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EFFECTS OF ENVIRONMENTAL HETEROGENEITY ON VICTIM–EXPLOITER COEVOLUTION

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We study victim–exploiter coevolution in a spatially heterogeneous island model. In each species, fitness consequences of between-species interactions are controlled by a single haploid diallelic locus. Our emphasis is on the conditions for the maintenance of genetic variation, the dynamic patterns observed, the extent of local adaptation and genetic differentiation between different demes, and on how different parameters (such as the strength and heterogeneity in selection, migration rates, and the number of sites) affect the dynamic and static behavior of the system. We show that under spatially homogeneous selection the maintenance of genetic variation is possible through asynchronous nonlinear dynamics where the allele frequencies in a majority of demes quickly synchronize but the rest do not. Spatially heterogeneous selection can maintain genetic variation even if migration rates are maximal. This happens in an oscillatory way. Genetic variation is most likely to be maintained at high levels if the heterogeneity in selection is large. If there are some restrictions on migration, genetic variation can be maintained at a stable equilibrium. This behavior is most likely at intermediate migration rates. In this case, the system can exhibit high spatial subdivision as measured by F_{ST} values but relatively low local adaptation.

KEY WORDS: Host, interaction, mathematical, model, parasite, subdivided.

Between-species interactions are ubiquitous in nature and are thought to result often in strong natural selection and reciprocal evolution (Futuyma and Slatkin 1983; Thompson 1994, 2005; Wade 2007). Victim–exploiter coevolution describes situations in which one species (exploiter) benefits at a cost to another (victim). Under such interactions the exploiter profits from strengthening the between-species interaction whereas the victim profits from weakening the interactions. One particularly important type of victim–exploiter system is represented by host–parasite species pairs. Evolutionary dynamics of host–parasite interactions have attracted a great deal of attention for several reasons. Host–parasite interactions are interesting in their own right because they concern a large part of biodiversity (de Meeus et al. 1998); they result in intriguing evolutionary and ecological processes, such as the evolution of virulence (Frank 1996), the evolution of offense–defense systems, e.g., the vertebrate immune system (Garrigan and Hedrick 2003), and the generation of patterns of local adaptation (Kaltz and Shykoff 1998; Kawecki and Ebert 2004; Greischar and Koskella 2007; Hoeksema and Forde 2008). These questions are central in public or animal health issues. Host–parasite interactions have also been involved in the evolution of several key traits of living organisms, and in particular in the evolution of sex (e.g., Hamilton et al. 1990; Howard and Lively 1994; West et al. 1999; Busch et al. 2004; Otto and Nuismer 2004), ploidy level (e.g., Nuismer and Otto 2004), and gene expression (e.g., Nuismer and Otto 2005).

Victim–exploiter interactions often result in complex and nonlinear coevolutionary dynamics that are difficult to understand

on the basis of verbal reasoning and generalizations from data. Mathematical modeling becomes an important tool for achieving better insights. A common approach for describing between-species interactions in a mathematical model is to assume that fitnesses depend on genetic composition of the interacting species, i.e., that fitnesses are frequency-dependent. The questions addressed using mathematical models of frequency-dependent selection include the conditions for the maintenance of genetic variation without mutation, the levels of genetic variation maintained, whether the system evolves toward an equilibrium state or some dynamic regime (e.g., cycles or chaos), and which species can be viewed as a "winner" of antagonistic interactions (Mode 1958; Leonard and Czochor 1980; May and Anderson 1983; Frank 1991a, 1996; Gavrilets 1997; Gavrilets and Hastings 1998; Kopp and Gavrilets 2006). When spatial subdivision is important, major questions include the extent of synchrony/asynchrony in the dynamics between different spatial locations and the levels of genetic differentiation (Frank 1991b; Gandon et al. 1996; Lively 1999; Nuismer et al. 2000; Gandon and Michalakis 2002; Thrall and Burdon 2002; Nuismer 2006; Nuismer and Gandon 2008). Additional questions that have received a lot of attention in the host–parasite literature concern the levels of local adaptation, and the effects of the type of between-species interactions (e.g., "gene-for-gene" vs. "matching alleles," Frank 1993; Agrawal and Lively 2002; Nuismer 2006) and of genetics of underlying characters (e.g., major vs. minor genes, effects of multiple alleles and multiple genes).

Spatial subdivision and spatial heterogeneity in environmental conditions (abiotic and biotic) are characteristic of most biological systems, including host–parasite systems. The importance of these effects is stressed in the influential geographic mosaic theory of coevolution (Thompson 1994, 2005; Gomulkiewicz et al. 2000), which holds that genotype-by-genotype-by-environment interactions drive coevolutionary changes as species interact with one another across heterogeneous landscapes. One of the aims of the geographic mosaic theory is to understand why some of these interactions can persist over long periods of time and how they shape coevolutionary dynamics. Some aspects of the geographic mosaic theory have been addressed using a variety of analytical and numerical models (e.g., Gandon et al. 1996; Lively 1999; Nuismer et al. 2000; Gandon and Michalakis 2002; Nuismer 2006).

The goal of this article is to investigate a relatively simple model of antagonistic coevolution in an island model with spatially heterogeneous selection (selection mosaic). Simplicity of the model implies that a relatively thorough analysis becomes feasible. This is in contrast to most previous works that used more complex models but typically focused on the effects of only one or two parameters (usually, the migration rates). The price of simplicity is, of course, biological realism. Our goal at this stage however is not to make precise predictions for concrete biological systems but rather to develop a better intuition about the effects of different factors that have been always present in the models but have remained largely unexplored theoretically. A better intuition gained from studying simple models can be used for deeper understanding of the previous empirical and modeling work and for attacking more complex and realistic models.

Our model is closely related to the single-deme models studied by Seger (1988) and Gavrilets and Hastings (1998) and generalized later by Nuismer et al. (2000) and Gandon (2002) for the case of spatially structured population. Simultaneously, our model can be viewed as a first step toward generalizing the classical Levene model of selection in a spatially heterogeneous environment (Levene 1953, Gavrilets 2004, Chap.7) for the case of coevolutionary interactions. We start by defining the model. Then we present analytical and numerical results on its dynamics and biologically relevant characteristics. At the end, we discuss biological significance of our results.

Model

We consider a host and a parasite species (or, more generally, a victim and an exploiter species) inhabiting a system of n sites (demes) connected by migration. Population sizes are sufficiently large to neglect the effects of random genetic drift. Generations are discrete and nonoverlapping. Both species are haploid and differ with regard to a single diallelic locus with alleles **A** and **a** in the host and alleles **B** and **b** in the parasite. Host allele **A** and parasite allele **B** and host allele **a** and parasite allele **b** are "complementary" (in a sense to be defined below). Before selection the frequencies of alleles **A** and **a** at site i are h_i and $1 - h_i$ and those of alleles **B** and **b** are p_i and $1 - p_i$.

SELECTION

Within each species selection is symmetric frequency-dependent. Fitnesses (viabilities) being given by linear functions of the genotype frequencies in the other species

$$w_{A,i} = 1 - \alpha_i p_i, \quad w_{a,i} = 1 - \alpha_i(1 - p_i), \tag{1}$$

$$w_{B,i} = 1 - \beta_i(1 - h_i), \quad w_{b,i} = 1 - \beta_i h_i, \tag{2}$$

where $0 < \alpha_i, \beta_i < 1$ are the coefficients measuring the sensitivity of fitness of each species at site i to changes in allele frequencies in the other species. These coefficients also measure the maximum possible strength of selection (observed when one of the alleles is close to fixation). For brevity, we will call them selection coefficients. In the host species, each genotype suffers the reduction in fitness when its "complementary" genotype in the parasite species increases in frequency. In the parasite species the opposite happens: each genotype benefits when its "complementary" genotype

in the host species increases in frequency. This model also implies that there are no fitness differences between the two genotypes of each species in a deme not related to their interactions with the other species. Whenever all α_i's are equal and β_i's are equal we will say that selection is homogeneous in space, and that it is heterogeneous otherwise. We emphasize that the fitness of a given genotype, however, may vary in space even in the case of homogeneous selection, because it depends on the frequencies of genotypes in the antagonistic species that can vary in space. In terms of the geographic mosaic theory of coevolution (Thompson 2005), coefficients α and β capture genotype-by-genotype interactions in fitness whereas the fact that these coefficients vary in space accounts for the "environment" part of genotype-by-genotype-by-environment interactions.

The allele frequencies after selection within deme i are

$$h_i^s = \frac{w_{A,i}}{\bar{w}_{h,i}} h_i, \tag{3}$$

$$p_i^s = \frac{w_{B,i}}{\bar{w}_{p,i}} p_i, \tag{4}$$

where

$$\bar{w}_{h,i} = w_{A,i} h_i + w_{a,i}(1 - h_i), \tag{5}$$

$$\bar{w}_{p,i} = w_{B,i} p_i + w_{b,i}(1 - p_i), \tag{6}$$

are the average fitnesses of the species in deme i.

MIGRATION

Migration occurs after selection. We assume migration to be uniform in space and to follow the island model, so that all immigrants come through a common migrants pool. Assuming that all demes contribute equally to the migrant pool, the allele frequencies in the migrant pool are

$$\bar{h} = \frac{\sum h_i^s}{n}, \tag{7}$$

$$\bar{p} = \frac{\sum p_i^s}{n}. \tag{8}$$

Assuming that the proportion of migrants coming into each deme is constant (m_h for hosts and m_p for parasites), the allele frequencies after migration are

$$h_i' = (1 - m_h) h_i^s + m_h \bar{h}, \tag{9}$$

$$p_i' = (1 - m_p) p_i^s + m_p \bar{p}. \tag{10}$$

Reproduction occurs after migration and does not change allele frequencies. Therefore, the allele frequencies in the next generation are the same as h'_i and p'_i.

