PhysiBoSS-COVID: the Boolean modelling of COVID-19 signalling pathways in a multicellular simulation framework allows for the uncovering of mechanistic insights

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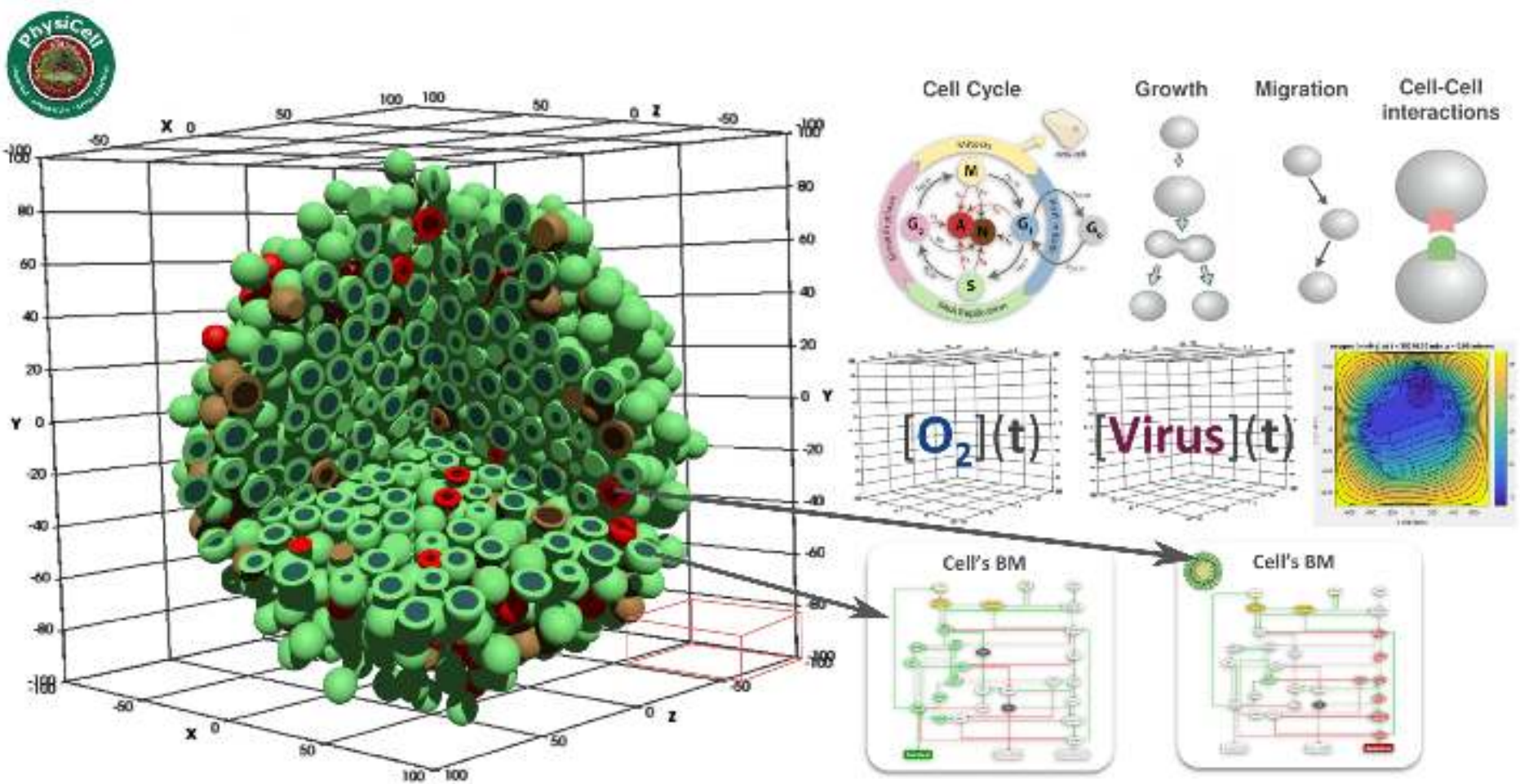
[1]Institut Curie, INSERM, Mines ParisTech, University PSL, Paris, France
[2]Barcelona Supercomputing Center, Barcelona, Spain
[3]Inria Saclay Ile de France, Palaiseau, France
[4]Univ. Evry, University of Paris-Saclay, Evry, France

5th Disease Maps Community Meeting
November 10, 2020

Introduction

- 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 Disease Maps community

PhysiCell + PhysiBoSS : Agent-based Modelling Framework



PhysiBoSS-COVID model structure

- Virus as a substrate diffusing in the environment
- Epithelial cells as tissue
- Immune system interacting with virus & infected cells
- Each cell type is running a specific Boolean model

⇒ Needs cell-type-specific models

⇒ Needs intercellular 'high level' model

⇒ Needs to fit a lot of parameters !

