Abstract

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Mathematical models are useful tools for understanding disease dynamics, but often assume a “well-mixed” population. In reality, populations usually violate this assumption, exhibiting heterogeneous mixing. Spatial structure is one mechanism that creates heterogeneous mixing by limiting the number of possible contacts. One-pathogen models show that inclusion of spatial structure decreases the prevalence of infection. In this paper, we extend spatial models to a two-pathogen system based on cereal and barley yellow dwarf viruses (C/BYDVs). By comparing the spatial model to a nonspatial model, we can determine how prevalence of coinfection and single infection changes with localized pathogen transmission. The model predicts that when pathogens do not interact within hosts, coinfection decreases as pathogen transmission becomes increasingly localized. Spatial aggregation of the pathogens explains this result. We also examine a model with decreased transmission due to cross-protection, a model with increased transmission due to synergism, and a model with increased host mortality due to synergism. Most notably, when hosts infected by multiple pathogens experience greater mortality than singly infected hosts, localized pathogen transmission makes pathogen persistence more likely. Thus, these models predict that overall pathogen diversity should be greater when pathogens are transmitted locally.
Spatial Dynamics of Infection by Multiple Pathogens: A Case Study with Yellow Dwarf Viruses

by
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A thesis submitted to the Graduate Faculty of North Carolina State University in partial fulfillment of the requirements for the Degree of Master of Science in Biomathematics

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Biography

Rebecca was raised in northern Virginia, where she graduated from Oakton High School in 2004. She proceeded to St. Mary’s College of Maryland where she began as a psychology major. Quickly she learned that her true passions were mathematics and biology. After her junior year of college, Rebecca participated in a mathematical biology Research Experience for Undergraduates at Penn State Erie, The Behrend College. The internship opened up to her the world of research in mathematical modeling and taught her about graduate programs in biomathematics. After graduating from St. Mary’s College of Maryland with a double major in mathematics and biology, Rebecca continued to North Carolina State University where she received a Masters of Science degree in Biomathematics.
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Introduction

1. Overview

Mathematical models are useful tools for understanding disease dynamics. They allow us to explore questions about topics such as pathogen transmission, virulence, disease prevalence, and infectiousness. The classic epidemic models function on the assumption of a “well-mixed” population in which all individuals are equally likely to come into contact with each other (Bailey 1975; Boylan 1991; Brauer 2008; Brown and Bolker 2004; Lefevre 1983). However, real populations often violate this assumption through individual differences, such as differences in susceptibility, infectiousness, behaviors, and number of contacts (Brauer 2008; Boylan 1991; Lefevre 1983). Here, we will focus on the effects of spatial structure created by heterogeneous mixing.

The spatial structure of a host population affects the dynamics of diseases spread through contact. When spatial structure is considered, the path of the disease becomes limited. Hosts close to an infected individual are at high risk for infection whereas hosts far away have little chance of becoming infected (Tildesley et al. 2010). This limits the number of susceptible hosts that the disease can reach, affecting the total number of individuals that could potentially become infected (Brown and Bolker 2004; Keeling 1999; Tildesley et al. 2010). To explore the extent to which spatial structure changes disease dynamics, epidemic models can be used to make comparisons between a spatial and a nonspatial structure.
Mathematical models for one-pathogen systems have provided a good basis for studying the differences between spatial and nonspatial structures, but multiple pathogens are often capable of inhabiting a single host organism at the same time, creating a more complex system (Seabloom et al. 2009). This system adds pathogen interactions as a factor in determining disease dynamics, which brings up new questions. Can the pathogens coexist and under what conditions? Does the presence of multiple pathogens increase infection prevalence? Does the presence of multiple pathogens increase host mortality? These are only some of the questions of concern for a system with multiple pathogens.

These questions arise in many biological systems, including the system involving cereal and barley yellow dwarf viruses (C/BYDV) and the host plants infected by C/BYDVs. C/BYDVs exist as at least five different species, which can coinfect grasses in the family Poaceae including cereal crops like barley and wheat (Miller and Rasochova 1997; D’Arcy 1995). Depending on the combination, C/BYDV species exhibit cross protection, where one pathogen prevents infection by another, and synergism, where pathogen interaction increases transmission or virulence (Miller and Rasochova 1997). Some symptoms of C/BYDVs include growth reduction, yellowing, and sterility, which can lead to yield reduction and significant agricultural losses (Miller and Rasochova 1997; Jensen and D’Arcy 1995; Lister and Ranieri 1995). C/BYDVs are obligately transmitted by both winged and wingless aphids (Halbert and Voegtlin 1995; Seabloom et al. 2009). In modeling C/BYDV dynamics, a spatial model can be used to describe the
limited movement of wingless aphids while a nonspatial model can describe the wider range of movement by winged aphids (Chaussalet et al. 2000).

In this paper, we will focus on exploring the effect of spatial structure on coinfection dynamics by using extensions of the well-known susceptible-infected (SI) model. Specifically, we will apply a two-pathogen, one-host model to C/BYDV to ask the following questions. 1. Does spatial structure affect the number of coinfected hosts relative to a well-mixed population? 2. Could pathogen clustering in the spatial model be responsible for a change in the number of coinfected hosts? 3. How does spatial structure affect disease dynamics when pathogens exhibit cross-protection, that is, when infection by one pathogen reduces the possibility of infection by a second pathogen? 4. How does spatial structure affect disease dynamics when pathogens exhibit synergism in the form of increased transmission? 5. How does spatial structure affect disease dynamics when pathogens exhibit synergism in the form of increased mortality? We will explore each of these questions with mathematical models and computer simulations.


Many mathematical models assume a “well-mixed” population, making them simpler and easier to analyze. However, most real populations do not follow this assumption, so the methods for analyzing nonspatial models are being expanded to assess more complicated spatial models. Here we discuss some of the mathematical tools used to analyze nonspatial and spatial models.
2.1 Tools for Nonspatial Models

A deterministic ordinary differential equation (ODE) model is one of the simplest methods for analyzing disease dynamics under the assumption of a “well-mixed” population. The ordinary differential equations can be analyzed to give us information about the number of individuals in each state, the stability of the infection, the possibility of an outbreak, and more (Kermack and McKendrick 1932). However, an ODE model always gives the same results for a given set of initial conditions, which is unrealistic for an actual population. Real populations usually exhibit more variation than these deterministic models account for, so these models can be expanded to include stochastic events.

Stochastic nonspatial models for epidemics are commonly analyzed in two ways, through simulations and analytical tools (Dangerfield et al. 2009). Simulations of stochastic nonspatial models typically use Markov processes and the memoryless property to create a random walk in the number of individuals in each state (Ross 2007; Keeling and Ross 2008). These simulations are usually run using computer programs designed for numerical analysis. More analytical approaches to exploring the behavior of stochastic nonspatial models include exact Kolmogorov forward equations for determining the probabilities of each state and diffusion approximations for determining the proportion of individuals in each state and the variability of the system (Keeling and Ross 2008; Dangerfield et al. 2009).
2.2 Tools for Spatial Models

Similar to stochastic nonspatial models, stochastic spatial models can be analyzed through either simulations or analytical methods, but these tools become more difficult to use without the assumption of a “well-mixed” population. Computer simulations can expand upon the methods used in stochastic nonspatial models to include spatial structure. These simulations obtain the number of infected individuals over time as determined by a stochastic spatial model (Chaussalet et al. 2000; Keeling 1999). The analytical method of pairwise approximations also determines the approximate number of infected individuals for a stochastic spatial model by taking into account the number of pairs and type of pairs in the system (Dangerfield et al. 2009). Moment closure analysis provides another approximation approach for exploring disease dynamics in spatial systems through the use of differential equations (Brown and Bolker 2004). In this paper, we will focus on the use of simulations to explore disease dynamics for both a stochastic nonspatial model and a stochastic spatial model.

3. Spatial Structure in One-Pathogen Models

Epidemic models for a one-pathogen system set the groundwork for understanding the difference in disease dynamics between a spatial and a nonspatial structure. A susceptible-infected-recovered (SIR) model shows that the total number of hosts infected during an epidemic is smaller for a spatial network model than for a nonspatial or mean-field model (Keeling 1999). This occurs because hosts have fewer
possible contacts in a spatial model. In spatial models a host can only infect its neighbors, the number of neighbors being determined by the connectivity level. Once all of the neighbors are infected, the original infected host no longer has susceptible hosts to spread the pathogen to, so the epidemic is slowed (Tildesley et al. 2010, Brown and Bolker 2004). Moment-closure analysis confirms that epidemics become slowed with the addition of spatial structure (Brown and Bolker 2004). The slowed epidemic spread can also be explained through susceptible-infected-susceptible (SIS) model extensions, which have shown that the limited contact structure of a spatial model results in lower transmission rates (Boots and Sasaki 1999). This occurs because small spatial neighborhoods limit resource availability to only a few hosts, creating the greatest intraspecific competition for pathogens (Keeling 1999). In addition to there being fewer infected hosts in a spatial model, SIS models together with pairwise approximations show that spatial structure produces a small increase in the variation of the number of infected hosts. This increase becomes more apparent for small neighborhood sizes combined with low levels of infection (Dangerfield et al. 2009). Understanding these results for a one-pathogen system provides the foundation for expansion to more complex systems.

4. Two-Pathogen Models

Two-pathogen SIS models provide a good starting place for exploring the new questions that arise with interactions among multiple pathogens. May and Nowak were among the first to define some of these interactions and create mathematical models that demonstrate those interactions. These models offer insight into the two extremes of
within host pathogen interactions: superinfection and coinfection (May and Nowak 1995; Nowak and May 1994). These extremes are important to understand as they may give insight to the more complicated scenarios that lie in between superinfection and coinfection (May and Nowak 1995).

Superinfection occurs when competition between two pathogens drives out the less virulent pathogen, replacing it with the more virulent pathogen. In this case, only the more virulent pathogen is transmitted. Adding superinfection to an epidemic model decreases the number of infected hosts, increases the average virulence level, and decreases the rate of transmission (Nowak and May 1994). The addition of spatial structure to a superinfection model decreases virulence and the number of infected hosts even more while increasing the possibility of strain replacement and extinction (Nunes et al. 2006; Caraco et al. 2006).

The other type of within host pathogen interaction is coinfection, which will be the focus of this paper. Unlike superinfection where one pathogen drives another pathogen out of the host, coinfection occurs when multiple pathogens are able to stably coexist within a host (May and Nowak 1995). This definition can also be expanded to the broader definition of multiple pathogens infecting the same host at the same time (Seabloom et al. 2009). In this case, all pathogens within the host can be transmitted to another host (May and Nowak 1995). The results of epidemic models incorporating coinfection depend on how the pathogens interact. In this paper we will consider three types of pathogen interaction: no interaction, cross-protection, and synergism.
4.1 Pathogen Interactions

When coinfection occurs with no interaction between the pathogens, transmission rates for each pathogen remain unchanged. The only difference assumed by a mathematical model is that a coinfected host acquires the death rate associated with the most virulent pathogen (May and Nowak 1995). Coinfection under the no interaction scenario can be explored using neutral null models, which model the dynamics of indistinguishable pathogens by allowing both pathogens to stay at their initial conditions rather than coming together at the same stable equilibrium (Lipsitch et al. 2009).

Cross protection, another type of pathogen interaction, occurs when one pathogen already present within the host prevents another pathogen from infecting the host (Zhang and Holt 2001). Especially in plants, this pathogen-provided immunity often occurs because the resident pathogen triggers resistance pathways within the host, which can provide protection against a variety of other pathogens (Barrett et al. 2009). With increased resistance to infection, cross protection models result in a decrease in coinfection prevalence and transmission rates. In some cases, cross protection has also been shown through epidemic models to decrease overall infection prevalence (Seabloom et al. 2009).

