Interactions between Genetic Drift, Gene Flow, and Selection Mosaics Drive Parasite Local Adaptation

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ABSTRACT: Interactions between gene flow, spatially variable selection, and genetic drift have long been a central focus of evolutionary research. In contrast, only recently has the potential importance of interactions between these factors for coevolutionary dynamics and the emergence of parasite local adaptation been realized. Here we study host-parasite coevolution in a metapopulation model when both the biotic and the abiotic components of the environment vary in space. We provide a general expression for parasite local adaptation that allows local adaptation to be partitioned into the contributions of spatial covariances between host and parasite genotype frequencies within and between habitats. This partitioning clarifies how relative rates of gene flow, spatially variable patterns of selection, and genetic drift interact to shape parasite local adaptation. Specifically, by using this expression in conjunction with coevolutionary models, we show that genetic drift can dramatically increase the level of parasite local adaptation under some models of specificity. We also show that the effect of migration on parasite local adaptation depends on the geographic mosaic of selection. We discuss how these predictions could be tested empirically or experimentally using microbial systems.

Keywords: host-parasite coevolution, local adaptation, metapopulation, migration, spatial heterogeneity, genetic drift.

Introduction

Antagonistic interactions between parasites and their hosts are expected to yield coevolutionary cycles of adaptation and counteradaptation. Coevolution may thus generate temporal variation in selection for both species (Flor 1956; Mode 1961; Jaenike 1978; Hamilton 1982, 1993; Lenski and Levin 1985; Burdon 1987). In a spatially structured environment, coevolution may also generate spatial variation in selection pressures (Frank 1991; Thompson 1994, 1999; Judson 1995; Burdon and Thrall 1999; Gomulkiewicz et al. 2000; Nuismer et al. 2000). The dynamics of adaptation in such spatially and temporally variable en-

vironments has been extensively studied experimentally with reciprocal transplant experiments (Parker 1985; Lively 1989; Ebert 1994; Kaltz and Shykoff 1998; Forde et al. 2004; Morgan et al. 2005). Although most transplant experiments have shown that parasites perform better on sympatric than on allopatric hosts (Parker 1985; Lively 1989; Ebert 1994; Manning et al. 1995; Morand et al. 1996; Lively and Dybdhal 2000), other experiments either did not find any evidence of parasite local adaptation (LA; Dufva 1996; Morand et al. 1996; Mutikainen et al. 2000) or found local maladaptation of the parasite (Imhoof and Schmid-Hempel 1998; Kaltz et al. 1999; Oppliger et al. 1999). These results suggest that the parasite might not always be ahead in the coevolutionary arms race.

Theoretical studies of coevolutionary interactions between hosts and parasites have identified multiple evolutionary forces that promote the emergence of LA. In general, all of these operate by promoting or at least maintaining asynchrony in coevolutionary dynamics across populations (Gandon et al. 1998). This asynchrony is a prerequisite for differentiation among populations and thus for LA. In the absence of gene flow between populations, asynchronous coevolutionary dynamics can be maintained in perpetuity, even if the abiotic environment is homogenous, because spatial variation in selection is produced by coevolution alone (Gandon et al. 1998; Gandon 2002). In contrast, if some gene flow takes place among populations, then coevolutionary synchrony generally occurs, eroding LA (Gandon 2002). In some cases, however, asynchrony can be maintained even in a purely deterministic model (Sasaki et al. 2002; Gavrilets and Michalakis 2008). This require specific conditions (low migration, a large number of populations, strong selection) and is thus likely to be a less important source of asynchrony in natural populations than three other factors. First, if population sizes are sufficiently small, stochasticity (genetic drift) can maintain genetic variation among populations despite the homogenizing force of migration (Burdon 1992; Thompson and Burdon 1992; Gandon

2002). Second, asynchrony can be maintained if isolation by distance is incorporated in the migration process. Localized dispersal allows the maintenance of spatial variation in genotype frequencies through the emergence of fixed or moving spatial patterns (Gandon 2002; Sasaki et al. 2002; Switkes and Moody 2004). Third, spatial variation may also be maintained by host genotype by parasite genotype by environment (G × G × E) interactions for fitness. Such "selection mosaics" arise anytime fitness consequences of species interactions vary across space for reasons independent of the interacting species genotypes (Thompson 1994, 1999; Nuismer et al. 2000; Nuismer 2006; Gavrilets and Michalakis 2008). Specific examples will be examined in the "Discussion."

Assuming that spatial genetic structure is maintained, the extent of parasite LA has been shown to depend on several factors. Initial theoretical studies of LA identified two critical determinants: (1) the relative intensity of selection acting on each species and (2) the relative rates of gene flow (Gandon et al. 1996, 1998). When host and parasite migration rates are similar, the species under more intense selection is expected to be locally adapted (Gandon 2002). When migration rates are low and selection intensities are similar, the species with the higher migration rate is expected to be locally adapted (Gandon et al. 1996; Gandon 2002). Thus, in contrast with classical population genetics models, where the environment does not vary through time (Slatkin 1987; Lenormand 2002), migration allows adaptation to local conditions because it increases the genetic variance on which selection can act (see also Lande and Shannon 1996). Recent meta-analyses of studies on LA in parasites support these predictions (Greischar and Koskella 2007; Hoeksema and Forde 2008). In contrast to these earlier theoretical predictions, Nuismer (2006) found very little evidence for an influence of relative rates of migration of host and parasites in a model incorporating extrinsic spatial variation in the selection intensity acting on host and parasite. Instead, the results of this model suggested that patterns of parasite LA were primarily explained by the underlying model of specificity (i.e., gene-for-gene vs. matching allele) and the type of selection mosaic. The aim of this article is to reconcile these contrasting views using a model that incorporates both genetic drift and selection mosaics as means to maintain spatial variation in selection.

We first derive a simple and general expression demonstrating that parasite LA can be expressed as a function of the spatial covariance of host and parasite genotype frequencies among populations. This expression is particularly useful because it allows LA to be naturally partitioned into contributions made by adaptive genetic variation within and between habitats. Second, we derive approximations for LA under weak selection and high mi-

gration rate in the absence of genetic drift in order to analyze the effects of selection mosaics as well as biased migration rates. Third, we use numerical simulations to study the robustness of these predictions and to study the effect of finite population sizes and genetic drift. We also explore the effects of multiple loci and diploidy with simulations. The combination of analytical approximations and numerical simulations clarifies the interplay among multiple factors (e.g., specificity of the interaction, host and parasite migration rates, selection mosaics, genetic drift) influencing parasite LA and yields new and experimentally testable predictions.

