# Knowledge systematization of COVID-19 infectious processes based on Homeostasis Imbalance Process (HoIP) Ontology

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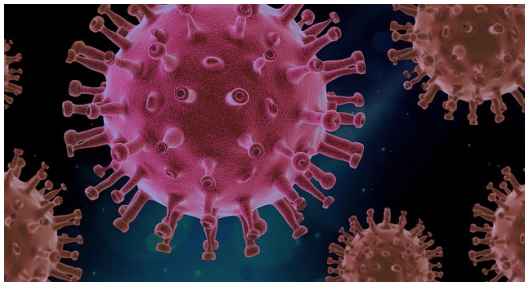
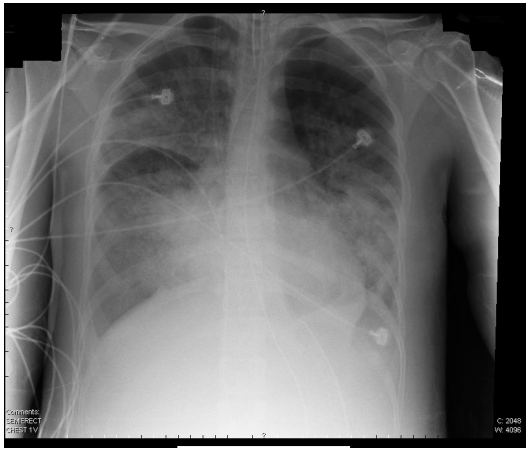
## BACKGROUND

- One of the major issues in COVID-19 is the risk management of severity
  E.g. Acute respiratory distress syndrome (ARDS)
- We need an understanding of the mechanisms of COVID-19

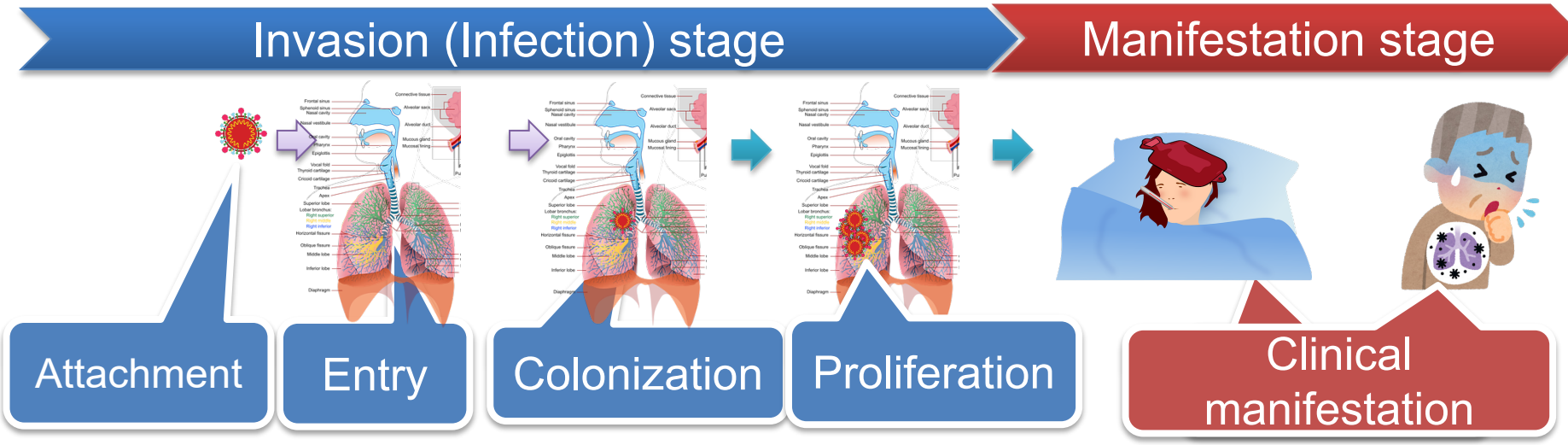


## Objective

- Knowledge systematization of COVID-19 infectious processes based on ontology



ARDS X-Ray
https://commons.wikimedia.org/wiki/File:ARDS_X-Ray.jpg#/media/ファイル:ARDS_X-Ray.jpg




Infectious course: A series of process in an organism from viral attachment to clinical manifestations, which is not part of the life of the organism.

Concerning COVID-19,
A wide variety of processes among patients:

- No symptoms
- microthrombus formation
- processes related to acute respiratory distress syndrome (ARDS)

Focus on homeostasis imbalance processes from non-symptoms to severe manifestation

# Development of Homeostasis imbalance process (HoIP) ontology

## Issue

- Clarifying processes from no symptoms to severe manifestation
- Coping with granularities in the body
- Distinction between COVID-19 and other diseases such as MERS
- Finding commonalities across multiple diseases

## Our approach

- Introducing homeostasis imbalance model
- Functional decomposition approach
- Developing three-layer ontological structure

# Homeostatic imbalance model

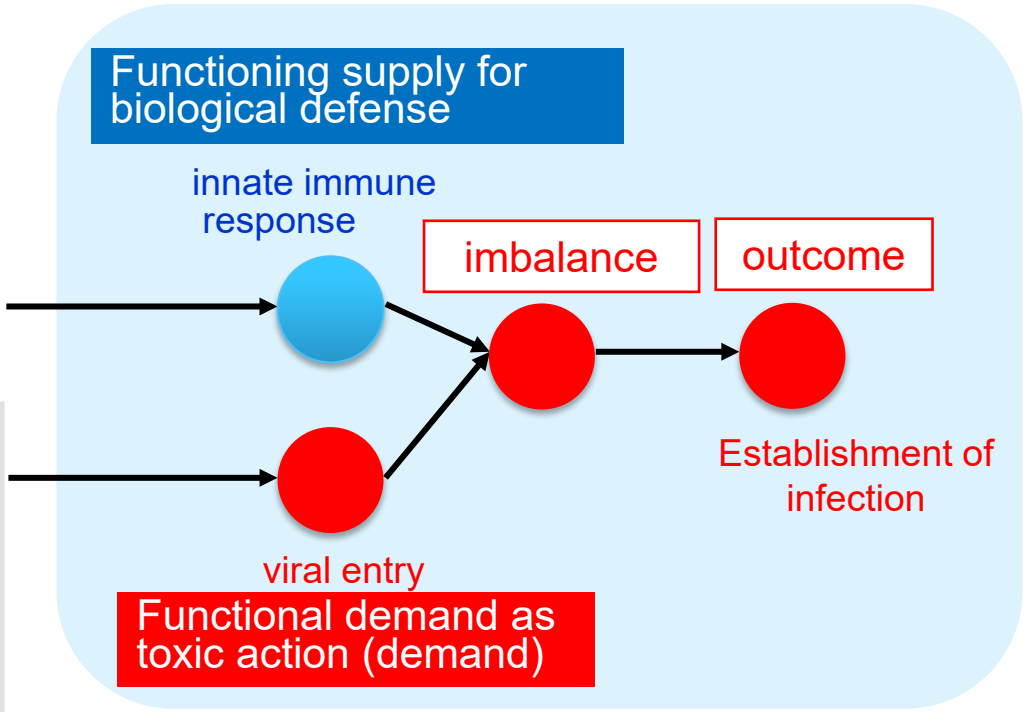
- Homeostatic imbalance model has four basic units:
  1. functional supply for biological defense,
  2. functional demand triggered by viral action,
  3. balance/imbalance,
  4. outcome from organelles, cells, to the organ of pathological manifestation

