

ESTABLISHMENT AND MAINTENANCE OF ADAPTIVE GENETIC DIVERGENCE UNDER MIGRATION, SELECTION, AND DRIFT

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There is a long tradition in population genetics of exploring the maintenance of variation under migration–selection balance using deterministic models that assume infinite population size. With finite population size, stochastic dynamics can greatly reduce the potential for the maintenance of polymorphism, but this has yet to be explored in detail. Here, classical two-patch models are extended to predict: (1) the probability of a locally beneficial mutation rising in frequency in the patch where it is favored and (2) the critical threshold migration rate above which the maintenance of polymorphism is much less likely. Individual-based simulations show that these approximations provide accurate predictions across a wide range of parameter space.

KEY WORDS: Dispersal, environmental heterogeneity, gene flow, genetic drift, local adaptation, migration–selection balance.

Understanding how evolutionary processes affect the establishment and maintenance of genetic divergence between populations is critical to interpreting empirical evidence for local adaptation and speciation. Most theoretical research on population divergence under migration–selection balance has focused on deterministic models (reviewed in Felsenstein 1976; Karlin 1982; Lenormand 2002; Nagylaki and Lou 2008; also see Nagylaki and Lou 2007; Star et al. 2007; Bürger 2009a,b; Nagylaki 2009). The earliest studies by Haldane (1930) and Wright (1931) considered a continent-island model, showing that a locally adapted allele would be deterministically maintained in an island patch as long as the rate of immigration, m , of the alternate allele (fixed on the continent) was lower than the selection coefficient, s , favoring the locally adapted allele ($m/s < 1$). Moran (1962), Maynard Smith (1966), and Bulmer (1972) generalized this result to a two-patch model with reciprocal migration (m_{ij} from patch j into patch i) with population size regulated independently in each patch (soft selection). A mutant allele spreads deterministically when $m_{12}/s_1 + m_{21}/s_2 < 1$, where the fitnesses of the resident

homozygote in the two patches are defined as $1 - s_1$ and $1 - s_2$ relative to the mutant-bearing heterozygotes, with s_1 and s_2 assumed to have opposite signs (Bulmer 1972). Counterintuitively, this result predicts the maintenance of polymorphism across a wide region of parameter space when selection coefficients and migration rates are closely balanced. In the extreme case, where $s_1 = -s_2$ and $m_1 = m_2$, a polymorphism is maintained regardless of the migration rate, even when selection is very weak. We would expect polymorphism to be readily lost in finite populations with very weak selection, however.

Although several studies have explored the effects of population size on the probability of a single mutant allele fixing in both patches of a finite two-patch model (Tachida and Iizuka 1991; Gavrillets and Gibson 2002; Whitlock and Gomulkiewicz 2005), previous work has not yet determined the conditions under which a polymorphism is likely to be maintained. Billiard and Lenormand (2005) approximated equilibrium allele frequencies under selection, drift, and low rates of migration, but their approach breaks down with moderate levels of migration and so

cannot be used to determine when local adaptation is likely to persist. Alternatively, the allele frequency dynamics under selection, drift, and migration can be described using a diffusion model in the case where the migrant pool arriving at a patch never changes (yielding, e.g., Wright's 1931 allele frequency distribution), but this assumes that migrants carry an allele, *A*, into the patch at a fixed frequency and that migration out of the patch has negligible effect on the dynamics elsewhere.

The aim of this article is to understand the effect of drift on the maintenance of polymorphism between two interconnected patches of finite size. Specifically, we develop approximations for the probability that locally adapted alleles increase when rare and the critical migration threshold below which adaptive divergence among patches is likely to persist. These predictions are then tested using individual-based simulations.