Results

We assume a number n of host and parasite populations with local sizes N_H and N_P, respectively. When population sizes are assumed to be extremely large, we neglect the effect of genetic drift on coevolutionary dynamics. Coevolution occurs locally (within sympatric populations), and movement occurs globally (no isolation by distance) and independently among host and parasite populations, at rates m_H and m_P, respectively. The specificity of the interaction is determined in a general way by $\pi_{h,p}$, the probability of infection of host genotype h by parasite genotype p. Specific models of host-parasite interactions are detailed below. Successful infection is assumed to reduce host fitness by an amount $s_{H,E}$, whereas unsuccessful infection is assumed to reduce parasite fitness by an amount $s_{P,E}$, where the subscript E denotes the potential effect of the abiotic environment on the intensity of selection imposed by biotic interactions. Note that these coefficients depend on the environment but not on host and parasite genotypes; in contrast, the probability of infection depends on host and parasite genotypes but not on the environment. Therefore, the overall fitness consequences of a particular interaction depend on host and parasite genotypes as well as on the environment. For the sake of generality, we also allow our model to take into account constitutive costs associated with some host and parasite genotypes, denoted c_h and c_p, respectively, as in the classical gene-for-gene model (Flor 1956). These costs are assumed to act multiplicatively and to be independent of the environment. The fitness of host genotype h in an interaction with parasite p in the environment E is thus $W^H_{E,h,p} = (1 - c_h)(1 - s_{H,E}\pi_{h,p})$. Similarly, $W^P_{E,h,p} = (1 - c_p)[1 - s_{P,E}(1 - \pi_{h,p})]$ refers to the fitness of parasite p in an interaction with host h in habitat E. Although we restrict our analysis to antagonistic interactions where the coefficients $s_{H,E}$ and $s_{P,E}$ are positive, the same approach can be readily extended to mutualistic interactions where these coefficients take negative values.

This model allows us to take into account host genotype

by parasite genotype by environment interactions (G × G × E) and thus many forms of selection mosaic (Thompson 2005; Gomulkiewicz et al. 2007). Let us assume that there is a finite number (max) of these habitats (i.e., $E \in [1, \text{max}]$) differing only in the intensity of the selection occurring in the host and/or in the parasite. Each habitat may consist of a variable number of populations, and n_E refers to the number of populations in habitat E ($\sum_{E=1}^{\text{max}} n_E = n$).

Local Adaptation as a Spatial Covariance of Genotype Frequencies

Local adaptation (LA) is generally measured in two different ways (Kawecki and Ebert 2004). The mean local fitness of a population may be compared to the mean fitness of the same population in a foreign environment ("home vs. away" criteria, denoted Δ) or to the mean fitness of allopatric organisms (immigrants) when placed in the same local environments ("local vs. immigrant" criteria, denoted ∇). As pointed out by Kawecki and Ebert (2004), these two criteria may lead to different estimated values of LA for a single population. When averaged among populations, however, these two measures are equal ($\overline{\Delta} = \overline{\nabla}$), although they may have different variances (Morgan et al. 2005). For this reason, this article focuses on the average value of LA as a property of the whole metapopulation. Furthermore, the mean fitness of populations is assumed to be measured in a common abiotic environment. This definition is appropriate for common-garden experiments, where cross-infection experiments are realized in a controlled and constant test environment T. The use of reciprocal transplant experiments (where fitness is evaluated in different environments) is explored in another article (Nuismer and Gandon 2008).

We focus here on parasite LA (but similar arguments can be used for the host), which depends on (1) the frequency x_h of the different host genotypes ($h \in [1, h_{\text{max}}]$) in all populations, (2) the frequency y_p of the different parasite genotypes ($p \in [1, p_{\text{max}}]$) in all populations, and (3) the fitness $W^P_{T,h,p}$ of parasite genotype p in an interaction with host genotype h when measured in the test environment T. It can be shown that parasite LA can be written in the following way (app. A in the online edition of the *American Naturalist*):

$$\overline{\Delta} = \sum_{h=1}^{h_{\text{max}}} \sum_{p=1}^{p_{\text{max}}} W^P_{T,h,p} \, \text{Cov}\,(x_h, y_p), \tag{1}$$

where $\text{Cov}\,(x_h, y_p)$ is the spatial covariance of host and parasite genotype frequencies (see also Switkes and Moody 2004). Note that this formulation of LA is very general.

It does not depend on the underlying model of specificity of the interaction, on the number of loci, or on the ploidy level. All the details of the genetic determinism of the interaction are acting through the $W^P_{T,h,p}$ coefficients. This formulation demonstrates that LA can be viewed in a very general way as a correlation between the heterogeneity of the environment (here the host genotype frequencies) and the distribution of parasite genotype frequencies.

Equation (1) further allows LA to be partitioned into the contributions of covariance within and between different types of habitats (app. A):

$$\overline{\Delta} = \text{E}(\overline{\Delta}_{\text{w}}) + \overline{\Delta}_{\text{b}}, \tag{2a}$$

where

$$\overline{\Delta}_{\text{w}} = \sum_{h=1}^{h_{\text{max}}} \sum_{p=1}^{p_{\text{max}}} W^P_{T,h,p} \, \text{Cov}_E\,(x_h, y_p), \tag{2b}$$

$$\overline{\Delta}_{\text{b}} = \sum_{h=1}^{h_{\text{max}}} \sum_{p=1}^{p_{\text{max}}} W^P_{T,h,p} \, \text{Cov}\,(\bar{x}_h, \bar{y}_p); \tag{2c}$$

$\overline{\Delta}_{\text{w}}$ is the level of parasite LA within habitat E, which is a function of $\text{Cov}_E\,(x_h, y_p)$, the spatial covariance of host and parasite genotype frequencies in habitat E. The first term in equation (2a), $\text{E}(\overline{\Delta}_{\text{w}})$, is thus the expected level of parasite LA within each habitat. The second term in equation (2a) refers to the level of parasite LA between different habitats. Thus, the two terms in equation (2a) have clear biological meanings and may be easily obtained using an experimental design in which host and parasite individuals used in the common-garden experiment come from the same or different habitats (fig. 1).

