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Host mating system and the spread of a disease-resistant allele in a population

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ABSTRACT

The model presented here modifies a susceptible-infected (SI) host–pathogen model to determine the influence of mating system on the outcome of a host–pathogen interaction. Both deterministic and stochastic (individual-based) versions of the model were used. This model considers the potential consequences of varying mating systems on the rate of spread of both the pathogen and resistance alleles within the population. We assumed that a single allele for disease resistance was sufficient to confer complete resistance in an individual, and that both homozygote and heterozygote resistant individuals had the same mean birth and death rates. When disease invaded a population with only an initial small fraction of resistant genes, inbreeding (selfing) tended to increase the probability that the disease would soon be eliminated from a small population rather than become endemic, while outcrossing greatly increased the probability that the population would become extinct due to the disease.

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1. Introduction

A major objective of epidemiological modeling of plant populations has been to understand the factors and mechanisms that affect the spread of disease (e.g. Gibson (1997), Kleczkowski et al. (1997), Power (1991), Xu and Ridout (1998) and Zhang et al. (2000)). Here we examine the effect of plant mating system on the rate of spread of resistance to disease. Plant populations vary in the relative rates of selfing and outcrossing (Schemske and Lande, 1985; Vogler and Kalisz, 2001). Previous theoretical work has shown that variation in the mating system affects both probability of fixation (Caballero and Hill, 1992; Charlesworth, 1992) and the time to fixation (Caballero and Hill, 1992) for mutant alleles under positive selection.

Disease is an important agent of natural selection (Bergelson et al., 2001; Roy and Kirchner, 2000). Resistance genes are expected in plant populations exposed to diseases, but these can also be expected to have negative effects on other fitness aspects of individuals carrying them (Bergelson et al., 1996; Tian et al., 2003). In previous work we developed an epidemiological host–pathogen model of a diploid population that contained both a susceptible and a resistant allele at a single locus, where the resistant allele carried a negative tradeoff in terms of a lower intrinsic population growth rate in the absence of disease (Koslow and DeAngelis, 2006). In that model we were able to consider the potential consequences of varying mating systems on the equilibrium values of absolute numbers and proportions of resistance alleles and diseased individuals in the population. We found that if a single allele for disease resistance is sufficient to confer complete resistance in an individual, and if both homozygote and heterozygote resistant individuals have the same mean birth and death rates, then for any parameter set, the selfing or inbreeding rate (probability of an individual being fertilizing by itself versus being fertilized by another individual) does not affect the proportions of resistant, susceptible, or infected individuals at equilibrium. If homozygote and heterozygote individual birth rates differ, however, the mating system can make a difference in these proportions. In that case, depending on other parameters, increased selfing can either increase or decrease the rate of infection in the population. Results from this model also predict higher frequencies of resistance alleles in predominantly selfing as compared to predominantly outcrossing populations.

In the present work we use the same model, but we now study the rate of spread of the resistance allele in a plant population as a function of the mating system. The effect of selfing on the prevalence of disease and rate of spread of resistance in a population is of broad conservation interest. How fast a resistant allele can spread in a population could determine whether a plant species can survive a deadly disease and reach some equilibrium with the pathogen. Humans are causing loss and fragmentation of habitat of many species, which is likely to have an effect on the amount of selfing, and in turn affect spread of resistance.

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For example, if a plant population has been free of disease for some time, so that resistance genes are low in proportion, the mating system may affect how rapidly those genes can spread to prevent major decline in the population or influence its rate of recovery. Another issue, prompted by the development of genetic engineering, is the possibility that resistance genes developed for protecting crops escape to natural plant populations, including weedy species, increasing their resistance to natural biological controls (Dale, 1992; Hails and Morley, 2005; Pollack, 2006; Wolfenbarger and Phifer, 2000). In that case also, the mating system of the plant may affect the rate at which the resistance allele spreads in the populations. Our model is aimed at intermediate time scales. In our model, the spread of the pathogen throughout the population can potentially occur well within a generation, while the dynamics of allele spread may take tens of generations. Thus our model covers a time scale longer than the time scale of the disease spread, but shorter than that of evolutionary dynamics; mutations are not modeled. It is aimed at following the dynamics of allele frequencies under the selective pressure of occasional occurrence of a disease over many generations.

Relevant to these issues, we consider three specific questions:

Question 1. Will the degree of selfing influence the rate at which the frequencies of alleles in the population approach their new equilibrium values in response to the introduction of a pathogen into the population?

We used a modeling approach to address this question by initiating a population with a high frequency of susceptible (r) alleles, with only a small number of resistance (R) alleles present. Then we introduced the pathogen and determined the temporal response of the resistance alleles in approaching the new equilibrium. We anticipated that a high degree of selfing might slow the spread of resistance genes.

Question 2. Will the new equilibrium be stable? We examined this question using Routh–Hurwitz stability criteria on the model.

Question 3. Will the degree of selfing influence the persistence of disease in the population after an outbreak, or the possibility of extinction of a local population if a disease enters the population after it has been free of disease for long enough that the resistant allele is in low relative numbers?

We examined this question using an individual-based version of the model (DeAngelis and Mooij, 2005; Grimm and Railsback, 2005) that allowed for demographic stochasticity. We anticipated that a high degree of selfing, by slowing the rate of spread of resistance genes, might increase the persistence time of the disease in the population and also increase the probability of extinction of the population from the disease.

2. The model

Models with compartments containing susceptible, infected, and recovered individuals are frequently used in epidemiology (for example Anderson and May (1981)), including the spread of pathogens in plant populations (Segarra et al., 2001). The model presented here modifies a continuous time SIR host–pathogen model to determine the influence of mating system on the outcome of the host–pathogen interaction. We added a genetic component of host resistance to infection and a host mating system that can be varied. We assumed a diploid host with a single locus for resistance to infection. A dominant resistance allele (R) confers complete resistance. The model is suitable for pathogens that spread through horizontal, density-dependent pathogen transmission, where the host is a perennial. The pathogen was assumed to have no alternative hosts, and all of the offspring were healthy, regardless of the infection status of the parent(s). Justifications for these assumptions are given in Koslow and DeAngelis (2006). Resistant individuals had lower fecundity than susceptible individuals, which is consistent with empirical work showing a cost of resistance (Bergelson and Purrington, 1996; Burdon and Thrall, 2003; Tian et al., 2003). However, we also extend our analysis to more general assumptions.

