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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Introduction

PhysiBoSS-COVID is an effort to integrate MaBoSS[1], a stochastic Boolean modelling software, into PhysiCell-COVID[4] to allow the leverage of cell- and pathway-specific Boolean models. To obtain these COVID-19-specific models, we have taken advantage of CaSQ[2] ability to convert all C19DM maps into SBML-qual files, that can subsequently be transformed to MaBoSS-format Boolean models, ready-to-use with PhysiBoSS-COVID. As a proof of concept, we have incorporated to our prototype a model of apoptosis on human epithelial host cells as a consequence of SARS-CoV-2 infection or T cell induction and hereby present preliminary results.

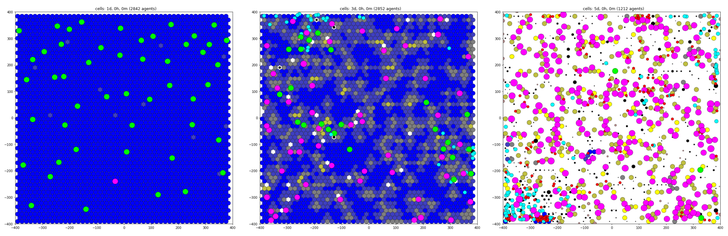
PhysiBoSS-COVID, which is based on our previous work PhysiBoSS[3], provides a framework that enables testing of combined genetic and environmental perturbations, and can offer mechanistic insights of SARS-CoV-2 infection, its dissemination among human host cells and its competition against immune cells. Finally, PhysiBoSS-COVID was incorporated as a use case into the European HPC/Exascale Centre of Excellence in Personalized Medicine (PerMedCoE, http://permedcoe.eu/), whose purpose is to adapt cell-level simulation tools to supercomputing environments and to provide an easy-to-use interface to systems biology end users.

PhysiCell-COVID19

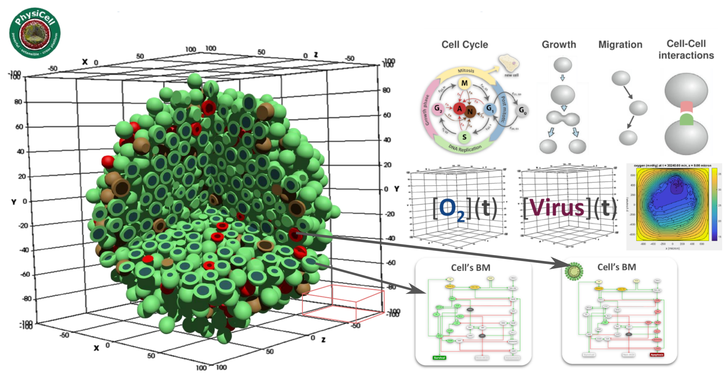
PhysiCell-COVID19[4] is a prototype of a multi-scale model of SARS-CoV-2 dynamics in lung tissue aimed at addressing the complexity of the problem and the acute need for an actionable model to guide therapy discovery and optimization.

Several model components cover all the infection progression from the virus dissemination on lung epithelium to the immune cells behaviour and it is based on PhysiCell[5], a multiscale multicellular agent-based software.

Below are three snapshots illustrating a simulation of this model, taken at time t=1d, t=3d, and t=5d.



PhysiBoSS = PhysiCell + MaBoSS



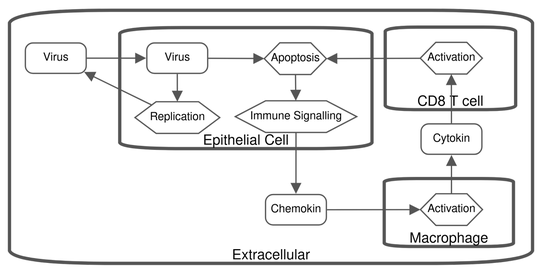
PhysiBoSS[3] merges PhysiCell[5] and MaBoSS[1], a time-continuous Markovian simulator for Boolean models.

