Limits of a multi-patch SIS epidemic model

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Abstract

We start from a stochastic SIS model for the spread of epidemics among a population partitioned into M sites, each containing N individuals; epidemic spread occurs through within-site ('local') contacts and global contacts. We analyse the limit behaviour of the system as M and N increase to ∞. Two limit procedures are considered, according to the order in which M and N go to ∞; independently of the order, the limiting distribution of infected individuals across sites is a probability measure, whose evolution in time is governed by the weak form of a PDE. Existence and uniqueness of the solutions to this problem is shown. Finally, it is shown that the infected distribution converges, as time goes to infinity, to a Dirac measure at the value x^*, the equilibrium of a single-patch SIS model with contact rate equal to the sum of local and global contacts.

1 Introduction

The stochastic SIS model under discussion describes the spread of an epidemic among a population partitioned into M sites, each of N individuals, as it has been introduced by Ball [1]. It is assumed that susceptible individuals can become infected through contacts within the same site (at rate c), and through global contacts (at rate d) that do not depend on the site of individuals. The sites can be interpreted as households within a city, as in Ball's formulation [1], but may also be towns within a country [15], or habitable sites within the range of an animal population. In household model, the number of individual per site has to be small, while in other situation, it could be relevant to consider a larger local population.

From a mathematical point of view, this process can be modeled by a continuous time Markov chain, which involves the two size-parameters M and N, the local infection rate c, the global infection rate d, and the recovery rate γ. The same mathematical setting arises also in different biological and epidemiological contexts: for example, models of macroparasites infections [5] and metapopulation dynamics [19].

We are interested in the approximation of this stochastic model by deterministic systems, along the lines of Kurtz [20] or Barbour [4], [3]. In Section 2, we report two different deterministic approximations, which have been suggested in [1]. The first one is suitable for not so many sites, each with large population; the resulting system of M ordinary differential equations is a particular case of the SIS multigroup epidemic studied in [21] and [8], for which one has a complete description of the equilibria and of their stability. The second deterministic approximation describes instead a situation of a population of a large number of patches, each with small local population and derives a system of N ODE's for the proportion of patches with j infectives: for $N = 2$, [1] studies the equilibria and their stability, while for $N \geq 3$, only numerical investigations are performed.

It must be remarked that, within the context of structured metapopulation dynamics, Gyllenberg and co-workers [16, 17] have proposed models consisting of a PDE whose variable is the distribution of population densities across patches. Although there are no rigorous derivations, such models should correspond to the limiting case of infinitely many patches, each with infinitely large population.

Our aim here is indeed to study the behaviour of the process as both parameters M and N go to infinity: in Section 3, we introduce a new variable $Y^{N,M}(t)$, that gives a global description of the system at time t: it is a random probability measure that, roughly speaking, represents the fraction of patches with a percentage of infectives in an assigned range; its limit will also be a measure. The choice of a measure-valued function to describe the evolution over time of structured populations has been suggested in several papers by Diekmann and co-workers [9, 10]. Here, as in [17], the individual level is that of the single sites, the population level is actually the metapopulation one, and the state x is the infectious load.

We show in Sections 4 and 5 that, independently of the order in which the double limit is performed, the process $Y^{N,M}(t)$ converges to a deterministic measure $\mu(t)$. The convergence is proved by applying results of compactness for families of probability measures [7] and employing "laws of large numbers" for density-dependent Markov processes [14, 22].

The limiting measure $\mu(t)$ satisfies a non-linear evolution equation, that can be considered the weak form of a partial differential equation.

From an epidemiological point of view, the main result (Section 6) is that, in the limit of infinitely many sites each with infinitely large population, the measure $\mu(t)$ converges, as t goes to infinity to a Dirac measure, centred at an endemic state x^*, if the threshold condition $\frac{c+d}{\gamma} > 1$ holds; centred at 0, below the threshold. We discuss (Section 7) how to interpret this condition in terms of the basic reproduction number: we define R_0 for the approximating models, according to the approach presented by Diekmann and Heesterbeek [], and, going to the limit, we can obtain a definition of R_0 for the limiting case for which the threshold condition becomes $R_0 > 1$. We also present some numerical examples to illustrate how large patch population size N must be to be accurately approximated by the limiting case, at least in terms of R_0.

It may be noticed that the threshold condition, and the infection level x^*, are exactly the same as an SIS epidemic spreading in a single population with infection rate $c + d$. In this sense, we may say that, at least in the limiting case, the metapopulation structure does not add new biological features; this, however, probably depends on the monotone structure of SIS epidemic models that makes them very stable [21, 8]. The present paper provides a rigorous framework where deterministic systems can be derived for different models, such as SIR epidemic models [2], or structured metapopulation models [17], whose qualitative behaviour may be richer, even in the limiting case.

2 The stochastic model

The epidemic spreads among a population consisting of M patches, labelled $1, \ldots, M$, each containing N individuals. We describe this process by means of a continuous time Markov chain with values in the lattice $\mathbb{Z}^M$:

$$\underline{Y} = (Y_1, Y_2, \ldots, Y_M)$$

where $Y_i(t)$ denotes the number of infectives at time t in the i-th patch; the constants involved are c (the local infection rate), d (the global infection rate) and γ (the recovery rate). Let $\underline{e}_j$ the j-th coordinate vector; $\underline{Y}$ is a jump Markov process with transition rates

$$\begin{cases} \underline{Y} & \rightarrow \underline{Y} + \underline{e}_j \text{ at rate } \quad (\mathrm{N} - \mathrm{Y_j})(\mathrm{c}\frac{\mathrm{Y_j}}{\mathrm{N}} + \frac{\mathrm{d}}{\mathrm{M}} \sum_{\mathrm{i}=1}^{\mathrm{M}} \frac{\mathrm{Y_i}}{\mathrm{N}}) \\ \underline{Y} & \rightarrow \underline{Y} - \underline{e}_j \text{ at rate } \quad \gamma \mathrm{Y_j} \end{cases}$$

To start with, we recall two results of approximation of the stochastic model with a deterministic one. In the first case, we let the number of individuals in each site go to infinity, keeping the number of sites fixed; in the second formulation, we let the number of sites go to infinity, with fixed population for each patch.

- Let $X_N(t)$ be the Markov process, whose components represent the fraction of infectives in each patch

$$\underline{X}_N(t) = \left(\frac{Y_1(t)}{N}, \ldots, \frac{Y_M(t)}{N}\right).$$

$\underline{X}_N$ is the density process associated to $\underline{Y}(t)$. A result of [14] (Theorem 11.2.1, page 456) for density-dependent Markov processes shows that if $\underline{X}_N(0) \to \underline{X}^0$ a.s. for $N \to \infty$, then

$$\lim_{N\to\infty} \sup_{t\in[0,T]} \|\underline{X}_N(t) - \underline{X}(t)\| = 0 \qquad a.s.$$

where the vector function $\underline{X} = (X_1, \ldots X_M)$ satisfies the following ODE system

$$\begin{cases} \dot{X}_i(t) = (1 - X_i(t))(cX_i(t) + \frac{d}{M}\sum_{j=1}^{M} X_j(t)) - \gamma X_i(t) \\ X_i(0) = X_i^0 \end{cases} \tag{2.1}$$

for $i = 1, \ldots M$.

