Analysis of the spread of tuberculosis in heterogeneous complex metapopulations

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Abstract

This paper describes and analyzes the spatial spread of tuberculosis (TB) on complex metapopulation, that is, networks of populations connected by migratory flows whose configurations are described in terms of connectivity distribution of nodes (patches) and the conditional probabilities of connections among classes of nodes sharing the same degree. The migration and transmission processes occur simultaneously. For uncorrelated networks under the assumption of standard incidence transmission, we compute the disease-free equilibrium and the basic reproduction number, and show that the disease-free equilibrium is locally asymptotically stable. Moreover, for uncorrelated networks and under assumption of simple mass action transmission, we give a necessary and sufficient conditions for the instability of the disease-free equilibrium. The existence of endemic equilibria is also discussed. Finally, the prevalence of the TB infection across the metapopulation as a function of the path connectivity is studied using numerical simulations.

Keywords: Tuberculosis, metapopulation, uncorrelated networks, basic reproduction number, stability.

AMS Classification: 34A34, 34D23, 34D40, 92D30
1 Introduction

Despite significant advances in medical science, infectious diseases continue to impact human populations in many parts of the world. Tuberculosis (abbreviated as TB for tubercle bacillus) is a common deadly infectious disease caused mainly by *Mycobacterium tuberculosis*. It basically attacks the lungs (pulmonary TB), but can also affect the central nervous system, circulatory system, the genital-urinary system, bones, joints and even the skin. Tuberculosis can spread through cough, sneeze, speak, kiss or spit from active pulmonary TB persons. It can also spread through use of an infected person’s unsterilized eating utensils and in rare cases a pregnant woman with active TB can infect her foetus (vertical transmission) [1,2]. Transmission can only occur from people with active TB but not latent TB. This transmission from one person to another depends upon the number of infectious droplets expelled by a carrier, the effectiveness of ventilation, duration of the exposure and virulence of the MTB strain. The chain of transmission can therefore be broken by isolating patients with active disease and starting effective anti-tuberculosis therapy [1-5]. At present, about 95% of the estimated 8 million new cases of TB occurring each year are in developing countries, where 80% occur among people between the ages of 15-59 years [1]. In sub-Saharan Africa, TB is the leading cause of mortality and in developing countries, it accounts for an estimated 2 million deaths which accounts for a quarter of avoidable adult deaths [1]. It is known that factors such as endogenous reactivation, emergence of multi-drug resistant TB, and increase in HIV incidence in the recent years call for improved control strategies for TB. A full understanding of the effectiveness of treatment and control strategies within different regions of the world is still needed. It is worth emphasizing that mathematical analysis of biomedical and disease transmission models can contribute to the understanding of the mechanisms of those processes and to design potential therapies (see [6-9] and references therein). A number of theoretical studies have been carried out on the mathematical modeling of TB transmission dynamics [3-9,38,39].

However, the analysis of the spread of infectious diseases on complex networks has become a central issue in modern epidemiology [10] and, indeed, it was one of the main motivations for the development of percolation theory [11]. While the initial approach was focussed on local contact networks [12-16], that is, social networks within single populations (cities, urban areas), a new approach has been recently introduced for dealing with the spread of diseases in ensembles of (local) populations with a complex spatial arrangement and connected by the migrations. Such sets of connected populations living in a patchy environment are called metapopulations in ecology, and their study began in 1967 with the theory of island biogeography [17].

Unfortunately, when considering dispersal models, there is an approach based on the metapopulation concept. The population is subdivided into a number of discrete patches which are supposed to be well mixed. Then, in each patch the population is subdivided into compartments corresponding to different epidemic status. This leads to a multi-patch, multi-compartment system. At this point two formulations
are possible.

The first one assumes that an infective in one patch can infect susceptible individuals in another patch. This assumption gives rise to a family of models which have been well studied [18,19]. This formulation assumes that there is a spatial coupling between patches, but that individuals (vectors or hosts) do not migrate between patches. They make short ‘visits’ from their home patches to other patches.

The second one considers migration of individuals between patches. The infection does not take place during the migration process. The situation is that of a directed graph, where the vertices represent the patches and the arcs represent the links between patches. Recently, there has been increased interest in these deterministic metapopulation disease models. For instance, in some recent models of epidemic spreading, the location of the patches in space is treated explicitly (without taking into account the number of connections $k$ (degree) that any given patch in the network may have) thanks to the increasing of computational power (see for instance [20, 21]). In Refs. [16, 22, 23], however, an alternative approach based on the formalism used in the statistical mechanics of complex networks is presented. Under this approach, the structure of the spatial network of patches (nodes) is encapsulated by means of the connectivity (degree) distribution $p(k)$ defined as the probability that a randomly chosen patch has connectivity $k$. In contrast, in [24, 25], the authors consider reaction diffusion processes to take place simultaneously, which turns out to be correct assumption for a suitable continuous-time formulation of metapopulation models for the spread of infectious diseases.

In this paper, we consider the spread of TB on complex metapopulations, that is, networks of populations connected by migratory flows whose configurations are described in terms of the conditional probabilities of connections among classes of nodes sharing the same degree. For uncorrelated networks under the assumption of standard incidence [37] (or frequency-dependent) transmission, we compute the disease-free equilibrium and the basic reproduction number and show that the disease-free equilibrium is locally asymptotically stable. Moreover, for uncorrelated networks and under assumption of simple mass action [37] (or density-dependent) transmission, we give a necessary and sufficient conditions for the instability of the disease-free equilibrium. We find that there exists a more precise bound of the largest eigenvalue of the Jacobian matrix of the system around the disease-free equilibrium. This condition says that, for fixed values of the migration rates of latently-infected and infectious individuals, a high enough density of individuals and/or large enough maximum connectivity in the metapopulation guarantee the instability of the disease-free equilibrium and, hence, TB spread. In the limit of infinite networks with bounded average degree, this condition implies the existence of a TB threshold for any distribution with large value. The existence of endemic equilibria is also discussed. Additionally, through numerical simulations, the forecasted prevalence of the infection is not constant but increases with the patch connectivity. Interestingly, close the epidemic threshold, there are always patches with low connectivities where TB is not able to progress unless infectious individuals
arrive from (crowded) patches with higher connectivities. Comparing to existing results in the literature, our work treats a specific disease which is not the case in Refs. [24, 25, 26]. We point out that in Refs. [24, 25, 26], the authors have neglected some important epidemiological features of the propagation of a disease such as births, natural mortality, mortality due to the disease, natural recovery and the basic models studied are of dimension 2 which are very simple. In addition, the authors have supposed that the total population is constant which is not always the case. Our basic model is of dimension 4 and incorporates the essential biological and epidemiological features of TB such as birth, mortality due to the disease, slow and fast progression, effective chemoprophylaxis of latently-infected individuals, natural recovery and treatment of infectious, relapse from the disease and re-infection after recovery. Also in our model, the total population is not constant. It is our view fact that this study represents the first work that provides an in-depth the spread of TB on complex metapopulation using a degree of distribution and conditional probabilities.

2 A TB metapopulation model

2.1 The model

We consider the spread of TB in heterogeneous metapopulations. The model consists of $n$ patches representing $n$ different degree of connectivities. We assume that the architecture of the network of patches (nodes) where local populations live is mathematically encoded by means of the connectivity (degree) distribution $p(k)$, defined as the probability that a randomly chosen patch has degree $k$. At any given time, in each patch, an individual is in one of the following states: susceptible, latently infected (exposed to TB but not infectious), infectious (has active TB) and recovered. These states are average number (density) of $\rho_{S,k}$, $\rho_{E,k}$, $\rho_{I,k}$ and $\rho_{R,k}$ in the patches of connectivity $k$, respectively. The total variable population size at time $t$ is given by,

$$\rho_k(t) = \rho_{S,k}(t) + \rho_{E,k}(t) + \rho_{I,k}(t) + \rho_{R,k}(t).$$

It is assumed that births are recruited into the population at per capita rate $\Lambda$. The transmission of Mycobacterium tuberculosis occurs following adequate contacts between a susceptible and infectious in each sub-population. The rate at which susceptible are infected is $\beta \frac{\rho_{I,k} \rho_{S,k}}{\rho_k}$ for standard incidence (or frequency-dependent) transmission and $\beta \rho_{I,k} \rho_{S,k}$ for simple mass action (or density-dependent) transmission, where $\beta$ is the effective contact rate of infectious that is sufficient to transmit infection to susceptible (it also denotes how contagious of the disease is). On adequate contacts with active individuals, a susceptible individual becomes infected but not yet infectious. A fraction $q$ of newly infected individuals is assumed to undergo a fast progression directly to the infectious class, while the remainder is latently infected and enter the latent class. Latently infected individuals are assumed to acquire some immunity as a result of the infection, which reduces the risk of subsequent infection but does not fully prevent it. We assume that chemoprophylaxis
of latently infected individuals reduces their reactivation at a rate \( \theta \) and that the initiation of therapeutics immediately remove individuals from active status and place them into a latent state. This last assumption is realistic. Indeed, the classic works of Jindani et al. [40] showed that a bactericidal treatment reduced the number of bacilli 20 times during the first two days and about 200 times during the 12 days. After two weeks of treatment, the sputum of a patient contain on average 1000 times less bacilli before treatment, a number generally too low to be detected on direct examination. Latently infected individuals who received successful chemoprophylaxis can recover at a constant rate \( \eta \). Successful chemoprophylaxis can have a partial immunity. Hence, they can relapse from the disease with a rate \( (1-\xi)\beta \frac{D_{I,k}}{\rho_k} \) and enter class \( E \). The rate for non-disease related death is \( \mu \), thus, \( 1/\mu \) is the average lifetime. Infectious have addition death rate due to disease with a rate \( d \).

This model description is summarized in the flow diagram given below.

