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E-Article

Spatial Structure Mitigates Fitness Costs in Host-Parasite Coevolution

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abstract: The extent of population mixing is known to influence the coevolutionary outcomes of many host and parasite traits, including the evolution of generalism (the ability to resist or infect a broad range of genotypes). While the segregation of populations into interconnected demes has been shown to influence the evolution of generalism, the role of local interactions between individuals is unclear. Here, we combine an individual-based model of microbial communities with a well-established framework of genetic specificity that matches empirical observations of bacterium-phage interactions. We find the evolution of generalism in well-mixed populations to be highly sensitive to the severity of associated fitness costs, but the constraining effect of costs on the evolution of generalism is lessened in spatially structured populations. The contrasting outcomes between the two environments can be explained by different scales of competition (i.e., global vs. local). These findings suggest that local interactions may have important effects on the evolution of generalism in host-parasite interactions, particularly in the presence of high fitness costs.

Keywords: host-parasite coevolution, spatial structure, resistance and infectivity range, fitness costs.

Introduction

Antagonistic coevolution between hosts and parasites is often associated with the emergence of generalism, where populations develop the ability to resist or infect a broad range of genotypes. This means that contemporary populations may be well adapted to ancestral lineages but perform poorly against future populations (Buckling and Rainey 2002*a*; Mizoguchi et al. 2003; Scanlan et al. 2011). The fundamental principles of these "coevolutionary arms races" are captured by the gene-for-gene (GFG) framework, in which hosts can avoid infection by accumulating resistance alleles at multiple loci but parasites can counter these adaptations by gaining infectivity alleles at matching loci (Flor 1956; Sasaki 2000). Hence there is a gene-for-gene correspondence between resistance and infectivity alleles. (Note that the literature often refers to these parasite adaptations as "virulence" alleles, but to avoid confusion with disease severity we will refer to them as "infectivity" alleles instead). Under the GFG framework, parasites must match or exceed the host's resistance alleles at each locus to have a high probability of causing an infection, which naturally leads to the evolution of generalism in the form of broader resistance and infectivity ranges. These dynamics have been observed in a variety of real host-parasite relationships, including bacterium-phage (Bohannan and Lenski 2000; Buckling and Rainey 2002*a*; Mizoguchi et al. 2003; Brockhurst et al. 2006; Forde et al. 2008; Scanlan et al. 2011), plant-pathogen (Flor 1956; Thompson and Burdon 1992; Thrall and Burdon 2003) and nematode-bacterium systems (Schulte et al. 2010). Recent studies of bacterium-phage coevolution have found that infectivity range is correlated with the number of amino acid changes in tail fibers relative to the ancestral genotype (Scanlan et al. 2011), providing further support for the GFG framework. However, coevolutionary arms races are unlikely to be maintained indefinitely as fitness costs associated with generalism (usually in the form of lower growth/infectivity rates) can reduce selection for broad ranges (Chao et al. 1977; Webster and Woolhouse 1999; Sasaki 2000; Bohannan et al. 2002; Lopez-Pascua and Buckling 2008; Poullain et al. 2008). Sasaki (2000) predicted that fitness costs will lead to fluctuations between specialism (narrow range) and generalism (broad range), but empirical observations suggest that fitness costs may instead lead to fluctuating selection among genotypes with similar ranges (Hall et al. 2011).

Fitness costs clearly have considerable influence on the extent of range expansion among hosts and parasites, but other factors are known to have an equally profound im-

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pact on coevolutionary dynamics. In particular, it is well established that spatial structure affects both epidemiological dynamics and the scale of competition within a population (Thrall and Burdon 2003; Forde et al. 2004, 2007; Morgan et al. 2007) and can allow polymorphism to be maintained even in the absence of fitness costs (Damgaard 1999). In a spatially structured environment the optimal genotype for a particular location will depend on local selection pressures, which may differ between locations and from what would be considered the globally optimal genotype in a well-mixed population (Thompson 1994). Experiments with the bacterium *Pseudomonas fluorescens* and the lytic phage Φ2 suggest that while limited population mixing will slow down the rate of coevolution (Brockhurst et al. 2003), it may also provide more stable conditions for coexistence (Brockhurst et al. 2006). Most empirical studies exploring the effects of spatial structure on range expansion have focused on scenarios where the population is split into interconnected demes, mainly to address questions associated with local adaptation (Burdon and Thrall 1999; Thrall and Burdon 2002, 2003; Forde et al. 2004, 2007; Morgan et al. 2007). Similarly, theoretical studies have generally been limited to metapopulation analyses (Frank 1993; Gandon et al. 1996, 2008; Damgaard 1999), which incorporate a certain degree of spatial structure but do not capture local interactions between individuals within subpopulations, which are known to be critical in many epidemiological scenarios (Rand et al. 1995; Rhodes and Anderson 1996; Keeling et al. 2001; Eames and Keeling 2002). Individual-based models are able to capture local interactions and have been used to study a diverse set of biological phenomena including the evolution of life histories and virulence (Boots and Sasaki 1999; Haraguchi and Sasaki 2000; Read and Keeling 2003; Heilmann et al. 2010), altruism (Jansen and van Baalen 2006), and various other aspects of coevolution (Hartvigsen and Levin 1997; Kerr et al. 2006; Mitchell et al. 2006; Best et al. 2011; Haerter et al. 2011; Zaman et al. 2011; Heilmann et al. 2012). However, the role of local interactions on range expansion has yet to be determined. Here, we attempt to address this gap in the literature by adapting an individual-based model of bacteria and phages first proposed by Heilmann et al. (2010). Although the model was originally used to explore the evolution of virulence in spatially structured populations, it can be readily adapted to serve our focus on range expansion by incorporating the multilocus GFG framework of Sasaki (2000). The model implements spatial structure by situating hosts and parasites on a two-dimensional grid, which is of particular relevance to bacteria (Kerr et al. 2006; Hellweger and Bucci 2009) as colonies often live attached to surfaces in biofilms (Matz et al. 2005; Faruque et al. 2006), providing potential spatial refuges to infection by phages (Levin and Bull 2004; Gallet et al. 2009).

