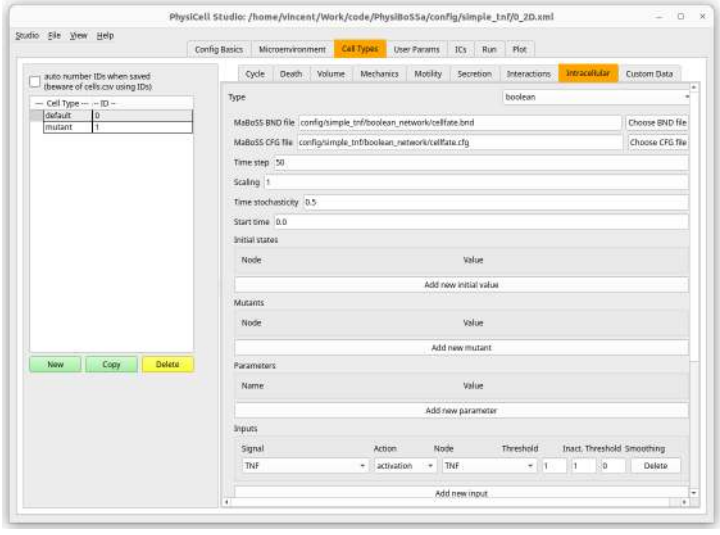
PhysiCell Studio

› Visualize simulation results



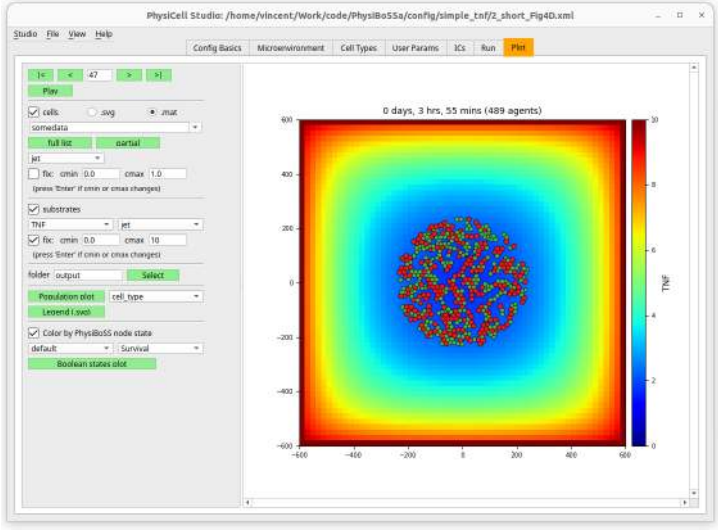
PhysiCell Studio

› Modify PhysiBoSS configuration



PhysiCell Studio

› Visualize PhysiBoSS results



TNF model

TNF model

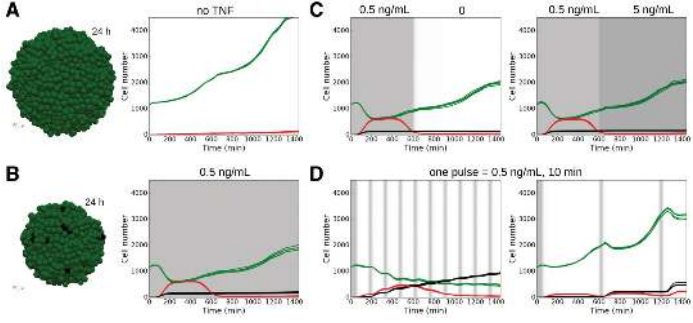
› Reproducing original results

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

Gaelle Letort ✉, Arnau 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** ▾

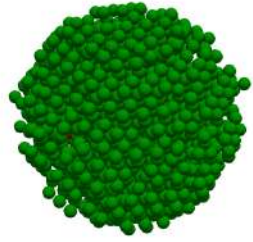


TNF model