Results

Here we describe analytical and numerical results on the behavior of our model as specified by dynamic equations (1–5). This dynamical system has always four monomorphic equilibria at which the frequencies of alleles **A** and **B** are (0,0), (0,1), (1,0), and (1,1), respectively. Also, there always exists a symmetric polymorphic equilibrium (1/2,1/2) at which all alleles have frequency 1/2. Below we describe our results in different sections, depending on the extent of migration and on whether selection is homogeneous or heterogeneous in space. In all cases, we examine the stability of the four monomorphic equilibria and of the symmetric polymorphic equilibrium and characterize the corresponding dynamic regimes.

Besides looking at whether genetic variation is maintained and interpreting general dynamics of allele frequencies, we will also analyze genetic differentiation and local adaptation. The level of genetic differentiation between different demes is measured by coefficient F_{ST}

$$F_{\mathrm{ST}} = \frac{\mathrm{var}(x)}{x(1 - x)}, \tag{11}$$

where x and var (x) are the average and variance of the frequencies of a particular allele in a particular species across all n demes. Following previous work (e.g., Gandon et al. 1996; Gandon and Michalakis 2002; Nuismer and Gandon 2008), we define the level of local adaptation Δ of the species (host or parasite) as the expectation (across all demes) of the difference between its fitness in the population of origin, w_{home}, and its average fitness, $\bar{w}_{away}$, over remaining $n - 1$ demes

$$\Delta = E\{w_{home} - \bar{w}_{away}\}. \tag{12}$$

The average fitness $\bar{w}_{away}$ is measured using the current genetic composition of the antagonistic species in the other demes. Note that substantial local adaptation requires substantial genetic differentiation. For the model under consideration, the expected local adaptation of hosts and parasites can be written as

$$\Delta_h = \frac{n}{n - 1} \mathrm{cov}(h_i, w_{A,i} - w_{a,i}), \tag{13}$$

$$\Delta_p = \frac{n}{n - 1} \mathrm{cov}(p_i, w_{B,i} - w_{b,i}), \tag{14}$$

where the covariances are computed over all n demes (see Appendix and also Nuismer and Gandon 2008 for a more general treatment). With spatially homogeneous selection (i.e., with $\alpha_i = \alpha$, $\beta_i = \beta$ for all i), the above equations simplify to

$$\Delta_h = -2\alpha \frac{n}{n - 1} \mathrm{cov}(h_i, p_i), \tag{15}$$

$$\Delta_p = 2\beta \frac{n}{n - 1} \mathrm{cov}(h_i, p_i). \tag{16}$$

Equations (15) and (16) show that host local adaptation is a negative function of the covariance of host and parasite allele frequencies, whereas parasite local adaptation is a positive function of this covariance. This makes intuitive sense, because the fitness of a given host genotype decreases as the frequency of the complementary parasite genotype increases; thus if host and parasite genotype frequencies are positively correlated we would expect hosts to "suffer" and parasites to benefit.

In performing numerical simulations with spatially heterogeneous selection, we will draw the values of parameters α_i and β_i for each deme randomly and independently from uniform distributions on intervals $[\alpha_{min}, \alpha_{max}]$ and $[\beta_{min}, \beta_{max}]$. We will interpret coefficients α_{max} and β_{max} as characterizing the overall strength of selection. We will interpret the relative differences $\kappa_\alpha = (\alpha_{max} - \alpha_{min})/\alpha_{max}$ and $\kappa_\beta = (\beta_{max} - \beta_{min})/\beta_{max}$ as measures of spatial heterogeneity of selection ($0 \leq \kappa_\alpha, \kappa_\beta \leq 1$). Except where explicitly noted otherwise, our simulations ran for 5000 generations.

Our major qualitative results are summarized in Table 1. The details of our analytical methods are given in the Appendix.

NO MIGRATION ($m_h = m_p = 0$)

In the case of an isolated deme, all four monomorphic equilibria are saddle points, whereas the polymorphic equilibrium is an unstable focus. On the (p, h)-phase plane, the resulting dynamics are represented by trajectories that spiral out approaching the boundaries closer and closer, with only one species polymorphic at a time (Fig. 1A,B; Seger 1988; Gavrilets and Hastings 1998). Unless selection is very weak, genetic variation disappears on the time scale of few hundred to few thousand generations (Fig. 1C). Note that if we allow for recurrent mutation, genetic variation will be maintained and the system will evolve toward a mutation–selection balance cycle positioned close to the boundaries of the (p, h)-phase plane (Gavrilets and Hastings 1998).

HOMOGENEOUS SELECTION ($\alpha_i = \alpha$, $\beta_i = \beta$), ARBITRARY MIGRATION

When selection is homogeneous in space, intuition for the island model suggests that allele frequencies in different demes will quickly synchronize and the behavior of the system will become similar to that in an isolated deme case considered above (Fig. 1). This is indeed what one often sees in numerical simulations. However, simulations also show that there is a different regime in which the system maintains genetic variation in a nonequilibrium fashion so that the average allele frequencies (Fig. 2A), F_{ST} values (Fig. 2B), and the degree of local adaptation (Fig. 2C) continuously fluctuate. In this regime, the majority of allele frequencies are synchronized (i.e., equal) but a few remaining are not. For example, in the case shown in Figure 2, 13 of 16 demes were synchronized whereas each of the three remaining demes followed its own dynamics.

To understand the dynamics of F_{ST} and local adaptation in these cases, consider a situation in which host populations are highly differentiated, i.e., host's F_{ST} is large, whereas parasite populations have very similar allele frequencies, i.e. parasite's F_{ST} is very small. The host is then facing spatially homogeneous selection, precisely because parasite's F_{ST} is close to 0, and therefore host populations will tend to homogenize, leading to low host's F_{ST}. At the same time, because host's F_{ST} is large, parasites are facing spatially heterogeneous selection, and thus their populations will diverge, leading to large parasite's F_{ST}. Local adaptation requires that both species exhibit spatial differentiation. It is thus close to 0 when either species has a very small F_{ST}, and reaches its maximal absolute value soon after the F_{ST} curves of the two species cross. Host local adaptation is positive whereas host F_{ST} increases. During this phase each host population is adapting to its sympatric parasite population. When host F_{ST} decreases, host local adaptation decreases as well, precisely

Table 1. Summary of major qualitative results. "U" stands for locally unstable and "S" stands for locally stable equilibria; "mono" and "poly" stand for the monomorphic and the symmetric polymorphic equilibria.

Condition	Mono	Poly	Dynamic patterns and features
No migration	U	U	Quick loss of variation via growing oscillations
Homogeneous selection	U	U	(1) synchronization and quick loss of variation, or
			(2) asynchronous nonlinear dynamics, maintenance
			of variation, substantial genetic differentiation, and
			Low local adaptation
Maximal migration	U	U	Stable cycling; low variation
General case	U	(1) S for intermediate migration,	(1) maintenance of variation, no genetic differentiation, or
		(2) U otherwise	(2) asynchronous nonlinear dynamics, maintenance
			of variation, substantial genetic differentiation, and
			some local adaptation

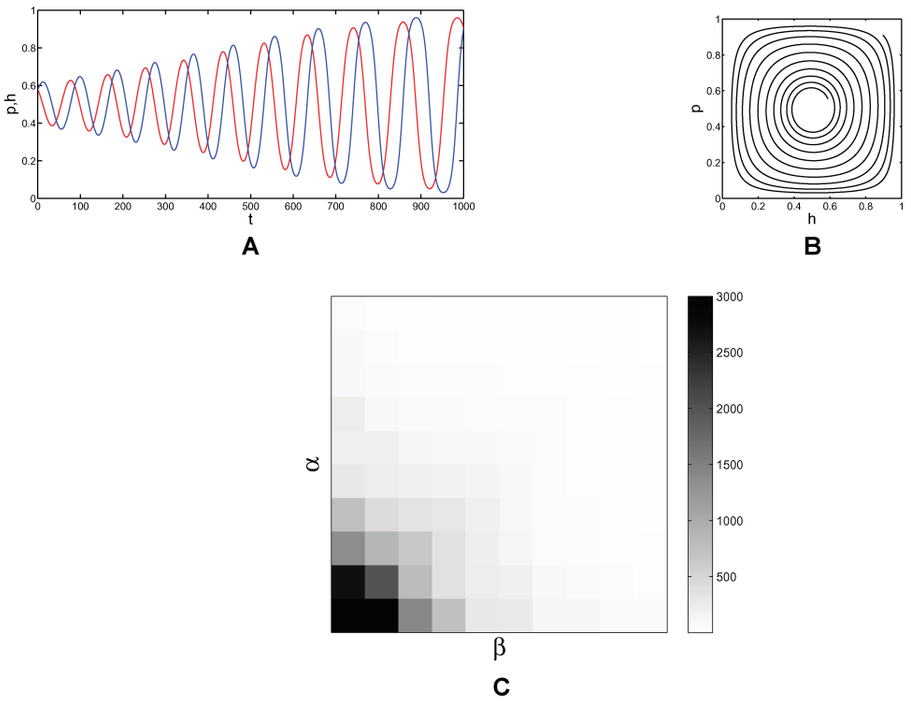

Figure 1. The dynamics in a single deme. (A) The dynamics of p (blue) and h (red) in time. (B) The corresponding dynamics on the (p, h)-phase plane. The trajectory spirals counter-clock wise. (C) The average time for an allele frequency to reach 10^{-4} with different α and β changing between 0 and 1. Random uniform initial conditions. Twenty runs for each parameter combination. For the smallest values of α and β used, the allele frequencies have not reached 10^{-4} within the time span used (10^4 generations).

because host populations have more and more similar genetic compositions. The reverse arguments hold for the parasite.

Asynchronous behavior maintaining genetic variation requires significant initial variation in allele frequencies between demes and is typically observed when migration rates are small, selection is intermediate, and the number of demes is large (see Fig. 3). Larger migration requires stronger selection. The differences in migration rates between the species do not affect these conclusions strongly (see Fig. 4).

