Lecture 4
Heterogeneity and Networks

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Five Lectures by
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From a Mathematics of Living Systems

to Modeling Virus Pandemics

P.1. Plan of the Lectures

Nicola Bellomo **Lecture 1. A Quest Towards a Mathematical Theory of Living Systems**

Diletta Burini **Lecture 2. Mathematical Tools of the Kinetic Theory of Active Particles**

Nicola Bellomo, Diletta Burini and Nisrine Outada **Lecture 3. Towards a Mathematical Theory of Virus Pandemics - Models with Mutations, Variants and Vaccination Programs**

Damian Knopoff **Lecture 4. Heterogeneity and Networks**

Pietro Terna **Lecture 5. Agent Methods to Modeling Virus Pandemics - A quick reference to complexity**

Pietro Terna **Closure, Description of the material support to the Lectures, Acknowledgments**

4.1. Heterogeneity and Networks

This lecture introduces network structures capable of capturing connectivity and some degree of spatial distribution of the population. Moreover, heterogeneity is also considered: in the case of modeling infectious diseases, e.g., the population can be stratified according to age or risk groups, and the impact on the overall dynamics will be discussed.

4.2. Heterogeneity and Networks

Main sources

* M. Aguiar, G. Dosi, D. A. Knopoff, and M. E. Virgillito, **A multiscale network-based model of contagion dynamics: heterogeneity, spatial distancing and vaccination**, *Math. Models Methods Appl. Sci.*, (2021).
* A.L. Barabasi, **Network Science**, Cambridge Univ. Press, 2016.
* 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.*, 30, 1591–1651, (2020).
* D. Knopoff and F. Trucco, **A compartmental model for antibiotic resistant bacterial infections over networks**, *Int. J. Biomath.* 13(1): 2050001 (16 pages), (2020).
* M. Aguiar, V. Anam, N. Cusimano, D. Knopoff, and N. Stollenwerk, **Understanding COVID-19 epidemics: a multi-scale modeling approach** In: Predicting Pandemics in a Globally Connected World, Volume 1 - N. Bellomo and M. Chaplain, Eds., Birkhäuser-Springer Series "Modeling and Simulation in Science, Engineering and Technology", to appear (2021).

4.3. Mathematical model

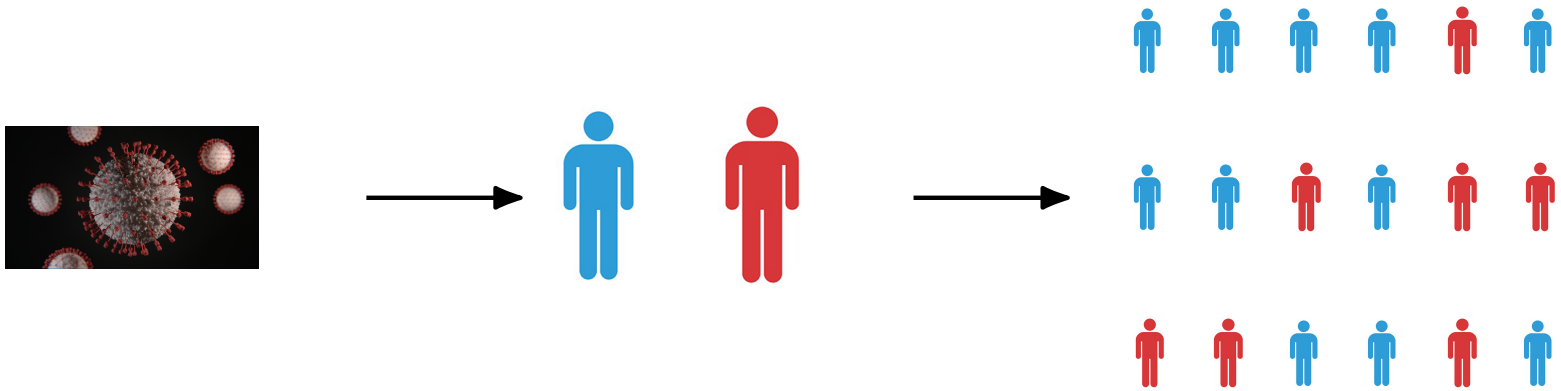
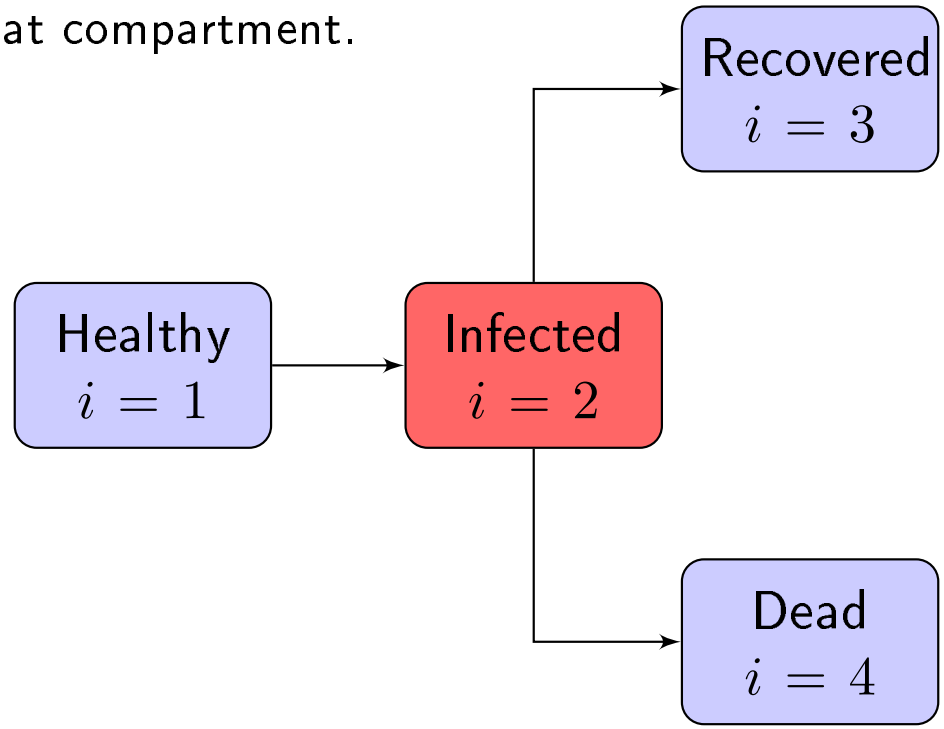


Figure – Schematic representation of different scale dynamics. COVID-19 virus image on the left credit: Photo by Viktor Forgacs on Unsplash.