- Spheroid model

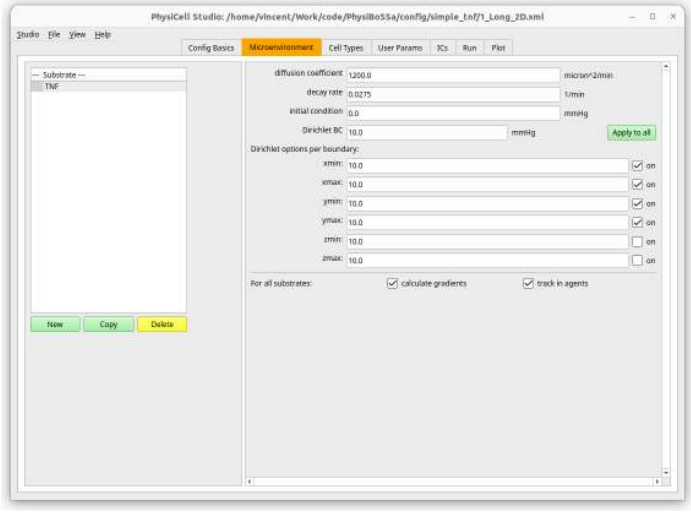
  - Simple model of a growing spheroid

  - Based on PhysiBoSS template



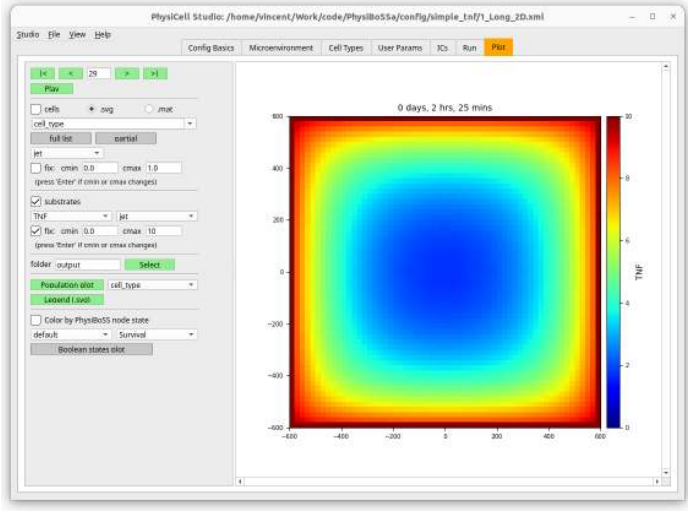
TNF model

› Adding TNF to the microenvironment



TNF model

› Adding TNF to the microenvironment



TNF model

- Long TNF treatment

OPEN ACCESS Freely available online

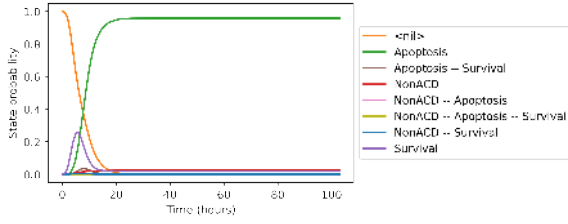
PLOS COMPUTATIONAL BIOLOGY

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 Zhivotovsky[6], Emmanuel Barillot[1,2,3¶], Andrei Zinovyev[1,2,3¶]

