# PhysiBoSS, an agent-based framework with boolean intracellular signalling

Vincent Noël[1]

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

Hybrid models and methods in systems medicine

July 6, 2022

institut Curie

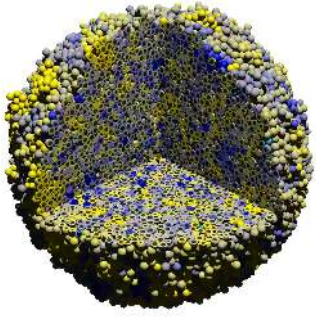
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# Modeling 3D cell populations and their microenvironment

- Tumor composition
- Tumor growth
- Nutrients (Necrosis)
- Immune cells
- Resistant cells



Ghaffarizadeh et al, 2018

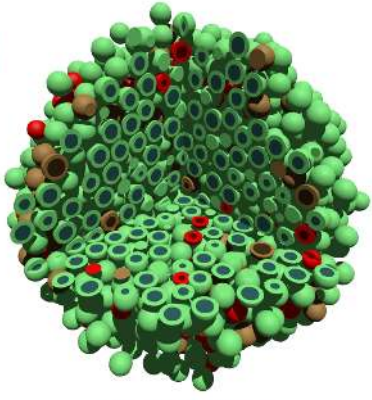
# PhysiCell : Multiscale Modelling Framework



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



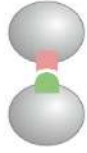

Growth



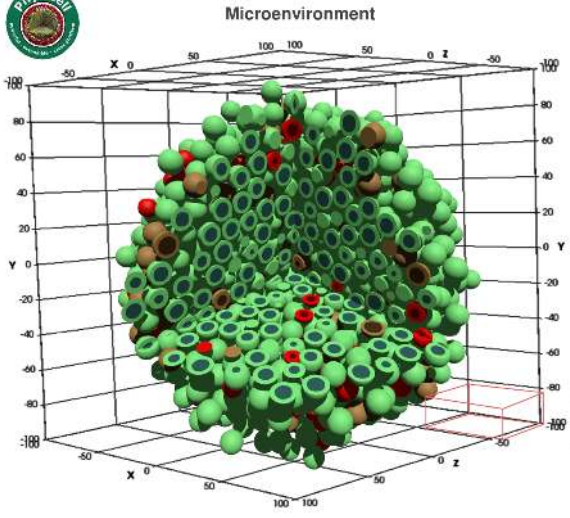
Migration



Cell-Cell interactions



# PhysiCell : Multiscale Modelling Framework



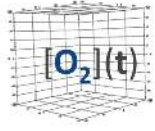

**Diffusion equations**

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

System of PDEs for each molecule:

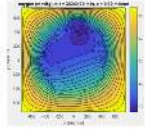
- Diffusion term
- Decay
- Uptake/Production