PhysiBoSS allows for the combined study of genetic and environmental perturbations in many different set-ups.

PhysiBoSS-COVID prototype

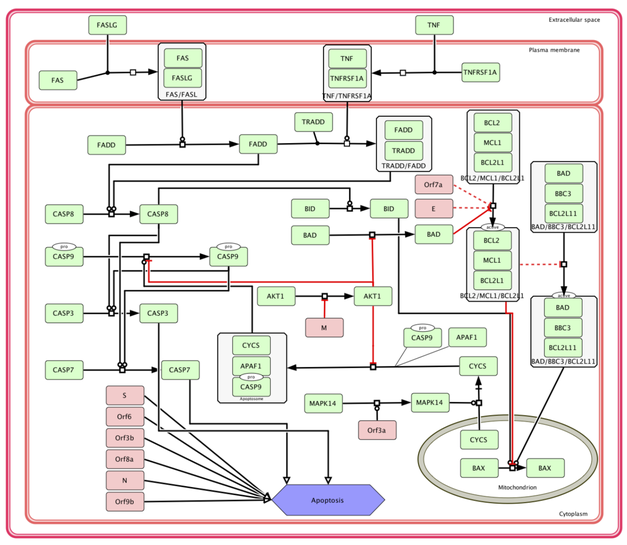
As a proof of concept, we integrated the apoptosis model from the COVID-19 Disease Map[6] project into PhysiBoSS-COVID.

Top-level interaction model



The framework integrates virus infection, epithelial host cell demise and different immune cells' response

Apoptosis map from COVID-19 Disease Map project



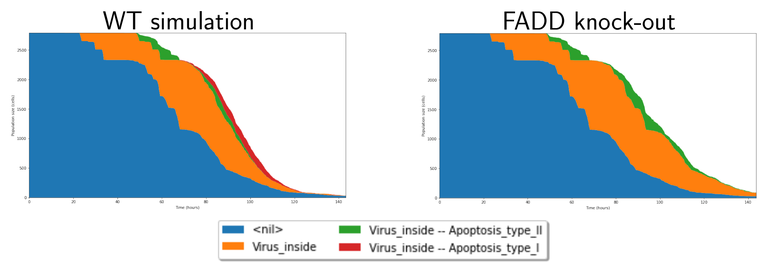
Converting the map to a functional Boolean model:

- Modified some connections:
  - To show mechanisms
  - To capture cell-type-specific mechanisms
- Input and output nodes:
  - Modified to be readouts
  - Connected to agent-based variables

Study of mutants

We identified two mutations that evade apoptosis in infected human host cells.

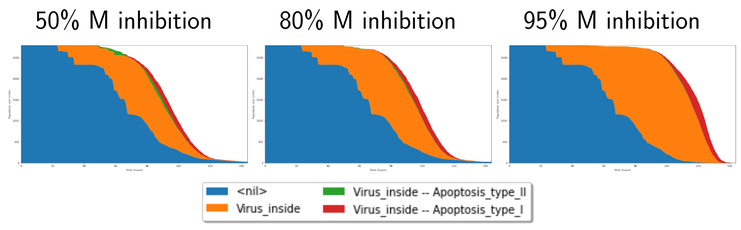
One is the inhibition of the virus' M protein that inhibits AKT1 protein, promoting apoptosis. The other is the inhibition of FADD, which is a downstream actuator of FASLG reception upon T cell activation promoting apoptosis.



While we indeed inactivated type I apoptosis, we don't observe a qualitative difference added by this mutant.

Study of heterogeneous cell populations

We simulated populations of cells with different proportion of wild type and M mutant cells.



We observe that the main effect of this inhibition is to delay the initiation of the immune response.

Perspectives

- Integrating models of immune cells' differentiation
- Expanding the epithelial cell model
- Personalising Boolean models with patients' data
- Scaling up the computation to HPC clusters as one of the use case of the Personalised Medicine HPC Center of Excellence - PerMedCoE

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