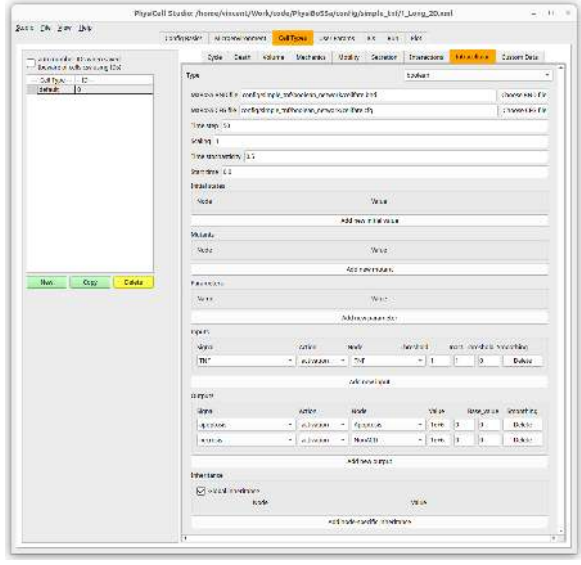
1 Institut Curie, Paris, France, 2 École des Mines ParisTech, Paris, France, 3 INSERM U900, Paris, France, 4 TAGC – INSERM U826 & Université de la Méditerranée, Marseille, France, 5 CONTRAINTES Project, INRIA Paris-Rocquencourt, France, 6 Karolinska Institutet, Stockholm, Sweden

- Cell Fate Boolean model
- Predicts cell response to TNF treatment
- Heterogenous response
- A population becomes resistant



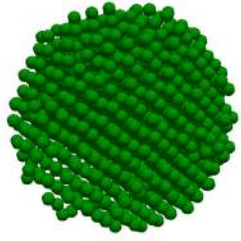
TNF model

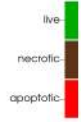
- Long TNF treatment
  - Setting BND/CFG
  - TNF activates the TNF Input node of MaBoSS model
  - Apoptosis output node activates PhysiCell's apoptosis
  - NonACD output node activates PhysiCell's necrosis



TNF model

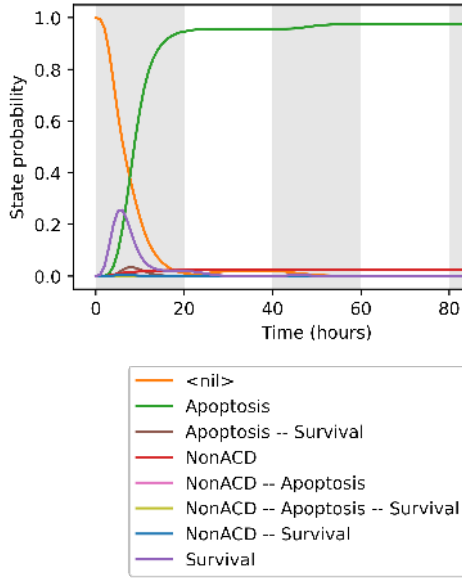
› Long TNF treatment





TNF model

- Pulsed TNF treatment



- Model also describe the effect of stopping treatment
- Resistant cells go back to naive state
- Resistant population gets smaller with repeated treatments

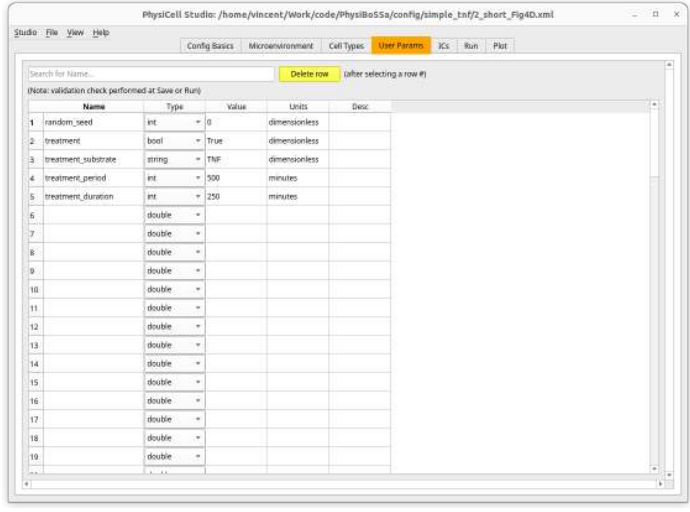
TNF model

- Pulsed TNF treatment

  - Simple mechanism to program periodic treatments

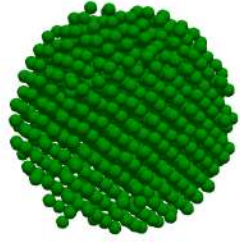
  - Custom C++ code added to the example

