Synthesis

The Consequences of Spatial Structure for the Evolution of Pathogen Transmission Rate and Virulence

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abstract: The distribution of organisms in space can be an important mediator of species interactions, but its evolutionary effects on those interactions are only beginning to be explored. These effects may be especially relevant to pathogen-host interactions. A detailed understanding of how and when spatial structure will affect the evolution of pathogen traits is likely to aid our ability to control rapidly emerging infectious diseases. Here we review a growing body of theoretical studies suggesting that spatial structure can lead to the evolution of an intermediate pathogen transmission rate and virulence. We explain the results of these studies in terms of a competition-persistence trade-off. These studies strongly suggest that local host interactions, local host dispersal, and relatively low host reproduction rates create a host population spatial structure that enforces this trade-off and leads to the evolution of lower pathogen transmission rates and virulence. They also suggest that when spatial structure exists, it can dominate over the shape of the transmission-virulence trade-off in determining pathogen traits. We also identify important areas of future research, including quantifying pathogen fitness in a spatial context in order to gain a more mechanistic understanding of the effects of spatial structure and observationally and experimentally testing theoretical predictions.

Keywords: spatial structure, pathogen virulence, transmission rate, competition-persistence trade-off, pathogen evolution.

Introduction

Far from the straightforward descriptions found in many traditional mathematical models, species interactions are frequently mediated by external factors. Classic examples include indirect mediation by a third species (Abrams 1995; Werner and Peacor 2003) and direct mediation by the environment (Chesson 1985; Taylor 1998; Chesson et al. 2004). Although often ignored, the spatial distribution of organisms can be an equally important mediator. Individuals within a population do not always mix randomly in space. Instead, interactions between individuals may be structured by extrinsic and intrinsic limitations on movement and dispersal. Besides potentially affecting the ecological dynamics of interacting species (reviewed in Kareiva 1990; Gilpin and Hanski 1991), reciprocal feedback between ecological and evolutionary dynamics suggests that spatial structure may have significant evolutionary effects (Thompson 1998; Hoffmeister et al. 2005; Fussmann et al. 2007; Kokko and López-Sepulcre 2007).

Particular attention has been paid to the potential evolutionary effects of spatial structure on species involved in exploitative interactions, such as predators and parasites. Interest in exploitative interactions stems from the long-standing paradox of "prudent predation," or "the tragedy of the commons" (Hardin 1968; Rankin et al. 2007). Consider a group of consumers that share the same resource. If the consumers overexploit the resource, they will drive it, and eventually themselves, to extinction. In contrast, if the consumers are prudent and conserve the resource, they will ensure long-term survival. The paradox is that a selfish consumer that utilizes the resource to a greater extent than other consumers has a higher relative fitness than nonselfish consumers. Over evolutionary time, then, selfish behavior and subsequent extinction should be favored by selection (Lewontin 1970). Spatial structure offers one possible resolution to this paradox, under certain conditions promoting the evolution of nonselfish, altruistic traits such as prudence (Lion and van Baalen 2008).

The evolutionary effects of spatial structure are likely to be especially relevant to pathogen-host interactions, one type of exploitative interaction. Pathogen populations are inherently structured in space by their division into discrete subpopulations within individual hosts. Host populations are also frequently, but not necessarily, spatially structured. Host population spatial structure arises when the opportunity for pathogen transmission between hosts depends on the spatial arrangement of hosts. In the case of an immobile host species such as a plant, spatial structure may arise as a consequence of distance-limited path-

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ogen dispersal (e.g., Roumagnac et al. 2004; Moreno et al. 2007). Or, in the case of a mobile host species such as an animal, spatial structure may be imposed by limitations on host movement or dispersal. For example, many animals have restricted home ranges, so that only individuals with home ranges in close proximity are likely to interact and transmit disease (e.g., Fulford et al. 2002).

Prudent predation is easily framed in the context of disease, with a prudent pathogen being one with an exploitation strategy that conserves susceptible hosts. A pathogen's exploitation strategy is largely determined by its virulence and transmission rate. Simple nonspatial models of disease dynamics predict that a pathogen will evolve to become avirulent and have infinitely fast transmission. However, many pathogens actually have intermediate to high virulence (e.g., tuberculosis, malaria, and many others), leading to the hypothesis that pathogen virulence and transmission are related through the within-host population growth rate (Levin and Pimentel 1981; Anderson and May 1982; Levin et al. 1982; May and Anderson 1982; Lenski 1988). With this trade-off incorporated, nonspatial models no longer predict avirulence. If the trade-off is one of increasing returns in transmission as virulence increases, the pathogen is predicted to evolve both infinitely high virulence and infinitely fast transmission, a nonprudent strategy that will lead to extinction. If, however, the trade-off is one of decreasing returns in transmission as virulence increases, the pathogen is instead predicted to evolve a more prudent strategy, in the form of intermediate virulence and intermediate transmission rates.

Alternatively, a growing number of studies in the literature suggest that host population spatial structure can also lead to the evolution of intermediate transmission rates and virulence. Here we review spatial structure as an explanation for the evolution of pathogen prudence. In the first section of our article, we explain background concepts that the reader must be familiar with to understand our review: common mathematical approaches to modeling pathogen-host dynamics, methods for predicting pathogen evolution in spatial and nonspatial contexts, and the evolutionary effects of a transmission-virulence trade-off and other aspects of host and pathogen ecology in a nonspatial context.

In the second section, we provide an in-depth review of spatial pathogen-host models from the literature, identifying key aspects of host and pathogen ecology that lead to the evolution of pathogen prudence and comparing the potential effects of space with those of the transmission-virulence trade-off. Although the general conditions that promote the evolution of altruism in a spatial context have been summarized (Lion and van Baalen 2008), the conditions specific to pathogen-host interactions have not. By comparing and interpreting spatial pathogen-host models, we show that spatially dependent host interactions (i.e., spatially dependent disease transmission), spatially dependent host dispersal, and relatively slow host reproduction can create a spatial structure that enforces a competition-persistence trade-off. We also point out that these models predict pathogen prudence regardless of the shape of the transmission-virulence trade-off. Finally, we review the handful of spatial models from the literature that include more complex aspects of host and pathogen ecology (host immunity, more-complicated host network structures, coinfection, superinfection, and free-living propagules) and discuss their potential importance for the evolution of pathogen transmission rate and virulence.