Genetic differentiation observed in asynchronous regimes can be rather substantial (Fig. 5A). In contrast, local adaptation remains relatively slight—at the level of 10^{-3} to 10^{-4} when averaged across all demes (Fig. 5B) and at the level of a few percent for an "average" pair of demes (Fig. 5C). [The latter interpretation assumes that the average of the absolute values of pairwise Δ's can be roughly approximated by the standard deviation of Δ's.] These conclusions are true for both species.

MAXIMUM MIGRATION ($m_h = m_p = 1$), HETEROGENEOUS SELECTION

If all individuals come to each deme via a common migrants pool (as in the classical Levene (1953) model), the allele frequencies become the same across all demes in one generation. Therefore the system state is completely characterized just by two dynamic variables: the average frequencies of alleles **A** and **B** in the migrants pool that we denote as h and p. The dynamic equations are

$$h' = \frac{1}{n}\sum_i \frac{h(1-\alpha_i p)}{h(1-\alpha_i p)+g(1-\alpha_i q)}, \tag{17}$$

$$p' = \frac{1}{n}\sum_i \frac{p(1-\beta_i g)}{p(1-\beta_i g)+q(1-\beta_i h)}, \tag{18}$$

where $q = 1 - p$ and $g = 1 - h$. As before, all four monomorphic equilibria are saddle points and the symmetric polymorphic equilibrium is an unstable focus. However, now analytical derivations (see the Appendix) indicate that the system evolves to a stable limit cycle so that in an infinitely large population genetic variation can be protected (see Fig. 6).

For many parameter values, the cycle gets very close to the boundaries of the phase-plane with allele frequencies reaching very low values that from the practical point of view implies the loss of genetic variation. Figure 7 illustrates the effects of parameters on the probability that all allele frequencies stay above a certain threshold (here, arbitrarily set at 10^{-4}) for a relatively long period of time (here, 10^4 generations). The figure shows

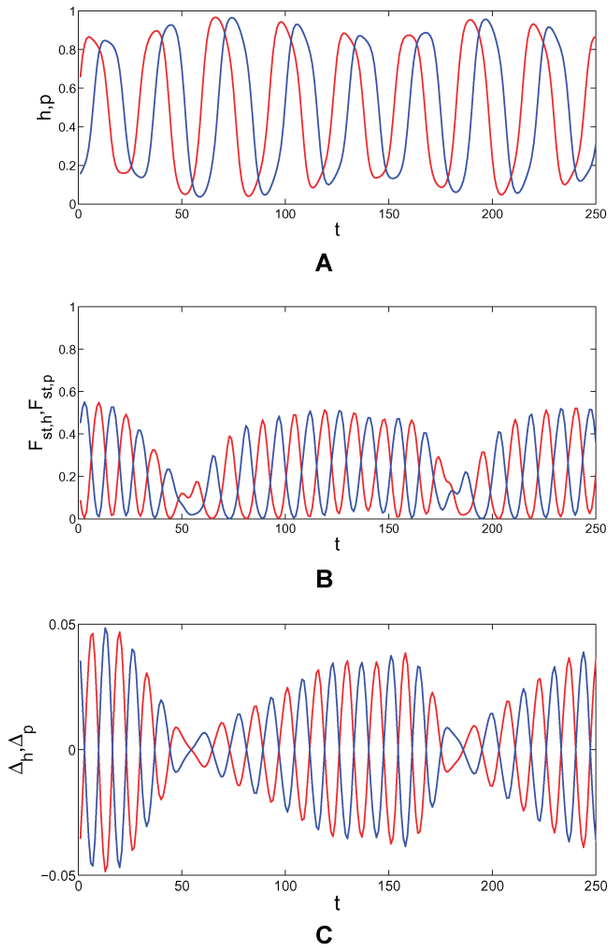

Figure 2. Nonequilibrium dynamics under spatially homogeneous selection. (A) The average allele frequencies. (b) F_{ST} values. (C) The degree of local adaptation Δ. Parameters: $\alpha = \beta = 0.5$, $m_h = m_p = 0.03$, $n = 16$. Red lines, host. Blue lines, parasite. Both F_{ST} and Δ values are computed before selection.

that the most important condition for the maintenance of genetic variation is significant heterogeneity in selection ($\kappa = 0.75$ or 1.00). There is also a slight trend toward increasing the probability of the maintenance of genetic variation with the number of demes n. This trend is probably explained by the fact that with large n the actual range of variation of α's and β's and the range of variation of initial allele frequencies (which are chosen randomly from a uniform distribution) slightly increase. The dark square in the bottom left corner in all graphs is an artifact of the method: with very small values of α's and β's, 10,000 generations of selection is not enough to reduce allele frequencies significantly. In the Appendix we use an analytical method to identify a coefficient ρ predicting the closeness of trajectories of the limit cycle to the axes in terms of selection coefficients.

LIMITED MIGRATION ($m_h < 1$, $m_p < 1$), HETEROGENEOUS SELECTION

When selection is spatially heterogeneous and there are some restrictions on migration, a qualitatively new behavior is possible: genetic variation can be stably maintained at the symmetric polymorphic equilibrium with all allele frequencies at 1/2. Analytical results for the two-deme case show that this stability is most likely at intermediate migration rates (see the Appendix). Our numerical simulations support the generality of this conclusion (Fig. 8). Note that although the symmetric polymorphic equilibrium is always unstable for very small migration rates (on the order of 0.001), the small white areas in the bottom left corner of the graphs are not always visible at the resolution level used.

If the system is at the symmetric polymorphic equilibrium, there is no genetic heterogeneity ($F_{ST} = 0$) and both Δ_h and Δ_p are zero. If however the system does not synchronize, the allele frequencies keep changing in an oscillatory way that can result in substantial F_{ST} values (Fig. 9A). As expected, genetic heterogeneity grows with increasing selection and decreasing migration. The measures of local adaptation Δ_h and Δ_p fluctuate around zero (Fig. 9B), but the magnitude of fluctuations grows with the strength of selection and decreasing migration (Fig. 9C). This implies that at each particular moment of time, the value of Δ for one species can be substantially larger than that for another species.

Discussion

Our motivation in this article was to study both analytically and numerically a relatively simple population-genetic model of host–parasite interactions in a spatially subdivided and heterogeneous environment. Our emphasis was on the conditions for the maintenance of genetic variation, the dynamic patterns observed, the extent of genetic differentiation between different demes, and on how different parameters (such as the strength and heterogeneity in selection, migration rates, and the number of demes) affect the dynamic and static behavior of the system. We also looked at measures of local adaptation that have been the focus of many theoretical studies using similar models. Our overall goal was to extend the scope of recent modeling work (discussed throughout the paper) on various aspects of the geographic mosaic theory of coevolution.

Coevolutionary models necessarily include components specifying genetics, spatial structure, environment, and demography, and a large number of parameters specifying these components. The more realistic the model, the more difficult its analysis. As a consequence, studies of many coevolutionary models typically focus on the effects of only one or two parameters (such as the migration rates) whereas all other parameters remain fixed in numerical simulations and, thus, their influence on the model

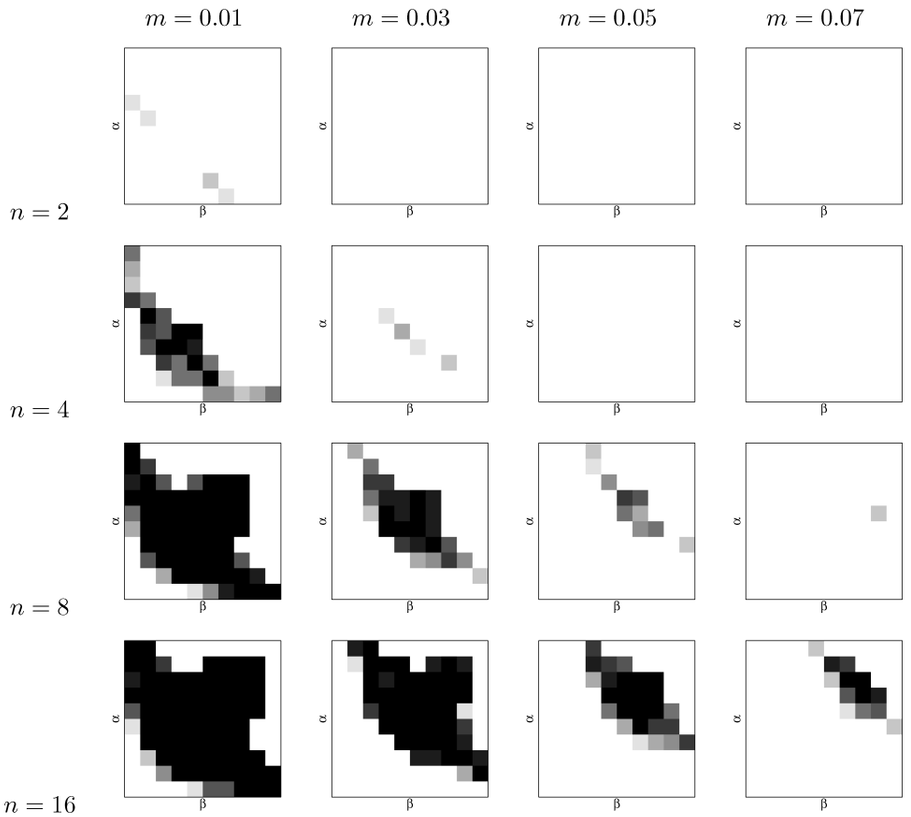

Figure 3. The probability that for randomly chosen initial allele frequencies the system does not synchronize under spatially homogeneous selection for different α and β changing between 0 and 1. Grayscale from zero (white) and one (black). Migration rates equal for host and parasite ($m_h = m_p = m$). First, second, third, and fourth rows are for $n = 2$, 4, 8, and 16 demes, respectively. First, second, third, and fourth columns are for $m = 0.01$, 0.03, 0.05, and 0.07, respectively. Ten runs for each parameter combination with initial conditions chosen randomly and independently from a uniform distribution on [0, 1].

dynamics remain unknown. As a result, the generality of the effects observed cannot be assured even within a particular model with well-defined components. Here, we used a complementary approach: use a simple, idealized model but study it as extensively as possible, with the hope that the intuition we would gain from such an analysis may help to both better understand coevolutionary dynamics and better interpret the results of more complex models.

