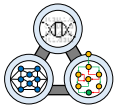
Building cell-line specific models of tumor growth using PhysiBoSS

Vincent Noël[1]

[1]Computational Systems Biology of Cancer,
Institut Curie, INSERM U900, Mines ParisTech, PSL Research University, Paris

BC2 - Mechanistic and AI digital twins in personalized medicine
two sides of the same coin

September 11, 2023





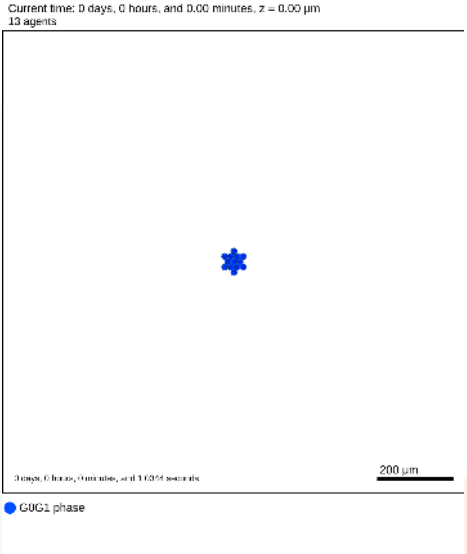








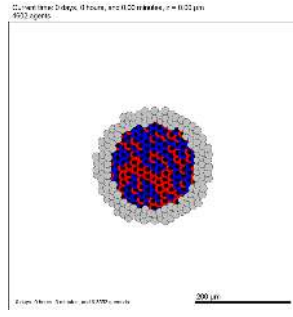
- Agent-based modeling
- PhysiBoSS
- Cell cycle model
- Personalisation using GDSC data



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

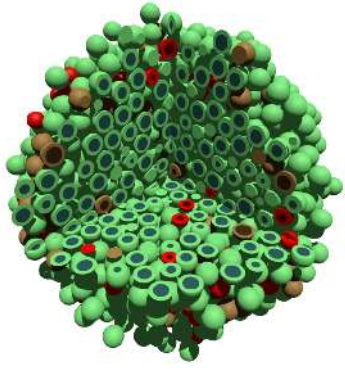
› PhysiCell



Paul Macklin



Randy Heiland



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

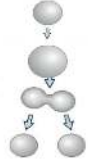
Cell agent properties

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

Cell Cycle



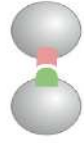
Growth



Migration

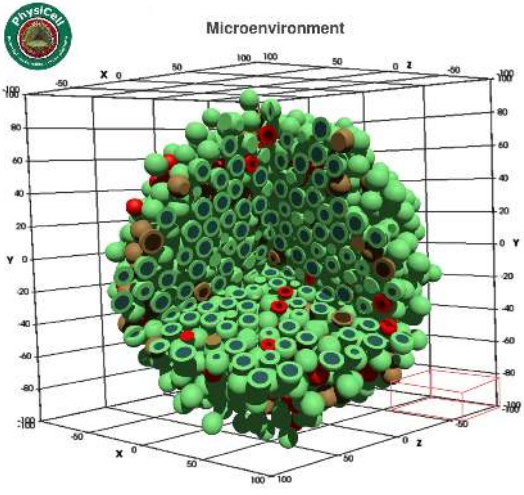


Cell-Cell interactions



Agent-based modeling

› PhysiCell



Diffusion equations

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

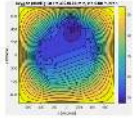
System of PDEs for each molecule:

