JTB 258 (2009), 550-560.

The Effects of Human Movement on the Persistence of Vector Borne Diseases

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Keywords: discrete diffusion

Abstract

vectorborne

1 Introduction

Vector-borne diseases are a major public health problem. They include long-established scourges, such as malaria and dengue fever, as well as emerging diseases such as West Nile virus. The maintenance and resurgence of vector-borne diseases is related to ecological changes that favor increased vector densities or vector-host interactions, among other factors. There have been profound increases in the magnitude of vector-borne disease problems as the result of urbanization, deforestation and development. Experts recognize urbanization as one of the most important drivers of global change, and predict that rapid increases in urban populations throughout the world will have major implications for human health in general and vector-borne diseases specifically (Sutherst 2004). Travel and transport have also contributed to the spread of vector-borne diseases. There are reasons to believe that the spatial movement of humans may be important for the epidemiology of vector-borne diseases. Malaria remains surprising prevalent among residents of some urban areas where there are very few mosquitoes; however, many of those residents visit rural or periurban areas where the disease is much more prevalent, so it is plausible that those visits might make the persistence of malaria in the urban setting more likely. Empirical studies supporting the idea that travel outside urban areas is an important factor in maintaining malaria in urban areas where transmission is low are described by Osorio et al. (2004), Domarle et al. (2006), and Ronald et al. (2006). Ronald et al. (2006) also noted that lower socioeconomic status was correlated with increased risk of infection. The use of personal protection such as bednets may vary between locations or socio-economic classes; such an effect was explored using simple models by Kileen et al. (2003).

We will use spatial models to examine how the the movements of humans in heterogeneous environments affect the transmission of vector-borne diseases. Specifically, we will study how diseases can be maintained in regions of low transmission by the movement of humans between regions of high and low transmission or the immigration of humans into regions of low transmission from regions of high transmission. Our study of this phenomenon is motivated by the specific case of malaria but may be relevant to other vector-borne diseases. Our analysis will be based on spatial versions

of the classical Ross-Macdonald model. A review of the derivation of Ross-Macdonald models is given in (Smith and McKenzie 2004). Although our goal is to understand spatial effects, our modeling approach could also be used to treat movement between different socio-economic classes or lifestyles. Because we want to consider the movement of humans we will use the populations of infected humans and mosquitoes as state variable rather than the proportions of the human and mosquito populations that are infected. This is also how mosquito populations are treated in (Smith et al. 2004), where mosquitoes are assumed to move but humans are not. We will model space as a network of patches. We will use two different sorts of descriptions of movement. . One description identifies humans as resident in a given patch or belonging to a certain social group and assumes that that remain in that patch or group most of the time, but may visit other patches or groups often enough for pathogen transmission to occur there. In that case the infection rate for humans in a given class or location depends on the numbers of infectious vectors in other patches and the fraction of their time that individual humans spend in those patches but is not directly to an explicit description of human movement between classes or patches. This type of formulation has been used by (Dye and Hasibeder 1986, Hasibeder and Dye 1988, Rodriguez and Torres-Sorando 2001, Ruan et al.2006). This approach is related to the Lagrangian approach to modeling in fluid dynamics because it in effect labels individuals (by patch or class) and tracks what happens to them. A type of movement we envision this modeling approach as describing is where people and/or vectors are commuting between locations (or changing their activities) on a regularly scheduled basis, so that there is a well defined fraction of time that any given individual spends in any given location or state of activity. Another description is to assume that pathogen transmission to humans in a given class or patch occurs only within that class or patch but there is mobility between classes or patches that can be explicitly described via something like discrete diffusion. This type of approach has been used by (Allen et al. 2007, Arino and van den Driessche 2003, Arino et al. 2005, Dhirasakdanon et al. 2007, Hsieh et al. al. 2007, Liu et al. 2006, Smith et al. 2004, Wang and Mulone 2003, Wang and Zhao 2004, 2005). It is related to the Eulerian approach to modeling in fluid mechanics because it labels locations (or classes) and tracks what happens in them but does not distinguish individuals by residence, only by current location. A type of movement we envision this modeling approach as describing is migration from one location to another, because discrete diffusion explicitly describes such movement and can result in changes in the total number of individuals in a given patch, at least until a population

equilibrium is attained.. Sattenspiel and Dietz (1995) use a combined approach but do not consider vector-borne diseases. The models in (Dye and Hasibeder 1986, Hasibeder and Dye 1988, Rodriguez and Torres-Sorando 2001, Smith et al. 2004, Liu et al. 2006) describe various aspects of the transmission of vector-borne diseases in networks of patches or classes but are used to address specific questions that are different from those we will consider here.

2 Modeling Framework

2.1 A single-patch model

Within a single patch, we base our description of disease dynamics on the Ross-Macdonald type model of (Smith and McKenzie, 2004). Our notation is slightly different from theirs but our model is equivalent to theirs. The model assumes that human and mosquito populations are fixed but there is turnover in the mosquito population because of adult mortality. The state variables in the model are the proportions x and z of the human and mosquito populations respectively consisting of infectious individuals. The parameters in the model are as follows:

- a represents the human feeding rate of mosquitoes (number of bites on humans, per mosquito, per unit time),
- b represents the transmission efficiency from infected mosquitoes to humans,
- c represents the transmission efficiency from infected humans to mosquitoes,
- m represents the mortality rate of mosquitoes,
- r represents the recovery rate of humans,
- n represents the incubation period from the time a mosquito becomes infected until it becomes infectious,
- M represents the ratio of mosquitoes to humans.

In our notation the model is

$$\begin{aligned}\frac{dx}{dt} &= Mabz(1-x) - rx,\\ \frac{dz}{dt} &= abx(e^{-mn} - z) - mz.\end{aligned} \tag{2.1}$$

A detailed derivation of the model and a discussion of how the parameters can be related to data and various indices such as the human blood index (HBI) and entomological inoculation rate (EIR) is given by Smith and MacKenzie (2004). The term e^{-mn} in the equation for the proportion of infectious mosquitoes arises because the rate of mosquito turnover due to adult mortality is typically high enough that a significant fraction of infected mosquitoes can be expected to die before they become infectious.

We need to rewrite (2.1) in terms of populations rather than fractions of populations for our derivation of spatial models. In parts of the derivation we will want to consider the human and mosquito populations in each patch as variables that can change over time due to the movement of humans or mosquitoes. Furthermore, we will find it convenient to use the number of infected mosquitoes rather than the number of infectious mosquitoes as a state variable. To that end we introduce the following variables:

H represents the total human population,

X represents the number of infected humans,

V represents the total mosquito population,

Y represents the number of infected mosquitoes.

