Supplementary material

1. *Criteria for a framework of a COVID-19 disease model.*

Studies used as conceptual reference for the model framework
Wang and colleagues[1]:
Main characteristics of this study
Multi-scale tissue simulator, that can be used to investigate mechanisms of intracellular viral replication, infection of epithelial cells, host immune response, and tissue damage, has been developed by an international, multi-disciplinary coalition. It is a prototype of multiscale model of SARS-CoV-2 dynamics in lung tissue iteratively refined.
The first prototype model was built and shared internationally as open-source code and an online interactive model. Last version of the model (number 3) released on 29 July 2020.
The following critical components are identified by this model:
1) Virus dissemination in epithelial tissue ;
2) Virus binding, endocytosis, replication, and exocytosis ;
3) Infected cell responses, including changes to metabolism, secreted signals, and death ;
4) Inflammatory response ;
5) Ramp up of the immune response (particularly in lymph nodes) ;
6) Immune cell infiltration ;
7) Immune cell predation of infected and other cells ;
8) Tissue damage by death of cells due to infection or host response.
A modular design was used: an overall tissue-scale model integrates an array of targeted submodels that simulate critical processes (e.g., receptor binding and trafficking and virus replication). Each submodel is clearly specified to enable interoperability and to make it feasible for subteams to simultaneously develop and test the model components in parallel.

Perfetto and colleagues [2]:
Main characteristics of this study
Dataset of physical molecular interactions, manually extracted by IMEx Consortium curators focused on proteins from SARS-CoV-2, SARS-CoV and other members of the Coronaviridae family. Currently, the dataset comprises over 2,200 binarized interactions extracted from 86 publications. Data on 70 organisms are included, most interactions refer to SARS-CoV-2 and SARS-CoV-1 - human interactions (992 and 351 unique interactions, respectively).
The dataset can be accessed in the standard formats recommended by the Proteomics Standards Initiative (HUPO-PSI) at the IntAct database website (www.ebi.ac.uk/intact) and will be continuously updated as research on COVID-19 progresses. Most SARS-CoV-2 data comes from two studies: Gordon and colleagues (2020) [3] and Li and colleagues [4].

2. *Modelling of infectious diseases: principles and referral concepts.*

Infectious disease systems are identified as complex multilevel and multiscale systems. The need for multiscale modelling as opposed to single scale modelling[5], for infectious disease comes from:
- the need to study infectious disease processes at the scale at which they occur: some disease processes are most easily observed and have their greatest impact at a particular scale.
- the need to reduce errors in modelling infectious disease systems: if a disease process is studied at inappropriate scale than its characteristic scale, there is the possibility of making errors.
- the need to incorporate more details in modelling of infectious disease systems: disease dynamics are generally a multiscale phenomenon.

- The need to study factors that influence disease dynamics at scales at which they have greatest impact: the impact of many factors that influence disease dynamics such as immune response, health interventions and environmental change are typically most strongly expressed, most easily observed.

In an infectious disease system, it is possible to recognize the following properties[6]:

a. diseases that always arise (emerge) from the interaction of an infectious disease system's sub-systems (host sub-system, pathogen sub-system, and environmental sub-system);
b. dynamic process of ongoing reciprocal change (co-evolution) where the pathogen sub-system imposes a selective influence on the host sub-system which respond to the selection;
c. self-sustained multiscale cycles/loops (self-organization), that is an overall order which is spontaneous and robust i.e self-reinforcing mechanism to persist and spread;
d. local and global exchange of organisms implicated in disease dynamics (pathogen sub-system and host sub-system) among the levels and scales of an infectious disease system (openness);
e. the past helps to shape the present behavior e.g.: due to development of partial immunity due to prior exposure to the disease system or development of herd immunity due to prior exposure to vaccination. (history).

The study of infectious disease systems has been informed by two main theories.

- The infectious disease causation theory: series of theories progressively refined, one after another, to explain the cause of infectious disease systems. In the era of modern medicine, the germ theory postulates that infectious diseases are caused by germs/microbes/ pathogens. An infectious disease system is a result of the interaction of three sub-systems: (i) the host sub-system, (ii) the pathogen sub-system, and (iii) the environment sub-system. This theory constitutes the current and modern infectious disease causation theory, resulting in infectious disease systems organized into hierarchical multilevel and multiscale complex systems, with levels ranging from cellular to macroecosystem one[7].

