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Spatiotemporal dynamics of epidemics: synchrony in metapopulation models

Alun L. Lloyd [a,b,*], Vincent A.A. Jansen [c]

[a] *Program in Theoretical Biology, Institute for Advanced Study, Einstein Drive, Princeton, NJ 08540, USA*
[b] *Biomathematics Graduate Program and Department of Mathematics, North Carolina State University, Raleigh, NC 27695, USA*
[c] *School of Biological Sciences, Royal Holloway, University of London, Egham, Surrey TW20 0EX, UK*

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Abstract

Multi-patch models – also known as metapopulation models – provide a simple framework within which the role of spatial processes in disease transmission can be examined. An n-patch model which distinguishes between k different classes of individuals is considered. The linear stability of spatially homogeneous solutions of such models is studied using an extension of an analysis technique previously described for a population setting in which individuals migrate between patches according to a simple linear term. The technique considerably simplifies the analysis as it decouples the nk dimensional linearized system into n distinct k-dimensional systems. An important feature of the spatial epidemiological model is that the spatial coupling may involve non-linear terms. As an example of the use of this technique, the dynamical behavior in the vicinity of the endemic equilibrium of a symmetric SIR model is decomposed into spatial modes. For parameter values appropriate for childhood diseases, expressions for the eigenvalues corresponding to in-phase and out-of-phase modes are obtained, and it is shown that the dominant mode of the system is an in-phase mode. Furthermore, the out-of-phase modes are shown to decay much more rapidly than the in-phase mode for a broad range of coupling strengths.

Keywords: Epidemiological model; Metapopulation; Spatial dynamics; Linear stability analysis

* Corresponding author. Current address: Biomathematics Graduate Program and Department of Mathematics, North Carolina State University, Raleigh, NC 27695, USA.
E-mail address: alun@alunlloyd.com (A.L. Lloyd).

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1. Introduction

Space plays an important role in many infectious disease processes. This is hardly surprising as populations are not well-mixed: interactions between individuals tend to be mainly local in nature. Disease incidence records clearly illustrate non-uniformities in the spatial distribution of cases, and in many instances highlight striking examples of spatial patterns [7,25,28]. As spatial patterns of disease are dependent on an often complex interplay between several factors (such as the dynamics intrinsic to a given host/pathogen interaction and the nature of mixing exhibited by a given population), mathematical models provide an excellent framework within which spatial processes and the emergence of patterns can be studied.

This study considers metapopulation models, in which the population is subdivided into a number of discrete patches, each of which is treated as being well-mixed. This formulation is commonly used as a model for the transmission of disease within and between different population centers. As an example, such models have been used to study the spatial dynamics of childhood diseases, such as measles, on a city-by-city level in an attempt to understand the mechanisms which give rise to the often high levels of synchronization seen between disease outbreaks in different cities [7,25].

Just as the analysis of equilibrium states often forms the first step in analyses of non-spatial models, a natural starting point for the study of a spatially extended model involves an analysis of spatially homogeneous states (which we term 'flat solutions') of the system. With the increased dimensionality of spatial models, even linear stability analysis becomes much more involved compared to non-spatial settings. Transform techniques, in which perturbations about the flat solution are decomposed into a collection of modes, can often simplify the analysis since the (linearized) equations describing the time-evolution of different modes are decoupled from each other.

In recent work, a transform methodology appropriate for metapopulation models was developed [15]. Here, this technique will be used to decompose the behavior of the metapopulation disease model, in the vicinity of its flat endemic equilibrium, into spatial modes. Furthermore, expressions for the eigenvalues which determine the stability (and characteristic decay times) of the modes will be obtained. The analysis shows that the dominant (i.e. the least slowly decaying) mode is always an in-phase mode, in which the densities of individuals in each patch oscillate together, and that the remaining out-of-phase modes decay much more rapidly provided that the coupling strength is neither too weak nor too strong. This analysis provides a more intuitive method for the derivation of the results of Lloyd and May [19], as well as providing a basis for obtaining generalizations of their results.

This paper is organized as follows. Section 2 briefly recaps and extends the results of Jansen and Lloyd [15] for an ecologically motivated spatial metapopulation model with a linear migration term. Section 3 discusses the formulation of metapopulation extensions of standard epidemiological models, including a discussion of the 'beta matrix' which describes the non-linear epidemiological coupling between patches. In Section 4, the analysis technique discussed in Section 2 is applied to the epidemiological metapopulation model. Section 5 studies the stability of the spatially homogeneous endemic equilibrium using the results of Section 4, and provides improved approximations for the eigenvalues describing the decay of in- and out-of-phase modes. Section 6 briefly discusses the analysis of an epidemiological metapopulation model in which the between-patch coupling arises from migration of individuals between patches.

2. The stability of flat solutions of spatial metapopulation models with linear migration

Jansen and Lloyd [15] considered the following simple, ecologically motivated, n-patch metapopulation model describing an interaction between k different species

$$\frac{\mathrm{d}\boldsymbol{x}_j}{\mathrm{d}t} = \boldsymbol{f}(\boldsymbol{x}_j) + \sum_{i=1}^{n} c_{ij} M \boldsymbol{x}_i. \tag{1}$$

Here, each $\boldsymbol{x}_j$ is a k-dimensional vector describing the densities of all species in patch j. The right hand side of (1) is made up of two terms. The first term, given by the function $\boldsymbol{f}$, describes the within-patch interactions between species; this function would describe the single patch dynamics if there were no spatial coupling. The second term describes the migration of individuals between patches.

It is assumed that the pattern of migration between patches, as described by the $n \times n$ matrix C, is the same for all species, but that different species may have different migration rates, m_k, which form the entries of the diagonal $k \times k$ matrix M. The patches are assumed to be of equal size, although as noted in [15], this assumption can be relaxed.