In addition, partitioning LA within and between habitats may help reconcile contrasting results obtained with different types of models. For instance, Nuismer (2006) analyzed the emergence of LA in a heterogeneous population with only two habitats and two populations. In this case, $\text{E}(\overline{\Delta}_{\text{w}}) = 0$ because when there is a single population per habitat, there is no spatial covariance between host and parasite genotype frequencies in each habitat (see eq. [2b]) and LA is governed only by the between-habitats component of the covariance, $\overline{\Delta}_{\text{b}}$. In contrast, in Gandon et al. (1996) and subsequent studies, a large number of populations is considered, but all the populations belong to the same habitat (i.e., max = 1). In this case, $\overline{\Delta}_{\text{b}} = 0$ and LA is governed only by the within-habitat component of the covariance, $\text{E}(\overline{\Delta}_{\text{w}})$. The aim of this article is to show that these contrasting conclusions result from the fact that these different models focus on different components of LA. The two types of models fall at the two extremes of a continuum of situations that is explored below. In what follows, we study the dynamics of LA in
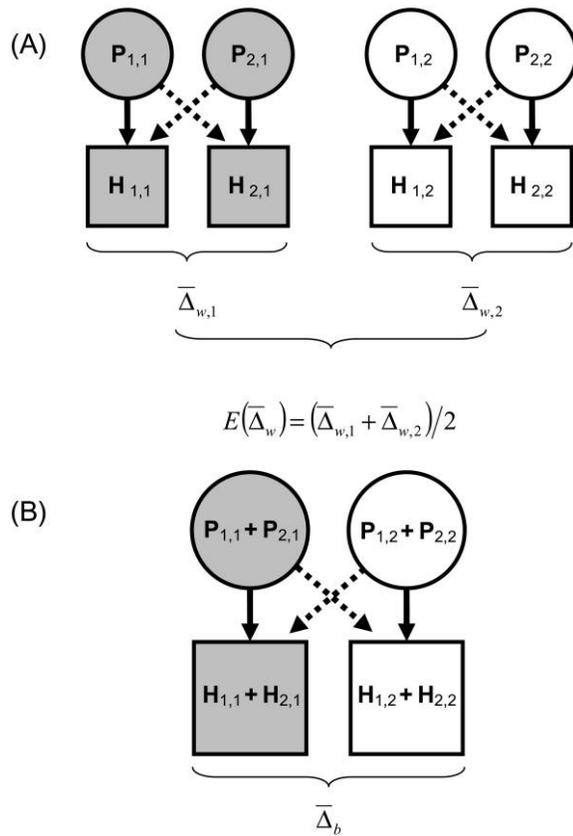
$$E(\overline{\Delta}_w) = (\overline{\Delta}_{w,1} + \overline{\Delta}_{w,2})/2$$

Figure 1: Schematic representation of different ways to measure local adaptation in the presence of abiotic heterogeneity. As in the numerical simulations, we consider two different types of habitats. In each habitat, we focus on two sites, and in each site a parasite population interacts with a host population. Thus, there are four parasite populations ($P_{1,1}$ and $P_{2,1}$ in habitat 1, $P_{1,2}$ and $P_{2,2}$ in habitat 2) and four host populations ($H_{1,1}$ and $H_{2,1}$ in habitat 1, $H_{1,2}$ and $H_{2,2}$ in habitat 2). Parasite local adaptation is defined here as the difference between parasite performance "at home" and "global" parasite performance (see "Local Adaptation as a Spatial Covariance of Genotype Frequencies"). The overall parasite local adaptation, $\overline{\Delta}$, is the average local adaptation (over the four different parasite populations) when the "global" performance is based on all the possible pairwise comparisons, irrespective of the habitat of origin. This overall measure of local adaptation can be partitioned into within- and between-habitat components of local adaptation (eq. [2]). *A*, Within-habitat local adaptation, $\overline{\Delta}_w$, measures the difference between "at home" performance (*solid arrows*) and "global" performance (*dashed arrows*), when only populations from the same habitat are considered, and $E(\overline{\Delta}_w)$ takes the average over the different habitats. *B*, Between-habitat local adaptation, $\overline{\Delta}_b$, measures the difference between the performance "at home" (on host from the same habitat; *solid arrows*) and "global" performance (*dashed arrows*).

intermediate situations with several habitats (i.e., max > 1) and several populations in each habitat (i.e., $n_E > 1$ for $E \in [1, \text{max}]$).

Local Adaptation in Simple Models of Coevolution

Equation (1) provides an explicit prediction for LA as a function of the spatial distributions of host and parasite genotype frequencies. In order to further evaluate how selection mosaics, gene flow, and genetic drift interact to shape patterns of LA, we must specify an underlying model of host-parasite interaction that determines the spatial and temporal dynamics of host and parasite genotype frequencies. We begin by exploring the dynamics of LA in a simple model (fig. 2*A*), where the host and the parasite are assumed to be haploid and asexual and the determinism of specificity is governed by a single diallelic locus in both the host (alleles A and a) and the parasite (alleles B

Figure 2: Genetic determinism of specificity with a single diallelic locus when both the host and the parasite are haploid (*A*) and when they are both diploid (*B*). The outcomes (I = infect, R = resist) of encounters between parasite and host genotypes for various genetic models of infection/resistance are indicated in braces. In both the haploid and the diploid cases, we study three classical models of coevolution: the matching-allele model (MAM), the inverse matching-allele model (IMAM), and the gene-for-gene model (GFGM). Note that the MAM and the IMAM are equivalent in haploids but not in diploids. The fitness of a particular genotype depends on (1) whether there is infection, (2) the coefficients of selection ($s_{H,E}$ and $s_{P,E}$ for the host and the parasite, respectively), and (3) in the GFGMs, the costs of resistance, c_a, and virulence, c_b, in the host and the parasite, respectively (see text for more details on genotype fitness).

and b). The frequencies of alleles A and B are denoted x and y, respectively. The effects of multiple loci and diploidy are explored only in this section.

Although there is overwhelming evidence supporting the existence of specificity in many host-parasite systems (Flor 1956; Burdon 1987; Carius et al. 2001; Poullain et al. 2008), it is statistically difficult to infer the genetics underlying these interactions (Frank 1996). Here we consider three commonly used models of specificity (fig. 2*A*): the matching-allele model (MAM), the inverse matching-allele model (IMAM), and the gene-for-gene model (GFGM). In the MAM, the A hosts resist infection by b parasites but are completely susceptible to B parasites, and the a hosts resist infection by B parasites but are susceptible to b parasites (fig. 2*A*). In the IMAM, the outcome of the interactions (i.e., infection or resistance) is simply reversed (fig. 2*A*). Consequently, in this case (haploid organisms with a single specificity locus), MAM and IMAM are equivalent, and thus we present only the results obtained with the MAM and the GFGM. The GFGM, in contrast with the other models, is intrinsically asymmetric (fig. 2*A*): the "virulent" allele (allele b) allows the parasite to infect both the "susceptible" and the "resistant" hosts (alleles A and a, respectively). As a consequence, additional costs of virulence (c_b in the parasite) and resistance (c_a in the host) are generally necessary to maintain some polymorphism at these loci in the GFGM. These two models have been shown to exhibit qualitatively different coevolutionary dynamics and thus lead to different patterns of LA (Lively 1999; Morgan et al. 2005; Nuismer 2006). We begin our analysis of these simple genetic models by studying LA in scenarios where host and parasite population sizes are very large. In these cases, the models can be analyzed deterministically, allowing analytical solutions. Next, we study how including stochastic effects of genetic drift in finite populations may affect the emergence and magnitude of LA, using numerical simulations.