PDEs are solved using BioFVM

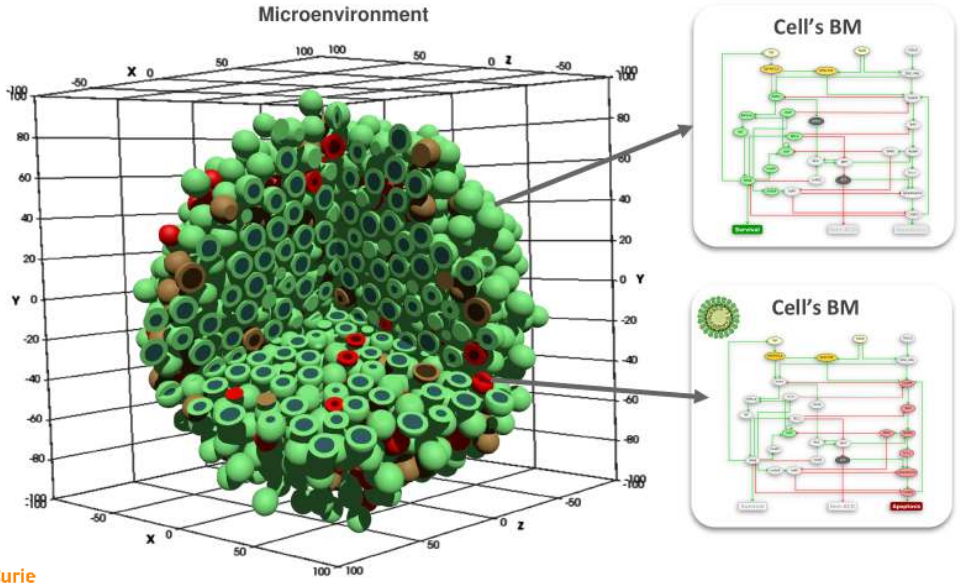








# PhysiCell + MaBoSS = PhysiBoSS



# PhysiCell + MaBoSS = PhysiBoSS




- Boolean
- Stochastic
- Physical time



Gautier Stoll



Laurence Calzone

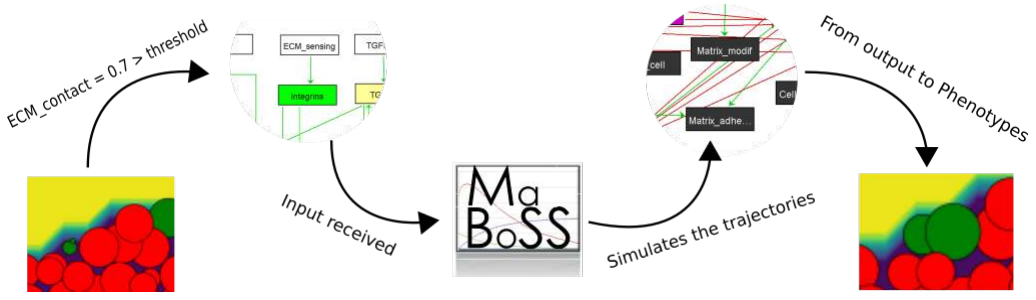
Continuous time Markov process applied on a Boolean network state space

Transition rate :

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

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

# PhysiCell + MaBoSS = PhysiBoSS



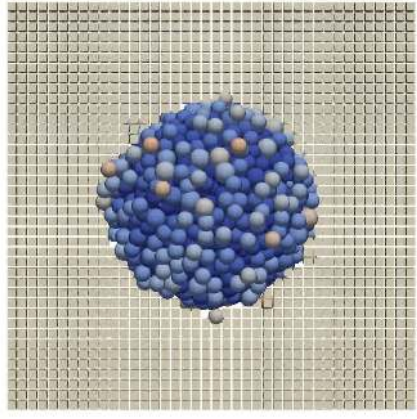

› Each cell runs one single (stochastic) simulation

Multiscale model of the different modes of invasion

# Multiscale model of the different modes of invasion

- Starts from a spheroid tumor
- Surrounding cells start evading
- Different migration modes :
  - Single
  - Collective
  - Trail

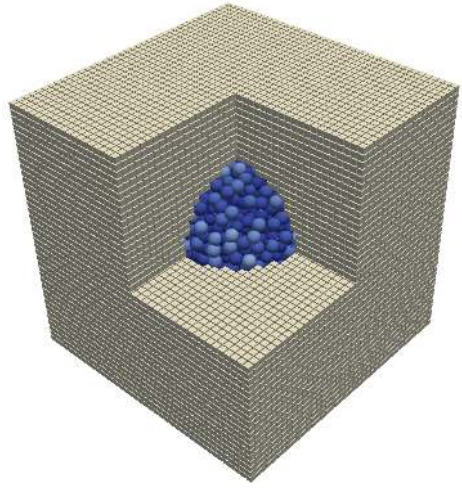




M. Ruscone et al., in preparation

# Multiscale model of the different modes of invasion

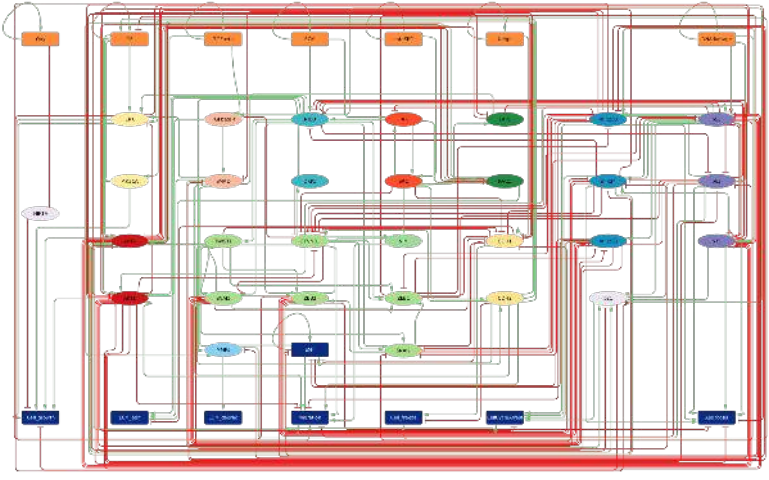
- A substrate of the microenvironment
- A barrier for the cells
- Cell-ECM contact triggers signalling
- Cells produce metaloprotease to destroy ECM



