

# Playing by Different Rules: The Evolution of Virulence in Sterilizing Pathogens

Kara J. O'Keefe<sup>1,\*</sup> and Janis Antonovics<sup>2,†</sup>

1. Department of Biology, Duke University, Durham, North Carolina 27708;

2. Department of Biology, University of Virginia, Charlottesville, Virginia 22904

Submitted February 7, 2001; Accepted December 1, 2001

---

**ABSTRACT:** We investigate the evolution of virulence of pathogens that reduce their hosts' fitness primarily by affecting host fecundity. We show that, under many conditions, such sterilizing pathogens evolve high rather than intermediate levels of virulence, and this pushes the pathogen population and sometimes the host population toward extinction. We also show that spatial population structure can reverse this evolutionary result and allow the persistence of intermediate-virulence pathogens. Thus, spatial population structure may be vital to the persistence of sterilizing pathogens in nature.

*Keywords:* disease, evolution of virulence, host-pathogen, individual-based model, sterilization, spatial population structure.

---

Models of the evolution of virulence have been developed over the past 20 yr to determine the conditions under which we expect pathogens to evolve to become more harmful or benign. Anderson and May (1982) established this line of investigation by using mathematical models (based on Kermack and McKendrick 1927) to demonstrate that, under certain basic assumptions, we should not necessarily expect pathogens to become benign, as conventional wisdom suggests. Rather, we should expect some well-adapted pathogens to inflict intermediate or even severe damage on their hosts.

Nearly all theory on the evolution of virulence (Anderson and May 1982; Bremermann and Pickering 1983; Bremermann and Thieme 1989; Lenski and May 1994; Nowak and May 1994; Claessen and de Roos 1995; van

Baalen and Sabelis 1995a; Bonhoeffer et al. 1996; Lipsitch et al. 1996; Taylor et al. 1998) makes two key assumptions. First, models equate pathogen virulence with extra host mortality, ignoring other possible disease symptoms. Second, the evolution of pathogen virulence is constrained by a positive, nonlinear relationship between virulence and pathogen transmission. As a result, pathogens that kill their hosts quickly are rewarded with high transmission rates but experience diminishing returns as virulence increases further. Thus, in the most basic form of these models, virulence evolution is constrained by a trade-off between longevity and transmission. Depending on the precise form of the trade-off, the pathogen settles into an evolutionarily stable state of intermediate added mortality and intermediate transmission rate.

We investigate the evolution of virulence of a large class of pathogens ("sterilizing pathogens") that reduce host fitness primarily through their effect on host fecundity. We maintain the relationship between virulence and pathogen transmission by assuming that the fecundity of infected hosts is a function of the pathogen's transmission rate. While we know of only one study that has looked for such a relationship explicitly (Bull and Molineux [1992] found that phage production is unchanged after selection on the phage to allow increased bacterial growth rate), such a relationship might be expected where pathogen reproduction destroys host reproductive tissue, as occurs in another smuts (Alexander and Antonovics 1995) and many animal sexually transmitted diseases. Sterilizing effects are characteristic of a variety of plant pathogens (Agrios 1997), parasitic castrators of invertebrate animals (Baudoin 1974), and sexually transmitted diseases (Lockhart et al. 1996). These diseases may have little or no effect on host mortality, and, therefore, we assume no relationship between infection-induced host mortality and pathogen transmission.

We begin with a simple differential equation model (Anderson and May 1979, 1982) generalized to allow infection to reduce host reproduction. Transmission rate and the sterility component of virulence will be the only pathogen

\* E-mail: kjo2@duke.edu.

† E-mail: ja8n@virginia.edu.

traits allowed to evolve, and, because of the relationship we assume between them, they will evolve in tandem.

We then present an individual-based, stochastic computer simulation model of a host-pathogen population in which time and space are discrete. We use the simulation to compare randomly mixing (nonspatial) host-pathogen populations with spatially structured ones in which population structure emerges from local dispersal of the host and pathogen.

### Analytical Model

We incorporate a pathogen's effect on host fecundity into a differential equation host-pathogen model similar to that presented by Anderson and May (1979, 1982). For simplicity, we assume that hosts do not recover and that they are all identical (i.e., there is no genetic, age-based, or sex-based variation among hosts). The following model tracks the density of susceptible and infectious hosts in a randomly mixing population:

$$\frac{dS_{\circ}}{dt_{\circ}} = b(S_{\circ} + \rho I_{\circ}) \left( \frac{K - N_{\circ}}{K} \right) - \beta_{\circ} S_{\circ} I_{\circ} - \mu_{\circ} S_{\circ},$$

$$\frac{dI_{\circ}}{dt_{\circ}} = \beta_{\circ} S_{\circ} I_{\circ} - (\alpha_{\circ} + \mu_{\circ}) I_{\circ},$$

where symbols are as defined in the top section of table 1. (The subscript  $\circ$  appears on parameters that are scaled by the nondimensionalization below.) This model can be simplified with the symbols in the bottom section of table 1. The following nondimensionalized form will be discussed in the rest of this article:

$$\frac{dS}{dt} = (S + \rho I)(1 - S - I) - \beta SI - \mu S, \quad (1)$$

$$\frac{dI}{dt} = \beta SI - (\mu + \alpha)I. \quad (2)$$

Note that  $S$  and  $I$  are host densities relative to the carrying capacity  $K$ . The rate parameters of the model ( $\beta$ ,  $\mu$ , and  $\alpha$ ) are in terms of the birth rate,  $b$ , which has become the unit of time.