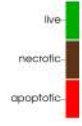
  - PhysiPKPD will replace this in the future



TNF model

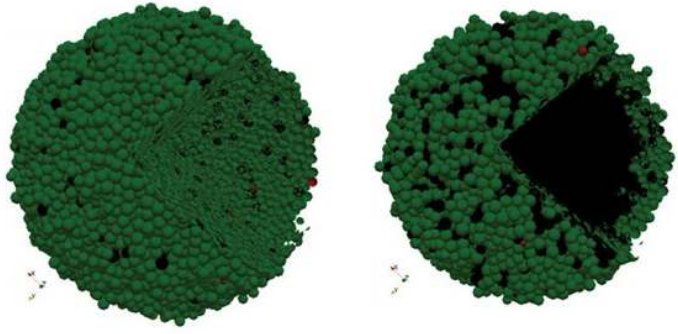
› Pulsed TNF treatment





TNF model

› Necrotic core

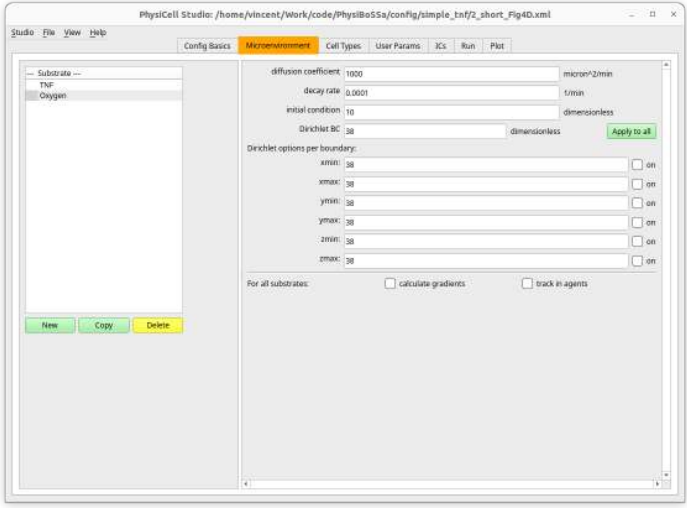


Letort et al., 2018

⇒ Necrotic core due to lack of oxygen in the center of the tumor

TNF model

› Necrotic core

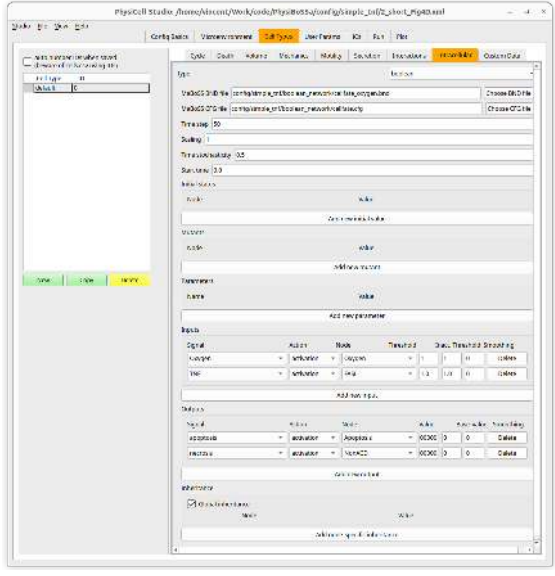


TNF model

- Necrotic core

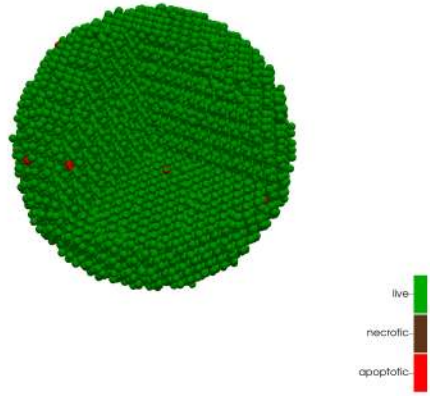
```
node OXYGEN
{
  rate_up = 0.0;
  rate_down = 0.0;
}

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;
}
```



