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Evolution of gene-for-gene systems in metapopulations: the effect of spatial scale of host and pathogen dispersal

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The concept of gene-for-gene coevolution is a major model for research on disease resistance in crop plants. However, few theoretical or empirical studies have examined such systems in natural situations, and as a consequence, there is little knowledge of how spatial effects are likely to influence the evolution of host resistance and pathogen virulence in gene-for-gene interactions. In this work, a simulation approach was used to investigate the epidemiological and genetic consequences of varying host and pathogen dispersal in metapopulation situations. The results demonstrate clear impacts of dispersal distance on the total number of host and pathogen genotypes that are maintained, as well as on genetic variation at individual host resistance and pathogen virulence loci. Several other important results also emerged from this study. In contrast to the predictions of many earlier nonspatial models, so-called 'super-races' of pathogens do not always evolve and dominate, indicating that it is not necessary to assume costs of resistance or virulence to maintain high levels of polymorphism in biologically realistic situations. The rate of evolution of both resistance and virulence depend on the scale of dispersal, with greater mixing (as a function of dispersal scale) resulting in a faster approach to a dynamic endpoint. The model in this paper also predicts that, despite the greater total genotypic diversity of pathogens across the metapopulation, variation in host resistance will generally be greater than variation in pathogen virulence within local populations.

Keywords: coevolution, disease dynamics, genetic polymorphism, resistance, virulence

Introduction

A general theme emerging from theoretical studies is that for a broad range of genetic and ecological assumptions, consideration of spatial structure leads to qualitatively different outcomes than would be predicted from single population models (Comins *et al.*, 1992; Gandon *et al.*, 1996; Hochberg & van Baalen, 1998; Boots & Sasaki, 1999; Kirchner & Roy, 1999; Roy & Kirchner, 2000). In such situations, coevolutionary processes have the potential to generate considerable spatial variation in the genetic structure of interacting species (Nuismer *et al.*, 1999, 2000). A recent review of long-term investigations of several natural plant–pathogen metapopulation systems (Burdon & Thrall, 1999) showed that they all exhibited substantial rates of colonization and extinction, and considerable among-population asynchrony in disease incidence (presence/absence) and prevalence (percentage of plants infected), indicating the central role of spatial structure in determining regional persistence. Empirical studies of plant host–pathogen systems have also demonstrated high diversity in resistance, virulence, and the distribution of genes controlling these traits, at both individual and population levels (Parker, 1985; Burdon, 1987; de Nooij & van Damme, 1988; Bevan *et al.*, 1993a,b,c; Burdon, 1994; Burdon *et al.*, 1999).

A major challenge is to elucidate conditions under which new resistance and virulence genes evolve and persist, and the factors that maintain genetic polymorphisms. For example, the Red Queen Hypothesis, which states that selection for increased variation in host resistance by pathogens and parasites can lead to an advantage for sexual reproduction, has been extensively explored both theoretically (e.g. Hamilton, 1980; Hamilton *et al.*, 1990) and empirically (e.g. Lively, 1987; Dybdahl & Lively, 1998; Ooi & Yahara, 1999). Realistic models must account, not only for the high diversity seen in natural plant–pathogen interactions, but also for the well documented potential for individual pathogen genotypes to be simultaneously adapted to multiple host resistance genes (unlike most existing models demonstrating Red Queen-type dynamics; Parker, 1994). This situation is problematic for gene-for-gene interactions in single populations. Without costs, it is predicted that 'super races' of pathogens (i.e. those carrying virulences effective against all resistance genes present) should evolve, at which point variation in resistance becomes effectively neutral.

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Recently, it was proposed that the spatial scale of dispersal may be a major determinant of ecological and genetic dynamics in host–pathogen interactions (Thrall & Burdon, 1997, 1999). In the present paper, the specific question of how entire assemblages of hosts and pathogens evolve in a gene-for-gene system involving host resistance and pathogen virulence (where virulence is used in the standard plant pathology context to mean the ability of a pathogen isolate to attack a host carrying a particular resistance gene) is investigated. In particular, two questions are addressed: (i) the epidemiological question of how the spatial scale of dispersal influences population size, disease incidence (presence/absence) and prevalence (percentage of individuals infected), and (ii) the evolutionary question of how dispersal influences the distribution of resistance and virulence genes at metapopulation, population and individual levels, as well as the total diversity of host and pathogen genotypes within the system.

Many host and pathogen life-history features are likely to interact to determine coevolutionary trajectories. In this paper, generalized parameter values are assumed for host birth and death rates and disease transmission (based on knowledge of the *Linum–Melampsora* system), while dispersal is focused on for several reasons. Consideration of a spatial (metapopulation) context (Thompson & Burdon, 1992; Burdon & Thrall, 1999) provides a realistic framework in which coevolutionary interactions evolve in space and time as a function of the interplay between local genetic drift, extinction, recolonization, migration and selection. Exactly how these processes interact will depend to a large extent on the degree of among-population connectedness. Previous work (Burdon & Thrall, 1999) suggests that pathogen dynamics and persistence are highly dependent on the spatial scale of spore dispersal relative to that of the host. In turn, variation in dynamics and persistence are likely to have a significant impact on the development of different patterns of disease resistance and pathogen virulence, as well as on the long-term maintenance of host and pathogen polymorphisms.

Materials and methods

The model

A spatially explicit simulation approach was used to investigate ecological and genetic dynamics in a gene-for-gene interaction without costs of resistance or virulence. In the gene-for-gene hypothesis (Flor, 1955), hosts and pathogens interact at each of n loci, with a susceptible reaction occurring unless there is a match between a resistant host allele and an avirulent pathogen allele (in general, resistance is dominant and virulence is recessive). This can be modelled by distinguishing resistance/susceptibility and avirulence/virulence alleles at each resistance or virulence locus by 1 or 0, respectively. A given host–pathogen combination leads to infection whenever there are no matching '1' alleles at any of the host and pathogen loci (see Frank, 1993a for a similar approach). Haploid asexual genetics were assumed for both host and pathogen, with five resistance and virulence loci, respectively (a total of 32 possible genotypes). Simulations assuming either four or six loci showed similar dynamics to those presented here, although the total numbers of possible genotypes were substantially different for these cases (16 and 64, respectively). Note that because this is a true gene-for-gene model it is possible to have pathogen genotypes that can attack all host genotypes.

The model assumes deterministic within-population dynamics, whereas the dispersal and extinction/recolonization phases are stochastic. Although the primary goal was to investigate the evolution of resistance and virulence in relation to the spatial scale of host and pathogen dispersal, the model was also used to examine several aspects of pathogen epidemiology (e.g. disease incidence and prevalence). Model structure and design of the simulation experiments are detailed below.

Within-population dynamics

Assuming strictly horizontal transmission, and that multiple pathogen types can simultaneously infect a single susceptible host, the year-to-year dynamics of healthy (X) and infected (Y) hosts within local populations are described as follows [only the equations for a single host genotype (j) are presented to avoid excessive complexity in notation]:

$$X_{j,t+1} = X_{j,t}[b + (1 - \mu)\exp(-\beta p_j)] + Y_{j,t}(b' + \nu) \quad (1)$$

$$Y_{j,t+1} = \{X_{j,t}[1 - \exp(-\beta p_j)] + Y_{j,t}\}(1 - \mu')(1 - \nu) \quad (2)$$

where p_j is the fraction of pathogens that can attack the jth host genotype [for each host genotype, p represents a different subset of the pathogen population (including migrants), depending on the specific resistance genes carried by that host]; ν is the rate at which infected hosts recover; β is the disease transmission parameter (all pathogen genotypes are assumed to be equally transmissible, given that infection is possible); μ is the disease-free mortality rate; μ' is the mortality rate of infected hosts ($\mu' \geq \mu$), and b and b' are the birth rates for healthy and infected hosts, respectively ($b' \leq b$). The mortality experienced by infected hosts is a function of disease severity (S = the mean pathogen load/infected host) such that

$$\mu' = \alpha + (\mu - a)\exp(-K_\alpha S) \quad (3)$$

In Eqn 3, α is the maximum mortality caused by infection and K_α is a constant that determines the slope of the relationship. Note that disease severity within a diverse host and pathogen population will vary among host genotypes according to the abundance of the subset of pathogens that can attack a particular host. The birth rate for healthy hosts (b), is given by the density-dependent function:

$$b = b_0/(1 + \zeta N_t) \quad (4)$$

where N_t is the total host population size, b_0 is the maximum per capita reproduction, and ζ determines the strength of density dependence on host establishment. For infected hosts, the birth rate (b') is assumed to be a

function of disease severity, where the numerator of the density-dependent function (Eqn 4) is replaced by

$$\varepsilon + (b_0 - \varepsilon)\exp(-K_\varepsilon S) \quad (5)$$

The minimum per capita reproduction for infected hosts is given by ε, with K_ε a constant, and S the disease severity as for Eqn 3.

