Modeling of a Virus Pandemic in a Globally Connected World

A multi-scale active particles approach

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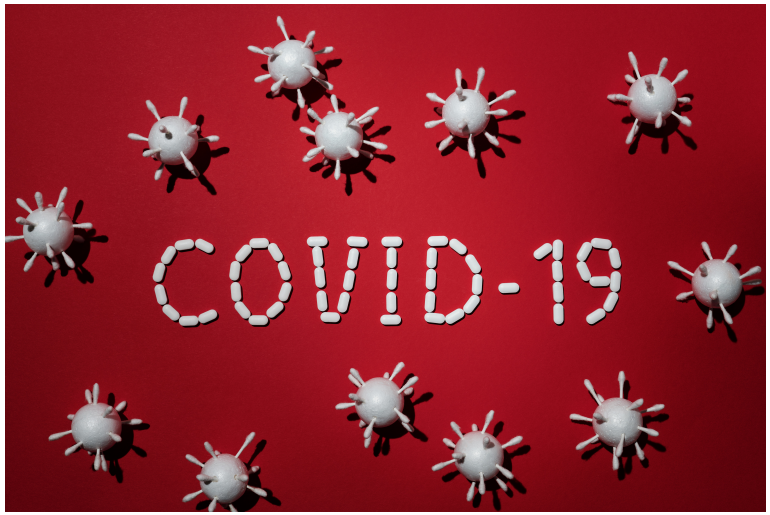

Main Sources

• N. Bellomo, R. Bingham, M. A. J. Chaplain, G. Dosi, G. Forni, D. A. Knopoff, J. Lowengrub, R. Twarock, and M. E. Virgillito, **A multi-scale model of virus pandemic: Heterogeneous interactive entities in a globally connected world**, *Math. Models Methods Appl. Sci.*, doi: 10.1142/S0218202520500323.

• **RAPID ASSISTANCE IN MODELLING THE PANDEMIC: RAMP**

https://epcced.github.io/ramp/

A call for assistance, addressed to the scientific modelling community *Coordinated by the Royal Society*

Within Host Dynamics *Coordinated by Mark Chaplain, St Andrew University, UK*

1.1. A multiscale vision in a globally connected world

What is COVID19

• The onset of *SARS–CoV–2* responsible for the initial *COVID-19* outbreak and the subsequent pandemic, has brought to almost all countries and societies across the globe huge problems affecting health, safety/security, economics, and practically all expressions of collective behaviors.

• A significant percentage of governments believed this to be a so-called *black swan* event for our society, including a number of scientists. However, this event is definitely not a black swan as the event should have been predictable (and indeed was predicted by a few) but many of our societies appear to be unprepared to tackle this problem.

• *SARS–CoV–2* is mainly transmitted through the respiratory route 10-12 via respiratory droplets, up to 1 millimetre in diameter, that an infected person expels.

1.2. A multiscale vision in in a globally connected world

- The large Spike protein forms a sort of crown on the surface of the viral particles and acts as an anchor allowing the virus to bind to the Angiotensin-Converting Enzyme 2 (ACE2) receptors on the host cell. After binding, the host cell transmembrane proteases cut the Spike proteins, allowing the virus surface to approach the cell membrane, fuse with it and the viral RNA enter the cell.
- The virus hijacks the cell machinery and the cell dies releasing millions of new viruses thus generating a virus infection. COVID-19 starts with the arrival of *SARS–CoV–2* virions to the respiratory mucosal surfaces of the nose and throat that express high levels of ACE-2 receptors on the surface .
- *Immune system actions:* When the virus manages to overcome the barrier of the mechanisms and the mucus secreted by goblet cells from a first effective reaction, a rapid release of danger signals activates the reaction of the host's innate immunity. Corona viruses are successful at suppressing various mechanisms, but not all of them, in an immune response.

1.3. A multiscale vision in a globally connected world

Mathematical reasonings on pandemic modeling

• Modeling approach should go far beyond deterministic population dynamics, as individual reactions to the infection and pandemic events are heterogeneously distributed throughout the population. Spatial dynamics is an important feature as the dynamics are generated by nonlocal interactions and transportation devices.

• The modeling ought to be developed within a multiscale vision, as the dynamics of individuals depend on the dynamics at smaller scales inside each individual by the competition between virus particles and the immune system.

• The approach described in this lecture looks firstly for a model local-in-space accounting for the infection dynamics and, subsequently for the competition inside each individual, between the proliferating virus and the immune-system specific to the individual. Subsequently the approach focuses on collective behaviors.

1.4. A multiscale vision in a globally connected world

Mathematical reasonings on virus pandemic

• Applied mathematicians cannot tackle the modeling problem by a stand-alone approach – an interdisciplinary vision is necessary through mutually enriching and beneficial interactions with scientists in other fields including virology, epidemiology, immunology and biology in general.

• The scope of such a research project should not be confined only to "biological and medical sciences", but also be addressed to wider aspects of and other communities in our society.

• Once refined and informed by empirical data, mathematical models can produce insightful provisional simulations which can even uncover dynamics which were not previously observed (cf. emergent behavior). Hence mathematical models can and should also be viewed as a tool to generate dialogue and wider communication between the hard and applied sciences. This dialogue can in turn lead to a perspective on and insight into possible future events.

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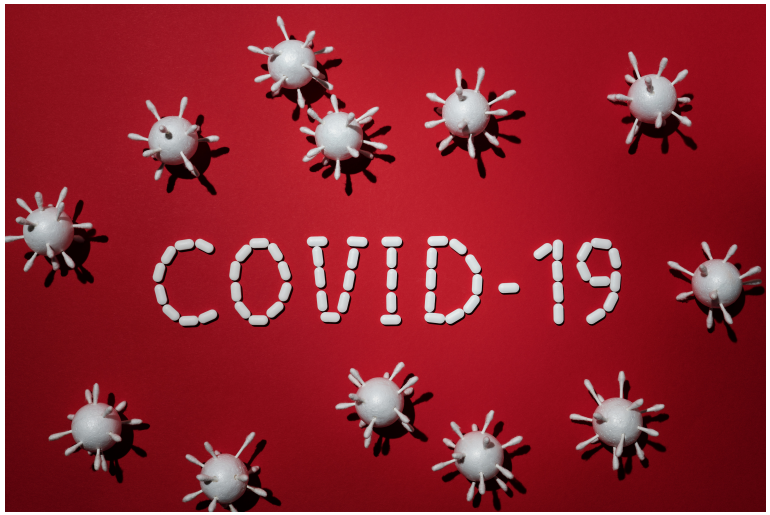


2.1. Modeling strategy

What we can learn from the Lecture by Lee Hartwell

• Nobel Laureate Lee Hartwell (born 1939) has well in mind that the mathematical approach to the description of the dynamics of the inert matter cannot be straightforwardly applied to living systems:

> *Biological systems are very different from the physical or chemical systems of the inanimate matter. In fact, although living systems obey the laws of physics and chemistry, the notion of function or purpose differentiate biology from other natural sciences. Indeed, cells are not molecules, but have a living dynamics induced by the lower scale of genes and is organized into organs.*

• This statement directly looks forward a challenging research perspective whose first step consists in acknowledging that the mathematics used for the inert matter fails when applied to the living matter.

