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The effects of dominance, linkage, and gene flow on local adaptation and differentiation

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Preface

In this thesis, I present my research in the area of mathematical population genetics conducted during my graduate studies in Mathematics. This work focuses mainly on the joint effects of the evolutionary forces selection, recombination, and migration on genetic architecture, on local adaptation, and on differentiation. Throughout this thesis, we study a subdivided population with two linked diallelic loci under locally heterogeneous selection.

This thesis is structured into three parts, each corresponding to a published or submitted paper:

In the first part (*The effects of linkage and gene flow on local adaptation: a two-locus continent-island model*) we study a continent-island model, which is the easiest scenario for describing population subdivision. We assume that selection is genic and time is continuous.

In the second part (*The consequences of gene flow for local adaptation and differentiation: a two-locus two-deme model*) we extend the scenario in our first work and study a population inhabiting two demes connected by migration in both directions. Analogous to the first part of this thesis, we assume genic selection and continuous time.

In the last part (*The consequences of dominance and gene flow for local adaptation and differentiation at two linked loci*), we introduce several generalizations: We admit dominance and assume discrete and nonoverlapping generations. We consider a population subdivided into two demes, which exchange migrants in both directions.

In the subsequent introduction, we motivate and relate the considered scenarios in more detail and discuss several implications of the work presented in this thesis.

In accordance with the formal criteria of a cumulative dissertation, each paper is followed by a separate section containing information about the status of submission (as of September 2013) and my personal contribution. All papers share a common bibliography at the end of this thesis.

Contents

Introduction

The research presented in this thesis focuses on the interplay of the evolutionary forces selection, recombination, and migration, and their joint effects on genetic architecture, on local adaptation, and on differentiation in subdivided populations. Although previous work studied each evolutionary force separately in great detail, their interaction is far from being well understood. Understanding how selection and gene flow simultaneously shape multilocus variation is essential for a correct interpretation of genetic data obtained from geographically structured populations. With the work presented in this thesis, we try to shape our intuition about these complicated interactions using comprehensive mathematical models.

Recent years showed some advances in the study of the interaction of gene flow, selection and linkage. Population structure may cause linkage disequilibrium between the loci even under genic selection, i.e., in the absence of epistasis and dominance, making the analysis of the models incorporating these forces challenging. In panmictic populations, linkage disequilibrium occurs if and only if there is epistasis. Due to the increased complexity by considering several evolutionary forces simultaneously, the theory of multilocus migration-selection models focuses on limiting or special cases. These include weak or strong migration (Bürger 2009a, b) or the Levene model (Nagylaki 2009; Bürger 2009c, 2010; Barton 2010). In all of these cases, linkage disequilibrium is weak or absent.

Several one-locus migration-selection models investigate the effect of dominance on the maintenance of polymorphisms (Prout, 1968; Nagylaki and Lou, 2001, 2007; Nagylaki 2009; Peischl 2010). In these models dominance is intermediate, which is of particular interest as it is common in nature and as stable polymorphisms can be maintained in structured populations. With panmixia, stable polymorphisms are admissible if and only if alleles exhibit overdominance. As dominance leads to substantial mathematical complications, only few multilocus migration-selection models investigate the evolutionary consequences of dominance (Bürger 2009a, b, c, 2010; Nagylaki 2009; Chasnov 2012).

In our work we incorporate linkage, gene flow, and selection (in particular dominance) and investigate models where high levels of linkage disequilibrium may be maintained. Beside determining the equilibrium and stability structure of the investigated

models, we try to shed light on several important questions: What genetic architectures can be expected to evolve under various forms of spatially heterogeneous selection? What are the consequences for genetic variation at linked neutral sites? What are the consequences of the genetic architecture on the degree of local adaptation and of differentiation achieved for a given amount of gene flow?

To this aim, we assume the simplest setting of mulitlocus dynamics, where we consider two arbitrarily linked diallelic loci (A and B) under selection. The alleles are denoted by A_1 and A_2, and by B_1 and B_2 at locus A and B, respectively. Throughout this thesis we ignore epistasis, mutation and drift. In general, we assume an infinitely large population subdivided into two demes connected by migration. Alleles A_1 and B_1, and A_2 and B_2 are favored in deme 1 and deme 2, respectively.

Throughout this work we use deterministic models. These are either systems of ordinary differential or difference equations. Our analysis is based on mathematical techniques such as local stability analysis and perturbation theory.

The effects of linkage and gene flow on local adaptation: a two-locus continent-island model. In this part of the thesis (published; see Bürger and Akerman, 2011), we investigate a continent-island model. We assume that there is gene flow only from deme 2 (continent) to deme 1 (island), and that the specialist A_2B_2 is fixed on the continent. We need to keep track only of the genetic constitution on the island, which simplifies the analysis significantly. We also assume absence of dominance and consider a model in continuous time. These simplifications (which are generalized in the two subsequent papers) allow a complete and explicit description of the equilibrium configuration (and of their stability for large sets of the parameter space). We present all possible equilibrium configurations as functions of the migration rate, and we determine how these depend on linkage. We determine the parameter sets explicitly which admit a stable multilocus polymorphism on the island.

We demonstrate that under maladaptive gene flow, weakly beneficial mutants linked to a locus under selection-migration balance can invade successfully provided linkage is sufficiently tight. This implies the emergence of clusters of beneficial alleles in populations subject to maladaptive gene flow.

Linkage may act as a strong barrier to maladaptive gene flow: Compared to two independent loci (i.e., ignoring linkage disequilibrium), linkage increases the critical migration rate below which a multilocus polymorphism is admissible. We determine the amount of linkage disequilibrium exhibited at the two-locus polymorphism. To this aim, we compute two measures of linkage disequilibrium: the classical measure from population genetics, D ($= x_1x_4 - x_2x_3$), and a measure used for statistical purposes, r^2

(the squared correlation in allelic state). We study local adaptation by computing the migration load at the multilocus polymorphism. Finally, we consider a neutral locus located between the loci under selection and derive the effective migration rate at the neutral locus explicitly.

The consequences of gene flow for local adaptation and differentiation: a two-locus two-deme model. In this part (published; see Akerman and Bürger, 2013), we consider a population inhabiting two demes where migrants are exchanged in both directions. As in our first paper, selection is genic and time is assumed continuous. Thus, the continent-island model considered in our first work is included here as a special case.

Admitting gene flow in both directions increases the complexity of the model substantially, so that equilibria cannot be calculated explicitly in general. Instead, we derive the equilibrium and stability structure for several important special cases (weak, strong, highly asymmetric, and super-symmetric migration, no or weak recombination, independent or strongly recombining loci, and absence of genotype-environment interaction) and weak or strong recombination.

We introduce a new multilocus fixation index (F_{ST}^{X}), which we use to measure the effect of linkage and gene flow on local adaptation and on differentiation. We investigate how the invasion conditions for a mutant of small effect that is beneficial in one deme but disadvantageous in the other deme depends on the migration pattern, where we assume that the mutant is linked to a polymorphic locus which is in selection-migration balance. We extend the model of the neutral locus linked to loci A and B introduced in our first paper by migration in both directions, and compute the effective migration rate at the neutral locus.

The consequences of dominance and gene flow for local adaptation and differentiation at two linked loci. In the third part of this thesis (Akerman, submitted), we generalize the models treated in the first and second paper by admitting intermediate dominance and assuming discrete and nonoverlapping generations.

The equilibrium and stability structure is obtained for the special cases of weak migration and of weak selection. Assuming sufficiently weak selection, weak recombination, and weak one-way migration, we obtain the continent-island model with dominance in continuous time. For this model we investigate weak migration, independent loci, and complete linkage, where we derive the possible equilibrium structure and the bifurcation patterns as functions of the migration rate. We show that the equilibrium and stability structure maintained in the population depends crucially on the degree of dominance, in particular if linkage is loose. One explanation may be that strong recombination facilitates the formation of heterozygotes, where dominance becomes evident only.

We determine how D and r^2, and the amount of local adaptation (measured by the migration load) depend on the degree of dominance and on the amount of linkage. We study the strength of barriers to gene flow at neutral sites linked to the selected loci by deriving an explicit approximation for the effective migration rate at a linked neutral site and determine its dependence on linkage and dominance. As another application, we investigate a quantitative trait subject to diversifying selection and determine the amount of differentiation under maladaptive gene flow. To this aim, we compute three different measures of differentiation: (i) $\bar{F}_{ST}$, which is F_{ST} averaged over the two loci, (ii) F^X_{ST}, a multilocus F_{ST} introduced in our second paper, and (iii) Q_{ST}, which measures differentiation of the trait. Using these, we determine the effects of dominance and linkage on the differentiation of the measured trait and of the genotypes.

Synopsis and Outlook. Our results suggest the emergence of clusters of beneficial alleles in populations subject to maladaptive gene flow if epistasis is absent (Bürger and Akerman, 2011). This should be in particular the case if migration between the two demes is asymmetric, as in the continent-island model (Akerman and Bürger, 2013). These analytical findings complement the conclusion drawn by Yeaman and Whitlock (2011), who performed a simulation study on the evolution of genetic architecture when two populations connected by migration experience stabilizing selection on a polygenic trait towards different optima.

We extended the effective migration rate at a neutral site linked to one locus under selection (introduced by Petry, 1983; Bengtsson, 1985; Barton and Bengtsson, 1986) to two linked loci under selection. We proved that the effective migration rate at neutral sites crucially depends on the degree of dominance exhibited by the loci under selection. If the locally adaptive alleles are recessive or exhibit no dominance, the linked loci under selection act as strong barriers to neutral gene flow. If the locally adaptive alleles are dominant, the effective migration rate is not reduced significantly below the actual one (Bürger and Akerman, 2011; Akerman and Bürger, 2013; Akerman, submitted).

For a population inhabiting two demes interchanging migrants, we proved that a monomorphism is globally asymptotically stable and all variation is lost if it experiences sufficiently strong gene flow (Akerman and Bürger, 2013). If the migration rates are asymmetric or symmetric, a specialist (A_1B_1 or A_2B_2) or generalist (A_1B_2 or A_2B_1) becomes fixed, respectively. For several informative special cases, we determined the maximum migration rate below which a stable, two-locus polymorphic equilibrium is maintained, and the minimum migration rate above which the population is monomorphic. We showed that for large sets of the parameter space, tighter linkage increases the

maximum migration rate below which a stable, two-locus polymorphic equilibrium is maintained.

If migration is weak, tighter linkage elevates the amount of local adaptation. For the continent-island model we showed that for arbitrary intermediate dominance or absence of dominance, the migration load is about twice as high if recombination is strong compared to tight linkage (Bürger and Akerman, 2011; Akerman, submitted). We expect the highest amount of local adaptation if linkage is tight and if the island alleles are completely dominant. Our results suggest that reduced recombination will be favored in populations subject to (sufficiently weak) maladaptive gene flow. An efficient mechanism in suppressing recombination among a set of genes is provided by chromosome inversions (Kirkpatrick and Barton, 2006). Assuming genic selection, we derived an explicit approximation of the invasion rate of an inversion capturing two adaptive alleles (Bürger and Akerman, 2011). If migration is strong and migration occurs in both directions, the migration load may be minimized at intermediate recombination rates (Akerman and Bürger, 2013).

For the continent-island model, we obtained simple and informative formulas for the linkage disequilibrium measures D and r^2, which reveal their different behavior with respect to migration and to dominance. Whereas r^2 is a monotone decreasing function of the migration rate, D is maximized at intermediate migration rates (Bürger and Akerman, 2011). If the island alleles are dominant, we expect elevated levels of D and reduced levels of r^2 (i.e., the correlation between the alleles decreases). Independently of the degree of dominance, tighter linkage leads to increased levels of D and r^2 (Akerman, submitted).

Our results show that Q_{ST} and F_{ST} (measured by $\bar{F}_{ST}$ or F^X_{ST}) may show a different behavior with respect to linkage and to dominance. We proved that for sufficiently weak migration, tighter linkage elevates the levels of genetic differentiation (measured by $\bar{F}_{ST}$ and F^X_{ST}). Differentiation of the trait (measured by Q_{ST}) is independent of the strength of linkage (up to first order of the migration rate); cf. Akerman, submitted. If migration is sufficiently strong, differentiation may be minimized at intermediate recombination rates (Akerman and Bürger, 2013).

Our results may lay the basis for further investigations, which we briefly discuss in the subsequent paragraphs.

We studied the invasion of beneficial mutants linked to established adaptive alleles in an infinitely large population subject to maladaptive gene flow. This lays the foundations for deriving the probability of invasion in a population of finite size (for details, we refer to Aeschbacher and Bürger; unpublished manuscript). For finite populations, the genetic background on which the beneficial mutant appears must be taken into account. It is

worthwhile to study also the actual amount and pattern of diversity at neutral sites linked to selected loci in finite populations.

Further work will have to incorporate epistasis. This was done by Bank et al. (2012) who studied the evolution of genetic incompatibilities assuming a continent-island model. Their model could be extended by other patterns of population structure. This should help shape our intuition on the evolution of recombination, as the actual pattern of gene flow, and the form of selection and epistasis determine if recombination between loci is favored or not: Our results suggest that, in the absence of epistasis, reduced recombination between selected loci is favored, except when migration rates are sufficiently symmetric and high (Akerman and Bürger, 2013). Certain forms of epistasis may favor high recombination in structured populations more easily (Pylkov et al. 1998; Lenormand and Otto, 2000; Bank et al. 2012).

The effects of linkage and gene flow on local adaptation: a two-locus continent-island model

R. BÜRGER, A. AKERMAN

ABSTRACT. *Population subdivision and migration are generally considered to be important causes of linkage disequilibrium (LD). We explore the combined effects of recombination and gene flow on the amount of LD, the maintenance of polymorphism, and the degree of local adaptation in a subdivided population by analyzing a diploid, deterministic continent-island model with genic selection on two linked loci (i.e., no dominance or epistasis). For this simple model, we characterize explicitly all possible equilibrium configurations. Simple and intuitive approximations for many quantities of interest are obtained in limiting cases, such as weak migration, weak selection, weak or strong recombination. For instance, we derive explicit expressions for the measures D ($= p_{AB} - p_A p_B$) and r^2 (the squared correlation in allelic state) of LD. They depend in qualitatively different ways on the migration rate. Remarkably high values of r^2 are maintained between weakly linked loci, especially if gene flow is low. We determine how the maximum amount of gene flow that admits preservation of the locally adapted haplotype, hence of polymorphism at both loci, depends on recombination rate and selection coefficients. We also investigate the evolution of differentiation by examining the invasion of beneficial mutants of small effect that are linked to an already present, locally adapted allele. Mutants of much smaller effect can invade successfully than predicted by naive single-locus theory provided they are at least weakly linked. Finally, the influence of linkage on the degree of local adaptation, the migration load, and the effective migration rate at a neutral locus is explored. We discuss possible consequences for the evolution of genetic architecture, in particular, for the emergence of clusters of tightly linked, slightly beneficial mutations and the evolution of recombination and chromosome inversions.*

1. Introduction

Evolution in geographically structured populations is governed by two potentially conflicting forces: selection for improved local adaptation may be opposed by migration and concomitant maladaptive gene flow. For one-locus models, both general theory as well as the study of numerous particular models have provided considerable insight into the evolutionary consequences of this interaction (reviewed by Karlin 1982, Lenormand 2002, Nagylaki and Lou 2008).

Frequently, however, selection acts on multiple loci which may be linked. For this situation much less is known. The recently developed multilocus theory for the evolution in subdivided populations focuses mainly on limiting or special cases, such as weak or strong migration (Bürger 2009a,b) or the Levene model (Nagylaki 2009, Bürger 2009c, 2010), in which LD is weak or absent. The applications treated there concern primarily conditions for the maintenance of multilocus polymorphism.

The main goal of this paper is to explore and quantify the role of selection on linked loci for local adaptation in the presence of maladaptive gene flow. To this aim, we study a diploid continent-island model with genic selection (i.e., no dominance or epistasis) acting on two recombining loci. Continent-island models seem to be the simplest scenario to investigate this topic, and they have been justified by and applied in studies of local adaptation in natural populations (e.g., King and Lawson 1995). A key role in our analysis will be played by the (LD) generated by the interaction of selection and migration.

Population subdivision and admixture are known to be important agents in generating LD (Charlesworth and Charlesworth 2010), and recent studies revealed high levels of LD in geographically structured species as well as substantial differences among species and subpopulations (e.g., Remington et al. 2001, Conrad et al. 2006, Cutter et al. 2006, Hernandez et al. 2007). However, analytical estimates for the expected amount of LD have been obtained mainly for neutral loci. In particular, the expectation and variance of measures of pairwise LD, such as $D(= p_{AB} - p_A p_B)$ or r^2 (the squared correlation in allelic state), have been derived for various island models (Ohta 1982, McVean 2002, Wakeley and Lessard 2003, De and Durrett 2007). Such estimates are particularly useful in testing hypotheses about neutral evolution (Nordborg and Tavaré 2002, Slatkin 2008).

For large subdivided populations in which selection and migration are the dominating forces, little quantitative information is available on the extent of LD. Li and Nei (1974) and Christiansen and Feldman (1975) investigated a two-deme model with symmetric migration and genic selection on two dialellic loci. They showed that for weak migration an equilibrium exhibiting LD exists. Li and Nei also provided numerical examples showing that considerable LD can be maintained. Slatkin (1975) studied gene flow and selection on two linked loci in a cline. He found that substantial LD is maintained if the recombination rate is of the same order of magnitude as the selection coefficients or smaller. In addition to studying the influence of linkage among multiple loci on the width of a cline, Barton (1983) derived a weak-migration approximation for the allele frequencies and the linkage disequilibria in a two-deme model with heterozygote inferiority at finitely many equivalent loci. Spichtig and Kawecki (2004) observed high levels of LD in a model of antagonistic directional selection on a quantitative trait in two

demes. However, in general, their fitness functions induce epistasis and dominance, and the dependence of LD on the degree of epistasis was not reported.

For our model, we can quantify explicitly the role of linkage in generating LD and in maintaining genetic polymorphism and local adaptation in the presence of gene flow. On the island, locally adapted alleles A_1 and B_1 may occur at two linked loci. Evolution occurs in continuous time and we ignore dominance and epistasis. Thus, the model also describes selection on haploids. All immigrants from the continent carry the (maladapted) haplotype A_2B_2. Mutation and random drift are ignored. Our parameters are the selection coefficients at the two loci, the recombination rate, and the migration rate. Section 2 contains a detailed description of the model.

In Section 3, the complete equilibrium and stability structure is derived. Below a critical migration rate, which can be determined explicitly and depends strongly on the recombination rate and the selection coefficients, there is a unique, stable, fully polymorphic equilibrium. If recombination is approximately as strong as selection, an additional, unstable fully polymorphic equilibrium can exist. In this case, the stable polymorphic equilibrium is simultaneously stable with a boundary equilibrium.

In Section 4, we consider various applications. (i) We derive simple and intuitive approximations for the stable, fully polymorphic equilibrium for several limiting cases. (ii) We obtain explicit conditions for the maintenance of both locally adapted alleles in the presence of gene flow. These reveal the role of linkage, and illustrate how it interacts with migration and selection in maintaining polymorphism. (iii) From an explicit analytical formula for the measure D of LD at the stable fully polymorphic equilibrium, we derive simple and informative approximations for D and r^2 in important limiting cases. Interestingly, D and r^2 show qualitatively different dependence on the migration rate. In particular, r^2 may be high for a large range of parameters. (iv) Assuming that a locally adapted allele (B_1) is in migration-selection balance on the island, we study the invasion condition for and the final frequency of a linked beneficial mutation of smaller effect (A_1). In the absence of LD, only mutations can invade whose selective advantage exceeds the immigration rate of the maladapted (continental) allele. We show that mutants having a much smaller effect than the immigration rate can invade if they are sufficiently (but not extremely) tightly linked to the already polymorphic locus. Such an invasion always entails an increase of B_1; the tighter the linkage, the higher this increase. (v) We derive explicit formulas for the migration load and examine how the load and the degree of local adaptation depend on the parameters of the model. (vi) We derive an approximation for the effective migration rate at a linked neutral marker locus.

In Section 5, we summarize and discuss these results. In particular, we elaborate on their consequences for the evolution of the genetic architecture, such as linkage groups or chromosome inversions, in the presence of gene flow.

2. The model

We extend the classical continent-island model (Haldane 1930, Nagylaki 1992) to two loci. We consider a sexually reproducing population of monoecious diploid individuals in which two diallelic loci are under selection. On the continent, the alleles A_2 and B_2 are fixed. On the island, the alleles A_1 and B_1 are selectively favored. We call them the island alleles, and A_2 and B_2 the continental alleles. We ignore mutation and random genetic drift and employ a deterministic continuous-time model to describe evolution on the island. We assume one-way migration from the continent to the island at rate $m \geq 0$. Thus, all immigrants on the island are of haplotype A_2B_2. The recombination rate between the two loci is denoted by $\rho \geq 0$.

The population can be described in terms of x_1, x_2, x_3, x_4, the frequencies of the four gametes A_1B_1, A_1B_2, A_2B_1, A_2B_2 on the island. The state space is the probability simplex $S_4 = \left\{(x_1, x_2, x_3, x_4) : x_i \geq 0 \text{ and } \sum_{i=1}^4 x_i = 1\right\}$. Its vertices correspond to the monomorphic states at which one of the gametes has frequency 1. The edges connecting the states $x_4 = 1$ and $x_3 = 1$, or $x_4 = 1$ and $x_2 = 1$, correspond to the marginal single-locus systems in which the island allele A_1, or B_1, respectively, is absent.

We assume absence of dominance and of epistasis, hence genic selection, and assign the Malthusian parameters $\frac{1}{2}\alpha$ and $-\frac{1}{2}\alpha$ to the alleles A_1 and A_2, and $\frac{1}{2}\beta$ and $-\frac{1}{2}\beta$ to B_1 and B_2. The resulting fitness matrix for the genotypes reads

$$\begin{array}{c} \\ A_1A_1 \\ A_1A_2 \\ A_2A_2 \end{array} \begin{array}{c} \begin{array}{ccc} B_1B_1 & B_1B_2 & B_2B_2 \end{array} \\ \begin{pmatrix} \alpha+\beta & \alpha & \alpha-\beta \\ \beta & 0 & -\beta \\ -\alpha+\beta & -\alpha & -\alpha-\beta \end{pmatrix} \end{array}. \tag{2.1}$$

Assuming continuous time, standard population genetics modeling (e.g. Bürger 2000, Chap. II.1) yields the following system of differential equations for the evolution of gamete frequencies on the island:

$$\dot{x}_1 = x_1[\alpha(x_3+x_4)+\beta(x_2+x_4)] - \rho D - mx_1\,, \tag{2.2a}$$

$$\dot{x}_2 = x_2[\alpha(x_3+x_4)-\beta(x_1+x_3)] + \rho D - mx_2\,, \tag{2.2b}$$

$$\dot{x}_3 = x_3[-\alpha(x_1+x_2)+\beta(x_2+x_4)] + \rho D - mx_3\,, \tag{2.2c}$$

$$\dot{x}_4 = x_4[-\alpha(x_1+x_2)-\beta(x_1+x_3)] - \rho D + m(1-x_4)\,, \tag{2.2d}$$

where $D = x_1x_4 - x_2x_3$ denotes the classical measure of LD.

For our purposes, it is convenient to describe the population composition by the frequencies $p = x_1 + x_2$ and $q = x_1 + x_3$ of the alleles A_1 and B_1 and by the LD measure D. The gamete frequencies are calculated from p, q, and D by

$$x_1 = pq + D\,,\ x_2 = p(1-q) - D\,,\ x_3 = q(1-p) - D\,,\ x_4 = (1-p)(1-q) + D\,. \quad (2.3)$$

The constraints $x_i \geq 0$ ($i = 1, 2, 3, 4$) and $\sum_{i=1}^{4} x_i = 1$ transform into $0 \leq p, q \leq 1$ and

$$-\min\{pq, (1-p)(1-q)\} \leq D \leq \min\{p(1-q), (1-p)q\}\,. \quad (2.4)$$

It follows that p, q, and D evolve according to

$$\dot{p} = \frac{dp}{dt} = \alpha p(1-p) - mp + \beta D\,, \quad (2.5a)$$

$$\dot{q} = \frac{dq}{dt} = \beta q(1-q) - mq + \alpha D\,, \quad (2.5b)$$

$$\dot{D} = \frac{dD}{dt} = [\alpha(1-2p) + \beta(1-2q)]D + m(pq - D) - \rho D\,. \quad (2.5c)$$

We note that by rescaling time, for instance to units of ρ or m (provided ρ or m is positive), the number of independent parameters can be reduced by one (i.e., to α/ρ, β/ρ, m/ρ or to α/m, β/m, ρ/m, respectively). We refrain from doing so because in our applications it will be illuminating to use either ρ or m as an independent parameter.

We have also studied the corresponding discrete-time model which allows for strong evolutionary forces and converges to the continuous-time model in the limit of weak selection, recombination, and migration. It yields more complicated expressions for most quantities of interest and, therefore, is less amenable to an explicit analysis. Qualitatively, however, it appears to give analogous results.

3. Equilibrium structure and stability

To present all possible equilibrium and stability configurations, it is most instructive to describe the equilibrium and stability properties as functions of the migration rate m. Thus, we use m as a bifurcation parameter. We treat the boundary equilibria first, then the internal, fully polymorphic equilibria. Section 3.3 contains the main results. In Section 3.4, we prove global stability results for a number of special cases. The results derived below provide the basis for the applications treated in Section 4.

Throughout, we posit without loss of generality that selection on the B-locus is at least as strong as on the A-locus, i.e.,

$$0 < \alpha \leq \beta\,. \quad (3.1)$$

Therefore, we call A and B the minor and major locus, respectively.

3.1. Boundary equilibria.

Monomorphic equilibria. (i) The state E_I at which both island alleles are fixed,

$$E_I: \quad \hat{p} = 1\,, \quad \hat{q} = 1\,, \quad \hat{D} = 0\,, \tag{3.2}$$

is an equilibrium if and only if $m = 0$. In this case, it is globally asymptotically stable (in the sense that it attracts all solutions with the property that both island alleles are initially present; see Section 3.4). If $m = 0$, there also exist the three other monomorphic equilibria. They are unstable and will not be needed.

(ii) The equilibrium E_C, at which both continental alleles are fixed, exists always:

$$E_C: \quad \hat{p} = 0\,, \quad \hat{q} = 0\,, \quad \hat{D} = 0\,. \tag{3.3}$$

A linear stability analysis yields the eigenvalues $\alpha - m, \beta - m$, and $\alpha + \beta - \rho - m$. Therefore, E_C is asymptotically stable if and only if $m > \max(\beta, m_C)$, where

$$m_C = \alpha + \beta - \rho\,. \tag{3.4}$$

Thus, if linkage is sufficiently tight ($\rho \leq \alpha$), the continental haplotype can become fixed if the critical migration rate m_C is exceeded. It will be proved in Section 3.4 that E_C is globally asymptotically stable if $m \geq \alpha + \beta$, independently of ρ.

Single-locus polymorphisms. There may exist two single-locus polymorphisms.

(i) If $0 < m < \alpha$, there exists the equilibrium

$$E_A: \quad \hat{p} = 1 - \frac{m}{\alpha}\,, \quad \hat{q} = 0\,, \quad \hat{D} = 0\,, \tag{3.5}$$

at which the A-locus is polymorphic and the B-locus is fixed for the continental allele B_2. As $m \to \alpha$, E_A approaches E_C. Although E_A is globally attracting within its one-locus marginal system whenever it is admissible (Nagylaki 1975; Nagylaki 1992, p. 128-132), it is always unstable with respect to the full two-locus system. The latter statement follows because the eigenvalues are

$$\lambda_1^A = m - \alpha \quad \text{and} \quad \lambda_\pm^A = \tfrac{1}{2}\left(2\beta - \alpha - \rho \pm \sqrt{(\alpha + \rho)^2 - 4m\rho}\right). \tag{3.6}$$

Since admissibility of E_A requires $m < \alpha$, we infer immediately that

$$\sqrt{(\alpha + \rho)^2 - 4m\rho} \geq |\alpha - \rho| \geq 0\,.$$

Hence, all eigenvalues are real and a simple calculation invoking $\alpha \leq \beta$ shows that $\lambda_+^A > 0$.

It follows that E_A is not hyperbolic (i.e., no eigenvalue has vanishing real part) if and only if $m = m_A$, where

$$m_A = \beta\left(1 - \frac{\beta - \alpha}{\rho}\right). \tag{3.7}$$

This observation will be of importance below. If $m = m_A$, we have $\hat{p} = \dfrac{(\beta-\alpha)(\beta-\rho)}{\alpha\rho}$, which is in $(0,1)$ if and only if

$$\beta - \alpha < \rho < \beta\,, \tag{3.8}$$

i.e., if and only if $0 < m_A < \alpha$.

(ii) If $0 < m < \beta$, there exists the equilibrium

$$E_B: \quad \hat{p} = 0\,, \quad \hat{q} = 1 - \frac{m}{\beta}\,, \quad \hat{D} = 0\,, \tag{3.9}$$

at which the B-locus is polymorphic and the A-locus is fixed for the continental allele A_2. As $m \to \beta$, E_B approaches E_C. If E_B is admissible, it is globally attracting within its one-locus marginal system. Moreover, the eigenvalues are

$$\lambda_1^B = m - \beta \quad \text{and} \quad \lambda_\pm^B = \tfrac{1}{2}\left(2\alpha - \beta - \rho \pm \sqrt{(\beta+\rho)^2 - 4m\rho}\right). \tag{3.10}$$

Because E_B is admissible only if $m < \beta$, we infer immediately that

$$\sqrt{(\beta+\rho)^2 - 4m\rho} \geq |\beta - \rho| \geq 0\,.$$

Hence, all eigenvalues are real. A simple calculation shows that this implies $\lambda_-^B < 0$. Finally, we find that $\lambda_+^B < 0$ if and only if $m > m_B$, where

$$m_B = \alpha\left(1 + \frac{\beta-\alpha}{\rho}\right), \tag{3.11}$$

and $\lambda_+^B = 0$ if $m = m_B$. We note that $\alpha \leq m_B$ holds always, and $m_B < \beta$ is fulfilled if and only if

$$\alpha < \min(\rho, \beta)\,. \tag{3.12}$$

Thus, we have shown that E_B is asymptotically stable if and only if

$$m_B < m < \beta\,, \tag{3.13}$$

and E_B is hyperbolic except when $m = m_B$. If $m = m_B$, then $\hat{q} = \dfrac{(\beta-\alpha)(\rho-\alpha)}{\beta\rho}$, and $\hat{q} \in (0,1)$ if and only if (3.12) holds, i.e., if and only if $m_B < \beta$.

No recombination. If $\rho = 0$, there is the following boundary equilibrium at which only the two gametes A_1B_1 and A_2B_2 are present:

$$E_0: \quad \hat{p} = \hat{q} = 1 - \frac{m}{\alpha+\beta}\,, \quad \hat{D} = \frac{m}{\alpha+\beta}\left(1 - \frac{m}{\alpha+\beta}\right). \tag{3.14}$$

The equilibrium E_0 is admissible (and polymorphic) if and only if $0 < m < \alpha+\beta$. (3.14) shows that $E_0 \to E_I$ if $m \to 0$, and $E_0 \to E_C$ if $m \to \alpha+\beta$. Because the eigenvalues are $-\alpha$, $-\beta$, and $-\alpha-\beta+m$, E_0 is asymptotically stable whenever it is admissible. If, initially, only the two gametes A_1B_1 and A_2B_2 are present, single-locus theory (Nagylaki

1992, p. 128-132) implies convergence to E_0. We shall prove global convergence from arbitrary initial conditions in Section 3.4.

3.2. Internal equilibria. We assume $\rho > 0$. Somewhat unexpectedly, the internal equilibria can be calculated explicitly. This is shown by substituting the value D obtained from solving $\dot{p} = 0$ (2.5a) into the right-hand side of (2.5c), which remains linear in q. Now, solving $\dot{D} = 0$ for q, substituting the solution into the right-hand side of (2.5b) and solving the resulting quadratic equation in p yields the following coordinates for fully polymorphic equilibria:

$$\hat{p}_\pm = \frac{1}{8\alpha\rho}\left[\beta^2 - \alpha^2 + 6\alpha\rho - \rho^2 - 4m\rho \pm (\alpha - \beta + \rho)R\right], \tag{3.15a}$$

$$\hat{q}_\pm = \frac{1}{8\beta\rho}\left[\alpha^2 - \beta^2 + 6\beta\rho - \rho^2 - 4m\rho \pm (\beta - \alpha + \rho)R\right], \tag{3.15b}$$

$$\begin{aligned}\hat{D}_\pm = \frac{1}{32\alpha\beta\rho^2}\Big\{&(\alpha - \beta - \rho)(\alpha + \beta - \rho)(\alpha - \beta + \rho)\Big[(\alpha + \beta + \rho) \mp R\Big] \\ &- 4m\rho(\alpha^2 + \beta^2 + \rho^2 - 2\alpha\beta - 2\alpha\rho - 2\beta\rho) - 8m^2\rho^2\Big\},\end{aligned} \tag{3.15c}$$

where

$$R = \sqrt{(\alpha + \beta + \rho)^2 - 8m\rho}\,. \tag{3.15d}$$

We call these equilibria E_+ and E_-. The calculations show that no other internal equilibrium can exist. It is straightforward to show that E_+ converges to E_I if $m \to 0$ and E_+ converges to E_0 as $\rho \to 0$.

Our first task is to determine when the equilibria E_+ and E_- are biologically feasible, i.e., in the state space S_4. Obviously, the equilibria can exist only if the root R is real, which is the case if and only if $m \le m^*$, where

$$m^* = \frac{(\alpha + \beta + \rho)^2}{8\rho}\,. \tag{3.16}$$

We have $E_+ = E_-$ if and only if $m = m^*$. The following proposition states the admissibility conditions for the fully polymorphic equilibria.

PROPOSITION 3.1. *(a)* E_+ *is an admissible internal equilibrium if and only if one of the following three, mutually exclusive conditions is satisfied:*

$$0 < \rho \le \min(\alpha, \tfrac{1}{3}(\alpha + \beta)) \quad \textit{and} \quad 0 < m < m_C\,, \tag{3.17a}$$

$$\tfrac{1}{3}(\alpha + \beta) < \rho \le 3\alpha - \beta \quad \textit{and} \quad 0 < m < m^*\,, \tag{3.17b}$$

$$\max(\alpha, 3\alpha - \beta) < \rho \quad \textit{and} \quad 0 < m < m_B\,. \tag{3.17c}$$

Therefore, the equilibrium E_+ *is admissible whenever m is positive and below a critical value.*

(b) E_- *is an admissible internal equilibrium if and only if*

$$\beta < 2\alpha \quad \textit{and} \quad \tfrac{1}{3}(\alpha+\beta) < \rho \le \alpha \quad \textit{and} \quad m_{\mathrm{C}} < m < m^*\,, \tag{3.18a}$$

or

$$\beta < 2\alpha \quad \textit{and} \quad \alpha < \rho < 3\alpha - \beta \quad \textit{and} \quad m_{\mathrm{B}} < m < m^*\,. \tag{3.18b}$$

Therefore, the equilibrium E_- *is never admissible if m is below or above a critical value. It is also not admissible if* $\beta \ge 2\alpha$*, i.e., if the locus effects differ by more than a factor of two.*

The tedious proof is given in Appendix A.1. The cases in Proposition 3.1(a), as well as those in (b), are indeed mutually exclusive and cover the whole parameter range for ρ because of the following simple observation:

$$\beta > 2\alpha \quad \text{if and only if} \quad \tfrac{1}{3}(\alpha+\beta) > \alpha > 3\alpha - \beta\,, \tag{3.19a}$$

$$\beta = 2\alpha \quad \text{if and only if} \quad \tfrac{1}{3}(\alpha+\beta) = \alpha = 3\alpha - \beta\,, \tag{3.19b}$$

$$\beta < 2\alpha \quad \text{if and only if} \quad \tfrac{1}{3}(\alpha+\beta) < \alpha < 3\alpha - \beta\,. \tag{3.19c}$$

Therefore,

$$\min(\alpha, \tfrac{1}{3}(\alpha+\beta)) = \begin{cases} \tfrac{1}{3}(\alpha+\beta) & \text{if} \quad \beta \le 2\alpha\,, \\ \alpha \quad \text{if} \quad \beta \ge 2\alpha\,, \end{cases} \tag{3.20a}$$

$$\max(\alpha, 3\alpha - \beta) = \begin{cases} 3\alpha - \beta & \text{if} \quad \beta \le 2\alpha\,, \\ \alpha \quad \text{if} \quad \beta \ge 2\alpha\,. \end{cases} \tag{3.20b}$$

Now we briefly describe the bifurcation patterns underlying Proposition 3.1. If (3.17a) applies, then E_+ leaves the state space through E_{C} as m increases above m_{C}. If (3.17c) applies, then E_+ leaves the state space through E_{B} as m increases above m_{B}. The condition (3.17b) can be satisfied only if $\beta < 2\alpha$. In this case, E_- coexists with E_+. Then E_- enters the state space through E_{C} (if (3.18a) holds) or through E_{B} (if (3.18b) holds). As m increases further and approaches m^* from below, E_+ and E_- merge and get extinguished at $m = m^*$. In Figure 1, the possible equilibrium configurations and bifurcation patterns for $\alpha < \beta$ are displayed as a function of m.

We note that neither E_+ nor E_- can leave or enter the state space through E_{A}. This is easy to understand because B is the major locus and E_{A} exists only if $m < \alpha$, hence $m < \beta$. Therefore, whenever E_{A} exists, selection on locus B is strong enough to increase the frequency q of B_1 near E_{A} (as is reflected by the fact that the eigenvalue λ_+^{A} at E_{A} is always positive). Hence, no admissible equilibrium can be arbitrarily close to E_{A}.

It remains to explore the stability properties of the internal equilibria. Apparently, and also supported by numerical results, the equilibrium E_+ is asymptotically stable whenever it exists, and E_- is always unstable. We could prove the following: (i) E_+ is globally asymptotically stable if m is small (Section 3.4) or if ρ is small (Section 3.4). (ii) E_+ is asymptotically stable if ρ is large (Appendix A.2) or if m is close to (and below) a bifurcation value of E_+ (Appendix A.2). (iii) E_- is unstable if m is close to (and above) a bifurcation value of E_- (Appendix A.2). As shown by diagrams (b), (d), (e), and (f) of Figure 1 (which are based on these results), E_+ may be simultaneously stable with either E_B or E_C for sufficiently large migration rates, intermediate recombination rates, and similar locus effects. The above results support our conjecture that E_+ is globally asymptotically stable whenever it is the only fully polymorphic equilibrium. In Section 3.4, we will prove that E_C is globally asymptotically stable if $m \geq \alpha + \beta$.

3.3. Main results. We now formulate our main theorem from which most further conclusions will be derived. It is an immediate consequence of the above results about existence and stability of equilibria.

THEOREM 3.2. *Let $\alpha < \beta$. Then all possible equilibrium configurations, displayed as functions of the migration rate, are given by the schematic bifurcation diagrams (a) – (g) of Figure 1.*

Diagram (a) applies if and only if

$$\beta \geq 2\alpha \quad \textit{and} \quad \rho < \alpha \tag{3.21a}$$

or

$$\beta < 2\alpha \quad \textit{and} \quad \rho \leq \tfrac{1}{3}(\alpha + \beta)\,. \tag{3.21b}$$

Diagram (b) applies if and only if

$$\beta < 2\alpha \quad \textit{and} \quad \tfrac{1}{3}(\alpha + \beta) < \rho < \alpha\,. \tag{3.22}$$

Diagram (c) applies if and only if

$$\beta \geq 2\alpha \quad \textit{and} \quad \rho = \alpha\,. \tag{3.23}$$

Diagram (d) applies if and only if

$$\beta < 2\alpha \quad \textit{and} \quad \rho = \alpha\,. \tag{3.24}$$

Diagram (e) applies if and only if

$$\beta < 2\alpha \quad \textit{and} \quad \alpha < \rho \leq 3\beta - \alpha - 2\sqrt{2}\,\sqrt{\beta(\beta - \alpha)}\,. \tag{3.25}$$

Diagram (f) applies if and only if

$$\beta < 2\alpha \quad \textit{and} \quad 3\beta - \alpha - 2\sqrt{2}\sqrt{\beta(\beta-\alpha)} < \rho < 3\alpha - \beta\,. \tag{3.26}$$

Diagram (g) applies if and only if

$$\beta \geq 2\alpha \quad \textit{and} \quad \rho > \alpha \tag{3.27a}$$

or

$$\beta < 2\alpha \quad \textit{and} \quad \rho \geq 3\alpha - \beta\,. \tag{3.27b}$$

As a brief guide to these results and Figure 1, we note that, by (3.19), diagrams (a) or (c) of Figure 1 apply if (3.17a) holds. This is the case whenever $\rho \leq \frac{2}{3}\alpha$. Similarly, diagram (g) applies if (3.17c) holds, which is satisfied whenever $\rho > 2\alpha$. Thus, diagrams (a) or (g) apply whenever linkage is sufficiently tight or sufficiently weak, respectively. If α and β are fixed and $\beta \geq 2\alpha$, then for increasing ρ the diagrams (a), (c), and (g) apply in this order. If $\beta < 2\alpha$, then for increasing ρ diagrams apply in the order (a), (b), (d), (e), (f), and (g). Diagrams (b), (d), (e), (f) are covered by (3.17b). We distinguished cases (e) and (f) because E_+ can be simultaneously stable with E_B or E_C in (e), but only with E_B in (f).

The following arguments offer an explanation why qualitatively different equilibrium configurations can occur for $\beta \geq 2\alpha$ and $\beta < 2\alpha$. At $\alpha = \frac{1}{2}\beta$, the order of fitnesses of diploid genotypes changes. If $\beta \geq 2\alpha$ (i.e., the selection coefficients are very different), the three genotypes of highest fitness are those composed by the two gametes A_1B_1 and A_2B_1. If $\beta < 2\alpha$ (i.e., similar locus effects), the three genotypes of highest fitness are A_1B_1/A_1B_1, A_1B_1/A_2B_1, and A_1B_1/A_1B_2. Hence, A_1 experiences a higher (relative) fitness advantage than in the other case and, by symmetry, A_2 a higher fitness disadvantage. Recombination between the island and the continental haplotype always produces both gametes A_2B_1 and A_1B_2. If $\beta < 2\alpha$, moderately strong recombination can maintain the fully polymorphic equilibrium even if one of the boundary equilibria E_B or E_C is already (locally) stable. In addition, if β is given, the overall strength of selection increases with increasing α, thus facilitating the maintenance of polymorphism in the presence of gene flow.

Since the case $\alpha = \beta$ of equivalent loci is degenerate, we formulate it separately.

