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DYNAMICS OF THE SPREAD OF TUBERCULOSIS IN HETEROGENEOUS COMPLEX METAPOPULATIONS

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This paper analyzes the dynamics of the 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, we give a necessary and sufficient condition 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: Dynamical systems; tuberculosis; complex metapopulation; uncorrelated networks; basic reproduction number; stability.

Tuberculosis (abbreviated as TB for tubercle bacillus) is a common deadly infectious disease caused mainly by the *Mycobacterium tuberculosis* (MTB). It basically attacks the lungs (pulmonary TB), but can also affect the central nervous system, the 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

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unsterilized eating utensils and in rare cases a pregnant woman with active TB can infect her foetus (vertical transmission) [Global Fund to Fight AIDS, Tuberculosis and Malaria, 2006; WHO, 2009]. 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 [Global Fund to Fight AIDS, Tuberculosis and Malaria, 2006; WHO, 2009; Dye, 2000; Snider *et al.*, 1994; Bloom, 1994]. 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 [Global Fund to Fight AIDS, Tuberculosis and Malaria, 2006]. More than 36 million patients have been successfully treated via the World Health Organization (WHO) strategy for tuberculosis control since 1995. Despite predictions of a decline in global incidence, the number of new cases continues to grow, approaching 10 million in 2010 [Global Fund to Fight AIDS, Tuberculosis and Malaria, 2006; WHO, 2009]. This rise has been attributed to the spread of HIV, the collapse of public health programs, the emergence of drug-resistant strains of MTB [Dye, 2000; Snider *et al.*, 1994; Bloom, 1994] and exogenous re-infections, where a latently-infected individual acquires a new infection from other infections [Feng *et al.*, 2000]. 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 the mathematical analysis of biomedical and disease transmission models can contribute to the understanding of the mechanisms of those processes and to design potential therapies [Hethcote, 2000; Murphy *et al.*, 2002; Feng *et al.*, 2000; Murphy *et al.*, 2003; Bhunu *et al.*, 2008; Bowong & Tewa, 2009; Blower & Gerberding, 1998].

However, the analysis of the spread of infectious diseases on complex networks has become a central issue in modern epidemiology [Keeling & Eames, 2005; Kuperman & Abramson, 2001; Auger *et al.*, 2009] and, indeed, it was one of the main motivations for the development of percolation theory [Newman, 2004]. While the initial approach was focussed on local contact networks [Lloyd & May, 1996; Pastor-Satorras & Vespignani, 2001; Newman, 2001; Colizza *et al.*, 2007a], i.e. 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 migration. 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 [MacArthur & Wilson, 1967].

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 multipatch, multicompartment 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 [Lloyd & Jansen, 2004; Lajmanovich & Yorke, 1976]. 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 ones.

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 thanks to the increasing of computational power [Colizza *et al.*, 2007a]. However, an alternative approach based on the formalism used in statistical mechanics of complex networks is presented in [Colizza *et al.*, 2007b; Colizza & Vespignani, 2007, 2008]. 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 [Saldana, 2008;

Juher *et al.*, 2009], the authors consider reaction diffusion processes to take place simultaneously, which turns out to be a correct assumption for a suitable continuous-time formulation of metapopulation models for the spread of infectious diseases.

In this paper, motivated by the usefulness of and the current investigation on the complexity of the spread of infectious diseases on heterogeneous populations, we intend to systematically analyze the dynamics of the spread of tuberculosis in the modeling framework. We consider the spread of TB on complex metapopulations, i.e. 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. We give a necessary and sufficient condition for the instability of the disease-free equilibrium for uncorrelated networks. 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. Comparing to existing results in the literature, our work treats a specific disease which is not the case in [Saldana, 2008; Juher *et al.*, 2009; Saldana, 2010]. We point out that in [Saldana, 2008; Juher *et al.*, 2009; Saldana, 2010], the authors have neglected some important epidemiological features of a disease propagation such as birth, natural mortality, disease related mortality 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. The proposd model is of dimension 3 and incorporates 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 and treatment of infectious. Also, the total population is not constant. It is our view, this study represents the first work that provides an in-depth spread of TB on complex metapopulations using a degree of distribution and conditional probabilities.

1. A TB Metapopulation Model

1.1. *The model*

We consider the spread of TB in heterogeneous metapopulations. The model consists of n patches. 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) and infectious (has active TB). These states are average number (density) of $\rho_{S,k}$, $\rho_{E,k}$ and $\rho_{I,k}$ in the patches of connectivity k, respectively. The total variable population size at time t is given by,

$$\rho_k(t) = \rho_{S,k}(t) + \rho_{E,k}(t) + \rho_{I,k}(t). \tag{1}$$

It is assumed that births are recruited into the population at per capita rate Λ. The transmission of MTB occurs following adequate contacts between a susceptible and infectious in each subpopulation. The rate at which susceptible are infected is $\beta\rho_{I,k}\rho_{S,k}$ which is a mass action (or density-dependent) transmission, where β is the effective contact rate of infectious that is sufficient to transmit the infection to susceptible (it also denotes how contagious the disease is). On adequate contacts with active TB 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 enters 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 θ 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.* [1980] 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 then before treatment, a number generally too low to be detected on direct examination. Latently infected individuals who did not received effective chemoprophylaxis progress to active TB at a rate $\alpha(1-\theta)$ where α is the rate at which latently infected individuals become infectious (this value is connected with the average time of incubations). After receiving an effective therapy, an individual leaves the class of infectious to the class of latently infected at a constant rate γ which is the probability that an infectious individual will recover.

The rate for nondisease-related death is μ, thus, $1/\mu$ is the average lifetime. Infectious individuals have additional death rate due to disease by a rate d.

According to the derivation in [Saldana, 2008; Juher *et al.*, 2009] of the continuous-time formulation for the progress of diseases on metapopulations, the equations governing the dynamics of TB propagation are

$$\begin{cases} \dot{\rho}_{S,k} = \Lambda - \beta\rho_{I,k}\rho_{S,k} - \mu\rho_{S,k} - D_S\rho_{S,k} \\ \qquad + kD_S\sum_{k'} P(k'\,|\,k)\dfrac{\rho_{S,k'}}{k'}, \\ \dot{\rho}_{E,k} = \beta(1-q)\rho_{I,k}\rho_{S,k} + \gamma\rho_{I,k} \\ \qquad - [\mu+\alpha(1-\theta)]\rho_{E,k} - D_E\rho_{E,k} \\ \qquad + kD_E\sum_{k'} P(k'\,|\,k)\dfrac{\rho_{E,k'}}{k'}, \\ \dot{\rho}_{I,k} = \beta q\rho_{I,k}\rho_{S,k} + \alpha(1-\theta)\rho_{E,k} \\ \qquad - (\mu+d+\gamma)\rho_{I,k} - D_I\rho_{I,k} \\ \qquad + kD_I\sum_{k'} P(k'\,|\,k)\dfrac{\rho_{I,k'}}{k'}, \end{cases} \tag{2}$$

where k is the degree of the patches where local population live ($k = k_1, \ldots, k_{\max}$), and $P(k'\,|\,k)$ is the conditional probability that a path of degree k has a connection to a path of degree k'. As in classical reaction–diffusion processes, Eq. (2) expresses the time variation of susceptible, latently infected individuals and infectious 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 k 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 ($D_s, D_E, D_I > 0$).