The model considers three genotypes, one of which can be either in the infected state or in the uninfected (susceptible) state. Following Anderson and May (1981), a possible set of differential equations for the system is:

$$\frac{dX_{RR}}{dt} = new\, X_{RR} - bX_{RR} \tag{1a}$$

$$\frac{dX_{Rr}}{dt} = new\, X_{Rr} - bX_{Rr} \tag{1b}$$

$$\frac{dX_{rr}}{dt} = new\, X_{rr} - (b + \beta Y_{rr})X_{rr} \tag{1c}$$

$$\frac{dY_{rr}}{dt} = \beta Y_{rr} X_{rr} - (b + \alpha)Y_{rr} \tag{1d}$$

where X_{RR}, X_{Rr}, and X_{rr} are the numbers of healthy individuals carrying two R alleles, one R and one r allele, and two r alleles, while Y_{rr} is the number of infected individuals with two r alleles. Because we assumed that individuals with an R allele are completely resistant, or immune, to infection, there is no need for equations for Y_{RR} and Y_{Rr}. Other assumptions incorporated into the above equations are as follows.

It was assumed that the infection is systemic, so that once an individual host was infected it either remained infected or died. Although recovery by plants from some diseases is possible through shedding of leaves or other organs, we followed here the observation that in plants, unlike many vertebrates, recovery from a systemic pathogen infection is extremely rare.

The pathogen was transmitted directly and equally from any infected individual. An X_{rr} individual's chance of getting the pathogen depended on the number of infected individuals in the population, with an infection rate coefficient, β.

For healthy individuals (X_{RR}, X_{Rr}, and X_{rr}) the death rate was b, so that $1/b$ is roughly the natural turnover time of the population, whereas for infected individuals (Y_{rr}) the death rate was $(b + \alpha)$, where α is referred to as 'aggressiveness' in the plant pathology literature. The parameter α was varied over a range of values.

New individuals were figured as the number of gametes produced for resistant and susceptible genotypes, such that the birth rates for the two gametes were

$$gam\, X_R = \frac{a_{RR}X_{RR} + 0.5a_{Rr}X_{Rr}}{1 + \rho N} \tag{2a}$$

$$gam\, X_r = \frac{a_{rr}X_{rr} + a_{rr,dis}Y_{rr} + 0.5a_{Rr}X_{Rr}}{1 + \rho N}. \tag{2b}$$

Here a_{RR}, a_{Rr}, and a_{rr}, are the birth rates of the three genotypes, while the reproductive rate of diseased plants is $0 \le a_{rr,dis} < a_{rr}$. Thus the reproductive cost of infection could be varied. In the analyses that follow, we considered the case in which $a_{RR} = a_{Rr} < a_{rr}$. Generalization to cases in which $a_{RR} < a_{Rr} < a_{rr}$ or $a_{RR} < a_{Rr} = a_{rr}$ is possible (see Koslow and DeAngelis (2006)), although those cases are less tractable analytically. The factor ρN represents density-dependent self-limitation on reproduction, where

$$N = X_{RR} + X_{Rr} + X_{rr} + Y_{rr}. \tag{3}$$

Other forms of density dependent regulation can be used if desired.

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In animal-pollinated plants, the mating system can be considered a continuous variable from complete selfing to complete outcrossing (Vogler and Kalisz, 2001). The mating system of a population can be estimated using the inbreeding coefficient (F), which ranges from 0 to 1 (Hartl and Clark, 1997). In comparison to a population composed of randomly mating (i.e. outcrossing) individuals, complete selfing halves the frequency of heterozygotes each generation (Wright, 1921). Selfing decreases the frequency of heterozygotes by F, which is the probability that two alleles in the same individual are identical by descent (Hartl and Clark, 1997). Therefore, offspring genotype frequencies are determined by the following equations:

$$f\,seed\,X_{RR} = (f\,gam\,X_R)^2 + F \times f\,gam\,X_R \times f\,gam\,X_r \tag{4a}$$

$$f\,seed\,X_{Rr} = 2 \times (1-F) \times f\,gam\,X_R \times f\,gam\,X_r \tag{4b}$$

$$f\,seed\,X_{rr} = (f\,gam\,X_r)^2 + F \times f\,gam\,X_R \times f\,gam\,X_r. \tag{4c}$$

The frequencies, $f\,gam\,X_R$ and $f\,gam\,X_r$, of each gamete in the population are simply $gam\,X_R/(gam\,X_R + gam\,X_r)$ and $gam\,X_r/(gam\,X_R + gam\,X_r)$, respectively. The total numbers of the three offspring genotypes, $new\,X_{RR}$, $new\,X_{Rr}$, and $new\,X_{rr}$, used in Eqs. (1a)–(1c) are determined, respectively, by multiplying each of the above functions, $f\,seed\,X_{RR}$, $f\,seed\,X_{Rr}$, and $f\,seed\,X_{rr}$ by the total number of offspring, $(gam\,X_R + gam\,X_r)$. This completes the development of the model.