SARS-CoV-2 Tissue Modelling Coalition





New Results

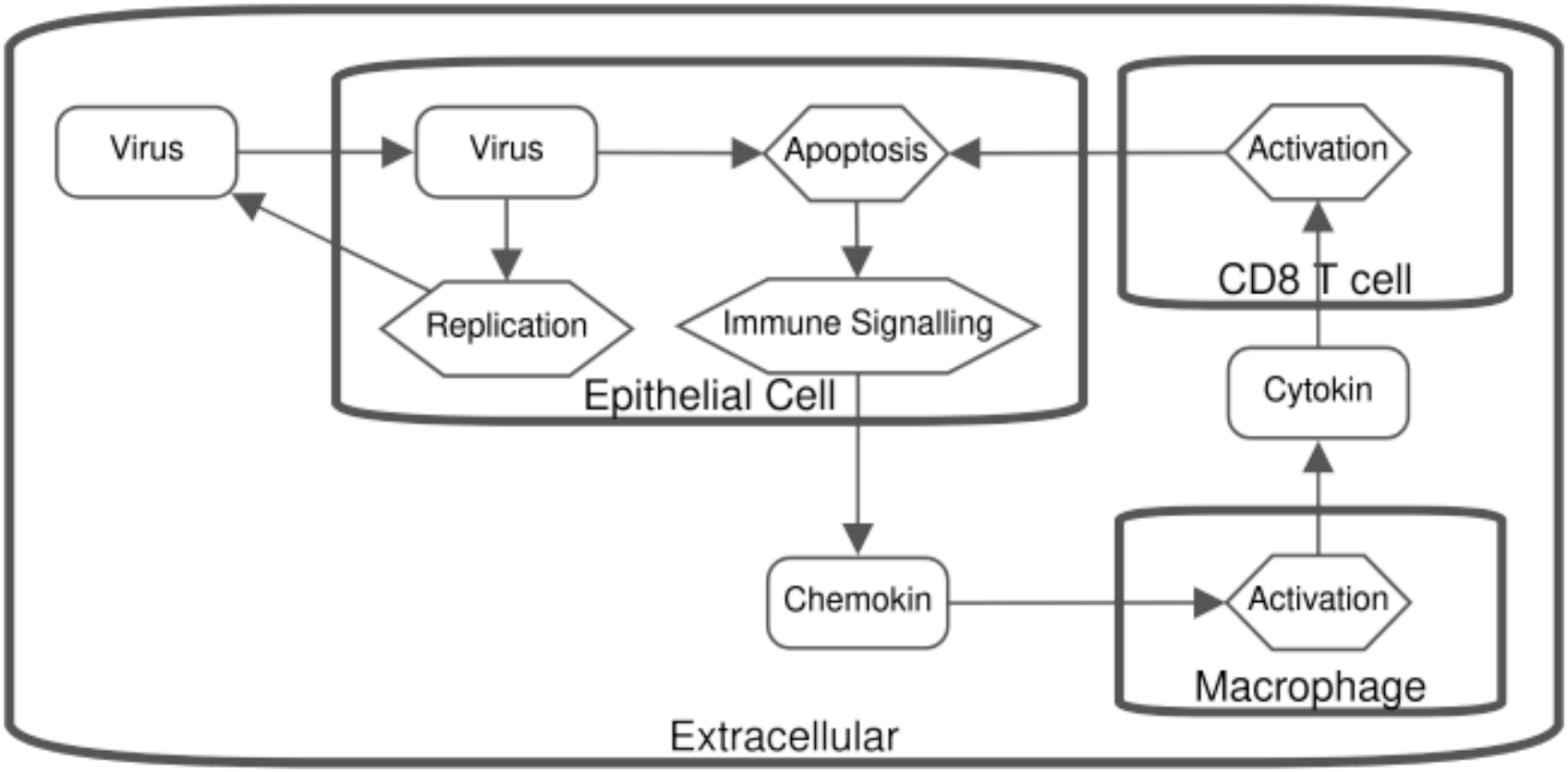
Comments (1)