H.L. Hartwell, J.J. Hopfield, S. Leibler, and A.W. Murray, From molecular to modular cell biology *Nature*, **402**, c47–c52, (1999).

2.2. Modeling strategy

Preliminary step towards a strategy

We suggest to replace the definition of Soft sciences with

Science of Living Systems

and to develop a strategy to take into account that in the case of the living matter the approach cannot be supported by field theory.

> ***The strategy consists in replacing the field theory by a mathematical structure (say mathematical theory) suitable to capture, as far as possible, the complexity features of living systems. This structure defines the conceptual framework for the derivation of models in different fields of science of living systems.***

• **P. Ball**, *Why Society is a Complex Matter*, Springer-Verlag, Heidelberg, (2012).

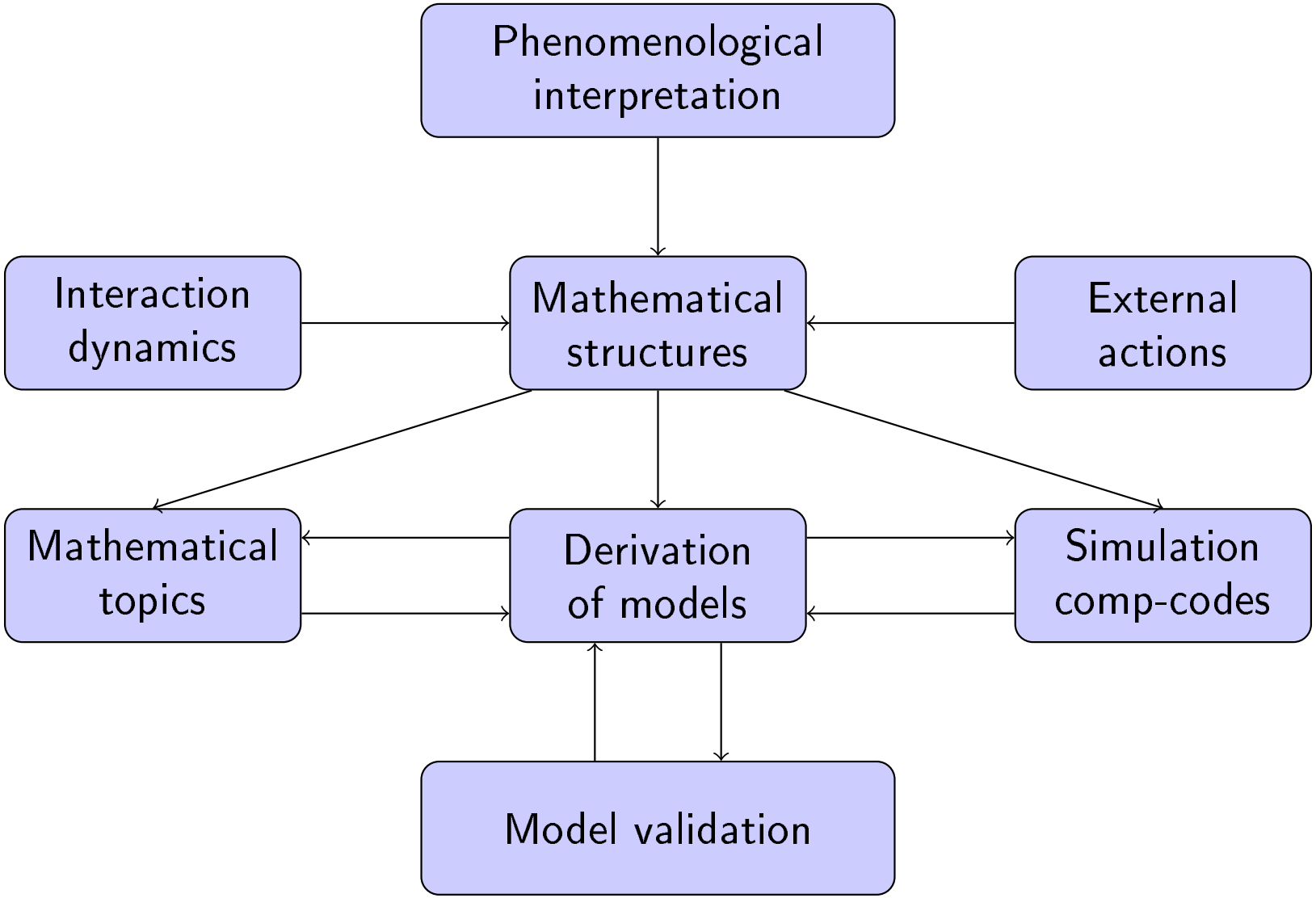
• **N. Bellomo, A. Bellouquid, L. Gibelli, and N. Outada**, *A Quest Towards a Mathematical Theory of Living Systems*, Birkhäuser-Springer, New York, (2017).

2.3. Modeling strategy

Rationale towards a strategy

- Understanding the links between the dynamics of living systems and their complexity features;
- Derivation of a general mathematical structure, consistent with the aforesaid features. The aim consists in offering the conceptual framework toward the derivation of specific models;
- Design of specific models corresponding to well defined classes of systems by implementing the said structure with suitable models of individual-based, micro-scale, interactions;
- Validation of models by quantitative comparison of the dynamics predicted by them with that one delivered by empirical data. In addition, models are required to reproduce qualitatively emerging behaviors.

2.4. Modeling strategy



2.5. Modeling strategy

Five Common Features and Sources of Complexity

1. Ability to express a strategy: Living entities are capable to develop specific *strategies* and *organization abilities* that depend on the state of the surrounding environment.