According to the derivation in [24, 25] of the continuous-time formulation for the progress of diseases on metapopulations and assuming non-limited or frequency-dependent transmission, the equations governing the dynamics of TB propagation are

\[
\begin{align*}
\dot{S}_{k} &= \Lambda - \beta \frac{\rho_{I,k}\rho_{S,k}}{\rho_k} - \mu S_{k} - D_{S} \rho_{S,k} + kD_{S} \sum_{k'} P(k'|k) \frac{\rho_{S,k'}}{k'}, \\
\dot{E}_{k} &= \beta (1-q) \frac{\rho_{I,k}\rho_{S,k}}{\rho_k} + \beta (1-\xi) \frac{\rho_{I,k}\rho_{R,k}}{\rho_k} + \gamma \rho_{I,k} - (\mu + \eta + \alpha(1-\theta)) \rho_{E,k} \\
&\quad - D_{E} \rho_{E,k} + kD_{E} \sum_{k'} P(k'|k) \frac{\rho_{E,k'}}{k'}, \\
\dot{I}_{k} &= \beta q \frac{\rho_{I,k}\rho_{S,k}}{\rho_k} + \alpha(1-\theta) \rho_{E,k} - (\mu + d + \gamma + \delta) \rho_{I,k} + \xi \rho_{R,k} \\
&\quad - D_{I} \rho_{I,k} + kD_{I} \sum_{k'} P(k'|k) \frac{\rho_{I,k'}}{k'}, \\
\dot{R}_{k} &= -\beta (1-\xi) \frac{\rho_{E,k}\rho_{R,k}}{\rho_k} + \eta \rho_{E,k} + \delta \rho_{I,k} - (\mu + \xi) \rho_{R,k} - D_{R} \rho_{R,k} + kD_{R} \sum_{k'} P(k'|k) \frac{\rho_{R,k'}}{k'}, \\
\end{align*}
\]

(2)

where \( k \) is the degree of the patches where local population live (\( k = k_{1}, \ldots, k_{\text{max}} \)), and \( P(k'|k) \) is the conditional probability that a patch of degree \( k \) has a connection to a patch of degree \( k' \). As in classical reaction-diffusion processes, Eq. (2) expresses the time variation of susceptible, latently infected individuals, recovered individuals and infections as the sum of two independent contributions: reaction and diffusion. In particular, the diffusion term includes the outflow of individuals (diffusing particles) from patches of degree
and the inflow of migratory individuals from the nearest patches of degree $k'$. For the sake of brevity, in the sequel we consider strictly positive diffusion rates $(D_s, D_E, D_I, D_R > 0)$.

For limited or frequency-dependent transmission model, we simple replace in Eq. (2) the transmission term $\beta \frac{p_{l,k} \rho_{S,k}}{\rho_k}$ by $\beta \rho_{l,k} \rho_{S,k}$.

2.2 Positively-invariant set

Notice that, since births and deaths are considered in model (2), the total number of individuals is not constant at the metapopulation level. More precisely, multiplying equations in system (2) by $p(k)$, and summing over all $k$, we have the following differential equations for $\rho_S, \rho_E, \rho_I$ and $\rho_R$, the average number of susceptible, latently infected, infectious and recovered individuals per path at time $t$, respectively,

\[
\dot{\rho}_S = \Lambda - \beta \sum_k p(k) \frac{p_{l,k} \rho_{S,k}}{\rho_k} - \mu \rho_S - D_S \rho_S + D_S \sum_k k p(k) P(k|k') \frac{\rho_{S,k'}}{k'},
\]

\[
\dot{\rho}_E = \beta (1-q) \sum_k p(k) \frac{p_{l,k} \rho_{S,k}}{\rho_k} + \beta (1-\xi) \sum_k p(k) \frac{p_{l,k} \rho_{R,k}}{\rho_k} + \gamma \rho_I - [\mu + \eta + \alpha(1-\theta)] \rho_E
\]

\[-D_E \rho_E + D_E \sum_k k p(k) P(k'|k) \frac{\rho_{E,k'}}{k'},\]

\[
\dot{\rho}_I = \beta q \sum_k p(k) \frac{p_{l,k} \rho_{S,k}}{\rho_k} + \alpha (1-\theta) \rho_E - (\mu + d + \gamma + \delta) \rho_I
\]

\[+ -D_I \rho_I + D_I \sum_k k p(k) P(k'|k) \frac{\rho_{I,k'}}{k'} + \xi \rho_R,
\]

\[
\dot{\rho}_R = -\beta (1-\xi) \sum_k p(k) \frac{p_{l,k} \rho_{R,k}}{\rho_k} + \eta \rho_E + \delta \rho_I - (\mu + \xi) \rho_R
\]

\[-D_R \rho_R + D_R \sum_k k p(k) P(k'|k) \frac{\rho_{R,k'}}{k'},\]

where $\rho_j(t) = \sum_k p(k) \rho_{j,k}, j = S, E, I, R$. Now, since the number of links emanating from nodes of degree $k$ to nodes of degree $k'$ must be equal to the number of links emanating from nodes of degree $k'$ to nodes of degree $k$ in non-directed graphs, we have the following relationship between $p(k)$ and $P(k'|k)$ [27]:

\[k P(k'|k) p(k) = k' P(k|k') p(k').\]  

Using this restriction and the fact that $\sum_k P(k|k') = 1$ after changing the order of summations, Eq. (3)
becomes
\[
\begin{align*}
\dot{\rho}_S &= \Lambda - \beta \sum_k p(k) \frac{\rho_{I,k} \rho_{S,k}}{\rho_k} - \mu \rho_S, \\
\dot{\rho}_E &= \beta (1-q) \sum_k p(k) \frac{\rho_{I,k} \rho_{S,k}}{\rho_k} + \beta (1-\xi) \sum_k p(k) \frac{\rho_{I,k} \rho_{R,k}}{\rho_k} + \gamma \rho_I - [\mu + \eta + \alpha (1-\theta)] \rho_E, \\
\dot{\rho}_I &= \beta q \sum_k p(k) \frac{\rho_{I,k} \rho_{S,k}}{\rho_k} + \alpha (1-\theta) \rho_E - (\mu + d + \gamma + \delta) \rho_I + \xi \rho_R, \\
\dot{\rho}_R &= -\beta (1-\xi) \sum_k p(k) \frac{\rho_{I,k} \rho_{R,k}}{\rho_k} + \eta \rho_E + \delta \rho_I - (\mu + \xi) \rho_R.
\end{align*}
\] (5)

Adding the expressions in the right-hand side of the equations in system (5) yields
\[
\frac{d\rho}{dt} = \Lambda - \mu \rho - d \rho_I.
\] (6)

From the above equation, one can deduce that \( \frac{d\rho}{dt} \leq \Lambda - \mu \rho \). Thus, \( \frac{d\rho}{dt} < 0 \) if \( \rho > \frac{\Lambda}{\mu} \). Since \( \frac{d\rho}{dt} \leq \Lambda - \mu \rho \), it can be shown that using a standard comparison theorem [28], that
\[
\rho(t) \leq \rho(0) e^{-\mu t} + \frac{\Lambda}{\mu} (1 - e^{-\mu t}).
\]

If \( \rho(0) \leq \frac{\Lambda}{\mu} \), then \( \rho(t) \leq \frac{\Lambda}{\mu} \).

Hence, all feasible solutions of components of system (5) enters the region:
\[
\Omega = \left\{ (\rho_S, \rho_E, \rho_I, \rho_R) \in \mathbb{R}_0^4, \rho(t) \leq \frac{\Lambda}{\mu} \right\}.
\] (7)

Thus, it follows from Eq. (7) that all possible solutions of system (5) will enter the region \( \Omega \). Hence, the region \( \Omega \), of biological interest, is positively-invariant under the flow induced by system (5). Further, it can be shown using the theory of permanence [26] that all solutions on the boundary of \( \Omega \) eventually enter the interior of \( \Omega \). Furthermore, in \( \Omega \), the usual existence, uniqueness and continuation results hold for system (5). Hence, system (5) is well posed mathematically and epidemiologically and it is sufficient to consider the dynamics of the flow generated by system (5) in \( \Omega \). The same conclusions on \( \Omega \) hold for the simple mass action (or density-dependent) model.

For networks with a connectivity pattern defined by a set of conditional probabilities \( P(k'|k) \), we define the elements of the connectivity matrix \( C \) as
\[
C_{kk'} = \frac{k}{k'} P(k'|k).
\]

Note that these elements are the average number of individuals that patches of degree \( k \) receive from neighboring patches of degree \( k' \) assuming that one individual leaves each of these patches by choosing at random one of the \( k' \) connections [9]. One should notice that, for those degrees \( k \) that are not present in the network, \( P(k'|k) = 0, \forall k' \). Hereafter in the paper, when talking about degrees, we implicitly mean those degrees that are present in the network. Furthermore, the case with patches having all the same
connectivity is excluded from our considerations because, under the present approach, the model equations reduce to those of a single patch SEIR model.

3 Uncorrelated networks

In order to obtain analytical results about the TB metapopulation dynamics, we need to be precise about the form of $P(k'|k)$. The easiest and usual assumption is to restrict ourselves to uncorrelated networks. In these networks, the degrees of the nodes at the ends of any given link are independent, that is, no degree-degree correlation between the connected nodes. In this case, we have that $P(k'|k) = k'p(k')/\langle k \rangle$ which corresponds to the degree distribution of nodes (patches) that arrive at by following a randomly chosen link [29].

3.1 Analysis of standard incidence (or frequency-dependent) model

After replacing the expression of $P(k'|k)$ into Eq.(2), one obtains the following equations for TB spread in metapopulations described by uncorrelated networks and limited transmission:

$$
\begin{aligned}
\dot{\rho}_{S,k} &= \Lambda - \beta \frac{\rho_{I,k}\rho_{S,k}}{\rho_k} - \mu \rho_{S,k} - D_S \left( \rho_{S,k} - \frac{k}{\langle k \rangle} \rho_S \right), \\
\dot{\rho}_{E,k} &= \beta (1-q) \frac{\rho_{I,k}\rho_{S,k}}{\rho_k} + \beta (1-\xi) \frac{\rho_{I,k}\rho_{R,k}}{\rho_k} + \gamma \rho_{I,k} - [\mu + \eta + \alpha (1-\theta)] \rho_{E,k} - D_E \left( \rho_{E,k} - \frac{k}{\langle k \rangle} \rho_E \right), \\
\dot{\rho}_{I,k} &= \beta q \frac{\rho_{I,k}\rho_{S,k}}{\rho_k} + \alpha (1-\theta) \rho_{E,k} - (\mu + d + \gamma + \delta) \rho_{I,k} - D_I \left( \rho_{I,k} - \frac{k}{\langle k \rangle} \rho_I \right) + \xi \rho_{R,k}, \\
\dot{\rho}_{R,k} &= -\beta (1-\xi) \frac{\rho_{I,k}\rho_{R,k}}{\rho_k} + \eta \rho_{E,k} + \delta \rho_{I,k} - (\mu + \xi) \rho_{R,k} - D_R \left( \rho_{R,k} - \frac{k}{\langle k \rangle} \rho_R \right),
\end{aligned}
$$

where $\langle k \rangle = \sum_k kp(k)$ is the average network degree.