Our primary focus in this study is to explore how the impact of fitness costs associated with range expansion is affected by the degree of population mixing. We show that global competition in well-mixed populations leads to rapid selective sweeps, preventing range expansion at high fitness costs. In spatially structured environments however, we find that local competition and spatial clustering can maintain selection for broader ranges even when fitness costs are high.

Methods: Model Description

Genetic Specificity

The genetic specificity of our model is based on the multilocus GFG framework proposed by Sasaki (2000). Host and parasite genotypes are represented by binary strings of length n ($h_1^i \ \ldots \ h_n^i$ for host genotype i and $p_1^j \ \ldots \ p_n^j$ for parasite genotype j), where each locus corresponds to the presence (1) or absence (0) of a resistance or infectivity allele. For example, a string of 000 represents a highly susceptible host (or a specialist parasite), whereas a string of 111 represents a highly resistant host (or a generalist parasite). We follow Sasaki (2000) by assuming a resistance allele at a particular locus is only effective against parasites that do not have a corresponding infectivity allele at that location and each effective resistance allele reduces the probability of infection by a factor of σ. The parameter σ represents the strength of resistance conferred by each locus: when $\sigma \approx 0$, the acquisition of a single resistance allele will lead to a strong reduction in susceptibility, but when $\sigma \approx 1$, each allele has only a mild effect. We define Q_{ij} to be the infectivity of parasite j on host i, such that

$$Q_{ij} = \sigma^{d_{ij}}, \ d_{ij} = \sum_{k=1}^{n} h_k^i(1 - p_k^j), \tag{1}$$

where d_{ij} is the sum of effective resistance alleles.

Simulation Rules

We adapt the bacterium-phage model proposed by Heilmann et al. (2010) to incorporate the GFG framework outlined above, thus allowing the evolution of varying degrees of generalism. We conduct simulations on a square grid of side length $N = 100$, where boundary effects are removed by wrapping the grid around the surface of a torus, so that all grid sites have exactly four orthogonal neighbors. A maximum of one host is allowed per grid site, so that each location is either empty or contains an infected or uninfected host; there are no restrictions on parasite density. The initial grid consists of uninfected

hosts at every site and 500 parasites at one location; both populations start without any resistance or infectivity alleles (i.e., $\sum_k h_k^i = \sum_k p_k^j = 0$). The grid is updated synchronously at the end of each time step. We implement two versions of our model (spatial and well-mixed) based on the following rules, which mostly follow those of Heilmann et al. (2010):

Host Replication. Spatial version. A host is only able to replicate if it satisfies the following criteria: (i) The host is uninfected, and (ii) at least T time steps have elapsed since the host's previous replication event (tracked by individual replication timers). If these criteria are satisfied, then replication proceeds with probability $Ec_{\mathrm{H}}(i)$, where E is the proportion of empty grid sites adjacent to the host and $c_{\mathrm{H}}(i)$ is a fitness cost associated with resistance, given by

$$c_{\mathrm{H}}(i) = \exp(-\eta_{\mathrm{H}}|i|), \tag{2}$$

with $|i| = \sum_k h_k^i$ equal to the total number of resistance alleles for host genotype i and η_{H} a scaling parameter for the strength of the fitness cost. Note that fitness costs were not included in the original model by Heilmann et al. (2010) due to the absence of host range expansion. Offspring are placed in a randomly chosen empty grid site adjacent to their parent; if multiple offspring attempt to occupy the same grid location, then one is chosen at random to survive and the others are removed from the population. The replication timers for successful parents and offspring are reset following this procedure. Mutations occur with probability ε_{H} at each locus, with the restriction that parents and offspring can only differ by one bit.

Well-mixed version. As per the spatial version, except that (i) the probability of replication is equal to $\overline{E}c_{\mathrm{H}}(i)$, where $\overline{E}$ is the proportion of sites across the entire grid that are empty, and (ii) new offspring are placed at randomly chosen empty grid sites.

Infection. Both versions. We modify the overall probability of infection derived by Heilmann et al. (2010) to allow competition between multiple host and parasite genotypes. Given a probability of infection (α) and decay (δ) per free parasite, the probability that genotype j is able to infect host genotype i is given by

$$\rho_\alpha(i, j) = 1 - \exp\left\{-\alpha P(j) c_{\mathrm{P}}(j) Q_{ij}\left[\frac{1 - \exp(-\delta)}{\delta}\right]\right\}, \tag{3}$$

where Q_{ij} is the strength of interaction between host and parasite and $P(j)$ is the local density of the parasite. Broader infectivity ranges are associated with fitness costs, which reduce the probability of infection, captured here by $c_{\mathrm{P}}(j) = \exp(-\eta_{\mathrm{P}}|j|)$, where η_{P} scales the strength of the fitness cost and $|j| = \sum_k p_k^j$ is the total number of infectivity alleles for the parasite. The probability that at least one parasite is able to infect the host is given by

$$z_1(i) = 1 - \prod_k (1 - \rho_\alpha(i, k)). \tag{4}$$

If a uniform random number, $\mathrm{RAND}_1 \in (0, 1)$, satisfies $\mathrm{RAND}_1 < z_1(i)$, then one parasite strain is chosen at random to infect the host. The probability of parasite j causing the infection is then equal to $\rho_\alpha(i, j)/\sum_k \rho_\alpha(i, k)$. We assume that coinfection does not occur.