In the model under consideration, it is known that genetic variation cannot be stably maintained in an isolated deme without mutation (Seger 1988; Gavrilets and Hastings 1998). In a single deme, allele frequencies experience growing oscillations

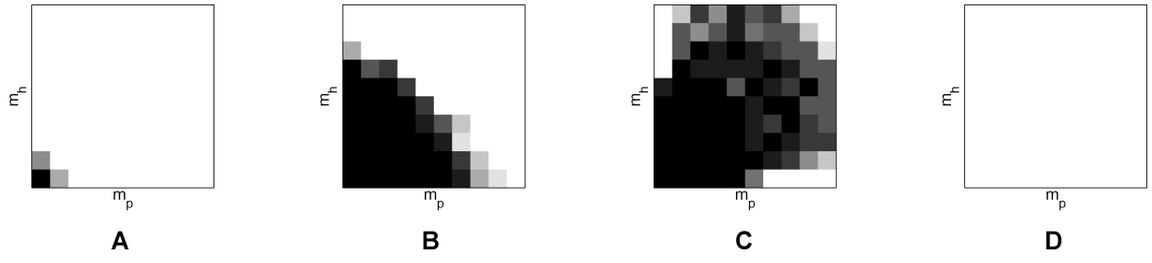

Figure 4. The probability that for randomly chosen initial allele frequencies the system does not synchronize under spatially homogeneous selection for different migration rates m_h and m_p changing between 0 and 0.1. Grayscale from zero (white) and one (black). (A) $\alpha = 0.25$. (B) $\alpha = 0.50$. (C) $\alpha = 0.75$. (D) $\alpha = 1.00$. $n = 16$, $\beta = \alpha$. Ten runs for each parameter combination with initial conditions chosen randomly and independently from a uniform distribution on [0, 1].

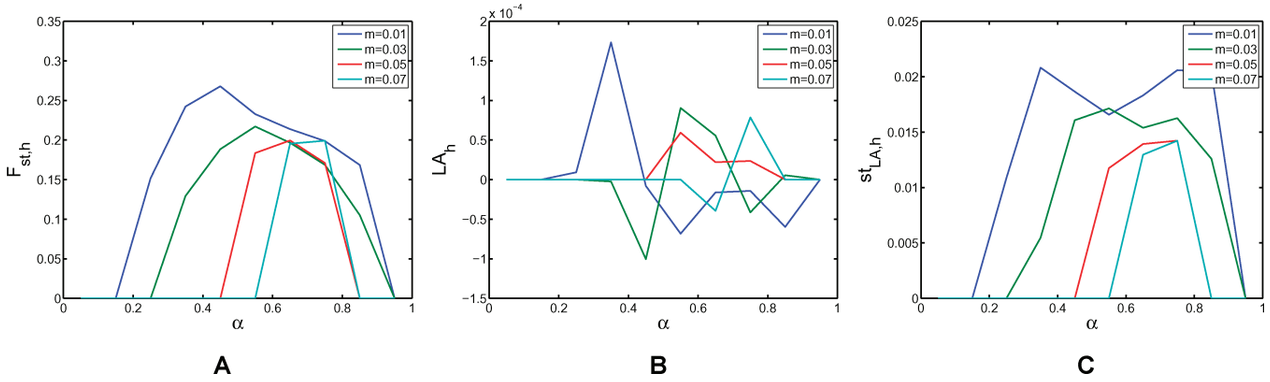

Figure 5. Spatial subdivision and local adaptation of host species under spatially homogeneous selection for different strengths of selection α and migration rates m (equal for both species) with $n = 16$ demes. $\beta = \alpha$. (A) Average F_{ST} values. (B) Average local adaptation Δ. (C) The standard deviation of local adaptation. All values are based on the last 250 generations over the runs resulting in the maintenance of genetic variation. Ten runs for $T = 5000$ generations for each parameter combination. For the parasite, the behavior of the average F_{ST} values and the standard deviation of local adaptation is very similar to those in Figures (A) and (C), whereas that of the average local adaptation is described by a mirror image of Figure (B).

eventually resulting in one allele being fixed in each species. Note that if instead of difference equations we approximated the dynamics by differential equations, the resulting model would predict the existence of neutrally stable cycles (Gavrilets and Hastings 1998). However, in the presence of random genetic drift, genetic variation would still be quickly lost even in a continuous-time model. With mutation genetic variation will be maintained in a dynamic mutation–selection balance cycle (Gavrilets and Hastings 1998).

When considering a subdivided population it is important to distinguish the case in which selection is homogeneous in space from the case in which it is heterogeneous. In the case of host–parasite interactions, where fitnesses of genotypes of one species depend on the frequencies of genotypes of the other species, we must be very clear on what the term homogeneous implies—and what it does not. Here, homogeneous selection means that the selection coefficients, i.e., parameters α_i and β_i of our model, have the same value in all demes. Because fitnesses of genotypes of one species depend on genotype frequencies of the other species and because the latter may vary across space, however, fitnesses of host and parasite genotypes may vary across space even in the case of homogeneous selection. Such heterogeneity in fitness may help to maintain polymorphism and population differentiation as has been observed in simulation studies using more complex stepping-stone systems and/or more complex genetics and/or genetic drift (Gandon et al. 1996; Lively 1999; Gandon and Michalakis 2002). All these factors have been argued to promote the maintenance of genetic variation in host-parasite systems. For example, isolation by distance which is always present in stepping-stone models is known to reduce the homogenizing effect of migration relative to that in island models. Similarly, genetic drift can contribute to maintaining polymorphism by desynchronizing different populations. Polymorphism is also promoted by more complex genetics. For example, Seger (1988) showed that either increasing the number of alleles per locus, or increasing the number of loci involved in the host–parasite recognition may lead to genotype frequency cycling in single population systems that would not sustain polymorphism otherwise (see also Kawecki 1998).

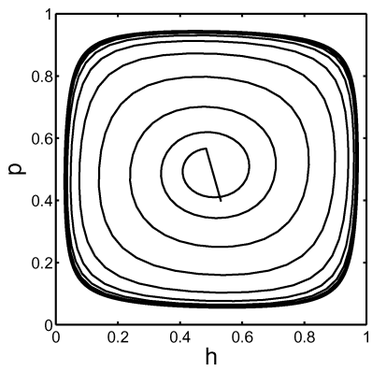

Figure 6. The dynamics with maximum migration. Shown is a single trajectory on the (p, h)-phase plane in a random deme. Parameters: $n = 8$, $\alpha_{max} = \beta_{max} = 0.75$, $\kappa_{min} = \kappa_{min} = 1.0$. The discontinuity in the trajectory corresponds to the change in the first generation. The trajectory spirals counterclockwise.

However, similar behavior, that is the maintenance of genetic variation under spatially homogeneous selection, can be observed in our much simpler island model. This suggests that isolation by distance, genetic drift, and complex genetics are not necessary for the maintenance of variation in host–parasite systems. Our detailed numerical study shows that the maintenance

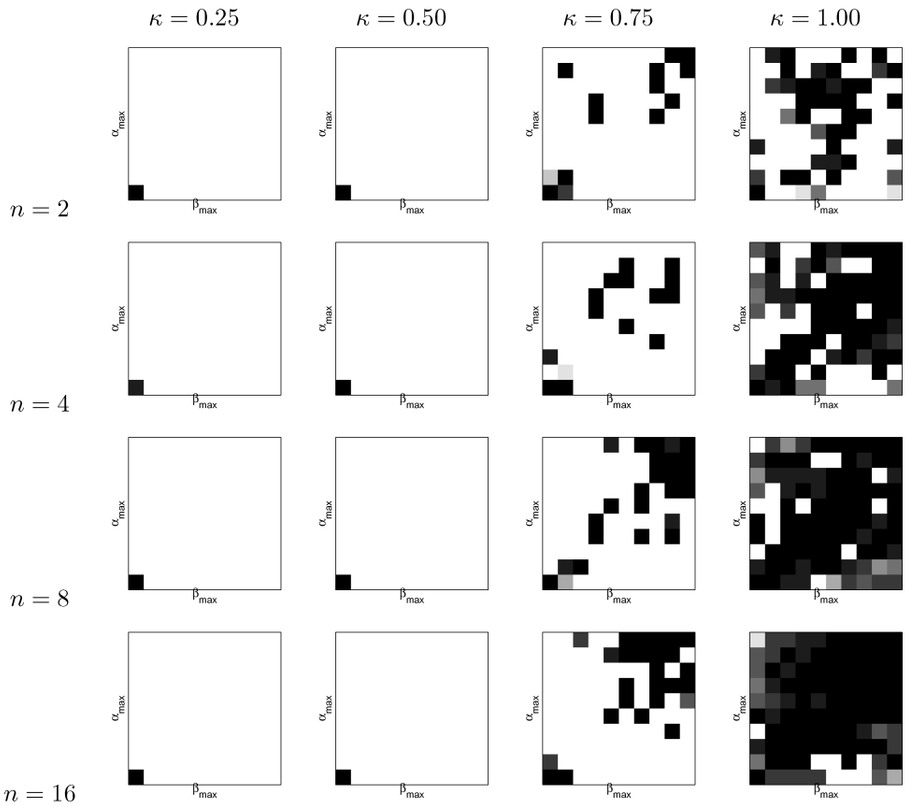

Figure 7. The probability that for randomly chosen initial allele frequencies and randomly chosen coefficients α and β the system maintains genetic variation for 10^4 generations with maximum migration rates. Grayscale from zero (white) and one (black). α_{max} and β_{max} change between 0 and 1. $\alpha_{min} = (1 - \kappa)\,\alpha_{max}$, $\beta_{min} = (1 - \kappa)\,\beta_{max}$ where κ is a parameter measuring heterogeneity in selection. First, second, third, and fourth rows are for $n = 2$, 4, 8, and 16 demes, respectively. First, second, third, and fourth columns are for $\kappa = 0.25$, 0.50, 0.75, and 1.00, respectively. Ten runs for each parameter combination with initial conditions were chosen randomly and independently from a uniform distribution on [0,1].

of genetic variation happens through asynchronous nonlinear dynamics where the majority of demes quickly synchronize but the rest do not. This regime requires substantial initial variation in allele frequencies and is more likely to be observed if migration rates are small, the strength of selection is intermediate, and the number of demes is large. It can result in substantial F_{ST} values but only in relatively low values of the measures of local adaptation Δ_h and Δ_p. If the above requirements are not satisfied, allele frequencies quickly synchronize between different demes, and after that the system exhibits the same behavior as in an isolated deme. That is, genetic polymorphism is not maintained.