1.2. *Positively-invariant set*

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

$$\begin{cases} \dot{\rho}_S = \Lambda - \beta\sum_k p(k)\rho_{I,k}\rho_{S,k} - \mu\rho_S - D_S\rho_S \\ \qquad + D_S\sum_k\sum_{k'} kp(k)P(k'\,|\,k)\dfrac{\rho_{S,k'}}{k'}, \\ \dot{\rho}_E = \beta(1-q)\sum_k p(k)\rho_{I,k}\rho_{S,k} + \gamma\rho_I \\ \qquad - [\mu+\alpha(1-\theta)]\rho_E - D_E\rho_E \\ \qquad + D_E\sum_k\sum_{k'} kp(k)P(k'\,|\,k)\dfrac{\rho_{E,k'}}{k'}, \\ \dot{\rho}_I = \beta q\sum_k p(k)\rho_{I,k}\rho_{S,k} + \alpha(1-\theta)\rho_E \\ \qquad - (\mu+d+\gamma)\rho_I - D_I\rho_I \\ \qquad + D_I\sum_k\sum_{k'} kp(k)P(k'\,|\,k)\dfrac{\rho_{I,k'}}{k'}, \end{cases} \tag{3}$$

where $\rho_j(t) = \sum_k p(k)\rho_{j,k}$, $j = S, E, I$. 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 nondirected graphs, we have the following relationship between $p(k)$ and $P(k'\,|\,k)$ [Boguna & Pastor-Satorras, 2002]:

$$kP(k'\,|\,k)p(k) = k'P(k\,|\,k')p(k'). \tag{4}$$

Using this restriction and the fact that $\sum_k \times P(k\,|\,k') = 1$ after changing the order of summations, Eq. (3) becomes

$$\begin{cases} \dot{\rho}_S = \Lambda - \beta \sum_k p(k) \dfrac{\rho_{I,k}\rho_{S,k}}{\rho_k} - \mu\rho_S, \\ \dot{\rho}_E = \beta(1-q) \sum_k p(k)\rho_{I,k}\rho_{S,k} + \gamma\rho_I \\ \qquad - [\mu + \alpha(1-\theta)]\rho_E, \\ \dot{\rho}_I = \beta q \sum_k p(k)\rho_{I,k}\rho_{S,k} + \alpha(1-\theta)\rho_E \\ \qquad - (\mu + d + \gamma)\rho_I. \end{cases} \tag{5}$$

Adding all the expressions on the right-hand side of model system (5) yields

$$\frac{d\rho}{dt} = \Lambda - \mu\rho - d\rho_I. \tag{6}$$

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 [Lakshmikantham *et al.*, 1989], 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) enter the region:

$$\Omega = \left\{ (\rho_S, \rho_E, \rho_I) \in \mathbb{R}^{3n}_{\geq 0}, \rho(t) \leq \frac{\Lambda}{\mu} \right\}. \tag{7}$$

Thus, it follows from Eq. (7) that all possible solutions of model system (5) will enter the region Ω. Hence, the region Ω, of biological interest, is positively-invariant under the flow induced by model system (5). Further, it can be shown using the theory of permanence [Berman & Plemmons, 1994] that all solutions on the boundary of Ω eventually enter the interior of Ω. Furthermore, in Ω, the usual existence, uniqueness and continuation results hold for model system (5). Hence, model system (5) is well posed mathematically and epidemiologically and it is sufficient to consider the dynamics of the flow generated by model system (5) in Ω.

For networks with a connectivity pattern defined by a set of conditional probabilities $P(k' \mid k)$, we define the elements of the connectivity matrix C as

$$C_{kk'} = \frac{k}{k'} P(k' \mid k).$$

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 [Pastor-Satorras & Vespignani, 2001]. One should notice that, for those degrees k that are not present in the network, $P(k' \mid k) = 0$, $\forall k'$. 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 SEI model.

2. Uncorrelated Networks

In order to obtain analytical results about the TB metapopulation dynamics, we need to be precise about the form of $P(k' \mid k)$. 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 $P(k' \mid k) = k'p(k')/\langle k \rangle$ which corresponds to the degree distribution of nodes (patches) as a result of following a randomly chosen link [Newman *et al.*, 2001].

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

$$\begin{cases} \dot{\rho}_{S,k} = \Lambda - \beta\rho_{I,k}\rho_{S,k} - \mu\rho_{S,k} \\ \qquad - D_S\left(\rho_{S,k} - \dfrac{k}{\langle k \rangle}\rho_S\right), \\ \dot{\rho}_{E,k} = \beta(1-q)\rho_{I,k}\rho_{S,k} + \gamma\rho_{I,k} \\ \qquad - [\mu + \alpha(1-\theta)]\rho_{E,k} \\ \qquad - D_E\left(\rho_{E,k} - \dfrac{k}{\langle k \rangle}\rho_E\right), \\ \dot{\rho}_{I,k} = \beta q\rho_{I,k}\rho_{S,k} + \alpha(1-\theta)\rho_{E,k} \\ \qquad - (\mu + d + \gamma)\rho_{I,k} - D_I\left(\rho_{I,k} - \dfrac{k}{\langle k \rangle}\rho_I\right), \end{cases} \tag{8}$$

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 and infectious individuals in patches of connectivity k, $D_s\rho_{S,k}$, $D_E\rho_{E,k}$ and $D_I\rho_{I,k}$ and the total inflow of susceptible, latently infected and infectious individuals across all their k connections, which is k times the average flow of individuals across a connection in the network, $D_S\rho_S/\langle k\rangle$, $D_E\rho_E/\langle k\rangle$ and $D_I\rho_I/\langle k\rangle$. Note that this average flow across a connection does not depend on the degree k of the considered path because we assume that the architecture of the metapopulation is described by an uncorrelated network.

