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Approximate aggregation of a two time scales periodic multi-strain SIS epidemic model: A patchy environment with fast migrations

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ABSTRACT

In this work we consider a spatially distributed periodic multi strain SIS epidemic model. We let susceptible and infected individuals migrate between patches, with periodic migration rates. Considering that migrations are much faster than the epidemic process, we build up a less dimensional (aggregated) system that allows to study some features of the asymptotic behavior of the original model. In particular, we are able to define global reproduction numbers in the non-spatialized aggregated system that serve to decide the eradication or endemicity of the epidemic in the initial spatially distributed nonautonomous model. Comparing these global reproductive numbers with those corresponding to isolated patches we show that adequate periodic fast migrations can in many cases reverse local endemicity and get global eradication of the epidemic.

1. Introduction

Periodic patterns have been observed in the behavior of many infectious diseases as influenza, pertussis, mumps or chicken-pox. A classical example is the weekly measles reports in England and Wales for the period 1948–1968, Anderson and May (1991). Scientists have focused on explaining these periodic behavior, finding out a variety of plausible scenarios as Hethcote and Levin (1989) did. Diseases with periodic transmission rates are among the possible explanations. After the pioneering work of Hethcote (1973), several authors have pursued his approach studying periodic, or more general nonautonomous, SIS or SEIR models, see Schwartz (1989) for a review (see also Hethcote, 2008).

A central 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. Ma and Ma (2006) suggested defining the reproduction numbers of several periodic SIS and SEIR 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) that they denoted $\overline{\mathcal{R}}$. With this definition, they found that the free-disease equilibrium is always reached when $\overline{\mathcal{R}}<1$ though this is not a necessary condition; they showed, via numerical simulations, that it might happen $\overline{\mathcal{R}}>1$ together with the number of infected individuals tending to zero.

Recently, Martcheva (2009) has considered a nonautonomous multi-strain SIS epidemic model with periodic coefficients and has defined its corresponding reproduction numbers similarly to what is done in Ma and Ma (2006) and Thieme (2000). In this case, conditions on reproduction numbers ensure the global stability of the disease-free equilibrium and the single-strain periodic solution.

Reproduction numbers for the simplified Kermack–McKendrick periodic systems were defined in Bacaër and Gomes (2009). There, authors show that the corresponding reproduction number is a threshold for the eradication of epidemics. However, unlike in constant environments, the final epidemic size may not be an increasing function of the basic reproduction number or of the initial fraction of infected individuals.

We consider a population affected by a periodic multi-strain SIS epidemic models similar to that found in Martcheva (2009). We distinguish population clusters according to epidemic behavior, which may evolve different within the whole population, for instance, due to spatial heterogeneity of environmental conditions (different salubriousness conditions, infrastructures,...). We represent these clusters by patches which can be distant from each

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other, typically, are not isolated. Our interest relies in understanding how epidemic behavior depends on the exchange of individuals between patches and if any class of control on population flow can contribute to handle epidemic. Thus, our model incorporates individual displacements (migrations) between patches which are assumed also to be periodic. We are considering processes of different nature and we distinguish between local (individual)–global (population) scales in order to tune our model. Individual displacements between patches happen at global scale while epidemic takes place at individual level, despite of how high the infection/recovery rate are. Therefore, the spread of an epidemic within each patch has small impact on the whole population and migrations is considered to be a faster process than epidemic.

The inclusion of two different processes in the same model has the disadvantage of increasing its number of variables and, in general, its complexity. In some cases this difficulty can be overcome via reduction methods. In particular, when the processes included in the model act at different time scales the so-called aggregation methods allow to perform an analysis of its asymptotic behavior in terms of that of a reduced system. These methods are well developed for autonomous ordinary differential equations, see Auger et al. (2008a,b, this issue). In Kouokam et al. (2008) it is proposed an autonomous system coupling constant migrations and SIRS epidemic local models where migrations rates are considered much higher than epidemic rates; the use of aggregation techniques allowed defining the reproduction number corresponding to the complete model through the aggregated (reduced) system and so carrying out a tractable mathematical analysis.

Section 2 is devoted to the presentation of the model. In Section 3 we justify the reduction of the system using the results of Hoppensteadt (1966, 1993, 2010) presented in Appendix A; we build up the aggregated system, that turns out to be similar to that treated in Martcheva (2009), and state the result giving asymptotic information on the complete model in terms of that obtained for the aggregated one. In Section 4 the reproduction numbers for the complete model are defined as those associated to the reduced system; with the help of the results in Section 3 and in Martcheva (2009) conditions on the reproduction numbers are established for the epidemic eradication and for the existence of an endemic periodic state with a single dominant strain. Section 5 presents two important particular cases where it is shown that periodic fast migrations tend to reduce the risk of epidemic and that adequately chosen can in many cases even reverse local endemicity and get global eradication of the epidemic. The conclusions are included in Section 6. Finally, in the appendices the technical details concerning the reduction technique are presented.

2. Multi strain SIS epidemic model with fast migrations

We consider a population inhabiting a p patches environment. Individuals move between patches and an infection evolves within each patch according to a SIS model with multiple strains. Let $S_k(t)$ denote the number of susceptible individuals in patch $k = 1, \ldots, p$ at time t. In each patch k the number of individuals infected by strain $j = 1, \ldots, n$ is denoted by $I_{jk}(t)$. We assume that migrations act at a faster time scale than the changes of state with respect to infection, so individuals leaving a patch in a particular infection state get to the arrival patch in the same state.

The migration rate from patch k to patch i, $k \neq i$, at time t for susceptibles is denoted by $m_{ik}(t)$ and for infected by strain j by $m^j_{ik}(t)$. Functions m_{ik} and m^j_{ik} are assumed non-negative and periodic. Let us call $M(t) = (m_{ik}(t))_{1\leq i,k\leq p}$, where $m_{ii}(t) = -\sum_{\substack{k=1\\k\neq i}}^{p} m_{ki}(t)$, the matrix of susceptibles migration rates and $M^j(t) = (m^j_{ik}(t))_{1\leq k,i\leq p}$, where $m^j_{ii}(t) = -\sum_{\substack{k=1\\k\neq i}}^{p} m^j_{ki}(t)$, the corresponding matrices of migration rates for individuals infected by strains $j = 1, \ldots, n$. We notice that the entries of the columns of all these matrices sum up to 0.