The simulation tracks the dynamics of healthy and infected hosts, as well as the numbers of each host and pathogen genotype in local populations. Within a host generation, pathogen increase is determined by the fraction of susceptible hosts (healthy plus those already infected); this varies for each pathogen genotype depending on the virulence genes it carries. For infected hosts, the number of new infections that can establish depends on disease severity (the probability of new pathogens establishing on infected host individuals is a decreasing function of the mean density of pathogens already present). Thus, changes in numbers of a single pathogen genotype are given by:

$$P_{j,t+1} = P_{j,t}(1 + \gamma\{x_{j,t}(1 - \exp(-\beta)) + y_{j,t}[1 - \exp(-\beta/(1 + \delta S))]\})(1 - \mu')(1 - \nu) \quad (6)$$

where x_j and y_j represent the fractions of healthy and infected hosts, respectively, that are susceptible to the jth pathogen genotype, γ is the per capita spore production, and δ is the strength of density-dependence on pathogen establishment. Equation 6 assumes that pathogen survival across host generations depends entirely on the mortality rate of infected hosts and the probability of host recovery (i.e. no free-living stage). Thus, the overall dynamic is one of epidemic increase of pathogen populations within a growing season, followed by a crash and subsequent re-establishment and spread the following year. The severity and amplitude of this 'boom and bust' cycle depend on the mortality rate of infected hosts, and the number of episodes of pathogen increase during each host generation.

Among-population dynamics

The metapopulation simulations consisted of a two-dimensional (100×100) array of sites with absorbing boundaries, as such scenarios best mimic metapopulations of definite size beyond which propagules are essentially lost from the system. Each site was assigned a carrying capacity from a log-normal distribution; these were reassigned at random for each simulation run. In the simulation, ζ was solved in each site based on the assigned carrying capacity, using Eqn 4.

In each time interval, a fraction of the spores and seeds produced in each population disperse according to a negative exponential probability curve. To investigate the evolutionary consequences of different spatial scales of pathogen dispersal, host and pathogen dispersal distances were varied such that 99% of migrating spores or seeds fell within the specified distance (maximum dispersal distances = 1, 2, 5, 10, 20, 50 and 100 units, giving a total of 7 pathogen $\times$ 7 host dispersal combinations). The actual probability of landing within a site was determined by the Euclidean distance from the source population. Thus, the total infection probability within a population was a function of immigrating spores as well as the pathogens already present (three infection cycles were assumed per host generation to allow for epidemic-type dynamics). Similarly, host population growth included both within-population reproduction and seeds immigrating from other populations. This allowed dispersal to be examined in situations ranging from small isolated populations with little among-population connectedness to those which behaved essentially as a single large population with varying degrees of spatial substructuring (Thrall *et al.*, 1998; Thrall & Burdon, 1999). In this paper dispersal scales of 1 and 2 are referred to as 'local', those between 5 and 20 as 'intermediate', and those between 50 and 100 as 'global'. Clearly, though, what constitutes local versus intermediate or global dispersal in any real-world system will depend heavily on details of host and pathogen life history and their interaction (Thrall & Burdon, 1997).

Following within-population reproduction, dispersal and establishment of new host and pathogen populations, over-winter death of adults and recovery of infected plants occurred. At the beginning of each time interval, prior to the within-population-dynamics phase, a probability of extinction was calculated for each occupied patch as a function of population size (Thrall & Antonovics, 1995). Each simulation ran for 1000 host generations, by which time both genetic and numerical dynamics had generally stabilized (particularly for the pathogen) apart from stochastic fluctuations.

Simulation runs were initiated with a subset of sites (10%) being occupied by hosts, of which 10% were randomly chosen to be diseased. All populations initially consisted of a single host (completely susceptible: 00000) and, where disease was present, a single pathogen genotype (completely avirulent: 11111). Subsequent variation was generated by random mutation at the five resistance and virulence loci (see below). For each set of initial conditions, 10 random runs were performed. Data on host and pathogen colonization and extinction rates were taken at the beginning of each growing season after over-winter mortality, recovery and disturbance; data on the fraction of occupied sites, the fraction of populations with disease present, and disease prevalence within populations were taken at the midpoint of the epidemic in each host generation. To further quantify whether dynamics were epidemic or endemic, the fraction of host populations changing disease status (from present to absent or vice-versa) from one generation to the next was calculated for each simulation run.

During the reproduction phase, new genotypes could be generated by mutation. For each host or pathogen genotype present in the metapopulation, the total number of seeds or spores produced was determined and then multiplied by a fixed mutation rate (1×10^{-5}) to give the number of mutants for that genotype. The identity of mutant progeny was set by randomly choosing a locus for the parental genotype and changing it from 0 to 1 or vice-versa (forward and backward mutation rates were assumed to be equal). Mutant seeds or spores were then

dispersed as outlined above. Because pathogens had multiple cycles of increase per host generation, the opportunities for mutation and evolution were correspondingly greater on a per-individual basis (although the total number of mutants was dependent on population size).

Spatial and temporal variation in resistance and virulence

To investigate the effects of varying spatial scales of dispersal on the evolution of resistance and virulence, changes in the total number of host and pathogen genotypes present in the metapopulation, the mean number of host and pathogen genotypes per population, and the mean number of resistance or virulence genes per host or pathogen individual were tracked in each simulation run. The mean virulence of pathogens (fraction of hosts in the metapopulation that could be attacked) was also calculated. At several time intervals (0, 250, 500, 750 and 1000 host generations) information was also collected on the distribution of resistance and virulence genes at the individual level (the fraction of individuals across the metapopulation carrying 0–5 resistance or virulence genes), as well as on the average fraction of hosts that could be attacked by pathogens within their own local host population.

Simulation results

Patterns of disease incidence and prevalence

Dynamic patterns for disease prevalence (percentage of individuals infected) showed that temporal variability (amplitude across generations within runs) was dependent on the spatial scale of pathogen dispersal, being much greater when the latter was very local. This was also true for other ecological parameters such as percentage occupancy (fraction of potential sites with host populations), and the fraction of populations with disease. With respect to the fraction of host populations with disease present, there was always an initial rise followed by a sharp decline in incidence (usually within the first 50 generations). The severity of this decline was greater (more closely approaching global pathogen extinction) for larger scales of host dispersal, and was accompanied by larger initial declines in average virulence, particularly when pathogen dispersal was very local. This may partially explain why long-term pathogen persistence within the metapopulation was least likely when the host dispersed over very large distances.

In terms of the metapopulation structure after 1000 generations, pathogen dispersal distance had a large effect on percentage occupancy and the fraction of populations with disease present, but relatively little effect resulted from changes in the scale of host dispersal. For these two variables, there was a clear decrease over low-to-intermediate scales of pathogen dispersal, followed by some increase at the most global scales (Fig. 1a and b). In contrast, there were significant interactions between the scale of host and pathogen dispersal with respect to the average prevalence of disease (Fig. 1c). When host dispersal was most local, disease prevalence decreased sharply at intermediate scales of pathogen dispersal, increasing again to near unity for broadly dispersed pathogens. However, for intermediate and large scales of host dispersal, there was essentially a monotonic increase in disease prevalence for increasingly global scales of pathogen dispersal.