Synergism, a third type of pathogen interaction, arises when two pathogens infecting the same organism lead to an increase in virus replication, virulence, and/or transmission rate (Zhang et al. 2001). In plants, synergism can occur when one pathogen decreases the plant’s resistance by down-regulating signaling pathways involved in plant
defense (Barrett et al. 2009). When synergism leads to increased host mortality, coinfection levels decrease. With substantial increases in synergistic mortality, overall infection prevalence decreases (Seabloom et al. 2009). All of these coinfection processes can be modeled using SIS model extensions (Lipsitch et al. 2009; Zhang and Holt 2001; Zhang et al. 2001). However, little research has been conducted on using these SIS model extensions to incorporate spatial structure (Seabloom et al. 2009).
Methods

1. Models and Their Architecture

In this paper, we consider three one-host, two-pathogen models: a nonspatial ODE model, a stochastic nonspatial model, and a stochastic spatial model. The nonspatial ODE model allows us to achieve a basic understanding of the system. The stochastic nonspatial model allows us to expand upon the ODE model to incorporate variation to capture the random events of real populations. Lastly, the stochastic spatial model allows us to explore disease dynamics without the assumption of a “well-mixed” population.

1.1 Nonspatial ODE Model

To explore C/BYDV dynamics, we use a one-host, two-pathogen SI model that assumes the pathogens are indistinguishable and includes the potential for coinfection (Bailey 1975; Kermack and McKendrick 1932; Lipsitch 2009). We assume the two pathogens, labeled here as A and B, are indistinguishable to simplify our model. This assumption allows for transmission and virulence rates to be the same for both pathogens, reducing the number of parameters needed. Our model envisions a landscape of \(N\) distinct patches, each of which can either be vacant or occupied by a single host. Hosts can be uninfected (‘susceptible’), infected by one pathogen, or infected by both pathogens. In total, our model includes five host states: vacant, susceptible, infected by pathogen A, infected by pathogen B, and coinfected. These five state variables are
represented by $V, S, I_A, I_B,$ and $I_X$, respectively and can be described by the following differential equations.

\[
\dot{S} = \frac{\alpha(S + \phi I_A + \phi I_B + \phi I_X)(N - S - I_A - I_B - I_X)}{N} - \nu_0 S - \lambda_A S - \lambda_B S \\
\dot{I}_A = \lambda_A S - \nu_1 I_A - k\lambda_B I_A \\
\dot{I}_B = \lambda_B S - \nu_1 I_B - k\lambda_A I_B \\
\dot{I}_X = k\lambda_B I_A + k\lambda_A I_B - (\nu_1 + \nu_2)I_X
\]

In these equations, $N$ represents the total number of hosts and vacant patches ($N = V + S + I_A + I_B + I_X$) and is considered a constant term. This allows us to reduce the necessary number of differential equations from five to four by rewriting the number of vacant patches ($V$) as $N - S - I_A - I_B - I_X$.

The transmission rates $\lambda_A$ and $\lambda_B$ quantify the rate at which susceptible hosts become infected with pathogen A or pathogen B, respectively. These rates are the product of a transmission rate constant, $\beta$, and the number of infected hosts capable of spreading the pathogen of interest, written as

\[
\lambda_A = \beta\left(\frac{I_A}{N} + \frac{qI_X}{N}\right) \\
\lambda_B = \beta\left(\frac{I_B}{N} + \frac{qI_X}{N}\right)
\]

$\beta$ is assumed to be the same for both pathogens. The transmission rates include both singly infected and coinfected hosts, because both can spread the pathogen to a susceptible host. However, the infectiousness of a coinfected host may differ from that of
a singly infected host, so coinfected hosts are weighted by the parameter $q$. In the transmission rate equations, the number of infected hosts is represented as a proportion of the total number of hosts and vacant patches.

These transmission rates can also be used to describe the rate at which a singly infected individual becomes infected by a second pathogen. The rate at which a singly infected host is infected by the other pathogen to become coinfected can be determined by multiplying $\lambda_A$ and $\lambda_B$ by the parameter $k$. Using $k$ allows the coinfection transmission rate to be different from the single infection transmission rate. Once transmission occurs and a host becomes either singly infected or coinfected, the host never recovers, just as a plant infected with C/BYDV never recovers.

Our model includes host births and deaths. Both susceptible and infected hosts produce offspring at a rate $\alpha$. Offspring can only be born into a vacant patch and the new host always starts as a susceptible individual, because C/BYDV is not transmitted vertically. $\phi_1$ and $\phi_2$ allow the number of offspring contributed by singly infected hosts and coinfected hosts, respectively, to differ from the number of offspring produced by healthy, susceptible hosts. We assume $\phi_2 \leq \phi_1 \leq 1$, because infection by C/BYDV can decrease fecundity (Seabloom 2009).

In addition to a birth rate, our model also has a death rate corresponding to each type of host. Susceptible hosts die naturally at a rate $\nu_0$. When a host becomes infected by a single pathogen, the death rate changes to $\nu_1 \geq \nu_0$. The death rate for both hosts
infected by A and hosts infected by B is the same, because pathogens are assumed to be indistinguishable. A coinfected host has at least the same death rate as a singly infected host, but can have a higher death rate by adding the parameter $\nu_2 \geq 0$ to $\nu_1$. Once a host of any kind dies, the patch occupied by that host becomes vacant. All these transmission, birth, and death rates allow for a total of nine possible state changes (Figure 1).

![Figure 1. Cereal and barley yellow dwarf viruses model. The rates given here are per capita rates. $V$ represents vacant patches. $S$ represents susceptible hosts. $I_A$ represents hosts infected by pathogen A. $I_B$ represents hosts infected by B. $I_X$ represents coinfected hosts. $(* ) = \alpha(S + \phi_1 I_A + \phi_1 I_B + \phi_2 I_X)$]
1.2 Stochastic Models

Here we analyze two stochastic models: a nonspatial model and a spatial model. The dynamics of C/BYDVs spread by winged aphids is well represented by a nonspatial model while a spatial model better represents the dynamics of C/BYDVs spread by wingless aphids. By comparing the two models, we can reach a better understanding of how C/BYDVs are spread in real populations.

1.2.1 Stochastic Nonspatial Model

The stochastic nonspatial model is very similar to the nonspatial ODE model. For both models, the rates are the same as given by the arrows in Figure 1. Both the ODE and stochastic nonspatial models also multiply the rates by the total number of individuals in the state of interest. For example, the forces of infection $\lambda_A$ and $\lambda_B$ are multiplied by the total number of susceptible individuals. This occurs because the stochastic nonspatial model functions under the assumption that the population is “well-mixed.” As long as one individual in the population is infected by a pathogen, then any susceptible individual in the population can become infected by that pathogen. For coinfection, as long as both pathogens are present somewhere in the population, then any singly infected individual can become coinfected.

The stochastic nonspatial model functions as a continuous-time Markov model where the state space of the model is the number of $S$, $I_A$, $I_B$, and $I_X$ individuals present at a given time. The model is event-driven with events occurring singly as determined by
the transition rates as given by Table 1, where [.] denotes the “concentration” in a given ‘neighborhood’. Each concentration is defined as the number of hosts in that state divided by the neighborhood size, such as $[S] = S/N$. For the nonspatial model, the ‘neighborhood’ is the entire lattice. Therefore, the overall rates depend on the total number of individuals in each state. In this case, $N$ is the total number of individuals and vacant patches. A more extensive description of the algorithm used for this model can be found in Section 3 of the Methods.

Table 1. Stochastic model events and rates where [.] denotes the “concentration”.

<table>
<thead>
<tr>
<th>Event</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V \rightarrow S$</td>
<td>$\alpha([S] + \phi_I[I_A] + \phi[I_B] + \phi_2[I_X])$</td>
</tr>
<tr>
<td>$S \rightarrow V$</td>
<td>$\nu_0$</td>
</tr>
<tr>
<td>$S \rightarrow I_A$</td>
<td>$\lambda_A = \beta([I_A] + q[I_X])$</td>
</tr>
<tr>
<td>$S \rightarrow I_B$</td>
<td>$\lambda_B = \beta([I_B] + q[I_X])$</td>
</tr>
<tr>
<td>$I_A \rightarrow V$</td>
<td>$\nu_1$</td>
</tr>
<tr>
<td>$I_A \rightarrow I_X$</td>
<td>$k\lambda_B = k\beta([I_B] + q[I_X])$</td>
</tr>
<tr>
<td>$I_B \rightarrow V$</td>
<td>$\nu_1$</td>
</tr>
<tr>
<td>$I_B \rightarrow I_X$</td>
<td>$k\lambda_A = k\beta([I_A] + q[I_X])$</td>
</tr>
<tr>
<td>$I_X \rightarrow V$</td>
<td>$(\nu_1 + \nu_2)$</td>
</tr>
</tbody>
</table>
1.2.2 Stochastic Spatial Model

Unlike the stochastic nonspatial model, the stochastic spatial model does not assume that the population is “well-mixed”. This means that instead of using the total number of individuals in a certain state, we only consider the individuals within a given neighborhood size. In the spatial model, individuals are distributed on a square lattice and each individual in the lattice has a neighborhood around it of \( n \) other individuals.

Here we examine two neighborhood sizes: \( n=4 \) and \( n=8 \). For a neighborhood size of \( n=4 \), each individual has one neighbor above, one below, one to the left, and one to the right (Figure 2a). For a neighborhood size of \( n=8 \), each individual has the same neighbors as in the \( n=4 \) model, but with the addition of the neighbors on the diagonals (Figure 2b).

For both neighborhood sizes, the edges of the lattice wrap around so that each individual has a complete neighborhood. For example, the individuals on the top row of the lattice have a neighbor on the bottom row of the lattice and vice versa. Similarly, the individuals in the left-most column of the lattice have a neighbor in the right-most column and vice versa. The neighbors of an individual determine whether or not an individual can become infected or coinfected. If the individual is susceptible then it can only become infected if one of its neighbors is infected. If the individual is singly infected with one pathogen, it can only become coinfected if one of its neighbors is infected by the other pathogen.
Similar to the stochastic nonspatial model, the stochastic spatial model is a continuous-time Markov model. The state space for the spatial model is every possible configuration of $V$, $S$, $I_A$, $I_B$, and $I_X$ individuals on the lattice. This model is also event-driven with events occurring singly as determined by the transition rates given by Table 1. The overall rates only take into account the state of the neighbors of the chosen cell. This means that where there is an $S$, $I_A$, $I_B$, or $I_X$ in the rate equations only the number of neighbors in that state is counted not the total number of individuals in that state. With only neighbors being considered, $N$ is now the neighborhood size rather than the total number of individuals.
number of individuals and vacant patches. A more extensive description of the algorithm used for this model can be found in section 3 of the methods.

2. Biological Scenarios and Parameter Values

We start with a set of baseline conditions to represent no pathogen interaction and then extend this case to incorporate three different variations. For the baseline model and the three extensions, all parameters other than $k$ and $\nu_2$ remain the same. To allow the pathogen to persist, the death rate needs to be less than the transmission rate ($\nu < \beta$), so we fix $\beta = 1$ and keep all the $\nu$ parameters less than one. In exploring each type of model, we allow $\nu_1$ to vary and keep $\nu_0$ constant. To determine the value of $\nu_0$ we would like to use, we look into a simpler model for insight. In a model that includes only vacant patches and susceptible hosts, the equilibrium number of susceptibles is $1 - \frac{\nu_0}{\alpha}$. If we fix $\alpha = 1$, then setting $\nu_0 = 0.1$ allows ninety percent of the population to be susceptible and ten percent to be vacant patches. Based on this calculation, we use these parameter values for $\alpha$ and $\nu_0$ in our model.

The rest of the parameters we determined based on assumptions. For simplicity, we assume that hosts infected by one or both pathogens do not experience a change in fecundity, so we set $\phi_1 = \phi_2 = 1$. With the assumption that the pathogens are indistinguishable, we set $q = \frac{1}{2}$ so that the total infectivity of doubly infected hosts
equals the infectivity of singly infected hosts. In all these models, we set the total number of patches equal to $N = 2500$.

2.1 Baseline

We start our exploration of spatial effects on coinfection with a baseline model that assumes no pathogen interactions and then extend this model to incorporate pathogen interactions. In the baseline model, the properties of the pathogens remain unchanged in the presence of each other. To keep the transmission rate unchanged, we set $k = 1$ so that the rate at which a singly infected host is infected by the second pathogen to become coinfected remains the same as the rate at which a susceptible host is infected by either pathogen A or pathogen B. We also assume $\nu_2 = 0$ so that there is no change in the death rate when both pathogens are present. The baseline model allows us to understand the basic system and make comparisons to models with pathogen interaction.