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

$$C_{kk'} = \frac{kp(k')}{\langle k\rangle}. \tag{9}$$

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" model system (8), using the following vectors of $\mathbb{R}^n$:

$$S = (\rho_{S,k_1}, \rho_{S,k_2}, \ldots, \rho_{S,k_n})^T,$$
$$E = (\rho_{E,k_1}, \rho_{E,k_2}, \ldots, \rho_{E,k_n})^T,$$
$$I = (\rho_{I,k_1}, \rho_{I,k_2}, \ldots, \rho_{I,k_n})^T,$$
$$N = (\rho_1, \rho_2, \ldots, \rho_n)^T$$

and

$$\mathbb{I} = (1, 1, \ldots, 1)^T.$$

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

$$\begin{cases} \dot{S} = \Lambda\mathbb{I} - \beta\,\mathrm{diag}(I)S - (\mu + D_S)S \\ \qquad + D_S CS, \\ \dot{E} = \beta(1-q)\mathrm{diag}(I)S + \gamma I \\ \qquad - [\mu + \alpha(1-\theta) + D_E]E + D_E CE, \\ \dot{I} = \beta q\,\mathrm{diag}(I)S + \alpha(1-\theta)E \\ \qquad - (\mu + d + \gamma + D_I)I + D_I CI, \end{cases} \tag{10}$$

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

We point out that in the case where the parameters β, q, γ, μ, α, θ and d are not the same for all patches, they are replaced in model system (10) by diagonal non-negative matrices and this does not change the fundamental structure of the system.

2.1. *Disease-free equilibrium (DFE) for generic networks*

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

$$\begin{cases} \Lambda - \beta\rho^0_{I,k}\rho^0_{S,k} - \mu\rho^0_{S,k} - D_S\rho^0_{S,k} \\ \qquad + kD_S\sum_{k'} P(k'\,|\,k)\dfrac{\rho^0_{S,k'}}{k'} = 0, \\ \beta(1-q)\beta\rho^0_{I,k}\rho^0_{S,k} + \gamma\rho^0_{I,k} - [\mu + \alpha(1-\theta)]\rho^0_{E,k} \\ \qquad - D_E\rho^0_{E,k} + kD_E\sum_{k'} P(k'\,|\,k)\dfrac{\rho^0_{E,k'}}{k'} = 0, \\ \beta q\rho^0_{I,k}\rho^0_{S,k} + \alpha(1-\theta)\rho^0_{E,k} - (\mu + d + \gamma)\rho^0_{I,k} \\ \qquad - D_I\rho^0_{I,k} + kD_I\sum_{k'} P(k'\,|\,k)\dfrac{\rho^0_{S,k'}}{k'} = 0. \end{cases} \tag{11}$$

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

$$(\mu + D_S)\rho^0_{S,k} = \Lambda + D_S\sum_{k'} C_{kk'}\rho^0_{S,k'}.$$

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

$$\rho^0_{S,k} = \frac{\Lambda}{\mu + D_S}\left(1 + \frac{D_S}{\mu}\frac{k}{\langle k\rangle}\right), \quad \forall k. \qquad (12)$$
$$\rho^0_{E,k} = \rho^0_{I,k} = 0,$$

2.2. *Basic reproduction number and local stability of the DFE*

The global behavior for model system (10) crucially depends on the basic reproduction number, that is, an average number of secondary cases produced by a single infective individual which is introduced into an entirely susceptible population. Model system (10) has an evident equilibrium $Q_0 = (S^0, 0, 0)$ with $S^0_k = \rho^0_{S,k}$ defined as in Eq. (12) and 0 is the zero vector of dimension n when there is no disease.

Linearizing model system (10) around the disease-free equilibrium $S^0 = (\rho^0_{S,1}, \rho^0_{S,2}, \ldots, \rho^0_{S,n})^T$ where $\rho^0_{S,k}$ is defined as in Eq. (12), one obtains that the Jacobian matrix is the following block matrix:

$$J = \begin{bmatrix} J_1 & 0 & J_2 \\ 0 & J_3 & J_4 \\ 0 & J_5 & J_6 \end{bmatrix},$$

where

$$J_1 = D_S C - (\mu + D_S) I_n,$$
$$J_2 = -\beta\,\mathrm{diag}(S^0),$$
$$J_3 = D_E C - [\mu + D_E + \alpha(1-\theta)] I_n,$$
$$J_4 = \beta(1-q)\mathrm{diag}(S^0) + \gamma I_n,$$
$$J_5 = \alpha(1-\theta) I_n,$$
$$J_6 = D_I C - (\mu + d + \gamma + D_I) I_n + \beta q\,\mathrm{diag}(S^0),$$

and 0 are $n \times n$ matrices with 0 being the zero matrix and n the number of degrees in the metapopulation.

Note that the upper blocks of the Jacobian matrix are computed differentiating equations in model system (10) with respect to susceptible, latently-infected and infectious individuals in patches of degree k, respectively. The triangular structure of the Jacobian implies that its characteristic polynomial factorizes as $Q(s) = Q_{J_1}(s) Q_{J_0}(s)$ with $Q_{J_1}(s)$ and $Q_{J_0}(s)$ being the characteristic polynomial of the main diagonal blocks with

$$J_0 = \begin{bmatrix} J_3 & J_4 \\ J_5 & J_6 \end{bmatrix}.$$

The submatrix J_0 defines the linear dynamics of latently infected individuals and infectious around the disease-free equilibrium. Therefore, a positive dominant eigenvalue of J_0 implies an increase of the number of latently infected individuals and infectious initially added to a resident population of susceptible individuals at the equilibrium.

Hence, the eigenvalues of J are those of the submatrix J_1 plus those of the submatrix J_0. From the knowledge of the eigenvalues of C, the eigenvalues of J_1 are those of $D_S C$ shifted by $-(D_S + \mu)$. It follows that $Q_{J_1}(s) = (s+\mu)(s + D_S + \mu)^{n-1}$ and, hence, the largest eigenvalue of J_1 is always $s = -\mu$. This implies that the submatrix J_1 is stable. On the other hand, using the results in [Kamgang & Sallet, 2005] on the computation of eigenvalues of an arbitrary matrix of dimension n, the eigenvalues of the submatrix J_0 are associated with the eigenvalues of the following $n \times n$ matrix:

$$J_6 - J_5 J_3^{-1} J_4.$$

To compute the expression of $J_6 - J_5 J_3^{-1} J_4$, we need to compute the inverse matrix of J_3. To do so, we shall used the following Lemma 1 stated below and proved in Appendix A.