The analysis involves the use of a book-keeping system to keep track of all nk state variables in a simple fashion, achieved by arranging the densities in a matrix, $X = (\boldsymbol{x}_1, \ldots, \boldsymbol{x}_n)$. The columns of X contain the densities of the k species within a patch and the rows contain the densities of a given species across the n patches. With this notation, the model (1) can be cast into the following form:

$$\frac{\mathrm{d}X}{\mathrm{d}t} = F(X) + MXC, \tag{2}$$

where $F(X) = (\boldsymbol{f}(\boldsymbol{x}_1), \ldots, \boldsymbol{f}(\boldsymbol{x}_n))$, and, as discussed above, the function $\boldsymbol{f}$ describes the within-patch interactions.

An important property that follows from the definition of X is that post-multiplication of the matrix of densities (e.g. a term of the form XC) represents interactions of a given species between different patches (i.e. migration), whereas pre-multiplication of the matrix (e.g. a term of the form JX) represents interactions between different species within the same patch.

It is straightforward to show that the linearized equation describing the time evolution of a small perturbation about a flat solution, $S_{\mathrm{flat}} = (\boldsymbol{s}(t), \ldots, \boldsymbol{s}(t))$, is given by

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = J(\boldsymbol{s}(t))Y + MYC, \tag{3}$$

where $J(\boldsymbol{s}(t))$ is the matrix of partial derivatives (also known as the Jacobian matrix) of the function describing the between-species (i.e. within-patch) interactions, evaluated at $\boldsymbol{s}(t)$. An important property of (3) is that the only term which involves post-multiplication of Y is the term YC.

The analysis of [15] shows that the linearized system (3) can be decomposed into n decoupled k-dimensional systems. The matrix C can be diagonalized by a similarity transformation, A, giving $A^{-1}CA = \Lambda$. The transformation has a simple construction: the columns of A are the (right) eigenvectors of C, and the entries of Λ are the corresponding eigenvalues, written as Λ_i. We order the eigenvalues of C such that Λ_1 is the maximal eigenvalue (i.e. the one with largest real part). Writing $\Psi(t) = Y(t)A$, Eq. (3) becomes

$$\frac{\mathrm{d}\Psi}{\mathrm{d}t} = J(\boldsymbol{s}(t))\Psi + M\Psi\Lambda. \tag{4}$$

Since the only term which post-multiplies Ψ is the diagonal matrix Λ, the equations for the time evolution of each column of Ψ are decoupled. This reduces the analysis from that of an nk dimensional system to n decoupled k-dimensional systems, and thus represents a considerable simplification.

Writing the ith column of Ψ as $\boldsymbol{\psi}_i$, and noting that the effect of (post)multiplying this column vector by Λ is to multiply the vector by Λ_i, the decoupled equations describing the linearization can be written as

$$\frac{\mathrm{d}\boldsymbol{\psi}_i}{\mathrm{d}t} = \{J(\boldsymbol{s}(t)) + \Lambda_i M\}\boldsymbol{\psi}_i. \tag{5}$$

We remark that this analysis can be carried out without the use of the matrix notation, but is considerably more complex, requiring the use of Kronecker product constructs (see [23]).

We see that if the migration rate, m, is the same for all species, the linearization takes a particularly simple form, with the matrix on the right hand side of (5) given by $J(\boldsymbol{s}(t)) + m\Lambda_i I^{(k)}$, where $I^{(k)}$ is the k-dimensional identity matrix. In this case, the eigenvalues of the full spatial system in an equilibrium setting are simply obtained by adding $m\Lambda_i$ to those of the single patch system.

Eq. (5) can be used to investigate the linear stability of both equilibrium and non-equilibrium behaviors of the system. For instance, the Floquet multipliers of a periodic orbit (which describe the linearization of the Poincaré map corresponding to the periodic orbit) can be obtained from the integration of (5) over one orbital period. Similarly, integration over longer timescales can be used to determine the Lyapunov exponent spectrum of a given attractor of the system. Notice that even though (5) is a linear system, its integration for non-equilibrium situations is usually difficult because the Jacobian matrix depends on the trajectory $\boldsymbol{s}(t)$.

2.1. A generalization of the spatial analysis

The linearization (3) is a particular example of the general form

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = PY + QYC, \tag{6}$$

where C is a constant $k \times k$ matrix, and P and Q are arbitrary $k \times k$ matrices, which need not be constant.

We remark that in this more general setting, the interpretation of the matrices P, Q and C may differ from their counterparts in the original ecological setting (3). In the particular case (3), P is the within-patch Jacobian matrix, which depends on $\boldsymbol{s}(t)$, whilst Q is a constant diagonal matrix. As another example, the more general model of [12] allows migration rates to be dependent on the densities of the species. Linearization around a flat solution of this model leads to an equation of the form (6), with P equal to the appropriate within-patch Jacobian matrix but for which Q is neither diagonal nor constant, reflecting the dependence of migration rates on the densities of the other species.

Since the only term that involves post-multiplication of Y in (6) is the YC term, it is clear that the analysis of [15] can be directly applied to linearizations of this more general type. Hence, the following n decoupled k-dimensional equations are obtained

$$\frac{\mathrm{d}\boldsymbol{\psi}_i}{\mathrm{d}t} = \{P + \Lambda_i Q\}\boldsymbol{\psi}_i. \tag{7}$$

In the next section, we shall see that the linearization that results from a metapopulation formulation of a standard epidemiological model can be written in the form (6), enabling the deployment of the results of this section.