Deterministic Models of Very Large Populations

In the absence of drift and/or isolation by distance, host and parasite migration generally yield synchronous coevolutionary dynamics among the populations within a habitat (Gandon 2002). Sasaki et al. (2002) and Gavrilets and Michalakis (2008) showed (for the GFGM and the MAM, respectively), however, that this deterministic model can sometimes yield asynchronous coevolutionary fluctuations. This requires somewhat specific conditions (strong selection, low migration, and a large number of populations) and appears to generally cause only low levels of LA (Gavrilets and Michalakis 2008). Our analytical model capitalizes on this observation by assuming that even if there are several populations in each habitat, mi-

gration within habitats synchronizes populations and results in the disappearance of LA within each habitat, such that $E(\overline{\Delta}_w) = 0$ (this assumption is confirmed by numerical simulations we report below). As a consequence, significant levels of LA in the absence of genetic drift are expected to emerge only if there are different habitats. In appendix B in the online edition of the *American Naturalist*, we focus on the simple case with two habitats and, as in Nuismer (2006), derive approximations for host and parasite LA when selection is weak and when the difference in genotype frequencies between populations is also small, which may occur when migration is sufficiently high. These assumptions are directly analogous to the weak-selection and high-recombination-rate assumptions used to obtain quasi–linkage equilibrium approximations in population genetics (Crow and Kimura 1970). Under these assumptions, one can derive approximations for parasite LA, or "quasi-synchronous dynamics" (QSD), for the GFGM and the MAM, respectively (app. B):

$$\overline{\Delta}_{\text{QSD}}^{\text{GFG}} \propto \text{Cov}_{\text{S}}, \tag{3a}$$

$$\overline{\Delta}_{\text{QSD}}^{\text{MAM}} \propto \text{Cov}_{\text{S}} \overline{X}\,\overline{Y}, \tag{3b}$$

with $\overline{X} = \bar{x} - 1/2$ and $\overline{Y} = \bar{y} - 1/2$, where Cov_{S} is the spatial covariance of selection acting on the host and the parasite. This covariance emerges whenever the intensity of selection on the host is variable among populations and is correlated with the intensity of selection on the parasite. It thus allows different types of selection mosaic to be distinguished. Approximation (3a) indicates that the sign of parasite LA in GFGMs is governed by the sign of Cov_{S} and should not be affected by the relative migration rates of hosts and parasites. Approximation (3b), in contrast, depends on the product of Cov_{S} and $\overline{X}\,\overline{Y}$. Given that mean host and parasite allele frequencies ($\bar{x}$ and $\bar{y}$) oscillate around 1/2 with a lag close to $\pi/2$ (Nee 1989; Gandon 2002), the product $\overline{X}\,\overline{Y}$ will oscillate from positive to negative values over time, and consequently, the sign of $\overline{\Delta}_{\text{QSD}}^{\text{MAM}}$ is also expected to oscillate over time. We were unable to make general predictions on the expected value of $\overline{\Delta}_{\text{QSD}}^{\text{MAM}}$ over several generations, except in one extreme case of positive spatial covariance of selection. In that case, the environment consists of hotspots of coevolution, where reciprocal selection is intense, and coldspots, where there is no selection. Negative frequency-dependent selection generates large fluctuations in allele frequencies in the hotspots. In the coldspots, however, allele frequencies oscillate only because of the migration from the hotspots. Thus, the dynamics of the mean allele frequency is mainly governed by the dynamics in the hotspot. Following this argument, we show in appendix B that the average over one period of oscillation of the product $\overline{X}\,\overline{Y}$ (denoted
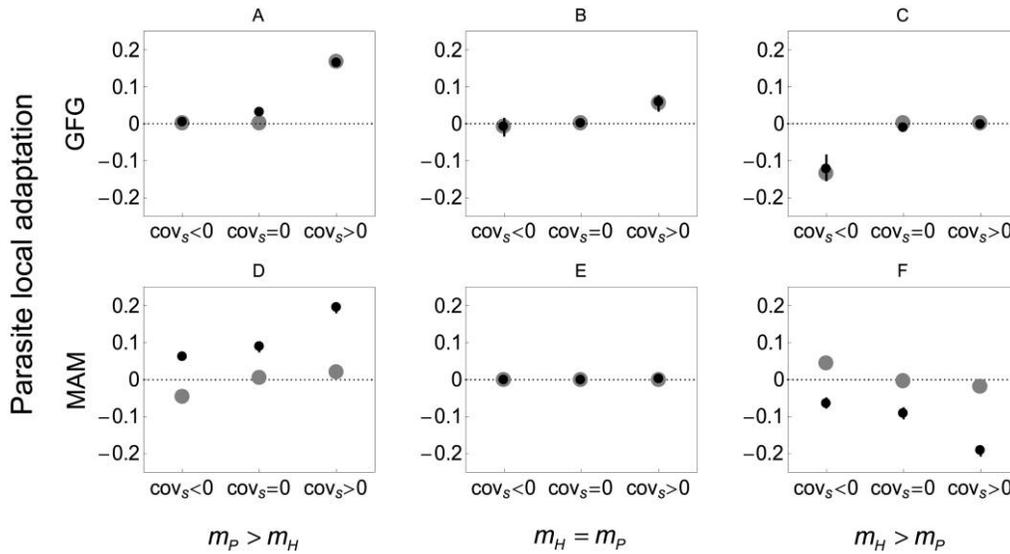
Figure 3: Interactions between biased migration rates, spatial covariance of selection, and the underlying model of specificity on the overall level of parasite local adaptation, $\overline{\Delta}$. We plot the average (*dots*) as well as the fifth and ninety-fifth percentiles (*error bar*) of parasite local adaptation obtained from 50 runs with identical parameter values. In most cases, the range between the fifth and the ninety-fifth percentiles interval is smaller than the symbols. We present the results obtained with the gene-for-gene (GFG) model and the matching-allele model (MAM) in the top and bottom rows, respectively. Gray dots refer to deterministic simulations (i.e., no genetic drift), while black dots are used when host and parasite population sizes are finite and equal to $N_H = N_P = 100$. In the first column (*A, D*) we assume $m_P = 5.10^{-2} > m_H = 10^{-3}$. In the second column (*B, E*), we assume $m_P = m_H = 10^{-2}$. In the third column (*C, F*), we assume $m_P = 10^{-3} < m_H = 5.10^{-2}$. In each plot, we consider three different types of selection mosaic: $Cov_S < 0$, $Cov_S = 0$, and $Cov_S > 0$ (see app. C in the online edition of the *American Naturalist* for more details on the simulation procedure).