Rapid community-driven development of a SARS-CoV-2 tissue simulator

Michael Getz, Yafei Wang, Gary An, Andrew Becker, Chase Cockrell, Nicholson Collier, Morgan Craig, Courtney L. Davis, James Faeder, Ashlee N. Ford Versypt, Juliano F. Gianlupi, James A. Glazier, Sara Hamis, Randy Heiland, Thomas Hillen, Dennis Hou, Mohammad Aminul Islam, Adrianne Jenner, Furkan Kurtoglu, Bing Liu, Fiona Macfarlane, Pablo Maygrundter, Penelope A Morel, Aarthi Narayanan, Jonathan Ozik, Elsje Pienaar, Padmini Rangamani, Jason Edward Shoemaker, Amber M. Smith, Paul Macklin

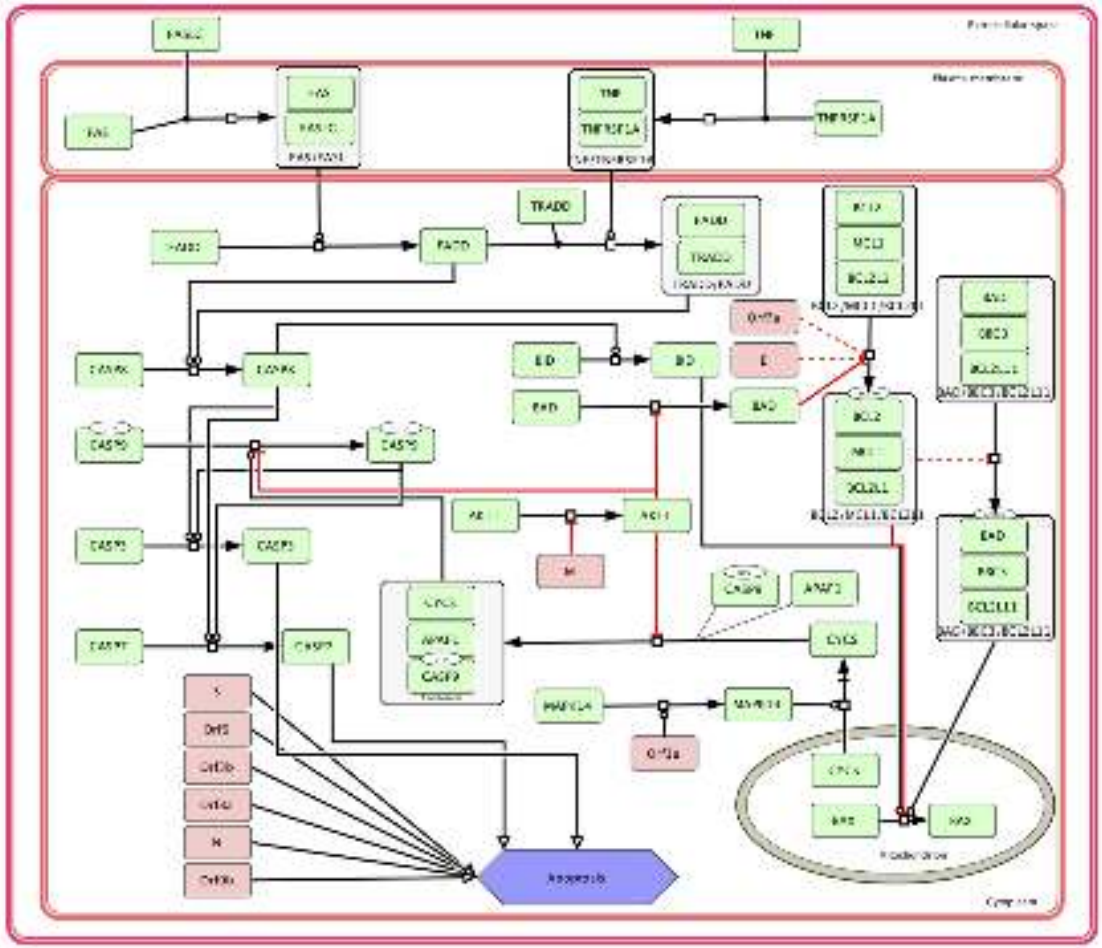
doi: https://doi.org/10.1101/2020.04.02.019075

