

Slides, videos, links and more:

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



Session 10: Introduction to intracellular models



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PhysiCell Project

July 27, 2022

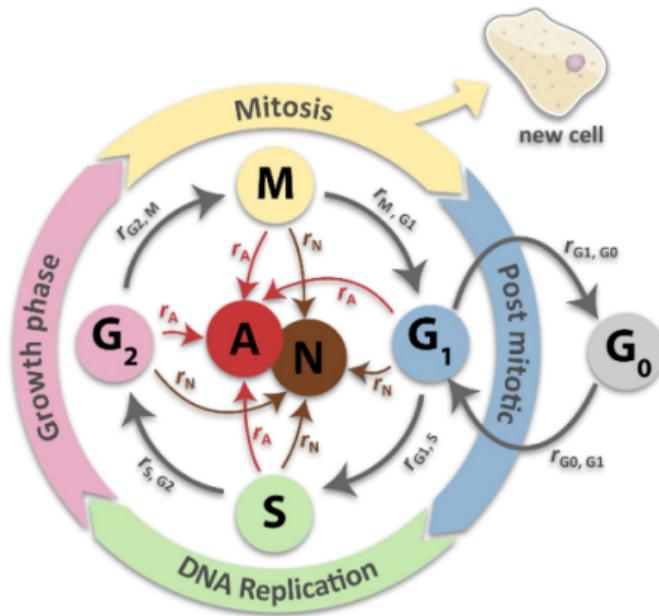


Outline

- › Modeling intracellular signaling
- › PhysiCell + MaBoSS = PhysiBoSS
- › PhysiBoSS 2.0
- › Intracellular interface

Modeling intracellular signaling

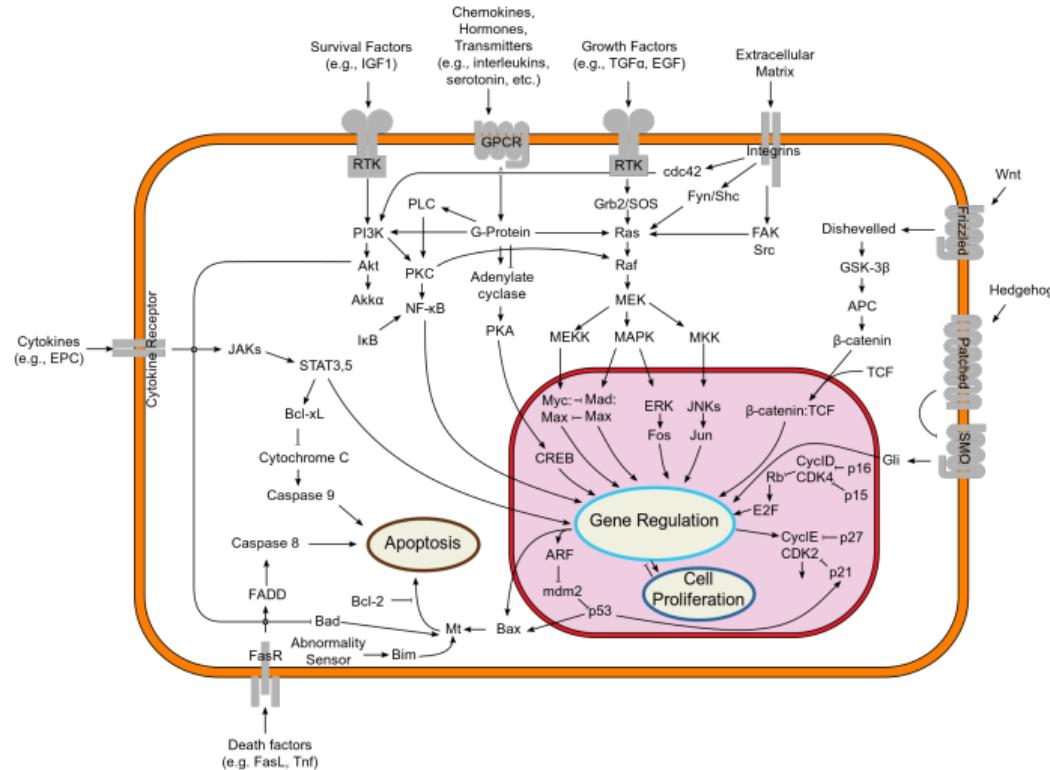
- PhysiCell have a very simple view of intracellular signaling