THEOREM 3.3. *Let $\alpha = \beta$. Then all possible equilibrium configurations, displayed as functions of the migration rate, are given by the schematic bifurcation diagrams (a) – (d) of Figure 2.*

Diagram (a) applies if and only if

$$\rho \leq \tfrac{2}{3}\alpha\,. \tag{3.28}$$

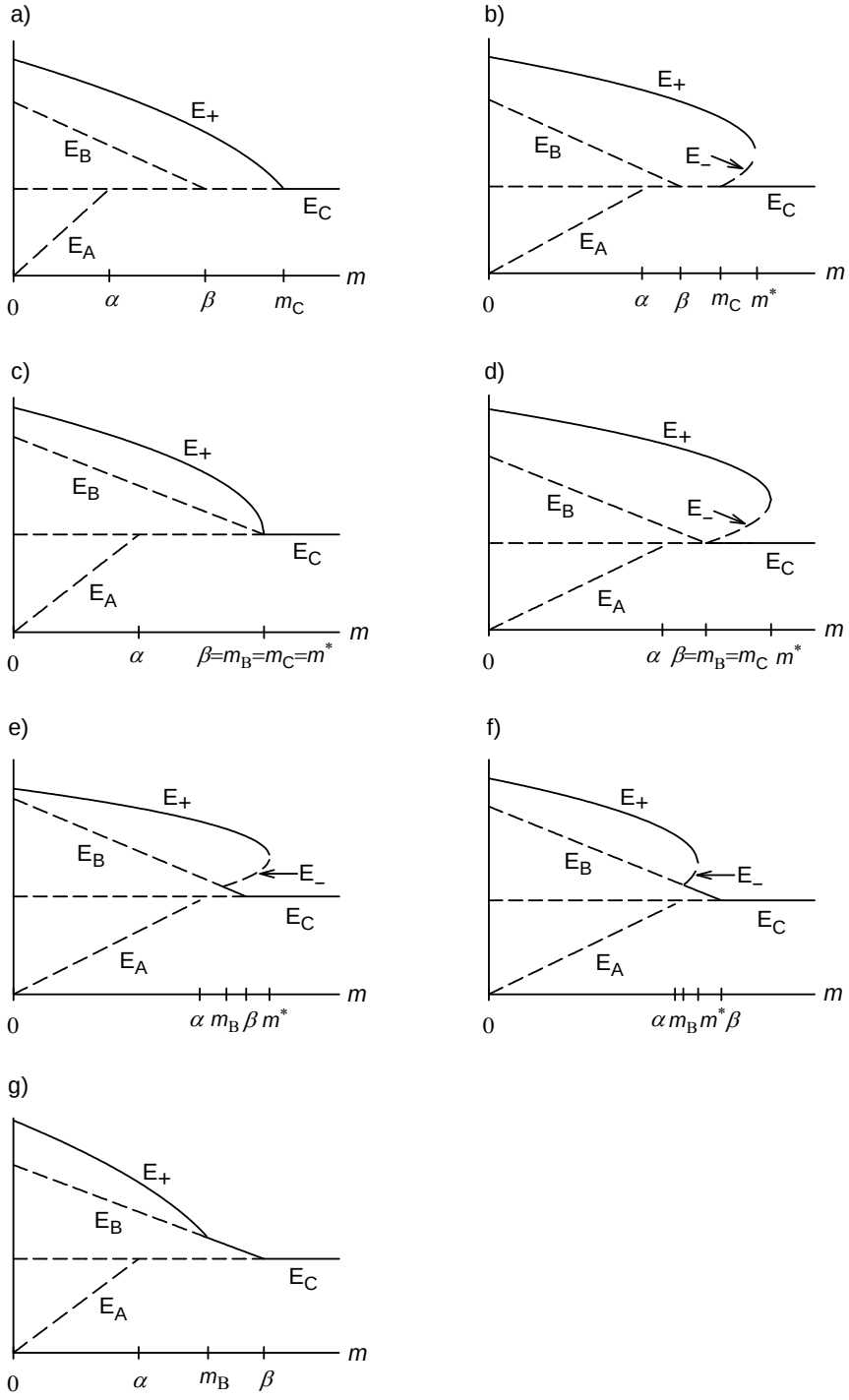

FIGURE 1. Bifurcation diagrams for the case $\alpha < \beta$. Diagrams (a) - (g) represent all possible equilibrium configurations, corresponding to the cases (a) - (g) in Theorem 3.2. Each diagram displays the possible equilibria as a function of the migration rate m. Each line indicates one equilibrium. The lines are drawn such that intersections occur if and only if the corresponding equilibria bifurcate. Solid lines represent asymptotically stable equilibria, dashed lines unstable equilibria. Equilibria are shown if and only if they are admissible. (The curves in this diagrams can be produced by using the function $f(m) = \sqrt{\hat{x}_1(m)} + \frac{1}{2}(\hat{x}_3(m) - \hat{x}_2(m)) = \sqrt{\hat{p}(m)\hat{q}(m) + \hat{D}(m)} + \frac{1}{2}(\hat{q}(m) - \hat{p}(m))$. For optimal visibility, diagrams have been drawn for different parameter choices and on different scales.)

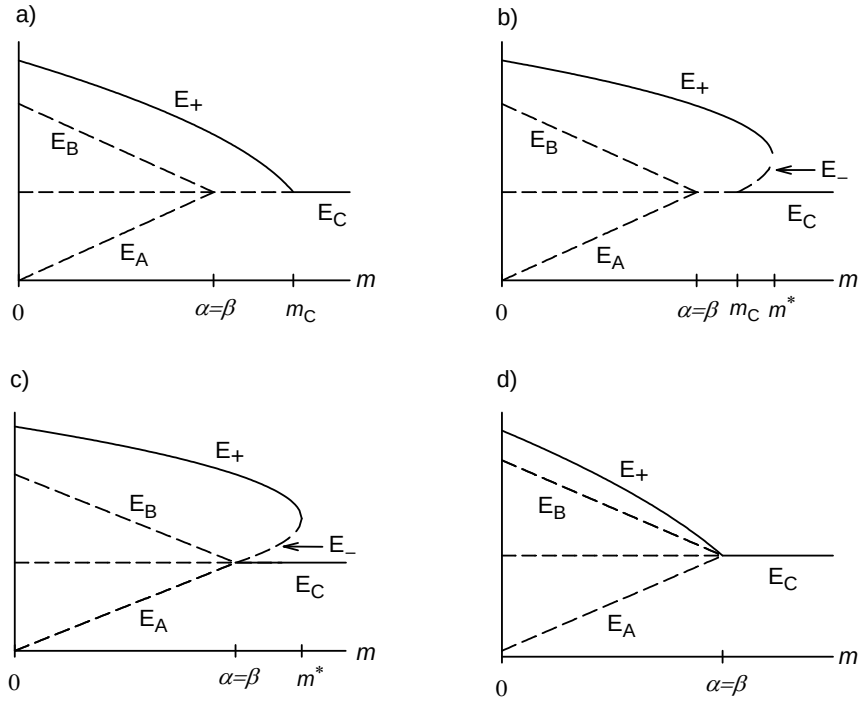

FIGURE 2. Bifurcation diagrams for the case $\alpha = \beta$. Diagrams (a) – (d) represent all possible equilibrium configurations, corresponding to the cases (a) – (d) listed in Theorem 3.3. Note that in this case we have $m_A = m_B = \alpha = \beta$. Everything else is as in Figure 1.

Diagram (b) applies if and only if

$$\tfrac{2}{3}\alpha < \rho < \alpha\,. \tag{3.29}$$

Diagram (c) applies if and only if

$$\alpha \le \rho \le 2\alpha\,. \tag{3.30}$$

Diagram (d) applies if and only if

$$\rho > 2\alpha\,. \tag{3.31}$$

Because $m_A = m_B = \alpha = \beta$ holds in Theorem 3.3, E_A and E_B bifurcate through E_C simultaneously. Hence, coexistence of E_+ and E_- occurs if and only if $\frac{2}{3}\alpha < \rho < 2\alpha$ and $\max(\alpha, 2\alpha - \rho) < m < m^*$. Using (A.13) and (3.18), it is straightforward to show that the interval (of values m) of coexistence of E_+ and E_- is maximized if $\alpha = \rho$. Then, $m^* = \frac{9}{8}\alpha$.

3.4. Global convergence results. Here, we prove global convergence results for some limiting cases.

$m = 0$. We show that E_I is globally asymptotically stable. For additive fitnesses, mean fitness increases strictly monotonically in time, except at equilibria (Ewens 1969). In our special case, mean (Malthusian) fitness on the island is given by $\bar{w} = \alpha(2p - 1) + \beta(2q - 1)$ which is maximized at E_I. Employing the well-known inequality $D \geq -\sqrt{p(1-p)q(1-q)}$, we obtain

$$\dot{\bar{w}} = 2\alpha\dot{p} + 2\beta\dot{q} \geq 2\left(\alpha\sqrt{p(1-p)} - \beta\sqrt{q(1-q)}\right)^2 \geq 0\,, \tag{3.32}$$

where $\dot{\bar{w}} = 0$ holds only at equilibrium. Because the only equilibria are the four monomorphic states, and E_I is the only stable equilibrium, all trajectories such that initially both alleles are present converge to E_I (Theorem 6.4 and Corollary 6.5 in LaSalle 1976). This conclusion can also be deduced from Theorem 3 of Karlin and Feldman (1970).

Small m. We prove global convergence to E_+ if m is sufficiently small. The proof follows immediately from Theorem 5.4 in Bürger (2009a), which is a general global perturbation result for weak migration. This applies here because, for $m = 0$, all equilibria (which are exactly the four monomorphic states) are hyperbolic, E_I is globally asymptotically stable (Section 3.4), and E_+ is the perturbation of E_I if m is small. We note that the results by Karlin and McGregor (1972) imply only asymptotic stability.

Large m. We demonstrate global convergence to E_C if $m \geq \alpha + \beta$. Because $D \leq p(1-q)$ holds always, we obtain from (2.5a)

$$\dot{p} \leq p(\alpha + \beta - m - \alpha p - \beta q) \leq 0\,, \tag{3.33}$$

and $\dot{p} = 0$ if and only if $p = 0$. Analogously, $D \leq q(1-p)$ implies $\dot{q} \leq 0$ with equality if and only if $q = 0$. Thus, we have two global Lyapunov functions, and all trajectories must converge to $p = q = 0$, i.e., to E_C (LaSalle 1976).

$\rho = 0$. We prove that E_0 is globally asymptotically stable whenever it exists (i.e., if $0 < m < \alpha + \beta$). Asymptotic stability follows immediately from the eigenvalues, which are given by $-\alpha$, $-\beta$, and $m - (\alpha + \beta)$. We prove global convergence to E_0 if initially the island haplotype A_1B_1 is present, i.e., if $x_1 > 0$. (Note that $x_1(t) = 0$ for every $t > 0$ if $x_1(0) = 0$.) We observe that

$$\left(\frac{x_3}{x_1}\right)^{\cdot} = -\alpha x_1 x_3\,, \tag{3.34}$$

and

$$\left(\frac{x_2}{x_1}\right)^{\cdot} = -\beta x_1 x_2\,. \tag{3.35}$$

Thus, we infer that the ω-limit of every trajectory with $x_1 > 0$ is contained in the invariant edge $x_2 = x_3 = 0$ (LaSalle 1976). On this edge, single-locus theory guarantees global convergence to E_0.

If, initially, $x_1 = 0$ and $x_3 > 0$, then $(x_2/x_3)^{\cdot} = (\alpha - \beta)x_2x_3 < 0$ (provided $\alpha \neq \beta$) and convergence to E_B occurs whenever it is admissible; otherwise, all trajectories converge to E_C. Of course, if $x_1 = x_3 = 0$ holds initially, then all trajectories converge to E_A (if it is admissible) or to E_C. The simple case $\alpha = \beta$ is left to the reader.

We note that for $\rho = 0$, the dynamics (2.2) has the global Lyapunov function

$$V = V(x_1, x_2, x_3, x_4) = \frac{1}{2}\bar{w} + m \ln x_4 \,. \tag{3.36}$$

This follows immediately from equations (2.13) - (2.16) on p. 103 in Bürger (2000) because, if $\rho = 0$, the system (2.2) is formally equivalent to a one-locus selection-mutation model with four alleles and so-called house-of-cards mutation. To see this, set all mutation rates to types 1, 2, and 3 (gametes A_1B_1, A_1B_2, A_2B_1) zero, and assume that each of types 1, 2, and 3 mutates to type 4 (A_2B_2) at rate m. Therefore (p. 103 in Bürger 2000), (2.2) is a generalized gradient system.

Small ρ. We prove global convergence of all trajectories to E_+ if ρ is sufficiently small and $m < m_C$. The crucial point is that the results in Section 3.4 imply that, if $\rho = 0$, the chain-recurrent points of (2.2) are exactly the equilibria (see Lemma 2.2 in Nagylaki et al. 1999). The only possible equilibria are E_A, E_B, and E_C, and they are hyperbolic if ρ is small (except when $m = \alpha$ or $m = \beta$). As a consequence, the proof of Theorem 2.3 in Nagylaki et al. (1999) applies unaltered and yields global convergence to E_+ for sufficiently small ρ. Asymptotic (local) stability of E_+ can also be inferred from Theorem 4.4 of Karlin and McGregor (1972).

4. Applications

We now treat a number of applications. We begin by deriving simple approximations for the stable fully polymorphic equilibrium E_+ in several limiting cases. Then we discuss the potential of maintaining both loci polymorphic on the island. Next, we explore the LD that is maintained by calculating and approximating the measures D and r^2. We continue by studying the invasion of a new beneficial mutation of small effect which is linked to a locus that is maintained polymorphic on the island by migration-selection balance. Then we investigate the degree of local adaptation and the migration load. Finally, we compute an approximation for the effective migration rate at a neutral locus that is linked to both selected loci.

4.1. Limiting cases. The following limiting cases are highly instructive and will be used in the applications treated below. In each case, we give the coordinates of the stable internal equilibrium E_+. They are readily deduced from equations (3.15) by using a formula manipulation program, such as *Mathematica*.

Weak migration. We assume that migration is much weaker than selection and recombination, i.e., $m \ll \min(\alpha, \rho)$. Then E_+ is given by

$$\hat{p}_+ = 1 - \frac{m}{\alpha}\left(1 - \frac{\beta}{\alpha+\beta+\rho}\right) + m^2 \frac{\rho(\beta-\alpha-\rho)}{\alpha(\alpha+\beta+\rho)^3} + O(m^3)\,, \tag{4.1a}$$

$$\hat{q}_+ = 1 - \frac{m}{\beta}\left(1 - \frac{\alpha}{\alpha+\beta+\rho}\right) - m^2 \frac{\rho(\beta-\alpha+\rho)}{\beta(\alpha+\beta+\rho)^3} + O(m^3)\,, \tag{4.1b}$$

$$\hat{D}_+ = \frac{m}{\alpha+\beta+\rho} - m^2 \frac{\alpha\beta(\alpha+\beta) + \rho(\alpha^2+\alpha\beta+\beta^2) + \rho^2(\alpha+\beta)}{\alpha\beta(\alpha+\beta+\rho)^3} + O(m^3)\,, \tag{4.1c}$$

where the second-order terms will be needed to derive the series expansion of the LD measure r^2. We note that for equivalent loci ($\alpha = \beta$), the first-order terms can be obtained from Barton's (1983) weak-migration approximation (8) for multiple equivalent loci.

Tight linkage. If we assume that recombination is much weaker than selection and migration, i.e., $\rho \ll \min(\alpha, m)$, then E_+ is given by

$$\hat{p}_+ = 1 - \frac{m}{\alpha+\beta} - \frac{\rho m}{(\alpha+\beta)^2}\left[\frac{\beta}{\alpha} - \frac{m}{\alpha+\beta}\left(\frac{\beta}{\alpha} - 1\right)\right] + O(\rho^2)\,, \tag{4.2a}$$

$$\hat{q}_+ = 1 - \frac{m}{\alpha+\beta} - \frac{\rho m}{(\alpha+\beta)^2}\left[\frac{\alpha}{\beta} - \frac{m}{\alpha+\beta}\left(\frac{\alpha}{\beta} - 1\right)\right] + O(\rho^2)\,, \tag{4.2b}$$

$$\hat{D}_+ = \frac{m}{\alpha+\beta}\left(1 - \frac{m}{\alpha+\beta}\right) \tag{4.2c}$$

$$- \frac{\rho m}{(\alpha+\beta)^2}\left[1 - \frac{m}{\alpha+\beta}\left(1 - \frac{m}{\alpha+\beta}\right)\left(2 - \frac{\beta}{\alpha} - \frac{\alpha}{\beta}\right)\right] + O(\rho^2)\,. \tag{4.2d}$$

It is a straightforward exercise to show that this is admissible if $m < m_\mathrm{C} + O(\rho^2)$.

Strong recombination. If recombination is strong relative to selection and migration, i.e., $\rho \gg \max(\beta, m)$, then the internal equilibrium E_+ is given by

$$\hat{p}_+ = 1 - \frac{m}{\alpha} + \frac{m}{\rho}\frac{\beta - m}{\alpha} + O(\rho^{-2})\,, \tag{4.3a}$$

$$\hat{q}_+ = 1 - \frac{m}{\beta} + \frac{m}{\rho}\frac{\alpha - m}{\beta} + O(\rho^{-2})\,, \tag{4.3b}$$

$$\hat{D}_+ = \frac{m}{\rho}\left(1 - \frac{m}{\alpha}\right)\left(1 - \frac{m}{\beta}\right) + O(\rho^{-2})\,. \tag{4.3c}$$

To leading order in $1/\rho$, this equilibrium is admissible if

$$m < m_\mathrm{B}\,. \tag{4.4}$$

In the limit $\rho \to \infty$, this condition simplifies to $m < \alpha$. Obviously, $\hat{D}_+ \to 0$ as $m/\rho \to 0$ or $m/\alpha \to 1$. (4.3) may be called the quasi-linkage equilibrium approximation.

4.2. Maintenance of polymorphism. The above results admit some worthwhile conclusions about the maintenance of polymorphism at two linked loci. It is well known that at an isolated single locus, i.e., if LD is ignored, a polymorphism is maintained on the island if and only if $0 < m < s$, where the fitnesses of the three genotypes are $1 - s$, 1, and $1 + s$ (Haldane 1930, Nagylaki 1975). Naive application of this result to our model would imply that both loci can be maintained polymorphic only if $m < \min(\alpha, \beta) = \alpha$. However, as we show below, the effects of linkage, even if weak, cannot be ignored. Our analysis is simplified by the facts that (i) E_+ is the only stable equilibrium at which the island haplotype, hence a polymorphism at both loci, is maintained, and (ii) E_+ is (apparently) asymptotically stable whenever it exists.

If (3.27) holds (Figure 1g), which is always the case if recombination is at least twice as strong as selection on the minor locus, the full polymorphism E_+ is maintained if

$$m < m_B \,. \tag{4.5}$$

As (3.11) shows, we have $\alpha < m_B < \beta$ if $\rho > \alpha$ (and $\alpha < \beta$), where the upper bound m_B tends to α as $\rho \to \infty$, and m_B tends to β as $\rho \to \alpha$. Therefore, if recombination is not much stronger than selection on the minor locus, a fully polymorphic equilibrium can be maintained for considerably higher migration rates than predicted by single-locus theory, namely up to values of m that are only slightly smaller than β.

If linkage is tight, i.e., if $\rho \ll \min(\alpha, m)$, then a two-locus polymorphism is maintained if (Section 4.1)

$$m < m_C + O(\rho^2) \,. \tag{4.6}$$

In the limit $\rho \to 0$, this yields $m < \alpha + \beta$, the bound obtained from a diallelic one-locus model if the alleles are identified with the non-recombining haplotypes A_1B_1 and A_2B_2.

For moderately strong linkage and if the effects of the two loci are similar, polymorphism at both loci can be maintained for migration rates higher than $\max(\beta, m_C)$. This occurs if and only if diagrams (b), (d), or (e) of Figure 1 apply (corresponding to the conditions (3.22), (3.24), or (3.25)), or if diagrams (b) or (c) of Figure 2 apply (corresponding to conditions (3.29) or (3.30)). Then the polymorphic equilibrium E_+ is simultaneously stable with the equilibrium E_C at which the continental haplotype is fixed. Although, in general, this range of parameters is not large, it becomes significant for loci of approximately equal effects. As noted above, this range is maximized if $\alpha = \beta = \rho$. Then $m_B = m_C = \beta$ and a full polymorphism is maintained if $m < m^* = \frac{9}{8}\beta$.

In summary, polymorphism at both loci can be maintained for higher migration rates than expected from simple one-locus considerations. Once $m \geq \alpha + \beta$, migration is strong enough to fix the continental haplotype independently of linkage and initial conditions (Section 3.4).

4.3. Linkage disequilibrium. The amount of LD maintained by migration-selection balance on the island can be computed readily because we have the explicit expression (3.15c) for the measure D of LD maintained at E_+. We also know that this is the only fully polymorphic equilibrium that can be stable. In Appendix A.3 it is proved that the measure D is always positive at E_+. Thus, the interaction of nonepistatic selection on the island and immigration from the continent generates positive LD.

For statistical purposes, the following measure of LD is often used (e.g., Nordborg and Tavaré 2002, Slatkin 2008):

$$r^2 = \frac{D^2}{p(1-p)q(1-q)}\,. \tag{4.7}$$

It can be interpreted as the squared correlation in allelic state between the two loci. A general, though complicated, expression for r^2 can be obtained directly from (3.15). We investigate D and r^2 analytically for limiting cases and numerically otherwise.

We start by examining weak migration, i.e., $m \ll \min(\alpha, \rho)$. At the polymorphic equilibrium E_+, we obtain from equations (4.1)

$$\hat{D}_+ = \frac{m}{\alpha+\beta+\rho} + O(m^2) \tag{4.8}$$

and, by series expansion (for which the second-order terms in equations (4.1) are needed),

$$\hat{r}^2 = \frac{\alpha\beta}{(\alpha+\rho)(\beta+\rho)} - \frac{m\rho^2[\alpha^2+\beta^2+\rho(\alpha+\beta)]}{(\alpha+\rho)^2(\beta+\rho)^2(\alpha+\beta+\rho)} + O(m^2)\,. \tag{4.9}$$

Notably, $\hat{r}^2$ does not vanish as $m \to 0$. In fact, $\hat{r}^2$ is a decreasing function of both ρ and m. It decays rapidly as a function of ρ, and very slowly as a function of m if ρ is small. Thus, for tightly linked loci, $\hat{r}^2$ is close to its maximum value one. Even if selection and recombination are of comparable strength, $\hat{r}^2$ may assume relatively high values if migration is weak. This is illustrated by Figure 3b, in which $\beta/\rho = 2$ is assumed, and by the following examples. If $\rho = \alpha$, the leading order term in (4.9) becomes $\beta/(2(\alpha+\beta))$, which is between $\frac{1}{2}$ (if $\alpha = 0$) and $\frac{1}{4}$ (if $\alpha = \beta$). The leading-order term in (4.9) is small if α/ρ is small, and very small if β/ρ is small. If $\alpha = \beta$, the expression (4.8) is also obtained from Barton's (1983) weak-migration approximation (8b); cf. Section 4.1.

For weak recombination, i.e., if $\rho \ll \min(\alpha, m)$, we obtain from Section 4.1 the expansion

$$\hat{r}^2 = 1 - \rho\,\frac{\alpha+\beta}{\alpha\beta} + \rho^2\,\frac{\alpha^3+2\alpha^2\beta+2\alpha\beta^2+\beta^3-m(\alpha^2+\beta^2)}{\alpha^2\beta^2(\alpha+\beta)} + O(\rho^3)\,, \tag{4.10}$$

where the first-order term is independent of m. Setting $\beta = n\alpha$, we observe that $\hat{r}^2 = 1 - (1+1/n)\rho/\alpha + O(\rho^2)$. Thus, for small ρ, $\hat{r}^2$ decreases from unity at a linear rate between $1/\alpha$ and $2/\alpha$.

In the limit of large ρ, we obtain from Section 4.1 that $\hat{r}^2$ decays quadratically in ρ:

$$\hat{r}^2 = \frac{(\alpha - m)(\beta - m)}{\rho^2} + O(\rho^{-3})\,. \tag{4.11}$$

This approximation requires $m < \alpha$. Obviously, we have $\hat{r}^2 \to 0$ as $m \to \alpha$.

Figure 3 displays $\hat{D}_+$ and $\hat{r}^2$ as functions of m/ρ for various parameter combinations.

It seems remarkable that $\hat{D}$ and $\hat{r}^2$ show such different behavior if considered as functions of m. Whereas $\hat{D}$ always assumes its maximum at intermediate migration rates, the squared correlation $\hat{r}^2$ always decreases as m increases. The latter fact is clearly indicated by the approximations (4.9) and (4.11).

That $\hat{r}^2$ tends to a positive value (as opposed to zero) as $m \to 0$ follows from its definition because, as shown by (4.8), at migration-selection balance D is of order m and, of course, the frequencies of both continental alleles are of order m. That D is of order m, and not smaller, follows because immigration of the continental haplotype increases the rate of change of D by $m(pq - D) = mpq + o(m) = m + o(m)$, whereas the contributions of selection and recombination are proportional to D, hence of order m only if $D = O(m)$; see (2.5c). A more intuitive explanation is that for arbitrarily weak migration and tight linkage, the population exists predominantly of A_1B_1 and A_2B_2 haplotypes because the other haplotypes are produced only at the small rate ρ. The stronger selection on A_2B_2 is insufficient to decrease the frequency of A_2B_2 to values below those of the recombinant haplotypes. Clearly, this leads to a high correlation in allelic state.

We note without proof that Lewontin's (1964) measure $D' = D/\max(p(1-q), q(1-p))$ behaves qualitatively similar to $r = \sqrt{r^2}$. In summary, migration may be a very efficient agent in inducing quite strong LD, even if selection is genic and weak.

4.4. Invasion of a linked beneficial mutation. In accordance with the general model, immigrants from the continent are of gametic type A_2B_2. Let us assume that at locus B a locally adapted allele, B_1, is segregating at migration-selection balance on the island. By single-locus theory, this requires $\beta > m$. The corresponding equilibrium in our model is $\mathrm{E_B}$. Now suppose that on the island a favorable mutant, A_1, occurs at the linked locus A. Because our model is deterministic, the mutant can invade if and only if $\mathrm{E_B}$ is unstable. By (3.13) this is the case if and only if

$$0 < m < \min(m_{\mathrm{B}}, \beta)\,. \tag{4.12}$$

Mutants of effect $\alpha > m$ can invade for every recombination rate ρ (which is consistent with the fact $\alpha < m_{\mathrm{B}}$). In addition, mutants of effect $\alpha \geq \rho$ can invade for every migration rate $m < \beta$ because this implies $m < \beta \leq m_{\mathrm{B}}$, hence (4.12). This reflects the intuition

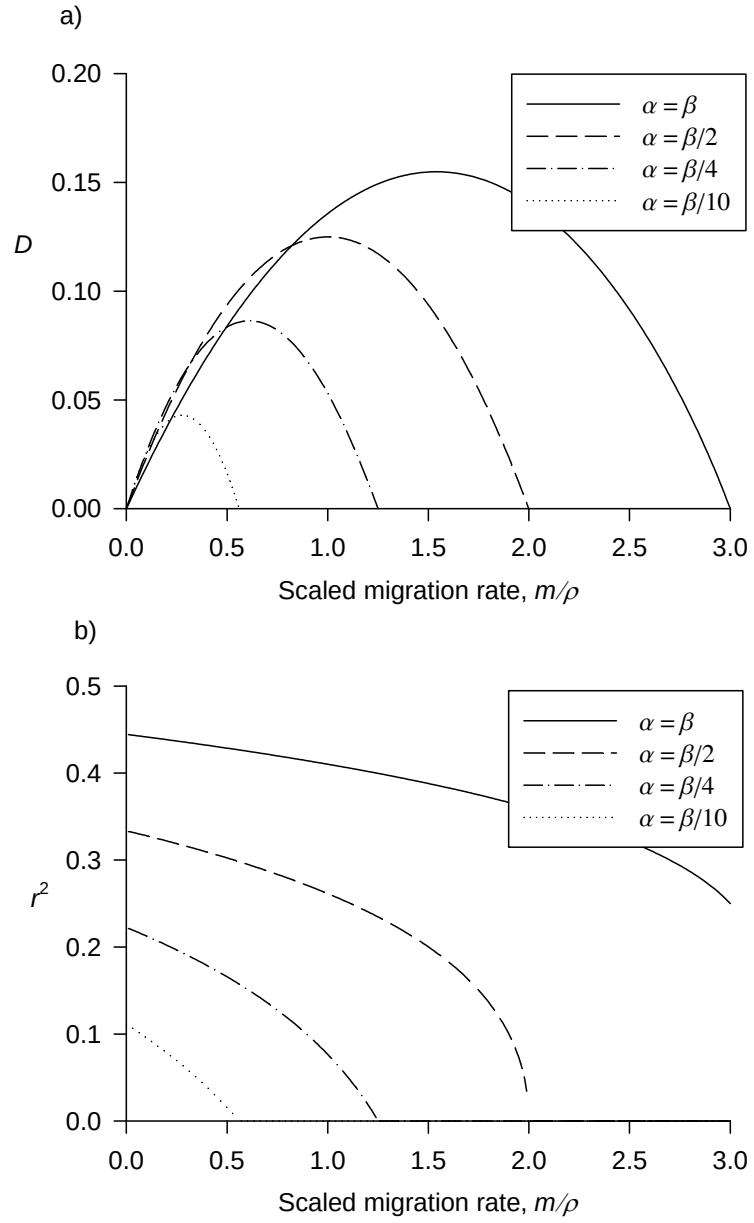

FIGURE 3. Linkage disequilibrium at the stable two-locus polymorphism. Respectively, diagrams (a) and (b) display the measures D and r^2 of LD as a function of m/ρ. D is calculated from (3.15c) ($D = \hat{D}_+$) and r^2 from D and (4.7). We note that D and r^2 are represented in terms of the compound parameters α/ρ, β/ρ, and m/ρ, which determine the model and all derived quantities uniquely. In both figures, $\beta/\rho = 2$ is assumed and α is as indicated in the legend. Diagram (b) might give the impression that LD decreases with decreasing recombination rate ρ. This, however, is not the case (e.g., (4.9)) because the compound parameters $\alpha/\rho, \beta/\rho$, and m/ρ are used. Hence, a decrease in ρ implies a decrease in α and β.

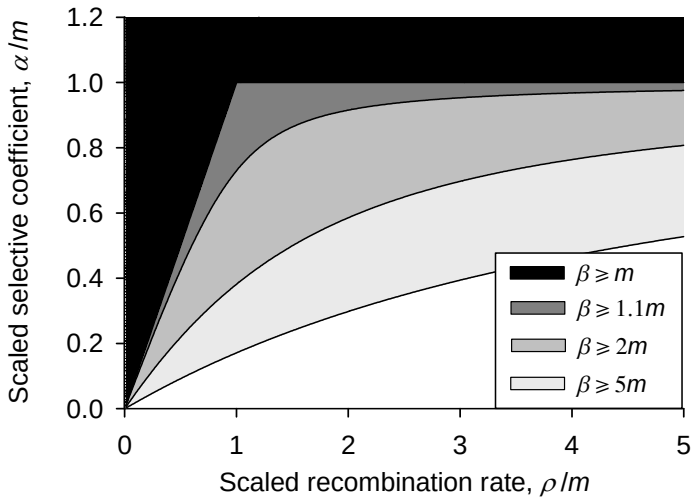

FIGURE 4. Regions of invasion of mutants of small effect. The shaded regions display the scaled fitness advantage α/m admitting invasion of a mutant linked to a beneficial allele that is in migration-selection balance on the island. The curves are obtained from (4.13) and show $\alpha_{\min}/m$ as a function of ρ/m for different values of β/m. As explained in the main text, mutants of effect $\alpha \geq \max(m, \rho)$ can invade whenever $m < \beta$ (black region).

that sufficiently strong linkage leads to reinforcement between the loci, thereby enabling invasion of A_1.

However, condition (4.12) implies that even mutants of effect $\alpha < \min(m, \rho)$ can invade. Indeed, straightforward rearrangement shows that $m < m_{\mathrm{B}}$ holds if and only if

$$\alpha > \alpha_{\min} = \frac{1}{2}\left(\beta + \rho - \sqrt{(\beta+\rho)^2 - 4m\rho}\right). \tag{4.13}$$

Hence, $\alpha_{\min}$ is the minimum selective advantage required for invasion. Figure 4 displays the dependence of $\alpha_{\min}$ on ρ and m.

If $\rho \ll \beta$, the condition (4.13) for the invasion of A_1 becomes approximately

$$\alpha \geq m\frac{\rho}{\beta}, \tag{4.14}$$

where the right hand side is much smaller than m. The invasion condition (4.13) can also be rewritten as

$$\rho < \frac{\alpha(\beta-\alpha)}{m-\alpha} \approx \frac{\alpha\beta}{m}, \tag{4.15}$$

where the approximation holds if $\alpha \ll m$. Thus, for given effect α, (4.15) puts an upper bound on the recombination rate that permits invasion.

After invasion of A_1, the asymptotically stable equilibrium E_+ is approached. Because $\hat{q}_+ > 1 - m/\beta$ if E_{B} is unstable (Appendix A.3), the frequencies of both island

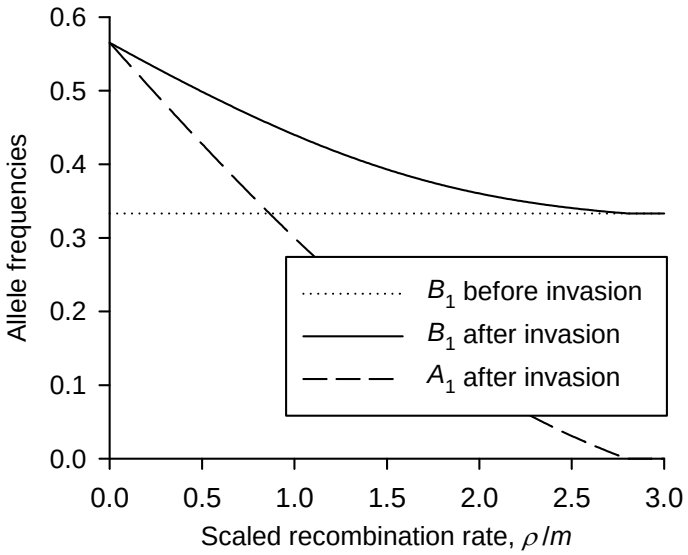

FIGURE 5. Frequencies of island alleles after invasion of a new mutant. The solid lines show the frequencies $\hat{p}_+$ and $\hat{q}_+$ of the island alleles reached at the equilibrium E_+, (3.15), after invasion of a mutant (A_1) of small effect α. The frequency of A_1 decreases faster as a function of ρ/m and vanishes if ρ/m is such that equality is attained in (4.13). The dashed lines signify the equilibrium frequency $\hat{q} = 1 - m/\beta$ of B_1 before invasion of A_1. The selection coefficients are $\alpha = 0.8m$ and $\beta = 1.5m$. Qualitatively similar graphs are obtained for other choices of selection coefficients.

alleles increase. This is demonstrated by Figure 5, in which the frequencies of the alleles before and after invasion are displayed as functions of ρ/m.

Not surprisingly, the largest increase occurs if the new mutant is completely linked ($\rho = 0$). Then the frequencies of both island alleles increase to $1 - m/(\alpha + \beta)$ because E_0 is the (unique) stable equilibrium. The figure shows that the frequencies of the island alleles at the polymorphic equilibrium decrease with increasing recombination rate, and this is proved in Appendix A.3. Figure 5 demonstrates that the invasion of a tightly linked mutant of smaller effect can elevate the frequency of the previously present island allele (B_1) considerably. In the displayed example, if ρ/m is small, the frequency of B_1 is pushed above 50%. Thus, B_1 becomes more frequent than the continental allele B_2.

4.5. Local adaptation and migration load. Local adaptation is impossible if gene flow is so strong that the equilibrium E_C, at which the continental haplotype is fixed, is globally asymptotically stable. By Theorem 3.2, this is the case if

$$\rho \le \min(\alpha, \tfrac{1}{3}(\alpha + \beta)) \quad \text{and} \quad m \ge m_C\,, \tag{4.16}$$

or if

$$\rho > \min(\alpha, \tfrac{1}{3}(\alpha+\beta)) \quad \text{and} \quad m \geq \max(\beta, m^*)\,. \tag{4.17}$$

Because the mean (Malthusian) fitness on the island is $\bar{w} = \alpha(2p-1) + \beta(2q-1)$, the mean fitness at E_C is $\bar{w} = -\alpha - \beta$, whereas in the absence of gene flow (at E_I) it is $\bar{w} = \alpha + \beta$.

However, local adaptation may already be severely reduced if gene flow is strong enough to eradicate the island haplotype A_1B_1 (but not the island allele B_1). Then the single-locus polymorphism E_B is asymptotically stable. By Theorem 3.2, this occurs if

$$\rho \geq \max(\alpha, 3\alpha - \beta) \quad \text{and} \quad m_B < m < \beta \tag{4.18}$$

holds, but also if (3.25) or (3.26) are satisfied and $m_B < m < \beta$ (Figure 1). The mean fitness at E_B is $\bar{w} = \beta - \alpha - 2m$.

If gene flow is sufficiently weak to maintain both alleles in the population, the degree of local adaptation can be measured by the migration load, by the frequencies of the island alleles, or by the frequency of the island haplotype.

First, we briefly investigate the migration load at the fully polymorphic equilibrium E_+. Because $\hat{p}_+$ and $\hat{q}_+$ are decreasing functions of m and of ρ (Appendix A.3), the same is true for mean fitness. For the mean fitness at E_+, we obtain

$$\hat{\bar{w}} = \frac{1}{2}\left(\alpha + \beta - \rho - 4m + \sqrt{(\alpha+\beta+\rho)^2 - 8m\rho}\right) \tag{4.19a}$$

$$= \alpha + \beta - 2m\left(1 + \frac{\rho}{\alpha+\beta+\rho}\right) + O(m^2)\,, \tag{4.19b}$$

where the approximation holds for weak migration (Section 4.1). Thus, the migration load increases from (approximately) $2m$ for completely linked loci to $4m$ for independent loci. Simple approximations for other limiting cases are readily derived from Section 4.1.

For weak gene flow, the frequencies of the island alleles are given by (4.1). From (4.1) and (2.3), the following first-order approximation in m is obtained for the frequency of the island haplotype:

$$\hat{x}_{+,1} \approx 1 - m\,\frac{\alpha\beta + \rho(\alpha+\beta)}{\alpha\beta(\alpha+\beta+\rho)}\,. \tag{4.20}$$

This, as well as (4.1), is accurate for a fairly large range of parameters. Remarkably, if $\rho = 0$, the linear approximations for the allele and gamete frequencies give the exact solutions, i.e., the equilibrium values at E_0. Therefore, (4.1) and (4.20) provide highly accurate approximations if $\rho < \min(\alpha, \frac{1}{3}(\alpha+\beta))$ and $m < \frac{1}{2}m_C$. Figure 6 displays the exact value and the weak-migration approximation of $\hat{x}_{+,1}$ for various parameter combinations.

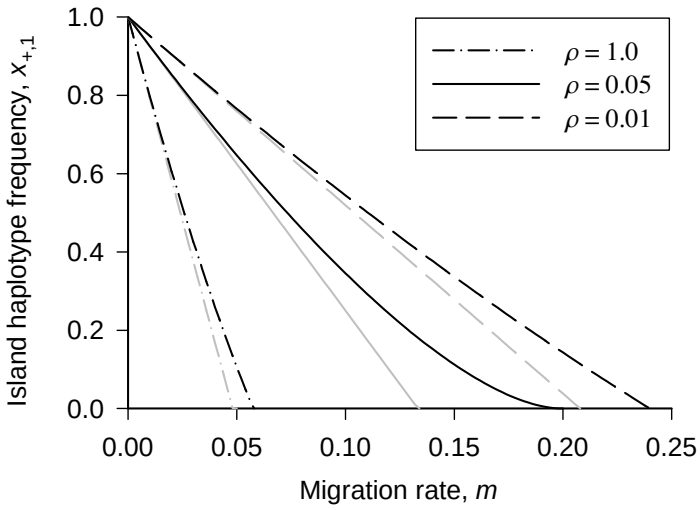

FIGURE 6. Frequency of the island haplotype A_1B_1 as a function of the migration rate for various parameter combinations. The exact value of $\hat{x}_{+,1}$ is displayed by black lines, the corresponding approximation (4.20) by gray lines of the same line type. Dashing indicates different recombination rates, as given in the legends. The selection coefficients are $\alpha = 0.05$ and $\beta = 0.2$.

As this figure shows, (4.20) is also very accurate if $\rho > \min(\alpha, \frac{1}{3}(\alpha+\beta))$ and $m < \frac{1}{2}m_B$. In general, (4.20) provides a useful approximation if $\hat{x}_{+,1} > \frac{1}{2}$.

Finally, we explore the case when the island alleles are maintained at frequencies greater than $\frac{1}{2}$, so that they are more frequent than the alternative continental alleles, and when the island haplotype has a frequency greater than $\frac{1}{2}$. As is suggested by Figures 5 and 6, and proved in Appendix A.3, the frequencies of both island alleles at the stable fully polymorphic equilibrium E_+ increase with increasing linkage and are maximized if $\rho = 0$. A rough estimate for the maximum value m that guarantees that $\hat{x}_{+,1} \geq \frac{1}{2}$ is obtained from (4.20):

$$m_{\frac{1}{2}} = \frac{\alpha\beta(\alpha+\beta+\rho)}{2(\alpha\beta+\rho(\alpha+\beta))}. \tag{4.21}$$

For small ρ, the following slightly more accurate approximation for the critical value of m is obtained directly from the tight-linkage approximation (4.2):

$$m'_{\frac{1}{2}} = \tfrac{1}{2}(\alpha+\beta) - \rho\,\frac{(\alpha+\beta)^2}{4\alpha\beta}. \tag{4.22}$$

Here, the error (i.e., $\left|\hat{x}_{+,1} - \frac{1}{2}\right|$) is $\frac{3}{8}\rho^2/(\alpha\beta) + O(\rho^3)$. If $\rho \geq \min(\alpha, \frac{1}{3}(\alpha+\beta))$, the approximation (4.22) fails, and (4.21) is more accurate.

We treat two examples. If $\rho = \alpha = \beta$, we compute from (3.15) that both island alleles are more frequent than the respective continental alleles if $m < \beta/\sqrt{2} \approx 0.707\beta$, and $\hat{x}_{+,1} > \frac{1}{2}$ if $m < (1 - 2^{-1/3} - 2^{1/3})\beta \approx 0.534\beta$. The approximation (4.21) produces $m < \frac{1}{2}\beta$.

In the extreme case that LD is negligible, i.e., if selection is very weak relative to recombination, the more advantageous allele (B_1) has a frequency greater than $\frac{1}{2}$ if $m < \frac{1}{2}\beta$. Both island alleles are more frequent than the respective continental alleles if $m < \frac{1}{2}\alpha$. The island haplotype frequency exceeds $\frac{1}{2}$ if $m < \frac{1}{2}(\alpha + \beta - \sqrt{\alpha^2 + \beta^2})$. If $\alpha = \beta$, this gives $m < (1 - 1/\sqrt{2})\beta \approx 0.293\beta$. From (4.21), one obtains $\alpha\beta/(2(\alpha + \beta))$ and $\frac{1}{4}\beta$, respectively.

In summary, these results show that the linkage disequilibria generated by at least moderately tight linkage improve local adaptation much more than would occur under linkage equilibrium.

4.6. Effective migration rate. The concept of the effective migration rate was introduced as a measure of gene flow at a neutral marker locus because the flow of alleles may be impeded or enhanced by linkage to selected loci (Bengtsson 1985, Barton and Bengtsson 1986). Recently, Kobayashi et al. (2008) proposed a precise definition of the effective migration rate for quite general models and derived approximate formulas that facilitate the computation of the effective migration rate under a variety of scenarios.

Here, we calculate the effective migration rate for a neutral locus that is linked to the two selected loci based on a continuous-time variant of the treatments of Bengtsson (1985), Barton and Bengtsson (1986), and Kobayashi et al. (2008). Since we assume one-way migration, the rate of change of allele frequency at an isolated neutral locus is $\dot{n} = -mn + mn_c$, where $n = n(t)$ denotes the (relative) frequency of the allele N_1 on the island and n_c is the (constant) fraction of alleles N_1 on the continent. Thus, the fraction of alternative alleles at the neutral locus on the continent, subsumed under N_2, is $1 - n_c$. In this simple scenario, the migration rate satisfies

$$m = \frac{\dot{n}(t)}{n_c - n(t)} = -\frac{(n(t) - n_c)^{\cdot}}{n(t) - n_c} \tag{4.23}$$

for every $t \geq 0$. Thus, m determines the rate of approach to equilibrium and $-m$ can be interpreted as the leading eigenvalue of the (one-dimensional) Jacobian at equilibrium.

