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REGULAR ARTICLE

Reproductive Numbers for Nonautonomous Spatially Distributed Periodic SIS Models Acting on Two Time Scales

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Abstract In this work we deal with a general class of spatially distributed periodic SIS epidemic models with two time scales. We let susceptible and infected individuals migrate between patches with periodic time dependent migration rates. The existence of two time scales in the system allows to describe certain features of the asymptotic behavior of its solutions with the help of a less dimensional, *aggregated*, system. We derive *global reproduction numbers* governing the general spatially distributed nonautonomous system through the aggregated system. We apply this result when the mass action law and the frequency dependent transmission law are considered. Comparing these global reproductive numbers to their non spatially distributed counterparts yields the following: adequate periodic migration rates allow global persistence or eradication of epidemics where locally, in absence of migrations, the contrary is expected.

Keywords Nonautonomous differential equations · SIS model · Two patches model · Two time scales system approximate aggregation

1 Introduction

In nature, individuals are affected by different processes, each of them evolving within its own characteristic time scale. Therefore, sometimes we are faced to

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consider models coupling two (or more) dynamics evolving at different time scales. For instance, populations suffer seasonal or yearly epidemics, while individuals move around very often, even if the corresponding migration rates do not change very much in the short term. As contacts between individuals is a crucial aspect in the spread of many diseases, it is of full interest considering two time scales systems coupling *fast* migrations with *slow* epidemics.

Many authors have studied autonomous spatial models of epidemics spread where the environment is represented as a set of discrete patches connected by migrations (Arino et al. 2005, 2007; Auger et al. 2008c; Lloyd and Jansen 2004). In most of these works migration and epidemic processes are assumed to act at the same time scale. A work were time scales are explicitly considered is Kouokam et al. (2008): a spatial SIRS model with migrations being faster than disease transmission and recovery. In the present work we also study a two time scales model coupling migrations and local disease spread but letting migration, transmission and recovery rates to be represented by periodic functions of time.

An important problem in the analysis of nonautonomous epidemic models is defining the reproduction number (the expected number of secondary cases caused by a primary case in a fully susceptible population) which value, greater or lower than 1, characterizes in the autonomous case the existence of an epidemic or the disease eradication, respectively. In Thieme (2000), Ma and Ma (2006), and Martcheva (2009) it is suggested defining the reproduction numbers of different periodic epidemics models through the reproduction numbers of the corresponding averaged systems (the autonomous systems obtained by replacing the time-varying parameters with their long-term time averages). This definition of reproductive numbers does not work as clearly as in the autonomous case but in some cases (Martcheva 2009) it is useful to characterize the global stability of the disease-free equilibrium and of the endemic periodic solution.

The model treated in this work is at the same time nonautonomous and spatially distributed. We take advantage of the existence of two time scales to reduce the system to a nonautonomous but spatially implicit one. In this way, the asymptotic results based on reproduction numbers for periodic systems can be applied. The reproduction numbers so obtained can be considered as extension of the usual ones to a patchy environment.

There are different methods to try to simplify complex models involving many variables. One of such method is the so-called aggregation of variables which was first introduced in the field of economy and imported to the field of population dynamics (Iwasa et al. 1987, 1989). These methods consist in deriving simplified global models governing a few global variables that allow to study to a certain extent the asymptotic behavior of the original system. A review of approximate aggregation methods based on time scales separation can be found in Auger et al. (2008a, b). Those aggregation techniques are particularly well developed for autonomous ordinary differential equations, the Fenichel center manifold theorems (Fenichel 1971) and the geometric singular perturbation theory (Verhulst 2005, 2007) being their mathematical basis, but they do not apply directly to our model because they only consider autonomous systems. To reduce, or aggregate, the nonautonomous system presented in this work we use the results on quasistatic-state

approximation for nonlinear initial-value problems, due to Hoppensteadt (1966, 1993, 2010), that are summarized in Sect. 6.1.

The aim of the work is analyzing the influence of fast periodic migrations on disease dynamics. In particular, it is motivated by the results presented in McCallum et al. (2001) where it is discussed how to model pathogen transmission. There, with the help of non spatially distributed autonomous models, it is claimed that epidemics behave the same whether transmission follows the mass action law or the frequency dependent law. We are interested in studying if epidemic dynamics are sensitive to these transmission laws in more complex situations as the one including fast periodic migrations of individuals affected by a periodic SIS. For that, we derive global reproductive numbers and, subsequently, we compare them with their local counterparts (those that were to be obtained *in absence* of migrations). This comparison yields that considering fast periodic migrations may change drastically the outcome of the model.

The paper is organized as follows. In Sect. 2, we present the complete two time scales spatial model with two patches. Section 3 is devoted to the reduction of the model, based on these results summarized in Appendices 1 and 2. In Sect. 4 we analyze the general SIS model by means of the reduced system. Two important cases are investigated by considering the mass action law and the frequency dependent transmission law. We particularly focus on the derivation of reproduction numbers for these models and on the effects of migrations on disease dynamics. Reproduction numbers allow to make suitable predictions about the spread of the epidemic and the appearance of an endemic situation. Section 5 contains the conclusions and the aforementioned appendices can be found in Sect. 6.

2 Spatially Distributed SIS Epidemics Model

Consider a population inhabiting a two patches environment. Individuals are affected by two processes; migrations between patches and a SIS-epidemic process. Let us note $S_k(t)$ and $I_k(t)$ the susceptible and infected individuals at time t and patch $k = 1, 2$, respectively.