For a given pathogen with transmission rate  $\beta$ , added mortality  $\alpha$ , and fecundity coefficient  $\rho$ , equations (1) and (2) predict a stable equilibrium point at which the pathogen and host can coexist:

**Table 1:** Symbols used in the analytical models

Symbol	Meaning
$S_{\circ}$	Density of susceptible hosts
$I_{\circ}$	Density of infected hosts
$K$	Carrying capacity
$t_{\circ}$	Time
$b$	Birth rate per susceptible host
$\rho$	Fecundity of infected host
$\beta_{\circ}$	Infection rate per infected host
$\mu_{\circ}$	Background mortality
$\alpha_{\circ}$	Disease-induced mortality
$S$	$S_{\circ}/K$
$I$	$I_{\circ}/K$
$t$	$t_{\circ}b$
$\beta$	$\beta_{\circ}K/b$
$\mu$	$\mu_{\circ}/b$
$\alpha$	$\alpha_{\circ}/b$

$$S^* = \frac{\mu + \alpha}{\beta}, \quad (3)$$

$$I^* = \frac{A + \sqrt{A^2 + 4\rho B}}{2\rho}, \quad (4)$$

where

$$A = \rho - \mu - \alpha - \frac{\mu + \alpha}{\beta}(1 + \rho),$$

$$B = \frac{\mu + \alpha}{\beta} \left( 1 - \frac{\mu + \alpha}{\beta} \right) - \frac{\mu(\mu + \alpha)}{\beta}.$$

The equilibrium densities of susceptible and infected hosts will change if  $\beta$ ,  $\alpha$ , and  $\rho$  change by evolution of the pathogen.

We introduce selection by allowing a host-pathogen system at equilibrium to be invaded by a new pathogen (of density  $I'$ ) with  $\beta'$ ,  $\alpha'$ , and  $\rho'$  and characteristic equilibria  $S'^*$  and  $I'^*$ . The two pathogens compete, and the winner becomes the resident for the next invasion. Successful invasion occurs if, at the resident's equilibrium, the invader's per capita growth rate is positive, that is, if

$$\left. \frac{1}{I'} \frac{dI'}{dt} \right|_{S^*, I^*} > 0,$$

$$\beta' S^* - (\mu + \alpha') > 0,$$

$$S^* > \frac{\mu + \alpha'}{\beta'}.$$

The quantity on the right is  $S^*$ , the density of susceptible hosts at the invader's equilibrium. It follows that an invader is successful and displaces a resident if the invader's characteristic  $S^{/*}$  is less than the current resident's equilibrium  $S^*$ . Evolution therefore always favors pathogen strains associated with lower equilibrium density of susceptible hosts; the pathogen with the  $\beta$ ,  $\alpha$ , and  $\rho$  that minimize  $S^*$ , if it exists, is uninventable. The same invasion criterion has been found for other models of the evolution of virulence (Anderson and May 1982; Dwyer et al. 1990).

For a sterilizing pathogen, which reduces host fecundity but does not affect the host's mortality, we assume that  $\alpha$ , the added mortality, is fixed at 0. We also assume that virulence and transmission are linked by a negative relationship between  $\rho$  and  $\beta$  so that high infected host fecundity corresponds to low transmission and vice versa. (The exact nature of the relationship will not matter, so long as it is strictly negative.)

Note that  $\rho$  appears in  $I^*$  in (4) but not in  $S^*$  in (3), which selection minimizes. Since  $\rho$  is absent from  $S^*$  and  $\alpha$  is fixed, transmission alone is under selection. To decrease  $S^*$ ,  $\beta$  has to increase, which means that, by assumption, host fecundity  $\rho$  decreases. In other words, this simple model predicts that if host fecundity declines with increasing pathogen transmission, then selection on the pathogen will cause host fecundity to decline toward 0.

Furthermore, if the relationship between infected host fecundity and transmission is such that fecundity can decrease all the way to 0 and  $\beta$  increases toward positive infinity, then as virulence and transmission increase, both  $S^*$  and  $I^*$  also fall toward 0. For  $I^*$ , we have shown this through numerical calculation over the full range of other parameters. Selection on the pathogen drives the host and pathogen toward extinction.

### The Individual-Based Simulation

To model spatial dynamics, we have constructed a stochastic, discrete-time, discrete-space, individual-based host-pathogen computer simulation in which individuals occupy sites in a square grid with edges that wrap together to form a torus. Each site can have one of three states: it can be occupied by a susceptible host, occupied by an infected host, or vacant. In a given time step, each site can remain in its current state or make one of the following possible transitions. A site occupied by a susceptible host can become infected (infection) or become vacant (death). An infected site can become vacant (death). A vacant site can become occupied by a susceptible host (birth) or become occupied by an infected host (birth plus infection). We permit newborn susceptible hosts to be infected before they reproduce (birth plus infection) so that the pathogen has the potential to sterilize its host completely, which is

consistent with the assumptions of our analytical model. As in the analytical model, all susceptible hosts are identical, and hosts do not recover from infection.