$E_T(\overline{X}\,\overline{Y})$) depends on the phase difference between these two dynamics. Interestingly, as pointed out in the absence of selection mosaic (Gandon 2002; Gandon and Otto 2007), this phase difference is governed by the relative rates of migration of the host and the parasite (app. B):

$$\text{sign}[E_T(\overline{X}\,\overline{Y})] \approx \text{sign}(m_P - m_H). \quad (4)$$

This approximation is derived in an extreme case of positive covariance of selection. In order to evaluate the robustness of approximate solutions (eqq. [3], [4]), we used numerical simulations to follow the dynamics of LA over a broad range of parameter combinations (app. C in the online edition of the *American Naturalist*).

We simulated coevolution in a metapopulation consisting of two habitats with five populations in each habitat ($n = 10$). To test the validity of predictions (3a) and (3b), we considered infinitely large populations (no genetic drift). At the beginning of each run, host and parasite genotype frequencies were randomly chosen from a uniform distribution. Each simulation run lasted 3,000 generations, and the summary statistics were recorded over the final 1,000 generations. The summary statistics are the mean level of LA at different spatial scales: (1) LA within

habitat, $E(\overline{\Delta}_w)$, (2) LA between habitats, $\overline{\Delta}_b$, and (3) the overall parasite LA, $\overline{\Delta}$. For each set of parameter values, 50 simulations were run to obtain means, as well as the fifth and ninety-fifth percentiles, for LA at the three spatial scales. Simulations confirmed that in the absence of genetic drift, even very small amounts of gene flow generally yield synchronous coevolutionary dynamics, causing LA within habitats to vanish ($E(\overline{\Delta}_w) \rightarrow 0$). Although asynchrony was maintained in some simulation runs, as suggested by the results of Sasaki et al. (2002) and Gavrilets and Michalakis (2008), these runs produced only very low levels of LA (0.5% or less). We thus focus our analysis on the overall measure of LA, $\overline{\Delta}$, which, in this case, is also equal to LA between habitats $\overline{\Delta}_b$ (see eqq. [2]).

Approximation (3a) predicts that the sign of LA in the GFGM should be governed by the sign of the spatial covariance of selection between host and parasites. Numerical simulations are consistent with this prediction (fig. 3A–3C). Another prediction of this approximation is the lack of an effect of biased migration rates on the sign of LA. Although simulations show that biased migration rates affect the magnitude of parasite LA in the GFGM, the qualitative pattern (whether it is the host or the parasite that is locally adapted) remains mainly governed by the

sign of the covariance of selection, thus supporting our analytical prediction (see fig. 3A–3C).

In the MAM, numerical simulations reveal that in the absence of a selection mosaic (i.e., $\text{Cov}_\text{S} = 0$), LA does not emerge (fig. 3E). This result agrees with equation (3b), which predicts no parasite LA in this case. When there is a positive covariance of selection, equations (3b) and (4) predict an effect of the relative rates of migration of the host and the parasite. Numerical simulations are consistent with this prediction. When $\text{Cov}_\text{S} > 0$, higher parasite migration yields parasite LA (fig. 3F). In contrast, when $\text{Cov}_\text{S} < 0$, higher parasite migration may yield parasite local maladaptation (fig. 3D). Indeed, numerical simulations indicate that prediction (4) holds over a broad range of selection mosaics, even when the spatial covariance of selection is negative. This explains why the sign of parasite LA averaged over several generations should be governed by the relative rates of migration of the parasite and the host and the type of selection mosaic.

Although the results of these simulations confirm our analytical approximations, they also reveal that the magnitude of LA is generally quite small (less than 5% in most of the cases) for both the GFGM and the MAM. The reason for these overall low levels of LA is that spatial variation in the strength of selection alone maintains only limited levels of genetic differentiation across space in the presence of gene flow. In the next section, we use simulations of finite populations to explore how genetic drift alters our analytical predictions and, in many cases, greatly increases the magnitude of LA.

Stochastic Models of Finite Populations

Our results reveal that genetic drift has important consequences for the magnitude and sign of LA (app. C). As in previous studies (Gandon 2002), our simulation results show that genetic drift allows LA to emerge even in the absence of a spatial covariance of selection as long as rates of host and parasite gene flow are low and unequal (fig. 3). Specifically, our results confirm those of earlier studies (Gandon et al. 1996; Gandon 2002; Gandon and Michalakis 2002) showing that increasing migration rates can promote LA (fig. 3).

In addition, our simulations demonstrate that the effect of drift is more pronounced in the MAM than in the GFGM. This differential effect of drift is likely explained by the different stability properties of the two models. Specifically, the haploid single-locus MAM is characterized by a single locally unstable internal equilibrium. Perturbation from this equilibrium yields cyclical dynamics. Consequently, genetic drift can readily generate spatial variability in this model. In contrast, for many parameter combinations, the GFGM is characterized by a locally sta-

ble internal equilibrium (Sasaki 2000). Because this internal equilibrium is locally stable, small amounts of genetic drift do not destabilize it and genotype frequencies remain spatially homogenous, precluding LA. Because we find that genetic drift plays such a limited role in the dynamics of the GFGM, we focus on the effects of varying population size in the MAM only.

We varied the intensity of genetic drift by altering the local population sizes of host and parasite in our numerical simulations. Figure 4 shows that the magnitude of LA is maximized for intermediate population sizes and thus intermediate levels of genetic drift. When population sizes are very large relative to rates of gene flow (i.e., when $N_\text{P} m_\text{P} \gg 1$), genetic drift is weak and cannot prevent synchronization among populations (fig. 4). In contrast, when population sizes are very small, genetic drift is intense and prevents adaptation. In particular, we expect drift to overwhelm parasite adaptation if $N_\text{P} \bar{s}_\text{P} < 1$, where $\bar{s}_\text{P}$ is the intensity of selection imposed by the host on the parasite, averaged over the different habitats. Because $\bar{s}_\text{P}$ is actually the maximum possible strength of selection, with the realized strength of selection depending on host genotype frequencies, genetic drift may overwhelm adaptation for local population sizes substantially larger than $1/\bar{s}_\text{P}$. In line with these expectations, our simulations show that LA is maximized for intermediate population sizes (between 10 and 100 in fig. 4), where drift prevents synchronization without overwhelming natural selection. In addition, simulations reveal that finite population sizes yield much higher values of LA than deterministic models. Figure 4E, for example, shows that parasite LA can reach values up to 0.26 for $N_\text{P} = N_\text{H} = 15$, more than 50 times that in the deterministic case (i.e., in the absence of genetic drift). Even greater levels of LA can be reached (even for larger population sizes) with increased strength of selection and decreased migration rates (not shown).