2.2 Variations

2.2.1 Cross Protection

Some species of C/BYDVs exhibit cross protection, resulting in decreased transmission (Seabloom et al. 2009). Typically this occurs between two closely related species (Haber 1995). In our model, we represent cross protection by setting $k < 1$. This decreases the rate of transmission from single infection to coinfection.
2.2.2 Synergism – Increased Transmission

For C/BYDVs, synergism usually occurs when two dissimilar species are present (Miller and Raschova 1997). One result of synergism between two species of C/BYDVs is an increase in transmission (Seabloom 2009). This type of interaction is represented in the model by setting $k > 1$, increasing the transmission rate from single infection to coinfection.

2.2.3 Synergism – Increased Mortality

Synergism can also increase the mortality of a coinfected host due to interactions between the pathogens (Zhang et al. 2001). In this case, we assume that the mortality rate of a coinfected host is the sum of the mortality rates of the two types of singly infected hosts. For our model the pathogens inflict the same mortality rates upon their hosts, so we set $\nu_2 = \nu_1$.

3. Simulation Details for Stochastic Models

3.1 Description of the Algorithm

Both the stochastic nonspatial and stochastic spatial models are continuous-time Markov models. The random variables that determine the processes of the continuous-time Markov model depend on the rates, which we will represent here by $\varphi_1, \ldots, \varphi_z$, where $z$ is the total number of rates. In the nonspatial model, $z = 9$ since we have nine transition rates. The continuous time period of each model is divided up into sojourn times as
calculated by an exponential random variable. The mean of the exponential random variable is the inverse of the sum of all the rates given in Table 1. Alternatively, this variable can be written as \( \text{Exp}(\frac{1}{\sum_{i=1}^{z} q_i}) \). At each sojourn time, one event or state change occurs. Which event occurs is determined by a multinomial random variable with one trial. The number of probabilities determining the multinomial random variable depends on the number of rates. For the nonspatial model, there are nine transition rates, so there are nine probabilities. Each probability is one rate divided by the sum of all the rates. For example, the first probability is \( p_i = \frac{q_1}{\sum_{i=1}^{z} q_i} \). After each event occurs, the rates are recalculated to account for the state change. The variables determining both sojourn times and events are memoryless, so only the current state determines the future state (Bartlett 1956, 1960; Kendall 1950; Ross 2007).

### 3.2 Implementation Details for Spatial Model

In implementing the algorithm, the stochastic spatial model is more difficult to implement than the stochastic nonspatial model. For each cell in the spatial model, we need to keep track of the state of the cell, the rates of the cell, and the state of the cell’s neighbors at each sojourn time. The number of probabilities that are used by the multinomial random variable in the spatial model is equal to the number of cells on the lattice. This is because each cell has a different transition rate, so we have \( N \) transition rates instead of only nine like in the nonspatial model. In addition, our spatial model only
uses the multinomial random variable to choose the cell to change, which simplifies the code. Once a cell is chosen, a uniform random variable ranging from zero to one determines which of the cell’s rates will be used to change the state of the cell. To simplify the code, the rates are recalculated only for the chosen cell and its neighbors, because those are the only cells affected by the state change.

3.3 Further Details

In this paper, we use MATLAB to run simulations for both the stochastic nonspatial and stochastic spatial model. Each simulation runs from time 0 to a maximum time of 250 with sojourn times being chosen throughout. As each simulation runs, the program keeps track of the number of patches in each state ($V, S, I_A, I_B, \text{ and } I_X$) and the amount of time in which the state variables have that number of patches. After the simulation is done, the vector of time each state variable spends in each state, 1 to $N$, is used to calculate the means and standard deviations over time for each state variable.

3.4 Conditional Probabilities

In addition, the program keeps track of conditional probabilities over time, indicating if aggregation is occurring. Each conditional probability represents the probability that individuals in certain states are neighbors. These probabilities allow us to examine whether pathogens are clumping together and whether the two pathogens are spatially segregated. All together we calculate four probabilities: $P(A|A)$, $P(A|B)$, $P(B|B)$, and $P(B|A)$. We will call these the neighboring probabilities of infection. These
probabilities include coinfected hosts as neighbors. The probabilities use the following formulas.

\[ P(A|A) = [I_A]_A + q[I_X]_A \]  \hspace{1cm} (1) 

\[ P(A|B) = [I_A]_B + q[I_X]_B \]  \hspace{1cm} (2) 

\[ P(B|B) = [I_B]_B + q[I_X]_B \]  \hspace{1cm} (3) 

\[ P(B|A) = [I_B]_A + q[I_X]_A \]  \hspace{1cm} (4) 

In these formulas [.] denotes the concentration of individuals in the neighborhood. The subscript next to the [.] represents the host whose neighbors we are concerned with. For example, the subscript A outside of the brackets in \([I_A]_A\) means the given host is one infected by pathogen A and \([I_A]\) in \([I_A]_A\) represents the proportion of hosts infected by pathogen A that are neighbors of the given host. Equations 1 and 4 represent the probability that a host infected by pathogen A will have a neighbor infected by pathogen A or pathogen B, respectively. Similarly, equations 2 and 3 represent the probability that a host infected by pathogen B will have a neighbor infected by pathogen A or pathogen B, respectively. Based on these formulas, the probabilities calculate the proportion of individuals in the neighborhood that are infected by each pathogen. At each sojourn time, the probabilities are first calculated for each individual host and then averaged over all A or B sites to find the mean probability. Once each simulation finishes, the means and standard deviations of each probability are calculated.
Results

1. Nonspatial Models

First, I report the internal fixed points of the deterministic ODE model and then compare these to the mean prevalence of infected hosts from the stochastic nonspatial model. The fixed points we find here are informative because they appear to represent the stable equilibrium solution to the differential equations. Thus we can expect the prevalence of infected hosts in the population to proceed toward these fixed points at least in a nonspatial setting when the population sizes are sufficiently large. Here, we define the prevalence of infected hosts as the number of infected hosts divided by the total number of patches, \( N \). This definition is for simplicity because the number of patches, \( N \), stays constant over time and for all simulations. When stochasticity is added to the model, the prevalence of infected hosts should fluctuate around the fixed points resulting in a mean approximately equal to the fixed points.

The fixed points for the deterministic ODE model are obtained using MATLAB. I use the solver ode45 to solve the differential equations of the deterministic model. The solver is run for a time period of 250, a sufficiently long amount of time for the state variables to settle at the fixed points. The state variables typically reach the fixed points before time 50, so allowing the simulation to run for 200 extra time steps assures us that we have reached the fixed points. The fixed points are taken to be the values of \( I_A \), \( I_B \), and \( I_X \) at the end of the time period.
To compare the fixed points and stochastic model means, I start by finding the fixed points for the baseline model parameters. When the fixed points of the baseline model are added together, we can see that the overall prevalence of infection 
\[ \left( \frac{I_A + I_B + I_X}{N} \right) \] decreases as the death rate, \( \nu_1 \), increases (Fig. 3). Similarly, the fixed point for the prevalence of coinfected hosts \( \left( \frac{I_X}{N} \right) \) decreases as the death rate increases. However, when the slopes of the coinfection and overall infection lines are compared, the rate at which coinfection decreases is different from the rate at which the overall

![Figure 3. Deterministic ODE model fixed points and stochastic nonspatial model means for the baseline model. The circles represent the stochastic nonspatial means for overall infection. The solid line connecting the circles represents the fixed points for overall infection from the ODE model. The vertical lines represent the standard deviation for each stochastic mean. Triangles and dashed lines represent stochastic nonspatial means and fixed points for (a) coinfection and (b) single infection.](image)
prevalence of infection decreases (Fig. 3). For $0.1 < \nu_1 < 0.3$, there is a greater decrease in the prevalence of coinfection than in the prevalence of overall infection. With the number of coinfected hosts decreasing more than overall infected hosts, the prevalence of singly infected hosts $((I_A + I_B)/N)$ must increase so that the number of coinfected hosts plus the number of singly infected hosts equals the overall number of infected hosts (Fig. 3). However, for $0.3 < \nu_1 < 0.5$, overall prevalence of infection decreases more than the prevalence of coinfection. As the difference between coinfection and overall infection decreases, the fixed point for the prevalence of singly infected hosts also must decrease.

To compare the ODE model to the stochastic nonspatial model, we overlay the mean prevalence of infection from the stochastic nonspatial model on the fixed points from the deterministic ODE model (Fig. 3). For coinfection, single infection, and overall infection, the comparison shows that the fixed points and the mean prevalence of infection are approximately equal. The fixed points from the ODE model and the means from the stochastic nonspatial model are also approximately equal in all the model variations.

2. Baseline Model

The baseline model simulates a system in which there is no interaction between the two pathogens. We explore the simulations under this scenario to compare the mean prevalence of infected hosts for a nonspatial model and a spatial model. In addition, we
examine the neighboring probabilities of infection (eqs. 1-4) to determine if aggregation is responsible for the difference in prevalence of infection between the two models.

### 2.1 Stochastic Nonspatial Model

Results from the stochastic nonspatial model parallel the results from the nonspatial ODE model, but are provided again here for comparison with the stochastic spatial model. Simulations of the baseline model were run for $\nu_1 = 0.1, 0.2, 0.3, 0.4, \text{ and } 0.5$. The baseline simulations result in a decrease in coinfection as the death rate increases (Fig. 4a). For small values of $\nu_1$, the prevalence of singly infected hosts increases while the prevalence of coinfecte hosts decreases. However, when the infection-induced death rate becomes larger, both the prevalence of coinfecte hosts and the prevalence of singly infected hosts decrease (Fig. 4). The overall prevalence of infection also decreases as the death rate increases.

### 2.2 Stochastic Spatial Model

The stochastic spatial model simulations result in similar trends to the stochastic nonspatial model. As $\nu_1$ increases, the prevalence of coinfecte hosts decreases in both models (Fig. 4a). Similar to the nonspatial model, the spatial model also shows an increase in the prevalence of singly infected hosts followed by a decrease as the death rate increases (Fig. 4b).
Figure 4. The mean prevalence of infection for the baseline model. Symbols represent mean prevalence of infected hosts. Vertical lines represent standard deviations. Dashed line is spatial $n=4$ model. Solid line is spatial $n=8$ model. Dashed-dotted line is nonspatial model. (a) Prevalence of coinfected hosts for each model. (b) Prevalence of singly infected hosts for each model. (c) Overall prevalence of infection for each model.
Although similar in some respects, the spatial and nonspatial models result in some differences too. The effect of spatial structure on the mean prevalence of singly infected hosts depends on the value of the infection death rate. For small values of $\nu_1$, the mean prevalence of singly infected hosts increases with localized transmission (Fig. 4b). This result may be a product of aggregation, which we explore through the neighboring probabilities of infection (eqs. 1-4). However, for larger values of $\nu_1$, the mean prevalence of singly infected hosts decreases with localized transmission. Some of this behavior can be explained by looking at the overall prevalence of infection (Fig. 4c).

At low values of the death rate, overall infection is similar for both the nonspatial and spatial model so aggregation appears to explain the increase in singly infected hosts with localization. However, as the death rate increases, overall infection decreases more rapidly with localization, causing the prevalence of singly infected hosts to also decrease with localization.

As transmission becomes more localized, the mean number of coinfected hosts decreases for all the infection death rates analyzed (Fig. 4a). This result also reflects the decrease in overall infection as transmission becomes more localized. Both the decrease in coinfected hosts and the decrease in overall infection with increased localization are similar to results from a one-pathogen model, where localization decreases overall prevalence of infection (Keeling 1999). In the one-pathogen model, the decrease is due to a limited number of susceptible contacts (Tildesley et al. 2010, Brown and Bolker 2004). Similar reasoning could be used in the two-pathogen model where contact
between hosts infected by different pathogens becomes limited with localization, especially if aggregation occurs.

To determine the mechanism causing the decrease in coinfected hosts with increased localization, we examine the neighboring probabilities of infection (eqs. 1-4). By comparing $P(A|A)$ to $P(B|A)$, we can determine if hosts infected by pathogen A are spatially aggregated. Pathogen A and pathogen B are indistinguishable, so the results of the neighboring probabilities of infection for pathogen A can also be extended to pathogen B. Probabilities from the simulations run for $\nu_1 = 0.5$ are not included, because no infected individuals remained by the end of the simulation for the spatial $n=4$ model.