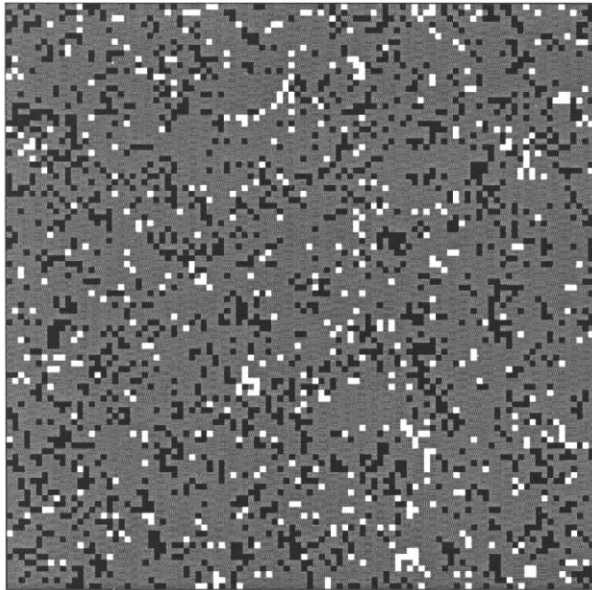
Births and infections are governed by explicit host progeny and pathogen spore dispersal. From each susceptible site, a random number of progeny (chosen from a Poisson distribution with a fixed mean) disperse. In what we refer to as a spatial simulation, dispersal moves each progeny to a nearby site. The distances moved from the source in the  $X$  and  $Y$  directions are chosen from a Gaussian distribution with mean 0. Dispersal distances used in the simulation are presented in the next section. In what we call a nonspatial simulation, progeny are dispersed globally to any site on the grid with uniform probability. (Note that in both the spatial and nonspatial simulations, the individual hosts themselves do not move.) Pathogen spores as well as progeny (if sterilization is not complete) disperse in the same way from each infected site. One or more progeny landing on a vacant site allows a birth at that site. One or more spores landing on a susceptible site or a site where progeny have landed allows the site to become infected in the next time step. If spores from more than one pathogen (which may differ from each other) land at the same susceptible site during the same time step, one of the spores is chosen at random to infect at that site. No secondary infections are allowed at an already infected site.

The rate of transmission  $\beta$  from a particular infected site (i.e., the mean number of spores dispersed per generation from that site) is an inherent characteristic of the pathogen at that site. It also determines the infected host's fecundity  $\rho$  by a negative function of one of several possible forms (detailed in the next section).

As with the analytical model, the only traits evolving in the simulation are infected host fecundity and pathogen transmission rate, which evolve in concert according to the functional relationship we have assumed. Mutations in pathogen transmission rate occur with a constant probability per pathogen. At every time step, one site in the grid is randomly selected. If the selected site is occupied by an infected host, that pathogen's transmission rate either increases or decreases by a fixed magnitude. The mutated transmission rate (along with the corresponding virulence) is passed to subsequent infections by spores from that site.

### Simulation Results

We present results from a  $100 \times 100$ -site grid. Unless otherwise stated, parameter values are as follows. The birth rate (the number of seeds produced per time step) of susceptible hosts is 1.0. Background mortality is 0.4. Initial pathogen transmission rate (the number of spores produced per infected individual per time step) is 4.0. In



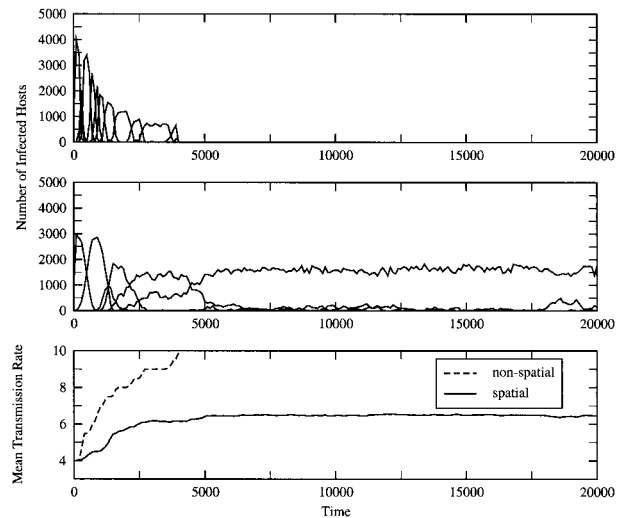
**Figure 1:** Image from a typical run of the spatial simulation at time step 25,000 with the default parameters listed in the text. White cells represent healthy hosts, black cells represent infected hosts, and gray cells are vacant.

simulation runs with local dispersal, the average dispersal distance of host and pathogen is 1.0 site. The fertility of infected hosts  $\rho$  is related to the transmission rate  $\beta$  by the quadratic form  $\rho = 1 - c\beta^2$ , where  $c = 0.01$ . The value of  $\rho$  can vary between 0 and 1.0, and therefore  $\beta$  can vary between 0 and  $(1/c)^{1/2} = 10$ . In the figures, we plot the transmission rate rather than virulence because it is the quantity directly undergoing mutation. One mutation occurs per time step with probability  $I \times 10^{-4}$  on a grid with  $10^4$  sites, where  $I$  is the number of infected hosts. The magnitude of mutations is 0.5 spores. Simulation runs begin with 50% of sites occupied by susceptible hosts and 10% occupied by infected hosts, randomly distributed on the grid. Spatial structure readily develops but remains fluid (fig. 1).