If the neutral locus is linked to one or more selected loci, the right side of (4.23) is no longer constant because evolution at the neutral locus will depend on allele frequencies at the selected loci and on the linkage disequilibria. If the selected loci are in equilibrium, the asymptotic rate of convergence of $n(t)$ can be defined by the leading eigenvalue λ_N of the Jacobian of the system that describes evolution of the frequency of N_1 and the

corresponding linkage disequilibria. Therefore, we define the effective migration rate as $m_{\text{eff}} = -\lambda_N$ (cf. Bengtsson 1985, Kobayashi et al. 2008). We explicate this approach below.

It is straightforward to derive the differential equations for the gamete frequencies. We order the gametes as $A_1N_1B_1$, $A_1N_1B_2$, $A_2N_1B_1$, $A_2N_1B_2$, $A_1N_2B_1$, $A_1N_2B_2$, $A_2N_2B_1$, $A_2N_2B_2$, and denote their frequencies by $y_1, \dots, y_8$, respectively. The rates of change caused by selection and immigration are immediately obtained from (2.2) because the locus N is neutral. We denote the recombination rate between loci A and N by ρ_1 and that between N and B by ρ_2. Because our model is continuous in time, in the absence of interference we have $\rho = \rho_1 + \rho_2$. The rate of change of $A_1N_1B_1$ due to recombination is

$$\dot{y}_1^{(\text{rec})} = -\rho_1[y_1(1-p) - y_3 p] - \rho_2[y_1(1-q) - y_2 q]\,, \tag{4.24}$$

and analogous expressions are obtained for the other gametes. The total rate of change is the sum of those caused by selection, migration, and recombination. The changes due to selection and migration follow immediately from (2.2).

As above, for our purposes it is more convenient to work with allele frequencies and linkage disequilibria. Let D_{AB}, D_{AN}, and D_{NB} denote the linkage disequilibria between the indicated pairs of loci, and let $D_{ANB} = y_1 - pqn - pD_{NB} - qD_{AN} - nD_{AB}$ denote the three-way linkage disequilibrium.

Of course, the equations for the change of p, q, and D_{AB} are given by (2.5). The allele frequency at the neutral locus evolves according to

$$\dot{n} = m[(n_c - n)(p + q - pq) - D_{AN}(1-q) - D_{NB}(1-p) + D_{ANB}] + \alpha D_{AN} + \beta D_{NB}\,, \tag{4.25}$$

and the equations for the linkage disequilibria involving the neutral locus are

$$\begin{aligned}
\dot{D}_{AN} &= -[\rho_1 + m(1 - p + pq) - \alpha(1-2p)]D_{AN} + mp(1-p)D_{NB} \\
&\quad + m(n_c - n)pD_{AB} + (\beta - mp)D_{ANB} + m(n_c - n)p(p + q - pq)\,, && \text{(4.26a)} \\
\dot{D}_{NB} &= -[\rho_2 + m(1 - q + pq) - \beta(1-2q)]D_{NB} + mq(1-q)D_{AN} \\
&\quad + m(n_c - n)qD_{AB} + (\alpha - mq)D_{ANB} + m(n_c - n)q(p + q - pq)\,, && \text{(4.26b)} \\
\dot{D}_{ANB} &= mpq(n_c - n)(p + q - pq) + mq[1 - (1-q)p]D_{AN} + mp[1 - (1-p)q]D_{NB} \\
&\quad - m(n_c - n)(p+q)D_{AB} - [\rho + m(1 - pq) - \alpha(1-2p) - \beta(1-2q)]D_{ANB} \\
&\quad + m(n_c - n)D_{AB}^2 + [m(1-q) - 2\alpha]D_{AB}D_{AN} + [m(1-p) - 2\beta]D_{AB}D_{NB} \\
&\quad - mD_{AB}D_{ANB}\,. && \text{(4.26c)}
\end{aligned}$$

This system has an (asymptotically stable) equilibrium such that the selected loci are at the equilibrium E_+ (3.15), and $n = n_c$ and $D_{AN} = D_{NB} = D_{ANB} = 0$ hold. We

denote this equilibrium by $E_+^{(N)}$. We use the order p, q, D_{AB}, n, D_{AN}, D_{NB}, D_{ANB} for the allele frequencies and linkage disequilibria. With the help of *Mathematica*, it is straightforward to show that the Jacobian at the equilibrium $E_+^{(N)}$ has the block structure

$$J = \begin{pmatrix} J_S & 0 \\ 0 & J_N \end{pmatrix}. \tag{4.27}$$

Here, J_S is the Jacobian approximating convergence of (p, q, D_{AB}) to E_+, and J_N is that approximating convergence of $(n, D_{AN}, D_{NB}, D_{ANB})$ to $(n_c, 0, 0, 0)$:

$$J_N = \begin{pmatrix} -m & \alpha & \beta & m \\ m & -\alpha-\rho_1+\frac{m(\alpha-\beta+\rho)}{\alpha+\beta+\rho} & 0 & \beta-m \\ m & 0 & -\beta-\rho_2+\frac{m(\beta-\alpha+\rho)}{\alpha+\beta+\rho} & \alpha-m \\ -m & \frac{m(\beta-\alpha+\rho)}{\alpha+\beta+\rho} & \frac{m(\alpha-\beta+\rho)}{\alpha+\beta+\rho} & -\alpha-\beta-\rho+\frac{2m(\alpha+\beta+2\rho)}{\alpha+\beta+\rho} \end{pmatrix}. \tag{4.28}$$

The rate of convergence to equilibrium at the neutral locus is determined by the leading eigenvalue of J_N. In the limit of weak migration, the following approximation for this leading eigenvalue is deduced (as can be checked easily with *Mathematica*):

$$\lambda_N = -m\frac{\rho_1\rho_2}{(\rho_1+\alpha)(\rho_2+\beta)} + O(m^2). \tag{4.29}$$

Since we define the effective migration rate as $m_{\mathrm{eff}} = -\lambda_N$, we obtain the approximation

$$m_{\mathrm{eff}} = m\frac{\rho_1\rho_2}{(\rho_1+\alpha)(\rho_2+\beta)} = m\left(1+\frac{\alpha}{\rho_1}\right)^{-1}\left(1+\frac{\beta}{\rho_2}\right)^{-1}. \tag{4.30}$$

This shows that the factor by which the effective migration rate is reduced relative to the actual migration rate, m_{eff}/m, is the product of the factors resulting from linkage to a single selected locus (cf. Petry 1983). Bengtsson (1985) called m_{eff}/m the gene-flow factor. It is a measure of the penetrability of a genetic barrier.

We note that also approximations for the other eigenvalues can be derived. As a consequence, asymptotic stability of this equilibrium has been shown for weak migration.

A simple calculation yields that m_{eff} is maximized at the recombination rate

$$\rho_1^* = \rho\left(1+\sqrt{\frac{\beta(\alpha+\rho)}{\alpha(\beta+\rho)}}\right)^{-1}, \tag{4.31}$$

and

$$m_{\mathrm{eff}}^* = \frac{2\alpha\beta+\rho(\alpha+\beta+\rho)-\sqrt{\alpha\beta(\alpha+\rho)(\beta+\rho)}}{(\alpha+\beta+\rho)^2} \tag{4.32}$$

is the corresponding maximum value of m_{eff}. In the simple case $\alpha = \beta$, we obtain $\rho_1^* = \frac{1}{2}\rho$ and

$$m_{\mathrm{eff}}^* = m\frac{\rho^2}{(2\alpha+\rho)^2}. \tag{4.33}$$

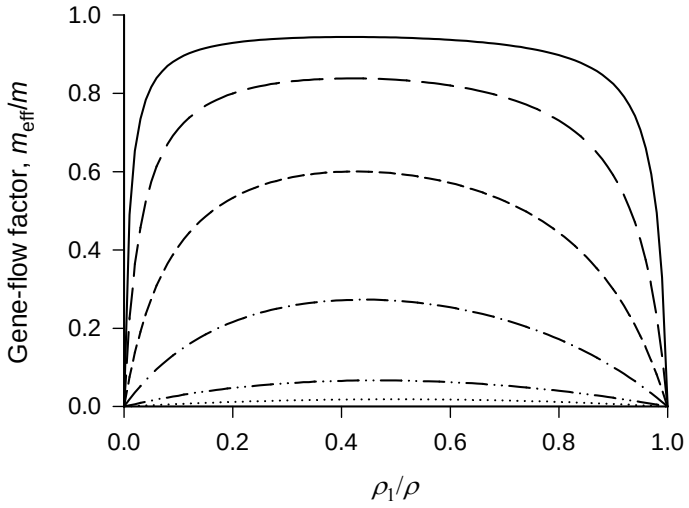

FIGURE 7. Gene-flow factor. The lines in the figure display the gene-flow factor m_{eff}/m (4.30) as a function of ρ_1/ρ for $\beta = 2\alpha$ and $\rho_1 + \rho_2 = \rho$. The lines from top to bottom are for $\alpha/\rho = 1/100$, $\sqrt{10}/100$, $1/10$, $\sqrt{10}/10$, 1, and $\sqrt{10}$. The gene-flow factor is maximized at ρ_1^*/ρ which is given by (4.31). For the given parameters, these values are between 0.415 and 0.484 (from top to bottom).

Therefore, the effective migration rate is massively reduced unless ρ is much larger than $2\alpha = 2\beta$. For instance, if $\rho = \alpha$, it is reduced to at least $\frac{1}{9}$ of m. Figure 7 displays the gene-flow factor for various parameter combinations.

5. Discussion

For a diploid two-locus continent-island model with genic selection on two loci, we investigated the combined effects of gene flow and linkage on the maintenance of polymorphism, the amount of LD, the degree of local adaptation, and the fate of newly arising slightly beneficial mutations that would be eliminated by gene flow in the absence of LD. Such a model appears to be an appropriate choice for studying evolution in a derived (island) population that experiences altered environmental conditions and maladaptive gene flow from the ancestral (continental) population.

Our prime analytical achievement (Theorem 3.2 and Figure 1) is the complete characterization of all equilibrium configurations. In particular, equations (3.15) provide explicit analytical formulas for the feasible fully polymorphic equilibria, and equations (3.17) and (3.18) give their admissibility conditions. From these results, simple and informative approximations are derived for the measures D and r^2 of LD and for the migration load, as well as simple criteria for the invasion of slightly beneficial mutants

and expressions for their final frequency. In the following we discuss the implications on a number of biological issues.

5.1. Maintenance of genetic variation. Theorem 3.2 and the concomitant evaluation of the potential for the maintenance of polymorphism show that both selectively favored alleles can be maintained in the population for higher levels of gene flow than would be concluded by ignoring LD. Under the assumption of independent loci, both loci can be maintained polymorphic if and only if the migration rate is less than the smaller of the selection coefficients ($m < \alpha$). The actual upper bounds are given by equations (3.17a) - (3.17c), which show that, essentially, three scenarios have to be distinguished: low, intermediate, and strong recombination. In the first case, the approximate condition $m < \alpha + \beta - \rho$ (4.6) is obtained, in the last case, the upper bound, (4.5) and (3.11), is between α and β.

The case of moderately strong linkage is more complicated, although the upper bound is always m^* (3.16). Interestingly, if the selection coefficients of the alleles differ by a factor of less than two and if the recombination rate is about as large as the selection coefficient at the minor locus, two fully polymorphic equilibria (E_+ and E_-) may exist, one stable, the other unstable (Figure 1, diagrams (b), (d), (e), (f); see the discussion above Theorem 3.3). Then the stable fully polymorphic equilibrium E_+ coexists with a stable boundary equilibrium (either E_B or E_C).

This bistable situation occurs for migration rates slightly below the maximum rate that admits coexistence of island and continental alleles at both loci. Which equilibrium is approached depends on the initial conditions. If, initially the island haplotype (A_1B_1) prevails, then the fully polymorphic equilibrium E_+ is approached. If, initially, the island haplotype is rare, then recombination breaks up this haplotype sufficiently quickly so that it is lost and, depending on the parameters, the continental haplotype A_2B_2 becomes fixed or the single-locus polymorphism E_B, at which A_2 is fixed, is approached.

5.2. Linkage disequilibrium under gene flow. In large panmictic populations, LD can be maintained only if there is epistasis. This changes in spatially structured populations. Li and Nei (1974), Christiansen and Feldman (1975), and Slatkin (1975) demonstrated that nonepistatic selection can maintain LD within local subpopulations. For sufficiently weak migration between two demes, so that each subpopulation is close to fixation, Barton (1983) derived a simple recursion for the linkage disequilibria of arbitrary order among a finite set of equivalent loci carrying a deleterious mutant. For our continent-island model we were able to derive the explicit analytical formula (3.15c) for the amount of LD maintained under migration-selection balance. It holds for arbitrary

relative strength of selection, recombination, and migration, and admits simple approximations in several limiting cases (eqs. (4.8) - (4.11) and Section 4.1).

Our results show that the measure D of LD is maximized at intermediate migration rates, whereas the measure r^2 is a monotone decreasing function of the migration rate m (Figure 3). As shown by (4.9) and explained at the end of Section 4.3, r^2 decays very slowly as a function of m if ρ is small.

Both D and r^2 decay slowly as functions of ρ if ρ is small (eqs. (4.8) – (4.10)), but faster for large ρ (4.11). For instance, if the recombination rate is equal to the larger of the two selection coefficients ($\rho = \beta$), then D is reduced by less than 50% of its maximum value attained at $\rho = 0$. The measure r^2 is somewhat more sensitive to changes in ρ, but even for loci of equal effects and $\rho = \alpha = \beta$, r^2 is reduced only by a factor of $\frac{1}{4}$ relative to the case $\rho = 0$. Thus, LD is high if the recombination rate is of the same order of magnitude as the larger of the selection coefficients.

5.3. Consequences for linked neutral variation. The results above provide information about the LD to be expected among selected loci but not about the consequences for linked neutral variation. Therefore, we performed a preliminary analysis of a model with a third neutral locus that is located between the two selected loci. It shows that, at least for weak migration, linkage equilibrium between the neutral locus and the selected loci will be established. For weak migration, we derived the simple formula (4.30) for the so-called effective migration rate (Bengtsson 1985, Barton and Bengtsson 1986, Kobayashi et al. 2008). This is a measure for the strength of gene flow at a neutral locus embedded in a selected background. From this formula and Figure 7, the extent of impediment of gene flow caused by linked selected loci becomes apparent. The formula shows that the linked loci contribute multiplicatively to the reduction in migration rate and thereby build an efficient barrier to neutral gene flow. A detailed study of the effects on linked neutral variation will have to examine the effects of random genetic drift and is an interesting topic for future research.

5.4. Dominance. Our analysis is based on the assumption of genic selection because this is the simplest case and almost all inference methods of selection are based on it. However, we also briefly investigated the influence of dominance (results not shown). In short, small deviations from no dominance lead to the same qualitative model behavior. If both island alleles are partially dominant, a two-locus polymorphism can be maintained for higher migration rates, whereas the opposite is true if they are partially recessive. For weak migration, to leading order in m, the equilibrium values $\hat{p}_+$, $\hat{q}_+$, and

$\hat{D}_+$ at the fully polymorphic equilibrium are obtained from equations (4.1) by the substitutions $\alpha \to \alpha(1-\vartheta)$ and $\beta \to \beta(1-\sigma)$, where $\alpha\vartheta$ and $\beta\sigma$ ($-1 < \vartheta, \sigma < 1$) are the selection coefficients of the single-locus genotypes A_1A_2 and B_1B_2, respectively.

If the island alleles are completely dominant ($\vartheta = \sigma = 1$), the maximum migration rate admitting polymorphism is about twice as high as without dominance. If the island alleles are highly or completely recessive, the equilibrium structure of the model is much more complicated because at least four fully polymorphic equilibria can coexist. This occurs for weak migration and strong recombination. In view of the fact that in the one-locus model, two polymorphic equilibria can coexist if the island allele is sufficiently strongly recessive (Nagylaki 1992, Chap. 6.1), this is not too surprising, but the model behavior could become more complicated at higher migration rates (as it is the case for genic selection).

5.5. Local adaptation. The present model enables us to study several aspects of local adaptation in the presence of gene flow. Simple measures of the degree of local adaptation are the migration load and the frequencies of the island alleles or the island haplotype. The effects of linkage on the migration load are relatively straightforward. If gene flow is low, so that the island haplotype is maintained at appreciable frequency, eq. (4.19) shows that the load is twice as high for very strong recombination as for no recombination. This is easy to understand because recombination predominantly breaks up the well adapted island haplotype if it is frequent. Tighter linkage always increases the frequency of the island alleles and of the island haplotype; see Figures 5 and 6, Appendix A.3, and eq. (4.20).

Simple instructive approximations are derived for the maximum rate of gene flow such that the frequency of the island haplotype exceeds $\frac{1}{2}$; e.g. (4.21). Figure 6 illustrates the finding that, in the presence of gene flow, already moderately strong linkage enhances the degree of local adaptation substantially. Thus, although gene flow diminishes local adaptation, linkage among advantageous genes may reduce the adverse effects of gene flow considerably in comparison to conclusions from single-locus models (Lenormand 2002).

For a given rate m of gene flow, and disregarding LD, a mutant can invade in our deterministic model if and only if its selective advantage exceeds m. The present analysis demonstrates that mutants of much smaller effect can invade successfully provided they occur close to a locus at which an advantageous allele is segregating in migration-selection balance (which requires a selective advantage greater than m). This may be interpreted as a form of hitch-hiking. Equations (4.13), (4.14), and (4.15) provide simple explicit estimates on the relation between linkage and the selective advantage required

for invasion. Figure 4 documents the extent to which linkage decreases the minimum selective advantage that admits invasion. In addition, invasion of a linked mutant of small effect increases the frequency of the already previously present island allele at the major locus (Figure 5). It would be a challenging, though worthwhile, enterprise to derive the probability of invasion in a population of finite size. Then it will matter whether the allele A_1 occurs on a B_1 or B_2 background.

5.6. Evolution of genetic architecture. We showed that weakly advantageous alleles can invade if and only if they are sufficiently tightly linked to an already segregating mutant of large effect. This suggests that long-term evolution under continued gene flow should lead to the emergence of clusters, or linkage groups, of locally adapted alleles. A similar conclusion was drawn recently by Yeaman and Whitlock (2011), who performed a simulation study on the evolution of genetic architecture when two populations connected by migration experience stabilizing selection on a polygenic trait towards different optima. Griswold (2006) investigated a model similar to that of Yeaman and Whitlock, but (mainly) with divergent directional selection. He explored the distribution of allelic effects but presented no information about linkage relations among loci causing phenotypic differentiation.

Our model can also be interpreted in terms of selection on a quantitative trait if the two loci contribute additively to the trait, i.e., without epistasis and dominance, and if on the island linear directional selection acts on the trait (cf. Bürger 2010). Therefore, clusters, or linkage groups, of adaptive loci can also evolve under directional selection. Our results not only support the main finding of Yeaman and Whitlock (2011), but they provide quantitative relations between the selective advantage and the degree of linkage to the major locus required for invasion and, hence, the emergence of such clusters (eqs. (4.13) - (4.15), Figure 4). It would be worthwhile to study the generality of the hypothesis that evolution in spatially structured populations leads to the emergence of clustered genetic architectures. For frequency-dependent disruptive selection, similar hypotheses have been raised (Kopp and Hermisson 2006, van Doorn and Dieckmann 2006), but slightly different model assumptions may lead to deviating conclusions (Schneider 2007). For a discussion of the evidence from and the consequences for QTL analysis, we refer to Yeaman and Whitlock (2011); see also Griswold (2006).

The expression (4.19) shows that the mean fitness at the polymorphic equilibrium increases with decreasing recombination rate between the selected loci. This suggests that reduced recombination rates will be evolutionarily favored in populations subject to new selective challenges but suffering from gene flow through maladapted individuals. As shown by Lenormand and Otto (2000), recombination can also be favored in spatially

structured populations, and predicting whether increased or decreased recombination is evolutionary advantageous requires detailed information on the pattern and intensity of migration as well as on the variability of selection across environments.

An efficient mechanism in suppressing recombination among a set of genes is provided by chromosome inversions. Indeed, Kirkpatrick and Barton (2006) suggested that chromosome inversions that capture locally adapted alleles should spread in a population exposed to gene flow by maladapted genotypes. Their arguments are based on the calculation of the invasion rate of such an inversion using a continent-island framework similar to ours. Their derivation assumed weak migration and strong recombination, and either multiplicative effects among a set of loci in a haploid population or additive effects in a diploid population. Below, we show that the true invasion rate may be higher than their approximation suggests.

In our continuous-time model, the invasion rate of the inversion is $\gamma = \dot{x}_1/x_1$, which is calculated from (2.2a) by omitting the term ρD and evaluating at the fully polymorphic equilibrium E_+. The result is

$$\gamma = \alpha(1-\hat{p}_+) + \beta(1-\hat{q}_+) - m = \frac{1}{4}\left(\alpha+\beta+\rho-\sqrt{(\alpha+\beta+\rho)^2-8m\rho}\right). \tag{5.1}$$

If migration is weak, the invasion rate is approximated by

$$\gamma_{\text{app}} = \frac{m\rho}{\alpha+\beta+\rho} \approx \rho\hat{D}_+ . \tag{5.2}$$

This is a highly accurate approximation if m is small or if ρ is either much smaller or much larger than both selection coefficients. If ρ is approximately as large as the selection coefficients and if the migration rate is not much smaller than the maximum migration rate under which the island haplotype (with recombination) can be maintained, then γ_{app} may underestimate the actual fitness gain γ substantially. For instance, if $\rho = \alpha = \beta$ and $m = m^* = \frac{9}{8}\beta$ (which, as we showed below Theorem 3.3, is the maximum migration rate), then (5.2) predicts $\gamma_{\text{app}} = \frac{3}{8}\beta$, whereas the precise value is $\gamma = \frac{3}{4}\beta$. Similarly, if $\rho = \alpha = \beta/n$, $n \geq 2$, and $m = m_{\text{B}} = \beta$, then (5.2) predicts $\gamma_{\text{app}} = \alpha n/(n+2)$, whereas the exact rate is $\gamma = \alpha$. Again, the approximation (5.2) may underestimate the true value up to a factor of two.

We also note that the gain in mean fitness resulting from the establishment of a chromosomal inversion capturing the locally advantageous alleles is twice the invasion rate γ. This follows because the (mean) fitness after the inversion has spread is $\alpha+\beta-2m$ (independently of the recombination rate between the loci since the subpopulation carrying the inversion is fixed for the island alleles); hence, the fitness gain can be approximated by $\alpha+\beta-2m-\hat{\bar{w}}$, where $\hat{\bar{w}}$ is evaluated at E_+, and (4.19a) yields the result.

For two loci of equal effects, γ_{app} is (after correcting for haploidy and a misprint) equivalent to equation (3) in Kirkpatrick and Barton (2006), who assumed strong recombination. From the above arguments, we conclude that if recombination rates are of the same order of magnitude as the selective coefficients and migration is moderately strong (such that the island genotype is maintained), the simple approximation γ_{app} may underestimate the true invasion rate by up to a factor of two. Therefore, chromosome inversions may spread even if they capture relatively tightly linked, locally adapted alleles. Thus, this mechanism may be even more general and efficient than suggested by Kirkpatrick and Barton (2006).

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A. Appendix

In this appendix we prove some of the results stated in the main text.

A.1. Proof of Proposition 3.1. As stated in the main text, we explore admissibility of E_+ and E_- as functions of m, i.e., we use m as a bifurcation parameter. We begin with E_+. Because $\mathrm{E}_+ = \mathrm{E}_\mathrm{I}$ if $m = 0$ and E_I is hyperbolic and globally asymptotically stable if $m = 0$ (Section 3.4), a general global perturbation result for multilocus selection-migration models (Bürger 2009a, Theorem 5.4) implies that E_+ moves into the interior of the state space as m increases from zero, and it remains globally asymptotically stable for small values of m (Section 3.4).

By continuity, as m increases further, E_+ remains in the state space until it leaves it through one of the three boundary equilibria, E_A, E_B, or E_C, which may occur if that equilibrium is not hyperbolic, or E_+ ceases to exist, which may occur at $m = m^*$. In the latter case, we have $\mathrm{E}_+ = \mathrm{E}_-$ and

$$\hat{p}_\pm = \frac{1}{16\alpha\rho}(3\rho - \alpha - \beta)(3\alpha - \beta - \rho)\,, \tag{A.1a}$$

$$\hat{q}_\pm = \frac{1}{16\alpha\rho}(3\rho - \alpha - \beta)(3\beta - \alpha - \rho)\,, \tag{A.1b}$$

$$\hat{D}_\pm = \frac{1}{256\alpha\beta\rho^2}(3\rho - \alpha - \beta)(3\alpha - \beta - \rho)(3\beta - \alpha - \rho)(\alpha + \beta + \rho)\,. \tag{A.1c}$$

If $m = 0$, then E_- is given by

$$\hat{x}_{-,1} = \frac{1}{8\alpha\beta\rho}(\beta+\rho-\alpha)(\alpha+\beta-\rho)(\beta-\alpha-\rho)\,, \tag{A.2a}$$

$$\hat{x}_{-,2} = \frac{1}{8\alpha\beta\rho}(\beta+\rho-\alpha)(\alpha+\beta-\rho)(\alpha+\beta+\rho)\,, \tag{A.2b}$$

$$\hat{x}_{-,3} = -\frac{1}{8\alpha\beta\rho}(\alpha+\beta-\rho)(\beta-\alpha-\rho)(\alpha+\beta+\rho)\,, \tag{A.2c}$$

$$\hat{x}_{-,4} = -\frac{1}{8\alpha\beta\rho}(\beta+\rho-\alpha)(\beta-\alpha-\rho)(\alpha+\beta+\rho)\,. \tag{A.2d}$$

It is easy to show that this equilibrium is never in the simplex. Therefore, as m increases, E_- can enter the simplex only through one of the three boundary equilibria E_A, E_B, or E_C.

From now on, we assume $m > 0$. Straightforward calculations show that

(α) $\mathrm{E}_+ = \mathrm{E}_\mathrm{A}$ if and only if

$$m = m_\mathrm{A} \quad \text{and} \quad \rho \geq 3\beta - \alpha\,; \tag{A.3}$$

(β) $\mathrm{E}_- = \mathrm{E}_\mathrm{A}$ if and only if

$$m = m_\mathrm{A} \quad \text{and} \quad \rho \leq 3\beta - \alpha\,; \tag{A.4}$$

(γ) $\mathrm{E}_+ = \mathrm{E}_\mathrm{B}$ if and only if

$$m = m_\mathrm{B} \quad \text{and} \quad \rho \geq 3\alpha - \beta\,; \tag{A.5}$$

(δ) $\mathrm{E}_- = \mathrm{E}_\mathrm{B}$ if and only if

$$m = m_\mathrm{B} \quad \text{and} \quad \rho \leq 3\alpha - \beta\,; \tag{A.6}$$

(ϵ) $\mathrm{E}_+ = \mathrm{E}_\mathrm{C}$ if and only if

$$m = m_\mathrm{C} \quad \text{and} \quad \rho \leq \tfrac{1}{3}(\alpha+\beta)\,; \tag{A.7}$$

(φ) $\mathrm{E}_- = \mathrm{E}_\mathrm{C}$ if and only if

$$m = m_\mathrm{C} \quad \text{and} \quad \rho \geq \tfrac{1}{3}(\alpha+\beta)\,. \tag{A.8}$$

It remains to determine the admissible parameter ranges for which these cases can occur, i.e., when the respective equilibria (E_A, E_B, E_C) are admissible.

Case (α) cannot occur because the condition $\rho \geq 3\beta - \alpha$ in (A.3) is incompatible with the condition $\rho < \beta$ required for E_A to be admissible; cf. (3.8).

Case (β) occurs if and only

$$\beta - \alpha < \rho < \min(3\beta - \alpha, \beta)\,; \tag{A.9}$$

cf. (3.8). By series expansion of E_- at $m = m_A$, it is straightforward to show that E_- passes through E_A at $m = m_A$, but does not enter the interior of the simplex S_4.

Case (γ) occurs if and only if

$$\max(\alpha, 3\alpha - \beta) < \rho\,; \tag{A.10}$$

cf. (3.12). By series expansion of E_+ at $m = m_B$, it is straightforward to show that E_+ leaves the simplex through E_B as m increases above m_B.

Case (δ) occurs if and only

$$\alpha < \rho \leq 3\alpha - \beta\,; \tag{A.11}$$

cf. (3.12). Obviously, this case requires $\beta < 2\alpha$. By series expansion of E_- at $m = m_B$, it is straightforward to show that, in this case, E_- enters the simplex through E_B at $m = m_B$.

Case (φ) occurs if and only if

$$\tfrac{1}{3}(\alpha + \beta) \leq \rho < \alpha + \beta \tag{A.12}$$

because $m_C > 0$ is required. In this case, series expansion shows that E_- enters the simplex through E_C as m increases above m_C if and only if $\rho < \alpha$. By (3.19), $\frac{1}{3}(\alpha + \beta) \leq \rho < \alpha$ is feasible if and only if $\beta < 2\alpha$.

The most delicate case is (ϵ). E_+ does not necessarily leave the simplex when m increases above m_C (and $\rho \leq \frac{1}{3}(\alpha + \beta)$ holds). The reason is that, by (γ), E_+ leaves the simplex through E_B as m increases above m_B if (A.10) holds. To explore the possible behaviors, according to (3.19) we distinguish three major cases.

(i) If $\beta > 2\alpha$ and $\rho \leq \max(\alpha, 3\alpha - \beta)$, (3.19a) yields $\max(\alpha, 3\alpha - \beta) = \alpha < \frac{1}{3}(\alpha + \beta)$. Hence, E_+ leaves the simplex through E_C. If $\beta > 2\alpha$ and $\rho > \max(\alpha, 3\alpha - \beta) = \alpha$, then, by ($\gamma$), E_+ leaves the simplex through E_B as m increases above m_B. As m increases further and if $\rho \leq \frac{1}{3}(\alpha + \beta)$, then, consistent with (ϵ), E_+ passes through E_C at $m = m_C$, but without entering the interior of the state space.

(ii) If $\beta = 2\alpha$, then E_+ leaves the simplex through E_C if $\rho < \frac{1}{3}(\alpha + \beta) = \alpha$, and E_+ leaves the simplex through E_B if $\rho > 3\alpha - \beta = \alpha$. At $\rho = \alpha$, we have $m = m_B = m_C = m^* = 2\alpha$ and $E_+ = E_B = E_C$.

(iii) If $\beta < 2\alpha$ and $\rho \leq \frac{1}{3}(\alpha + \beta)$, then E_+ leaves the simplex through E_C because, by (A.9) and (3.19c), case (γ) cannot occur. If $\beta < 2\alpha$ and $\rho \geq 3\alpha - \beta$, then ($\epsilon$) cannot occur and E_+ leaves the simplex through E_B. To treat the remaining case $\frac{1}{3}(\alpha + \beta) < \rho < 3\alpha - \beta$, in which neither ($\gamma$) nor ($\epsilon$) can occur, we note that

$$m^* = m_C + \frac{(\alpha + \beta - 3\rho)^2}{8\rho} \geq m_C \tag{A.13a}$$

and

$$m^* = m_B + \frac{(\beta + \rho - 3\alpha)^2}{8\rho} \geq m_B \tag{A.13b}$$

hold always.

It follows that E_+ is admissible if and only if $0 < m < m^*$, and coexistence of E_+ and E_- occurs if and only if (3.18a) or (3.18b) holds.

There are a number of degenerate cases. If $\beta = 2\alpha$ and $\rho = \alpha$, then $m^* = m_C = m_B$, and we have $E_+ = E_- = E_B = E_C$ if $m = m^*$. If $\rho = 3\alpha - \beta$, then $m^* = m_B$, and we have $E_+ = E_- = E_B$ if $m = m_B$. If $\rho = \frac{1}{3}(\alpha + \beta)$, then $m^* = m_C$, and we have $E_+ = E_- = E_C$ if $m = m_C$.

If $\alpha = \beta$, then $m_A = m_B = \alpha = \beta$. Therefore, E_B (and also E_A) is always hyperbolic except when $E_B = E_C$. Hence, no internal equilibrium can leave or enter the simplex through E_B.

Thus, we have established the admissibility conditions of the internal equilibria.

A.2. Asymptotic stability of internal equilibria. Although we can prove that real eigenvalues of the Jacobian of E_+ are always negative, this is insufficient to conclude asymptotic stability of E_+ because we have not been able to exclude the possibility of complex, non-real eigenvalues. In the following we prove that E_+ is asymptotically stable near the possible bifurcation points. Then we prove asymptotic stability of E_+ for strong recombination, and instability of E_- near the bifurcation points.

Asymptotic stability of E_+ *near bifurcation points.* If $E_+ = E_B$, the eigenvalues are $0, -(\beta - 2\alpha + \rho), -(\beta - \alpha)(\rho - \alpha)/\rho$. By (3.17c), the second and third are negative. Therefore, this is also the case if $m = m_B - \epsilon$, where $\epsilon > 0$. Because the characteristic polynomial at E_+ has the leading coefficient -1 and assumes the value $(\beta-\alpha)(\alpha-\rho)\epsilon < 0$ at $x = 0$ if $m = m_B - \epsilon$, also the first eigenvalue is negative.

If $E_+ = E_C$, the eigenvalues are $0, \rho - \alpha, \rho - \beta$. By (3.17a), the second and third are negative. Therefore, this is also the case if $m = m_C - \epsilon$, where $\epsilon > 0$. Because the characteristic polynomial has the leading coefficient -1 and assumes the value $(\alpha - \rho)(\rho - \beta)\epsilon < 0$ at $x = 0$ if $m = m_C - \epsilon$, also the first eigenvalue is negative.

If $E_+ = E_-$, the characteristic polynomial is of the form $-xP(x)/(32\rho)$, where

$$P(x) = 32\rho x^2 - 4[(\alpha + \beta)^2 - 6\rho(\alpha + \beta) + \rho^2]x + 32\alpha\beta\rho - (\alpha + \beta + \rho)^3 . \tag{A.14}$$

Because the discriminant of $P(x)$ can be written as

$$\frac{1}{16}\left[64(\beta - \alpha)^2\rho^2 + (\alpha + \beta + \rho)^2(3\rho - \alpha - \beta)^2\right] > 0 , \tag{A.15}$$

the zeros of P are real. They are negative because $(\alpha+\beta)^2 - 6\rho(\alpha+\beta) + \rho^2 < 0$ if $3 - \sqrt{10} < (\alpha+\beta)/\rho < 3 + \sqrt{10}$ and, as we show below,

$$32\alpha\beta\rho - (\alpha+\beta+\rho)^3 > 0 \text{ if } \tfrac{1}{3}(\alpha+\beta) < \rho < 3\alpha - \beta\,; \tag{A.16}$$

cf. (3.17b). By setting $\alpha = a\rho$, $\beta = b\rho$, and rearranging, (A.16) combined with (3.1) becomes

$$32ab - (a+b+1)^3 > 0 \text{ if } \tfrac{1}{3}(b+1) \le a \le \min(b, 3-b)\,. \tag{A.17}$$

We note that the constraints on a and b imply $\frac{1}{2} < a < \frac{3}{2}$ and $\frac{1}{2} < b < 2$. It is easy to check that we can write

$$32ab - (a+b+1)^3 = \frac{32}{27}(b+1)(2-b)(2b-1) + Q(a - \tfrac{1}{3}(b+1))\,, \tag{A.18}$$

where $Q(x) = \frac{1}{3}x\left[16(4b - b^2 - 1) - 12(b+1)x - 3x^2\right]$. The first term on the right-hand side of (A.18) is positive because $\frac{1}{2} < b < 2$. Straightforward calculations show that $Q(x) > 0$ if $0 < x < \frac{1}{3}(2b-1)$. This proves (A.17), hence (A.16), because $0 < x < \frac{1}{3}(2b-1)$ is equivalent to $\frac{1}{3}(b+1) \le a \le b$. Therefore, E_+ (and E_-) have two negative eigenvalues if m is slightly smaller than m^*.

It remains to show that the third eigenvalue of E_+ is also negative. As in the cases above, this follows because the characteristic polynomial has a negative leading coefficient and assumes the value $-\sqrt{\epsilon}(3\rho - \alpha - \beta)(3\alpha - \beta - \rho)(3\beta - \alpha - \rho)/(16\sqrt{2\rho}) < 0$ at $x = 0$ if $m = m^* - \epsilon$ and $\epsilon > 0$.

Asymptotic stability of E_+ *if* ρ *is large.* In the limiting case $\rho \to \infty$, the linkage-equilibrium manifold is globally attracting and the dynamics on $D = 0$ is given by

$$\dot{p} = \frac{dp}{dt} = \alpha p(1-p) - mp\,, \tag{A.19a}$$

$$\dot{q} = \frac{dq}{dt} = \beta q(1-q) - mq\,. \tag{A.19b}$$

Then it is immediate that if $m < \alpha \le \beta$, the equilibrium $\hat{p} = 1 - m/\alpha$, $\hat{q} = 1 - m/\beta$ is globally asymptotically stable. Therefore, Proposition 5.1 in Bürger (2009a) shows that the perturbed equilibrium, which is given by (4.3), is asymptotically stable.

Instability of E_-. If $\mathrm{E}_- = \mathrm{E}_\mathrm{B}$, the eigenvalues are $0, -(\beta - 2\alpha + \rho), -(\beta - \alpha)(\rho - \alpha)/\rho$. By (3.18b), the second and third are negative. Therefore, this is also the case if $m = m_\mathrm{B} + \epsilon$, where $\epsilon > 0$. Because the characteristic polynomial at E_- has the leading coefficient -1 and assumes the value $(\beta - \alpha)(\rho - \alpha)\epsilon > 0$ if $m = m_\mathrm{B} + \epsilon$, the first eigenvalue is positive.

If $\mathrm{E}_- = \mathrm{E}_\mathrm{C}$, the eigenvalues are $0, \rho - \alpha, \rho - \beta$. By (3.18a), the second and third are negative. Therefore, this is also the case if $m = m_\mathrm{C} + \epsilon$, where $\epsilon > 0$. Because the characteristic polynomial has the leading coefficient -1 and assumes the value $(\alpha - \rho)(\beta - \rho)\epsilon > 0$ if $m = m_\mathrm{C} + \epsilon$, the first eigenvalue is positive.

Instability of E_- if $m = m^* - \epsilon$ follows immediately from the above proof of stability of E_+ if $m = m^* - \epsilon$.

A.3. Further properties of the fully polymorphic equilibria.

Linkage disequilibrium. We prove that $D > 0$ at E_+ and E_-. If m is small, then (4.1c) shows that $\hat{D}_+ > 0$. A straightforward calculation shows that $\hat{D}_+$, considered as a function of m has the possible zeros 0, m_A, m_B, and m_C, where $m = 0$ is always a zero. For the others, we have

$$\hat{D}_+ = 0 \text{ at } m = m_A \text{ if and only if } \rho \geq 3\beta - \alpha\,, \tag{A.20a}$$

$$\hat{D}_+ = 0 \text{ at } m = m_B \text{ if and only if } \rho \geq 3\alpha - \beta\,, \tag{A.20b}$$

and

$$\hat{D}_+ = 0 \text{ at } m = m_C \text{ if and only if } \rho \leq \tfrac{1}{3}(\alpha + \beta)\,. \tag{A.20c}$$

Now we distinguish the five nondegenerate cases of Theorem 3.2, i.e., those corresponding to diagrams (a), (b), (e), (f), and (g) in Figure 1, and keep (3.19) in mind.

If (3.21a) applies, then we have $m_A < 0 < m_C < m_B$; hence, $\hat{D}_+ > 0$ if $0 < m < m_C$.

If (3.21b) applies, then $0 < m_C$ and we may have $0 < m_A, m_B < m_C$. However, (A.20a) and (A.20b) show that m_A and m_B are no zeros. Thus, $\hat{D}_+ > 0$ if $0 < m < m_C$.

If (3.22), (3.25), or (3.26) applies, i.e., if $\beta < 2\alpha$ and $\frac{1}{3}(\alpha + \beta) < \rho < 3\alpha - \beta$, then (A.20) shows $\hat{D}_+$ has no zeros except $m = 0$. Hence, $\hat{D}_+$ is positive if $0 < m < m^*$.

If (3.27a) applies and $\rho \leq \beta - \alpha$, then $m_A \leq 0 < m_B < m_C$. If $\rho > \beta - \alpha$, then $\rho > \frac{1}{3}(\alpha + \beta)$, and $\hat{D}_+$ cannot vanish at m_C. If, in addition, $\rho < 3\beta - \alpha$, then $\hat{D}_+$ can also not vanish at m_A. If $\rho > 3\beta - \alpha$, then $m_C < 0 < m_B < m_A$. In both cases, $\hat{D}_+$ is positive if $0 < m < m_B$.

If (3.27b) applies, then $\rho > \frac{1}{3}(\alpha + \beta)$, so that m_C cannot be a zero. If $\frac{1}{3}(\alpha + \beta) < \rho < 3\beta - \alpha$, then m_A can also not be a zero. $\rho > 3\beta - \alpha$, then $\rho > \alpha + \beta$, hence $m_A > m_B$. Thus, in both cases, we have shown that $\hat{D}_+$ is positive if $0 < m < m_B$.

We leave the simple cases (3.23) and (3.24) to the reader.

Monotonicity properties. (i) We prove that $\hat{p}_+$ and $\hat{q}_+$ are strictly decreasing functions of ρ if E_+ leaves the state space through E_B at $m = m_B$. Straightforward differentiation produces

$$8\alpha^2\rho^2 R\,\frac{\partial \hat{p}_+}{\partial \rho} = (\beta^2 - \alpha^2 + \rho^2)(\alpha + \beta + \rho - R) - 4m\rho(\beta - \alpha + \rho) \tag{A.21}$$

and

$$8\beta^2\rho^2 R\,\frac{\partial \hat{q}_+}{\partial \rho} = (\alpha^2 + \rho^2 - \beta^2)(\alpha + \beta + \rho - R) - 4m\rho(\alpha + \rho - \beta)\,, \tag{A.22}$$

where R is given by (3.15d). Then $\partial \hat{p}_+/\partial \rho = \partial \hat{q}_+/\partial \rho = 0$ if $m = 0$, $\partial \hat{p}_+/\partial \rho = 0$ if $m = m_+ = \beta(\beta^2 - \alpha^2 + \rho^2)/(\beta - \alpha + \rho)^2$, and $\partial \hat{q}_+/\partial \rho = 0$ if $m = m_- = \alpha(\alpha^2 + \rho^2 - \beta^2)/(\alpha + \rho - \beta)^2$.

There are no other zeros and $\partial\hat{p}_+/\partial\rho < 0$ if and only if $0 < m < m_+$, and $\partial\hat{q}_+/\partial\rho < 0$ if and only if $0 < m < m_-$. A simple calculation shows that

$$\frac{\partial\hat{p}_+}{\partial\rho} = -\frac{(\beta-\alpha)(\rho-\alpha)}{\rho^2(\rho-3\alpha+\beta)} \tag{A.23}$$

if $\rho > 3\alpha - \beta$. Hence, $\partial\hat{p}_+/\partial\rho < 0$ if $\max(\alpha, 3\alpha-\beta) < \rho$ and $0 < m < m_{\mathrm{B}}$, and our assertion about $\hat{p}_+$ follows from (3.17c) and (3.27). Similarly,

$$\frac{\partial\hat{q}_+}{\partial\rho} = -\frac{\alpha^2(\beta-\alpha)}{\rho^2\beta(\rho-3\alpha+\beta)} \tag{A.24}$$

yields that $\hat{q}_+$ is decreasing in ρ if E_+ leaves the state space through E_{B}.