Susceptible and infected individuals can remain or leave a given patch. Let us note the corresponding migration rates from patch $k = 1, 2$ by $m_k^S(t) > 0$ and $m_k^I(t) > 0$, which are assumed to be periodic.

At local scale, we consider a general SIS epidemic process. Fertility and mortality rates are the same and represented by the periodic functions $\mu_k(t)$ for patch $k = 1, 2$, thus population can be considered to be globally constant. Periodic functions $\beta_k(t)$ and $\gamma_k(t)$ stand for the transmission and recovery rates at patch $k = 1, 2$. The epidemic process affecting susceptible individuals at patch $k = 1, 2$ is represented by the general function $\Psi_k(\mu_k, \beta_k, \gamma_k, S_k, I_k)$ and so the corresponding function for the infected individuals is $-\Psi_k(\mu_k, \beta_k, \gamma_k, S_k, I_k)$. We assume that $\Psi_k(\cdot, \cdot, \cdot, \cdot, 0) = 0$ for $k = 1, 2$, what reflects the fact that infected individuals cannot spontaneously appear in the population. Functions Ψ_k are taken to be $\mathscr{C}^2$ on their respective domains for technical reasons.

The model coupling fast migrations and slow local SIS-epidemic dynamics reads as follows:

$$\begin{cases} \varepsilon \frac{dS_1}{dt} = -m_1^S(t)S_1 + m_2^S(t)S_2 + \varepsilon\Psi_1(\mu_1(t), \beta_1(t), \gamma_1(t), S_1, I_1), \\ \varepsilon \frac{dS_2}{dt} = m_1^S(t)S_1 - m_2^S(t)S_2 + \varepsilon\Psi_2(\mu_2(t), \beta_2(t), \gamma_2(t), S_2, I_2), \\ \varepsilon \frac{dI_1}{dt} = -m_1^I(t)I_1 + m_2^I(t)I_2 - \varepsilon\Psi_1(\mu_1(t), \beta_1(t), \gamma_1(t), S_1, I_1), \\ \varepsilon \frac{dI_2}{dt} = m_1^I(t)I_1 - m_2^I(t)I_2 - \varepsilon\Psi_2(\mu_2(t), \beta_2(t), \gamma_2(t), S_2, I_2). \end{cases} \tag{1}$$

Positive small parameter ϵ represents the ratio between time scales. All periodic function appearing in the model are assumed to have a common period ω and to be $\mathscr{C}^2(\mathbb{R})$. The period is related to the slow time scale, the underlying idea is that coefficients exhibit periodic patterns and we expect small changes of the value of these functions in the short term but which may become larger as the time passes by. For instance, if the period is yearly, the value of a given migration rate should be more or less the same in a time interval of few days, but can experiment large variations after several months. Besides, individual displacements are related with encounters but, for not so contagious diseases, it is a plausible hypothesis that several encounters are needed for a single transmission event. These assumptions support the existence of different time scales.

The total population given by $N(t) = S_1(t) + S_2(t) + I_1(t) + I_2(t)$ verifies $dN/dt = 0$. Then, we can assume from now on that the total population size is constant and rescaled to 1, so that we consider system (1) on the set

$$\Omega = \left\{(S_1, S_2, I_1, I_2) \in \mathbb{R}_+^4 : N(t) = 1\right\}$$

which is positively invariant.

3 Reduction of Model (1)

The results we are presenting here are derived from Hoppensteadt results on quasistatic-state approximation for nonlinear initial-value problems, Hoppensteadt (1966, 1993, 2010). For the convenience of the reader, we have summarized these results in Sect. 6 and, in particular, in Theorem 2 (Appendix 1).

Model (1) couples two different processes acting at different time scales and it fits in the general form (22) presented in Appendix 2. Thus, we proceed to write it into the so-called slow-fast form so that we get the associated reduced system.

To transform system (1) into slow-fast form we seek for an appropriate change of variables making emerge the slow variables of the model. In this case, the natural choice is the total number of susceptible and infected individuals because these variables are kept constant through migrations (the fast dynamics) and so they evolve at the slow time scale, the one that infectious process acts at. We denote them by

$$S = S_1 + S_2 \quad \text{and} \quad I = I_1 + I_2.$$

According to Appendix 2 notation, the change of variables

$$n = (S_1, S_2, I_1, I_2) \mapsto T(n) := (x, y),$$

where $x = (S_1, I_1)$ and $y = (S, I)$, leads system (1) into the desired slow-fast form.

$$\begin{cases} \varepsilon \frac{dS_1}{dt} = -m_1^S(t)S_1 + m_2^S(t)(S - S_1) - \varepsilon \Psi_1(\mu_1(t), \beta_1(t), \gamma_1(t), S_1, I_1), \\ \varepsilon \frac{dI_1}{dt} = -m_1^I(t)I_1 + m_2^I(t)(I - I_1) + \varepsilon \Psi_1(\mu_1(t), \beta_1(t), \gamma_1(t), S_1, I_1), \\ \frac{dS}{dt} = -\Psi_1(\mu_1(t), \beta_1(t), \gamma_1(t), S_1, I_1) - \Psi_2(\mu_2(t), \beta_2(t), \gamma_2(t), S - S_1, I - I_1), \\ \frac{dI}{dt} = \Psi_1(\mu_1(t), \beta_1(t), \gamma_1(t), S_1, I_1) + \Psi_2(\mu_2(t), \beta_2(t), \gamma_2(t), S - S_1, I - I_1). \end{cases} \tag{2}$$

We define also the transformations $T_x\ (n) := x$ and $T_y\ (n) := y$, and denote $\Omega_T = T(\Omega), \Omega_T^x = T_x(\Omega)$ and $\Omega_T^y = T_y(\Omega)$. First we proceed to construct the reduced model and for that we need to prove that system (2) fulfills hypotheses H1, H2 and H3 stated in Appendix 1.