- When $M \to \infty$, it is useful to consider the fraction of patches with j infectives:

$$\begin{aligned} \underline{x}^M(t) &= (x_0, \ldots, x_N) \\ x_j^M(t) &= \frac{\sum_{j=1}^{M} 1\!\!1_{[Y_i=j]}(t)}{M} \end{aligned}$$

$\{\underline{x}^M(t), t \in [0,\infty)\}$ is a continuous time Markov chain with state-space $\left([0,1] \cap \frac{\mathbb{Z}}{M}\right)^{N+1}$ and transition rates

$$\begin{cases} \underline{x}^M \to \underline{x}^M + \frac{1}{M}(\underline{e}_{j+1} - \underline{e}_j) \quad \text{at rate} \quad M(N-j)x_j^M(c\frac{j}{N} + \frac{d}{N}\sum_{l=1}^{N} l x_l^M) \\ \\ \underline{x}^M \to \underline{x}^M + \frac{1}{M}(\underline{e}_{j-1} - \underline{e}_j) \quad \text{at rate} \quad M\gamma j x_j^M \\ \end{cases}$$

Ethier and *Kurtz* [14] and *Barbour* and *Kafetzaki* [5] show that assuming that $\underline{x}^M(0)$ converges a.s., as M goes to infinity, to $y \in [0,1]^{N+1}$ with $\sum_{j=1}^{N} y_j = 1$, the stochastic process $\underline{x}^M(t)$ converges a.s. to $\xi = (\xi_0, \ldots, \xi_N) \in C_T^{N+1} = \{\ 0 \le \xi_i(t) \le 1, \quad i = 0, \ldots, N \quad \xi_i \in C[0,T]\}$ solution of the following deterministic ODE system:

$$\begin{cases} \dot{\xi}_j(t) & = \gamma[(j+1)\xi_{j+1} - j\xi_j] + \\ & +c\left[(N-j+1)\frac{j-1}{N}\xi_{j-1} - (N-j)\frac{j}{N}\xi_j\right] + \\ & +\frac{d}{N}\sum_{l=0}^{N}\xi_l l\left[(N-j+1)\xi_{j-1} - (N-j)\xi_j\right] \\ \dot{\xi}_0(t) & = \gamma\xi_1 - \xi_0 d\sum_{l=0}^{N}\xi_l l \\ \xi_j(0) & = y_j \end{cases} \tag{2.2}$$

where $j = 0 \ldots N$, $\xi_{N+1}(t) \equiv 0$, and $\xi_{-1}(t) \equiv 0$.

3 Limit equation

Our aim is to study the behaviour of the process as both parameters go to infinity.
In order to do that, we construct a family of probability measures on the interval $[0,1]$ depending on the time parameter t; for every measurable set $I \subset [0,1]$, let us define

$$Y^{N,M}(t)(I) := \frac{\sum_{i=1}^{M} \mathbb{1}_{[\frac{Y_i(t)}{N} \in I]}}{M} = \frac{1}{M}\sum_{i=1}^{M} \delta_{\frac{Y_i}{N}}(I). \tag{3.1}$$

If $I = (a,b]$, $Y^{N,M}(t)$ is the fraction of patches with a fraction of infectives between a and b at time t; if $a = \frac{k-1}{N}$and $b = \frac{k}{N}$, we have $Y^{N,M}(t)(I) = x_k^M(t)$.
$Y^{N,M}(t)$ is a stochastic process indexed by two parameters and values in the space of probability measure on the unit interval; with the notation of the previous section, we get

$$Y^{N,M}(t)(I) = \sum_{j=0}^{N} x_j^M(t)\delta_{\frac{j}{N}}(I).$$

The following sections deal with two limits:

A) $\lim_{M\to\infty}\lim_{N\to\infty} Y^{N,M}(t)$

B) $\lim_{N\to\infty}\lim_{M\to\infty} Y^{N,M}(t)$

They could be a 'priori' different, but it will be shown that they both lead to the same measure on the interval $[0,1]$, whose evolution is described by the following non-linear equation

$$< f, \mu(t) > = < f, \mu_0 > + \int_0^t < H_{\mu(s)} f, \mu(s) > ds \qquad \forall f \in C^1([0,1]) \tag{3.2}$$

where we denote the action of the generic measure of probability μ on a continuous function $f : [0,1] \to \mathbb{R}$ with $< \cdot, \cdot >$

$$< f, \mu > = \int_0^1 f(x)\mu(dx)$$

and

$$\begin{aligned} H_\mu f &= -\gamma R f + cSf + dE(\mu)Tf \\ Rf(x) &= xf'(x) \\ Sf(x) &= x(1-x)f'(x) \\ Tf(x) &= (1-x)f'(x) \\ E(\mu) &= \textstyle\int_0^1 x\mu(dx) \end{aligned} \tag{3.3}$$

In order to show existence and uniqueness of solutions of (3.2), we follow the strategy adopted in [10]: pretending that the 'environmental' input (the severity of the global epidemics at time t) is known, we have a non-autonomous linear dynamical system that, for a given μ_0 yields a unique solution; then, by a contraction argument, we obtain the requested solution of (3.2). Hence, we first consider the linear equation

$$< f, \mu(t) > = < f, \mu(0) > + \int_0^t < r(s,\cdot)f'(\cdot), \mu(s) > ds \qquad \forall f \in C^1([0,1]) \tag{3.4}$$

where $r(t,x)$ is a given continuous function defined on $[0,T]\times[0,1]$ and $\mu(t)$ are measures on the Borel σ-field. Formally, we can write $\partial_t \mu = A^\star(t)\mu$ where $A^\star$ denotes the adjoint of the time dependent operator $(A(t)f)(x) = r(t,x)f'(x)$.
Note that if we assume that the measure $\mu(t)$ solution of (3.4) is absolutely continuous with respect to the Lebesgue measure, that is $d\mu_t(x) = v(t,x)\,dx$ with $v \in \mathbb{C}^1([0,T]\times[0,1])$, then if $r(t,0)$ and $r(t,1)$ are different from 0, the density function v must satisfy the partial differential equation

$$\partial_t v(t,x) = -\partial_x (r(t,x)v(t,x))$$

with boundary conditions

$$v(t,0) = v(t,1) = 0$$

as one can see by integrating by parts.

Let us denote by $\Phi(t;t_0,x)$ the solution to the Cauchy problem

$$\begin{cases} \dot{y}(t) & = r(t,y(t)) \\ y(t_0) & = x \end{cases} \tag{3.5}$$

extending $r(t,x) = r(t,1)$ for $x > 1, t \in \mathbb{R}$ and $r(t,x) = r(t,0)$ for $x < 0, t \in \mathbb{R}$ and assume that this solution is defined for each $t \in \mathbb{R}$ and $x \in \mathbb{R}$.

Lemma 3.1 *Let* $r(t,0) \geq 0 > r(t,1)$ *for all* $t \geq 0$. *Then* $0 \leq \Phi(t;t_0,x) \leq 1, \quad \forall\, x \in [0,1], t \geq t_0 \geq 0$

Proof It is enough considering the sign of $\frac{\partial}{\partial t}\Phi(t;t_0,x)$ when $\Phi(t;t_0,x) = 0$ or $\Phi(t;t_0,x) = 1$.

As in the case of an absolutely continuous measure, we can construct the measure solution of (3.4) carrying the initial μ_0 along the flow: for every Borel measurable set A in $[0,1]$, let

$$\begin{aligned} \phi_t(x) & = \Phi(t;0,x) \\ \psi_t(x) & = \phi_t^{-1}(x) = \Phi(0;t,x) \\ \mu_t(A) & = \mu_0\left[\phi_t^{-1}(A) \cap [0,1]\right] \end{aligned} \tag{3.6}$$

In order to show that μ_t is the unique solution of (3.4), we need some identities. Note first that, since the solution of (3.5) is unique , we have

$$\Phi(t;s,\Phi(s;t,x)) = x. \tag{3.7}$$

Taking the derivatives with respect to t and to x of both sides of (3.7) ($\partial_i,\ i = 1,2,3$ denotes the partial derivative of Φ with respect to the $i-th$ variable), we have

$$\begin{aligned} (\partial_1\Phi)(t,s,\Phi(s,t,x)) + (\partial_3\Phi)(t,s,\Phi(s,t,x))(\partial_2\Phi(s,t,x)) & = 0 \\ (\partial_3\Phi)(t,s,\Phi(s,t,x))(\partial_3\Phi(s,t,x)) & = 1. \end{aligned}$$