We conclude our article by discussing three important directions for future research. First, it is essential to clarify and further develop our quantitative understanding of the evolutionary effects of spatial structure. The ability to quantitatively predict the evolutionary trajectory of a pathogen's transmission rate in a spatial context can contribute to our ability to design appropriate intervention strategies for newly emerging infectious diseases (see, e.g., Débarre et al. 2007). Second, it is important to continue to develop existing, and create new, theoretical models of pathogen-host interactions, improving and refining our understanding of both the overall dynamics and the individual causal factors. Finally, in order to practically apply the knowledge gained from theoretical models, it is crucial to test the growing body of theoretical hypotheses both observationally and experimentally.

Background

Pathogen-Host Models

Nonspatial Models. The canonical nonspatial pathogen-host model for horizontally transmitted diseases consists of a set of ordinary differential equations describing the population of susceptible hosts S, infected hosts I, and hosts removed by recovery or death R (Anderson and May 1979; Diekmann and Heesterbeek 2000; Hethcote 2000). A simple example, often used as the basic framework for many spatial and nonspatial models, is given by the following equations:

$$\frac{ds}{dt} = (\lambda - \mu) \cdot s - \beta \cdot i \cdot s, \tag{1}$$

$$\frac{di}{dt} = \beta \cdot i \cdot s - (\alpha + \mu) \cdot i. \tag{2}$$

In this formulation, $s = S/N$ and $i = I/N$, where N is the total population size, such that s and i represent the fractions of the total population that are susceptible and in-

fected, respectively; λ is the host birth rate, μ is the host death rate, β is the pathogen's transmission rate, and α is the pathogen's virulence. The fraction of hosts removed at a given time t is $r(t) = 1 - s(t) - i(t)$, and the amount of time an individual spends in the pool of infected hosts is $1/(\alpha + \mu)$.

This relatively simple model is only one of a large family of models characterized by different assumptions. All models in this family share some common features. First, the pathogen population is not explicitly modeled but is inferred from the number of infected hosts. Second, each host is assumed to interact equally with all other hosts: pathogen transmission depends only on the relative numbers of infected and susceptible hosts in the population. Finally, the ability of a pathogen to invade a host population is determined by its basic reproductive ratio (R_0; Anderson and May 1979; May and Anderson 1979).

The concept of R_0 (reviewed and discussed in Diekmann et al. 1990; Heesterbeek and Dietz 1996; Hethcote 2000; Dieckmann 2002; Heesterbeek 2002; Heffernan et al. 2005; Roberts 2007) is closely related to the ecological and demographic concept of an individual's lifetime reproductive success (R). For a pathogen, R is the number of secondary infections caused by an average infected host or the number of secondary infections caused by a single infected individual per unit time ($\beta \cdot s(t)$) multiplied by the time spent in the infectious pool ($1/(\alpha + \mu)$). A more specific metric, R_0 is the lifetime reproductive success of a pathogen specifically when the host population is entirely susceptible ($s(t) = 1$),

$$R_0 = \frac{\beta}{\alpha + \mu}. \tag{3}$$

If $R_0 > 1$, then the pathogen will be able to successfully invade the host population.

Spatial Models. The majority of spatially explicit pathogen-host models are individual-based models (but see, e.g., Débarre et al. 2007; House and Keeling 2008) that track the state of individual hosts through time. Like nonspatial models, individual-based models (IBMs) simply track the presence or absence of the pathogen in each host. Most individual-based pathogen-host models assume fixed host location. These discrete state and space models are typically implemented as probabilistic cellular automata (PCAs). By definition, PCAs treat the host population size as a discrete variable. In addition, since space is limiting, host reproduction is inherently density dependent. Finally, PCAs are typically stochastic rather than deterministic.

Whether the host population in an IBM is spatially structured depends on how individual hosts interact. In this context, it is useful to think of the host population as a network where each node is an individual host and two nodes are connected if there is an opportunity for disease transmission between them. The connection kernel that describes the probability of interaction between nodes dictates the structural properties of the network and therefore the disease dynamics on that network (see, e.g., Keeling and Eames 2005; Eames and Keeling 2006; Webb et al. 2007). If all individuals have an equal probability of interacting with and transmitting disease to every other individual in the population, then the population is randomly mixing and nonspatial. If, however, each individual interacts with only a limited subset of other individuals, then the population may not be randomly mixing. For example, if the probability of two hosts interacting depends on the physical distance between them, then the population is spatially structured. If, on the other hand, the probability of two hosts interacting is random, then the population is effectively randomly mixed. Complex spatial models of host-pathogen interactions may allow the number of connections per individual host to vary across the population or in time (e.g., Bansal et al. 2007; Volz and Meyers 2007), or they may allow connections to be asymmetric, such that the disease can be unidirectionally transmitted between hosts (e.g., Meyers et al. 2006).

In general, there are two approaches to characterizing the dynamics of an IBM: simulation and correlation equations. In the former case, the dynamics are characterized by the statistical analysis of multiple independent simulations. In the latter case, the dynamics are characterized by a set of differential equations that describe the spatial moments or the spatial covariance of the system. Through the use of a pair-approximation method, the dynamics of the correlation equations are simplified so that they approximately describe correlations between pairs of neighboring hosts that can then be analyzed. Results obtained by simulation and pair approximation closely match each other (Sato et al. 1994; Haraguchi and Sasaki 2000; Kamo et al. 2007). Recently, it has been shown that including the effects of higher moments can improve the accuracy of the approximation (Peyrard et al. 2008).