The fact that Ω_T is positively invariant for system (2) ensures that Hypothesis H1 is met.

To find function $x = \Phi(t, y)$ of Hypothesis H2 we have to solve for $x = (S_1, I_1)$ the following system:

$$\begin{cases} -m_1^S(t)S_1 + m_2^S(t)(S - S_1) = 0, \\ -m_1^I(t)I_1 + m_2^I(t)(I - I_1) = 0. \end{cases} \tag{3}$$

we note

$$\begin{aligned} (S_1^*(t,S), I_1^*(t,S)) &= \left(\frac{m_2^S(t)S}{m_1^S(t) + m_2^S(t)}, \frac{m_2^I(t)I}{m_1^I(t) + m_2^I(t)} \right) \\ &= \left(\mathscr{S}_1^*(t)S, \mathscr{I}_1^*(t)I \right) = \Phi(t, S, I). \end{aligned} \tag{4}$$

Straightforward calculations also give that $\det(f_x(t, x, y)) > 0$ for $x = \Phi(t, S, I)$ where $f(t, x, y) = \left(-m_1^S(t)S_1 + m_2^S(t)(S - S_1), -m_1^I(t)I_1 + m_2^I(t)(I - I_1)\right)$. Thus, Hypothesis H2 is also met.

To verify Hypothesis H3 we need to prove that the fast equilibrium $\Phi(\alpha, \beta)$ are asymptotically stable uniformly in the parameters $(\alpha, \beta) \in \mathbb{R} \times \Omega_T^y, \beta = (b_1, b_2)$, for system

$$\begin{cases} \frac{dS_1}{d\tau} = -m_1^S(\alpha)S_1 + m_2^S(\alpha)(b_1 - S_1), \\ \frac{dI_1}{d\tau} = -m_1^I(\alpha)I_1 + m_2^I(\alpha)(b_2 - I_1). \end{cases} \tag{5}$$

The global asymptotic stability of $\Phi(\alpha, \beta) = \left(S_1^*(\alpha, b_1), I_1^*(\alpha, b_2)\right)$ is straightforward as equations in (5) are uncoupled and each of them is linear. The uniformity follows from the fact that Ω_T^y is compact and the functions appearing in the system are periodic on α. Furthermore, the domain of attraction of the equilibrium $\Phi(t_0, y_0)$, for each $t_0 \geq 0$ and each $y_0 \in \Omega_T^y$, includes all $x_0 \in \Omega_T^x$.

Now that hypotheses H1, H2 and H3 are verified we can write the reduced system (21) (see Hypothesis 4) with variables $\bar{y} = (\bar{S}, \bar{I})$ and defined in the domain $\bar{\Omega} = \left\{(\bar{S}, \bar{I}) \in \mathbb{R}_+^2 : \bar{S} + \bar{I} = 1\right\}$, associated to system (2):

$$\begin{cases} \frac{d\bar{S}}{dt} = \Psi_1\left(\mu_1(t), \beta_1(t), \gamma_1(t), S_1^*(t, \bar{S}), I_1^*(t, \bar{I})\right) \\ \qquad + \Psi_2\left(\mu_2(t), \beta_2(t), \gamma_2(t), \bar{S} - S_1^*(t, \bar{S}), \bar{I} - I_1^*(t, \bar{I})\right), \\ \frac{d\bar{I}}{dt} = -\Psi_1\left(\mu_1(t), \beta_1(t), \gamma_1(t), S_1^*(t, \bar{S}), I_1^*(t, \bar{I})\right) \\ \qquad - \Psi_2\left(\mu_2(t), \beta_2(t), \gamma_2(t), \bar{S} - S_1^*(t, \bar{S}), \bar{I} - I_1^*(t, \bar{I})\right). \end{cases} \tag{6}$$

A further reduction in system (6) is still possible having in mind that $\bar{S}(t) + \bar{I}(t)$ is constant and we have normalized it to 1. The equation for $\bar{I}$ equivalent to system (6) is:

$$\begin{aligned} \frac{d\bar{I}}{dt} &= -\Psi_1\big(\mu_1(t), \beta_1(t), \gamma_1(t), S_1^*(t, 1-\bar{I}), I_1^*(t, \bar{I})\big) \\ &\quad -\Psi_2\big(\mu_2(t), \beta_2(t), \gamma_2(t), 1-\bar{I}-S_1^*(t, 1-\bar{I}), \bar{I}-I_1^*(t, \bar{I})\big) \\ &= \Psi(\mu_1(t), \mu_2(t), \beta_1(t), \beta_2(t), \gamma_1(t), \gamma_2(t), S_1^*(t), I_1^*(t), I). \end{aligned} \tag{7}$$

4 Analysis of the Model: Global Reproductive Numbers

In this section we address the analysis of the general model (1) (a 4 dimensional) through the aggregated system (7) (a scalar equation) using Theorem 2. The study of the aforementioned reduced system yields criteria predicting persistence or eradication of epidemics for the general two time scales system (1).