Genetic drift may also qualitatively alter the results obtained with deterministic models. In particular, our deterministic simulations show that when $\text{Cov}_\text{S} < 0$ and the parasite migrates more than the host, parasites are locally maladapted in the MAM (see figs. 3D, 4D). With finite population sizes, however, the parasite tends to be locally adapted anytime it has a higher rate of migration, irrespective of the sign of Cov_S (see figs. 3D, 4D). Thus, it seems that as soon as population sizes are relatively small (i.e., $N_\text{P} m_\text{P} < 1$; see fig. 4D), the sign of LA is governed mainly by the relative rates of migration and only weakly depends on the sign of the spatial covariance of selection.

To understand the effect of genetic drift and its interaction with host and parasite migration rates, we contrast the measures of LA within and between habitats. Finite population size prevents synchronization of coevolutionary dynamics among populations from the same habitat
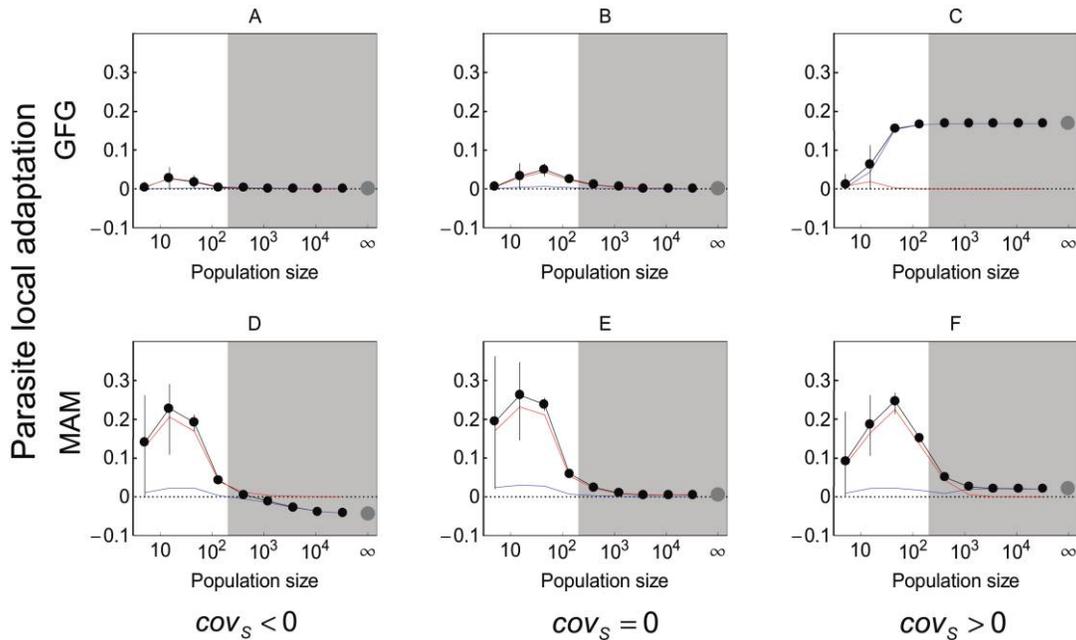
Figure 4: Interactions between the size of host and parasite populations ($N_H = N_P$), spatial covariance of selection, and the underlying model of specificity on overall parasite local adaptation, $\overline{\Delta}$ (*black dots, black line*), on parasite within-habitat local adaptation, $E(\overline{\Delta}_w)$ (*red line*), and on parasite between-habitat local adaptation, $\overline{\Delta}_b$ (*blue line*). We plot the average and, for $\overline{\Delta}$ only, the fifth and ninety-fifth percentiles (*vertical line*) for parasite local adaptation obtained from 50 runs under the same parameter values. As in figure 3, the first and second rows are the results obtained with the gene-for-gene (GFG) model and the matching-allele model (MAM), respectively. In the left, middle, and right columns we assume $Cov_S < 0$, $Cov_S = 0$, and $Cov_S > 0$, respectively (see app. C for more details on the simulation procedure). At the right edge of each plot, we also report the overall level of parasite local adaptation obtained with deterministic simulations (i.e., when N_H, $N_P \to \infty$; *gray dots*). The gray area at the right-hand side of each plot refers to parameter values where $N_P m_P > 1$. In all the panels we further assume $m_P = 5 \times 10^{-2} > m_H = 10^{-3}$.

and thus allows some level of LA within habitats to build up. In fact, the importance of the within-habitat component increases with the intensity of drift and thus with decreasing population sizes (fig. 5). It is this effect that explains the increase in the overall level of LA when population sizes are intermediate. It is also this increasing influence of LA within habitat that explains why biased migration rates are more important in finite populations. In the absence of selection mosaics, but with genetic drift, it has been shown that higher migration rates tend to promote LA (Gandon 2002). Figure 4 shows that we obtain this result even when there is a mosaic of selection, as long as populations are small. Figure 4 further shows that the effect of migration within habitats may counteract the effect of migration rates on LA between habitats that we found in a fully deterministic model (fig. 4*D*). In the GFGM, we observed similar effects of drift on the relative contribution of within- and between-habitat components of LA (figs. 4, 5). Yet the overall level of parasite LA seems to be governed mainly by the type of selection mosaic rather than by migration and drift.