There was a strong positive correlation between the percentage of sites occupied by host populations and disease incidence ($r = 0{\cdot}77$, $P < 0{\cdot}0001$), and negative correlations between these variables and disease prevalence ($r = -0{\cdot}74$ and $-0{\cdot}56$ for occupancy and incidence, respectively; $P < 0{\cdot}0001$ for both). The overall epidemiological picture is one in which site occupancy by hosts is highest when pathogen dispersal is most local, generally with a high percentage of populations having disease present. In this case, disease dynamics were endemic – an assessment supported by the low frequency of change in the disease status of host populations (presence/absence) across generations. In contrast, intermediate scales of pathogen dispersal generated situations in which site occupancy and disease incidence were lower, but prevalence was generally high (except when pathogen dispersal was very local). Dynamics at these intermediate scales, where there was limited between-population dispersal, were strongly epidemic, with a large fraction of host populations changing disease status from one generation to the next, leading to high pathogen colonization and extinction rates.

Resistance and virulence structure

Diversity of host and pathogen genotypes

The evolutionary dynamics of the pathogen generally showed a rapid increase in the total number of pathogen genotypes within the first 200–300 host generations, followed by a gradual decline as less fit genotypes were selected out of the metapopulation. The magnitude of this initial increase in diversity was dependent on the spatial scale of pathogen dispersal, with the greatest increase when dispersal was most local, little or no increase for pathogens dispersing over intermediate distances, and the greatest initial increase when pathogen dispersal became more global (Fig. 2a). This initial increase in the diversity of pathogen genotypes corresponded with a decline in mean pathogen virulence across the metapopulation (Fig. 2b). In contrast, overall variation in host resistance generally showed a gradual increase. For any given scale of host dispersal, the total number of host genotypes increased most rapidly when pathogen dispersal was very local, and either increased more slowly or did not change at intermediate scales of pathogen dispersal, before tending to increase again at very large scales (Fig. 3). The results indicated that the number of host genotypes was often still increasing even after 1000 generations when pathogen dispersal was very local, but not when pathogen dispersal became more global. Moreover, increasing host dispersal led to equilibration of resistance diversity at smaller and smaller scales of pathogen dispersal (compare Fig. 3a and b). This suggests that host evolution will 'equilibrate'

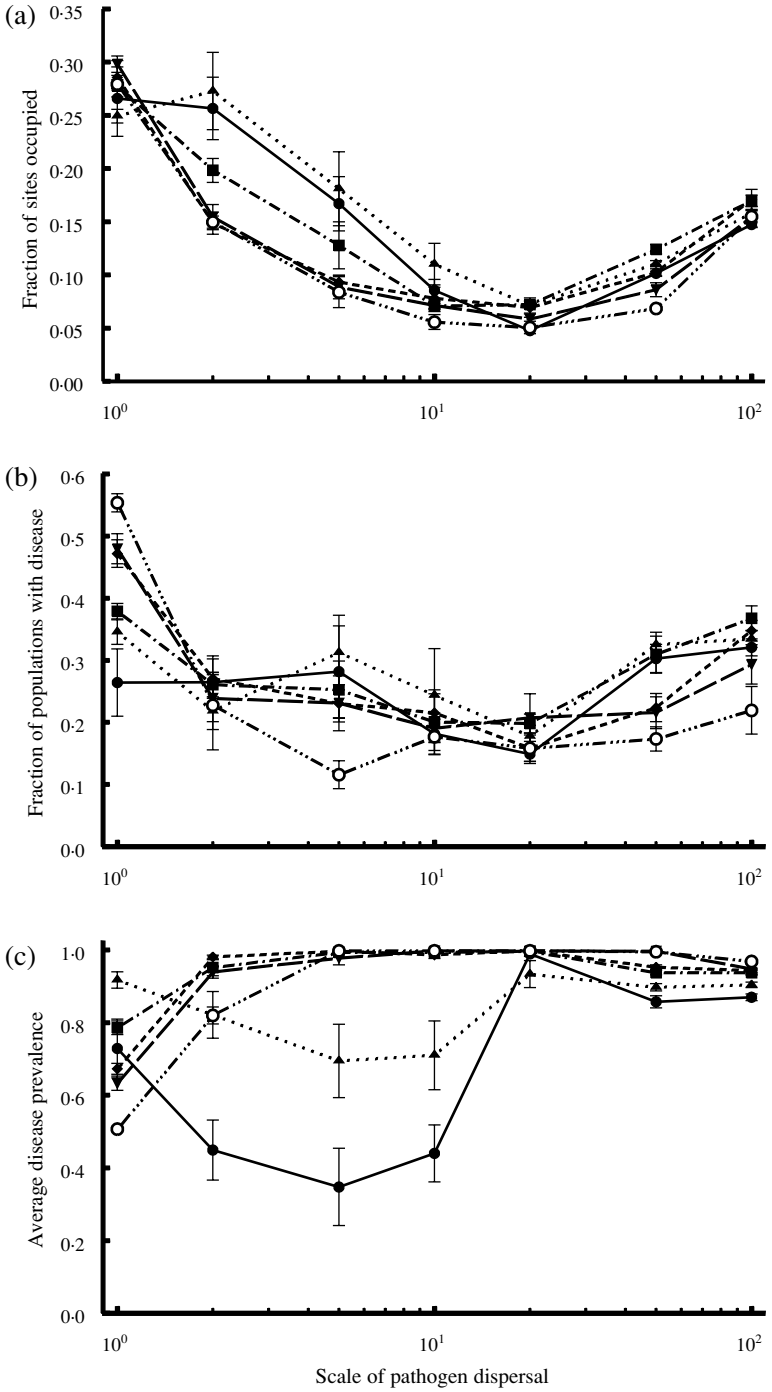

Figure 1 Effects of altering the spatial scale of dispersal on (a) the fraction of sites occupied in the metapopulation (100 × 100 two-dimensional grid), (b) the fraction of populations with disease present (incidence), and (c) average population disease prevalence after 1000 generations. The scale of pathogen dispersal (D_P) is represented along the *x*-axis (log scale), while each plotted line is for a different level of host dispersal (D_H): $D_H = 1$ (●), $D_H = 2$ (▲), $D_H = 5$ (■), $D_H = 10$ (◆), $D_H = 20$ (▼), and $D_H = 50$ (○). Each point represents the mean of 10 random runs at 1000 generations (standard errors are shown). For all runs, parameter values assumed were: $b_0 = 2{\cdot}5$, $\varepsilon = 1{\cdot}25$, $\nu = 0{\cdot}25$, $\mu = 0{\cdot}25$, $\beta = 5{\cdot}855$, $\alpha = 0{\cdot}95$, $\gamma = 10{\cdot}0$ and $\delta = 1{\cdot}0$ (see Eqns 1–6 in text).

faster across the metapopulation under these conditions, due to a greater degree of mixing.

The total number of virulence genotypes present after 1000 generations was highest for local pathogen dispersal, declined substantially for intermediate scales, and then increased again when pathogen dispersal was more global (Fig. 4a). Generally, decreases in equilibrium levels of diversity with increasing pathogen dispersal were greater