4.4. Mathematical model

Model recap

- Let us consider a population of spatially homogeneous distributed individuals. Each individual can belong, at each time t, to one of the following compartments or FSs: susceptible (S-FS), infected (I-FS), recovered (R-FS) or deceased (D-FS). The S-FS is assumed to have only an outlet flow (into the I-FS), while R-FS and D-FS have only an inlet flow (from I-FS).
- We assume that recovered individuals get a long lasting immunity and remain in that compartment.



4.5. Mathematical model

Model recap

- The micro-state of every individual is described by a variable $w \in [0,1]$ corresponding to the level of activation of the immune defence. It is convenient to discretize into a set

$$\mathbf{w} = \{w_1 = 0, \ldots, w_k = \frac{k-1}{n-1}, \ldots, w_n = 1\},$$

such that n risk groups (e.g., according to age or presence of co-morbidities) are considered. In this way, $w_1 = 0$ and $w_n = 1$ correspond, respectively, to the lowest and highest immune system activation.

- Within the I-FS individuals are also characterized by a variable $u \in [0,1]$ representing the level of progression of the viral infection (e.g., from mild to severe). If m possible states are considered, we have

$$\mathbf{u} = \{u_1 = 0, \ldots, u_p = \frac{p-1}{m-1}, \ldots, u_m = 1\}.$$

Here, if an individual reaches the state $u_1 = 0$ we assume that it is recovered from the infection (transition into R), while reaching the state $u_m = 1$ implies a decease (transition into D).

4.6. Mathematical model

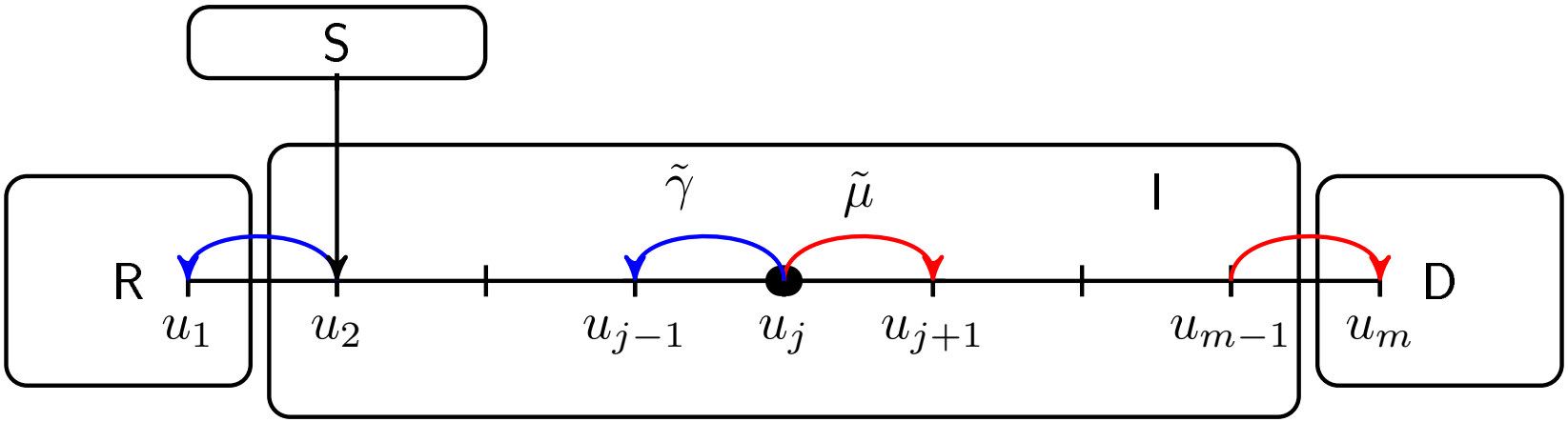


Figure – Illustration of the transitions: susceptible individuals can get infected with an infection rate $\tilde{\beta}$, entering to the infected compartment (wide box in the middle) with state u_2. Then, competitive interactions between the pathogen that replicates with rate $\tilde{\mu}$ towards more aggressive infection states and the immune system, which acts with rate $\tilde{\gamma}$, with resulting transition into the R or D compartment.

4.7. Mathematical model

$$
\begin{cases}
\dfrac{d}{dt} f_S^k(t) = -\displaystyle\sum_{l=1}^{n} \sum_{q=2}^{m-1} \alpha^k \, u_q \, f_S^k(t) \, f_I^{q,l}(t), \\
\dfrac{d}{dt} f_I^{p,k}(t) = \displaystyle\sum_{l=1}^{n} \sum_{q=2}^{m-1} \alpha^k \, u_p \, f_S^k(t) \, f_I^{q,l}(t) \, \delta_{2p} \; + \beta u_{p-1} \, f_I^{p-1,k}(t) \\
\qquad\qquad + \gamma \, w_k \, f_I^{p+1,k}(t) - \beta \, u_p \, f_I^{p,k}(t) - \gamma \, w_k \, f_I^{p,k}(t), \\
\dfrac{d}{dt} f_R(t) = \gamma \displaystyle\sum_{k=1}^{n} w_k \, f_I^{2,k}(t), \\
\dfrac{d}{dt} f_D(t) = \beta \, u_{m-1} \displaystyle\sum_{k=1}^{n} f_I^{m-1,k}(t),
\end{cases}
\tag{1}
$$

4.8. Network structure

- Let us now consider that the dynamics takes place within several nodes of an undirected weighted network $\mathcal{G} = (V, E)$, where V is a set of N nodes and E is a set of edges joining some pairs of nodes. Let $A = [a_{ij}]_{i,j=1\ldots,N}$ be the adjacency matrix of $\mathcal{G}$.
- Entries $a_{ij} \in [0, 1]$ weigh the "intensity" of the interaction between nodes i and j.
- Within each node there is a subpopulation of individuals belonging to one of the classes S, I, R or D.
- To keep the model as a generalization of the one presented above, there is an edge connecting each node to itself, namely a self-loop. Let $a_{ii} = 1$ for $i = 1, \ldots, N$.
- The network is undirected. Consequently, A is symmetric.