- Diffusion term
- Decay
- Uptake/Production

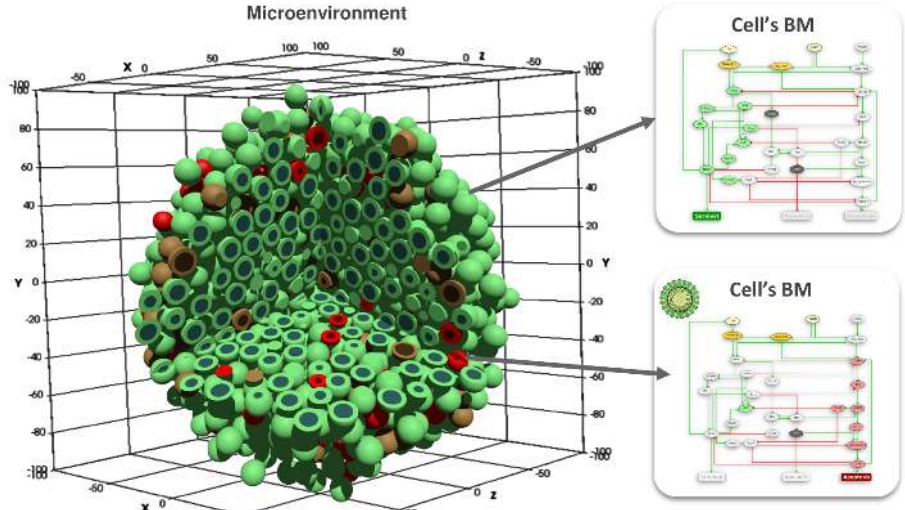
PDEs are solved using BioFVM







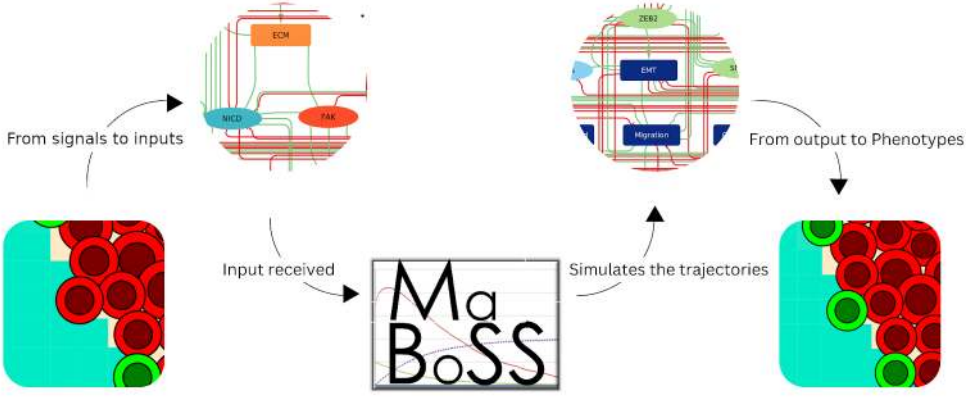
PhysiBoSS



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

- PhysiBoSS XML settings
  - MaBoSS BND and 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>
```

PhysiBoSS

- Automatic Mapping

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>
```

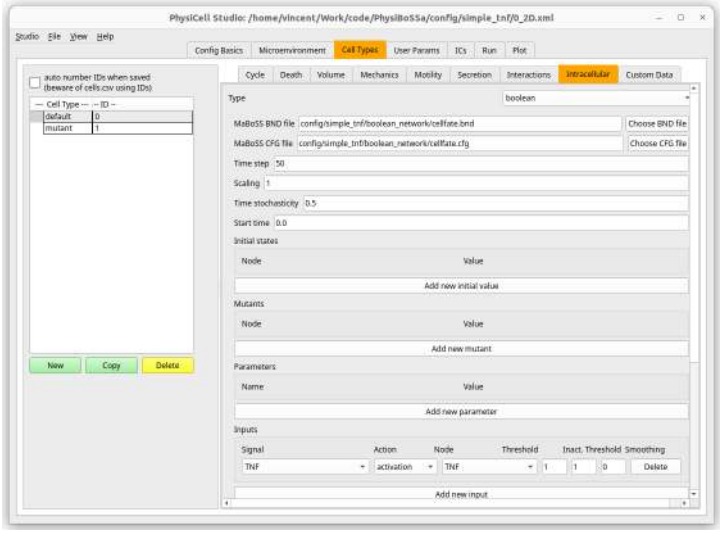
Output Mapping : *MaBoSS output node → PhysiCell Behavior*