Predicting the Evolution of Pathogen Transmission Rate and Virulence

For some nonspatial pathogen-host models, the evolutionarily stable transmission rate and virulence can be analytically determined by maximizing the pathogen's basic reproductive ratio (R_0; Bremermann and Thieme 1989; Roberts 2007). In those cases, the pathogen with the highest initial growth rate, quantified by R_0, is competitively superior to all other pathogens from the moment of invasion to equilibrium. Although attractive for its simplicity, the R_0 maximization approach to determining the evo-

lutionarily stable transmission rate and virulence is not without limitations. Perhaps the biggest limitation is that this approach is accurate only if selection is not frequency dependent and the demographic and epidemiological rates are not density dependent (Dieckmann 2002). In those cases, a pathogen with the highest initial growth rate may not be competitively superior later, when the host population is not entirely susceptible. In addition, the R_0 maximization approach ignores short-term evolutionary dynamics, giving only the long-term evolutionary end point. To avoid these limitations, a different approach is required. One commonly used alternative is an adaptive-dynamics approach (Hofbauer and Sigmund 1990; Nowak and Sigmund 1990; Dieckmann 1997; Waxman and Gavrilets 2005), which uses the pathogen's invasion fitness rather than R_0 to determine the evolutionarily stable transmission rate and virulence, if one exists. Another, less utilized alternative is a quantitative-genetics approach (e.g., Day and Proulx 2004).

Because of their complexity, the evolutionary dynamics of spatial host-pathogen models have to be analyzed with an adaptive-dynamics approach utilizing either pair-correlation equations to derive a pathogen's invasion fitness (Matsuda et al. 1992; Sato et al. 1994) or simulation. By simulation, the evolutionarily stable transmission rate or virulence (again, if one exists) can be estimated with stochastic invasion sequences. Starting with a host population in equilibrium with a resident pathogen strain, a mutant strain with a trait value close to that of the resident strain is introduced. The process continues until a mutant strain with the evolutionarily stable transmission rate or virulence invades so that the trait under selection no longer changes. To be accurate, such simulations should allow the system to reach equilibrium before new mutant strains are introduced. However, especially in large spatial systems, equilibration may take an inordinate amount of time, and many authors instead infer the evolutionarily stable trait value by averaging across all pathogen strains in the population at a given time. The evolutionarily stable trait values estimated by simulation generally match those estimated with correlation equations (Kamo et al. 2007).

Transmission Rate and Virulence Evolution in a Nonspatial Context

Through the development of nonspatial models, a multitude of potential controls on pathogen evolution have been identified. Perhaps the most prominent—and sometimes controversial—aspect of pathogen ecology that can theoretically influence the evolution of a pathogen's transmission rate and virulence is a trade-off between the two (Levin and Pimentel 1981; Anderson and May 1982; Levin et al. 1982; May and Anderson 1982; Lenski 1988; Lipsitch and Moxon 1997). The trade-off theory of pathogen evolution arose from the observation that in simple disease models, selective maximization of R_0 should lead to the evolution of maximum transmission rates and minimal virulence (according to eq. [3], maximum β plus minimum α maximizes R_0). In reality, among the known pathogens in the world, many exhibit intermediate to high virulence. The existence of a trade-off between transmission and virulence is one explanation for this variation. This trade-off could arise because of a linkage between transmission and virulence through the within-host population growth rate of the pathogen or because of other within-host mechanisms.

A transmission-virulence trade-off can take one of three basic shapes: linear, concave up, or concave down. A linear transmission-virulence trade-off occurs, for example, if an increase in within-host reproduction proportionally increases both transmission rate and virulence. In contrast, a concave-up trade-off occurs when an increase in within-host reproduction disproportionately increases transmission rate over virulence. Finally, a concave-down trade-off occurs when an increase in within-host reproduction disproportionately increases the virulence over the transmission rate. In other words, the benefits of an increased transmission rate are offset by the accelerating costs of virulence.

When the conditions for R_0 maximization are met, the evolutionary effects of different transmission-virulence trade-off shapes can easily be assessed. Rather than avirulence and maximum transmission rates, both linear and concave-up trade-offs lead to the evolution of maximal virulence and transmission rates. In contrast, a concave-down trade-off leads to the evolution of intermediate virulence and transmission rates, or prudence. When the conditions for R_0 maximization are not met, the evolutionary effects of different transmission-virulence trade-off shapes may or may not differ from these general patterns (Dieckmann 2002). For example, if the simple model presented in equations (1) and (2) is modified to include density-dependent host reproduction, the evolutionary predictions generated by R_0 maximization and invasion analysis are quantitatively identical for all trade-off shapes. In contrast, a similar model with density-dependent host mortality and a concave-up transmission-virulence trade-off produces an evolutionary dimorphism not predicted by R_0 maximization (Pugliese 2002).

Many other aspects of host and pathogen ecology have been shown to influence the evolution of a pathogen's transmission rate and virulence in a nonspatial context: for example, the mode of transmission (Ewald 1993); the ability of a pathogen to coinfect or superinfect already infected hosts (Levin and Pimentel 1981; Bonhoeffer and Nowak 1994; Levin and Bull 1994; Mosquera and Adler

1998; Nowak and Sigmund 2002); disease life-history events, such as the time lag between the onset of transmission and the onset of pathogen-induced mortality (Day 2003); host mortality (Anderson and May 1982; Kakehashi and Yoshinaga 1992; Lenski and May 1994; Ebert and Weisser 1997; Choo et al. 2003); and free-living propagule survival rate (Bonhoeffer et al. 1996; Gandon 1998). More recently, theoretical evidence has been accumulating that host population spatial structure can also affect the evolution of a pathogen's transmission rate and virulence. In the following sections, we review the results of several spatial pathogen-host models. By comparing these models with each other and their nonspatial counterpart, we find that the evolutionary effects of space are strongest when host interactions are local, host dispersal is local, and the host reproduction rate is low. Together, these conditions enforce a competition-persistence trade-off.