M. Ruscone et al., in preparation

# Multiscale model of the different modes of invasion

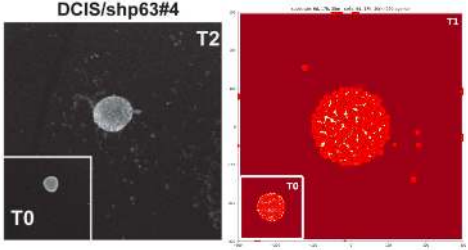
› 7 input nodes and 7 output nodes



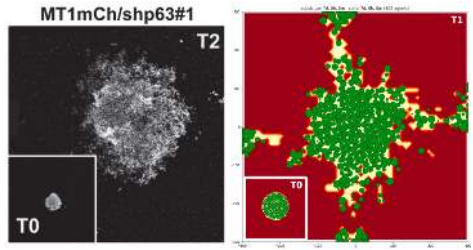
M. Ruscone et al., in preparation

# Multiscale model of the different modes of invasion

› Comparison with Figure 6.a from *"MT1-MMP and P63 in DCIS to IDC transition" C. Lodillinsky et al*




Red cells have p63 node OFF

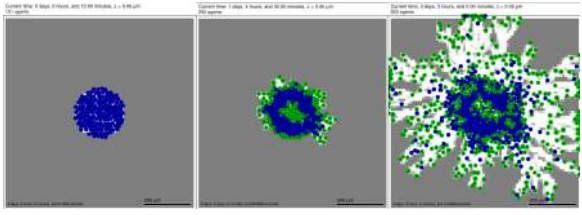



Green cells have p63 node ON

M. Ruscone et al., in preparation

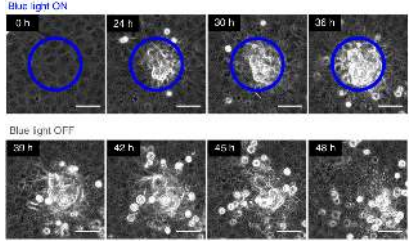
# Multiscale model of the different modes of invasion

- up/down-regulation induced by light
- reproduce collective extrusion of cells



**Local light-activation of the Src oncoprotein in an epithelial monolayer promotes collective extrusion**

Sarah Moitrier, Nastassia Pricoupenko, Adèle Kerjouan, Christiane Oddou, Olivier Destaing, Aude Battistella, Pascal Silberzan & Isabelle Bonnet




M. Ruscone et al., in preparation

# Multiscale model of the different modes of invasion

- Performing sensitivity analysis
- Improvement of ECM representation
- Work on PhysiBoSS model fitting


Marco Ruscone


Gaelle Letort


Arnau Montagud


Laurence Calzone


Andrei Zinovyev


Philippe Chavrier


Olivier Destaing

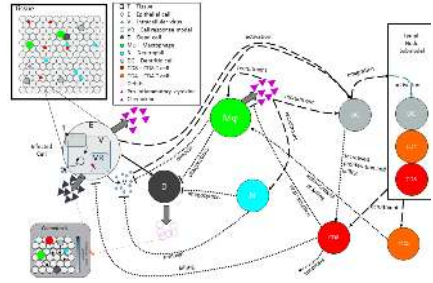
# PhysiBoSS-COVID : Lung tissue infection by SARS-CoV-2

# PhysiBoSS-COVID : Lung tissue infection by SARS-CoV-2

- Build a multi-scale model of COVID infection
- Using PhysiCell formalism + PhysiBoSS addon
- Starting with existing model from PhysiCell creators
- With mechanistic Boolean models produced by the COVID-19 Disease Maps community

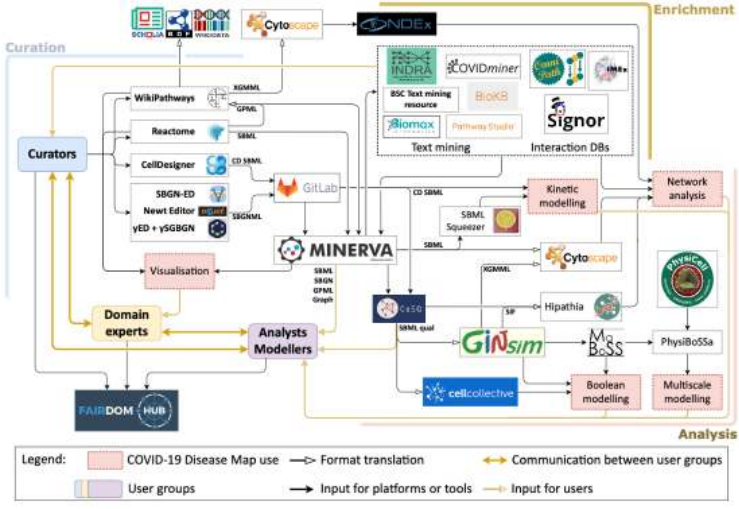
# PhysiBoSS-COVID : Lung tissue infection by SARS-CoV-2