from Miguel Ponce de Leon

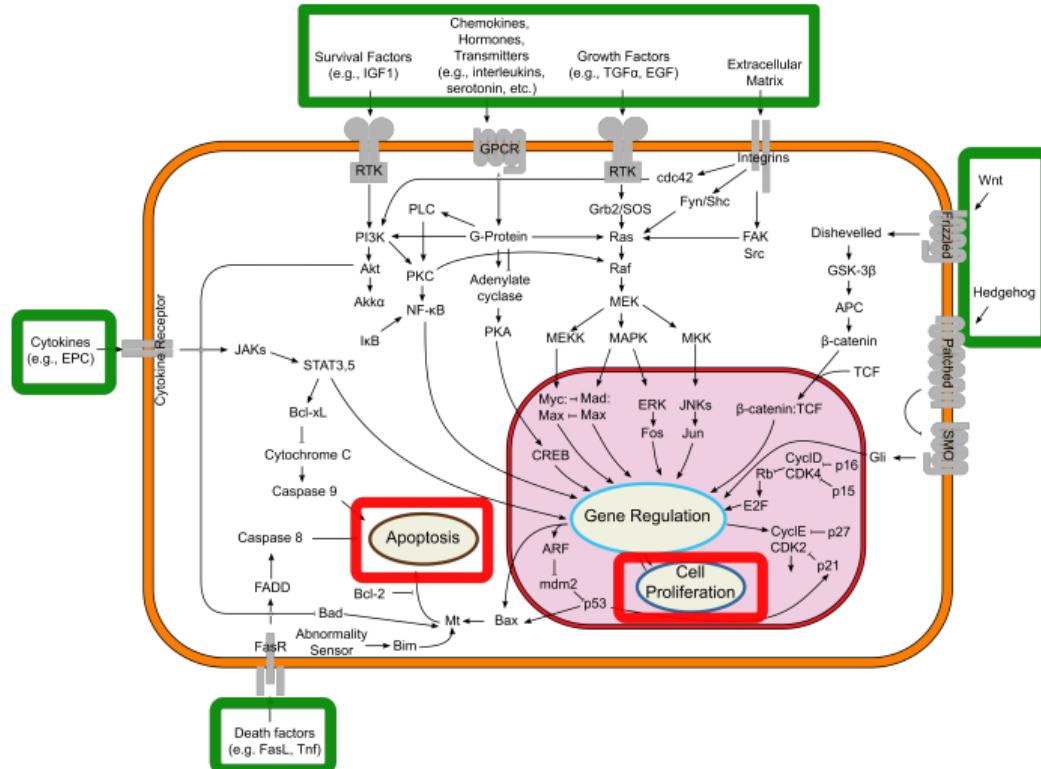
Modeling intracellular signaling

- But a lot of complexity (and regulation) is at the intracellular level



Modeling intracellular signaling

- Fortunately, PhysiCell provides Signals and Behaviors

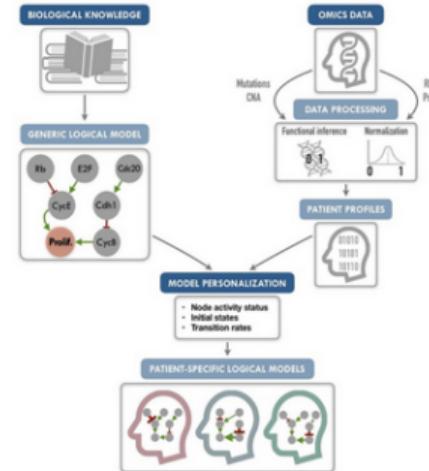


adapted from Wikipedia

Modeling intracellular signaling

Existing intracellular models could be interfaced with PhysiCell to "compute" behaviours from signals

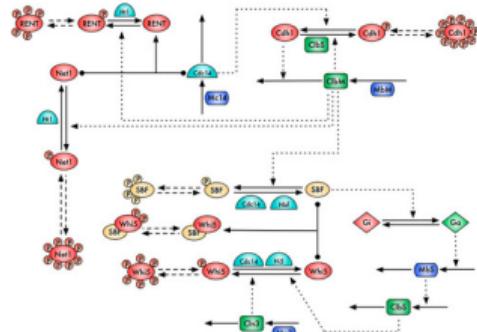
- › Drug treatments
 - › Mutants
 - › Personalisation
- ⇒ And simplify the description of multi-scale models !



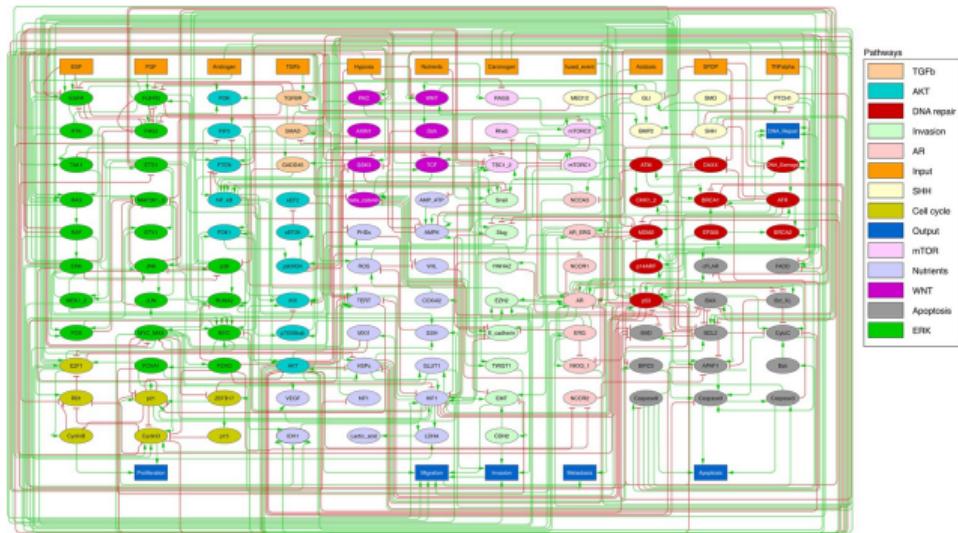
Béas et al, 2019

Modeling intracellular signaling

- Most of the modeling community is working on intracellular models
- Many existing models