4.9. Network structure

Let f_{iS}^{k}, $f_{iI}^{p,k}$, f_{iR} and f_{iD} denote the distribution functions of susceptible, infected, recovered and deceased individuals within node i, for $i = 1, \ldots, N$, $k = 1, \ldots, n$ and $p = 1, \ldots, m$. System (1) can be now formulated for the entire network as follows:

$$
\begin{cases}
\dfrac{d}{dt} f_{iS}^{k}(t) = -\displaystyle\sum_{j=1}^{N} \sum_{l=1}^{n} \sum_{q=2}^{m-1} a_{ij}\, \alpha_i^k\, u_q\, f_{iS}^{k}(t)\, f_{jI}^{q,l}(t), \\
\dfrac{d}{dt} f_{iI}^{p,k}(t) = \displaystyle\sum_{j=1}^{N} \sum_{l=1}^{n} \sum_{q=2}^{m-1} a_{ij}\, \alpha_i^k\, u_p\, f_{iS}^{k}(t)\, f_{jI}^{p,l}(t)\, \delta_{2p} + \beta u_{p-1}\, f_{iI}^{p-1,k}(t) \\
\qquad\qquad + \gamma\, w_k\, f_{iI}^{p+1,k}(t) - \beta\, u_p\, f_{iI}^{p,k}(t) - \gamma\, w_k\, f_{iI}^{p,k}(t), \\
\dfrac{d}{dt} f_{iR}(t) = \gamma \displaystyle\sum_{k=1}^{n} w_k\, f_{iI}^{2,k}(t), \\
\dfrac{d}{dt} f_{iD}(t) = \beta\, u_{m-1} \displaystyle\sum_{k=1}^{n} f_{iI}^{m-1,k}(t),
\end{cases}
\tag{2}
$$

where α_i^k is the contagion rate of individuals with state w_k within node i.

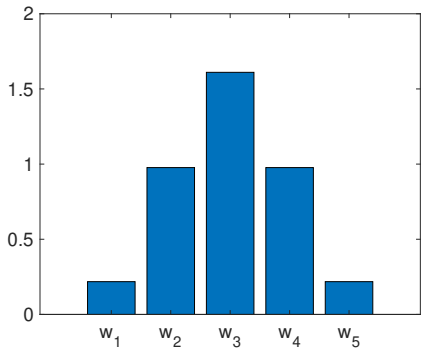
4.10. Within node dynamics

To characterize each node as a distinct metapopulation, we consider 4 classes of nodes which are distinguished in terms of three attributes: size, immune distribution, multiplicity of each class of node:

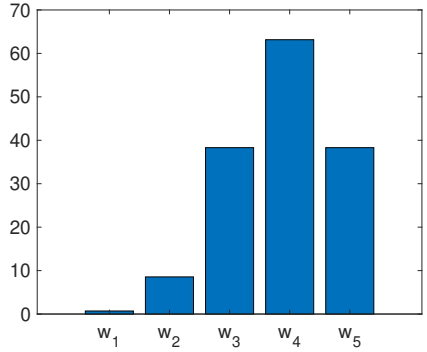
- **Household**
- **School**
- **Hospital/nursing home**
- **Company/working place**

Node type	Size	Immune distribution	Color
Household	5	Centered	Green
School	150	Skewed-right	Blue
Hospital	150	Skewed-left	Red
Company	150	Centered	Black

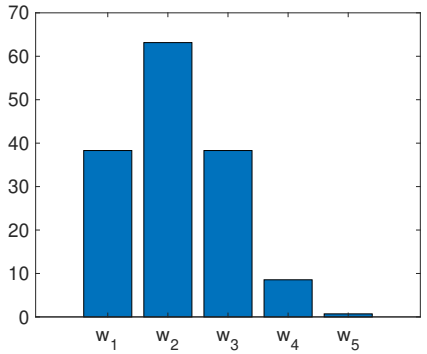
Table – Parametrization of each node type.



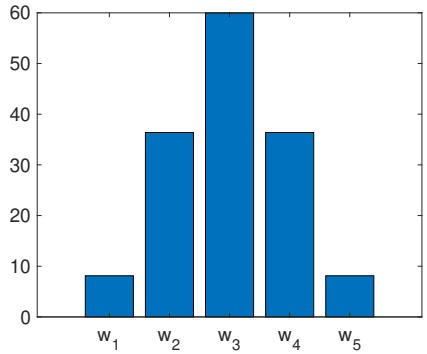
Household



School



Nursing home



Working place

4.11. Network dynamics

Erdös-Rényi random network

A random network consists of N nodes where each node pair is connected with wiring probability p. Each node is statistically equivalent to another. Such a network can be constructed as follows:

Erdös-Rényi random network

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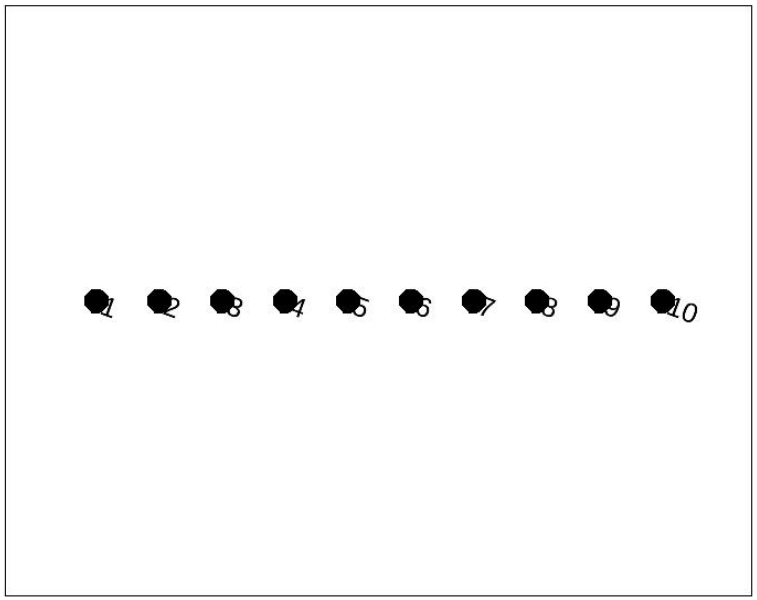
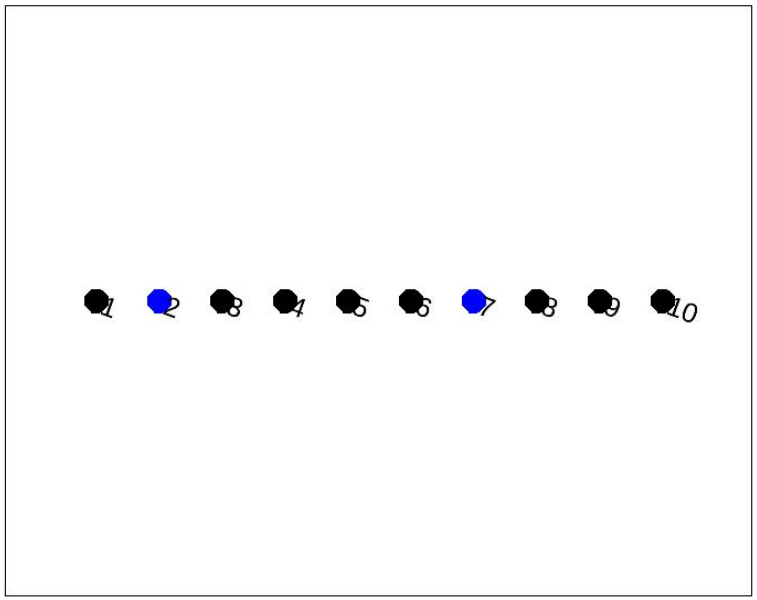
1) Start with N isolated nodes.



Erdös-Rényi random network

A random network consists of N nodes where each node pair is connected with wiring probability p. Each node is statistically equivalent to another. Such a network can be constructed as follows:

2) Select a node pair and generate a random number between 0 and 1. If the number exceeds p, connect the selected node pair with a link, otherwise leave them disconnected.



Erdös-Rényi random network

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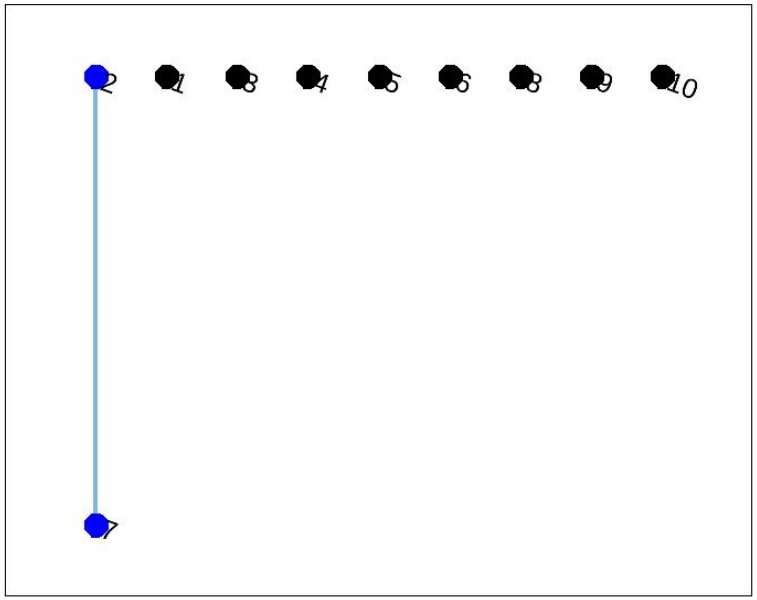
3) Repeat the previous step for each of the $N(N-1)/2$ pairs of nodes.



Erdös-Rényi random network

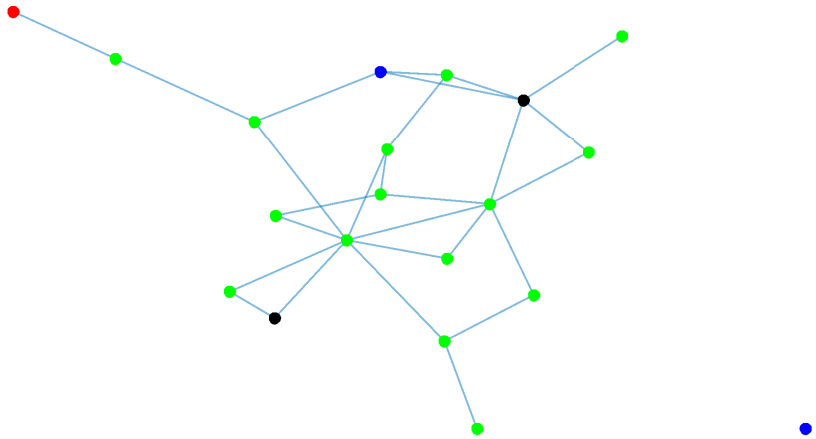


Figure – Random network with $N = 20$ and $p = 0.15$. The color node code is: green = household; blue = school; red = hospital; black = company.