3. Results: Analysis of model equations

It is difficult to analyze or even anticipate the behavior of the model in the above form. However, with our assumption that the R-allele not only carries immunity to disease, but that the RR-homozygote and R, r-heterozygote share the same birth rate coefficient (i.e., $a_{RR} = a_{Rr} < a_{rr}$), the above equations can be reduced to a form from which one can more readily see how F influences the equations and thus affects the spread of the R-allele. In particular, the basic equations can then be reduced to the following set, after a change to the set of variables that includes the number of R-alleles ($Allele_R$), as well as N, X_{rr}, and Y_{rr}:

$$\frac{d(Allele_R)}{dt} = \left(\frac{a_{RR}}{1+\rho N} - b\right) Allele_R \tag{5a}$$

$$\frac{dN}{dt} = \frac{a_{RR}(N - X_{rr} - Y_{rr}) + a_{rr}X_{rr} + a_{rr,dis}Y_{rr}}{1+\rho N} - bN - \alpha Y_{rr} \tag{5b}$$

$$\frac{dX_{rr}}{dt} = \left[\frac{(gam\,X_r)^2 + F(gam\,X_R)(gam\,X_r)}{gam\,X_r + gam\,X_R}\right] - (b + \beta Y_{rr})X_{rr} \tag{5c}$$

$$\frac{dY_{rr}}{dt} = \beta Y_{rr}X_{rr} - (b+\alpha)Y_{rr} \tag{5d}$$

where (3) also holds and the number of R-alleles in the population is

$$Allele_R = 2X_{RR} + X_{Rr}. \tag{5e}$$

The other terms are the following:

$$gam\,X_R = \frac{a_{RR}X_{RR} + 0.5a_{RR}X_{Rr}}{1+\rho N} = \frac{0.5a_{RR}\,Allele_R}{1+\rho N} \tag{5f}$$

$$gam\,X_r = \frac{a_{rr}X_{rr} + a_{rr,dis}Y_{rr} + 0.5a_{RR}X_{Rr}}{1+\rho N}$$

or, using (5e) to substitute for X_{Rr} in $gam\,X_r$,

$$gam\,X_r = \frac{a_{RR}(N - X_{rr} - Y_{rr}) + a_{rr}X_{rr} + a_{rr,dis}Y_{rr}}{1+\rho N} - \frac{0.5a_{RR}\,Allele_R}{1+\rho N}. \tag{5g}$$

Table 1
Parameter values for numerical evaluation of Eqs. (5a)–(5g)

$a_{RR} = 0.7$
$a_{Rr} = 0.7$
$a_{rr} = 0.8$
$a_{rr,dis} = 0.8$
$b = 0.2$
$\alpha = 0.1$
$\beta = 0.0004$
$\rho = 0.0002$

Note that the only place where F occurs is in Eq. (5c). Only the total population size N has a direct effect on the rate of change of the R-allele. However, the rate of change of N depends on X_{rr}, and thus implicitly on F through the reproductive rate of these susceptibles.

4. Results: Model evaluations and simulations

The equilibrium values for this system are presented in online Appendix. We did not try to analyze the model Eqs. (5a)–(5g) any further, but resorted directly to numerical simulations to study the behavior of this system. Two types of model simulations were used. First, the deterministic version of the model was studied by numerically evaluating Eqs. (5a)–(5g) for different sets of parameter values. The purpose was to determine whether the type of breeding system had any effects on the spread of the R-allele during a disease outbreak. Second, a stochastic version of the model was created by developing an individual-based model (IBM) that is analogous to the above model, except that each individual plant in the population was simulated, rather than continuous variables for the four classes of plants. The purpose was to determine if the type of breeding system had any effect on the persistence of the disease in the population or the possibility of extinction of a small population.

Deterministic model numerical evaluation

We numerically evaluated Eqs. (5a)–(5g) in the following way using, for a typical case, the parameter values shown in Table 1, which produced an equilibrium population size of 15,000 susceptibles in the absence of disease. We began the simulation in the absence of disease. According to Eq. (1d), the disease can spread in the population when the number of susceptibles, $X_{rr} > (b+\alpha)/\beta$ (which is equivalent to the well-known R_0 criterion for epidemics, that each infected produce more than one secondary infection). But in our simulations the population was allowed to be free of disease for a long enough period of time, 400 time steps (or 80 generations, given that the mean turnover time of the population is approximately $1/b$, or 5 time units, in the simulations here), that resistant individuals were reduced to a tiny fraction (about the same in all simulations) of the total alleles in the population, and X_{rr} was more than 99% of the total population size N. The subsequent dynamics shown by the simulations, starting at time $t = 400$, can be divided into five temporal phases (Fig. 1a, b for outcrossing and selfing, respectively). First, there was a rapid spread of disease through the whole non-immune population, with Y_{rr} sharply increasing and X_{rr} sharply decreasing to around 1400. Second, there was a rapid decline in Y_{rr} to a lower 'plateau' of about 8000 individuals after the reduction of the susceptibles. Third, there was a period of approximate steady state, or quasi-equilibrium, of Y_{rr} on this plateau, during which R-alleles were still only a small part of the population and the number of diseased individuals, Y_{rr}, stayed roughly constant at around 8000. Although the R-alleles were increasing exponentially during that period, as Eq. (5a) implies and is seen in the increases in X_{RR} and X_{Rr} in the figures, they were still a relatively small component of the population. Fourth, as the R-alleles increased to be a sizable fraction

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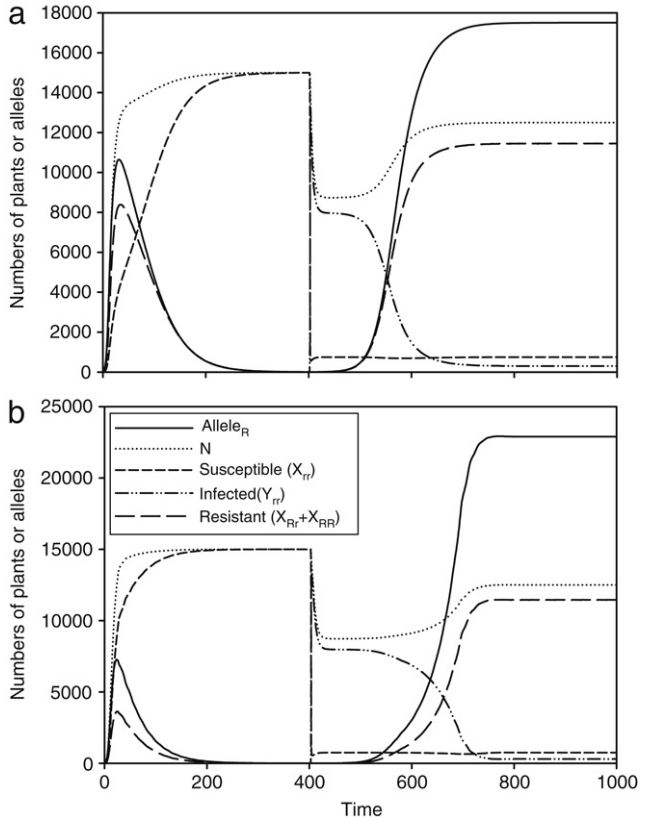

