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HPC-enabled multiscale simulation to uncover mechanistic insights in the COVID-19 infection

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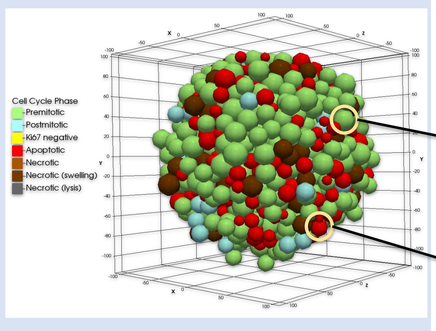
The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has experienced an extremely fast worldwide spreading, producing an unprecedented pandemic situation. We hereby present the use of a framework, termed PhysiBoSS[1], that integrates MaBoSS[2], a stochastic Boolean modelling software, into PhysiCell-COVID[3,4] to allow the leverage of cell- and pathway-specific Boolean models for the study of the COVID infection. Currently, 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 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. In parallel we have developed PhysiCell-MPI, that support distributed parallelism using MPI, allowing for the simulation of large-scale agent-based models of billions of cells and complex heterogeneous environments by efficiently using HPC clusters.

PhysiCell

Multiscale modelling frameworks prove useful in integrating mechanisms that have very different time and space scales, as in the study of viral infection, human host cell demise and immune cells response.

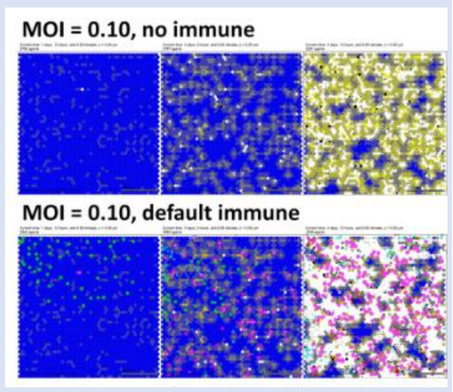
PhysiCell[3] is a multiscale multicellular agent-based tool with the highest potential to be expanded and built upon. It is used for the modelling of the population of cells and can help understand the role of the interactions between cells and their environment.

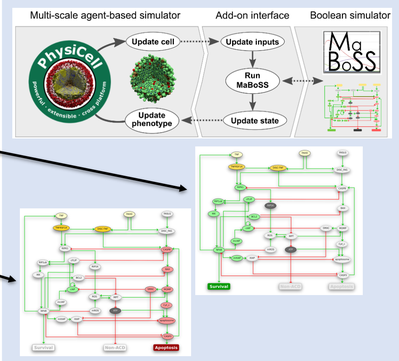


PhysiCell for COVID initiative

Our work builds upon the PC4COVID[4], a multiscale 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[3].

For instance, PC4COVID allows to simulate dynamics such as a multiplicity of infection (MOI) of 0.10 with and without an immune response (figure on the right).

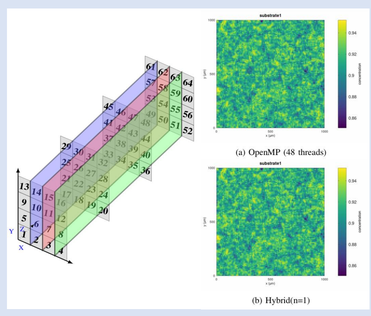




PhysiBoSS

PhysiBoSS[1] merges PhysiCell[3] and MaBoSS[2] and allows for the combined study of genetic and environmental perturbations in many different set-ups. The use of **MaBoSS**[3], a tool that uses Monte-Carlo kinetic algorithm to perform **continuous time stochastic simulations on logical models**, allows for semi-quantitative evaluation of the model's phenotypes and perturbations.

The solutions can be represented in different forms: a **probability** of network states equivalent to the **asymptotic solutions** of the stochastic simulations, or **time evolution** of the nodes of interest.



PhysiCell-MPI

PhysiCell[3] supports only shared memory parallelization using OpenMP. We are currently restructuring PhysiCell to support distributed parallelism using MPI and parallelize the generic core kernels of PhysiCell including simulation initialization, domain partitioning and agents' generation.