In a situation where H and V can vary, M will no longer be a constant parameter, but in any case $M = V/H$. In general, $X = xH$ and $e^{-mn}Y = zV$. Using those relations we can rewrite (2.1) as

$$\begin{aligned}\frac{dX}{dt} &= \frac{abe^{-mn}}{H}Y(H-X) - rX,\\ \frac{dy}{dt} &= \frac{ac}{H}X(V-Y) - mY.\end{aligned} \tag{2.2}$$

We will use the formulation in (2.2) to build our spatial models. In those models we will write parameters analogous to those appearing in (2.2) in condensed form, indexed by patch.

2.2 The spatial models

In our models models we will treat space as a network of connected patches. The patches (or nodes) typically will represent different geographical locales such as rural areas, villages, or city districts, but the same modeling approach could be used to describe networks of different groups within a population (schoolchildren, factory workers, night watchmen, etc.) We will examine models based on two different ways of describing the movement of humans and/or mosquitoes among the patches. In the first type of model we will label individuals as residents of a particular patch and describe their interactions with individuals from their own or other patches in terms of the rate of exposure to infection from residents of those patches. We will assume that individuals do not move permanently from their patch of residence to another patch, but may visit other patches. The rate at which individuals become infected will then depend upon the fraction of their time that they spend in each patch together with the transmission rates in those patches. We will sometimes refer to this approach as Lagrangian in that it labels and in some sense tracks individual humans or mosquitoes. In the second type of model we will assume that humans and mosquitoes can migrate between patches and thus do not have a specified patch of residence. The rate at which individuals become infected will depnd only on the patch where they are located. We will sometimes refer to this approach as Eulerian because we will track what happens in a given location (patch) rather than what happens to labeled individuals. The first or Lagrangian approach has been used in (Dye and Hasibeder 1986, Hasibeder and Dye 1988, Rodriguez and Torres-Sorando 2001, Ruan et al.2006). The second or Eulerian approach has been used in (Allen et al.2007, Arino and van den Driessche 2003, Arino et al. 2005, Dhirasakdanon et al. 2007, Hsieh et al. al. 2007, Liu et al. 2006, Smith et al. 2004, Wang and Mulone 2003, Wang and Zhao 2004, 2005). Models using a combination of these approaches have been used in Sattenspiel and Dietz (1995). Throughout our discussion we will use N to denote the total number of patches:

N represents the total number of patches in the network.

To formulate spatial models using the Lagrangian approach, we need to define transmission rates by averaging the rates across patches weighted

by the fraction of their time that individual spend in each patch. We will denote those as follows:

p_{ij} represents the fraction of time a human resident in patch i spends visiting patch j,

q_{ij} represents the fraction of time a mosquito resident in patch i spends visiting patch j.

Note that

$$\sum_{j=1}^{N} e_{ij} = \sum_{j=1}^{N} f_{ij} = 1.$$

Let $a_i, b_i, c_i, m_i, r_i, n_i, H_i, V_i$ denote the values of the parameters appearing in (2.2) in the case of the ith patch. Define

$$\begin{aligned} A_{ij} &= \frac{a_j b_j p_{ij} e^{-m_j n_j}}{H_j} \\ B_{ij} &= \frac{a_j c_j q_{ij}}{H_j}. \end{aligned} \tag{2.3}$$

Our Lagrangian models then have the form

$$\begin{aligned} \frac{dX_i}{dt} &= (\sum_{j=1}^{N} A_{ij} Y_j)(H_i - X_i) - r_i X_i, \\ \frac{dY_i}{dt} &= (\sum_{j=1}^{N} B_{ij} X_j)(V_i - Y_i) - m_i Y_i, \\ i &= 1, \ldots, N. \end{aligned} \tag{2.4}$$

It is clear that the set $\{(X_1, \ldots, X_N, Y_1, \ldots, Y_N) : 0 \leq X_i \leq H_i,\ 0 \leq Y_i \leq V_i,\ i = 1, \ldots, N\}$ is invariant for (2.4). We will always assume that $0 \leq X_i(0) \leq H_i$ and $0 \leq Y_i(0) \leq V_i$ for all i.

In some cases we may want to assume that the total vector populations in one or more of the patches are zero, so that the numbers of infected vectors in those patches are also zero (so there is no equation for the number of infected vectors in that patch) and thus some of the transmission terms in

(2.4) are zero since some of the variables Y_i are always zero. Such models can be cast in the form

$$\begin{aligned} \frac{dX_i}{dt} &= (\sum_{j=1}^{N_1} A_{ij}Y_j)(H_i - X_i) - r_i X_i \quad \text{for} \quad i = 1, \ldots, N \\ \frac{dY_i}{dt} &= (\sum_{j=1}^{N} B_{ij}X_j)(V_i - Y_i) - m_i Y_i \quad \text{for} \quad i = 1, \ldots, N_1 \end{aligned} \tag{2.4A}$$

where $N_1 < N$.

In deriving our Eulerian models we must address the issue that the total human and/or vector populations in a given patch might change sufficiently over time to affect the model. We will start by formulating a model where those populations are viewed as dynamic variables, but then we will make the assumption that those populations have come to the equilibrium predicted by the migration rates, at least relative to the the time scale on which we want to study the system. That will allow us to examine how vector-borne diseases might be propagated through populations that are distributed in space in situations where a migration pattern is relatively stable over time. It would be of interest to study transient effects, and even systems where migration rates can vary over time, but we will not do that in the present article. To derive Eulerian models we will initially use H_i and V_i to denote human and vector populations on the ith patch, but we will consider them as dynamic variables. We will use C_{ij} to denote the migration rate of humans from patch j to patch i and D_{ij} to denote the corresponding rate for vectors:

C_{ij} represents the rate of human migration from patch j to patch i,

D_{ij} represents the rate of vector migration from patch j to patch i

The movement model for migration then takes the form of a discrete diffusion:

$$\frac{dH_i}{dt} = \sum_{\substack{j=1 \\ j\neq i}}^{N} C_{ij}H_j - (\sum_{\substack{j=1 \\ j\neq i}}^{N} C_{ji})H_i,$$

$$\frac{dV_i}{dt} = \sum_{\substack{j=1 \\ j\neq i}}^{N} D_{ij}V_j - (\sum_{\substack{j=1 \\ j\neq i}}^{N} D_{ji})V_i, \tag{2.5}$$

$$i = 1, \ldots, N.$$

Define

$$C_{ii} = -\sum_{\substack{j=1 \\ j\neq i}}^{N} C_{ji}, \qquad D_{ii} = -\sum_{\substack{j=1 \\ j\neq i}}^{N} D_{ji}, \qquad i = 1, \ldots, N, \tag{2.6}$$

and

$$H = \sum_{i=1}^{N} H_i, \qquad V = \sum_{i=1}^{N} V_i.$$

By summing the equations forH_i in (2.5) we can see that $\frac{dH}{dt} = 0$, and similarly $\frac{dV}{dt} = 0$. Thus, $H(t) = H(0)$ and $V(t) = V(0)$. Also, $(1, \ldots, 1)((C_{ij})) = 0$, so zero is an eigenvalue of $((C_{ij}))$, and similarly for $((D_{ij}))$. Under an additional assumption of irreducibility, zero can be seen to be principal eigenvalue of $((C_{ij}))$ and $((D_{ij}))$ by the Perron-Frobenius theorem (because it has a positive left eigenvector), so it is simple and any other eigenvalue has real part less than zero. (See for example (Berman and Plemmons 1979,Graham 1987). Thus we have:

Lemma 1: Suppose that the matrix with off-diagonal entries C_{ij} and diagonal entries equal to 0 is irreducible. If $(H_1(t), \ldots, H_N(t))$ is a solution to the first system of equations in (2.5) with $H_i(0) \geq 0$ for $i = 1, \ldots, N$ and $H_i(0) > 0$ for some i, then $H_i(t) \to H_i^*$ as $t \to \infty$ for $i = 1, \ldots, N$, where $(H_1^*, \ldots, H_N^*)$ is the solution to

$$\sum_{j=1}^{N} C_{ij}H_j^* = 0, \quad \sum_{j=1}^{N} H_j^* = H(0). \tag{2.7}$$

(In other words, $(H_1^*, \ldots, H_N^*)^T$ is the right eigenvector of $((C_{ij}))$ corresponding to the eigenvalue 0 normalized so that its components sum to H(0).) Similarly, suppose that the matrix with off-diagonal entries D_{ij} and diagonal entries equal to 0 is irreducible. If $(V_1(t), \ldots, V_N(t))$ is a solution to the second system of equations in (2.5) with $V_i(0) \geq 0$ for $i = 1, \ldots, N$ and $V_i(0) > 0$ for some i, then $V_i(t) \to V_i^*$ as $t \to \infty$ for $i = 1, \ldots, N$, where $(V_1^*, \ldots, V_N^*)$ is the solution to

$$\sum_{j=1}^{N} D_{ij} V_j^* = 0, \quad \sum_{j=1}^{N} V_j^* = V(0). \tag{2.8}$$

Proof: See Appendix.

In formulating our Eulerian models we will assume that the migration process has reached a steady state, so that there may be exchange of individuals between patches but there is no net change in the total human or vector population in each patch. Thus, we will assume that $H_i(t) = H_i^*$ and $V_i(t) = V_i^*$with H_i^* and V_i^* are as in Lemma 1 for $i = 1, \ldots, N$. We will assume that disease transmission occurs only between individuals that are in the same patch at the same time. Let

$$\begin{aligned} A_i &= \frac{a_i b_i e^{-m_i n_i}}{H_i^*}, \\ B_i &= \frac{a_i c_i}{H_i^*}. \end{aligned} \tag{2.9}$$

Our Eulerian model with infected individuals present would take the form

$$\begin{aligned} \frac{dX_i}{dt} &= A_i Y_i (H_i^* - X_i) - r_i X_i + \sum_{\substack{j=1 \\ j \neq i}}^{N} C_{ij} X_j - (\sum_{\substack{j=1 \\ j \neq i}}^{N} C_{ji}) X_i, \\ \frac{dY_i}{dt} &= B_i X_i (V_i^* - Y_i) - m_i Y_i + \sum_{\substack{j=1 \\ j \neq i}}^{N} D_{ij} Y_j - (\sum_{\substack{j=1 \\ j \neq i}}^{N} D_{ji}) Y_i, \\ i &= 1, \ldots, N, \end{aligned} \tag{2.10}$$

It is clear from (2.7) and (2.8) that the set $\{(X_1, \ldots, X_N, Y_1, \ldots, Y_N) : 0 \leq X_i \leq H_i^*,\ 0 \leq Y_i \leq V_i^*,\ i = 1, \ldots, N\}$ is invariant for (2.10). We will always assume that $0 \leq X_i(0) \leq H_i^*$ and $0 \leq Y_i(0) \leq V_i^*$ for all i.

To address the issue of how diseases can be maintained in regions of low transmission by the movement of humans between regions of high and low transmission we again will want to consider cases where there are no vectors and thus no transmission in certain patches. Then (2.10) becomes

$$\frac{dX_i}{dt} = A_iY_i(H_i^* - X_i) - r_iX_i + \sum_{\substack{j=1\\j\neq i}}^{N} C_{ij}X_j - (\sum_{\substack{j=1\\j\neq i}}^{N} C_{ji})X_i \quad \text{for } i = 0,\ldots,N_1,$$

$$\frac{dX_i}{dt} = -r_iX_i + \sum_{\substack{j=1\\j\neq i}}^{N} C_{ij}X_j - (\sum_{\substack{j=1\\j\neq i}}^{N} C_{ji})X_i \qquad \text{for } i = N_1+1,\ldots,N,$$

$$\frac{dY_i}{dt} = B_iX_i(V_i^* - Y_i) - m_iY_i + \sum_{\substack{j=1\\j\neq i}}^{N_1} D_{ij}Y_j - (\sum_{\substack{j=1\\j\neq i}}^{N_1} D_{ji})Y_i \quad \text{for } i = 0,\ldots,N_1. \tag{2.10A}$$

where again as in (2.4A) we have $N_1 < N$.