Fig. 1. Numerical evaluation of Eqs. (5a)–(5g) for the case of (a) complete outcrossing ($F = 0$), and (b) complete selfing ($F = 1$). Parameter values are given in Table 1. Explanation is in the text.

of the total alleles, and approached an inflection point, the number of diseased individuals declined rapidly. In the fifth phase, the new equilibrium of about 12,000 total individuals was then approached slowly. The population in this case consisted mostly of resistant individuals, but also of about 700 susceptible and 300 diseased individuals, as disease remained endemic in the population. As in Koslow and DeAngelis (2006), it is clear here that the same equilibrium values $X_{rr}{}^*$, $Y_{rr}{}^*$, N^*, and $X_{RR} * + X_{Rr} *$ are approached, regardless of whether $F = 0$ or $F = 1$. However, as can be seen in comparing Fig. 1a, b, the *Allele*$_R$ is greater in the selfing case. Solutions always exhibited local stability. Although we did not attempt to prove that is the case in general, an on-line Appendix provides a proof for the limiting case of pure selfing, $F = 1$. The outcrossing case, $F = 0$, is too complex to evaluate in general, but use of Routh–Hurwitz criteria over a range of parameter values produced only stability. This suggests that the answer to Question 2 is "yes"; the equilibrium will be stable.

Although the breeding system did not affect the potential final equilibrium values, the breeding system did affect the dynamics. The two extremes, $F = 0$ and $F = 1$, are compared here. When there was complete selfing ($F = 1$, Fig. 1b), the diseased part of the population was maintained at a high level (about 8000) for a somewhat longer period of time (greater than 100 time steps) than when there is outcrossing ($F = 0$, less than 100 time steps, Fig. 1a). Another difference is visible in comparison of the $F = 0$ and $F = 1$ cases (Fig. 1a, b): As the number of diseased individuals declined to smaller values, after about 600 time steps, the approach to the new equilibrium became slower, or more gentle, in the case of outcrossing than for complete selfing. In fact, in the case of selfing, the decline in Y_{rr} produced a slight undershoot of the new equilibrium before increasing again and asymptotically approaching the final state, although this undershoot is not easily visible in Fig. 1b.

Table 2
Parameter values for simulations of individual-based analog of Eqs. (5a)–(5g)

$a_{RR} = 0.7$
$a_{Rr} = 0.7$
$a_{rr} = 0.8$
$a_{rr,dis} = 0.8$
$b = 0.3$
$\alpha = 0.35$
$\beta = 0.009$
$\rho = 0.0025$

Simulations with different costs of disease resistance were performed to determine the effect on dynamics. When the cost of resistance was decreased (e.g., reproduction increased from $a_{RR} = a_{Rr} = 0.7$ to 0.75), the time required for resistant alleles to nearly disappear from the system increased by slightly over 50%, and the time for resistant alleles to reach 1/2 their asymptotic level following disease outbreak decreased by about 20%.

Individual-based (stochastic) model simulations

The results of the deterministic model suggest that there may be differences between selfing and outcrossing populations in whether the disease in a small population is likely to persist in or disappear from the population after an outbreak, or whether one or the other of the alleles, or even the population as a whole, might be threatened with extinction. We drew the former inference concerning disease persistence from the observation that in the case of selfing the number of infecteds, Y_{rr}, declined in numbers faster than for outcrossing after the plateau period of Y_{rr} in Fig. 1a, b was passed, slightly undershooting the final equilibrium, a difference that seemed to be inherent in the two different cases. Although the disease remained endemic in the deterministic model, we conjectured that it might not in a model with a small population size in which demographic stochasticity was included. While the persistence or loss of the disease depended heavily on the total size of the population and the exact circumstances regarding the outbreak (e.g., proportion of *R*-alleles at the time), it was possible to compare simulations of varying degrees of selfing when all other circumstances were held the same. It seemed likely that the disease would have a greater chance of being lost from the population in the selfing case. We tested this using the individual-based analog of the model, which incorporated both discrete individuals and demographic stochasticity, which are both needed to simulate possible extinctions of components of the model, including disease (see on-line Appendix for a description of the individual-based model).

First, simulations were performed to determine if differences in breeding affected the outbreak of the disease, assuming disease propagules were always available, using the values in Table 1. Twelve simulations each were performed for selfing and outcrossing populations, in which disease was introduced (a single diseased individual) every few time steps. The result was that a major disease outbreak occurred, on average, when the number of *rr*-individuals reached 815.75 (sd 200.29) in the case of selfing and 858.42 (sd 131.09) in the case of outcrossing. These did not differ significantly, and both satisfied the deterministic R_0 criterion, $X_{rr} > (b + \alpha)/\beta$, though stochasticity delayed the occurrence of significant outbreaks beyond the deterministic value of $(b + \alpha)/\beta = 750$.