In the nonspatial model, the conditional probabilities $P(A|A)$ and $P(B|A)$ are approximately the same, meaning that hosts with pathogen A are as likely to be next to a host with pathogen A as to be next to a host with pathogen B (Fig. 5). This occurs because in the nonspatial model the neighboring probabilities of infection depend on the total number of infected individuals in the population. With the total number of hosts infected by pathogen A and pathogen B being approximately equal in the nonspatial model, the probabilities $P(A|A)$ and $P(B|A)$ are approximately equal. This makes it easy to determine the differences between $P(A|A)$ and $P(B|A)$ in the spatial model.

Comparing $P(A|A)$ to $P(B|A)$ in the spatial model shows that a host infected with pathogen A is more likely to be next to another host infected by pathogen A than next to a host infected by pathogen B. Because $P(A|A)$ is greater than $P(B|A)$, these probabilities indicate spatial aggregation of pathogen A. In addition, the difference between $P(A|A)$
Figure 5. Aggregation of pathogen A. Symbols represent the mean prevalence of infecteds. Vertical lines represent standard deviations. The dashed line is the nonspatial model. The solid line is the spatial $n=8$ model. The dashed-dotted line is the spatial $n=4$ model. (a) The probability of a host infected by pathogen A neighboring another host infected by pathogen A. (b) The probability of a host infected by pathogen A neighboring a host infected by pathogen B.
and P(B|A) increases with increased localization, indicating that spatial aggregation of pathogen A increases with localization (Fig. 5). The same results occur for the probabilities for pathogen B indicating that hosts infected by pathogen B are also spatially aggregated. These results indicate that spatial aggregation is keeping the two pathogens separated, providing a possible explanation for why there is less coinfection in the spatial model. The separation becomes apparent when examining a map of the lattice, where we can see clumps of pathogen A and clumps of pathogen B (Fig. 6). Coinfected

Figure 6. Map of the lattice to show aggregation in the baseline model. Taken from the spatial n=4 model. Time=250, v_1=0.3. White represents vacant patches. Green represents susceptible hosts. Blue represents hosts infected by A. Red represents hosts infected by B. Purple represents coinfected hosts. This figure is best viewed in color.
hosts can be included with either pathogen A or pathogen B to extend the clumps further. The clumps of pathogen A and the clumps of pathogen B are usually separated by susceptible hosts and vacant patches, creating spatial segregation.

Why does aggregation lead to a decrease in coinfection and an increase in single infection? Aggregation causes a host infected only by pathogen A to be surrounded by other hosts infected only by pathogen A. This means that the host has no neighbors with pathogen B, so the host cannot become infected by pathogen B. A similar argument holds for a host with pathogen B. Thus aggregation leads to a decrease in the number of coinfected hosts and an increase in the number of singly infected hosts. Aggregation in the spatial model provides a reason for why we see a decrease in coinfection and an increase in single infection.

3. Cross-Protection

In a system with cross-protection, one pathogen prevents a second pathogen from infecting the host. Consequently, the rate at which hosts become coinfected is reduced. To demonstrate cross-protection in this set of simulations, we set $k = 0.5$ to reduce the rate of coinfection.

3.1 Stochastic Nonspatial Model

In the cross-protection model, the overall prevalence of infection is approximately the same as in the baseline model (compare Fig. 4c & Fig. 7e). However, the cross-protection model results in fewer coinfected hosts than the baseline model regardless of
Figure 7. The mean prevalence of infection for the cross-protection model. Symbols represent the mean prevalence of infected hosts. Vertical lines represent standard deviations. Dashed line is the spatial $n=4$ model. Solid line is the spatial $n=8$ model. Dashed-dotted line is the nonspatial model. (a) Prevalence of coinfectd hosts. (b) Prevalence of singly infected hosts. (c) Overall prevalence of infection.
the value of $\nu_1$, because of the slowed rate at which hosts transition from single infection to coinfection in the cross-protection model (compare Fig. 4a & Fig. 7a). In order to keep the overall infection prevalence the same in both the cross-protection model and the baseline model, the prevalence of singly infected hosts must compensate for the decrease in coinfectected hosts. Therefore, the cross-protection model results in an increase in the prevalence of singly infected hosts compared to the baseline model for each $\nu_1$ analyzed (compare Fig. 4b & Fig. 7b). This result shows that as the rate at which hosts gain a second pathogen decreases, the prevalence of coinfectected hosts also decreases. The case when this rate is zero, or in terms of the model when $k=0$, is a limiting case that helps build intuition. In this case, hosts do not become coinfectected so we would expect only singly infected hosts to remain.

3.2 Stochastic Spatial Model

Similar to the nonspatial model, the spatial cross-protection model results in approximately the same overall prevalence of infection as in the spatial baseline model, but with a decrease in coinfection and an increase in single infection (compare Fig. 4 & Fig. 7). In addition to being the result of a lower coinfection rate, the decrease in coinfectected hosts and increase in singly infected hosts is the result of a difference in aggregation between the spatial models. The cross-protection model produces a small increase in aggregation compared to the baseline model. The probability of a host infected by pathogen A having a neighbor also infected by pathogen A increases by 0.025 to 0.05 and the probability of a host infected by pathogen A having a neighbor infected
by pathogen B decreases by 0.02 to 0.047 in the cross-protection model, except for when \( \nu_1 = 0.4 \) where the difference is almost equal to 0.

Similar to the baseline model, the cross-protection model maintains the same relationship between the spatial and nonspatial model. The mean number of coinfected hosts decreases with increased localization (Fig. 7a). At the same time, the mean number of singly infected hosts increases with increased localization for small values of \( \nu_1 \) and decreases with localization for large values of \( \nu_1 \) (Fig. 7b). This relationship between the spatial and nonspatial models remains the same for all variations unless otherwise stated.

### 4. Synergism – Increased Transmission

One effect that occurs when two pathogens interact within the same organism is an increased pathogen transmission rate. To represent increased transmission rates due to synergism, we set \( k=5 \) to increase the rate at which a singly infected host becomes doubly infected.

#### 4.1 Stochastic Nonspatial Model

Again, the overall prevalence of infection is the same in the increased transmission model as in the baseline model. However, hosts are becoming coinfected at a faster rate in the increased transmission model than in the baseline model, so the prevalence of coinfected hosts increases in the increased transmission model (compare Fig. 4a & Fig. 8a). While the rate at which singly infected hosts become coinfected increases, the rate at which hosts become singly infected remains the same, resulting in a
Figure 8. The mean prevalence of infection for the increased transmission model. Symbols represent the mean prevalence of infected hosts. Vertical lines represent standard deviations. Dashed line is the spatial $n=4$ model. Solid line is the spatial $n=8$ model. Dashed-dotted line is the nonspatial model. (a) Prevalence of coinfected hosts. (b) Prevalence of singly infected hosts. (c) Overall prevalence of infection.
decrease in the prevalence of singly infected hosts (compare Fig. 4b & Fig. 8b). The increase in coinfection and similar decrease in single infection allows the overall prevalence of infection in the increased transmission model to remain approximately equal to the overall prevalence of infection in the baseline model (compare Fig. 4c & Fig. 8c).

4.2 Stochastic Spatial Model

The spatial model with increased transmission results in a decrease in aggregation compared to the baseline model. This decreased aggregation is shown through a decrease in $P(A|A)$ of 0.032-0.11 and an increase in $P(B|A)$ of 0.016-0.071, depending on the value of $\nu_1$ and the degree of localization. The decreased aggregation means that the two pathogens are not as spatially separated in the increased transmission model. With less pathogen separation, the two pathogens are more likely to come into contact with each other. Therefore, the increased transmission model results in an increase in the prevalence of coinfected hosts compared to the baseline model. However, the overall prevalence of infection is approximately the same in both the increased transmission model and the baseline model, so the increase in coinfected hosts is reflected by a decrease in the prevalence of singly infected hosts.
5. Synergism – Increased Mortality

A second effect of pathogen interaction within a host is increased host mortality. To represent increased mortality due to synergism, we set $\nu_2 = \nu_1$ to increase the rate at which coinfected hosts die.

5.1 Stochastic Nonspatial Model

With $\nu_2 = \nu_1$, the death rate for coinfected hosts is double the death rate for singly infected hosts. This means that when $\nu_1 = \nu_2 = 0.25$ the death rate for coinfected hosts is 0.5, which is the highest death rate we examined under the other scenarios. In addition, the rate at which singly infected hosts become coinfected remains unchanged from the baseline model, but coinfected hosts die faster. This produces a large decrease in the prevalence of coinfected hosts in the increased mortality model compared to the baseline model (compare Fig. 4a & Fig. 9a). The overall prevalence of infection also decreases in the increased mortality model, but not as much as coinfection decreases (compare Fig. 4c & Fig. 9c). Reflecting the difference between coinfection and overall infection, the prevalence of singly infected hosts increases in the increased mortality model compared to the baseline model (compare Fig. 4b & Fig. 9b).

For these simulations, we are only able to draw conclusions from $\nu_1, \nu_2 \in [0.05, 0.25]$, because larger values of $\nu_2$ cause one of the pathogens to become extinct. In the simulations where one pathogen becomes extinct, the means are not very
Figure 9. The mean prevalence of infection for the increased mortality model. Symbols represent the mean prevalence of infected hosts. Vertical lines represent standard deviations. Dashed line is the spatial $n=4$ model. Solid line is the spatial $n=8$ model. Dashed-dotted line is the nonspatial model. (a) Prevalence of coinfectd hosts. (b) Prevalence of singly infected hosts. (c) Overall prevalence of infection.
informative, because the number of infected hosts does not oscillate around an equilibrium point. Rather the number of infected hosts decreases until there are no more infected hosts. This result produces a very large standard deviation, making the mean unreliable for large values of $\nu_2$. Instead, we explore the cases where $\nu_2 > 0.25$ by looking at extinction probabilities in section 5.3.

5.2 Stochastic Spatial Model

Similar to the nonspatial model, the spatial model with increased mortality results in a decrease in the prevalence of coinfected hosts and an increase in the prevalence of singly infected hosts compared to the baseline model. The rapid decrease in coinfection in the spatial model can be explained through aggregation. With increased mortality, the $P(A|A)$ increases as the death rate increases unlike in the baseline model where $P(A|A)$ decreases as the death rate increases (compare Fig. 5a & Fig. 10a). In addition, $P(B|A)$ exhibits a large decrease in the increased mortality model compared to the baseline model, almost reaching zero by the time the death rate is 0.2 (compare Fig. 5b & Fig. 10b). Considering these conditional probabilities and comparing them to the baseline model, the increased mortality model indicates a large amount of aggregation of pathogen A especially at larger death rates. With the pathogens being indistinguishable, we see similar results for pathogen B.
Figure 10. Aggregation of pathogen A in the increased mortality model. Symbols represent the mean prevalence of infecteds. Vertical lines represent standard deviations. The dashed line is the nonspatial model. The solid line is the spatial $n=8$ model. The dashed-dotted line is the spatial $n=4$ model. (a) The probability of a host infected by pathogen A neighboring another host infected by pathogen A. (b) The probability of a host infected by pathogen A neighboring a host infected by pathogen B.
5.3 Extinction Probability

The simulations for the nonspatial model with increased mortality resulted in extinction of one pathogen for the larger values of $\nu_1$. Because of this result, we decided to study the extinction times for the increased mortality scenario. To determine extinction times, we ran 100 simulations of each model for a maximum time of 500 under both $\nu_2 = \nu_1 = 0.3$ and $\nu_2 = \nu_1 = 0.4$. The results of these simulations are studied by comparing the probability of extinction for the nonspatial model to the spatial model.

The results of these simulations show that extinction occurs faster and more often in the nonspatial model compared to the spatial model. For both death rates, all 100 of the nonspatial model simulations reached extinction before reaching the maximum time of 500 (Fig. 11). Only a few of the spatial model simulations reached extinction by time 500. Specifically, only one simulation for a neighborhood size of four and only six simulations for a neighborhood size of eight reached extinction before time 500 when $\nu_2 = \nu_1 = 0.3$ (Fig. 11a). For $\nu_2 = \nu_1 = 0.4$, only five simulations for a neighborhood size of four and only nine simulations for a neighborhood size of eight reached extinction before time 500 (Figure 11b). To understand the extinction behavior better, we can look at the average time to extinction. For the nonspatial model, the average time to extinction is 206.2 for $\nu_2 = \nu_1 = 0.3$ and 118.0 for $\nu_2 = \nu_1 = 0.4$. On the other hand, the average time to extinction for both spatial models under both death rates is greater than 500.
Figure 11. Time of extinction of one pathogen. The dashed line is the spatial $n=4$ model. The solid line is the spatial $n=8$ model. The dashed-dotted line is the nonspatial model. (a) Time of extinction of one pathogen for $\nu_2 = \nu_1 = 0.3$. (b) Time of extinction of one pathogen for $\nu_2 = \nu_1 = 0.4$.  