How it works



⇒ We have begun by adding a detailed description of the apoptosis

Adding apoptosis pathway



From COVID-19 Disease Map project:

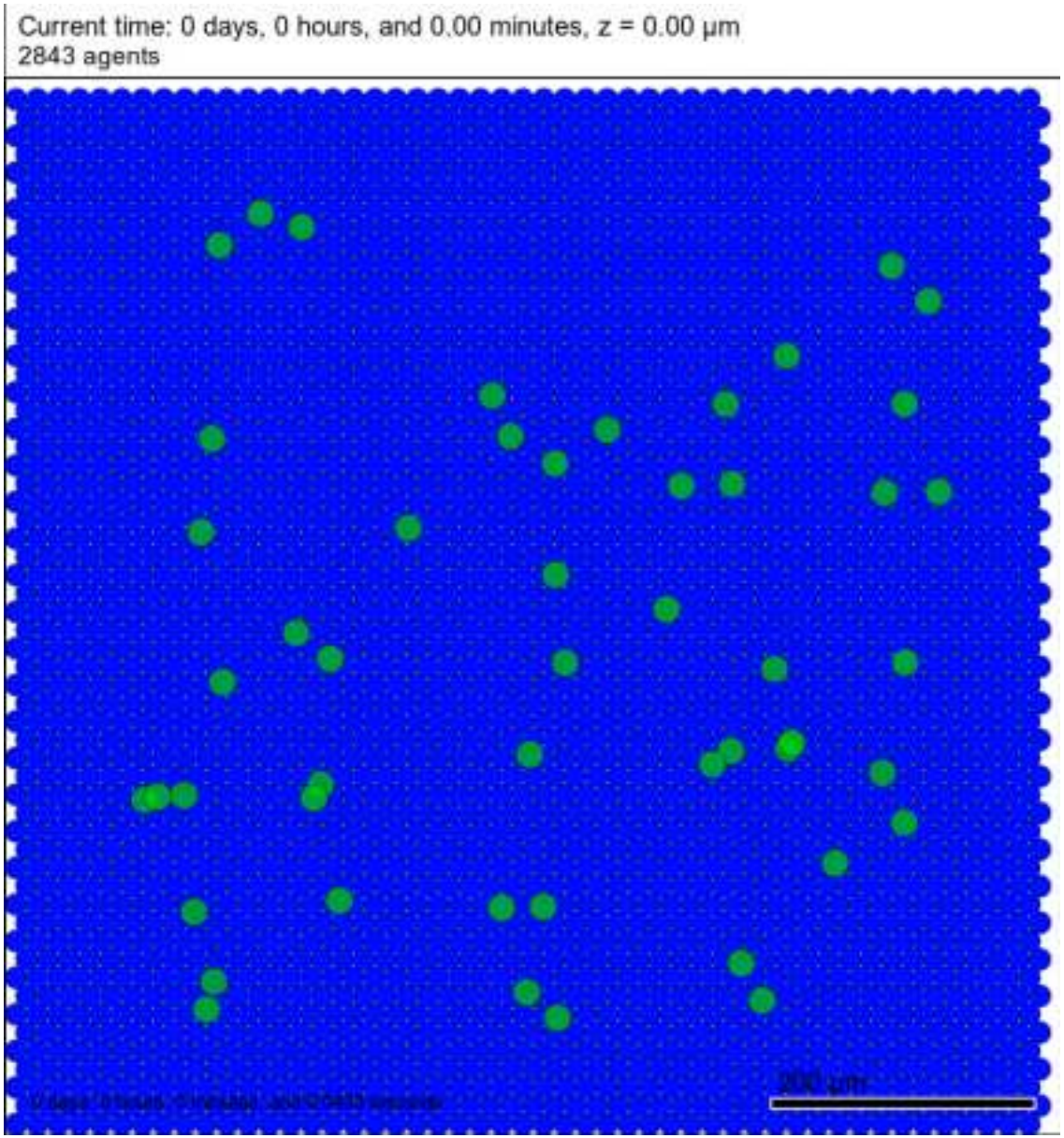
⇒ https://fairdomhub.org/models/712

Apoptosis Boolean model

Starting from CaSQ, we generated a Boolean model :