3. Metapopulation SEIR models

A standard metapopulation version of the deterministic susceptible/exposed/infective/recovered (SEIR) model for a non-fatal disease which confers permanent immunity upon recovery can be written as

$$\frac{\mathrm{d}S_i}{\mathrm{d}t} = \mu - \mu S_i - S_i \sum_{j=1}^{n} \beta_{ij} I_j, \tag{8}$$

$$\frac{\mathrm{d}E_i}{\mathrm{d}t} = S_i \sum_{j=1}^{n} \beta_{ij} I_j - (\mu + \sigma) E_i, \tag{9}$$

$$\frac{\mathrm{d}I_i}{\mathrm{d}t} = \sigma E_i - (\mu + \gamma) I_i. \tag{10}$$

Here, S_i, E_i and I_i denote the fractions of the occupants of the ith patch which are susceptible, exposed and infective. It is assumed that the population sizes of each patch are identical and remain constant. This corresponds to assuming that the population birth and death rates, denoted by μ, are equal and implies that the density of recovered individuals, R_i, is given by $R_i = 1 - S_i - E_i - I_i$. The average lifespan of individuals, L, can be seen to equal $1/\mu$.

A simple description of the disease process is employed: individuals are born susceptible and can acquire infection from infective individuals, at which point they enter the exposed class. After a latent period, lasting an average of $1/\sigma$ time units, individuals are infectious for an average of $1/\gamma$ time units. Since the population is subject to a disease-independent mortality rate, μ, the mortality-corrected average duration of infectiousness, written as τ, equals $1/(\gamma + \mu)$, and the fraction, f_S, of exposed individuals who will become infectives is $\sigma/(\mu + \sigma)$. Notice that when the latent and infectious periods are short compared to the lifespan, then $\tau \approx 1/\gamma$ and $f_S \approx 1$.

The beta matrix, whose entries equal β_{ij}, describes the transmission between and within patches. This formulation of the model assumes that there is an epidemiological cross-coupling between patches, but that individuals do not migrate between patches. This might be thought of as arising from a situation in which individuals make short-lived visits from their home patch to other patches. It is often assumed that within-patch mixing is stronger (and often considerably stronger) than between-patch mixing, and hence that the between-patch transmission parameters are small compared to the within-patch transmission parameters.

An alternative model formulation considers the mechanism by which cross-coupling arises in more detail, explicitly modeling the migration of individuals between patches [16]. This formulation was extensively used in an early Russian attempt to model influenza epidemics (see, for example, [5], and the review of Bailey [3]; see also [26]). Such a model can be written in the form

$$\frac{\mathrm{d}S_i}{\mathrm{d}t} = \mu - \mu S_i - \beta_i S_i I_i + \Omega_i^{(1)}(\boldsymbol{S}), \tag{11}$$

$$\frac{\mathrm{d}E_i}{\mathrm{d}t} = \beta_i S_i I_i - (\mu + \sigma)E_i + \Omega_i^{(2)}(\boldsymbol{E}), \tag{12}$$

$$\frac{\mathrm{d}I_i}{\mathrm{d}t} = \sigma E_i - (\mu + \gamma)I_i + \Omega_i^{(3)}(\boldsymbol{I}), \tag{13}$$

where the $\Omega_i^{(k)}$ are functions describing the transport of individuals of different types between patches. These functions need not be the same for all types of individuals: for instance, it might be assumed that sick individuals are less likely to travel.

In uses of this formulation, transport has generally been described by a linear function which mimics simple diffusion, and so the resulting model is exactly of the form (1), with migration being described by matrices M and C that can be written in terms of the $\Omega_i^{(k)}$. The study of the stability of its flat solutions proceeds exactly as in the general analysis of [15]. This study shall, therefore, mainly focus on the first, cross-coupled, formulation. Interestingly, there are correspondences between these two model formulations [4,16]. Notice that, as mentioned in Section 2.1, both the interpretation and the properties of the matrix describing spatial coupling differ between the cross-coupled and linear migration cases; detailed properties of the C matrix in the latter setting are discussed in [15].

3.1. The structure of the beta matrix in the cross-coupled model

Throughout this study, we shall assume that the between-patch transmission process is symmetric and that the infection can be passed between any pair of patches, albeit possibly via intermediate patches. This second assumption essentially means that the n-patch system cannot be decomposed into non-interacting subsystems. In mathematical terms, the beta matrix is symmetric and irreducible [22].

Symmetry of the beta matrix implies that its eigenvalues are real. Further information about the eigenvalues is provided by the Perron–Frobenius theory for non-negative irreducible matrices [22]. Such matrices can be shown to have a positive maximal eigenvalue, i.e. a real positive eigenvalue whose modulus is greater than, or equal to, those of the remaining eigenvalues. The corresponding maximal eigenvector is positive, and is the only (linearly independent) eigenvector corresponding to this eigenvalue. Furthermore, the maximal eigenvector is the only non-negative eigenvector of the matrix. If, as mentioned earlier, the maximal eigenvalue is denoted by Λ_1, these results show that the remaining eigenvalues of the beta matrix lie in the interval $[-\Lambda_1, \Lambda_1)$.

The beta matrix must exhibit certain symmetries in order for flat solutions of the cross-coupled model to exist. Eq. (8) shows that the sum of the entries of each row of the beta matrix must be equal; this common row sum is written as β_T. It is clear that β_T is an eigenvalue of the beta matrix,

with corresponding eigenvector $(1,\ldots,1)^{\mathrm{T}}$. Therefore, according to the Perron–Frobenius theory, this eigenvalue is the maximal eigenvalue of the beta matrix.

Standard expressions for the basic reproductive number, R_0, in heterogeneous populations [8,11,17], show that $R_0 = \beta_T f_S \tau$, where the product $f_S\tau$ gives the average duration of infectiousness, corrected for mortality in the exposed and infectious classes.