**Functional supply**

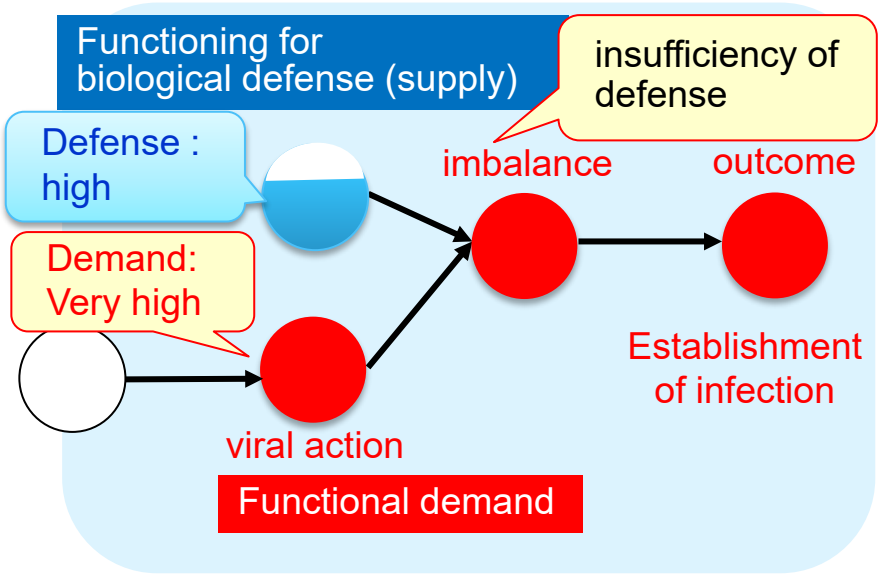
- Performing biological defense function (supply)
- E.g., innate immune response

**Functional demand**

- Process of required defense function (functional demand)
- E.g., viral entry

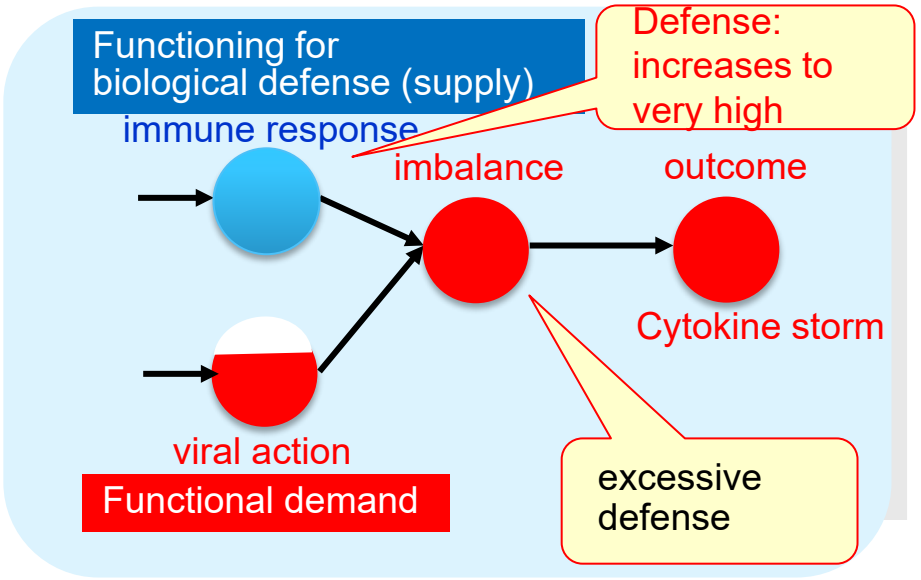


## Severe outcome ( excessive demand)



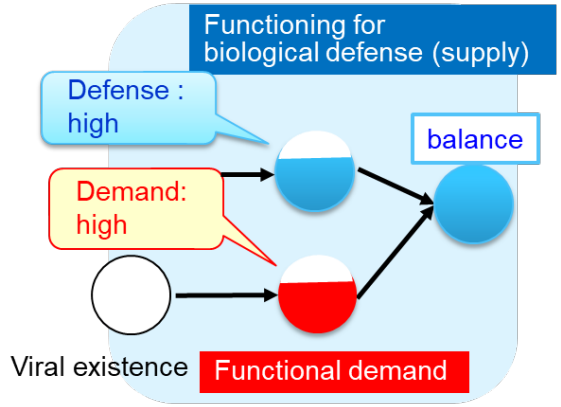

When demand becomes very high, the imbalance occurs, which brings about an outcome.

## Severe outcome (excessive defense)



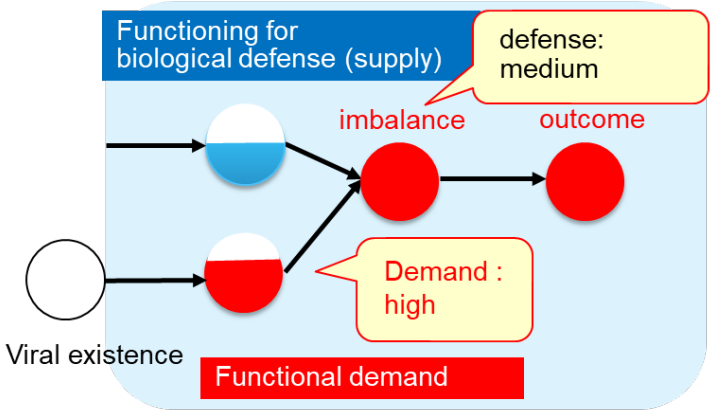

When defense becomes very high (excessive defense), the imbalance can also occur, which brings about an outcome.

Latent (to maintain high-level homeostasis)