In this form, it becomes clearer that the diffusion term is simply given by the difference between the outflow of susceptible, latently infected, infectious and recovered individuals in patches of connectivity $k$, $D_s\rho_{S,k}$, $D_E\rho_{E,k}$, $D_I\rho_{I,k}$, and $D_R\rho_{R,k}$ and the total inflow of susceptible, latently infected, infectious and recovered individuals across all their $k$ connections, which is $k$ times the average flow of individuals across a connection in the network, $D_S\rho_S/\langle k \rangle$, $D_E\rho_E/\langle k \rangle$, $D_I\rho_I/\langle k \rangle$ and $D_R\rho_R/\langle k \rangle$. Note that this average flow across a connection does not depend on the degree $k$ of the considered patch because we have assumed that the architecture of the metapopulation is described by an uncorrelated network.

In these networks, the elements of the connectivity matrix $C$ are simply

$$
C_{kk'} = \frac{kp(k')}{\langle k \rangle},
$$

Clearly, $C$ is a rank-one matrix and has the vector with components $v_k = k$ as eigenvector of eigenvalue 1. So, if there are $n$ different degrees in the network, then the eigenvalues of this matrix are $\lambda = 0$, with
algebraic multiplicity $n - 1$ and $\lambda = 1$ which is a simple eigenvalue. This fact will be used in the stability of equilibria of the model. To do this, we are going to ‘vectorialize’ system (8), using the following vectors of $\mathbb{R}^n$:

\[
S = (\rho_{S,k_1}, \rho_{S,k_2}, \ldots, \rho_{S,k_n})^T, \quad E = (\rho_{E,k_1}, \rho_{E,k_2}, \ldots, \rho_{E,k_n})^T, \quad I = (\rho_{I,k_1}, \rho_{I,k_2}, \ldots, \rho_{I,k_n})^T,
\]

\[
R = (\rho_{R,k_1}, \rho_{R,k_2}, \ldots, \rho_{R,k_n})^T, \quad N = (\rho_{k_1}, \rho_{k_2}, \ldots, \rho_{k_n})^T \quad \text{and} \quad I = (1, 1, \ldots, 1)^T.
\]

If $X \in \mathbb{R}^n$ is a vector, we denote by $\text{diag}(X)$ the $n \times n$ matrix whose diagonal is given by the components of $X$. With these notations and conventions, system (8) becomes

\[
\begin{align*}
\dot{S} &= \Lambda I - \beta \text{diag}(N)^{-1} \text{diag}(I) S - (\mu + D_S) S + D_S CS, \\
\dot{E} &= \beta (1 - q) \text{diag}(N)^{-1} \text{diag}(I) S + \beta (1 - \xi) \text{diag}(N)^{-1} \text{diag}(I) R \\
&\quad + \gamma I - [\mu + \eta + \alpha (1 - \theta) + D_E] E + D_E CE, \\
\dot{I} &= \beta q \text{diag}(N)^{-1} \text{diag}(I) S + \alpha (1 - \theta) E - (\mu + d + \gamma + \delta + D_I) I + D_I C I + \xi R, \\
\dot{R} &= -\beta (1 - \xi) \text{diag}(N)^{-1} \text{diag}(I) R + \eta E + \delta I - (\mu + \xi + D_R) R + D_R C R,
\end{align*}
\]

where $C$ is the connectivity matrix defined as in Eq. (9).

We point out that in the case where the parameters $\beta$, $q$, $\gamma$, $\mu$, $\delta$, $\theta$, $\alpha$, $\xi$, $\eta$ and $d$ are not the same for all patches, they are replaced in system (10) by diagonal non-negative matrices and this does not change the fundamental structure of the system.

### 3.1.1 Disease-free equilibrium (DFE) for generic networks

The disease-free equilibrium of model system (2) are the solutions $\rho_{S,k}^0$, $\rho_{E,k}^0$ and $\rho_{I,k}^0$ to the equations:

\[
\begin{align*}
\Lambda - \beta \frac{\rho_{I,k}^0 \rho_{S,k}^0}{\rho_{k}^0} - \mu \rho_{S,k}^0 - D_S \rho_{S,k}^0 + k D_S \sum_{k'} P(k'|k) \frac{\rho_{S,k'}^0}{k'} &= 0, \\
\beta (1 - q) \frac{\rho_{I,k}^0 \rho_{S,k}^0}{\rho_{k}^0} + \beta (1 - \xi) \rho_{I,k}^0 \rho_{I,k}^0 \rho_{k}^0 + \gamma \rho_{I,k}^0 - [\mu + \eta + \alpha (1 - \theta)] \rho_{E,k}^0 &= 0, \\
-D_E \rho_{E,k}^0 + k D_E \sum_{k'} P(k'|k) \frac{\rho_{E,k'}^0}{k'} &= 0, \\
\beta q \frac{\rho_{I,k}^0 \rho_{E,k}^0}{\rho_{k}^0} + (\mu + d + \gamma + \delta) \rho_{I,k}^0 - D_I \rho_{I,k}^0 + k D_I \sum_{k'} P(k'|k) \frac{\rho_{S,k'}^0}{k'} + \xi \rho_{R,k}^0 &= 0, \\
\rho_{I,k}^0 \rho_{E,k}^0 \rho_{R,k}^0 + \eta \rho_{E,k}^0 + \delta \rho_{I,k}^0 - (\mu + \xi) \rho_{R,k}^0 - D_R \rho_{R,k}^0 + k D_R \sum_{k'} P(k'|k) \frac{\rho_{R,k'}^0}{k'} &= 0.
\end{align*}
\]

For the analysis of the infection’s spread, the so-called disease-free equilibrium is particularly relevant. By definition, this is obtained by replacing $\rho_{I,k}^0 = 0$ in Eq.(2), leading to an explicit expression for the number of susceptible individuals in patches with degree $k$ that can be written as

\[(\mu + D_S) \rho_{S,k}^0 = \Lambda + D_S \sum_{k'} C_{kk'} \rho_{S,k'}^0.\]
As $\sum_{k'} P(k'|k) = 1$, it follows that, for any generic network, one has

$$\rho^0_{S,k} = \frac{1}{\mu + D_S} \left( \Lambda + D_S \frac{k}{\langle k \rangle} \rho^0_S \right).$$

Note that Eq. (6) at the disease-free equilibrium yields

$$\rho^0 = \rho^0_S = \frac{\Lambda}{\mu}.$$ 

Then, the disease-free equilibrium is given by

$$\rho^0_{S,k} = \frac{\Lambda}{\mu + D_S} \left( 1 + \frac{D_S}{\mu} \frac{k}{\langle k \rangle} \right), \quad \rho^0_{E,k} = \rho^0_{I,k} = \rho^0_{R,k} = 0, \quad \forall k.$$ 

Equation (12) is also the disease free equilibrium for the simple mass action transmission model.

3.1.2 Basic reproduction number and local stability of (DFE)

The global behavior for this model crucially depends on the basic reproduction number, that is, the average number of secondary cases produced by a single infective individual which is introduced into an entirely susceptible population. System (8) has an evident equilibrium $Q_0 = (S^0, 0, 0, 0)$ with $S^0_k = \rho^0_{S,k}$ defined as in Eq. (12) and $0$ the zero vector of dimension $n$ when there is no disease. We calculate the basic reproduction number, $R_0$, using the next generation approach, developed in Ref. [30].

Using the notations in Ref. [30], the matrices $F$ and $V$, for the new infections and the remaining transfers, are, respectively, given by

$$F = \begin{bmatrix} 0 & F_1 & 0 \\ 0 & F_2 & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} A_E I_n - D_E C & -\gamma I_n & 0 \\ -\alpha (1 - \theta) I_n & A_I I_n - D_I C & -\xi I_n \\ -\eta I_n & -\delta I_n & A_R I_n - D_R C \end{bmatrix},$$

where $I_n$ is the identity matrix of dimension $n$,

$F_1 = \beta (1 - q) I_n, \quad F_2 = \beta q I_n, \quad A_E = [\mu + \eta + \alpha (1 - \theta) + D_E], \quad A_I = \mu + d + \gamma + \delta + D_I, \quad A_R = \mu + \xi + D_R.$

Set

$$F = \begin{bmatrix} F_{11} & F_{12} \\ F_{21} & F_{22} \end{bmatrix},$$

where

$$F_{11} = \begin{bmatrix} 0 & F_1 \\ 0 & F_2 \end{bmatrix}, \quad F_{12} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \quad F_{21} = [0, 0] \quad \text{and} \quad F_{22} = 0.$$

Also, let

$$V = \begin{bmatrix} V_1 & V_2 \\ V_3 & V_4 \end{bmatrix},$$

where

$$V_1 = \begin{bmatrix} A_E I_n - D_E C & -\gamma I_n \\ -\alpha (1 - \theta) I_n & A_I I_n - D_I C \end{bmatrix}, \quad V_2 = \begin{bmatrix} 0 \\ -\xi I_n \end{bmatrix}, \quad V_3 = [-\eta I_n, -\delta I_n] \quad \text{and} \quad V_4 = A_R I_n - D_R C.$$

We stress that since $V$ is a M-matrix and $-V$ is stable, then one can deduce that $V^{-1} \geq 0$. 

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Now, we need to compute the inverse of the matrix $V$. To this end, suppose that the inverse matrix of $V$ can be written in the following form:

$$
V^{-1} = \begin{bmatrix} W_{11} & W_{12} \\ W_{21} & W_{22} \end{bmatrix},
$$

where $W_{11}$ and $W_{22}$ are square matrices of dimension $(2n \times 2n)$ and $(n \times n)$, respectively.