We note that the eigenvalues of the beta matrix need be known in order to obtain the decoupled equations corresponding to (7). Since one need not explicitly construct the transformation matrix, A, the eigenvectors of the beta matrix need not be known explicitly. Their entries do, however, contain useful spatial information regarding the nature of the modes. For instance, the Perron–Frobenius theory shows that the eigenvector that corresponds to the maximal eigenvalue of the beta matrix is positive and, therefore, always corresponds to an in-phase mode. Furthermore, none of the remaining eigenvectors are non-negative: they must contain two entries that have opposite sign and hence represent out-of-phase modes.

In the analysis of Section 5, we shall make use of the quantities δ_i, defined as $\delta_i = 1 - \Lambda_i/\Lambda_1$. For a given mode, δ_i is a measure of how far away the corresponding eigenvalue of the beta matrix is from the maximal eigenvalue. By definition, δ_1 is equal to zero and the constraints on the eigenvalues of the beta matrix imply that the remaining δ_i lie between zero and two. When the between-patch coupling is weak, the δ_i take values close to zero. Values close to two can only be achieved when between-patch transmission is much stronger than within-patch transmission, a situation that is epidemiologically unlikely. The limiting value of two can only possibly be attained when there is between-patch transmission but no within-patch transmission.

Some limited insight into the dependence of the eigenvalues of the beta matrix on the strengths of within and between-patch coupling can be gained if the beta matrix can be written in the form

$$\beta(I^{(n)} + \phi B). \tag{14}$$

Here $I^{(n)}$ is the n-dimensional identity matrix. The constant row sum property of the beta matrix means that the matrix B, which describes the pattern of cross-coupling between patches, must have constant row sums. This sum can be taken to be unity, and the parameter ϕ is then a measure of the relative strengths of between and within patch transmission.

If the eigenvalues of the B matrix are written as l_i, then the eigenvalues of the beta matrix (14) are equal to $\beta(1 + \phi l_i)$. Because B is a non-negative symmetric matrix with row sums equal to one, its eigenvalues are real and lie between -1 and 1 [22], and so the eigenvalues of the beta matrix lie between $\beta(1 - \phi)$ and $\beta(1 + \phi)$, with the latter value being attained by the maximal eigenvalue, β_T. Notice that when ϕ is small, i.e. the between-patch coupling is relatively weak, all of these eigenvalues are close to the maximal eigenvalue.

The description of the beta matrix provided by (14) assumes that the within-patch transmission parameter is a constant, independent of the strength of between-patch transmission. This implies that R_0 increases as the between-patch coupling, ϕ, becomes stronger. This simplest cross-coupled formulation essentially allows individuals to simultaneously infect others in more than one patch: traveling individuals can still infect those in their 'home' patch during their visits to other patches. Many authors instead assume that R_0 (and hence β_T) is independent of the spatial coupling: this can easily be achieved by an appropriate renormalization of β. Since this assumption is routinely made in the literature, we shall employ it here, partly to facilitate comparison of our results with those of other authors. (In fact, this change has little impact on the analyses or results that follow.)

For the beta matrix described by (14), the renormalization is achieved by replacing β with $\beta/(1+\phi)$. The maximal eigenvalue of the beta matrix, β_T, is then independent of ϕ and equals β, whilst the remaining eigenvalues lie between $\beta(1-\phi)/(1+\phi)$ and β.

3.1.1. Particular forms of the beta matrix

Since expressions for the eigenvalues of certain symmetric matrices are well known, such matrices suggest themselves as analytically useful choices for beta matrices. We shall discuss two particular forms, although it should be realised that there are many other symmetric matrices whose eigenvalues can be explicitly calculated (see [23] or appendix II of [21]).

The 'equal coupling' beta matrix assumes that there is a certain transmission parameter, β, within a patch and that there is an equal coupling between this patch and any other patch, with the between-patch transmission parameter written as $\epsilon\beta$. The between-patch transmission parameter is usually assumed to be smaller, and in most cases much smaller, than the within-patch transmission parameter. As mentioned above, the parameter β is usually renormalized so that R_0 is independent of ϵ. This corresponds to scaling the beta matrix by the factor $1/(1+\{n-1\}\epsilon)$. (Notice the intuitive origin of this scaling: the factor arises because each patch is connected to $(n-1)$ other patches.)

The (renormalized) beta matrix has maximal eigenvalue $\beta_T = \beta$ and $(n-1)$ repeated eigenvalues equal to $\beta(1-\epsilon)/(1+\{n-1\}\epsilon)$. As mentioned above, the maximal eigenvalue corresponds to an eigenvector of the form $(1,\ldots,1)^{\mathrm{T}}$, which represents a mode in which perturbations about the endemic equilibrium are in phase. The eigenvectors corresponding to the repeated eigenvalues can be written in the form $(1,-1,0,\ldots,0)^{\mathrm{T}}$, with $(n-2)$ zero entries and the remaining two entries (which can be in any position in the vector) being non-zero but having opposite signs. Written in this way, these eigenvectors describe modes in which $(n-2)$ patches exhibit no fluctuations and the perturbations in the remaining pair of patches have opposite phases (i.e. they are 180 degrees out of phase). Notice, however, that this description of the out-of-phase modes is not unique: because of the repeated eigenvalue, one can generate alternate sets of independent eigenvectors (by taking linear combinations of the eigenvectors just discussed). In any case, the eigenvectors always contain a mixture of negative and positive entries and therefore correspond to out-of phase modes of the system.

The value of δ_i corresponding to the out-of-phase modes is equal to $n\epsilon/(1+\{n-1\}\epsilon)$. When the between-patch transmission parameter is smaller than the within-patch transmission parameter, we see that these δ_i lie between 0 and 1. As ϵ tends to infinity, the value tends to $n/(n-1)$: values approaching 2 are only possible for a two-patch setting in which the between-patch coupling is very strong.