- PhysiCell model representing SARS-CoV-2 infection
- Developed by a consortium led by Paul Macklin's lab
- Represents Virus, Epithelial cells, CD4, CD8, Macrophages, Dendritic cells, Neutrophils
- Good phenomenological model
- Lacks mechanistic details



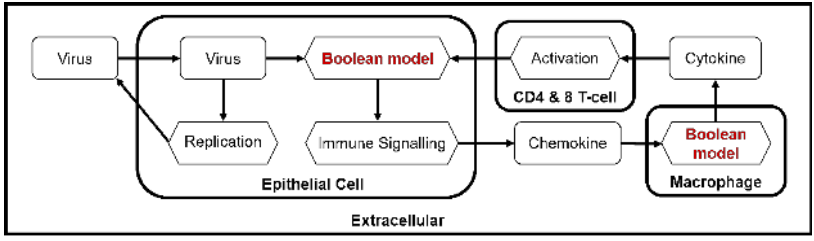
M. Getz et al. (2021)

# PhysiBoSS-COVID : Lung tissue infection by SARS-CoV-2



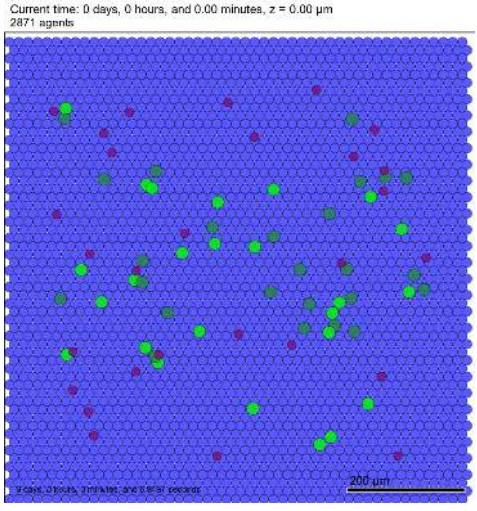

M. Ostaszewski et al. (2021)

# PhysiBoSS-COVID : Lung tissue infection by SARS-CoV-2




- Epithelial cells Apoptosis model from Anna Niarakis' lab (40 nodes)
- Macrophage model from Martin Kuiper's lab (157 nodes)

# PhysiBoSS-COVID : Lung tissue infection by SARS-CoV-2

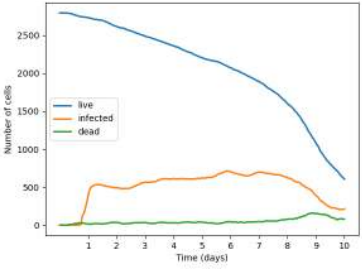


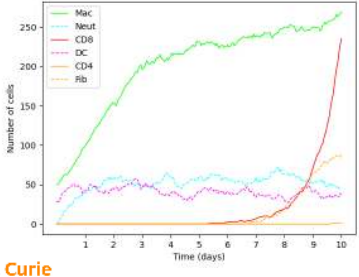

- **lung epithelium:** are colored by their (assembled) virion loads in four colors
  - Cells with 0 assembled virions.
  - Cells with 1-9 assembled virions.
  - Cells with 10-99 assembled virions.
  - Cells with 100-999 assembled virions.
  - Cells with 1000+ assembled virions.
  - Apoptotic (dead from viral load)
- **CD8⁺ T cells:** are colored by their cell cycle status
  - G0G1, S, G2, M cycle
- **CD4⁺ T cells:** are colored by their cell cycle status
  - G0G1, S, G2, M cycle
- **macrophage:** are colored by their cell cycle status
  - G0G1, S, G2, M cycle
  - Activated macrophage
  - Exhausted macrophage
  - Hyperactivated macrophage
- **neutrophil:** are colored by their cell cycle status
  - G0G1, S, G2, M cycle
- **fibroblast:** are colored by their cell cycle status
  - G0G1, S, G2, M cycle
- **Dendritic cells:** are colored by their cell cycle status
  - G0G1, S, G2, M cycle
  - Activated DC

  Apoptotic immune cells
  - Apoptotic
- **Background:** Contour plot of released virus that is diffusing in and above the tissue.