Observe that

$$
FV^{-1} = \begin{bmatrix} A & B \\ 0 & 0 \end{bmatrix},
$$

where $A = F_{11} W_{11}$ and $B = F_{11} W_{12}$. Thus, the basic reproduction ratio is defined, following [30], as the spectral radius of the next generation matrix, $FV^{-1}$:

$$
R_0 = \rho(FV^{-1}) = \rho(A) = \rho(F_{11} W_{11}).
$$

(13)

To compute the explicit expression of the basic reproduction number, we need to compute the inverse matrix of $V$. To this end, we need the following lemma stated above and proved in Appendix A.

Lemma 1: Let $N$ be a square block matrix of the following form:

$$
N = \begin{bmatrix} N_1 & N_2 \\ N_3 & N_4 \end{bmatrix},
$$

where $N_1$ and $N_4$ are square matrices.

If $N_1$ and $D = N_4 - N_3 N_1^{-1} N_2$ are invertible, then the inverse matrix of $N$ is given by

$$
N^{-1} = \begin{bmatrix} N_1^{-1} + N_1^{-1} N_2 D^{-1} N_3 N_1^{-1} & -N_1^{-1} N_2 D^{-1} \\ -D^{-1} N_3 N_1^{-1} & D^{-1} \end{bmatrix}.
$$

Note that the matrix $V_1$ has the form of the matrix $N$ defined in Lemma 1 with $N_1 = A_E I_n - D_E C$, $N_2 = -\gamma I_n$, $N_3 = -\alpha(1 - \theta) I_n$ and $N_4 = A_I I_n - D_I C$.

Note also that the matrix $V$ has the form of the matrix $N$ defined in Lemma 1 with $N_1 = V_1$, $N_2 = V_2$, $N_3 = V_3$ and $N_4 = V_4$. So, if all the hypotheses in Lemma 1 are satisfied for the matrices $V_1$ and $V_4$, then Lemma 1 can be used twice to compute $V^{-1}$.

Thus using Lemma 1, one can prove that $V_1^{-1}$ has the following form:

$$
V_1^{-1} = \begin{bmatrix} V_{11} & V_{12} \\ V_{21} & V_{22} \end{bmatrix},
$$

where

$$
V_{11} = (A_E I_n - D_E C)^{-1} + \gamma (A_E I_n - D_E C)^{-1} V_{21},
$$

$$
V_{12} = \gamma (A_E I_n - D_E C)^{-1} V_{22},
$$

$$
V_{21} = \alpha(1 - \theta) V_{22} (A_E I_n - D_E C)^{-1},
$$

$$
V_{22} = \left[ A_I I_n - D_I C - \alpha \gamma(1 - \theta) (A_E I_n - D_E C)^{-1} \right]^{-1}.
$$
From the above expressions, it appears that to compute the explicit expressions of $V_{11}$, $V_{12}$, $V_{21}$ and $V_{22}$, we need to compute the inverse matrices of $[A_I I_n - D_I C - \alpha \gamma (1 - \theta) (A_E I_n - D_E C)^{-1}]$ and $(A_E I_n - D_E C)$. To do so, we shall use the following Lemma 2 stated below and proved in Appendix C.

**Lemma 2** : Let $G = U + X W Z$ be an $n \times n$ invertible matrix. Suppose that the matrices $U$, $W$ and $W^{-1} + Z U^{-1} X$ are invertible. Then, the inverse matrix of $R$ is defined as

$$G^{-1} = U^{-1} - U^{-1} X [W^{-1} + Z U^{-1} X]^{-1} Z U^{-1}. \quad (14)$$

Using the above Lemma 2 and the fact that $C^m = C, \forall m \in \mathbb{N}^*$, one can easily prove that

$$(A_E I_n - D_E C)^{-1} = \frac{1}{A_E} \left( I_n + \frac{D_E}{A_E - D_E} C \right),$$

$$\left[ A_I I_n - D_I C - \alpha \gamma (1 - \theta) (A_E I_n - D_E C)^{-1} \right]^{-1} = \frac{1}{a} \left( I_n + \frac{b}{a - b} C \right),$$

where

$$a = \frac{A_I (\mu + \eta + D_E) + \alpha (1 - \theta)(\mu + d + \delta + D_I)}{A_E} \quad \text{and} \quad b = \frac{A_E D_I [\mu + \eta + \alpha(1 - \theta)] + \gamma \alpha (1 - \theta) D_E}{A_E [\mu + \eta + \alpha(1 - \theta)]}.$$  

With this in mind, after some substitutions, one has:

$$V_{22} = \frac{1}{a} \left[ I_n + \frac{b}{a - b} C \right],$$

$$V_{21} = \frac{\alpha (1 - \theta)}{a A_E} \left[ I_n + \frac{b[\mu + \alpha(1 - \theta)] + a D_E}{(a - b)[\mu + \alpha(1 - \theta)]} \right],$$

$$V_{21} = a_1 I_n + b_1 C,$$

$$V_{12} = \frac{\gamma}{a A_E} \left[ I_n + \frac{b[\mu + \alpha(1 - \theta)] + a D_E}{(a - b)[\mu + \alpha(1 - \theta)]} C \right],$$

$$V_{12} = a_2 I_n + b_2 C,$$

$$V_{11} = \frac{a A_E + \gamma \alpha (1 - \theta)}{a A_E} \left[ I_n + \frac{\gamma \alpha (1 - \theta) A_E [b[\mu + \alpha(1 - \theta)] + a D_E]}{(a - b)[a A_E + \gamma \alpha(1 - \theta)] [\mu + \alpha(1 - \theta)]^2 C} \right]$$

$$+ \frac{a A_E + \gamma \alpha (1 - \theta)}{a A_E} \left[ D_E [\mu + \alpha(1 - \theta)] [a A_E + \gamma \alpha (1 - \theta)] [\mu + \alpha(1 - \theta)]^2 C \right]$$

$$= a_3 I_n + b_3 C,$$
where,

\[ a_0 = \frac{1}{a} = \frac{A_E}{A_I (\mu + \eta + D_E) + \alpha (1 - \theta)(\mu + d + \delta + D_I)} \]

\[ b_0 = \frac{b}{a(a - b)} \]

\[ a_1 = \frac{\alpha (1 - \theta)}{a A_E} \]

\[ b_1 = \frac{\alpha (1 - \theta) b [\mu + \alpha (1 - \theta)] + a D_E}{a A_E (a - b) [\mu + \alpha (1 - \theta)]} \]

\[ a_2 = \frac{1}{a A_E} \]

\[ b_2 = \frac{b [\mu + \alpha (1 - \theta)] + a D_E}{a A_E (a - b) [\mu + \alpha (1 - \theta)]} \]

\[ a_3 = \frac{a A_E + \gamma \alpha (1 - \theta)}{a A_E^2} \]

\[ b_3 = \frac{a A_E + \gamma \alpha (1 - \theta)}{a A_E^2} \left[ \frac{\gamma \alpha (1 - \theta) A_E [b [\mu + \alpha (1 - \theta)] + a D_E] + (a - b) D_E [\mu + \alpha (1 - \theta)] [a A_E + \gamma \alpha (1 - \theta)]}{(a - b) [a A_E + \gamma \alpha (1 - \theta)] [\mu + \alpha (1 - \theta)]^2} \right] \]

This achieve the computation of \( V_1^{-1} \).

Now, we need to compute \( V^{-1} \). To this end, we need to prove the invertibility of matrix \( D = V_4 - V_3 V_1^{-1} V_2 \). Simple substitutions show that:

\[ D = V_4 - (\eta \xi V_{11} + \delta \xi V_{21}), \]

\[ = [A_R - \xi (\eta a_3 + \delta a_1)] I_n - [D_R + \xi (\eta b_3 + \delta b_1)] C. \]

Applying Lemma 2 one again, the inverse of \( D \) is given by

\[ D^{-1} = \frac{1}{[A_R - \xi (\eta a_3 + \delta a_1)]} \left[ I_n + \frac{D_R + \xi (\eta b_3 + \delta b_1)}{[A_R - \xi (\eta a_3 + \delta a_1)] - [D_R + \xi (\eta b_3 + \delta b_1)]} C \right], \]

\[ = a_4 I_n - b_4 C, \]

where

\[ a_4 = \frac{1}{[A_R - \xi (\eta a_3 + \delta a_1)]}, \]

\[ b_4 = \frac{1}{[A_R - \xi (\eta a_3 + \delta a_1)]} \frac{D_R + \xi (\eta b_3 + \delta b_1)}{[A_R - \xi (\eta a_3 + \delta a_1)] - [D_R + \xi (\eta b_3 + \delta b_1)]}. \]

Since \( V_1 \) and \( D \) are invertible matrices, applying Lemma 1, after simple calculations we have:

\[ W_{11} = V_1^{-1} + V_1^{-1} V_2 D^{-1} V_3 V_1^{-1}, \]

\[ = \begin{bmatrix} V_{11} + \xi V_{12} D^{-1} (\eta V_{11} + \delta V_{21}) & V_{12} + \xi V_{12} D^{-1} (\eta V_{12} + \delta V_{22}) \\ V_{21} + \xi V_{22} D^{-1} (\eta V_{11} + \delta V_{21}) & V_{22} + \xi V_{22} D^{-1} (\eta V_{12} + \delta V_{22}) \end{bmatrix}. \]
At this stage, we need to compute the expression of $A$. Note that $A$ can be written as follows:

$$ A = F_{11} W_{11}, $$

$$ = \begin{bmatrix} F_1 \left[ V_{21} + \xi V_{22} D^{-1} (\eta V_{11} + \delta V_{21}) \right] & F_1 \left[ V_{22} + \xi V_{22} D^{-1} (\eta V_{12} + \delta V_{22}) \right] \\
F_2 \left[ V_{21} + \xi V_{22} D^{-1} (\eta V_{11} + \delta V_{21}) \right] & F_2 \left[ V_{22} + \xi V_{22} D^{-1} (\eta V_{12} + \delta V_{22}) \right] \end{bmatrix}. $$

On the other hand, to have the explicit expression of the basic reproduction ratio, we need the following lemma whose proof is given in Appendix B.

**Lemma 3**: Let $M$ be a square block matrix of the following form:

$$ M = \begin{bmatrix} M_1 & M_2 \\ M_3 & M_4 \end{bmatrix}, $$

where $M_1$, $M_2$, $M_3$ and $M_4$ are also square matrices.