Parasite Decay. Both versions. Free parasites decay with probability $1 - \exp(-\delta)$ and are immediately removed from the environment.

Parasite Diffusion. Both versions. We assume that parasites move between adjacent grid sites with probability proportional to the negative concentration gradient between those locations, with diffusion constant D. Parasites are restricted to one grid site movement per time step.

Parasite-Induced Host Mortality. Spatial version. Infected hosts are killed after a fixed number of time steps (latent period), τ, which results in the release of β new parasites into the environment. New parasites are placed at the same grid site as the newly deceased host. If a uniform random number, $\mathrm{RAND}_2 \in (0, 1)$, satisfies $\mathrm{RAND}_2 < n\varepsilon_{\mathrm{P}}$, then one of the new parasites mutates at a random locus, gaining or losing an infectivity allele accordingly.

Well-mixed version. As per the spatial version, except parasites are distributed to randomly chosen grid sites.

Natural Host Mortality. Both versions. All hosts die with probability μ per time step. Parasites are not released into the environment if an infected host dies before the full latent period has expired.

Host Mixing. Well-mixed version only. Hosts are randomly assigned new grid sites at the end of each time step.

Analysis

We draw all parameters from uniform random distributions (table A1; tables A1–A4 available online), except for the strength of the fitness cost for hosts (η_{H}), the probability of natural death (μ) and the number of loci (n). A total of 500 simulations are conducted for each combination (s) of these parameters in both spatially structured and well-mixed environments. We run simulations for a maximum of 10,000 time steps and parameter combinations where hosts or parasites die out in either environment are discarded from further analysis. We allow a burn-