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These results imply that the probability of extinction of one pathogen increases as localization decreases. One reason that localization increases the probability that both pathogens persist may be that localization produces aggregation as can be seen through the conditional probabilities for the spatial model. In the spatial $n=4$ model where $\nu_2 = \nu_1 = 0.3$, $P(A|A)$ is 0.4645 and $P(B|A)$ is 0.0164. In the spatial $n=4$ model where $\nu_2 = \nu_1 = 0.4$, $P(A|A)$ is 0.3854 and $P(B|A)$ is 0.0028. Although these numbers are taken from one simulation, these conditional probabilities give approximately the same values as all other simulations run. For both death rates, the neighboring probabilities of infection indicate that a host with pathogen A is much more likely to be next to another host with pathogen A than next to a host with pathogen B. This large degree of aggregation is due to coinfected hosts dying quickly and being replaced by vacant patches. The vacant patches provide spatial separation of hosts infected by A and hosts infected by B. With this large amount of spatial separation through aggregation, contact between the two pathogens is limited in the spatial model, making it more difficult for one pathogen to outcompete the other pathogen. Therefore, both pathogens are able to persist by being separated into different areas of the lattice.
Discussion

1. Conclusions and Biological Implications

Mathematical models are useful, noninvasive tools for making predictions about disease dynamics, which can then be tested in the field. However, most of the current models assume a “well-mixed” population (Bailey 1975; Boylan 1991; Brauer 2008; Brown and Bolker 2004; Lefevre 1983). This assumption is unrealistic in many cases, especially for plant communities where the hosts are incapable of moving to interact with other hosts (Brown and Bolker 2004). In this case, spatial structure must be taken into consideration to explore the spread of infection. Some one-pathogen models incorporate spatial structure, providing a good foundation, but often multiple pathogens are capable of inhabiting a single organism requiring a more complicated model (Seabloom 2009). The addition of both multiple pathogens and spatial structure to a host-pathogen model raises some new questions. How does spatial structure affect the prevalence of single infection and coinfection? Is pathogen clustering responsible for the changes in infection? How do within-host interactions among pathogens (e.g. cross-protection and synergism) affect the prevalence of single infection and coinfection? With the use of the two-pathogen model presented here, we can begin to answer these questions.

Through examining and comparing two-pathogen nonspatial and spatial models, we learn that the dynamics of coinfection depend on the infection-induced death rate and the degree of localization. When pathogens do not interact directly, increasing the infection-induced death rate causes coinfection to decrease while the prevalence of single
infection first increases and then decreases. When spatial structure is added to the model without pathogen interaction, coinfection decreases with localized infection. This result resembles findings from a one-pathogen model in which overall infection prevalence decreases with localization (Keeling 1999). On the other hand, the prevalence of singly infected hosts increases with localization for small death rates and decreases with localization for large death rates. The changes associated with increased localization can be explained by aggregation in the spatial model. When spatial structure is added to the model, the pathogens aggregate to become spatially separated, resulting in less coinfection.

Localized disease transmission has similar effects when pathogens interact directly within a host, but the prevalence of infection changes with pathogen interaction. Cross-protection, in which one pathogen prevents infection by the other pathogen, decreases the prevalence of coinfection while increasing the prevalence of single infection (Zhang and Holt 2001). The decrease in coinfection is consistent with previous research on cross-protection using a C/BYDV models (Seabloom et al. 2009). Increased transmission due to synergism, having the opposite effect, increases the prevalence of coinfection while decreasing the prevalence of single infection. This is similar to a previous plant virus model, which showed increased coexistence of pathogens with increased transmission due to synergism (Zhang et al. 2001). When pathogens interact to increase host mortality, previous studies found a reduction in the prevalence of coinfection (Seabloom et al. 2009; Zhang et al. 2001). Here, the result is also low levels
of coinfection, but with the possibility of extinction of one pathogen when the death rate is large. However, localized transmission promotes pathogen persistence when coinfected hosts suffer increased mortality, because pathogens aggregate to create spatial separation.

Although the results presented here are for a system with only two pathogens, these results give some insight into what may occur in a system with more than two pathogens, such as C/BYDVs, which exist as five pathogen species (Miller and Raschova 1997). Assuming that aggregation still increases with localization no matter how many pathogen species are present, we can predict that the number of hosts infected by more than one pathogen will decrease with localization. Aggregation in a model with multiple pathogens will still cause hosts with a single pathogen to clump together forming a spatial separation between pathogens. This makes it less likely that hosts with different pathogens will come into contact with the same vector, decreasing the prevalence of infection by two species. Similarly we could expect doubly infected hosts to aggregate in the middle of the singly infected hosts. For example, hosts coinfectd by pathogen A and pathogen B would be expected to aggregate in between hosts infected by pathogen A and hosts infected by pathogen B. With doubly infected hosts being surrounded by hosts with the same pathogens, the probability of contacting a host with a third type of pathogen becomes less likely, decreasing the prevalence of infection by three species. Using this reasoning, we could continue adding more pathogens and
predict that the number of hosts with multiple pathogens will decrease with localization because of aggregation.

For C/BYDVs, the viruses that motivated this model, there are implications that depend on which vectors are spreading the disease. Both wingless and winged aphids act as vectors to spread C/BYDVs (Halbert and Voegtlin 1995). In a system where wingless aphids are the primary vectors of C/BYDVs, we can conclude that there should be a lower prevalence of coinfection due to the limited number of plants with which the wingless aphid comes into contact. In a system where winged aphids are abundant, we can conclude that there should be a higher prevalence of coinfection because winged aphids can travel longer distances. In general, there will be more coinfection as the aphids disperse farther.

In addition to the type of vector determining disease dynamics for C/BYDVs, the prevalence of infection also depends on the virulence of the species. Less virulent species will cause more single infections when spread by a wingless aphid, because wingless aphids are predicted to decrease the prevalence of coinfection more than they decrease the overall prevalence of infection. When spread by a winged aphid, less virulent species are predicted to cause fewer single infections and more coinfection. More virulent species will have the opposite effect for single infection while maintaining the same effect for coinfection, because overall infection is predicted to be much lower in systems with wingless aphids than in systems with winged aphids. Therefore, when more
virulent species are spread by winged aphids, the model predicts that there will be more single infection and coinfection than when spread by a wingless aphid.

In addition, the prevalence of infection will depend on the interactions between the species of C/BYDV. Cross-protection is one type of interaction that some species of C/BYDV express that changes the prevalence of infection. Cross-protection only occurs between similar species of C/BYDV in Group I, which consists of PAV, MAV, and SGV. In particular, cross-protection is seen between PAV and MAV where MAV is the protecting species and PAV is the challenging species (Haber 1995; Miller and Raschova 1997; Zhang and Holt 2001). When similar species of C/BYDV are present, a model by Seabloom et al. (2009) showed that there should not be coexistence of both species. Similarly, our model predicts that coinfection by both MAV and PAV will decrease and infection by only one of these species will increase compared to when two non-interacting species are present.

Species of C/BYDV can also interact through synergism, either increasing transmission or increasing mortality. Synergism occurs between dissimilar species of C/BYDV, specifically between one species from Group I and one species from Group II, which consists of RPV and RMV (Miller and Raschova 1997). When increased transmission due to synergism occurs between two species of C/BYDV, our model predicts that coinfection will increase while single infection will decrease. On the other hand, if two species of C/BYDV interact to increase mortality, our model predicts that coinfection will decrease and single infection will increase. These results are similar to
those presented in a paper by Seabloom et al. (2009) where increasing transmission between two dissimilar species increased coexistence, but increasing mortality due to synergism decreased coinfection prevalence. However, our model also shows that if synergism increases mortality too much, coinfection is eliminated through the extinction of one species. We can expect this to occur especially when winged aphids spread C/BYDV.

Although the model presented here gives some insight into the spatial effects on multiple pathogen systems like C/BYDVs, the model has some limitations that could be explored in more detail through future research. One limitation of the model is that seasonality is excluded to make the model easier to implement. For C/BYDVs, seasonality would be an important factor to include because the vectors change between winged and wingless aphids depending on the time of year (Halbert and Voegtlin 1995). Another limitation is that the model presented here assumes that the two pathogens have identical properties in order to reduce the number of variables. Therefore, our model does not account for the possibility that transmission and virulence may be different for the two pathogens. For C/BYDVs, the virulence differs depending on the species, for example PAV is a virulent species and MAV is a mild species (Miller and Rasochova 1997; Zhang and Holt 2001). Also the transmission rate differs depending on the type of vector, which determines the efficiency of transmission. For example, the aphid species *Rhopalosiphum padi* efficiently transmits PAV and RPV, but not the other C/BYDV species (Seabloom et al. 2009). Therefore, allowing for changes in virulence and
transmission would be a beneficial model extension for C/BYDV (Miller and Raschova 1997; Seabloom 2009). This model also leaves out the possibility of unequal competition between the two pathogens, because the pathogens in our model are assumed to be equally good competitors. The inclusion of unequal competitors could make one pathogen less prevalent than the other or make extinction of one pathogen more likely (Power 1996). All of these limitations could be explored through future research with the use of mathematical tools and fieldwork.

2. Future Work

In future work, our mathematical model could be adjusted to account for the limitations of the model. For example, our model could be expanded to include seasonality by allowing the parameters to depend on the time. The birth rate could change during the planting season and the death rate could change during the harvest season. In addition, the transmission rate could depend on the time of year, which determines whether winged or wingless aphids are the primary vector of BYDV (Halbert and Voegtlin 1995). To account for this change in aphids throughout the year, the nonspatial and spatial models could also be combined so that how many contacts a host has would depend on the time of year and therefore on the type of vector.

Once the model with indistinguishable pathogens is well understood, the coinfection model presented here could also be expanded to include competition. To make the pathogens different, transmission rates and virulence rates could be different for
each pathogen. Each pathogen could have a unique $\beta$ transmission parameter and a unique $\nu$ mortality parameter. Depending on the parameters in this scenario, we would get only pathogen A, only pathogen B, or coexistence (Durrett and Neuhauser 1997).

When one pathogen has a larger transmission rate and a larger death rate than the other pathogen, we would expect the pathogen with the larger rates to outcompete the other pathogen similar to a superinfection scenario (Caraco et al. 2006; Nowak and May 1994). Coexistence would also depend on the transmission and death rates of the two pathogens, but may also depend on the degree of localization. Similar to the case with increased mortality, we may see that increased aggregation with increased localization allows the two pathogens to coexist in a spatial model when they cannot coexist in a nonspatial model. In this case, aggregation would provide some separation of the two pathogens, reducing the effects of competition by isolating the two pathogens so that they do not interact (Lipsitch et al. 2009). By including competition, we could begin to explore the scenarios between coinfection and superinfection.

To acquire a better understanding of the dynamics of coinfection, a study of the variance-covariance structure could also be added to the results presented here. Determining the variance-covariance structure of the nonspatial and spatial model would allow us to explore differences in how the state variables change under these two structures. In a one-pathogen model, it has already been shown that the addition of spatial structure produces a small increase in variation of the number of infected hosts with increasing variation as the neighborhood size decreases (Dangerfield et al. 2009).
To look at the variance-covariance structure, we would construct a matrix that had the variance over time for each state variable on the diagonal and the covariances between each pair of state variables filling the rest of the matrix. A large difference in the variance-covariance structure between the nonspatial and spatial model may indicate a difference in infection prevalence from year to year. The variance-covariance matrix could also give us some information on how informative field sampling is in determining infection prevalence. If the variance and covariance are large, then more field samples need to be taken at more times throughout the season than if the variance and covariance are small.