1. If $M_2$ is invertible and $M_2 M_3 - M_2 M_4 M_2^{-1} M_1 = 0$, then

$$ \rho(M) = \max \{ 0, \rho(M_1 + M_2 M_4 M_2^{-1}) \}. \quad (15) $$

2. Moreover, if $M_2 M_4 = M_4 M_2$, then

$$ \rho(M) = \max \{ 0, \rho(M_1 + M_2) \}. \quad (16) $$

Note that $A = F_{11} W_{11}$ has the form of the matrix $M$ defined in Lemma 3 with

$M_1 = F_1 \left[ V_{21} + \xi V_{22} D^{-1} (\eta V_{11} + \delta V_{21}) \right]$, $M_2 = F_1 \left[ V_{22} + \xi V_{22} D^{-1} (\eta V_{12} + \delta V_{22}) \right]$, $M_3 = F_2 \left[ V_{21} + \xi V_{22} D^{-1} (\eta V_{11} + \delta V_{21}) \right]$ and $M_4 = F_2 \left[ V_{22} + \xi V_{22} D^{-1} (\eta V_{12} + \delta V_{22}) \right]$.

Since $F_1 = \beta (1 - q) I_n$ and $F_2 = \beta q I_n$, are diagonal matrices, one has,

$$ M_2 M_4 = F_1 \left[ V_{22} + \xi V_{22} D^{-1} (\eta V_{12} + \delta V_{22}) \right] F_2 \left[ V_{22} + \xi V_{22} D^{-1} (\eta V_{12} + \delta V_{22}) \right] $$

$$ = F_1 F_2 \left[ V_{22} + \xi V_{22} D^{-1} (\eta V_{12} + \delta V_{22}) \right] \left[ V_{22} + \xi V_{22} D^{-1} (\eta V_{12} + \delta V_{22}) \right], $$

$$ = F_2 F_1 \left[ V_{22} + \xi V_{22} D^{-1} (\eta V_{12} + \delta V_{22}) \right] \left[ V_{22} + \xi V_{22} D^{-1} (\eta V_{12} + \delta V_{22}) \right], $$

$$ = F_2 \left[ V_{22} + \xi V_{22} D^{-1} (\eta V_{12} + \delta V_{22}) \right] F_1 \left[ V_{22} + \xi V_{22} D^{-1} (\eta V_{12} + \delta V_{22}) \right], $$

$$ = M_4 M_2, $$

and

$$ M_2 M_3 - M_2 M_4 M_2^{-1} M_1 = M_2 M_3 - M_4 M_2 M_2^{-1} M_1, $$

$$ = M_2 M_3 - M_4 M_1, $$

$$ = F_1 \left[ V_{22} + \xi V_{22} D^{-1} (\eta V_{12} + \delta V_{22}) \right] F_2 \left[ V_{22} + \xi V_{22} D^{-1} (\eta V_{11} + \delta V_{21}) \right] - F_2 F_1 \left[ V_{22} + \xi V_{22} D^{-1} (\eta V_{12} + \delta V_{22}) \right] F_1 \left[ V_{22} + \xi V_{22} D^{-1} (\eta V_{11} + \delta V_{21}) \right], $$

$$ = F_1 F_2 \left[ V_{22} + \xi V_{22} D^{-1} (\eta V_{12} + \delta V_{22}) \right] \left[ V_{22} + \xi V_{22} D^{-1} (\eta V_{11} + \delta V_{21}) \right] - F_2 F_1 \left[ V_{22} + \xi V_{22} D^{-1} (\eta V_{12} + \delta V_{22}) \right] \left[ V_{22} + \xi V_{22} D^{-1} (\eta V_{11} + \delta V_{21}) \right], $$

$$ = 0. $$
With this in mind, since \( A > 0 \), by applying Lemma 3, Eq. (13) becomes

\[
\mathcal{R}_0 = \rho [M_1 + M_2],
\]

\[
= \rho \left( F_1 [V_{21} + \xi V_{22} D^{-1} (\eta V_{11} + \delta V_{21})] + F_2 [V_{22} + \xi V_{22} D^{-1} (\eta V_{12} + \delta V_{22})] \right),
\]

\[
= \beta \rho \left[ (1 - q) [V_{21} + \xi V_{22} D^{-1} (\eta V_{11} + \delta V_{21})] + q [V_{22} + \xi V_{22} D^{-1} (\eta V_{12} + \delta V_{22})] \right],
\]

\[
(17)
\]

\[
= \beta \rho \left[ (1 - q)V_{21} + qV_{22} + \xi V_{22} D^{-1} [\eta ((1 - q)V_{11} + qV_{12}) + \delta((1 - q)V_{21} + qV_{22})] \right],
\]

\[
= \beta \rho \left[ (I_n + \delta \xi V_{22} D^{-1}) ((1 - q)V_{21} + qV_{22}) + \xi \delta V_{22} D^{-1} ((1 - q)V_{11} + qV_{12}) \right].
\]

From the above expressions, it is evident that \( V_{11}, V_{12}, V_{21}, V_{22}, D^{-1} > 0 \). We point out that as \( V_{11} \) and \( V_{22} \) are irreducible and nonnegative, one has \( V_{12}, V_{21} > 0 \). This implies that \( A \) is also irreducible and nonnegative. Then, using the Perron-Frobenius theorem [31], one can deduce that \( \rho(A) \) is a positive eigenvalue of \( A \). Additionally, a simple calculation can prove that

\[
[(1 - q)V_{21} + qV_{22}] = \left[ \frac{(1 - q) \alpha (1 - \theta) + q A_E}{a A_E} \right] I_n +
\]

\[
\left[ \frac{(1 - q) \alpha (1 - \theta) [a D_E + b (A_E - D_E)] + q b A_E (A_E - D_E)}{a (a - b) A_E (A_E - D_E)} \right] C,
\]

\[
= a_5 I_n + b_5 C,
\]

\[
I_n + \delta \xi V_{22} D^{-1} = I_n + \xi \delta (a_0 I_n + b_0 C)(a_4 I_n + b_4 C)
\]

\[
= [(1 + \xi \delta a_0 a_4) I_n + \xi \delta (a_0 b_4 + b_0 a_4 + b_0 b_4) C]
\]

\[
= a_6 I_n + b_6 C,
\]

\[
\xi \delta V_{22} D^{-1} [(1 - q)V_{11} + qV_{12}] = [(a_6 - 1) I_n + b_6 C] [((1 - q)a_3 + qa_2) I_n + ((1 - q)b_3 + qb_2)]
\]

\[
= (a_6 - 1) [(1 - q)a_3 + qa_2] I_n
\]

\[
+ [(a_6 - 1) [(1 - q)b_3 + qb_2] + b_6[(1 - q)a_3 + qa_2] + b_6[(1 - q)b_3 + qb_2}] C
\]

\[
= a_7 I_n + b_7 C.
\]

Finally

\[
\beta \left(I_n + \delta \xi V_{22} D^{-1} \right) [(1 - q)V_{21} + q V_{22}] + \xi \delta V_{22} D^{-1} [(1 - q)V_{11} + qV_{12}]
\]

\[
= \beta \left[ (a_5 I_n + b_5 C)(a_6 I_n + b_6 C) + a_7 I_n + b_7 C \right]
\]

\[
= \beta \left[ (a_5 a_6 + a_7) I_n + (a_5 b_6 + b_5 a_6 + b_5 b_6 + b_7) C \right]
\]

\[
= a_8 I_n + b_8 C.
\]
where

\[
\begin{align*}
a_5 &= \frac{(1-q)\alpha(1-\theta)+qAE}{AE}, \\
b_5 &= \frac{(1-q)\alpha(1-\theta)[aDE+b(AE-DE)]+qbAE(AE-DE)}{a(a-b)AE(AE-DE)}, \\
a_6 &= (1+\xi \delta a_0 a_4), \\
b_6 &= \xi \delta (a_0 b_4 + b_0 a_4 + b_0 b_4), \\
a_7 &= (a_6 - 1) [(1-q)a_3 + qa_2], \\
b_7 &= [(a_6 - 1) [(1-q)b_3 + qb_2] + b_6[(1-q)a_3 + qa_2] + b_5[(1-q)b_3 + qb_2]], \\
a_8 &= a_5 a_6 + a_7, \\
b_8 &= a_5 b_6 + b_5 a_6 + b_5 b_6 + b_7.
\end{align*}
\]

Now, since \(C\) is a rank-one matrix that admits 1 as a unique positive eigenvalue, the greatest eigenvalue of the matrix is \(\beta \left(a_8 I_n + a_8 C\right)\) is \(\beta \left[a_8 + b_8\right]\) and consequently, the basic reproduction ratio of system (8) is

\[
R_0 = \beta \left[a_8 + b_8\right],
\]

\[
= \beta \left[(a_5 + b_5)(a_6 + b_6) + a_7 + b_7\right].
\]

The following result is established from Theorem 2 of [30]:

**Lemma 4**: The disease-free equilibrium \(Q_0\) of system (8) is locally asymptotically stable whenever \(R_0 < 1\), and instable if \(R_0 > 1\).

Biologically speaking, Lemma 4 implies that TB can be eliminated from the community (when \(R_0 \leq 1\)) if the initial sizes of the population are in the basin of attraction of the disease-free equilibrium \(Q_0\).

Now, let us analyze the basic reproduction number (19). The parameter values used for numerical simulation are given in Table 1.