Besides, a deeper analysis is carried out for two important epidemiological models by considering the mass action law and the frequency transmission law (McCallum et al. 2001). As a result, we define *global reproductive numbers* $\bar{\mathcal{R}}$ for these two time scales spatially distributed SIS models. $\bar{\mathcal{R}}$ is a threshold for the global persistence of epidemics; whenever $\bar{\mathcal{R}} < 1$, epidemics globally disappear, while $\bar{\mathcal{R}} > 1$ allows epidemics globally to persists (according to Theorem 2). Global reproductive numbers are defined in terms of local parameters and migration rates. Finally, we compare these global reproductive numbers with their local counterparts. Doing so, we get knowledge on the influence of considering migrations and time scales in these epidemic processes.

Equation (7) is a scalar periodic one and its solutions are confined in the [0,1] interval. We already know about the existence of the trivial solution $I_0(t) = 0$ (disease free state) of (7) and we seek for the existence of non trivial periodic solutions. Thanks to the fact that the solutions of (7) are bounded, we can derive the existence of positive asymptotically stable solutions of (7) when the trivial solution $I_0(t)$ is unstable. In terms of Floquet's theory (see, for instance, Farkas 1994) the stability of a periodic solution of a periodic system can be established in terms of the sign of the corresponding characteristics exponents (noted by a_0 in the following result). Using these ideas along with Theorem 2 (see Appendix 1) we get the following information on the complete system (1) through the reduced system (7).

Theorem 1 *Let us note*

$$a_0 := \int_{t_0}^{t_0+\omega} \frac{\partial}{\partial I}\big(\Psi(\mu_1(t), \mu_2(t), \beta_1(t), \beta_2(t), \gamma_1(t), \gamma_2(t), S_1^*(t), I_1^*(t), I)\big)\big|_{I=0} dt, \tag{8}$$

which is the characteristic exponent of the zero solution of system (7). *We consider* $n^\varepsilon(t) = (S_1^\varepsilon(t), S_2^\varepsilon(t), I_1^\varepsilon(t), I_2^\varepsilon(t))$ *the solution of system* (1) *with initial values* $n^\varepsilon(t_0) = n_0^\varepsilon \in \Omega$. *Let us recall that the total population size has been rescaled to 1. Then*,

1. *If $a_0 < 0$, then the trivial solution $I_0^*(t) = 0$ of system (7)is uniform asymptotically stable. Besides, if $n^\varepsilon(t)$ is such that $I_1^\varepsilon(t_0) + I_2^\varepsilon(t_0) = \xi_0$ is in the domain of attraction of $I_0^*(t)$ then, for any $\delta > 0$, there exist $\varepsilon_\delta > 0$ and $t_\delta > t_0$ such that*

$$|n^\varepsilon(t) - \big(\mathscr{S}_1^*(t), (1 - \mathscr{S}^*(t)), 0, 0\big)| < \delta$$

for every $\varepsilon \leq \varepsilon_\delta$ and every $t \geq t_\delta$, where $\mathscr{S}_1^*$ was defined in (4).

2. *If $a_0 > 0$, then there exists a positive periodic uniform asymptotically stable solution $I^*(t)$ of system (7). If $n^\varepsilon(t)$ is such that $I_1^\varepsilon(t_0) + I_2^\varepsilon(t_0) = \xi_0$ is in the domain of attraction of $I^*(t)$ then, for any $\delta > 0$, there exist $\varepsilon_\delta > 0$ and $t_\delta > t_0$ such that*

$$|n^\varepsilon(t) - \big(\mathscr{S}_1^*(t)(1 - I^*(t)), (1 - \mathscr{S}_1^*(t))(1 - I^*(t)), \mathscr{I}_1^*(t)I^*(t), \big(1 - \mathscr{I}_1^*(t))I^*(t)\big)| < \delta$$

for every $\varepsilon \leq \varepsilon_\delta$ and every $t \geq t_\delta$, where $\mathscr{S}_1^*$ and $\mathscr{I}_1^*$ were defined in (4).

Proof We are proving the existence of uniformly asymptotically stable solutions of (7) and that Hypothesis H4 holds. Doing so, 1. and 2. in the theorem will be direct consequence of Theorem 2.

We already know that $I_0^*(t) := 0$ for all $t \geq t_0$ is a solution of (7). It is known that a periodic solution of a periodic scaler equation is asymptotically stable it the corresponding characteristic multiplier is less than 0. Otherwise, $I_0^*(t)$ is unstable.

Let us assume the later condition. In this case, solutions are bounded away from $I_0^*(t)$. In addition, $I(t)$ varies in the compact set [0, 1], so that every solution of (7) is bounded. In this case, there exists an asymptotically stable periodic solution $I^*(t)$ of (7) (see, for instance, Theorem 4.11 in Chow and Hale 1982). As $I_0(t)$ is unstable when $a_0 > 0$, then $I^*(t)$ is positive.

Finally, in Chow and Hale (1982) it is also proved that a bounded solution of a periodic scalar equation monotonically converges to a periodic solution. Thus, in case of being stable, the aforementioned solutions $I_0^*(t)$ and $I^*(t)$ are, in fact, uniformly asymptotically stable. □

It is now apparent that expression a_0 is the key for studying the outcome of epidemics and we will use it for defining the global reproductive numbers. In the sequel, we apply the previous general results to study the effect of fast migrations when considering the mass action law and the frequency dependent transmission law.