Now we introduce an assumption on migration matrices that reflects the fact that there always exists a path through which individuals can get any patch from any other patch. We assume that matrices $M(t)$ and $M^j(t)$ $(j = 1, \ldots, n)$, are irreducible for every t. As a consequence, see Seneta (1981) th. 2.6, 0 is a simple eigenvalue larger than the real part of any other eigenvalue. The left eigenspace of each of these matrices associated with the eigenvalue 0 is generated by vector $\mathbf{1} := (1, \ldots, 1) \in \mathbf{R}^p$. The right eigenspace is generated by vectors $\boldsymbol{\nu}(t) = (\nu_1(t), \ldots, \nu_p(t))$ and $\boldsymbol{\nu}^j(t) = (\nu^j_1(t), \ldots, \nu^j_p(t))$ $(j = 1, \ldots, n)$, respectively, which we choose to have positive entries that sum up to 1 and so they are unique.

The entries of these eigenvectors, $\boldsymbol{\nu}(t)$ and $\boldsymbol{\nu}^j(t)$ $(j = 1, \ldots, n)$, for a constant time t, represent the stable proportions that the distribution among patches of the different types of individuals would attain, at the fast time scale, if the migration process were the only change affecting the population.

The ratio of migrations to infection time scales is represented by the small parameter $\varepsilon > 0$. The model takes the form:

$$\begin{cases} \varepsilon \dfrac{dS_k}{dt} = \displaystyle\sum_{i=1}^{p} m_{ki}(t) S_i + \varepsilon \left[\mu_k(t) \left(S_k + \sum_{j=1}^{n} I_{jk} \right) - \sum_{j=1}^{n} \beta_{jk}(t) S_k I_{jk} - \mu_k(t) S_k + \sum_{j=1}^{n} \gamma_{jk}(t) I_{jk} \right] \\ \varepsilon \dfrac{dI_{jk}}{dt} = \displaystyle\sum_{i=1}^{p} m^j_{ki}(t) I_{ji} + \varepsilon \left[\beta_{jk}(t) S_k I_{jk} - (\mu_k(t) + \gamma_{jk}(t)) I_{jk} \right] \end{cases} \quad (k = 1, \ldots, p; \quad j = 1, \ldots, n) \tag{1}$$

The local SIS epidemic model with multiple strains for each patch $k = 1, \ldots, p$ is represented by the terms preceded by ε in the right-hand sides of the equations. The mortality rate is the same for all individuals in the same patch and denoted by $\mu_k(t)$. We assume all newly recruited individuals are susceptible and the recruitment rate equals mortality rate so that in absence of migrations the total population in a patch remains constant. The transmission rate of strain $j = 1, \ldots, n$ in patch k is denoted by $\beta_{jk}(t)$. Finally we denote $\gamma_{jk}(t)$ the recovery rate from strain j in patch k.

All the rates (migration, death, recruitment, transmission and recovery) appearing in the model are assumed to be periodic functions on t in $C^2(\mathbb{R})$ with common period ω.

The total population is given by

$$N(t) = \sum_{k=1}^{p} \left(S_k(t) + \sum_{j=1}^{n} I_{jk} \right).$$

Summing up all the equations in (1) we see that $dN/dt = 0$. We assume henceforth that the total population size is constant and rescaled to one, and consider the system on the set:

$$\Omega = \left\{ (S_1, \ldots, S_p, I_{11}, \ldots, I_{1p}, \ldots, I_{n1}, \ldots, I_{np}) \in \mathbb{R}^{p(n+1)}_{+} : N(t) = 1 \right\}$$

which is easy to see that it is positively invariant.

3. Reduction of the model

Model (1) is written by coupling two different processes that act at different time scales and so it fits in the general form (B.1) presented in Appendix B. We now proceed to transform it into the so-called slow–fast form so that we get the associated reduced system that serves to study some aspects of its asymptotic behavior. The precise results we are presenting are derived from the Hoppensteadt results on quasistatic-state approximation for nonlinear initial-value problem, Hoppensteadt (1966, 1993, 2010), summarized in Theorem 6 of Appendix A.

To transform system (1) into slow–fast form the key point is making emerge its slow variables. The natural choice is the total number of susceptible and of individuals infected by each of the different strains because these variables are kept constant through migrations, the fast dynamics, and so they evolve at the slow time scale, the one that infection process acts at. We denote them:

$$S=\sum_{k=1}^{p}S_k \text{ and } I_j=\sum_{k=1}^{p}I_{jk},\quad j=1,\dots,n.$$

The change of variables, using Appendix B notation, that transforms the system (1) into slow–fast form is the following:

$$n=(S_1,\dots,S_p,I_{11},\dots,I_{1p},\dots,I_{n1},\dots,I_{np})\in\mathbb{R}^{p(n+1)}.$$

is transformed into $(x,y)\in\mathbb{R}^{(p-1)(n+1)}\times\mathbb{R}^{n+1}$ where

$$x=(S_1,\dots,S_{p-1},I_{11},\dots,I_{1p-1},\dots,I_{n1},\dots,I_{np-1}) \text{ and}$$
$$y=(S,I_1,\dots,I_n).$$

We define the following transformations $\mathfrak{T}(n):=(x,y)$, $\mathfrak{T}_x(n):=x$ and $\mathfrak{T}_y(n):=y$.