Analytical Model

We briefly rederive the conditions for a protected polymorphism for the deterministic two-allele model with two patches connected by migration (Bulmer 1972), which is the foundation for our results with finite patch sizes. We use the following notation for parameters in patch *i*: the allele frequencies of the two competing alleles (*A* and *a*) are p_i and q_i ; W_i represents the fitness of each genotype; m_{ij} represents the proportion of gametes in patch *i* that have arrived from patch *j*; finally, \bar{W}_i represents the mean fitness. A generation consists of random mating, followed by selection on diploids, gamete production, and gamete migration. The allele frequencies in the next generation then become:

$$\begin{aligned} p'_i &= (1 - m_{ij}) p_i^s + m_{ij} p_j^s \\ q'_i &= (1 - m_{ij}) q_i^s + m_{ij} q_j^s, \end{aligned} \tag{1}$$

where,

$$\begin{aligned} p_i^s &= p_i(p_i W_{i,AA} + q_i W_{i,Aa}) / \bar{W}_i \\ q_i^s &= q_i(q_i W_{i,aa} + p_i W_{i,Aa}) / \bar{W}_i. \end{aligned} \tag{2}$$

We assume throughout that selection favors allele *a* in patch 1 and allele *A* in patch 2; to emphasize this assumption, we will use the following alternative fitness definitions where convenient: $W_{1,AA} = 1 - s$, $W_{1,Aa} = 1 - hs$, $W_{1,aa} = 1$, $W_{2,AA} = 1$, $W_{2,Aa} = 1 - kt$, and $W_{2,aa} = 1 - t$.

The standard approach to finding the regions of parameter space that allow the maintenance of polymorphism is to consider the stability of the monomorphic equilibria when either allele is fixed (e.g., Moran 1962; Maynard Smith 1966; Bulmer 1972). If both fixation states are unstable, it follows that a polymorphism will be maintained. The stability of the equilibrium where *A* is fixed can be found by evaluating the Jacobian matrix at $q_i = 0$. The leading eigenvalue of this matrix ($\lambda_{i,a}$) represents the rate of

change in frequency of allele *a* when rare:

$$\lambda_{i,a} = \frac{1}{2} \psi + \frac{1}{2} \sqrt{\psi^2 - 4(1 - m_{12} - m_{21}) \frac{W_{1,Aa}}{W_{1,AA}} \frac{W_{2,Aa}}{W_{2,AA}}}, \tag{3}$$

where,

$$\psi = (1 - m_{12}) \frac{W_{1,Aa}}{W_{1,AA}} + (1 - m_{21}) \frac{W_{2,Aa}}{W_{2,AA}}. \tag{4}$$

A similar result holds for the invasion of *A* when rare ($\lambda_{i,A}$, interchanging *A* and *a* as well as m_{12} and m_{21}). In an infinite population, we expect the population to remain polymorphic as long as both $\lambda_{i,a}$ and $\lambda_{i,A}$ are greater than one because both alleles increase in frequency when rare.

To simplify the presentation, we now assume that migration is symmetric between the two patches ($m_{ij} = m_{ji}$); analogous results can be obtained for unequal migration using the approach that follows. To begin, we find the critical migration rates below which each allele invades by solving for when $\lambda_{i,a} = 1$ and $\lambda_{i,A} = 1$. For the invasion of allele *a* when rare, the critical migration threshold is

$$m_{crit,a}^\infty = \frac{1}{\frac{W_{1,Aa}}{W_{1,AA} - W_{1,AA}} - \frac{W_{2,Aa}}{W_{2,AA} - W_{2,Aa}}}, \tag{5}$$

where, the ∞ superscript indicates that the population size is assumed to be infinite. Equation (5) is equivalent to the threshold found by Bulmer (1972) using his fitness definitions ($W_{1,AA}/W_{1,Aa} = 1 - s_1$ and $W_{2,AA}/W_{2,Aa} = 1 - s_2$). We have written equation (5) so that the two fractions in the denominator are positive under the assumption that allele *a* is favored in patch 1 and allele *A* in patch 2. If the difference between these two fractions is negative ($m_{crit,a}^\infty < 0$) or is zero, then allele *a* can invade for any migration rate. If there is intermediate dominance with $h = 0.5$ and $k = 0.5$, equation (5) reduces to:

$$m_{crit,a}^\infty = \frac{st}{2t - 2s}. \tag{6}$$

Similarly, $m_{crit,A}^\infty$ can be obtained by interchanging the allelic designations, *A* and *a*, in equation (5).