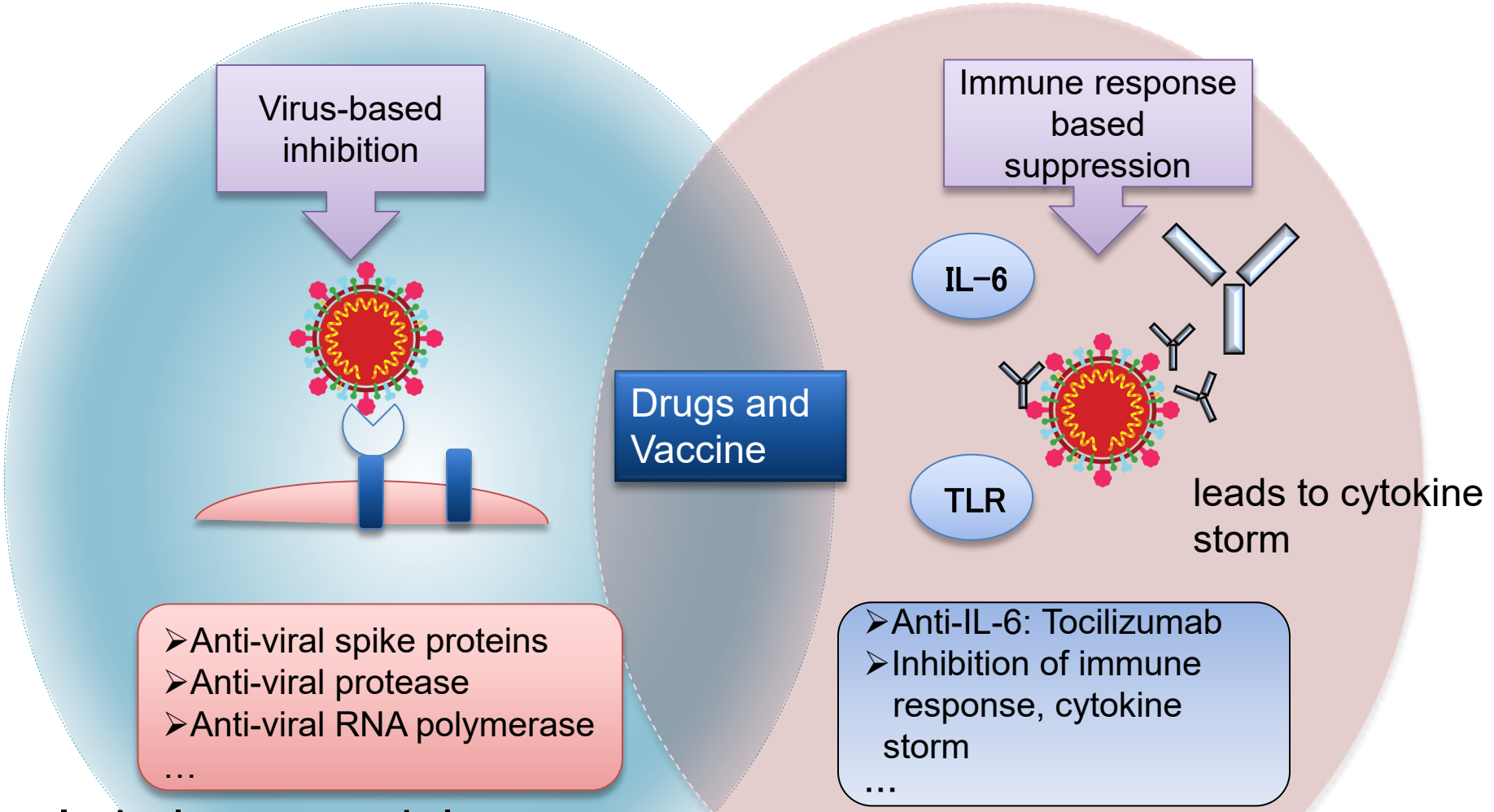



When demand increases to high, biological defense also increases and the balanced keeps at high level homeostasis than normal condition.

Manifestation (Adaptation failure)




When function decreases, an **imbalance** (insufficiency of biological defense function) occurs, which leads to manifestation as an **outcome**.



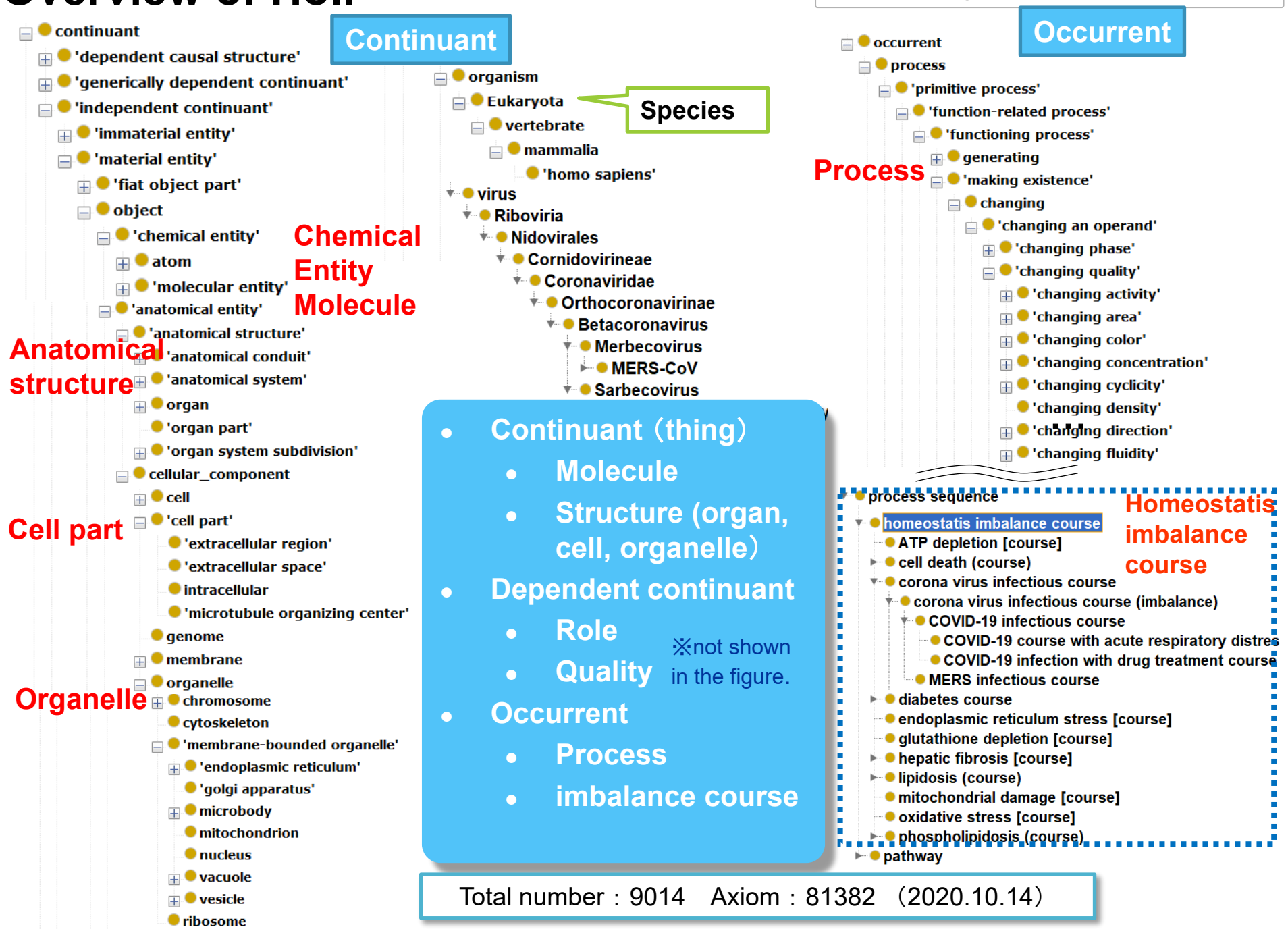

Imbalance model can

- distinguish viral action and innate immune response
- represent excessive defense, i.e., immune response, leading to the severe manifestation