- The infectious disease transmission mechanism theory: based on the idea that infectious disease dynamics consist of transmission as main dynamic process at each hierarchical level (cell, tissue, host, etc.) and that specific transmission models can be developed to study an infectious disease system at a particular level of organization. The standard approach in the development of such models, is to classify the population (which may be a population of cells for the cell level or a population of tissues for the tissue level, or a population of hosts for the host level) into compartments within which unit (cells, tissues, hosts, etc.) behave homogeneously[5,8].

This theory lies on three main transmission mechanisms:

(i) Direct transmission, based on compartmentalizing the population (cells, tissues, hosts, etc.) into susceptible, exposed, infected, recovered (SEIR), and variations of this paradigm at each hierarchical level;
(ii) Environmental transmission, based on compartmentalizing the population (cells, tissues, hosts, etc.) into susceptible, exposed, infected, recovered, and environmental pathogen load (SEIRP), and variations of this paradigm;
(iii) Vector-borne transmission: the pathogen has a complex life cycle, so it needs two hosts (a vertebrate host and vector host) to complete its life cycle. These infectious disease systems can be environmentally or directly transmitted (as malaria). Transmission models at host level are developed by compartmentalizing the host population into susceptible, exposed, infected, recovered (SEIR), and variations of this paradigm include two-host infections (the vertebrate host and the vector host).

Considering the above, the infectious disease causation theory, in the form of epidemiological triad theory, is adequate to explain the causes of infectious diseases, while the infectious disease transmission mechanism theory is not capable of providing a systems level description of infectious disease and is not adequate to describe infectious disease phenomena that vary through time and space and at different scales, using

multiscale modelling approaches. This is expected because transmission at any level of organization of an infectious disease system (cell, tissue, host, etc.) is a single scale disease process.
Furthermore, complex systems are multilevel and multiscale, and are organized differently: for some complex systems, a scale is the same as a level, for others, a level is different from a scale.
For example, for some complex systems, such as the immune response system at the site of infection, a level is the same as a scale, because it is organized into three main levels/scales (molecular, cellular, and the tissue); in this case we can interchangeably use the words level and scale. For other biological systems, this interchangeability is not possible.
Infectious disease systems are complex systems in which a scale is different from a level, and a level is different from a scale: each level can be resolved into two limiting adjacent scales which are microscale and macroscale.
W. Garira proposed a new theory which incorporates events (i.e. pathogen replication) that give rise to transmission and thus accommodate variations in time and space.
This theory, called "replication-transmission relativity theory", is considered an extension of the relativity principle in physics, and provides scientific basis for a systems level description of infectious disease systems using multiscale modelling methods. The Garira model considers multilevel and multiscale infectious disease systems, organized into seven main hierarchical levels (see Fig. 2 in main test).
Each level of organization of an infectious disease system has two limiting adjacent scales (microscale and a macroscale), which allows for bidirectional flow of information between scales, making infectious disease dynamics at each hierarchical level, a multiscale loop involving the reciprocal influences of macroscale and microscale.
At any level of organization of an infectious disease system there is no privileged/absolute scale which would determine disease dynamics, only interactions between microscale and macroscale.
At every level of an infectious disease system, the reciprocal influences among microscale and macroscale establish a pathogen replication-transmission multiscale cycle (see Fig.2 in main test) [5,8,9].

Microscale and the macroscale influence each other at each hierarchical level of an infectious disease system, through interactions of four key disease processes:

- infection/super-infection by pathogen;
- pathogen replication;
- pathogen shedding/excretion;
- pathogen transmission.

At each hierarchical level, disease dynamics involve a pathogen replication-transmission multiscale cycle. This happens because, at each of the hierarchical levels of organization of an infectious disease system, the characteristic scale at which pathogen replication and pathogen transmission occur, often do not match. In fact, the macroscale influences the microscale through infection/super-infection (involving movement of pathogen from macroscale into microscale) while the microscale influences the macroscale through pathogen shedding/excretion (which also involves movement of pathogen from microscale into the macroscale). Therefore, at each hierarchical level of organization of an infectious disease system, infection/super-infection and shedding/excretion of the pathogen introduce a multiscale cycle of influence between pathogen replication at the microscale, and pathogen transmission at the macroscale, respectively.