In simulation runs with global dispersal and in the absence of mutation, the population dynamics of the simulation runs match very precisely the dynamics of a randomly mixing difference equation model. In this nonspatial, non-evolving scenario, the host and pathogen populations persist (beyond time step 30,000) in more than 50% of runs for  $\beta$  between 0.85 and 9.90. When  $\beta < 0.85$ , the pathogen is usually lost and the host persists. When  $\beta > 9.90$ , the pathogen is usually lost and the host may or may not go extinct. When mutation is introduced, the pathogen population experiences successive invasions of mutants of higher and higher virulence and transmission. Just as in the analytical model, the pathogen does not reach an evo-

lutionarily stable state. Instead, its transmission rate increases to its maximum, and the pathogen population drives itself extinct (fig. 2).

When dispersal is local, the range of transmission rates that lead to host and pathogen persistence in a nonevolving system is only slightly narrower; more than 50% of runs result in host and pathogen coexistence when transmission rate is between 1.42 and 9.90. When the transmission rate is allowed to mutate, the population undergoes successive invasions by pathogen mutants. But in this instance, the system settles on one mutant with a particular virulence and transmission rate and remains there indefinitely (fig. 2). The transmission rate converges to the same value regardless of the size of the mutational change or the initial transmission rate (so long as the initial transmission rate lies within the range where the host and pathogen coexist), indicating that the predominant pathogen mutant at the



**Figure 2:** *Top*, dynamics of infected hosts in a typical simulation run with global dispersal. Each curve represents the population numbers of a pathogen mutant with a particular transmission rate. The system undergoes successive invasions by pathogens with higher and higher transmission rates (and virulence levels) until it exceeds the maximum transmission rate at which the pathogen can sustain itself. The pathogen may also drive the susceptible host population (not shown) extinct. Otherwise, the susceptible population recovers to its infection-free carrying capacity. *Middle*, dynamics of infected hosts in a typical spatial simulation run in which the mean dispersal distance is 1.0 cell. Here the host population is invaded by a succession of mutant pathogens with successively higher transmission rates until one mutant becomes dominant and persists. *Bottom*, change over time in the mean transmission rate (measured as the average number of pathogen propagules dispersed per time step from one infected site) of the pathogen population in the same nonspatial and spatial simulation runs as depicted above. In the nonspatial case, transmission evolves upward until the pathogen population drives itself extinct. In the spatial case, transmission rate evolves to a stable value where it will remain indefinitely.

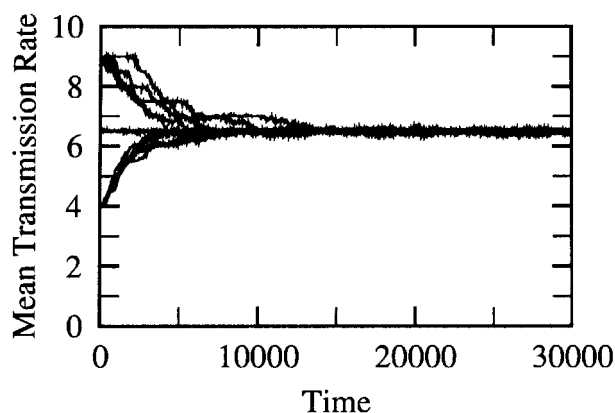
evolutionary equilibrium is almost certainly a global evolutionarily stable strategy (ESS; fig. 3). As dispersal distance increases, the conditions for intermediate levels of transmission and virulence become more difficult to meet, and the ESS virulence level increases (fig. 4).

Two pathogen strategies persist whenever the precise ESS cannot be achieved because the magnitude of mutations is discrete. However, we have never observed a polymorphism consisting of two genotypes with widely different transmission rates.

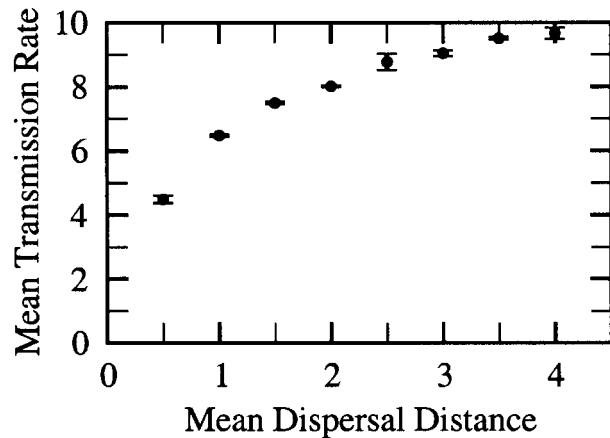
The outcome of the simulation runs is highly repeatable. In 20 replicate simulation runs, the average transmission rate at time step 50,000 is 6.496 with standard deviation 0.052, corresponding to an infected host fecundity of 0.578 with standard deviation 0.00678.

We explored the full range of combinations of the parameters  $\mu$  (the mortality rate) and  $c$  (the steepness of the relationship between sterility and transmission). We found a threshold mortality  $\mu_t$ , above which the host population cannot sustain itself. For the default parameters that we have defined,  $\mu_t$  occurs at 0.7. In the majority of the region below  $\mu_t$ , we observed host-pathogen coexistence and the evolution of the pathogen to intermediate sterility. The exception to this occurred at high values of both  $\mu$  and  $c$  (but below  $\mu_t$ ), where the pathogen is lost. It is clear that pathogen extinction in this region is caused by stochastic fluctuations at a low density of infected hosts. However, it remains unclear whether an ESS exists in this region, albeit at low pathogen densities.

We observed the persistence of intermediate sterility levels for a range of negative fecundity-transmission relationships, including linear, accelerating, and decelerating



**Figure 3:** Evolutionary trajectories of transmission rate in 18 spatial simulation runs, six from each of three initial transmission rates. From all three initial conditions, transmission rate converges to the same value, indicating that the endpoint transmission rate is an evolutionarily stable strategy.