Our approach will support new drug development

# Overview of HoIP

Tool: Protégé 5.5.0



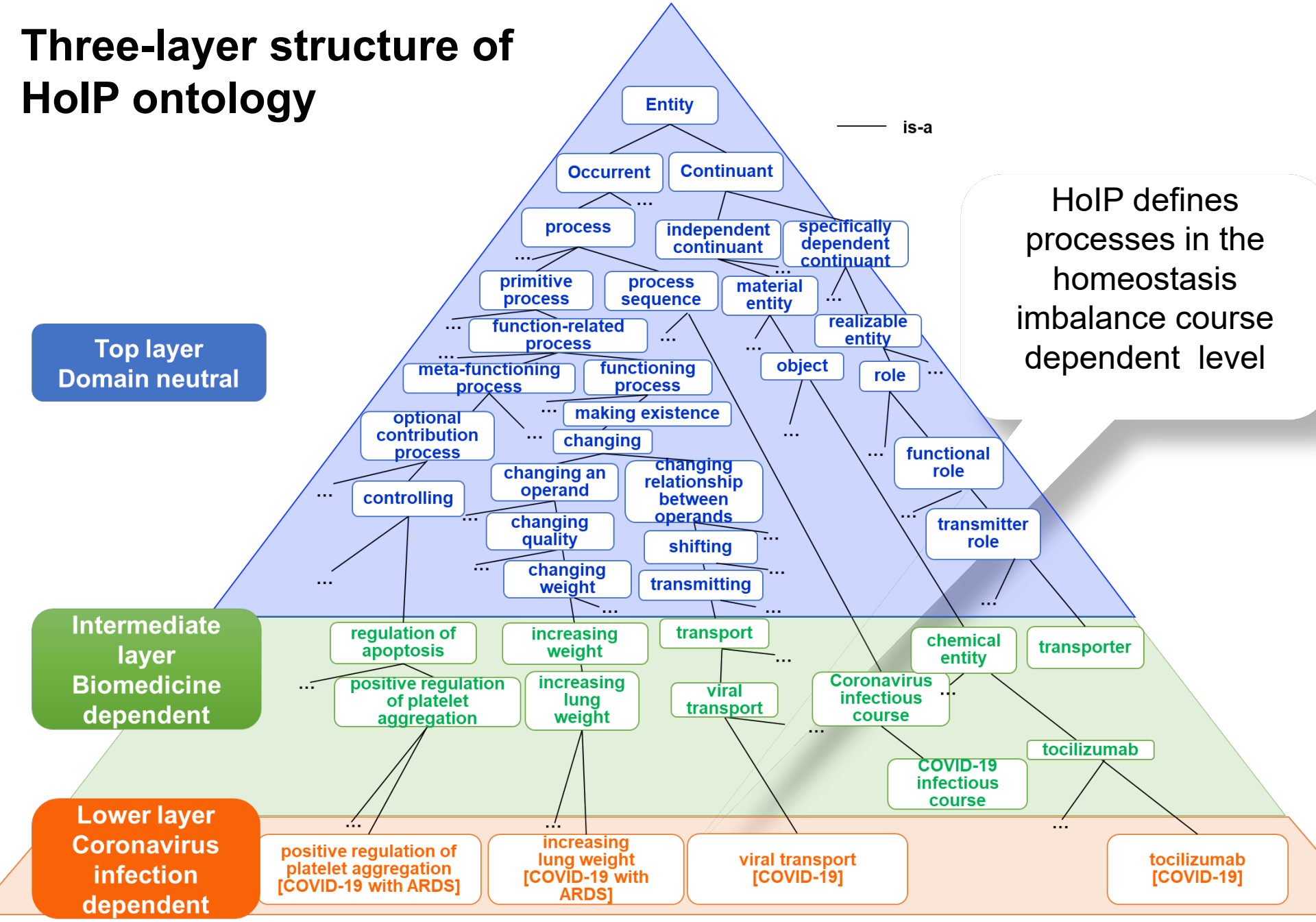

- Continuant（thing）
  - Molecule
  - Structure (organ, cell, organelle)
- Dependent continuant
  - Role
  - Quality

※not shown in the figure.

- Occurrent
  - Process
  - imbalance course

Total number：9014　Axiom：81382　(2020.10.14)

# Three-layer structure of HoIP ontology



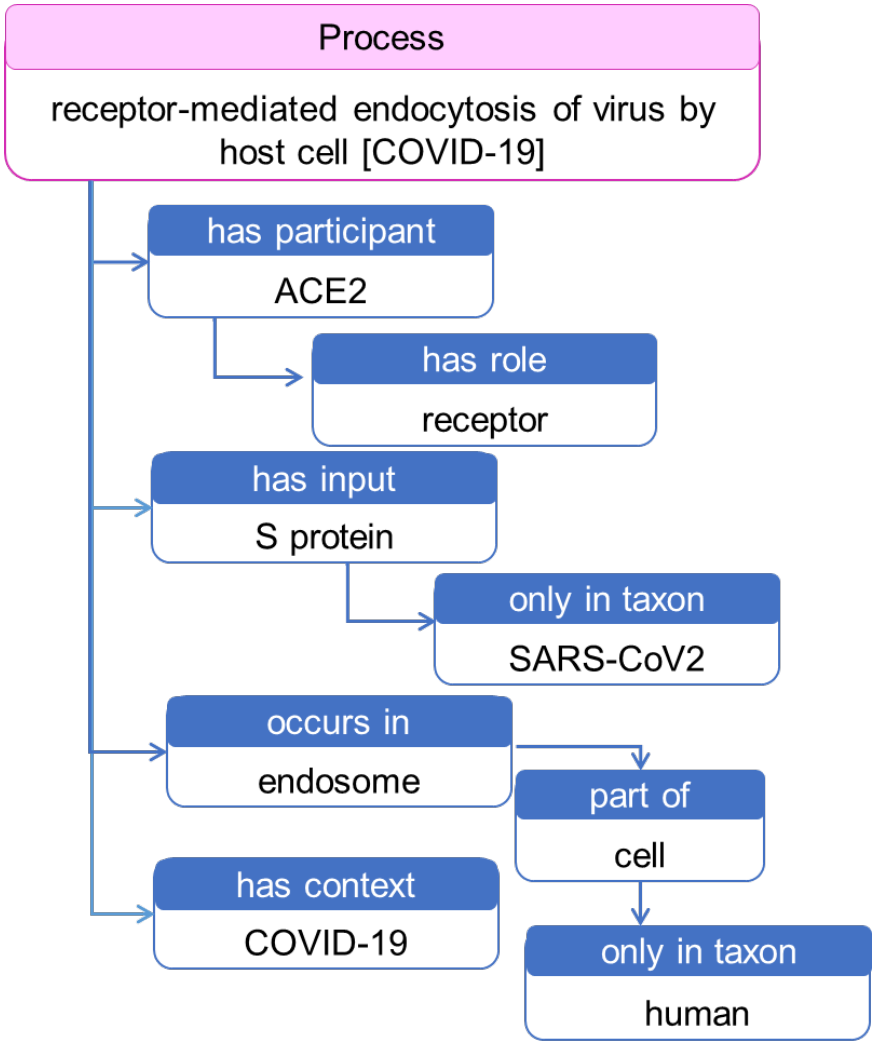
# How to specifies the COVID-19 infectious process?