The critical threshold for the invasion of allele *a*, given by equation (5), is more restrictive than the equivalent threshold for the invasion of *A* whenever their selection and dominance coefficients satisfy:

$$\begin{aligned} \frac{W_{1,Aa}}{W_{1,aa} - W_{1,Aa}} + \frac{W_{1,Aa}}{W_{1,Aa} - W_{1,AA}} \\ > \frac{W_{2,Aa}}{W_{2,Aa} - W_{2,aa}} + \frac{W_{2,Aa}}{W_{2,AA} - W_{2,Aa}}. \end{aligned} \tag{7}$$

Without loss of generality, we assume that the alleles are labeled such that equation (7) is satisfied, and we define the patches

such that patch 1 is where allele a is favored. For example, in the additive case, equation (7) reduces to $t > s$, indicating that we should label allele a as the one that is more deleterious in the patch where it is locally maladapted. Defining the alleles such that equation (7) is satisfied, it is then sufficient to ask whether $m < m_{crit,a}^\infty$ to determine whether a polymorphism will be maintained in an infinite population, and we refer to this deterministic critical threshold as m_{crit}^∞ for simplicity.

For some combinations of parameters, the critical threshold rises above one, implying that both alleles will be maintained deterministically for any migration rate. It can be shown that for m_{crit}^∞ to be greater than one, the geometric mean fitness of the heterozygotes across patches must be higher than that of the resident homozygotes:

$$\sqrt{\frac{W_{1,Aa} W_{2,Aa}}{W_{1,AA} W_{2,AA}}} > 1. \quad (8)$$

Equation (8) is most likely to be satisfied when the dominance coefficients (h and k) are small, causing the heterozygotes to have a high relative fitness.

In this deterministic model, we expect a polymorphism to be maintained as long as the smaller of the two leading eigenvalues ($\lambda_{l,a}$ or $\lambda_{l,A}$ from eq. 3) rises above one, as illustrated in Figure 1A for the simple additive case ($h = 0.5, k = 0.5$) with symmetric migration ($m_{ij} = m_{ji} = m$). When selection is much stronger in one patch than the other, the criterion for polymorphism approaches the threshold in the continent-island model (Haldane 1930; Wright 1931; $m/(s/2) < 1$ when $t \gg s$, $m/(t/2) < 1$ when $s \gg t$, selection is divided by two to account for the fitness definitions used here) because the patch with strong selection exhibits little polymorphism, as assumed for the continent (dashed lines in Fig. 1A). Similar behavior is seen in the continuous-time model of Gavrillets and Gibson (2002; their Fig. 1).

With finite population size, the magnitude of $\lambda_l - 1$ is important, not just its sign, as alleles experiencing very weak diversifying selection will be easily lost due to the combined effects of migration and drift. Here, we splice together the above deterministic results with standard diffusion results for a single patch to predict when both locally adapted alleles are likely to be maintained in finite populations. For a mutation experiencing selection of constant strength S in a single population of size N , Kimura (1962) showed that the probability of rising from a single copy to fixation is

$$\Pr[fix] = \frac{1 - e^{-2S}}{1 - e^{-4NS}}. \quad (9)$$

Because $\lambda_l - 1$ describes the asymptotic rate of increase of a rare allele in a deterministic analysis, we define the “diversification coefficient” to be $\delta = \lambda_l - 1$ and use δ in place of S in equation (9)