Earlier Sasaki et al. (2002) found that a similar asynchronous nonequilibrium behavior can be exhibited by a single deme in a different gene-for-gene haploid model of coevolution in a spatially homogeneous island model. In Sasaki et al. (2002) both the number of demes and migration rates were much higher than used here ($n = 10,000$ and $m_h = m_p = 0.2$, respectively). The fact that genetic variation can be preserved under spatially homogeneous selection if migration is sufficiently small is analogous to that in classical models of constant disruptive selection (Gavrilets (2004), Chap.7). This happens when the corresponding dynamic system allows for multiple attractors within a single deme. [In our case, "attractors" differ in the phase of fluctuations.] Then if different demes start with different allele frequencies they may experience somewhat divergent selection so that in isolation they would evolve to different attractors. If migration is weak relative to selection, it is not able to overcome spatial heterogeneity in selection (induced by initial differentiation in allele frequencies) and genetic differentiation will be preserved. With isolation by distance (e.g., as present in stepping-stone models), asynchronous fluctuations can result in rather interesting dynamic spatial patterns (Sasaki et al., 2002). We note that stable maintenance of variation under spatially homogeneous selection was not observed in Nuismer et al., (2000) who used a stepping-stone system. The reason for this is probably that selection was weak in their simulations.

We note that in general nonequilibrium dynamics are not required for the maintenance of spatial structure in genotype

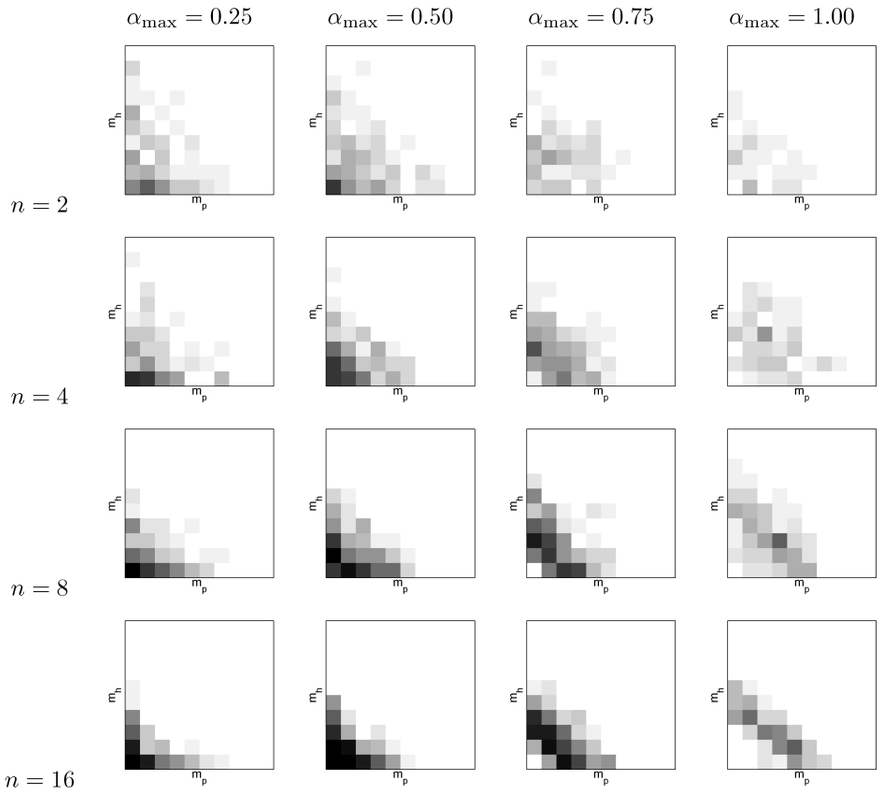

Figure 8. The probability that for randomly chosen coefficients α and β the symmetric polymorphic equilibrium is locally stable with spatially heterogeneous selection and limited migration. Grayscale from zero (white) and one (black). m_p and m_h change between 0.0 and 0.1. First, second, third, and fourth columns are for $\alpha_{max} = 0.25$, 0.50, 0.75, and 1.00, respectively. First, second, third, and fourth rows are for $n = 2$, 4, 8, and 16, respectively. Maximum heterogeneity in selection ($\kappa = 1$), $\beta_{max} = \alpha_{max}$. Twenty runs with randomly chosen α and β and initial conditions for each parameter combination.

frequencies under spatially homogeneous selection. The same can happen when the system evolves to a migration-selection equilibrium. For example, spatial structure will be maintained in the diploid version of the matching allele model studied by Nuismer (2006). This model is characterized by strong underdominance in the host population. Therefore if initially different demes are close to fixation of alternative alleles and migration is small enough, genetic differentiation will be preserved in the same

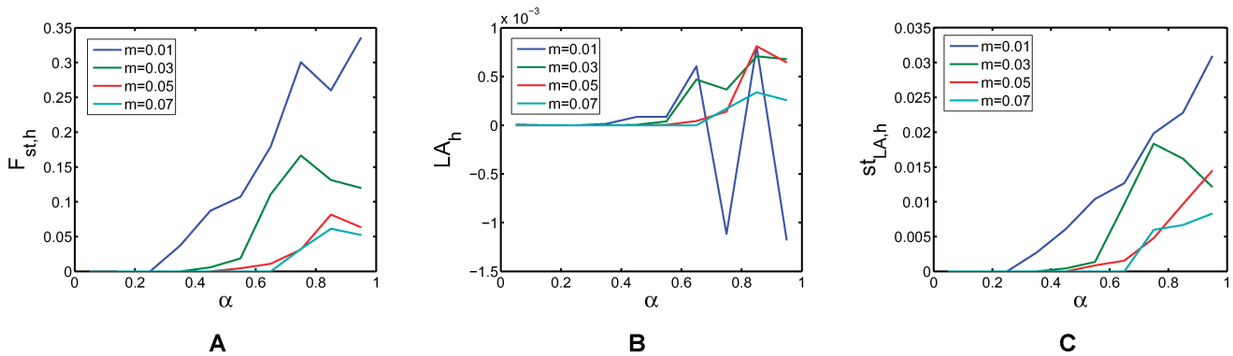

Figure 9. Spatial subdivision and local adaptation of the host species under spatially heterogeneous selection for different strengths of selection α_{max} and migration rates m (equal for both species) with $n = 16$ demes. Maximum heterogeneity in selection ($\kappa = 1$), $\beta_{max} = \alpha_{max}$. (A) Average F_{ST} values. (B) Average local adaptation. (C) The standard deviation of local adaptation. All values are based on the last 250 generations over the runs resulting in the maintenance of genetic variation. Ten runs for $T = 5000$ generations for each parameter combination. The corresponding graphs for the parasite species look similar.

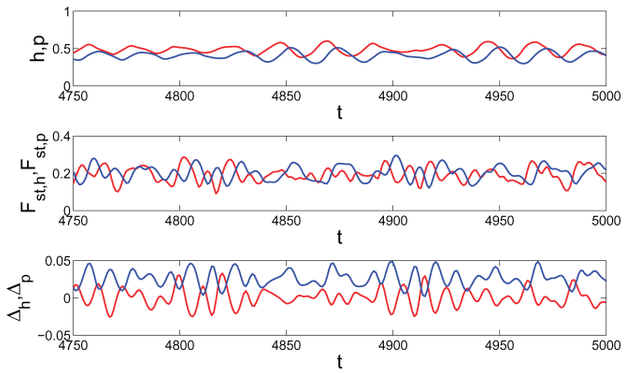

Figure 10. **The dynamics of the average allele frequencies, F_{ST}'s and the measures of local adaptation in the asymetric model (11). Blue lines: parasite, red lines: host. Parameters ζ's and ξ's were chosen randomly and independently from a uniform distribution on [− 0.1, 0.1]. Other parameters: $n = 16$, $m_h = 0.01$, $m_p = 0.05$, $\alpha_{max} = \beta_{max} = 0.75$, $\kappa = 1.00$.**

way as in models of underdominant selection (Svirezhev 1968; Karlin and McGregor 1972; Gavrilets 2004, Chap.7). This shows that Nuismer's (2006) conclusion that spatially heterogeneous selection "is required for spatial structuring of allele frequencies to be maintained indefinitely" (p.26) is justified only within the weak-selection strong-migration approximation he used.

Spatially heterogeneous selection can maintain genetic variation even if migration rates are maximal. This happens in an oscillatory way with allele frequencies periodically reaching low values. Genetic variation is most likely to be maintained at high levels relatively long if the heterogeneity in selection is large. Increasing the number of demes and the strength of selection both promote the maintenance of variation however the effect of these two factors is relatively small.