Simulations were next run using the individual-based model to determine whether the degree of selfing affected the possibility of elimination of the disease. After confirming that the individual-based model could roughly duplicate the mean values of the deterministic equations for the values in Table 1, the population parameters were changed somewhat from those of Table 1 to increase the effects of demographic stochasticity (Table 2). For these parameters, in the absence of disease, the population, dominated

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Table 3
Number of time steps that the disease persists in the population after time step 600 in the individual-based version of the model

	$\alpha = 0.25, \beta = 0.006$	$\alpha = 0.25, \beta = 0.009$	$\alpha = 0.25, \beta = 0.012$
Outcrossing	128.94 (50.14)*	105.10 (34.91)	99.40 (35.05)
Selfing	120.03 (47.67)*	83.31 (31.78)	76.93 (26.27)
	$\alpha = 0.35, \beta = 0.006$	$\alpha = 0.35, \beta = 0.009$	$\alpha = 0.35, \beta = 0.012$
Outcrossing	98.89 (40.18)	77.27 (27.01)	71.61 (22.21)
Selfing	85.17 (34.36)	63.71 (22.89)	53.29 (17.00)
	$\alpha = 0.45, \beta = 0.006$	$\alpha = 0.45, \beta = 0.009$	$\alpha = 0.45, \beta = 0.012$
Outcrossing	73.05 (26.49)*	59.51 (17.43)	57.45 (17.55)
Selfing	67.66 (24.18)*	51.47 (14.58)	44.94 (13.26)

In all cases the disease persisted longer in the outcrossing case. Standard deviations are shown in parentheses. All differences were significant at level $p < 0.01$ except two cases marked with asterisks.

by susceptibles, could reach approximately 700 individuals. Simulations were run for both the selfing and outcrossing cases. We allowed the population to undergo dynamics in the absence of disease until only about 12 resistant (*RR* or *Rr*) individuals, and thus over 680 *rr*-individuals, remained before disease was introduced (although the R_0 criterion predicts that fewer than 80 *rr*-individuals are sufficient for disease outbreak to be possible in the case of the parameter values of Table 2).

All simulations that compared the two reproductive extremes showed that disease disappeared from the population earlier in the selfing case. A typical comparison of a pair of simulations is shown in Fig. 2a, b. In these figures we plot X_{RR}, X_{Rr}, X_{rr}, and Y_{rr}, as these were easy to simulate directly in an individual-based model. In the outcrossing case (Fig. 2a), the disease disappeared at about 175 time units following disease outbreak, while in the selfing case (Fig. 2b), the disease disappeared at about 80 time units after the outbreak. The smaller population sizes in the individual-based model shortened the time scale relative to the deterministic case (Fig. 1a, b), but aside from the stochasticity and extinction of disease, these results resemble those of the deterministic case. To determine if the difference observed between selfing and outcrossing was a general one, and specifically to examine the effects of key parameters on disease dynamics, comparisons were made between outcrossing and selfing breeding strategies for nine combinations of three different values of α and three different values of β, with 100 simulations in each case (Table 3). In all nine cases the disease died out in the selfing population before it died out in the outcrossing population, and these differences were highly significant in almost all cases.

In order to test for any influence of whether the tradeoff for disease resistance was manifested in a higher mortality rate rather than lower fecundity, the above set of simulations were rerun with the parameter values $a_{RR} = a_{Rr} = a_{rr} = 0.8$ and $b_{RR} = b_{Rr} = 0.34$ and $b_{rr} = 0.30$. All differences between selfing and outcrossing were qualitatively the same and the quantitative results for the 'mortality tradeoff' were similar to those for which the tradeoff involved fecundity.

We also examined the effects of another assumption on model parameters. Following Bergelson et al. (1996), Burdon and Thrall (2003), and Tian et al. (2003), we had initially assumed a cost of disease resistance in terms of lower birth rates ($a_{RR} = a_{Rr} = 0.7$, versus $a_{rr} = 0.8$) for disease resistant individuals. However, a tradeoff of this size has been questioned by others (e.g. Brown (2003)). Some authors have not found costs (Bronson and Ellingboe, 1986; Vera Cruz et al., 2000), and Bergelson and Purrington (1996) found a cost of only about 5% compared with the cost of about 12% (0.7 vs. 0.8 that we assumed for reproductive rates in our model). It can be shown in our model that if the cost of disease resistance is not high, that is $(a_{rr} - a_{RR})/a_{RR} \ll 1$, then disease is not likely to be maintained under stochastic conditions, because the size of Y^*_{rr} at equilibrium point is proportional to the difference;

$$Y^*_{rr} = \frac{(a_{rr} - a_{RR})(b + \alpha)b}{(a_{RR}(b + \alpha) - a_{rr,dis}b)\beta}. \quad (6)$$

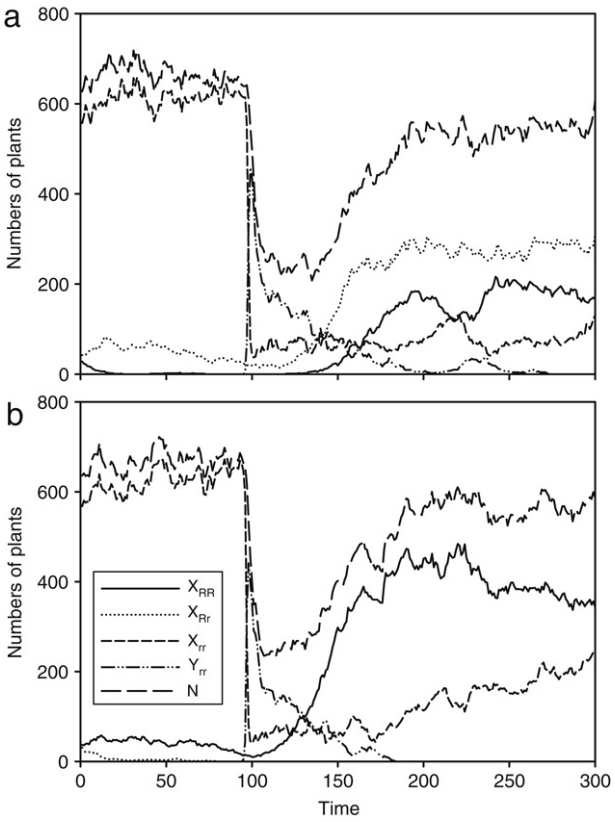

Fig. 2. Typical simulations of the stochastic individual-based analog of Eqs. (5a)–(5g) for the case of (a) complete outcrossing ($F = 0$), and (b) complete selfing ($F = 1$). The pathogen becomes extinct near time 275 in (a) and near 180 in (b). Parameter values are given in Table 2. Explanation is in the text.