(ii) Analogous calculations and arguments demonstrate that $\hat{p}_+$ and $\hat{q}_+$ are both decreasing in ρ if E_+ leaves the simplex through E_{C}.

Thus, tighter linkage leads to a higher frequency of both island alleles. Their frequencies are maximized if the loci are completely linked.

(iii) Finally, we show that B_1 increases after invasion of A_1, i.e., $\hat{q}_+ > 1 - m/\beta$ if (4.13), or equivalently, $m < m_{\mathrm{B}}$ holds. We can write

$$\hat{q}_+ - (1 - m/\beta) = [A + (\beta - \alpha + \rho)R]/(8\beta\rho)\,, \tag{A.25}$$

where $A = \alpha^2 - (\beta+\rho)^2 + 4m\rho$ and R is given by (3.15d). If $A \geq 0$, we are finished. If $A < 0$, a simple calculation shows that $(\beta-\alpha+\rho)^2R^2 > A^2$ if and only if $m < m_{\mathrm{B}}$, which proves the assertion.

B. Erratum

Equations (4.25), (4.26), and (4.28) in Bürger and Akerman (2011) contain errors which we correct below. We point out that neither the main result of that section, formula (4.30) for the effective migration rate, nor any other results in the paper are affected by these errors.

Instead of (4.25), the allele frequency at the neutral locus evolves according to

$$\dot{n} = \alpha D_{AN} + \beta D_{NB} + m(n_c - n). \tag{B.1}$$

Instead of (4.26), the equations for the rate of change of the linkage disequilibria involving the neutral locus should read

$$\dot{D}_{AN} = -\rho_1 D_{AN} + \alpha(1-2p)D_{AN} + \beta D_{ANB} - mD_{AN} - mp(n_c - n)\,, \tag{B.2a}$$

$$\dot{D}_{NB} = -\rho_2 D_{NB} + \beta(1-2q)D_{NB} + \alpha D_{ANB} - mD_{NB} - mq(n_c - n)\,, \tag{B.2b}$$

$$\begin{aligned}\dot{D}_{ANB} = {} & -\rho D_{ANB} + [\alpha(1-2p) + \beta(1-2q)]D_{ANB} - 2D_{AB}(\alpha D_{AN} + \beta D_{NB}) \\ & - m(D_{ANB} - pD_{NB} - qD_{AN}) + m(pq - D_{AB})(n_c - n)\,.\end{aligned} \tag{B.2c}$$

Finally, the fourth column, $(m, \beta - m, \alpha - m, -\alpha - \beta - \rho + \frac{2m(\alpha+\beta+2\rho)}{\alpha+\beta+\rho})$, of the Jacobian matrix J_N given in equation (4.28) must be replaced by $(0, \beta, \alpha, -\alpha - \beta - \rho + \frac{m(\alpha+\beta+3\rho)}{\alpha+\beta+\rho})$.

We thank Dr. Simon Aeschbacher for pointing out the errors.

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The consequences of gene flow for local adaptation and differentiation: a two-locus two-deme model

A. AKERMAN, R. BÜRGER

ABSTRACT. *We consider a population subdivided into two demes connected by migration in which selection acts in opposite direction. We explore the effects of recombination and migration on the maintenance of multilocus polymorphism, on local adaptation, and on differentiation by employing a deterministic model with genic selection on two linked diallelic loci (i.e., no dominance or epistasis). For the following cases, we characterize explicitly the possible equilibrium configurations: weak, strong, highly asymmetric, and super-symmetric migration, no or weak recombination, and independent or strongly recombining loci. For independent loci (linkage equilibrium) and for completely linked loci, we derive the possible bifurcation patterns as functions of the total migration rate, assuming all other parameters are fixed but arbitrary. For these and other cases, we determine analytically the maximum migration rate below which a stable fully polymorphic equilibrium exists. In this case, differentiation and local adaptation are maintained. Their degree is quantified by a new multilocus version of F_{ST} and by the migration load, respectively. In addition, we investigate the invasion conditions of locally beneficial mutants and show that linkage to a locus that is already in migration-selection balance facilitates invasion. Hence, loci of much smaller effect can invade than predicted by one-locus theory if linkage is sufficiently tight. We study how this minimum amount of linkage admitting invasion depends on the migration pattern. This suggests the emergence of clusters of locally beneficial mutations, which may form 'genomic islands of divergence'. Finally, the influence of linkage and two-way migration on the effective migration rate at a linked neutral locus is explored. Numerical work complements our analytical results.*

1. Introduction

Migration in a geographically structured population may have opposing effects on the genetic composition of that population and, hence, on its evolutionary potential. On the one hand, gene flow caused by migration may be so strong that it not only limits but hinders local adaptation by swamping the whole population with a genotype that has high fitness in only one or a few demes. On the other hand, if migration is sufficiently weak, gene flow may replenish local populations with genetic variation and contribute to future adaptation. In this case, locally adapted genotypes may coexist in the population

and maintain high levels of genetic variation as well as differentiation between subpopulations. For reviews of the corresponding, well developed one-locus theory, see Karlin (1982), Lenormand (2002), and Nagylaki and Lou (2008).

If selection acts on more than one locus, additional questions arise immediately. For instance, what are the consequences of the genetic architecture, such as linkage between loci, relative magnitude of locus effects or epistasis, on the degree of local adaptation and of differentiation achieved for a given amount of gene flow? What are the consequences for genetic variation at linked neutral sites? What genetic architectures can be expected to evolve under various forms of spatially heterogeneous selection?

For selection acting on multiple loci, the available theory is much less well developed than for a single locus. One of the main reasons is that the interaction of migration and selection, even if the latter is nonepistatic, leads to linkage disequilibrium (LD) between loci (Li and Nei 1974, Christiansen and Feldman 1975, Slatkin 1975, Barton 1983). LD causes substantial, often insurmountable, complications in the analysis of multilocus models. Therefore, many multilocus studies are primarily numerical and focus on quite specific situations or problems. For instance, Spichtig and Kawecki (2004) investigated numerically the influence of the number of loci and of epistasis on the degree of polymorphism if selection acts antagonistically in two demes. Yeaman and Whitlock (2011) showed that concentrated genetic architecture, i.e., clusters of linked, locally beneficial alleles, evolve if stabilizing selection acts on a trait such that the fitness optima in two demes differ.

Linkage disequilibrium is also essential for the evolution of recombination. The evolution of recombination in heterogeneous environments has been studied by a number of authors (e.g., Charlesworth and Charlesworth 1979, Pylkov et al. 1998, Lenormand and Otto 2000), and the results depend strongly on the kind of variability of selection across environments, the magnitude of migration, and the sign and strength of epistasis.

Recent years have seen some advances in developing general theory for multilocus migration-selection models. The focus of this work was on the properties of the evolutionary dynamics and the conditions for the maintenance of multilocus polymorphism in limiting or special cases, such as weak or strong migration (Bürger, 2009a,b), or in the Levene model (Nagylaki 2009; Bürger 2009c, 2010; Barton 2010; Chasnov 2012). This progress was facilitated by the fact that in each case, LD is weak or absent.

Using a continent-island-model framework, Bürger and Akerman (2011) and Bank et al. (2012) analyzed the effects of gene flow on local adaptation, differentiation, the emergence of Dobzhansky-Muller incompatibilities, and the maintenance of polymorphism at two linked diallelic loci. They obtained analytical characterizations of the possible equilibrium configurations and bifurcation patterns for wide ranges of parameter

combinations. In these models, typically high LD is maintained. In particular, explicit formulas were derived for the maximum migration rate below which a fully polymorphic equilibrium can be maintained, as well as for the minimum migration rate above which the island is swamped by the continental haplotype.

Here, we explore the robustness of some of these results by admitting arbitrary (forward and backward) migration between two demes. This generalization leads to substantial mathematical complications, but also to new biological insight. Because our focus is on the consequences of gene flow for local adaptation and differentiation, we assume divergent selection among the demes, i.e., alleles A_1 and B_1 are favored in deme 1, and A_2 and B_2 are favored in deme 2. The loci may recombine at an arbitrary rate. By ignoring epistasis and dominance, we assume genic selection. Mutation and random drift are neglected. Because we assume evolution in continuous time, our model also describes selection on haploids.

The model is set up in Section 2. In Section 3, we derive the equilibrium and stability structure for several important special cases. These include weak, strong, highly asymmetric, and super-symmetric migration, no or weak recombination, independent or strongly recombining loci, and absence of genotype-environment interaction. In Section 4, we study the dependence of the equilibrium and stability patterns on the total migration rate while keeping the ratio of migration rates, the recombination rate, and the selection coefficients constant (but arbitrary). In particular, we derive the possible bifurcation patterns for the cases of independent loci (linkage equilibrium) and for completely linked loci. With the help of perturbation theory, we obtain the equilibrium and stability configurations for weak or strong migration, highly asymmetric migration, and weak or strong recombination. For these cases, we determine the maximum migration rate below which a stable, fully polymorphic equilibrium is maintained, and the minimum migration rate above which the population is monomorphic. Numerical work complements our analytical results.

The next four sections are devoted to applications of the theory developed in Sections 3 and 4. In Section 5 and 6, we use the migration load and a new, genuine multilocus, fixation index (F_{ST}), respectively, to quantify the dependence of local adaptation and of differentiation on various parameters, especially, on the migration and the recombination rate. In Section 7, we investigate the invasion conditions for a mutant of small effect (A_1) that is beneficial in one deme but disadvantageous in the other deme. We assume that the mutant is linked to a polymorphic locus which is in selection-migration balance. We show that linkage between the loci facilitates invasion. Therefore, in such a scenario, clusters of locally adapted alleles are expected to emerge (cf. Yeaman and Whitlock 2011, Bürger and Akerman 2011). In Section 8, we study the strength of barriers to gene

flow at neutral sites linked to the selected loci by deriving an explicit approximation for the effective migration rate at a linked neutral site. Our results are summarized and discussed in Section 9. Several purely technical proofs are relegated to the Appendix.

2. The model

We consider a sexually reproducing population of monoecious, diploid individuals that is subdivided into two demes connected by genotype-independent migration. Within each deme, there is random mating. We assume that two diallelic loci are under genic selection, i.e., there is no dominance or epistasis, and different alleles are favored in different demes. We assume soft selection, i.e., population regulation occurs within each deme. We ignore random genetic drift and mutation and employ a deterministic continuous-time model to describe evolution. A continuous-time model is obtained from the corresponding discrete-time model in the limit of weak evolutionary forces (here, selection, recombination, and migration).

We denote the rate at which individuals in deme 1 (deme 2) are replaced by immigrants from the other deme by $m_1 \geq 0$ ($m_2 \geq 0$). Then $m = m_1 + m_2$ is the total migration rate. The recombination rate between the two loci is designated by $\rho \geq 0$.

Alleles at locus A are denoted by A_1 and A_2, at locus B by B_1 and B_2. We posit that A_1 and B_1 are favored in deme 1, whereas A_2 and B_2 are favored in deme 2. In deme k ($k = 1, 2$), we assign the Malthusian parameters $\frac{1}{2}\alpha_k$ and $-\frac{1}{2}\alpha_k$ to A_1 and A_2, and $\frac{1}{2}\beta_k$ and $-\frac{1}{2}\beta_k$ to B_1 and B_2. Because we assume absence of dominance and of epistasis, the resulting fitness matrix for the genotypes reads

$$\begin{array}{c} \\ A_1A_1 \\ A_1A_2 \\ A_2A_2 \end{array} \begin{array}{c} \begin{array}{ccc} B_1B_1 & B_1B_2 & B_2B_2 \end{array} \\ \begin{pmatrix} \alpha_k + \beta_k & \alpha_k & \alpha_k - \beta_k \\ \beta_k & 0 & -\beta_k \\ -\alpha_k + \beta_k & -\alpha_k & -\alpha_k - \beta_k \end{pmatrix} \end{array}. \tag{2.1}$$

By relabeling alleles, we can assume without loss of generality $\alpha_1 > 0 > \alpha_2$ and $\beta_1 > 0 > \beta_2$. Hence, A_1B_1 and A_2B_2 may be called the locally adapted haplotypes in deme 1 and deme 2, respectively. By relabeling loci, we can assume $\beta_1 \geq \alpha_1$. We define

$$\theta = \alpha_1\beta_2 - \alpha_2\beta_1. \tag{2.2}$$

By exchanging demes, i.e., by the transformation $\tilde{\alpha}_k = -\alpha_{k^*}$ and $\tilde{\beta}_k = -\beta_{k^*}$ (where k^* denotes the deme $\neq k$), or by exchanging loci, i.e., by the transformation $\tilde{\alpha}_k = \beta_k$ and $\tilde{\beta}_k = \alpha_k$, we can further assume $\theta \geq 0$ without loss of generality, cf. Appendix A.1.

The fitness matrix (2.1) is also obtained if the two loci contribute additively to a quantitative trait that is under linear directional selection in each deme (Bürger 2009c).

Then $\theta = 0$ if the genotypic values are deme independent, i.e., if there is no genotype-environment interaction on the trait level.

Because in the case $\theta = 0$ degenerate features can occur, it will be treated separately (Sections 3.9 and 3.10). Therefore, unless stated otherwise, we always impose the following assumptions on our parameters:

$$\alpha_1 > 0 > \alpha_2 \text{ and } \beta_1 > 0 > \beta_2, \tag{2.3a}$$

and

$$\beta_1 > \alpha_1, \tag{2.3b}$$

and

$$\theta > 0. \tag{2.3c}$$

From (2.3a) and (2.3c), we infer

$$\beta_2 < \alpha_2 \Rightarrow \alpha_1 < \beta_1. \tag{2.4}$$

Therefore, locus A is under weaker selection than locus B in both demes, i.e., $|\alpha_k| \leq |\beta_k|$ for $k = 1, 2$, if and only if $\beta_2 < \alpha_2$ holds.

The population can be described by the gamete frequencies in each of the demes. We denote the frequencies of the four possible gametes A_1B_1, A_1B_2, A_2B_1, and A_2B_2 in deme k by $x_{1,k}$, $x_{2,k}$, $x_{3,k}$, and $x_{4,k}$. Then the state space is $S_4 \times S_4$, where $S_4 = \left\{(x_1, x_2, x_3, x_4) : \ x_i \geq 0 \text{ and } \sum_{i=1}^4 x_i = 1\right\}$ is the simplex.

The following differential equations for the evolution of gamete frequencies in deme k can be derived straightforwardly:

$$\dot{x}_{i,k} = \frac{d}{dt}x_{i,k} = x_{i,k}(w_{i,k} - \bar{w}_k) - \eta_i \rho D_k + m_k(x_{i,k^*} - x_{i,k}). \tag{2.5}$$

Here the marginal fitness $w_{i,k}$ of gamete i and the mean fitness $\bar{w}_k$ in deme k are calculated from (2.1), $\eta_1 = \eta_4 = -\eta_2 = -\eta_3 = 1$, and $D_k = x_{1,k}x_{4,k} - x_{2,k}x_{3,k}$ is the linkage-disequilibrium (LD) measure. We note that $D_k > 0$ corresponds to an excess of the locally adapted haplotypes in deme k. The equations (2.5) also describe the dynamics of a haploid population if in deme k we assign the fitnesses α_k, $-\alpha_k$, β_k, $-\beta_k$ to the alleles A_1, A_2, B_1, B_2, respectively.

Instead of gamete frequencies it is often more convenient to work with allele frequencies and the LD measures D_k. We write $p_k = x_{1,k} + x_{2,k}$ and $q_k = x_{1,k} + x_{3,k}$ for the frequencies of A_1 and B_1 in deme k. Then the gamete frequencies $x_{i,k}$ are calculated from the p_k, q_k, and D_k by

$$x_{1,k} = p_k q_k + D_k, \qquad x_{2,k} = p_k(1 - q_k) - D_k, \tag{2.6a}$$

$$x_{3,k} = (1 - p_k)q_k - D_k, \quad x_{4,k} = (1 - p_k)(1 - q_k) + D_k\,. \tag{2.6b}$$

The constraints $x_{i,k} \geq 0$ and $\sum_{i=1}^{4} x_{i,k} = 1$ for $i = 1, 2, 3, 4$, and $k = 1, 2$ transform into $0 \leq p_k, q_k \leq 1$ and $-\min\{p_k q_k, (1-p_k)(1-q_k)\} \leq D_k \leq \min\{p_k(1-q_k), (1-p_k)q_k\}$. It follows that p_k, q_k, and D_k evolve according to

$$\dot{p}_k = \alpha_k p_k(1-p_k) + \beta_k D_k + m_k(p_{k^*} - p_k), \tag{2.7a}$$

$$\dot{q}_k = \beta_k q_k(1-q_k) + \alpha_k D_k + m_k(q_{k^*} - q_k), \tag{2.7b}$$

$$\begin{aligned}\dot{D}_k = {} & \left[\alpha_k(1-2p_k) + \beta_k(1-2q_k) - \rho\right] D_k \\ & + m_k\left[(D_{k^*} - D_k) + (p_{k^*} - p_k)(q_{k^*} - q_k)\right].\end{aligned} \tag{2.7c}$$

We emphasize that, because we are treating a continuous-time model, the parameters ρ, m_k, α_k, and β_k are rates (of recombination, migration, growth), whence they can be arbitrarily large. Their magnitude is determined by the time scale. By rescaling time, for instance to units of ρ or m, the number of independent parameters could be reduced by one without changing the equilibrium properties.

3. Equilibria and their stability

We distinguish three types of equilibria: (i) monomorphic equilibria (ME), (ii) single-locus polymorphisms (SLPs), and (iii) full (two-locus) polymorphisms (FPs). The first two types are boundary equilibria, whereas FPs are internal equilibria (except when $\rho = 0$). The stability properties of the ME and the coordinates and conditions for admissibility of the SLPs can be derived explicitly. However, the stability conditions for the SLPs and the conditions for existence or stability of FPs could be derived only for a number of limiting cases. These include strong recombination, weak or no recombination, weak, strong, or highly asymmetric migration.

3.1. Existence of boundary equilibria. The four ME, corresponding to fixation of one of the gametes, exist always. Their coordinates are as follows:

$$\begin{aligned}
&\mathsf{M}_1\ (A_1B_1 \text{ fixed}): && \hat{p}_k = 1,\ \hat{q}_k = 1,\ \hat{D}_k = 0 \ \text{ for } k = 1, 2,\\
&\mathsf{M}_2\ (A_1B_2 \text{ fixed}): && \hat{p}_k = 1,\ \hat{q}_k = 0,\ \hat{D}_k = 0 \ \text{ for } k = 1, 2,\\
&\mathsf{M}_3\ (A_2B_1 \text{ fixed}): && \hat{p}_k = 0,\ \hat{q}_k = 1,\ \hat{D}_k = 0 \ \text{ for } k = 1, 2,\\
&\mathsf{M}_4\ (A_2B_2 \text{ fixed}): && \hat{p}_k = 0,\ \hat{q}_k = 0,\ \hat{D}_k = 0 \ \text{ for } k = 1, 2,
\end{aligned}$$

where a $\hat{}$ signifies an equilibrium. There are up to four SLPs, one in each marginal one-locus system. We denote the SLPs where B_1 or B_2 is fixed by $\mathsf{P}_{\mathsf{A},1}$ or $\mathsf{P}_{\mathsf{A},2}$, respectively, and the SLPs where A_1 or A_2 is fixed by $\mathsf{P}_{\mathsf{B},1}$ or $\mathsf{P}_{\mathsf{B},2}$. Their coordinates and the conditions

for their admissibility can be calculated explicitly (Eyland 1971). We define

$$\sigma_k = \frac{m_k}{\alpha_k} \quad \text{and} \quad \tau_k = \frac{m_k}{\beta_k}\,. \tag{3.1}$$

By (2.3a), we have

$$\sigma_1 > 0 > \sigma_2 \quad \text{and} \quad \tau_1 > 0 > \tau_2\,. \tag{3.2}$$

In addition, it is easy to show that the assumptions (2.3) imply:

$$\sigma_1 + \sigma_2 \geq 0 \;\Rightarrow\; \tau_1 + \tau_2 < \sigma_1 + \sigma_2, \tag{3.3a}$$

$$\sigma_1 + \sigma_2 < 0 \;\Rightarrow\; \tau_1 + \tau_2 < 0. \tag{3.3b}$$

If locus B is fixed (for B_1 or B_2), the equilibrium allele frequencies at locus A are

$$\hat{p}_1^{\mathsf{A}} = \frac{1}{2}\left(1 - 2\sigma_1 + \sqrt{1 - 4\sigma_1\sigma_2}\right), \quad \hat{p}_2^{\mathsf{A}} = \frac{1}{2}\left(1 - 2\sigma_2 - \sqrt{1 - 4\sigma_1\sigma_2}\right). \tag{3.4}$$

If locus A is fixed, the equilibrium allele frequencies at locus B are given by

$$\hat{q}_1^{\mathsf{B}} = \frac{1}{2}\left(1 - 2\tau_1 + \sqrt{1 - 4\tau_1\tau_2}\right), \quad \hat{q}_2^{\mathsf{B}} = \frac{1}{2}\left(1 - 2\tau_2 - \sqrt{1 - 4\tau_1\tau_2}\right). \tag{3.5}$$

Thus, the four SLPs have the following coordinates:

$$\mathsf{P}_{\mathsf{A},1}: \quad \hat{p}_1 = \hat{p}_1^{\mathsf{A}},\ \hat{p}_2 = \hat{p}_2^{\mathsf{A}},\ \hat{q}_1 = \hat{q}_2 = 1,\ \hat{D}_1 = \hat{D}_2 = 0, \tag{3.6a}$$

$$\mathsf{P}_{\mathsf{A},2}: \quad \hat{p}_1 = \hat{p}_1^{\mathsf{A}},\ \hat{p}_2 = \hat{p}_2^{\mathsf{A}},\ \hat{q}_1 = \hat{q}_2 = 0,\ \hat{D}_1 = \hat{D}_2 = 0, \tag{3.6b}$$

$$\mathsf{P}_{\mathsf{B},1}: \quad \hat{p}_1 = \hat{p}_2 = 1,\ \hat{q}_1 = \hat{q}_1^{\mathsf{B}},\ \hat{q}_2 = \hat{q}_2^{\mathsf{B}},\ \hat{D}_1 = \hat{D}_2 = 0, \tag{3.6c}$$

$$\mathsf{P}_{\mathsf{B},2}: \quad \hat{p}_1 = \hat{p}_2 = 0,\ \hat{q}_1 = \hat{q}_1^{\mathsf{B}},\ \hat{q}_2 = \hat{q}_2^{\mathsf{B}},\ \hat{D}_1 = \hat{D}_2 = 0, \tag{3.6d}$$

The equilibria $\mathsf{P}_{\mathsf{A},1}$ and $\mathsf{P}_{\mathsf{A},2}$ are admissible if and only if

$$|\sigma_1 + \sigma_2| < 1, \tag{3.7}$$

and the equilibria $\mathsf{P}_{\mathsf{B},1}$ and $\mathsf{P}_{\mathsf{B},2}$ are admissible if and only if

$$|\tau_1 + \tau_2| < 1. \tag{3.8}$$

The SLPs leave the state space through one of their 'neighboring' ME if $|\sigma_1 + \sigma_2|$ or $|\tau_1 + \tau_2|$ increases above 1. In particular, we find

$$\sigma_1 + \sigma_2 \downarrow -1 \iff \mathsf{P}_{\mathsf{A},1} \to \mathsf{M}_1 \text{ and } \mathsf{P}_{\mathsf{A},2} \to \mathsf{M}_2, \tag{3.9a}$$

$$\sigma_1 + \sigma_2 \uparrow 1 \iff \mathsf{P}_{\mathsf{A},1} \to \mathsf{M}_3 \text{ and } \mathsf{P}_{\mathsf{A},2} \to \mathsf{M}_4, \tag{3.9b}$$

$$\tau_1 + \tau_2 \downarrow -1 \iff \mathsf{P}_{\mathsf{B},1} \to \mathsf{M}_1 \text{ and } \mathsf{P}_{\mathsf{B},2} \to \mathsf{M}_3, \tag{3.9c}$$

$$\tau_1 + \tau_2 \uparrow 1 \iff \mathsf{P}_{\mathsf{B},1} \to \mathsf{M}_2 \text{ and } \mathsf{P}_{\mathsf{B},2} \to \mathsf{M}_4. \tag{3.9d}$$

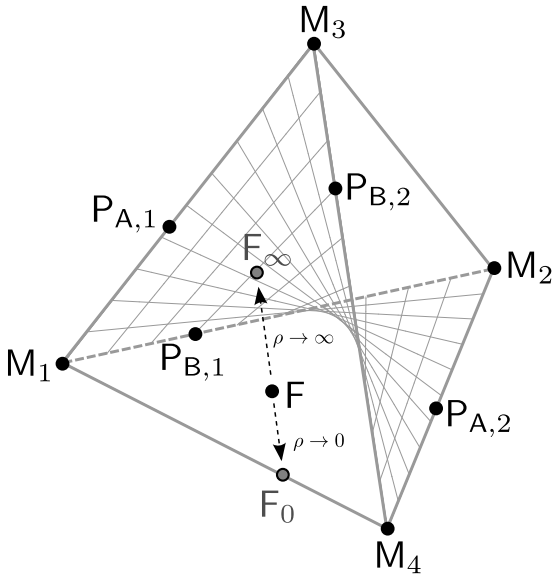

FIGURE 1. Location of equilibria. In terms of gamete frequencies, the state space is $S_4 \times S_4$, where each S_4 corresponds to one deme. This figure shows (schematically) the location in S_4 of all boundary equilibria and of the stable internal equilibrium F. F converges to F_∞ if $\rho \to \infty$ and to F_0 if $\rho \to 0$. The LE manifold is indicated by hatching.

Throughout, we use $\downarrow$ to indicated convergence from above and $\uparrow$ to indicate convergence from below. Figure 1 illustrates the location of the possible equilibria.

The SLPs are asymptotically stable within their marginal one-locus system if and only if they are admissible. Then they are also globally asymptotically stable within their marginal system (Eyland 1971). (We use globally stable in the sense that at least all trajectories from the interior of the designated set converge to the equilibrium.) The reader may notice that (3.7) and (3.8) are precisely the conditions for maintaining a protected polymorphism at locus A and B, respectively.

3.2. Stability of monomorphic equilibria. At each monomorphic equilibrium, the characteristic polynomial factors into three quadratic polynomials. Two of them determine stability with respect to the marginal one-locus systems, whereas the third determines stability with respect to the interior of the state space. The stability properties of the monomorphic equilibria are as follows. The proof is given in Appendix A.2.

PROPOSITION 3.1. M_1 *is asymptotically stable if*

$$\sigma_1 + \sigma_2 < -1 \text{ and } \tau_1 + \tau_2 < -1 \tag{3.10}$$

and one of the following conditions hold

$$\rho \geq \min\{-\alpha_2, -\beta_2\} \tag{3.11a}$$

or

$$\rho < \min\{-\alpha_2, -\beta_2\} \text{ and } m_2 > -\frac{(\alpha_1+\beta_1+\rho+m_1)(\alpha_2+\beta_2+\rho)}{\alpha_1+\beta_1+\rho}. \tag{3.11b}$$

M_2 *is always unstable.*

M_3 *is asymptotically stable if*

$$\sigma_1+\sigma_2 > 1 \text{ and } \tau_1+\tau_2 < -1. \tag{3.12}$$

M_4 *is asymptotically stable if*

$$\sigma_1+\sigma_2 > 1 \text{ and } \tau_1+\tau_2 > 1 \tag{3.13}$$

and one of the following conditions hold

$$\rho \geq \alpha_1 \tag{3.14a}$$

or

$$\rho < \alpha_1 \text{ and } m_2 > \frac{(\alpha_1+\beta_1-\rho-m_1)(\alpha_2+\beta_2-\rho)}{\alpha_1+\beta_1-\rho}. \tag{3.14b}$$

If one of the inequalities in (3.10)*,* (3.12)*, or* (3.13)*, or one of the inequalities for* m_2 *in* (3.11b) *or* (3.14b) *is reversed, the respective equilibrium is unstable.*

If we assumed $\theta < 0$, then M_3 would always be unstable and M_2 would be stable if $\sigma_1+\sigma_2 < -1$ and $\tau_1+\tau_2 > 1$.

The above result shows that each of M_1, M_3, or M_4 can be stable, but never simultaneously. For sufficiently loose linkage, the stability of a ME is determined solely by its stability within the two marginal one-locus systems in which it occurs. Stability of M_3 is independent of the recombination rate. For given migration rates, the equilibria M_1 and M_4 may be stable for high recombination rates but unstable for low ones. For a low total migration rate ($m_1 + m_2$), no ME is stable. For a sufficiently high total migration rate, there is a globally asymptotically stable ME (Section 4.5).

3.3. Stability of single-locus polymorphisms. As already mentioned, a single-locus polymorphism is globally attracting within its marginal one-locus system whenever it is admissible. Although the coordinates of the SLPs are given explicitly, the conditions for stability within the full, six-dimensional system on $S_4 \times S_4$ are uninformative because the four eigenvalues that determine stability transversal to the marginal one-locus system are solutions of a complicated quartic equation.

In the following we treat several limiting cases in which the conditions for stability of the SLPs and for existence and stability of FPs can be obtained explicitly.

3.4. Weak migration. The equilibrium and stability structure for weak migration can be deduced from the model with no migration by perturbation theory. In the absence

of migration ($m_1 = m_2 = 0$), the two subpopulations evolve independently. Because selection is nonepistatic and there is no dominance, in each deme the fittest haplotype becomes eventually fixed. In fact, mean fitness is nondecreasing (Ewens 1969). Our assumptions about fitness, i.e., (2.1) and (2.3a), imply that in deme 1 the equilibrium with $\hat{p}_1 = \hat{q}_1 = 1$ and $\hat{D}_1 = 0$ is globally attracting, and in deme 2 the equilibrium with $\hat{p}_2 = \hat{q}_2 = 0$ and $\hat{D}_2 = 0$ is globally attracting. Therefore, in the combined system, i.e., on $S_4 \times S_4$, but still with $m_1 = m_2 = 0$, the (unique) globally attracting equilibrium is given by

$$\hat{p}_1 = \hat{q}_1 = 1, \quad \hat{p}_2 = \hat{q}_2 = 0, \quad \hat{D}_1 = \hat{D}_2 = 0\,. \tag{3.15}$$

All other equilibria are on the boundary and unstable.

Because, generically, all equilibria in the system without migration are hyperbolic and it is a gradient system (Shahshahani 1979; Bürger 2000, p. 42), Theorem 5.4 in Bürger (2009a) applies and shows that the perturbation F of the equilibrium (3.15) is globally asymptotically stable for sufficiently small migration rates m_1 and m_2. Boundary equilibria remain unstable for sufficiently small migration rates. It is straightforward to calculate the coordinates of the perturbed equilibrium to leading order in m_1 and m_2. They are given by

$$\hat{p}_1 = 1 - \frac{m_1}{\alpha_1}\frac{\alpha_1 + \rho}{\alpha_1 + \beta_1 + \rho}\,, \quad \hat{q}_1 = 1 - \frac{m_1}{\beta_1}\frac{\beta_1 + \rho}{\alpha_1 + \beta_1 + \rho}\,, \quad \hat{D}_1 = \frac{m_1}{\alpha_1 + \beta_1 + \rho}\,, \tag{3.16a}$$

$$\hat{p}_2 = \frac{m_2}{-\alpha_2}\frac{\rho - \alpha_2}{\rho - \alpha_2 - \beta_2}\,, \qquad \hat{q}_2 = \frac{m_2}{-\beta_2}\frac{\rho - \beta_2}{\rho - \alpha_2 - \beta_2}\,, \qquad \hat{D}_2 = \frac{m_2}{\rho - \alpha_2 - \beta_2}\,. \tag{3.16b}$$

Therefore, we conclude

Proposition 3.2. *For sufficiently weak migration, there is a unique, globally attracting, fully polymorphic equilibrium* F. *To leading order in* m_1 *and* m_2, *its coordinates are given by* (3.16).

Proposition 3.2 remains valid if the assumptions (2.3b) and (2.3c) are dropped. Apart from the obvious fact that migration reduces differences between subpopulations, the above approximations show that the lower the recombination rate, the smaller is this reduction. Thus, for given (small) migration rates, differentiation between subpopulations is always enhanced by reduced recombination. Linkage disequilibria within subpopulations are always positive.

3.5. Linkage equilibrium. If recombination is so strong relative to selection and migration that linkage equilibrium (LE) can be assumed, i.e., if $\frac{1}{\rho}\max_{k=1,2}\{|\alpha_k|, |\beta_k|, m_k\} \to 0$, the dynamics (2.7) simplifies to

$$\dot{p}_1 = \alpha_1 p_1(1 - p_1) + m_1(p_2 - p_1)\,, \tag{3.17a}$$

$$\dot{p}_2 = \alpha_2 p_2(1 - p_2) + m_2(p_1 - p_2)\,, \tag{3.17b}$$

$$\dot{q}_1 = \beta_1 q_1(1 - q_1) + m_1(q_2 - q_1)\,, \tag{3.17c}$$

$$\dot{q}_2 = \beta_2 q_2(1 - q_2) + m_2(q_1 - q_2)\,, \tag{3.17d}$$

which is defined on $[0, 1]^4$.

In (3.17), the differential equations for the two loci are decoupled, i.e., (3.17a) and (3.17b) as well as (3.17c) and (3.17d) form closed systems. Thus, the dynamics of the full system is a Cartesian product of the two one-locus dynamics. Therefore, in addition to the ME and to the SLPs determined above, the following internal equilibrium, denoted by F_∞, may exist

$$\hat{p}_1^\infty = \hat{p}_1^{\mathsf{A}}, \quad \hat{p}_2^\infty = \hat{p}_2^{\mathsf{A}}, \quad \hat{q}_1^\infty = \hat{q}_1^{\mathsf{B}}, \quad \hat{q}_2^\infty = \hat{q}_2^{\mathsf{B}}, \tag{3.18}$$

where the $\hat{p}_k^{\mathsf{A}}$ and $\hat{q}_k^{\mathsf{B}}$ are given by (3.4) and (3.5), respectively. No other internal equilibrium can exist. This equilibrium is admissible if and only if (3.7) and (3.8) are satisfied, i.e., if and only if all four SLPs are admissible.

Because in the one-locus model the FP is globally asymptotically stable (hence, it attracts all trajectories from the interior of the state space) whenever it is admissible (Eyland 1971; Hadeler and Glas 1983, Theorem 2; Nagylaki and Lou 2008, Section 4.3.2), and because the full dynamics is the Cartesian product of the one-locus dynamics, the fully polymorphic equilibrium F_∞ is globally asymptotically stable whenever it is admissible. Similarly, we conclude that a boundary equilibrium is globally asymptotically stable whenever it is asymptotically stable in the full system. These results in combination with those in Sections 3.1 and 3.2 yield the following proposition.

Proposition 3.3. *Assume* (3.17)*. Then a globally asymptotically stable equilibrium exists always. This equilibrium is internal, hence equals* F_∞ (3.18)*, if and only if* (3.7) *and* (3.8) *hold. It is a SLP if one of* (3.7) *or* (3.8) *is violated, and a ME if both* (3.7)*and* (3.8) *are violated.*

If, by variation of parameters, the internal equilibrium leaves (or enters) the state space, generically, it does so through one of the SLPs. The precise conditions are:

$$\mathsf{F}_\infty \to \mathsf{P}_{\mathsf{A},1} \iff \tau_1 + \tau_2 \downarrow -1 \text{ and } |\sigma_1 + \sigma_2| < 1, \tag{3.19a}$$

$$\mathsf{F}_\infty \to \mathsf{P}_{\mathsf{A},2} \text{ does not occur}, \tag{3.19b}$$

$$\mathsf{F}_\infty \to \mathsf{P}_{\mathsf{B},1} \iff \sigma_1 + \sigma_2 \downarrow -1 \text{ and } |\tau_1 + \tau_2| < 1, \tag{3.19c}$$

$$\mathsf{F}_\infty \to \mathsf{P}_{\mathsf{B},2} \iff \sigma_1 + \sigma_2 \uparrow 1 \text{ and } |\tau_1 + \tau_2| < 1. \tag{3.19d}$$

When, upon leaving the state space, F_∞ *collides with a boundary equilibrium (SLP or ME), the respective boundary equilibrium becomes globally asymptotically stable.*

We note that $\mathsf{F}_\infty \to \mathsf{P}_{A,2}$ does not occur because it requires $\tau_1+\tau_2 \uparrow 1$ and $|\sigma_1+\sigma_2| < 1$, which is impossible by (3.3). We leave the simple determination of the conditions for bifurcations of F_∞ with one of the ME to the interested reader.

Proposition 3.3 can be extended straightforwardly to an arbitrary number of loci because the dynamics at each locus is independent of that at the other loci. This decoupling of loci occurs because there is no epistasis.

3.6. Strong recombination: quasi-linkage equilibrium. If recombination is strong, a regular perturbation analysis of the internal equilibrium F_∞ of (3.17) can be performed. The allele frequencies and linkage disequilibria can be calculated to order $1/\rho$. Formally, we set

$$m_k = m_k/\rho \quad (k = 1, 2), \tag{3.20}$$

keep σ_k and τ_k constant, and let $\rho \to \infty$. Then, we obtain

$$\hat{p}_1 = \hat{p}_1^\infty + \frac{\sigma_1}{\rho}\frac{\sigma_2(\beta_1-\beta_2)+\beta_1\sqrt{1-4\sigma_1\sigma_2}}{\sqrt{1-4\sigma_1\sigma_2}}(\hat{q}_1^\infty-\hat{q}_2^\infty)+O(\rho^{-2}), \tag{3.21a}$$

$$\hat{q}_1 = \hat{q}_1^\infty + \frac{\tau_1}{\rho}\frac{\tau_2(\alpha_1-\alpha_2)+\alpha_1\sqrt{1-4\tau_1\tau_2}}{\sqrt{1-4\tau_1\tau_2}}(\hat{p}_1^\infty-\hat{p}_2^\infty)+O(\rho^{-2}), \tag{3.21b}$$

$$\hat{D}_1 = \frac{m_1}{\rho}(\hat{p}_1^\infty-\hat{p}_2^\infty)(\hat{q}_1^\infty-\hat{q}_2^\infty)+O(\rho^{-2}), \tag{3.21c}$$

and analogous formulas hold for the second deme. Because LD is of order $1/\rho$, this approximation may be called the quasi-linkage equilibrium approximation of the fully polymorphic equilibrium (Kimura 1965, Turelli and Barton 1990, Nagylaki et al. 1999). We note that LD is positive in both demes and increases with increasing differentiation between the demes, increasing migration, or decreasing recombination.

Proposition 5.1 in Bürger (2009a) shows that in every small neighborhood of an equilibrium of the model with LE (3.17), there is one equilibrium of the perturbed system, and it has the same stability properties as the unperturbed equilibrium. Because of the simple structure of (3.17), a stronger result can be obtained. In an isolated one-locus system on $[0,1]^2$ (e.g., (3.17a) and (3.17b)), every trajectory from the interior converges to the unique asymptotically stable equilibrium (Section 3.5), and the chain-recurrent points (Conley 1978) are the equilibria. Therefore, the same holds for the LE dynamics (3.17), and the regular global perturbation result of Nagylaki et al. (1999) (the proof of their Theorem 2.3) applies for large ρ. Hence the dynamical behavior with strong recombination is qualitatively the same as that under LE. We conclude that for sufficiently strong recombination every asymptotically stable equilibrium is globally asymptotically stable.

3.7. No recombination. Let recombination be absent, i.e., $\rho = 0$. Then, effectively, we have a one-locus model in which the four alleles correspond to the four gametes A_1B_1, A_1B_2, A_2B_1, A_2B_2. In deme k, they have the selection coefficients $\frac{1}{2}(\alpha_k + \beta_k)$, $\frac{1}{2}(\alpha_k - \beta_k)$, $\frac{1}{2}(-\alpha_k + \beta_k)$, $-\frac{1}{2}(\alpha_k + \beta_k)$, respectively. According to Theorem 2.4 of Nagylaki and Lou (2001), generically, no more than two gametes can be present at an equilibrium. We will prove a stronger result and characterize all possible equilibria and their local stability.

Because $\rho = 0$, there may be a polymorphic equilibrium at which only the gametes A_1B_1 and A_2B_2 are present. We call it F_0 and set

$$\kappa_k = \frac{m_k}{\alpha_k + \beta_k} \quad (k = 1, 2)\,. \tag{3.22}$$

Then one-locus theory (Section 3.1) informs us that F_0 is admissible if and only if

$$|\kappa_1 + \kappa_2| < 1. \tag{3.23}$$

Its coordinates are given by

$$\hat{p}_1^0 = \hat{q}_1^0 = \frac{1}{2}\left(1 - 2\kappa_1 + \sqrt{1 - 4\kappa_1\kappa_2}\right), \tag{3.24a}$$

$$\hat{p}_2^0 = \hat{q}_2^0 = \frac{1}{2}\left(1 - 2\kappa_2 - \sqrt{1 - 4\kappa_1\kappa_2}\right), \tag{3.24b}$$

$$\hat{D}_k^0 = \hat{p}_k(1 - \hat{p}_k) \quad (k = 1, 2)\,, \tag{3.24c}$$

where $\hat{p}_k^0 = \hat{q}_k^0 = \hat{x}_{1,k}^0$, $\hat{x}_{2,k}^0 = \hat{x}_{3,k}^0 = 0$, and $\hat{x}_{4,k}^0 = 1 - \hat{x}_{1,k}^0$ $(k = 1, 2)$. Within the subsystem in which only the gametes A_1B_1 and A_2B_2 are present, F_0 is asymptotically stable whenever it is admissible. One-locus theory implies that

$$\kappa_1 + \kappa_2 \downarrow -1 \iff \mathsf{F}_0 \to \mathsf{M}_1, \tag{3.25a}$$

$$\kappa_1 + \kappa_2 \uparrow 1 \iff \mathsf{F}_0 \to \mathsf{M}_4. \tag{3.25b}$$

A simple application of Corollary 3.9 of Nagylaki and Lou (2007) shows that the gamete A_1B_2 will always be lost (to apply their result, recall assumptions (2.3) and use $\gamma_{22} = \gamma_{23} = 0$, $\frac{\alpha_1}{\alpha_1+\beta_1} < \gamma_{21} < \frac{\alpha_2}{\alpha_2+\beta_2}$, $\gamma_{24} = 1 - \gamma_{21}$). This strengthens the result in Section 3.2 that M_2 is always unstable. Thus, we are left with the analysis of the tri-gametic system consisting of A_1B_1, A_2B_1, and A_2B_2. (If $\theta < 0$, then gamete A_2B_1 is lost.)

In Appendix A.3 it is proved that F_0 is the only equilibrium at which both loci are polymorphic except when

$$m_1 m_2 = \tilde{m} \tag{3.26}$$

holds, where

$$\tilde{m} = -\alpha_1\alpha_2\beta_1\beta_2(\alpha_1 + \beta_1)(\alpha_2 + \beta_2)/\theta^2. \tag{3.27}$$

If (3.26) holds, then there is a line of internal equilibria connecting F_0 with $\mathsf{P}_{A,1}$ or $\mathsf{P}_{B,2}$ (or M_3); see Appendix A.3.

We find that F_0 is asymptotically stable if

$$m_1 m_2 < \tilde{m}, \tag{3.28}$$

and unstable if the inequality is reversed (Appendix A.4). For sufficiently small migration rates, Proposition 3.2 implies that $\mathsf{F}_0 = \mathsf{F}$ and F_0 is globally asymptotically stable. If the inequality in (3.28) is reversed, F_0 may or may not be admissible.