By summing up from $k=1$ to $k=p$ in (1) the equations for S_k and I_{jk} ($j=1,\dots,n$) and substituting S_p and I_{jp} by $S-\sum_{k=1}^{p-1}S_k$ and $I_j-\sum_{k=1}^{p-1}I_{jk}$, respectively, we obtain the equations for the global variables where the fast part, corresponding to migrations, has disappeared. To get the transformed equations for the rest of the variables it suffices to perform the aforementioned substitution. The resulting system has the standard slow–fast form (B.2) presented in Appendix B

$$\begin{cases}\varepsilon\dfrac{dx}{dt}=F(t,x,y)+\varepsilon H(t,x,y),\\ \dfrac{dy}{dt}=G(t,x,y).\end{cases}\tag{2}$$

System (2) is a particular case of system (A.1) in Appendix A, taking

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

Next, we follow the hypotheses of Theorem 6 to obtain some results on the asymptotic behavior of system (1). Let us denote $\Omega_{\mathfrak{T}}=\mathfrak{T}(\Omega)$, $\Omega^x_{\mathfrak{T}}=\mathfrak{T}_x(\Omega)$ and $\Omega^y_{\mathfrak{T}}=\mathfrak{T}_y(\Omega)$.

Hypothesis H1 is met because $\Omega_{\mathfrak{T}}$ is positively invariant for the slow–fast system associated to system (1).

Hypothesis H2 asks for the existence of a function $x=\Phi(t,y)$ that solves the equation $F(t,x,y)=0$ which, in the present case, is equivalent to find the eigenvectors associated to 0 of matrices $M(t)$ and $M^j(t)$ ($j=1,\dots,n$) which entries sum up to S and I_j ($j=1,\dots,n$), respectively. To be precise $\Phi(t,y)$ is defined as follows, for $i=1,\dots,p-1$ and $j=1,\dots,n$:

$$S_i=\nu_i(t)S,\quad I_{ji}=\nu_i^j(t)I_j.\tag{3}$$

The assumptions made on migration rates implies that Hypothesis H2 is also met.

Hypothesis H3 requires that the fast equilibria $\Phi(\alpha,\beta)$ are asymptotically stable uniformly in the parameters $(\alpha,\beta)\in[t_0,\infty)\times\Omega^y_{\mathfrak{T}}$. System (A.3) has in this case the following form:

$$\frac{dX}{d\tau}=F(\alpha,X,\beta).$$

The assumptions on matrices $M(t)$ and $M^j(t)$ ($j=1,\dots,n$), that are taken to be irreducible and periodic, ensure the asymptotic stability of equilibria $x=\Phi(\alpha,\beta)$ uniformly on $\mathbb{R}\times\Omega^y_{\mathfrak{T}}$. Furthermore, the domain of attraction of the equilibrium $\Phi(t_0,y_0)$, for each $t_0\geq 0$ and each $y_0\in\Omega^y_{\mathfrak{T}}$, includes all $x_0\in\Omega^x_{\mathfrak{T}}$.

Using the expressions (3) for the fast equilibria we obtain the reduced or aggregated system (A.4), with variables $\overline{y}=(\overline{S},\overline{I}_1,\dots,\overline{I}_n)$ and domain $\overline{\Omega}=\left\{(\overline{S},\overline{I}_1,\dots,\overline{I}_n)\in\mathbb{R}^{n+1}_+:\overline{S}+\sum_{j=1}^{n}\overline{I}_j=1\right\}$, associated to system (2):

$$\begin{cases}\dfrac{d\overline{S}}{dt}=\sum_{j=1}^{n}\overline{\mu}_j(t)\overline{I}_j-\sum_{j=1}^{n}\overline{\beta}_j(t)\overline{S}\overline{I}_j+\sum_{j=1}^{n}\overline{\gamma}_j(t)\overline{I}_j,\\ \dfrac{d\overline{I}_j}{dt}=\overline{\beta}_j(t)\overline{S}\overline{I}_j-\left(\overline{\mu}_j(t)+\overline{\gamma}_j(t)\right)\overline{I}_j,\quad j=1,\dots,n\end{cases}\tag{4}$$

where we use the following notation:

$$\overline{\mu}_j(t)=\sum_{k=1}^{p}\mu_k(t)\nu_k^j(t),\quad \overline{\gamma}_j(t)=\sum_{k=1}^{p}\gamma_{jk}(t)\nu_k^j(t) \text{ and}$$
$$\overline{\beta}_j(t)=\sum_{k=1}^{p}\beta_{jk}(t)\nu_k(t)\nu_k^j(t).$$

Now Theorem 6 implies the following result that we use in the next section to analyze some asymptotic features of system (1) with the help of system (4).

Theorem 1. *Assume that system* (4) *has a solution, say* $y^*(t)$*, that it is uniformly asymptotically stable and let* $n(t)$ *be the solution of system* (1) *with initial conditions* $n(t_0)=n_0\in\Omega$ *such that* $T_y(n_0)$ *is in the domain of attraction of* $y^*(t)$*. Then, calling* $\mathbf{\Upsilon}(t)=\operatorname{diag}\{\boldsymbol{\nu}(t),\boldsymbol{\nu}^1(t),\dots,\boldsymbol{\nu}^n(t)\}$*, we have that for any* $\delta>0$ *there exist* $\varepsilon_\delta>0$ *and* $t_\delta>t_0$ *such that*

$$|n(t)-\overline{y}^*(t)\mathbf{\Upsilon}(t)|<\delta$$

for every $\varepsilon\leq\varepsilon_\delta$ *and every* $t\geq t_\delta$.

4. Analysis of the model

In this section we proceed to study system (1) with the help of the aggregated system (4) via Theorem 1.

System (4) is similar to that study in Martcheva (2009) and we are recovering some of her results that are susceptible of being exported to the asymptotic behavior of system (1). The results we present next are expressed in terms of the reproductions numbers of the strains as defined in Ma and Ma (2006) or Martcheva (2009).

To define the reproduction numbers of the strains, we first introduce the average of a periodic function over its period. If $f(t)$ is a periodic function of period ω, then the average of f is given by

$$\left\langle f\right\rangle=\frac{1}{\omega}\int_0^{\omega}f(t)dt$$

which verifies that

$$\left\langle f\right\rangle=\lim_{t\to\infty}\frac{1}{t-t_0}\int_{t_0}^{t}f(s)ds.\tag{5}$$

We define the reproduction numbers of the strains as

$$\overline{\mathcal{R}}_j=\frac{\left\langle\overline{\beta}_j\right\rangle}{\left\langle\overline{\mu}_j\right\rangle+\left\langle\overline{\gamma}_j\right\rangle}\quad j=1,\dots,n.\tag{6}$$

These reproduction numbers are defined for the aggregated system, that is, for the global variables and so we call them *global reproduction numbers*. Though the aggregated system is not spatially distributed, the initial migration process is reflected in its parameters. We will see that the global reproduction numbers decide the asymptotic stability of the disease-free equilibrium and other asymptotic features of system (1) so that we can consider their definition as an extension from non-spatial systems to some patchy systems.