It is natural to ask whether it is possible to translate models between the forms (2.4) and (2.10). Suppose we denote the number of infected human residents of patch i in (2.4) as X_i, that is, let the variables X_i correspond to the state variables for humans in (2.4). Denote the number of infected humans currently located in patch i as $\hat{X}_i$, that is, let the variables $\hat{X}_i$ correspond to the state variables for humans in (2.10). Similarly, denote the number of infected vector residents of patch i as Y_i and the number of infected vectors currently located in patch i as $\hat{Y}_i$. Since the infected humans currently in patch i could be from any patch, but human residents of patch j spend a fraction p_{ji} of their time in patch i, and similarly for vectors with p_{ji} replaced by q_{ji}, we should have

$$\hat{X}_i = \sum_{j=1}^{N} p_{ji}X_j \quad \text{and} \quad \hat{Y}_i = \sum_{j=1}^{N} q_{ji}Y_j.$$

Clearly we generally cannot solve this system unless the matrices $((p_{ji}))$ and $((q_{ij}))$ are invertible, but that need not be the case under the asumptions of our models. In cases where the matrices are invertible, the system resulting from translating the model (2.4) into a model with state variables X_i, Y_i into a system in terms of $\hat{X}_i, \hat{Y}_i$ is generally not of the form (2.10). Except in special cases where the amount of time individuals spend in patches other

than their patch of residence is small, it is not even approximately of the form (2.10). Thus, the two modeling formulations are not equivalent, although in some cases they might both be reasonable as approximate descriptions of a given system. Hence, we will want to analyze both types of models.

3 Analysis and Application of the Models

3.1 General properties

The models (2.4) and (2.10) are cooperative systems on the invariant sets $\{(X_1,\dots,X_N,Y_1,\dots,Y_N) : 0 \le X_i \le H_i,\ 0 \le Y_i \le V_i,\ i = 1,\dots,N\}$ and $\{(X_1,\dots,X_N,Y_1,\dots,Y_N) : 0 \le X_i \le H_i^*,\ 0 \le Y_i \le V_i^*,\ i = 1,\dots,N\}$ respectively, so they generate flows that are order preserving on those sets; see for example (Smith 1995). Since the models are epidemiological in character it is sensible to describe the stability or instability of the disease free equilibrium $X_i = Y_i = 0, i = 1,\dots,N$ in terms of a basic reproduction number R_0. That number can be computed by the methods of (van den Driessche and Watmough 2002). (Since the models describe vector-borne diseases that require the two-step process of a human transmitting the disease to a vector and the vector transmitting the disease to another human to achieve transmission from one human to another, some authors would consider the basic reproduction number for such models to be R_0^2 if R_0 were the value computed as in (van den Driessche and Watmough 2002). We will use that convention here. In the case of (2.4), a formula for R_0 and a description of the dynamics of the model were already obtained by Hasibeder and Dye (1988), partly on the basis of results of Lajmanovich and Yorke (1976). We will consider that case first. Throughout our discussion we will use $\rho(M)$ to denote the spectral radius of the matrix M. In some cases, for example if M is primitive, $\rho(M)$ will be the principal eigenvalue of M.

Theorem 1. (Hasibeder and Dye 1988): Let $\mathcal{A} = ((A_{ij}H_i/m_j))$, $\mathcal{B} = ((B_{ij}V_i/r_j))$, where the entries in $\mathcal{A}$ and $\mathcal{B}$ are taken from (2.4). Assume that the matrices $\mathcal{A}, \mathcal{B}$ are irreducible. Then for (2.4) we may take $R_0^2 = \rho(\mathcal{A}\mathcal{B})$. If $R_0 < 1$ then the disease-free equilibrium in (2.4) is stable while if $R_0 > 1$ it is unstable. If the disease-free equilibrium in (2.4) is stable then there is no positive equilibrium and the disease-free equilibrium is globally stable among nonnegative solutions. If the disease-free equilibrium is unstable there is a unique positive equilibrium which is globally stable among positive solutions.

Remarks: It follows from the theory of monotone dynamical systems that in the case of Theorem 1 where the disease-free equilibrium is unstable there will be a monotone trajectory connecting the disease-free equilibrium to the positive equilibrium; see (Smith 1995). Furthermore $(H_1, \ldots, H_N, V_1, \ldots, V_N)$ is a supersolution to the equilibrium problem for (2.4) so a a solution of (2.4) with that initial data will decrease toward an equilibrium. Thus, when it exists, the positive equilibrium is globally stable in the set $\{(X_1, \ldots, X_N, Y_1, \ldots, Y_N) : 0 \leq X_i \leq H_i,\ 0 \leq Y_i \leq V_i,\ i = 1, \ldots, N\}$. It follows from the structure of $\mathcal{A}$ and $\mathcal{B}$ that if one of the parameters A_{ij}, B_{ij}, H_i, or V_i is increased then R_0 will increase but if r_i or m_i is increased then R_0 will decrease. This is sensible biologically since increasing transmission rates or the initial number of susceptible individuals typically increase R_0 while increasing recovery or mortality rates decrease typically decrease it.

Theorem 2. Consider the system (2.10) restricted to the invariant region $\{(X_1, \ldots, X_N, Y_1, \ldots, Y_N) : 0 \leq X_i \leq H_i^*,\ 0 \leq Y_i \leq V_i^*,\ i = 1, \ldots, N\}$. Let $C = ((C_{ij}))$ and $D = ((D_{ij}))$. Let $\mathcal{A}^* = ((A_i H_i^* \delta_{ij})), \mathcal{B}^* = ((B_i M_i^* \delta_{ij}))$, $\mathcal{C}^* = ((C_{ij} - r_i \delta_{ij}))$, and $\mathcal{D}^* = ((D_{ij} - m_i \delta_{ij}))$, where δ_{ij} is the Kronecker delta. Assume that the matrices C and D are irreducible. Then for (2.10) we may take $R_0^2 = \rho(\mathcal{A}^* \mathcal{D}^{*-1} \mathcal{B}^* \mathcal{C}^{*-1})$. If $R_0 < 1$ then the disease-free equilibrium in (2.10) is stable while if $R_0 > 1$ it is unstable. If the disease-free equilibrium in (2.10) is stable then there is no positive equilibrium and the disease-free equilibrium is globally stable among nonnegative solutions. If the disease-free equilibrium is unstable there is a unique positive equilibrium which is globally stable among positive solutions.

Proof: See Appendix.