Of course, if F_0 is asymptotically stable, then the equilibria M_1 and M_4 are unstable; cf. (3.25). The following argument shows that M_3 cannot be simultaneously stable with F_0. We rewrite (3.28) as

$$\kappa_1 \kappa_2 > -\frac{\alpha_1 \alpha_2 \beta_1 \beta_2}{\theta^2} = -\frac{\sigma_1 \sigma_2 \tau_1 \tau_2}{(\sigma_1 \tau_2 - \sigma_2 \tau_1)^2}\,. \tag{3.29}$$

Because

$$\kappa_k^{-1} = \sigma_k^{-1} + \tau_k^{-1}\,, \tag{3.30}$$

(3.29) becomes

$$(\sigma_1 \tau_2 - \sigma_2 \tau_1)^2 + (\sigma_1 + \tau_1)(\sigma_2 + \tau_2) < 0\,. \tag{3.31}$$

Since M_3 is asymptotically stable if (3.12) holds and because, as is easy to show, (3.12) and (3.31) are incompatible, the assertion follows. It can also be shown from (3.12) and (3.31) that M_3 cannot become stable when F_0 loses its stability except in the degenerate case when $\sigma_1 + \sigma_2 = 1$ and $\tau_1 + \tau_2 = -1$.

In our tri-gametic system, $\mathsf{P}_{A,1}$ and $\mathsf{P}_{B,2}$ are the only possible SLPs. They may exist simultaneously with F_0 if (3.28) holds, i.e., if F_0 is stable, but not otherwise (Appendix A.5). If (3.28) holds, both are unstable (if admissible). $\mathsf{P}_{A,1}$ or $\mathsf{P}_{B,2}$ have an eigenvalue 0 if and only if (3.26) holds or if they leave or enter the state space through a ME. In Appendix A.5 it is shown that $\mathsf{P}_{A,1}$ is asymptotically stable if and only if

$$\tau_1 + \tau_2 < -1 \;\text{ and }\; |\sigma_1 + \sigma_2| < 1 \;\text{ and }\; m_1 m_2 > \tilde{m}, \tag{3.32}$$

and $\mathsf{P}_{B,2}$ is asymptotically stable if and only if

$$1 < \sigma_1 + \sigma_2 \;\text{ and }\; |\tau_1 + \tau_2| < 1 \;\text{ and }\; m_1 m_2 > \tilde{m}. \tag{3.33}$$

Hence, if $m_1 m_2$ increases above $\tilde{m}$, the SLP that is admissible becomes asymptotically stable. Upon collision of the stable SLP with one of the adjacent ME, the corresponding ME becomes stable and remains so for all higher migration rates. We summarize these findings as follows:

PROPOSITION 3.4. *Except in the degenerate case when* (3.26) *holds, only equilibria with at most two gametes present exist. If* (3.23) *is satisfied, the equilibrium* F_0 *given by* (3.24) *is admissible. If, in addition,* (3.28) *is fulfilled, then* F_0 *is asymptotically stable. For sufficiently small migration rates, it is globally asymptotically stable. If* F_0 *is unstable or not admissible, then one of the ME* (M_1, M_3, M_4) *or one of the SLPs* ($\mathsf{P}_{\mathsf{A},1}$, $\mathsf{P}_{\mathsf{B},2}$) *is asymptotically stable. If* (3.26) *holds, then there is a line of equilibria with three gametes present.*

The proposition shows that, except for the nongeneric case when (3.26) holds, there is always precisely one stable equilibrium point. Numerical results support the conjecture that the stable equilibrium is globally asymptotically stable. Bifurcation patterns as functions of m are derived in Section 4.8.

In addition to F_0, there exists a second FP on the edge connecting M_2 and M_3. Although its coordinates can be calculated easily, it is not of interest here as it is unstable for every choice of selection and migration parameters. This unstable equilibrium leaves the state space under small perturbations, i.e., if $\rho > 0$.

3.8. Highly asymmetric migration. All special cases treated above suggest that there always exists a globally asymptotically stable equilibrium. This, however, is generally not true as was demonstrated by the analysis of the two-locus continent-island (CI) model in Bürger and Akerman (2011). There, all possible bifurcation patterns were derived and it was shown that the fully polymorphic equilibrium can be simultaneously stable with a boundary equilibrium. For highly asymmetric migration rates, the equilibrium and stability structure can be obtained by a perturbation analysis of this CI model.

Therefore, we first summarize the most relevant features of the analysis in Bürger and Akerman (2011). Because in that analysis the haplotype A_2B_2 is fixed on the continent (here, deme 2) and there is no back migration ($m_2 = 0$), it is sufficient to treat the dynamics on the island (here, deme 1) where immigration of A_2B_2 occurs at rate m_1. Thus, the state space is S_4.

It was shown that up to two internal (fully polymorphic) equilibria, denoted by E_+ and E_-, may exist. Only one (E_+) can be stable. Two SLPs, E_A and E_B, may exist. At E_A, locus A is polymorphic and allele B_2 is fixed; at E_B, locus B is polymorphic and allele A_2 is fixed. E_A (E_B) is admissible if and only if $m_1 < \alpha_1$ ($m_1 < \beta_1$). E_A is always unstable. Finally, there always exists the monomorphic equilibrium E_C at which the haplotype A_2B_2 is fixed on the island. The equilibrium coordinates of all equilibria were obtained explicitly. In addition, it was proved (see also Bank et al. 2012, Supporting Information, Theorem S.4) that precisely the following two types of bifurcation patterns can occur:

Type 1. There exists a critical migration rate $m^\bullet > 0$ such that:

- If $0 < m_1 < m^\bullet$, a unique internal equilibrium, E_+, exists. It is asymptotically stable and, presumably, globally asymptotically stable.
- At $m_1 = m^\bullet$, E_+ leaves the state space through a boundary equilibrium (E_B or E_C) by an exchange-of-stability bifurcation.
- If $m_1 > m^\bullet$, a boundary equilibrium (E_B or E_C) is asymptotically stable and, presumably, globally stable.

Type 2. There exist critical migration rates m° and $m^\bullet$ satisfying $m^\bullet > m^\circ > 0$ such that:

- If $0 < m_1 < m^\circ$, there is a unique internal equilibrium (E_+). It is asymptotically stable and, presumably, globally stable.
- At $m_1 = m^\circ$, an unstable equilibrium (E_-) enters the state space by an exchange-of-stability bifurcation with a boundary equilibrium (E_B or E_C).
- If $m^\circ < m_1 < m^\bullet$, there are two internal equilibria, one asymptotically stable (E_+), the other unstable (E_-), and one of the boundary equilibria (E_B or E_C) is asymptotically stable.
- At $m_1 = m^\bullet$, the two internal equilibria merge and annihilate each other by a saddle-node bifurcation.
- If $m_1 > m^\bullet$, a boundary equilibrium (E_B or E_C) is asymptotically stable and, presumably, globally stable.

For sufficiently large migration rates ($m > m^{\bullet\bullet} \geq m^\bullet$), E_C is globally asymptotically stable in both cases. Bifurcation patterns of Type 2 occur only if the recombination rate is intermediate, i.e., if ρ is about as large as α_1.

By imbedding the CI model into the two-deme dynamics, (2.5) or (2.7), perturbation theory can be applied to obtain analogous results for highly asymmetric migration, i.e., for sufficiently small m_2/m_1 (Karlin and McGregor 1972). This is so because all equilibria in the CI model are hyperbolic except when collisions between equilibria occur (Bürger and Akerman 2011). Since the coordinates of the internal equilibria E_+ and E_- were derived, the perturbed equilibrium frequencies can be obtained. Because they are too complicated to be informative, we do not present them. The perturbation of E_+, denoted by F, is asymptotically stable. As E_- is internal, it cannot be lost by a small perturbation. Also the boundary equilibria and their stability properties are preserved under small perturbations. In particular, E_C gives rise to M_4, and the SLPs E_A and E_B give rise to $\mathsf{P}_{\mathsf{A},2}$ and $\mathsf{P}_{\mathsf{B},2}$, respectively,

If recombination is intermediate, (at least) under highly asymmetric two-way migration, one stable and one unstable FP can coexist. In this case the stable FP, F, is simultaneously stable with either M_4 or $\mathsf{P}_{\mathsf{B},2}$. Although there is precisely one (perturbed)

equilibrium in a small neighborhood of every equilibrium of the CI model, we can not exclude that other internal equilibria or limit sets are generated by perturbation.

3.9. The case $\theta = 0$. The analyses in the previous sections are based on the assumptions (2.3), in particular, on $\theta > 0$. However, many of the results obtained above remain valid if $\theta = 0$. Here, we point out the necessary adjustments.

Without loss of generality, we can assume

$$|\alpha_k| \le |\beta_k| \text{ for } k = 1, 2 \tag{3.34}$$

in addition to $\theta = 0$ and (2.3a). Then we observe that

$$\sigma_1 + \sigma_2 = \frac{\beta_2}{\alpha_2}(\tau_1 + \tau_2) \ge \tau_1 + \tau_2 \text{ and } \kappa_1 + \kappa_2 = \frac{\beta_2}{\alpha_2 + \beta_2}(\tau_1 + \tau_2) < \tau_1 + \tau_2. \tag{3.35}$$

Therefore, either

$$0 < \kappa_1 + \kappa_2 < \tau_1 + \tau_2 \le \sigma_1 + \sigma_2 \tag{3.36a}$$

or

$$0 > \kappa_1 + \kappa_2 > \tau_1 + \tau_2 \ge \sigma_1 + \sigma_2 \tag{3.36b}$$

or

$$\kappa_1 + \kappa_2 = \tau_1 + \tau_2 = \sigma_1 + \sigma_2 = 0 \tag{3.36c}$$

applies, where equality in (3.36a) and (3.36b) holds if $\alpha_k = \beta_k$ ($k = 1, 2$). In addition,

$$\kappa_1 + \kappa_2 = 0 \iff \tau_1 + \tau_2 = 0 \iff \sigma_1 + \sigma_2 = 0. \tag{3.37}$$

With these preliminaries, we can treat the changes required in the above propositions if $\theta = 0$.

From (3.36) we infer that, in Proposition 3.1, not only M_2 but also M_3 is always unstable. In addition, if $0 > \tau_1 + \tau_2 \ge \sigma_1 + \sigma_2$, then M_1 is asymptotically stable for sufficiently strong migration, whereas M_4 is stable for sufficiently strong migration if $0 < \tau_1 + \tau_2 \le \sigma_1 + \sigma_2$ holds.

As already noted, Proposition 3.2 remains valid independently of the value of θ.

In Proposition 3.3, the only SLPs through which the internal equilibrium F_∞ can leave the state space are $\mathsf{P}_{\mathsf{B},1}$ and $\mathsf{P}_{\mathsf{B},2}$; see (3.19c) and (3.19d). The reason is that, except when $\sigma_1 + \sigma_2 = 0$ (and (3.37) applies), $\mathsf{P}_{\mathsf{A},1}$ and $\mathsf{P}_{\mathsf{A},2}$ are only admissible if $\mathsf{P}_{\mathsf{B},1}$ and $\mathsf{P}_{\mathsf{B},2}$ are. Thus, the locus under weaker selection always becomes monomorphic at lower rates of gene flow than the locus under stronger selection.

If $\rho = 0$ (Proposition 3.4), F_0 is asymptotically stable whenever it is admissible because $\tilde{m} \to \infty$ as $\theta \to 0$; see (3.28). In addition, (3.36) implies that F_0 persists stronger gene flow than the SLPs, which are always unstable; see (3.32) and (3.33).

In the highly symmetric case of (3.36c), SLPs cannot be lost. Thus, F_∞ is always admissible and globally stable, cf. Proposition 3.3. If $\rho = 0$, (3.37) implies that F_0 exists always (and is stable). In the next section we show that in this highly symmetric case the FP is always admissible for arbitrary recombination rates.

3.10. The super-symmetric case. In many, especially ecological, applications highly symmetric migration-selection models are studied. Frequently made assumptions are that the migration rates between the demes are identical ($m_1 = m_2$), selection in deme 2 mirrors that in deme 1 ($\alpha_k = -\alpha_{k^*}$), and the loci are equivalent ($\alpha_k = \beta_k$). Thus, $\theta = 0$ and (3.36c) holds, which we assume now.

Conditions (3.7) and (3.8) imply that all four SLPs are admissible. Hence, all monomorphisms are unstable. In addition, it can be proved that all SLPs are unstable (Appendix A.6). If migration is weak, a globally asymptotically stable, fully polymorphic equilibrium (F) exists (Proposition 3.2).

Because every boundary equilibrium is hyperbolic for every parameter choice, the index theorem of Hofbauer (1990) can be applied. Since none of the boundary equilibria is saturated, it follows that an internal equilibrium with index 1 exists. For small migration rates, this is F because it is unique. Since the boundary equilibria are always hyperbolic, no internal equilibrium can leave the state space through the boundary. However, we cannot exclude that the internal equilibrium undergoes a pitchfork or a Hopf bifurcation. Numerical results support the conjecture that the internal equilibrium is unique and globally attracting, independently of the strength of migration. This is a very special feature of this super-symmetric case; cf. Proposition 4.3.

3.11. General case. Because a satisfactory analysis for general parameter choices seems out of reach, we performed extensive numerical work to determine the possible equilibrium structures. In no case did we find more complicated equilibrium structures than indicated above, i.e., apparently there are never more than two internal equilibria. If there is one internal equilibrium, it appears to be globally asymptotically stable. If there are two internal equilibria, then one is unstable and the other is simultaneously stable with one boundary equilibrium (as in the CI model). Apparently, two internal equilibria occur only for sufficiently asymmetric migration rates and only if the recombination rate is of similar magnitude as the selective coefficients.

A glance at the dynamical equations (2.7) reveals that an internal equilibrium can be in LE only if $p_1 = p_2$ or $q_1 = q_2$. From (3.18), (3.4) and (3.5), we find that this can occur

only if $|\sigma_1 + \sigma_2| = 1$ or $|\tau_1 + \tau_2| = 1$, i.e., for a boundary equilibrium. Thus, internal equilibria always exhibit LD.

For low migration rates as well as for high recombination rates, there is a unique, fully polymorphic equilibrium which is globally asymptotically stable and exhibits positive LD (Sections 3.4 or 3.6). We denote the (presumably unique) asymptotically stable, fully polymorphic equilibrium by F. If migration is weak, or recombination is weak, or recombination is strong, we have proved that F is unique. Useful approximations are available for weak migration or strong recombination; see (3.16) or (3.21). Finally, for sufficiently high migration rates one of the monomorphic equilibria is globally asymptotically stable.

4. Bifurcation patterns and maintenance of polymorphism

Here we study how genetic variation and polymorphism depend on the strength and pattern of migration. In particular, we are interested in determining how the maximum migration rate that permits genetic polymorphism depends on the other parameters. For this end, we explore properties of our model, such as the possible bifurcation patterns, as functions of the total migration rate m. We do this by assuming that $\alpha_1, \alpha_2, \beta_1, \beta_2, \rho$, and the migration ratio

$$\phi = \frac{m_1}{m}, \tag{4.1}$$

where $m > 0$ and $0 \le \phi \le 1$, are constant. The values $\phi = 0$ and $\phi = 1$ correspond to one-way migration, as in the CI model. If $\phi = \frac{1}{2}$, migration between the demes is symmetric, an assumption made in many studies of migration-selection models. Fixing ϕ and treating m as the only migration parameter corresponds to the migration scheme introduced by Deakin (1966).

4.1. Important quantities. We define several important quantities that will be needed to describe our results and summarize the relevant relations between them. Let

$$\phi^{\mathsf{A}} = \frac{\alpha_1}{\alpha_1 - \alpha_2}, \tag{4.2a}$$

$$\phi^{\mathsf{B}} = \frac{\beta_1}{\beta_1 - \beta_2}, \tag{4.2b}$$

$$\phi^{\mathsf{F}_0} = \frac{\alpha_1 + \beta_1}{\alpha_1 + \beta_1 - (\alpha_2 + \beta_2)}, \tag{4.2c}$$

$$\tilde{\phi}^{\mathsf{AB}} = \frac{\alpha_1\beta_1(\alpha_2 - \beta_2)}{\alpha_1\beta_1(\alpha_2 - \beta_2) - \alpha_2\beta_2(\alpha_1 - \beta_1)}, \tag{4.2d}$$

$$\phi^{\mathsf{AB}} = \frac{\alpha_1\beta_1(\alpha_2 + \beta_2)}{\alpha_1\beta_1(\alpha_2 + \beta_2) - \alpha_2\beta_2(\alpha_1 + \beta_1)}, \tag{4.2e}$$

$$\phi^{\mathsf{M}_1} = \frac{\alpha_1(\beta_2+\rho)(\alpha_1+\beta_1+\rho)}{\alpha_1(\beta_2+\rho)(\alpha_1+\beta_1+\rho)-\alpha_2(\beta_1+\rho)(\alpha_2+\beta_2+\rho)}, \tag{4.2f}$$

$$\tilde{\phi}^{\mathsf{M}_1} = \frac{\beta_1(\alpha_2+\rho)(\alpha_1+\beta_1+\rho)}{\beta_1(\alpha_2+\rho)(\alpha_1+\beta_1+\rho)-\beta_2(\alpha_1+\rho)(\alpha_2+\beta_2+\rho)}, \tag{4.2g}$$

$$\phi^{\mathsf{M}_4} = \frac{\beta_1(\alpha_2-\rho)(\alpha_1+\beta_1-\rho)}{\beta_1(\alpha_2-\rho)(\alpha_1+\beta_1-\rho)-\beta_2(\alpha_1-\rho)(\alpha_2+\beta_2-\rho)}, \tag{4.2h}$$

$$\tilde{\phi}^{\mathsf{M}_4} = \frac{\alpha_1(\beta_2-\rho)(\alpha_1+\beta_1-\rho)}{\alpha_1(\beta_2-\rho)(\alpha_1+\beta_1-\rho)-\alpha_2(\beta_1-\rho)(\alpha_2+\beta_2-\rho)}, \tag{4.2i}$$

$$\phi^{\mathsf{AF}_0} = \frac{\alpha_1(\alpha_1+\beta_1)(2\alpha_2+\beta_2)}{\alpha_1(\alpha_1+\beta_1)(2\alpha_2+\beta_2)-\alpha_2(\alpha_2+\beta_2)(2\alpha_1+\beta_1)}, \tag{4.2j}$$

$$\phi^{\mathsf{BF}_0} = \frac{\beta_1(\alpha_1+\beta_1)(\alpha_2+2\beta_2)}{\beta_1(\alpha_1+\beta_1)(\alpha_2+2\beta_2)-\beta_2(\alpha_2+\beta_2)(\alpha_1+2\beta_1)}, \tag{4.2k}$$

and

$$m^{\mathsf{A}} = \frac{\alpha_1\alpha_2}{\alpha_1-\phi(\alpha_1-\alpha_2)}, \tag{4.3a}$$

$$m^{\mathsf{B}} = \frac{\beta_1\beta_2}{\beta_1-\phi(\beta_1-\beta_2)}, \tag{4.3b}$$

$$m^{\mathsf{F}_0} = \frac{(\alpha_1+\beta_1)(\alpha_2+\beta_2)}{\alpha_1+\beta_1-\phi(\alpha_1+\beta_1-\alpha_2-\beta_2)}, \tag{4.3c}$$

$$m^{\mathsf{M}_1} = \frac{-(\alpha_1+\beta_1+\rho)(\alpha_2+\beta_2+\rho)}{\alpha_1+\beta_1+\rho-\phi(\alpha_1+\beta_1-\alpha_2-\beta_2)}, \tag{4.3d}$$

$$m^{\mathsf{M}_4} = \frac{(\alpha_1+\beta_1-\rho)(\alpha_2+\beta_2-\rho)}{\alpha_1+\beta_1-\rho-\phi(\alpha_1+\beta_1-\alpha_2-\beta_2)}, \tag{4.3e}$$

$$m^{*} = \frac{1}{\theta}\sqrt{\frac{-\alpha_1\alpha_2\beta_1\beta_2(\alpha_1+\beta_1)(\alpha_2+\beta_2)}{\phi(1-\phi)}}. \tag{4.3f}$$

We set $m^{\mathsf{A}} = \infty$, $m^{\mathsf{B}} = \infty$, and $m^{\mathsf{F}_0} = \infty$ if $\phi = \phi^{\mathsf{A}}$, $\phi = \phi^{\mathsf{B}}$, and $\phi = \phi^{\mathsf{F}_0}$, respectively. Similarly, we set $m^{*} = \infty$ if $\theta = 0$, $\phi = 0$, or $\phi = 1$.

The quantities m^{A}, m^{B}, and m^{F_0} yield the bounds for the intervals of total migration rates m in which the SLPs at A, B, and the polymorphic equilibrium F_0, respectively, are admissible:

$$-1 < \sigma_1+\sigma_2 < 1 \iff -1 < \frac{m}{m^{\mathsf{A}}} < 1, \tag{4.4a}$$

$$-1 < \tau_1+\tau_2 < 1 \iff -1 < \frac{m}{m^{\mathsf{B}}} < 1, \tag{4.4b}$$

$$-1 < \kappa_1+\kappa_2 < 1 \iff -1 < \frac{m}{m^{\mathsf{F}_0}} < 1. \tag{4.4c}$$

Here, the left and the right inequalities correspond, and we have

$$m^{\mathsf{A}} > 0 \iff \phi > \phi^{\mathsf{A}}, \tag{4.5a}$$

$$m^{\mathsf{B}} > 0 \iff \phi > \phi^{\mathsf{B}}, \tag{4.5b}$$

$$m^{\mathsf{F}_0} > 0 \iff \phi > \phi^{\mathsf{F}_0}. \tag{4.5c}$$

From (2.3), we obtain

$$m^{\mathsf{A}} \neq 0, \quad m^{\mathsf{B}} \neq 0, \quad m^{\mathsf{F}_0} \neq 0, \quad m^* > 0, \tag{4.6}$$

$$\alpha_2 \leq m^{\mathsf{A}} \leq \alpha_1, \quad \beta_2 \leq m^{\mathsf{B}} \leq \beta_1, \quad \alpha_2 + \beta_2 \leq m^{\mathsf{F}_0} \leq \alpha_1 + \beta_1. \tag{4.7}$$

The quantities m^{M_1} and m^{M_4} occur in the stability conditions of the monomorphic equilibria M_1 and M_4 (Proposition 4.1), and m^* determines the range of stability of F_0; see (4.56). They satisfy

$$-(\alpha_1 + \beta_1 + \rho) \leq m^{\mathsf{M}_1} \leq -(\alpha_2 + \beta_2 + \rho), \quad \alpha_2 + \beta_2 - \rho \leq m^{\mathsf{M}_4} \leq \alpha_1 + \beta_1 - \rho. \tag{4.8}$$

We note that m^{A}, m^{B}, m^{F_0}, and m^{M_4} assume their minima if $\phi = 0$ and their maxima if $\phi = 1$, whereas m^{M_1} assumes its minimum or maximum at $\phi = 1$ or $\phi = 0$, respectively. m^* is a convex function of ϕ, and symmetric around its minimum $\phi = 1/2$.

The definitions of (several of) the quantities ϕ^{X} are motivated by the following relations:

$$m^{\mathsf{A}} = m^{\mathsf{B}} \iff \phi = \tilde{\phi}^{\mathsf{AB}} \text{ and } m^{\mathsf{A}} < 0, \tag{4.9a}$$

$$m^{\mathsf{A}} = -m^{\mathsf{B}} \iff \phi = \phi^{\mathsf{AB}} \text{ and } m^{\mathsf{A}} > 0, \tag{4.9b}$$

$$m^{\mathsf{M}_1} = -m^{\mathsf{A}} \iff \phi = \phi^{\mathsf{M}_1} \text{ and } m^{\mathsf{A}} < 0, \tag{4.9c}$$

$$m^{\mathsf{M}_1} = -m^{\mathsf{B}} \iff \phi = \tilde{\phi}^{\mathsf{M}_1} \text{ and } m^{\mathsf{B}} < 0, \tag{4.9d}$$

$$m^{\mathsf{M}_4} = m^{\mathsf{A}} \iff \phi = \tilde{\phi}^{\mathsf{M}_4} \text{ and } m^{\mathsf{A}} > 0, \tag{4.9e}$$

$$m^{\mathsf{M}_4} = m^{\mathsf{B}} \iff \phi = \phi^{\mathsf{M}_4} \text{ and } m^{\mathsf{B}} > 0, \tag{4.9f}$$

$$m^{\mathsf{F}_0} = -m^{\mathsf{B}} \iff \phi = \phi^{\mathsf{BF}_0} \text{ and } m^{\mathsf{B}} < 0, \tag{4.9g}$$

$$-m^{\mathsf{F}_0} = m^{\mathsf{A}} \iff \phi = \phi^{\mathsf{AF}_0} \text{ and } m^{\mathsf{A}} > 0, \tag{4.9h}$$

where we have

$$m^{\mathsf{F}_0} = m^{\mathsf{M}_4} = -m^{\mathsf{M}_1} \iff \rho = 0. \tag{4.10}$$

The following relations apply to m^*:

$$m^{\mathsf{A}} = -m^{\mathsf{B}} = m^* \iff \phi = \phi^{\mathsf{AB}}, \tag{4.11a}$$

$$m^{\mathsf{A}} = m^{\mathsf{F}_0} = m^* \iff \phi = \phi^{\mathsf{M}_4}, \tag{4.11b}$$

$$-m^{\mathsf{B}} = -m^{\mathsf{F}_0} = m^* \iff \phi = \phi^{\mathsf{M}_1}, \tag{4.11c}$$

where we derived (4.11b) and (4.11c) from (4.9c) and (4.9f) using (4.10).

In the following, we summarize the most important inequalities between the quantities ϕ^{X}:

$$0 < \phi^{\mathsf{A}} < \phi^{\mathsf{AF}_0} < \phi^{\mathsf{AB}} < \phi^{\mathsf{BF}_0} < \phi^{\mathsf{B}} < 1, \tag{4.12}$$

$$\beta_2 < \alpha_2 \iff 0 < \tilde{\phi}^{\mathsf{AB}} < \phi^{\mathsf{A}}, \tag{4.13}$$

$$\phi^{\mathsf{AF}_0} < \phi^{\mathsf{F}_0} < \phi^{\mathsf{BF}_0}. \tag{4.14}$$

They can be derived straightforwardly from their definitions and our general assumption (2.3). Finally, if $\rho = 0$ and $\tilde{\theta} = \alpha_1\alpha_2 - \beta_1\beta_2$, the following relations hold:

$$0 < \phi^{\mathsf{M}_1} < \phi^{\mathsf{A}} < \phi^{\mathsf{AF}_0} < \phi^{\mathsf{F}_0} \le \phi^{\mathsf{AB}} < \phi^{\mathsf{BF}_0} < \phi^{\mathsf{B}} < \phi^{\mathsf{M}_4} < 1 \iff \tilde{\theta} \le 0, \tag{4.15a}$$

$$0 < \phi^{\mathsf{M}_1} < \phi^{\mathsf{A}} < \phi^{\mathsf{AF}_0} < \phi^{\mathsf{AB}} < \phi^{\mathsf{F}_0} < \phi^{\mathsf{BF}_0} < \phi^{\mathsf{B}} < \phi^{\mathsf{M}_4} < 1 \iff \tilde{\theta} > 0, \tag{4.15b}$$

and

$$\tilde{\phi}^{\mathsf{AB}} < \phi^{\mathsf{M}_1} \text{ if } \beta_2 < \alpha_2. \tag{4.15c}$$

Additional relations that are needed only in the proofs may be found in Appendix A.7.

4.2. Admissibility of SLPs. We begin by expressing the conditions for admissibility of the SLPs in terms of the total migration rate m and the migration ratio ϕ. Since, by (3.7), (3.8), and (4.4), every SLP is admissible if m is sufficiently small and leaves the state space at a uniquely defined critical migration rate, it is sufficient to determine this critical rate and the monomorphism through which it leaves the state space. Using (4.3a), (4.3b), (4.5), and (4.4), we infer from (3.9) that

$$\phi < \phi^{\mathsf{A}} \text{ and } m \uparrow -m^{\mathsf{A}} \iff \mathsf{P}_{\mathsf{A},1} \to \mathsf{M}_1 \text{ and } \mathsf{P}_{\mathsf{A},2} \to \mathsf{M}_2, \tag{4.16a}$$

$$\phi > \phi^{\mathsf{A}} \text{ and } m \uparrow m^{\mathsf{A}} \iff \mathsf{P}_{\mathsf{A},1} \to \mathsf{M}_3 \text{ and } \mathsf{P}_{\mathsf{A},2} \to \mathsf{M}_4, \tag{4.16b}$$

$$\phi < \phi^{\mathsf{B}} \text{ and } m \uparrow -m^{\mathsf{B}} \iff \mathsf{P}_{\mathsf{B},1} \to \mathsf{M}_1 \text{ and } \mathsf{P}_{\mathsf{B},2} \to \mathsf{M}_3, \tag{4.16c}$$

$$\phi > \phi^{\mathsf{B}} \text{ and } m \uparrow m^{\mathsf{B}} \iff \mathsf{P}_{\mathsf{B},1} \to \mathsf{M}_2 \text{ and } \mathsf{P}_{\mathsf{B},2} \to \mathsf{M}_4. \tag{4.16d}$$

Å In particular, no SLP is admissible if

$$m > \max\{|m^{\mathsf{A}}|, |m^{\mathsf{B}}|\}. \tag{4.17}$$

We observe that locus A is polymorphic and locus B is monomorphic if and only if

$$|m^{\mathsf{B}}| < m < |m^{\mathsf{A}}|. \tag{4.18}$$

If $\beta_2 < \alpha_2$, we infer from (A.18c) and (A.18d) that (4.18) holds if and only if

$$\tilde{\phi}^{\mathsf{AB}} < \phi < \phi^{\mathsf{AB}}. \tag{4.19}$$

Therefore, (2.4) implies that if locus A is under weaker selection than locus B in both demes ($|\beta_k| > |\alpha_k|$), then there is a range of values ϕ and m such that locus A is polymorphic whereas B is monomorphic. This is in contrast to the CI model or highly asymmetric migration rates or $\theta = 0$, where it is always the locus under weaker selection that first loses its polymorphism while m increases. This is a pure one-locus result and a consequence of the classical condition for a protected polymorphism, e.g., (3.7). With two-way migration, a locus with alleles of small and similar (absolute) effects in the demes ($\alpha_1 \approx -\alpha_2$) may be maintained polymorphic for higher migration rates than a locus with alleles of large and very different (absolute) effects.

4.3. Stability of monomorphic equilibria. Here, we reformulate the stability conditions of the ME derived in Section 3.2 in terms of m and ϕ.

PROPOSITION 4.1. M_1 *is asymptotically stable if*

$$\phi < \phi^{\mathsf{A}} \text{ and } m > \max\{-m^{\mathsf{A}}, -m^{\mathsf{B}}, m^{\mathsf{M}_1}\}. \tag{4.20}$$

M_2 *is always unstable.*

M_3 *is asymptotically stable if*

$$\phi^{\mathsf{A}} < \phi < \phi^{\mathsf{B}} \text{ and } m > \max\{m^{\mathsf{A}}, -m^{\mathsf{B}}\}. \tag{4.21}$$

M_4 *is asymptotically stable if*

$$\phi > \phi^{\mathsf{B}} \text{ and } m > \max\{m^{\mathsf{A}}, m^{\mathsf{B}}, m^{\mathsf{M}_4}\}. \tag{4.22}$$

If in these conditions one inequality is reversed, the corresponding equilibrium is unstable.

PROOF. We prove only that the statement about M_1 is equivalent to that in Proposition 3.1. The others follow analogously or are immediate.

From Proposition 3.1 and (4.3a), (4.3b), (4.3d), and (4.4), we infer immediately that M_1 is asymptotically stable if and only if

$$1 < \frac{m}{-m^{\mathsf{A}}} \text{ and } 1 < \frac{m}{-m^{\mathsf{B}}} \tag{4.23}$$

and

$$m > m^{\mathsf{M}_1}. \tag{4.24}$$

The possible inequalities between $-m^{\mathsf{A}}$, $-m^{\mathsf{B}}$, and m^{M_1} are given in (A.32) and (A.33). By (4.5a), (4.5b), and (4.12), it follows that (4.23) is feasible if and only if $\phi < \phi^{\mathsf{A}}$. Thus if $\phi \geq \phi^{\mathsf{A}}$, M_1 is unstable. Therefore, (4.23) and (4.24) are equivalent to (4.20). □

REMARK 4.2. (i) We have $\max\{-m^{\mathsf{A}}, -m^{\mathsf{B}}, m^{\mathsf{M}_1}\} = m^{\mathsf{M}_1}$ in (4.20) if and only if

$$\phi < \min\{\phi^{\mathsf{M}_1}, \tilde{\phi}^{\mathsf{M}_1}\} \text{ and } \rho < -\alpha_2 \text{ and } \beta_2 < \alpha_2, \text{ or} \tag{4.25a}$$

$$\phi < \phi^{\mathsf{M}_1} \text{ and } \rho < -\beta_2 \text{ and } \beta_2 \geq \alpha_2. \tag{4.25b}$$

(ii) We have $\max\{m^{\mathsf{A}}, m^{\mathsf{B}}, m^{\mathsf{M}_4}\} = m^{\mathsf{M}_4}$ in (4.22) if and only if

$$\phi > \phi^{\mathsf{M}_4} \text{ and } \rho < \alpha_1. \tag{4.26}$$

(iii) An internal equilibrium in LD can leave or enter the state space through M_1 or M_4 only if $m = m^{\mathsf{M}_1}$ or $m = m^{\mathsf{M}_4}$, respectively. If (4.25) or (4.26) holds, then M_1 or M_4, respectively, become asymptotically stable by the bifurcation.

PROOF OF REMARK 4.2. If $\beta_2 \geq \alpha_2$, statement (i) is an immediate consequence of (A.32a) and (A.32b) because $\phi < \phi^{\mathsf{A}}$ implies $0 < \min\{-m^{\mathsf{A}}, -m^{\mathsf{B}}\}$. If $\beta_2 < \alpha_2$, then (A.32a), (A.32b), and (A.32c) show that $\max\{-m^{\mathsf{A}}, -m^{\mathsf{B}}, m^{\mathsf{M}_1}\} = m^{\mathsf{M}_1}$ if (a) $\rho < \rho^{\mathsf{M}_1}$ (A.23) and $\tilde{\phi}^{\mathsf{AB}} < \phi < \phi^{\mathsf{M}_1}$ or (b) $\rho < \rho^{\mathsf{M}_1}$ and $\phi \leq \tilde{\phi}^{\mathsf{AB}}$ or (c) $\rho^{\mathsf{M}_1} < \rho < -\alpha_2$ and $\phi < \tilde{\phi}^{\mathsf{M}_1}$, where $\rho^{\mathsf{M}_1} < -\alpha_2$ by (A.26a). Invoking (A.31), we can combine conditions (a), (b), and (c) to obtain (4.25a).

Statement (ii) follows directly from (A.18f) and (A.35a).

Statement (iii) follows by observing that only internal equilibria in LD will depend on ρ, the factor t_3 (A.4) in the characteristic polynomial at M_1 is the only one that depends on ρ, and t_3 gives rise to an eigenvalue zero if and only if $m = m^{\mathsf{M}_1}$. An analogous argument holds for M_4. □

The asymmetry between (4.25) and (4.26) results from the fact that $\alpha_1 < \beta_1$ is assumed, whereas $\beta_2 < \alpha_2$ or $\beta_2 \geq \alpha_2$ is possible. The reader may recall the comments made below Proposition 3.1. In addition, we note that if the fitness parameters and ρ and ϕ are fixed, a stable ME remains stable if m is increased. This is not necessarily so if m and ϕ are varied simultaneously. For related phenomena in the one-locus case, see Karlin (1982) and Nagylaki (2012). In Section 4.5, we will prove global convergence to one of the asymptotically stable ME if m is sufficiently large.

4.4. Weak migration. We recall from Proposition 3.2 that for sufficiently weak migration, there is a fully polymorphic equilibrium, it is globally asymptotically stable, and exhibits positive LD in both demes.

4.5. Strong migration.

PROPOSITION 4.3. *For sufficiently large m, one of the monomorphic equilibria* M_1, M_3, *or* M_4 *is globally attracting. This equilibrium is* M_1, M_3, *or* M_4 *if* $\phi < \phi^{\mathsf{A}}$, $\phi^{\mathsf{A}} < \phi < \phi^{\mathsf{B}}$, *or* $\phi^{\mathsf{B}} < \phi$, *respectively.*

PROOF. The proof is based on the perturbation results about the strong-migration limit in Section 4.2 of Bürger (2009a). The strong-migration limit is obtained if $\max_{k=1,2}\{|\alpha_k|, |\beta_k|, \rho\}/m \to 0$. In this limit, the demes become homogeneous and the system of differential equations (2.7) converges to a system, where in each deme

$$\dot{p} = \alpha p(1-p) + \beta D, \tag{4.27a}$$

$$\dot{q} = \beta q(1-q) + \alpha D, \tag{4.27b}$$

$$\dot{D} = \left[\alpha(1-2p) + \beta(1-2q) - \rho\right] D \tag{4.27c}$$

holds with $p_1 = p_2 = p$, $q_1 = q_2 = q$, $D_1 = D_2 = D$. Here,

$$\alpha = (1-\phi)\alpha_1 + \phi\alpha_2 \quad \text{and} \quad \beta = (1-\phi)\beta_1 + \phi\beta_2 \tag{4.28}$$

are the spatially averaged selection coefficients and averaging is performed with respect to the Perron-Frobenius eigenvector $(1-\phi, \phi)$ of the migration matrix (see Section 4.2 in Bürger (2009a) for a much more general treatment starting with a multilocus model in discrete time). Therefore, Proposition 4.10 in Bürger (2009a) applies and, provided m is sufficiently large, all trajectories of (2.7) converge to a manifold on which the allele frequencies and the linkage disequilibria in both demes are nearly identical. In addition, in the neighborhood of each hyperbolic equilibrium of (4.27) there is exactly one equilibrium of (2.7), and it has the same stability.

In the present case, the conclusion of Proposition 4.10 in Bürger (2009a) can be considerably strengthened. Because the system (4.27) describes evolution in an ordinary two-locus model under genic selection, the ME representing the gamete of highest fitness is globally asymptotically stable. In fact, (4.27) is also a generalized gradient system for which Lemma 2.2 of Nagylaki et al. (1999) holds. Therefore, the analog of statement (c) in Theorem 4.3 of Bürger (2009a) applies and yields global convergence to the unique stable equilibrium.

Finally, it is an easy exercise to show that, in the strong-migration limit, i.e., with fitnesses averaged according to (4.28), gamete A_1B_1, A_2B_1, or A_2B_2 has highest fitness if $\phi < \phi^{\mathsf{A}}$, $\phi^{\mathsf{A}} < \phi < \phi^{\mathsf{B}}$, or $\phi > \phi^{\mathsf{B}}$, respectively. Since there is no dominance, the corresponding ME is the unique stable equilibrium. □

4.6. Linkage equilibrium. We shall establish all possible equilibrium configurations and their dependence on the parameters under LE. In Figure 2, the equilibrium configurations are displayed as schematic bifurcation diagrams with the total migration rate m as the bifurcation parameter. In Theorem 4.4, we assign to each diagram its pertinent parameter combinations.

In order to have only one bifurcation diagram covering cases that can be obtained from each other by simple symmetry considerations but are structurally equivalent otherwise, we use the sub- and superscripts X, and Y in the labels of Figure 2. For an efficient presentation of the results, we define

$$\mathsf{P}_\mathsf{X} = \mathsf{P}_{\mathsf{B},1},\ \mathsf{P}_\mathsf{Y} = \mathsf{P}_{\mathsf{A},1},\ \mathsf{M}_\mathsf{i} = \mathsf{M}_1,\ m^\mathsf{X} = -m^\mathsf{B},\ m^\mathsf{Y} = -m^\mathsf{A}, \tag{L1}$$

$$\mathsf{P}_\mathsf{X} = \mathsf{P}_{\mathsf{A},1},\ \mathsf{P}_\mathsf{Y} = \mathsf{P}_{\mathsf{B},1},\ \mathsf{M}_\mathsf{i} = \mathsf{M}_1,\ m^\mathsf{X} = -m^\mathsf{A},\ m^\mathsf{Y} = -m^\mathsf{B}, \tag{L2}$$

$$\mathsf{P}_\mathsf{X} = \mathsf{P}_{\mathsf{A},1},\ \mathsf{P}_\mathsf{Y} = \mathsf{P}_{\mathsf{B},2},\ \mathsf{M}_\mathsf{i} = \mathsf{M}_3,\ m^\mathsf{X} = m^\mathsf{A},\ m^\mathsf{Y} = -m^\mathsf{B}, \tag{L3}$$

$$\mathsf{P}_\mathsf{X} = \mathsf{P}_{\mathsf{B},2},\ \mathsf{P}_\mathsf{Y} = \mathsf{P}_{\mathsf{A},1},\ \mathsf{M}_\mathsf{i} = \mathsf{M}_3,\ m^\mathsf{X} = -m^\mathsf{B},\ m^\mathsf{Y} = m^\mathsf{A}, \tag{L4}$$

$$\mathsf{P}_\mathsf{X} = \mathsf{P}_{\mathsf{B},2},\ \mathsf{P}_\mathsf{Y} = \mathsf{P}_{\mathsf{A},2},\ \mathsf{M}_\mathsf{i} = \mathsf{M}_4,\ m^\mathsf{X} = m^\mathsf{B},\ m^\mathsf{Y} = m^\mathsf{A}. \tag{L5}$$

THEOREM 4.4. *Assume LE, i.e.,* (3.17). *Figure 2 shows all possible bifurcation diagrams that involve bifurcations with equilibria that can be stable for some m given the other parameters.*

A. Diagram (a) in Figure 2 occurs generically. It occurs if and only if one of the following cases applies:

$$\phi < \tilde{\phi}^{\mathsf{AB}} \text{ and } \beta_2 < \alpha_2 \text{ and (L1)} \tag{4.29}$$

or

$$\tilde{\phi}^{\mathsf{AB}} < \phi < \phi^{\mathsf{A}} \text{ and } \beta_2 < \alpha_2 \text{ and (L2)} \tag{4.30}$$

or

$$\phi < \phi^{\mathsf{A}} \text{ and } \alpha_2 \le \beta_2 \text{ and (L2)} \tag{4.31}$$

or

$$\phi^{\mathsf{A}} < \phi < \phi^{\mathsf{AB}} \text{ and (L3)} \tag{4.32}$$

or

$$\phi^{\mathsf{AB}} < \phi < \phi^{\mathsf{B}} \text{ and (L4)} \tag{4.33}$$

or

$$\phi^{\mathsf{B}} < \phi \text{ and (L5).} \tag{4.34}$$

B. The following two diagrams occur only if the parameters satisfy particular relations. Diagram (b) in Figure 2 applies if one of the following two cases holds:

$$\phi = \tilde{\phi}^{\mathsf{AB}} \text{ and } \beta_2 < \alpha_2 \text{ and (L1)} \tag{4.35}$$

or

$$\phi = \phi^{\mathsf{AB}} \text{ and (L4).} \tag{4.36}$$

Diagram (c) in Figure 2 applies if one of the following two cases holds:

$$\phi = \phi^{\mathsf{A}} \text{ and } \mathsf{P}_\mathsf{X} = \mathsf{P}_{\mathsf{A},1} \text{ and } m^\mathsf{Y} = -m^\mathsf{B} \tag{4.37}$$

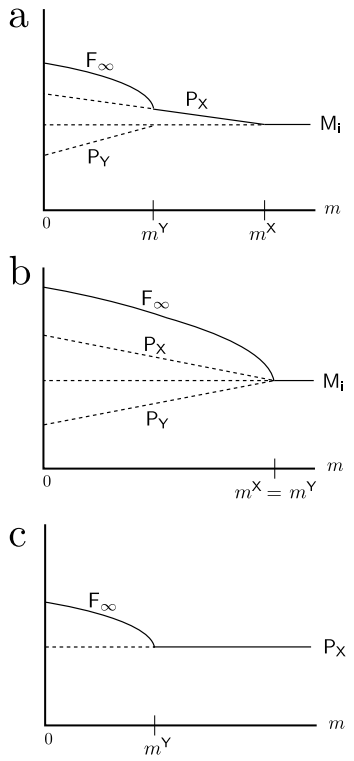

FIGURE 2. Bifurcation diagrams for LE. Diagrams (a)-(c) display the equilibrium configurations listed in Theorem 4.4. Each line indicates one admissible equilibrium as a function of the total migration rate m. Only equilibria are shown that can be stable or are involved in a bifurcation with an equilibrium that can be stable. Lines are drawn such that intersections occur if and only if the corresponding equilibria collide. Solid lines represent asymptotically stable equilibria, dashed lines unstable equilibria. The meaning of the superscripts X and Y is given in (L1) – (L5).