The following theorem states conditions on the global reproductive numbers for the global asymptotic stability of the disease-free equilibrium.

Theorem 2. *Let $\overline{y}_0^* = (1, 0, \ldots, 0) \in \mathbb{R}^{n+1}$ be the disease-free equilibrium of the aggregated system (4). If $\overline{\mathcal{R}}_j < 1$ for $j = 1, \ldots, n$ then $\overline{y}_0^*$ is globally uniformly asymptotically stable.*

Proof. For every $j = 1, \ldots, n$ we have $d\overline{I}_j/dt = \overline{\beta}_j(t)\overline{S}\overline{I}_j - (\overline{\mu}_j(t) + \overline{\gamma}_j(t))\overline{I}_j$. Now, having in mind that $\overline{S}(t) \in [0, 1]$ for every t, we obtain the following inequality

$$\frac{d\overline{I}_j}{dt} \le \overline{\beta}_j(t)\overline{I}_j - \left(\overline{\mu}_j(t) + \overline{\gamma}_j(t)\right)\overline{I}_j$$

that yields

$$\overline{I}_j(t) \le \overline{I}_j(t_0)\exp\left(\int_{t_0}^{t}\left[\overline{\beta}_j(s) - (\overline{\mu}_j(s) + \overline{\gamma}_j(s))\right]ds\right).$$

Condition $\overline{\mathcal{R}}_j < 1$ together with equality (5) implies that

$$\lim_{t\to\infty}\frac{1}{t - t_0}\int_{t_0}^{t}\left[\overline{\beta}_j(s) - (\overline{\mu}_j(s) + \overline{\gamma}_j(s))\right]ds < 0$$

so we can find a constant $\sigma > 0$ and a time $t_1 > 0$ such that for every $j = 1, \ldots, n$, every t_0 and every t such that $t - t_0 \ge t_1$ we have

$$\int_{t_0}^{t}\left[\overline{\beta}_j(s) - (\overline{\mu}_j(s) + \overline{\gamma}_j(s))\right]ds < -\sigma(t - t_0)$$

from which we obtain that $\overline{I}_j(t) \to 0$ as $t \to \infty$ for every $j = 1, \ldots, n$, uniformly in t_0 and for any initial conditions in $\overline{\Omega}_x$.

The fact that $\overline{S}(t) = 1 - \sum_{j=0}^{n}\overline{I}_j(t)$ for every $t \ge 0$ completes the proof.□

After presenting conditions for the eradication of the epidemic we treat some simple cases where epidemic becomes endemic. Sometimes, in multiple strain epidemic, one of these strains manages to persist while the others die out. This fact is known as single strain solution. In the next theorem it is shown that a global reproductive number $\overline{\mathcal{R}}_i$ being larger than one implies the existence of a periodic solution, where strain i becomes endemic, that attracts every solution starting with some individuals infected by strain i and none infected by the rest of strains. This solution is called the single-strain periodic solution.

Theorem 3. *For each i for which $\overline{\mathcal{R}}_i > 1$, there exists a unique, positive periodic function $\overline{I}_i^*(t)$ such that $(1 - \overline{I}_i^*(t), 0, \ldots, 0, \overline{I}_i^*(t), 0, \ldots, 0)$ is a solution of the aggregated system (4). Furthermore, if $(1 - \overline{I}_i(t), 0, \ldots, 0, \overline{I}_i(t), 0, \ldots, 0)$ is a solution of system (4) starting from $\overline{I}_i(0) > 0$, we have*

$$\lim_{t\to\infty}|\overline{I}_i(t) - \overline{I}_i^*(t)| = 0.$$

Proof. This result is proved in Martcheva (2009) (th. 3.1). The proof uses de Poincaré map, $\mathcal{P}$, associated to the equation

$$\frac{d\overline{I}_i}{dt} = \overline{\beta}_i(t)(1 - \overline{I}_i)\overline{I}_i - (\overline{\mu}_i(t) + \overline{\gamma}_i(t))\overline{I}_i$$

considered in the domain $\Omega_i = \{\overline{I}_i : \overline{I}_i \in [0, 1]\}$ that it is defined: if $\overline{I}_i(0) = \overline{I}_i^0$ then $\mathcal{P}(\overline{\mathcal{I}}_\rangle) = \overline{\mathcal{I}}_\rangle(\omega, \overline{\mathcal{I}}_\rangle')$, to demonstrate the existence, uniqueness and attractivity of the periodic solution.□

Next theorem gives simple conditions on the reproductive numbers so that the single-strain periodic solution be globally uniformly asymptotically stable.

Theorem 4. *If $\overline{\mathcal{R}}_i > 1$ and $\overline{\mathcal{R}}_j < 1$ for $j \ne i$, then the single-strain periodic solution $(1 - \overline{I}_i^*(t), 0, \ldots, 0, \overline{I}_i^*(t), 0, \ldots, 0)$ is globally uniformly asymptotically stable.*

Proof. The global asymptotic stability is proved in Martcheva (2009) (th. 4.2). The proof is based on the fact that $\overline{\mathcal{R}}_j < 1$ implies $\overline{I}_j(t) \to 0$ as $t \to \infty$, see the proof of Theorem 2, that yields the following inequalities:

$$\overline{\beta}_i(t)(1 - \varepsilon - \overline{I}_i)\overline{I}_i - (\overline{\mu}_i(t) + \overline{\gamma}_i(t))\overline{I}_i \le \frac{d\overline{I}_i}{dt}$$
$$\le \overline{\beta}_i(t)(1 - \overline{I}_i)\overline{I}_i - (\overline{\mu}_i(t) + \overline{\gamma}_i(t))\overline{I}_i.$$

Now, using the proof of Theorem 3 with equations

$$\frac{dX}{dt} = \overline{\beta}_i(t)(1 - X)X - (\overline{\mu}_i(t) + \overline{\gamma}_i(t))X$$

and

$$\frac{dY}{dt} = \overline{\beta}_i(t)(1 - \varepsilon - Y)Y - (\overline{\mu}_i(t) + \overline{\gamma}_i(t))Y$$

it is shown that as $\overline{I}_i(t)$ is bounded between two periodic functions that converge to $\overline{I}_i^*(t)$ as $\varepsilon \to 0$.