**Figure 4:** As the mean dispersal distance of host and pathogen increases, the evolutionarily stable strategy transmission rate increases. Plotted points represent the average of 10 simulation runs. Error bars indicate the standard deviation.

functions, of the forms  $\rho = 1 - c_1\beta^n$  and  $\rho = 1 + c_2 - c_2e^{\lambda\beta}$ , where  $n > 0$ ,  $c_1 > 0$ , and either  $\lambda > 0$  and  $c_2 > 0$  or  $\lambda < 0$  and  $c_2 \leq -1$ . Under these relationships and parameter ranges, as transmission rate increases from  $\beta = 0$ , infected host fecundity declines from  $\rho = 1$  toward 0. We do not allow  $\rho$  to fall below 0 in the simulation.

## Discussion

Invasion analysis of our differential equation model of a host-pathogen system predicts that, for pathogens that do not affect host longevity, a higher pathogen transmission rate will always be favored in well-mixed populations. This is the case even for sterilizing pathogens, for which we assume a negative relationship between host fecundity and pathogen transmission. Furthermore, as infected host fecundity decreases and transmission rate increases, the host and pathogen populations decline.

However, in an explicitly spatial population model, under analogous assumptions regarding the relationship between fecundity and transmission, the persistence of intermediate-virulence pathogens is possible. Therefore, in a spatial model, virulence evolution does not necessarily lead to pathogen or host extinction, as it does in the well-mixed model. This indicates that, in order to make predictions about virulence evolution, it may be vital to consider the spatial structure of the host-pathogen population.

Evolution to high virulence in our analytical model differs from the classic prediction of evolution of intermediate virulence for pathogens that increase host mortality. The contrast between the evolutionary outcomes for these two types of pathogens can be understood most easily by

considering the cost to the pathogen of evolving a higher transmission rate. In the classic case of pathogens that increase host mortality, the pathogen suffers a fitness cost from a reduced life span along with a fitness benefit from an increased transmission rate. It is the balance between cost and benefit to the pathogen that results in an ESS virulence and transmission strategy.

In contrast, in the sterilizing pathogen, there is no fitness cost associated with high transmission. For sterilizing pathogens, we assume that the transmission rate  $\beta$  is linked not to  $\alpha$  but to the infected host fecundity  $\rho$ . However,  $\rho$  does not appear in equation (2) nor, therefore, in  $S^*$  (3). As  $S^*$  decreases and  $\beta$  increases, infected host fecundity  $\rho$  evolves downward because of its relationship with  $\beta$ .

More intuitively, a higher transmission rate for a sterilizing pathogen means fewer host offspring, but in a randomly mixing population, a pathogen can transmit to the offspring of any host. Thus, sterilization of the host presents no fitness cost to the individual pathogen, and a higher transmission rate is always favored.

We can think of the evolution of virulence in our analytical model as the coordinate evolution of one pathogen trait (transmission rate) under directional selection and another pathogen trait (virulence) that is neutral and pleiotropic with the first.

The only other theoretical study addressing the evolution of the sterility component of virulence is Jaenike (1996), whose results support those we present here. Jaenike develops a nonspatial analytical model of a semelparous host and parasite with fixed, externally determined population sizes. The parasite in Jaenike's model diverts some fraction of the host's reproductive resources toward its own reproduction, reducing the reproductive output of the host. Jaenike finds that the maximum number of secondary infections occurs when the pathogen maximizes the fraction of host resources it diverts for its own reproduction.

The current paradigm of evolution toward intermediate virulence rests entirely on its assumptions regarding the existence and form of trade-offs between various pathogen characters. Nearly all models rely on a relationship between infection-induced host mortality and pathogen transmission that is similar to one of Anderson and May's (1982) assumptions regarding the myxoma virus. (A trade-off between transmission and the rate of host recovery has also been explored in a few studies; Anderson and May 1982; Frank 1996.) The increasing, nonlinear relationship between infection-induced mortality and transmission rate results in a fitness trade-off for the pathogen and a single ESS. Other functional relationships predict different evolutionary outcomes for the differential equation model. For example, if the virulence-transmission relationship were positive and linear, or if transmission increased at an

accelerating rate with increasing extra mortality, then both mortality and transmission would continually increase. The same is true for pathogens for which transmission is unrelated to extra host mortality, as we have shown for sterilizing pathogens. Thus, without evidence that virulence and transmission are related, as they appear to be for the myxoma virus, intermediate virulence should not be our a priori expectation.

We still have no clear picture of how frequently the standard mortality-transmission relationship is found in real host-pathogen systems. Since the classic myxoma study (Fenner and Ratcliff 1965), empirical studies have documented the relationship for only a few other pathogens (reviewed in Messenger et al. 1999). About half of these studies suggest a positive association. However, most studies do not measure both mortality and transmission rate directly, and none of them have the resolution to confirm diminishing returns in transmission rate. For many other pathogens, although a positive, decelerating mortality-transmission relationship seems like a reasonable expectation, we lack any empirical evidence (Ewald 1983, 1994; Bull 1994; Frank 1996).