2. Heterogeneity: The ability to express a strategy is not the same for all entities as *expression of heterogeneous behaviors* is a common feature of a great part of living systems.

3. Nonlinear interactions: Interactions are nonlinearly additive and involve immediate neighbors, but in some cases also distant entities.

4. Learning ability: Living systems receive inputs from their environments and have the ability to learn from past experience.

5. Darwinian mutations and selection: All living systems are evolutionary, as birth processes can generate entities more fitted to the environment, who in turn generate new entities again more fitted to the outer environment.

2.6. Modeling strategy

Understanding living systems

• ***Multiscale aspects:*** Modeling always needs a *multiscale approach*, where the dynamics at the large scale needs to be properly related to the dynamics at the low scales. For instance, the functions expressed by a cell are determined by the dynamics at the molecular (genetic) level.

• ***Role of the environment:*** The environment evolves in time, in several cases also due to interactions with the internal living system.

• ***Large deviations:*** Emerging behaviors often present large deviations although the qualitative behaviors is reproduced. In this case, small deviations in the input create large deviations in the output.

• ***Individuals within a certain population can aggregate into groups of affinity:*** Communications and subsequent dynamics can take advantage (or disadvantage) from the said aggregation by creating a new communication network.

2.7. Modeling strategy

What is the Black Swan?

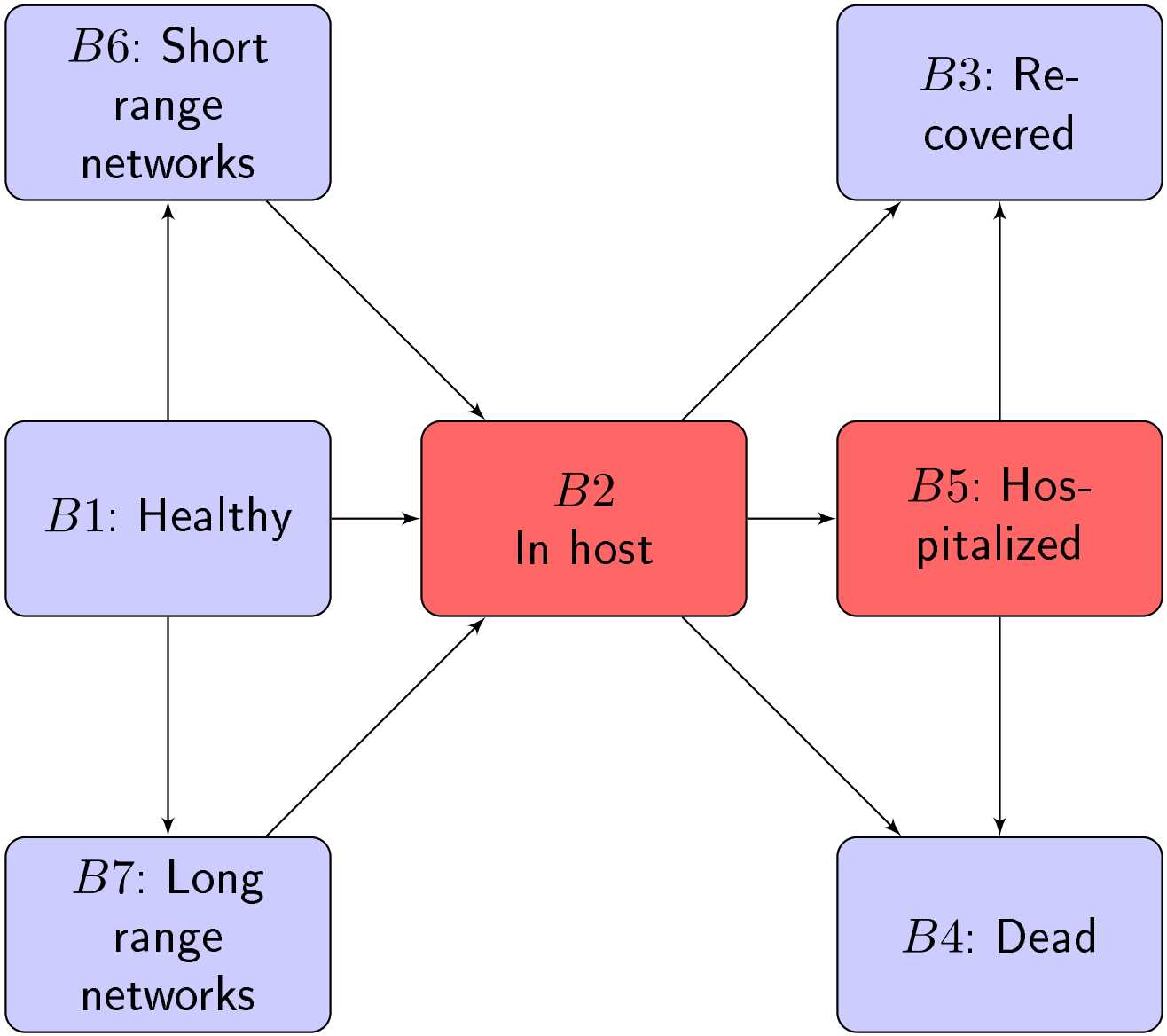
It is worth detailing a little more the expression **Black Swan**, introduced in the specialized literature for indicating unpredictable events, which are far away from those generally observed by repeated empirical evidence. According to the definition by Taleb a Black Swan is specifically characterized as follows:

"A Black Swan is a highly improbable event with three principal characteristics: It is unpredictable; it carries a massive impact; and, after the fact, we concoct an explanation that makes it appear less random, and more predictable, than it was."

***** N. N. Taleb, **The Black Swan: The Impact of the Highly Improbable**, Random House, New York City, 2007.

2.8. Modeling strategy

On a systems approach



2.9. Modeling strategy

Blocks of the systems approach

Block 1: Contagion occurs between individuals depending on the level of confinement only in the case of spatial homogeneity, and to local densities for crowd movement in complex venues.

Block 2: The dynamics follows inside each individual depending on the interaction at the small scale between virus infection and immune particles, *within host dynamics*. The modeling takes into account the heterogeneous behavior of individuals, as well as heterogeneity, progression and competition inside each individual entity. The dynamics of the virus is coupled with that of the lung.

Blocks 3,4: Show the output of the interactions consisting in recovery or death of patients, where this final exit can go through the passage across the hospitalization which is related to the level of the pathology.