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

$$R^{-1} = U^{-1} - U^{-1}X[W^{-1} + ZU^{-1}X]^{-1}ZU^{-1}. \qquad (13)$$

Note that the matrix J_3 may be written in the form $R = U + XWZ$ with $U = -(\mu + D_S) I_n$, $X = [k_1, k_2, \ldots, k_n]^T$, $W = 1$ and $Z = \frac{D_S}{\langle k\rangle}[p(k_1), \ldots, p(k_n)]$. Then using Lemma 1, one can easily prove that the inverse matrix of J_3 is given by

$$J_3^{-1} = \frac{-1}{[\mu + D_E + \alpha(1-\theta)]}\left[I_n + \frac{D_E C}{\mu + \alpha(1-\theta)}\right].$$

With this in mind, using the above expression of J_3^{-1}, one has

$$J_5 J_3^{-1} J_4 = J_3^{-1} J_5 J_4 = -\left[I_n + \frac{D_E C}{\mu + \alpha(1-\theta)}\right] \times \mathrm{diag}\left(\frac{\alpha(1-\theta)[\beta(1-q)S^0 + \gamma\mathbb{I}]}{\mu + D_E + \alpha(1-\theta)}\right).$$

Then, one can deduce that

$$\begin{aligned} J_6 - J_5 J_3^{-1} J_4 &= D_I C + \operatorname{diag}(\beta q S^0 - (\mu + d + \gamma + D_I)\mathbb{I}) \\ &\quad + \left[I_n + \frac{D_E C}{\mu + \alpha(1-\theta)} \right] \operatorname{diag}\left(\frac{\alpha(1-\theta)[\beta(1-q)S^0 + \gamma\mathbb{I}]}{[\mu + D_E + \alpha(1-\theta)]} \right), \\ &= C \operatorname{diag}\left(\frac{D_E \alpha(1-\theta)[\beta(1-q)S^0 + \gamma\mathbb{I}]}{[\mu + D_E + \alpha(1-\theta)][\mu + \alpha(1-\theta)]} + D_I \mathbb{I} \right) \\ &\quad + \operatorname{diag}\left(\frac{\beta[\alpha(1-\theta) + q(\mu + D_E)]S^0}{[\mu + D_E + \alpha(1-\theta)]} \right) \\ &\quad - \operatorname{diag}\left(\frac{[(\mu + D_E)(\mu + d + \gamma + D_I) + \alpha(1-\theta)(\mu + d + D_I)]\mathbb{I}}{[\mu + D_E + \alpha(1-\theta)]} \right), \\ &= C \operatorname{diag}(V^*) + \operatorname{diag}(W^*), \end{aligned}$$

where

$$V^* = \frac{D_E \alpha(1-\theta)[\beta(1-q)S^0 + \gamma\mathbb{I}]}{[\mu + D_E + \alpha(1-\theta)][\mu + \alpha(1-\theta)]} + D_I \mathbb{I} \gg 0,$$

$$W^* = \frac{\beta[\alpha(1-\theta) + q(\mu + D_E)]S^0 - [(\mu + D_E)(\mu + d + \gamma + D_I) + \alpha(1-\theta)(\mu + d + D_I)]\mathbb{I}}{[\mu + D_E + \alpha(1-\theta)]}.$$

Thus, the eigenvalues of $J_6 - J_5 J_3^{-1} J_4$ reduce to the eigenvalues of the matrix $L = C \operatorname{diag}(V^*) + \operatorname{diag}(W^*)$. Note that the matrix L is the sum of a rank-one matrix and a diagonal matrix. Then, 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 [Anderson, 1996], the eigenvalues $\lambda_{k_1} < \lambda_{k_2} < \cdots < \lambda_{k_n} = \lambda_{k_{\max}}$ of L interlace with the eigenvalues $W^*_{k_1} < W^*_{k_2} < \cdots < W^*_{k_n}$ of $\operatorname{diag}(W^*)$ as follows

$$\begin{aligned} W^*_{k_1} < \lambda_{k_1} < W^*_{k_2} < \lambda_{k_2} \\ < \cdots < \lambda_{k_{n-1}} < W^*_{k_n} < \lambda_{k_n} = \lambda_{k_{\max}}. \end{aligned}$$

Then, it follows that the greatest eigenvalue λ_{k_n} of L satisfies $\lambda_{k_{\max}} > W^*_{k_n} = W^*_{k_{\max}} > 0$. In summary, all eigenvalues of the Jacobian matrix of model system (10) at the disease-free equilibrium Q_0 are real and the largest one is $\lambda_{\max} = \lambda_{k_{\max}}$, with

$$\lambda_{k_n} > \frac{\beta[\alpha(1-\theta) + q(\mu + D_E)]\rho^0_{S,k_n} - [(\mu + D_E)(\mu + d + \gamma + D_I) + \alpha(1-\theta)(\mu + d + D_I)]}{[\mu + D_E + \alpha(1-\theta)]} > 0.$$

Therefore, a sufficient condition for this equilibrium to be unstable is given by

$$\rho^0_{S,k_{\max}} > \frac{[(\mu + D_E)(\mu + d + \gamma + D_I) + \alpha(1-\theta)(\mu + d + D_I)]}{\beta[\alpha(1-\theta) + q(\mu + D_E)]}. \tag{14}$$

This condition simply says that, if the number of individuals inhabiting those patches with lowest connectivity in the metapopulation, for fixed values of μ, γ, D_E, D_I, q, θ, β, d and α, a large enough $\rho^0_{S,k_{\max}}$ guarantee the instability of the disease-free equilibrium. This implies that the infection reaches all patches.

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 number $\mathcal{R}_0$, 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 $\mathcal{R}_0 > 1$. Note that $\rho^0_{S,k_{\max}}$ is defined as

$$\rho^0_{S,k_{\max}} = \frac{\Lambda}{\mu\langle k\rangle(\mu + D_S)}[\mu\langle k\rangle + k_{\max}D_S].$$

Thus, large values of the patch connectivity lead to a large enough $\rho^0_{S,k_{\max}}$. Now, rearranging Eq. (14) yields

$$\frac{\Lambda\beta[k_{\max}D_S + \mu\langle k\rangle][\alpha(1-\theta) + q(\mu + D_E)]}{\mu\langle k\rangle(\mu + D_S)[(\mu + D_E)(\mu + d + \gamma + D_I) + \alpha(1-\theta)(\mu + d + D_I)]} > 1.$$

Note that in the limit of very large networks with bounded average degree $\langle k\rangle$, the above sufficient condition implies that there always exists an epidemic threshold for any degree distribution.

Using the above condition, it then follows that the basic reproduction ratio $\mathcal{R}_0 > 1$ is given by

$$\mathcal{R}_0 = \frac{\Lambda\beta[k_{\max}D_S + \mu\langle k\rangle][\alpha(1-\theta) + q(\mu + D_E)]}{\mu\langle k\rangle(\mu + D_S)[(\mu + D_E)(\mu + d + \gamma + D_I) + \alpha(1-\theta)(\mu + d + D_I)]}. \tag{15}$$

Thus, crossing the threshold reduces the basic reproductive number $\mathcal{R}_0$ below unity and the infection is prevented from propagating.