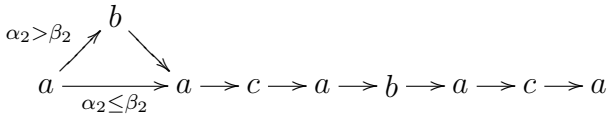

FIGURE 3. Order in which the bifurcation diagrams of Figure 2 occur as ϕ increases from 0 to 1.

or

$$\phi = \phi^{\mathsf{B}} \text{ and } \mathsf{P}_{\mathsf{X}} = \mathsf{P}_{\mathsf{B},2} \text{ and } m^{\mathsf{Y}} = m^{\mathsf{A}}. \tag{4.38}$$

C. Figure 3 shows the order in which the bifurcation diagrams of Figure 2 arise if ϕ is increased from 0 to 1.

PROOF. We prove parts A and B simultaneously, essentially by rewriting the conditions in Proposition 3.3 on admissibility and stability of the equilibria in terms of m, m^{A}, and m^{B} (4.3).

From (3.19) and (4.4), we infer easily:

$$\mathsf{F}_\infty \to \mathsf{P}_{\mathsf{A},1} \iff m \uparrow -m^{\mathsf{B}} \text{ and } 0 < -m^{\mathsf{B}} < |m^{\mathsf{A}}|, \tag{4.39a}$$

$$\mathsf{F}_\infty \to \mathsf{P}_{\mathsf{A},2} \text{ does not occur,} \tag{4.39b}$$

$$\mathsf{F}_\infty \to \mathsf{P}_{\mathsf{B},1} \iff m \uparrow -m^{\mathsf{A}} \text{ and } 0 < -m^{\mathsf{A}} < -m^{\mathsf{B}}, \tag{4.39c}$$

$$\mathsf{F}_\infty \to \mathsf{P}_{\mathsf{B},2} \iff m \uparrow m^{\mathsf{A}} \text{ and } 0 < m^{\mathsf{A}} < |m^{\mathsf{B}}|, \tag{4.39d}$$

$$\mathsf{F}_\infty \to \mathsf{M}_1 \iff m \uparrow -m^{\mathsf{A}} = -m^{\mathsf{B}} \text{ and } 0 < -m^{\mathsf{A}} = -m^{\mathsf{B}}, \tag{4.39e}$$

$$\mathsf{F}_\infty \to \mathsf{M}_3 \iff m \uparrow m^{\mathsf{A}} = -m^{\mathsf{B}} \text{ and } 0 < m^{\mathsf{A}} = -m^{\mathsf{B}}, \tag{4.39f}$$

$$\mathsf{F}_\infty \to \mathsf{M}_2 \text{ or } \mathsf{F}_\infty \to \mathsf{M}_4 \text{ do not occur.} \tag{4.39g}$$

Invoking the relations (A.18), we can rewrite conditions (4.39a), (4.39c)-(4.39f) in the form

$$\begin{aligned} \mathsf{F}_\infty \to \mathsf{P}_{\mathsf{A},1} \iff\ & m \uparrow -m^{\mathsf{B}} \text{ and either} \\ & \phi < \phi^{\mathsf{AB}} \text{ if } \alpha_2 \le \beta_2 \text{ or } \tilde{\phi}^{\mathsf{AB}} < \phi < \phi^{\mathsf{AB}} \text{ if } \beta_2 < \alpha_2, \end{aligned} \tag{4.40a}$$

$$\mathsf{F}_\infty \to \mathsf{P}_{\mathsf{B},1} \iff m \uparrow -m^{\mathsf{A}} \text{ and } \beta_2 < \alpha_2 \text{ and } \phi < \tilde{\phi}^{\mathsf{AB}}, \tag{4.40b}$$

$$\mathsf{F}_\infty \to \mathsf{P}_{\mathsf{B},2} \iff m \uparrow m^{\mathsf{A}} \text{ and } \phi > \phi^{\mathsf{AB}}, \tag{4.40c}$$

$$\mathsf{F}_\infty \to \mathsf{M}_1 \iff m \uparrow -m^{\mathsf{A}} = -m^{\mathsf{B}} \text{ and } \beta_2 < \alpha_2 \text{ and } \phi = \tilde{\phi}^{\mathsf{AB}}, \tag{4.40d}$$

$$\mathsf{F}_\infty \to \mathsf{M}_3 \iff m \uparrow m^{\mathsf{A}} = -m^{\mathsf{B}} \text{ and } \phi = \phi^{\mathsf{AB}}. \tag{4.40e}$$

We conclude immediately that (4.40b) applies in case (4.29) (Part A), (4.40d) in case (4.35) (Part B), and (4.40e) in case (4.36) (Part B). From (4.12) and (4.13) we conclude that (4.40a) applies in the following cases: (4.30)-(4.32) (Part A), or (4.37) (Part B). Analogously we conclude that (4.40c) applies in the following cases: (4.33), (4.34) (Part A), or (4.38) (Part B).

From Proposition 3.3 and (4.16) we obtain:

$$\mathsf{P}_{\mathsf{A},1} \text{ is globally asymptotically stable} \iff -m^{\mathsf{B}} < m < |m^{\mathsf{A}}|, \tag{4.41a}$$

$$\mathsf{P}_{\mathsf{B},1} \text{ is globally asymptotically stable} \iff -m^{\mathsf{A}} < m < -m^{\mathsf{B}}, \tag{4.41b}$$

$$\mathsf{P}_{\mathsf{B},2} \text{ is globally asymptotically stable} \iff m^{\mathsf{A}} < m < |m^{\mathsf{B}}|. \tag{4.41c}$$

As $m \to \max\{|m^{\mathsf{A}}|, |m^{\mathsf{B}}|\}$, the stable SLP leaves the state space according to (4.16), which gives precisely the cases corresponding to diagrams (a) and (c). If $\phi = \phi^{\mathsf{A}}$ ($m^{\mathsf{A}} = \infty$),

$\mathsf{P}_{\mathsf{A},1}$ is always admissible, cf. (4.37). If $\phi = \phi^{\mathsf{B}}$ ($m^{\mathsf{B}} = \infty$), $\mathsf{P}_{\mathsf{B},2}$ is always admissible, cf. (4.38).

A ME is globally asymptotically stable and only if

$$m \geq \max\{|m^{\mathsf{A}}|, |m^{\mathsf{B}}|\}. \tag{4.42}$$

By Proposition 4.1 and Remark 4.2 this equilibrium is M_1 if $\phi < \phi^{\mathsf{A}}$ (cases (4.29)-(4.31), (4.35)), or M_3 if $\phi^{\mathsf{A}} < \phi < \phi^{\mathsf{B}}$ (cases (4.32), (4.33), (4.36)), or M_4 if $\phi^{\mathsf{B}} < \phi$ (4.34). □

The bifurcations of equilibria that cannot be stable can be derived easily from Sections 4.2 and 4.3 and the above theorem by noting that these are boundary equilibria and corresponding pairs of SLPs are admissible for the same parameters; see (3.7) and (3.8). Inclusion of these bifurcations would require the introduction of subcases.

Corollary 4.5. *Under the assumption of LE, the maximum migration rate, below which a stable two-locus polymorphism exists, is given by*

$$m^{\infty}_{\max} = \min\{|m^{\mathsf{A}}|, |m^{\mathsf{B}}|\}. \tag{4.43}$$

The corollary is a simple consequence of Proposition 3.3 and (4.40).

4.7. Strong recombination: quasi-linkage equilibrium. We recall from Section 3.6 that for sufficiently strong recombination, global convergence to the unique stable equilibrium occurs. From the coordinates (3.21) of the perturbed internal equilibrium, which is in quasi-linkage equilibrium, approximations could be derived for the critical migration rates at which the internal equilibrium collides with a boundary equilibrium and leaves the state space. It is not difficult to check with *Mathematica* that for large ρ, F collides with $\mathsf{P}_{\mathsf{B},2}$ if $m = m^{\rho}_{\max}(\mathsf{P}_{\mathsf{B},2}) + O(\rho^{-2})$, where

$$m^{\rho}_{\max}(\mathsf{P}_{\mathsf{B},2}) = m^{\mathsf{A}} - \frac{(m^{\mathsf{A}})^3}{\rho}\left[\frac{\beta_1}{\alpha_1}\phi - \frac{\beta_2}{\alpha_2}(1-\phi)\right]\left[\frac{\phi}{\beta_1} - \frac{1-\phi}{\beta_2} - \sqrt{(m^{\mathsf{A}})^{-2} - \frac{4\phi(1-\phi)}{\beta_1\beta_2}}\right]. \tag{4.44}$$

We note that $m^{\rho}_{\max}(\mathsf{P}_{\mathsf{B},2}) > 0$ if and only if $\phi > \phi^{\mathsf{AB}}$, as is expected from (4.40c). Closer examination of (4.44) reveals that both $m^{\rho}_{\max}(\mathsf{P}_{\mathsf{B},2}) > m^{\mathsf{A}}$ and $m^{\rho}_{\max}(\mathsf{P}_{\mathsf{B},2}) < m^{\mathsf{A}}$ may hold.

Thus, the fully polymorphic equilibrium may be maintained for higher or lower migration rates than in the case of LE. This does not conform with the intuitive expectation that for reduced recombination, $m^{\rho}_{\max}(\mathsf{P}_{\mathsf{B},2}) > m^{\infty}_{\max}$ should hold because the locally adapted haplotypes (A_kB_k in deme k) are less frequently broken apart. However, numerical evaluation of (4.44) shows that $m^{\rho}_{\max}(\mathsf{P}_{\mathsf{B},2}) < m^{\infty}_{\max}$ occurs only for about 3% of the admissible parameter combinations and if it holds, $m^{\rho}_{\max}(\mathsf{P}_{\mathsf{B},2})$ is only very slightly less than $m^{\infty}_{\max}$ (results not shown). If ρ is about as large as the largest selection coefficient

or smaller, $m_{\max}$ increases with decreasing ρ. Expressions analogous to (4.44) can be obtained for collisions of F with the other equilibria.

4.8. No recombination. Our aim is to establish all possible equilibrium configurations and their dependence on the parameters if recombination is absent. In Figure 4, the equilibrium configurations are displayed as schematic bifurcation diagrams with the total migration rate m as the bifurcation parameter. In Theorem 4.6, we assign to each diagram its pertinent parameter combinations.

In order to have only one bifurcation diagram covering cases that can be obtained from each other by simple symmetry considerations but are structurally equivalent otherwise, we use the sub- and superscripts X and Y in the labels of Figure 4. For an efficient presentation of the results, we define

$$\mathsf{P}_\mathsf{X} = \mathsf{P}_{\mathsf{A},1},\ \mathsf{P}_\mathsf{Y} = \mathsf{P}_{\mathsf{B},2},\ \mathsf{M}_\mathsf{i} = \mathsf{M}_1,\ m^\mathsf{X} = |m^\mathsf{A}|,\ m^\mathsf{Y} = |m^\mathsf{B}|, \tag{R1}$$

$$\mathsf{P}_\mathsf{X} = \mathsf{P}_{\mathsf{B},2},\ \mathsf{P}_\mathsf{Y} = \mathsf{P}_{\mathsf{A},1},\ \mathsf{M}_\mathsf{i} = \mathsf{M}_4,\ m^\mathsf{X} = |m^\mathsf{B}|,\ m^\mathsf{Y} = |m^\mathsf{A}|, \tag{R2}$$

$$\mathsf{P}_\mathsf{X} = \mathsf{P}_{\mathsf{A},1},\ \mathsf{P}_\mathsf{Y} = \mathsf{P}_{\mathsf{B},2},\ \mathsf{M}_\mathsf{i} = \mathsf{M}_4,\ m^\mathsf{X} = |m^\mathsf{A}|,\ m^\mathsf{Y} = |m^\mathsf{B}|, \tag{R3}$$

$$\mathsf{P}_\mathsf{X} = \mathsf{P}_{\mathsf{B},2},\ \mathsf{P}_\mathsf{Y} = \mathsf{P}_{\mathsf{A},1},\ \mathsf{M}_\mathsf{i} = \mathsf{M}_1,\ m^\mathsf{X} = |m^\mathsf{B}|,\ m^\mathsf{Y} = |m^\mathsf{A}|, \tag{R4}$$

$$\mathsf{P}_\mathsf{X} = \mathsf{P}_{\mathsf{A},1},\ \mathsf{M}_\mathsf{i} = \mathsf{M}_1,\ m^\mathsf{X} = |m^\mathsf{A}|, \tag{R1'}$$

$$\mathsf{P}_\mathsf{X} = \mathsf{P}_{\mathsf{B},2},\ \mathsf{M}_\mathsf{i} = \mathsf{M}_4,\ m^\mathsf{X} = |m^\mathsf{B}|, \tag{R2'}$$

$$\mathsf{P}_\mathsf{X} = \mathsf{P}_{\mathsf{A},1},\ \mathsf{P}_\mathsf{Y} = \mathsf{P}_{\mathsf{B},2},\ m^\mathsf{X} = |m^\mathsf{A}|,\ m^\mathsf{Y} = |m^\mathsf{B}|, \tag{R3'}$$

$$\mathsf{P}_\mathsf{X} = \mathsf{P}_{\mathsf{B},2},\ \mathsf{P}_\mathsf{Y} = \mathsf{P}_{\mathsf{A},1},\ m^\mathsf{X} = |m^\mathsf{B}|,\ m^\mathsf{Y} = |m^\mathsf{A}|. \tag{R4'}$$

THEOREM 4.6. *Let $\rho = 0$. Figure 4 shows all possible bifurcation diagrams that involve bifurcations with equilibria that can be stable for some m given the other parameters.*

A. The following diagrams occur for an open set of parameters:

(1) Diagram (a) in Figure 4 applies if one of the following two cases holds:

$$0 \le \phi < \phi^{\mathsf{M}_1} \text{ and (R1')} \tag{4.45a}$$

or

$$\phi^{\mathsf{M}_4} < \phi \le 1 \text{ and (R2')}. \tag{4.45b}$$

(2) Diagram (c) in Figure 4 applies if one of the following two cases holds:

$$\phi^{\mathsf{M}_1} < \phi < \phi^\mathsf{A} \text{ and (R1')} \tag{4.46a}$$

or

$$\phi^\mathsf{B} < \phi < \phi^{\mathsf{M}_4} \text{ and (R2')}. \tag{4.46b}$$

(3) Diagram (e) in Figure 4 applies if one of the following two cases holds:

$$\phi^{A} < \phi < \phi^{AF_0} \text{ and (R4)} \tag{4.47a}$$

or

$$\phi^{BF_0} < \phi < \phi^{B} \text{ and (R3).} \tag{4.47b}$$

(4) Diagram (g) in Figure 4 applies if one of the following four cases holds:

$$\phi^{AF_0} < \phi < \min\{\phi^{F_0}, \phi^{AB}\} \text{ and (R4)} \tag{4.48a}$$

or

$$\phi^{F_0} < \phi < \phi^{AB} \text{ and (R2)} \tag{4.48b}$$

or

$$\phi^{AB} < \phi < \phi^{F_0} \text{ and (R1)} \tag{4.48c}$$

or

$$\max\{\phi^{F_0}, \phi^{AB}\} < \phi < \phi^{BF_0} \text{ and (R3).} \tag{4.48d}$$

B. The following diagrams are degenerate, i.e., occur only if the parameters satisfy particular relations.

(5) Diagram (b) in Figure 4 applies if one of the following two cases holds:

$$\phi = \phi^{M_1} \text{ and (R1')} \tag{4.49a}$$

or

$$\phi = \phi^{M_4} \text{ and (R2').} \tag{4.49b}$$

(6) Diagram (d) in Figure 4 applies if one of the following two cases holds:

$$\phi = \phi^{A} \text{ and (R1')} \tag{4.50a}$$

or

$$\phi = \phi^{B} \text{ and (R2').} \tag{4.50b}$$

(7) Diagram (f) in Figure 4 applies if one of the following two cases holds:

$$\phi = \phi^{AF_0} \text{ and (R2)} \tag{4.51a}$$

or

$$\phi = \phi^{BF_0} \text{ and (R1).} \tag{4.51b}$$

(8) Diagram (h) in Figure 4 applies if

$$\phi = \phi^{F_0} = \phi^{AB}. \tag{4.52}$$

(9) Diagram (i) in Figure 4 applies if one of the following two cases holds:

$$\phi = \phi^{F_0} > \phi^{AB} \text{ and (R3').} \tag{4.53a}$$

or

$$\phi = \phi^{\mathsf{F}_0} < \phi^{\mathsf{AB}} \text{ and (R4')} \tag{4.53b}$$

(10) Diagram (j) in Figure 4 applies if one of the following two cases holds:

$$\phi = \phi^{\mathsf{AB}} < \phi^{\mathsf{F}_0} \text{ and } \mathsf{M}_i = \mathsf{M}_1 \tag{4.54a}$$

or

$$\phi = \phi^{\mathsf{AB}} > \phi^{\mathsf{F}_0} \text{ and } \mathsf{M}_i = \mathsf{M}_4. \tag{4.54b}$$

C. Figure 5 shows the order in which the bifurcation diagrams of Figure 4 arise if ϕ is increased from 0 to 1.

Proof. We prove parts A and B simultaneously and derive the statements about admissibility and stability of the equilibria by rewriting the conditions in Section 3.7 in terms of m, m^{A}, m^{B}, m^{F_0}, and m^* (4.3). These critical migration rates satisfy the relations given in (4.9), (4.11), (A.19) and (A.37).

We start by treating the bifurcations and stability of F_0. Using (4.5c) and (4.4c), we infer from (3.25):

$$\mathsf{F}_0 \to \mathsf{M}_1 \iff m \uparrow -m^{\mathsf{F}_0} \text{ and } \phi < \phi^{\mathsf{F}_0}, \tag{4.55a}$$

$$\mathsf{F}_0 \to \mathsf{M}_4 \iff m \uparrow m^{\mathsf{F}_0} \text{ and } \phi > \phi^{\mathsf{F}_0}. \tag{4.55b}$$

From (4.15) we conclude that (4.55a) applies precisely in the following cases: (4.45a), (4.46a), (4.47a), (4.48a), (4.48c) (Part A), or (4.49a), (4.50a), (4.51a), (4.54a) (Part B). Similarly, (4.55b) applies in precisely the following cases: (4.45b), (4.46b), (4.47b), (4.48b), (4.48d) (Part A) or (4.49b), (4.50b), (4.51b), (4.54b) (Part B). F_0 is admissible for every $m > 0$ if and only if $\phi = \phi^{\mathsf{F}_0}$, which corresponds to the remaining three cases (4.52) and (4.53b), (4.53a).

Condition (3.26), which determines when F_0 changes stability, is equivalent to $m = m^*$. Therefore, Proposition 3.4 and the definitions of m^{F_0} and m^* imply that F_0 is asymptotically stable if and only if either

$$0 < m < |m^{\mathsf{F}_0}| \le m^* \tag{4.56a}$$

or

$$0 < m < m^* < |m^{\mathsf{F}_0}| \tag{4.56b}$$

holds, where

$$0 < |m^{\mathsf{F}_0}| \le m^* \iff \phi \le \phi^{\mathsf{M}_1} \text{ or } \phi \ge \phi^{\mathsf{M}_4}, \tag{4.57a}$$

$$0 < m^* < |m^{\mathsf{F}_0}| \iff \phi^{\mathsf{M}_1} < \phi < \phi^{\mathsf{M}_4}. \tag{4.57b}$$

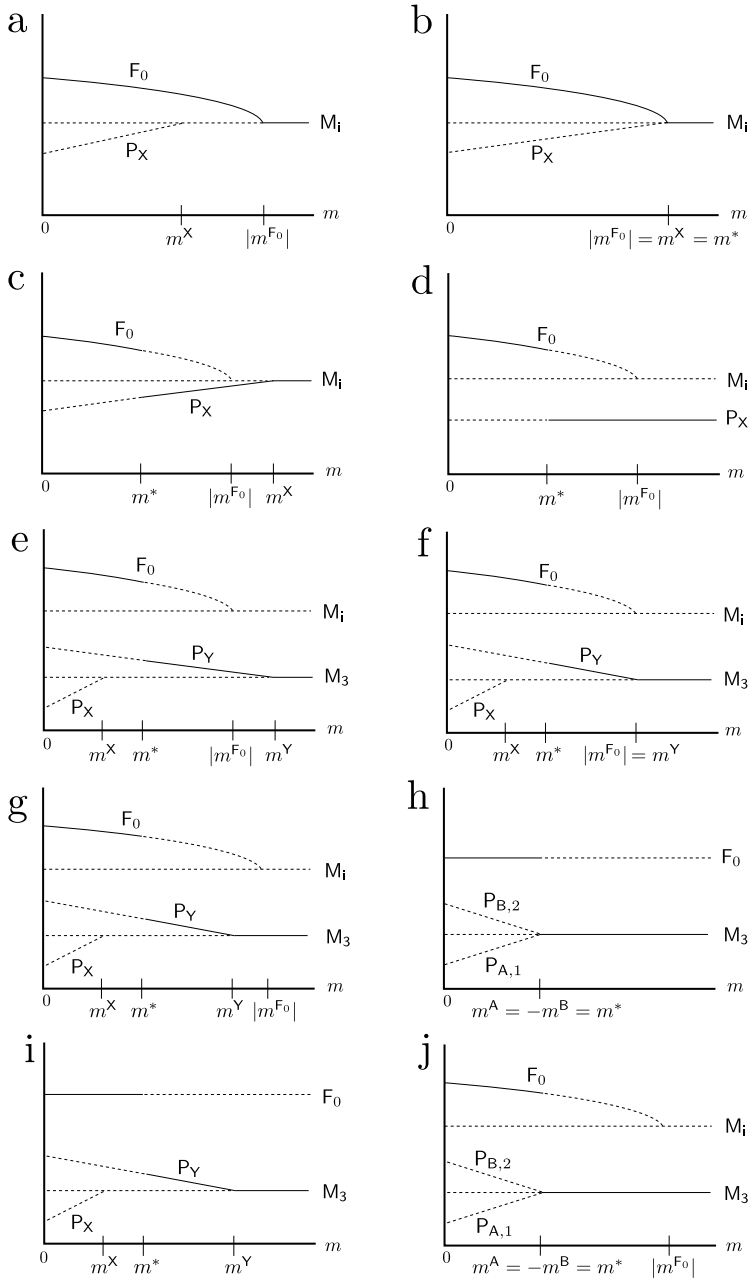

FIGURE 4. Bifurcation diagrams for $\rho = 0$. Diagrams (a) – (j) represent all equilibrium and stability configurations listed in Theorem 4.6. Each diagram displays the possible equilibria as a function of the total migration rate m. Each line indicates one admissible equilibrium, drawn if and only if it is admissible. Only equilibria are shown that can be stable or are involved in a bifurcation with an equilibrium that can be stable. Lines are drawn such that intersections occur if and only if the corresponding equilibria collide. Solid lines represent asymptotically stable equilibria, dashed lines unstable equilibria.

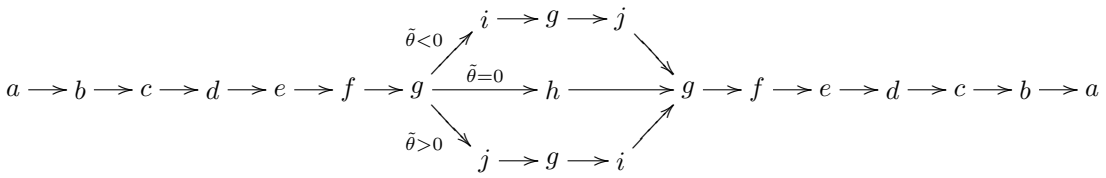

FIGURE 5. Order in which the bifurcation diagrams of Figure 4 occur as ϕ increases from 0 to 1.

If (4.56a) applies, according to (4.55), F_0 leaves the state space at $m = -m^{\mathsf{F}_0}$ or $m = m^{\mathsf{F}_0}$ and exchanges stability with the respective monomorphism. By (4.57a), this occurs in the cases (4.45) or (4.49) of the theorem.

If (4.56b) applies, F_0 loses stability at $m = m^*$ and, generically, either $\mathsf{P}_{\mathsf{A},1}$ or $\mathsf{P}_{\mathsf{B},2}$ is asymptotically stable if $m > m^*$ (see below). F_0 remains admissible up to $m = |m^{\mathsf{F}_0}|$, when it collides with M_1 or M_4. By (4.15) and (4.57b), this occurs in the cases (4.46) – (4.48), (4.50), (4.51), (4.53), and (4.54).

Finally, if $\phi = \phi^{\mathsf{AB}}$ (cases (4.52) and (4.54) in the theorem), M_3 becomes stable. This follows from the statement below (3.31) together with (4.11a).

Next, we treat the bifurcations of the SLPs. The SLPs are admissible in intervals of the form $0 < m < |m^{\mathsf{A}}|$ or $0 < m < |m^{\mathsf{B}}|$ and leave the state space upon collision with a ME (Section 4.2). From (3.32) we conclude by simple calculations that $\mathsf{P}_{\mathsf{A},1}$ is asymptotically stable if and only if

$$m^* < m < |m^{\mathsf{A}}| \text{ and } \phi^{\mathsf{M}_1} < \phi < \phi^{\mathsf{AB}}, \tag{4.58}$$

as is the case in (4.46a), (4.47a), (4.48a) (if $\min\{\phi^{\mathsf{F}_0}, \phi^{\mathsf{AB}}\} = \phi^{\mathsf{AB}}$), and (4.48b), as well as in (4.50a), (4.51a), and (4.53b).

From (3.33), we conclude that $\mathsf{P}_{\mathsf{B},2}$ is asymptotically stable if and only if

$$m^* < m < |m^{\mathsf{B}}| \text{ and } \phi^{\mathsf{AB}} < \phi < \phi^{\mathsf{M}_4}, \tag{4.59}$$

as is the case in (4.46b), (4.47b), (4.48c), and (4.48d) (if $\max\{\phi^{\mathsf{F}_0}, \phi^{\mathsf{AB}}\} = \phi^{\mathsf{AB}}$), as well as in (4.50b), (4.51b), and (4.53a).

It remains to study the stability of the ME. For $\rho = 0$, we infer from Section 4.1 and Proposition 4.1:

$$\mathsf{M}_1 \text{ is asymptotically stable} \iff \begin{cases} m > -m^{\mathsf{F}_0} \text{ and } \phi < \phi^{\mathsf{M}_1}, \text{ or} \\ m > -m^{\mathsf{A}} \text{ and } \phi^{\mathsf{M}_1} \le \phi < \phi^{\mathsf{A}}, \end{cases} \tag{4.60a}$$

$$\mathsf{M}_3 \text{ is asymptotically stable} \iff m > \max\{|m^{\mathsf{A}}|, |m^{\mathsf{B}}|\} \text{ and } \phi^{\mathsf{A}} < \phi < \phi^{\mathsf{B}}, \tag{4.60b}$$

$$\mathsf{M}_4 \text{ is asymptotically stable} \iff \begin{cases} m > m^{\mathsf{B}} \text{ and } \phi^{\mathsf{B}} < \phi \le \phi^{\mathsf{M}_1}, \text{ or} \\ m > m^{\mathsf{F}_0} \text{ and } \phi^{\mathsf{M}_4} < \phi. \end{cases} \tag{4.60c}$$

In conjunction with the above results on F_0 and the SLPs, this shows that, except in the degenerate cases (4.49), (4.50), (4.52), and (4.54), a ME becomes stable through a transcritical bifurcation with either F_0, $\mathsf{P}_{\mathrm{A},1}$, or $\mathsf{P}_{\mathrm{B},2}$. In particular, M_1 becomes asymptotically stable for large m if (4.45a), (4.46a), or (4.49a) applies, M_3 becomes asymptotically stable if one of (4.47), (4.48), (4.51), (4.52), (4.53), or (4.54) applies, and M_4 becomes asymptotically stable if (4.45b), (4.46b), or (4.49b) applies. If $\phi = \phi^{\mathsf{A}}$ or $\phi = \phi^{\mathsf{B}}$ (4.50), then $\mathsf{P}_{\mathrm{A},1}$ or $\mathsf{P}_{\mathrm{B},2}$, respectively, is admissible and asymptotically stable for every m, and every ME is unstable. This finishes the proof of parts A and B.

Part C of Theorem 4.6 follows immediately from parts A and B by applying the relations in (4.15). □

This theorem demonstrates that, for given selection parameters, the equilibrium structure, hence also the evolutionary dynamics, depends strongly on the degree ϕ of asymmetry of the migration rates. However, it is also important to note (and maybe counter intuitive) that for symmetric migration ($\phi = 1/2$) any of the ten possible bifurcation diagrams may apply, simply by choosing the selection parameters accordingly.

The bifurcations of equilibria that cannot be stable can be derived easily from Sections 4.2, 4.3, 3.7, and the above theorem by noting that these are boundary equilibria and corresponding pairs of SLPs are admissible for the same parameters. Inclusion of these bifurcations would require the introduction of subcases. In particular, $\mathsf{P}_{\mathrm{A},2}$, $\mathsf{P}_{\mathrm{B},1}$, and M_2 are always unstable because gamete A_1B_2 is eventually lost. We observe from (A.20) and (A.38) that at most one pair of SLPs can be admissible if F_0 is either unstable or not admissible. If this is the case, then one of these SLPs is asymptotically stable (Figure 4).

Corollary 4.7. *If $\rho = 0$, the maximum migration rate, below which a stable two-locus polymorphism exists, is given by*

$$m^0_{\max} = \min\{|m^{\mathsf{F}_0}|, m^*\}. \tag{4.61}$$

The corollary follows from the arguments surrounding (4.56) and (4.57).

4.9. Weak recombination. If $m \neq m^*$, a regular perturbation analysis of F_0 yields the coordinates of a fully polymorphic (internal) equilibrium to leading order in ρ. This equilibrium, F, is asymptotically stable (Karlin and McGregor 1972). We denote the first-order approximation of F by F_ρ. Therefore, we have $\mathsf{F} = \mathsf{F}_\rho + o(\rho)$ and $\mathsf{F}_\rho = \mathsf{F}_0 + O(\rho)$

as $\rho \to 0$. Because the coordinates of F_ρ are much too complicated to be informative, we refrain from presenting them.

For sufficiently small ρ, the following properties of F_ρ (hence, of F) can be inferred from Proposition 4.1, Remark 4.2, and Theorem 4.6, Part A.1:

$$\mathsf{F}_\rho \to \mathsf{M}_1 \iff m \uparrow m^{\mathsf{M}_1} \text{ and } \phi \le \phi^{\mathsf{M}_1}, \tag{4.62a}$$

$$\mathsf{F}_\rho \to \mathsf{M}_4 \iff m \uparrow m^{\mathsf{M}_4} \text{ and } \phi^{\mathsf{M}_4} \le \phi. \tag{4.62b}$$

The above perturbation analysis can not be used to investigate the properties of the internal equilibrium F for given small positive ρ when m is varied in the proximity of m^*. Therefore, we performed numerical calculations to study the fate of F when ρ is small and fixed, and m increases. It suggests the following:

$$\mathsf{F} \to \mathsf{P}_{\mathsf{A},1} \iff m \uparrow m^*_{\mathsf{A}} \text{ and } \phi^{\mathsf{M}_1} < \phi < \phi^{\mathsf{AB}}, \tag{4.63a}$$

$$\mathsf{F} \to \mathsf{M}_3 \iff m \uparrow m^* = m^{\mathsf{A}} = -m^{\mathsf{B}} \text{ and } \phi = \phi^{\mathsf{AB}}, \tag{4.63b}$$

$$\mathsf{F} \to \mathsf{P}_{\mathsf{B},2} \iff m \uparrow m^*_{\mathsf{B}} \text{ and } \phi^{\mathsf{AB}} < \phi < \phi^{\mathsf{M}_4}, \tag{4.63c}$$

where m^*_{A} and m^*_{B} are close to m^*. Thus, if ρ is small, F stays close to F_0 as m increases from 0 until a value close to m^* is reached. Then, within a very short interval of m, F moves 'quickly' along the manifold given by (A.8) and (A.11) to one of the boundary equilibria ($\mathsf{P}_{\mathsf{A},1}$, $\mathsf{P}_{\mathsf{B},2}$, or M_3) on the 'opposite' side of the state space, where it exchanges stability upon collision with the respective equilibrium (at m^*_{A}, m^*_{B}, or m^*). F appears to be asymptotically stable whenever it is admissible.

If one of the cases in (4.62) applies, then F_0 can be maintained for higher migration rates than F because m^{M_1} and m^{M_4} are decreasing functions in ρ. Numerical investigations support the conjecture that F_0 can be maintained for higher migration rates than F whenever recombination is weak but positive. Thus, when recombination is weak, decreasing ρ increases the maximum migration rate below which a stable, fully polymorphic equilibrium can be maintained.

4.10. Highly asymmetric migration. As already discussed in Section 3.8, by introducing weak back migration (i.e., ϕ close to 0 or 1) to the CI model, every equilibrium in the CI model gives rise to a unique equilibrium in a small neighborhood. This (perturbed) equilibrium has the same stability as the unperturbed. For weak or strong recombination, we can strengthen this conclusion. Because the CI model with $\rho = 0$ is a generalized gradient system (Bürger and Akerman 2011, Section 3.4.4) and the LE dynamics (3.17) has a globally asymptotically stable equilibrium (Theorem 4.4), the proof of Theorem 2.3 of Nagylaki et al. (1999) applies and shows that in both cases the global

dynamics remains qualitatively unchanged under small perturbations. In particular, no new equilibria or limit sets are generated by a small perturbation.

Therefore, if ρ is sufficiently small and ϕ is sufficiently close to 0 or 1, we infer from Section 3.8 and Theorem 2 in Bürger and Akerman (2011) that the following bifurcation pattern applies (where $i = 1$ or 4):

- If $0 < m < m^{\mathsf{M}_i}$, a unique internal equilibrium, F, exists. It is globally asymptotically stable.
- At $m = m^{\mathsf{M}_i}$, F leaves the state space through the ME M_i by an exchange-of-stability bifurcation.
- If $m > m^{\mathsf{M}_i}$, M_i is globally asymptotically stable.

This pattern is displayed in diagram (a) of Figure 4, where F_0 needs to be substituted by F. We conjecture that it applies whenever ρ is sufficiently small and either $\phi < \phi^{\mathsf{M}_1}$ or $\phi > \phi^{\mathsf{M}_4}$ holds. The bounds ϕ^{M_1} and ϕ^{M_4} follow from Remark 4.2 because $\tilde{\phi}^{\mathsf{M}_1}$ is not needed if ρ is sufficiently small; see (A.32b). However, the upper bounds for ρ given in Remark 4.2 are, in general, too large to guarantee the above bifurcation pattern. This is known from the CI model in which the monomorphic equilibrium (M_i) may be simultaneously stable with the internal equilibrium F because an unstable internal equilibrium enters the state space at $m = m^{\mathsf{M}_i}$ through M_i. If $\phi = 1$, this may occur if $\frac{1}{3}(\alpha_1 + \beta_1) < \rho < 3\alpha_1 - \beta_1$, cf. (4.65b). For $\phi \neq 0$ or $\phi \neq 1$, we have not been able to determine the upper bound for ρ below which F indeed leaves the state space through M_i.

Now we treat large ρ. Proposition 4.1 and Remark 4.2 show that if $\rho > \max\{-\alpha_2, -\beta_2\}$, then M_1 is asymptotically stable if and only if $\phi < \phi^{\mathsf{A}}$ and $m > \max\{-m^{\mathsf{A}}, -m^{\mathsf{B}}\}$, and if $\rho > \alpha_1$, then M_4 is asymptotically stable if and only if $\phi > \phi^{\mathsf{B}}$ and $m > \max\{m^{\mathsf{A}}, m^{\mathsf{B}}\}$.

If, in addition to ρ being sufficiently large, ϕ is small or large, then Theorem 4.4 implies that the internal equilibrium (F) leaves the state space through $\mathsf{P}_{\mathsf{A},1}$, $\mathsf{P}_{\mathsf{B},1}$, or $\mathsf{P}_{\mathsf{B},2}$. The respective conditions are small perturbations of those given in (4.40a), (4.40b), of (4.40c), respectively. Combining theses conditions with those for the stability of the ME and observing (4.12) and (4.13), we conclude that the following bifurcation pattern applies if one of the conditions (a) $\alpha_2 \leq \beta_2$ and $\phi < \phi^{\mathsf{A}}$, or (b) $\beta_2 < \alpha_2$ and $\phi < \tilde{\phi}^{\mathsf{AB}}$, or (c) $\phi > \phi^{\mathsf{B}}$ holds approximately:

- If $0 < m < m^{\bullet}$, a unique internal equilibrium, F, exists. It is asymptotically stable.
- At $m = m^{\bullet}$, F leaves the state space through a SLP by an exchange-of-stability bifurcation.
- If $m^{\bullet} < m < m^{\bullet\bullet}$, this SLP is asymptotically stable.

- If $m \geq m^{\bullet\bullet}$, then a ME is asymptotically stable.

If (a) holds, then $m^{\bullet} \approx -m^{\mathsf{B}}$ and the SLP and the ME are $\mathsf{P}_{\mathsf{A},1}$ and M_1, respectively; if (b) holds, then $m^{\bullet} \approx -m^{\mathsf{A}}$ and the SLP and the ME are $\mathsf{P}_{\mathsf{B},1}$ and M_1, respectively; if (c) holds, then $m^{\bullet} \approx m^{\mathsf{A}}$ and the SLP and the ME are $\mathsf{P}_{\mathsf{B},2}$ and M_4, respectively. Finally, $m^{\bullet\bullet} = \max\{-m^{\mathsf{A}}, -m^{\mathsf{B}}\}$ in (a) and (b), and $m^{\bullet\bullet} = \max\{m^{\mathsf{A}}, m^{\mathsf{B}}\}$ in (c).

4.11. Maintenance of polymorphism. As already noted in Section 3.11, for general parameters the equilibrium configurations could not be determined analytically. To explore the potential of spatially heterogeneous selection in maintaining genetic variation in the presence of gene flow, we investigate the maximum total migration rate, $m_{\max}$, that admits a stable, fully polymorphic equilibrium. We have already shown that $m_{\max} = m^{\infty}_{\max}$ holds in the LE approximation (Corollary 4.5), and $m_{\max} = m^{0}_{\max}$ holds if $\rho = 0$ (Corollary 4.7). From (A.20) and (A.38) we conclude that

$$m^{\infty}_{\max} \leq m^{0}_{\max}, \tag{4.64}$$

where, as is not difficult to show, equality holds if and only if $\phi = \phi^{\mathsf{AB}}$.

For the CI model with $\phi = 1$, Proposition 1 in Bürger and Akerman (2011) yields

$$m_{\max} = \begin{cases} \alpha_1 + \beta_1 - \rho & \text{if } 0 < \rho \leq \min\{\alpha_1, \tfrac{1}{3}(\alpha_1 + \beta_1)\}, \quad (4.65a) \\ \dfrac{(\alpha_1 + \beta_1 + \rho)^2}{8\rho} & \text{if } \tfrac{1}{3}(\alpha_1 + \beta_1) < \rho \leq 3\alpha_1 - \beta_1, \quad (4.65b) \\ \alpha_1 \left(1 + \dfrac{\beta_1 - \alpha_1}{\rho}\right) & \text{if } \max\{\alpha_1, 3\alpha_1 - \beta_1\} < \rho. \quad (4.65c) \end{cases}$$

In this case, the fully polymorphic equilibrium is globally asymptotically stable if (4.65a) or (4.65c) apply, but only locally stable if (4.65b) and m is close to $m_{\max}$. A formula analogous to (4.65), but with $-\alpha_2$ and $-\beta_2$ instead of α_1 and β_1, holds if $\phi = 0$.

In general, we have no explicit formula for $m_{\max}$. However, extensive numerical work, as well as (4.65) and the considerations in Section 4.9 suggest that

$$m_{\max} \leq m^{0}_{\max} \tag{4.66}$$

holds always. This is illustrated by Figure 6, which displays the dependence of $m_{\max}$ on the migration ratio ϕ (Figures 6a and 6c) and on the recombination rate ρ (Figures 6b and 6d) for two selection regimes. In Figures 6a and 6b, locus B is under stronger selection in both demes. In Figures 6c and 6d, each locus is under stronger selection in one deme.

In Figures 6a and 6c, $m^{\infty}_{\max}$ and $m^{0}_{\max}$ are shown as functions of ϕ. The inequality (4.64) is a conspicuous feature in both cases. Also the shapes of $m^{\infty}_{\max}$ and $m^{0}_{\max}$ are conspicuous. The following properties are easy to prove: $m^{\infty}_{\max}$ is not differentiable at $\phi = \phi^{\mathsf{AB}}$ and $\phi = \tilde{\phi}^{\mathsf{AB}}$, and $m^{0}_{\max}$ is not differentiable at $\phi = \phi^{\mathsf{M}_1}$ and $\phi = \phi^{\mathsf{M}_4}$. $m^{\infty}_{\max}$

and $m^0_{\max}$ are piecewise convex functions in ϕ. If $\phi < \phi^{M_1}$, $m^0_{\max}$ increases in ϕ; if $\phi^{M_4} < \phi$, $m^0_{\max}$ decreases in ϕ; if $\phi^{M_1} < \phi < \phi^{M_4}$, $m^0_{\max}$ assumes its minimum at $\frac{1}{2}$ provided $\phi^{M_1} \le \frac{1}{2} \le \phi^{M_4}$. Therefore, $m^0_{\max}$ attains its maximum at ϕ^{M_1} or ϕ^{M_4}. $m^\infty_{\max}$ increases if $\phi < \phi^{AB}$ and decreases if $\phi > \phi^{AB}$. It assumes its maximum at ϕ^{AB}.

Notably, $m^\infty_{\max} = m^0_{\max}$ holds if $\phi = \phi^{AB}$. Numerical work suggests that indeed $m_{\max} = m^\infty_{\max} = m^0_{\max}$ holds independently of ρ if $\phi = \phi^{AB}$. If $\theta = 0$, then $\phi^A = \phi^B = \phi^{AB} = \phi^{F_0}$ and $m^\infty_{\max} = m^0_{\max}$ if $\phi = \phi^{AB}$. The latter condition is equivalent to (3.36c). Therefore, the analysis in Section 3.10 applies and shows that an internal equilibrium, which presumably is globally asymptotically stable, exists always.

Figures 6b and 6d illustrate the effect of recombination on $m_{\max}$ for different values of ϕ. In all cases investigated, $m_{\max}$ decreased monotonically with increasing ρ. These findings support the conjecture that (4.66) is always valid. Therefore, $m^0_{\max} - m^\infty_{\max}$ serves as a useful estimate for the sensitivity of $m_{\max}$ to variation in ρ. We can prove that $m^0_{\max} - m^\infty_{\max}$ is maximized at $\phi = \phi^{M_1}$, or at $\phi = \phi^{M_4}$, or at $\phi = 0$ if $\beta_2 < \alpha_2$.

Although we proved that $m_{\max} < m^\infty_{\max}$ can occur (Section 4.7), all numerical examples showed that $m_{\max}$ is only very slightly smaller than $m^\infty_{\max}$ in this case (results not shown). Therefore, our results suggest that the cases of LE (infinitely strong recombination) and of no recombination 'essentially' bracket the range of parameters for which both loci can be maintained polymorphic.