2.10. Modeling strategy

Block 5: Refers to the passage from Block 2 to an organized hospitalization dynamics. If the dynamics within Block 5 are properly modelled accounting for medical care, the number of patients which are recovered should increase, while that of dead persons should decrease.

Block 6: Refers to the dynamics by which the contagion spreads over a territory made of a sequence of interconnected areas. The dynamics might include aggregation through endogenous networks.

Block 7: Studies the dynamics by which the contagion spreads over a territory through long range exogenous networks, where connections between nodes depend on the transportation system.

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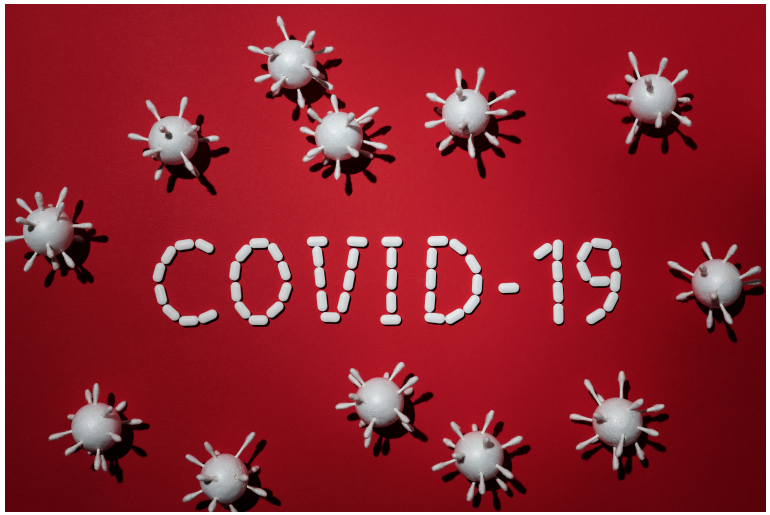


3.1. A multiscale vision of contagion and in-host dynamics

Contagion in crowds: Consider a population of N_0 individuals homogeneously distributed in space. A small number εN_0 is initially infected, while $(1-\varepsilon) N_0$ is considered healthy. Contagion depends on the frequency of contacts, on the level of the infection within each individual, on the level of physical protection used by individuals aware of the risk of contagion, and on the so-called *social distance*.

3.2. A multiscale vision of contagion and in-host dynamics

A simple model of contagion: The contagion dynamics, followed by the competition for survival within each individual, can be modeled according to the following rationale:

1. Individuals are viewed as *active particles* which are carriers of an internal state, called *activity*. The level of infection of each a-particle can progress (or regress) in time due to a prevalence (or lack of prevalence) of the virus aggressiveness over the immune defence.
2. Contagion depends on the level of the infection as well as on the *social distance* between individuals which is a constant parameter in the case of spatial homogeneity.
3. Dynamics within each individual depends on the heterogeneous *competition between a proliferative virus and the immune system*.

In-host dynamics

– The overall population is subdivided into four sub-populations labeled by the subscripts $i = 1, 2, 3, 4$. The abbreviation i-FS is used to denote the i-th population viewed as a functional subsystem.

– The micro-state of a-particles includes two variables $u \in [0, 1]$ and $w \in [0, 1]$ corresponding, respectively, to the progression of virus invasion and to the level of activation of the immune defence. In this sense, $u = 0$ represents the absence of the viral infection, while $u > 0$ characterizes the presence of the disease, where increasing values of u towards 1 correspond to more aggressive states. Similarly, $w = 0$ and $w = 1$ correspond, respectively, to the lowest and highest immune system activation. If discrete variables are used one has

$$\mathbf{u} = \{u_j = \frac{j-1}{m-1}, j = 1, \dots, m\}, \quad \text{and} \quad \mathbf{w} = \{w_k = \frac{k-1}{n-1}, k = 1, \dots, n\},$$

where $u_1 = 0$ corresponds to the healthy level and $w_1 = 0$ to the lack of immune defence and $u_m = 1$, $w_n = 1$

3.4. A multiscale vision of contagion and in-host dynamics

Within host dynamics

- $i = 1$: Healthy individuals with distribution $f_1^{1,k}(t, u_1, w_k)$, where t is the time belonging to the interval $[0, T]$.
- $i = 2$: Infected individuals with distribution $f_2^{j,k}(t, u_j, w_k)$, with $1 < j < m$.
- $i = 3$: Individuals recovered from the infection with distribution $f_3(t)$, namely infected individuals that succeed in reaching back to the state $j = 1$.
- $i = 4$: $f_4(t)$ is the number of individuals of the infected population who do not succeed to recover, that are infected individuals who reach the state $j = m$.

3.5. A multiscale vision of contagion and in-host dynamics

Within host dynamics A general structure is reported as it provides the conceptual basis for these developments.

$$\begin{aligned}\frac{d}{dt}f_{ij}^{r} &= G_{ij}^{r}(\mathbf{f}) - L_{ij}^{r}(\mathbf{f}) \\ &= \sum_{s=1}^{m}\sum_{h,k,p,q=1}^{n} \eta_{hk}^{pq}(r,s)(\mathbf{f})\mathcal{A}_{hk}^{pq}(hk \to ij)(\mathbf{f}) f_{hk}^{r} f_{pq}^{s} \\ &\quad - f_{ij}^{r}\sum_{s=1}^{m}\sum_{p,q=1}^{n} \eta_{ij}^{pq}(\mathbf{f})\, f_{pq}^{s},\end{aligned}$$

The subscripts h, k and p, q denote the micro-states corresponding to the r, s FSs which by interactions lead to the dynamics of f^r. In addition, η_{hk}^{pq}, η_{ij}^{pq}, denote the interaction rates, and $\mathcal{A}_{hk}^{pq}$ the transition rate into the micro-state i, j of the r-FS. The time dynamics are then ruled by a *gain* term of particles which at time t gain the state (i, j) and a *loss* term related to particles which lose such a state.

3.6. Towards a multiscale vision of contagion and in-host dynamics

Within host dynamics: Modeling of interactions.

1. $i = 1$: Active 1-FS particles interact with a-particles from 2-FS and can become, in probability, infected. The rate of infection depends on the physical interaction rate η_0, supposed to be constant, and to the level of progression u_j of the infected individuals as the probability of infection grows with u_j.
2. $i = 1, 2$: The interaction rate depends on the social distance. Interactions do not modify the levels of the immune defence, while particles which move from 1-FS to 2-FS take the value u_2 and start their competition to survive the attack from the immune system.
3. $i = 2$: Viral particles progress (proliferate) thanks to foraging of the surrounding tissues, while the immune defence counteracts the progression by inducing a regression.
4. $i = 2, 3, 4$: A-particles from 2-FS move to 3-FS if the immune defence succeeds to obtain a regression down to u_1, while a-particles from 2-FS move to 4-FS if the immune defence does not succeed to obtain a regression.