4.1 Mass Action Transmission Law

In this case we consider

$$\Psi_k(\mu_k, \beta_k, \gamma_k, S_k, I_k) = -\beta_k(t)S_kI_k + (\mu_k(t) + \gamma_k(t))I_k, \quad k = 1, 2. \tag{9}$$

Straightforward calculations yield the corresponding reduced system

$$\begin{cases} \frac{dS}{dt} = -\beta^*(t)SI + (\mu^*(t) + \gamma^*(t))I, \\ \frac{dI}{dt} = \beta^*(t)SI - (\mu^*(t) + \gamma^*(t))I, \end{cases} \tag{10}$$

where

$$\beta^*(t) = \beta_1(t)\mathscr{I}_1^*(t)\mathscr{S}_1^*(t) + \beta_2(t)(1-\mathscr{I}_1^*(t))(1-\mathscr{S}_1^*(t)),$$
$$\mu^*(t) = \mu_1(t)\mathscr{I}_1^*(t) + \mu_2(t)(1-\mathscr{I}_1^*(t)), \quad \gamma^*(t) = \gamma_1(t)\mathscr{I}_1^*(t) + \gamma_2(t)(1-\mathscr{I}_1^*(t)),$$

and $\mathscr{S}_1^*(t), \mathscr{I}_1^*(t)$ were defined in (4). Keeping in mind (7), system (10) can be studied by means of the scaler equation

$$\frac{dI}{dt} = -(\mu^*(t) + \gamma^*(t))I + \beta^*(t)(1-I)I. \tag{11}$$

If function $f(t)$ is ω-periodic on t, we note $\langle f(t)\rangle = \frac{1}{\omega}\int_{t_0}^{t_0+\omega} f(s)ds$. In addition, direct calculations yield that, in the present case,

$$a_0 = \int_{t_0}^{t_0+\omega} \beta^*(t) - (\mu^*(t) + \gamma^*(t))ds.$$

If we define the *global reproductive number* as

$$\bar{\mathscr{R}} := \frac{\langle \beta^*(t)\rangle}{\langle \mu^*(t)\rangle + \langle \gamma^*(t)\rangle} \tag{12}$$

it is apparent that the relation between a_0 and $\bar{\mathscr{R}}$ is as follows

Proposition 1 *If holds that*

$$\bar{\mathscr{R}} < 1 \Leftrightarrow a_0 < 0 \quad \textit{and} \quad \bar{\mathscr{R}} > 1 \Leftrightarrow a_0 > 0.$$

Proof It can be easily checked by direct calculations. □

Formally, expression (12) is that defined in Martcheva (2009), where a non spatially distributed SIS epidemic model with multiple strains was addressed. Nevertheless, coefficients involved in (12) depend on the equilibrium of the fast dynamics (5) as well as on local epidemic parameters, extending those defined in Martcheva (2009). In particular, it turns out that migration rates are relevant when computing the value of the global reproductive numbers.

Next, we accomplish the analysis of the effect of fast migrations in two different scenarios. On the one hand we let coefficients describing epidemics to be equal in both regions. On the other hand, we set epidemic coefficients so that local disease behavior is asymmetric, being epidemics stronger in one of the regions. In both cases the behavior of infected individuals is determined by the solutions of equation

$$\frac{dI_k}{dt} = -(\mu_k(t) + \gamma_k(t))I_k + \beta_k(t)(1-I_k)I_k, \quad k = 1,2, \tag{13}$$

having normalized the total population at each patch up to 1. We compare the global reproductive number $\bar{\mathscr{R}}$ with the local reproductive numbers

$$\mathscr{R}_k = \frac{\langle \beta_k(t)\rangle}{\langle \mu_k(t)\rangle + \langle \gamma_k(t)\rangle}, \quad k = 1,2, \tag{14}$$

which are obtained in a similar way as we got (12) and determine the outcome of the epidemic process at patch $k = 1,2$ in *absence* of migrations.

We recall also that

Proposition 2 *Under the assumptions in Sect. 4.1,*

1. *If $\bar{\mathscr{R}} < 1$ (resp. $\mathscr{R}_k < 1, k = 1,2$), then the trivial solution of (11) (resp. (13)) whose existence follows from the proof of Theorem 1 is globally uniformly asymptotically stable.*
2. *If $\bar{\mathscr{R}} > 1$ (resp. $\mathscr{R}_k > 1, k = 1,2$), then the positive periodic solution of (11) (resp. (13)) whose existence follows from the proof of Theorem 1 is globally uniformly asymptotically stable.*

Proof

1. Consider, for instance, (13). It follows easily from the fact that solutions of (13) are bounded from above by the solutions of equation
$$\frac{dz_k}{dt} = -(\mu_k(t) + \gamma_k(t))z_k + \beta_k(t)z_k,$$
which converge to zero when $\mathscr{R}_k < 1, k = 1,2$. A similar reasoning is valid for (11).
2. Equations (11) and (13) are the periodic Bernoulli equation, which has received much attention. Different proofs of the existence of an unique periodic positive solution can be found in Thieme (2003) and Martcheva (2009). Therefore, b) follows from the proof of Theorem 1.

Remark In particular, Proposition 2 implies that these results in Theorem 1 are global, meaning that any $0 \neq \xi_0$ is in the domain of attraction of the corresponding solution in the statement of Theorem 1.

4.1.1 Effect of Migrations: Symmetric Regions

Let us assume that disease parameters are the same in both patches. Namely

Proposition 3 *Assume that $\beta_1 = \beta_2$, $\gamma_1 = \gamma_2$ and $\mu_1 = \mu_2 \equiv \mu$. It follows that*
$$\bar{\mathscr{R}} \leq \mathscr{R}_k \quad k = 1,2,$$
where $\bar{\mathscr{R}}$ and $\mathscr{R}_k$ are these given by (12) and (14), resp.