Erdös-Rényi random network

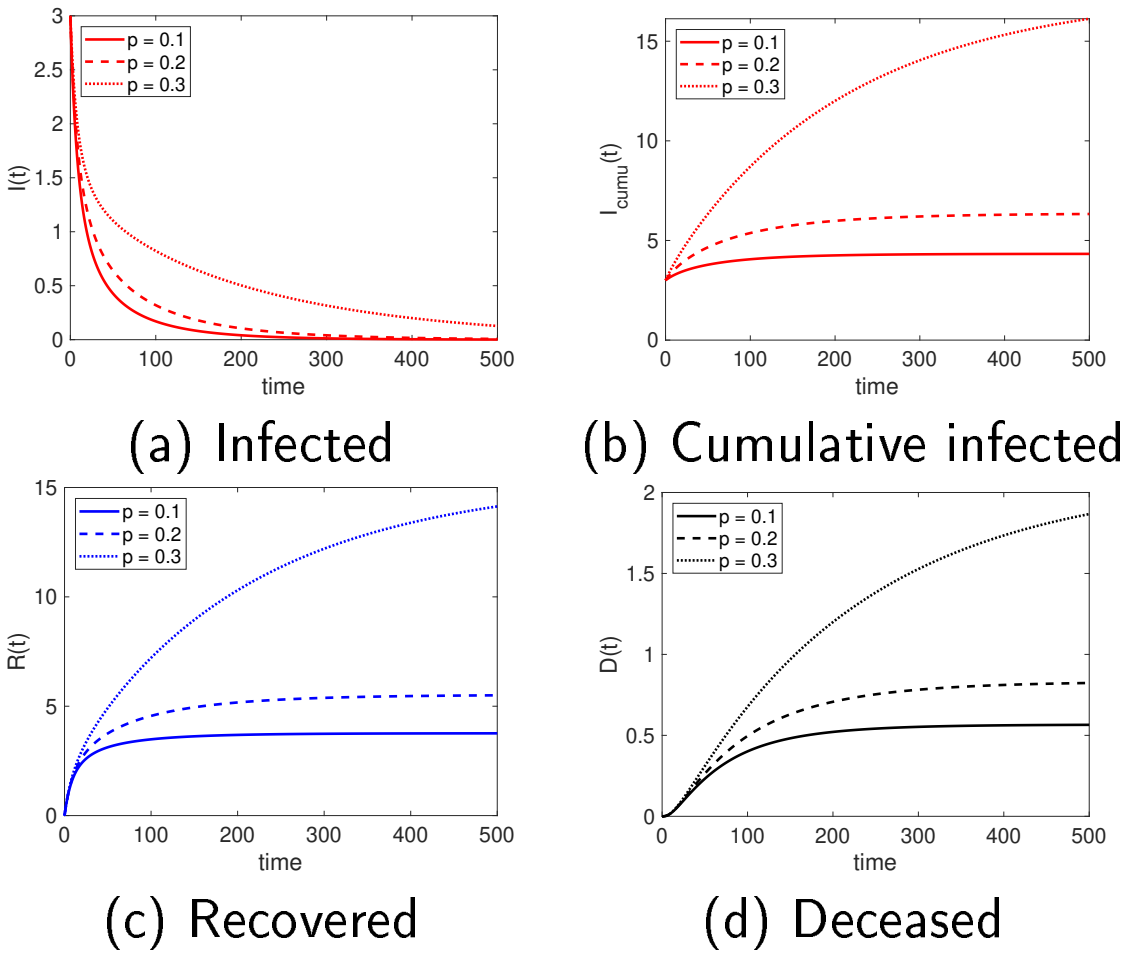


Figure – **Random network with $N = 200$ and $p = 0.1, 0.2, 0.3$, with 195 households, 2 schools, 1 hospital and 2 companies. The total population is 1725 with 5 initial infected individuals. Parameter values are $\alpha_i^k = 0.4$, $\beta = 0.1$ and $\gamma = 0.2$. Curves represent (a) prevalence $I(t)$, (b) cumulative infected $I_{cumu}(t)$, (c) recovered $R(t)$ and (d) deceased $D(t)$.**

Watts-Strogatz small world graph

A small world network with N nodes is constructed in the following way:

1. Create a ring lattice with N nodes of mean degree $2K$. Each node is connected to its K nearest neighbours.
2. For each edge in the graph, with independent and uniform probability $\tilde{p}$, that edge is removed and replaced by a new edge between two nodes that are chosen uniformly at random from the N nodes, without duplicating or self-looping edges.

When $\tilde{p} = 0$, a ring graph in which each node is coupled to its K nearest neighbours is obtained. On the other hand, when $\tilde{p} = 1$, the result is a random graph.

(a) $\tilde{p} = 0$ (b) $\tilde{p} = 0.1$

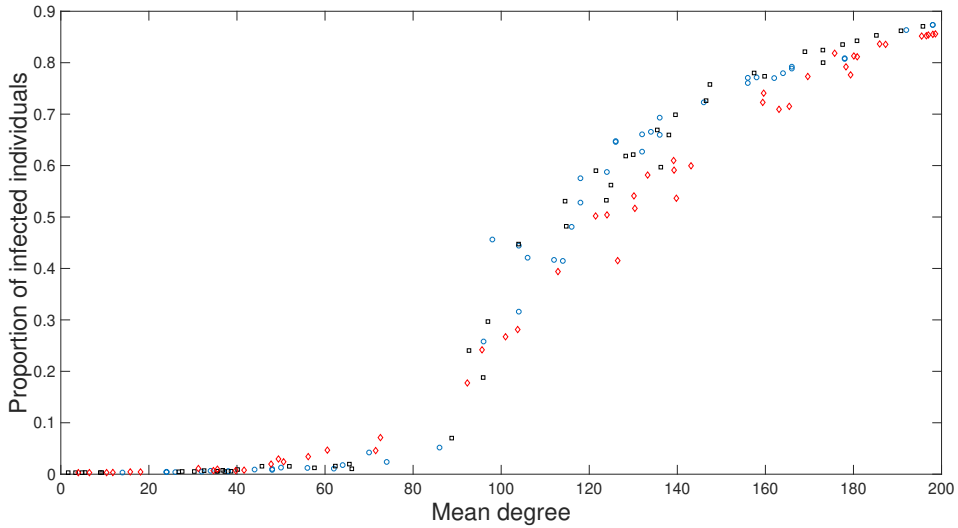
Figure – **Watts-Strogatz small world network with $N = 20$, $K = 2$ (the mean degree is thus 4) and wiring probabilities (a) $\tilde{p} = 0$ and (b) $\tilde{p} = 0.1$. The color node code is: green = household; blue = school; red = hospital; black = company.**