Consequently, we can distinguish two kinds of reciprocal influences between microscale and macroscale[9]:

- Type I reciprocal influence between the macroscale and microscale within a hierarchical level:

the microscale influences the macroscale through pathogen shedding/excretion. This involves the movement of pathogen from the microscale to the macroscale.
Further, the macroscale influences the microscale through initial infection. At each of the hierarchical levels, disease dynamics involves a pathogen replication-transmission multiscale cycle.
From a mathematical point of view the macroscale in this case influences the microscale through initial conditions of the microscale submodel variables (initial infection).

- Type II reciprocal influence between the macroscale and microscale within a hierarchical level:

the macroscale influences the microscale also through super-infection (i.e. repeated infection before the host recovers from an infectious episode), which also involves movement of pathogen from the macroscale to the microscale.
From a mathematical point of view the macroscale influences the microscale through scaled down macroscale variables and parameters.
For a conceptual representation of this model framework regarding mutual influence macro/micro scale, see Tab. 1S.

Furthermore, following this logic it is possible to identify three different types of environmentally transmitted infectious disease systems [10-16]:

A. Type A environmentally transmitted infectious disease systems: Infectious disease systems in which there is no pathogen replication at the microscale (within-host scale)

Macroparasites (mostly parasitic worms called helminths and parasitic arthropods such as lice) are larger, longer-lived, and rarely complete their life cycle within a single host. Instead, adult macroparasites usually shed infective stages such as eggs or larvae into the environment, and these may or may not infect the same host that the adult macroparasites live in. For these pathogens, the host's immune response is often incomplete or short-lived, resulting in persistent infections and continuous re-infection. Because the impacts of macroparasites on their hosts, and often parasite survival and fecundity, depend strongly on the number of adult parasites in each host, disease ecologists keep track of the number of macroparasites in each host and mathematically quantify their distribution across hosts. For these infectious disease systems, the pathogen load at the within-host scale is directly related to the number of infective stages encountered by the host (i.e. taken up by the host) in the environment (water, soil, food, air, contact surfaces, etc.) through super-infection (i.e. repeated infection before the host recovers from an infectious episode). Host behavior is a major factor influencing the disease burden in a particular community because certain ways of behaving, particularly regarding sanitation and hygiene will result in greater disease transmission. Such infectious disease systems can be modelled by embedded multiscale models in which type II reciprocal influence describes the relationship between the microscale and the macroscale at host level of organization of an infectious disease system.

B. Type B environmentally transmitted infectious disease systems:

Infectious disease systems in which the pathogen only replicates at the microscale (within-host scale). Some viral infections such as influenza and some bacterial infections such as NT Mycobacteria species and Mycobacterium tuberculosis are good examples of Type B environmentally transmitted infectious disease systems. Such infectious disease systems can be modelled by nested multiscale models in which type I reciprocal influence describes the relationship between the microscale and the macroscale at host level of organization of an infectious disease system.

C. Type C environmentally transmitted infectious disease systems:

environmentally transmitted infectious disease systems in which the pathogen replicates at both the microscale (within-host scale) and at the macroscale (between-host scale), as opportunistic infections, as cholera, Salmonella enterica and anthrax. For these infectious disease systems, a combination of type I reciprocal influence and type II reciprocal influence describe the relationship between the microscale and the macroscale at host level of organization of an infectious disease system
For a conceptual representation of this aspect, see Tab. 1S.

Tab. 1 S: Conceptual representation of mutual macro/micro scale influences and infections environmentally transmitted. This framework was adapted and modified from Garira (2019) [9].

Mutual influence Macro/micro scale		Environmentally transmitted Infectious disease Type A	Environmentally transmitted Infectious disease Type B	Environmentally transmitted Infectious disease Type C
Type I	**Macroscale** Initial infection Excretion/shedding Pathogen			pathogen replicates at the macroscale (between-host scale)
	Microscale Pathogen replication		pathogen only replicates at the microscale (within-host scale).	pathogen replicates at both the microscale (within-host scale)
Type II	**Macroscale** Repeated infection Excretion/shedding Pathogen			pathogen replicates at the macroscale (between-host scale)
	Microscale No pathogen replication	no pathogen replication at the microscale (within-host scale)		pathogen replicates at both the microscale (within-host scale)