Multiplying the first equality by $\partial_3\Phi(s,t,x)$ and recalling that

$$\partial_1\Phi(t,s,\Phi(s,t,x)) = r(t,\Phi(t,s,\Phi(s,t,x)) = r(t,x),$$

we have

$$\partial_2\Phi(s,t,x) + r(t,x)\partial_3\Phi(s,t,x) = 0 \tag{3.8}$$

and for $s = 0$

$$\partial_x\psi_t(x)r(t,x) + \partial_t\psi_t(x) = 0. \tag{3.9}$$

Lemma 3.2 *Let $r(t,0) \geq 0 > r(t,1)$ for all $t \geq 0$. Then μ_t, defined in (3.6) is the only solution of (3.4).*

Proof First, note that $\mu(t)$ satisfies (3.4). In fact, for every measurable function f defined on $[0,1]$

$$\int_0^1 f(x)\mu_t(dx) = \int_0^1 f(\phi_t(y))\mu_0(dy)$$

(see for example [13],Th.III.10.8). Hence, if $f \in C^1([0,1])$

$$\begin{aligned}
\tfrac{d}{dt} < f, \mu_t > &= \tfrac{d}{dt}\left[\textstyle\int_0^1 f(\phi_t(y))\mu_0(dy)\right] \\
&= \textstyle\int_0^1 \frac{\partial}{\partial t} f(\phi_t(y))\mu_0(dy) = \\
&= \textstyle\int_0^1 f'(\phi_t(y))\frac{\partial\phi_t(y)}{\partial t}\mu_0(dy) \\
&= \textstyle\int_0^1 f'(\phi_t(y))r(t,\phi_t(y))\mu_0(dy) \\
&= \textstyle\int_0^1 f'(x)r(t,x)\mu_t(dx).
\end{aligned}$$

so that (3.4) holds.
Let ν_t be a solution of the equation (3.4). First note that, if $g \in C^2([0,T] \times [0,1])$

$$\frac{d}{dt} < g(t,\cdot), \nu_t > = \int_0^1 \frac{\partial}{\partial t} g(t,y)\nu_t(dy) + \int_0^1 \frac{\partial}{\partial y} g(t,y)r(t,y)\nu_t(dy). \tag{3.10}$$

To show that the family of measures (3.6) is the only solution of equation (3.4), we extend the measures ν_t and μ_0 to measures $\tilde{\nu}_t$ and $\tilde{\mu}_0$ on $\mathbb{R}$ by setting

$$\begin{aligned}
\tilde{\nu}_t(A) &= \nu_t(A \cap [0,1]), \qquad & A \in \mathcal{B}(\mathbb{R}) \\
\tilde{\mu}_0(A) &= \mu_0(A \cap [0,1]), \qquad & A \in \mathcal{B}(\mathbb{R})
\end{aligned}$$

where $\mathcal{B}(\mathbb{R})$ is the Borel σ-field, and construct the family of measures on $\mathbb{R}$

$$\lambda_t(B) = \tilde{\nu}_t\left[\psi_t^{-1}(B)\right]. \tag{3.11}$$

Since

$$\int_{\mathbb{R}} f(x)\lambda_t(dx) = \int_{\mathbb{R}} f(\psi_t(x))\tilde{\nu}_t(dx) = \int_0^1 f(\psi_t(x))\nu_t(dx)$$

for all $f \in C^2(\mathbb{R})$, we have, using (3.10)

$$\begin{aligned}
\frac{d}{dt}\int_0^1 f(\psi_t(y))\nu_t(dy) &= \int_0^1 \left[\frac{\partial}{\partial t} f(\psi_t(y))\right]\nu_t(dy) + \int_0^1 \left[\frac{\partial}{\partial y}\left(f(\psi_t(y))\right)\right] r(t,y)\nu_t(dy) = \\
&= \int_0^1 f'(\psi_t(y))\partial_t\psi_t(y)\nu_t(dy) + \int_0^1 f'(\psi_t(y))\partial_y(\psi_t(y))r(t,y)\,\nu_t(dy) \\
&= \int_0^1 f'(\psi_t(y))\left[\partial_y\psi_t(y)r(t,y) + \partial_t\psi_t(y)\right]\nu_t(dy) = 0
\end{aligned}$$

because of (3.9). Hence, $\int_{\mathbb{R}} f(x)\lambda_t(dx) = \int_{\mathbb{R}} f(x)\lambda_0(dx) = \int_{\mathbb{R}} f(x)\tilde{\mu}_0(dx)$ so that, for every measurable set $B \subset \mathbb{R}$

$$\lambda_t(B) = \lambda_0(B) = \tilde{\mu}_0(B) = \mu_0(B \cap [0,1]). \tag{3.12}$$

For each measurable set $A \subset [0,1]$, take $B = \phi_t^{-1}(A)$; from (3.12) and (3.11) we have

$$\begin{aligned}
\nu_t(A) = \tilde{\nu}_t(A) &= \tilde{\nu}_t\big(\psi_t^{-1}(\phi_t^{-1}(A))\big) = \lambda_t\big(\phi_t^{-1}(A)\big) \\
&= \mu_0\big(\phi_t^{-1}(A) \cap [0,1]\big) = \mu_t(A).
\end{aligned}$$

Remark The measure $\mu(t)$ may be considered as the measure associated to a Markov process $Z(t)$, which is actually random only in the distribution μ_0 at the initial time $t=0$, while its evolution is deterministic, with transition function $\delta_{\Phi(s;t,x)}$.

In our original equation, the function r depends on the measure μ, but we can apply the previous argument to construct a contraction map: a fixed point of this map is the solution of our original problem. Note first

Lemma 3.3 *Let $E \in C([0,T])$ with $0 \le E(t) \le 1$, $x \in [0,1]$ and $\phi^E(t,x)$ be the solution of (3.5) with $t_0 = 0$ and $r(t,y) = cy(1-y) - \gamma y + E(t)d(1-y)$.*
Then $0 \le \phi^E(t,x) \le 1, \quad x \in [0,1], t \in [0,T]$.

Proof Clearly, $r(t,y)$ satisfies the assumptions of Lemma 3.1.

Theorem 3.4 *There exists a unique solution to the equation (3.2).*

Proof Let us consider $\mathcal{M} = \{E \in C([0,T]), 0 \leq E(t) \leq 1\}$ equipped with the supremum norm , and let μ_t^E be the solution of (3.4) where $r(t,y) = cy(1-y) - \gamma y + d(1-y)E(t)$. Let $\mathbf{T} : \mathcal{M} \to \mathcal{M}$

$$\mathbf{T}(E)(t) = \int_0^1 x\mu_t^E(dx).$$

We will show that if $T < T_0$, where T_0 is such that $dT_0 \exp((c+\gamma+d)T_0) = 1$, then $\mathbf{T}$ is a contraction.

Let $E, F \in \mathcal{M}$ and $\phi^E(t,x)$, $[\phi^F(t,x)]$ the solution of (3.5) with $r^E(t,y) = cy(1-y) - \gamma y + d(1-y)E(t)$ $[r^F(t,y) = cy(1-y) - \gamma y + d(1-y)F(t)]$; using (3.6) we can write

$$\mathbf{T}(E)(t) = \int_0^1 \phi^E(t,x)\mu_0(dx)$$

and

$$\begin{aligned}
|\phi^E(t,x) \quad & -\phi^F(t,x)| = \left|\int_0^t r^E(s,\phi^E(s,x)) - r^F(s,\phi^F(s,x))\,ds\right| \\
& \leq \int_0^t \left|r^E(s,\phi^E(s,x)) - r^F(s,\phi^E(s,x)) + r^F(s,\phi^E(s,x)) - r^F(s,\phi^F(s,x))\right| ds \\
& \leq \Big(\sup_{[0,1]\times[0,T]} |r^E - r^F|\Big) t + \Big(\sup_{[0,1]\times[0,T]} \left|\frac{\partial r^F}{\partial y}\right|\Big) \int_0^t |\phi^E(s,x) - \phi^F(s,x)|\, ds \\
& \leq d \sup_{[0,T]} |E(t) - F(t)| t + (c+\gamma+d) \int_0^t |\phi^E(s,x) - \phi^F(s,x)|\, ds
\end{aligned}$$

By Gronwall inequality

$$|\phi^E(t,x) - \phi^F(t,x)| \leq dt\|E - F\| \exp[(c+\gamma+d)t]$$

Hence $\forall\, t \in [0,T]$,

$$\big|\big(\mathbf{T}(E) - \mathbf{T}(F)\big)(t)\big| = \left|\int_0^1 [\phi^E(t,x) - \phi^F(t,x)]\,\mu_0(dx)\right| \leq dt\|E-F\| \exp[(c+\gamma+d)t].$$

The contraction mapping theorem shows that there exists a unique solution of (3.2) on $[0,T]$, for any $T < T_0$; since T_0 depends only on the constants c, d, γ, the previous procedure can be iterated, yielding a solution of (3.2) on any compact interval $[0,T]$.