'Nearest neighbour coupling' assumes that the n patches have a one-dimensional arrangement, with between-patch interactions restricted to neighboring patches. To avoid the edge effects that would be associated with a linear chain, we imagine that the patches are arranged on a circle, so the first and nth patches are neighbors. Making the assumption that R_0 is independent of coupling strength, the (renormalized) within-patch transmission parameter is taken to be $\beta/(1+2\epsilon)$, and the between-patch transmission parameter is $\epsilon\beta/(1+2\epsilon)$. The eigenvalues of this beta matrix are of the form $\beta\{1-2\epsilon\cos(j\pi/n)\}/(1+2\epsilon)$. If n is even then j takes the values $2,4,\ldots,2n$, whereas if n is odd then j takes the values $1,3,\ldots,2n-1$. The maximal eigenvalue, β_T, is achieved when $j=n$ and equals β.

It is straightforward to see that the values of δ_i for the out-of-phase modes in the nearest neighbour case must be less than or equal to $4\epsilon/(1+2\epsilon)$. When ϵ lies between 0 and 1, the largest value of δ_i for these modes lies between 0 and 4/3. In this case, the maximal possible value of 2 can be attained regardless of the number of patches, but this only occurs as ϵ tends to infinity.

4. Analysis of the cross-coupled epidemiological model

Writing $x_{1j}(t) = S_j(t)$, $x_{2j}(t) = E_j(t)$ and $x_{3j}(t) = I_j(t)$, the linearization of the model (8)–(10) about a flat solution (for which $S_j(t) = S(t)$, $E_j(t) = E(t)$ and $I_j(t) = I(t)$) is easily performed. Taking partial derivatives of the right hand sides of (8)–(10) with respect to the variables x_{ij}, it is immediately clear that most non-zero entries in this linearization arise from within-patch terms. The only non-zero between-patch terms result from the partial derivatives of the cross-coupling term, $S_i \Sigma \beta_{ij} I_j$, with respect to the Is; these partial derivatives are equal to $S\beta_{ij}$. It is then straightforward to see that the linearization can be written in the form (6). The matrix P, corresponding to the within-patch terms, is given by

$$P = \begin{pmatrix} -\mu - I(t)\beta_T & 0 & 0 \\ I(t)\beta_T & -(\mu+\sigma) & 0 \\ 0 & \sigma & -(\mu+\gamma) \end{pmatrix}, \tag{15}$$

the entries of Q, corresponding to the between-patch terms, are zero, except for $q_{13} = -S(t)$ and $q_{23} = S(t)$, and the entries of C are β_{ij}. (In general, C is the transpose of the beta matrix, but here this matrix is assumed to be symmetric.) Notice that the matrix Q is not a diagonal matrix, reflecting the between-species nature of the between-patch coupling employed in the epidemiological model (cf. the earlier discussion of [12]).

Use of the similarity transformation (defined above in terms of the eigenvectors of the beta matrix, C) allows the linearization of the model to be written in the decoupled form (7). Since Q contains only two non-zero entries, the transformed system can be written in the simple form

$$\frac{\mathrm{d}\boldsymbol{\psi}_i}{\mathrm{d}t} = D_i(\boldsymbol{s}(t))\boldsymbol{\psi}_i, \tag{16}$$

where the 3×3 matrix $D_i(\boldsymbol{s}(t))$ has the following form

$$D_i(\boldsymbol{s}(t)) = \begin{pmatrix} -\mu - I(t)\beta_T & 0 & -S(t)\Lambda_i \\ I(t)\beta_T & -(\mu+\sigma) & S(t)\Lambda_i \\ 0 & \sigma & -(\mu+\gamma) \end{pmatrix}. \tag{17}$$

The eigenvalues, λ, of the Jacobian of the full spatial system at any time point can now be obtained as the eigenvalues of the matrices D_i. It is straightforward to show that they satisfy the following cubic equations:

$$(\lambda + \mu + \beta_T I(t))(\mu + \sigma + \lambda)(\lambda + \mu + \gamma) - S(t)\Lambda_i\sigma(\lambda + \mu) = 0. \tag{18}$$

In the case of an SIR model, in which individuals become infectious as soon as they are infected (i.e. the $\sigma \to \infty$ limit of the SEIR model), (18) simplifies to

$$(\lambda + \mu + \beta_T I(t))(\lambda + \mu + \gamma) - S(t)\Lambda_i(\lambda + \mu) = 0. \tag{19}$$

In an equilibrium situation, Eqs. (18) or (19) can be used directly to determine the linear stability of the equilibrium. (This is not the case for non-equilibrium situations, such as periodic orbits, since the Floquet multipliers that determine the stability of such orbits must be obtained by integrating an equation of the form (7) over a complete orbit.) At the endemic equilibrium, for which $S = 1/R_0$ and $I = \mu\tau(1 - 1/R_0)$, Eqs. (18) and (19) reduce to those given in [19] (Eqs. (32) and (33)).

5. An application: behavior near the endemic equilibrium of the SIR model

The behavior near the endemic equilibrium of the SIR model will now be examined in more detail. Parameter values appropriate for a childhood disease, such as measles, will be employed. For such diseases there is often a separation of timescales between the duration of infectiousness, τ (infection often lasts on the order of days), the average age at infection, denoted by A, and the average lifespan, L. (Using the standard result $R_0 = L/A$ [1], the separation between L and A can be seen to reflect the large value of R_0 for such diseases: e.g., $R_0 \approx 15$ for measles [1].) In the following analyses, therefore, it shall be assumed that $\tau \ll A \ll L$.