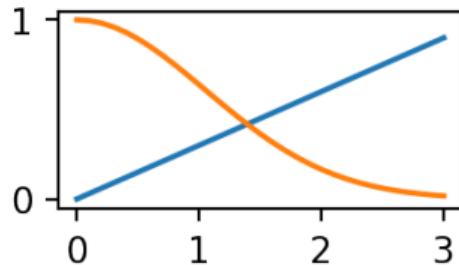
Barik et al, 2010



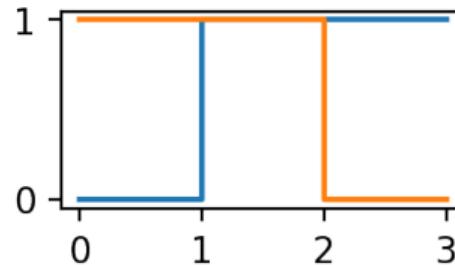
Montagud et al, 2022

Modeling intracellular signaling

Quantitative (ODEs)



Qualitative (Boolean)



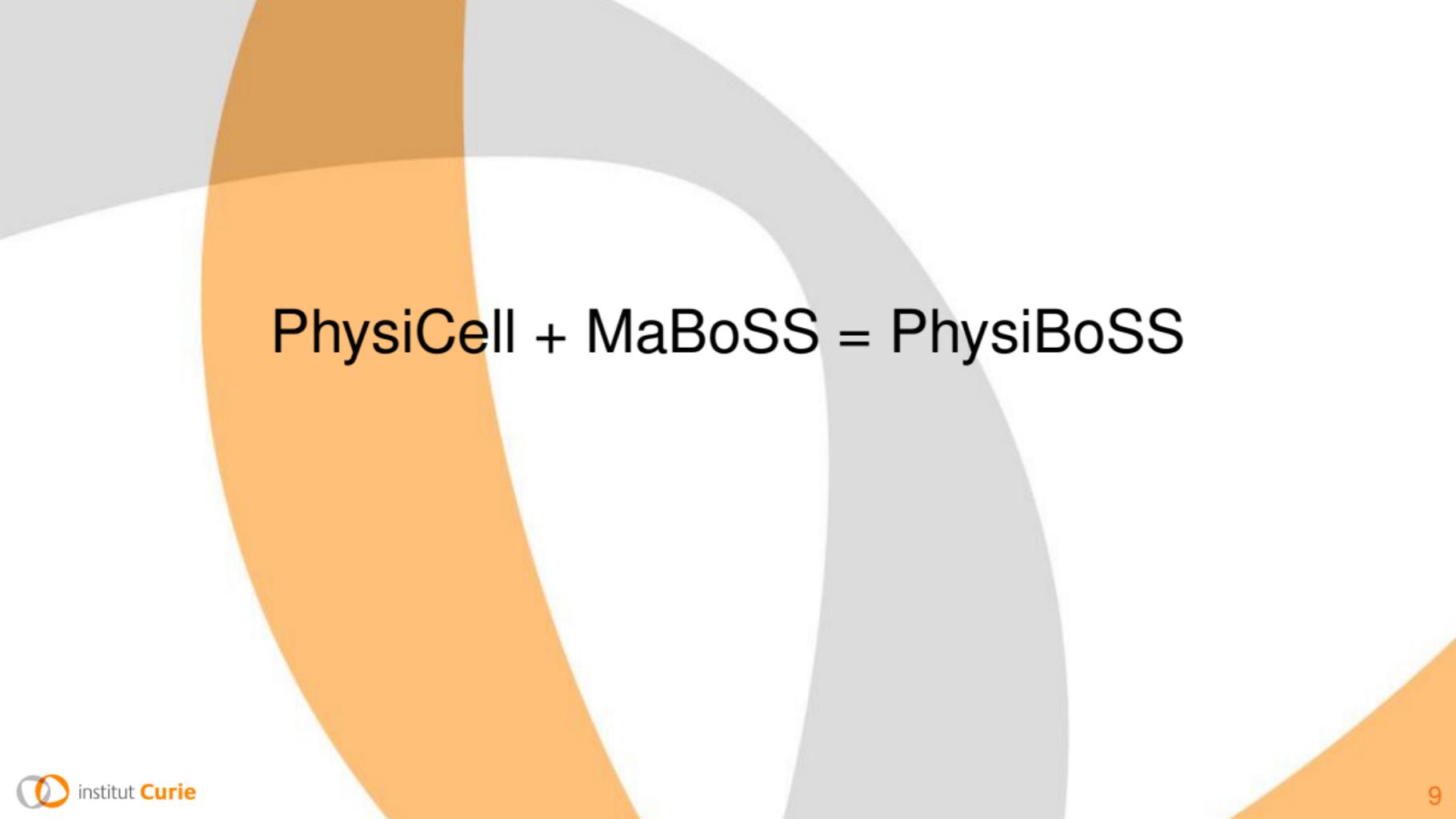
- › Values can be any quantity
- › Continuous time
- › Difficult to write
- › Difficult to simulate large models

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

Modeling intracellular signaling

Goals:

- › Simplify inclusion of existing signaling models
- › Allowing multiple frameworks
- › Integration with Signals and Behaviors