4 First limit

We saw in Section 2 that, if $\lim_{N\to\infty} \underline{X}_N(0) = \underline{X}^0$ *a.s.* then weakly

$$\lim_{N\to\infty} Y^{N,M}(t) = \lim_{N\to\infty} \frac{1}{M} \sum_{i=1}^{M} \delta_{\frac{Y_i}{N}(t)} = \frac{1}{M} \sum_{i=1}^{M} \delta_{X_i^M(t)}$$

where $\{X_j^M\}_{j=1}^M$ are the solution of the ODE system (2.1) (see, for instance, [5] and [20]). Hence, we consider the probability measures for $t \in [0, T]$

$$\mu_t^M = \frac{1}{M} \sum_{i=1}^{M} \delta_{X_i^M(t)} \tag{4.1}$$

Since the trajectories X_i^M belong to the space of continuous functions, we can consider the sequence of probability measure μ_M on the space $C([0, T])$, each with a finite support consisting of the M functions X_i^M:

$$\mu_M = \frac{1}{M} \sum_{i=0}^{M} \delta_{X_i^M}.$$

First we have:

Lemma 4.1 *The sequence of probability measures $\{\mu_M\}$ is tight.*

Proof We remind that a sequence of probability measures P_N on $C([0, T])$ is tight iff the next two conditions hold

i) For each positive η, there exists an a such that

$$P_N\{x : |x(0)| > a\} \le \eta \qquad N \ge 1$$

ii) For each positive ϵ and η, there exist a δ and an integer N_0 such that

$$P_N\{x : \sup_{|s-t|<\delta} |x(s) - x(t)| \ge \epsilon\} \le \eta, \quad N \ge N_0$$

The first condition, which is equivalent to the tightness of the initial finite-dimensional measure is automatically fulfilled because we deal with measures on a compact space. Since the functions X_i^M are Lipschitz with a uniform Lipschitz constant

$$\begin{aligned} |\dot{X}_i(t)| &\le c|1 - X_i(t)|\,|X_i(t)| + |1 - X_i(t)| \tfrac{d}{M} \textstyle\sum_{i=0}^{M} |X_i^M| + \gamma |X_i(t)| \\ &\le c + d + \gamma, \end{aligned}$$

so that the second condition is satisfied.

Tightness implies the relative compactness of the sequence via Prokhorov theorem [7]. Improving on this, we obtain:

Theorem 4.2 *Let us assume that the sequence $\{\mu_M(0)\}$ converges weakly to μ_0; then the sequence $\{\mu_M(t)\}$ converges weakly to $\mu(t)$ solution of (3.2).*

Proof For every M, $\mu_M(t)$ satisfies the weak equation :

$$\begin{aligned} < f, \mu_M(t) > \; & - < f, \mu_M(0) >= \int_0^t \frac{d}{ds} < f, \mu_M(s) > \, ds = \int_0^t \sum_{i=1}^M \frac{1}{M} \frac{d}{ds} f(X_i^M(s))\, ds \\ & = \int_0^t \sum_{i=1}^M \frac{1}{M} f'(X_i^M(s)) \left[(1 - X_i(s))(cX_i(s) + \frac{d}{M} \sum_{j=1}^M X_j(s)) - \gamma X_i(s) \right] ds \\ & = \int_0^t \left[c < Sf, \mu_M(s) > + dE(\mu_M) < Tf, \mu_M(s) > - \gamma < Rf, \mu_M(s) > \right] ds \\ & = \int_0^t < H_{\mu_M(s)} f, \mu_M(s) > ds \qquad \forall f \in C^1([0,1]) \end{aligned} \tag{4.2}$$

with R, S, T, H_μ defined in (3.3).

Take a sequence $\{\mu_{M_k}(t)\}$ weakly converging to a limit $\bar{\mu}(t)$. Since $\mu_M(0) \to \mu_0$, as $M \to \infty$, one can pass to the limit in (4.2) and see that $\bar{\mu}(t)$ must satisfy equation (3.2); because of the uniqueness of the solutions of (3.2), we have that the whole sequence μ_M has μ as weak limit.

5 Second limit

First of all, according to the result of Section 2, if $\lim_{M\to\infty} \underline{x}^M(0) = \underline{y}$ we have that

$$\lim_{M\to\infty} \sum_{j=0}^N x_j^M(t) \delta_{\frac{j}{N}} = \sum_{j=0}^N \xi_j^N(t) \delta_{\frac{j}{N}}$$

where $\{\xi_j^N(t)\}_{j=0}^N$ satisfies (2.2).

Let us define the sequence of probability measures

$$\mu_N(t) = \sum_{j=0}^N \xi_j^N(t) \delta_{\frac{j}{N}}.$$

In order to prove the convergence for $N \to \infty$ of this family of measures, we give a probabilistic interpretation of the measures: considering $E^N(t) = \sum_{j=0}^N \xi_j^N(t) \frac{j}{N}$ as a given function, we construct continuous time Markov chains $Z^N(t)$ on the same probability space $(\Omega, \mathcal{F}, \mathbb{P})$

with state space $S_N = (\frac{\mathbb{Z}}{N} \cap [0,1])$, and inhomogeneous transitions: $\mu_N(t)$ will be the distribution of that process at time t.
First of all, let us construct a family of Markov processes $Z^N_{x_N}$, $N \in \mathbb{N}$, $x_N \in S_N$ on a probability space $(\Omega', \mathcal{F}', \mathcal{P}')$ with state space S_N such that, as $h \to 0$

$$\begin{aligned} P'[Z^N_{x_N}(t+h) = \frac{j+l}{N} | Z^N_{x_N}(t) = \frac{j}{N}] &= q^N(j, j+l, t)\, h + o(h) \qquad l \neq 0 \\ P'[Z^N_{x_N}(0) = x_N] &= 1 \end{aligned} \tag{5.1}$$

where $j, l \in \mathbb{Z}$ and the transition rates are

$$\begin{aligned} q^N(j, j+1, t) &= c(N-j)\tfrac{j}{N} + d(N-j)E^N(t) \\ &= N\left[c(1-\tfrac{j}{N})\tfrac{j}{N} + d(1-\tfrac{j}{N})E^N(t)\right] \\ q^N(j, j-1, t) &= \gamma j = \gamma N(\tfrac{j}{N}) \\ q^N(j, j+l, t) &= 0 \qquad |l| > 1 \end{aligned}$$

Note that $\xi_j(t) = P'[Z^N_{x_N}(t) = j]$ satisfy (2.2) with $y = \delta_{x_N}$.

The functions $q^N(j, j+l, t)$ satisfy the definition of asymptotically density dependence (see the Appendix) with

$$\begin{aligned} \beta^N(x, 1, t) &= c(1-x)x + d(1-x)E^N(t) \\ \beta^N(x, -1, t) &= \gamma x \\ \beta^N(x, l, t) &= 0 \qquad |l| > 1 \\ F^N(x, t) &= c(1-x)x + d(1-x)E^N(t) - \gamma x \end{aligned}$$

In order to apply Theorem 8.1 of the Appendix, we need the convergence of the sequence $\{F^N(x,t)\}$. One can easily show that

Lemma 5.1 *The family of functions $E^N(t)$ is equicontinuous and uniformly bounded on the compact time interval $[0,T]$.*

Proof It is enough to give an uniform estimate for $\frac{dE^N}{dt}(r) = \sum_{i=1}^N \frac{i}{N}\xi'_i(r)$, $r \in [0,T]$; from (2.2), we see that $|\frac{dE^N}{dt}(r)| \leq (c+d+\gamma)$ (the explicit calculation can be found in 5.6, if we choose $f(x) = x$).