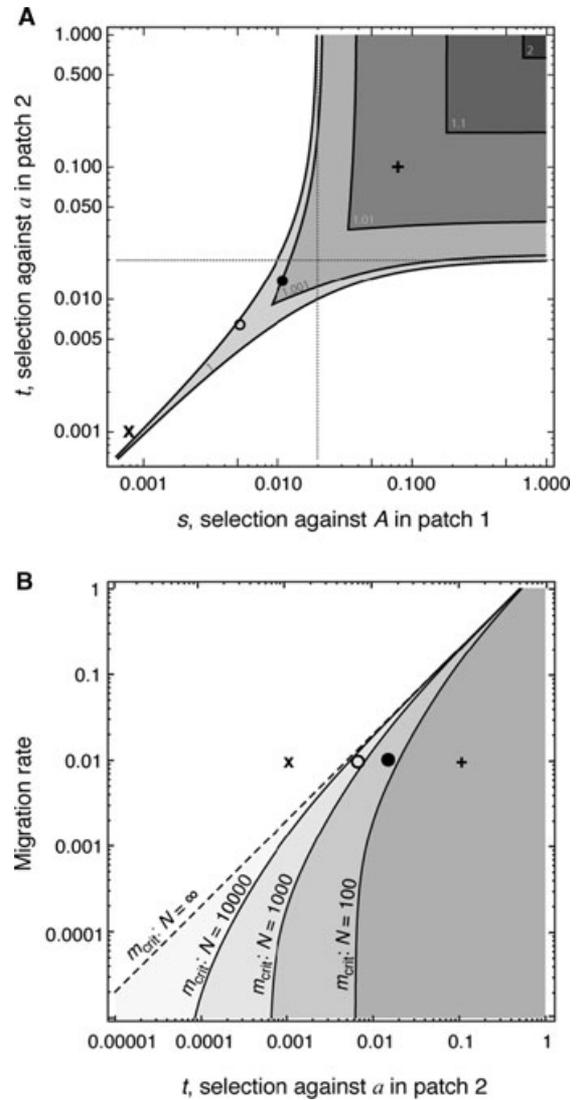


Figure 1. Regions maintaining a balanced polymorphism as a function of the selection coefficients (s, t) and migration rate (m). (A) Contour plot showing the smaller of the two leading eigenvalues ($\lambda_{l,a}$ or $\lambda_{l,A}$; contour values in gray) from a deterministic analysis with $h = k = 0.5$ and $m = 1/100$. Within the white region, deterministic selection does not maintain a balanced polymorphism, and we expect loss of one of the alleles. (B) The critical migration rate, below which polymorphism will be maintained using equation (5) for infinitely large populations and equation (11) for finite populations, assuming $s = 0.8 t$ and $h = k = 0.5$. The four points correspond to the same parameter sets in both panels and illustrate the fact that even though $\lambda_l > 1$ in a deterministic analysis (points “o” “•” and “+”), the evolutionary forces can be too weak to maintain a polymorphism in the face of drift in finite populations (when $N < 2643$ for “o” and when $N < 220$ for “•”).

to approximate the probability that a locally adapted mutation rises to high frequency, given that it is introduced into the patch where it is favored (hereafter, invasion probability). Here, N is assumed to equal the local patch size, and the allele is assumed

to be nearly additive (see Supporting information for the general case with dominance).

Alternatively, the “diversification coefficient” could be defined based on branching process results, setting $\delta = P/2$, where P is the probability of establishment of a rare allele in the patch where it is favored in a two-patch model (see Supporting information; Barton 1987). The branching process approach also assumes that the total population size is infinitely large, but it accounts for chance loss of the allele while rare. As shown in the Supporting information (Fig. S6), defining δ using the asymptotic rate of increase, $\lambda_l - 1$, or the probability of establishment, $P/2$, yields qualitatively similar results, and both approaches accurately describe the invasion probability in finite populations once δ is plugged into equation (9). Because the λ_l is more easily solved, however, we focus the text on the former approach. The branching process approach can, however, be easily adapted to give the invasion probability when the mutation is first introduced into the patch where it is disfavored (see Supporting information).