Proof It can be easily established directly comparing $\bar{\mathscr{R}}$ and $\mathscr{R}_k, k = 1,2$. □

Therefore, it may happen either $\bar{\mathscr{R}} = \mathscr{R}_k$ or $\bar{\mathscr{R}} < \mathscr{R}_k$ for $k = 1, 2$. In the first case, the output of epidemics is the same globally and locally, meaning that it does not matter considering migrations in the final outcome of the epidemic process. On the contrary, the second case allows
$$\bar{\mathscr{R}} < 1 < \mathscr{R}_k \quad k = 1,2,$$
so that epidemics will be globally eradicated while, in *absence* of migration, the contrary was expected at each patch.

4.1.2 Asymmetric Regions

We consider now that the epidemic process has stronger incidence in one of the regions, for instance, at patch one. The following result holds

Proposition 4 *Let us set* $\beta_1 < \beta_2$, $\gamma_2 < \gamma_1$ *and we let* $\mu_1 = \mu_2 \equiv \mu$. *If*

$$\langle \beta_1(t)(1 - \mathscr{I}_1^*(t)\mathscr{S}_1^*(t))\rangle < \langle \beta_2(t)(1 - \mathscr{I}_1^*(t))(1 - \mathscr{S}_1^*(t))\rangle$$

then

$$\mathscr{R}_1 < \bar{\mathscr{R}} < \mathscr{R}_2,$$

where $\bar{\mathscr{R}}$ *and* $\mathscr{R}_k$ *are these given by* (12) *and* (14), *resp.*

Proof On the one hand, it is clear that

$$\bar{\mathscr{R}} < \frac{\langle \beta_2(t)\mathscr{I}_1^*(t)\mathscr{S}_1^*(t) + \beta_2(t)(1 - \mathscr{I}_1^*(t))(1 - \mathscr{S}_1^*(t))\rangle}{\langle \mu(t)\rangle + \langle \gamma_2(t)\rangle} < \mathscr{R}_2$$

because

$$\langle \beta_2(t)\big[\mathscr{I}_1^*(t)(\mathscr{S}_1^*(t) - 1) + \mathscr{S}_1^*(t)(\mathscr{I}_1^*(t) - 1)\big]\rangle < 0.$$

On the other hand,

$$\frac{\langle \beta_1(t)\mathscr{I}_1^*(t)\mathscr{S}_1^*(t) + \beta_2(t)(1 - \mathscr{I}_1^*(t))(1 - \mathscr{S}_1^*(t))\rangle}{\langle \mu(t)\rangle + \langle \gamma_1(t)\rangle} < \bar{\mathscr{R}}.$$

Comparing $\mathscr{R}_1$ with the left hand side quotient in the previous expression finishes the proof. □

As particular cases,

$$\mathscr{R}_1 < 1 < \bar{\mathscr{R}} < \mathscr{R}_2$$

or

$$\mathscr{R}_1 < \bar{\mathscr{R}} < 1 < \mathscr{R}_2$$

produce global behaviors which are different of those expected at local level. This analysis is not exhaustive and do not exclude the case $\mathscr{R}_k > \bar{\mathscr{R}}$ for $k = 1, 2$, which was addressed in the symmetric regions case.

4.2 Frequency Dependent Transmission Law

Following the schema of the previous Sect. 4.1, we turn our attention to the case

$$\Psi_k(\mu_k, \beta_k, \gamma_k, S_k, I_k) = (\mu_k(t) + \gamma_k(t))I_k - \beta_k(t)\frac{S_k I_k}{S_k + I_k}, \quad k = 1, 2. \tag{15}$$

Reasoning as before we define the corresponding global reproductive number as

$$\bar{\mathscr{R}} := \frac{\left\langle \frac{\beta_1(t)}{\mathscr{S}_1^*(t)} \right\rangle + \left\langle \frac{\beta_2(t)}{1-\mathscr{S}_1^*(t)} \right\rangle}{\langle \mu^*(t) \rangle + \langle \gamma^*(t) \rangle}. \tag{16}$$

As we did in the case of mass action transmission law, we finish this section analyzing the effect of fast migrations in epidemics outcome in two different cases considering again epidemiological symmetric and asymmetric regions. Hence, we compare the global reproductive number (16) with the corresponding local reproductive numbers. In absence of migrations, local epidemic process (15) simplifies in

$$\begin{cases} \frac{dS_k}{dt}(\mu_k(t) + \gamma_k(t))I_k - \beta_k(t)\frac{S_k I_k}{S_k + I_k}, \\ \frac{dI_k}{dt} = -(\mu_k(t) + \gamma_k(t))I_k + \beta_k(t)\frac{S_k I_k}{S_k + I_k}, \end{cases} \quad k = 1, 2.$$

In addition, hypothesis $S_k(t) + I_k(t) = 1$ yields the following expression for the local reproductive numbers

$$\mathscr{R}_k = \frac{\langle \beta_k(t) \rangle}{\langle \mu_k(t) \rangle + \langle \gamma_k(t) \rangle}, \quad k = 1, 2. \tag{17}$$

4.2.1 Effect of Migrations: Symmetric Regions

Proposition 5 *In case of $\beta_1 = \beta_2 = \beta$, $\gamma_1 = \gamma_2 = \gamma$ and $\mu_1 = \mu_2 = \mu$, it follows that*

$$\mathscr{R}_k < \bar{\mathscr{R}}, \quad k = 1, 2,$$

where $\bar{\mathscr{R}}$ and $\mathscr{R}_k$ are these given by (16) and (17), respectively.