(see online Appendix). This equation shows that in the deterministic equation the pathogen can be maintained in steady state even for very small advantages in reproductive rates of the non-resistant, a_{rr}, over the resistant, a_{RR} and a_{Rr}, individuals. In the stochastic model, with a maximum population size of only about 700, a decrease in cost of resistance (i.e., a change from $a_{RR} = a_{Rr} = 0.70$ to 0.77) made it impossible to maintain the disease for more than several time steps in our simulations, because Y^*_{rr} decreased in proportion to very low levels and the pathogen ceased to spread. This confirms theoretical results that low costs for resistance may not be sufficient to maintain polymorphism in plant–parasite co-evolutionary interactions (Damgaard, 1999; Thrall and Burdon, 2003; Tellier and Brown, 2007).

Another aspect of disease dynamics is whether the mating system has any effect on the possibility of extinction of the population due to disease. To explore this, we eliminated reproduction of the infected individuals (i.e., we set $a_{rr,dis} = 0$). We did this because, when infecteds were able to reproduce with

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Table 4
Fraction of times, out of 100 simulations, that the population goes to extinction within 250 steps after the outbreak of disease in the individual-based version of the model

	$\alpha = 0.25, \beta = 0.006$	$\alpha = 0.25, \beta = 0.009$	$\alpha = 0.25, \beta = 0.012$
Outcrossing	58%	64%	65%
Selfing	1%	2%	4%
	$\alpha = 0.35, \beta = 0.006$	$\alpha = 0.35, \beta = 0.009$	$\alpha = 0.35, \beta = 0.012$
Outcrossing	28%	48%	43%
Selfing	0%	2%	0%
	$\alpha = 0.45, \beta = 0.006$	$\alpha = 0.45, \beta = 0.009$	$\alpha = 0.45, \beta = 0.012$
Outcrossing	12%	34%	34%
Selfing	0%	2%	0%

In all cases the population persisted longer in the selfing case.

the same probability as non-infected *rr*-homozygotes, extinction of the population did not occur in simulations of populations this size; but when diseased individuals could not reproduce, extinction could easily occur. The simulations were run long enough without the pathogen present to the point where the total number of *R*-alleles in the population was reduced to about 50 (at which point the number of susceptible individuals, X_{rr}, reached close to 700). At that point in time, ten infected individuals from outside were assumed to be present for a few time steps and during that time to randomly infect members of the population.

Comparisons were made between outcrossing and selfing populations for all nine combinations of three different values of α and three different values of β, with 100 simulations in each case (Table 4). For both breeding types, after the introduction of the disease the number of infecteds grew rapidly and dominated the population. As the results in Table 4 show, selfing populations tended to be much more successful than outcrossing populations in escaping population extinction for all values of α and β. An example of a particular simulation of each breeding extreme is shown to demonstrate typical behaviors (Fig. 3a, b). In the case of complete selfing ($F = 1$) the population size declined to a low of 38 and then started to recover, eventually approaching the new equilibrium point of over 500 resistant individuals. The susceptible *r*-allele was lost through disease from the population in this simulation. The disease also extinguished itself from the population. For the complete outcrossing example ($F = 0$), not only did the *r*-allele go to extinction, but the *R*-allele did as well, and thus the whole population.

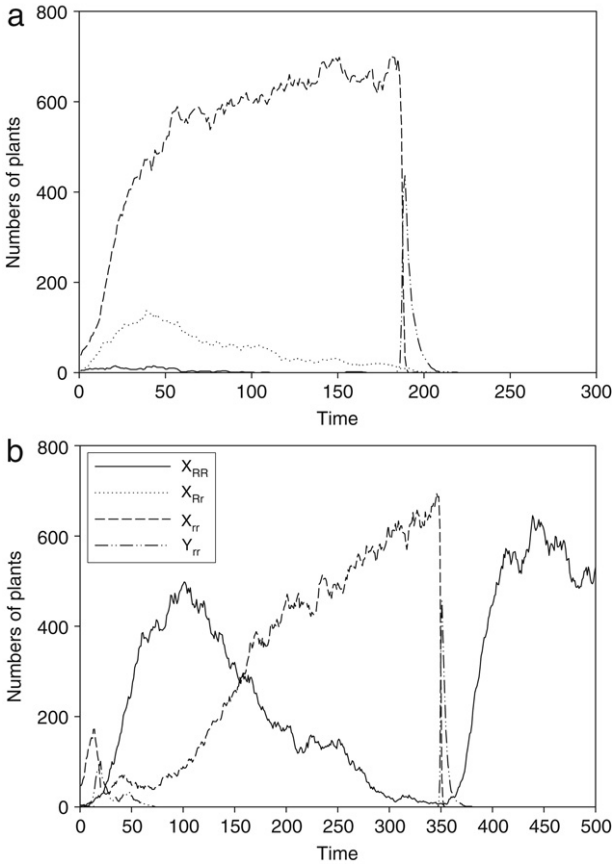

Fig. 3. Typical simulations of the stochastic individual-based analog of Eqs. (5a)–(5g) for the case of (a) complete outcrossing ($F = 0$), and (b) complete selfing ($F = 1$). Parameter values are given in Table 2. Note that in the case of selfing the population is able to recover, but it consists only of *RR*-homozygotes. In the outcrossing case, the population goes to extinction.