If selection is spatially heterogeneous and there are some restrictions on migration, a different type of behavior is possible: the maintenance of genetic variation at a stable equilibrium with all allele frequencies at 1/2. This kind of behavior, which was already observed by Nuismer et al. (2000) in a similar stepping-stone model, is most likely at intermediate migration rates.

The reason why intermediate migration rates are required for the stable maintenance of genetic variation is as follows. If migration rates are very high, different demes synchronize and the system evolves in a cyclic way (as illustrated in Fig. 6). If migration rates are very low, each deme evolves largely independently exhibiting the tendency to approach the boundaries of the unit square in a cyclical way as illustrated in Figure 1. The effects of low migration are felt only when an allele frequency approaches 0 or 1 very closely. Then migration will only result in the allele frequency moving slightly toward 1/2 which would maintain cycling but no stabilization at 1/2 will be observed.

Overall, spatial heterogeneity of the environment (translated in a spatial heterogeneity of selection coefficients) dramatically affects the evolutionary dynamics by greatly simplifying the maintenance of genetic variation and amplifying genetic differentiation. These effects are observed even in the island model studied here that lacks isolation by distance. The influence of spatial heterogeneity on the maintenance of genetic variation is much stronger than in the classical Levene (1953) model in which fitnesses are spatially variable but not frequency dependent. The effect of spatial heterogeneity is expected to be even greater if isolation by distance is present (as observed in Nuismer et al. 2000). The overall behavior is also affected by other parameters (the number of sites, strength of selection, and migration rates) as discussed above.

Our model does not show any substantial levels of local adaptation measures Δ_h and Δ_p. Although the differences in fitness that an individual would have if placed in any two unsynchronized demes can be very large, when averaged across time and space, these differences (as measured by Δ_h and Δ_p) are very low (Figs. 5B and 9B). Further, although previous theoretical models (e.g., Gandon et al. 1996; Lively 1999; Gandon and Michalakis 2002; Gandon 2002) and reviews of empirical work (e.g. Greischar and Koskella 2007; Hoeksema and Forde 2008) found that parasite local adaptation was present when parasites had greater migration rates than their hosts, we never observed such outcomes consistently over time.

Several reasons explain why the measures of local adaptation can be small despite the large F_{ST} values. The first two are structural: F_{ST} is a normalized variance, although as equation (9) shows the local adaptation measures we used correspond to unnormalized covariances, and covariances are always smaller than the corresponding variances. Additionally, F_{ST} is not sensitive to different demes being synchronized. For example, if nine demes have allele frequency 0 and one deme has allele frequency 1, $F_{ST} = 1$, but the measures of local adaptation will obviously be small. These reasons however do not completely explain why Δ_h and Δ_p in our model are that close to zero as we observe. The small local adaptation measures in our model also result from the fact that F_{ST} values of the two species are often out of synchrony: when F_{ST} is large among host populations, it is negligible among parasite populations, and vice versa (see Fig. 2B). The fact that genotype frequencies of the antagonist species are similar across space leads to low local adaptation measures. For example, if we measure local adaptation when F_{ST} is large for hosts but almost zero for parasites, then any given host population will have very similar mean fitness against its sympatric parasite population as against allopatric parasite populations. Finally, the symmetric nature of our model severely limits the behavior of the local adaptation measures we use. In our model, the allele frequencies either stabilize at 1/2 in all demes (so that no local

adaptation is possible at all) or fluctuate around 1/2 so that the averages over time are very close to 1/2 for all demes. As a result, not much local adaptation on average is possible.

The symmetry around 1/2 can be broken by straightforward generalizations of the model. For example, we can assume that different genotypes have different maximum fitness in different demes. A simple way to account for this would be to assume that fitnesses of **A** and **a** instead of being given by equation (1a) are

$$w_{A,i} = 1 + \zeta_i - \alpha_i p_i, \quad w_{a,i} = 1 - \alpha_i(1 - p_i), \qquad (19)$$

$$w_{B,i} = 1 + \xi_i - \beta_i(1 - h_i), \quad w_{b,i} = 1 - \beta_i h_i, \qquad (20)$$

where ζ_i and ξ_i varies across demes. Such a behavior will increase genetic differentiation and is expected to result in more local adaptation. The few runs of this more complex model that we have performed support this intuition (see Fig. 10). In particular, we observed an increase in local adaptation in parasites if their migration rate is significantly higher than that of hosts, which is what is expected from both theoretical (Gandon et al. 1996; Lively 1999; Gandon and Michalakis 2002; Gandon 2002) and empirical perspectives (Greischar and Koskella 2007; Hoeksema and Forde 2008).

Despite the fact that in our symmetric model overall we find very low levels of local adaptation, our analysis indicates that spatial heterogeneity in selection coefficients yields much larger local adaptation values than those observed under homogeneous selection (the Δ_h axis in Fig. 9B is an order of magnitude larger than in Fig. 5B). This is compatible with the results reported by Nuismer (2006) and Nuismer et al. (2000) and with the discussions on the possible effects of spatial variation in selection coefficients and/or the effects of variation in the abiotic environment by Hochberg and van Baalen (1998), Hochberg et al. (2000), Kawecki and Ebert (2004), and Nuismer and Gandon (2008) (this last reference provides a very thorough discussion on the issue). The fact that the strength and outcome of host–parasite interactions is variable, depending on host and parasite genotypes but also on abiotic environmental conditions, has been established in so many cases that it is impossible to cite them all and seems unfair to single out any. Nevertheless, it is striking to see that, to our best knowledge, none of the empirical local adaptation studies conducted so far on natural systems has taken variability of selection coefficients or abiotic environment explicitly into account and we are aware only of a single experimental study in which the effect of abiotic variation has been addressed (Forde et al. 2004). There is a clear need for empirical studies addressing these issues. Our model, along with Nuismer (2006) and Nuismer et al. (2000), predicts that there should be higher levels of local adaptation in systems with spatially heterogeneous selection coefficients than when these coefficients are similar across space. Further theoretical work is needed to elaborate predictions on the effects of abiotic variation on local adaptation patterns.

Our fitness model (given by eq. 1) includes a modified "matching allele model" (Nee 1989; Frank 1991a,b, 1994; Gandon et al. 1996; Gandon 2002) as a special case. The latter assumes that each host is fully susceptible to its complementary parasite but confers resistance against the other parasite genotype such that infection occurs with a probability s. The parameter s ($0 \leq s \leq 1$) measures parasite specificity. When $s = 0$, there is no specificity and each host type is equally susceptible to both parasite types. When $s = 1$, each parasite can only infect its complementary host (as in the classical "matching allele model"; Agrawal and Lively 2002; Nuismer 2006). The other parameter of the model is parasite virulence, v ($0 \leq v \leq 1$), measuring the deleterious effect of parasites on the fitness of infected hosts. Parameters α and β of our model are related to parameters s and v of the modified matching allele model via the relationships

$$\alpha = \frac{sv}{1 - v(1 - s)}, \beta = s. \qquad (21)$$

That is, β is identical to "virulence" whereas α depends on both "specificity" and "virulence." Gandon (2002) analyzed a spatially homogeneous version of the modified matching allele model. Rather than studying the multideme system explicitly, he modeled the dynamics of a single deme assuming that the average allele frequencies in the metapopulation are all equal to one half, and that therefore the allele frequencies in migrants are all equal to one half as well. Our model shows that under spatially homogeneous selection either the allele frequencies synchronize and genetic variation is quickly lost or the system as a whole goes through cycles in which the average allele frequencies in the whole population and among migrants cycle. The average allele frequencies are very rarely at one half, and indeed never for both species at the same time (e.g. see Fig. 2A). Therefore, the main assumption of Gandon's approach is never satisfied. Gandon (2002) argues however that his approximations provide an accurate description of local adaptation if additional factors maintaining spatial asynchrony (such as random genetic drift and isolation by distance) are introduced in the model.

Frequency-dependent selection within a single species is well known for the ability to maintain genetic variation under relatively broad conditions (Cockerham et al. 1972; Asmussen and Basnayake 1990; Trotter and Spencer 2007). Frequency-dependent selection can also easily produce nonlinear dynamics including classical cycle and chaos (Altenberg 1991; Yi et al. 1999) and more exotic behaviors like intermittency and transient chaos (Gavrilets and Hastings 1995). Frequency-dependent selection resulting from between-species interactions has been shown to be able to both maintain genetic variation and result in nonequilibrium dynamics (Seger 1988; Kawecki 1998).

Our haploid multideme model, fits this general pattern in that nonequilibrium dynamics are common. We note that in a related single-deme model of a diploid population with multiple loci and nonequal allelic effects, cycling and chaos were observed readily (Kopp and Gavrilets 2006). In the model studied here, the period of cycling is at least on the order of a few dozen generations, which will make it difficult to identify empirically.

The question to what extent our results generalize to more complex genetic systems (e.g., diploid, multilocus, and multiallele) subject to the influence of additional factors present in natural systems (e.g., mutation, genetic drift, and isolation by distance) is a very important one. Unfortunately given the inherent complexity of the coevolutionary process in the spatially explicit and environmentally heterogeneous context, to answer this question one needs either to have solid theoretical results or to use verbal arguments. We do not have the former and are skeptical about the utility of the latter. Therefore answering this question is delegated to future work.

Our findings support the major claim of the geographic mosaic theory (Thompson 2005) that the true dynamics of coevolution in real populations, and the persistence of interactions over long periods of time, cannot be understood without explicit consideration of spatial structuring of natural populations and heterogeneity in their environment. Our results should provide a firm basis for analyzing and interpreting more complex and realistic models of victim–exploiter interactions, in particular by allowing to evaluate the effects of specific factors such as the strength of selection, heterogeneity of selection, complexity of the genetic system, or the importance of drift.

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Appendix

THE DERIVATION OF EQUATION (8).