Restricting ourselves to a converging subsequence, we set

$$E(t) = \lim_{k\to\infty} E^{N_k}(t) \qquad \text{and} \qquad F(x,t) = c(1-x)x + d(1-x)E(t) - \gamma x, \tag{5.2}$$

so that $\lim_{k\to\infty} F^{N_k}(x,t) = F(x,t)$.

Let us assume that the sequence of measures $\mu_0^N = \sum_{j=0}^{N} y_j^N \delta_{\frac{j}{N}}$ converges in distribution to a probability measure μ_0 on $[0,1]$. First we have the result ([6], Theorem 25.6)

Lemma 5.2 *If $\lim_{N\to\infty} \mu_0^N = \mu_0$ then there exist random variables Z_0^N, Z_0 on a common probability space Ω" such that Z_0^N has distribution μ_0^N, Z_0 has distribution μ_0, and $\lim_{N\to\infty} Z_0^N = Z_0$ for all $\omega'' \in \Omega''$.*

We can consider now the sequence of random processes $Z_N(t,\omega',\omega'') = Z_{Z_0^N(\omega'')}(t,\omega')$ on the probability space $\Omega = \Omega' \otimes \Omega''$ with the product measure $\mathbb{P} = P' \otimes P''$. Moreover, the measure $\mu_N(t)$ is the distribution of the process $Z^N(t,\omega',\omega'')$, that is, for a measurable set $A \in [0,1]$

$$\mu_N(t)(A) = \mathbb{P}\left[Z^N(t,\omega',\omega'') \in A\right].$$

Since, for a fixed $\omega'' \in \Omega$", $\lim\limits_{N\to\infty} Z_N(0,\omega',\omega'') = Z_0^N(\omega'')$ applying Theorem 8.1, we obtain

Corollary 5.3 *Take a subsequence $\{N_k\}$ such that $\lim_{k\to\infty} E^{N_k}(t) = E(t)$. Then for every $\omega'' \in \Omega''$ there exists a set $\Gamma'(\omega'') \in \Omega'$ of measure zero such that*

$$\lim_{k\to\infty} \sup_{t\in[0,T]} |Z^{N_k}(t,\omega',\omega'') - Z(t,\omega'')| = 0 \qquad (\omega',\omega'') \in (\Omega' \setminus \Gamma'(\omega'')) \times \Omega'' \tag{5.3}$$

where $Z(t,\omega'')$ satisfies

$$Z(t,\omega'') = Z_0(\omega'') + \int_0^t F\left(Z(s,\omega''),s\right) ds \tag{5.4}$$

Now we can obtain

Lemma 5.4 *For every $t \in [0,T]$, the sequence of measures $\mu^{N_k}(t)$ converge weakly to the measure $\tilde{\mu}(t)$ given by*

$$\tilde{\mu}(t)(A) = \mathbb{P}\left[Z(t,\omega'') \in A\right] = P''\left[Z(t,\omega'') \in A\right].$$

Moreover, $E(t) = \int_0^1 x\tilde{\mu}_t(dx)$.

Proof Take $f \in C([0,1])$: for every ω'', we have $\lim\limits_{k\to\infty} f(Z^{N_k}(t,\omega',\omega'') = f(Z(t,\omega''))$ a.e.

Hence, from the dominated convergence theorem we have

$$\lim_{k\to\infty}\int_{\Omega'} f(Z^{N_k}(t,\omega',\omega''))\,dP' = \int_{\Omega'} f(Z(t,\omega''))\,dP' = f(Z(t,\omega'')) \quad \forall\ \omega'' \in \Omega''$$

and

$$\begin{aligned}
\lim_{k\to\infty}\int_0^1 f(x)\mu^{N_k}(t)(dx) &= \lim_{k\to\infty}\int_{\Omega} f(Z^{N_k}(t,\omega',\omega''))\,d\mathbb{P} \\
&= \lim_{k\to\infty}\int_{\Omega''} dP''\int_{\Omega'} f(Z^{N_k}(t,\omega',\omega''))\,dP' = \int_{\Omega''} dP''\int_{\Omega'} f(Z(t,\omega''))\,dP' \\
&= \int_{\Omega''} f(Z(t,\omega''))\,dP'' = \int_0^1 f(x)\mu(t)(dx)
\end{aligned}\tag{5.5}$$

i.e. $\mu^{N_k}(t)$ converge weakly to $\tilde{\mu}(t)$.

If we choose the function $f(x) = x$, we have that

$$E(t) = \lim_{k\to\infty} E^{N_k}(t) = \lim_{k\to\infty}\int_0^1 x\mu_t^{N_k}(dx) = \int_0^1 x\tilde{\mu}_t(dx).$$

In principle, the measure $\tilde{\mu}$ could depend on the function $E(t)$ defined in (5.2), and hence on the choice of the subsequence N_k. Instead, we show that $\tilde{\mu}$ is actually the solution $\mu(t)$ of equation (3.2).

Theorem 5.5 *If* $\lim_{N\to\infty}\mu_0^N = \mu_0$ *weakly, then* $\mu^N(t)$ *converges weakly to* $\mu(t)$ *solution of (3.2).*

Proof The family of measures $\mu_N(t)$ satisfies the following equation

$$< f, \mu_N(t) >=< f, \mu_N(0) > + \int_0^t \sum_{j=0}^N \dot{\xi}_j(s) f(\frac{j}{N})\,ds \qquad \forall f \in C([0,1])$$

and from (2.2)

$$\begin{aligned}
\textstyle\sum_{j=0}^N \dot{\xi}_j(t) f(\frac{j}{N}) &= \gamma \textstyle\sum_{j=0}^N f(\frac{j}{N})[(j+1)\xi_{j+1} - j\xi_j] + \\
&\quad + c\textstyle\sum_{j=0}^N f(\frac{j}{N})\left[(1-\frac{j-1}{N})(j-1)\xi_{j-1} - (1-\frac{j}{N})j\xi_j\right] + \\
&\quad + d\left(\textstyle\sum_{l=0}^N (\frac{l}{N})\xi_l\right)\textstyle\sum_{j=0}^N f(\frac{j}{N})\left[(1-\frac{j-1}{N})\xi_{j-1} - (1-\frac{j}{N})\xi_j\right] \\
&= -\gamma\textstyle\sum_{j=0}^N \nabla_-^N f(\frac{j}{N})\frac{j}{N}\xi_j + c\textstyle\sum_{j=0}^N (1-\frac{j}{N})\frac{j}{N}\xi_j\nabla_+^N f(\frac{j}{N}) + \\
&\quad + dE^N(t)\textstyle\sum_{j=0}^N (1-\frac{j}{N})\nabla_+^N f(\frac{j}{N})\xi_j
\end{aligned}\tag{5.6}$$

where

$$\begin{aligned}\nabla_+^N f(x) &= \frac{f(x+\frac{1}{N})-f(x)}{\frac{1}{N}}, \quad x\in[0,1-\tfrac{1}{N}]\\ \nabla_-^N f(x) &= \frac{f(x)-f(x-\frac{1}{N})}{\frac{1}{N}}, \quad x\in[\tfrac{1}{N},1]\end{aligned}$$

Hence we have

$$\begin{aligned}&< f,\mu_N(t)> - < f,\mu_N(0)>\\ &= \int_0^t \big[-\gamma < \nabla_-^N f(\cdot)\cdot,\mu_N(s)> + c < (1-\cdot)\cdot\nabla_+^N f(\cdot),\mu_N(s)> \\ &\qquad + E^N(s) < (1-\cdot)\nabla_+^N f(\cdot),\mu_N(s)>\big]\, ds.\end{aligned} \tag{5.7}$$