Functional subsystems

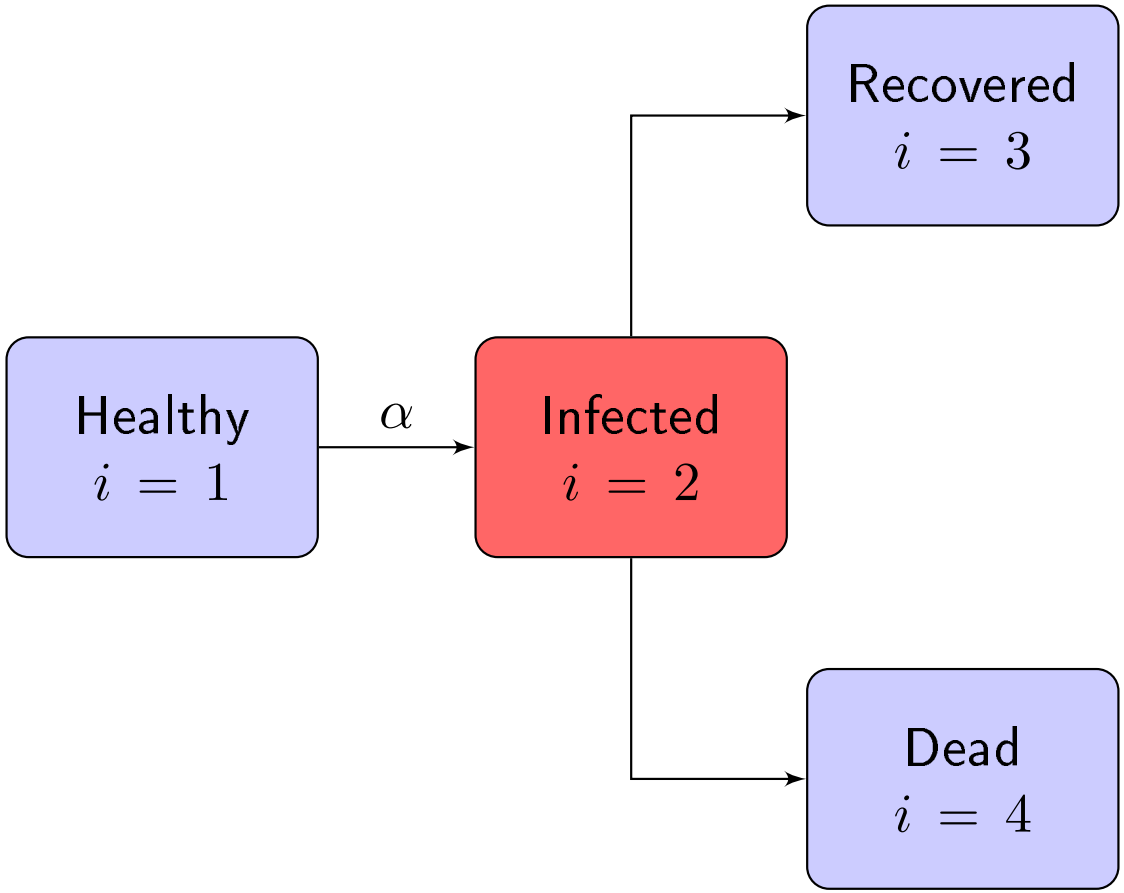


Figure – Transfer diagram of the model. Boxes represent functional subsystems and arrows indicate transition of individuals.

Flow chart of the systems approach

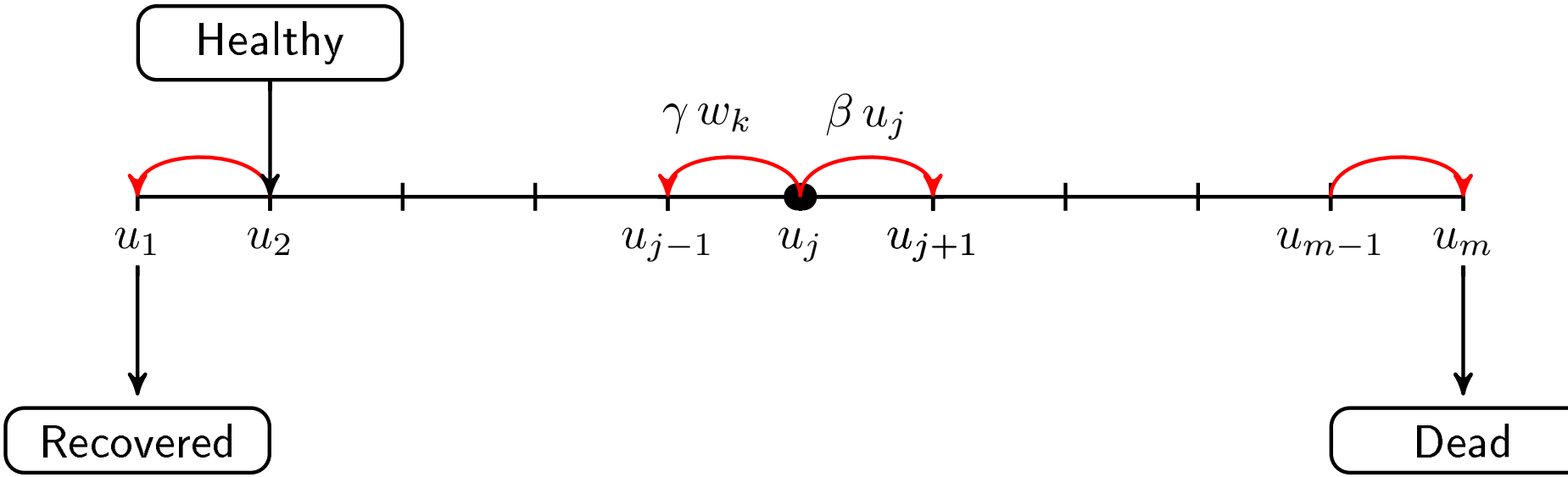


Figure – Dynamics within infected population.