Proof Simple calculations yield

$$\bar{\mathscr{R}} = \frac{\left\langle \frac{\beta(t)}{\mathscr{S}_1^*(t)(1-\mathscr{S}_1^*)} \right\rangle}{\langle \mu^*(t) \rangle + \langle \gamma^*(t) \rangle}$$

and the fact that $\mathscr{S}_1^*(t) \in (0, 1)$ for all t finishes the proof.

Surprisingly, concrete migratory schemes may let epidemics to persist whether eradication was expected at local level. This result is, in any sense, the "converse" of that obtained for the mass action transmission law.

4.2.2 Asymmetric Regions

We consider now that epidemics has stronger incidence in one of the regions, for instance, at patch one. Thus, we set $\beta_1 < \beta_2$, $\gamma_2 < \gamma_1$ and we let $\mu_1 = \mu_2$.

It is straightforward that $\mathscr{R}_1 < \bar{\mathscr{R}}$.

On the other hand, it is not possible to find out a general relation between $\mathscr{R}_2$ and $\bar{\mathscr{R}}$. In fact, it may happen $\mathscr{R}_2 < \bar{\mathscr{R}}$, $\mathscr{R}_2 = \bar{\mathscr{R}}$ or $\mathscr{R}_2 > \bar{\mathscr{R}}$. Therefore, once more time, the outcome of the model can change drastically depending on the migratory scheme.

5 Discussion and Conclusions

In this work we deal with a general two time scales periodic nonautonomous spatially distributed system coupling fast migrations with a slow SIS epidemic process. As pointed out in the introduction, the purpose of the study is twofold. On the one hand, we seek for defining global reproduction numbers and, on the other hand, we want to contrast those results presented in McCallum et al. (2001) in a more complex realistic scenario, as that described by the aforementioned hypotheses.

Under these general settings and using approximate aggregation methods, we are able to derive a reduced model and a threshold quantity a_0 describing whether epidemics become globally endemic or are globally eradicated. Obviously, dealing with a system as general as (1), with no explicit expression describing epidemics, does not allow to do deeper analysis. Then, we carry on analyzing the aforementioned pathogen transmission laws (McCallum et al. 2001): the mass action law and the frequency dependent transmission law. We derive *global reproductive numbers* $\bar{\mathscr{R}}$ based on a_0 for models considering each of these transmission laws. Then, we compare these global reproductive numbers to the *local reproductive numbers*, that is, the reproductive numbers corresponding with isolated patches (those calculated for each patch in absence of migration). Our results are the following:

1. In the symmetric case, i.e. when the two patches are the same from an epidemiological point of view, an interesting result holds for the mass action transmission law: the global reproductive number is smaller than the local ones. This result is similar to that obtained in Kouokam et al. (2008) for a two patch SIRS autonomous model with fast migration, which was extended in that contribution to a set of $N > 2$ patches. On the contrary, considering the frequency dependent transmission law yields global reproduction number greater than local ones.
2. The asymmetric patches case leads to more complex results in both the mass action law and the frequency dependent transmission law. Namely, global reproduction number can be greater or smaller than local ones according to the set of parameter values.

The analysis performed in Sect. 4 yields evidences of the importance of identifying heterogeneous clusters on the epidemiological behavior of a disease within a population, identifying individual displacement patterns and/or choosing an appropriate pathogen transmission law. Namely, an appropriate combination of the previous factors may allow epidemics to globally persist whether at local level (that is, in absence of migrations) the contrary was expected, and conversely. For instance, let us consider an homogeneous environment. Compared to the local reproductive numbers, the global reproductive number is smaller for the mass action law and larger for the frequency dependent law. Then, the outcome of the model can be completely different depending on how transmission in modeled. Summing up, we have achieved the proposed aims.

Our results point out fast periodic migrations as a suitable mechanism for promoting disease eradication/endemicity. In general, the relation between the global reproduction numbers and the local ones is sophisticated. Paying attention to these relations may help to getting knowledge on how individual displacements may lead to epidemics eradication/persistence. In particular, once the local epidemiological and demographic parameters are estimated, a control of epidemics can be considered by an adequate management of individual displacements.

Considering just periodic fast migrations with respect to the dynamics of the epidemics, the present model could be quite easily extended to a series of $N > 2$ patches using aggregation methods. It would also be very interesting to study the effects of the migration connection graph for infected as well as susceptible individuals on the global dynamics of the epidemics, leading either to eradication or to an endemic situation.

We also believe that these models could be applied to some concrete epidemics in an heterogeneous environment which can be represented by a set of patches connected by fast migrations and we expect to achieve this goal in a future contribution.

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Appendix 1: Quasistatic-State Approximation for Nonlinear Initial-Value Problems

We summarize here the results on quasistatic-state approximation for nonlinear initial-value problems, due to Hoppensteadt (1966, 1993, 2010), that allow to extend aggregation methods, see Auger et al. (2008a, b), to some two time scales nonautonomous systems of ordinary differential equations, in particular to system (1).