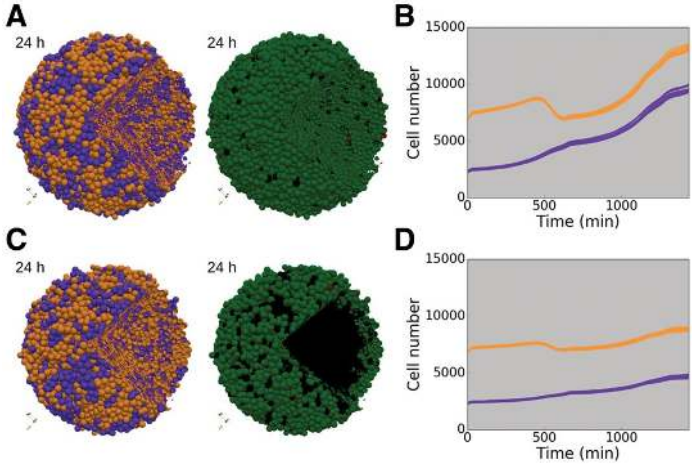
TNF model

› Necrotic core



TNF model

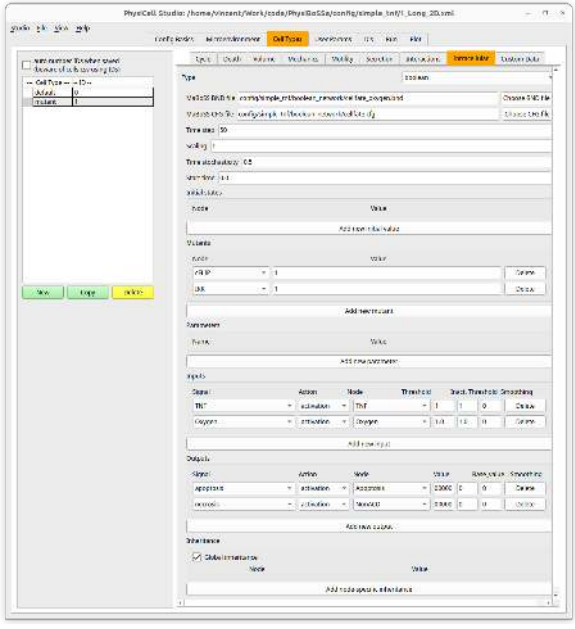
› IKK++, cFLIP++



Letort et al., 2018

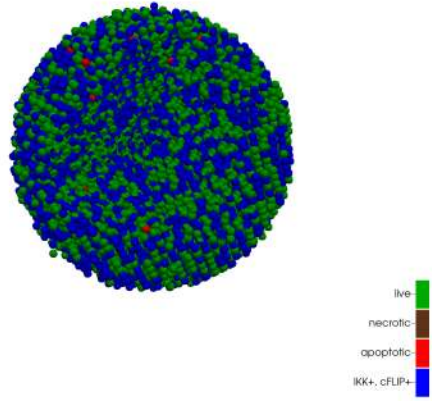
TNF model

- IKK++, cFLIP++



TNF model

› IKK++, cFLIP++



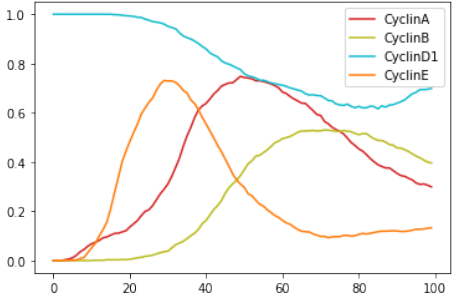
Cell cycle model

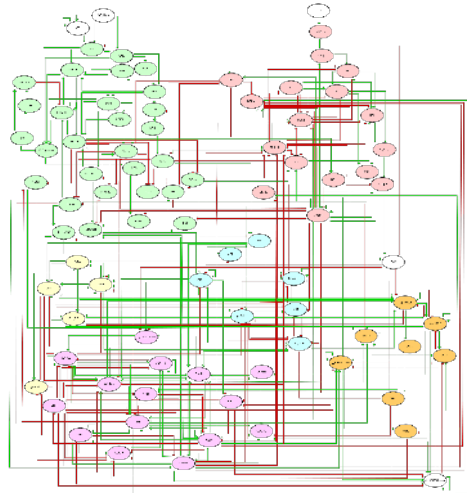
Cell cycle model

› Creating a signaling controlled cell cycle model

Boolean model of growth signaling, cell cycle and apoptosis predicts the molecular mechanism of aberrant cell cycle progression driven by hyperactive *PI3K*