3.9. A multiscale vision of contagion and in-host dynamics

How do parameters influence on the dynamics? Let us introduce the key number:

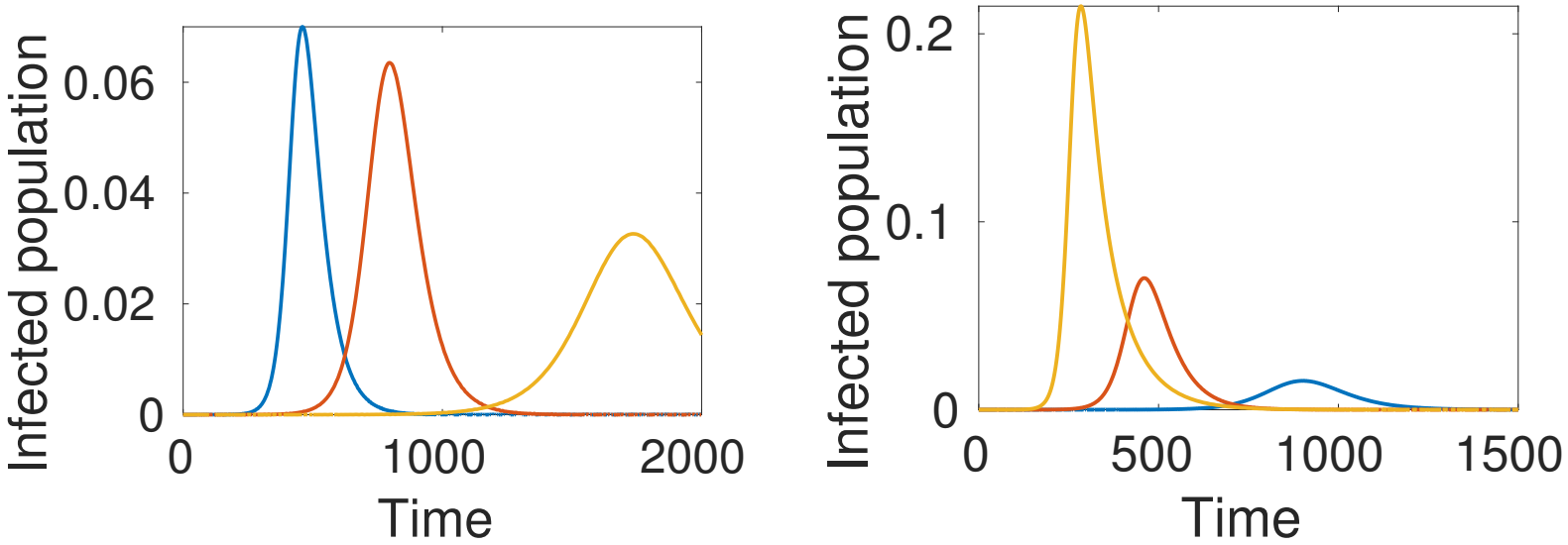
$$\kappa = \frac{\alpha \cdot \beta}{\gamma}$$

which refers the intensity of the infection $\alpha \cdot \beta$ to the immune defence γ, where α and β refer to infectivity and the progression of the virus, respectively. Increasing values of κ denote an increasing level of the infection attack.

A very first, and rapid, biological interpretation is as follows:

> *The defence of the immune system applies an effective contrast to the virus progression. However the efficacy of the action is more relevant if the defence keeps a fixed value independently on the level of infection or progression. If the defence increases with increasing values of α and β, the efficacy is even higher.*

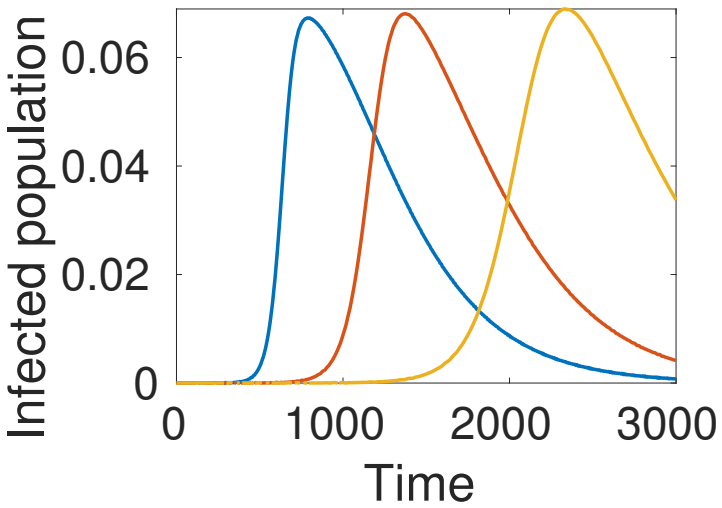
3.10. A multiscale vision of contagion and in-host dynamics



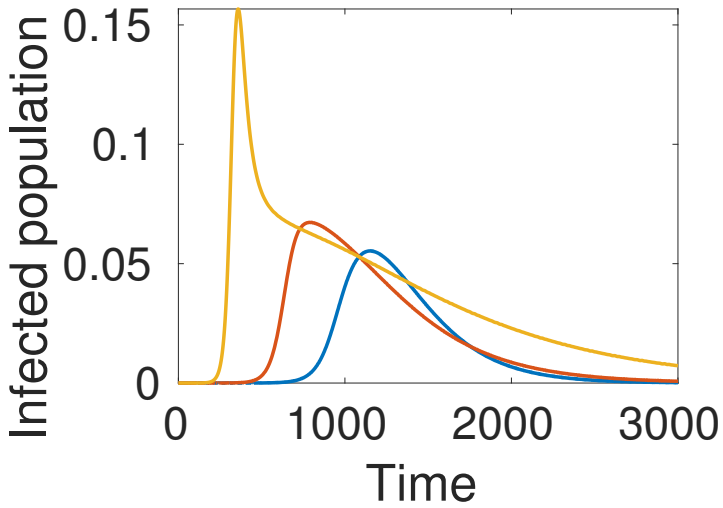
(a) $\kappa = 0.2$, fixed $\beta = 0.1$ (b) $\kappa = 0.2$, fixed $\alpha = 0.4$

Figure – Sensitivity to κ.
(a) Blue: $\alpha = 0.4$, $\gamma = 0.2$, Red: $\alpha = 0.2$, $\gamma = 0.1$, Yellow: $\alpha = 0.1$, $\gamma = 0.05$.
(b) Blue: $\beta = 0.15$, $\gamma = 0.3$, Red: $\beta = 0.1$, $\gamma = 0.2$, Yellow: $\beta = 0.05$, $\gamma = 0.1$.

