Development of QSP model of COVID-19 based on Immune Response Template

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Purpose.

Coronavirus disease 2019 (COVID-19) is associated with several respiratory symptoms that can progress to acute respiratory distress syndrome (ARDS). QSP modeling approach can potentially contribute to the fight of the global public health system with the COVID-19 via increasing certainty in mechanism-based understanding of virus interaction with host cell leading to immune response and associated inflammation. Immune response template (IRT) is ODE-based simulation platform focusing on interactions of multiple immune cell types, cancer cells, soluble mediators (cytokines, chemokines), cell-cell contact effects. We have applied IRT to develop the prototype of QSP model of innate immune response to COVID-19.

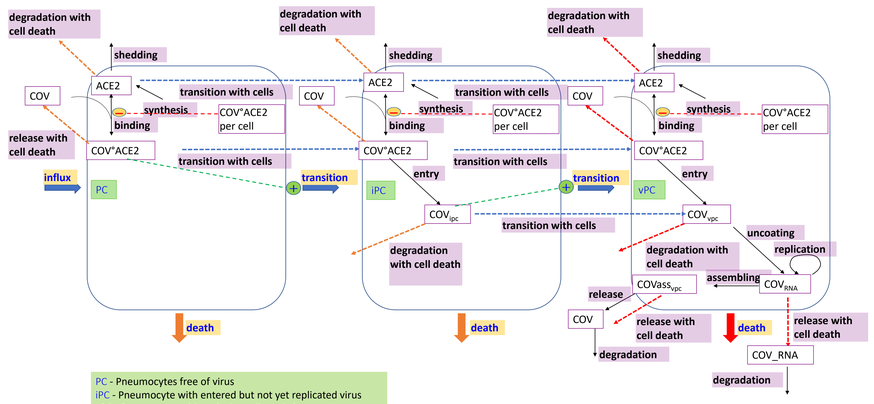
Objectives.

1. Develop a model describing SARS-CoV-2 virus replication in the type 2 pneumocytes with empirical immune response implementation.
2. Develop an algorithm to create an immune response QSP platform by merging of the IRT sub-models with pre-developed virus replication model.
3. Apply this algorithm to create a prototype of a QSP platform describing immune response in SARS-CoV-2 infection. Replace an empirical response description by detailed one for further practical implication of the platform.

Methods.

Virus replication model was developed as an ODE system describing infection of alveolar cell type II (pneumocytes type II) with SARS-CoV-2 via binding to ACE2 located on the cell surface. Virus ACE2 complex internalization with subsequent virus penetration to cytoplasm, uncoating, replication, assembling of newly produced viral particles and their release was added to the model. Empirical immune response (IR) was described as Spike specific antibodies interfered binding of virus and stimulation of infected cells death by IR. For detailed immune response module addition different IRT sub-models were exported from online IRT version 3.5 using IRT Navigator in the Heta XLSX format and merged with virus replication model In Heta compiler. Calibration to describe steady state in healthy patient was performed in DBSolve Optimum 2020 using values from Cytocon DB.

SARS-CoV2 replication cycle model scheme.



Results.

Virus replication model

Developed virus replication model (see scheme on the left) with empirical IR allows to reproduce average data on:

1. Viral load taken from different sources
2. % of viral subgenomic mRNA in sputum (see figures on the right).

QSP platform development with IRT templates

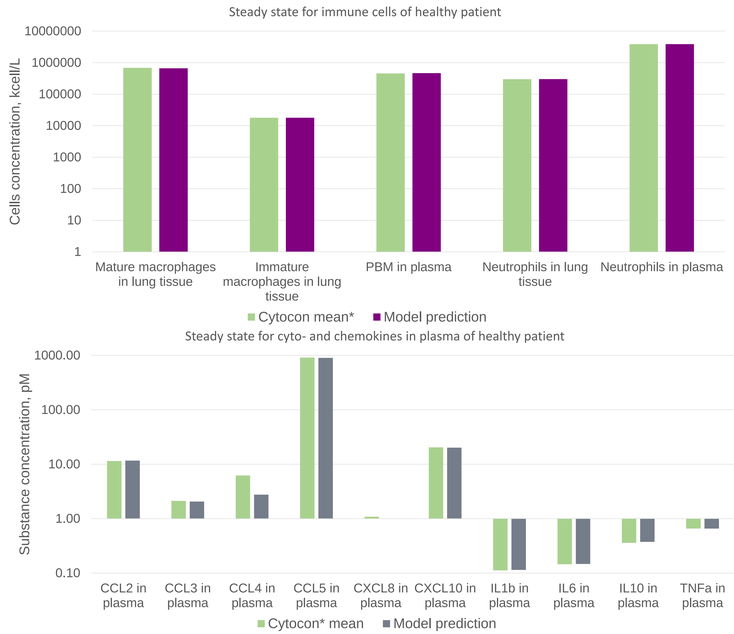
An algorithm for IRT templates merge with pre-developed models was described. It includes 6 steps:

- additional models pre-development
- IRT sub-models templates for immune response selection and export
- IRT templates modifications and parameters re-identification (if needed)
- General species and parameters values identification
- Building a QSP platform from pre-developed models, modified IRT export templates and general values module
- Calibration of the platform (see figures on the right)

Algorithm was applied to replace an empirical immune response in the SARS-CoV-2 virus replication model by detailed innate immune response description with exported and modified IRT templates, as well as additionally developed secretion models. Developed QSP platform prototype now includes processes for macrophages, neutrophils, pneumocytes type 2 and endothelial cells dynamics description in plasma and lung tissue. IL1b, IL6, IL10, TNFa, CCL2, CCL3, CCL4, CCL5, CXCL8, CXCL10 synthesis, distribution and degradation is included as well. QSP platform prototype describes steady state value for healthy subject and is merged with virus replication model (see figures on the bottom).

Prototype QSP platform steady state for healthy patient description.

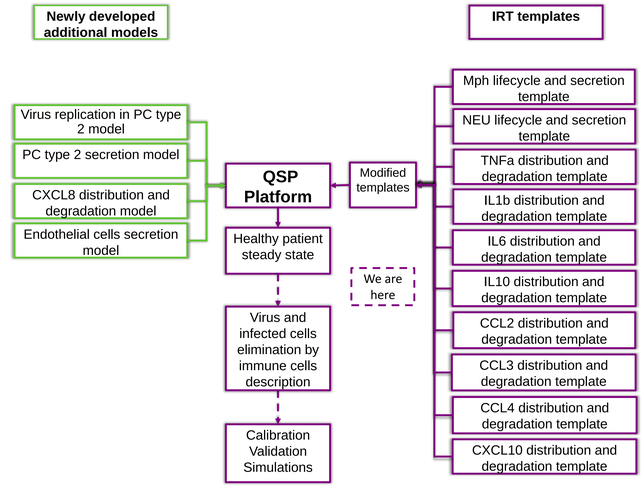
Innate immune response to SARS-CoV2 infection model prototype was calibrated to describe steady state for healthy patient



(*) Mean values for healthy patient were obtained from Cytocon DB. If there were several data sources available in Cytocon, the truncated mean was taken with 30% of outlying values excluded

Prototype QSP platform of SARS-CoV2 innate immune response content.

Innate immune response to SARS-CoV2 infection model prototype was developed by merge of an IRT templates with pre-developed sub-models of virus replication and cytokines dynamics.



Virus replication model with immune response described empirically