To prove that the asymptotic stability is uniform we use a result in Farkas (1994) (th. 1.4.12):

For the system $\dot{w} = h(t, w)$ if h is periodic in t and $h(t, 0) \equiv 0$ then the asymptotic stability of $w = 0$ implies its uniform asymptotic stability

which can be extended to a periodic solution $\varphi(t)$ by performing the change of variables $z = w - \varphi(t)$.□

We summarize in the next theorem the results on the asymptotic behavior of system (1) that can be deduced from Theorems 2–4 using Theorem 1.

Theorem 5. *Let $n(t)$ be the solution of system (1) with initial conditions $n(t_0) = n_0 \in \Omega$.*

1. *If $\overline{\mathcal{R}}_j < 1$ for $j = 1, \ldots, n$ then for any $\delta > 0$ there exist $\varepsilon_\delta > 0$ and $t_\delta > t_0$ such that*
$$|n(t) - (\boldsymbol{\nu}(t), 0, \ldots, 0)| < \delta$$
for every $\varepsilon \le \varepsilon_\delta$ and every $t \ge t_\delta$.
2. *If $\overline{\mathcal{R}}_i > 1$ and n_0 is such that $\sum_{k=1}^{p} I_{ik}(t_0) > 0$ and $\sum_{k=1}^{p} I_{jk}(t_0) = 0$ for $j \ne i$ then for any $\delta > 0$ there exist $\varepsilon_\delta > 0$ and $t_\delta > t_0$ such that*
$$|n(t) - \left(\left(1 - \overline{I}_i^*(t)\right)\boldsymbol{\nu}(t), 0, \ldots, 0, \overline{I}_i^*(t)\boldsymbol{\nu}^i(t), 0, \ldots, 0\right)| < \delta$$
for every $\varepsilon \le \varepsilon_\delta$ and every $t \ge t_\delta$.
3. *If $\overline{\mathcal{R}}_i > 1$ and $\overline{\mathcal{R}}_j < 1$ for $j \ne i$ then for any $\delta > 0$ there exist $\varepsilon_\delta > 0$ and $t_\delta > t_0$ such that*
$$|n(t) - \left(\left(1 - \overline{I}_i^*(t)\right)\boldsymbol{\nu}(t), 0, \ldots, 0, \overline{I}_i^*(t)\boldsymbol{\nu}^i(t), 0, \ldots, 0\right)|\delta$$
for every $\varepsilon \le \varepsilon_\delta$ and every $t \ge t_\delta$.

Proof.

1. Direct consequence of Theorems 1 and 2.

2. Considering system (4) on the domain $\overline{\Omega}_i = \{\overline{x} \in \overline{\Omega} : \overline{I}_j = 0 \text{ for } j \neq i\}$ from Theorem 3 it is easy to establish that the single-strain periodic solution is globally uniformly asymptotically stable (see the proof of Theorem 4). Now, if we correspondingly consider system (1) on the domain

$$\Omega_i = \{n \in \Omega : I_{jk} = 0 \quad \text{for } j \neq i \text{ and } k = 1, \ldots, p\},$$

the result is a direct consequence of Theorem 1.
3. Direct consequence of Theorems 1 and 4. □

Theorem 5 states that if every global reproduction number is less than 1 we can consider that epidemic will be eradicated. It suffices that one single reproduction number be larger than 1 to get an endemic situation depending on initial conditions. In the case where a strain is dominant, in the sense that its reproduction number is larger than one while those of the others are less than one, the behavior of epidemic evolves certainly towards an endemic periodic state with all individuals in the population being either susceptible or infected by the dominant strain.

5. Effects of fast migrations on epidemic behavior

In this section we compare strain reproduction numbers at single patches not linked by migrations to the global strain reproduction numbers obtained in Section 4 where a fast migration process linking all patches was considered.

The reproduction number of strain j ($j = 1, \ldots, n$) at patch k ($k = 1, \ldots, p$) when it is considered isolated is

$$\mathcal{R}_{jk} = \frac{\langle \beta_{jk} \rangle}{\langle \mu_k \rangle + \langle \gamma_{jk} \rangle}$$

while the global reproduction number of strain j is $\overline{\mathcal{R}}_j$ as defined in (6).

The comparison should provide some insights on how fast periodic migrations might modify the global outcome of the epidemic process. Due to the large number of involved parameters it is difficult to obtain clear consequences in very general cases. That is why we treat next two simplified cases which still keep interest because they illustrate the fact that periodic fast migrations can induce outcomes which are different from those expected if patches were isolated. Next, we tackle the mathematical analysis. A brief discussion on the underlying mechanism can be found in Section 6.

5.1. Homogeneous patches

The first case we treat considers that epidemic behaves exactly the same at every patch, that is, for every $j = 1, \ldots, n$:

$$\beta_{jk}(t) = \beta_j(t), \ \gamma_{jk}(t) = \gamma_j(t), \ \mu_k(t) = \mu(t) \qquad \forall\, k = 1, \ldots, p. \tag{7}$$

In this case we have the same reproduction number of strain j at every patch

$$\mathcal{R}_{jk} = \mathcal{R}_j = \frac{\langle \beta_j \rangle}{\langle \mu \rangle + \langle \gamma_j \rangle}$$

and so the comparison should be established taking into account $\mathcal{R}_j$ and $\overline{\mathcal{R}}_j$.