We next adjust the critical migration rate to account for the role of drift by solving for the migration rate that results in $2\delta > 1/(2N)$, which is roughly where the invasion probability based on equation (9) transitions from being dominated by drift ($\sim 1/2N$) to being dominated by selection ($\sim 2\delta$) (Crow and Kimura 1970). In essence, this approach finds the boundary where the net evolutionary force acting deterministically on the allele frequencies (migration and selection) has the same probability of explaining the spread of the rare allele as the stochastic noise generated by sampling error in a finite population. Throughout, we assume that the fitness differences are not so small that drift would overwhelm selection and hamper the spread of the alleles where they are locally favored, even without the swamping effects of migration. Specifically, we assume that

$$2 \left(\frac{W_{1,Aa}}{W_{1,AA}} - 1 \right) \gg \frac{1}{2N} \text{ and } 2 \left(\frac{W_{2,Aa}}{W_{2,aa}} - 1 \right) \gg \frac{1}{2N}. \quad (10)$$

Solving for when $2\delta > 1/(2N)$, we obtain a new threshold for the migration rate below which the system is expected to maintain polymorphism

$$m_{crit}^N = \frac{1}{\frac{W_{1,Aa}}{W_{1,AA} - W_{1,AA} \left(1 + \frac{1}{4N}\right)} - \frac{W_{2,Aa}}{W_{2,AA} \left(1 + \frac{1}{4N}\right) - W_{2,Aa}}}. \quad (11)$$

Decreasing the population size makes it more difficult to maintain a polymorphism, both because m_{crit}^N is more likely to be positive and because m_{crit}^N , when positive, tends to be smaller (recall that negative values of m_{crit}^N allow polymorphism to be maintained for any migration rate, provided assumption eq. 10 is satisfied).

Again, the critical threshold can rise above one for some parameters, implying that both alleles will be maintained for any migration rate when:

$$\sqrt{\frac{W_{1,Aa}}{W_{1,AA}} \frac{W_{2,Aa}}{W_{2,AA}}} > \left(1 + \frac{1}{4N}\right). \quad (12)$$

Drift in smaller populations makes equation (12) more restrictive.

Individual-based Simulations

To assess the accuracy of the above splicing approach, we used a modification of the Nemo platform (Guillaume and Rougemont 2006) to run individual-based simulations (as per Yeaman and Whitlock 2011) based on the above lifecycle and parameters. We measured: (1) the probability of a novel mutation rising to high frequency in the patch where it is favored; (2) the persistence time of a polymorphism (Supporting information); and (3) the fraction of time in which populations exhibited local adaptation. For the latter, we measured whether populations in each patch had a higher fitness than they would have had if transplanted to the other patch.

PROBABILITY OF A NEW MUTATION RISING TO HIGH FREQUENCY

We first tested the accuracy of the splicing approach in predicting the invasion probability of a locally adapted allele. In these simulations, all individuals in both patches were initially AA homozygotes and a single a mutant was introduced in one randomly chosen individual in the patch where it was beneficial. No mutations occurred thereafter and simulations were run for 5000 generations, with between 20,000 and 1,000,000 replicates for each parameter set, adjusted so that the standard errors were roughly the size of the symbols on the plots. The observed invasion probability was calculated from the fraction of simulations in which the a mutant either rose to a frequency above 0.5 (in the entire meta-population) or persisted for 5000 generations (we note that for cases with strongly asymmetrical selection and/or dominance, invasion may yield stable polymorphism at frequencies below 0.5; in such cases, as long as the allele persists for at least 5000 generations, it would still be recorded as a successful invasion).

Substituting the diversification coefficient δ for S in Kimura’s equation (9) provided an accurate prediction for the invasion probability for a range of selection coefficients when mutations were codominant ($h = k = 0.5$; Fig. 2B). Alleles introduced where they were locally favored had a much higher invasion probability when selection was stronger, and in all cases, invasion probability increased with decreasing migration. Although it is intuitive that strongly selected mutations should have a higher establishment probability, this result runs counter to the