Effects of Multiple Loci and Diploidy on Local Adaptation

We used our stochastic simulation model to further explore the effects of multiple loci and diploidy. Allowing more loci to govern the outcome of the interaction requires assumptions about the form of epistasis for the specificity of the interaction. We assumed that resistance was an all-or-nothing response and that resistance at a single locus was enough to allow recognition of the parasite by the host and to prevent infection. In the GFGM, we also assume that costs of carrying resistance and virulence alleles (in the host and the parasite, respectively) acted multiplicatively across loci. All simulation results presented in figure D1 in the online edition of the *American Naturalist* assume no recombination between loci, although cases with free recombination were also explored and did not affect qualitatively the main results we discuss here. Studying the effects of diploidy also requires additional assumptions regarding the dominance of resistance and virulence. For the sake of comparison, we studied the same models of specificity used by Nuismer (2006; fig. 2*B*). Note
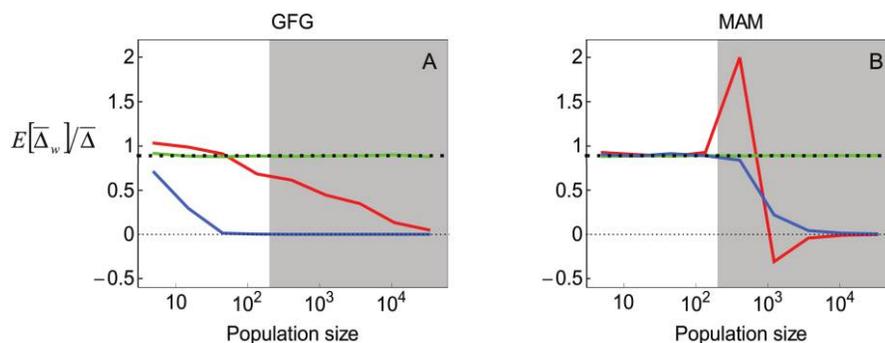
Figure 5: Contribution of within-habitat component to the overall level of parasite local adaptation, $E(\overline{\Delta}_w)/\overline{\Delta}$, for variable population sizes. We use the same parameter values as in figure 4 for the gene-for-gene model (GFG; *A*) and the matching-allele model (MAM; *B*) and for the three different types of selection mosaics: $\mathrm{Cov}_S < 0$ (*red*), $\mathrm{Cov}_S = 0$ (*green*), and $\mathrm{Cov}_S > 0$ (*blue*). The black dotted line indicates the expected value of $E(\overline{\Delta}_w)/\overline{\Delta} = \max(n-1)/(n\max -1)$ in the absence of a selection mosaic. As in figure 4, the gray area on the right-hand side of each plot refers to parameter values where $N_p m_p > 1$.

that under these assumptions, the IMAM and the MAM are no longer equivalent, as they are in the haploid case.

Figure D1 shows that increasing the number of loci does not change how biased migration rates and genetic drift interact to determine parasite LA. In particular, we recover the effects of biased migration rates on LA when population sizes are relatively low. The main effect of adding more loci is to decrease the absolute level of LA. Under the epistasis rule that we used, adding more loci decreases the expected infectivity of the parasite population when the host and the parasite genotypes are all at the equifrequent equilibrium. Lower average infectivity leaves less room for LA to emerge. Additional simulations (not shown) using a different rule for epistasis (where resistance on all loci is required for the host to prevent infection) revealed an opposite effect of increasing the number of loci on LA.

In figure D2 in the online edition of the *American Naturalist*, we explore the robustness of our results when both the host and the parasite are assumed to be diploid. The asymmetry of the models of specificity yields more complicated interactions between the effects of biased migration rates, population size, and selection mosaic. Some cases deserve investigation beyond what can be accomplished in this article. In particular, figure D2 shows that high levels of LA can be maintained in the absence of selection mosaics and genetic drift, provided that the host and the parasite have different migration rates. Yet we recover the main results pointed out above in the haploid version of the model: the overall level of LA is governed by biased host and parasite migration rates, and finite

population sizes can alter qualitatively and quantitatively the level of LA.

At first glance, the dominance of biased migration rates contrasts with the results of Nuismer (2006), who concluded that LA was governed mainly by the selection mosaic and less by biased migration rates. The fact that our study focused only on three extreme cases of selection mosaics and biased migration rates might explain some of the differences with Nuismer (2006), who explored a broader range of ecological situations. It is more likely, however, that the apparent discrepancy between these studies arises for two main reasons. First, the maintenance of LA in the deterministic version of our diploid MAM (fig. D2*A*, D2*B*) is due to the emergence of stable spatial patterns in which populations end up being (almost) fixed for different homozygous genotypes. Yet the maintenance of this spatial differentiation requires a sufficient number of populations. Because he studied the emergence of LA in a model with only two populations, Nuismer (2006) simply did not get these spatial patterns and always obtained very low levels of LA in the absence of selection mosaics. Second, the effect of biased migration rates is apparent mostly for intermediate population sizes (fig. D2), whereas Nuismer (2006) analyzed the coevolutionary dynamics of deterministic models with no genetic drift. This leads us to reiterate the conclusion obtained with the haploid model that the effect of biased migration rates is mostly apparent with finite population sizes because it allows within-habitat LA to emerge. We also ran simulations of the diploid model with more loci (not shown) that confirmed the results obtained with the haploid

model. Adding more loci does not qualitatively alter our results but reduces the absolute level of LA under our assumption for epistasis (see fig. D1).

Discussion

We have studied the interactions among (1) gene flow, (2) mosaics of selection, (3) genetic drift, and (4) the genetic specificity of pathogen resistance on the emergence of parasite LA in a geographically structured model of host-parasite coevolution. The analysis of the coevolutionary dynamics is greatly clarified by the use of a general expression for the level of LA as a function of the spatial covariance between the genotype frequencies of hosts and parasites. This spatial covariance measures the association between the spatial distribution of genotype frequencies of the focal species and the heterogeneity of the environment (i.e., the heterogeneity of the genotype frequencies of the interacting species). We use this expression to follow the dynamics of haploid organisms when coevolution is governed by a single diallelic locus in both the host and the parasite. This expression can, however, be readily used for any ploidy level, model of host-parasite specificity, or number of loci and alleles. In particular, we used this expression to explore the effects of multiple loci and diploidy (figs. D1, D2). Similar expressions can also be obtained when the focal species adapts to spatially variable but temporally constant biotic or abiotic components of the environment (Nuismer and Gandon 2008).

The definition of LA as a spatial covariance can be viewed as a special kind of "interspecific linkage disequilibrium" (Wade 2003, 2007; Nuismer 2006; Day et al. 2008). In classical population genetics, linkage disequilibrium between two loci can be defined as a covariance between allele frequencies at different loci (Barton and Turelli 1991; Kirkpatrick et al. 2002). Thus, one may also define LA as the linkage disequilibrium between allele frequencies in different species. Note that, because linkage disequilibrium can be extended to more than two loci, this definition could be extended to study LA at the scale of whole communities of species. We propose that the study of interspecific linkage disequilibrium may yield important insights into the evolutionary process shaping interspecific interactions, as has been the case with the classical intraspecific linkage disequilibrium of population genetics (Crow and Kimura 1970).

Mosaics of Selection, Biased Migration, and Genetic Drift

Our general covariance formulation for LA is particularly useful when the environment consists of different habitats. This is because it allows LA to be partitioned into within- and between-habitat components. Partitioning LA in this way clarifies how selection mosaics, biased migration rates, and genetic drift lead to LA. For instance, the positive effect of migration on LA is mainly acting on the within-habitat component of LA. The between-habitat component, however, is more strongly affected by the selection mosaic and, in particular, by the sign of the spatial covariation between the intensities of selection acting on the host and the parasite. This is particularly true in the GFGM, where both analytic approximations and numerical simulations indicate that the sign of parasite LA is governed by the type of selection mosaic. For the MAM, however, there is a strong interaction between the effects of selection mosaics and biased migration rates on parasite LA. Parasite migration can promote or hamper LA, depending on the type of selection mosaic.