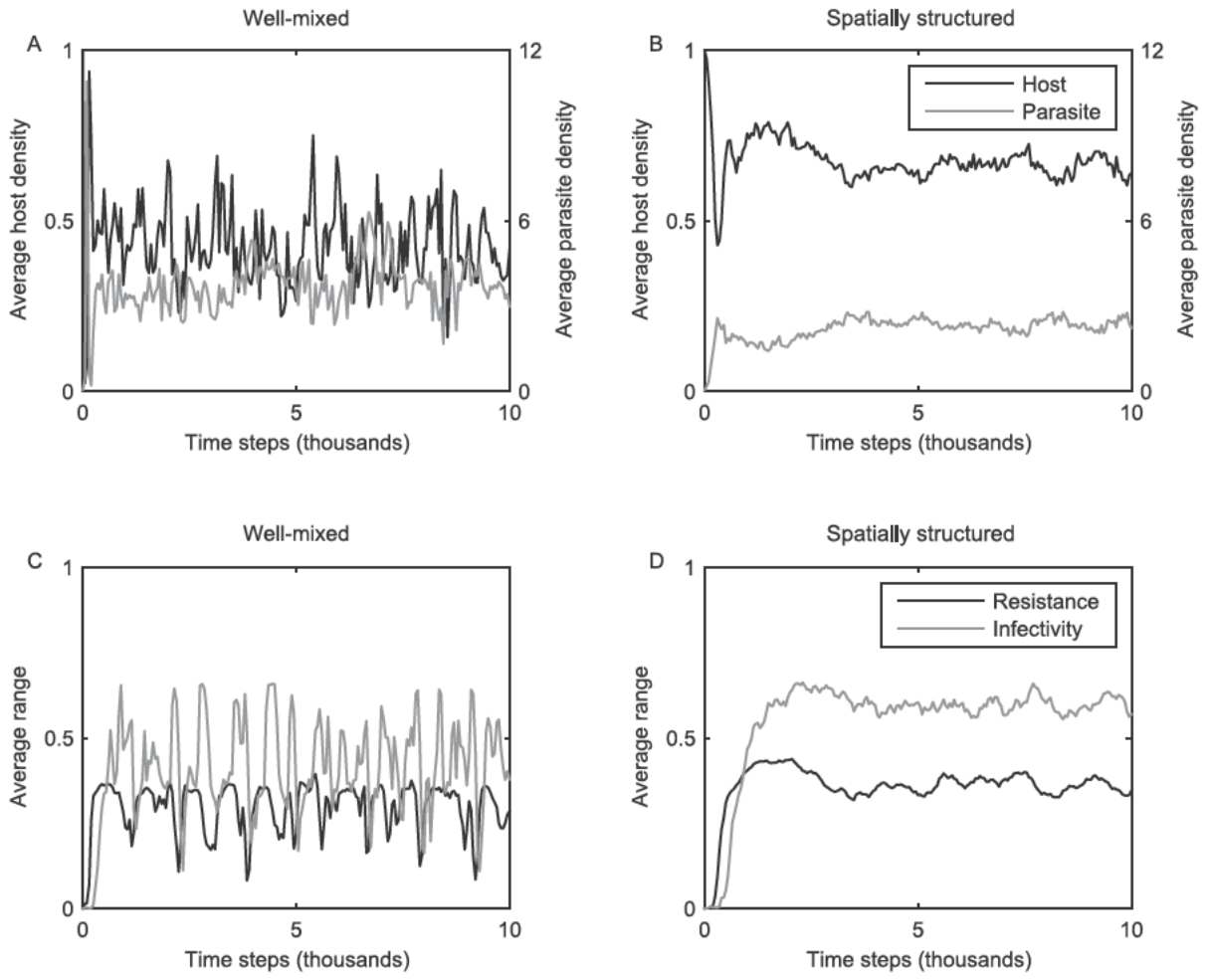

Figure 1: Example coevolutionary dynamics from well-mixed (*left panels*) and spatially structured (*right panels*) populations. *A*, *B*, Average density of host (black) and parasite (gray) populations. *C*, *D*, Average resistance (black) and infectivity (gray) ranges. Well-mixed populations are prone to rapid fluctuating dynamics, whereas spatially structured populations generally produce more stable dynamics. Parameters: $\alpha = 0.15$; $\beta = 50$; $\delta = 0.75$; $\varepsilon_H = 0.001$; $\varepsilon_P = 0.01$; $\eta_H = 1$; $\eta_P = 0.4$; $\mu = 0.001$; $\sigma = 0.25$; $\tau = 3$; $D = 0.5$; $N = 100$; $n = 3$; $T = 3$.

in period for the first half of each simulation before measuring the mean resistance, $R^*(s)$, and infectivity, $I^*(s)$, ranges over the final 5,000 time steps. Each measure varies between 0 and 1, where 0 indicates no range expansion by any members of the population and 1 corresponds to full range expansion by all members of the population. The resistance range of the host population at time step t is given by $R(s, t) = \sum_{i=1}^{n} ix(i, s, t)/n$, where $x(i, s, t)$ is the proportion of the host population that has i resistance alleles. Similarly, the infectivity range of the parasite population at time step t is given by $I(s, t) = \sum_{i=1}^{n} iy(i, s, t)/n$, where $y(i, s, t)$ is the proportion of the parasite population that has i infectivity alleles. We $\log_{10}$ transform the data and use ANCOVA to explore the extent to which spatial structure influences range expansion. In addition, we define the following two pairwise comparisons to visualize differences between the environments:

$$C_R(s) = \frac{R^*_{\text{mixed}}(s) - R^*_{\text{spatial}}(s)}{R^*_{\text{mixed}}(s) + R^*_{\text{spatial}}(s)}, \tag{5}$$

$$C_I(s) = \frac{I^*_{\text{mixed}}(s) - I^*_{\text{spatial}}(s)}{I^*_{\text{mixed}}(s) + I^*_{\text{spatial}}(s)}, \tag{6}$$

where the subscripts "mixed" and "spatial" correspond to the two environments. These measures vary between -1 and 1, indicating whether ranges are on average broader (>0) or narrower (<0) in well-mixed environments. Values close to the extremes correspond to a large disparity in evolutionary outcomes between the environments.