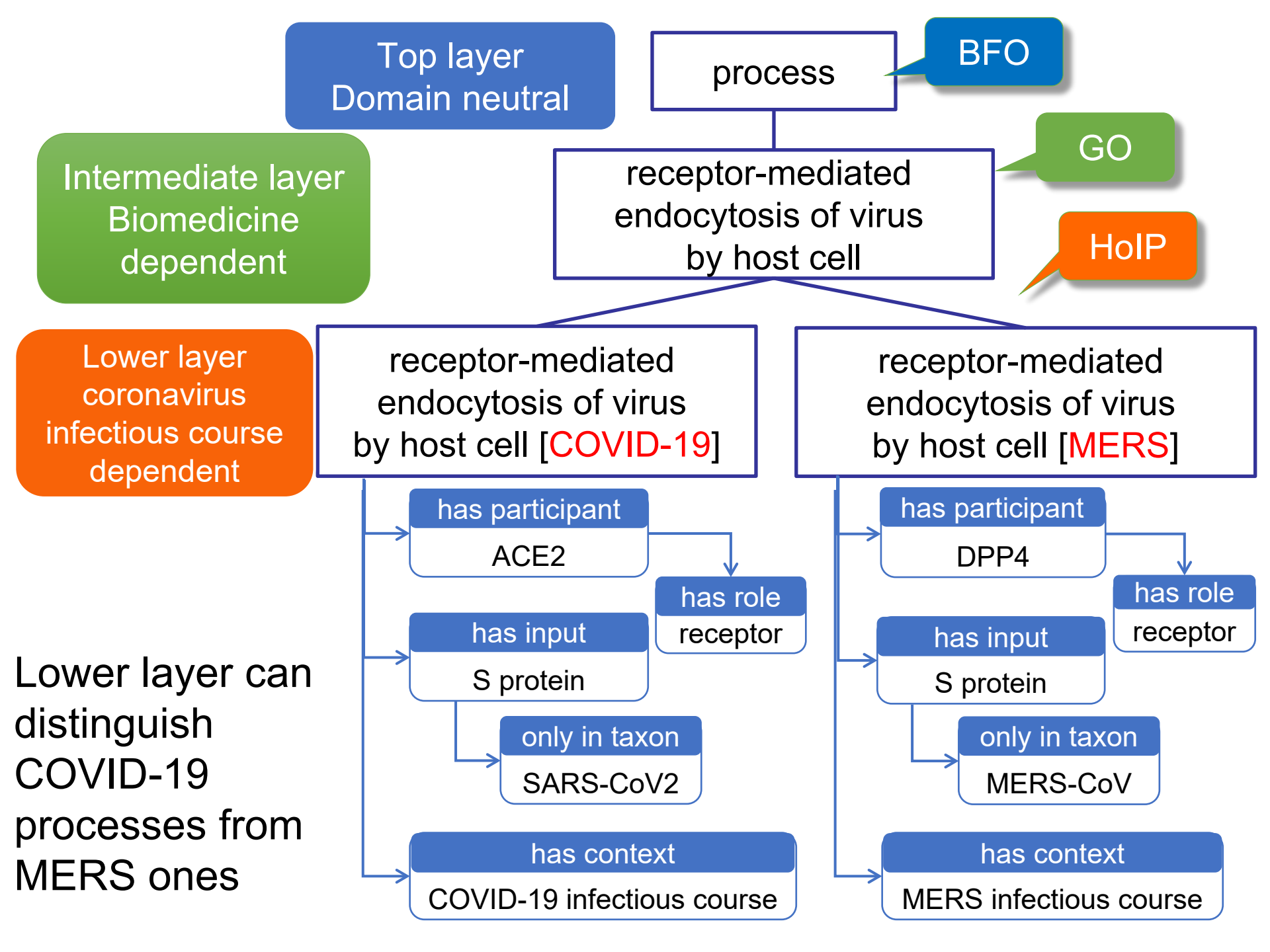
HoIP lower layer define processes:

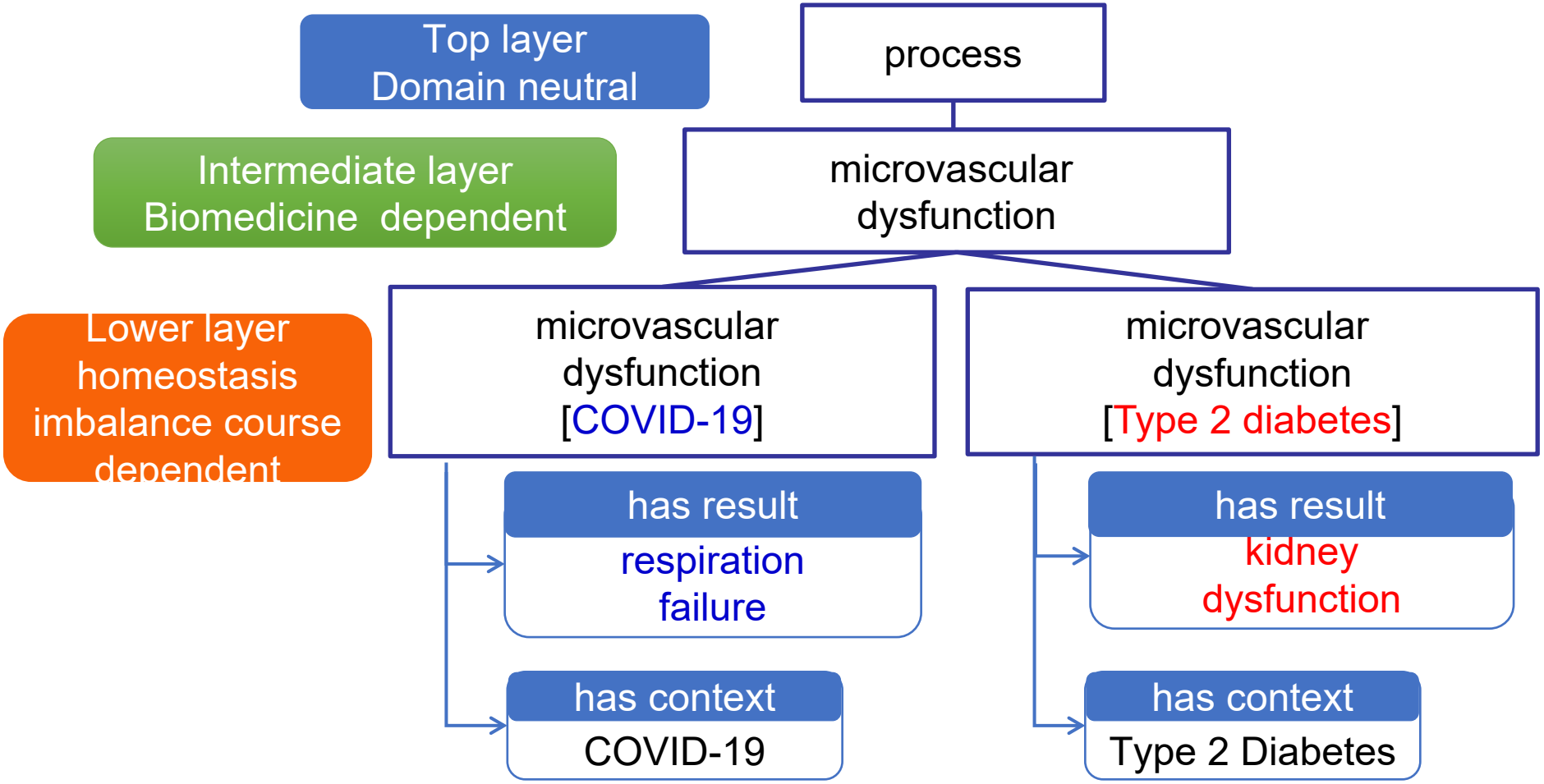
- constitute a specific course
- restrict properties in the particular description.