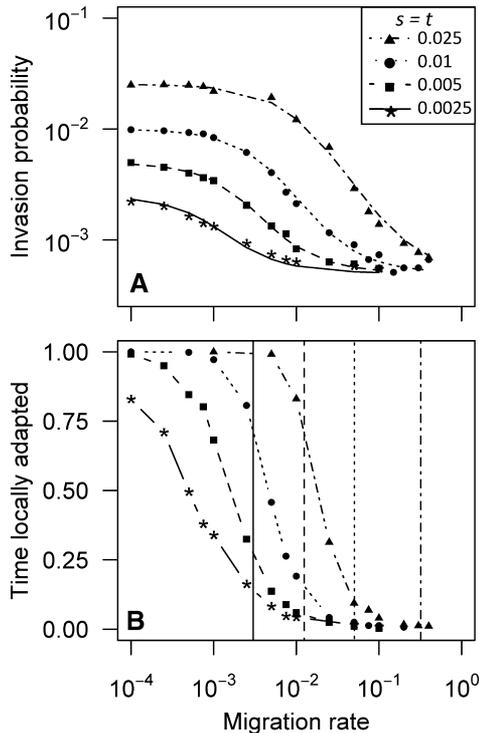


Figure 2. Invasion probability of a new mutation in a finite population (A) and fraction of time points at which both populations were locally adapted under recurrent mutation (B). For the four selection regimes shown, the curves in (A) correspond to predictions from Kimura's fixation probability using δ for S in equation (9), and the vertical lines in (B) correspond to m_{crit}^N . Other parameters: $h = k = 0.5$ and $N = 1000$.

deterministic result that locally adapted alleles should always invade when selection coefficients and migration rates are symmetrical (Bulmer 1972; Spichtig and Kawecki 2004). For very low migration rates, the fixation probability of the introduced allele was, as expected, nearly twice its selective advantage ($2(W_{1,Aa}/W_{1,AA} - 1)$). The fixation probability dropped with increasing migration, because the rare allele spent an increasing amount of time in the patch where it was disfavored.

We also find similar results with a smaller patch size ($N = 100$; Fig. S1), with discrepancies only when selection is so weak that inequality (10) begins to break down. The splicing approach using equation (9) is less accurate, however, when the alleles are not codominant (Fig. S2), but we found that using Kimura's general solution for arbitrary dominance provided good agreement in these cases (Fig. S3), even when selection and dominance coefficients were asymmetrical (Fig. S4). As selection tends toward neutrality, the success of the invading allele will increasingly depend upon dynamics in the patch where it is disfavored, so that using the single patch size for N in equation (9) may yield inaccurate results (but this will usually be in the region of parameter space that fails to satisfy inequality (10)).

CRITICAL MIGRATION THRESHOLD AND MAINTENANCE OF POLYMORPHISM

We next tested the accuracy of the critical migration threshold, m_{crit}^N , below which we expect local adaptation to persist, asking whether populations were more likely to exhibit local adaptation for $m < m_{crit}^N$. Simulations were initialized with all Aa individuals and run for 20,000 generations. Because our interest here was on whether polymorphic populations exhibited local adaptation, we included bidirectional mutation (from A to a or vice versa) at a rate of $\mu = 10^{-4}$ to facilitate the maintenance of both alleles. Populations were censused every 50 generations for the final 5000 generations, with at least 60 independent replicates per parameter combination. At each census, populations were considered to be locally adapted if, in both patches, the mean fitness of individuals in a patch was higher than had those individuals been transplanted to the other patch.

The critical threshold m_{crit}^N provided an accurate prediction for the migration rate below which populations were locally adapted for a substantial fraction of time in each patch (Fig. 2B; $h = k = 0.5$). In all cases, m_{crit}^∞ was infinite and, therefore, failed to predict this transition between maintenance and loss of local adaptation. Similar results were obtained for asymmetrical selection and dominance coefficients ($h \neq k$ and $s \neq t$; Fig. S9B) and for other population sizes (Fig. S10). In Figures S8–S10, we show that the persistence time of locally adapted alleles rises dramatically for migration rates below m_{crit}^N .