PhysiCell + MaBoSS = PhysiBoSS

PhysiCell + MaBoSS = PhysiBoSS

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 

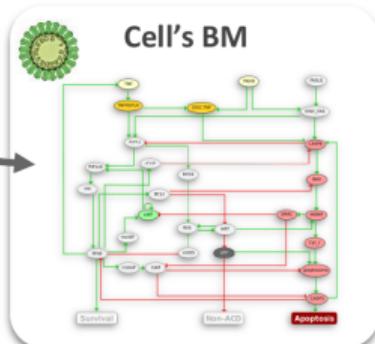
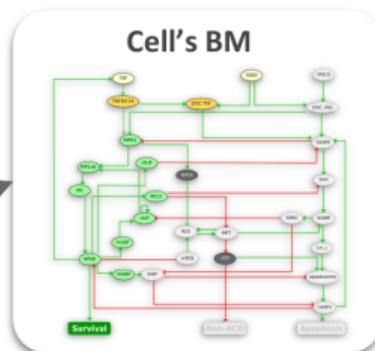
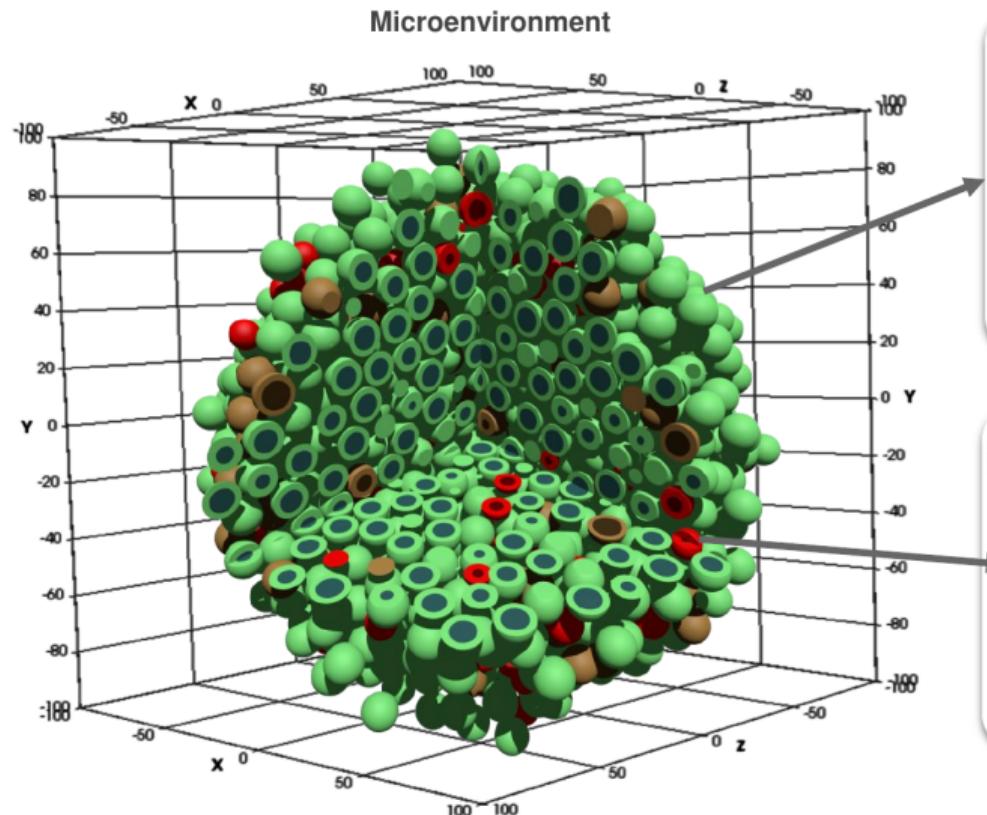
Bioinformatics, Volume 35, Issue 7, 01 April 2019, Pages 1188–1196, <https://doi.org/10.1093/bioinformatics/bty766>