- 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>
```

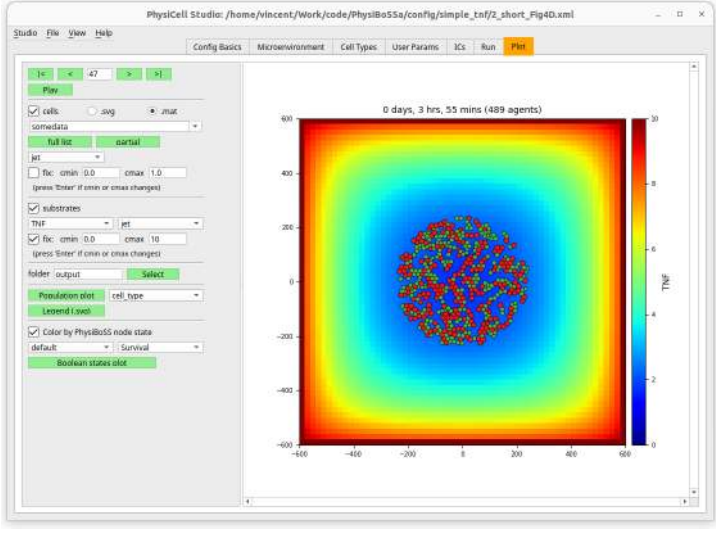
PhysiBoSS

› Modify PhysiBoSS configuration



PhysiBoSS

› Visualize PhysiBoSS results



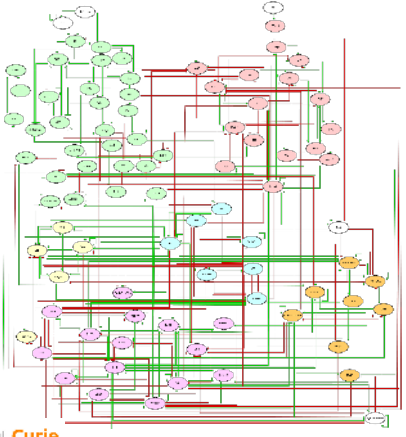
Cell cycle model

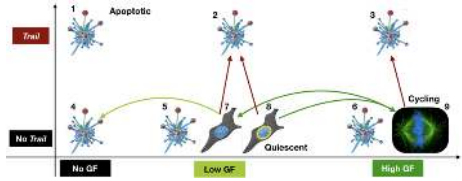
Cell cycle model

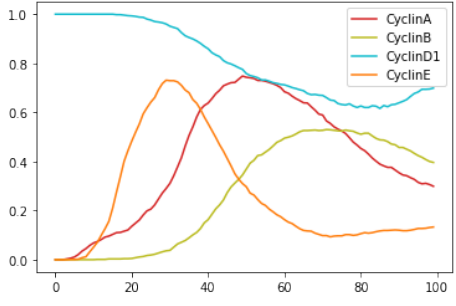
› Creating a signaling controlled cell cycle model

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

Herbert Sizek, Andrew Hamal, Dávid Deritei, Sarah Campbell, Erzsébat Ravasz Regan







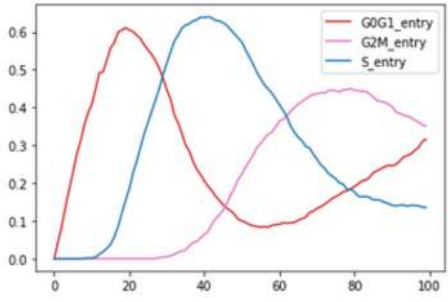
Cell cycle model

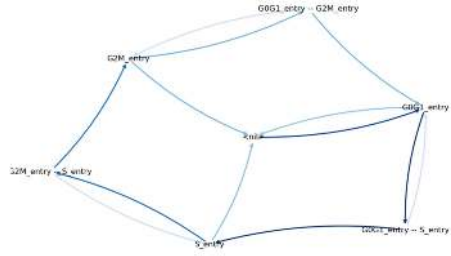
› Creating a signaling controlled cell cycle model