In a well-mixed population, the evolution of high virulence and transmission in a sterilizing pathogen causes host and pathogen population numbers to drop toward 0 in the absence of evolutionary constraints on sterility and transmission. However, this pattern of events is not repeated in our spatial model. When multiple pathogen strains find themselves together in small, approximately well-mixed patches of hosts, we can think of the effect of spatial structure on virulence evolution as the result of a conflict between short-term and long-term evolution. In these patches, pathogens experience selection for higher virulence and transmission and subsequent decline or extinction of the patch. But the rate of evolution and decline varies across space because of stochasticity and local dispersal. Thus, a local area in which the pathogen drives itself to extinction might subsequently be colonized by milder strains from another area. The result is a tug-of-war between short-term evolution to high virulence and rescue by pathogens from longer-lived patches. In contrast, when infected hosts are instead spaced widely enough that their pathogens are not in direct competition for the same pool of host offspring, we can think of pathogen transmission as essentially vertical. In this case, pathogens that allow host reproduction enhance their own reproduction and, thus, have an advantage. In our simulation, stochasticity and local dispersal cause population structure and the degree of competition between strains to vary across the spatial grid.

Virulence evolution in our simulation always appeared to result in no more than one ESS. It is likely that polymorphism would be possible if heterogeneity in spatial

structure were forced on the system by external conditions. However, it remains an open question whether and under what conditions self-generating spatial structure can maintain virulence polymorphisms.

The idea that spatial structure moderates virulence evolution is not new; rather, it is closely related to the conventional wisdom, that is, the perceived evolutionary trend toward pathogen benevolence. This trend is sometimes blamed on the extinction of populations or patches of highly virulent pathogens that overexploit their hosts (Alexander 1981; Parlevliet 1981; Lederberg 1993), a mechanism that requires spatial structure. When Anderson and May (1982) discredited the conventional wisdom, they provided an alternative model with a different outcome, which, in contrast to spatial models, describes explicitly well-mixed populations. However, they did not test whether the conventional wisdom might be plausible in spatially structured populations.

Our findings can readily be interpreted in the context of kin and group selection. Kin-selection theory (Hamilton 1964) finds that altruistic traits, or traits that benefit the group at a cost to the individual, more easily spread when individuals interact disproportionately with relatives (e.g., as a result of spatial substructure) and locally successful groups can export their productivity. Although no clearly delineated groups are identifiable in our model, local dispersal of host and pathogen ensures that pathogens are situated near their relatives. Here the altruistic trait is low virulence, which has the effect of providing fresh hosts that neighboring and related pathogens can colonize. As we expect, the altruistic trait prevails only in the spatially structured model and disappears when the system is well mixed (see also, e.g., Nowak and May 1992; Frank 1994; Bever and Simms 2000).

The effect of spatial structure on evolution is also a topic of recent theoretical interest. Using models that are individual-based and consist of an interconnected lattice of sites, Claessen and de Roos (1995), Haraguchi and Sasaki (2000), and van Baalen (2001) investigate the evolution of virulence in spatial populations for pathogens that increase host mortality. These three studies show that, under the standard virulence-transmission relationship, virulence evolves to a lower level in spatial models than in randomly mixing models. Their results agree with those of related spatial predator-prey models (van Baalen and Sabelis 1995*b*). Our results show that, for sterilizing pathogens, spatial structure may similarly impose moderation on virulence evolution. However, its role is especially striking because selection in the nonspatial case is completely directional. In other words, the effect of spatial structure on virulence evolution in sterilizing pathogens is qualitative rather than quantitative.

Spatial and nonspatial models in Rand et al. (1995)

differ from our models in both formulation and results, but they too find a qualitative change in evolutionary trajectory caused by spatial population structure. Rand et al. model a host with a pathogen that sterilizes completely, increases host mortality by a fixed amount, and has a freely evolving transmission rate. In a nonspatial, deterministic model with discrete individuals and discrete time steps, they find that transmission evolves to its maximum value. In an analogous individual-based connected-lattice simulation with nearest-neighbor dispersal, they find an evolutionarily stable intermediate transmission rate. The randomly mixing model presented by Rand et al. is similar to our analytical model in that transmission alone is under selection. As a result, a high transmission rate is favored, but because transmission rate is capped at an intermediate value in their model, pathogen extinction is not observed. In the spatial case, although the diseases in both their model and ours evolve to an ESS transmission rate, they do so by different mechanisms. In Rand et al. (1995), it is only the transmission rate that is evolving. In contrast, the ESS in our spatial simulation is caused by conflicting selection on sterility and transmission. Indeed, we can show that the pathogen is under selection for reduced sterility effects by fixing the transmission rate and allowing mutation and selection on sterilization alone. It is interesting that the sterilizing effect of the pathogen, which is neutral in the well-mixed model, comes under selection in the presence of spatial structure.

Diseases with a sterilization component are common in natural and domesticated plant and animal populations. Some examples of sterilizing pathogens include fungal smuts (Alexander and Antonovics 1995), loose smuts and bunts (*Ustilago sp.* and *Tilletia sp.*) on grains and grasses (Fischer and Holton 1957), the bacterium that causes fire blight (*Erwinia amylovora*) on fruit trees (Johnson and Stockwell 1998), the parasitic castrators of barnacles (Blower and Roughgarden 1989), some herpes viruses in equids (Borchers et al. 1999), *Brucella sp.* (bacteria) in cattle and other bovids (Meagher and Meyer 1994), and the mumps virus in humans (Craighead 2000). It has been our aim to show that the evolution of virulence in these important pathogens may not necessarily follow the same pattern as has been set out for pathogens that affect host mortality.