References

1. Wang, Y.; An, G.; Becker, A.; Cockrell, C.; Collier, N.; Craig, M.; Davis, C.L.; Faeder, J.; Versypt, A.N.F.; Gianlupi, J.F.; et al. Rapid community-driven development of a SARS-CoV-2 tissue simulator. bioRxiv. 2020, doi:10.1101/2020.04.02.019075.
2. Perfetto, L.; Pastrello, C.; Del-Toro, N.; Duesbury, M.; Iannuccelli, M.; Kotlyar, M.; Licata, L.; Meldal, B.; Panneerselvam, K.; Panni, S.; et al. The IMEx coronavirus interactome: an evolving map of Coronaviridae-host molecular interactions. Database (Oxford). 2020, 2020, doi:10.1093/database/baaa096.
3. Gordon, D.E.; Jang, G.M.; Bouhaddou, M.; Xu, J.; Obernier, K.; White, K.M.; O'Meara, M.J.; Rezelj, V.V.; Guo, J.Z.; Swaney, D.L.; et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature. 2020, 583, 459-468, doi:10.1038/s41586-020-2286-9.
4. Li, J.; Guo, M.; Tian, X.; Wang, X.; Yang, X.; Wu, P.; Liu, C.; Xiao, Z.; Qu, Y.; Yin, Y.; et al. Virus-Host Interactome and Proteomic Survey Reveal Potential Virulence Factors Influencing SARS-CoV-2 Pathogenesis. Med (N Y). 2021, 2, 99-112 e117, doi:10.1016/j.medj.2020.07.002.
5. Garira, W. A primer on multiscale modelling of infectious disease systems. Infect Dis Model. 2018, 3, 176-191, doi:10.1016/j.idm.2018.09.005.
6. Garira, W. The research and development process for multiscale models of infectious disease systems. PLoS Comput Biol. 2020, 16, e1007734, doi:10.1371/journal.pcbi.1007734.
7. Karamanou, M.; Panayiotakopoulos, G.; Tsoucalas, G.; Kousoulis, A.A.; Androutsos, G. From miasmas to germs: a historical approach to theories of infectious disease transmission. Infez Med. 2012, 20, 58-62.

8. Garira, W. A complete categorization of multiscale models of infectious disease systems. J Biol Dyn. 2017, 11, 378-435, doi:10.1080/17513758.2017.1367849.
9. Garira, W. The Replication-Transmission Relativity Theory for Multiscale Modelling of Infectious Disease Systems. Sci Rep. 2019, 9, 16353, doi:10.1038/s41598-019-52820-3.
10. Garira, W.; Mathebula, D.; Netshikweta, R. A mathematical modelling framework for linked within-host and between-host dynamics for infections with free-living pathogens in the environment. Math Biosci. 2014, 256, 58-78, doi:10.1016/j.mbs.2014.08.004.
11. Netshikweta, R.; Garira, W. A Multiscale Model for the World's First Parasitic Disease Targeted for Eradication: Guinea Worm Disease. Comput Math Methods Med. 2017, 2017, 1473287, doi:10.1155/2017/1473287.
12. Spicknall, I.H.; Koopman, J.S.; Nicas, M.; Pujol, J.M.; Li, S.; Eisenberg, J.N. Informing optimal environmental influenza interventions: how the host, agent, and environment alter dominant routes of transmission. PLoS Comput Biol. 2010, 6, e1000969, doi:10.1371/journal.pcbi.1000969.
13. Beggs, C.B.; Noakes, C.J.; Sleigh, P.A.; Fletcher, L.A.; Siddiqi, K. The transmission of tuberculosis in confined spaces: an analytical review of alternative epidemiological models. Int J Tuberc Lung Dis. 2003, 7, 1015-1026.
14. Fung, I.C. Cholera transmission dynamic models for public health practitioners. Emerg Themes Epidemiol. 2014, 11, 1, doi:10.1186/1742-7622-11-1.
15. Chikerema, S.M.; Murwira, A.; Matope, G.; Pfukenyi, D.M. Spatial modelling of Bacillus anthracis ecological niche in Zimbabwe. Prev Vet Med. 2013, 111, 25-30, doi:10.1016/j.prevetmed.2013.04.006.
16. Breban, R.; Drake, J.M.; Rohani, P. A general multi-strain model with environmental transmission: invasion conditions for the disease-free and endemic states. J Theor Biol. 2010, 264, 729-736, doi:10.1016/j.jtbi.2010.03.005.