5. Discussion

The deterministic model shows that the effect of complete selfing on the spread of the *R*-allele, compared with complete outcrossing, is noticeable, although it is not huge. There are two main features of how the *R*-alleles change through time that differ between the extreme cases, $F = 0$ and $F = 1$. In the complete selfing case, after the introduction of disease causes a crash of the X_{rr} population, the number of diseased individuals stays at a high value for a somewhat longer period of time. The size of the susceptible population, X_{rr}, stays relatively constant at a low level over the entire period, as it is subjected to strong top-down effects from the disease. The second main feature is that, as the populations start to approach their new steady state equilibrium values asymptotically, in the complete selfing case, in approaching its new equilibrium value, Y_{rr}, undershoots this equilibrium value, at least slightly, coming closer to the axis than does Y_{rr} in the outcrossing case.

Eqs. (5a)–(5g) help us to understand the differences between the complete selfing and complete outcrossing cases (and cases in between). We can use those equations in a very rough way to interpret the disease and genetic trajectories, which we can view as divided into five phases (Fig. 1):

Phase 1. Following the outbreak of the disease in a population in which there is only a small proportion of the *R*-allele, the disease spreads very rapidly through the population on a time scale much faster than genetic response. The rate of increase of infecteds, Y_{rr}, is approximately $(\beta X_{rr} - b - \alpha)$, where X_{rr} is the size of the susceptible component of the population at the start of the outbreak. The term βX_{rr} is very large relative to the others.

Phase 2. After a large fraction of the susceptibles has become infected, the population of susceptibles is nearly exhausted and the infected population declines at a rate $b + \alpha$, until Y_{rr} settles to a plateau where further decline is very slow for a certain time interval.

Phase 3. Over that interval, the 'plateau' period, the number of *R*-alleles in the population, while growing exponentially according to Eq. (5a), is still small, so that X_{RR} and X_{Rr}, while competing with X_{rr} and Y_{rr} for resources, are not large enough to have an impact on the X_{rr} and Y_{rr} populations, which are in equilibrium with each other. The duration of this quasi-equilibrium plateau

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of Y_{rr} depends on the fraction of R-alleles in the population when this quasi-equilibrium is reached, and is longer the smaller that fraction is. The duration is also longer for pure selfing than for outcrossing (confirming our anticipation of that result under Question 1). We can see how this happens by noting in Eq. (5c) that the rate of input of new individuals of X_{rr} differs between the pure selfing and outbreeding cases. For pure selfing ($F = 1$), the input rate is $gam\,X_r$, while for random mating ($F = 0$) it is $gam\,X_r\left(\frac{gam\,X_r}{gam\,X_r+gam\,X_R}\right)$, and thus smaller to a degree that depends on the size of $gam\,X_R$. Therefore, as the resistant individuals, X_{RR} and X_{Rr}, increase, Y_{rr} starts to decline from its quasi-equilibrium sooner in the outcrossing case. This results from the fact that in the outcrossing case the input to X_{rr} declines due to two factors, competition from X_{RR} and X_{Rr}, which have lower mortality rates, and because of a faster loss of r-homozygotes from mating. In a selfing population, only the competition factor is at work. Outcrossing leads to faster depletion of X_{rr} and faster production of X_{Rr}'s, which are disease resistant. Thus the source of susceptibles is diminished at a faster rate with outcrossing, and the plateau period of Y_{rr} is shorter.

Phase 4. During this phase, the R-allele ($Allele_R$) starts to become a substantial fraction of the population. In its early growth, it is governed largely by Eq. (5a) alone, which means that its growth rate is approximately $a_{RR}/(1+\rho N^*)-b$, where N^* is approximately $X_{rr}+Y_{rr}$. When $Allele_R$ approaches its inflection point, Y_{rr} decreases rapidly, as it and X_{rr} (which is held at a relatively steady level by top-down control by the disease) are out-competed by X_{RR} (and X_{Rr}, if outcrossing occurs). In the selfing case ($F = 1$) Y_{rr} declines more sharply than when $F = 0$, and undershoots its new equilibrium level. The reason seems to be that in the selfing case the interaction between the disease and the susceptibles, X_{rr}, is somewhat like a Lotka–Volterra predator–prey relationship, and produces dynamics similar to a rapidly damped oscillation, causing X_{rr} to decline to values below those reached in the outcrossing ($F = 0$) case. This undershoot by Y_{rr} increases the probability of extinction of the disease from the population when demographic stochasticity is added. In the outcrossing case, the mating between rr-homozygotes and Rr-heterozygotes tends to moderate that Lotka-Volterra predator–prey effect.

Phase 5. In this phase, both $Allele_R$ and Y_{rr} are approaching their new equilibrium values (i.e., where resistance alleles dominate in the population, and endemic disease persists at a low level).

The individual-based (stochastic) model demonstrated that there is a substantial effect of selfing on the persistence of the disease in the population. Selfing, relative to outcrossing, tends to decrease disease persistence time, due to a higher influx of new susceptibles because of Rr–Rr and Rr–rr matings in the latter case. The IBM also shows an effect of the type of breeding on the possible extinction of the population, but not in the way that might have been anticipated (see Question 3). When disease drastically reduces the population of susceptibles, the only remaining individuals are RR-homozygotes in the selfing case, whereas in the outbreeding case they are mostly Rr-heterozygotes. In the selfing case, these homozygotes, although low in numbers, have a high probability of reproducing new homozygotes. However, in the outcrossing case, even though the same total number of R-alleles exist at the time of outbreak of the disease, enough of the offspring are rr-homozygotes that the resistant population could not build up. In those cases population extinction occurs. Hence the selfing population is generally more successful at avoiding extinction. The stochastic models also predict the occasional extinction of one of the alleles. Severe oscillations in host-parasite models can lead to possible extinction of genetic variants (Seger, 1988); our model does not undergo cycles, but can produce undershoots in population levels.