Remarks: The proof for Theorem 2 could be adapted to give an alternate proof of Theorem 1. A related result giving a similar formula for R_0 in a discrete-diffusion type model for a disease with direct transmission in a patchy environment was obtained by Dhirasakdanon et al. (2007). The proof of Theorem 2 shows that the matrix $\mathcal{A}^* \mathcal{D}^{*-1} \mathcal{B}^* \mathcal{C}^{*-1}$ is nonnegative. Increasing the transmission rates and populations A_i, B_i, H_i^* or V_i^* will increase some of its entries and thus R_0 will be monotone increasing in those parameters. In the proof of Theorem 2 it is also shown that the matrices $-\mathcal{C}^* = -C + ((r_i \delta_{ij}))$ and $-\mathcal{D}^* = -D + ((m_i \delta_{ij}))$ are nonsingular M-matrices . It follows that they are invertible with nonnegative inverses (see Berman and Plemmons 1979). To see how their entries depend on $r_i$and m_i, suppose

that $R_i > 0$ for $i = 1, \ldots, N$ and observe that

$$[-C + ((R_i\delta_{ij}))]^{-1} - [-C + ((r_i\delta_{ij}))]^{-1} = \\ [-C + ((R_i\delta_{ij}))]^{-1}(([r_i - R_i]\delta_{ij}))[-C + ((r_i\delta_{ij}))]^{-1} \quad .$$

Hence, if $r_i \geq R_i$ for all i then $[-C + ((R_i\delta_{ij}))]^{-1} - [-C + ((r_i\delta_{ij}))]^{-1}$is nonnegative. Thus, the entries in $\mathcal{A}^*\mathcal{D}^{*-1}\mathcal{B}^*\mathcal{C}^{*-1} = \mathcal{A}^*(-\mathcal{D}^{*-1})\mathcal{B}^*(-\mathcal{C}^{*-1})$ are monotone decreasing with respect to the recovery rates r_i. Similarly, they are also monotone decreasing with respect to the mortality rates m_i. It follows that $\rho(\mathcal{A}^*\mathcal{D}^{*-1}\mathcal{B}^*\mathcal{C}^{*-1})$ and hence R_0 are monotone decreasing in those parameters. The dependence on the movement rates C_{ij}, D_{ij} is more subtle in general but sometimes can be determined in particular cases. We will return to that point later.

The analysis used to prove Theorems 1 and 2 also applies to models such as (2.4A) and (2.10A) where vectors are present only in some patches and the equations for the infected vectors in the patches where vectors are absent are dropped from the model. In such cases the dimensions of the matrices $\mathcal{A}$ or $\mathcal{A}^*$ will be different from those of $\mathcal{B}$ or $\mathcal{B}^*$ so the short formulations for R_0 given in those theorems cannot be used; however, we can still compute R_0 as the spectral radius of an appropriate matrix by using the methods of (van den Driessche and Watmough 2002), or perhaps directly, and the arguments for the existence and uniqueness, or nonexistence, of a positive equilibrium are unchanged. In particular, for (2.4A) we can define the matrices $\mathcal{A}$ and $\mathcal{B}$ as in Theorem 1, except that $\mathcal{A}$ is $N \times N_1$ and $\mathcal{B}$ is $N_1 \times N$; then the results of (van den Driessche and Watmough 2002) imply that

$$R_0 = \rho \begin{pmatrix} 0 & \mathcal{A} \\ \mathcal{B} & 0 \end{pmatrix}. \tag{3.1}$$

For (2.10A) we can define the entries in $\mathcal{A}^*$, $\mathcal{B}^*$, $\mathcal{C}^*$, and $\mathcal{D}^*$ as before, but with $\mathcal{A}^*$, $\mathcal{B}^*$, and $\mathcal{D}^*$ now being $N_1 \times N_1$ matrices. Define the $N \times N$ matrix $\hat{\mathcal{A}}^*$ by

$$\hat{\mathcal{A}}^* = \begin{pmatrix} 0 & \mathcal{A}^* \\ 0 & 0 \end{pmatrix}. \tag{3.2}$$

We can then compute R_0 by the methods of (van den Driessche and Watmough 2002) as

$$R_0 = \rho \left[\begin{pmatrix} 0 & \hat{\mathcal{A}}^* \\ \mathcal{B}^* & 0 \end{pmatrix} \begin{pmatrix} -\mathcal{C}^* & 0 \\ 0 & -\mathcal{D}^* \end{pmatrix}^{-1} \right]. \tag{3.3}$$

3.2 Two-patch models with no transmission in one patch

To understand how movement between patches might sustain infection in patches with no transmission we will study models with two patches but with transmission only in one patch. We will denote the patch with no transmission as patch number 2. We will assume that there is no movement of vectors between patches, so that there are no infected vectors in patch number 2, that is, $Y_2 = 0$. Since $Y_2 = 0$ we omit the equation for Y_2 from the models.

The first such model we will consider has the form (2.4A) with $N = 2$ and $N_1 = 1$, that is

$$\begin{aligned}
\frac{dX_1}{dt} &= A_{11}Y_1(H_1 - X_1) - r_1X_1 \\
\frac{dX_2}{dt} &= A_{21}Y_1(H_2 - X_2) - r_2X_2 \\
\frac{dY_1}{dt} &= (B_{11}X_1 + B_{12}X_2)(V_1 - Y_1) - m_1Y_1.
\end{aligned} \tag{3.4}$$

Computing R_0 by the method of van den Driessche and Watmough (2002) as described in the previous subsection yields

$$R_0^2 = \frac{A_{11}B_{11}H_1V_1}{r_1m_1} + \frac{A_{21}B_{12}H_2V_1}{r_2m_1}. \tag{3.5}$$

The first term on the right in (3.5) is the value of R_0^2 that would result if patch number 1 were isolated. Note that it is possible to have that value less than 1, so that the disease would not persist in patch number 1 in the absence of patch number 2, but still have $R_0^2 > 1$ in (3.5). If $R_0 > 1$ in (3.5) then (3.4) has a unique positive equilibrium (X_1^*, X_2^*, Y_1^*) that is globally stable among positive solutions.

Suppose that $R_0 > 1$ in (3.5). The components X_1^* and X_2^* satisfy

$$X_1^* = \frac{A_{11}H_1Y_1^*}{A_{11}Y_1^* + r_1}, \qquad X_2^* = \frac{A_{21}H_2Y_1^*}{A_{21}Y_1^* + r_2}. \tag{3.6}$$

The component Y_1^* satisfies

$$\frac{A_{11}B_{11}H_1V_1}{A_{11}Y_1^* + r_1} + \frac{A_{21}B_{12}H_2V_1}{A_{21}Y_1^* + r_2} = \frac{m_1}{V_1 - Y_1^*}. \tag{3.7}$$

It is possible to compute Y_1^* explicitly by solving (3.7), but that yields a quadratic equation with coefficients depending on the parameters of the

model in a complicated way, so the result is not very illuminating. For our purposes we can obtain reasonably satisfactory results by making some simple observations and estimates.