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



Gaëlle Letort

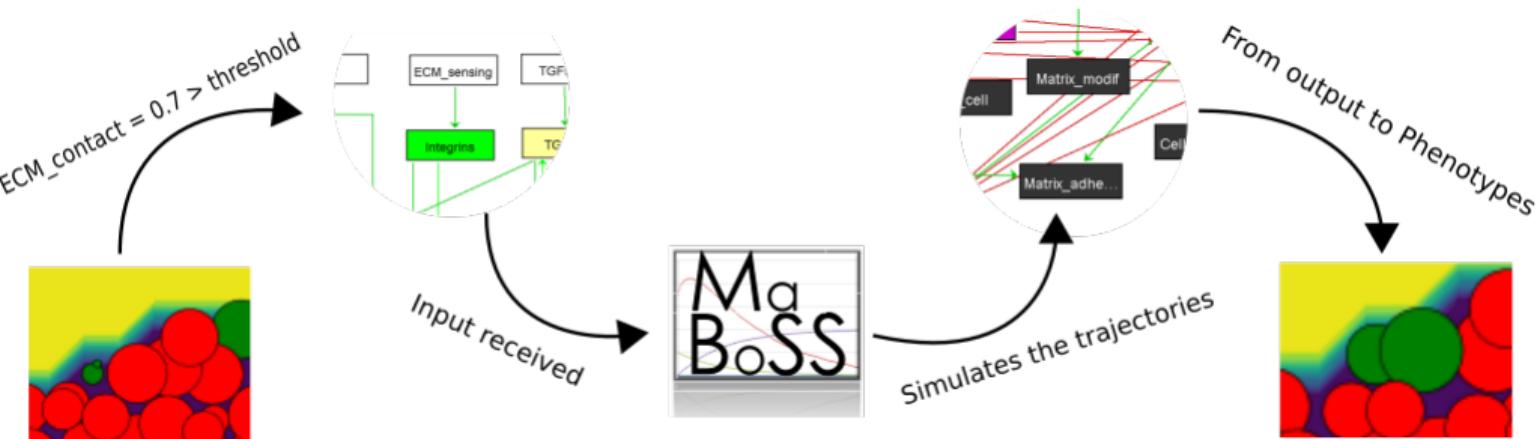
PhysiCell + MaBoSS = PhysiBoSS



Ponce de Leon et al, 2022

PhysiCell + MaBoSS = PhysiBoSS

- › Every *intracellular_dt*



- › Each cell runs one single (stochastic) simulation

PhysiCell + MaBoSS = PhysiBoSS



- › Boolean
- › Stochastic
- › Physical time



Gautier Stoll



Laurence Calzone

Continuous time Markov process applied on a Boolean network state space

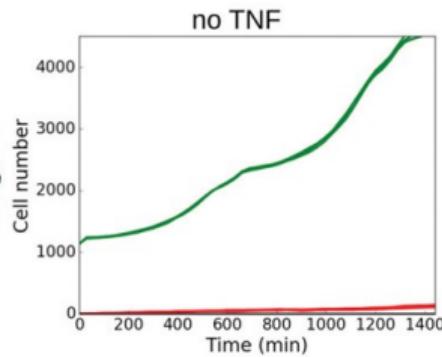
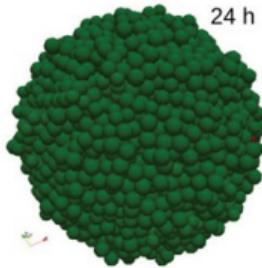
Transition rate :

$$p(S \rightarrow S') = \begin{cases} R_{up}(S), & \text{if } S_i = 0 \\ R_{down}(S), & \text{if } S_i = 1 \end{cases}$$

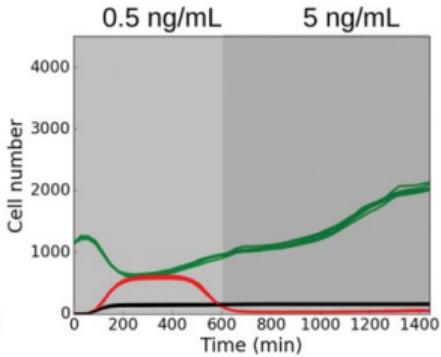
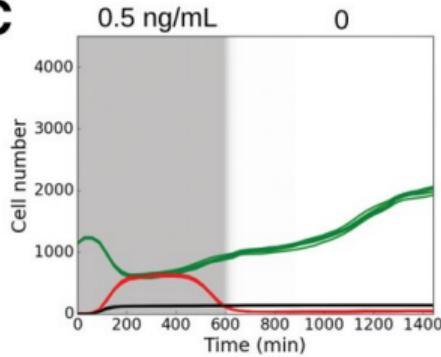
⇒ We have a notion of time in our boolean simulation, that we can couple with PhysiCell's time

PhysiCell + MaBoSS = PhysiBoSS

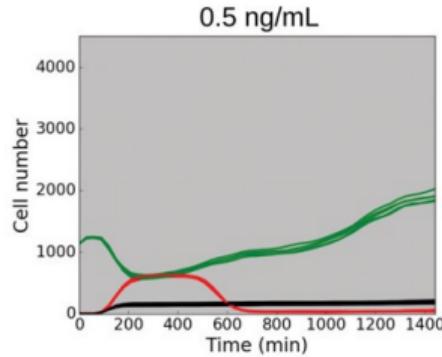
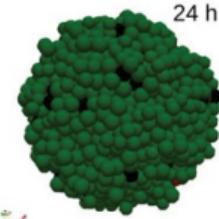
A



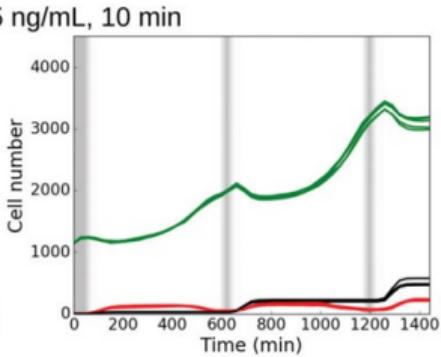
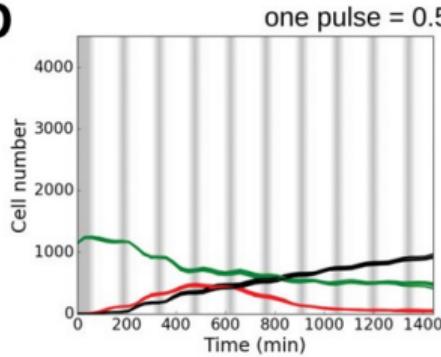
C