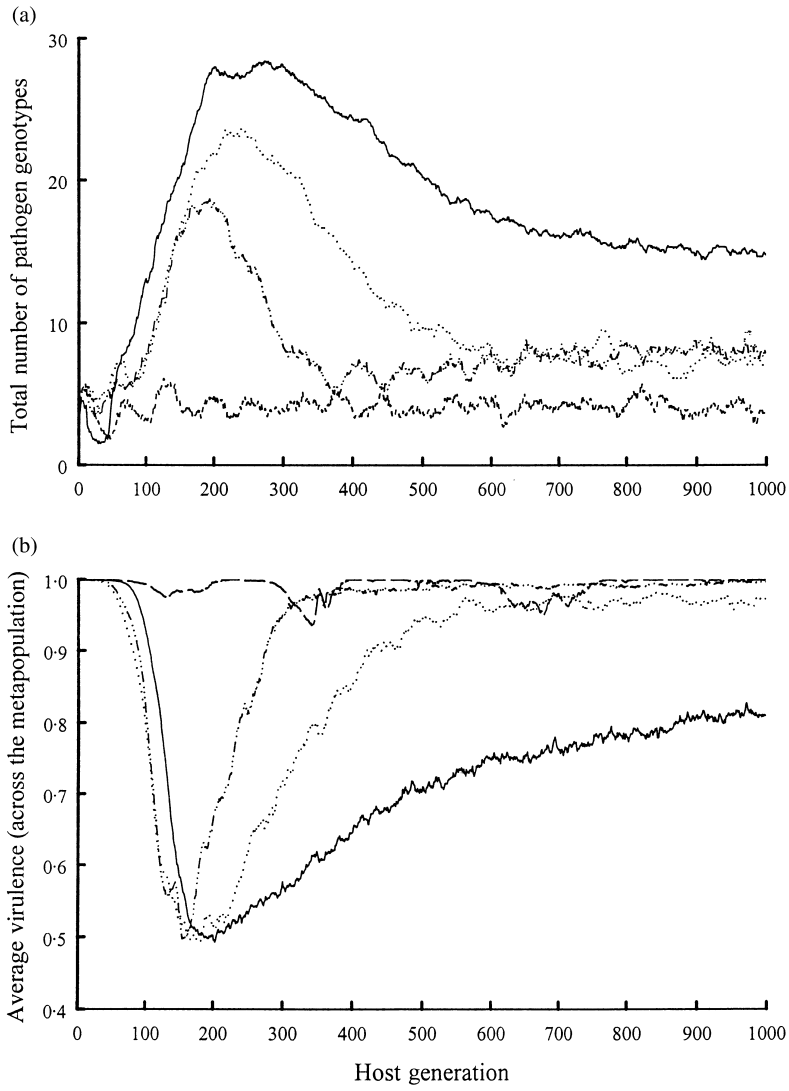

Figure 2 Evolutionary dynamics of the pathogen when D_H = 20 (these patterns are representative of all scales of host dispersal). (a) Total number of virulence genotypes occurring in the metapopulation. (b) Average virulence of the pathogens present calculated for each pathogen genotype as the fraction of susceptible hosts occurring in the metapopulation. Lines on the graph represent different scales of pathogen dispersal (solid lines, D_P = 1; dotted lines, D_P = 2; short dashed lines, D_P = 10; dashed-dotted lines, D_P = 100). See Fig. 1 for parameter values used.

when host dispersal was at larger scales, with the lowest levels of virulence diversity across the metapopulation occurring when hosts dispersed globally but pathogens dispersed over intermediate scales.

With respect to host resistance structure, the total number of resistance genotypes across the metapopulation after 1000 generations was also greatest when pathogens dispersed very locally, decreasing substantially as pathogen dispersal increased, and then increasing somewhat as pathogen dispersal became essentially global (Fig. 4b). The results also indicated significant effects of changing the scale of host dispersal on levels of diversity, in that at very local scales, resistance diversity increased somewhat as pathogen dispersal increased, before declining. For larger scales of host dispersal, this did not occur.

Population structure

There were tight correlations between the total number of resistance or virulence genotypes that evolved and the average number of these genotypes found per population (r = 0·90 for the host, and r = 0·87 for the pathogen; $P < 0{\cdot}0001$ for both). More unexpected, however, were the differences in the relationships between total and population diversity. As overall diversity of resistance genotypes increased, the number of host genotypes found per population also rose dramatically (Fig. 5b). In contrast, the average number of pathogen genotypes per population remained very low, regardless of overall pathogen diversity. A similar relationship occurred between the number of resistance genes per individual and genotypic diversity at the population level (Fig. 5a). Overall, these results indicate qualitative differences between hosts and pathogens in how variation is partitioned within and among populations, a pattern that may also be representative of host–parasitoid interactions (Tuda & Bonsall, 1999).

Mean and distribution of virulence genes per individual

A consistent dynamic pattern emerged, with the accumulation of virulence genes rising to an asymptote in the first several hundred generations. This was most evident for

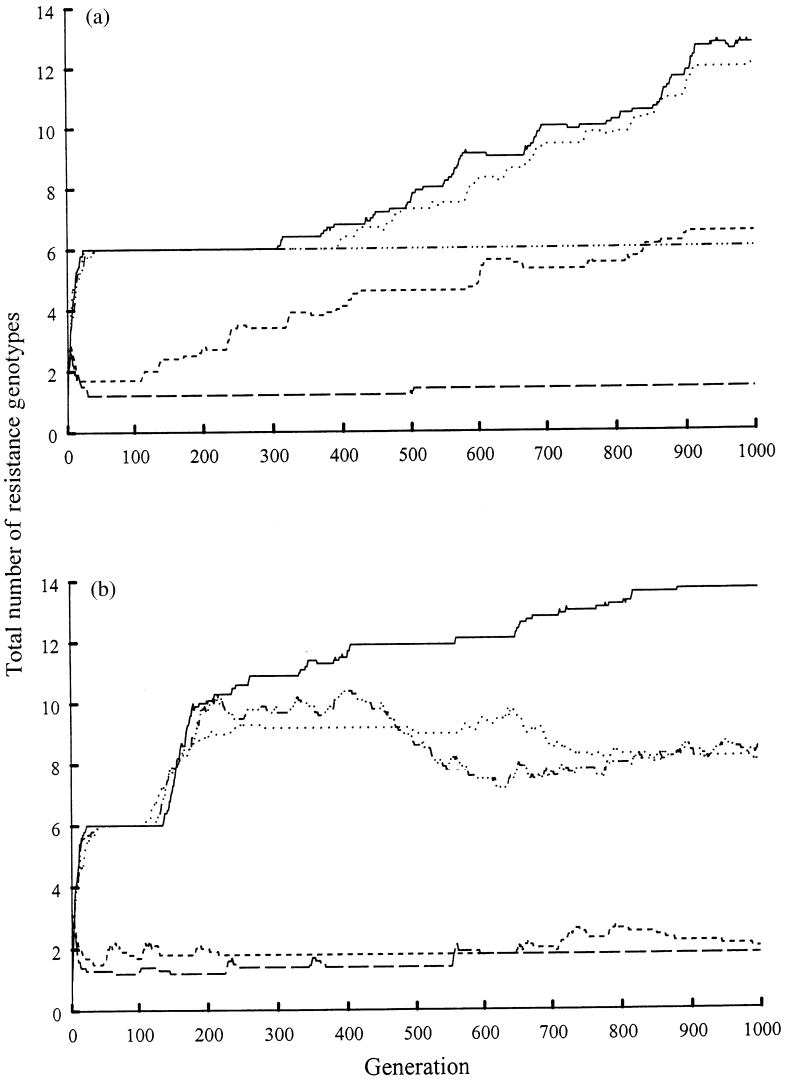

Figure 3 Evolutionary dynamics of the host with respect to the total number of resistance genotypes present in the metapopulation for (a) local host dispersal (D_H = 1), and (b) intermediate host dispersal (D_H = 20). Lines on the graph represent different scales of pathogen dispersal (solid lines, D_P = 1; dotted lines, D_P = 2; short dashed lines, D_P = 10; long dashed lines, D_P = 20; dashed-dotted lines, D_P = 100). See Fig. 1 for parameter values used.

very local or global pathogen dispersal, suggesting that pathogen evolution equilibrated fastest in these situations. As for total genotypic diversity, the mean number of virulence genes per pathogen was very high when pathogen dispersal was very local, generally declining as dispersal distance increased, but then rising again when pathogen dispersal was global (Fig. 6a). In fact, at the most global scales of dispersal, the number of virulence genes per pathogen was as high as, if not higher than, that seen for the most local scales of pathogen dispersal (e.g. pathogen dispersal = 100; host dispersal = 1; mean number of virulence genes = 4·655, indicating that most pathogens were capable of attacking all host genotypes). In contrast, for intermediate pathogen dispersal scales, the number of virulence genes per pathogen was always low (e.g. pathogen dispersal = 20; host dispersal = 1; mean number of virulence genes = 0·160). There was also an interaction with the scale of host dispersal such that the decline in the average number of virulence genes per pathogen was greatest when host dispersal was most local (e.g. at a pathogen dispersal scale of 20, the mean number of virulence genes/individual was 0·16 and 2·21 for host dispersal scales of 1 and 20, respectively). For host dispersal scales > 2, rather than an immediate decline in the number of virulence genes per individual, there was either no change or a slight increase for pathogen dispersal scales between 1 and 5 (Fig. 6a).