Spatial Models of the Evolution of Pathogen Transmission and Virulence

The Competition-Persistence Trade-Off

Qualitatively, the effects of spatial structure on horizontally transmitted pathogens can best be understood in the framework of a trade-off between a pathogen's competitive ability and its persistence. Decomposed, the lifetime reproductive success of a pathogen (R) is the pathogen's basic reproductive ratio (R_0; eq. [3]) multiplied by the fraction of susceptible hosts in the population ($s(t)$). The first component, R_0, quantifies a pathogen's competitive ability when host resources are not limiting: of two different pathogen strains introduced into the same host population, the one with the higher R_0 will have a competitive advantage. The second component, $s(t)$, determines the length of time the pathogen will persist in the population when resources are limiting (i.e., there is not a constant supply of susceptible hosts): of two identical pathogen strains introduced into two different host populations of the same total size, the one in the population with the higher fraction of susceptible hosts will persist longer.

A competition-persistence trade-off arises when the factors that increase the pathogen's competitive ability also decrease its persistence time. For example, in the model captured by equations (1) and (2), a higher transmission rate increases the pathogen's competitive ability (R_0) but also decreases the size of the susceptible population ($s(t)$) and therefore the pathogen's persistence time (see, e.g., fig. 1 in Keeling 2000). Virulence, on the other hand, decreases the pathogen's competitive ability and increases its persistence time by decreasing the size of the pool of infected hosts and thus the likelihood that a susceptible host will interact with an infected host. For this model, then, a competition-persistence trade-off has the potential to lead to the evolution of an intermediate transmission rate and virulence, with selection balancing the benefits of higher competitive ability with the costs of lower persistence times. It is important to note that in some cases, the effects of virulence on persistence are not so straightforward. For example, if infected hosts can reproduce, less virulent pathogens will increase persistence by maintaining a large pool of infected hosts to reproduce. Ultimately, then, the effect of virulence on persistence will depend on the balance between the benefits and the costs of maintaining a large pool of infected hosts.

Although a competition-persistence trade-off conceptually exists in a nonspatial context, it does not affect the evolutionary trajectory of the pathogen because all pathogen strains share the same pool of susceptible hosts: if that shared pool disappears, all pathogen strains relying on it will become extinct. Therefore, in a nonspatial context, the persistence time of all pathogens is determined by the least persistent pathogen in the group. (A notable exception is when host population size is small enough that persistence time is influenced not just by the initial fraction of susceptibles but also by the possibility of stochastic extinction due to fluctuations in the fraction of infected hosts inherent in some host-pathogen dynamics; King et al. 2009.) In contrast, if the host population is spatially structured, two individuals infected by different pathogen strains do not necessarily share the same pool of host resources: one particular pathogen strain may overutilize its own pool of susceptible hosts and become extinct without also causing the extinction of every other pathogen strain. As a result, different pathogen strains can determine their own persistence time, and selection can act on the competition-persistence trade-off.

Simple Models

By far the most common spatial pathogen-host models in the literature are susceptible-infected individual-based PCAs in which coinfection and recovery are not allowed and the number of connections per host is constant across the population and fixed through time. These simple models are ideal for exploring the effects of a few basic aspects of host and pathogen ecology. Table 1 lists models of this type from the literature with their references, organized by the different aspects of host-pathogen ecology they capture, including the range of host interactions, the range of host dispersal, the host reproduction rate, and the shape of the transmission-virulence trade-off. The ranges of host interactions and host dispersal can vary from local to random, the host reproduction rate can be high (empty sites in the PCA are instantaneously colonized by susceptible hosts) or low (colonization of empty sites by susceptible

Table 1: Predicted transmission rates for a set of spatial models

Model type, reference	Trade-off type	Host interactions	Host reproduction rate	Host dispersal	β and α
1:					
Rand et al. 1995	None	Local	Low	Local	Different
Haraguchi and Sasaki 2000	None	Local	Low	Local	Different
Rauch et al. 2002	None	Local	Low	Local	Different
2:					
Boots and Sasaki 1999	Linear and concave up	Local	Low	Local	Different
Haraguchi and Sasaki 2000	Linear	Local	Low	Local	Different
Kamo et al. 2007	Linear	Local	Low	Local	Different
Boots and Sasaki 2000	Concave up	Local	Low	Local	Different
3:					
Boots and Sasaki 2000	Concave up	Local	Low	Random	Different[a]
4:					
Kamo et al. 2007	Linear	Intermediate	Low	Local	Different
Boots and Sasaki 1999	Concave up	Intermediate	Low	Local	Different
5:					
Kamo et al. 2007	Linear	Random	Low	Local	Same
Boots and Sasaki 1999	Concave up	Random	Low	Local	Same
6:					
Claessen and de Roos 1995	Concave down	Local	High	Local or random[b]	Same
7:					
Kamo et al. 2007	Concave down	Local	Low	Local	Different
8:					
Kamo et al. 2007	Concave down	Intermediate	Low	Local	Different[c]
9:					
Kamo et al. 2007	Concave down	Random	Low	Local	Same

Note: All models are probabilistic cellular automata where the number of contacts per host (4) is constant both across the population and in time. Host interactions are local when interactions occur only between directly adjacent hosts and random when interactions occur randomly. Host dispersal is similarly defined, with hosts reproducing into empty sites either locally or randomly. Coinfection is not allowed. Models with similar host and pathogen ecologies are grouped together by number. For the models that do not have a trade-off between transmission rate and virulence (type 1), the virulence is held fixed and only the transmission rate evolves. The last column indicates whether the model qualitatively predicts the same transmission rate (β) as a nonspatial model with the same transmission-virulence trade-off.

[a] The predicted value is smaller than that predicted by the nonspatial model but larger than that predicted by type 2 models.

[b] Because of the high reproduction rate, there is no effective difference between the cases of local and random host dispersal.

[c] The predicted value is larger than that for the equivalent nonspatial model.

hosts is determined by the demography of the host population), and the shape of the trade-off, if present, can be linear, concave up, or concave down. For each case of host-pathogen ecology, we indicate whether the model (or models) predicts the same or a different evolutionary outcome as a nonspatial model (i.e., the model in eqq. [1], [2]) with the same type of trade-off between transmission rate and virulence.