In addition to exploring the variance-covariance structure of the model, the results could be supported through other techniques. The use of analytical tools like pairwise approximations would give further mathematical support for justifying that the number of singly infected and coinfected hosts found through the simulations are correct. Pairwise approximations can be used to approximate the prevalence of infection in a stochastic spatial model, so these approximations could be compared to the spatial model results presented in this paper (Dangerfield et al. 2009). If the results of our spatial model and the results of the pairwise approximations are similar, then we can be more confident about our results.

Lastly, fieldwork studying the prevalence of C/BYDVs would give biological support for the results presented here. One field study that could be conducted would be an observational study in which the researchers keep track of the pathogen species and
the degree of spatial segregation. To do this, samples from each plant in a plot of land need to be analyzed for which species of C/BYDV are present. The location of each sample also needs to be recorded to determine if spatial segregation is present. If the majority of species found are from Group I, we can expect there to be cross-protection (Haber 1995; Miller and Raschova 1997). Based on the model results from the cross-protection scenario, we would then expect to find a greater degree of spatial segregation of the species and less coinfection. If the species analyzed are from different groups, then we can expect synergism to be occurring (Miller and Raschova 1997). In this case, we would expect to find a lesser degree of spatial segregation and more coinfection. If the expected results occur in the field, then we can be more confident that our model predicts real biological behavior.

Another field study that could be conducted would be to record the types of aphids found in the system and the degree of pathogen aggregation. If our model predicts biological behavior well, then the degree of aggregation will be correlated with the types of aphids found in the system. If the majority of aphids are winged, then we would expect there to be little aggregation. If the majority of aphids are wingless, then we would expect there to be more aggregation.

A laboratory experiment could also be conducted in which single plants are placed in pots arranged in a lattice formation. Two lattices of plants would be set up to represent one spatial setting and one nonspatial setting. For the spatial setting, the pots would remain unmoved for the whole experiment. For the nonspatial setting, the pots
could be moved around to create a well-mixed population. The plants could then be sampled to determine the prevalence of infection and the degree of aggregation. From this experiment, we would expect to see less coinfection and more aggregation in the spatial setting compared to the nonspatial setting.
References


Appendix
clear all

alpha = 1;       % rate from V to S
phi1 = 1;        % rate at which singly infecteds produce susceptibles compared to susceptibles producing susceptibles
phi2 = 1;        % rate at which doubly infecteds produce susceptibles compared to susceptibles producing susceptibles
nu0 = .1;        % death rate for S
beta = 1;        % rate of becoming singly infected
q = 1/2;         % how infectious doubly infecteds are compared to singly infecteds
nu1 = .1;        % death rate of singly infecteds
k = 1;           % coefficient to scale infection rate from singly infected to doubly infected
nu2 = 0;         % increase in death rate for doubly infecteds

maxtime = 250;   % maximum time
size=50;         % lattice size (size x size)
z=4;             % neighborhood size

stream = RandStream('mt19937ar','Seed',floor(rem(now,1)*1e8));

thestate=randsrc(size,size,[0 1 2 3 4 ; .1 .3 .2 .2 .2]);  % initial state of the lattice

j=1;             % start the counter
s(1)=0;          % initial time is 0
timespent=zeros(4,size^2+1);  % preallocation for time spent in each state
rate=zeros(size); % preallocation for rate matrix

PAS=zeros(size,size);  % preallocation for conditional probabilities
PBS=zeros(size,size);
PBA=zeros(size,size);
PAB=zeros(size,size);
PAA=zeros(size,size);
PBB=zeros(size,size);
rate1=zeros(size,size);
rate2=zeros(size,size);
rate3=zeros(size,size);
snapshot=zeros(size,size,maxtime);  % preallocation to take snapshots of the state matrix

I=zeros(1,5);  % preallocation vector for number of individuals in each state
local=zeros(size,size,5);  % counts the number of each type of individual in the neighborhood [ #V #S #IA #IB #IAB ]

for n=1:size  %go through rows
   for m=1:size  %go through columns

   %look to the north
   if n==1
      local(n,m,thestate(size,m)+1)=local(n,m,thestate(size,m)+1)+1;
   else
      local(n,m,thestate(n-1,m)+1)=local(n,m,thestate(n-1,m)+1)+1;
   end

   %look to the west
   if m==1
      local(n,m,thestate(n,size)+1)=local(n,m,thestate(n,size)+1)+1;
   else
      local(n,m,thestate(n,m-1)+1)=local(n,m,thestate(n,m-1)+1)+1;
   end

   %look to the south
   if n==size
      local(n,m,thestate(1,m)+1)=local(n,m,thestate(1,m)+1)+1;
   else
      local(n,m,thestate(n+1,m)+1)=local(n,m,thestate(n+1,m)+1)+1;
   end

   %look to the east
   if m==size
if thestate(n,m)==0 %if the current state of the cell is V
    l(j,1)=l(j,1)+1; %add one V to the V column of I for time step j
    rate(n,m)=alpha*(local(n,m,2)+phi1*local(n,m,3)+phi1*local(n,m,4)+phi2*local(n,m,5))/z; %calculate rate from V to S
else if thestate(n,m)==1 %if the current state of the cell is S
    l(j,2)=l(j,2)+1; %add one S to the S column of I for time step j
    rate1(n,m)=beta*(local(n,m,3)/z + q*local(n,m,5)/z); %calculate rate from S to IA
    rate2(n,m)=beta*(local(n,m,4)/z + q*local(n,m,5)/z); %calculate rate from S to IB
    rate3(n,m)=nu0; %calculate rate from S to V
    PAS(n,m)=(local(n,m,3)+q*local(n,m,5))/z; %probability of a neighbor with A
    PBS(n,m)=(local(n,m,4)+q*local(n,m,5))/z; %probability of a neighbor with B
else if thestate(n,m)==2 %if the current state is IA
    l(j,3)=l(j,3)+1; %add one IA to the IA column of I for time step j
    rate1(n,m)=k*beta*(local(n,m,3)/z+q*local(n,m,5)/z); %calculate rate from IA to IX
    rate2(n,m)=nu1; %calculate rate from IA to V
    rate(n,m)=rate1(n,m)+rate2(n,m);
    PBA(n,m)=(local(n,m,3)+q*local(n,m,5))/z; %probability of a neighbor with B
    PAA(n,m)=(local(n,m,3)+q*local(n,m,5))/z; %probability of a neighbor with A
else if thestate(n,m)==3 %if the current state of the cell is IB
    l(j,4)=l(j,4)+1; %add one IB to the IB column of I for time step j
    rate1(n,m)=k*beta*(local(n,m,3)/z+q*local(n,m,5)/z); %calculate rate from IB to IX
    rate2(n,m)=nu1; %calculate rate from IB to V
    rate(n,m)=rate1(n,m)+rate2(n,m);
    PBB(n,m)=(local(n,m,3)+q*local(n,m,5))/z; %probability of a neighbor with B
    PAB(n,m)=(local(n,m,3)+q*local(n,m,5))/z; %probability of a neighbor with A
else I(j,5)=I(j,5)+1; %rate from IX to V
end
end
end
end
while (s(j)<=maxtime && (l(j,3)+l(j,4)+l(j,5))>0) %run loop while s is less than max time and the # of infecteds is positive
    sumrate=sum(sum(rate)); %sum of all rates
    sojourn=exprnd(1/sumrate,stream); %sojourn time
    s(j+1)=s(j)+sojourn; %adding on sojourn time to current time
    if s(j) >= 50
        timespent(1,l(j,2)+1)=timespent(1,l(j,2)+1)+sojourn; %time spent in each state for each type of infected
        timespent(2,l(j,3)+1)=timespent(2,l(j,3)+1)+sojourn;
        timespent(3,l(j,4)+1)=timespent(3,l(j,4)+1)+sojourn;
        timespent(4,l(j,5)+1)=timespent(4,l(j,5)+1)+sojourn;
        meanPAS(j)=sum(sum(PAS))/l(j,2); %mean of PAS for each state
        meanPBS(j)=sum(sum(PBS))/l(j,2);
        meanPBA(j)=sum(sum(PBA))/l(j,3);
        meanPAB(j)=sum(sum(PAB))/l(j,4);
        meanPAA(j)=sum(sum(PAA))/l(j,3);
        meanPBB(j)=sum(sum(PBB))/l(j,4);
    end
rate4=reshape(rate,1,size^2); %turns the rate matrix into a vector
    cell=find(mnrnd(1,rate4/sumrate)==1); %picks a random cell to change
    myrow=mod(cell,size); %find the row of the randomly picked cell
    if myrow==0
        myrow=size;
    end
    mycol=cell(size); %find the column of the randomly picked cell
end
u=unifrnd(0,1);
myrowplus1=myrow+1;
myrowminus1=myrow-1;
mycolplus1=mycol+1;
mycolminus1=mycol-1;

if myrowplus1==size+1
    myrowplus1=1;
end;
if myrowminus1==0
    myrowminus1=size;
end;
if mycolplus1==size+1
    mycolplus1=1;
end;
if mycolminus1==0
    mycolminus1=size;
end;