Harbert Sizek, Andrew Hamel, Dávid Deritei, Sarah Campbell, Erzsébet Ravasz Regan





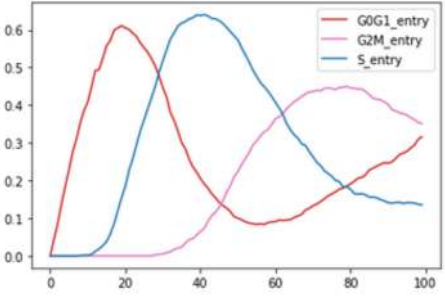
Cell cycle model

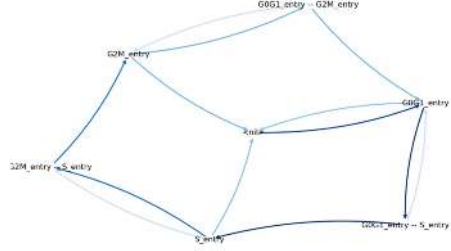
› Creating a signaling controlled cell cycle model

```
G0G1_entry : (CyclinD1 & !CyclinA) & !(G2M_entry & S_entry) & !S_entry

S_entry : ((CyclinE & G0G1_entry) | (CyclinA & G0G1_entry ) | (CyclinE & S_entry) | (CyclinA & S_entry)) & !(G0G1_entry & G2M_entry) & !G2M_entry

G2M_entry : ((CyclinB & S_entry) | (CyclinB & G2M_entry)) & !(G0G1_entry & S_entry) & !G0G1_entry
```