The results shown here for both the deterministic and stochastic models depend on the parameter values used in the models. We restricted our study to the case $a_{RR} = a_{Rr} < a_{rr}$, which is a reasonable assumption, and allowed us to focus on the dynamics of the interaction, as the equilibrium values are the same for selfing and outcrossing. Also, our examination of a range of key parameters, α and β, indicated that significant qualitative differences between selfing and outcrossing occurred over all of these parameter ranges. However, our results also confirmed that if costs of disease resistance are low, the polymorphism studied here might not be maintained in small populations.

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Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tpb.2008.07.001.

References

Anderson, R.M., May, R.M., 1981. The population dynamics of microparasites and their invertebrate hosts. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences 291, 451–524.
Bergelson, J., Dwyer, G., Emerson, J.J., 2001. Models and data on plant-enemy coevolution. Annual Review of Genetics 35, 469–499.
Bergelson, J., Purrington, C.B., 1996. Surveying patterns in the cost of resistance in plants. American Naturalist 148, 536–558.
Bergelson, J., Purrington, C.B., Palm, C.J., Lopez-Gutierrez, J.C., 1996. Costs of resistance: A test using transgenic *Arabidopsis thaliana*. Proceedings of the Royal Society of London Series B-Biological Sciences 263, 1659–1663.
Bronson, C.R., Ellingboe, A.H., 1986. The influence of 4 unnecessary genes for virulence on the fitness of *Ersiphe-Graminis* F sp. *Tritici*. Phytopathology 76, 154–158.
Brown, J.K.M., 2003. A cost of disease resistance: Paradigm or peculiarity?. Trends in Genetics 19, 667–671.
Burdon, J.J., Thrall, P.H., 2003. The fitness costs to plants of resistance to pathogens. Genome Biology 4, 227.
Caballero, A., Hill, W.G., 1992. Effects of partial inbreeding on fixation rates and variation of mutant genes. Genetics 131, 493–507.
Charlesworth, B., 1992. Evolutionary rates in partially self-fertilizing species. American Naturalist 140, 126–148.
Dale, P.J., 1992. Spread of engineered genes to wild relatives. Plant Physiology 100, 13–15.
Damgaard, C., 1999. Coevolution of a plant host–pathogen gene-for-gene system in a metapopulation model without cost of resistance or cost of virulence. Journal of Theoretical Biology 201, 1–12.
DeAngelis, D.L., Mooij, W.M., 2005. Individual-based modeling of ecological and evolutionary processes. Annual Review of Ecology, Evolution, and Systematics 36, 147–168.
Gibson, G.J., 1997. Investigating mechanisms of spatiotemporal epidemic spread using stochastic models. Phytopathology 87, 139–146.
Grimm, V., Railsback, S.F., 2005. Individual-based Modeling and Ecology. Princeton University Press, Princeton, New Jersey.
Hails, R.S., Morley, K., 2005. Genes invading new populations: A risk assessment perspective. Trends in Ecology & Evolution 20, 245–252.
Hartl, D.L., Clark, A.G., 1997. Principles of Population Genetics. Sinauer Associates, Inc., Sunderland, MA.
Kleczkowski, A., Gilligan, C.A., Bailey, C.J., 1997. Scaling and spatial dynamics in plant-pathogen systems: From individuals to populations. Proceedings of the Royal Society of London Series B-Biological Sciences 264, 979–984.
Koslow, J.M., DeAngelis, D.L., 2006. Host selfing and the prevalence of disease in a plant population. Proceedings of the Royal Society of London Series B-Biological Sciences 273, 1825–1831.
Pollack, A., 2006. Grass Created in the Lab is Found in the Wild. New York Times, New York, NY.
Power, A.G., 1991. Virus spread and vector dynamics in genetically diverse plant populations. Ecology 72, 232–241.

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Roy, B.A., Kirchner, J.W., 2000. Evolutionary dynamics of pathogen resistance and tolerance. Evolution 54, 51–63.
Schemske, D.W., Lande, R., 1985. The evolution of self-fertilization and inbreeding depression in plants. II Empirical observations. Evolution 39, 41–52.
Segarra, J., Jeger, M.J., van den Bosch, F., 2001. Epidemic dynamics and patterns of plant diseases. Phytopathology 91, 1001–1010.
Seger, J., 1988. Dynamics of some simple host-parasite models with more than 2 genotypes in each species. Philosophical Transactions of the Royal Society of London Series B-Biological Sciences 319, 541–555.
Tellier, A., Brown, J.K.M., 2007. Polymorphism in multilocus host-parasite coevolutionary interactions. Genetics 177, 1777–1790.
Thrall, P.H., Burdon, J.J., 2003. Evolution of virulence in a plant host–pathogen metapopulation. Science 299, 1735–1737.
Tian, D., Traw, M.B., Chen, J.Q., Kreitman, M., Bergelson, J., 2003. Fitness costs of R-gene-mediated resistance in *Arabidopsis thaliana*. Nature 423, 74–77.
Vera Cruz, C.M., Bai, J.F., Ona, I., Leung, H., Nelson, R.J., Mew, T.W., Leach, J.E., 2000. Predicting durability of a disease resistance gene based on an assessment of the fitness loss and epidemiological consequences of a virulence gene mutation. Proceedings of the National Academy of Sciences 97, 13500–13505.
Vogler, D.W., Kalisz, S., 2001. Sex among the flowers: The distribution of plant mating systems. Evolution 55, 202–204.
Wolfenbarger, L.L., Phifer, P.R., 2000. Biotechnology and ecology—The ecological risks and benefits of genetically engineered plants. Science 290, 2088–2093.
Wright, S., 1921. Systems of mating. II. The effects of inbreeding on the genetic composition of a population. Genetics 6, 124–143.
Xu, X.M., Ridout, M.S., 1998. Effects of initial conditions, sporulation rate, and spore dispersal gradient on the spatio-temporal dynamics of plant disease epidemics. Phytopathology 88, 1000–1012.
Zhang, X.S., Holt, J., Colvin, J., 2000. A general model of plant-virus disease infection incorporating vector aggregation. Plant Pathology 49, 435–444.