If $A_{11}B_{11}H_1V_1/r_1m_1 > 1$ so that the disease could persist in patch 1 if that patch were isolated, then it follows from the form of (3.7) that $Y_1^* \geq Y_1^{**}$ where Y_1^{**} is the equilibrium that would result if patch number 1 were isolated (equivalently if the second term on the left were dropped from (3.7)). We would then have

$$Y_1^* \geq Y_1^{**} = \frac{A_{11}B_{11}H_1V_1 - r_1m_1}{A_{11}(B_{11}H_1 + m_1)}, \tag{3.8}$$

which yields a lower bound on X_2^* in (3.6). However, our primary interest is in comparing X_1^* and X_2^*.

Suppose that $p_{11}/p_{21} \geq r_1/r_2$. (Recall that p_{ij} denotes the fraction of his or her time that a human resident of patch i spends in patch j, so if $r_1 = r_2$ this assumption would mean that residents of patch 1 spend a larger fraction of their time in patch 1 than do residents of patch 2, which is reasonable.) By (2.3) we then have $A_{11}Y_1^*/r_1 \geq A_{21}Y_1^*/r_2$. In that case it follows from (2.3) and (3.6) that

$$\frac{X_2^*}{X_1^*} = \frac{A_{21}H_2}{A_{21}Y^* + r_2} \cdot \frac{A_{11}Y_1^* + r_1}{A_{11}H_1} \geq \frac{A_{21}H_2r_1}{A_{11}H_1r_2} = \frac{p_{21}H_2r_1}{p_{11}H_1r_2}. \tag{3.9}$$

If the human populations and recovery rates are equal in the two patches then the last expression in (3.7) reduces to the ratio of the fractions of time spent in patch 1 by residents of patch 2 and patch 1 respectively. In any case, the model predicts that disease can indeed be maintained in patch 2 without transmission there, at a level that is proportional to the fraction of their time that residents of patch 2 spend in patch 1 relative to residents of patch 1.

Next we consider the case of models of the form (2.10A), again with transmission only in patch 1, and no movement of mosquitoes between patches, so that we do not include an equation for infected vectors in patch 2. This leads to models of the form

$$\begin{aligned}
\frac{dX_1}{dt} &= A_1Y_1(H_1^* - X_1) - r_1X_1 + C_{12}X_2 - C_{21}X_1, \\
\frac{dX_2}{dt} &= C_{21}X_1 - C_{12}X_2 - r_2X_2 \\
\frac{dY_1}{dt} &= B_1X_1(V_1^* - Y_1) - m_1Y_1.
\end{aligned} \tag{3.10}$$

In this case R_0 is given by

$$R_0^2 = \frac{A_1 B_1 H_1^* V_1^*}{m_1} \cdot \frac{C_{12} + r_2}{C_{12} r_1 + C_{21} r_2 + r_1 r_2}, \tag{3.11}$$

with coefficients as in (2.7)-(2.9). Note that $H_1^* \leq H(0)$ where $H(0)$ is the total initial human population in the two patches, so that if C_{21} is sufficiently large we will have $R_0 < 1$ in (3.11). Recall that the parameter C_{21} represents the rate of migration from the patch with transmission to the patch without transmission. Thus, a sufficiently high rate of migration from the patch with transmission into the patch without it can cause the disease to be eliminated. A similar observation was made in (Hsieh et al. 2007) for diseases that are directly transmitted between humans.

For $R_0 > 1$ in (3.11) the equilibrium (X_1^*, X_2^*, Y_1^*) of (3.10) satisfies

$$\begin{aligned} X_2^* &= \frac{C_{21} X_1^*}{C_{12} + r_2} \\ Y_1^* &= \frac{B_1 V_1^* X_1^*}{B_1 X_1^* + m_1} \\ X_1^* &= \frac{A_1 B_1 V_1^* H_1^* - Q m_1}{B_1 (A_1 V_1^* + Q)} = \frac{(R_0^2 - 1) Q m_1}{B_1 (A_1 V_1^* + Q)}, \end{aligned} \tag{3.12}$$

where

$$Q = \frac{C_{12} r_1 + C - 21 r_2 + r_1 r_2}{C_{12} + r_2}.$$

It is clear from the first equation in (3.12) that if the rates of migration as reflected by the size of the coefficients C_{12} and C_{21} are comparable to the recovery rate in patch 2 then disease can be sustained in patch 2 even though there is no transmission in that patch.

4 Conclusions

The models in (2.4),(2.4A), (2.10), (2.10A) describe vector borne disease systems on networks of patches. Those patches can reflect physical locations, socio-economic-behavioral classes, or other features that distinguish subpopulations of people or vectors. The models include terms describing the movement of humans and vectors between patches. The models can be parameterized in terms of coefficients that have clear biological interpretations and which in principle could be measured. The analysis shows that

the models are cooperative systems with simple dynamics. They predict that either the disease will disappear or that it will become established at a unique stable equilibrium, depending on the parameters. Which of these two possibilities will actually occur will depend on the basic reproduction number R_0, which is well defined for the models. The value of R_0 for any of the models can be characterized as the spectral radius of an associated matrix and can be explicitly calculated in simple cases. Analysis of models with two patches but with disease transmission only in one patch shows that if there is sufficient movement of humans between patches the disease can be sustained in the patch with no transmission. This suggests that a possible explanation for observations that vector borne diseases persist in some patches where mosquito densities and hence disease transmission rates are very low is that there is either immigration of humans from patches with higher transmission or that humans residing in patches with low transmission commute to patches with high transmission. The strength of those effects depend on the rate of migration or the fraction of time spent by commuters in patches with high transmission rates.