2.3. *Endemic equilibrium*

Herein, we investigate the existence of the endemic equilibrium of model system (10). To this end, it is more convenient to write model system (10) in a more compact form. In a more compact form, model system (10) may be written as follows:

$$\begin{cases} \dot{x} = \Lambda\mathbb{I} - \operatorname{diag}(By)x + [D_S C - (\mu + D_S)]x, \\ \dot{y} = \displaystyle\sum_{i=1}^{n}\langle e_i \,|\, By\rangle\langle e_i \,|\, x\rangle(\mathcal{K}_i + \mathcal{K}_{i+n}) - Vy, \end{cases} \tag{16}$$

where $x = S \in \mathbb{R}^n_{\geq 0}$, $y = (E, I)^T \in \mathbb{R}^{2n}_{\geq 0}$, $\mathcal{K}_i \in \mathbb{R}^{2n}$ and $\mathcal{K}_{i+n} \in \mathbb{R}^{2n}$ are constant vectors with

$$\mathcal{K}_1 = (\underbrace{1-q, 0, \ldots, 0}, \underbrace{0, \ldots, 0}), \quad \mathcal{K}_2 = (\underbrace{0, 1-q, 0, \ldots, 0}, \underbrace{0, \ldots, 0}), \ldots,$$

$$\mathcal{K}_n = (\underbrace{0, \ldots, 0, 1-q}, \underbrace{0, \ldots, 0}), \quad \mathcal{K}_{n+1} = (\underbrace{0, \ldots, 0, q}, \underbrace{0, \ldots, 0}),$$

$$\mathcal{K}_{n+2} = (\underbrace{0, \ldots, 0, 0}, \underbrace{q, \ldots, 0}), \ldots, \quad \mathcal{K}_{2n} = (\underbrace{0, \ldots, 0, 0}, \underbrace{0, \ldots, 0, q}),$$

e_i is the canonical basis of $\mathbb{R}^n$, $B = [0, \beta I_n]$ with 0 a $n \times n$ null matrix, $\mathbb{I}$ is defined as in model system (10) and V is the $2n \times 2n$ constant matrix:

$$V = \begin{bmatrix} [\mu + \alpha(1-\theta) + D_E]I_n - D_E C & -\gamma I_n \\ -\alpha(1-\theta)I_n & [\mu + d + \gamma + D_I]I_n - D_I C \end{bmatrix}.$$

We point out that the matrix $-V$ is a Metzler matrix, that is, a matrix with all its off-diagonal entries non-negative [Berman & Plemmons, 1994; Jacquez & Simon, 1993].

With this new notation, and using the method of [Van den Driessche & Watmough, 2002], the basic reproduction number (15) satisfies

$$\mathcal{R}_0 = \xi\left[\sum_{i=1}^{n}\langle e_i \,|\, x^*\rangle BV^{-1}(\mathcal{K}_i + \mathcal{K}_{i+n})e_i^T\right], \tag{17}$$

where ξ is the spectral radius.

Let $Q^* = (x^*, y^*)$ be the positive endemic equilibrium of model system (16). Then, the positive endemic equilibrium (steady state with $y > 0$) can be obtained by setting the right-hand side of equations in model system (16) at zero, giving

$$\begin{cases} \Lambda\mathbb{I} - \operatorname{diag}(By^*)x^* + [D_S C - (\mu + D_S)I_n]x^* = 0, \\ \displaystyle\sum_{i=1}^{n}\langle e_i \,|\, By^*\rangle\langle e_i \,|\, x^*\rangle(\mathcal{K}_i + \mathcal{K}_{i+n}) - Vy^* = 0. \end{cases} \tag{18}$$

Multiplying the second equation of (18) by V^{-1} yields

$$y^* = \sum_{i=1}^{n} \langle e_i \,|\, By^* \rangle \langle e_i \,|\, x^* \rangle V^{-1}(\mathcal{K}_i + \mathcal{K}_{i+n}).$$

Using the first equation of (18), one has

$$x^* = [\mathrm{diag}(By^*) - [D_S C - (\mu + D_S) I_n]]^{-1} \Lambda \mathbb{I}.$$

Then, one can deduce that

$$\begin{aligned} y^* = & \sum_{i=1}^{n} \langle e_i \,|\, By^* \rangle \\ & \times \langle e_i \,|\, [\mathrm{diag}(By^*) - [D_S C - (\mu + D_S) I_n]]^{-1} \Lambda \mathbb{I} \rangle \\ & \times V^{-1}(\mathcal{K}_i + \mathcal{K}_{i+n}). \end{aligned} \tag{19}$$

Remind that at the disease-free equilibrium, one has

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

Plugging the above expression in Eq. (19) yields

$$\begin{aligned} y^* = & \sum_{i=1}^{n} \langle e_i \,|\, By^* \rangle \\ & \times \langle e_i \,|\, -[\mathrm{diag}(By^*) - [D_S C - (\mu + D_S) I_n]]^{-1} \\ & \times [D_S C - (\mu + D_S) I_n] x^0 \rangle V^{-1}(\mathcal{K}_i + \mathcal{K}_{i+n}). \end{aligned}$$

Multiplying the above equation by B and setting $z^* = By^*$ gives

$$\begin{aligned} z^* = & \sum_{i=1}^{n} \langle e_i \,|\, z^* \rangle \\ & \times \langle e_i \,|\, -P^{-1}(z^*)[D_S C - (\mu + D_S) I_n] x^0 \rangle \\ & \times B V^{-1}(\mathcal{K}_i + \mathcal{K}_{i+n}), \end{aligned} \tag{20}$$

where

$$P(z^*) = \mathrm{diag}(z^*) - [D_S C - (\mu + D_S) I_n].$$

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 $R = U + XWZ$ given in Lemma 1 with $U = \mathrm{diag}[z^* + (\mu + D_S)\mathbb{I}]$, $X = [k_1, k_2, \ldots, k_n]$, $W = 1$ and $Z = \frac{D_S}{\langle k \rangle}[p(k_1), p(k_2), \ldots, p(k_n)]$. Then, using Lemma 1, a simple computation gives

$$\begin{aligned} P^{-1}(z^*) = & \mathrm{diag}\left[\frac{1}{z_k^* + \mu + D_S}\right] \\ & \times \left[I_n + \frac{D_S C\, \mathrm{diag}\left[\dfrac{1}{z_k^* + \mu + D_S}\right]}{1 - \dfrac{D_S}{\langle k \rangle} \displaystyle\sum_k \frac{k p(k)}{z_k^* + \mu + D_S}} \right]. \end{aligned} \tag{21}$$

Now, from Eq. (20), one has

$$\langle e_j \,|\, z^* \rangle = \sum_{i=1}^{n} \langle e_i \,|\, z^* \rangle \langle e_i \,|\, P^{-1}(z^*) P(0) x^0 \rangle \langle e_j \,|\, B V^{-1}(\mathcal{K}_i + \mathcal{K}_{i+n}) \rangle, \quad j = 1, 2, \ldots, n, \tag{22}$$

where $P(0) = -[D_S C - (\mu + D_S) I_n]$. From the above equation, one can deduce that

$$\sum_{j=1}^{n} \langle e_j \,|\, z^* \rangle = \sum_{i=1}^{n} \langle e_i \,|\, z^* \rangle \langle e_i \,|\, P^{-1}(z^*) P(0) x^0 \rangle \left\langle \sum_{j=1}^{n} e_j \,|\, B V^{-1}(\mathcal{K}_i + \mathcal{K}_{i+n}) \right\rangle. \tag{23}$$