Discussion

If two alleles experience opposing selection pressures in different parts of the range of a species, divergent selection and limited migration may favor the maintenance of both alleles. Because alleles can be lost stochastically, however, drift can reduce the potential for the maintenance of polymorphism, especially in small populations. The current study illustrates how the net effect of deterministic evolutionary processes (here, migration and selection) can be accurately approximated using the rate of change in frequency of a rare allele within an infinitely large population ($\delta = \lambda_l - 1$). This diversification coefficient can then be spliced into Kimura's equation for the fixation probability from a single-patch model to predict the invasion probability of an allele introduced into the patch where it is favored (Fig. 2A) and the critical migration rate below which populations tend to exhibit local adaptation (Fig. 2B). When the diversification coefficient is strong relative to drift (i.e., $2\delta \gg 1/(2N)$), locally favored alleles have a high probability of invading when rare and a long persistence time, and sampled populations are likely to exhibit local adaptation. As migration rates increase, however, the net diversification coefficient declines, resulting in less local adaptation.

Although the leading eigenvalue of the Jacobian matrix, λ_1 , integrates the effects of selection and migration to describe the asymptotic rate of increase of a rare allele, it is not obvious that splicing this into Kimura's equations for fixation probability would work as well as we observed in our simulations. Similarly, despite the coarseness of the splicing approach for calculating m_{crit}^N , the stochastic migration threshold functions agree well over a range of symmetrical and asymmetrical selection and dominance coefficients. In the extreme case of additive alleles with equal and opposite effects in the two patches, the deterministic analysis (m_{crit}^∞) predicts that polymorphism can be maintained regardless of the strength of selection (Fig. 1). This prediction is not met, however, in finite populations. Instead, we find that polymorphism is likely to be maintained only when the migration rate is less than m_{crit}^N , a more restrictive condition, especially when selection is weak.

We show that the interplay between migration, selection, and drift tends to result in threshold behavior of the system, with rapid transitions at the critical migration rate (m_{crit}^N) between regions of parameter space that do and do not maintain polymorphism. Drift in finite populations can dramatically change the conditions maintaining a polymorphism with locally adapted alleles because when migration and selection nearly balance, the net effect of these deterministic processes can be very weak and overwhelmed by drift, even when selection is not itself weak.

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Supporting Information

The following supporting information is available for this article:

Figure S1. Even in very small populations ($N = 100$), the predicted invasion probability is accurate as long as selection is strong relative to the inverse of the population size (purple and green curves).

Figure S2. Invasion probability of a new mutation in a finite population ($N = 1000$ in each patch).

Figure S3. Local invasion probability for dominant and recessive mutations.

Figure S4. Invasion probability for mutations with unequal dominance and selection coefficients ($s \neq t$, $h \neq k$; see legend), with curves giving the numerical solutions to equation (S1) for patches of size $N = 1000$.

Figure S5. Eigenvectors and the invasion of locally adapted alleles.

Figure S6. Predicted invasion probabilities according to the branching process solution (P_1 ; blue curves) versus the splicing approximation with either $\delta = \lambda_t - 1$ (red curves) or $\delta = P_1/2$ (black curves).

Figure S7. Predicted invasion probabilities according to the branching process solution when the mutation is introduced into the patch where it is disfavored (P_2 ; dashed lines) versus simulation results (points).

Figure S8. Persistence time of a pair of divergent alleles under migration and selection.

Figure S9. (A) The persistence time and (B) the fraction of time points at which both populations are locally adapted with asymmetrical selection ($s \neq t$) and dominance ($h \neq k$) coefficients, as shown in the legend.

Figure S10. (A) The persistence time of a pair of divergent alleles and (B) the fraction of time points at which both populations were locally adapted under recurrent mutation, both increase with increasing population size.

Figure S11. Change in the diversification coefficient (δ) with migration for the cases considered in Figures S8 (dashed black curves) and S9 (gray solid curves), ordered in the same manner as in those figures.

Supporting Information may be found in the online version of this article.

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