Assuming (7) we have:

$$\overline{\mu}_j(t) = \sum_{k=1}^{p} \mu_k(t) \nu_k^j(t) = \mu(t) \sum_{k=1}^{p} \nu_k^j(t) = \mu(t),$$

$$\overline{\gamma}_j(t) = \sum_{k=1}^{p} \gamma_{jk}(t) \nu_k^j(t) = \overline{\gamma}_j(t) \sum_{k=1}^{p} \nu_k^j(t) = \overline{\gamma}_j(t),$$

and

$$\overline{\beta}_j(t) = \sum_{k=1}^{p} \beta_{jk}(t) \nu_k(t) \nu_k^j(t) = \left(\sum_{k=1}^{p} \nu_k(t) \nu_k^j(t) \right) \overline{\beta}_j(t).$$

Function $\overline{\nu}_j(t) = \sum_{k=1}^{p} \nu_k(t) \nu_k^j(t)$, due to the definition of $\boldsymbol{\nu}(t)$ and $\boldsymbol{\nu}^j(t)$, verifies $\overline{\nu}_j(t) < 1$ and so $\overline{\beta}_j(t) < \beta_j(t)$, from which we obtain that reproduction numbers are smaller when migrations are considered

$$\overline{\mathcal{R}}_j = \frac{\langle \overline{\beta}_j \rangle}{\langle \overline{\mu}_j \rangle + \langle \overline{\gamma}_j \rangle} < \frac{\langle \beta_j \rangle}{\langle \mu \rangle + \langle \gamma_j \rangle} = \mathcal{R}_j \quad j = 1, \ldots, n. \tag{8}$$

We see then that migrations favour the eradication of the epidemic. It is easy to express sufficient conditions for global reproduction numbers being less than one while the local ones are larger than one:

$$\langle \overline{\nu}_j \cdot \beta_j \rangle < \langle \mu \rangle + \langle \gamma_j \rangle < \langle \beta_j \rangle \quad \text{for } j = 1, \ldots, n. \tag{9}$$

If condition (9) is met any strain can locally become endemic depending on initial conditions while, via fast periodic migrations, epidemic is globally eradicated.

Function $\overline{\nu}_j(t)$ can be as little as wanted provided we choose appropriately the migration patterns of susceptibles and individuals infected by strain j. It suffices to increase the mismatch of susceptible and infected individuals across the different patches to get $\sup \overline{\nu}_j(t)$ closer to zero. As $\langle \overline{\nu}_j \cdot \beta_j \rangle = \overline{\nu}_j(\xi) \langle \beta_j \rangle$ for a certain $\xi \in [0, \omega]$, we can conclude that for an isolated strain with $\mathcal{R}_j > 1$, i.e. locally endemic, it is always possible to find migration patterns so that $\overline{\mathcal{R}}_j < 1$, i.e. it is globally eradicated.

5.2. Asymmetric patches

Now we let epidemic behave different at each patch. We assume that regions can be grouped in two disjoint sets according with the following: transmission rates are larger at regions of the first group, while recovery rates are larger at patches of the second group, that is, disease has stronger incidence at patches belonging to the first group than at those belonging to the second one. To simplify we suppose a two patches environment for which the epidemic rates verify the following conditions

$$\begin{aligned} &\beta_{j2}(t) < \beta_{j1}(t) \text{ and } \gamma_{j1}(t) < \gamma_{j2}(t), \quad \text{for } j = 1, \ldots, n, \\ &\mu_1(t) = \mu_2(t) = \mu(t) \end{aligned} \tag{10}$$

so we have

$$\mathcal{R}_{j2} < \mathcal{R}_{j1}. \tag{11}$$

Assuming (10) we obtain for each $j = 1, \ldots, n$

$$\begin{aligned} &\nu_1(t) \nu_1^j(t) \beta_{j1}(t) + \nu_2(t) \nu_2^j(t) \beta_{j2}(t) < \beta_{j1}(t), \text{ i.e. } \overline{\beta}_j(t) < \beta_{j1}(t) \\ &\gamma_{j1}(t) < \nu_1^j(t) \gamma_{j1}(t) + \nu_2^j(t) \gamma_{j2}(t) < \gamma_{j2}(t), \text{ i.e. } \gamma_{j1}(t) < \overline{\gamma}_j(t) < \gamma_{j2}(t) \\ &\overline{\mu}(t) = \nu_1^j(t) \mu(t) + \nu_2^j \mu(t) = \mu(t). \end{aligned} \tag{12}$$

what yields

$$\overline{\mathcal{R}}_j < \mathcal{R}_{j1} \tag{13}$$

but allows both inequalities either $\overline{\mathcal{R}}_j < \mathcal{R}_{j2}$ or $\mathcal{R}_{j2} < \overline{\mathcal{R}}_j$.

We first consider the case where strain j is eradicated at patch 2 while it might become endemic at patch 1 depending on initial conditions, $\mathcal{R}_{j2} < 1 < \mathcal{R}_{j1}$. If we now take into account migrations