Comparing network structures

We now compare different network structures and we do not observe any systematic difference in the overall dynamics, as far as the three graphs are parametrized in "comparable" way.
For each kind of graph, we compute

- Mean degree
- Mean closeness
- Mean betweenness

Figure – ER (blue circles), WS (black squares), scale-free (red diamonds).



(a) Final epidemic size vs mean degree

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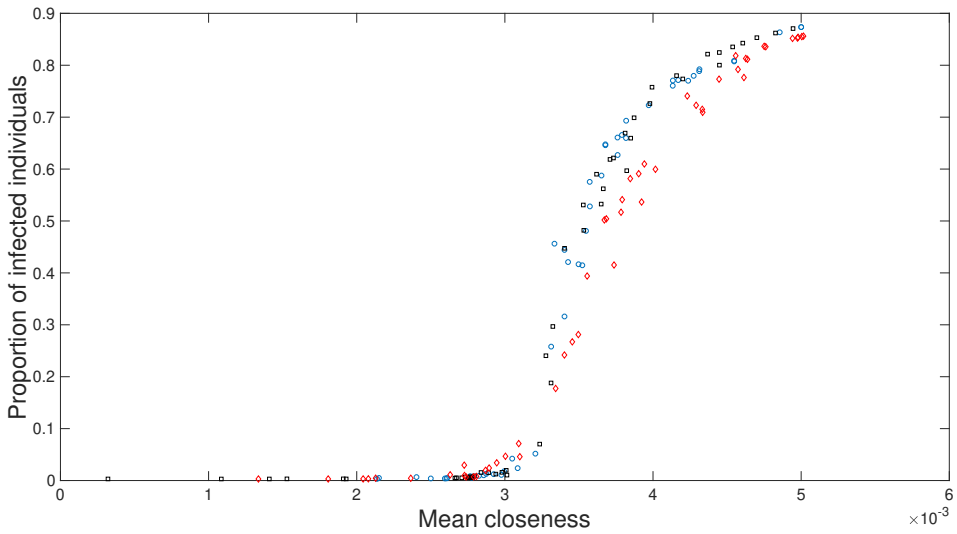

(b) Final epidemic size vs mean closeness

Comparing network structures

We now compare different network structures and we do not observe any systematic difference in the overall dynamics, as far as the three graphs are parametrized in "comparable" way.
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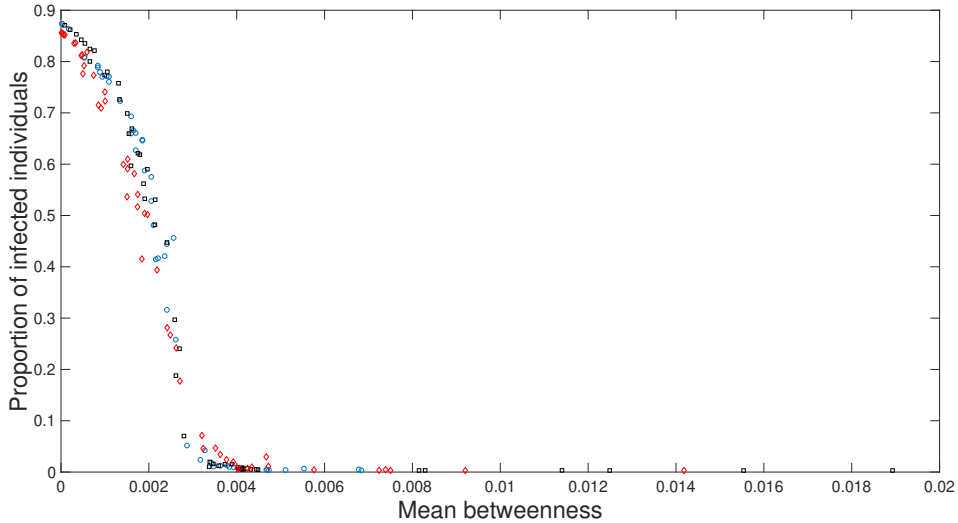