Let $g_i = 1 - h_i$ and $q_i = 1 - p_i$. For a randomly chosen host from deme i, its fitness in deme i is

$$\bar{w}_{h,i\to i} = h_i w_{A,i} + g_i w_{a,i},$$

its fitness in deme j is

$$\bar{w}_{h,i\to j} = h_i w_{A,j} + g_i w_{a,j},$$

and the difference between its fitness in deme i and in deme j is

$$\Delta_{h,i\to j} = h_i(w_{A,i} - w_{A,j}) + g_i(w_{a,i} - w_{a,j}).$$

For a randomly chosen host from deme i, the difference between its fitness in deme i and in a randomly chosen different deme is

$$\Delta_{h,i\to\text{away}} = h_i\left(w_{A,i} - \frac{\sum_{j\neq i} w_{A,j}}{n-1}\right) + g_i\left(w_{a,i} - \frac{\sum_{j\neq i} w_{a,j}}{n-1}\right)$$
$$= \frac{n}{n-1}[h_i(w_{A,i} - \bar{w}_A) + g_i(w_{a,i} - \bar{w}_a)],$$

where $\bar{w}_A = \sum_{i=1}^{n} w_{A,i}/n$ and $\bar{w}_a = \sum_{i=1}^{n} w_{a,i}/n$ are the average fitnesses of host alleles across demes at this generation. Finally, the expectation of $\Delta_{h,i\to}$ away across all i, which is the degree of local adaptation of a randomly chosen host from a randomly chosen deme, is

$$\Delta_h = \frac{n}{n-1}\left[\text{cov}(h_i, w_{A,i}) + \text{cov}(g_i, w_{a,i})\right].$$

In a similar way, the expectation of the degree of local adaptation of a randomly chosen parasite from a randomly chosen deme is

$$\Delta_p = \frac{n}{n-1}\left[\text{cov}(p_i, w_{B,i}) + \text{cov}(q_i, w_{b,i})\right].$$

The equations in the main text follow immediately because cov $(g_i, .) = -$ cov $(h_i, .)$ and cov $(q_i, .) = -$ cov $(p_i, .)$.

NO MIGRATION ($m_h = m_p = 0$)

This case is the same as if there is a single deme. There are four monomorphic equilibria and a single doubly polymorphic equilibrium.

The four monomorphic equilibria are saddles. For the monomorphic equilibria (0,0) and (1,1) the eigenvalues are

$$\lambda_1 = \frac{1}{1-\alpha} > 1, \lambda_2 = 1 - \beta < 1. \quad \text{(A1)}$$

For the monomorphic equilibria (1,0) and (0,1) the eigenvalues are

$$\lambda_1 = 1 - \alpha < 1, \lambda_2 = \frac{1}{1-\beta} > 1. \quad \text{(A2)}$$

For the polymorphic equilibrium (1/2,1/2) the characteristic equation is

$$\lambda^2 - 2\lambda + 1 + AB = 0,$$

where $A = \alpha/(2 - \alpha) > 0$ and $B = \beta/(2 - \beta) > 0$. The roots are $\lambda_{1,2} = 1 \mp \sqrt{-AB}$. Therefore, the roots are complex and with modules $|\lambda_{1,2}| = \sqrt{1 + AB} > 1$. Thus, this equilibrium is an unstable focus.

Numerical simulations suggest that the only dynamics are the cyclical evolution toward the boundaries accompanied by a quick loss of genetic variation.

TWO DEMES WITH SPATIALLY HOMOGENEOUS SELECTION ($\alpha_1 = \alpha_2 = \alpha$, $\beta_1 = \beta_2 = \beta$)

For the monomorphic equilibria ($h_1 = h_2 = 1, p_1 = p_2 = 1$) and ($h_1 = h_2 = 0, p_1 = p_2 = 0$), the eigenvalues are

$$1 - \beta < 1, (1 - m_p)(1 - \beta) < 1, \frac{1}{1 - \alpha} > 1, \frac{1 - m_h}{1 - \alpha}.$$

For the monomorphic equilibria ($h_1 = h_2 = 1, p_1 = p_2 = 0$) and ($h_1 = h_2 = 0, p_1 = p_2 = 1$), the eigenvalues are

$$1 - \alpha < 1, (1 - m_h)(1 - \alpha) < 1, \frac{1}{1 - \beta} > 1, \frac{1 - m_p}{1 - \beta}.$$

Note that the fourth eigenvalues can be smaller or large than one depending on the the levels of migration. This suggests that some change in the dynamics might happen as the relative values m_h/α or m_p/β cross one. Numerical simulations did not show this though.

Polymorphic equilibrium (1/2,1/2,1/2,1/2). Two eigenvalues satisfy a quadratic

$$\lambda^2 - 2\lambda + 1 + AB = 0.$$

These eigenvalues are complex: $\lambda = 1 \mp \sqrt{-AB}$, and have the modules larger than one. Therefore, the equilibrium is always unstable.

Two other eigenvalues satisfy a quadratic

$$\lambda^2 - 2\left(1 - \frac{m_h + m_p}{2}\right)\lambda + (1 - m_h)(1 - m_p)(1 + AB) = 0.$$

These eigenvalues are real (and, thus, are necessarily between 0 and 1) if

$$\frac{(m_p - m_h)^2}{(1 - m_h)(1 - m_p)} > 4AB.$$

The above condition assumes that the migration rates are different: $m_p \neq m_h$. If the migration rates are the same ($m_h = m_p = m$), the eigenvalues are $(1 - m)(1 \mp \sqrt{-AB})$.

MAXIMUM POSSIBLE MIGRATION ($m_h = m_p = 1$), ARBITRARY NUMBER OF DEMES

After one generation the allele frequencies become the same across all demes (as in the Levene model). Therefore the system state is completely characterized just by two dynamic variables: h and p. The dynamics are described by equation (10) of the main text. There are four monomorphic equilibria which all are saddle points. For the equilibria (1,1) and (0,0) the eigenvalues are

$$\mu_1 = \frac{1}{n}\sum(1 - \beta_i) < 1, \lambda_1 = \frac{1}{n}\sum\frac{1}{1 - \alpha_i} > 1. \quad \text{(A3)}$$

For the equilibria (1,0) and (0,1) the eigenvalues are

$$\mu_2 = \frac{1}{n}\sum(1 - \alpha_i) < 1, \lambda_2 = \frac{1}{n}\sum\frac{1}{1 - \beta_i} > 1. \quad \text{(A4)}$$

The polymorphic equilibrium (1/2,1/2) has two complex eigenvalues

$$\lambda_{1,2} = 1 \mp \sqrt{-\bar{A}\bar{B}},$$

where $\bar{A} = \sum A_i/n$, $A_i = \alpha_i/(2 - \alpha_i)$, $\bar{B} = \sum B_i/n$, $B_i = \beta_i/(2 - \beta_i)$. Thus, this equilibrium is always an unstable focus.

There also exists a heteroclinic cycle, that is a cycle comprised by saddle trajectories. Adapting the derivations in Hofbauer and Sigmund (1998) for the case of difference equations, the stability of a simple heteroclinic cycle is controlled by the coefficient

$$\rho = \Pi_j\left(\frac{\ln \mu_j^{-1}}{\ln \lambda_j}\right), \quad \text{(A5)}$$

where $\mu_j < 1$ and $\lambda_j > 1$ are the eigenvalues corresponding to "incoming" and "outcoming directions" for the jth saddle point. The cycle is locally stable if $\rho > 1$ and is unstable if $\rho < 1$. The smaller ρ, the more "repelling" the cycle. Because for any random variable x with expectation $E\{x\}$,

$$\frac{1}{1 - E\{x\}} \leq E\left\{\frac{1}{1 - x}\right\},$$

$\mu_1^{-1} \leq \lambda_2$ and $\mu_2^{-1} \leq \lambda_1$ with equality only when selection is homogeneous. Therefore, if selection is heterogeneous, $\rho < 1$ always, the heteroclinic cycle is unstable, the allele frequencies are pushed from the boundaries, and genetic variation is protected.

ARBITRARY MIGRATION

In derivations below, we will use the following notation and observations. Consider a quadratic equation $\lambda^2 - 2\lambda X + Y = 0$ where $X, Y > 0$. Its roots are $X \mp \sqrt{X^2 - Y}$. Assume that $X^2 > Y$ so that the roots are real. Both roots are between 0 and 1 if $X < 1$ and $1 - 2X + Y > 0$. Both roots are larger than 1 if $X > 1$ and $1 - 2X + Y > 0$. One root is larger than 1 and another is smaller than 1 if $1 - 2X + Y < 0$.

Monomorphic equilibria

There are four monomorphic equilibria and the corresponding eigenvalues all must be real. Consider first the monomorphic equilibria (1,1,1,1) and (0,0,0,0). There are two eigenvalues that satisfy a quadratic

$$\lambda^2 - 2\lambda\left(1-\frac{m_p}{2}\right)\left(1-\frac{\beta_1+\beta_2}{2}\right) + (1-m_p)(1-\beta_1)(1-\beta_2) = 0$$

Both these eigenvalues are always between 0 and 1 (because $X < 1$ and $1 - 2X + Y > 0$).