- Connected PhysiCell variables to model inputs and outputs
- Modified the direct activation of apoptosis by viral proteins
- Added nodes and connections to capture apoptosis type I and type II (mitochondria-mediated)
  - Details need to be further characterised
- Studied 148 mutants to find apoptosis-escaping mutations under two initial conditions :
  - Viral infection
  - T cell induction of apoptosis

Wild type simulation

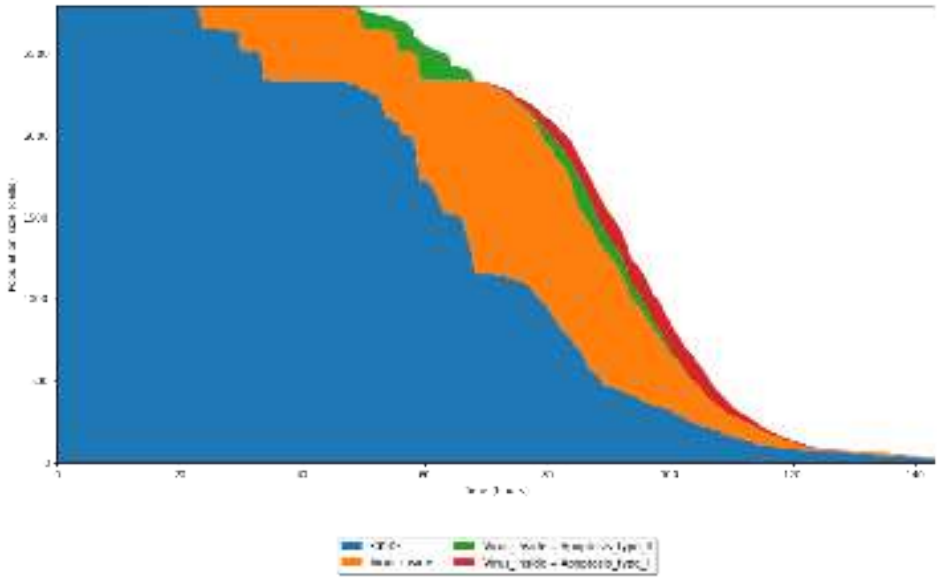


- **lung epithelium:** are colored by their (assembled) virion loads in four colors
  - Cells with 0 assembled virions.
  - Cells with 1-9 assembled virions.
  - Cells with 10-99 assembled virions.
  - Cells with 100-999 assembled virions.
  - Cells with 1000+ assembled virions.
  - Apoptotic (dead from viral load)
- **CD8⁺ T cells:** are colored by their cell cycle status
  - G0G1, S, G2, M cycle
  - Apoptotic
- **macrophage:** are colored by their cell cycle status
  - G0G1, S, G2, M cycle
  - Flag of activated_immune_cell > 0.5
  - Apoptotic
- **neutrophil:** are colored by their cell cycle status
  - G0G1, S, G2, M cycle
  - Apoptotic
- **Background:** Contour plot of released virus that is diffusing in and above the tissue.