(c) Final epidemic size vs mean betweenness

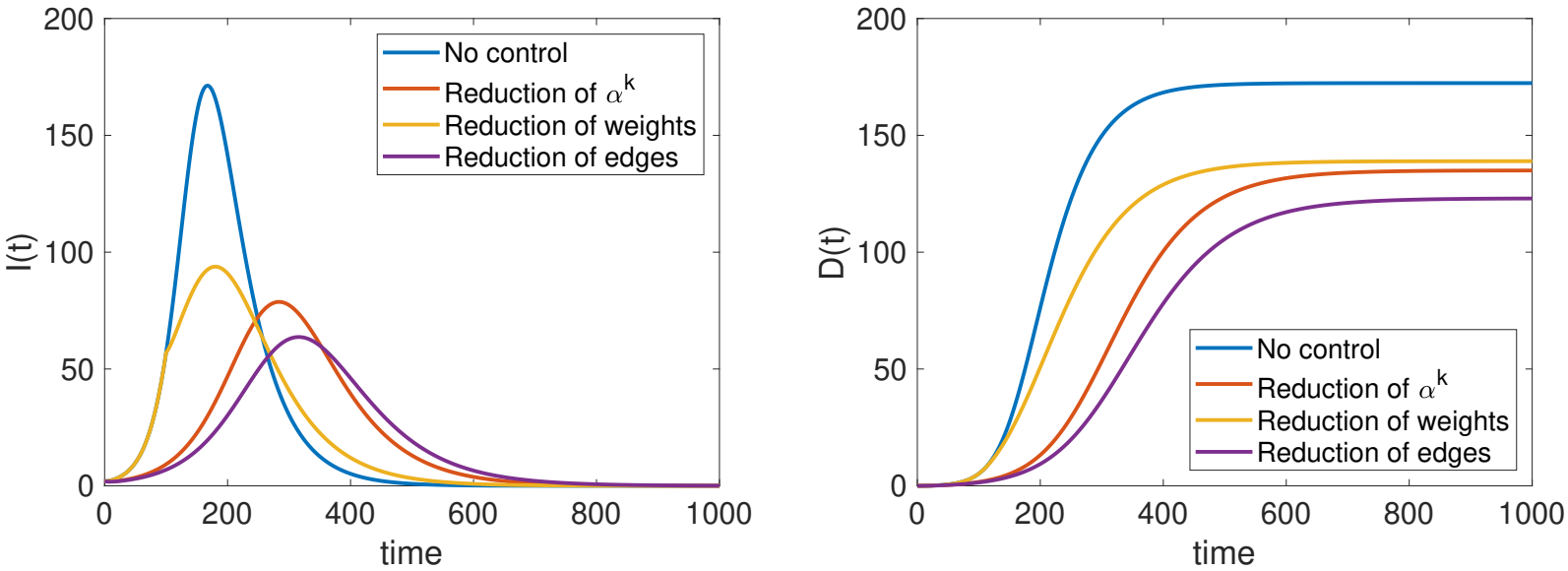
Social distancing measures

We now compare three alternative scenarios under a common random graph. At time $t = 100$ the lockdown might consist in:

a. reducing social interactions within each node via the parameter α_i^k;

b. reducing the diffusion across nodes via weights in the adjacency matrix;

c. reducing the number of edges that connect nodes.



(a) Infected (b) Deceased

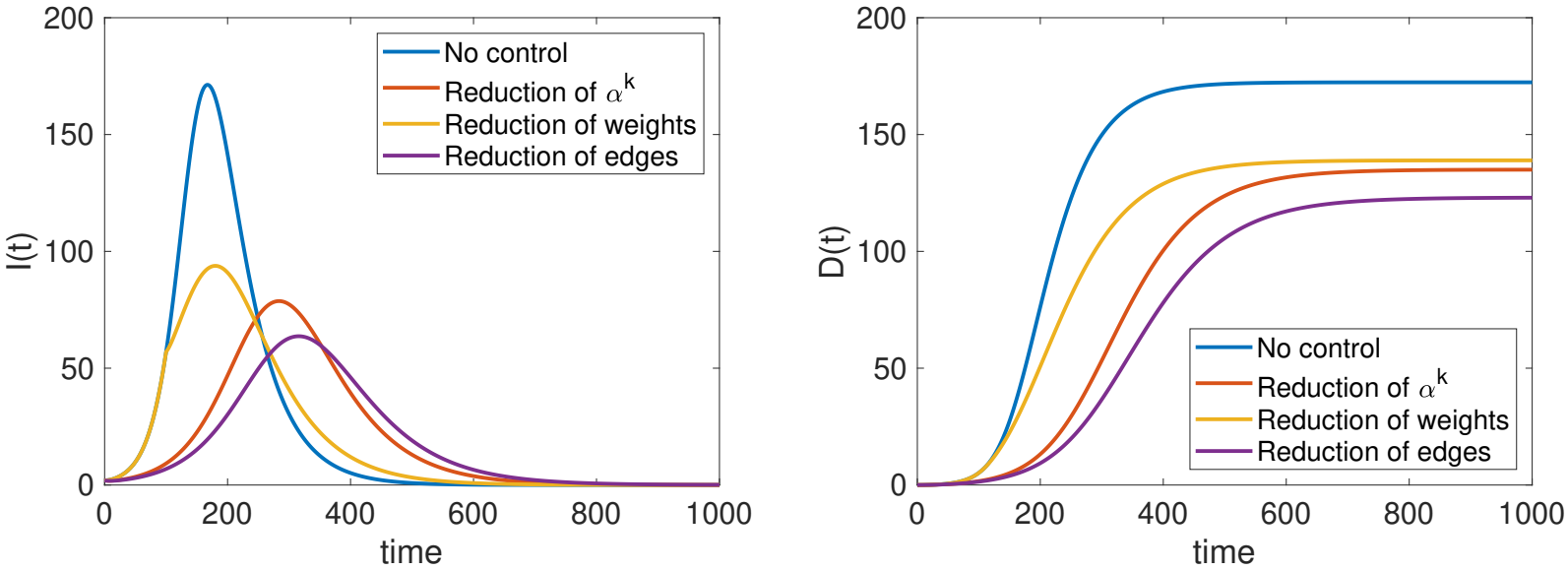
Figure – **(a) Infected and (b) deceased cases in a weighted Erdos-Renyi random network with $N = 200$ and $p = 0.9$. At time $T_{lock} = 100$, assuming a 25% reduction for each considered scenarios: social interactions α_i^k (red), edges weights (yellow) and the total number of edges randomly reduced (purple). The scenario with no reduction is shown in blue.**

Social distancing measures: protecting the vulnerable

We introduce a set-up in which we compare:

a. reduction of social interactions for the vulnerable segment of the population, denoted by α_i^1;

b. reducing weights of edges connecting to hospitals.



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4.17. Social distancing and vaccination

Immunization of the population

According to our model, virus transmission does not only depend on the number and structure of contacts, as the super-spreader strategy would entail, but also on the biological evolution of the virus. The within-host dynamics is equally if not more important than the structure of contacts in determining the transmission: most vulnerable individuals not only have higher chances to get infected but also of die out of the infection. Additionally, this fraction is not only more vulnerable but also more contagious because of high viral loads concentrating in elderly residency and hospitals.
In order to test the effectiveness of targeted vaccination toward the most vulnerable segment of the population, we define an experiment according to which:

- We employ the ER random network with $N = 200$ and $p = 0.9$ as a sample graph.
- Each realization of the experiment consists in choosing randomly a proportion of the total nodes, and within the chosen nodes we "vaccinate the vulnerable individuals". We model the effect of vaccination "moving" those individuals with states w_1 and w_2 to the highest level w_n.