**Table 1**: Description of parameters of model system

| Parameter | Description                                      | Estimated value   | Source |
|-----------|--------------------------------------------------|-------------------|--------|
| \(\Lambda\) | Recruitment rate | 1001 year\(^{-1}\) | [35]   |
| \(\beta\) | Transmission coefficient | Variable          |        |
| \(\mu\) | Per capita naturally death rate | 0.017 year\(^{-1}\) | [34]   |
| \(q\) | Fast route to active TB | 0.015              | [36]   |
| \(\alpha\) | Slow route to active TB | 0.0024 year\(^{-1}\) | [35]   |
| \(\theta\) | Per capital rate of effective chemoprophylaxis | 0.001 year\(^{-1}\) | [36]   |
| \(\delta\) | Recovery rate of infectious | 0.7372 year\(^{-1}\) | [35]   |
| \(\eta\) | Recovery rate due to chemoprophylaxis | year\(^{-1}\) | [35]   |
| \(\gamma\) | Natural recovery rate of infectious | 0.7372/4 year\(^{-1}\) | Assumed |
| \(d\) | Per capita disease-induced mortality rate | 0.0012 year\(^{-1}\) | [35]   |
| \(\xi\) | Relapse of recovered individuals | 0.0986 year\(^{-1}\) | [35]   |

Figure ?? shows the effects of the transmission rate \(\beta\) and the patch connectivity \(k\) on the basic reproduction ratio \(R_0\) given as in Eq. (19). We have taken a metapopulation with scale-free distribution \(p(k) \sim k^{-3}\)
with \(\langle k \rangle = 6, k_{\text{min}} = 3\) and \(D_S = D_E = D_I = D_R = 1\). All other parameters are as in Table 1. The part above the unity of the picture corresponds to the region of the instability of the disease-free equilibrium, while the part below the unity of the figure represents the region for the stability of the disease-free equilibrium. From this figure, one can see that \(R_0\) decreases if \(\beta\) decreases even in the case of large values of \(k\). This means that if the transmission coefficient \(\beta\) is sufficiently small, TB infection could be eliminated in the host population even if the number of the patch connectivity \(k\) is large. However, it is difficult to control \(\beta\). This figure also shows that for the chosen parameter values, if the patch connectivity \(k\) does not exceed 1.2 (\(k < 6\)), then TB can be controlled irrespective of the value of \(\beta\). The infection will equally persist for \(k > 6\).

The combined effects of the patch connectivity \(k\) and the recovery rate \(\delta\) on the basic reproduction number \(R_0\) when \(\beta = 0.0017\) are shown in Fig. ?? . This figure suggests that the basic reproduction ratio \(R_0\) decreases if \(\delta\) increases or \(k\) decreases. Thus, the treatment of TB will have beneficial effects on infectious populations if the recovery rate is large.

### 3.2 Analysis of the simple mass action (or density-dependent) model

In this section, we consider the analysis of the spread of TB in metapopulation uncorrelated networks under the assumption of simple mass action (or density-dependent). Under these assumptions, system (8) can be written as

\[
\begin{align*}
\dot{S}_{k} &= \Lambda - \beta \rho_{I,k} \rho_{S,k} - \mu \rho_{S,k} - D_S \left( \rho_{S,k} - \frac{k}{\langle k \rangle} \rho_S \right), \\
\dot{E}_{k} &= \beta (1 - q) \rho_{I,k} \rho_{S,k} + \beta (1 - \xi) \rho_{I,k} \rho_{R,k} + \gamma \rho_{I,k} - [\mu + \eta + \alpha (1 - \theta)] \rho_{E,k} - D_E \left( \rho_{E,k} - \frac{k}{\langle k \rangle} \rho_E \right), \\
\dot{I}_{k} &= \beta q \rho_{I,k} \rho_{S,k} + \alpha (1 - \theta) \rho_{E,k} - (\mu + d + \gamma + \delta) \rho_{I,k} - D_I \left( \rho_{I,k} - \frac{k}{\langle k \rangle} \rho_I \right) + \xi \rho_{R,k}, \\
\dot{R}_{k} &= -\beta (1 - \xi) \rho_{I,k} \rho_{R,k} + \eta \rho_{R,k} + \delta \rho_{I,k} - (\mu + \xi) \rho_{R,k} - D_R \left( \rho_{R,k} - \frac{k}{\langle k \rangle} \rho_R \right).
\end{align*}
\]

(20)

Using the same notations as in Eq. (10), system (20) can be written in the following compact form:

\[
\begin{align*}
\dot{S} &= \Lambda I - \beta \text{diag}(I) S - (\mu + D_S) S + D_S CS, \\
\dot{E} &= \beta (1 - q) \text{diag}(I) S + \beta (1 - \xi) \text{diag}(I) R + \gamma I - [\mu + \eta + \alpha (1 - \theta) + D_E] E + D_E C E, \\
\dot{I} &= \beta q \text{diag}(I) S + \alpha (1 - \theta) E - (\mu + d + \gamma + \delta + D_I) I + D_I C I + \xi R, \\
\dot{R} &= -\beta (1 - \xi) \text{diag}(I) R + \eta R + \delta I - (\mu + \xi + D_R) R + D_R C R,
\end{align*}
\]

(21)

where \(S, E, I, R\) and \(\text{diag}(I)\) are defined as in Eq. (10).

#### 3.2.1 Local stability of the DFE

We give the formulae of the basic reproduction number, \(R_0\), for the density-dependent model, using again
the next generation approach, developed in [30]. Then, derive bounds on $R_0$ in term of the connectivities of patches.

Using the notations in [30], the matrices $F$ and $V$, for the new infections and the remaining transfers, are defined analogously as for the frequency-dependent model except that

$$F_1 = \beta (1 - q) \text{diag}(S^0) \quad \text{and} \quad F_2 = \beta q \text{diag}(S^0).$$

Similarly, the techniques used in the previous subsection can be used to compute the basic reproduction number of the density-dependent model (20). Hence, Lemmas 1, 2 and 3 can be used to find the spectral radius of the following matrix:

$$L = \beta \text{diag}(S^0) \left((I_n + \delta \xi V_{22}D^{-1}) [(1 - q) V_{21} + q V_{22}] + \xi \delta V_{22}D^{-1} [(1 - q)V_{11} + qV_{12}]\right),$$

where $a_8$ and $b_8$ are defined as in Eq. (18). Thus

$$R_0 = \beta \rho \left[ (a_8 \text{diag}(S^0) + b_8 \text{diag}(S^0) C \right].$$

Since the spectral radius of $L$ is very difficult to compute, we shall only give some properties and estimates of its eigenvalues owing to its specific form.

We point out that $L$ is a sum of a diagonal matrix $a_8 \text{diag}(S^0)$ and a rank 1 matrix $b_8 \text{diag}(S^0) C$. Moreover, the diagonal elements of $a_8 \text{diag}(S^0)$ are positive and written in the increasing order. Thus, $L$ can be considered as a diagonal matrix perturbed by a rank-one matrix. Now, for a general interlacing theorem of eigenvalues for perturbations of a diagonal matrix by rank-one matrices [33], the eigenvalues $\lambda_{k_1} < \lambda_{k_2} < \ldots < \lambda_{k_n} = \lambda_{k_{\text{max}}}$ of $L$ interlace with the eigenvalues $\beta a_8 S_{k_1}^0 < \beta a_8 S_{k_2}^0 < \ldots < \beta a_8 S_{k_n}^0$ of $\beta a_8 \text{diag}(S^0)$ as follows

$$\beta a_8 S_{k_1}^0 < \beta a_8 S_{k_2}^0 < \lambda_{k_2} < \ldots < \beta a_8 S_{k_n}^0 < \lambda_{k_n} = \lambda_{k_{\text{max}}}. $$

Then, it follows that all the eigenvalues of $L$ are real, simple, positive and the greatest one is $\lambda_{k_{\text{max}}} = R_0$. Thus, the following inequality for $R_0$ holds:

$$R_0 > \beta a_8 \rho_{S,k_{\text{max}}},$$

Note that $\rho_{S,k_{\text{max}}}$ is defined as

$$\rho_{S,k_{\text{max}}} = \frac{\Lambda}{\mu \langle k \rangle (\mu + D_S)} [\mu \langle k \rangle + k_{\text{max}} D_S].$$

Therefore, a sufficient condition for the DFE to be unstable is given by the following lemma:

**Lemma 5** If

$$\beta a_8 \frac{\Lambda (\mu \langle k \rangle + D_S k_{\text{max}})}{\mu \langle k \rangle (\mu + D_S)} > 1,$$

then the disease-free equilibrium of the density dependent model is unstable.
Condition (24) implies that $R_0 > 1$, which is a sufficient condition for the DFE to be unstable. Rearranging condition (24) gives

$$\rho_{S,k_{\text{max}}}^0 > \frac{1}{\beta a_8}.$$  \hspace{1cm} (25)

Condition (25) simply says that, if the number of individuals inhabiting those patches with highest connectivity in the metapopulation, for fixed values of $\mu$, $\gamma$, $D_E$, $D_I$, $D_R$, $\delta$, $\xi$, $q$, $\theta$, $\beta$, $d$, $\gamma$, $\eta$ and $\alpha$, a large enough $\rho_{S,k_{\text{max}}}^0$ guarantee the instability of the disease-free equilibrium. This implies that the infection reaches all patches.

Now, we prove that $R_0$ is bounded above and below and give a sufficient condition of the instability of the DFE in term of the average density of patches of lowest connectivities.

Observe that $L$ is nonnegative ($L \geq 0$) and $S_k^0$ is an increasing function of the connectivity $k$. Thus

$$\beta \left[ a_8 (\min_k S_k^0) I_n + b_8 \text{diag}(S^0) C \right] < L < \beta \left[ a_8 (\max_k S_k^0) I_n + b_8 \text{diag}(S^0) C \right].$$

Since $S_k^0 = \rho_{S,k}^0$, one has

$$\beta \left[ S_{k_{\text{min}}}^0 a_8 I_n + b_8 \text{diag}(S^0) C \right] < L < \beta \left[ S_{k_{\text{max}}}^0 a_8 I_n + b_8 \text{diag}(S^0) C \right].$$

Then, one can deduce that

$$\beta \rho \left[ S_{k_{\text{min}}}^0 a_8 I_n + b_8 \text{diag}(S^0) C \right] < \rho(L) < \beta \rho \left[ S_{k_{\text{max}}}^0 a_8 I_n + b_8 \text{diag}(S^0) C \right],$$

which implies

$$\beta \left[ a_8 S_{k_{\text{min}}}^0 + b_8 \sum_k S_k^0 C_{kk} \right] < \rho(L) < \beta \left[ a_8 S_{k_{\text{max}}}^0 + b_8 \sum_k S_k^0 C_{kk} \right].$$

We have established the following lemma which give precise bounds on $R_0$ and then yield a sufficient condition for the instability of the DFE in term of the average density of patches of lowest connectivities.

**Lemma 6 :** The basic reproduction number of the density-dependent model satisfies

$$\beta \left[ a_8 S_{k_{\text{min}}}^0 + b_8 \sum_k S_k^0 \frac{kp(k)}{\langle k \rangle} \right] < R_0 < \beta \left[ a_8 S_{k_{\text{max}}}^0 + b_8 \sum_k S_k^0 \frac{kp(k)}{\langle k \rangle} \right].$$  \hspace{1cm} (26)

The proof of this lemma is straightforward since $b_8 \text{diag}(S^0)C$ is a rank one matrix, therefore, the only non zero eigenvalue of this matrix is the sum $b_8 \sum_k S_k^0 \frac{kp(k)}{\langle k \rangle}$ of its diagonal entries.