e.g.), receptor-mediated endocytosis of virus by host cell [COVID-19]

- ‘has participant’ ACE2
  - ‘has role’ receptor
- ‘occurs in’ endosome
  - ‘part of’ cell and ‘only in taxon’ human
- ‘has context’ only COVID-19 infectious course




Top layer
Domain neutral
process
BFO
Intermediate layer
Biomedicine
dependent
receptor-mediated
endocytosis of virus
by host cell
GO
HoIP
Lower layer
coronavirus
infectious course
dependent
receptor-mediated
endocytosis of virus
by host cell [COVID-19]
receptor-mediated
endocytosis of virus
by host cell [MERS]
has participant
ACE2
has role
receptor
has input
S protein
only in taxon
SARS-CoV2
has context
COVID-19 infectious course
has participant
DPP4
has role
receptor
has input
S protein
only in taxon
MERS-CoV
has context
MERS infectious course
Lower layer can
distinguish
COVID-19
processes from
MERS ones



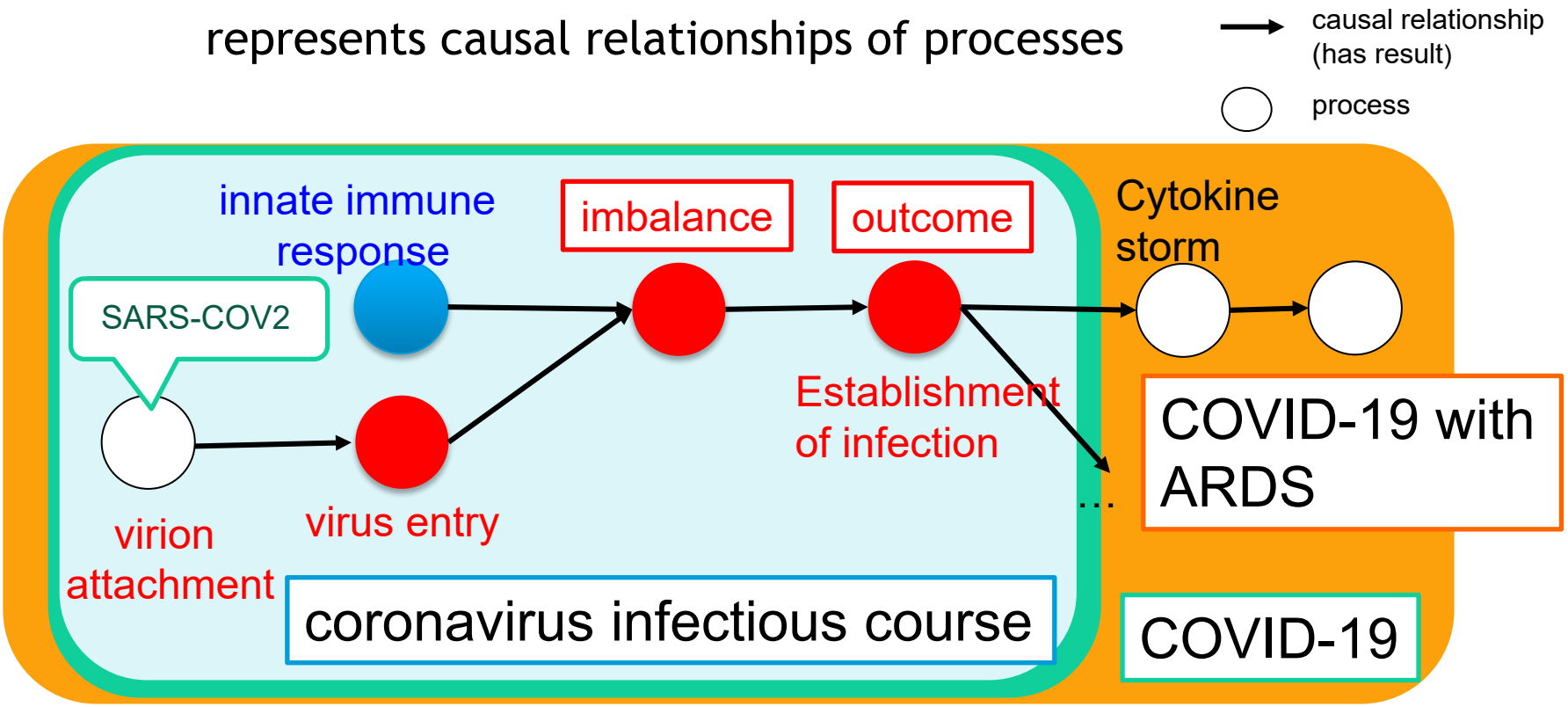

Our three-layer model can find

- common processes across multiple courses in the intermediate layer

e.g. microvascular dysfunction common to COVID-19 and Type2 diabetes

# Coronavirus infectious course map

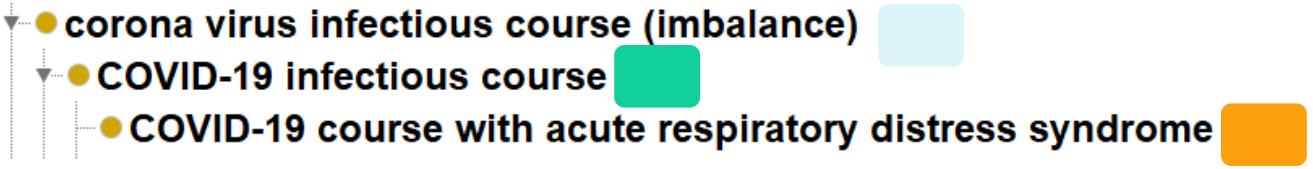
represents causal relationships of processes