B

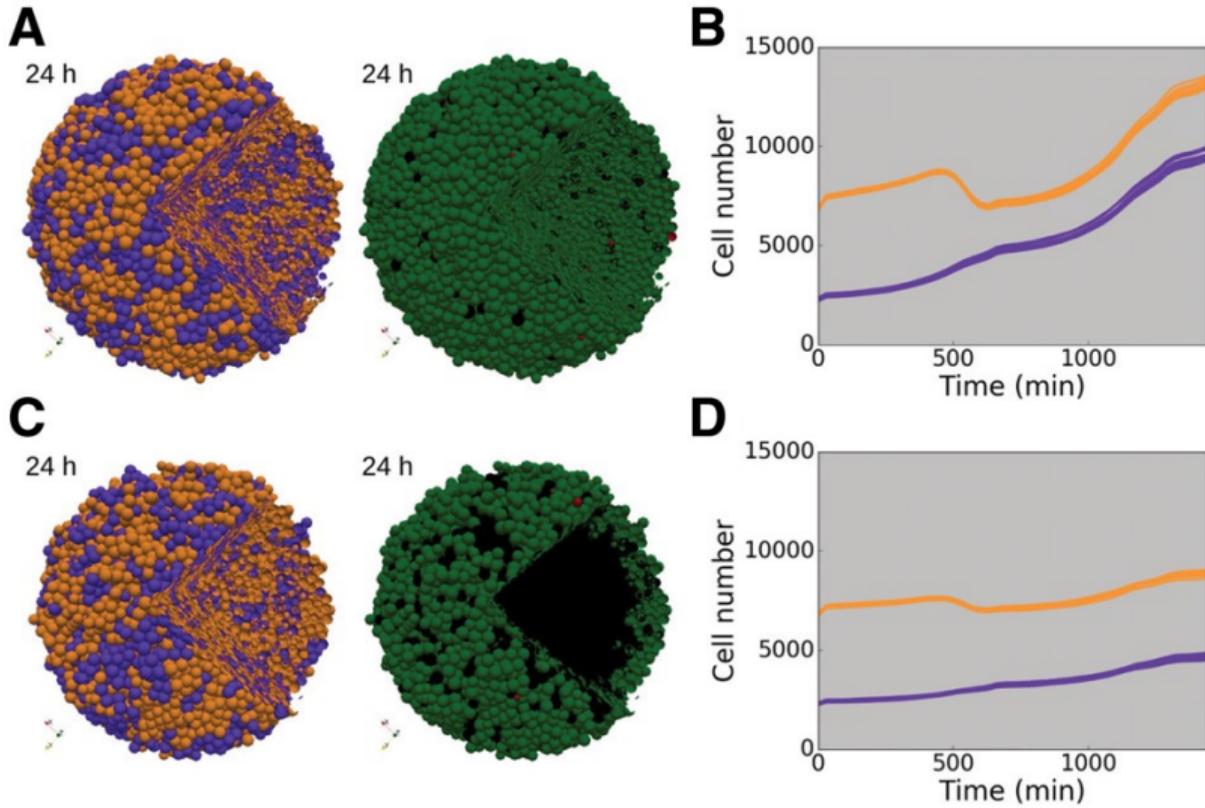


D



Letort et al, 2019

PhysiCell + MaBoSS = PhysiBoSS

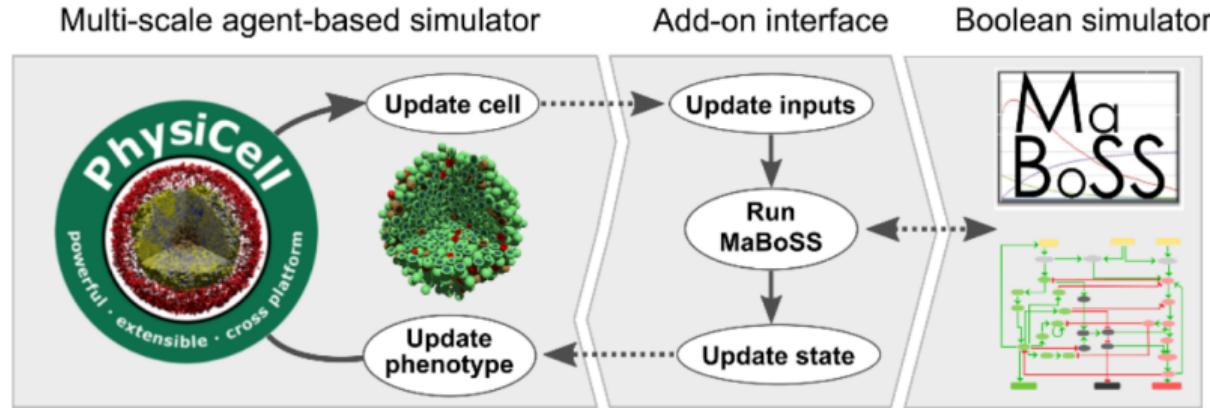


Letort et al, 2019

PhysiBoSS 2.0

PhysiBoSS 2.0

- › PhysiBoSS started from a fork of PhysiCell 1.1.0 (Nov 2017)
- › First meetings (Curie, BSC, IU) to merge PhysiBoSS into PhysiCell (Feb 2019)
- › PhysiBoSS 2.0 was merged into PhysiCell 1.9.0 (July 2021) as an add-on



Ponce de Leon et al, 2022

- › PhysiBoSS 2.2.0 release this summer (stochastic time step, automatic mapping)