As Figures 6a and 6c show, the range of values ϕ for which the equilibrium structure can be expected to be similar to the CI model, i.e., $\phi < \min\{\phi^{M_1}, \tilde{\phi}^{AB}\}$ or $\phi > \phi^{M_4}$ (Section 4.10), can vary considerably.

Finally, we infer from Proposition 4.1 that none of the ME is stable if $m < \max\{|m^A|, |m^B|\}$. Hence, in this case at least one locus is maintained polymorphic. By contrast, we have shown in Section 4.2 that no SLP is admissible if $m > \max\{|m^A|, |m^B|\}$. However, as demonstrated by our results for $\rho = 0$, an internal equilibrium may be asymptotically stable if $\max\{|m^A|, |m^B|\} < m < m^0_{\max}$. These results suggest that no genetic variability can be maintained if

$$m > \max\{|m^A|, |m^B|, m^0_{\max}\}. \tag{4.67}$$

This bound is best possible if $\rho = 0$. For sufficiently large ρ, the corresponding bound is $\max\{|m^A|, |m^B|\}$.

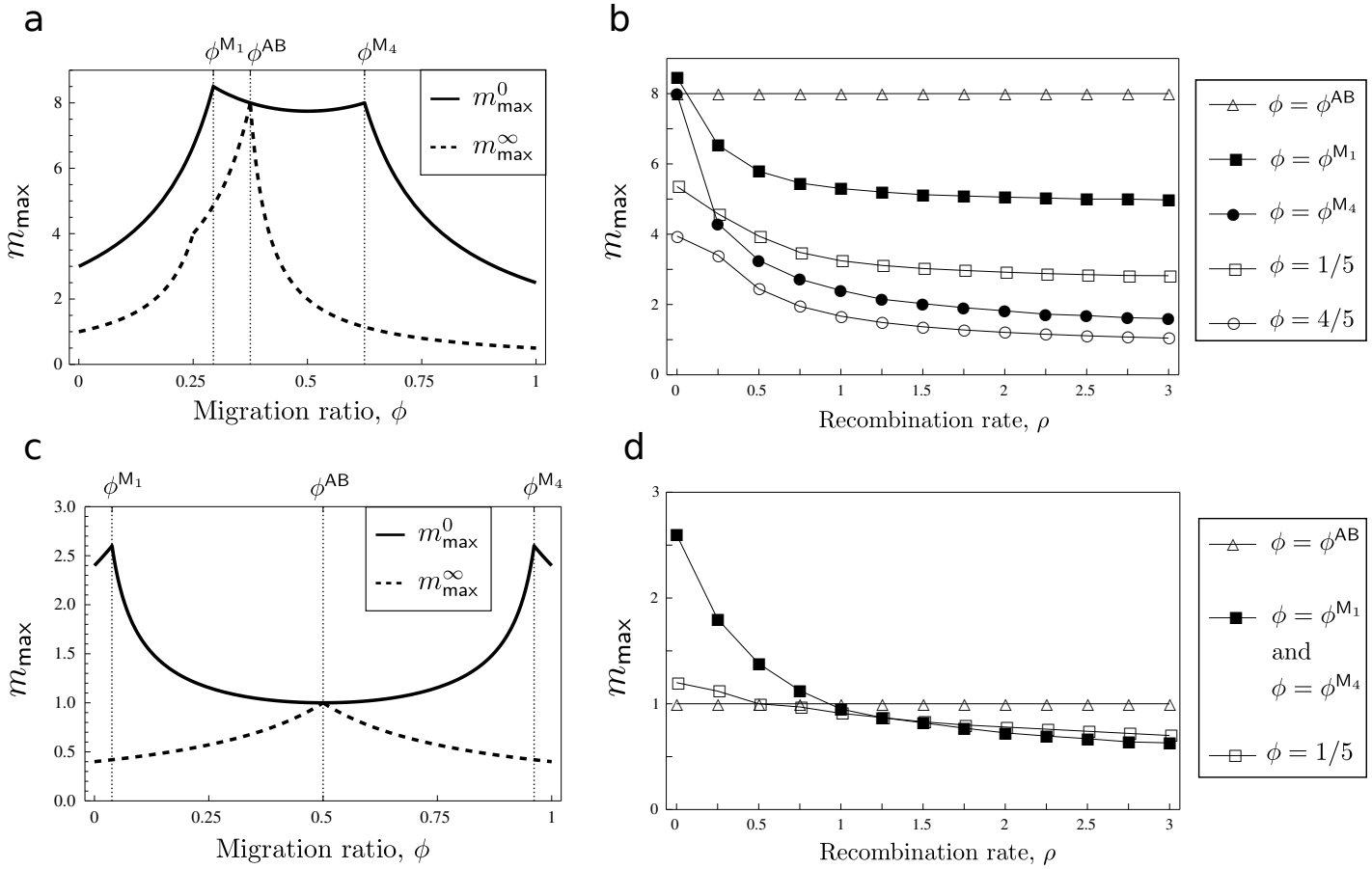

FIGURE 6. The maximum amount of gene flow, $m_{\max}$, admitting an asymptotically stable two-locus polymorphism as a function of ϕ or ρ. In panels a and b, locus B is under stronger selection than locus A in both demes ($\alpha_2 = -2\alpha_1 = -1$, $\beta_1 = -\beta_2 = 2$, $\theta = 1$). In c and d, different loci are under stronger selection in the two demes ($\alpha_1 = -\beta_2 = 0.4$, $\beta_1 = -\alpha_2 = 2$, $\theta = 3.84$). Panels a and c show $m_{\max}$ as a function of ϕ for complete linkage ($m^0_{\max}$, (4.61)) and under linkage equilibrium ($m^\infty_{\max}$, (4.43)). Panels b and d display $m_{\max}$ for the indicated values of ϕ as a function of ρ. Here, $m_{\max}$ is obtained by determining numerically the critical migration rate when the stable internal equilibrium hits the boundary. This is done by computing when the leading eigenvalue at the boundary equilibrium is zero and by calculating the coordinates of the fully polymorphic equilibrium in a small neighborhood. In a and b, we have $\tilde{\phi}^{AB} = \frac{1}{4}$ (indicated by the kink in the dashed line in a), $\phi^{M_1} = \frac{5}{17}$, $\phi^{A} = \frac{1}{3}$, $\phi^{AB} = \frac{3}{8}$, $\phi^{B} = \frac{1}{2}$, $\phi^{M_4} = \frac{5}{8}$. In c and d, we have $\phi^{M_1} = \frac{1}{26}$, $\phi^{A} = \frac{1}{6}$, $\phi^{AB} = \frac{1}{2}$, $\phi^{B} = \frac{5}{6}$, $\phi^{M_4} = \frac{25}{26}$.

5. Migration load and local adaptation

Here, we briefly investigate some properties of the migration load of the subpopulations and of the total population. We use these migration loads as simple measures for local adaptation (but see Blanquart et al. 2012). Mean fitness in deme k is given by $\bar{w}_k = \alpha_k(2p_k - 1) + \beta_k(2q_k - 1)$, with its maximum at $\alpha_k + \beta_k$. Therefore, the migration loads in demes 1 and 2, defined as the deviation of $\bar{w}_k$ from its maximum, are given by

$$L_1 = 2(\alpha_1(1 - p_1) + \beta_1(1 - q_1)) \quad \text{and} \quad L_2 = 2(-\alpha_2 p_2 - \beta_2 q_2). \tag{5.1}$$

Assuming that the subpopulations are of equal size, we define the load of the total population by $L = \frac{1}{2}(L_1 + L_2)$.

If migration is weak, we can calculate the migration load in each deme at the fully polymorphic equilibrium F (Proposition 3.2) to leading order in m_1 and m_2. For deme 1, we obtain

$$L_1 \approx 2m_1 \frac{\alpha_1 + \beta_1 + 2\rho}{\alpha_1 + \beta_1 + \rho}, \tag{5.2}$$

and an analogous formula holds for deme 2. Obviously, the migration load increases with increasing migration rates m_1 or m_2, hence with m, in each of the demes and in the total population. Simple calculations show that each of the loads also increases with increasing recombination rate ρ if migration is weak.

In general, however, the load in each deme does not always increase with increasing m. The reason is that for sufficiently strong migration, generically, first one locus, then one of the haplotypes becomes fixed (Proposition 4.3). If this is either A_1B_1 or A_2B_2, then the load in the corresponding deme will vanish for high migration rates, whereas that in the other deme will be very high. In such a case, the load of the total population may also decrease with increasing m. This occurs for large migration rates (not far below $m_{\max}$) and it can occur for completely linked loci as well as for loci in LE. In the CI model, the load always increases with the migration rate (Bürger and Akerman 2011)

Finally, although L is increasing in ρ if migration is weak, this is not necessarily so if migration is strong. By using a grid of parameter combinations, we showed numerically that in about 0.34% of more than 10^6 combinations of $\alpha_1, \alpha_2, \beta_1, \beta_2, m$, and ϕ, the total load L at the equilibrium F_∞ is lower than that at F_0 (results not shown). Again, this occurs for high migration rates, not far below the value $m^\infty_{\max}$ at which F_∞ leaves the state space. Then a population maintained fully polymorphic by tight linkage may have a higher total load than a population in which fixation of a locus or a haplotype is facilitated by high recombination. In all such cases, selection in one deme was (considerably) stronger than in the other, and in more than 70% of the cases, a specialist haplotype became fixed at very high migration rates. In summary, under a wide range of conditions

in this model, reduced recombination is favored, but there are instances where increased recombination is favored (cf. Pylkov et al. 1998; Lenormand and Otto 2000).

6. $F_{\rm ST}$ and differentiation

The most commonly used measure for quantifying differentiation in spatially structured populations is $F_{\rm ST}$. For diallelic loci, $F_{\rm ST}$ can be defined as $F_{\rm ST} = \frac{{\rm Var}(p)}{\bar{p}(1-\bar{p})}$, where ${\rm Var}(p)$ is the variance of the allele frequencies in the total population and $\bar{p}$ is the allele frequency averaged over the demes. Estimators of multilocus $F_{\rm ST}$ are usually defined as weighted averages of one-locus $F_{\rm ST}$ estimators (e.g., Weir and Cockerham 1984, Leviyang and Hamilton, 2011). Here, we extend Nagylaki's (1998) approach and define a genuine multilocus version of $F_{\rm ST}$ that measures the covariance of the frequencies of (multilocus) haplotypes. We restrict attention to the diallelic two-locus case, but the extension to multiple multiallelic loci is evident. A general multilocus theory of fixation indices will be developed elsewhere.

Let c_k denote the proportion of the population in deme k, so that $\sum_k c_k = 1$. Then the frequency of haplotype i in the entire population is $\bar{x}_i = \sum_k c_k x_{i,k}$. Because our subpopulations are randomly mating, the frequency of genotype ij in the entire population is given by $\overline{x_i x_j} = \sum_k c_k x_{i,k} x_{j,k}$. Following eqs. (6a) and (6b) in Nagylaki (1998), we define $F_{{\rm ST},ij}$ as a standardized measure of the covariance of the frequencies of haplotypes i and j:

$$\overline{x_i^2} = \bar{x}_i^2 + F_{{\rm ST},ii}\bar{x}_i(1-\bar{x}_i), \tag{6.1a}$$

$$\overline{x_i x_j} = (1 - F_{{\rm ST},ij})\bar{x}_i\bar{x}_j. \tag{6.1b}$$

The multilocus, or haplotype, heterozygosity in the entire population can be defined as

$$\bar{h}_S = \sum_{i,j:i\neq j} \overline{x_i x_j} = \sum_i (\bar{x}_i - \overline{x_i^2}), \tag{6.2}$$

where $\sum_i$ runs over all haplotypes. If the entire population were panmictic, its multilocus heterozygosity would be

$$h_T = \sum_i \bar{x}_i(1-\bar{x}_i). \tag{6.3}$$

Thus, $1 - h_T$ is the probability that two gametes chosen at random from the entire population are the same haplotype.

Following eq. (32) in Nagylaki (1998), we define $F_{\rm ST}$ by

$$F_{\rm ST} = \frac{1}{h_T}\sum_i \bar{x}_i(1-\bar{x}_i)F_{{\rm ST},ii}. \tag{6.4}$$

Then F_{ST} can be written as

$$F_{ST} = 1 - \frac{\bar{h}_S}{h_T} = \frac{\sum_i \mathrm{Var}(x_i)}{\sum_i \bar{x}_i(1-\bar{x}_i)}, \tag{6.5}$$

in direct generalization of the classical formula given above.

We focus on the dependence of the equilibrium value of F_{ST} on the migration parameters m and ϕ and on the recombination rate ρ. Because we obtained the coordinates of the stable, fully polymorphic equilibrium equilibrium F explicitly only in special or limiting cases, explicit formulas for F_{ST} can be derived only in these cases. For instance, if migration is weak, we obtain from (3.16) that, to leading order in m,

$$F_{ST} = 1 - m\left[\frac{\phi}{c_2}\,\frac{\alpha_1\beta_1 + (\alpha_1+\beta_1)\rho}{\alpha_1\beta_1(\alpha_1+\beta_1+\rho)} - \frac{1-\phi}{c_1}\,\frac{\alpha_2\beta_2 - (\alpha_2+\beta_2)\rho}{\alpha_2\beta_2(\alpha_2+\beta_2-\rho)}\right]. \tag{6.6}$$

Here, F_{ST} increases with decreasing ρ, and decreases with increasing m. Thus, stronger linkage leads to increased differentiation if migration is weak.

Figure 7 illustrates for two selection scenarios how F_{ST}, evaluated at the stable, fully polymorphic equilibrium F, depends on the total migration rate m and the recombination rate ρ. In diagrams (a) and (c) of Figure 7, it is assumed that locus B is under stronger selection than locus A in both demes. It shows that F_{ST} usually declines with increasing migration rate. However, there are a few instances, where F_{ST} increases if m is slightly below the migration rate at which the fully polymorphic equilibrium loses admissibility. In diagrams (a) and (c) of Figure 7, differentiation between the populations experiences the fastest decline for weak migration (relative to the selection parameters), whereas this is not necessarily so in diagrams (b) and (d). There, F_{ST} may experience its strongest decrease if migration is strong.

Figure 7 also shows that at large migration rates, F_{ST} may increase if the recombination rate increases, i.e., F_{ST} is not minimized under linkage equilibrium. However, this occurs only for large recombination rates, i.e., larger than the largest selection coefficient. This is compatible with the finding in Section 4.11 that at high recombination rates, $m_{\max}$ may (slightly) increase in ρ, and the finding in Section 5 that the load L may decrease with increasing m. We note that this 'aberrant' behavior of $m_{\max}$, L, and F_{ST} does not necessarily occur for the same parameter combinations. Among more than 10^6 parameter combinations of $\alpha_1, \alpha_2, \beta_1, \beta_2, m$, and ϕ, we found no instance where F_{ST} evaluated at the equilibrium F_∞ was higher than that at F_0 (results not shown). Importantly, if recombination is weak or migration is weak then F_{ST} apparently always increases with tighter linkage.

Comparison of our multilocus $F_{\rm ST}$ with averages of single-locus $F_{\rm ST}$ values showed that the multilocus $F_{\rm ST}$ declines somwehat faster at small migration rates than the averaged single-locus $F_{\rm ST}$. For large parameter regions, the qualitative behavior of these measures of differentiation is the same. Differences occur only for a subset of selection coefficients at high migration rates and high recombination rates. Finally, we mention that our multilocus $F_{\rm ST}$ is a sensitive measure of differentiation only if the effective number of haplotypes is low. This parallels the well known fact that the classical $F_{\rm ST}$ is a sensitive measure of differentiation only if the effective number of alleles is low (e.g., Nagylaki 1998, 2011). Thus, our multilocus $F_{\rm ST}$ may be most useful if applied to short sequences of DNA. A thorough and more general study is in preparation.

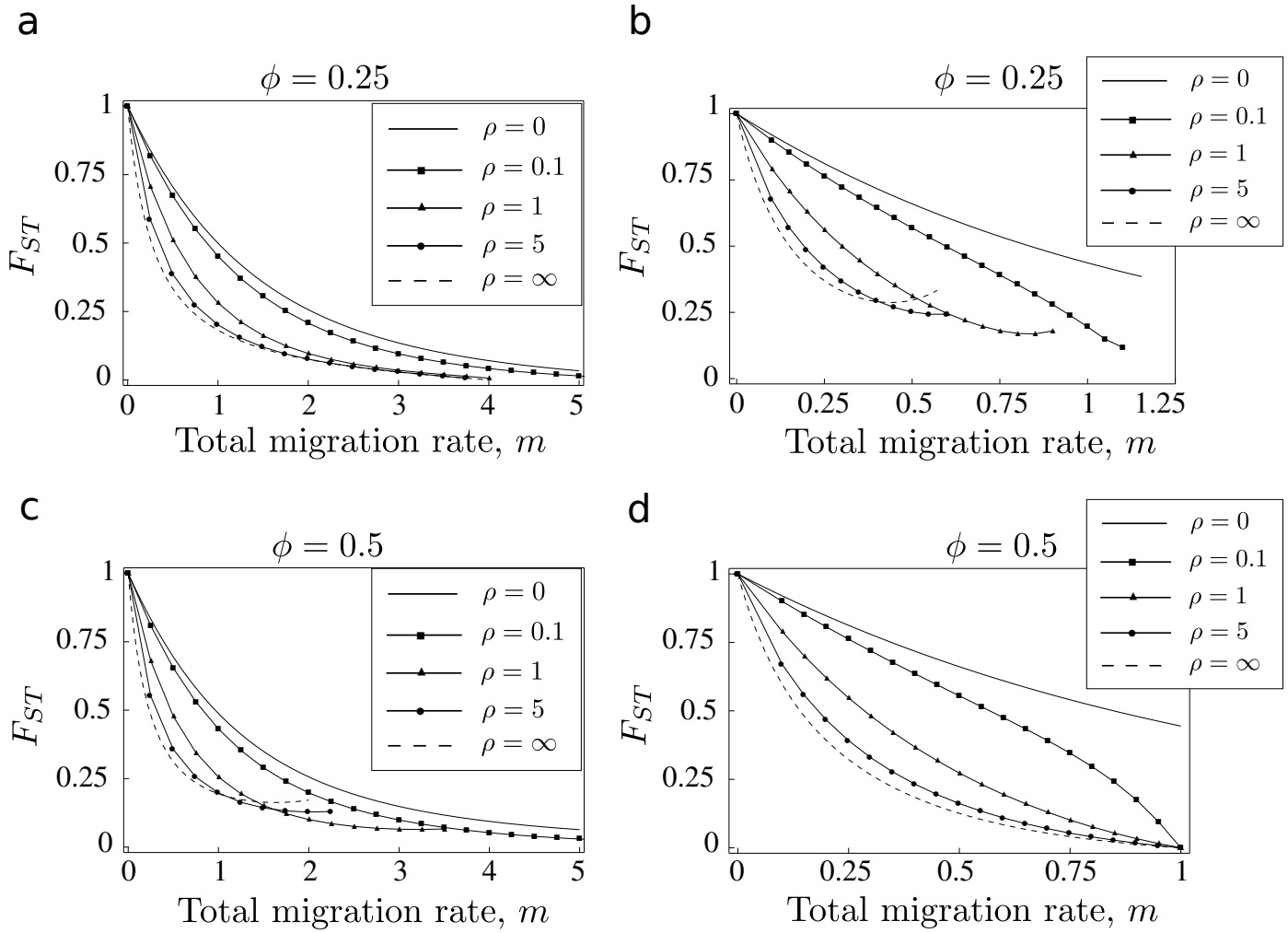

FIGURE 7. F_{ST} as a function of the total migration rate m. In panels a and c, locus B is under stronger selection in both demes ($\alpha_1 = \frac{1}{2}$, $\alpha_2 = -1$, $\beta_1 = -\beta_2 = 2$, $\theta = 1$). In panels b and d, locus A is under stronger selection than B in deme 2, and locus B is under stronger selection than A in deme 1 ($\alpha_1 = -\beta_2 = 0.4$, $\beta_1 = -\alpha_2 = 2$, $\theta = 3.84$). Note that in all cases, F_{ST} is also monotone decreasing in ρ. For $\rho = 0$ and $\rho = \infty$ (LE), the lines are from numerical evaluation of (6.5) by substitution of the coordinates of F_0 (3.24) or F_∞ (3.18). For other values of ρ, the numerically determined coordinates of the internal equilibrium are used.

7. Invasion of a locally beneficial mutant

Differentiation between subpopulations can be increased by the invasion of mutants that establish a stable polymorphism at their locus. Therefore, we consider a locus (A) at which a new mutant A_1 arises that is advantageous relative to the wild type A_2 in deme 1, but disadvantageous in deme 2. In terms of our model, we assume $\alpha_1 > 0 > \alpha_2$. If locus A is isolated, this mutant can invade and become established in a stable polymorphism if and only if $|\sigma_1 + \sigma_2| < 1$; cf. (3.7) and (3.9). Using m and ϕ, this condition can be rewritten as

$$m < |m^{\mathsf{A}}|, \tag{7.1}$$

see (4.3a) and (4.4a), or

$$\frac{m + \alpha_2}{m}\,\phi^{\mathsf{A}} < \phi < \frac{m - \alpha_2}{m}\,\phi^{\mathsf{A}} = \phi_{\text{inv}}. \tag{7.2}$$

We restrict attention to the case $\phi > \phi^{\mathsf{A}}$ (4.2a) when the influx of the deleterious allele A_2 into deme 1 is sufficiently strong such that A_2 is protected. (The case $\phi < \phi^{\mathsf{A}}$ is symmetric and more suitable to study invasion of A_2 under influx into deme 2 of A_1 which is deleterious there.) Then the mutant A_1 can invade if any of the following equivalent conditions hold:

$$m < m^{\mathsf{A}}, \tag{7.3a}$$

$$\alpha_1 > \frac{\alpha_2 m\phi}{\alpha_2 - m(1-\phi)} = \frac{m_1}{1 - m_2/\alpha_2}, \tag{7.3b}$$

or

$$\phi^{\mathsf{A}} < \phi < \phi_{\text{inv}}, \tag{7.3c}$$

where $\phi_{\text{inv}} > 1$ if and only if $m < \alpha_1$. Thus, A_1 can always invade if $m < \alpha_1$. For the CI model ($\phi = 1$), each of the conditions in (7.3) simplifies to the well known invasion condition $m < \alpha_1$ (Haldane 1930). The conditions (7.3) show that invasion is facilitated whenever back migration is increased, either by keeping m_1 constant and increasing m_2, or by fixing m and decreasing ϕ.

For the CI model it was proved that invasion of a locally beneficial mutant is always facilitated by increased linkage to a locus in migration-selection balance (Bürger and Akerman 2011). In fact, mutants of arbitrarily small effect can invade provided they are sufficiently tightly linked to this polymorphic locus which may be considered as the background in which the new mutant appears.

Here, we investigate whether this is also the case with two-way migration. Thus, we assume that locus B is in migration-selection balance (which requires that analogs of (7.3) are satisfied for β_1 and β_2) and a locally beneficial mutant A_1 arises at the linked locus A. Hence, the model in Section 2 applies and we assume (2.3).

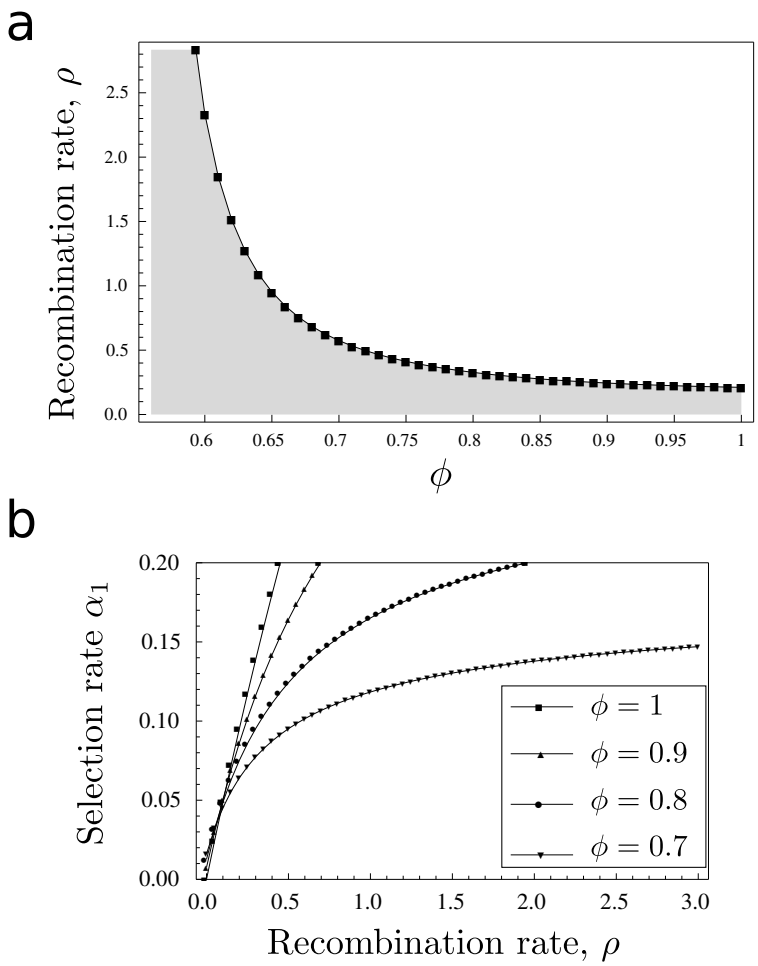

FIGURE 8. Invasion properties of locally beneficial alleles. In a, the maximum recombination rate between loci A and B, below which invasion of A_1 can occur, is displayed as a function of ϕ. The parameters $\alpha_1 = -\alpha_2 = 0.1, \beta_1 = -2\beta_2 = 2$, and $m = 1$ are fixed. Therefore, $\phi^{\mathsf{A}} = \frac{1}{2}$ and $\phi_{\text{inv}} = 0.55$. In b, the minimum selective advantage α_1 required for invasion of A_1 is shown as a function of ρ for different values of ϕ. The parameters $\alpha_2 = -0.1, \beta_1 = -2\beta_2 = 2$, and $m = 1$ are fixed.

Because we are mainly interested in the invasion properties of mutants of small effect, we assume that locus B is under stronger selection than A, i.e., $|\alpha_k| < |\beta_k|$ in deme $k = 1, 2$. Before the mutant A_1 arises, the population is at the equilibrium $\mathsf{P}_{\mathsf{B},2}$ (where $|\tau_1 + \tau_2| < 1$ must hold for admissibility; see Section 3). A_1 can invade if $\mathsf{P}_{\mathsf{B},2}$ is unstable. Since the eigenvalues determining external stability are zeros of a complicated quartic equations, the stability of $\mathsf{P}_{\mathsf{B},2}$ cannot be determined analytically. We expect that the new stable equilibrium that will be reached is the fully polymorphic equilibrium F. For

the CI model, this was be proved in (Bürger and Akerman 2011). For the case of LE, it follows from Theorem 4.4.

Figure 8 displays typical results about the invasion of the mutant A_1. In Figure 8a, the maximum recombination rate admitting invasion, denoted by $\rho_{\max}$, is shown as a function of ϕ. In the shaded region, A_1 can invade. If $\phi \leq \phi_{\text{inv}} = 0.55$, (7.3c) implies that A_1 can always invade. If $\phi > \phi_{\text{inv}}$, there exists $\rho_{\max} < \infty$, such that A_1 can invade only if $\rho < \rho_{\max}$, i.e., if A_1 is sufficiently tightly linked to locus B. In Figure 8b, the minimum selection coefficient α_1 necessary for invasion of A_1 is shown as a function of ρ/m for various values of ϕ. These values are obtained by computing when the leading eigenvalue that determines external stability of $\mathsf{P}_{\mathsf{B},2}$ equals zero.

We conclude that, as in the CI model, mutants of arbitrarily small effect can invade provided they are sufficiently tightly linked to a locus that is already maintained in migration-selection balance. In addition, as shown by both panels in Figure 8, increasingly symmetric migration facilitates the invasion and establishment of locally beneficial alleles.

8. The effective migration rate at a linked neutral site

Linkage to loci under selection may impede or enhance gene flow at a neutral marker locus. In the first case, linkage may act as a barrier to gene flow. This was shown by the work of Petry (1983), Bengtsson (1985), Barton and Bengtsson (1986), and Charlesworth et al. (1997), who developed and studied the concept of the effective migration rate as a measure of the 'effective' gene flow at a neutral site. More recently, the effective migration rate was studied for CI models with selection on a single locus in a class-structured population (Kobayashi et al. 2008) or with selection on two linked loci (Bürger and Akerman 2011). Fusco and Uyenoyama (2011) investigated the consequences of a selectively maintained polymorphism on the rate of introgression at a linked neutral site under symmetric migration between two demes.

Here, we derive an explicit expression for the effective migration rate at a neutral locus (N) that is located between the two selected loci, A and B. Recombination between locus A (B) and the neutral locus occurs with rate ρ_{AN} (ρ_{NB}) such that $\rho = \rho_{\mathsf{AN}} + \rho_{\mathsf{NB}}$. Thus, only one crossover event occurs in a sufficiently small time interval. We assume that ρ_{AN} and ρ_{NB} are positive, i.e., the neutral locus is not completely linked to a selected site. We consider two variants at the neutral locus, N_1 and N_2, each with arbitrary, positive initial frequency in at least one deme. The frequency of N_1 in deme $k(= 1, 2)$ is denoted by n_k. We model evolution at the three loci by a system of 7×2 ordinary differential equations for the allele frequencies and linkage disequilibria (p_1, p_2, q_1, q_2, D_1^{AB}, D_2^{AB}, n_1, n_2, D_1^{AN}, D_2^{AN}, D_1^{NB}, D_2^{NB}, D_1^{ANB}, D_2^{ANB}). We refrain from presenting the equations for the allele

frequencies at the neutral locus and the associated linkage disequilibria because they are a straightforward extension of those in Section 4.6 of Bürger and Akerman (2011).

Obviously, the equilibrium allele frequencies at the neutral locus are the same in each deme and given by the initial allele frequencies averaged over the two demes:

$$\hat{n}_1 = \hat{n}_2 = \hat{n} = \frac{m_2 n_1(0)}{m} + \frac{m_1 n_2(0)}{m}. \tag{8.1}$$

The equilibrium frequencies at the two selected loci are independent of the neutral locus andÅ, thus, the same as in the two-locus model treated above. The linkage disequilibria involving the neutral locus (D_k^{AN}, D_k^{NB}, and D_k^{ANB}) are zero at equilibrium. By (8.1), there is a one-dimensional manifold of equilibria resulting from the absence of selection at the neutral locus.

We assume that parameters are such that the fully polymorphic equilibrium F is admissible and globally asymptotically stable. Using the above order for the allele frequencies and linkage equilibria, the Jacobian at the equilibrium F has block structure,

$$J = \begin{pmatrix} J_S & 0 \\ 0 & J_N \end{pmatrix}, \tag{8.2}$$

where J_S is the Jacobian describing convergence of $(p_1, p_2, q_1, q_2, D_1^{\mathsf{AB}}, D_2^{\mathsf{AB}})$ to F, and J_N is the Jacobian describing convergence of $(n_1, n_2, D_1^{\mathsf{AN}}, D_2^{\mathsf{AN}}, D_1^{\mathsf{NB}}, D_2^{\mathsf{NB}}, D_1^{\mathsf{ANB}}, D_2^{\mathsf{ANB}})$ to $(\hat{n}, \hat{n}, 0, 0, 0, 0, 0, 0)$.

Because zero is the leading eigenvalue of J_N, the rate of convergence to equilibrium at the neutral locus is determined by the second largest eigenvalue of J_N, which we denote by λ_N. We define the effective (total) migration rate by $m_{\mathsf{eff}} = -\lambda_N$ (Bengtsson 1986, Kobayashi et al. 2008, Bürger and Akerman 2011). It can be checked that under weak migration, i.e., to leading order in m_1 and m_2, one obtains

$$m_{\mathsf{eff}} = -\lambda_N = m_1 \frac{\rho_{\mathsf{AN}}\rho_{\mathsf{NB}}}{(\rho_{\mathsf{AN}} + \alpha_1)(\rho_{\mathsf{NB}} + \beta_1)} + m_2 \frac{\rho_{\mathsf{AN}}\rho_{\mathsf{NB}}}{(\rho_{\mathsf{AN}} - \alpha_2)(\rho_{\mathsf{NB}} - \beta_2)} \tag{8.3}$$

(a *Mathematica* notebook is available on request). If the neutral site is linked only to one selected locus (e.g., because $\beta_1 = \beta_2 = 0$), then

$$m_{\mathsf{eff}} = m_1 \frac{\rho_{\mathsf{AN}}}{\rho_{\mathsf{AN}} + \alpha_1} + m_2 \frac{\rho_{\mathsf{AN}}}{\rho_{\mathsf{AN}} - \alpha_2} \tag{8.4}$$

is obtained. Thus, two linked selected loci act as a much stronger barrier to gene flow than a single selected locus, especially if the recombination rate between the two loci is not much larger than the selective coefficients. In Figure 9, the approximation (8.3) of the effective migration rate m_{eff} is displayed as a function of m for various parameter combinations and compared with the exact value obtained by numerical evaluation of λ_N.

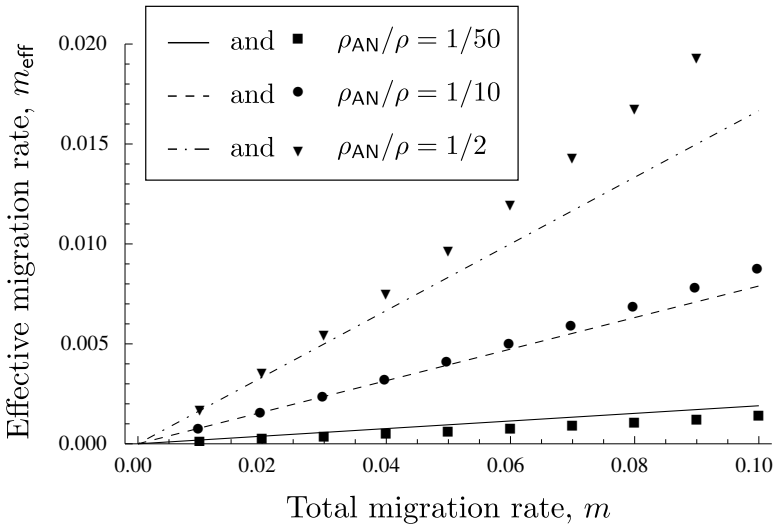

FIGURE 9. The effective migration rate m_{eff} as a function of m for $\alpha_1 = -\alpha_2 = 0.1$, $\beta_1 = -\beta_2 = 0.2$, $\phi = \frac{1}{2}$, and $\rho = 0.2$. Recall that $\rho = \rho_{\text{AN}} + \rho_{\text{NB}}$. Lines show the weak-migration approximation of m_{eff} (8.3). Symbols give the exact numerical value of $m_{\text{eff}} = -\lambda_N$.

We note that m_{eff} is (approximately) the sum of the two effective one-way migration rates (Bürger and Akerman 2011) and closely related to Kobayashi and Telschow's (2011) effective recombination rate. Our result complements their explicit example on two-locus incompatibilities. We refer to their paper for the discussion of the relation of this concept of an effective migration rate to that of Bengtsson (1985) and for applications in the context of speciation theory.

9. Discussion

The purpose of this investigation was to improve our understanding of how genetic architecture, in particular recombination and locus effects, as well as the pattern and amount of migration determine polymorphism, local adaptation, and differentiation in a subdivided population inhabiting a heterogeneous environment. For simplicity, we restricted attention to two linked, diallelic loci and to migration between two demes. The study of diversifying selection in just two demes may also shape our intuition about clinal variation if the two subpopulations are from different ends of the cline. If alleles are beneficial in only one environment and detrimental in the other, local adaptation of subpopulations and differentiation between them can be obtained only if a (multilocus) polymorphism is maintained. Therefore, most of our mathematical results focus on existence and stability of polymorphic equilibria and on the dependence of the equilibrium

configurations on the model parameters (migration rates, selection coefficients, recombination rate).

The model is introduced in Section 2. Sections 3 and 4 are devoted to the derivation of the possible equilibrium configurations and bifurcation patterns. They contain our main mathematical results. Explicit analytical results about existence and stability of equilibria were obtained for several limiting or special cases and are complemented by numerical work.

The conditions for admissibility of all single-locus polymorphisms (SLPs) are given in Section 3.1, those for asymptotic stability of the monomorphic equilibria (ME) in Proposition 3.1 in Section 3.2. The stability of SLPs could not generally be determined (Section 3.3). Weak migration is treated by perturbation methods in Section 3.4. For sufficiently weak migration, there exists a globally attracting fully polymorphic equilibrium, F (Proposition 3.2). Its approximate coordinates are given by (3.16).

The complete equilibrium and stability structure could be derived under the assumption of linkage equilibrium (Section 3.5). The unique, fully polymorphic equilibrium $\mathsf{F} = \mathsf{F}_\infty$ is admissible and globally attracting if and only if all four SLPs are admissible. Otherwise, one boundary equilibrium (SLP or ME) is globally asymptotically stable (Proposition 3.3). These results extend straightforwardly to an arbitrary number of diallelic loci. Based on these results, nonlinear perturbation theory establishes the existence of a globally stable, fully polymorphic equilibrium in a perturbed parameter range if recombination is sufficiently strong (Section 3.6). This equilibrium is in quasi-linkage equilibrium and given by (3.21).

Also for completely linked loci all equilibria and their local stability properties could be derived (Section 3.7). In this case, the fully polymorphic equilibrium F_0 (3.24) may lose stability while it is admissible (3.28). At this threshold a boundary equilibrium becomes stable by a 'jump bifurcation' (Proposition 3.4). In general, however, more complicated equilibrium patterns than determined by Propositions 3.3 and 3.4 can occur, in particular, multiple stable equilibria.

In Section 3.8, we apply perturbation theory to infer the equilibrium properties under highly asymmetric migration from those derived for the continent-island model in Bürger and Akerman (2011) and Bank et al. (2012). There, a stable (F) and an unstable fully polymorphic equilibrium may exist if recombination is intermediate, and F is simultaneously stable with a boundary equilibrium. In general (Section 3.11), we cannot exclude the existence of more than two internal equilibria or complicated dynamical behavior. Numerical searches produced no such instances. What can be shown easily is that, if $\rho < \infty$, any fully polymorphic equilibrium exhibits LD. In all cases, where

an internal equilibrium was calculated (numerically or analytically), it exhibited positive LD.

In the super-symmetric case, in which selection in deme 2 mirrors that in deme 1 and migration is symmetric, an assumption made in several applications, a fully polymorphic equilibrium exists always and, presumably, is stable (Section 3.10). This is a highly degenerate situation because if $\theta \neq 0$, only a monomorphic equilibrium can be stable for sufficiently large migration rates (Proposition 4.3). If $\theta = 0$ (Section 3.9), then a fully polymorphic equilibrium can exist for arbitrarily large migration rates if $\phi = \phi^{\mathsf{AB}}$ (see also Section 4.11).

Whereas in Section 3 the focus was on the efficient presentation of the existence and stability results of equilibria, in Section 4 these results are used to derive the possible bifurcation patterns with the total migration rate m as the bifurcation parameter. All possible bifurcation patterns could be derived under the assumption of LE (Theorem 4.4, Figures 2 and 3), and under the assumption of complete linkage (Theorem 4.6, Figures 4 and 5). The latter case is considerably more complex. Interestingly, in each case, every bifurcation pattern can occur for every ratio $\phi = m_1/m$ of migration rates by choosing the selection coefficients appropriately. Hence, the assumption of symmetric migration does not yield simpler equilibrium configurations than general migration if arbitrary selection coefficients are admitted.

In each of these cases (LE or $\rho = 0$), we determined the maximum migration rate $m_{\max}$ admitting an asymptotically stable, fully polymorphic equilibrium (Corollaries 4.5 and 4.7). The maximum migration rate $m^0_{\max}$ for $\rho = 0$ always exceeds or equals that ($m^\infty_{\max}$) for LE, i.e., $m^\infty_{\max} \leq m^0_{\max}$. Although for strong recombination, $m_{\max}$ can be very slightly smaller than $m^\infty_{\max}$ (Section 4.7), in the vast majority of investigated cases, $m_{\max}$ is bracketed by $m^\infty_{\max}$ and $m^0_{\max}$ (Figure 6, Section 4.11).

Proposition 4.3 demonstrates that a ME is globally attracting if migration is sufficiently strong (except in the degenerate case noted above). If we interpret the equilibria M_2 and M_3 as fixation of a generalist (A_1B_2 and A_2B_1 are haplotypes of intermediate fitness), and M_1 and M_4 as fixation of a specialist (A_1B_1 and A_2B_2 are the locally adapted haplotypes), then depending on the sign of θ one of the generalists becomes fixed for high m if ϕ is intermediate (i.e., $\phi^{\mathsf{A}} < \phi < \phi^{\mathsf{B}}$ if $\theta > 0$, $\phi^{\mathsf{B}} < \phi < \phi^{\mathsf{A}}$ if $\theta < 0$; but note that, depending on the selection coefficients, both ϕ^{A} and ϕ^{B} can be arbitrarily close to 0 or 1.). The critical value m as well as ϕ^{A} and ϕ^{B} are independent of ρ. Otherwise, one of the specialists becomes fixed for large m.

The fact that a generalist becomes fixed for strong migration is a distinct feature of (balanced) two-way migration: in the CI model or if migration is sufficiently asymmetric ($\phi < \phi^{\mathsf{A}}$ or $\phi > \phi^{\mathsf{B}}$ if $\theta > 0$), one of the specialist haplotypes swamps the populations

and becomes fixed. Another difference between highly asymmetric and more symmetric migration patterns is that in the first case, it is always the locus under weaker selection that first loses its polymorphism while m increases, whereas this not necessarily so in the latter case (see Section 4.2 and Theorem 4.6, cases A3 and A4).

In summary, we determined quantitatively when the following three evolutionarily stable states discussed by Kawecki and Ebert (2004) occur: (i) existence of a single specialist optimally adapted to one deme and poorly to the other, (ii) existence of a single generalist type which has higher average fitness in the whole population than than any of the specialists, and (iii) existence of a set of specialists each adapted to its deme, i.e., coexistence in a polymorphism. Local adaptation and differentiation occur only in case (iii).

In Section 5, we used the migration load in each deme to quantify the degree of local adaptation. In Section 6 we introduced a new multilocus version of F_{ST} to measure differentiation. If migration is weak, then local adaptation and differentiation decrease with increasing migration rate and increase with increasing linkage between the loci (Figure 7). In particular, for given (small) migration rate, local adaptation and differentiation are maximized if the fitness effects are concentrated on a single locus (corresponding to $\rho = 0$ in our model). However, as discussed in Section 5, for high migration rates, the migration load of the total population can decrease with increasing recombination or migration rate. Similarly, at high recombination and migration rates, F_{ST} can increase with increasing migration or recombination rate. Thus, for given, relatively high migration rate, F_{ST} may be minimized at intermediate recombination rates. Apparently, it is always maximized in the absence of recombination.

In Section 7, we investigated the conditions for invasion of locally beneficial mutants. At an isolated locus, such a mutant can invade and become established in a migration-selection equilibrium if and only if its advantage exceeds a threshold that increases with the immigration rate of the wild type; see (7.3b). If, however, this mutant occurs at a locus that is linked to a locus that is already in migration-selection balance, then its invasion is facilitated, i.e., its local selective advantage can be smaller (Figure 8b). Equivalently, for given selection coefficients and total migration rate, the minimum recombination rate needed for invasion increases if ϕ, or the influx of the (deleterious) wild type relative to the efflux of the new mutant, increases (Figure 8a). For the extreme case of one-way migration from a 'continental' population to an 'island' population that is adapting to a new environment, Bürger and Akerman (2011) proved that invasion of a locally beneficial mutant is always facilitated by increased linkage to a locus in migration-selection balance.