Note that in comparing the evolutionary dynamics of these spatial models with those of nonspatial models, it is important to consider the potential effects of discrete population sizes and stochasticity, both of which are characteristic of PCAs but not necessarily characteristic of nonspatial models and both of which can have significant consequences (Durrett and Levin 1994; Read and Keeling 2007). In the studies examined here, the authors have accounted for the potential effects of discreteness and stochasticity by comparing the dynamics of the spatial model with random mixing and the dynamics of an equivalent nonspatial, deterministic model. In the cases here, the dynamics are not significantly different, indicating that disparities that arise when other aspects of the spatial model are changed cannot be attributed to the effects of discreteness or stochasticity. Also important to consider is that density-dependent host reproduction, implicit in PCA models, does not influence the evolutionary effects of different transmission-virulence trade-off shapes.

Some interesting patterns emerge from comparisons across the models listed in table 1. First, it is clear that the most evolutionarily significant aspects of host and pathogen ecology among those that vary across these models are the range of host interactions and the rate of host reproduction. Regardless of the presence or form of the transmission-virulence trade-off or the range of host dis-

persal, if the host reproduction rate is low, local host interactions lead to the evolution of a transmission rate lower than that from either a nonspatial model (types 1–3, 7) or a similar model with a random interaction network (cf. types 2 and 5 and types 7 and 9). However, the effects of local host interactions can be overridden by a high host reproduction rate. The evolutionary trajectory of a spatial model with local host interactions and a high host reproduction rate is not different from that of a nonspatial model (type 6).

Table 1 also reveals that, although not essential to the qualitative outcome, the range of host dispersal is quantitatively important to the evolutionary effects of spatial structure. When host interactions are local and host reproduction is low, localized host dispersal amplifies the effects of spatial structure (cf. types 2 and 3), leading to transmission rates and virulence lower than those occurring when host dispersal is random. By itself, however, local host dispersal does not lead to the evolution of a transmission rate lower than that in a nonspatial model (type 9).

In the context of a competition-persistence trade-off, it becomes clear why the evolutionary effects of spatial structure on pathogen transmission rate and virulence are strongest when the host reproduction rate is low, host interactions are local, and host dispersal is local. A low host reproduction, in combination with local host interactions, ensures that different pathogen strains do not often share the same pool of susceptible hosts, so that selection can act on the competition-persistence trade-off. Low host reproduction allows the host population to segregate into distinct patches separated by dead hosts, and local host interactions limit the spread of the pathogen between patches, so that each host patch is typically infected by only one pathogen strain. If the host reproduction rate is high, there is no opportunity for the formation of distinct host population patches, and whether host interactions are local or not, the end result is that different pathogen strains will frequently share the same pool of susceptible hosts, so that selection cannot act on persistence. Note that these dynamics require that the space be large enough to contain multiple host patches. Otherwise, the dynamics are identical to those of a well-mixed system (Rauch and Bar-Yam 2006).

Recall that we define high host reproduction as the instantaneous colonization of empty sites by susceptible hosts and low host reproduction as anything that is not high. This definition is especially imprecise with respect to low host reproduction. Therefore, although a low host reproduction rate, as we define it, allows the potential for the host population to segregate into distinct patches, whether it does depends on the reproduction rate relative to the host's death rate and the pathogen's transmission rate and virulence. In the studies reviewed here, the demographic and epidemiological rates are such that the host population dynamics are characterized by a patchy distribution in space, but this is not necessarily always the case. Also note that empty space (or population regulation by the pathogen) is one of the conditions that Lion and van Baalen (2008) cite as favorable to the evolution of altruistic traits.

Finally, given a low host reproduction and local host interactions, local host dispersal further enforces the competition-persistence trade-off by restricting the effects of a particular pathogen strain to its own pool of susceptible hosts. Even if different pathogen strains do not share the same pool of susceptible hosts, host dispersal indirectly allows pathogen strains to influence pools of susceptible hosts other than their own. For example, random host dispersal from an area with a high density of susceptible hosts can replenish an area with a low density of susceptible hosts. However, because the effects are indirect, random host dispersal only weakens and cannot entirely negate the selective importance of the competition-persistence trade-off.

Comparing across the models in table 1 additionally suggests that in a spatial context and given local host interactions, local host dispersal, and low host reproduction, the shape of the transmission-virulence trade-off is not as critical as it is in a nonspatial context. In a nonspatial model, a linear or concave-up transmission-virulence trade-off leads to the evolution of infinite values of both, while a concave-down trade-off leads to finite, intermediate values of both. In contrast, spatial models with local host interactions, local host dispersal, and low host reproduction qualitatively predict intermediate transmission rates and virulence lower than that predicted by a nonspatial model for all forms of the trade-off and in the absence of a trade-off altogether (cf. types 1, 2, and 7).

Furthermore, a limited preliminary analysis of available results indicates that the quantitative difference in the evolutionary trajectory between spatial models with linear and concave-down trade-offs is small (see table 2). This suggests that when spatial structure exists with local host interactions, local host dispersal, and low host reproduction, spatial structure dominates over the form of transmission-virulence trade-off in determining pathogen transmission rate and virulence.

However, when host interactions are intermediate between local and random, the shape of the transmission-virulence trade-off can have important consequences (see types 4 and 8 in table 1). For example, assuming a linear (Kamo et al. 2007) or concave-up (Boots and Sasaki 1999) transmission-virulence trade-off, at some intermediate connectivity between local and random (the "critical connectivity") the evolutionarily stable pathogen virulence

Table 2: Quantitative comparison of evolutionarily stable transmission rate (β) and virulence (α) in spatial and nonspatial models

	Nonspatial model		Spatial model	
Trade-off shape	α	β	α	β
Linear or concave up	Maximal	Maximal	.15	.45
Concave down	.145	.29	.1	.21

Note: Virulence values for the spatial model were estimated from the cases with local host interactions ($L = 0.0$) in figures 1 and 5 in Kamo et al. (2007), and the transmission rates were calculated using the trade-off equations given by Kamo et al. (2007; first row: $\beta = 3\alpha$; second row: $\beta = 5 \cdot \log(\alpha + 1)$). The values for the nonspatial model were calculated by maximizing the expression for R_0, with the parameter values given for the spatial models: host death rate $d = 0.01$ and host growth rate $r = 3$.

quickly increases from an intermediate value to the value predicted by an equivalent nonspatial model. In contrast, with a concave-down trade-off, the evolutionarily stable virulence initially increases with the probability of random interactions, reaches a maximum value at some intermediate connectivity, and then declines slightly to the virulence predicted by an equivalent nonspatial model (Kamo et al. 2007). In addition, in the case of a linear trade-off, there is evolutionary bistability on a small interval below the critical connectivity, behavior that is not evident when the trade-off is concave down (Kamo et al. 2007).