Our aim is to show that, with notations of Lemma (5.4)

$$\lim_{N_k\to\infty} < \nabla_-^{N_k} f(\cdot)\cdot,\mu_{N_k}(s) >= \lim_{N_k\to\infty}\int_{\frac{1}{N_k}}^1 x\nabla_-^{N_k} f(x)\, d\mu_{N_k}(s) = \int_0^1 xf'(x)\, d\tilde{\mu}(s).$$

If we choose a function $f\in C^2([0,1])$, we have

$$\begin{aligned}&\left|\int_{\frac{1}{N_k}}^1 x\nabla_-^{N_k} f(x)\, d\mu_{N_k}(s) - \int_0^1 xf'(x)\, d\tilde{\mu}(s)\right| \le\\ &\left|\int_{\frac{1}{N_k}}^1 x\nabla_-^{N_k} f(x)\, d\mu_{N_k}(s) - \int_{\frac{1}{N_k}}^1 xf'(x)d\mu_{N_k}(s) + \int_{\frac{1}{N_k}}^1 xf'(x)d\mu_{N_k}(s) - \int_0^1 xf'(x)\, d\tilde{\mu}(s)\right|\\ &\le \sup_{[\frac{1}{N_k},1]}|x\nabla_f^{N_k}(x) - xf'(x)| + \left|\int_0^1 (xf'(x))(d\mu^{N_k}(s) - d\tilde{\mu}(s))\right|\\ &\le \tfrac{1}{N_k}\sup_{[0,1]}|f''(x)| + |\int_0^1 (xf'(x))(d\mu^{N_k}(s)-d\tilde{\mu}(s))|.\end{aligned}$$

Since $\mu^{N_k}(s)$ tends weakly to $\tilde{\mu}(s)$ and the function $g(x)=xf'(x)$ is continuous and bounded on $[0,1]$,the right-hand side of the inequality tends to zero, as $N_k\to\infty$. Analogously, one can prove that

$$\lim_{N_k\to\infty}\int_0^{1-\frac{1}{N_k}}(1-x)x\nabla_+^{N_k} f(x)\, d\mu_{N_k}(s) = \int_0^1 (1-x)xf'(x)d\tilde{\mu}(s)$$

and

$$\lim_{N_k\to\infty}\int_0^{1-\frac{1}{N_k}}(1-x)\nabla_+^{N_k} f(x)\, d\mu_{N_k}(s) = \int_0^1 (1-x)f'(x)d\tilde{\mu}(s).$$

We can apply the dominated convergence theorem and we have that $\tilde{\mu}(t)$ satisfies equation (3.2) with $\mu_0 = \lim_{N\to\infty}(\sum_{j=0}^N \xi_j(0)\delta_{\frac{j}{N}})$. Since there exists a unique solution $\mu(t)$ of (3.2), $\tilde{\mu}(t) = \mu(t)$; thus, every subsequence of $\{\mu_N(t)\}$ contains a subsequence that converges to $\mu(t)$, which shows that the whole sequence converges weakly to that limit.

6 Asymptotic behaviour of the measure $\mu(t)$

We search for an equilibrium measure for the equation (3.2) as a delta measure $\mu^\star = \delta_{x^\star}$ with support $x^\star \in (0,1)$. Since $E(\mu^\star) = x^\star$, $< H_{\mu^\star} f, \mu^\star >= 0 \quad \forall f \in C^1([0,1])$ if and only if we have

$$G(x^\star) := c(1-x^\star) + d(1-x^\star) - \gamma = 0. \tag{6.1}$$

(6.1) has a unique solution $x^\star \in (0,1)$ if and only if $c+d > \gamma$. We notice that, in this case, $G(z) > 0$ if and only if $z < x^\star$.

On the other hand, if $c+d \leq \gamma$, $G(z) < 0$ for all $z > 0$. It must also be noted that $\mu(t) \equiv \delta_0$ is always an equilibrium solution of (3.2).

In order to study the asymptotic behaviour of the measure $\mu(t)$ solution of (3.2), we can take advantage of its representation (5.4) as the measure associated at time t to the stochastic process $Z(t)$ solution of the Cauchy problem

$$\begin{cases} Z'(t) & = cZ(t)(1-Z(t)) + d(1-Z(t))E(t) - \gamma Z(t) := F(Z(t),t) \\ Z(0) & = Z_0 \end{cases} \tag{6.2}$$

where Z_0 is a random variable with distribution μ_0 and $E(t) = \int_0^1 x\mu_t(dx)$.
We consider the solution $Z_m(t)$ and $Z_M(t)$ of the Cauchy problems

$$\begin{cases} Z'_m(t) & = F(Z_m(t),t) \\ Z_m(0) & = 0 \end{cases} \qquad \begin{cases} Z'_M(t) & = F(Z_M(t),t) \\ Z_M(0) & = 1 \end{cases}$$

They bound the solution $Z(t)$, that is $0 \leq Z_m(t) \leq Z(t,\omega'') \leq Z_M(t) \leq 1$; hence

$$Z_m(t) \leq E(t) \leq Z_M(t) \tag{6.3}$$

with strict inequalities, unless $\mu_0 \equiv \delta_0$.

Proposition 6.1 *Let $x^\star$ be the unique positive solution of (6.1) if $c+d > \gamma$ and $x^\star = 0$ if $c+d \leq \gamma$: both $Z_m(t)$ and $Z_M(t)$ go to $x^\star$ for $t \to +\infty$, unless $x^\star > 0$, and $\mu \equiv \delta_0$ or $d = 0$.*

Proof First, note from (6.3) that

$$Z'_M(t) \leq Z_M(t) G(Z_M(t)) \tag{6.4}$$

and

$$Z'_m(t) \geq Z_m(t) G(Z_m(t)) \tag{6.5}$$

If $x^\star = 0$, (6.4), together with $G(z) < 0$ for all $z > 0$, yields immediately the conclusion.
Let $x^\star > 0$. If there exists t_0 such that $Z_m(t) \leq x^\star$, for $t > t_0$, then, using (6.5), we have $Z'_m(t) \geq 0$, hence $Z_m(t)$ is non- decreasing in t; then $\lim_{t\to\infty} Z_m(t) = m^\star \leq x^\star$. It is obvious that $m^\star = 0$ if and only if $\mu \equiv \delta_0$ or $d = 0$; take then $0 < m^\star < x^\star$: we have $Z'_m(t) \geq m^\star G(m^\star) > 0$ contradicting the assumption of the existence of a finite limit; so $m^\star = x^\star$. Analogously, we can prove that, if $Z_M(t) \geq x^\star$, for all $t \in [t_0, +\infty)$, then $\lim_{t\to\infty} Z_M(t) = x^\star$.
Assume now that there exists τ such that $x^\star = Z_m(\tau)$; from the uniqueness of solution of (6.2), we have $Z(t, z_0) > x^\star$ for all $z_0 > 0$; hence, $E(\tau) > x^\star$. Now we have

$$Z'_m(\tau) = F(Z_m(\tau), \tau) > x^\star G(x^\star) = 0. \tag{6.6}$$

It is then impossible that $Z_m(t)$ crosses $x^\star$ downward. Hence $Z_m(t) > x^\star$ for $t > \tau$. Since $x^\star < Z_m(t) \leq Z_M(t), \quad t \in (\tau, +\infty)$, we conclude from the previous case that $\lim_{t\to+\infty} Z_M(t) = x^\star$; from $x^\star < Z_m(t) < Z_M(t)$, we also have that $\lim_{t\to\infty} Z_m(t) = x^\star$.
The case where there exists τ such that $Z_M(\tau) = x^\star$ is dealt with analogously.