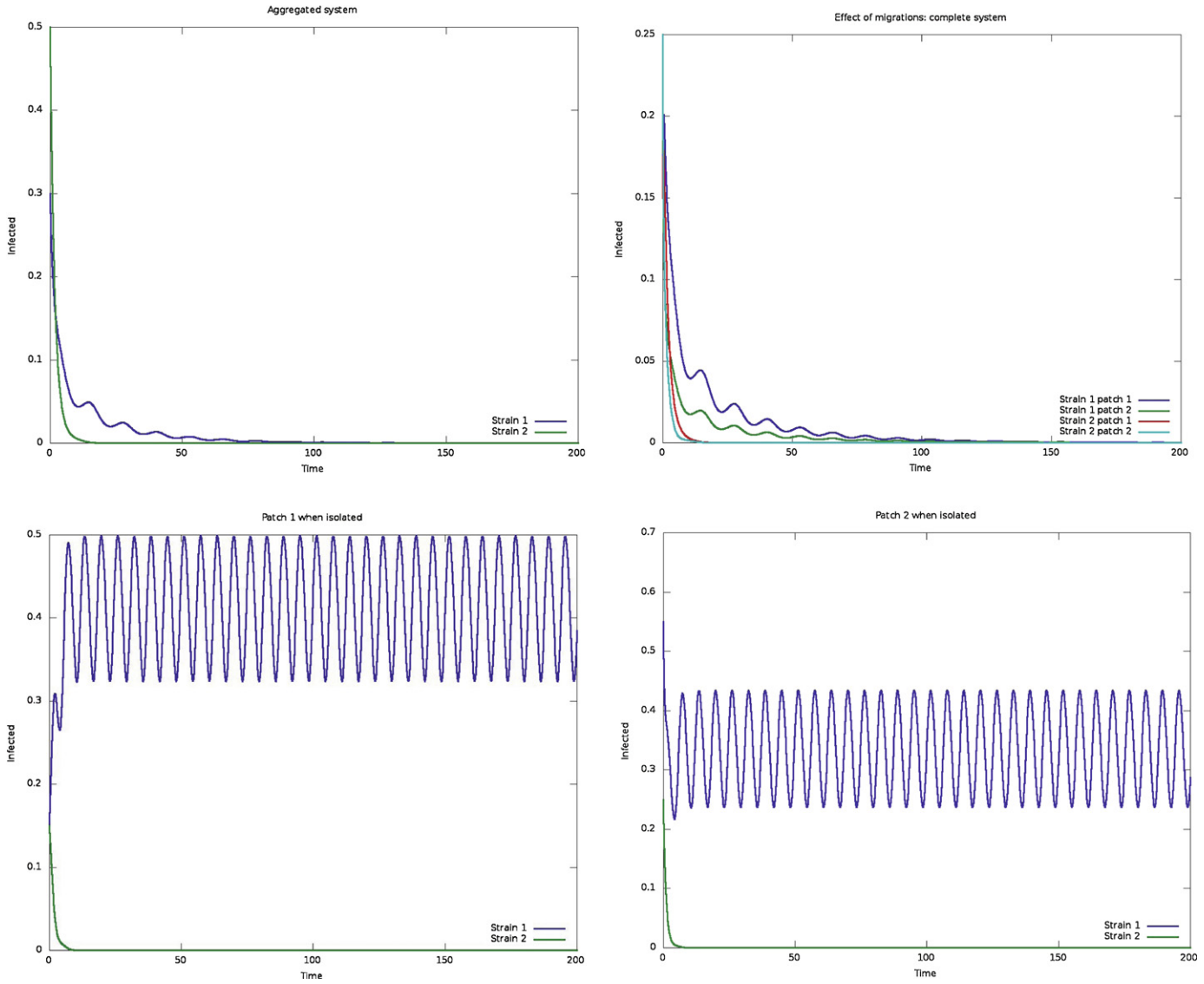

Fig. 1. Solutions of the reduced system, the complete system and, in absence of migrations, of the local subsystems. Global reproduction numbers $\overline{\mathcal{R}}_1 = 0.9362$, $\overline{\mathcal{R}}_2 = 0.4494$ entail global epidemic eradication (left top: aggregated system and right top: complete system). In absence of migrations $\overline{\mathcal{R}}_{11} = 1.7487$, $\overline{\mathcal{R}}_{21} = 0.84574$ and $\overline{\mathcal{R}}_{12} = 1.5371$, $\overline{\mathcal{R}}_{22} = 0.71378$ imply local persistence for strain 1 and local eradication for strain 2 at patch 1 (left bottom) and at patch two (right bottom). Parameter values: $m_1(t) = 1.1 + \cos(t)$, $m_2(t) = 2m_1(t)$, $m_{11}(t) = 1 + 0.5\cos(t) = m_{21}(t)$, $m_{12}(t) = 2 + \cos(t)$, $m_{22}(t) = 2 + 0.5\cos(t)$, $\mu_1(t) = 1 + 0.2\cos(t) = \mu_2(t)$, $\beta_{11}(t) = 2.1 + \cos(t)$, $\beta_{21}(t) = 1.1 + 0.5\cos(t)$, $\beta_{12}(t) = 2 + \cos(t)$, $\beta_{22}(t) = 1 + 0.5\cos(t)$, $\gamma_{11} = 0.2 + 0.1\cos(t)$, $\gamma_{21} = 0.3 + 0.2\sin(t)$, $\gamma_{12} = 0.3 + 0.1\cos(t)$, $\gamma_{22} = 0.4 + 0.1\sin(t)$, $\epsilon = 0.5$.

the global fate of strain j depends on $\overline{\mathcal{R}}_j$ with two different situations: $\overline{\mathcal{R}}_j < 1$, entailing that if strain j is not isolated then it is globally eradicated, and

$$\mathcal{R}_{j2} < 1 < \overline{\mathcal{R}}_j < \mathcal{R}_{j1} \tag{14}$$

yielding that strain j has the potential to become globally endemic. We notice, see (12), that these two situations are possible depending of the migration patterns of susceptibles and individuals infected by strain j.

It is also possible to find migration patterns ensuring

$$\overline{\mathcal{R}}_j < 1 < \mathcal{R}_{j2} < \mathcal{R}_{j1}, \tag{15}$$

that is, an isolated strain j is globally eradicated while it might become endemic at both patches when they are not linked by migrations (see Fig. 1). To get that it suffices that susceptibles tend to accumulate in one of the patches while the infected individuals tend to do it in the other one.

6. Conclusions

In this contribution we consider a population affected by a periodic multi-strain SIS epidemic and distinguish population patches according with epidemic behavior. We aim to investigate whether and how epidemic behavior depends on the exchange of individuals between zones through a two time scales nonautonomous periodic model.

The first result of our study is the definition of *global reproductive numbers* (6) generalizing those previously defined for single patch populations. In particular, global reproductive numbers combine the value of (local) reproductive numbers corresponding to each patch in absence of migrations (that is, if they were isolated) with information about individual displacement patterns. Then, the outcome of epidemic may depend somehow on migrations.

Subsequently, we compare the local and the global reproductive numbers seeking for measuring somehow the influence of migrations in the epidemic process. It follows that the relation

between these quantities is, in general, very sophisticated and cannot be analyzed in the most general case. Thus, we study two simplified but important cases.