More-Complex Models

The models reviewed above are relatively simple with respect to host and pathogen ecology. Here we briefly review a handful of spatial models that include more complicated aspects of host and pathogen ecology, such as host immunity, more complex host interaction networks, coinfection, superinfection, and propagule survival rate. While arguably more realistic, the complexity of these models makes it more difficult to interpret the dynamics in relation to the competition-persistence trade-off. Also, because these aspects of host and pathogen ecology can be modeled in numerous ways, it is not clear to what degree the results of these models are generalizable.

Host Immunity. Host immunity is an important aspect of host ecology that is not often included in spatial models. In a model with local host interactions, local host dispersal, relatively low host reproduction, and a constant transmission rate, if the rate of recovery (and therefore the acquisition of immunity) is inversely related to the virulence of the pathogen, then immunity leads to evolutionary bistability: high virulence or avirulence (Boots et al. 2004). Which strategy is realized depends on the prevalence and spatial arrangement of immune hosts, which, in addition to empty space, act as barriers to disease transmission. Because of the inverse relationship between virulence and the production of immune hosts, an initial epidemic caused by a low-virulence pathogen leads to the presence of numerous, widespread immune hosts, while a high-virulence strain results in fewer immune hosts and more empty space. In the former case, immune hosts retard the spread of all newly invading pathogen strains, and since high-virulence strains are more likely to kill their host before they have an opportunity to spread, selection favors avirulence. In the latter case, newly invading less virulent pathogens surround themselves with immune hosts before they have an opportunity to spread, and selection favors high virulence. Whether bistability occurs with other types of immunity (partial or temporary) or with other relationships between virulence and recovery has not been determined.

Host Network Structure. The simple spatial models reviewed above share the same basic host network structure, in which each host has the same number of connections and each connection is either local or random. Many other host network structures are possible, raising the question of whether the evolutionary role of local host interactions in enforcing the competition-persistence trade-off is consistent across all types of networks. Current evidence suggests that it may not be, at least in the context of pathogens for which there is permanent host immunity. In a model that includes permanent host immunity and a more complex host interaction structure, more-local host interactions lead to higher virulence than do global host interactions (Read and Keeling 2003). In this model, after an initial epidemic, the host population is fragmented into distinct host clusters separated from each other by barriers of immune hosts. When the network is structured locally, the clusters tend to be bigger (contain more hosts) and highly connected (hosts in the same cluster share many of the same contacts). As a consequence, new pathogen strains are more likely to arise in the same cluster and compete for the same susceptible hosts. In essence, each cluster is an isolated, well-mixed system where competition, not persistence, drives the evolutionary dynamics.

Coinfection. One study (Claessen and de Roos 1995) indicates that coinfection can allow for the evolution of reduced transmission and virulence even in the presence of high host reproduction. According to this model, the effect of coinfection on the evolutionary trajectory of pathogens in a spatial context depends on the combined virulence of the pathogens. Assuming that the combined virulence and transmission rate of pathogens in doubly infected hosts is independent of the virulence of pathogens on their

own, local host interactions, local host dispersal, a high host reproduction rate, and a concave-down transmission-virulence trade-off, this spatial model predicts that high combined virulence leads to the evolution of lower virulence, whereas low combined virulence leads to the evolution of high virulence. Like immune hosts or empty space, doubly infected hosts act as barriers to disease transmission because they cannot be infected a third time. When the virulence of doubly infected hosts is high, doubly infected hosts are not effective disease transmitters, and the host population segregates into distinct patches of singly infected hosts separated by doubly infected hosts. This spatial structuring selects for lower-virulence pathogens. When virulence of infected hosts is low, infected hosts are less spatially segregated, and higher virulence is selected.

Superinfection. Superinfection is a specific type of coinfection whereby higher-virulence pathogens displace low-virulence pathogens in doubly infected hosts. In a spatial model with local host interactions, local host dispersal, a relatively low host reproduction rate, and a linear trade-off between pathogen transmission and virulence, superinfection leads to the evolution of a lower transmission rate and virulence than does a similar model in a nonspatial context (Caraco et al. 2006). These results are qualitatively identical to the predictions of a simple spatial model without superinfection (e.g., type 2 in table 1) where local host interactions, local dispersal, and low host reproduction rates enforce a competition-persistence trade-off. Further studies are needed to determine whether superinfection quantitatively affects the evolutionarily stable transmission rate and virulence.

Free-Living Propagules. Many pathogens are able to persist for some time outside their host. For those pathogens, the length of time the free-living propagules can persist and the means of dissemination can affect the evolution of pathogen transmission rates and virulence. Here we consider a spatial model with local host interactions, local host dispersal, a low host reproduction rate, and host recovery in which infected hosts produce pathogen propagules that are disseminated (either throughout infection or upon the death of the infected host) to the site the host occupies plus the sites that it is in contact with (Kamo and Boots 2004). In this model, short-lived propagules lead to the evolution of transmission rates that are higher, though still intermediate, than those produced by long-lived propagules, regardless of the shape or existence of a transmission-virulence trade-off or the timing of propagule production. When there is a trade-off, the same pattern holds for the evolution of virulence. However, if there is no trade-off, then the evolutionarily stable virulence depends on the timing of propagule production. If the propagules are produced only when the host dies, then long-lived propagules lead to the evolution of higher virulence. Otherwise, both long- and short-lived propagules lead to the evolution of avirulence.