From this Lemma 6, we deduce a sufficient condition of the instability of the DFE in term of the average density of patches of lowest connectivities given as:

$$\beta \left[ a_8 S_{k_{\text{min}}}^0 + b_8 \sum_k S_k^0 \frac{kp(k)}{\langle k \rangle} \right] > 1.$$  \hspace{1cm} (27)

Since $S_k^0 = \rho_{S,k}^0$, condition (27) becomes

$$\rho_{S,k_{\text{min}}}^0 > \frac{1}{a_8} \left[ \frac{1}{\beta} - b_8 \sum_k \rho_{S,k}^0 \frac{kp(k)}{\langle k \rangle} \right].$$  \hspace{1cm} (28)
This condition (28) says that, if the number of individuals inhabiting those patches with lowest connectivity in the metapopulation, for fixed values of $\mu$, $\gamma$, $D_E$, $D_I$, $D_R$, $\delta$, $\xi$, $q$, $\theta$, $d$, $\gamma$, $\eta$ and $\alpha$, a large enough $\rho_{S,k_{\min}}^0$ guarantee the instability of the disease-free equilibrium. This implies that the infection reaches all patches.

In summary, it is classically known that if $R_0 < 1$, then the DFE is locally stable, and if $R_0 > 1$, then it is unstable. With this classic result in mind and the bounds on $R_0$ giving by condition (24) and condition (28), we have established the following result giving sufficient conditions for the instability of the DFE.

**Theorem 1**: For the model with density-dependent model (20),
if the average density of patches with highest connectivities satisfies

$$\rho_{S,k_{\max}}^0 > \frac{1}{\beta a_8}$$

(29)

or,

if the average density of patches with lowest connectivities satisfies

$$\rho_{S,k_{\min}}^0 > \frac{1}{a_8} \left[ \frac{1}{\beta} - b_8 \sum_k \rho_{S,k}^0 \frac{kp(k)}{\langle k \rangle} \right]$$

(30)

then, the DFE is unstable.

Model of this type demonstrates clear infection threshold. In the presence of a threshold, disease eradication requires the reduction of the infection rate below a critical level where a stable infection-free equilibrium is guaranteed. In epidemiological terminology, the infection threshold may be expressed in terms of the basic reproductive ratio $R_0$, the average number of infections produced by a single infected individual in a population of susceptible. From this definition, it is clear that TB infection can spread in a population only if $R_0 > 1$.

In conclusion, crossing the threshold reduces the basic reproductive ratio $R_0$ below unity and the infection is prevented from propagating.

### 3.2.2 Endemic equilibrium

Herein, we investigate the existence of an endemic equilibrium of system (21) in the special case where there is no re-infection after recovery (i.e. no flow from the recovered class to the latently infected class due to infection), but with possible relapse from the disease.

To this end, it is more convenient to write system (21) in a more compact form. In a more compact form, model (21) may be written as follows:

$$\begin{cases}
\dot{x} = \Lambda \mathbb{I} - \text{diag}(By) \ x + [D_S \ C - (\mu + D_S)] \ x, \\
\dot{y} = \sum_{i=1}^{n} (c_i \ | \ By)(c_i \ | \ x) K_i - V \ y,
\end{cases}$$

(31)
Using the first equation of (33), one has

\[ x = S \in \mathbb{R}^n_+, \quad y = (E, I, R)^T \in \mathbb{R}^{3n}_+, \quad K_i \in \mathbb{R}^{3n} \] are constant vectors with

\[
K_1 = (1 - q, 0, \ldots, 0, q, 0, \ldots, 0, 0, \ldots, 0)^T,
K_2 = (0, 1 - q, 0, \ldots, 0, q, 0, \ldots, 0, 0, \ldots, 0)^T,
\]

\[ \vdots \]

\[
K_n = (0, \ldots, 0, 1 - q, 0, \ldots, 0, q, 0, \ldots, 0, 0, \ldots, 0)^T,
\]
e_i is the canonical basis of \( \mathbb{R}^n \), \( B = [0, \beta I_n, 0] \) with 0 a \( n \times n \) null matrix, \( I \) is defined as in Eq. (21) and \( V \) is the \( 3n \times 3n \) constant matrix:

\[
V = \begin{bmatrix}
A_E I_n - D_E C & -\gamma I_n & 0 \\
-\alpha (1 - \theta) I_n & A_I I_n - D_I C & -\xi I_n \\
-\eta & -\delta I_n & A_R I_n - D_R C \\
\end{bmatrix}.
\]

We point out that the matrix \(-V\) is a Metzler matrix, that is, a matrix with all its off-diagonal entries nonnegative [31-34].

With this new notations, and using the method of [30], the basic reproduction ratio (23) satisfies

\[
R_0 = \rho \left[ \sum_{i=1}^{n} \langle e_i | x^0 \rangle B V^{-1} K_i e_i^T \right].
\]

(32)

where \( x^0 = S^0 = (\rho^0_{S,k})_k \).

Let \( Q^* = (x^*, y^*) \) be the positive endemic equilibrium of system (31). Then, the positive endemic equilibrium (steady state with \( y > 0 \)) can be obtained by setting the right hand side of equations in system (31) at zero, giving

\[
\left\{ \begin{array}{l}
\Lambda I - \text{diag}(B y^*) x^* + [D_S C - (\mu + D_S) I_n] x^* = 0, \\
\sum_{i=1}^{n} \langle e_i | B y^* \rangle \langle e_i | x^* \rangle K_i - V y^* = 0.
\end{array} \right.
\]

(33)

Multiplying the second equation of (33) by \( V^{-1} \) yields

\[
y^* = \sum_{i=1}^{n} \langle e_i | B y^* \rangle \langle e_i | x^* \rangle V^{-1} K_i.
\]

Using the first equation of (33), one has

\[
x^* = [\text{diag}(B y^*) - [D_S C - (\mu + D_S) I_n]]^{-1} \Lambda I.
\]

Then, one can deduce that

\[
y^* = \sum_{i=1}^{n} \langle e_i | B y^* \rangle \langle e_i | [\text{diag}(B y^*) - [D_S C - (\mu + D_S) I_n]]^{-1} \Lambda I \rangle V^{-1} K_i.
\]

(34)

Remind that at the disease-free equilibrium, one has

\[
\Lambda I = -[D_S C - (\mu + D_S) I_n] x^0 \gg 0.
\]

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Plugging the above expression in Eq. (34) yields
\[ y^* = \sum_{i=1}^{n} \langle e_i \mid B y^* \rangle \langle e_i \mid -[\text{diag}(B y^*) - [D_S C - (\mu + D_S)I_n]]^{-1}[D_S C - (\mu + D_S)I_n] x^0 \rangle V^{-1} K_i. \]

Multiplying the above equation by \( B \) and setting \( z^* = B y^* \) gives
\[ z^* = \sum_{i=1}^{n} \langle e_i \mid z^* \rangle \langle e_i \mid -P^{-1}(z^*)[D_S C - (\mu + D_S)I_n] x^0 \rangle B V^{-1} K_i, \] (35)
where
\[ P(z^*) = \text{diag}(z^*) - [D_S C - (\mu + D_S)I_n]. \]

We give the explicit expression of the inverse matrix of \( P(z^*) \) since we will need it later. Note that \( P(z^*) \) has the form of the matrix \( R = U + X W Z \) given in Lemma 2 with \( U = \text{diag}[z^* + (\mu + D_S)I] \), \( X = [k_1, k_2, \ldots, k_n] \), \( W = 1 \) and \( Z = \frac{D_S}{\langle k \rangle} p(k_1), p(k_2), \ldots, p(k_n) \). Then, using Lemma 2, a simple computation gives
\[ P^{-1}(z^*) = \text{diag} \left[ \frac{1}{z_k^* + \mu + D_S} \right] \left[ I_n + \frac{D_S C \text{diag} \left[ \frac{1}{z_k^* + \mu + D_S} \right]}{1 - \frac{D_S}{\langle k \rangle} \sum_k z_k^* + \mu + D_S} \right]. \] (36)

Now, from Eq. (35), one has
\[ \langle e_j \mid z^* \rangle = \sum_{i=1}^{n} \langle e_i \mid z^* \rangle \langle e_i \mid P^{-1}(z^*)P(0) x^0 \rangle \langle e_j \mid BV^{-1} K_i \rangle, \quad j = 1, 2, \ldots, n, \] (37)
where \( P(0) = -[D_S C - (\mu + D_S)I_n] \). From the above equation, one can deduce that
\[ \sum_{j=1}^{n} \langle e_j \mid z^* \rangle = \sum_{i=1}^{n} \langle e_i \mid z^* \rangle \langle e_i \mid P^{-1}(z^*)P(0) x^0 \rangle \left( \sum_{j=1}^{n} e_j \mid BV^{-1} K_i \right). \] (38)

Then, to find the endemic equilibrium of system (21), it suffices to find solutions of the following equation:
\[ H(z^*) = 1, \] (39)
where
\[ H(z^*) = \frac{\sum_{i=1}^{n} \langle e_i \mid z^* \rangle \langle e_i \mid P^{-1}(z^*)P(0) x^0 \rangle \left( \sum_{j=1}^{n} e_j \mid BV^{-1} K_i \right)}{\sum_{j=1}^{n} \langle e_j \mid z^* \rangle}. \] (40)

where \( P^{-1}(z^*) \) is defined as in Eq. (36). Note that \( z^* \) are the intersection points between the curve of \( H(z^*) \) and the line \( z = 1 \).

From Eq. (40), it follows that the function \( H(z^*) \) satisfies
\[ \lim_{z^* \to +\infty} H(z^*) = 0, \]
and
\[ \lim_{z^* \to 0} H(z^*) = \sum_{i=1}^{n} \langle e_i \mid x^0 \rangle \left( \sum_{j=1}^{n} e_j \mid BV^{-1} K_i \right). \]
We claim the following result.
Lemma 7: The inequality \( \lim_{z^* \to 0} H(z^*) \geq R_0 \) holds.