Mathematical models have tended to define “virulence” more narrowly than its generally accepted verbal meaning. Verbally, researchers describe virulence as the severity of disease symptoms or the effect of infection on the host’s well-being (Bremermann and Pickering 1983; Herre 1993; Ebert and Herre 1996; Frank 1996; Jaenike 1996; Lipsitch et al. 1996; Agnew and Koella 1997; Taylor et al. 1998; Messenger et al. 1999). In contrast, in nearly all mathematical models, virulence is the change in host mortality

caused by infection (Levin and Pimentel 1981; Bremermann and Pickering 1983; Bremermann and Thieme 1989; Dwyer et al. 1990; Antia et al. 1994; Lenski and May 1994; Nowak and May 1994; Claessen and de Roos 1995; Lipsitch and Nowak 1995; van Baalen and Sabelis 1995a; Bonhoeffer et al. 1996; Ebert and Herre 1996; Frank 1996; Lipsitch et al. 1996; Ebert and Weisser 1997; Taylor et al. 1998; but see Jaenike 1996). It would be satisfying (and less confusing) to have greater agreement between the verbal and mathematical definitions of virulence. (A similar point is made by M. A. Gilchrist, unpublished manuscript.) One way to remedy this discrepancy might be to take both sterility and mortality effects of pathogens into account mathematically. For example, it may be useful to express virulence  $V$  as the difference between the fitness of susceptible hosts  $W_s$  and the fitness of infected hosts (not of the pathogen)  $W_i$ . We calculate the fitness (i.e., the contribution of each host at time  $t$  to hosts at time  $t + dt$ ) of susceptible (or infected) hosts as the per capita birth rate contributed by susceptible (or infected) hosts minus per capita death rate of susceptible (or infected) hosts. From equations (1) and (2), we obtain

$$W_s = 1 - N - \mu,$$

$$W_i = \rho(1 - N) - (\mu + \alpha),$$

$$V = W_s - W_i = \alpha + (1 - \rho)(1 - N),$$

where  $N = S + I$  is the fraction of the habitat that is occupied. Here the extra host mortality  $\alpha$  and the fecundity of infected hosts  $\rho$  are components of virulence but are not synonymous with virulence itself. Note that the virulence of a single pathogen depends on the host population size  $N$ . This dependence reflects the greater impact of sterilization when the host population is below its carrying capacity than when it has reached equilibrium. For comparisons across different pathogens of different host species, the mathematical expression of virulence can be normalized by the fitness of susceptible hosts, that is,  $V_r = V/W_s$ . By taking this broader view of virulence, we may come to a better understanding of the evolution of disease characteristics in both spatial and nonspatial contexts.

#### Acknowledgments

We are extremely grateful to M. A. Gilchrist, M. W. Prior, and W. A. Rueff for technical aid and to S. A. Frank, W. G. Wilson, and an anonymous reviewer for helpful comments. This research was conducted with partial support from National Science Foundation doctoral dissertation improvement grant DEB-9972650 and National Institutes of Health grant GM-60766-01.

#### Literature Cited

- Agnew, P., and J. C. Koella. 1997. Virulence, parasitic mode of transmission, and host fluctuating asymmetry. *Proceedings of the Royal Society of London B, Biological Sciences* 264:9–15.
- Agrios, G. N. 1997. *Plant pathology*. Academic Press, London.
- Alexander, H. M., and J. Antonovics. 1995. Spread of anther-smut disease (*Ustilago violacea*) and character correlations in a genetically variable experimental population of *Silene alba*. *Journal of Ecology* 83:783–794.
- Alexander, M. 1981. Why microbial predators and parasites do not eliminate their prey and hosts. *Annual Review of Microbiology* 35:113–133.
- Anderson, R. M., and R. M. May. 1979. Population biology of infectious diseases. I. *Nature* 280:361–367.
- . 1982. Coevolution of hosts and parasites. *Parasitology* 85:411–426.
- Antia, R., B. R. Levin, and R. M. May. 1994. Within-host population dynamics and the evolution and maintenance of microparasite virulence. *American Naturalist* 144:457–472.
- Baudoin, M. 1974. Castration as a parasitic strategy. *Evolution* 29:335–352.
- Bever, J. D., and E. L. Simms. 2000. Evolution of nitrogen fixation in spatially structured populations of *Rhizobium*. *Heredity* 85:366–372.
- Blower, S., and J. Roughgarden. 1989. Population dynamics and parasitic castration: test of a model. *American Naturalist* 134:848–858.
- Bonhoeffer, S., R. E. Lenski, and D. Ebert. 1996. The curse of the pharaoh: the evolution of virulence in pathogens with long-living propagules. *Proceedings of the Royal Society of London B, Biological Sciences* 263:715–721.
- Borchers, K., K. Frolich, and H. Ludwig. 1999. Detection of equine herpesvirus types 2 and 5 (EHV-2 and EHV-5) in Prevalski's wild horses. *Archives of Virology* 144:771–780.
- Bremermann, H. J., and J. Pickering. 1983. A game-theoretical model of parasite virulence. *Journal of Theoretical Biology* 100:411–426.
- Bremermann, H. J., and H. R. Thieme. 1989. A competitive exclusion principle for pathogen virulence. *Journal of Mathematical Biology* 27:179–190.
- Bull, J. J. 1994. Perspective: virulence. *Evolution* 48:1423–1436.
- Bull, J. J., and I. J. Molineux. 1992. Molecular genetics of adaptation in an experimental-model of cooperation. *Evolution* 46:882–895.
- Claessen, D., and A. M. de Roos. 1995. Evolution of virulence in a host-pathogen system with local pathogen transmission. *Oikos* 74:401–413.