```
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
```

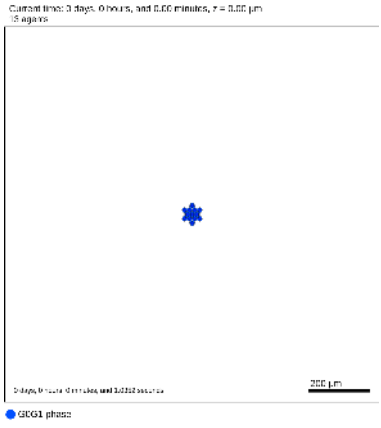




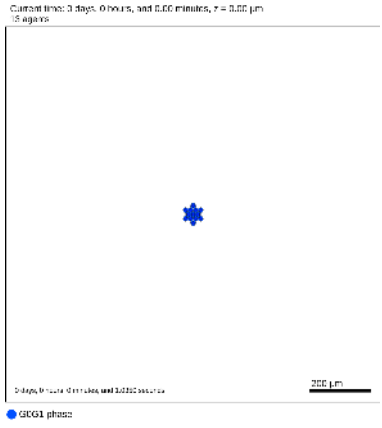
Cell cycle model

› Reproducing PhysiCell's cell cycle model

PhysiCell's cycle



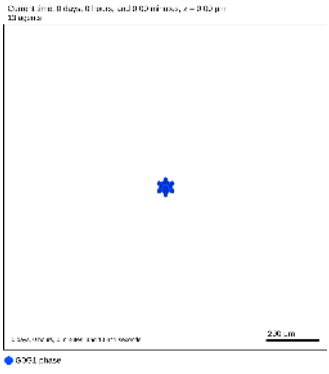
PhysiBoSS Sizek's cycle



Cell cycle model

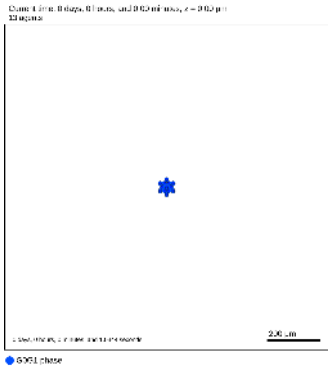
› Mutants analysis

Plk1 KO



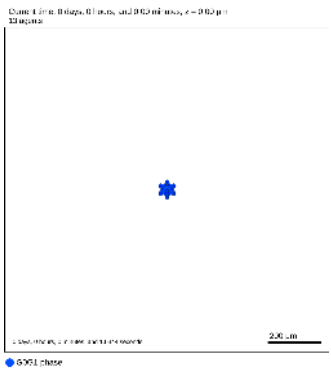
⇒ Cycle arrest in G2

FoxO3- -



⇒ Slower cell cycle

PI3KH++, p110++

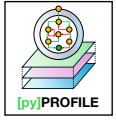


⇒ Faster cell cycle

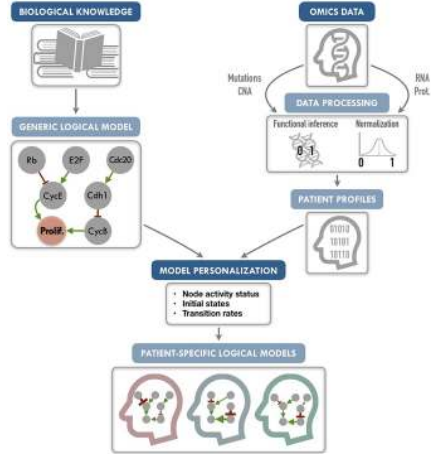
Personalisation using GDSC cell lines

WORK IN PROGRESS

- GDSC cells lines ($\sim$ 1000)
- Bulk RNAseq + mutations
- Personalized tumor growth/death

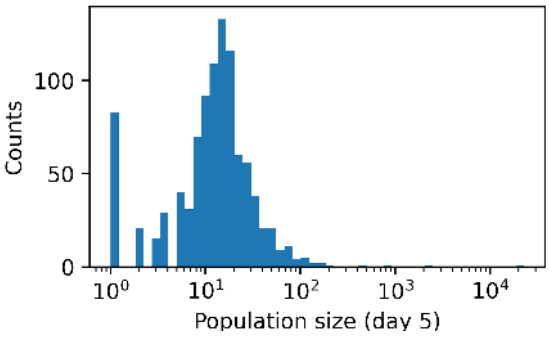




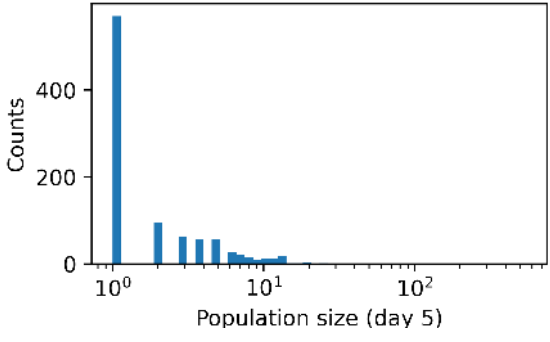


Personalisation using GDSC cell lines

High GF

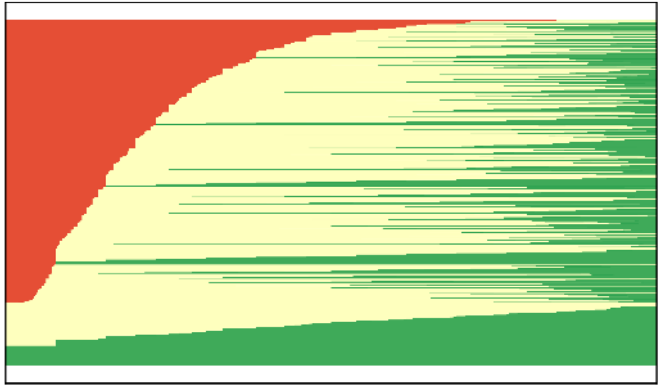


TRAIL



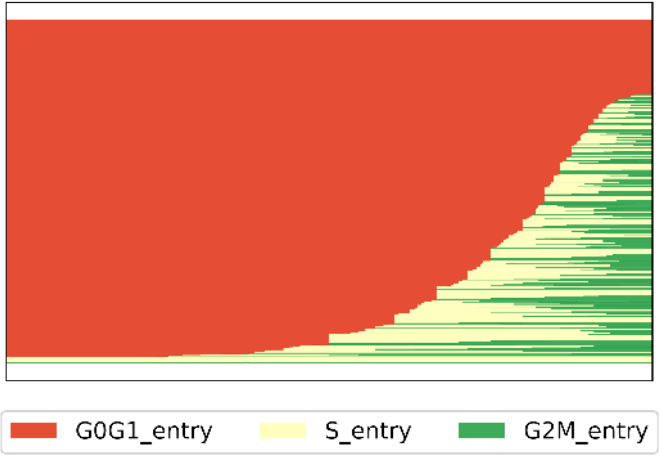
⇒ Lower growth rate than generic model, TRAIL mostly keeps working

Personalisation using GDSC cell lines



⇒ Most cells are cycling

Personalisation using GDSC cell lines



⇒ Many cells stuck in G1 (and no other phase ??!!)

Perspectives

Cell cycle personalization using GDSC

- Which nodes should (and shouldn't) be personalized (Caspases ?)
- Why so few S/G2/M blockages ?
- Next step : Comparing treatments with data

PhysiBoSS tutorial

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

Aknowledgments

Computational Systems Biology of Cancer

institutCurie

PSL RESEARCH UNIVERSITY PARIS

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Barcelona Supercomputing Center — Centro Nacional de Supercomputación

INDIANA UNIVERSITY


Marco Ruscone


Laurence Calzone


Gaëlle Letort


Emmanuel Barillot


Arnau Montagud


Miguel Ponce de Leon


Gerard Pradas


Alfonso Valencia


Randy Heiland


Paul Macklin


Sophia Orozco Ruiz


Adam Smelko


Marco Farinas Fernandez


Saran Pankaew


Paola Corbin Agusti

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