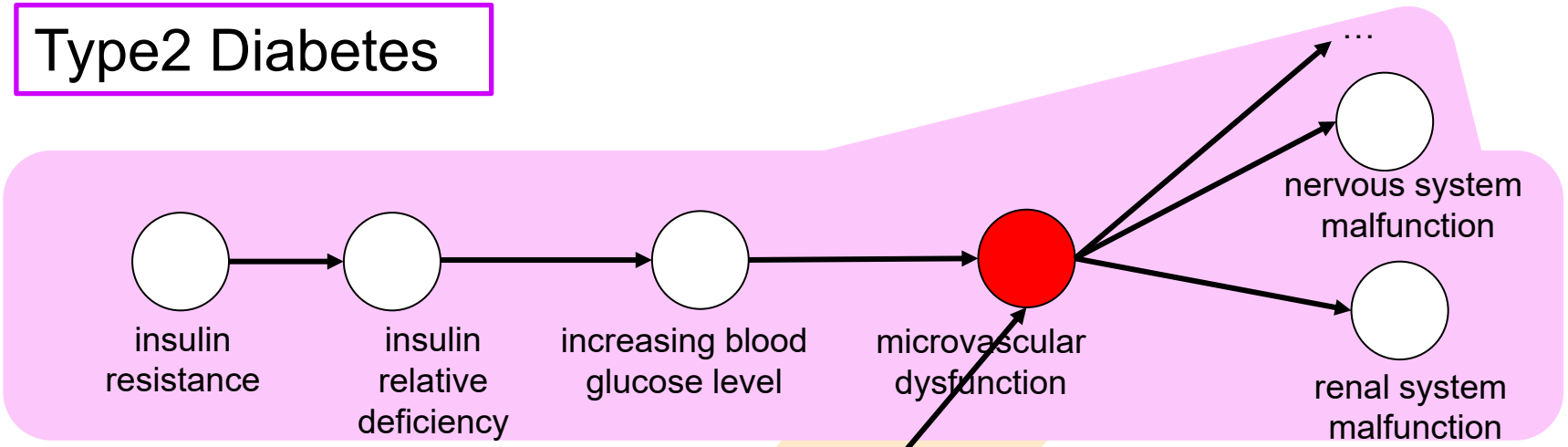

*Is-a* relation between courses is shown as an inclusion relationship

COVID-19 course includes the basic imbalance unit of the coronavirus course

*Is-a* relation

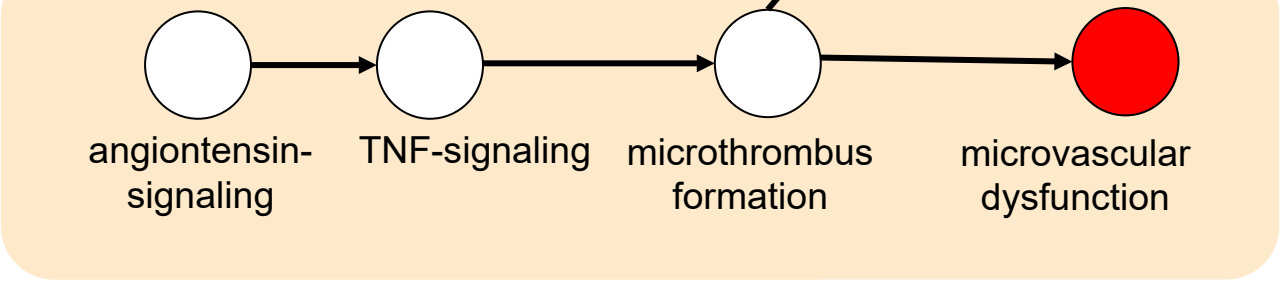


# Type2 Diabetes

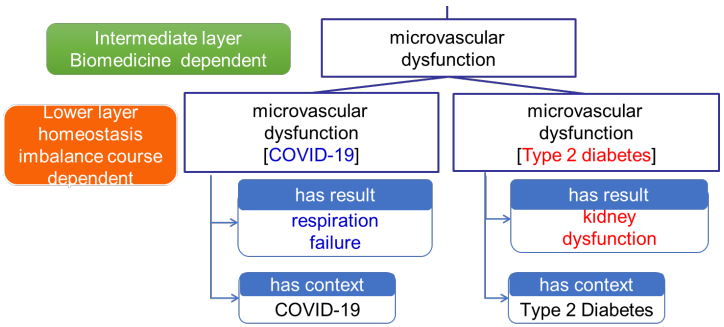



# COVID-19 with ARDS

general causal relationships

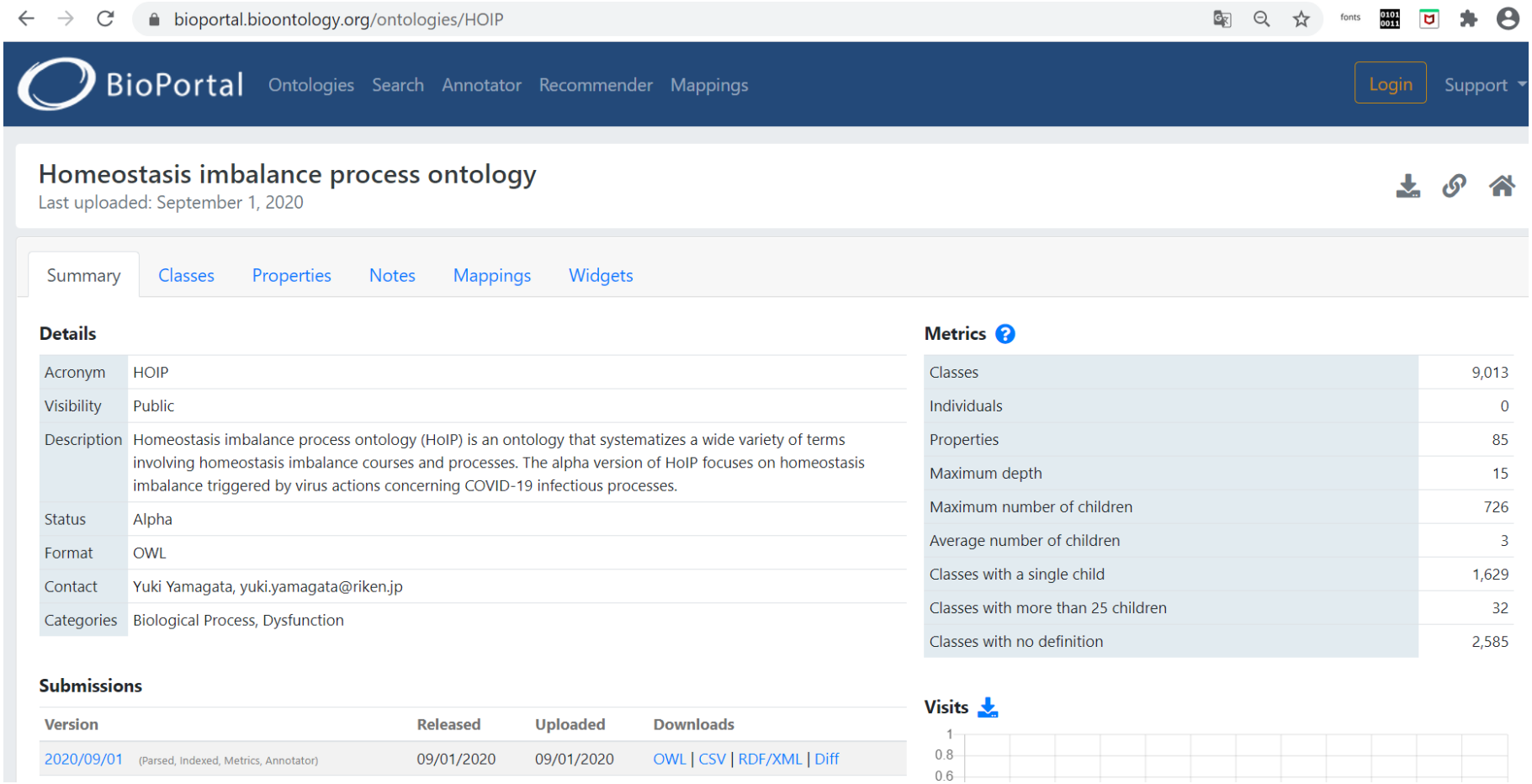



Our approach can find potential severe risk patients and explain the unexpected severe manifestation in diabetes