Two other eigenvalues satisfy a quadratic

$$\lambda^2 - 2\lambda\frac{\left(1-\frac{m_h}{2}\right)\left(1-\frac{\alpha_1+\alpha_2}{2}\right)}{(1-\alpha_1)(1-\alpha_2)} + \frac{1-m_h}{(1-\alpha_1)(1-\alpha_2)} = 0.$$

Here, $X > 1$, if

$$m_h < \frac{\alpha_1+\alpha_2-2\alpha_1\alpha_2}{1-\frac{1}{2}(\alpha_1+\alpha_2)}, \tag{A6}$$

and $1 - 2X + Y > 0$, if

$$m_h < \frac{2\alpha_1\alpha_2}{\alpha_1+\alpha_2}. \tag{A7}$$

From this, one can show that if condition (17) is satisfied, then both roots are larger than one. Otherwise, one root is larger than one and another root is smaller than one. For the equilibria (1,0,1,0) and (0,1,0,1) two eigenvalues satisfy a quadratic

$$\lambda^2 - 2\lambda\left(1-\frac{m_h}{2}\right)\left(1-\frac{\alpha_1+\alpha_2}{2}\right) + (1-m_h)(1-\alpha_1)(1-\alpha_2) = 0.$$

Both these eigenvalues are smaller than one. Two other equilibria satisfy

$$\lambda^2 - 2\lambda\frac{\left(1-\frac{m_p}{2}\right)\left(1-\frac{\beta_1+\beta_2}{2}\right)}{(1-\beta_1)(1-\beta_2)} + \frac{1-m_p}{(1-\beta_1)(1-\beta_2)} = 0.$$

Now both eigenvalues are larger than one if $m_p < \frac{2\beta_1\beta_2}{\beta_1+\beta_2}$. One eigenvalue is larger and one is smaller than one if the above inequality is not satisfied. These results suggest that some changes in the dynamics might happen as the relative values of $m_h/\frac{2\alpha_1\alpha_2}{\alpha_1+\alpha_2}$ or $m_p/\frac{2\beta_1\beta_2}{\beta_1+\beta_2}$ cross one.

Symmetric polymorphic equilibrium ($h_i = p_i = 1/2$ for all $i = 1, 2$)

Numerical simulations suggest this is the only polymorphic equilibrium that can be stable. Stability matrix has the following form:

$$S = \frac{1}{2}\begin{pmatrix} 1-m_h/2 & -A_1(1-m_h/2) & m_h/2 & -A_2m_h/2, \\ B_1(1-m_p/2) & 1-m_p/2 & B_2m_p/2 & m_p/2, \\ m_h/2 & -A_1m_h/2 & 1-m_h/2 & -A_2(1-m_h/2), \\ B_1m_p/2 & m_p/2 & B_2(1-m_p/2) & 1-m_p/2, \end{pmatrix} \tag{A8}$$

where $A_i = \alpha_i/(2-\alpha_i)$, $B_i = \beta_i/(2-\beta_i)$.

The eigenvalues of S controlling the conditions for stability are given by the roots of a fourth-order polynomial:

$$R = c_4\lambda^4 + c_3\lambda^3 + c_2\lambda^2 + c_1\lambda + c_0, \tag{A9}$$

where

$$c_4 = 1, \tag{A10}$$

$$c_3 = -(2 + \tilde{m}_p + \tilde{m}_h), \tag{A11}$$

$$c_2 = \left[1 + \frac{(A_1+A_2)(B_1+B_2)}{4}\right](1 + \tilde{m}_h\tilde{m}_p) \tag{A12}$$

$$+ \left[2 + \frac{(A_1-A_2)(B_1-B_2)}{4}\right](\tilde{m}_h + \tilde{m}_p), \tag{A13}$$

$$c_1 = -\left(1 + \frac{A_1B_1 + A_2B_2}{2}\right)(\tilde{m}_h + \tilde{m}_p + 2\tilde{m}_h\tilde{m}_p), \tag{A14}$$

$$c_0 = (1 + A_1B_1)(1 + A_2B_2)\tilde{m}_h\tilde{m}_p. \tag{A15}$$

with $\tilde{m}_h = 1 - m_h$, $\tilde{m}_p = 1 - m_p$. Let $\lambda = (1+\mu)/(1-\mu)$.

Then μ satisfies a polynomial

$$T = C_4\mu^4 + C_3\mu^3 + C_2\mu^2 + C_1\mu + C_0,$$

where

$$C_4 = c_0 - c_1 + c_2 - c_3 + c_4, \tag{A16}$$

$$C_3 = -4c_0 + 2c_1 - 2c_3 + 4c_4, \tag{A17}$$

$$C_2 = 6c_0 - 2c_2 + 6c_4, \tag{A18}$$

$$C_1 = -4c_0 - 2c_1 + 2c_3 + 4c_4, \tag{A19}$$

$$C_0 = c_0 + c_1 + c_2 + c_3 + c_4. \tag{A20}$$

According to the Liénard-Chipart version of the Routh-Hurwitz criterion, the roots of the polynomial T have negative real parts if and only if

$$C_0, C_1, C_3, C_4 > 0, \tag{A21}$$

$$\Delta_3 \equiv C_1C_2C_3 - C_0C_3^2 - C_1^2C_4 > 0. \qquad \text{(A22)}$$

If all μ's have negative real parts, then all λ's lie within a unit circle of the origin in the complex plane. Thus, inequalities (22) give the conditions for stability of the symmetric polymorphic equilibrium.

Let $s_1 = A_1B_1$, $s_2 = A_2B_2$, $\bar{A} = (A_1 + A_2)/2$, and $\bar{B} = (B_1 + B_2)/2$. Let migration rates be equal, i.e. $m_p = m_h = m$ and $\tilde{m} = 1 - m$. Performing straightforward calculations,

$$C_0 = \tilde{m}^2 s_1 s_2 + (1 - \tilde{m})^2 \bar{A}\bar{B} > 0$$

and

$$C_4 = \tilde{m}^2 s_1 s_2 + (1 - \tilde{m})^2 \bar{A}\bar{B} + 4(1 + \tilde{m})^2 + 2\tilde{m}(1 + \tilde{m})(s_1 + s_2) > 0.$$

Proceeding further,

$$C_1 = 2\tilde{m}(1 - \tilde{m})(s_1 + s_2) - 4\tilde{m}^2 s_1 s_2,$$

and is positive if

$$m > \frac{2s_1s_2}{s_1 + s_2 + 2s_1s_2}. \qquad \text{(A23)}$$

In a similar way,

$$C_3 = 8 - 2\tilde{m}(s_1 + s_2) - 2\tilde{m}^2(4 + 3s_1 + 3s_2 + 2s_1s_2).$$

Solving this quadratic for $\tilde{m}$, one finds that $C_3 > 0$ if

$$m > m_l \equiv 1 - \frac{1}{2}\frac{\sqrt{(s_1 + s_2)^2 + 16(4 + 3s_1 + 3s_2 + 2s_1s_2)} - (s_1 + s_2)}{4 + 3s_1 + 3s_2 + 2s_1s_2}. \qquad \text{(A24)}$$

If the above condition is satisfied, condition (23) is satisfied as well. That is, the migration rate must be higher than a threshold m_l. Note that $0 \le m_l \le 0.5$ and that stronger selection requires stronger migration.

Finally,

$$\Delta_3 = 64\tilde{m}[1 - \tilde{m}(1 + s_1)][1 - \tilde{m}(1 + s_2)] \times \left[3(1 + s_1)(1 + s_2)(s_1 + s_2 + s_1s_2)\tilde{m}^3 - (s_1 + s_2 + 2s_1s_2)\tilde{m}^2 - (s_1 + s_2 + 3s_1s_2)\tilde{m} + s_1 + s_2\right] - 64(1 - \tilde{m})^2[1 - \tilde{m}^2(1 + s_1)(1 + s_2)]^2\bar{A}\bar{B} \qquad \text{(A25)}$$

It can be shown that if condition (23) is satisfied then each of the factors of the first term is positive.

Let us consider a few special cases.

(1) If $\tilde{m} \to 0$ (or, equivalently, $m \to 1$), $\Delta_3 \to -64\bar{A}\bar{B}$. Therefore, the symmetric polymorphic equilibrium can be stable only for intermediate migration rates.

(2) Let $s_1 = s_2 = s$. Note that in this case $A_1/A_2 = B_2/B_1$ and thus $\delta < 0$. Then Δ_3 can be written as

$$\Delta_3 = (1 - \tilde{m})^2[1 + \tilde{m}(1 + s)]^2\delta - 4s[1 - \tilde{m}^2(1 + s)][(1 - \tilde{m})^2 + s\tilde{m}[2 + 2\tilde{m} + s\tilde{m})].$$

This shows that Δ_3 cannot be positive in this case.

(3) Assume that selection is weak so that $A_i = \sqrt{\varepsilon}a_i$, $B_i = \sqrt{\varepsilon}b_i$, where var *epsilon* $\ll 1$. Then

$$\Delta_3 = 64(1 + \tilde{m})(1 - \tilde{m})^4[\tilde{m}(\overline{AB} + \delta) - \bar{A}\bar{B}] + o(\varepsilon),$$

where $\overline{AB} = (A_1B_1 + A_2B_2)/2$ and $\delta = (A_1 - A_2)(B_1 - B_2)/4$. Note that $\delta = \overline{AB} - \bar{A}\bar{B}$ and, thus, has the meaning of covariance. First, assume that $\overline{AB} + \delta > 0$. Then $\Delta_3 > 0$ if

$$m < m_u \equiv \frac{2\delta}{\overline{AB} + \delta}. \qquad \text{(A26)}$$

Note that in this case stability requires that $\delta > 0$. Then, assume that $\overline{AB} + \delta < 0$ that requires $\delta < 0$. Now $\Delta_3 > 0$ if $m > 2\delta/(\overline{AB} + \delta)$ which however is not possible because with negative δ the expression in the right-hand side of the last inequality is larger than two. Therefore, if selection is weak, the necessary conditions for stability are $\delta > 0$ and $m < m_u$. Notice that increasing spatial heterogeneity (characterized by δ) widens the conditions for stability of the symmetric polymorphic equilibrium.

(4) Assume that migration is weak (i.e., $m \ll 1$). Then there are two critical migration rates (which can be found explicitly but are rather cumbersome), $m_1 = m_1(s_1, s_2)$ and $m_2 = m_2(s_1, s - 2, \delta)$ such that $\Delta_3 > 0$ for $m < m_1$ and $m > m_2$ but $\Delta_3 < 0$ for $m_1 < m < m_2$. Numerical solutions show that m_2 can be larger than m_l. Thus, in general, migration rates necessary for stability can be larger than the critical value predicted by condition (24).