- Craighead, J. E. 2000. Pathology and pathogenesis of human viral disease. Academic Press, London.
- Dwyer, G., S. A. Levin, and L. Buttel. 1990. A simulation model of the population dynamics and evolution of myxomatosis. *Ecological Monographs* 60:423–447.
- Ebert, D., and E. A. Herre. 1996. The evolution of parasitic disease. *Parasitology Today* 12:96–101.
- Ebert, D., and W. W. Weisser. 1997. Optimal killing for obligate killers: the evolution of life histories and virulence of semelparous parasites. *Proceedings of the Royal Society of London B, Biological Sciences* 264:985–991.
- Ewald, P. W. 1983. Host-parasite relations, vectors, and the evolution of disease severity. *Annual Review of Ecology and Systematics* 14:465–485.
- . 1994. *Evolution of infectious disease*. Oxford University Press, Oxford.
- Fenner, F., and F. N. Ratcliff. 1965. *Myxomatosis*. Cambridge University Press, Cambridge.
- Fischer, G. W., and C. S. Holton. 1957. *Biological control of the smut fungi*. Ronald, New York.
- Frank, S. A. 1994. Genetics of mutualism: the evolution of altruism between species. *Journal of Theoretical Biology* 170:393–400.
- . 1996. Models of parasite virulence. *Quarterly Review of Biology* 71:37–78.
- Hamilton, W. D. 1964. The genetics of evolution of social behavior. I. *Journal of Theoretical Biology* 7:1–16.
- Haraguchi, Y., and A. Sasaki. 2000. The evolution of parasite virulence and transmission rate in a spatially structured population. *Journal of Theoretical Biology* 203:85–96.
- Herre, E. A. 1993. Population structure and the evolution of virulence in nematode parasites of fig wasps. *Science (Washington, D.C.)* 259:1442–1445.
- Jaenike, J. 1996. Suboptimal virulence of an insect-parasitic nematode. *Evolution* 50:2241–2247.
- Johnson, K. B., and V. O. Stockwell. 1998. Management of fire blight: a case study in microbial ecology. *Annual Review of Phytopathology* 36:227–248.
- Kermack, W. O., and A. G. McKendrick. 1927. A contribution to the mathematical theory of epidemics. *Proceedings of the Royal Society of London A, Mathematical and Physical Sciences* 115:700–721.
- Lederberg, J. 1993. Viruses and humankind: intracellular symbiosis and evolutionary competition. Pages 3–9 in S. S. Morse, ed. *Emerging viruses*. Oxford University Press, Oxford.
- Lenski, R. E., and R. M. May. 1994. The evolution of virulence in parasites and pathogens: reconciliation between two competing hypotheses. *Journal of Theoretical Biology* 169:253–265.
- Levin, S., and D. Pimentel. 1981. Selection of intermediate rates of increase in parasite-host systems. *American Naturalist* 117:308–315.
- Lipsitch, M., and M. A. Nowak. 1995. The evolution of virulence in sexually transmitted HIV/AIDS. *Journal of Theoretical Biology* 174:427–440.
- Lipsitch, M., S. Siller, and M. A. Nowak. 1996. The evolution of virulence in pathogens with vertical and horizontal transmission. *Evolution* 50:1729–1741.
- Lockhart, A. B., P. H. Thrall, and J. Antonovics. 1996. Sexually transmitted diseases in animals: ecological and evolutionary implications. *Biological Reviews of the Cambridge Philosophical Society* 71:415–471.
- Meagher, M., and M. E. Meyer. 1994. On the origin of brucellosis in bison of Yellowstone National Park: a review. *Conservation Biology* 8:645–653.
- Messenger, S. L., I. J. Molineux, and J. J. Bull. 1999. Virulence evolution in a virus obeys a trade-off. *Proceedings of the Royal Society of London B, Biological Sciences* 266:397–404.
- Nowak, M. A., and R. M. May. 1992. Evolutionary games and spatial chaos. *Nature* 359:826–829.
- . 1994. Superinfection and the evolution of parasite virulence. *Proceedings of the Royal Society of London B, Biological Sciences* 255:81–89.
- Parlevliet, J. E. 1981. Disease resistance in plants and its consequences for plant breeding. Pages 309–347 in K. J. Frey, ed. *Plant breeding II*. Iowa State University Press, Ames.
- Rand, D. A., M. Keeling, and H. B. Wilson. 1995. Invasion, stability and evolution to criticality in spatially extended, artificial host-pathogen ecologies. *Proceedings of the Royal Society of London B, Biological Sciences* 259:55–63.
- Taylor, D. R., A. Jarosz, R. E. Lenski, and D. Fulbright. 1998. The acquisition of hypovirulence in host-pathogen systems with three trophic levels. *American Naturalist* 151:343–355.
- Van Baalen, M. 2001. Contact networks and the evolution of virulence. Pages 85–103 in U. Dieckmann, J. A. J. Metz, M. W. Sabelis, and K. Sigmund, eds. *Adaptive dynamics of infectious diseases: in pursuit of virulence management*. Cambridge University Press, Cambridge.
- Van Baalen, M., and M. W. Sabelis. 1995a. The dynamics of multiple infection and the evolution of virulence. *American Naturalist* 146:881–910.
- . 1995b. The milker-killer dilemma in spatially structured predator-prey interactions. *Oikos* 74:391–400.