For ascertaining the precise role of fast migrations we consider n homogeneous patches. In this case we get that local reproductive numbers are always larger than global reproductive numbers. This property allows global eradication when, in absence of migrations, the contrary was expected, as entailed by the sufficient condition (9).

We consider also the case of two patches, being the consequences of the disease largest in one of them. We get again that the outcome of epidemic can be drastically different depending on migrations. For instance, under adequate migrations scheme, global persistence is possible for a given strain when, if patches were isolated, this strain could only persist in one of them. Besides, we find scenarios of global strains eradication when in the isolated strains could potentially persist at each patch (see below).

Indeed, our analysis suggests epidemic management mechanisms based in controlling individual displacements and, most important, provides with quantifiable threshold values entailing eradication/persistence. The idea is in same way similar to vaccination problems: infection can be kept under control vaccinating a sufficient large fraction of the population. It is clear that if we consider patches formed exclusively by either susceptible or infected individuals and if these zones are always spatially separated, epidemic cannot develop and will be eradicated. This is an extreme situation which in many real situations is not feasible. Therefore, the question is, is eradication possible assuming a given amount of infected individuals moving around? Our results point out that epidemic control is possible through the control on individual displacements, as illustrated, for instance, in expression (9). Computing global reproductive numbers (which combine displacements and patch epidemic information) is a cornerstone for implementing effective eradication/persistence policies. The same reasoning can be applied to situation described in Section 5.2, where in some patches, the epidemic has a stronger incidence than in other patches.

When dealing with multi-strain epidemic, competition among strains is of interest. Let us consider just two strains which we note a and b. We recall that being the global reproduction number (grn) of a given strain less than 1 implies that the corresponding strain is eradicated. If there is any strain whith grn larger than one, the disease-free solution becomes unstable. Besides, if the grn of strain a is less than 1 and the grn of strain b is larger than 1, strain a is eradicated while strain b persists. Then, which is the outcome when considering two strains with its global reproduction number larger than 1? Using these results in Martcheva (2009) it is possible to define the corresponding *(global) invasion reproduction numbers* of each strain. Being both global invasion reproduction numbers larger than one implies strains coexistence. In addition, competitive exclusion occurs when the transmission rate is a product of a periodic contact rate and a constant probability of transmission, $\beta_{ij}(t) = c(t)p_{ij}$ and establishes, in this case, that the strain with the largest global reproduction number excludes, globally, the other strain. These results are local and can be easily achieved following this manuscript and Martcheva (2009).

Although the periodicity in epidemics is well documented, there is controversy about the underlying mechanisms. Namely, it is not clear whether periodicity comes across as an intrinsic property of epidemic dynamics or it is due to external periodic forcings. There is no doubt about the existence of external forcings and, in many cases, considering them is a natural assumption. To the best of our knowledge, "pure" autonomous epidemic models do not exhibit *per se* such a periodic behavior, which are found incorporating delays, demographic dynamics or community relations to the model. Perhaps neglecting external forcings and further underlying dynamics makes models too simple so that do not describe reality.

The effect of external forcings can be investigated in laboratories. In case of epidemic models including demographic dynamics, it is questionable if both, epidemics and demographic processes, evolve within the same time scale. If not, approximate aggregation techniques for autonomous ODEs are a suitable tool for studying such kind of systems.

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Appendix A. 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, this issue), to some two time scales nonautonomous systems of ordinary differential equations, in particular to system (1).

We consider the initial-value problem

$$\begin{cases} \varepsilon \dfrac{dx}{dt} = f(t,x,y,\varepsilon), \quad x(t_0) = \eta_0, \\ \dfrac{dy}{dt} = g(t,x,y,\varepsilon), \ y(t_0) = \xi_0, \end{cases} \tag{A.1}$$

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 $\mathcal{C}^2(\hat{\Omega})$ and any solution of the system (A.1) beginning in $B_R \times B_{R'}$ remains there for $t \in I$.

Setting $\varepsilon = 0$ in (A.1) we obtain the so-called *reduced problem*:

$$\begin{cases} 0 = f(t,x,y,0), \\ \dfrac{dy}{dt} = g(t,x,y,0), \quad y(t_0) = \xi_0. \end{cases} \tag{A.2}$$

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

Hypothesis H3. The system of equations

$$\frac{dX}{d\tau} = f(\alpha, X, \beta, 0) \tag{A.3}$$

has $X = \Phi(\alpha, \beta)$ as an equilibrium for each $(\alpha, \beta) \in I \times B_{R'}$ that it is asymptotically stable uniformly in the parameters $(\alpha, \beta) \in I \times B_{R'}$, and the initial condition η_0 is in the domain of attraction of the equilibrium $\Phi(t_0, \xi_0)$ for system (A.3) with $\alpha = t_0$ and $\beta = \xi_0$.

Hypothesis H4. The system of equations

$$\frac{dy_0}{dt} = g(t, \Phi(t, y_0), y_0, 0) \tag{A.4}$$

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 6. *Let Hypotheses H1–H4 be satisfied and let $y_0(t)$ be the solution of (A.4) for $y_0(t) = \xi_0$. Then, for sufficiently small values of ε the solution of problem (A.1), $(x(t), y(t))$, 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 B. Approximate aggregation methods: nonautonomous case

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

$$\varepsilon \frac{dn}{dt} = f(t, n) + \varepsilon s(t, n), \tag{B.1}$$

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, this issue) 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 (B.1) 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:

$$\begin{cases} \varepsilon \dfrac{dx}{dt} = F(t, x, y) + \varepsilon H(t, x, y), \\ \dfrac{dy}{dt} = G(t, x, y), \end{cases} \tag{B.2}$$

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 (B.2) of system (B.1). 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 susceptibles and of individuals infected by each strain, 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 (B.2) is reduced by means of Fenichel center manifold theorems, Auger et al. (2008a,b, this issue). 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 (B.2) is a particular case of system (A.1) taking

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

so we are using the Hoppensteadt results summarized in Theorem 6. System (A.4) 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 (B.2) asymptotic behavior via Theorem 6.

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