Then, to find the endemic equilibrium of model system (10), it suffices to find solutions of the following equation:

$$H(z^*) = 1, \tag{24}$$

where

$$H(z^*) = \frac{\displaystyle\sum_{i=1}^{n} \langle e_i \,|\, z^* \rangle \langle e_i \,|\, P^{-1}(z^*) P(0) x^0 \rangle \left\langle \sum_{j=1}^{n} e_j \,|\, B V^{-1}(\mathcal{K}_i + \mathcal{K}_{i+n}) \right\rangle}{\displaystyle\sum_{j=1}^{n} \langle e_j \,|\, z^* \rangle}, \tag{25}$$

where $P^{-1}(z^*)$ is defined as in Eq. (21). Note that z^* are the intersection points between the curve of $H(z^*)$ and the line $z = 1$.

From Eq. (25), it follows that the function $H(z^*)$ satisfies

$$\lim_{z^* \to +\infty} H(z^*) = 0,$$

and

$$\lim_{z^* \to 0} H(z^*) = \sum_{i=1}^{n} \langle e_i \,|\, x^0 \rangle \times \left\langle \sum_{j=1}^{n} e_j \,|\, BV^{-1}(\mathcal{K}_i + \mathcal{K}_{i+n}) \right\rangle.$$

We claim the following result.

Lemma 2. *The inequality* $\lim_{z^* \to 0} H(z^*) \geq \mathcal{R}_0$ *holds.*

Proof of Lemma. Let $A = \sum_{i=1}^{n} \langle e_i \,|\, x^* \rangle BV^{-1}(\mathcal{K}_i + \mathcal{K}_{i+n}) e_i^T$. Then, using Eq. (17), one has $\mathcal{R}_0 = \xi(A)$. Since A is a non-negative matrix, if $r_j = \sum_j^n A_{ji}$ is the sum of the jth column of A, one has

$$\min_j \{r_j\} \leq \xi(A) \leq \max_j \{r_j\}.$$

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

$$\begin{aligned} r_j &= e_j^T A \mathbb{I} \\ &= e_j^T \left(\sum_{i=1}^{n} \langle e_i \,|\, x^* \rangle BV^{-1}(\mathcal{K}_i + \mathcal{K}_{i+n}) e_i^T \right) \mathbb{I}, \\ &= e_j^T \left(\sum_{i=1}^{n} \langle e_i \,|\, x^* \rangle BV^{-1}(\mathcal{K}_i + \mathcal{K}_{i+n}) \right), \\ &= \left\langle e_j \,\middle|\, \sum_{i=1}^{n} \langle e_i \,|\, x^0 \rangle BV^{-1}(\mathcal{K}_i + \mathcal{K}_{i+n}) \right\rangle, \\ &= \sum_{i=1}^{n} \langle e_i \,|\, x^0 \rangle \langle e_j \,|\, BV^{-1}(\mathcal{K}_i + \mathcal{K}_{i+n}) \rangle. \end{aligned}$$

With this in mind, one can deduce that

$$\begin{aligned} \sum_{j=1}^{n} r_j &= \sum_{j=1}^{n} e_j^T A \mathbb{I}, \\ &= \sum_{i=1}^{n} \langle e_i \,|\, x^0 \rangle \left\langle \sum_{j=1}^{n} e_j \,|\, BV^{-1}(\mathcal{K}_i + \mathcal{K}_{i+n}) \right\rangle, \\ &= \lim_{z^* \to 0} H(z^*). \end{aligned}$$

Then, one has that

$$\mathcal{R}_0 = \xi(A) \leq \max_j \{r_j\} \leq \sum_j^n r_j,$$

which implies that $\lim_{z^* \to 0} H(z^*) \geq \mathcal{R}_0$. This completes the proof. ■

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 $\lim_{z^* \to 0} H(z^*) \geq \mathcal{R}_0$ and $\lim_{z^* \to +\infty} H(z^*) = 0$, $H(z^*)$ is a positive function. Thus, positive solutions of Eq. (24) exist if and only if $\lim_{z^* \to 0} H(z^*) > \mathcal{R}_0 > 1$. From the first equation of (18), one has $x^* = P^{-1}(z^*)\Lambda \mathbb{I}$. 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 $\mathcal{R}_0 > 1$, the equilibria are endemic. This means that there exists at least one endemic equilibrium of model system (10). Also, note that $z^* = By^*$ is not a bijection (it is a onto map, but not a one-to-one map), one can conclude that the TB model 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. (24) is very difficult to solve analytically due to the fact that H is a 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.

2.4. *Numerical studies*

To illustrate the various theoretical results contained in the previous section, model system (8) is simulated using the parameter value/range in Table 1. In all simulations, the initial conditions have been chosen randomly.

In Table 1, a^* denotes parameter values from [Bowong & Kurths, 2010], b^* from [Bhunu *et al.*, 2008] and c^* from [National Committee of Fight Against Tuberculosis of Cameroon, 2008].

Figure 1 shows the effects of the transmission rate β and the patch connectivity k on the basic reproduction number $\mathcal{R}_0$ given as in Eq. (15). We have taken a metapopulation with scale-free distribution $p(k) \sim k^{-3}$ with $\langle k \rangle = 6$, $k_{\min} = 3$ and $D_S = D_E = D_I = 1$ per year. 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

Table 1. Description and estimation of parameters.

Parameter	Description	Estimated Value	Source
Λ	Recruitment rate	1001 year^{-1}	a^*
β	Transmission coefficient	Variable	
μ	Per capita naturally death rate	0.017 year^{-1}	b^*
q	Fast route to active TB	0.015	b^*
α	Slow route to active TB	0.0024 year^{-1}	a^*
θ	Per capital rate of effective chemoprophylaxis	0.001 year^{-1}	c^*
γ	Recovery rate of infectious	0.7372 year^{-1}	a^*
d	Per capita disease-induced mortality rate	0.0012 year^{-1}	a^*
D_S	Diffusion rate of susceptible individuals	Variable	
D_E	Diffusion rate of latently-infected individuals	Variable	
D_I	Diffusion rate of infectious	Variable	