# Homeostasis infection process ontology (HoIP)

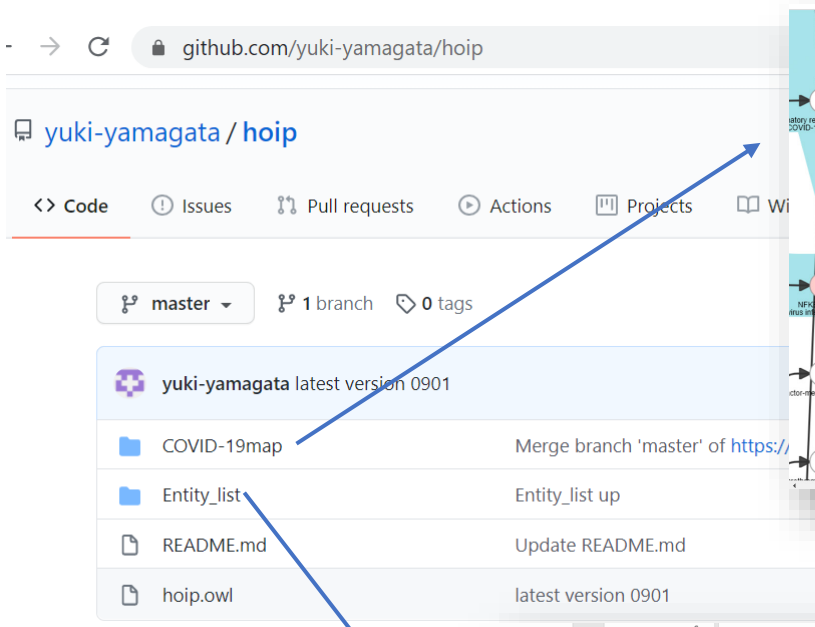
- HoIP is open to the public on BioPortal
- https://bioportal.bioontology.org/ontologies/HOIP

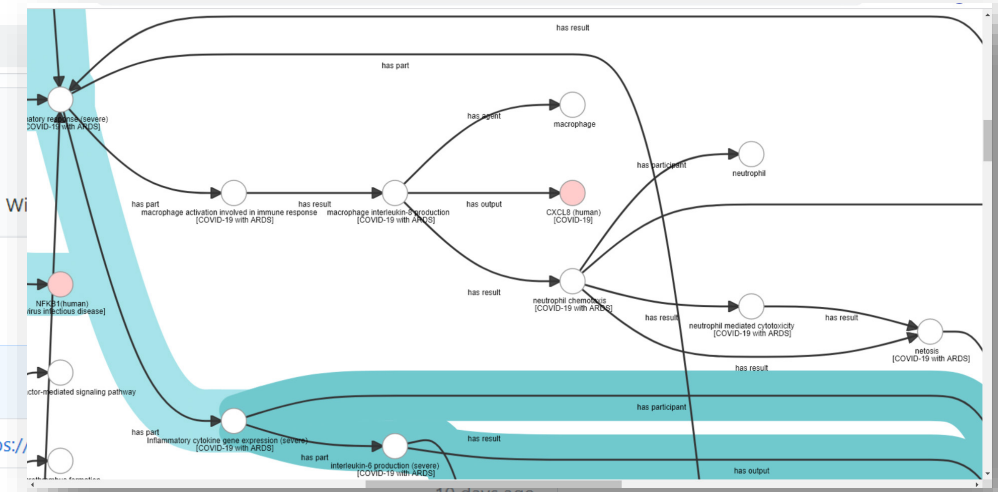


# GitHub [https://github.com/yuki-yamagata/hoip](https://github.com/yuki-yamagata/hoip)

provides COVID-19 related information in HoIP

- COVID-19 infectious course map
- Entity list concerning COVID-19 infectious course




README.md

## Homeostasis imba

Homeostasis imbalance process onto
homeostasis imbalance courses and
by virus actions concerning COVID-1
layers: the top layer contains general
contains biomedical terms, and the l

macrophage interleukin-8 production [COVID-19 with ARDS]

| Process_label | Participant | Participant_ label |
|---|---|---|
| inflammasome activation [COVID-19 with ARDS] | http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006043 | NLRP3 (human)[coronavirus infectious disease] |
| inflammasome activation [COVID-19 with ARDS] | http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006130 | PYCARD (human)[coronavirus infectious disease] |
| inflammasome activation [COVID-19 with ARDS] | http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006131 | CASP1 (human)[coronavirus infectious disease] |
| IL-1beta processing [COVID-19 with ARDS] | http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006131 | CASP1 (human)[coronavirus infectious disease] |
| IL-1beta processing [COVID-19 with ARDS] | http://bioportal.bioontology.org/ontology/HOIP/HOIP_0030051 | IL-1B (human)[COVID-19 with ARDS] |
| IL-1beta production [COVID-19 with ARDS] | http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006131 | CASP1 (human)[coronavirus infectious disease] |
| IL-1beta production [COVID-19 with ARDS] | http://bioportal.bioontology.org/ontology/HOIP/HOIP_0030051 | IL-1B (human)[COVID-19 with ARDS] |
| Inflammatory cytokine gene expression (severe)[COVID-19 with ARDS] | http://bioportal.bioontology.org/ontology/HOIP/HOIP_0007085 | IL-6(human)[coronavirus infectious disease] |
| IL-6 signaling(severe) [COVID-19 with ARDS] | http://bioportal.bioontology.org/ontology/HOIP/HOIP_0007085 | IL-6(human)[coronavirus infectious disease] |
| TLR9 signaling [COVID-19 with ARDS] | http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006156 | TLR9(human)[COVID-19] |
| release of DNA from mitochondria [COVID-19 with ARDS] | http://www.ebi.ac.uk/efo/EFO_0008480 | mitochondrial DNA |
| tumor necrosis factor production (severe) [COVID-19 with ARDS] | http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006151 | TNF A (human)[COVID-19] |
| increasing blood AST concentration [COVID-19 with ARDS] | http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006225 | GOT1 (human)[coronavirus infectious disease] |
| increasing blood ALT concentration [COVID-19 with ARDS] | http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006228 | GPT (human) [coronavirus infectious disease] |
| macrophage interleukin-8 production [COVID-19 with ARDS] | http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006009 | CXCL8 (human) [COVID-19] |
| macrophage interleukin-8 production [COVID-19 with ARDS] | http://purl.obolibrary.org/obo/CL_0000235 | macrophage |
| neutrophil chemotaxis[COVID-19 with ARDS] | http://purl.obolibrary.org/obo/CL_0000775 | neutrophil |
| IL-17 signaling [COVID-19 with ARDS] | http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006385 | IL-17A(human)[coronavirus infectious disease] |
| T-helper 17 cell cytokine production [COVID-19 with ARDS] | http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006385 | IL-17A(human)[coronavirus infectious disease] |

# Future Work

- Refinement and addition of processes of the COVID-19 in HoIP Ontology
  - Investigation of relationships of other diseases (diabetes, heart disease, etc.)
  - Investigation of differences in aging populations (elderly, child)
- Development of application system for visualization map
- Coordination of HoIP ontology with other ontologies such as CIDO and COVID-19-IDO for better understanding of COVID-19

Thank you