Since the support of the measure $\mu(t) \subset [Z_m(t), Z_M(t)]$, we can easily conclude

Theorem 6.2 *As $t \to \infty$, the measure $\mu(t)$ tends weakly to the Dirac measure $\delta_{x^\star}$, unless $x^\star > 0$, and $\mu \equiv \delta_0$ or $d = 0$.*

7 Basic reproduction ratios R_0

We discuss briefly the previous results in terms of the basic reproduction ratio R_0 for our $S - I - S$ metapopulation model. We have seen in Section 6 that if $c + d > \gamma$, the measure $\mu(t)$ tends to a delta measure concentrated at the positive state $x^\star$, otherwise the disease vanishes. How can this threshold condition be related to a basic reproduction ratio R_0 as defined in [11]?
Recently, Gyllenberg and Metz [18] have defined the mutant fitness in terms of a basic reproductive ratio for a class of structured metapopulation models similar to that studied in Section 6. However, it is not quite clear how to use that definition in our case. Therefore, we start by discussing the threshold condition for the approximating models (2.1) and (2.2). For the model (2.1), the disease-free equilibrium $(0, \dots, 0)$ is asymptotically stable if $c+d < \gamma$. This condition can be obtained in a classical way by estimating the spectral bound $s(J)$ of the Jacobian matrix of the system: $s(J) = c + d - \gamma$, thus is $s(J) < 0$, the disease-free equilibrium $(0, \dots, 0)$ is asymptotically stable. Indeed, it can be shown [21] that the stability is global, i.e. when $s(J) < 0$, the disease eventually vanishes.

The same threshold condition can be obtained by using the approach Diekmann and Heesterbeck give in [12]. We can define the operator T on the space $\mathbb{N}^M$

$$T(\underline{e}_j) = \frac{c}{\gamma}\underline{e}_j + \frac{d}{M\gamma}\underline{u}$$

where $\underline{e}_j = (0, \dots, 1, \dots, 0)$ and $\underline{u} = (1, 1, \dots, 1, 1)$. From the epidemiological point of view, the i-th component of the vector $T(\underline{e}_j)$ represents the number of infectives in the i-th patch of the metapopulation, generated by an infective in the j-th patch over its life as infectious, assuming that everybody else in the population is susceptible.

The basic reproduction number is defined as the dominant eigenvalue of T: in this case one computes easily $R_0 = \frac{c+d}{\gamma}$. Note that R_0 doesn't depend on the size parameter M.

In this case one sees immediately that $s(J) < 0$ if and only if $R_0 < 1$. This is true in more general cases, and can be proved using a property [12] that will be needed later:

(P) Let T be a positive matrix, Σ a positive off-diagonal matrix and D a positive diagonal matrix, with $s(\Sigma - D) < 0$ then

$$s(T + \Sigma - D) < 0 \Leftrightarrow \rho(-T(\Sigma - D)^{-1}) < 1.$$

In the second finite dimensional model (2.2), we can write down the linearization of the ODE system at the equilibrium point $(\xi_0, \dots, \xi_N) = (1, 0, \dots, 0)$; keeping in mind that $\xi_0(t) = 1 - \sum_{i=0}^{N} \xi_N(t)$, we can consider only N equations

$$\frac{d\xi_i}{dt} = \gamma(i+1)\xi_{i+1} - i\left[\gamma + c\frac{(N-i)}{N}\right]\xi_i + c(i-1)\left(\frac{N+1-i}{N}\right)\xi_{i-1} + \delta_{i1} d \sum_l l\xi_l \quad i = 1, \dots, N$$

where by definition $\xi_{N+1}(t) \equiv 0$; in matrix form we write $\frac{d\underline{\xi}}{dt} = B\underline{\xi}$.

In order to study the stability of the equilibrium $(\xi_1, \dots, \xi_N) = (0, \dots, 0)$, one can compute the spectral bound of the matrix B but there does not seem to be any explicit or illuminating formula. Instead, one could exploit the result (P) by choosing any decomposition $B = \Sigma - D$; the easiest choice would be setting D equal to the opposite of the diagonal terms of B and Σ equal to the off-diagonal part of B.

We prefer to present a different choice following the approach of Diekmann and Heesterbeck give in [12]; model (2.2) can be considered a structured epidemiological models, where the patches play the role of individuals (i.e. are the epidemic units); each patch can be in a finite number of different states, labelled by j, the number of infectives in the patch.

In such a case, one can write $B = T + \Sigma - D$ where T represent the production of new infected patches, Σ the transitions of the patches between the different states, and D takes into account the deaths, and in our case is the null-matrix, because patches cannot disappear.

Precisely, the entries T_{ij} represent the rate at which an infected patch with label j produce infected patches with label i. Hence, in our case

$$T_{i,j} = d\delta_{1i}j.$$

where δ_{ki} is the Kronecker symbol. The matrix Σ is the transpose of the generator of the Markov process describing the transitions among states. Hence

$$\Sigma_{ij} = \begin{cases} \Sigma_{i,i} & = -i(\gamma + \frac{N-i}{N}) \\ \Sigma_{i,i+1} & = \gamma(i+1) \\ \Sigma_{i,i-1} & = c(i-1)(1 - \frac{i-1}{N}) \end{cases}$$

From the property (P), we see that the equilibrium $\underline{0}$ is asymptotically stable if and only if the dominant eigenvalue R_0 of the next-generation operator $K = -T(\Sigma - D)^{-1}$ is less than one.

In order to describe R_0, it is convenient to go back to the representation of the matrix Σ^t as the generator of a defective birth and death Markov process $X^N(t)$, with rates

$$\begin{array}{ll} i \to i+1 & ci\left(1 - \frac{i}{N}\right) \\ i \to i-1 & \gamma i \end{array}$$

Then

$$(e^{t\Sigma})_{ij} = \mathbb{P}(X^N(t) = i | X^N(0) = j) \tag{7.1}$$

and letting $s_{ij} = -(\Sigma^{-1})_{ij}$ we have

$$s_{ij} = -(\Sigma)^{-1}_{ij} = \int_0^\infty (e^{t\Sigma})_{ij}\, dt = \int_0^\infty \mathbb{P}(X^N(t) = i | X^N(0) = j)\, dt. \tag{7.2}$$

Now we can compute the entries of the matrix $K = -T\Sigma^{-1}$

$$k_{ij} = \sum_{r=1}^N T_{ir} s_{rj} = \sum_{r=1}^N d\delta_{1i} r s_{rk}.$$

The basic reproduction number R_0 is the spectral radius of the matrix T; since K has one-dimensional range, it is easy to see that

$$\begin{aligned} R_0 = k_{11} &= -\sum_{j=1}^{N} dj s_{j1} = \sum_{j=1}^{N} dj \int_0^{+\infty} \mathbb{P}(X^N(t) = j \mid X^N(0) = 1)dt = \\ &= d \int_0^{+\infty} \sum_{j=1}^{N} j\mathbb{P}(X^N(t) = j \mid X^N(0) = 1)dt = d \int_0^{+\infty} \mathbb{E}^1(X^N(t))dt \end{aligned}$$

We have obtained the expression of R_0^N:

$$R_0^N = d \int_0^{+\infty} \mathbb{E}^1(X^N(t))dt$$

which depends on the size parameter N and is quite similar to the expression found in other structured metapopulation model [18].

Our aim is now to study the limit of R_0^N as $N \to \infty$. The sequence R_0^N is non-decreasing: in fact, by a coupling argument, one can show that $X^N(t)$ is stochastically dominated by $X^{N+1}(t)$, thus $\mathbb{E}^1(X^N(t)) \le \mathbb{E}^1(X^{N+1}(t))$.

Moreover, one can also see that $X^N(t)$ is stochastically dominated by a linear birth and death process $X(t)$ with per capita birth rate c and per capita death rate γ.