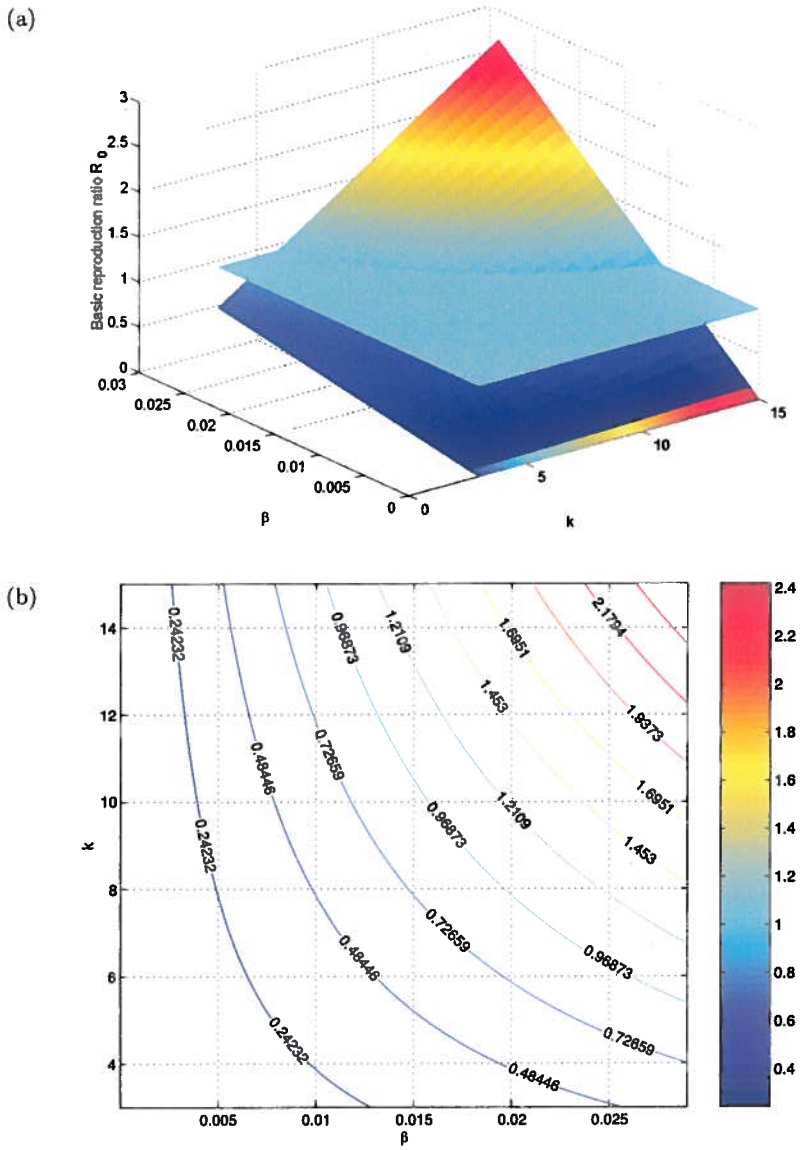
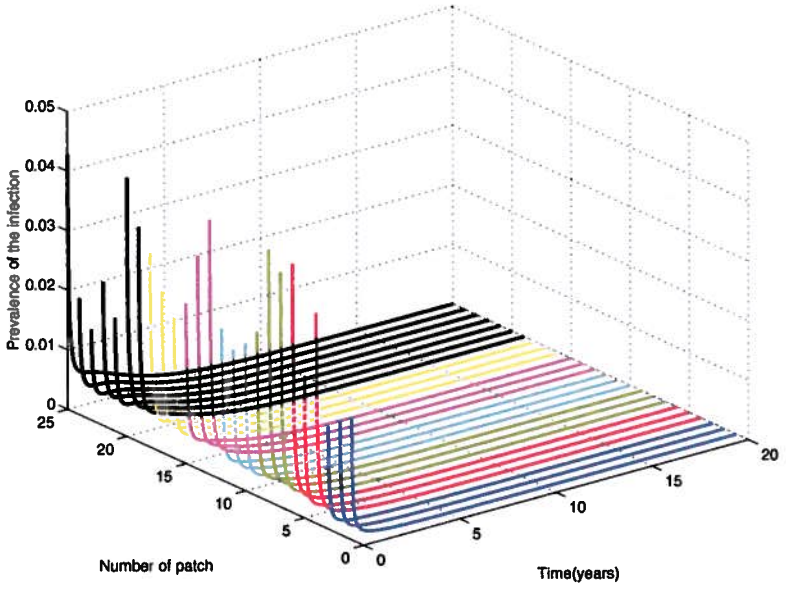


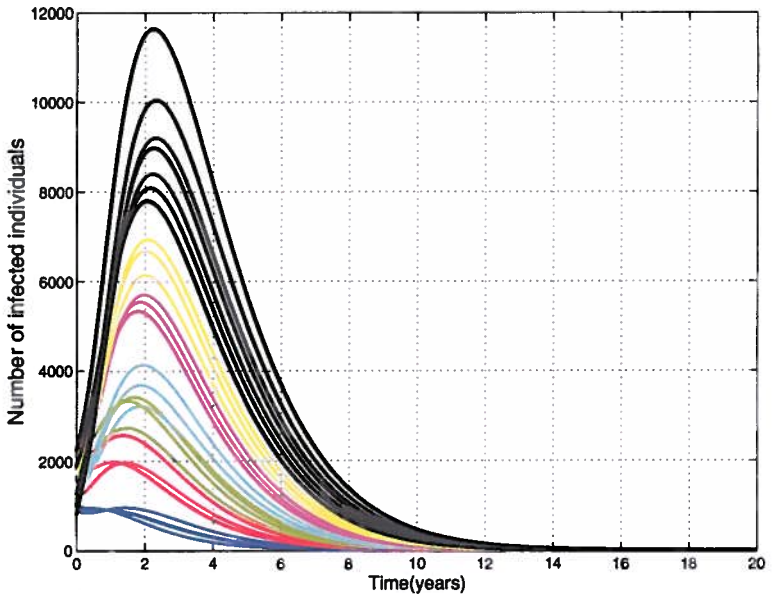
Fig. 1. Basic reproduction ratio given as in Eq. (15) as a function of the transmission rate and the patch connectivity when $D_S = D_E = D_I = 1$. All other parameters are as in Table 1.

the unity of the figure represents the region for the stability of the disease-free equilibrium. From this figure, one can see that $\mathcal{R}_0$ decreases if β decreases even in the case of large values of k. This means that if the transmission coefficient β 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 β. 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 β. The infection will equally persist for $k > 6$.