Eq. (19) describing the stability of the modes of the spatial system can be rewritten as

$$\lambda^2 + \lambda\left\{\frac{1}{A} + \frac{1}{\tau} - \frac{\Lambda_i}{R_0}\right\} + \mu\left[\frac{R_0}{\tau} - \frac{\Lambda_i}{R_0}\right] = 0. \tag{20}$$

Since $R_0 = \Lambda_1\tau$, it is convenient to rewrite this quadratic as

$$\lambda^2 + \lambda\left\{\frac{1}{A} + \frac{\delta_i}{\tau}\right\} + \frac{\mu}{\tau}[R_0 - (1 - \delta_i)] = 0, \tag{21}$$

where $\delta_i = 1 - \Lambda_i/\Lambda_1$, as defined above. We notice that, since $0 \leqslant \delta_i \leqslant 2$ and $R_0 \gg 1$, the constant term of the quadratic (21) is well approximated by $1/(A\tau)$. For simplicity, we employ this approximation in the following analysis.

Application of the Routh–Hurwitz conditions (see, for example, appendix II of [21]) to (21) immediately shows that all modes of the system are linearly stable when $R_0 > 1$, as both the linear and constant coefficients of the quadratic are positive in this case. This basic stability property is as expected from general analyses of the stability of endemic equilibria of multi-group epidemic models [11,17].

For the in-phase mode, which, as discussed above, corresponds to $\delta_1 = 0$, the quadratic (21) simplifies somewhat. Since $\delta_1 = 0$, the coefficient of the linear term reduces to $1/A$ as the second and third terms in the braces of the corresponding term of (20) cancel. The resulting quadratic is familiar as it is precisely the expression which determines the stability of the endemic equilibrium of the standard (homogeneous) SIR model [1], with R_0 appropriately redefined to account for the spatial coupling. The eigenvalue equation determining the stability of the in-phase mode is well approximated by

$$\lambda^2 + \frac{1}{A}\lambda + \frac{1}{A\tau} = 0, \tag{22}$$

which, given the separation of timescales in the model, has approximate roots

$$\lambda \approx -\frac{1}{2A} \pm \frac{i}{\sqrt{A\tau}}. \tag{23}$$

The in-phase mode exhibits weakly damped oscillations towards the endemic equilibrium, with oscillation period much shorter than the damping time.

For the out-of-phase modes, δ_i is non-zero and so the coefficient of the linear term in (21) consists of two terms. (Alternatively, this can be viewed as the non-cancellation of the second and third terms in the braces of the corresponding term of (20).) The eigenvalue equation determining the stability of the out-of-phase modes can be written as

$$\lambda^2 + \lambda\left\{\frac{1}{A} + \frac{\delta_i}{\tau}\right\} + \frac{1}{A\tau} = 0. \tag{24}$$

This quadratic has roots given by

$$\lambda = -\frac{1}{2A} - \frac{\delta_i}{2\tau} \pm \frac{1}{2}\sqrt{\left(\frac{1}{A} + \frac{\delta_i}{\tau}\right)^2 - \frac{4}{A\tau}}. \tag{25}$$

Examining the discriminant of (24), we see that these roots form a complex conjugate pair if $\delta_i < \sqrt{4\tau/A} - \tau/A$, otherwise they are both real.

In the former case, the roots have real parts equal to

$$\operatorname{Re}\lambda = -\frac{1}{2A} - \frac{\delta_i}{2\tau}. \tag{26}$$

Provided that δ_i is greater than zero (i.e. that there is some coupling between patches), the out-of-phase modes corresponding to these roots decay more rapidly than the in-phase mode.

In the latter case, comparison of the second and third terms of (25) shows that the out-of-phase modes decay more rapidly than the in-phase mode unless $\delta_i \geqslant 2 - \tau/(2A)$. Notice, however, that this constraint is extremely unlikely to be violated in reality: since τ is much smaller than A, this would require δ_i to be very close to its maximum possible value of 2, and hence that the between-patch coupling is much stronger than the within-patch coupling. (See the discussion of δ_i values in Sections 3.1 and 3.1.1.)

Taking the two cases together, we see that the in-phase mode is always the dominant mode of the system provided that the between-patch coupling is non-zero and is not considerably greater than the within-patch transmission parameter.

Use of the inequality $\sqrt{1-x} \leqslant 1 - x/2$ shows that when δ_i is such that the roots (25) are real, they satisfy $\lambda \leqslant -1/(\tau + A\delta_i)$. Approximate expressions for these roots can be obtained by using the fact that $\tau \ll A$. Returning to the discriminant of (24), we see that an approximate condition for there to be a pair of real roots of this equation is that $\delta_i > \sqrt{4\tau/A}$. If δ_i is neither too small, by which we mean that $A\delta_i$ is large compared to τ, nor too large, by which we mean that δ_i is not too close to two, then we see that, to a good approximation, the quadratic equation (25) has roots

$$\lambda = -\frac{\delta_i}{2\tau} \pm \frac{\delta_i}{2\tau}\sqrt{1 - \frac{4\tau}{A\delta_i^2}}. \tag{27}$$

We remark that the condition that δ_i is not too small implies that the second term in the braces of the linear coefficient of (24) dominates the first: the coefficient of the linear term is of the order of $1/\tau$, as opposed to $1/A$. The second condition on δ_i is required because as δ_i becomes large, the two terms in the expression (27) for the larger root almost cancel, in which case it is no longer safe to omit the terms of order $1/(2A)$.

The behavior of the out-of-phase modes, therefore, depends on the size of δ_i. There is a wide range of δ_i values for which the out-of-phase modes decay on the fast timescale of τ, as opposed to the decay of the in-phase mode which occurs on the slower timescale of A. Provided that the spatial coupling is weak enough that (26) holds, the ratio of the damping time of the in-phase mode to that of an out-of-phase mode is given by $1 + A\delta_i/\tau$. In the equal coupling case this expression simplifies to $1 + nA\epsilon/\tau$, assuming that ϵ is small. Notice that the value of ϵ required to make the decay of out-of-phase modes sufficiently rapid can then be obtained by rearranging this ratio (cf. Eq. (50) of [19]).