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Appendix

Proof of Lemma 1:
Choose $c_0 > max\{-C_{ii} : i = 1 \ldots N\}$. The matrix $((C_{ij}))+c_0 I$ is irreducible with positive diagonal elements, so it is primitive (see Graham 1987, pps. 137-138) and hence the Perron-Frobenius theorem applies to it. It follows that $((C_{ij})) + c_0 I$ has a principal eigenvalue characterized by having a positive eigenvector, and all other eigenvalues have real parts smaller than that principal eigenvalue. By the definition of the entries C_{ii}, the vector $(1, \ldots, 1)$ is a left eigenvector of $((C_{ij})) + c_0 I$ corresponding to the eigenvalue c_0, so c_0 must be the principal eigenvalue of $((C_{ij})) + c_0 I$. Since every eigenvalue of $((C_{ij}))$ is equal to $\lambda - c_0$, where λ is an eigenvalue of $((C_{ij})) + c_0 I$, it follows that 0 is an eigenvalue of $((C_{ij}))$ with positive left and right eigenvectors and that all other eigenvalues of $((C_{ij}))$must have real parts less than zero. Any nonnegative nontrivial initial data $(H_1(0), \ldots, H_N(0))$ will have a positive component in the direction of the right eigenvector $(H_1^*, \ldots, H_N^*)$ corresponding to the eigenvalue 0 of $((C_{ij}))$. Since all other eigenvalues of $((C_{ij}))$ have negative real parts and $H(t) = \sum_{i=1}^{N} H_i(t) = H(0)$, the conclusion of the lemma follows for $(H_1, \ldots, H_N)$. The proof for $(V_1, \ldots, V_N)$ is the same.

Proof of Theorem 2:
The proof will make use of results and ideas from (van den Driessche and Watmough 2002) as well as some other results on matrices and monotone dynamical systems. We will briefly review the key ideas from (van den Driessche and Watmough 2002) as they apply in this context. The models treated by van den Driessche and Watmough (2002) are formulated as

$$\frac{dx_i}{dt} = f_i(x_i) = \mathcal{F}_i(x) - \mathcal{V}_i(x) \qquad (A.1)$$

where $x = (x_1, \ldots, x_n$, $\mathcal{F}_i$ is the rate at which new infections occur in compartment i and $-\mathcal{V}_i$ is the rate of movement of individuals into or out of that compartment by other means. The rate $\mathcal{V}_i$ is broken down further as $\mathcal{V}_i = \mathcal{V}_i^+ - \mathcal{V}_i^-$ where $\mathcal{V}_i^+, \mathcal{V}_i^-$ are rates of individuals entering and leaving compartment i respectively. The linearizations of $\mathcal{F}$ and $\mathcal{V}$ at the disease free equilibrium are denoted by F and V repectively. In our situation, $n = 2N$ and each compartment describes the number of infected humans or vectors on one of the N patches. All compartments contain only infected individuals. We have $x = (X_1, \ldots, X_N, Y_1, \ldots Y_N)$. Then $\mathcal{F}_i(x) = A_i Y_i(H_i^* - X_i)$ for $i = 1, \ldots, N$

and $\mathcal{F}_i(x) = B_{i-N}X_{i-N}(V^*_{i-N} - Y_{i-N})$ for $i = N+1, \ldots, 2N$; $\mathcal{V}_i^+ = \sum_{\substack{j=1 \\ j\neq i}}^{N} C_{ij}X_j$ for $i = 1, \ldots, N$ and $\mathcal{V}_i^+ = \sum_{\substack{j=1 \\ j\neq i-N}}^{N} D_{(i-N)j}Y_j$ for $i = N+1, \ldots, 2N$; and $\mathcal{V}_i^- = (r_i + (\sum_{\substack{j=1 \\ j\neq i}}^{N} C_{ji}))X_i$ for $i = 1 \ldots N$ and $\mathcal{V}_i^- = (m_{i-N} + (\sum_{\substack{j=1 \\ j\neq i-N}}^{N} D_{j(i-N)}))Y_{i-N}$ for $i = N+1, \ldots, 2N$. The disease-free equilibrium in our models is $(0, \ldots, 0)$. The hypotheses A1-A4 of (van den Driessche and Watmough 2002) can be readily verified, at least for (X, Y) in the invariant region $\{(X_1, \ldots, X_N, Y_1, \ldots, Y_N) : 0 \leq X_i \leq H_i^*,\ 0 \leq Y_i \leq V_i^*,\ i = 1, \ldots, N\}$, from the forms of $\mathcal{F}$ and $\mathcal{V}$. The key hypothesis (A5) of (van den Driessche and Watmough 2002) is that if $\mathcal{F}$ is set to zero then all the eigenvalues of the Jacobian of what remains in $f(x)$ evaluated at the disease-free equilibrium have negative real parts. In our case the eigenvalues in question are those of $-V$. The matrix V consists of two$N \times N$ blocks on the diagonal and zeroes elsewhere. The blocks are $((C_{ij} - r_i\delta_{ij}))$ and $((D_{ij} - m_i\delta_{ij}))$ where δ_{ij} is the Kronecker delta. Let $C = ((C_{ij}))$. It follows as in the proof of Lemma 1 that $C - ((r_i\delta_{ij}))$ has an eigenvalue σ_0 that is real, characterized by having a positive eigenvector $\vec{\phi}$, and is larger than the real part of any other eigenvalue of $C - ((r_i\delta_{ij}))$. Let $r_0 = min\{r_i : i = 1, \ldots, N\}$. We have $([C - ((r_i\delta_{ij})]\vec{\phi})_i = \sigma_0\phi_i$ so that $(C\vec{\phi})_i = (r_i + \sigma_0)\vec{\phi}$, so componentwise $C\vec{\phi} \geq (r_0 + \sigma_0)\vec{\phi}$. It follows from Lemma 2 of (Cosner et al. 2007) that C has a real eigenvalue greater than or equal to $r_0 + \sigma_0$ with nonegative nonzero eigenvector. If $r_0 + \sigma_0 > 0$ that would contradict the fact that 0 is the eigenvalue of C with largest real part, as established in the proof of Lemma 1. It follows that we must have $\sigma_0 \leq -r_0 < 0$ so the eigenvalues of $C - ((r_i\delta_{ij}))$ must all have negative real parts, as required. (It then follows from (Berman and Plemmons 1979, p.135, G_{20} that $-C + ((r_i\delta_{ij}))$ is a nonsingular M-matrix.) A similar analysis yields the corresponding conclusion for $-D + ((m_i\delta_{ij}))$. Thus, Lemma 1 and Theorem 2 of (van den Driessche and Watmough 2002) apply to our model (2.10). In particular, V is a nonsingular M-matrix, and the basic reproduction number is the spectral radius of FV^{-1}, that is, $R_0 = \rho(FV^{-1})$. Using $\mathcal{A}^* = ((A_iH_i^*\delta ij)), \mathcal{B}^* = ((B_iM_i^*\delta ij)), \mathcal{C}^* = ((C_{ij} - r_i\delta_{ij}))$, and $\mathcal{D}^* = ((D_{ij} - m_i\delta_{ij}))$, we have that

$$F = \begin{pmatrix} 0 & \mathcal{A}^* \\ \mathcal{B}^* & 0 \end{pmatrix} \tag{A.2}$$

and

$$V = \begin{pmatrix} -\mathcal{C}^* & 0 \\ 0 & -\mathcal{D}^* \end{pmatrix}. \tag{A.3}$$