Immunization of the population

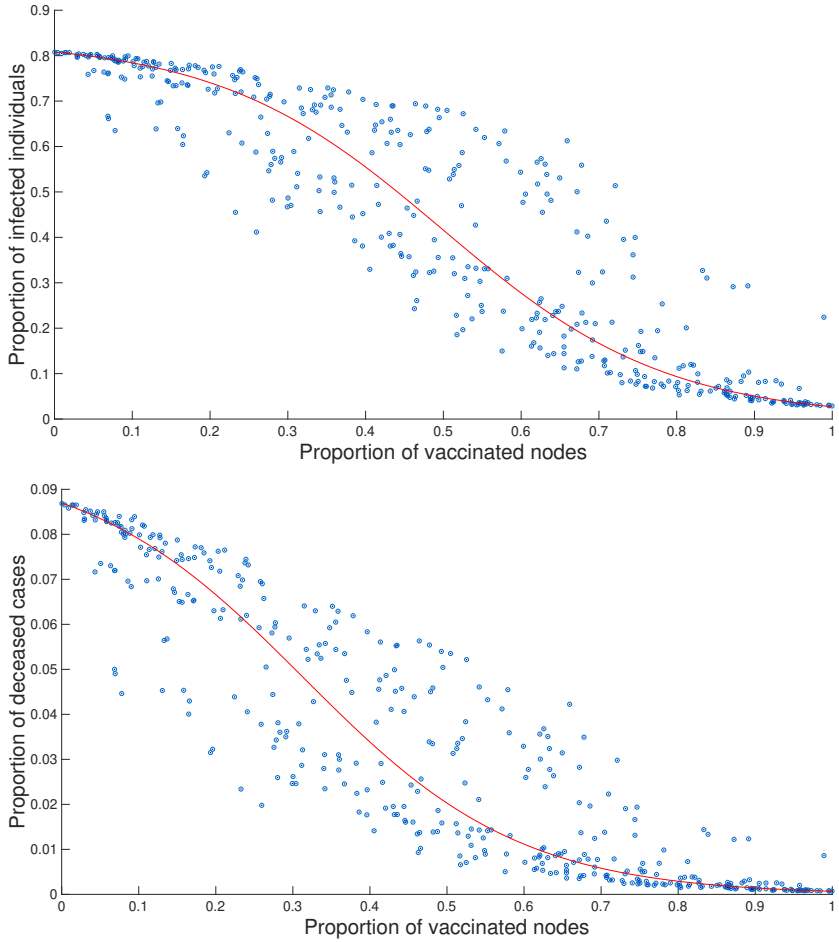


Figure – **(a) Final epidemic size and (b) cumulative deceased cases vs. fraction of vaccinated nodes for 200 realizations of the experiment. Spearman correlation coefficient of -0.9 in both cases. Blue markers represent the output of each realization, and the red curve is a sigmoidal LSQ robust filter.**

4.19. Summary

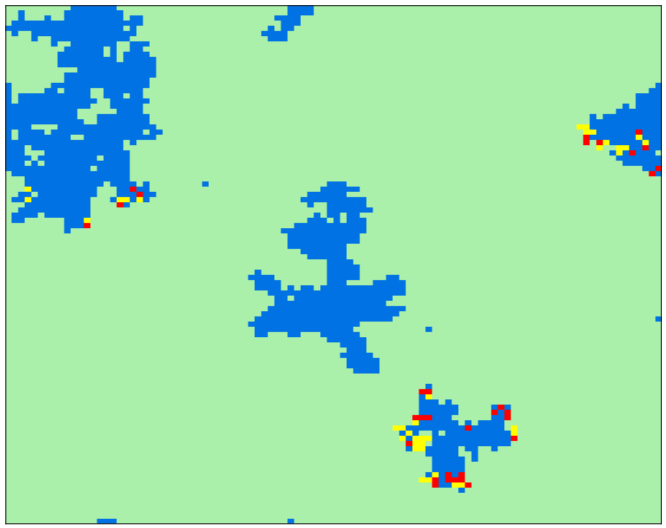
- We have seen a model able to study the impact of different lockdown policies and vaccination strategies, using a multiscale approach and considering heterogeneous interactions through network structures
- While the multiscale approach allows to tackle both the within- and between-host dynamics, modelling the problem of virus propagation as a competition process between immunity and the virus itself, contacts among individuals are structured within nodes via a constant probability, and across nodes via network dynamics.
- We characterize four alternative nodes in terms of their size and immunity distributions, namely households, companies, schools and hospitals/nursing homes. Methodologically, our model can be seen as a metapopulation multiscale model able to couple biological and social dynamics.

4.20. Summary

- Simulation results show that protecting the vulnerable hub would influence significantly the reduction of deaths, whereas reduction of contacts toward the most heterogeneous hubs would not affect the number of decease cases as much, but rather influencing on disease transmission. Clearly, controlling the diffusion of the virus *inside* nodes is very important and effective in containing the epidemics.
- The within-host dynamics allows to implement vaccine administration and to evaluate the impact of different strategies, which we are able to study acting on the immunity distribution of individuals.
- We show that protecting the most vulnerable segment of the population is very effective in reducing deaths and eventually transmission.
- There are many open research perspectives in this direction, considering epidemiological, behavioral and economic aspects of epidemic spreading.

4.21. Closure

Human mobility has a significant effect on the spreading of infectious diseases, speed and cluster formation. Its understanding has become assertive to monitor, control and prevent epidemic spreading.



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1. From https://www.technologynetworks.com/immunology/articles/epidemic-vs-pandemic-323471