Pathogen dispersal distance also had large effects on how virulence genes were distributed. For any given scale of host dispersal, distributions were skewed towards high numbers of genes/individual pathogen for either very local or global pathogen dispersal, and shifted towards lower numbers of genes/individual for intermediate dispersal scales (Fig. 7). However, even for highly skewed distributions, pathogen genotypes carrying intermediate numbers of virulence genes were always present, and it was often the case that similar mean values for the number of genes per individual reflected substantially different distributions across the metapopulation. For example, compare the distribution of virulence genes for pathogen

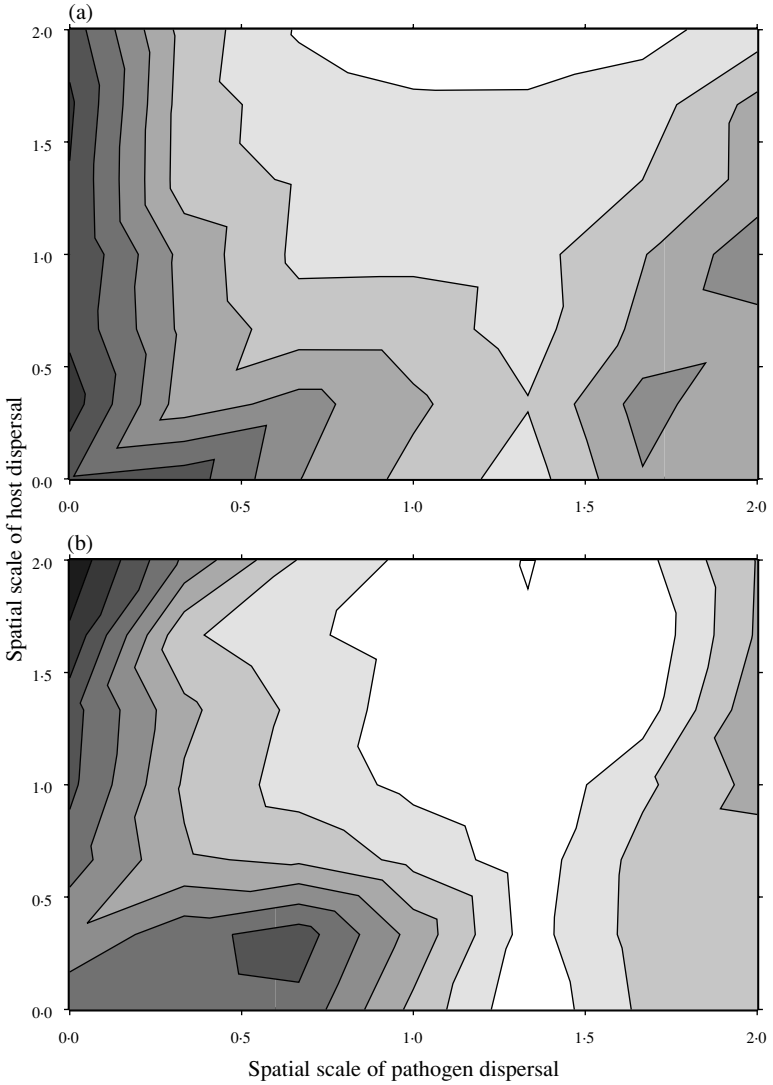

Figure 4 Contour plots showing the effect of altering the spatial scale of host and pathogen dispersal (log scale) on (a) the total number of pathogen virulence genotypes that are maintained in the metapopulation, and (b) the total number of host resistance genotypes. Contour lines are plotted at intervals of 2·0, with darker regions representing situations with greater overall diversity of resistance or virulence genotypes. The results shown represent the means of 10 random runs at 1000 generations. See Fig. 1 for parameter values used.

dispersal scales of 1 and 100, when host dispersal scale = 1, where the mean numbers of virulence genes per pathogen were 4·02 and 4·65, respectively (Fig. 7a).

In general, increasing host dispersal distance favoured the development of pathogen populations dominated by individuals with multiple virulence genes (Fig. 7a–c). This reflects a tendency for metapopulation structure to more closely approximate a single very large population as host dispersal becomes more global. This situation is roughly equivalent to the assumptions of classic population genetic models of hosts and pathogens, which predict that without fitness costs, evolution will lead to the domination of 'super races' of pathogens that can attack all hosts (Leonard, 1969; Groth, 1976; Leonard, 1977; Leonard & Czochor, 1980).

Mean and distribution of resistance genes per individual

The evolutionary dynamics of host resistance showed a similar pattern to that for pathogen virulence. For example, for any given scale of pathogen dispersal, the dynamics generally showed a monotonic increase in numbers of resistance genes per host individual over time (data not shown). However, rates of evolution of host resistance were most rapid when pathogen dispersal was very local, but host dispersal was global. The mean number of resistance genes per individual that evolved was thus clearly linked to the scale of pathogen dispersal, with very little resistance evolving for intermediate scales of dispersal, but higher values when dispersal was very local (Fig. 6b). In general, as host dispersal increased, the maximum number of resistance genes per host individual also increased (most evident when pathogen dispersal was very local).

With respect to the distribution of host resistance genes, regardless of the scale of pathogen dispersal, the majority of hosts either carried only single resistance genes or were completely susceptible (Fig. 8). This was in strong contrast to the pattern seen in the pathogen, where genotypes carrying multiple virulence genes often predominated. However, there was a tendency at the most local scales of pathogen dispersal for some hosts to carry a greater

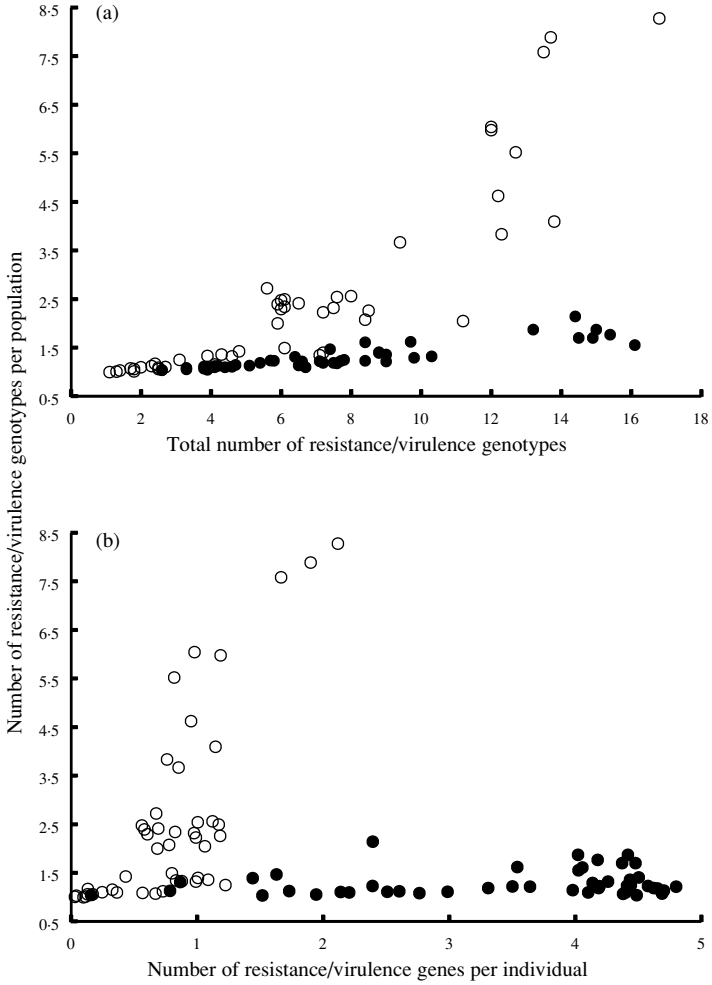

Figure 5 The relationship between the mean number of resistance (○) and virulence (●) genotypes per local population and (a) the mean number of resistance or virulence genes per host or pathogen population, respectively, and (b) the total number of host or pathogen genotypes across the metapopulation. Each point represents the mean of 10 random runs at 1000 generations. See Fig. 1 for parameter values used.

number of resistance genes. This effect became more pronounced as host dispersal became more global, to the extent that at very broad scales of host dispersal, a small fraction of hosts carried up to four resistance genes (compare Fig. 8a and c).

Discussion

Epidemiological and genetic patterns

The coevolutionary nature of most host–pathogen interactions and the importance of life-history features that determine the frequency and duration of encounters between different host and pathogen genotypes suggest that spatial structure is a crucial factor in how such associations evolve (Thrall & Burdon, 1997) and the levels of genetic diversity that are maintained. The results of the simulation model presented here confirm this idea, indicating that the scales of host and pathogen dispersal are important influences on the epidemiology and evolution of gene-for-gene interactions.