These results help clarify the apparent discrepancies between previous studies on the effect of migration on parasite LA. Earlier models relied on the simplifying assumption that the host-parasite interaction takes place in a homogeneous environment (Morand et al. 1996; Gandon et al. 1996; Lively 1999; Gandon 2002) when there is no between-habitat component of LA. These earlier studies thus focused on within-habitat LA, which explains why they found a positive effect of parasite migration on parasite LA (Gandon et al. 1996; Gandon 2002). In contrast, Nuismer (2006) analyzed a two-population model in which each population belonged to a different habitat. In this situation, there is no within-habitat component of LA because each habitat contains only a single population. This explains why Nuismer (2006) found that LA is only weakly affected by biased migration rates. Indeed, as we point out in this article, the between-habitat component of LA is mainly driven by the mosaics of selection.

The model we analyzed allowed us to explore situations between these two extremes. Simulations indicate that the relative weights of the within- and between-habitat components of LA are mediated by the intensity of genetic drift and thus by the size of host and parasite populations. When both host and parasite populations are very small, there is little LA (both within and between habitats) because selection cannot counteract the effect of genetic drift. When both host and parasite population sizes are relatively large (i.e., $N_H m_H > 1$ and $N_P m_P > 1$), LA is governed mainly by the between-habitat component. This is due to the synchrony in coevolutionary dynamics that occurs among populations from the same habitats, which reduces the within-habitat component of LA. When both the host and parasite populations are moderately small (the range of population sizes varies, depending on the strength of selection and migration rates), LA is driven by the within-habitat component. Genetic drift can thus affect levels of LA quantitatively (LA is maximized for intermediate population sizes) and qualitatively (e.g., the effect of biased

migration rates on LA). A similar argument can be used to explain the effect of biased population sizes on the emergence of LA (Gandon and Michalakis 2002). All else being equal, the species with the larger population size is often the one locally adapted because selection is less counteracted by drift.

Local Adaptation in the Field and in the Lab

Before discussing the relevance of this study for empirical and experimental research on LA, we want to recall that in this study we focus on average patterns of LA. We do not deal with the variation around this mean, which is likely to be large because of the intrinsic fluctuations of selection generated by the underlying coevolutionary process. Our simulations results are averaged over space (10 populations) and time (1,000 generations). In most experimental systems, however, estimates of LA will be determined only on the basis of a low number of populations and a single time point. How this will affect the likelihood of detecting the true pattern of LA clearly deserves more attention.

Our results have implications for the design of transplant experiments. If there is obvious habitat variation among populations (e.g., availability of resources for the host, temperature, altitude), one may sample populations from different habitats to try to contrast the measures of LA within and between habitats. These measures could then be compared to the expected value of $E(\overline{\Delta}_w)/\overline{\Delta}$, the expected proportion of total LA explained by LA within habitats, in the absence of spatial covariance of selection. In particular, if we sample the same number n_{pop} of populations in each habitat, we would expect this ratio to depend only on the number of populations and on the number of habitats (app. A):

$$\frac{E(\overline{\Delta}_w)}{\overline{\Delta}} = \frac{\max(n_{pop} - 1)}{n_{pop}\max - 1}. \tag{5}$$

However, figure 5 illustrates that when populations sizes are large (i.e., $N_P m_P > 1$), we expect a huge departure of $E(\overline{\Delta}_w)/\overline{\Delta}$ from equation (5) when there is some spatial covariance of selection in both the GFGM and the MAM. Provided that population sizes are large, this comparison could, in principle, reveal the existence of large amounts of between-habitats LA (relative to within-habitats LA) and thus the existence of selection mosaics in the field.

An alternative to the existence of selection mosaics, however, could be that the between-habitats LA is generated by uneven patterns of migration where migration is more frequent among populations belonging to the same habitats than among populations from different habitats.

This could easily occur in situations where populations from different habitats are more distant and migration rate decreases with distance but also when there is some habitat choice in the migration process. This alternative deserves further theoretical investigation, for example, with simulation models that could take these uneven migration patterns into account. In any case, the comparisons between the different components of LA (fig. 5) requires that the different habitats are already well characterized, since unknown environmental heterogeneities could obscure the expected patterns of LA.

Another way to detect mosaics of selection, even in the absence of obvious habitat heterogeneities, is to perform cross-infection experiments that take into account the abiotic heterogeneity of the environment. Classical common-garden experiments focus only on the biotic component of environmental heterogeneity and thus on the interactions between host and parasite genotypes (i.e., G × G interactions). Consequently, this prevents the estimation of statistical interactions between genotypes and the abiotic components of the environment (i.e., G × E and G × G × E interactions). Yet a full factorial experimental design taking into account the effects of host genotypes, parasite genotypes, and abiotic heterogeneity is feasible in some cases (Nuismer and Gandon 2008) and would allow estimation of different statistical interactions (i.e., G × E, G × G, and G × G × E). Such alternative experimental designs would thus be a way to detect and characterize selection mosaics, in the form of G × G × E statistical interactions.

The two experimental designs described above could be used in the field to study the emergence of LA in many different host-parasite systems. In addition, microbial systems offer wonderful opportunities to put some of the above predictions to the test by studying the emergence of LA experimentally. For instance, Morgan et al. (2005) used the bacterium *Pseudomonas fluorescens* and its phage $\phi2$ to show that, in accord with earlier models of coevolution (Gandon et al. 1996), increasing parasite migration experimentally increased parasite LA. Exploring the interaction between the effect of migration rates and other factors (genetic drift, selection mosaic) seems feasible in such experimental systems. Genetic drift could be manipulated by varying the size and/or the frequency of the bottleneck between each transfer. According to the above simulation results, we would expect LA to be maximized for intermediate levels of genetic drift.

Microbial systems could also be used to evaluate the effects of selection mosaics by varying the conditions among the different populations. For example, Brockhurst et al. (2003) showed that varying the intensity of shaking of the experimental populations may alter the rate of coevolution and thus the intensity of selection. This type of variation may be an easy way to generate a positive spatial

covariance of selection between species and would thus allow within- and between-habitat components of LA to be explored. It would be particularly interesting to test the effect of genetic drift on the relative effects of within- and between-habitat components on the overall level of LA (figs. 4, 5). These experiments, together with more detailed description of the underlying specificity of the bacteria-phage interaction (Poullain et al. 2008), should yield a better understanding of the coevolutionary dynamics of microbial systems in the lab. This would represent an important first step toward understanding coevolutionary interactions among multiple hosts and multiple parasites occurring in the field.

Acknowledgments

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