if thestate(myrow,mycol)==0                       %if the current state is V
    thestate(myrow,mycol)=1;                       %change the state to S
    I(j+1,1)=I(j,1)-1;
    I(j+1,2)=I(j,2)+1;
    I(j+1,3)=I(j,3);
    I(j+1,4)=I(j,4);
    I(j+1,5)=I(j,5);
    local(myrowplus1,mycol,1)=local(myrowplus1,mycol,1)-1;
    local(myrowplus1,mycol,2)=local(myrowplus1,mycol,2)+1;
    local(myrowminus1,mycol,1)=local(myrowminus1,mycol,1)-1;
    local(myrowminus1,mycol,2)=local(myrowminus1,mycol,2)+1;
    local(myrow,mycolplus1,1)=local(myrow,mycolplus1,1)-1;
    local(myrow,mycolplus1,2)=local(myrow,mycolplus1,2)+1;
    local(myrow,mycolminus1,1)=local(myrow,mycolminus1,1)-1;
    local(myrow,mycolminus1,2)=local(myrow,mycolminus1,2)+1;
else if thestate(myrow,mycol)==1                  %if the current state is S
    PAS(myrow,mycol)=0;
    PBS(myrow,mycol)=0;
    if u<(rate1(myrow,mycol)/rate(myrow,mycol))
        thestate(myrow,mycol)=2;                       %either change to IA
        I(j+1,1)=I(j,1);
        I(j+1,2)=I(j,2)-1;
        I(j+1,3)=I(j,3)+1;
        I(j+1,4)=I(j,4);
        I(j+1,5)=I(j,5);
        local(myrowplus1,mycol,2)=local(myrowplus1,mycol,2)+1;
        local(myrowplus1,mycol,3)=local(myrowplus1,mycol,3)+1;
        local(myrowminus1,mycol,2)=local(myrowminus1,mycol,2)+1;
        local(myrowminus1,mycol,3)=local(myrowminus1,mycol,3)+1;
        local(myrow,mycolplus1,2)=local(myrow,mycolplus1,2)+1;
        local(myrow,mycolplus1,3)=local(myrow,mycolplus1,3)+1;
    else if u<((rate1(myrow,mycol)+rate2(myrow,mycol))/rate(myrow,mycol))
        thestate(myrow,mycol)=3;          %or to IB
        I(j+1,1)=I(j,1);
        I(j+1,2)=I(j,2)-1;
        I(j+1,3)=I(j,3);
        I(j+1,4)=I(j,4)+1;
        I(j+1,5)=I(j,5);
        local(myrowplus1,mycol,2)=local(myrowplus1,mycol,2)-1;
    end;
end;
local(myrowminus1,mycol,2)=local(myrowminus1,mycol,2)-1;
local(myrowminus1,mycol,4)=local(myrowminus1,mycol,4)+1;
local(myrow,mycolplus1,2)=local(myrow,mycolplus1,2)-1;
local(myrow,mycolplus1,4)=local(myrow,mycolplus1,4)+1;
local(myrow,mycolminus1,2)=local(myrow,mycolminus1,2)-1;
local(myrow,mycolminus1,4)=local(myrow,mycolminus1,4)+1;
else thestate(myrow,mycol)=0;  %or to V
  I(j+1,1)=I(j,1)+1;
  I(j+1,2)=I(j,2)-1;
  I(j+1,3)=I(j,3);
  I(j+1,4)=I(j,4);
  I(j+1,5)=I(j,5);
  local(myrowplus1,mycol,2)=local(myrowplus1,mycol,2)-1;
  local(myrowplus1,mycol,1)=local(myrowplus1,mycol,1)+1;
  local(myrowminus1,mycol,2)=local(myrowminus1,mycol,2)-1;
  local(myrowminus1,mycol,1)=local(myrowminus1,mycol,1)+1;
  local(myrow,mycolplus1,2)=local(myrow,mycolplus1,2)-1;
  local(myrow,mycolplus1,1)=local(myrow,mycolplus1,1)+1;
end
else if thestate(myrow,mycol)==2                  %if the current state is IA
  PBA(myrow,mycol)=0;
  PAA(myrow,mycol)=0;
  if u<(rate1(myrow,mycol)/rate(myrow,mycol))   %
    thestate(myrow,mycol)=4;                  %either change to IX
    I(j+1,1)=I(j,1);
    I(j+1,2)=I(j,2);
    I(j+1,3)=I(j,3)-1;
    I(j+1,4)=I(j,4);
    I(j+1,5)=I(j,5)+1;
    local(myrowplus1,mycol,3)=local(myrowplus1,mycol,3)-1;
    local(myrowplus1,mycol,5)=local(myrowplus1,mycol,5)+1;
    local(myrowminus1,mycol,3)=local(myrowminus1,mycol,3)-1;
    local(myrowminus1,mycol,5)=local(myrowminus1,mycol,5)+1;
    local(myrow,mycolplus1,3)=local(myrow,mycolplus1,3)-1;
    local(myrow,mycolplus1,5)=local(myrow,mycolplus1,5)+1;
    local(myrow,mycolminus1,3)=local(myrow,mycolminus1,3)-1;
    local(myrow,mycolminus1,5)=local(myrow,mycolminus1,5)+1;
  else thestate(myrow,mycol)=0;                 %or to V
    I(j+1,1)=I(j,1)+1;
    I(j+1,2)=I(j,2);
    I(j+1,3)=I(j,3)-1;
    I(j+1,4)=I(j,4);
    I(j+1,5)=I(j,5);
    local(myrowplus1,mycol,3)=local(myrowplus1,mycol,3)-1;
    local(myrowplus1,mycol,1)=local(myrowplus1,mycol,1)+1;
    local(myrowminus1,mycol,3)=local(myrowminus1,mycol,3)-1;
    local(myrowminus1,mycol,1)=local(myrowminus1,mycol,1)+1;
    local(myrow,mycolplus1,3)=local(myrow,mycolplus1,3)-1;
    local(myrow,mycolplus1,1)=local(myrow,mycolplus1,1)+1;
    local(myrow,mycolminus1,3)=local(myrow,mycolminus1,3)-1;
    local(myrow,mycolminus1,1)=local(myrow,mycolminus1,1)+1;
end
else if thestate(myrow,mycol)==3              %if the current state is IB
  PAB(myrow,mycol)=0;
  PBB(myrow,mycol)=0;
  if u<(rate1(myrow,mycol)/rate(myrow,mycol))   %
    thestate(myrow,mycol)=4;                  %either change to IX
    I(j+1,1)=I(j,1);
    I(j+1,2)=I(j,2);
    I(j+1,3)=I(j,3);
    I(j+1,4)=I(j,4)-1;
    I(j+1,5)=I(j,5)+1;
  else thestate(myrow,mycol)=0;      %or to V
    I(j+1,1)=I(j,1)+1;
    I(j+1,2)=I(j,2);
    I(j+1,3)=I(j,3);
    I(j+1,4)=I(j,4);
    I(j+1,5)=I(j,5);
    local(myrowplus1,mycol,3)=local(myrowplus1,mycol,3)-1;
    local(myrowplus1,mycol,1)=local(myrowplus1,mycol,1)+1;
    local(myrowminus1,mycol,3)=local(myrowminus1,mycol,3)-1;
    local(myrowminus1,mycol,1)=local(myrowminus1,mycol,1)+1;
    local(myrow,mycolplus1,3)=local(myrow,mycolplus1,3)-1;
    local(myrow,mycolplus1,1)=local(myrow,mycolplus1,1)+1;
    local(myrow,mycolminus1,3)=local(myrow,mycolminus1,3)-1;
    local(myrow,mycolminus1,1)=local(myrow,mycolminus1,1)+1;
end
if thestate(myrow,mycol)==0   %if the current state of the cell is V
rate(myrow,mycol)=alpha*(local(myrow,mycol,2)+phi1*local(myrow,mycol,3)+phi1*local(myrow,mycol,4)+phi2*local(myrow,mycol,5))/z; %rate from V to S
else if thestate(myrow,mycol)==1   %if the current state is S
rate1(myrow,mycol)=beta*(local(myrow,mycol,3)/z + q*local(myrow,mycol,5)/z); %calculate rate from S to IA
rate2(myrow,mycol)=beta*(local(myrow,mycol,4)/z + q*local(myrow,mycol,5)/z); %calculate rate from S to IB
rate3(myrow,mycol)=nu0;       %calculate rate from S to V
rate(myrow,mycol)=rate1(myrow,mycol)+rate2(myrow,mycol)+rate3(myrow,mycol);
PAS(myrow,mycol)=(local(myrow,mycol,3)+q*local(myrow,mycol,5))/z;
PBS(myrow,mycol)=(local(myrow,mycol,4)+q*local(myrow,mycol,5))/z;
else if thestate(myrow,mycol)==2   %if the current state is IA
rate1(myrow,mycol)=k*beta*(local(myrow,mycol,4)/z+q*local(myrow,mycol,5)/z); %calculate rate from IA to IX
rate2(myrow,mycol)=nu1;       %calculate rate from IA to V
rate(myrow,mycol)=rate1(myrow,mycol)+rate2(myrow,mycol);
PBA(myrow,mycol)=(local(myrow,mycol,4)+q*local(myrow,mycol,5))/z;
PAA(myrow,mycol)=(local(myrow,mycol,3)+q*local(myrow,mycol,5))/z;
else if thestate(myrow,mycol)==3   %if the current state is IB
rate1(myrow,mycol)=k*beta*(local(myrow,mycol,3)/z+q*local(myrow,mycol,5)/z); %calculate rate from IB to IX
rate2(myrow,mycol)=nu1;       %calculate rate from IB to V
rate(myrow,mycol)=rate1(myrow,mycol)+rate2(myrow,mycol);
PAB(myrow,mycol)=(local(myrow,mycol,3)+q*local(myrow,mycol,5))/z;
end
end
if thestate(myrow,mycol)==0   %if the current state of the cell is V
rate(myrow,mycol)=alpha*(local(myrow,mycol,2)+phi1*local(myrow,mycol,3)+phi1*local(myrow,mycol,4)+phi2*local(myrow,mycol,5))/z; %rate from V to S
else if thestate(myrow,mycol)==1   %if the current state is S
rate1(myrow,mycol)=beta*(local(myrow,mycol,3)/z + q*local(myrow,mycol,5)/z); %calculate rate from S to IA
rate2(myrow,mycol)=beta*(local(myrow,mycol,4)/z + q*local(myrow,mycol,5)/z); %calculate rate from S to IB
rate3(myrow,mycol)=nu0;       %calculate rate from S to V
rate(myrow,mycol)=rate1(myrow,mycol)+rate2(myrow,mycol)+rate3(myrow,mycol);
PAS(myrow,mycol)=(local(myrow,mycol,3)+q*local(myrow,mycol,5))/z;
PBS(myrow,mycol)=(local(myrow,mycol,4)+q*local(myrow,mycol,5))/z;
else if thestate(myrow,mycol)==2   %if the current state is IA
rate1(myrow,mycol)=k*beta*(local(myrow,mycol,4)/z+q*local(myrow,mycol,5)/z); %calculate rate from IA to IX
rate2(myrow,mycol)=nu1;       %calculate rate from IA to V
rate(myrow,mycol)=rate1(myrow,mycol)+rate2(myrow,mycol);
PBA(myrow,mycol)=(local(myrow,mycol,4)+q*local(myrow,mycol,5))/z;
PAA(myrow,mycol)=(local(myrow,mycol,3)+q*local(myrow,mycol,5))/z;
else if thestate(myrow,mycol)==3   %if the current state is IB
rate1(myrow,mycol)=k*beta*(local(myrow,mycol,3)/z+q*local(myrow,mycol,5)/z); %calculate rate from IB to IX
rate2(myrow,mycol)=nu1;       %calculate rate from IB to V
rate(myrow,mycol)=rate1(myrow,mycol)+rate2(myrow,mycol);
PAB(myrow,mycol)=(local(myrow,mycol,3)+q*local(myrow,mycol,5))/z;
end
end
PBB(myrow,mycol)=(local(myrow,mycol,4)+q*local(myrow,mycol,5))/z;  
else rate(myrow,mycol)=nu1+nu2;   %rate from IX to V
end
end
end

if thestate(myrowplus1,mycol)==0   %if the current state of the cell is V
rate(myrowplus1,mycol)=alpha*(local(myrowplus1,mycol,2)+phi1*local(myrowplus1,mycol,3)+phi1*local(myrowplus1,mycol,4)+phi2*local(myrowplus1,mycol,5))/z; %rate from V to S
else if thestate(myrowplus1,mycol)==1 %if the current state of the cell is S
rate1(myrowplus1,mycol)=beta*(local(myrowplus1,mycol,3)/z + q*local(myrowplus1,mycol,5)/z); %calculate rate from S to IA
rate2(myrowplus1,mycol)=beta*(local(myrowplus1,mycol,4)/z + q*local(myrowplus1,mycol,5)/z); %calculate rate from S to IB
rate3(myrowplus1,mycol)=nu0; %calculate rate from S to V
rate(myrowplus1,mycol)=rate1(myrowplus1,mycol)+rate2(myrowplus1,mycol)+rate3(myrowplus1,mycol); %calculate rate from S to V
PAS(myrowplus1,mycol)=(local(myrowplus1,mycol,3)+q*local(myrowplus1,mycol,5))/z;
PBS(myrowplus1,mycol)=(local(myrowplus1,mycol,4)+q*local(myrowplus1,mycol,5))/z;
else if thestate(myrowplus1,mycol)==2 %if the current state is IA
rate1(myrowplus1,mycol)=k*beta*(local(myrowplus1,mycol,4)/z+q*local(myrowplus1,mycol,5)/z); %calculate rate from IA to IX
rate2(myrowplus1,mycol)=nu1; %calculate rate from IA to V
rate(myrowplus1,mycol)=rate1(myrowplus1,mycol)+rate2(myrowplus1,mycol); %calculate rate from IA to V
PBA(myrowplus1,mycol)=(local(myrowplus1,mycol,4)+q*local(myrowplus1,mycol,5))/z;
PAA(myrowplus1,mycol)=(local(myrowplus1,mycol,3)+q*local(myrowplus1,mycol,5))/z;
else if thestate(myrowplus1,mycol)==3 %if the current state is IB
rate1(myrowplus1,mycol)=k*beta*(local(myrowplus1,mycol,3)/z+q*local(myrowplus1,mycol,5)/z); %calculate rate from IB to IX
rate2(myrowplus1,mycol)=nu1; %calculate rate from IB to V
rate(myrowplus1,mycol)=rate1(myrowplus1,mycol)+rate2(myrowplus1,mycol); %calculate rate from IB to V
PBB(myrowplus1,mycol)=(local(myrowplus1,mycol,4)+q*local(myrowplus1,mycol,5))/z;
PAB(myrowplus1,mycol)=(local(myrowplus1,mycol,3)+q*local(myrowplus1,mycol,5))/z;
else rate(myrowplus1,mycol)=nu1+nu2;   %rate from IX to V
end
end
end