Total numbers of resistance and virulence genotypes evolved to their highest levels in the metapopulation when both host and pathogen dispersal were very local. In contrast, host and pathogen genotypic diversity was predicted to be very low for intermediate pathogen dispersal scales. The mean number of resistance or virulence genes per individual host or pathogen followed similar patterns to that seen for total genotypic diversity. These genetic variables were all highly positively correlated with disease incidence and the fraction of sites occupied by hosts, but negatively correlated with disease prevalence and average pathogen virulence. Thus, mean pathogen virulence was highest for intermediate scales of dispersal.

At low-to-intermediate dispersal scales, pathogens showed the greatest evenness of distribution across a larger number of genotypic classes (ranging from pathogens carrying 0–5 virulence genes). While complex pathogens carrying many virulence genes are more likely to establish and spread more widely than simple pathotypes within any given host population, they may also cause greater mortality due to higher average pathogen loads. When pathogens disperse globally (and the metapopulation resembles a single large subdivided population), abundant opportunities for transmission and reduced probabilities of extinction favour complex pathotypes. When dispersal is very local, pathogens carrying multiple virulence genes

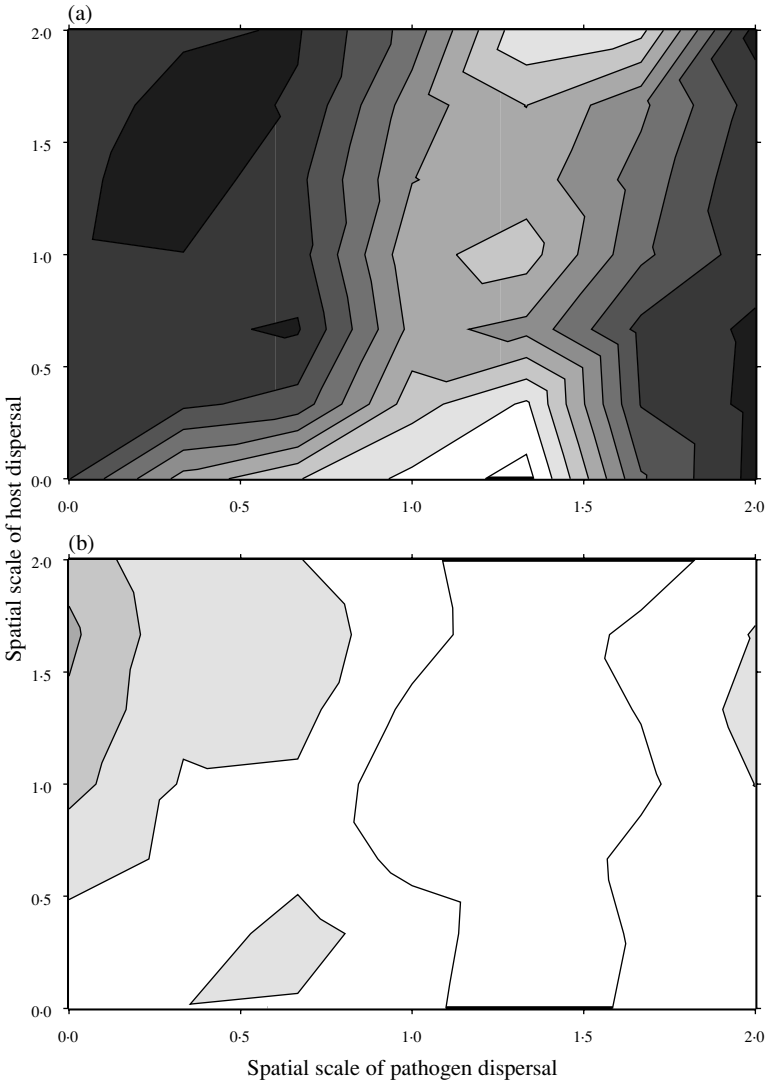

Figure 6 Contour plots showing the effect of altering the spatial scale of host and pathogen dispersal (log scales) on (a) the average number of virulence genes carried per pathogen, and (b) the average number of resistance genes carried per host. Contour lines are plotted at intervals of 0·5, with darker regions representing situations where pathogens or hosts carry greater numbers of virulence or resistance genes, respectively. The results shown represent the means of 10 random runs at 1000 generations. See Fig. 1 for parameter values used.

are also favoured within any single population, but stochastic effects (e.g. drift), the possibility of local extinction and low recolonization rates ensure that complex pathotypes do not always dominate (hence the greater distribution across genotypic classes observed for the most local scale of dispersal, relative to that seen for the most global scale of dispersal, e.g. Fig. 7a). Finally, at intermediate scales, where colonization and extinction rates are highest, but there is still substantial among-population asynchrony, a more diverse mixture of pathogens is favoured, most likely due to trade-offs between within-population spread, local extinction, and ability to colonize new host populations (see also May & Nowak, 1994). This idea was supported both by positive correlations between pathogen colonization and extinction rates and by overall evenness (Shannon-Weaver index) among genotypic classes. Moreover, results from additional simulations assuming a more severe effect of increasing pathogen loads on host mortality showed that distributions were shifted towards pathogens carrying fewer virulence genes (data not shown). Group selection scenarios of the sort outlined above have also been demonstrated in other theoretical metapopulation studies (e.g. Kirchner & Roy, 1999).

Overall, pathogens generally carried significantly greater numbers of virulence genes than hosts did resistance genes. However, this did not necessarily result in pathogens being locally well adapted to their host populations. Indeed, when both host and pathogen dispersal were very local, a high percentage of pathogens were able to attack 10% or less of the hosts present (e.g. pathogen dispersal = 2; host dispersal = 1; average percentage of 'maladapted' pathogens = 50·8%). On the other hand, for intermediate host and pathogen dispersal, most pathogens were able to attack more than 90% of their local hosts, while for global scales of host dispersal, the level of maladaption again increased to very high levels. It may well be that the low probabilities of pathogen persistence under conditions of global host dispersal are due to a combination of overall rapid early increases in disease, followed by population crashes and generally low site occupancy. Due to