With respect to the pathogen's transmission rate, the results of this model are consistent with those of the simple models reviewed above, except that the particular transmission rate that optimally balances the benefits of increased competitive ability with the costs of decreased persistence depends on the life span of the free-living propagule. The evolutionary dynamics of virulence in this model are more complicated, partially because the model includes host recovery, an assumption that changes the relationship between virulence and pathogen persistence. Ultimately, the evolutionarily stable virulence balances the effects of virulence and recovery on persistence with the effect of virulence on competitive ability.

Selection Mechanism

Given the conditions that enforce a competition-persistence trade-off, there are several ways to interpret the resulting evolutionary dynamics. Some authors attribute the dynamics to individual-level selection (e.g., Boots and Sasaki 1999; Rauch et al. 2002) and others to multilevel (kin or group) selection (e.g., Boerlijst et al. 1993 for a host-parasitoid interaction; Claessen and de Roos 1995; Haraguchi and Sasaki 2000). Under both interpretations, the evolutionary driving force behind the dynamics is local feedback between the pathogen and the environment. Pathogens, or groups of pathogens, that reduce the local availability of susceptible hosts ultimately reduce their fitness. From the perspective of individual-level selection, the fitness effects of the environmental feedback loop are assessed at the level of the individual—a single pathogen strain infecting a single host—and have variously been called "self-shading" (Boots and Sasaki 1999, 2000; Haraguchi and Sasaki 2000) or "time-dependent fitness" (Rauch et al. 2002, 2003). In contrast, from the perspective of multilevel selection, the fitness effects are assessed at the group level: a cluster of hosts, each infected by the same pathogen strain or closely related pathogen strains. Regardless of the interpretation, the key to these evolutionary dynamics is the spatial aggregation of pathogen types so that the environmental effects of a particular pathogen strain are experienced exclusively by it and similar or related pathogens. Importantly, spatial assortment been identified as the basis for the evolution of altruism in general (Fletcher and Doebeli 2009).

It is important to note that the competition-persistence trade-off induced by spatial structure is not the same as the trade-off between a pathogen's transmission rate and

its virulence. Because the two trade-offs can have similar consequences (lower evolutionarily stable pathogen transmission rates and virulence), it is tempting to assume that spatial structure is another explanation for the existence of a transmission-virulence trade-off (see, e.g., Johnson and Boerlijst 2002). There is a critical distinction, however, between the two trade-offs. A competition-persistence trade-off is enforced at the level of the host population, while the transmission-virulence trade-off is enforced at the level of individual hosts.

Future Research

Theoretical work examining pathogen-host interactions has contributed significant insight into the effects of spatial structure on evolutionary dynamics. In particular, the importance of selected host and pathogen life-history traits has been thoroughly explored. However, our understanding of the effects of spatial structure is still incomplete, offering opportunity for advancement in diverse directions. Below we identify and outline what we see as the next big steps.

Quantifying Pathogen Fitness

Currently, our ability to quantitatively predict pathogen evolution in a spatial context is limited to certain specific cases. For example, while the pathogen's invasion fitness derived from pair-correlation equations is an accurate predictor of the evolutionarily stable transmission rate and virulence, it has been developed for only a narrow range of spatial models not including those with a variable number of contacts per host, either across the population or in time, or those with more complicated host dispersal and connection kernels. Expanding the analytical framework within which we can quantitatively predict the evolution of pathogen transmission rate and virulence will be useful in the context of predicting the effects of newly emerging infectious diseases.

Beyond successfully predicting the evolution of pathogen transmission rates and virulence, our understanding of the mechanism driving it in a spatial context ultimately will depend on the quantitative development and subsequent comparison of the three possible interpretations of the dynamics: individual, kin, or group selection. It is possible that these three interpretations are indistinguishable, as argued by Fletcher and Doebeli (2009). To determine whether they are distinguishable, each must be (1) associated with quantitatively different predictions of pathogen evolution and (2) compared with simulation results.

To date, the mathematical argument for individual selection is the best developed. From the invasion fitness of individual pathogen strains derived from pair-correlation equations, one can quantitatively and accurately predict a pathogen's evolutionarily stable transmission rate and virulence without explicitly invoking either kin or group selection. However, because the invasion fitness derived in this way depends on the equilibrium density of susceptible hosts surrounding an invading pathogen, it is nonetheless suggestive of multilevel selection. In fact, by defining the relatedness of pathogens as a spatiotemporal variable and using the invasion fitness of the pathogen derived from the pair-correlation equations, Hamilton's rule for the spread of altruism can easily be derived from the pair-density dynamics (Lion and van Baalen 2008). Although this formulation of Hamilton's rule does not immediately permit one to quantitatively predict a pathogen's transmission rate or virulence, it does suggest that such a prediction, reliant only on kin selection, is possible.

An alternative approach to quantitatively predicting a pathogen's evolutionarily stable transmission rate and virulence by using the hypothesis of individual selection is to define the pathogen's invasion fitness as a function of time (Rauch et al. 2002). In this way, the effect of the pathogen on its local environment can be incorporated into the selection dynamics without explicitly including it in the expression of pathogen fitness, thus eliminating the suggestion of multilevel selection. However, this approach is limited by the fact that the explicit shape of the time-dependent invasion fitness of a pathogen has so far been estimated only from simulations. Consequently, generating quantitative predictions that can be compared with both simulations and predictions generated by other approaches has been impossible.

Group selection, an extension of kin selection, is the least mathematically developed hypothesis of the three. Although general formulations of group selection have been derived (see, e.g., chap. 10 in Rice 2004), they have not been adapted specifically to pathogen transmission rate and virulence. Until these three hypotheses are sufficiently quantitatively developed, we will remain unsure which interpretation is correct and hence be limited in our understanding of the dynamics.

Modeling Developments

Continued exploration and development of spatial pathogen-host models will be invaluable. In addition to advancing our understanding of the factors that influence the evolution of pathogen transmission rate and virulence, models like those discussed in this review are useful tools for directing observational and experimental research.