PhysiBoSS 2.0

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

```
<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>
  </settings>
  <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 2.0

Inputs : Signals to MaBoSS nodes

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

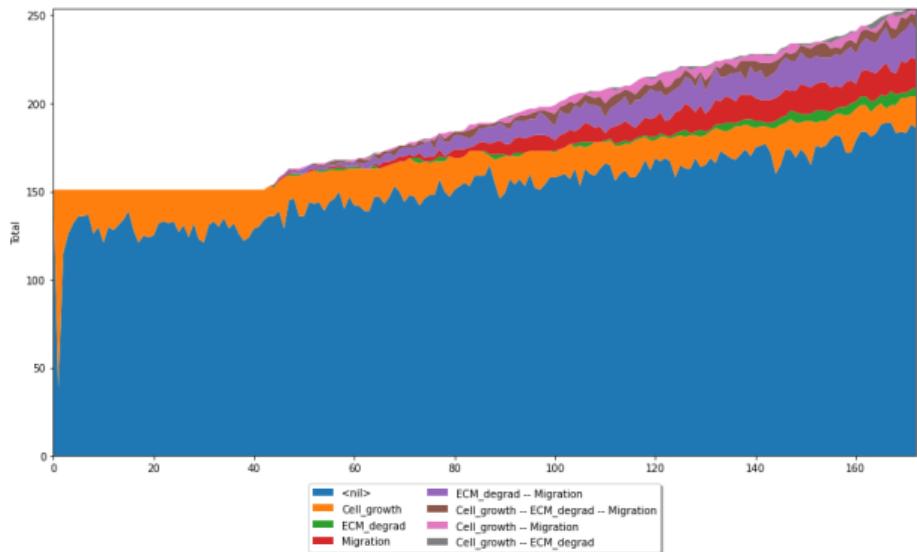
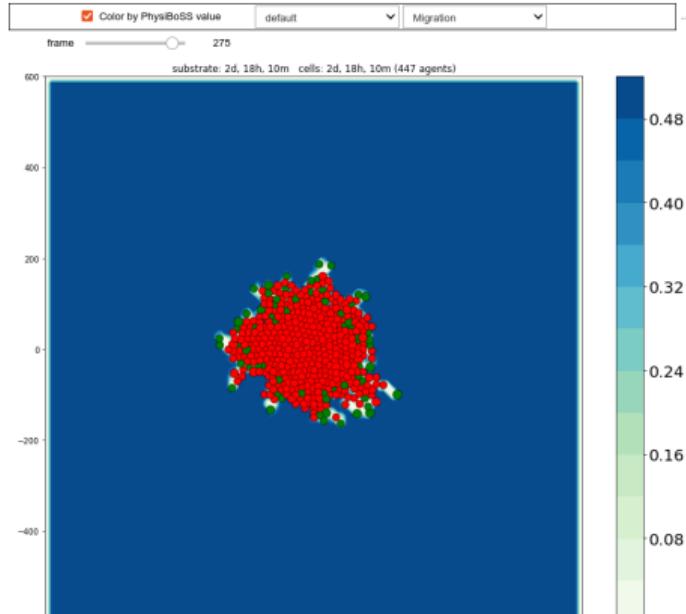
```
<input physicell_name="oxygen" intracellular_name="A">
  <settings>
    <action>inhibition</action>
    <threshold>10</threshold>
    <inact_threshold>10</inact_threshold>
  </settings>
</input>
```

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 2.0



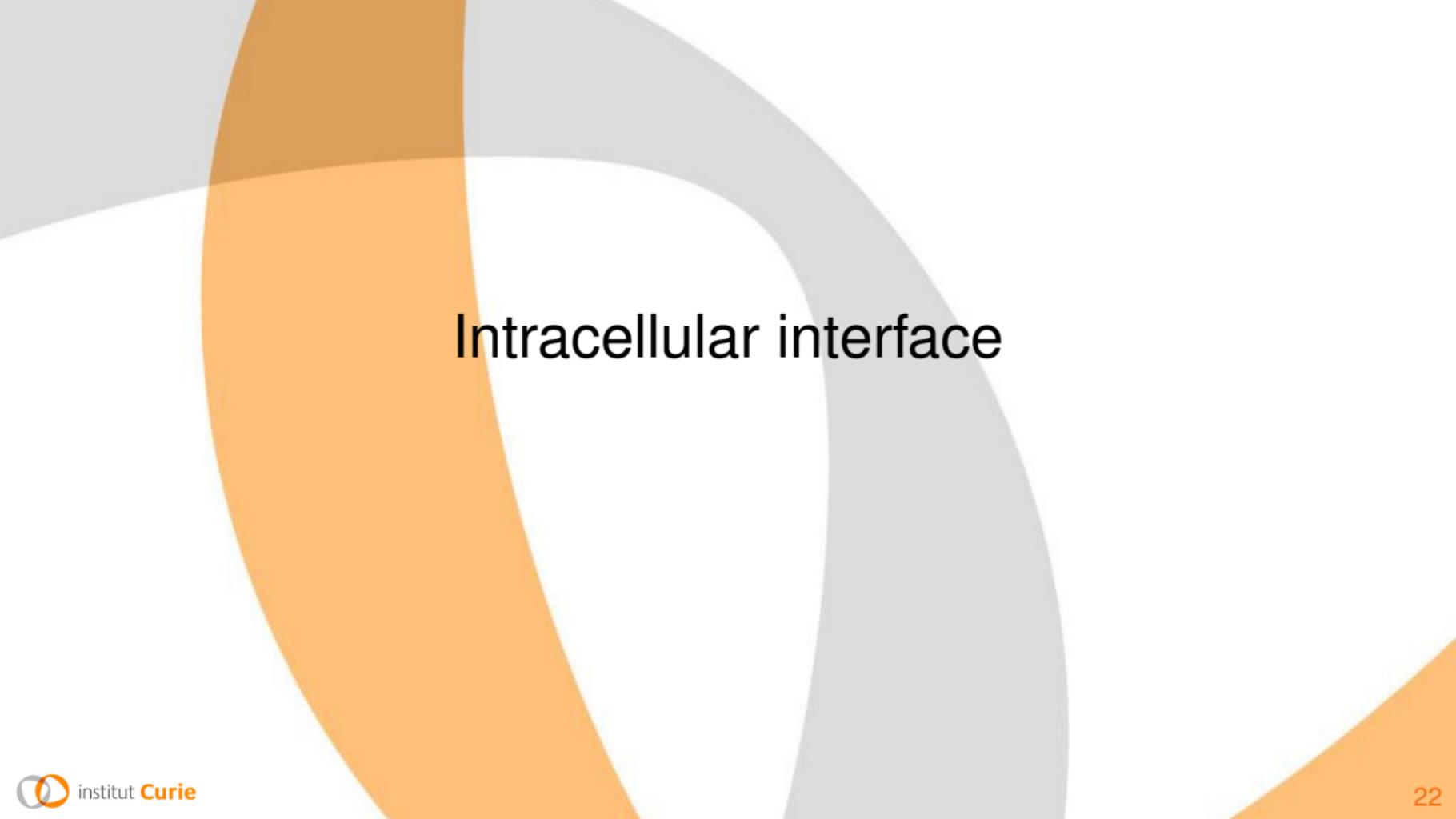
PhysiBoSS 2.0

- › Support of intracellular models in PhysiCell-model-builder
- › Still experimental. Please report bugs !

The screenshot shows the PhysiBoSS 2.0 software interface with the "Cell Types" tab selected. The left sidebar lists cell types: "default", "other", "another", "yet_another", "yet_yet_another", and "last_one". The main panel contains various configuration options:

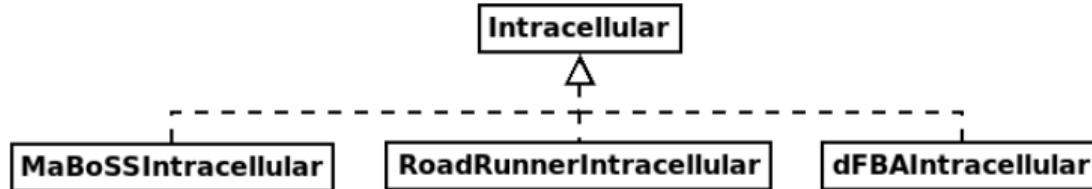
- Type:** boolean
- MaBoSS BND file:** ./data/model_0.bnd
- MaBoSS CFG file:** ./data/model.cfg
- Time step:** 1
- Scaling:** 1.0
- Time stochasticity:** (empty)
- Initial states:** A: 1, C: 0. Buttons: Add new initial value, Delete.
- Mutants:** (empty) Buttons: Add new mutant.
- Parameters:** (empty) Buttons: Add new parameter.
- Inputs:** oxygen: inhibition, Node: A, Threshold: 10, Inact. Threshold: 10, Smoothing: 0. Buttons: Add new input, Delete.
- Outputs:** apoptosis: activation, Node: C, Value: 5, Base_value: 0, Smoothing: 5. Buttons: Add new output, Delete.

Intracellular interface



Intracellular interface

- › Intracellular is a pure abstract class : it can be implemented in multiple ways



- › RoadRunnerIntracellular : Ordinary Differential Equations (Furkan Kurtoglu, Randy Heiland)
 - › dFBAIntracellular : Metabolic pathways (Miguel Ponce de Leon)
- ⇒ Other intracellular frameworks are welcome !

Intracellular interface