Proof: Let \( A = \sum_{i=1}^{n} \langle e_i | x^0 \rangle B V^{-1} K_i e_i^T \). Then, using Eq. (32), one has \( R_0 = \rho(A) \). Since \( A \) is a nonnegative matrix, if \( r_j = \sum_i A_{ij} \) is the sum of the \( j \)th column of \( A \), one has

\[
\min_j \{ r_j \} \leq \rho(A) \leq \max_j \{ r_j \}.
\]

If \( e_j \) denotes the canonical basis of \( \mathbb{R}^n \), \( I = (e_1 + e_2 + \cdots + e_n)^T \), using the fact that \( e_i^T I = 1, \forall i \), one has

\[
r_j = e_j^T A = e_j^T \left( \sum_{i=1}^{n} \langle e_i | x^0 \rangle B V^{-1} K_i \right) I,
\]

\[
= e_j^T \left( \sum_{i=1}^{n} \langle e_i | x^0 \rangle B V^{-1} K_i \right),
\]

\[
= \left( e_j \right| \sum_{i=1}^{n} \langle e_i | x^0 \rangle B V^{-1} K_i \),
\]

\[
= \sum_{i=1}^{n} \langle e_i | x^0 \rangle \langle e_j | B V^{-1} K_i \),
\]

With this mind, one can deduce that

\[
\sum_{j=1}^{n} r_j = \sum_{j=1}^{n} e_j^T A I = \sum_{i=1}^{n} \langle e_i | x^0 \rangle \left( \sum_{j=1}^{n} e_j | B V^{-1} K_i \right),
\]

\[
= \lim_{z^* \to 0} H(z^*).
\]

Then, one has that

\[
R_0 = \rho(A) \leq \max_j \{ r_j \} \leq \sum_j r_j,
\]

which implies that \( \lim_{z^* \to 0} H(z^*) \geq R_0 \). This completes the proof.

\( \square \)

Note that we use the expression of \( V^{-1} \) to put emphasis on the fact that \( V^{-1} \geq 0 \) because \( -V \) is a Metzler matrix. Since \( \lim_{z^* \to 0} H(z^*) \geq R_0 \) and \( \lim_{z^* \to +\infty} H(z^*) = 0, H(z^*) \) is a positive function. Thus, positive solutions of Eq. (39) exist if and only if \( \lim_{z^* \to 0} H(z^*) > R_0 > 1 \). From the first equation of (33), one has \( x^* = P^{-1}(z^*)A I \). Since \( P^{-1}(z^*) \) is a positive definite matrix, one has \( x^* > 0 \). On the other hand, since \( z^* \) are the intersection points between the curve of \( H(z^*) \) and the line \( z = 1 \), one has that \( z^* > 0 \). Then, when \( R_0 > 1 \), the equilibria are endemic. This means that there exists at least one endemic equilibrium of the model (21). Also, note that \( z^* = B y^* \) is not a bijection (it is a onto map, but not a one to one map), one can conclude that the TB model with simple mass action transmission could have multiple endemic equilibria. However, to know the number of endemic equilibria, we need to analyze the function \( H(z^*) \). We stress that Eq. (39) is very difficult to solve analytically due to the fact that \( H \) is a highly nonlinear function.
Nonetheless, one can numerically plot this curve and examine how the intersection point(s) with the line \( z = 1 \) change with model parameters. We have established the following theorem for the density-dependent model (21).

**Theorem 2**: For the model with density-dependent model (20), if the basic reproduction number \( R_0 > 1 \), then there exists at least one endemic equilibrium.

### 3.2.3 Numerical studies

To illustrate the various theoretical results contained in the previous section, system (20) are simulated using the parameter value/range in Table 1. In all simulations, the initial conditions have been chosen randomly. We have also taken a metapopulation with scale-free distribution \( p(k) \sim k^{-3} \) with \( \langle k \rangle = 6 \) and \( k_{\text{min}} = 3 \).

Figure ?? gives the evolution of the model (20) when \( \beta = 0.0001 \) and \( D_S = D_E = D_I = D_R = 1 \) (so that \( R_0 < 1 \)). All other parameters are as in Fig. ?? . Figure ??(a) presents the prevalence curves of the model while, the time evolution of the number of infected individuals in each patch is depicted in Fig. ??(b). From these figures, it clearly appears that the disease disappears in the host population even for higher values of the patch connectivity.

Figure ?? gives the evolution of the model (20) when \( \beta = 0.001 \) and \( D_S = D_E = D_I = D_R = 1 \) (so that \( R_0 > 1 \)). All other parameters are as in Fig. ?? . From this figure, one can observe that the disease persists in the host population. In addition, one can also observe that as the patch connectivity increases, the prevalence of the infection also increases.

Now, let us examine the influence of the migration on the propagation of TB in the host population.

Figure ?? presents the prevalence of the infection of model (20) in nodes of degree \( k \) of an uncorrelated scale-free network for different values of the migration rates. From this figure, the role of the migration rates \( D_S, D_E, D_I \) and \( D_R \) is remarkable. Increasing the value of the migration rates \( D_S, D_E, D_I \) and \( D_R \) causes a reduction in the prevalence of the infection. This is the only case we have observed in which the infection prevalence changes non-uniformly across the metapopulation when varying the value of a parameter.

### 4 Conclusion

In this paper, we have presented a system of differential equations of reaction-diffusion type describing the TB spread in heterogeneous complex metapopulations. The spatial configuration is given by the degree \( p(k) \) and the conditional probabilities \( P(k \mid k') \). For uncorrelated networks under the assumption of standard incidence transmission, we have computed the disease-free equilibrium and the basic reproduction number. We have also shown that the disease-free equilibrium is locally asymptotically stable. Moreover, for uncorrelated networks and under assumption of simple mass action transmission, necessary and sufficient
conditions for the instability of the disease-free equilibrium for uncorrelated networks have been given in term of the highest and lowest connectivities of patches. We have also shown that if the basic reproduction number \( R_0 > 1 \), then the simple mass action model could have multiple endemic equilibria. Through numerical simulations, we found that the prevalence of the infection increases with the path connectivity. Also, increasing the value of the migration rates cause a reduction in the prevalence of the infection.

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**Appendix A: Proof of Lemma 1**

In this appendix, we give the proof of Lemma 1. Note that the matrix \( N \) can be written as

\[
N = \begin{bmatrix}
N_1 & N_2 \\
N_3 & N_4
\end{bmatrix},
\]

\[
= \begin{bmatrix}
N_1 & 0 \\
N_3 & I
\end{bmatrix} \begin{bmatrix}
I & N_1^{-1}N_2 \\
0 & D
\end{bmatrix}.
\]

Then, one can deduce that

\[
N^{-1} = \begin{bmatrix}
I & N_1^{-1}N_2 \\
0 & D
\end{bmatrix}^{-1} \begin{bmatrix}
N_1 & 0 \\
N_3 & I
\end{bmatrix}^{-1},
\]

\[
= \begin{bmatrix}
I & -N_1^{-1}N_2D^{-1} \\
0 & D^{-1}
\end{bmatrix} \begin{bmatrix}
N_1^{-1} & 0 \\
-N_3N_1^{-1} & I
\end{bmatrix},
\]

\[
= \begin{bmatrix}
N_1^{-1} + N_1^{-1}N_2D^{-1}N_3N_1^{-1} - N_1^{-1}N_2D^{-1} \\
-D^{-1}N_3N_1^{-1} & D^{-1}
\end{bmatrix}.
\]

This ends the proof.

\[\Box\]

**Appendix B: Proof of Lemma 3**

In this appendix, we give the proof of Lemma 3. To do so, we shall use the properties of the determinant.
Let \( \lambda \) the spectrum of \( M \). Assume that \( M \) is a \( 2n \times 2n \) square matrix, then,
\[
\det(M - \lambda I_{2n}) = \det \begin{bmatrix} M_1 - \lambda I_n & M_2 \\ M_3 & M_4 - \lambda I_n \end{bmatrix},
\]
\[
= (-1)^n \det \begin{bmatrix} M_2 & M_1 - \lambda I_n \\ M_4 - \lambda I_n & M_3 \end{bmatrix},
\]
\[
= (-1)^n \det(M_2) \det \left[ M_3 - (M_4 - \lambda I_n)\left[M_2^{-1}(M_1 - \lambda I_n)\right] \right],
\]
\[
= (-1)^n \det \left[ M_2 M_3 - M_2 M_4 M_2^{-1} M_1 + \lambda (M_1 + M_2 M_4 M_2^{-1}) - \lambda^2 I_n \right].
\]

If \( M_2 M_3 - M_2 M_4 M_2^{-1} M_1 = 0 \), then
\[
\det(M - \lambda I_{2n}) = (-\lambda)^n \det \left[ M_1 + M_2 M_4 M_2^{-1} - \lambda I_n \right].
\]

Moreover if \( M_2 M_4 = M_4 M_2 \) then
\[
\det(M - \lambda I_{2n}) = (-\lambda)^n \det \left[ M_1 + M_4 - \lambda I_n \right].
\]

This ends the proof.

\[\Box\]

**Appendix C: Proof of Lemma 2**

In this Appendix, we give the proof of Lemma 2. To do so, it suffices to verified that \( GG^{-1} = I_n \). Indeed, one has
\[
GG^{-1} = UU^{-1} - X \left[ W^{-1} + ZU^{-1}X \right]^{-1} ZU^{-1} + XWZU^{-1}
\]
\[
= XWZU^{-1}X \left[ W^{-1} + ZU^{-1}X \right]^{-1} ZU^{-1},
\]
\[
= I_n - X \left[ W^{-1} + ZU^{-1}X \right]^{-1} W - WZU^{-1}X \left[ W^{-1} + ZU^{-1}X \right]^{-1} ZU^{-1},
\]
\[
= I_n - XW \left[ W^{-1} + ZU^{-1}X \right]^{-1} - I_n + ZU^{-1}X \left[ W^{-1} + ZU^{-1}X \right]^{-1} ZU^{-1},
\]
\[
= I_n - XW \left[ W^{-1} + ZU^{-1}X \right] \left[ W^{-1} + ZU^{-1}X \right]^{-1} I_n ZU^{-1},
\]
\[
= I_n - XW(I_n - I_n)ZU^{-1},
\]
\[
= I_n.
\]

This concludes the proof.

\[\Box\]

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