Finally, we measure the "patchiness" of spatially struc-

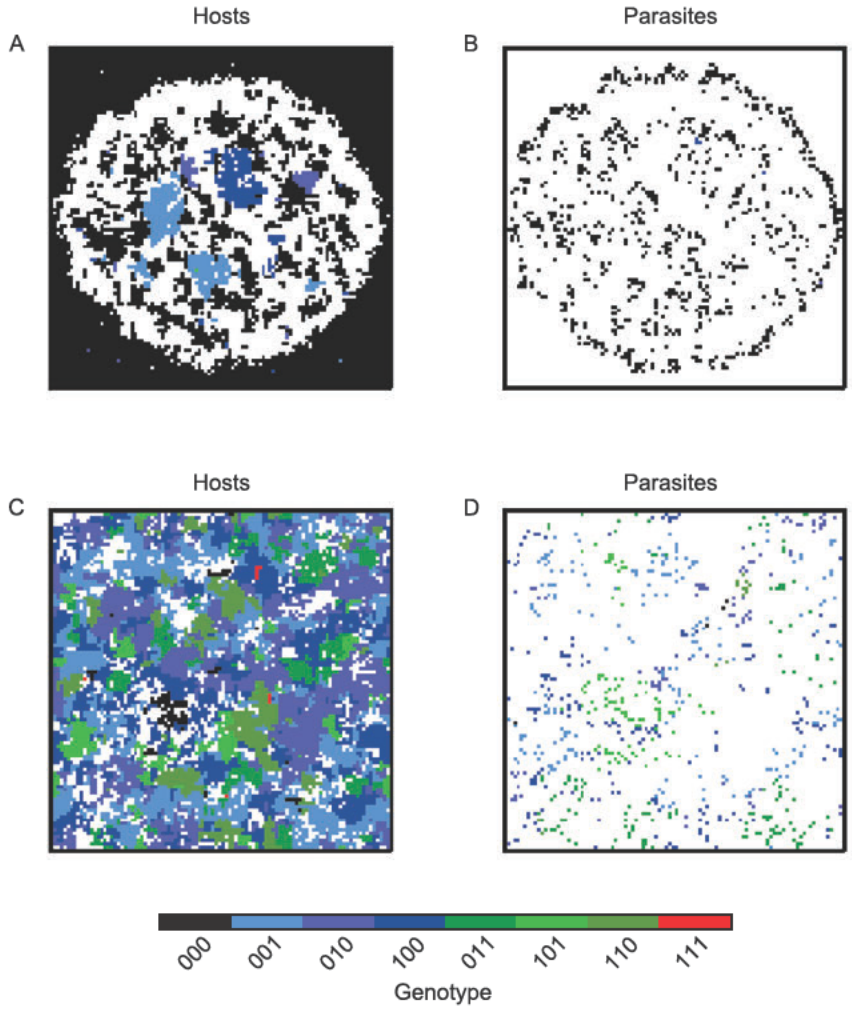

Figure 2: Snapshots of a simulation from the spatially structured population in figure 1 at two time points: *A*, *B*, 250 generations; *C*, *D*, 1,000 generations. Hosts (*left panels*) and intracellular parasites (*right panels*) are colored according to their genotype (i.e., number of resistance/infectivity alleles, where $n = 3$), with black = no alleles (000); blue = 1 allele (001, 01,0 or 100); green = 2 alleles (011, 101, or 110); and red = 3 alleles (111). White regions indicate no hosts/intracellular parasites. The Shannon index for the host population, $H(t)$, is equal to 2.19 (*A*) and 5.19 (*C*) at these two time points.

tured populations to assess how the distribution of host patch sizes varies with time. At a given time step, each patch, q, is defined by a unique set of orthogonally connected hosts sharing the same genotype. We measure the richness and evenness of these patches using the Shannon index, $H(s, t) = -\sum_q a(q, s, t) \ln a(q, s, t)$, where $a(q, s, t)$ is the number of hosts in patch q (Shannon 1948). This index increases as the number of patches grows and/or the distribution of patch sizes becomes more even. We define the "relative patchiness" of the population to be $H'(s, t) = H(s, t)/\overline{H}(s)$, where $\overline{H}(s)$ is the average value of $H(s, t)$ over the final 5,000 time steps of the simulation. Hence, if H' is consistently close to 1, then the patchiness of the population has reached a stable distribution.

Probabilistic Cellular Automata

We also explore a simplified version of our primary model using probabilistic cellular automata (PCA), which does not permit the existence of free-living parasites in the environment (Bak and Chao 1990). The model structure and analysis for the PCA are largely similar to the methods described above for our primary model; the full PCA simulation rules, MATLAB code, analysis, and results are detailed in appendix B (apps. A and B available online).[1]

[1] Code that appears in the *American Naturalist* is provided as a convenience to the readers. It has not necessarily been tested as part of the peer review.

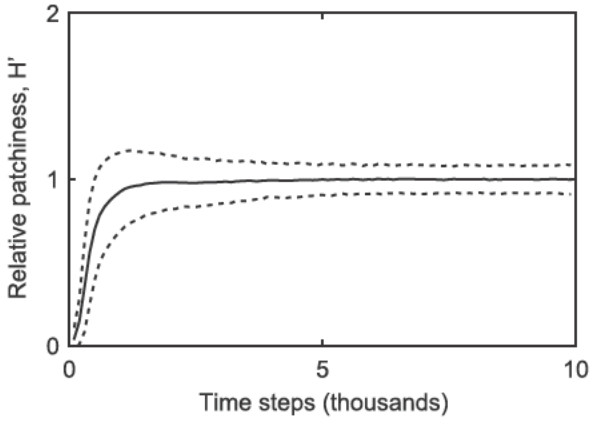

Figure 3: Relative patchiness of spatially structured populations as a function of time (mean ± standard deviation) for $n = 3$. Patchiness is defined by the Shannon index (as described in the main text), which measures the richness and evenness of patch sizes at a given time point; relative patchiness is equal to this value divided by the average over the final 5,000 generations, giving an indication as to how the spatial structure of the population tends to change during the course of a simulation. The first 1,000 generations are characterized by a rapid increase in patchiness, which then plateaus. The standard deviation does not increase over the final 5,000 generations, which implies that patchiness remains roughly constant within each simulation over this period.

Results

For the sake of brevity we present data for only $n = 3$ here, but similar results were obtained for other numbers of loci (see app. A).

Epidemiological Dynamics. We began our investigation by qualitatively comparing epidemiological dynamics in the presence and absence of spatial structure. Overall, 63% of simulations led to host-parasite coexistence for 10,000 generations in both environments. We observed that well-mixed environments were prone to large-amplitude epidemic cycles, whereas spatially structured populations typically demonstrated much steadier dynamics (fig. 1). The patchiness of spatially structured populations (H) typically increased sharply during the first 1,000 time steps of a simulation, before settling down to a stable distribution (figs. 2, 3). The snapshots in figure 2 demonstrate how these populations are typically structured into clusters of identical genotypes.

Resistance. We found that the evolution of broad resistance ranges was highly constrained by the severity of fitness costs (η_H) and to a lesser extent by the probability of natural mortality (μ; fig. 4*A*). When $\mu = 0.001$, R^* was on average 80% lower in the presence of high fitness costs ($\eta_H = 2$) compared to no fitness costs. This difference increased to 88% for $\mu = 0.01$ and to 98% for $\mu = 0.05$, as higher values of μ led to a faster turnover in the host population, reducing the benefits associated with broad resistance ranges.