It follows that

$$FV^{-1} = \begin{pmatrix} 0 & -\mathcal{A}^*\mathcal{D}^{*-1} \\ -\mathcal{B}^*\mathcal{C}^{*-1} & 0 \end{pmatrix}. \tag{A.4}$$

To obtain a formulation analogous to that given by Hasibeder and Dye (1988) and quoted in Theorem 1, observe that

$$(FV^{-1})^2 = \begin{pmatrix} \mathcal{A}^*\mathcal{D}^{*-1}\mathcal{B}^*\mathcal{C}^{*-1} & 0 \\ 0 & \mathcal{B}^*\mathcal{C}^{*-1}\mathcal{A}^*\mathcal{D}^{*-1} \end{pmatrix}, \tag{A.5}$$

so that $R_0^2 = \rho(\mathcal{A}^*\mathcal{D}^{*-1}\mathcal{B}^*\mathcal{C}^{*-1})$.

If $R_0 > 1$ then the disease-free equilibrium is unstable. The Jacobian of linearization of the model (2.10) around the disease-free equilibrium is $J = F - V$. Again, the proof of Lemma 1 implies that $F - V$ has a principal eigenvalue σ_0 that is real, larger than the real part of any other eigenvalue, and which has a positive eigenvector. In the case where (0,...,0) is unstable, we have $\sigma_0 > 0$. It is easy to see that in that case that if $\vec{\psi}$ is a positive eigenvector for σ_0 then for the model (2.10) written in the notation of (A.1) we have$f_i(\epsilon\vec{\psi}) > 0$ for all i as long as $\epsilon > 0$ is sufficiently small. It then follows by the order preserving property of (2.10) that a solution to (2.10) with initial data $\epsilon\vec{\psi}$ will increase componentwise toward an equilibrium $(X^*, Y^*) = (X_1^*, \ldots, X_N^*, Y_1^*, \ldots, Y_N^*)$ of (2.10) that is the minimal positive equilibrium of (2.10) in the invariant set $\{(X_1, \ldots, X_N, Y_1, \ldots, Y_N) : 0 \le X_i \le H_i^*,\ 0 \le Y_i \le V_i^*,\ i = 1, \ldots, N\}$. (See (Cantrell and Cosner 2003, section 3.6, for further discussion and references.) Similarly, if we let $\vec{\xi} = (H_1^*, \ldots, H_N^*, V_1^*, \ldots, V_N^*)$ we have $f_i(\vec{\xi}) < 0$ for all i, so that the solution to (2.10) with initial data $\vec{\xi}$ will decrease componentwise toward an equilibrium (X^{**}, Y^{**}) that is the maximal equilibrium of (2.10) in the invariant set $\{(X_1, \ldots, X_N, Y_1, \ldots, Y_N) : 0 \le X_i \le H_i^*,\ 0 \le Y_i \le V_i^*,\ i = 1, \ldots, N\}$.

The equilibrium (X^*, Y^*) (and any other positive equilibrium) must satisfy

$$\begin{pmatrix} \mathcal{C}^* & ((A_i(H_i^* - X_i^*)\delta_{ij})) \\ ((B_i(V_i^* - Y_i^*)\delta_{ij})) & \mathcal{D}^* \end{pmatrix} \begin{pmatrix} X^* \\ Y^* \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}. \tag{A.6}$$

In the invariant region for (2.10) the off-diagonal terms in the matrix in (A.6) are nonnegative, and the matrices $\mathcal{C}^*, \mathcal{D}^*$ are irreducible, so again as

in the proof of Lemma 1 the matrix in (A.6) has a principal eigenvalue that is characterized by having a positive eigenvector. In this case $(X^*, Y^*)^T$ is the eigenvector and the eigenvalue is 0. For any other positive equilibrium (X^{***}, Y^{***}) the relation analogous to (A.6) with (X^*, Y^*) replaced by (X^{***}, Y^{***}) would necessarily hold, implying that the matrix

$$\begin{pmatrix} \mathcal{C}^* & ((A_i(H_i^* - X_i^{***})\delta_{ij})) \\ ((B_i(V_i^* - Y_i^{***})\delta_{ij})) & \mathcal{D}^* \end{pmatrix} \qquad (A.7)$$

would also have principal eigenvalue 0. However, unless $(X^*, Y^*) = (X^{***}, Y^{***})$ that is impossible because the principal eigenvalue is increasing relative to the entries of the matrix. Hence the minimal equilibrium (X^*, Y^*) must be the unique equilibrium. (This proof is entirely analogous to that of the corresponding result in continuous space as in (Cantrell and Cosner 2003, Proposition 3.3). In particular, the minimal and maximal equilibria must be the same, so that the unique positive equilibrium is globally stable for solutions of (2.10) with positive initial data in the invariant set $\{(X_1, \ldots, X_N, Y_1, \ldots, Y_N) : 0 \leq X_i \leq H_i^*,\ 0 \leq Y_i \leq V_i^*,\ i = 1, \ldots, N\}$.

If $R_0 < 1$ then the disease-free equilibrium is stable and the principal eigenvalue σ_0 of the Jacobian of linearization of the model (2.10) around the disease-free equilibrium is negative. It follows that since the entries of the matrix in (A.7) at any positive equilibrium (X^{***}, Y^{***}) are less than or equal to those of the linearization around the disease free equilibrium $(0, \ldots, 0)$, the matrix in (A.7) also must have a principal eigenvalue that is negative. On the other hand, any positive equilibrium (X^{***}, Y^{***}) must satisfy (A.6) with (X^*, Y^*) replaced by (X^{***}, Y^{***}), so if such an equilibrium exists then the principal eigenvalue of the matrix in (A.7) must be zero, which is a contradiction. Thus, there can be no positive equilibrium, so the solution to (2.10) with initial data $\vec{\xi}$ will decrease toward the disease-free equilibrium. It then follows from the order preserving property of the system that the disease free equilibrium is globally stable in the invariant set $\{(X_1, \ldots, X_N, Y_1, \ldots, Y_N) : 0 \leq X_i \leq H_i^*,\ 0 \leq Y_i \leq V_i^*,\ i = 1, \ldots, N\}$.