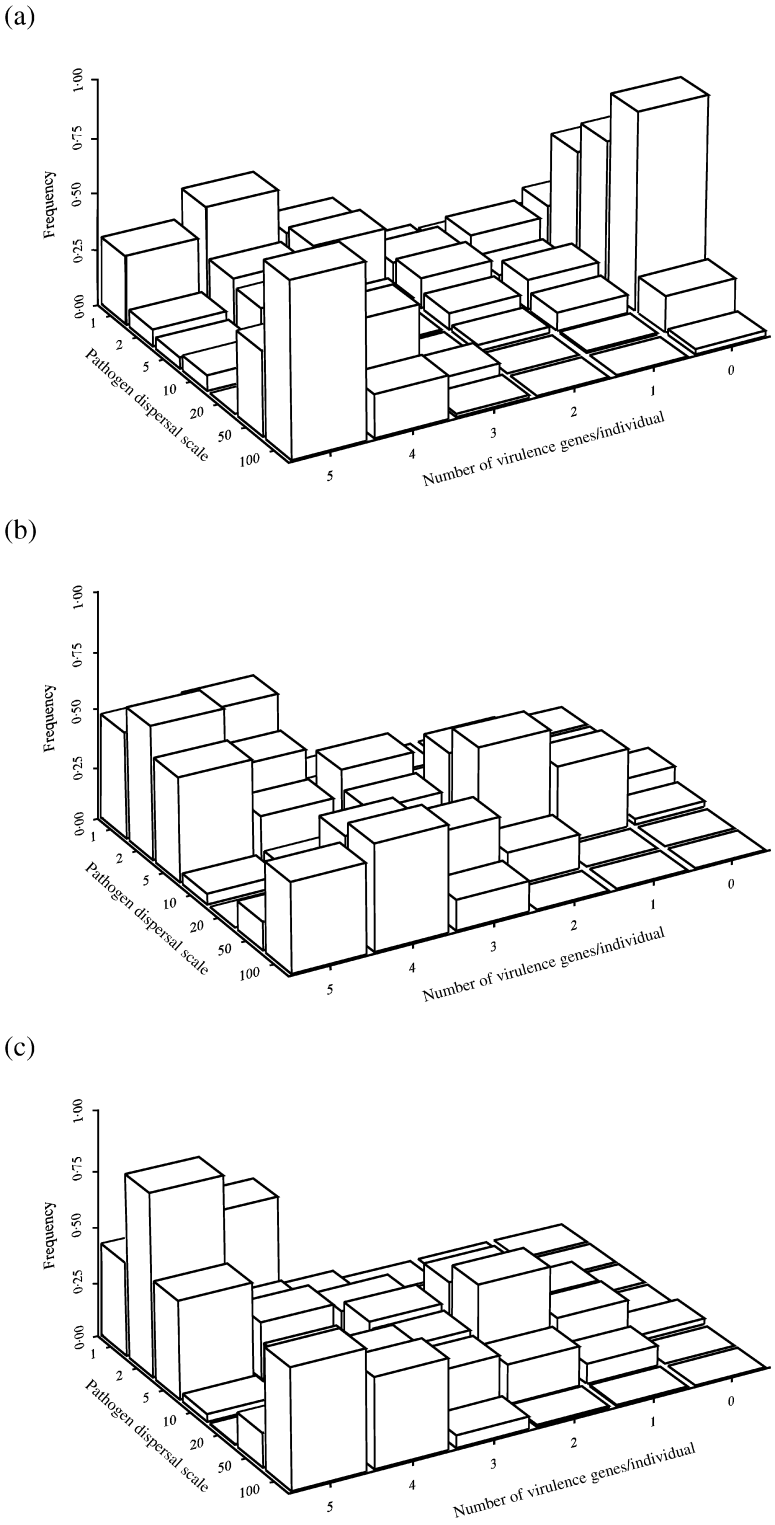

Figure 7 Bar graphs showing the frequency distributions for pathogens carrying different numbers of virulence genes (0–5) in relation to different scales of host and pathogen dispersal. Each graph represents a different scale of host dispersal (D_H) and a range of dispersal scales for the pathogen. (a) $D_H = 1$, (b) $D_H = 10$, (c) $D_H = 20$. Bars represent the mean of 10 random runs at 1000 generations. See Fig. 1 for parameter values used.

smaller population sizes, these conditions will result in slower rates of pathogen evolution which would also contribute to higher probabilities of extinction. It should be noted that in many cases, average virulence does not accurately reflect what is happening at the local scale.

Theoretical studies of coevolution in space and time

In recent years, a range of analytical and simulation approaches have been used to investigate coevolutionary dynamics in spatially structured interactions ranging from

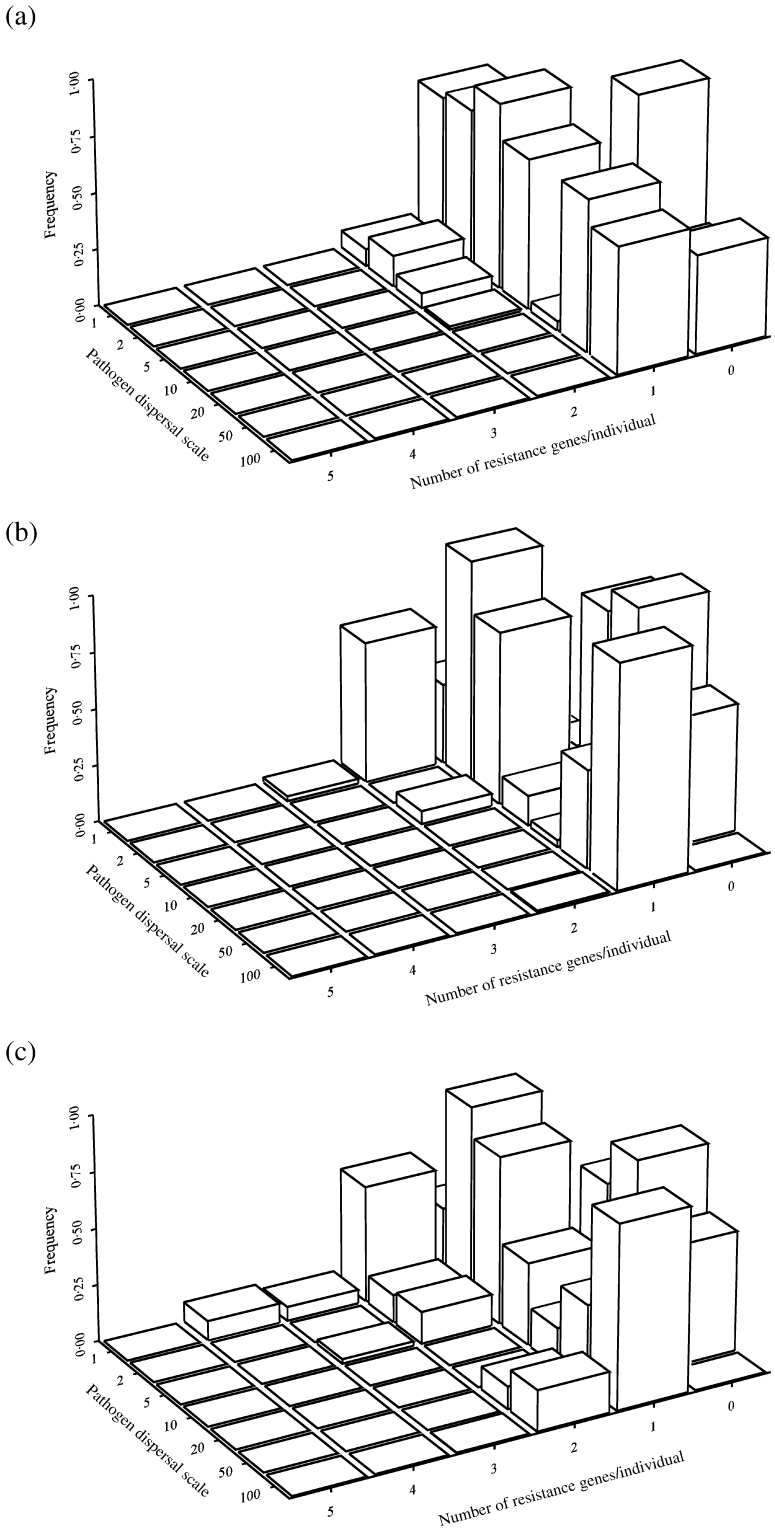

Figure 8 Bar graphs showing the frequency distributions for hosts carrying different numbers of resistance genes (0–5) in relation to different scales of host and pathogen dispersal. Each graph represents a different scale of host dispersal (D_H) and a range of dispersal scales for the pathogen. (a) $D_H = 1$, (b) $D_H = 10$, (c) $D_H = 20$. Bars represent the mean of 10 random runs at 1000 generations. See Fig. 1 for parameter values used.

predators and their prey (e.g. van Baalen & Sabelis, 1993; Hochberg & van Baalen, 1998) to mutualisms (Parker, 1999) and host–parasite systems (Gandon *et al.*, 1996; Morand *et al.*, 1996; Thrall & Burdon, 1999). A number of studies have focused on the geographic mosaic theory (Thompson, 1994) and exploration of the consequences of coevolutionary hot spots and selection mosaics (e.g. Nuismer *et al.*, 1999, 2000; Gomulkiewicz *et al.*, 2000). Despite the array of underlying ecological and genetic assumptions represented, an overarching theme linking

these studies is that spatial structure can result in coevolutionary outcomes that simply cannot occur in isolated local populations.

A number of other generalities have emerged with respect to the influence of spatial and geographic structure on coevolutionary dynamics. For example, polymorphisms in the genetics of interacting species are far easier to maintain in these situations (Thrall & Antonovics, 1995; Nuismer *et al.*, 1999), particularly in heterogeneous environments, where crucial parameters such as reproductive capacity (Hochberg & van Baalen, 1998; the present study) or risk of infection (Nuismer *et al.*, 2000) may vary across the landscape. Although the extent to which these assumptions influence coevolutionary outcomes in gene-for-gene interactions is not explored here, it may well be that 'super pathogens' would evolve much more rapidly in more homogeneous situations (cf. agricultural systems). In this context, Hochberg & van Baalen (1998) predicted that generalist predators would dominate in areas more productive of prey, whereas specialists would be favoured in marginal situations. This pattern is enhanced in situations where migration is local relative to the global case, and parallels other studies showing that genetic diversity is likely to depend on the life histories of the coevolving species, as well as on environmental heterogeneity (e.g. Thrall & Burdon, 1997; Nuismer *et al.*, 2000).