By applying a result of Kurtz for sequences of Markov chains (Ex. n.8, p. 262 in [14]), one can show that X_N converge in distribution to X as $N \to \infty$. For every fixed $t \ge 0$ the sequence of random variable $\{X_N(t)\}_n$ is uniformly integrable, because $P[X^N(t) \ge \alpha] \le P[X(t) \ge \alpha]$, thus $\lim_{N\to\infty} \mathbb{E}^1(X^N(t)) = \mathbb{E}^1(X(t))$. Hence, by Lebesgue's theorem, we obtain

$$\lim_{N\to+\infty} R_0^N = \lim_{N\to+\infty} d \int_0^{+\infty} \mathbb{E}^1(X^N(t))\, dt = d \int_0^{+\infty} e^{(c-\gamma)t}\, dt = \begin{cases} \frac{d}{\gamma-c} & \text{for } c < \gamma. \\ +\infty & \text{for } c \ge \gamma \text{ and } d > 0. \end{cases}$$

Note that there is an undetermined case if $c \ge \gamma$ and $d = 0$, when then there is no transmission of infection between patches.

In a sense, we could say that the definition of R_0 for the model of Section 6 depends on the order of the limits by which it was obtained: if we first let the number N of individuals per patch go to infinity, and then the number M of patches, we can define the basic reproduction ratio as $R_0^1 = \frac{c+d}{\gamma}$. On the other hand, if first M goes to infinity, and then N, we can use $R_0^2 = \frac{d}{\gamma-c}$ for $\gamma > c$ or $R_0^2 = +\infty$ if $c \ge \gamma$ and $d > 0$. However, in either case we see that $R_0^i > 1$ corresponds to $c + d > \gamma$, the condition we found in Section 6 for disease persistence. The limiting system has been introduced to approximate the more complex systems with finite M and/or N. In order to evaluate the approximation, we found it useful to study numerically how quickly R_0^N converge to R_0^2. In Figure 1, we show the values of R_0^N for some values of N and five different combinations of values for the parameters c and d (we

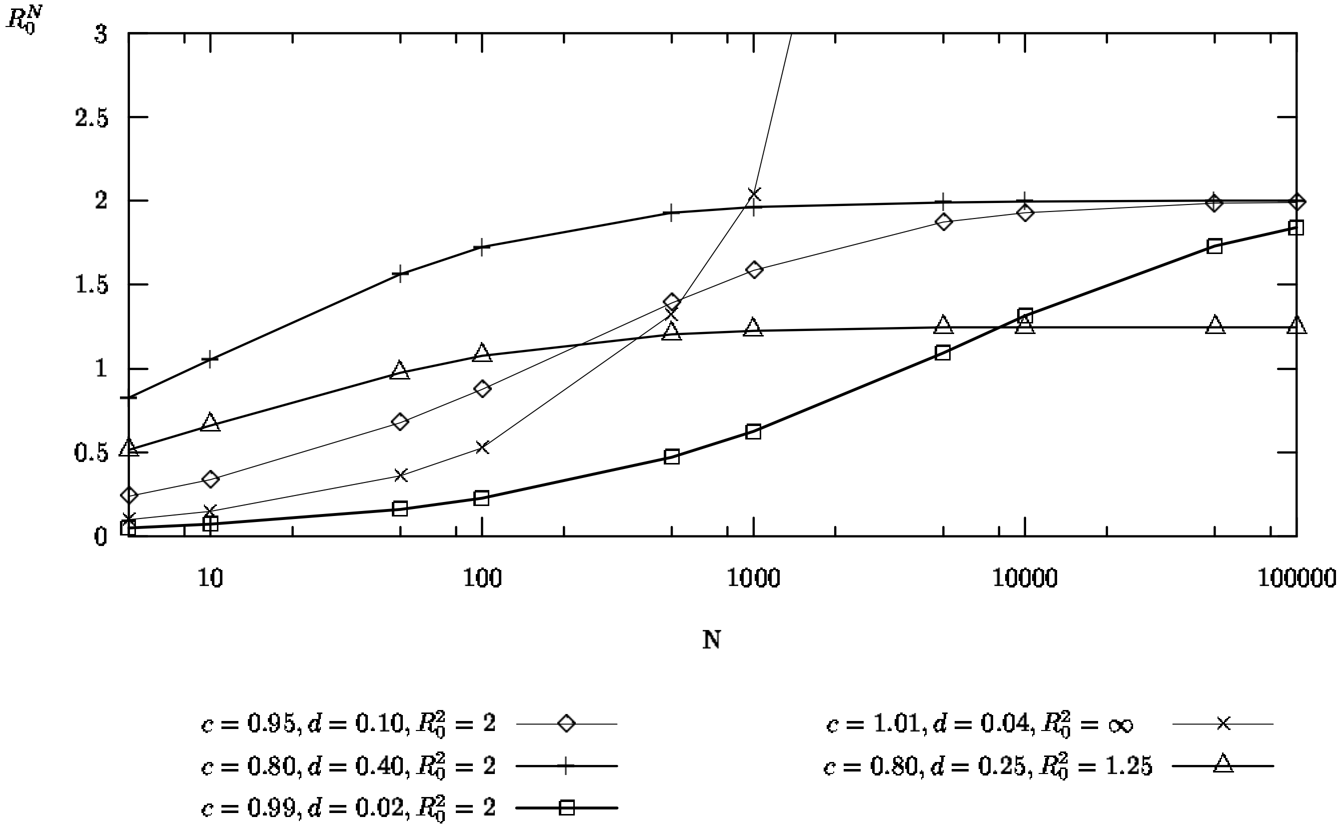

Figure 1: The value of R_0^N for different values of N, c and d; in all cases $\gamma = 1$.

always kept $\gamma = 1$). The numerical results show that the R_0^N indeed tends to R_0^2 for large N; however, if the value of the d is small, R_0^2 gives a good approximation of R_0^N only for large local populations (for $d = 0.02$, we can say N at least 10,000) while the approximation is better for larger values of d. Going to the other extreme, if $N = 1$, the metapopulation model reduces to an epidemic model consisting of individuals, instead of patches: in that case, the basic reproduction number is d/γ: indeed, when we compare the values of R_0^N for small N in the five different parameter combinations, we can see (see Fig. 1) that their order depends on the value of d/γ.

8 Appendix

Applying results of Kurtz ([14], Theorem 7.3, page 223) about existence and uniqueness of the martingale problem for some kind of pure jump Markov processes with non-homogenous transition rates, one can slightly extend Definition 3.1 and Theorem 3.1 of [22] as follows.

Definition A family of continuous-time Markov chains $\{J^N(t)\}_{N\in\mathbb{N}}$ with values in $S_N = \{0,1,2,\ldots,N\} \subset \mathbb{Z}$ and transition rates $q^N(j,k,t), \quad j,k \in S_N, t \in [0,T]$ is said asymptotically density dependent if there exists an open set $E \in \mathbb{R}$ and a family of continuous functions $\{\beta^N\} : E \times \mathbb{Z} \times [0,T]$ such that

$$q^N(k,k+l,t) = N\beta^N(\frac{k}{N},l,t) \qquad l \neq 0,$$

$\sum_l l\beta^N(x,l,t) < \infty$ for all $(x,t) \in E \times [0,T]$ and there exists a function F such that $F^N(x,t) := \sum_l l\beta^N(x,l,t)$ converges to $F(x,t)$ on $E \times [0,T]$.

Theorem 8.1 *If* $|F(x,t) - F(y,t)| < M|x-y|$ *and for all* N

$$\sup_{(x,t)\in E\times[0,T]} \sum |l|\beta_N(x,t,l) < \infty$$

$$\lim_{\delta\to\infty} \sup_{(x,t)\in E\times[0,T]} \sum_{l:|l|>\delta} |l|\beta_N(x,t,l) = 0$$

$$\lim_{N\to\infty} \sup_{E\times[0,T]} |F^N(x,t) - F(x,t)| = 0$$

and $\lim_{N\to\infty} \frac{J^N}{N}(0) = x$, *(with deterministic initial datum* $J^N(0)$*) then*

$$\lim_{N\to\infty} \sup_{[0,T]} \left| \frac{J^N}{N}(t) - Z_x(t) \right| = 0 \qquad a.e.$$

where

$$Z_x(t) = x + \int_0^t F(Z_x(s),s)\, ds$$

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