3.11. A multiscale vision of contagion and in-host dynamics



(c) $\kappa = 0.02$, fixed $\beta = 0.01$



(d) $\kappa = 0.02$, fixed $\alpha = 0.4$

Figure – Sensitivity to κ.
(c) Blue: $\alpha = 0.4$, $\gamma = 0.2$, Red: $\alpha = 0.2$, $\gamma = 0.1$, Yellow: $\alpha = 0.1$, $\gamma = 0.05$.
(d) Blue: $\beta = 0.15$, $\gamma = 0.3$, Red: $\beta = 0.1$, $\gamma = 0.2$, Yellow: $\beta = 0.05$, $\gamma = 0.1$.

3.12. A multiscale vision of contagion and in-host dynamics

When should locking be implemented? Let T_ℓ is the lapse of time, after the discovery of the infection, at which locking is imposed with α_ℓ; and T_d is the lapse of time from T_ℓ to impose less restrictive locking rules (locking-down) corresponding to $\alpha_d > \alpha_\ell$.

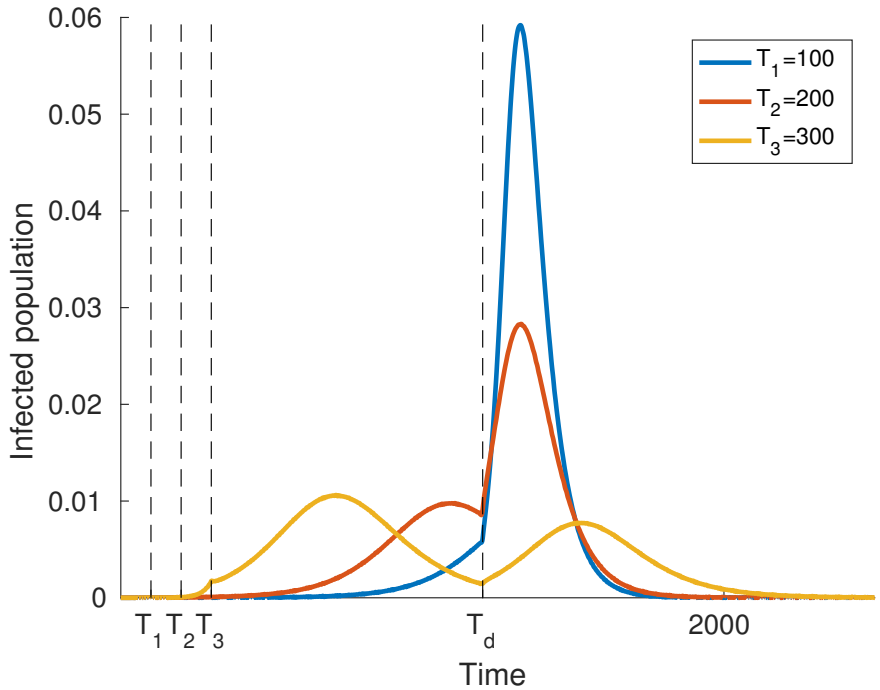


Figure – We take $T_\ell = 100, 200, 300$, and fixed lock-open time $T_d = 1200$. $\alpha = 0.4$ for $t \in [0, T_\ell) \cup [T_d, T_{max}]$ while $\alpha = 0.25$ during the locking interval.

3.13. A multiscale vision of contagion and in-host dynamics

And how long should locking last? Simulations show how delaying T_d reduces the peak, but increases the time interval of the persistence of the infection.

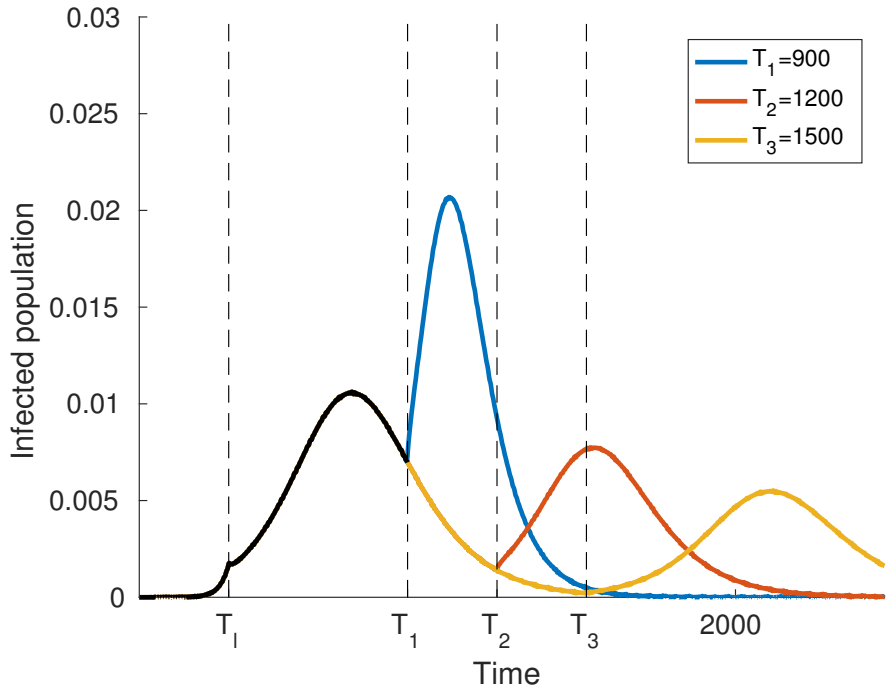


Figure – Varying de-locking times. We take a fixed locking time $T_\ell = 300$, and three different lock-open times $T_d = 900, 1200, 1500$. $\alpha = 0.4$ for $t \in [0, T_l) \cup [T_d, T_{max}]$ while $\alpha = 0.25$ during the locking interval.

3.14. A multiscale vision of contagion and in-host dynamics

How flexible shall lock-down relaxation be?

We study the influence of the relaxation level for fixed values of T_d and T_ℓ. Simulations show that a large relaxation can generate high level peaks.