While both spatially structured and well-mixed populations experienced a decrease in R^* with η_H, the magnitude of the constraint was generally much greater in the absence of spatial structure (figs. 4*B*, 6*A*; ANCOVA,

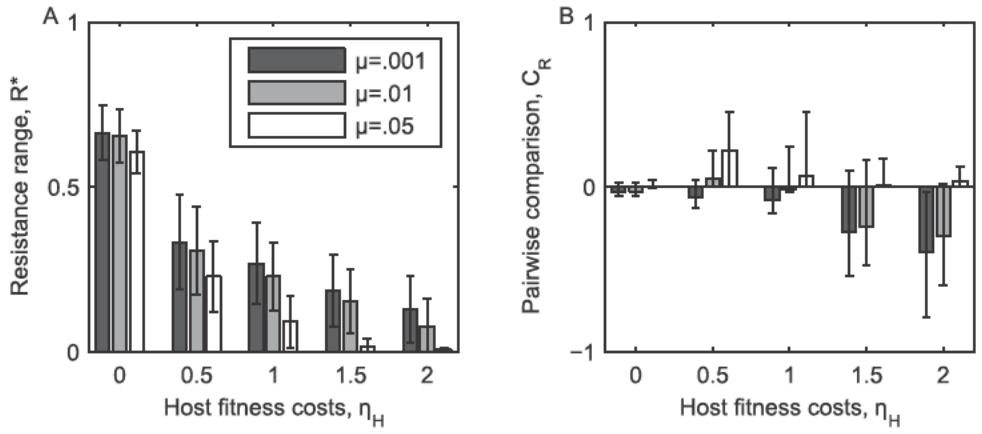

Figure 4: The effects of fitness costs, spatial structure, and the natural mortality rate on the resistance range of the host population for $n = 3$. *A*, The average resistance range (taken over both environments), R^*, tends to decrease with the host fitness cost parameter, η_H, and the natural mortality rate, μ. *B*, A pairwise comparison, C_R, of resistance range expansion in the two environments. If $C_R > 0$, then the mixed environment tends to produce broader resistance ranges than the spatially structured environment and vice versa if $C_R < 0$. Spatially structured populations generally exhibit broader resistance ranges than well-mixed populations as the associated fitness costs increase. However, high natural mortality rates can negate this effect, as resistance becomes less beneficial in both environments.

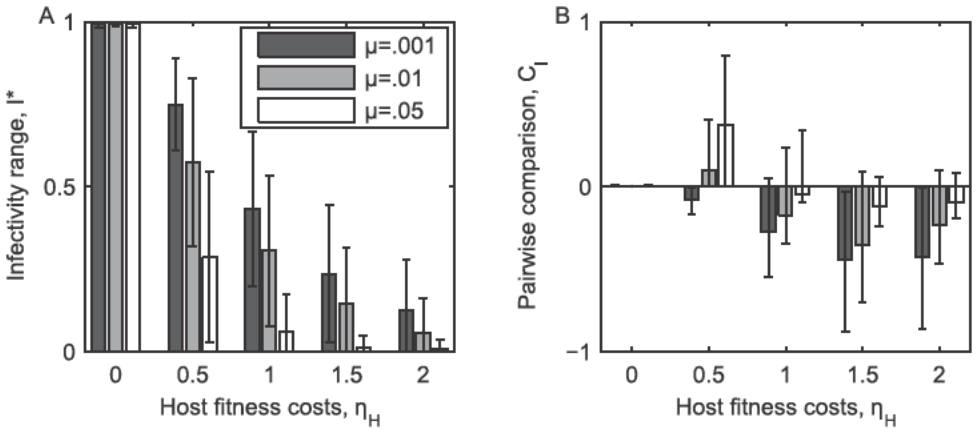

Figure 5: The effects of fitness costs, spatial structure, and the natural mortality rate on the infectivity range of the parasite population for $n = 3$. *A*, The average infectivity range (taken over both environments), I^*, tends to decrease with the host fitness cost parameter, η_H, and the natural mortality rate, μ. *B*, A pairwise comparison, C_I, of infectivity range expansion in the two environments. If $C_I > 0$, then the mixed environment tends to produce broader infectivity ranges than the spatially structured environment and vice versa if $C_I < 0$. Spatially structured populations generally exhibit broader infectivity ranges than well-mixed populations as the fitness costs for hosts increase. However, high natural mortality rates can negate this effect, as selection for infectivity decreases in both environments.

environment × fitness cost interaction for $\mu = 0.001$: $F_{1,\,3,234} = 194$, $P < .0001$; see table A3 for full ANCOVA results). The difference in evolutionary outcomes in the two environments is highlighted by the pairwise comparison (C_R) in figure 4*B*, which shows that spatially structured populations tended to evolve broader resistance ranges than comparable well-mixed populations and that this disparity increased with greater fitness costs, provided the turnover rate of the host population was not too fast. For sufficiently large values of μ, the two environments exhibited broadly similar levels of resistance in the presence of high fitness costs.

We examined the robustness of our results by varying the period during which resistance ranges were recorded. The median difference in resistance ranges between time steps 5,001–7,500 and 7,500–10,000 was 2.8%, indicating that the host population had reached a quasi-steady state prior to the beginning of the measurement window. Minor oscillations were often observed about the mean values of R^* (as shown in fig. 1), with slightly larger fluctuations more likely to occur in well-mixed populations (median difference between R^* and the peak value of R: 4.6% for well-mixed and 2.7% for spatially structured populations).