5.1. A numerical example

We shall illustrate these results using parameter values appropriate for a childhood disease such as measles, for which infection lasts on the order of a week and for which R_0 is fairly large. We take the average duration of infectiousness to be seven days, R_0 (in the absence of coupling between patches) equal to 15 and assume an average lifespan of 50 years [1].

The real parts of the eigenvalues corresponding to the in-phase and out-of-phase modes for a 10 patch equally coupled system over a range of values of the coupling are illustrated in Fig. 1(a). Also shown are the values obtained using expression (23) for the in-phase mode, the approximate expression (27) for the out-of-phase modes, which assumed that δ_i was neither too small nor too large, and expression (26) for the out-of-phase modes, which is an exact solution of (24) for values of δ_i small enough that the quadratic has a complex conjugate pair of roots.

As previous studies have shown, expression (23) provides an excellent approximation to the eigenvalues of the in-phase mode. Expression (27) provides a surprisingly good approximation to the real parts of the eigenvalues of the out-of-phase modes. Since the approximation that gave this expression neglected the $1/A$ term in the linear coefficient of (24), we notice that this leads to the discriminant of (24) being underestimated. The approximation, therefore, overestimates the strength of coupling at which the eigenvalues of the out-of-phase modes change from being complex to being purely real, as well as underestimating the difference between the real eigenvalues that are then seen. Recall that, as discussed in Section 3.1.1, the out-of-phase modes of this system can be viewed as modes in which a pair of patches exhibit antiphase fluctuations (with the eight remaining patches showing no fluctuations).

As long as the spatial coupling is not too weak, Fig. 1(a) confirms that the out-of-phase modes decay much more rapidly than the in-phase mode. As the system approaches the endemic equilibrium, it does so in such a fashion that the densities of infectives in each patch oscillate in phase. Numerical integrations of SIR and SEIR models which illustrate this behavior can be found in [19].

For comparison, Fig. 1(b) illustrates the real parts of the eigenvalues for in-phase and out-of-phase modes of a 10 patch system for which nearest neighbor coupling is employed. The figure

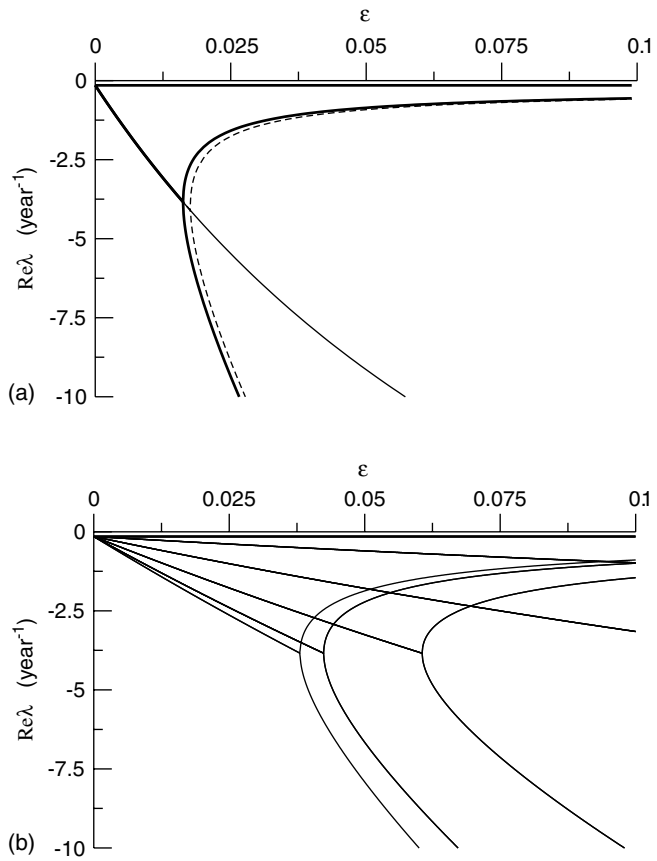

Fig. 1. (a) Real parts of the eigenvalues corresponding to the in-phase and out-of-phase modes of a 10 patch cross-coupled SIR system with equal coupling between distinct pairs of patches. Thick solid curves denote exact values, obtained by solving (21). The upper curve corresponds to the in-phase mode, and the lower curve, which has two branches when ϵ is sufficiently large, corresponds to the out-of-phase modes. The approximation (23) for the real part of the eigenvalues of the in-phase mode is indistinguishable from the exact solution on the scale of this figure. The light solid black curve denotes expression (26) for the real part of the eigenvalues of the out-of-phase modes, which is an exact solution of (21) as long as the spatial coupling is not too strong. (Notice that this curve coincides with the curve depicting the exact values when the roots corresponding to the out-of-phase modes form complex conjugate pairs.) The broken black curves depict the approximation (27). Parameter values, as discussed in the text, are $\mu = 1/50$ year^{-1}, $R_0 = 15$ (notice that, as discussed in the text, the corresponding value of β is renormalized so that R_0 is independent of ϵ) and $1/\gamma = 7$ days. (b) Real parts of the eigenvalues corresponding to the in-phase and out-of-phase modes of a 10 patch cross-coupled SIR system with nearest neighbor coupling. The heavy (horizontal) curve denotes the in-phase mode and the lighter curves the out-of-phase-modes. These eigenvalues were obtained numerically, although their values could have been obtained straightforwardly using the analysis developed in the text. All parameter values as in (a).

shares many of the features seen in the equal coupling case, although because the submaximal eigenvalues of the beta matrix are either non-repeated or just 2-fold repeated (as opposed to being $(n-1)$-fold repeated in the equal coupling case), many more distinct curves can be seen.