```
class Intracellular
{
private:
public:
    std::string intracellular_type; // specified in XML <intracellular type="...": "maboss", "sbml", ...

    // This function parse the xml cell definition
    virtual void initialize_intracellular_from_pugixml(pugi::xml_node& node) = 0;

    // This function initialize the model, needs to be called on each cell once created
    virtual void start() = 0;

    // This function checks if it's time to update the model
    virtual bool need_update() = 0;

    // This function update the model for the time_step defined in the xml definition
    virtual void update(Cell* cell, Phenotype& phenotype, double dt) = 0;

    // Get value for model parameter
    virtual double get_parameter_value(std::string name) = 0;

    // Set value for model parameter
    virtual void set_parameter_value(std::string name, double value) = 0;

    virtual std::string get_state() = 0;

    virtual void display(std::ostream& os) = 0;

    virtual Intracellular* clone() = 0;

    virtual ~Intracellular(){};
```

Perspectives

PhysiBoSS

- › More complex mapping rules (combination of signals, nodes)
- › Improve PhysiBoSS support in PhysiCell GUIs

Intracellular

- › Standardize intracellular data output
- › Improve visualization
- › Multiple intracellular models per cell

Acknowledgments



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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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PhysiCell Development:

- Breast Cancer Research Foundation
- 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)

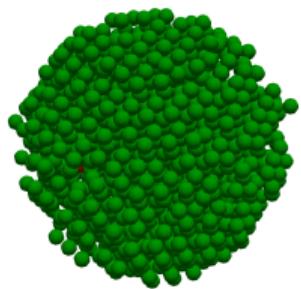
Other Funding:

- NCI / DOE / Frederick National Lab for Cancer Research (21X126F)
- DOD / Defense Threat Reduction Agency (HDTRA12110015)
- NIH Common Fund (3OT2OD026671-01S4)



Session 11 - Simulate a TNF treatment

No TNF



TNF