if thestate(myrowminus1,mycol)==0   %if the current state of the cell is V
rate(myrowminus1,mycol)=alpha*(local(myrowminus1,mycol,2)+phi1*local(myrowminus1,mycol,3)+phi1*local(myrowminus1,mycol,4)+phi2*local(myrowminus1,mycol,5))/z; %rate from V to S
else if thestate(myrowminus1,mycol)==1 %if the current state of the cell is S
rate1(myrowminus1,mycol)=beta*(local(myrowminus1,mycol,3)/z + q*local(myrowminus1,mycol,5)/z); %calculate rate from S to IA
rate2(myrowminus1,mycol)=beta*(local(myrowminus1,mycol,4)/z + q*local(myrowminus1,mycol,5)/z); %calculate rate from S to IB
rate3(myrowminus1,mycol)=nu0; %calculate rate from S to V
rate(myrowminus1,mycol)=rate1(myrowminus1,mycol)+rate2(myrowminus1,mycol)+rate3(myrowminus1,mycol); %calculate rate from S to V
PAS(myrowminus1,mycol)=(local(myrowminus1,mycol,3)+q*local(myrowminus1,mycol,5))/z;
PBS(myrowminus1,mycol)=(local(myrowminus1,mycol,4)+q*local(myrowminus1,mycol,5))/z;
else if thestate(myrowminus1,mycol)==2 %if the current state is IA
rate1(myrowminus1,mycol)=k*beta*(local(myrowminus1,mycol,4)/z+q*local(myrowminus1,mycol,5)/z); %calculate rate from IA to IX
rate2(myrowminus1,mycol)=nu1; %calculate rate from IA to V
rate(myrowminus1,mycol)=rate1(myrowminus1,mycol)+rate2(myrowminus1,mycol); %calculate rate from IA to V
PBA(myrowminus1,mycol)=(local(myrowminus1,mycol,4)+q*local(myrowminus1,mycol,5))/z;
PAA(myrowminus1,mycol)=(local(myrowminus1,mycol,3)+q*local(myrowminus1,mycol,5))/z;
else if thestate(myrowminus1,mycol)==3 %if the current state is IB
rate1(myrowminus1,mycol)=k*beta*(local(myrowminus1,mycol,3)/z+q*local(myrowminus1,mycol,5)/z); %calculate rate from IB to IX
rate2(myrowminus1,mycol)=nu1; %calculate rate from IB to V
rate(myrowminus1,mycol)=rate1(myrowminus1,mycol)+rate2(myrowminus1,mycol); %calculate rate from IB to V

if thestate(myrow,mycolplus1)==0   %if the current state of the cell is V
rate(myrow,mycolplus1)=alpha*(local(myrow,mycolplus1,2)+phi1*local(myrow,mycolplus1,3)+phi1*local(myrow,mycolplus1,4)+phi2*local(myrow,mycolplus1,5))/z; %rate from V to S
else if thestate(myrow,mycolplus1)==1 %if the current state of the cell is S
rate1(myrow,mycolplus1)=beta*(local(myrow,mycolplus1,3)/z + q*local(myrow,mycolplus1,5)/z);   %calculate rate from S to IA
rate2(myrow,mycolplus1)=beta*(local(myrow,mycolplus1,4)/z + q*local(myrow,mycolplus1,5)/z);   %calculate rate from S to IB
rate3(myrow,mycolplus1)=nu0;   %calculate rate from S to V
rate(myrow,mycolplus1)=rate1(myrow,mycolplus1)+rate2(myrow,mycolplus1)+rate3(myrow,mycolplus1);
PBA(myrow,mycolplus1)=(local(myrow,mycolplus1,4)+q*local(myrow,mycolplus1,5))/z;
PAA(myrow,mycolplus1)=(local(myrow,mycolplus1,3)+q*local(myrow,mycolplus1,5))/z;
else if thestate(myrow,mycolplus1)==2 %if the current state is IA
rate1(myrow,mycolplus1)=k*beta*(local(myrow,mycolplus1,4)/z+q*local(myrow,mycolplus1,5)/z);  %calculate rate from IA to IX
rate2(myrow,mycolplus1)= nu1;    %calculate rate from IA to V
rate(myrow,mycolplus1)=rate1(myrow,mycolplus1)+rate2(myrow,mycolplus1);
PBA(myrow,mycolplus1)=(local(myrow,mycolplus1,4)+q*local(myrow,mycolplus1,5))/z;
PAA(myrow,mycolplus1)=(local(myrow,mycolplus1,3)+q*local(myrow,mycolplus1,5))/z;
else if thestate(myrow,mycolplus1)==3 %if the current state is IB
rate1(myrow,mycolplus1)=k*beta*(local(myrow,mycolplus1,3)/z+q*local(myrow,mycolplus1,5)/z);  %calculate rate from IB to IX
rate2(myrow,mycolplus1)= nu1;    %calculate rate from IB to V
rate(myrow,mycolplus1)=rate1(myrow,mycolplus1)+rate2(myrow,mycolplus1);
PBA(myrow,mycolplus1)=(local(myrow,mycolplus1,4)+q*local(myrow,mycolplus1,5))/z;
PAA(myrow,mycolplus1)=(local(myrow,mycolplus1,3)+q*local(myrow,mycolplus1,5))/z;
else rate(myrow,mycolplus1)=nu1+nu2;      %rate from IX to V
end
end
end
if thestate(myrow,mycolminus1)==0   %if the current state of the cell is V
rate(myrow,mycolminus1)=alpha*(local(myrow,mycolminus1,2)+phi1*local(myrow,mycolminus1,3)+phi1*local(myrow,mycolminus1,4)+phi2*local(myrow,mycolminus1,5))/z; %rate from V to S
else if thestate(myrow,mycolminus1)==1 %if the current state of the cell is S
rate1(myrow,mycolminus1)=beta*(local(myrow,mycolminus1,3)/z + q*local(myrow,mycolminus1,5)/z);   %calculate rate from S to IA
rate2(myrow,mycolminus1)=beta*(local(myrow,mycolminus1,4)/z + q*local(myrow,mycolminus1,5)/z);   %calculate rate from S to IB
rate3(myrow,mycolminus1)=nu0;   %calculate rate from S to V
rate(myrow,mycolminus1)=rate1(myrow,mycolminus1)+rate2(myrow,mycolminus1)+rate3(myrow,mycolminus1);
PAS(myrow,mycolminus1)=(local(myrow,mycolminus1,3)+q*local(myrow,mycolminus1,5))/z;
PBS(myrow,mycolminus1)=(local(myrow,mycolminus1,4)+q*local(myrow,mycolminus1,5))/z;
else if thestate(myrow,mycolminus1)==2 %if the current state is IA
rate1(myrow,mycolminus1)=k*beta*(local(myrow,mycolminus1,4)/z+q*local(myrow,mycolminus1,5)/z);  %calculate rate from IA to IX
rate2(myrow,mycolminus1)= nu1;    %calculate rate from IA to V
rate(myrow,mycolminus1)=rate1(myrow,mycolminus1)+rate2(myrow,mycolminus1);
PBA(myrow,mycolminus1)=(local(myrow,mycolminus1,4)+q*local(myrow,mycolminus1,5))/z;
PAA(myrow,mycolminus1)=(local(myrow,mycolminus1,3)+q*local(myrow,mycolminus1,5))/z;
else if thestate(myrow,mycolminus1)==3 %if the current state is IB
rate1(myrow,mycolminus1)=k*beta*(local(myrow,mycolminus1,3)/z+q*local(myrow,mycolminus1,5)/z);  %calculate rate from IB to IX
rate2(myrow,mycolminus1)= nu1;    %calculate rate from IB to V
rate(myrow,mycolminus1)=rate1(myrow,mycolminus1)+rate2(myrow,mycolminus1);
PAS(myrow,mycolminus1)=(local(myrow,mycolminus1,3)+q*local(myrow,mycolminus1,5))/z;
PBS(myrow,mycolminus1)=(local(myrow,mycolminus1,4)+q*local(myrow,mycolminus1,5))/z;
else rate(myrow,mycolminus1)=nu1+nu2;      %rate from IX to V
end
end
end
rate(myrow,mycolminus1)=rate1(myrow,mycolminus1)+rate2(myrow,mycolminus1);
PAB(myrow,mycolminus1)=(local(myrow,mycolminus1,3)+q*local(myrow,mycolminus1,5))/z;
PBB(myrow,mycolminus1)=(local(myrow,mycolminus1,4)+q*local(myrow,mycolminus1,5))/z;
else rate(myrow,mycolminus1)=nu1+nu2; %rate from IX to V
end
end
end

if floor(s(j))==floor(s(j)+1) %take a snapshot of the state every time s(n) crosses an integer value
    snapshot(:,:,floor(s(j+1)))=thestate;
end;
j=j+1;
end

figure(1) %plots stairs of infecteds of all three types
sinit=find(s>=50,1);
x=s(1,sinit:j);
y=I(sinit:j,2);
y2=I(sinit:j,3);
y3=I(sinit:j,4);
y4=I(sinit:j,5);
stairs(x,y,'blue')
hold on
stairs(x,y2,'green')
stairs(x,y3,'red')
stairs(x,y4,'magenta')
axis([50 maxtime 0 size^2])
xlabel('time')
ylabel('# of individuals')
title('spatial one host-two pathogen model with host demography')
legend('S','IA','IB','IX')
hold off
saveas(figure(1),'figure 1')

figure(2) % grid of the state at time 150
pcolor(snapshot(:,:,150))
colormap([1 1 1; 0.6 1 0.6; 0.1 0.1 0.7; 0.7 0 0; 0.8 0.4 0.8])
colorbar
saveas(figure(2),'figure 2')

meanPAA=meanPAA(sinit:j-1);
meanPBB=meanPBB(sinit:j-1);
meanPAS=meanPAS(sinit:j-1);
meanPBS=meanPBS(sinit:j-1);
meanPAB=meanPAB(sinit:j-1);
meanPBA=meanPBA(sinit:j-1);

%PAA
PAAmean=diff(s(sinit:j))*transpose(meanPAA)/sum(diff(s(sinit:j)));
PAAvar=diff(s(sinit:j))*transpose(meanPAA)-PAAmean).^2/sum(diff(s(sinit:j)));
PAAstd=sqrt(PAAvar);

%PBB
PBBmean=diff(s(sinit:j))*transpose(meanPBB)/sum(diff(s(sinit:j)));
PBBvar=diff(s(sinit:j))*transpose(meanPBB)-PBBmean).^2/sum(diff(s(sinit:j)));
PBBstd=sqrt(PBBvar);

%PAB
PABmean=diff(s(sinit:j))*transpose(meanPAB)/sum(diff(s(sinit:j)));
PABvar=diff(s(sinit:j))*transpose(meanPAB)-PABmean).^2/sum(diff(s(sinit:j)));
PABstd=sqrt(PABvar);
%PBA
PBAmean=diff(s(sinit:j))*transpose(meanPBA)/sum(diff(s(sinit:j)));
PBAvar=diff(s(sinit:j))*(transpose(meanPBA)-PBAmean).^2/sum(diff(s(sinit:j)));
PBAstd=sqrt(PBAvar);

%PAS
PASmean=diff(s(sinit:j))*transpose(meanPAS)/sum(diff(s(sinit:j)));
PASvar=diff(s(sinit:j))*(transpose(meanPAS)-PASmean).^2/sum(diff(s(sinit:j)));
PASstd=sqrt(PASvar);

%PBS
PBSmean=diff(s(sinit:j))*transpose(meanPBS)/sum(diff(s(sinit:j)));
PBSvar=diff(s(sinit:j))*(transpose(meanPBS)-PBSmean).^2/sum(diff(s(sinit:j)));
PBSstd=sqrt(PBSvar);

%S
Smean=(timespent(1,:)/sum(timespent(1,:)))*transpose(0:size^2);
Svar=(timespent(1,:)/sum(timespent(1,:)))*(transpose(0:size^2)-Smean).^2;
Sstd=sqrt(Svar);

%IA
IAmean=(timespent(2,:)/sum(timespent(2,:)))*transpose(0:size^2);
IAvar=(timespent(2,:)/sum(timespent(2,:)))*(transpose(0:size^2)-IAmean).^2;
IAstd=sqrt(IAvar);

%IB
IBmean=(timespent(3,:)/sum(timespent(3,:)))*transpose(0:size^2);
IBvar=(timespent(3,:)/sum(timespent(3,:)))*(transpose(0:size^2)-IBmean).^2;
IBstd=sqrt(IBvar);

%IX
IXmean=(timespent(4,:)/sum(timespent(4,:)))*transpose(0:size^2);
IXvar=(timespent(4,:)/sum(timespent(4,:)))*(transpose(0:size^2)-IXmean).^2;
IXstd=sqrt(IXvar);