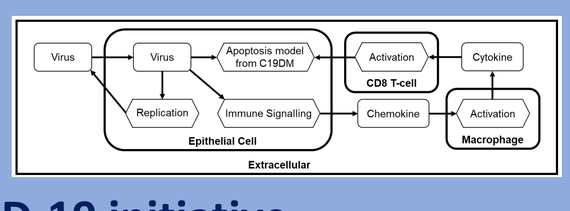
Preliminary results of PhysiCell-MPI expand the scope of the simulations by several orders of magnitude and enable the simulation of complex behaviours with different types of cells, substrates, drugs or three-dimensional domains.

PhysiBoSS-COVID

The use of PhysiBoSS on COVID offers mechanistic insights of SARS-CoV-2 infection and dissemination among human host cells. To obtain these models, we have taken advantage of CaSQ[5] ability to convert all COVID-19 Disease Maps (C19DM)[6] into SBML-qual files, that can subsequently be transformed to MaBoSS-format Boolean models, ready-to-use with PhysiBoSS-COVID.

For instance, we worked with an apoptosis model from C19DM, modified it to connect it to the agent-base model and identified two different mutants that affect apoptosis of the human lung epithelial cells: the inhibition of FADD and of the virus' M protein.

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

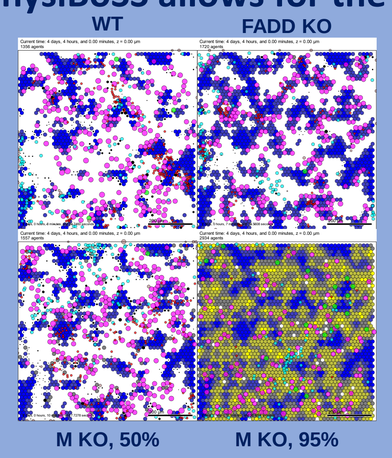


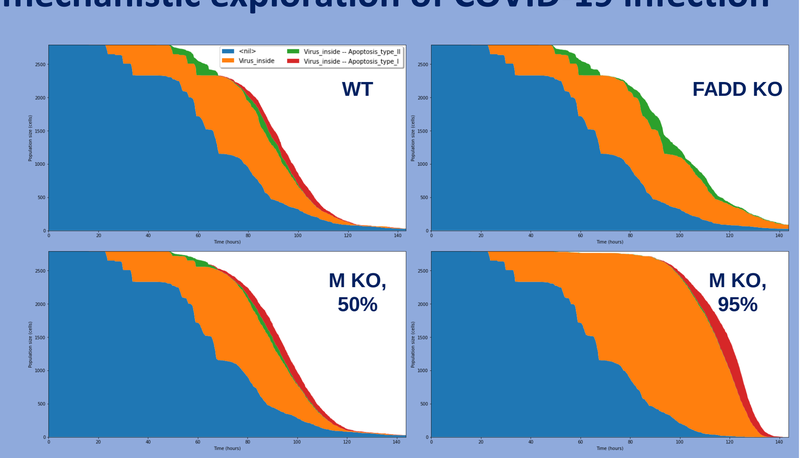
Disease Maps COVID-19 initiative

We incorporate cell- and pathway-specific Boolean models to detail the interactions of virus and human cells previously generated by CaSQ[5] from the COVID-19 Disease Map initiative[6], which integrates and formalises mechanistic knowledge, using current systems biology standards.

These Boolean models can then be simulated using MaBoSS allowing for the study of the cells' mechanisms and their perturbations upon mutation or virus infection, enabling the discovery of biomarkers and therapeutic targets.

PhysiBoSS allows for the mechanistic exploration of COVID-19 infection





With PhysiBoSS we can now inspect mutants that affect epithelial cells' apoptosis and heterogeneous cell populations

Perspectives

- Fully integrate MPI into PhysiBoSS-COVID to scale up the simulations using HPC clusters
- Benchmark it in MareNostrum4: memory allocation problem, we use now the *jemalloc* library
- Include models of immune cells' differentiation
- Personalise Boolean models with patients' data

References

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PerMedCoE — HPC/Exascale Centre of Excellence in Personalised Medicine

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