Infectivity. Parasite evolution was closely linked to changes in the host population, which meant that host fitness costs and natural mortality had similar effects on I^* to those described above for R^* (fig. 5*A*). This is unsurprising given that parasites also experienced a fitness cost associated with generalism (η_P), so that broader infectivity ranges were unlikely to be selected for unless resistance was widespread. Hence, I^* decreased with η_H and μ in both environments, but parasites in spatially structured populations tended to exhibit broader ranges than those in well-mixed populations as η_H increased, provided the host population did not exhibit rapid turnover (figs. 5*B*, 6*B*; ANCOVA, environment × fitness cost interaction for $\mu = 0.001$: $F_{1,\,3,234} = 157$, $P < .0001$; see table A3 for full ANCOVA results).

As observed in the host population, average ranges among parasites were found to be stable over different measurement windows (median difference of 3.9% between time steps 5,001–7,500 and 7,501–10,000) and minor oscillations about the mean values of I^* were common (median difference between I^* and the peak value of I within each simulation: 5% for well-mixed and 4.7% for spatially structured populations).

Probabilistic Cellular Automata. To test the generality of our results, we created a simplified version of our model based on probabilistic cellular automata (see app. B for full description and results). We found that both the epidemiological dynamics and coevolutionary outcomes were qualitatively similar to those observed in the primary model, especially when moving between environments. Most importantly, our key finding was replicated using this alternative approach: spatially structured populations tended to produce broader resistance and infectivity ranges than well-mixed populations as fitness costs increased.

Discussion

Using an individual-based model of host-parasite coevolution, we explored the effects of spatial structure on the

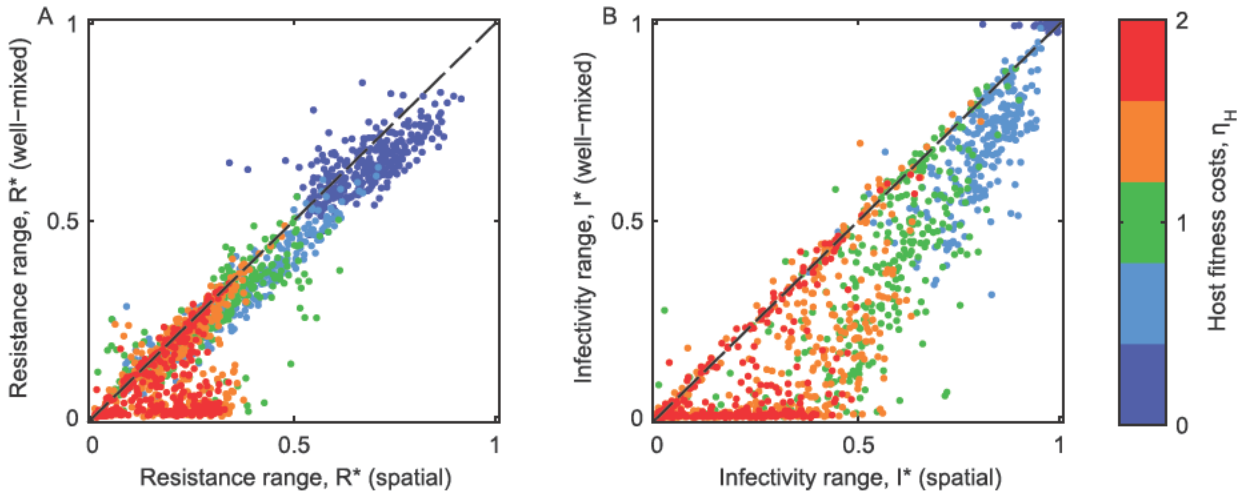

Figure 6: Scatter plots showing the resistance (*A*) and infectivity (*B*) ranges in the two environments for each simulation. Colors correspond to the host fitness cost parameter, η_H. Spatially structured populations consistently exhibit broader ranges than well-mixed populations, particularly when fitness costs are high. Parameters: $\mu = 0.001$; $n = 3$.

expansion of resistance and infectivity ranges. Consistent with previous theoretical (Hochberg and van Baalen 1998; Sasaki 2000; Agrawal and Lively 2002) and empirical studies (Bohannan et al. 2000; Forde et al. 2004, 2008; Buckling et al. 2006; Lopez-Pascua et al. 2008, 2012), we found resistance and infectivity range evolution to be constrained by fitness costs. Our novel result is that the magnitude of the constraint imposed by host fitness costs on range expansion is highly dependent on the degree of mixing in the population. More specifically, we found that high host fitness costs severely restricted range expansion in well-mixed environments, but the effect was much weaker in the presence of spatial structure. While host fitness costs did not have a direct impact on parasite fitness, we assumed that range expansion was still costly for parasites and so would only be selected for in the presence of resistant hosts (see Sasaki 2000). Thus, parasite infectivity behaved in a qualitatively similar way to resistance in response to greater host fitness costs.

To test the generality of our results we constructed a second model, replacing the free-living parasite population with one transmitted via direct contact between hosts (probabilistic cellular automata; app. B). We found the results to be broadly consistent, despite the stark contrast in transmission dynamics between the two models, which suggests that our findings are likely to have general applicability to a variety of host-parasite systems. Our study is closely linked to the work of Best et al. (2011), who reported an important effect of spatial structure on the coevolution of quantitative resistance and infectivity (as opposed to the resistance and infectivity ranges explored here): high resistance and low virulence were favored when dispersal was limited, but this trend was reversed in well-mixed environments.