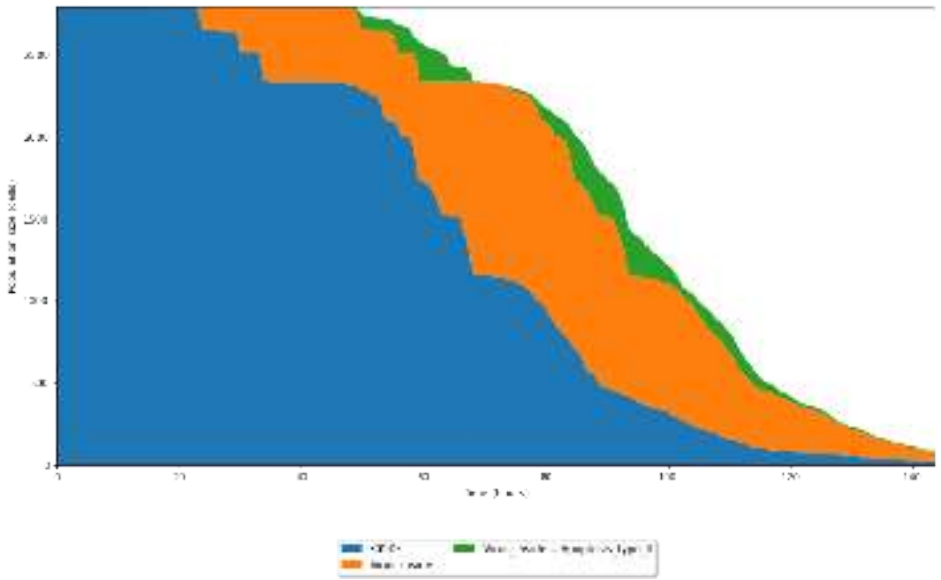
Results

› FADD knock-out in PhysiBoSS-COVID simulations

WT



FADD KO

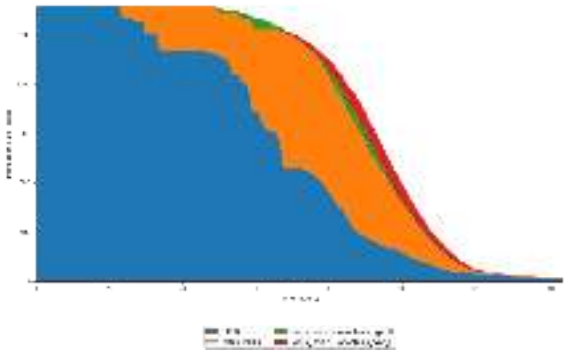


› FADD knock-out completely deactivates CD8-T-cell-mediated apoptosis

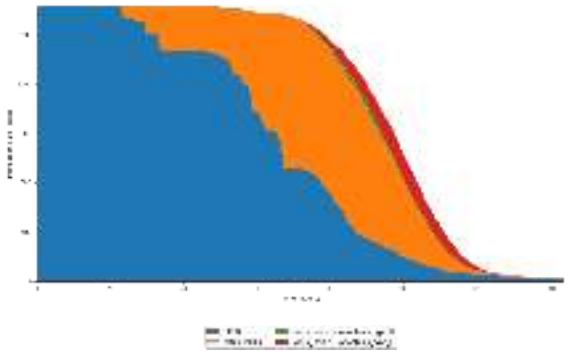
Results

- Partial M inhibition in PhysiBoSS-COVID simulations

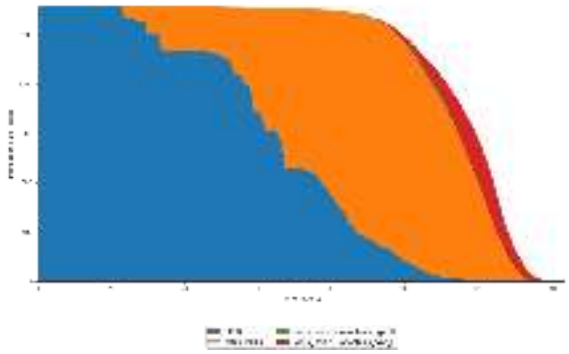
50% M inhibition



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

PerMedCoE

- Personalised Medicine HPC Center of Excellence (2020 - 2022)

PerMedCoE objectives:

1. Upscale cell-level simulations to HPC and Exascale
   - MaBoSS, PhysiCell, CellNOpt and COBRA
2. Integrate PerMed into the new European HPC/Exascale ecosystem
3. Set PerMed representative use cases
   - Cancer, drugs, rare diseases, single-cell cancer and COVID



HPC/Exascale Centre of Excellence in Personalised Medicine

- Use case 5: COVID multi-scale modelling using single-cell data
- PhysiCell + MaBoSS + HPC + COVID

⇒ Twitter: @PerMedCoE

⇒ Website: www.permedcoe.eu

Future work

- Cell-type-specific Boolean models
  - Immune cells' differentiation
- Transition rate parameters
  - Activation and deactivation of the different components
- Test the model by yourself !
  - GitHub : https://github.com/vincent-noel/pb4covid19
  - nanoHUB : https://nanohub.org/resources/pb4covid19

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