We consider the initial-value problem

$$\begin{cases} \varepsilon \frac{dx}{dt} = f(t,x,y,\varepsilon), & x(t_0) = \eta_0, \\ \frac{dy}{dt} = g(t,x,y,\varepsilon), & y(t_0) = \xi_0, \end{cases} \tag{18}$$

where $x \in \mathbb{R}^n, y \in \mathbb{R}^m$ and ε is a small positive parameter. We define the domain $\hat{\Omega} = I \times \Omega \times [0, \varepsilon_0]$ where $I = \{t : t_0 \le t \le T \le \infty\}, \Omega = B_R \times B_{R'}, B_R = \{x \in \mathbb{R}^n : |x| \le R\}, B_{R'} = \{y \in \mathbb{R}^m : |y| \le R'\}$, and ε_0 is a fixed constant. In what follows, the balls B_R and $B_{R'}$ can be replaced by any sets that are diffeomorphic to them.

Hypothesis H1 *Functions f and g are $\mathscr{C}^2(\hat{\Omega})$ and any solution of the system (18) beginning in $B_R \times B_{R'}$ remains there for $t \in I_T$*

Setting $\varepsilon = 0$ in (18) we obtain the so-called *reduced problem*:

$$\begin{cases} 0 = f(t,x,y,0), \\ \frac{dy}{dt} = g(t,x,y,0), y(t_0) = \xi_0. \end{cases} \tag{19}$$

Hypothesis H2 *There is a function $x = \Phi(t,y)$ such that $f(t,\Phi(t,y),y,0) = 0$ for $t \in I_T$ and $y \in B_{R'}$. Moreover $\Phi \in \mathscr{C}^2(I_T \times B_{R'})$ and $\det(f_x(t,\Phi(t,y),y,0)) \neq 0$ for $(t,y) \in I_T \times B_{R'}$.*

Hypothesis H3 *The system of equations*

$$\frac{dX}{d\tau} = f(\alpha, X, \beta, 0) \tag{20}$$

has $X = \Phi(\alpha, \beta)$ *as an equilibrium for each* $(\alpha, \beta) \in I_T \times B_{R'}$ *that it is asymptotically stable uniformly in the parameters* $(\alpha, \beta) \in I_T \times B_{R'}$, *and the initial condition* η_0 *is in the domain of attraction of the equilibrium* $\Phi(t_0, \xi_0)$ *for system* (20) *with* $\alpha = t_0$ *and* $\beta = \xi_0$.

Hypothesis H4 *The system of equations*

$$\frac{dy_0}{dt} = g(t, \Phi(t, y_0), y_0, 0) \tag{21}$$

has a solution for $t_0 \leq t < \infty$, *say* $y^*(t)$, *that it is uniformly asymptotically stable and* ξ_0 *is in the domain of attraction of* $y^*(t)$.

Theorem 2 *Let hypothesis H1, H2, H3 and H4 be satisfied and let* $y_0(t)$ *be the solution of 21 for* $y_0(t) = \xi_0$. *Then, for sufficiently small values of* ε *the solution of problem* (18), $(x(t), y(t))$, *exists for* $t_0 \leq t < \infty$ *and it satisfies*

$$x(t) = \Phi(t, y_0(t)) + o(1), \quad y(t) = y_0(t) + o(1)$$

as $\varepsilon \to 0^+$ *uniformly on any interval of the form* $t_0 < t_1 \leq t < \infty$.

Appendix 2: Approximate Aggregation Methods: Nonautonomous Case

System (1) belongs to a class of two time scales systems of the form

$$\varepsilon \frac{dn}{dt} = f(t, n) + \varepsilon s(t, n), \tag{22}$$

with $n \in \mathbb{R}^m_+$ and where f and s represent the fast and slow dynamics, respectively.

This kind of systems with f and s not depending on t have been extensively studied and applied to different biological models, see Auger et al. (2008a, b) for recent reviews, using approximate aggregation methods. The first step in applying these methods is to transform the system into slow-fast form by means of an appropriate change of variables. To reproduce this step with the nonautonomous system (22) we assume that it exists a change of variables $n \in \mathbb{R}^m \to (x, y) \in \mathbb{R}^{m-q} \times \mathbb{R}^q$ that yields the following system:

$$\begin{cases} \varepsilon \frac{dx}{dt} = F(t, x, y) + \varepsilon H(t, x, y), \\ \frac{dy}{dt} = G(t, x, y), \end{cases} \tag{23}$$

where x and y stand for the fast and the slow variables, respectively. It is not always easy to find the appropriate transformation leading to the slow-fast form (23) of system (22). Nevertheless, in some applications, the context gives a natural way to define the slow variables, also called *global variables*, which are the key of the transformation. In system (1) the obvious candidates for slow variables are the total

number of susceptible and of infected individuals, which are kept constant by fast dynamics (movements among patches) and so they evolve at the slow time scale.

The autonomous case of the slow-fast system (23) is reduced by means of Fenichel center manifold theorems (Auger et al. 2008a, b). The asymptotic behavior of the complete initial system is then studied with the help of a reduced system for the global variables called *aggregated system*. Here, for the nonautonomous case, we notice that system (23) is a particular case of system (18) taking

$$f(t,x,y,\varepsilon) = F(t,x,y) + \varepsilon H(t,x,y) \quad \text{and} \quad g(t,x,y,\varepsilon) = G(t,x,y)$$

so we are using the Hoppensteadt results summarized in Theorem 2. System (21) plays a similar role to the aggregated system of the nonautonomous case in the sense that some features of its asymptotic behavior can be translated in terms of system (23) asymptotic behavior via Theorem 2.

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