This review suggests several interesting questions that can be addressed with existing models. First, is there a quantitative difference between the effects of spatial structure alone and the effects of a trade-off between trans-

mission rate and virulence? Although we suggest that spatial structure may have evolutionary effects as significant as those of a trade-off, the relative effects may differ, depending on the details of the model or the shape of the trade-off. Because both are potential alternative hypotheses to explain the evolution of pathogen prudence, a thorough exploration of their relative effects is important. Second, what is the shape of the relationship between the evolutionarily stable transmission rate and the host reproduction rate? Although we present evidence that such a relationship exists, it is insufficient to determine whether the relationship is smooth and continuous or whether there is a critical threshold reproduction rate. Finally, are the conditions that enforce the competition-persistence trade-off consistent across different types of host interaction networks? Given that different network structures exhibit different disease dynamics, they could also easily exhibit different evolutionary dynamics.

Many other questions can be addressed by further developing existing models. For example, while the coevolutionary dynamics of pathogen-host interactions have been studied with nonspatial models and the evolution of host traits alone have been studied with spatially explicit models (Richards et al. 1999), no studies have addressed coevolution in a spatial context. Pathogen-host interactions are particularly good candidates for coevolutionary change (Godfray et al. 1994). It is likely that coevolutionary relationships exist between host resistance and pathogen virulence, between pathogen-avoidance and host-seeking behavior, and between the host's ability to clear infection and the pathogen's ability to evade host defenses (Woolhouse et al. 2002). Undoubtedly, these coevolutionary relationships will influence the effects of spatial structure on the evolution of pathogen transmission rate and virulence.

In addition, through the use of nested models (reviewed in Mideo et al. 2008), the effects of spatial structure can more explicitly be related to the dynamics of the pathogen populations. For example, nested models have been used to examine the emergence of the hypothesized trade-off between pathogen transmission rate and virulence (Antia et al. 1994; Gilchrist and Sasaki 2002; Alizon and van Baalen 2005; Gilchrist and Coombs 2006). Nested models may be especially important in considerations of coinfection because they can explicitly treat competitive dynamics between pathogen strains in the same host (see, e.g., Read and Keeling 2006).

Experimental and Observational Validation

A perennial problem with modeling evolutionary dynamics is that the model predictions are usually very difficult to test experimentally. One of the advantages associated with modeling pathogen evolution is that pathogens, because of their ability to quickly adapt, are exceptionally well suited to experimental investigations. Two such studies have been done, one using moth larvae infected with their species-specific granulosis virus (Boots and Mealor 2007) and one using *Escherichia coli* and its T4 bacteriophage (Kerr et al. 2006). Both studies supported the hypothesis that local host interactions, in combination with local host dispersal, can lead to reduced pathogen virulence. Future studies should test the effects of local interactions, local dispersal, and low host reproduction independently and together in varying degrees.

In addition to experimentation, it may be possible to observationally validate theoretical predictions with existing data. Comparison of the transmission rates and virulences of pathogens that affect host populations characterized by different ecologies may reveal consistent patterns. Ideally, comparisons can be made between host populations infected with the same or closely related pathogen strains but in slightly different contexts. For example, comparing pathogen strains that infect two host populations, one that is more structured in space, perhaps because of landscape fragmentation, and one that is subject to fewer spatial constraints, addresses the evolutionary importance of the range of host dispersal. Comparing pathogen strains that infect different species of animals, some more prolific than others, addresses the evolutionary importance of host reproduction rate.

Conclusions

Simple nonspatial models of pathogen evolution predict that natural selection should maximize the basic reproductive ratio (R_0). The particular pathogen virulence or transmission rate that maximizes R_0 depends on the existence and shape of the trade-off between the transmission rate and virulence. If there is no trade-off, selection leads to maximal transmission rate and minimal virulence. If the trade-off is linear or concave up, selection leads to maximal transmission rate and maximal virulence. If the trade-off is concave down, selection leads to a finite and intermediate transmission rate and virulence. Alternatively, if the host population is spatially structured, then the evolution of a pathogen's transmission rate and virulence can be constrained by a trade-off between competitive ability and persistence. Pathogens with a higher transmission rate are more competitive than those with a low transmission rate but are more likely to cause their own extinction by reducing their access to susceptible hosts. The models reviewed here suggest that the most important aspects of pathogen and host ecology in a spatial context are the range of host dispersal, the range of pathogen transmission, and the rate of host reproduction. All

three factors enforce a competition-persistence trade-off by inducing a spatially patchy host population structure.

From the results presented in this review, spatial structure offers several advantages over the transmission-virulence trade-off theory as an explanation for the evolution of pathogen prudence. First, while some pathogens show evidence of a transmission-virulence trade-off (Messenger et al. 1999; de Roode et al. 2007), others do not (Bull 1994; Ebert and Bull 2003; Stewart et al. 2005). In the absence of a transmission-virulence trade-off, spatial models can predict an intermediate transmission rate, unlike nonspatial models, which predict infinitely fast transmission. An intermediate transmission rate is arguably a more realistic prediction and, more important, is in some cases a necessary component of prudence. Further, for pathogens that do exhibit a transmission-virulence trade-off, whether it is one of decreasing returns is not clear. Unlike nonspatial models, which require a trade-off of decreasing returns to predict intermediate transmission rates and virulence, spatial models can predict the same regardless of the specific shape of the transmission-virulence trade-off. Finally, while the explanatory power of a transmission-virulence trade-off is specific to pathogen-host interactions, the evolutionary effects of spatial structure are likely to extend to other types of exploitative interactions (e.g., Rauch and Bar-Yam 2006).

The continual, world-wide emergence of new, drug-resistant diseases and the ubiquity of spatial structure in human host populations emphasize the critical importance of understanding the evolutionary effects of spatial structure on pathogen-host interactions. Future research should focus on quantifying pathogen fitness in a spatial context, on further theoretical developments and exploration of spatial models, and on experimental and observational validation of those models.

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