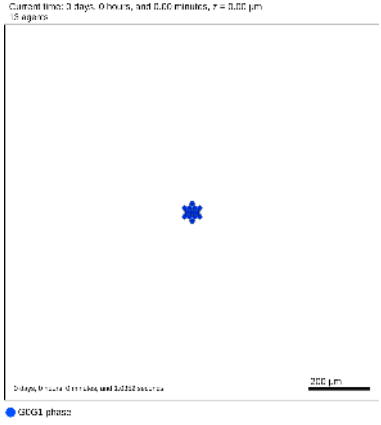




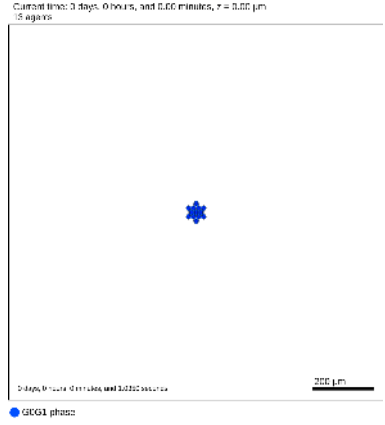
Cell cycle model

› Reproducing PhysiCell's cell cycle model

PhysiCell's cycle



PhysiBoSS Sizek's cycle

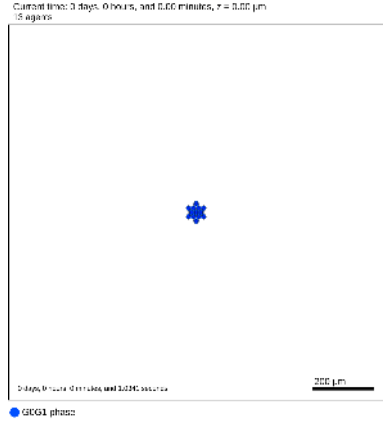


Cell cycle model

› PLK1 KO-induced blockage in G2

› Knocking out PLK1 leads to a cycle arrest in G2

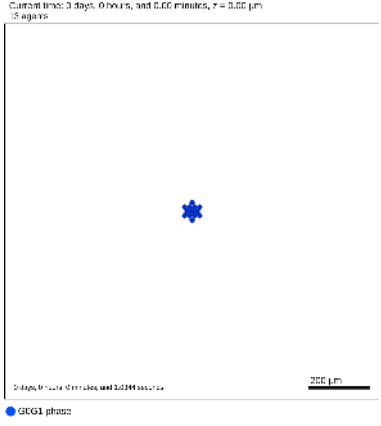
Plk1 KO



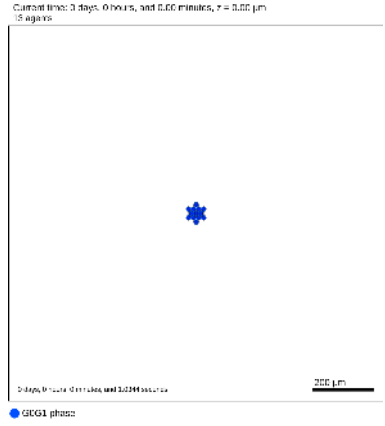
Cell cycle model

› Mutants modifying proliferation rate

FoxO3- -

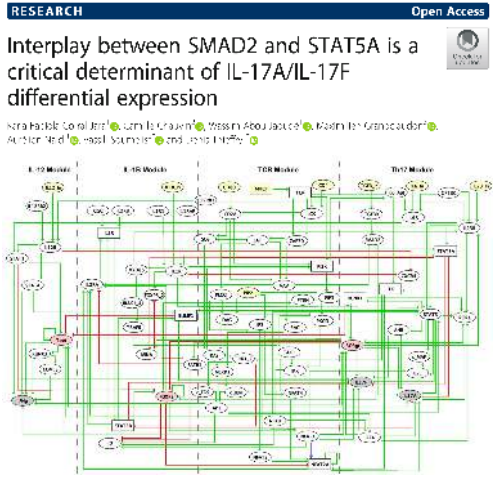


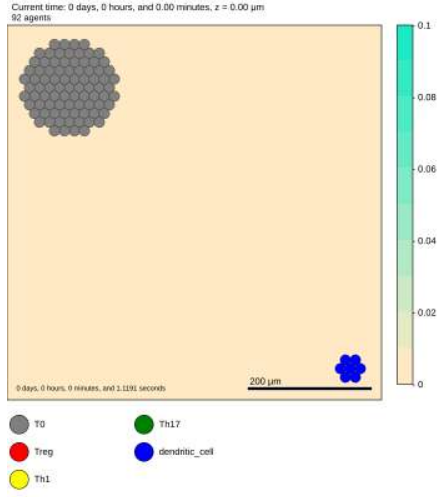
PI3KH++, p110++



Differentiation model

Differentiation model





Perspectives

PhysiBoSS tutorial

- PhysiBoSS is getting simpler !
- Tutorial in the coming months

Model personalization

- We can represent mutations in the signaling network
- We can use RNAseq data to personalize our MaBoSS models (PROFILE)
- New methods are needed to personalize agent-based models

Aknowledgments



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