We remark that the difference between the timescales on which the in-phase and out-of-phase modes decay is smaller than seen in Fig. 1(a), reflecting the fact that the submaximal eigenvalue of

the beta matrix is closer to the maximal eigenvalue of the beta matrix than it was in the equally coupled case (see Section 3.1.1). We should point out, however, that in order to make a fair direct comparison between the two cases, one should perhaps rescale ϵ to reflect the fact that each patch is only connected to two others under nearest neighbor coupling, as opposed to $(n-1)$ in the equal coupling case.

6. Analysis of the migration model

Although the analysis of the epidemiological model with linear migration is covered by the general analysis of [15], one special case is entirely straightforward, with simple and striking results, so we shall discuss it here.

If the migration term does not depend on the disease status of the individual, then the matrix M in (1) is a diagonal matrix with entries m. The notation can be simplified by absorbing the constant m into the matrix C, which now describes the pattern and strength of migration between patches. Recall that the interpretation of this matrix differs between the migration and cross-coupled models. For a flat solution, the migration terms must cancel and so C must have a zero eigenvalue corresponding to an eigenvector $(1,\ldots,1)^{\mathrm{T}}$. Furthermore, all other eigenvalues, again written as Λ_i, are real and negative (see [15] for a detailed discussion of the definition and properties of the matrix C in the linear migration model).

As mentioned previously, for a spatially homogeneous equilibrium situation in such a setting, (7) immediately shows that the eigenvalues of the full spatial system can be obtained by simply adding Λ_i to those of the corresponding single-patch system.

As in the cross-coupled model, the maximal eigenvalue of the migration matrix corresponds to an in-phase mode. Since this maximal eigenvalue equals zero, the equation determining the (linear) stability of the in-phase mode is precisely that which determines the stability of the single-patch system (i.e. Eq. (22) in the case of an SIR model). Since the remaining eigenvalues of the migration matrix are negative, the eigenvalues of the out-of-phase modes have smaller negative real parts and so decay more rapidly than the in-phase mode.

As an example, in the case of a two patch SIR model in which the (per capita) rate at which individuals move between patches is given by ϵ, it is easy to see that $\Lambda_1 = 0$ and $\Lambda_2 = -2\epsilon$. For the situation described above, in which the real parts of the eigenvalues of the in-phase mode are given by $-1/(2A)$, the real parts of the eigenvalues of the out-of-phase mode are given by $-1/(2A) - 2\epsilon$. The ratio between the damping times of the in-phase and out-of-phase modes is given by $1 + 4\epsilon A$.

7. Discussion

The transform method discussed in this paper considerably simplifies the linear stability analysis of spatially homogeneous states of a broad class of population models. In equilibrium situations, the analysis provides an alternative derivation of the results obtained by Othmer and Scriven in an important early paper [23]. This somewhat neglected study considered a general model which allowed for cross-species interactions (see also [12,24]). We remark that an almost

identical analysis can be carried out for discrete time metapopulation models, known as coupled map lattice models, (see [15] for details).

Given that the eigenvalues of the beta matrix only differ by a quantity of magnitude ϵ, which is usually assumed to be small, the often large difference in the decay times of the in-phase and out-of-phase modes might, at first, seem strange. This analysis shows that this behavior results from the exact cancellation of two terms in the eigenvalue equation (20) for the in-phase mode. Furthermore, as the difference in decay times between a given mode and the in-phase mode depends on the size of δ_i for that mode, the strength of coupling required for rapid synchronization can be large when the beta matrix has a submaximal eigenvalue which lies close to the maximal eigenvalue. An example is provided by the nearest neighbor coupling discussed earlier: when the number of patches, n, is large, the submaximal eigenvalue (which has the next-closest allowed value of j to n) can be close to the maximal eigenvalue.

Whilst the analysis presented here provides a starting point for understanding the patterns of synchrony seen in real-world outbreaks of childhood diseases, the model employed is an extremely simplified description of the biology underlying such diseases. The major influences of seasonal variations in disease transmission and demographic stochasticity on disease transmission have been highlighted in several analyses of incidence records and modeling studies [2,6,9,16,20,25]. Eq. (5) can be integrated to examine the linear stability of perturbations made to periodic solutions, although this integration would almost certainly have to be carried out numerically. Since periodic solutions allow a larger class of bifurcations than equilibrium solutions, such an analysis will often be worthwhile as there can be qualitatively different results [14].

Trajectories in the non-seasonal model (assuming that R_0 is greater than one) tend to the unique endemic equilibrium, and so, at least in symmetric situations, the above analysis of flat solutions is applicable. The inclusion of seasonality can lead to the maintenance of phase differences between patches: many non-flat attracting solutions exist [19,27]. Analyses of the form presented here are not applicable for such solutions. In those cases, understanding the synchrony or asynchrony seen between outbreaks requires a global analysis which accounts for the basins of attraction of different solutions. Even in situations for which the long-term behavior of each patch is of a simple periodic form, there can be sensitive dependence on initial conditions indicative of complex transient dynamics [19].

Stochasticity further complicates the situation: randomness tends to desynchronize patches, although in many cases this effect is not strong enough to overcome the synchronizing effect of spatial coupling described above. The importance of random effects can be assessed using moment equations [10,13,16,18], which can be used to estimate the correlation seen between the time series of infectives in different patches [16]. An interesting question which remains open is the extent to which the degree of correlation predicted by such moment equations corresponds to the relative decay rates of in-phase and out-of-phase modes of the corresponding deterministic system.

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