Rates of migration and gene flow also play crucial roles in determining patterns of local adaptation and maladaptation. Thus, Gandon *et al.* (1996) used a matching-allele model to investigate how patterns of local adaptation depended on host and pathogen migration rates. They concluded that when pathogen migration exceeded that of the host, pathogens were likely to be locally adapted to host populations, whereas the opposite pattern should be observed when hosts migrate more than their pathogens. Studies of coevolutionary clines suggest that spatially structured patterns of local adaptation are most likely to occur in situations where selection is strong but spatially variable, and where gene flow is weak (Nuismer *et al.*, 2000).

While much generality has emerged from spatial models of coevolution, it is unclear to what extent specific model outcomes depend on the form of the underlying genetics. The present paper focuses on gene-for-gene interactions in plant host–pathogen interactions as these are genetically the best known and characterized. Previous theoretical studies of host–pathogen systems have investigated various aspects of their ecological and evolutionary dynamics in spatial or pseudospatial contexts, assuming either some form of a symmetric matching-allele model (Frank, 1991, 1992, 1993b, 1996b; Gandon *et al.*, 1996; Morand *et al.*, 1996), or incorporating, as here, gene-for-gene formulations (Frank, 1993a; Damgaard, 1999; Thrall & Burdon, 1999) that mirror the asymmetries found in a number of real-world plant–pathogen interactions (Parker, 1994; Thompson & Burdon, 1992). Simulations of models based on matching-allele versus gene-for-gene situations predict both qualitative and quantitative differences in disease dynamics and persistence, as well as the relative levels of host and pathogen diversity that evolve (J. J. Burdon and P. H. Thrall, unpublished data).

The matching-allele model differs in several important aspects from the biologically realistic gene-for-gene scenario originally proposed by Flor (1942, 1955) and adopted in the current investigation. Despite Frank's statement that 'the current data are not sufficient' (Frank, 1996a) to draw strong conclusions about the nature of genetic specificity in plant–pathogen interactions, the available evidence (from both natural and agricultural systems) overwhelmingly supports a gene-for-gene interpretation (e.g. Islam & Shepherd, 1991; Thompson & Burdon, 1992; Parker, 1994; McIntosh *et al.*, 1995) in systems dominated by major gene effects. Moreover, although some forms of the matching-allele model (Frank, 1993b) predict resistance genes will be rare and virulence genes common (a pattern that is empirically supported), this is also an inevitable consequence of gene-for-gene systems in which any resistance gene gives protection against all except its specific matching virulence gene. In this context, it is noteworthy that the simulation presented in the current paper also produces realistic patterns with respect to numbers of host resistance and pathogen virulence genes per individual. Furthermore, the results demonstrate quite clearly that in a biologically realistic setting where pathogens can be simultaneously well adapted to multiple host resistance genes, high levels of polymorphism can be maintained without assuming costs.

In the only other model explicitly incorporating gene-for-gene dynamics in a metapopulation context, Damgaard (1999) also apparently showed that host and pathogen polymorphisms in resistance and virulence could be maintained without costs. However, his results were almost certainly artifactual, as pathogen populations were arbitrarily truncated in each generation to remove those with high virulence. Moreover, it is unclear to what extent that model represented biologically realistic host–pathogen interactions given the lack of distance-dependent dispersal, the assumption that all host populations were always diseased, and that recolonization of host sites was always from a pre-existing seedbank, and thus independent of the genetic or numerical dynamics of other local demes.

In another study, Frank (1993a), used a Lotka–Voltera approach to investigate the genetic dynamics of a true gene-for-gene interaction within a single population into which new resistance and virulence types could migrate. Assuming some fitness costs associated with resistance and virulence, his results again predicted that the number of resistance genes per host would generally be much lower than the number of virulence genes per pathogen (see also Sasaki, 2000), but also that increasingly epidemic dynamics would lead to the reverse situation, with lower overall genetic diversity in both host and pathogen. These latter results are in apparent contrast to observed patterns from the few wild host–pathogen interactions for which genetic structure has been assessed (Leonard, 1997; see also Table 1 in Thrall & Burdon, 1997).

Resistance and virulence structure in natural plant–pathogen systems

The simulation results in this study show a range of evolutionary outcomes that depend on the spatial scale of host and pathogen dispersal. Empirical studies of host–pathogen systems in nature also reveal a diversity of genetic resistance and virulence structures. These range from systems with little or no evidence for classic gene-for-gene interactions [e.g. *Silene* spp.–*Ustilago violacea* (Biere & Antonovics, 1996; Antonovics *et al.*, 1997; Carlsson-Granér, 1997), *Plantago lanceolata–Phomopsis subordinaria* (De Nooij & van Damme, 1988)] to those where qualitative major gene resistance is a central feature [*Linum marginale–Melampsora lini* (Jarosz & Burdon, 1991; Burdon, 1994; Burdon *et al.*, 1996, 1999), *Glycine canescens–Phakopsora pachyrhizi* (Burdon, 1987), *Avena* spp.–*Puccinia coronata* (Dinoor, 1970, 1977)]. Hosts in plant–pathogen interactions, such as that between wild barley grasses and *Rhynchosporium secalis* (Jarosz & Burdon, 1996) or *Populus trichocarpa–Melampsora occidentalis* (Hsiang & Chastagner, 1993), exhibit a mixture of different resistance types that fall between these extremes. Even within major gene-for-gene systems, there can be considerable variation in how resistance is structured; for example, it is not uncommon to find as many as three resistance genes in individual *Glycine* plants (Burdon, 1987), while for *L. marginale*, one resistance gene per host is the rule (Burdon, 1994).

Evidence from several natural plant–pathogen interactions [*Valeriana salina–Uromyces valerianae*, *Filipendula ulmaria–Triphragmium ulmariae*, *Linum marginale–Melampsora lini*, *Silene alba–Ustilago violacea* (Burdon & Thrall, 1999 and references therein)] indicates that local populations within these systems are at least partially isolated from one another. Indeed, interactions between adjacent populations in these systems range from essentially free movement to virtually none, with corresponding shifts in the asynchrony of among-population disease dynamics. The genetic and epidemiological consequences of this asynchrony have been most clearly documented in the *Linum–Melampsora* system, where interpopulation distances are significantly correlated with similarities in resistance structure (Thrall *et al.*, 2001); importantly, such among-population variation in resistance significantly influences the severity of local disease epidemics (Thrall & Burdon, 2000). Clearly, the assumption of global dispersal does not fit comfortably with the observed dynamics in natural host–pathogen interactions, but is rather a 'convenience' used in many models that stems from human perceptions of agricultural systems.

The model presented in this paper also predicts that host diversity may considerably exceed pathogen diversity within local populations, despite generally greater numbers of pathogen genotypes across the metapopulation as a whole. Support for this prediction comes from work on a metapopulation of the *Linum–Melampsora* interaction where comparisons between a range of host and pathogen populations frequently show a greater number of resistance phenotypes than virulence phenotypes at the local scale (P. H. Thrall and J. J. Burdon, unpublished data).

General conclusions

Beyond the demonstration of clear effects of dispersal distance on metapopulation dynamics and coevolution, several other important results emerge from this study. In contrast to the predictions of many earlier nonspatial models of genotype-specific interactions (e.g. Jayakar, 1970; Groth, 1976; Leonard, 1977), so-called 'super races' of pathogens do not always evolve and become totally dominant. In fact, the results of the current work indicate that contrary to much of the previous theory on host–pathogen interactions, it is not necessary to assume resistance or virulence costs to maintain high levels of polymorphism. Indeed, when host and pathogen dispersal were very local, while the majority of pathogens had high virulence, a significant fraction of pathogens had less than the maximum number of virulence genes, indicating that coevolutionary outcomes arising from many small isolated populations with high probabilities of extinction do not equal predictions based on a single very large population.

Finally, although it is clear that many isolated local populations do not equal one large population, at the same time it is at these extreme scales of dispersal that the dynamics and evolutionary outcomes of host–pathogen associations are most similar. It is at intermediate scales of dispersal, where colonization and extinction processes play significant roles in the interaction between host and pathogen, that the metapopulation paradigm predominates.

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