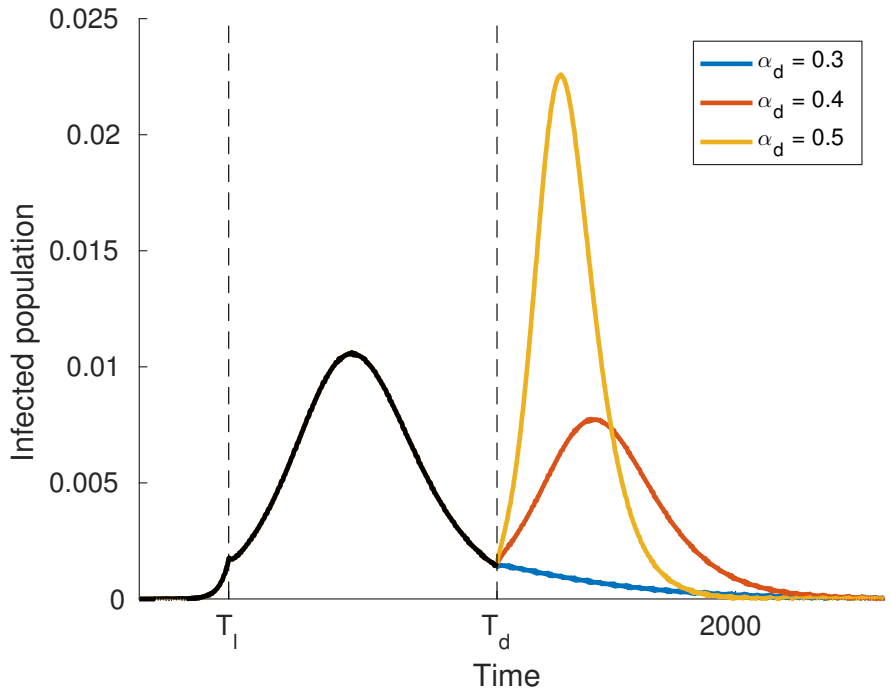


Figure – Varying the de-locking value α_d. We take fixed locking and lock-open times $T_l = 300$ and $T_d = 1200$, respectively. $\alpha = 0.4$ initially for $t \in [0, T_l)$ then reduced to $\alpha = 0.25$ during the locking interval and finally we consider three different lock-open values $\alpha_d = 0.3, 0.4, 0.5$.

3.15. A multiscale vision of contagion and in-host dynamics

On a research perspective:

Populations and representation: Three populations: Virus particles, immune cells, and lung tissue cells which feed the virus. The state of the FSs is delivered by the distribution functions $f_{ij}(t,u)$, $f_{ij}(t,v)$, and $f_{ij}(t,w)$, in each hexagon of the lung at time t over the activity variable. The following activities are linked to each FS, $i=1$: *u = reproductive ability*; $i=2$: *v = activation of the immune ability*; $i=3$: *feeding ability* the virus particles to contribute to reproduction with $u,v,w \in D=[0,1]$.

Virus interaction with local tissue, proliferation and space propagation: Virus particles interacting locally with lung cells proliferate depending on their level of progression up to when the virus load reaches a critical value. Then virus particles move to the boundary hexagons.

3.16. A multiscale vision of contagion and in-host dynamics

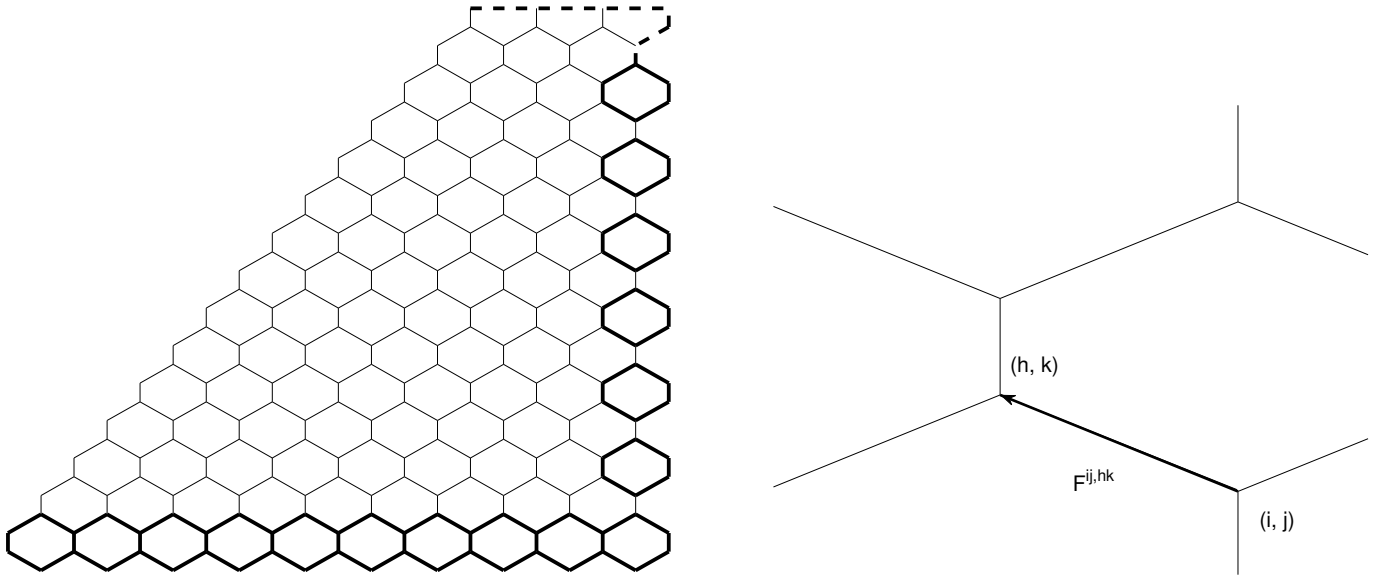


Figure – Upper Left Lung Parenchyma and internal forces

3.17. A multiscale vision of contagion and in-host dynamics

Activation of the immune system, virus regression or progression: The immune system activates from the sentinel level by a collective learning process which can reduce the speed of progression and even induce regression. The dynamics is sensitive to the initial virus load.

Recovery, need of hospitalization, and eventual death: Modeling can contribute to the strategy towards hospitalization by referring this choice to the pathological stage related to progression. Trends to low stages of the progression indicate trends to full recovery. Progression and trend of the virus load over critical levels are indicator of eventual death of the patient.

Lung dynamics and damage: The in-host dynamics should be coupled with the lung dynamics by an appropriate coupling of the two models. The study of lung damage can contribute to develop therapeutical strategies.

3.18. Closing

Thank to:

- Richard Bingham, University of York, U.K.,
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