Figure 2 gives the evolution of model system (8) when $\beta = 0.0001$ and $D_S = D_E = D_I = 1$ (so that $\mathcal{R}_0 < 1$). All other parameters are as in



(a)

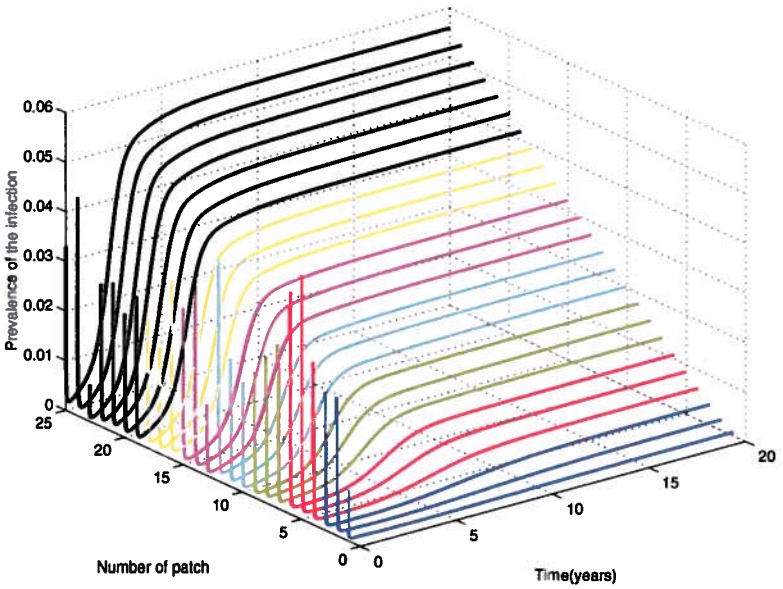


(b)

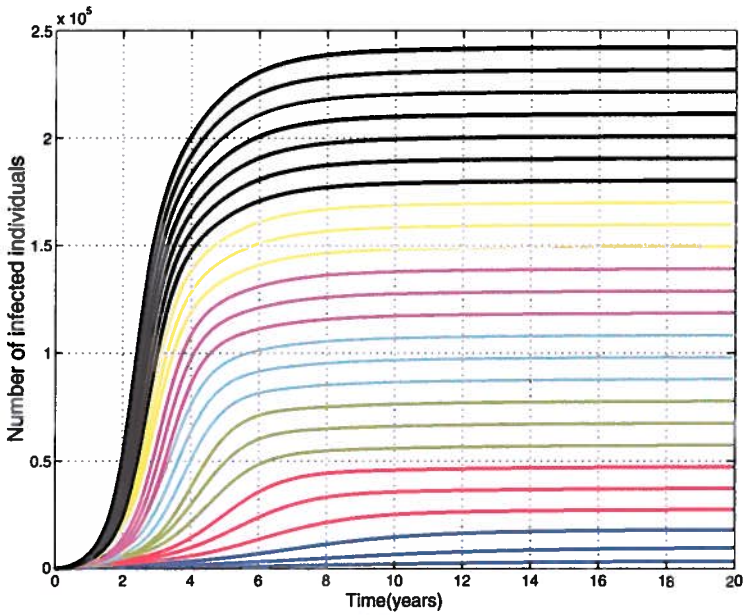
Fig. 2. Evolution of model system (8) when $\beta = 0.0002$ and $D_S = D_E = D_I = 1$ (so that $\mathcal{R}_0 < 1$). All other parameters are as in Fig. 1. (a) Prevalence curves and (b) time evolution of the number of infected individuals in each patch.

Fig. 1. Figure 2(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. 2(b). From these figures, it clearly appears that the disease disappears in the host population even for higher values of the patch connectivity.

Figure 3 gives the evolution of model system (8) when $\beta = 0.001$ and $D_S = D_E = D_I = 1$ (so that $\mathcal{R}_0 > 1$). All other parameters are as in Fig. 1. 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.



(a)



(b)

Fig. 3. Evolution of model system (8) when $\beta = 0.002$ and $D_S = D_E = D_I = 1$ (so that $\mathcal{R}_0 > 1$). All other parameters are as in Fig. 1. (a) Prevalence curves and (b) time evolution of the number of infected individuals in each patch.

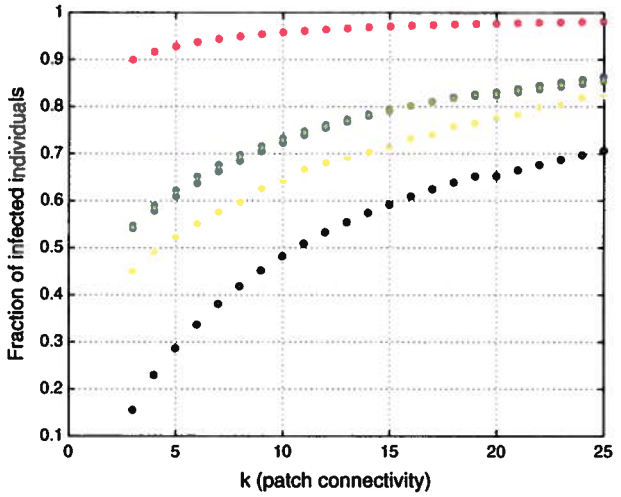


Fig. 4. Prevalence of the infection of model system (8) in nodes of degree k of an uncorrelated scale-free network when $\beta = 0.001$. All other parameters are as in Fig. 1. $D_S = 0.1$ and $D_E = D_I = 1$ (blue stars); $D_E = 0.1$ and $D_S = D_I = 1$ (red stars); $D_I = 0.1$ and $D_E = D_I = 1$ (green stars); $D_S = D_E = D_I = 1$ (yellow stars) and $D_S = D_E = D_I = 1.5$ (black stars).

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

Figure 4 presents the prevalence of the infection of model system (8) 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 and D_I is remarkable. Increasing the value of the migration rates D_S, D_E and D_I causes a reduction in the prevalence of the infection. This is the only case we have observed in which the infection prevalence changes nonuniformly across the metapopulation when varying the value of a parameter.

3. 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, a necessary and sufficient condition for the instability of the disease-free equilibrium for uncorrelated networks has been given. We have also shown that if the basic reproduction number $\mathcal{R}_0 > 1$, 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. To do so, it suffices to verify that $GG^{-1} = I_n$. Indeed, one has

$$\begin{aligned}
GG^{-1} &= UU^{-1} - X[W^{-1} + ZU^{-1}X]^{-1}ZU^{-1} \\
&\quad + XWZU^{-1} - XWZU^{-1}X \\
&\quad \times [W^{-1} + ZU^{-1}X]^{-1}ZU^{-1}, \\
&= I_n - X[[W^{-1} + ZU^{-1}X]^{-1} + W \\
&\quad - WZU^{-1}X[W^{-1} + ZU^{-1}X]^{-1}]ZU^{-1}, \\
&= I_n - XW[W^{-1}[W^{-1} + ZU^{-1}X]^{-1} - I_n \\
&\quad + ZU^{-1}X[W^{-1} + ZU^{-1}X]^{-1}]ZU^{-1}, \\
&= I_n - XW[[W^{-1} + ZU^{-1}X] \\
&\quad \times [W^{-1} + ZU^{-1}X]^{-1} - I_n]ZU^{-1}, \\
&= I_n - XW(I_n - I_n)ZU^{-1}, \\
&= I_n.
\end{aligned}$$

This concludes the proof. ■