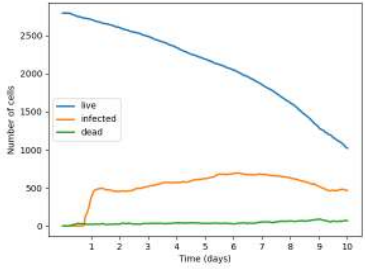
# PhysiBoSS-COVID : Lung tissue infection by SARS-CoV-2

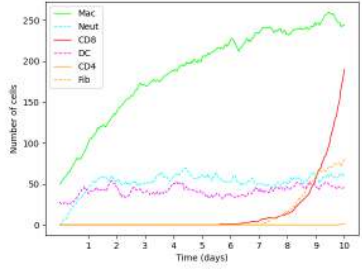
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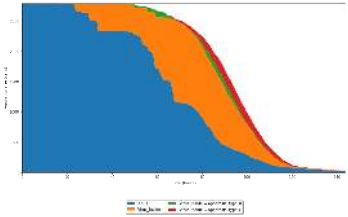

FADD KO



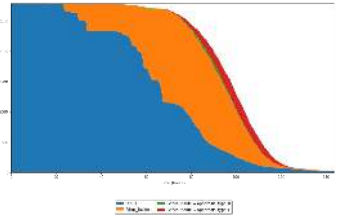



# PhysiBoSS-COVID : Lung tissue infection by SARS-CoV-2

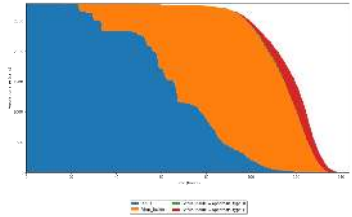
50% M inhibition



80% M inhibition



95% M inhibition



- 100% inhibition blocks the activation of the immune system
- 50% inhibition has little effect compared to no inhibition
- More inhibition adds more delay to the immune system activation

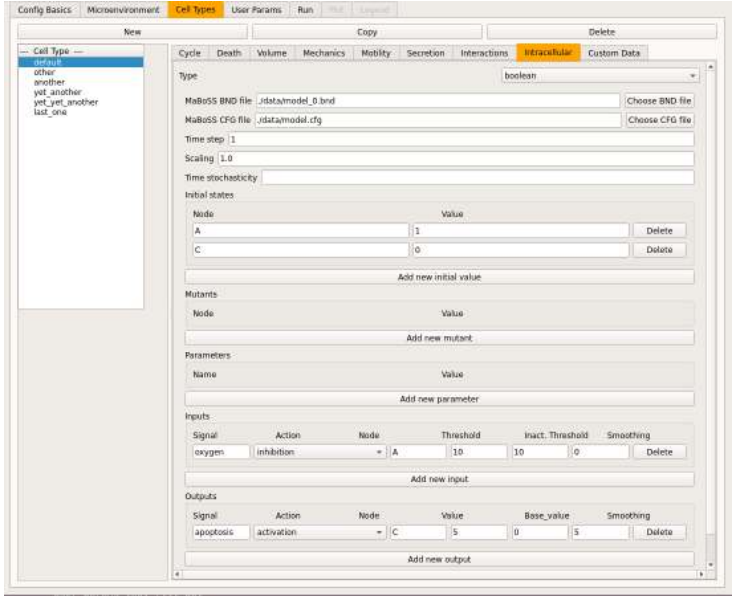
# PhysiBoSS-COVID : Lung tissue infection by SARS-CoV-2

- Update to latest version of SARS-CoV-2 tissue simulator
- Improve cell-type-specific boolean models
- Model personalization with patient's data
- Simulate possible treatments

# Conclusion

- Development of PhysiBoSS as PhysiCell first addon
- PhysiBoSS is officially included in PhysiCell 1.9.0
- Intracellular definition using PhysiCell's XML settings
- Automatic mappings for PhysiCell <=> MaBoSS
- PhysiCell Studio : PhysiCell future GUI

# PhysiCell Studio



# Aknowledgments



Vincent Noël



Gautier Stoll



Eric Viara



Laurence Calzone



Emmanuel Barillot



Marco Ruscone



Andrei Zinovyev



Arnau Montagud



Miguel Ponce de Leon



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