The contrasting dynamics observed in the two environments can be explained by two processes. First, individuals in poorly mixed populations only compete with a subset of the population at very small spatial scales, whereas individuals in well-mixed environments are in competition with the entire population. In structured environments, the fitness of a particular genotype will vary depending on the neighboring population, which means that different genotypes may be optimal at different locations and spatial scales (Thompson 1994; Gandon et al. 1996). Second, clustering and limited dispersal can limit the extent to which a genotype can spread in spatially structured populations, even if it is optimal for a given location (Campos et al. 2008).

As a specific example of the impact of these two related processes, first consider a well-mixed population initially composed of sensitive hosts and specialist (narrow range) parasites in a single locus GFG framework. If a resistant host emerges, it is likely to have a huge advantage over the sensitive population and will therefore rapidly increase in prevalence. Specialist parasites will then be at a disadvantage, so generalists that can infect both host types will eventually dominate. Assuming resistance is associated with slower growth, but provides no protection against the generalist parasite, the sensitive population will then gradually increase relative to the resistant population. Similarly, generalist parasites have a lower fitness than specialist parasites when the host population is not resistant. Hence, the specialist parasite increases in prevalence and the cycle repeats, giving fluctuations in range. In a spatially struc-

tured environment, the emergence of resistant hosts and generalist parasites will initially follow a similar pattern. Although sensitive hosts will then have the globally optimal genotype, they may not be able to realize their growth advantage as clustering may limit the extent to which they can spread before being wiped out by parasites. In addition, if small numbers of specialist parasites are maintained by these sensitive patches then resistance could still be the locally optimal trait. Thus, local competition and clustering provide ephemeral refuges for globally suboptimal genotypes, which make spatially structured populations less likely to exhibit fluctuations in range. Similar dynamics emerge in our multilocus framework, as shown in figure 1. Resistance initially spreads in both environments, but they respond differently to the emergence of generalist parasites, with broader ranges persisting in the presence of spatial structure.

We found that the difference in coevolutionary outcomes between the two environments was dependent on the probability of natural death for the host, given by the parameter μ. Higher values of μ correspond to faster turnover rates in the host population, which increases the severity of fitness costs to the point where resistance is no longer beneficial in either environment. In addition, a faster population turnover rate will reduce the effects of clustering, allowing sensitive hosts with faster growth rates to reestablish themselves in the presence of generalist parasites.

The genetic specificity in our model was based on a well-established multilocus GFG framework that can produce arms race coevolutionary dynamics as well as fluctuations in range (Sasaki 2000; Fenton et al. 2009). While there is considerable evidence for coevolutionary arms races taking place among bacteria and phages (Bohannan and Lenski 2000; Buckling and Rainey 2002*a*; Mizoguchi et al. 2003; Brockhurst et al. 2006; Forde et al. 2008; Scanlan et al. 2011) and various other host-parasite systems (Little et al. 2006; Schulte et al. 2010), there is limited evidence of fluctuations in range except for some plant-fungus interactions (e.g., Thrall and Burdon 2003). Recent work with *Pseudomonas fluorescens* and lytic phages has shown that fluctuating selection between genotypes with similar ranges is possible, either following (Hall et al. 2011) or in the absence of a coevolutionary arms race (Gomez and Buckling 2011). In addition, the frequent occurrence of local adaptation indicates that there may be multiple routes to generalism (Buckling and Rainey 2002*b*; Morgan et al. 2005; Vos et al. 2009; Koskella et al. 2011). These data indicate that the GFG framework may only be capturing part of the genetic interactions between bacteria and phages, which has led others to propose more complex specificities (Agrawal and Lively 2002, 2003; Weitz et al. 2005; Forde et al. 2008; Fenton et al. 2012).

Furthermore, some systems appear to be based on other forms of specificity that do not permit generalism. For example, Carius et al. (2001) observed that the bacterium *Pasteuria ramosa* specializes on different lineages of the freshwater crustacean *Daphnia magna*, which can lead to fluctuating selection between different genotypes rather than an escalatory arms race (Decaestecker et al. 2007). Similarly, coevolutionary dynamics between the freshwater snail *Potamopyrgus antipodarum* and trematode parasites of the genus *Microphallus* appear to be governed by fluctuating selection between specialists, a process which has been linked to the maintenance of sexual reproduction among the host population (Lively 1987; King et al. 2009). While generalists have not yet been observed in these systems, it is possible that the fitness costs associated with broad ranges are simply too high.

Our work complements the growing body of research on the effects of spatial structure on coevolutionary dynamics (Hartvigsen and Levin 1997; Boots and Sasaki 1999; Haraguchi and Sasaki 2000; Read and Keeling 2003; Jansen and van Baalen 2006; Kerr et al. 2006; Mitchell et al. 2006; Heilmann et al. 2010, 2012; Best et al. 2011; Haerter et al. 2011; Zaman et al. 2011). There are also strong links between this study and a variety of ecological models on victim-exploiter relationships. Of particular relevance is the work on host and parasitoids, in which variation in dispersal rate can lead to a range of complex dynamics, with high rates of dispersal increasing extinction risk and leading to fluctuations in population sizes, as observed here (Hassell et al. 1991; Comins et al. 1992; Pascual 1993). Together, these studies highlight the important role that spatial structure plays in shaping both ecological and evolutionary dynamics.

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