Thus, our results complement the numerical finding by Yeaman and Whitlock (2011) for a multilocus quantitative-genetic model that clusters of locally adaptive mutations, or concentrated genetic architectures, build up in spatially structured populations with opposing selection pressures in two demes. Because tighter linkage is required for invasion under increasingly asymmetric migration rates, more concentrated architectures and a greater advantage for recombination-reducing mechanisms (such as chromosome inversions) should be expected for highly asymmetric migration. In finite populations, invasion of new mutants occurs only with a certain probability, and genetic drift may erase polymorphism. Numerical work, supported by analytical methods, has already shed some light on the dependence of the probability of establishment of new, locally adaptive mutations on the recombination rate and other factors (Yeaman and Otto 2011, Feder et al. 2012). Analytical work on the role of genetic drift and finite population size on these issues is in progress.

Our results also show that, in the absence of epistasis and under the present form of balancing selection, reduced recombination between selected loci is favored, except when migration rates are sufficiently symmetric and high (Section 5). Selection inducing certain forms of epistasis may favor high recombination in structured populations more easily (Pylkov et al. 1998; Lenormand and Otto, 2000; Bank et al. 2012). Therefore, general predictions about the emergence of clusters of locally adaptive mutations in regions of reduced recombination, or of genomic islands of speciation (Wu and Ting 2004) or of differentiation (Feder et al. 2012), can not be made in the absence of detailed information about epistasis and the spatial pattern of selection and migration. At least in the absence of epistasis, the most favorable situation for the emergence of such clusters should occur in populations that are adapting to a new environment, still receiving maladaptive gene flow but sending out only very few or no migrants (corresponding to a continent-island model).

In Section 8, we derived the approximation (8.3) for the effective migration rate at a linked neutral locus that is located between the selected loci. This approximation is simply the sum of the two effective migration rates under one-way migration (Bürger and Akerman, 2011). Because in the present model, polymorphism at the selected loci is maintained by balancing selection, the effective migration rate may be greatly reduced compared with the actual migration rate (see Figure 9). Thus, strong barriers against gene flow may build up at such neutral sites and enhance (neutral) differentiation (see Charlesworth and Charlesworth 2010, Chap. 8.3). Future work will have to study the actual amount and pattern of neutral diversity at such sites in finite populations.

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A. Appendix

A.1. Sufficiency of the assumptions (2.3)**.** By relabeling alleles, we can assume without loss of generality (2.3a). Generically, one of the following nine parameter sets applies:

$$\theta > 0, \quad \alpha_1 < \beta_1, \quad \text{and} \quad \alpha_2 \geq \beta_2, \tag{A.1a}$$

$$\theta > 0, \quad \alpha_1 < \beta_1, \quad \text{and} \quad \alpha_2 < \beta_2, \tag{A.1b}$$

$$\theta > 0, \quad \alpha_1 \geq \beta_1, \quad \text{and} \quad \alpha_2 < \beta_2, \tag{A.1c}$$

$$\theta < 0, \quad \alpha_1 > \beta_1, \quad \text{and} \quad \alpha_2 \leq \beta_2, \tag{A.1d}$$

$$\theta < 0, \quad \alpha_1 > \beta_1, \quad \text{and} \quad \alpha_2 > \beta_2, \tag{A.1e}$$

$$\theta < 0, \quad \alpha_1 \leq \beta_1, \quad \text{and} \quad \alpha_2 > \beta_2. \tag{A.1f}$$

In addition, there are the following three parameter sets:

$$\theta = 0, \quad \alpha_1 < \beta_1 \quad \text{and} \quad \alpha_2 > \beta_2, \tag{A.1g}$$

$$\theta = 0, \quad \alpha_1 = \beta_1 \quad \text{and} \quad \alpha_2 = \beta_2, \tag{A.1h}$$

$$\theta = 0, \quad \alpha_1 > \beta_1 \quad \text{and} \quad \alpha_2 < \beta_2. \tag{A.1i}$$

The sets (A.1a) – (A.1i) yield the complete parameter space of the selection coefficients.

We show that the parameter sets (A.1c) – (A.1f) can be derived from (A.1a) and (A.1b) by simple transformations. Let f denote the exchange of loci, i.e., $f(\alpha_k) = \beta_k$ and $f(\beta_k) = \alpha_k$, and g the exchange of demes, i.e., $g(\alpha_k) = -\alpha_{k^*}$ and $g(\beta_k) = -\beta_{k^*}$. We observe that $\text{sign}(f(\theta)) = \text{sign}(g(\theta)) = -\text{sign}(\theta)$ and

$$\text{(A.1a)} \xrightarrow{f} \text{(A.1d)} \xrightarrow{g} \text{(A.1c)} \xrightarrow{f} \text{(A.1f)}, \tag{A.2a}$$

$$\text{(A.1b)} \xrightarrow{g} \text{(A.1e)} \tag{A.2b}$$

hold. Therefore, (2.3) is sufficient to describe the (generic) parameter region where $\theta \neq 0$. Since

$$\text{(A.1g)} \xrightarrow{f} \text{(A.1i)}, \tag{A.3}$$

(3.34) is sufficient to describe the degenerate cases $\theta = 0$.

A.2. Proof of Proposition 3.1. At each monomorphic equilibrium, the characteristic polynomial factors into three quadratic polynomials, $P(\lambda) = t_1(\lambda)t_2(\lambda)t_3(\lambda)$. Two of them, $t_1(\lambda)$ and $t_2(\lambda)$, determine stability with respect to the adjacent marginal one-locus systems. The corresponding conditions are already known from one-locus theory. The third, $t_3(\lambda)$, determines stability with respect to the interior of the state space.

In the following, we derive the stability conditions (3.10) and (3.11) for M_1. Those for M_4 can be deduced analogously or by symmetry considerations by taking into account that (2.3b) implies $\min\{\alpha_1,\beta_1\} = \alpha_1$. The stability analysis of M_2 and M_3 is much simpler and left to the reader.

For M_1, it is straightforward to show that

$$t_1(\lambda) = \lambda^2 + [\alpha_1(1+\sigma_1) + \alpha_2(1+\sigma_2)]\lambda + \alpha_1\alpha_2(1+\sigma_1+\sigma_2), \tag{A.4a}$$

$$t_2(\lambda) = \lambda^2 + [\beta_1(1+\tau_1) + \beta_2(1+\tau_2)]\lambda + \beta_1\beta_2(1+\tau_1+\tau_2), \tag{A.4b}$$

$$\begin{aligned} t_3(\lambda) = \lambda^2 &+ (\alpha_1+\alpha_2+\beta_1+\beta_2+2\rho+m_1+m_2)\lambda \\ &+ (\alpha_1+\beta_1+m_1+\rho)(\alpha_2+\beta_2+m_2+\rho) - m_1m_2. \end{aligned} \tag{A.4c}$$

Because $t_1''(\lambda) > 0$ for every λ, $t_1'(0) = \alpha_1(1+\sigma_1) + \alpha_2(1+\sigma_2) > 0$ if $\sigma_2 < -1$, $t_1(0) > 0$ if and only if $\sigma_1 + \sigma_2 < -1$, and $\min_\lambda\{t_1(\lambda)\} < 0$, we conclude that the two eigenvalues emanating from t_1 are negative if and only if

$$\sigma_1 + \sigma_2 < -1. \tag{A.5a}$$

Analogously, the two eigenvalues emanating from t_2 are negative if and only if

$$\tau_1 + \tau_2 < -1, \tag{A.5b}$$

and those originating from t_3 are negative if and only if

$$m_2 > -\frac{(\alpha_1+\beta_1+m_1+\rho)(\alpha_2+\beta_2+\rho)}{\alpha_1+\beta_1+\rho}. \tag{A.5c}$$

Conditions (A.5a) and (A.5b) yield (3.10).

Concerning (A.5c), we observe that it is always satisfied if $\rho > -(\alpha_2+\beta_2)$ because then the right-hand side is negative. Next we show, that (A.5c) is also satisfied if $\rho > -\alpha_2$. Because the right-hand side of (A.5c) is strictly monotone decreasing in ρ, it is sufficient to prove that (A.5c) holds if $\rho = -\alpha_2$. Then simple rearrangement of (A.5c) leads to the condition

$$\frac{m_2(\alpha_1+\beta_1-\alpha_2)}{\beta_1\beta_2} + \frac{\alpha_1+\beta_1-\alpha_2+m_1}{\beta_1} < 0, \tag{A.6}$$

which can be rewritten as

$$\tau_1 + \tau_2 + 1 + \frac{\alpha_1 - \alpha_2}{\beta_1}(1 + \tau_2) < 0. \tag{A.7}$$

This is satisfied if (A.5b) holds because this also implies $1+\tau_2 < 0$. One shows similarly that (A.5c) is satisfied if $\rho \geq -\beta_2$. Therefore, we have proved that M_1 is asymptotically stable if (3.10) and (3.11) hold.

A.3. Calculation of equilibria with two polymorphic loci if $\rho = 0$. As shown in the main text, by Corollary 3.9 of Nagylaki and Lou (2007) it is sufficient to assume that A_1B_2 is absent, which implies $D_k = p_k(1 - q_k)$ and $p_k \leq q_k$. Setting $\rho = 0$, we find from the equations $\dot{p}_1 = 0$ and $\dot{q}_1 = 0$ (2.7) that

$$p_2 = p_1[m_1 - \alpha_1(1 - p_1) - \beta_1(1 - q_1)]/m_1, \tag{A.8a}$$

$$q_2 = 1 - (1 - q_1)(m_1 + \alpha_1 p_1 + \beta_1 q_1)/m_1 \tag{A.8b}$$

holds at equilibrium. Substituting (A.8) into $\dot{p}_2$ and $\dot{q}_2$, we obtain at equilibrium,

$$0 = p_1[g_1(p_1, q_1) - \alpha_1^2\alpha_2 p_1^3 - \beta_1^2\beta_2 q_1^3]/m_1^2, \tag{A.9a}$$

$$0 = (1 - q_1)[g_2(p_1, q_1) - \alpha_1^2\alpha_2 p_1^3 - \beta_1^2\beta_2 q_1^3]/m_1^2, \tag{A.9b}$$

where g_1 and g_2 are quadratic polynomials in (p_1, q_1). The obvious substitution results in the equilibrium condition

$$\begin{aligned} 0 = {} & \alpha_1\alpha_2(\alpha_1 + \beta_1)p_1^2 + \beta_1\beta_2(\alpha_1 + \beta_1)q_1^2 + (\alpha_1 + \beta_1)(\alpha_1\beta_2 + \alpha_2\beta_1)p_1q_1 \\ & + [m_1(\alpha_1(2\alpha_2 + \beta_2) + \alpha_2\beta_1) - (\alpha_1 + \beta_1)(\alpha_2\beta_1 + \alpha_1(\alpha_2 + \beta_2))]p_1 \\ & + [m_1(\beta_2(\alpha_1 + 2\beta_2) + \alpha_2\beta_1) - \beta_1\beta_2(\alpha_1 + \beta_1)]q_1 \\ & + m_1[m_1(\alpha_2 + \beta_2) + m_2(\alpha_1 + \beta_1) - (\alpha_1 + \beta_1)(\alpha_2 + \beta_2)]. \end{aligned} \tag{A.10a}$$

It is easy to check that F_0 always fulfills this condition and it is the only solution satisfying $0 \leq p_1 = q_1 \leq 1$. Hence, unless there is curve (p_1, q_1) of solutions of (A.10) that passes through F_0 and through either a point on $p_1 = 0$ with $0 < q_1 \leq 1$ or on $q_1 = 1$ with $0 \leq p_1 < 1$, F_0 is the unique admissible solution of (A.10).

Because F_0 has an eigenvalue 0 only if either (3.26) is satisfied or if $|\kappa_1 + \kappa_2| = 1$ (which occurs if and only if F_0 collides with either M_1 or M_4), F_0 is the only equilibrium with both loci polymorphic, except when (3.26) is satisfied. In the latter case, a line of equilibria exists, as we show now.

We calculate m_2 from (3.26) and substitute into (A.10). The right-hand side factorizes into two linear terms. Only one of them gives rise to admissible equilibria and, in

fact, yields the manifold:

$$p_1 = \frac{\theta[\beta_1(1-q_1) - m_1] - \alpha_1\beta_1(\alpha_2+\beta_2)}{\alpha_1\theta}, \tag{A.11}$$

where $0 \le q_1 \le 1$. The allele frequencies in the other deme are obtained from (A.8). It is straightforward to check that not only F_0, but also the equilibria $\mathsf{P}_{\mathsf{A},1}$ and $\mathsf{P}_{\mathsf{B},2}$ lie on this manifold. In terms of the gamete frequencies, this manifold is a straight line.

A.4. Stability of F_0. In this section we derive the stability of F_0.

As A_1B_2 is lost if $\rho = 0$ and (2.3) hold, it is sufficient to consider the dynamics (2.5) in $S_3 \times S_3$. In this case, the characteristic polynomial at F_0 factors into two quadratic polynomials, $P(\lambda) = t_1(\lambda)t_2(\lambda)$. These are given by

$$\begin{aligned} t_1(\lambda) =& \lambda^2 + \left[(\alpha_1+\beta_1-\alpha_2-\beta_2)\sqrt{1-\kappa_1\kappa_2} - (m_1+m_2)\right]\lambda \\ &+ (\alpha_1+\beta_1)(\alpha_2+\beta_2)\left[1+(\kappa_1-\kappa_2)\sqrt{1-\kappa_1\kappa_2}\right], \end{aligned} \tag{A.12a}$$

$$\begin{aligned} t_2(\lambda) =& \lambda^2 + \frac{1}{2}\left[\alpha_1+\alpha_2-\beta_1-\beta_2+(\alpha_1-\alpha_2+\beta_1-\beta_2)\sqrt{1-\kappa_1\kappa_2}\right]\lambda \\ &+ \frac{1}{2}\left[-\alpha_1\beta_2(1+\sqrt{1-\kappa_1\kappa_2}) - \alpha_2\beta_1(1-\sqrt{1-\kappa_1\kappa_2})\right]. \end{aligned} \tag{A.12b}$$

The polynomial t_1 determines the stability with respect to the (effectively one-locus) system where only 'alleles' A_1B_1 and A_2B_2 are present. It is convex with $t_1(0) \ge 0$ if and only if $|\kappa_1 + \kappa_2| \le 1$ (where the equalities correspond), i.e., whenever F_0 is admissible, cf. (3.23). If $|\kappa_1+\kappa_2| < 1$, $t_1'(0) > 0$ and t_1 attains a negative value at its minimum (as can be shown easily). Therefore, all eigenvalues emanating from t_1 are real and negative whenever F_0 is admissible.

The polynomial t_2 determines stability with respect to the interior of $S_3 \times S_3$. It is convex and attains its minimum at

$$\lambda_{\min} = \frac{1}{4}\left[(\alpha_1+\beta_2-\alpha_2-\beta_2)(1-\sqrt{1-\kappa_1\kappa_2})\right] \tag{A.13}$$

where $\lambda_{\min} < 0$ by (2.3a) and (3.22). As $t_2(\lambda_{\min}) < 0$, the eigenvalues emanating from t_2 are real. As

$$t_2(0) \ge 0 \iff m_1m_2 \le \tilde{m}, \tag{A.14}$$

where the equalities correspond and $\tilde{m}$ is defined in (3.27), and because $t_2'(0) > 0$, we conclude that the two eigenvalues emanating from t_2 are negative if and only if (3.28) holds.

A.5. Stability of SLPs under $\rho = 0$. For $\rho = 0$ it is sufficient to study the dynamics (2.5) in $S_3 \times S_3$. SLPs where $\hat{x}_{k,2} > 0$ ($k = 1, 2$), i.e., $\mathsf{P}_{\mathsf{A},2}$ and $\mathsf{P}_{\mathsf{B},1}$, are unstable. It remains to study the stability of $\mathsf{P}_{\mathsf{A},1}$ and $\mathsf{P}_{\mathsf{B},2}$.

We present the analysis for $\mathsf{P}_{\mathsf{A},1}$ in detail, as results for $\mathsf{P}_{\mathsf{B},2}$ follow analogously.

At $\mathsf{P}_{\mathsf{A},1}$ the characteristic polynomial factors into two quadratic polynomials, $P(\lambda) = t_1(\lambda)t_2(\lambda)$, given by

$$\begin{aligned} t_1(\lambda) =& \lambda^2 + \left[\alpha_1(\sqrt{1-4\sigma_1\sigma_2} - \sigma_1) - \alpha_2(\sqrt{1-4\sigma_1\sigma_2} + \sigma_2)\right]\lambda \\ &+ \alpha_1\alpha_2\left[(\sigma_1 - \sigma_2)\sqrt{1-4\sigma_1\sigma_2} - (1-4\sigma_1\sigma_2)\right], \end{aligned} \tag{A.15a}$$

$$\begin{aligned} t_2(\lambda) =& \lambda^2 + \frac{1}{2}\left[2\beta_1 + 2\beta_2 + \alpha_1(1 - \sqrt{1-4\sigma_1\sigma_2}) + \alpha_1(1 + \sqrt{1-4\sigma_1\sigma_2})\right]\lambda \\ &+ \frac{1}{2}\left[\beta_1(\beta_2+\alpha_2) + \beta_2(\alpha_1+\beta_1) + \theta\sqrt{1-\sigma_1\sigma_2}\right]. \end{aligned} \tag{A.15b}$$

t_1 determines stability with respect to the one-locus system where B_1 is fixed. $t_1(0) = 0$ if and only if $|\sigma_1 + \sigma_2| = 1$, i.e., whenever $\mathsf{P}_{\mathsf{A},1}$ collides with a ME according to (3.9a) and (3.9b). Whenever $|\sigma_1 + \sigma_2| < 1$, i.e., $\mathsf{P}_{\mathsf{A},1}$ is admissible (3.7), $t_1(0) > 0$ and $t_1'(0) > 0$. As $t_1''(\lambda) > 0$ for every λ, t_1 attains a minimum, where it is straightforward to show that t_1 takes a negative value at its minimum. Thus, all eigenvalues emanating from t_1 are real and negative whenever $\mathsf{P}_{\mathsf{A},1}$ is admissible.

t_2 determines stability with respect to the interior of $S_3 \times S_3$. $t_2(0) \geq 0$, if and only if $m_1m_2 \geq \tilde{m}$, cf. (3.27), where the equalities correspond. Whenever $m_1m_2 > \tilde{m}$, $t_2'(0) > 0$. As $t_2''(\lambda) > 0$ for every λ, t_2 attains a minimum, where it is straightforward to show that t_2 takes a negative value at its minimum. Thus, all eigenvalues emanating from t_1 are real and negative whenever $m_1m_2 > \tilde{m}$ holds. Otherwise, at least one eigenvalue is positive.

Combining the results obtained for t_1 and t_2 it follows that $\mathsf{P}_{\mathsf{A},1}$ is asymptotically stable if and only if

$$-1 < \sigma_1 + \sigma_2 < 1 \text{ and } m_1m_2 > \tilde{m} \tag{A.16}$$

hold. We note that $m_1m_2 > \tilde{m}$ is equivalent to $(\sigma_1\tau_2 - \sigma_2\tau_1)^2 < -(\sigma_1+\tau_1)(\sigma_2+\tau_2)$, and our general assumption (2.3) implies $\tau_1 < \sigma_1$ and $\sigma_1\tau_2 - \sigma_2\tau_1 < 0$. Using these relations we can show with the help of *Mathematica* that (A.16) is incompatible with $-1 < \tau_1 + \tau_2$. Consequently, $\mathsf{P}_{\mathsf{B},2}$ is not admissible if $\mathsf{P}_{\mathsf{A},1}$ is asymptotically stable.

A.6. The super-symmetric case. We prove that in the super-symmetric case of Section 3.10, all SLPs are unstable.

We assume symmetric migration rates ($m_1 = m_2 = m$), equivalent loci ($\alpha_k = \beta_k = a$), and selection in deme 2 mirrors that in deme 1 ($\alpha_k = -\alpha_{k^*}$). Thus, $\theta = 0$. Equilibria may collide (thus leave or enter the state space) if and only if at least one of their eigenvalues is zero. Eigenvalues are zeros of the characteristic polynomial, which has the form $P(\lambda) = c_6\lambda^6 + \cdots + c_1\lambda + c_0$. If zero is an eigenvalue at an equilibrium, i.e., $P(0) = 0$, the constant term c_0 must vanish. In the super-symmetric case every characteristic polynomials at an

SLP has the same constant term

$$c_0 = -a^2\rho\left(2a^2\sqrt{a^2+m^2} + m(3m-\rho)\sqrt{a^2+m^2} - (a^2+m^2)(3m-\rho)\right). \tag{A.17}$$

One can show that $c_0 = 0$ is impossible if $m > 0$.

A.7. Important quantities and relations. The following section complements Section 4.1. Here, we derive all relations of ϕ^{X} (4.2) and m^{X} (4.3) needed in Sections 4.2 to 4.8 and in the proofs of the theorems there.

Using (4.9a), (4.9b), (4.5a), (4.5b), (4.12) and (4.13), we derive all possible inequalities between m^{A} and m^{B}:

$$0 < m^{\mathsf{A}} < m^{\mathsf{B}} \iff \phi^{\mathsf{B}} \le \phi, \tag{A.18a}$$

$$0 < -m^{\mathsf{A}} < -m^{\mathsf{B}} \iff \alpha_2 > \beta_2 \text{ and } \phi < \tilde{\phi}^{\mathsf{AB}}, \tag{A.18b}$$

$$0 < -m^{\mathsf{B}} < -m^{\mathsf{A}} \iff \begin{cases} \alpha_2 \le \beta_2 \text{ and } \phi < \phi^{\mathsf{A}}, \text{ or} \\ \alpha_2 > \beta_2 \text{ and } \tilde{\phi}^{\mathsf{AB}} < \phi < \phi^{\mathsf{A}}, \end{cases} \tag{A.18c}$$

$$0 < -m^{\mathsf{B}} < m^{\mathsf{A}} \iff \phi^{\mathsf{A}} \le \phi < \phi^{\mathsf{AB}}, \tag{A.18d}$$

$$0 < m^{\mathsf{A}} < -m^{\mathsf{B}} \iff \phi^{\mathsf{AB}} < \phi < \phi^{\mathsf{B}}, \tag{A.18e}$$

where

$$0 < m^{\mathsf{B}} \le m^{\mathsf{A}},\ 0 < -m^{\mathsf{A}} \le m^{\mathsf{B}}, \text{ and } 0 < m^{\mathsf{B}} \le -m^{\mathsf{A}} \text{ are infeasible.} \tag{A.18f}$$

Using (4.6), (4.5), and (4.12)-(4.15) we obtain the following inequalities for m^*:

$$0 < m^* < -m^{\mathsf{F}_0} \iff \phi^{\mathsf{M}_1}(\rho = 0) < \phi < \phi^{\mathsf{F}_0}, \tag{A.19a}$$

$$0 < -m^{\mathsf{F}_0} < m^* \iff \phi < \phi^{\mathsf{M}_1}(\rho = 0), \tag{A.19b}$$

$$0 < m^* < m^{\mathsf{F}_0} \iff \phi^{\mathsf{F}_0} < \phi < \phi^{\mathsf{M}_4}(\rho = 0), \tag{A.19c}$$

$$0 < m^{\mathsf{F}_0} < m^* \iff \phi^{\mathsf{M}_4}(\rho = 0) < \phi, \tag{A.19d}$$

$$0 < m^* < -m^{\mathsf{A}} \iff \phi^{\mathsf{M}_1}(\rho = 0) < \phi < \phi^{\mathsf{A}}, \tag{A.19e}$$

$$0 < m^* < -m^{\mathsf{B}} \iff \phi^{\mathsf{AB}} < \phi < \phi^{\mathsf{B}}, \tag{A.19f}$$

$$0 < m^* < m^{\mathsf{A}} \iff \phi^{\mathsf{A}} < \phi < \phi^{\mathsf{AB}}, \tag{A.19g}$$

$$0 < m^* < m^{\mathsf{B}} \iff \phi^{\mathsf{B}} < \phi < \phi^{\mathsf{M}_4}(\rho = 0), \tag{A.19h}$$

$$0 < -m^{\mathsf{A}} < m^* \iff \phi < \phi^{\mathsf{M}_4}(\rho = 0), \tag{A.19i}$$

$$0 < -m^{\mathsf{B}} < m^* \iff \phi < \phi^{\mathsf{AB}}, \tag{A.19j}$$

$$0 < m^{\mathsf{A}} < m^* \iff \phi^{\mathsf{AB}} < \phi, \tag{A.19k}$$

$$0 < m^{\mathsf{B}} < m^* \iff \phi^{\mathsf{M}_4}(\rho = 0) < \phi. \tag{A.19l}$$

From (4.12), (4.13), (A.18), and (A.19e) – (A.19l) we infer

$$\min\{|m^{\mathsf{A}}|, |m^{\mathsf{B}}|\} \leq m^{*}. \tag{A.20}$$

Next, we derive the relations between m^{F_0} and m^{A} or m^{B} needed in the proof of Theorem 4.6. As their derivation is lengthy, the reader may wish to skip the proof and go immediately to the results given by (A.37) and (A.38).

Our approach to derive the possible relations between m^{F_0} and m^{A} or m^{B} is as follows: First, we derive all relevant relations of ϕ^{X} (4.2) for arbitrary recombination ρ. We use these relations to determine the required relations between m^{A}, m^{B}, m^{M_1} and m^{M_4} for arbitrary ρ. By setting $\rho = 0$ in the results obtained and by the equivalence given in (4.10), the possible relations between m^{F_0} and m^{A} or m^{B} follow immediately.

By definition, the values ϕ^{A}, ϕ^{B}, ϕ^{F_0}, $\tilde{\phi}^{\mathsf{AB}}$, ϕ^{AB}, ϕ^{AF_0}, and ϕ^{BF_0} (4.2) are independent of the recombination rate ρ. Their relations under (2.3) are given in (4.12), (4.13), and (4.14).

The values ϕ^{M_1}, $\tilde{\phi}^{\mathsf{M}_1}$, ϕ^{M_4}, and $\tilde{\phi}^{\mathsf{M}_4}$ (4.2) depend on ρ, and we analyze this dependence in the following. The conditions which determine the admissibility of ϕ^{M_i} and $\tilde{\phi}^{\mathsf{M}_i}$ ($i = 1, 4$) are:

$$0 < \phi^{\mathsf{M}_1} < 1 \iff 0 \leq \rho < -\beta_2 \text{ or } \rho > -\alpha_2 - \beta_2, \tag{A.21a}$$

$$0 < \tilde{\phi}^{\mathsf{M}_1} < 1 \iff 0 \leq \rho < -\alpha_2 \text{ or } \rho > -\alpha_2 - \beta_2, \tag{A.21b}$$

$$0 < \phi^{\mathsf{M}_4} < 1 \iff 0 \leq \rho < \alpha_1 \text{ or } \rho > \alpha_1 + \beta_1, \tag{A.21c}$$

$$0 < \tilde{\phi}^{\mathsf{M}_4} < 1 \iff 0 \leq \rho < \beta_1 \text{ or } \rho > \alpha_2 + \beta_2, \tag{A.21d}$$

with the relations

$$0 \leq \rho < -\beta_2 \implies 0 < \phi^{\mathsf{M}_1} < \phi^{\mathsf{A}}, \tag{A.22a}$$

$$0 \leq \rho < \alpha_1 \implies \phi^{\mathsf{B}} < \phi^{\mathsf{M}_4} < 1. \tag{A.22b}$$

To determine further relations of ϕ^{M_1}, $\tilde{\phi}^{\mathsf{M}_1}$, ϕ^{M_4}, and $\tilde{\phi}^{\mathsf{M}_4}$, we define the following critical recombination rates:

$$\begin{aligned}\rho^{\mathsf{M}_1} = {} & \frac{\alpha_2\beta_1(\alpha_2+\beta_1) - \alpha_1\beta_2(\alpha_1+\beta_2)}{2\theta} \\ & + \frac{\sqrt{(\alpha_2\beta_1(\alpha_2+\beta_1) - \alpha_1\beta_2(\alpha_1+\beta_2))^2 - 4\theta^2(\alpha_2\beta_1+\alpha_1\beta_2)}}{2\theta},\end{aligned} \tag{A.23a}$$

$$\begin{aligned}\tilde{\rho}^{\mathsf{M}_1} = {} & \frac{-\theta(\alpha_1+\alpha_2) + \alpha_2\beta_1^2 - \alpha_1\beta_2^2}{2\theta} \\ & + \frac{\sqrt{(-\theta(\alpha_1+\alpha_2) + \alpha_2\beta_1^2 - \alpha_1\beta_2^2)^2 - 4\theta^2(\alpha_2\beta_1+\alpha_1(\alpha_2+\beta_2))}}{2\theta},\end{aligned} \tag{A.23b}$$

$$\rho^{\mathsf{M}_4} = \frac{\alpha_1\beta_2(\alpha_1+\beta_2)-\alpha_2\beta_1(\alpha_2+\beta_1)}{2\theta} + \frac{\sqrt{(\alpha_1\beta_2(\alpha_1+\beta_2)-\alpha_2\beta_1(\alpha_2+\beta_1))^2-4\theta^2(\alpha_2\beta_1+\alpha_1\beta_2)}}{2\theta}, \tag{A.23c}$$

$$\tilde{\rho}^{\mathsf{M}_4} = \frac{\theta(\beta_1+\beta_2)+\alpha_1^2\beta_2-\alpha_2^2\beta_1}{2\theta} + \frac{\sqrt{(-\theta(\beta_1+\beta_2)+\alpha_2^2\beta_1-\alpha_1^2\beta_2)^2-4\theta^2(\alpha_2\beta_1+\beta_2(\alpha_1+\beta_1))}}{2\theta}. \tag{A.23d}$$

Next, we determine the admissibility of ρ^{X} and $\tilde{\rho}^{X}$ defined in (A.23). Therefore, we partition the selection parameters satisfying (2.3) and $\beta_2 > \alpha_2$ according to

$$\beta_2 > \alpha_2 + \frac{\alpha_1\beta_2(\beta_2-\alpha_1)}{\beta_1(\alpha_1+\beta_1-\beta_2)} > \alpha_2 \tag{A.24a}$$

and

$$\alpha_2 + \frac{\alpha_1\beta_2(\beta_2-\alpha_1)}{\beta_1(\alpha_1+\beta_1-\beta_2)} > \beta_2 > \alpha_2. \tag{A.24b}$$

Analogously, the selection parameters satisfying (2.3) and $\beta_1 > \alpha_1$ can be partitioned according to

$$\beta_1 > \alpha_1 + \frac{\alpha_1\alpha_2(\alpha_1-\alpha_2)}{\beta_2(\alpha_1-\alpha_2-\beta_2)} > \alpha_1 \tag{A.25a}$$

and

$$\alpha_1 + \frac{\alpha_1\alpha_2(\alpha_1-\alpha_2)}{\beta_2(\alpha_1-\alpha_2-\beta_2)} > \beta_1 > \alpha_1. \tag{A.25b}$$

Using these partitions, we obtain that ρ^{X} and $\tilde{\rho}^{X}$ satisfy the following relations (as can be checked with *Mathematica*):

$$\tilde{\rho}^{\mathsf{M}_1} < \rho^{\mathsf{M}_1} < -\alpha_2 < -\beta_2 \iff \beta_2 < \alpha_2, \tag{A.26a}$$

$$\tilde{\rho}^{\mathsf{M}_1} < \rho^{\mathsf{M}_1} = -\alpha_2 = -\beta_2 \iff \beta_2 = \alpha_2, \tag{A.26b}$$

$$-\beta_2 < \tilde{\rho}^{\mathsf{M}_1} < -\alpha_2 < \rho^{\mathsf{M}_1} < -\alpha_2-\beta_2 \iff \text{(A.24a) holds}, \tag{A.26c}$$

$$\tilde{\rho}^{\mathsf{M}_1} < -\beta_2 < -\alpha_2 < \rho^{\mathsf{M}_1} < -\alpha_2-\beta_2 \iff \text{(A.24b) holds}, \tag{A.26d}$$

$$\alpha_1 < \tilde{\rho}^{\mathsf{M}_4} < \beta_1 < \rho^{\mathsf{M}_4} < \alpha_1+\beta_1 \iff \text{(A.25a) holds}, \tag{A.26e}$$

$$\tilde{\rho}^{\mathsf{M}_4} < \alpha_1 < \beta_1 < \rho^{\mathsf{M}_4} < \alpha_1+\beta_1 \iff \text{(A.25b) holds}. \tag{A.26f}$$

As $\rho \geq 0$ and (2.3) hold, we obtain that

$$\phi^{\mathsf{M}_1} = \tilde{\phi}^{\mathsf{M}_1} \iff \rho = -\alpha_2-\beta_2 \text{ or } \rho = \rho^{\mathsf{M}_1}, \tag{A.27a}$$

$$\tilde{\phi}^{\mathsf{AB}} = \phi^{\mathsf{M}_1} \iff \tilde{\phi}^{\mathsf{AB}} = \tilde{\phi}^{\mathsf{M}_1} \iff \rho = \rho^{\mathsf{M}_1}, \tag{A.27b}$$

$$\phi^{\mathsf{A}} = \tilde{\phi}^{\mathsf{M}_1} \iff \rho = \tilde{\rho}^{\mathsf{M}_1}, \tag{A.27c}$$

and

$$\phi^{\mathsf{M}_4} = \tilde{\phi}^{\mathsf{M}_4} \iff \rho = \alpha_1 + \beta_1 \text{ or } \rho = \rho^{\mathsf{M}_4}, \tag{A.28a}$$

$$\phi^{\mathsf{B}} = \tilde{\phi}^{\mathsf{M}_4} \iff \rho = \tilde{\rho}^{\mathsf{M}_4}, \tag{A.28b}$$

where

$$\phi^{\mathsf{A}} = \phi^{\mathsf{M}_1} \text{ and } \phi^{\mathsf{B}} = \phi^{\mathsf{M}_4} \text{ are infeasible.} \tag{A.28c}$$

We derive the following relations additinal to (A.22a) and (A.22b), using (A.26) and (A.27):

$$0 < \tilde{\phi}^{\mathsf{M}_1} < \phi^{\mathsf{A}} \iff \tilde{\rho}^{\mathsf{M}_1} < \rho < -\alpha_2, \tag{A.29a}$$

$$\phi^{\mathsf{A}} < \tilde{\phi}^{\mathsf{M}_1} < 1 \impliedby 0 \le \rho < \tilde{\rho}^{\mathsf{M}_1}, \tag{A.29b}$$

and

$$\phi^{\mathsf{B}} < \tilde{\phi}^{\mathsf{M}_4} < 1 \iff \tilde{\rho}^{\mathsf{M}_4} < \rho < \beta_1, \tag{A.30a}$$

$$0 < \tilde{\phi}^{\mathsf{M}_4} < \phi^{\mathsf{B}} \impliedby 0 \le \rho < \tilde{\rho}^{\mathsf{M}_4}, \tag{A.30b}$$

and by recalling (4.13):

$$\tilde{\phi}^{\mathsf{AB}} < \phi^{\mathsf{M}_1} < \phi^{\mathsf{A}} \iff \beta_2 < \alpha_2 \text{ and } 0 \le \rho < \rho^{\mathsf{M}_1}, \tag{A.31a}$$

$$0 < \phi^{\mathsf{M}_1} < \tilde{\phi}^{\mathsf{AB}} \iff \beta_2 < \alpha_2 \text{ and } \rho^{\mathsf{M}_1} < \rho < -\alpha_2. \tag{A.31b}$$

Now we derived all relations between ϕ^X necessary to deduce the relevant relations between m^{M_1} (m^{M_4}) and m^{A}, m^{B}.

First, we note that under (2.3), $m^{\mathsf{M}_1} > 0$ if $\phi < \phi^{\mathsf{A}}$ and $m^{\mathsf{M}_4} > 0$ if $\phi^{\mathsf{B}} < \phi$.

In the following, we derive all possible relations between m^{A}, m^{B}, and m^{M_1} where we assume that $\phi < \phi^{\mathsf{A}}$ (otherwise M_1 is unstable, cf. Proposition 4.1, and m^{M_1} is not of particular interest). By (4.5a), (4.5b), (4.12), (4.13), (A.22a), (A.27), (A.29), and (A.31), we obtain that

$$0 < -m^{\mathsf{B}} < -m^{\mathsf{A}} < m^{\mathsf{M}_1} \iff \begin{cases} \beta_2 < \alpha_2 \text{ and } \rho < \rho^{\mathsf{M}_1} \text{ and } \tilde{\phi}^{\mathsf{AB}} < \phi < \phi^{\mathsf{M}_1}, \text{ or} \\ \beta_2 \ge \alpha_2 \text{ and } \rho < -\beta_2 \text{ and } \phi < \phi^{\mathsf{M}_1}, \end{cases} \tag{A.32a}$$

$$0 < -m^{\mathsf{A}} < -m^{\mathsf{B}} < m^{\mathsf{M}_1} \iff \beta_2 < \alpha_2 \text{ and } \begin{cases} \rho < \rho^{\mathsf{M}_1} \text{ and } \phi < \tilde{\phi}^{\mathsf{AB}}, \text{or} \\ \rho^{\mathsf{M}_1} < \rho < -\alpha_2 \text{ and } \phi < \tilde{\phi}^{\mathsf{M}_1}, \end{cases} \tag{A.32b}$$

$$0 < -m^{\mathsf{A}} = -m^{\mathsf{B}} < m^{\mathsf{M}_1} \iff \beta_2 < \alpha_2 \text{ and } \rho < \rho^{\mathsf{M}_1} \text{ and } \phi = \tilde{\phi}^{\mathsf{AB}}, \tag{A.32c}$$

and

$$0 < -m^{\mathsf{B}} < m^{\mathsf{M}_1} < -m^{\mathsf{A}} \iff$$

$$\begin{cases} \beta_2 \le \alpha_2 \text{ and } \rho < \tilde{\rho}^{\mathsf{M}_1} \text{ and } \phi^{\mathsf{M}_1} < \phi < \phi^{\mathsf{A}}, \text{or} \\ \beta_2 \le \alpha_2 \text{ and } \tilde{\rho}^{\mathsf{M}_1} < \rho < \rho^{\mathsf{M}_1} \text{ and } \phi^{\mathsf{M}_1} < \phi < \tilde{\phi}^{\mathsf{M}_1}, \text{or} \\ \text{(A.24a) and } \rho < -\beta_2 \text{ and } \phi^{\mathsf{M}_1} < \phi < \phi^{\mathsf{A}}, \text{or} \\ \text{(A.24a) and } -\beta_2 < \rho < \tilde{\phi}^{\mathsf{M}_1} \text{ and } \phi < \phi^{\mathsf{A}}, \text{or} \\ \text{(A.24a) and } \tilde{\rho}^{\mathsf{M}_1} < \rho < -\alpha_2 \text{ and } \phi < \tilde{\phi}^{\mathsf{M}_1}, \text{or} \\ \text{(A.24b) and } \rho < \tilde{\rho}^{\mathsf{M}_1} \text{ and } \phi^{\mathsf{M}_1} < \phi < \phi^{\mathsf{A}}, \text{or} \\ \text{(A.24b) and } \tilde{\rho}^{\mathsf{M}_1} < \rho < -\beta_2 \text{ and } \phi^{\mathsf{M}_1} < \phi < \tilde{\phi}^{\mathsf{M}_1}, \text{or} \\ \text{(A.24b) and } -\beta_2 < \rho < -\alpha_2 \text{ and } \phi < \tilde{\phi}^{\mathsf{M}_1}, \end{cases} \tag{A.33a}$$

$$0 < -m^{\mathsf{A}} < m^{\mathsf{M}_1} < -m^{\mathsf{B}} \iff$$

$$\beta_2 < \alpha_2 \text{ and } \begin{cases} \rho^{\mathsf{M}_1} < \rho < -\alpha_2 \text{ and } \tilde{\phi}^{\mathsf{M}_1} < \phi < \phi^{\mathsf{M}_1}, \text{or} \\ -\alpha_2 < \rho < -\beta_2 \text{ and } \phi < \phi^{\mathsf{M}_1}, \end{cases} \tag{A.33b}$$

$$0 < m^{\mathsf{M}_1} < -m^{\mathsf{B}} < -m^{\mathsf{A}} \iff$$

$$\begin{cases} \beta_2 < \alpha_2 \text{ and } \tilde{\rho}^{\mathsf{M}_1} < \rho < \rho^{\mathsf{M}_1} \text{ and } \tilde{\phi}^{\mathsf{M}_1} < \phi < \phi^{\mathsf{A}}, \text{or} \\ \beta_2 < \alpha_2 \text{ and } \rho^{\mathsf{M}_1} < \rho \text{ and } \tilde{\phi}^{\mathsf{AB}} < \phi < \phi^{\mathsf{A}}, \text{or} \\ \beta_2 \ge \alpha_2 \text{ and } \tilde{\rho}^{\mathsf{M}_1} < \rho < -\beta_2 \text{ and } \tilde{\phi}^{\mathsf{M}_1} < \phi < \phi^{\mathsf{A}}, \text{or} \\ \beta_2 \ge \alpha_2 \text{ and } -\beta_2 < \rho \text{ and } \phi < \phi^{\mathsf{A}}, \text{or} \end{cases} \tag{A.33c}$$

$$0 < m^{\mathsf{M}_1} < -m^{\mathsf{A}} < -m^{\mathsf{B}} \iff$$

$$\beta_2 < \alpha_2 \text{ and } \begin{cases} \rho^{\mathsf{M}_1} < \rho < -\beta_2 \text{ and } \phi^{\mathsf{M}_1} < \phi < \tilde{\phi}^{\mathsf{AB}}, \text{or} \\ -\beta_2 < \rho \text{ and } \phi < \tilde{\phi}^{\mathsf{AB}}. \end{cases} \tag{A.33d}$$

From (A.18f) it follows that

$$0 < -m^{\mathsf{A}} < -m^{\mathsf{B}} < m^{\mathsf{M}_1} \text{ occurs never if } \beta_2 \ge \alpha_2, \tag{A.34a}$$

$$0 < -m^{\mathsf{A}} < m^{\mathsf{M}_1} < -m^{\mathsf{B}} \text{ occurs never if } \beta_2 \ge \alpha_2, \tag{A.34b}$$

$$0 < m^{\mathsf{M}_1} < -m^{\mathsf{A}} < -m^{\mathsf{B}} \text{ occurs never if } \beta_2 \ge \alpha_2. \tag{A.34c}$$

To derive all possible relations between m^{A}, m^{B}, and m^{M_4} we assume $\phi > \phi^{\mathsf{B}}$ (cf. Proposition 4.1). By (4.5a), (4.5b), (4.12), (4.13), (A.22b), (A.28), and (A.30), we obtain that

$$0 < m^{\mathsf{A}} < m^{\mathsf{B}} < m^{\mathsf{M}_4} \iff \rho < \alpha_1 \text{ and } \phi^{\mathsf{M}_4} < \phi, \tag{A.35a}$$

$$0 < m^{\mathsf{A}} < m^{\mathsf{M}_4} < m^{\mathsf{B}} \iff$$

$$\begin{cases} \text{(A.25a) and } \rho < \alpha_1 \text{ and } \phi^{\mathsf{B}} < \phi < \phi^{\mathsf{M}_4}, \text{or} \\ \text{(A.25a) and } \alpha_1 < \rho < \tilde{\rho}^{\mathsf{M}_4} \text{ and } \phi^{\mathsf{B}} < \phi, \text{or} \\ \text{(A.25a) and } \tilde{\rho}^{\mathsf{M}_4} < \rho < \beta_1 \text{ and } \tilde{\phi}^{\mathsf{M}_4} < \phi, \text{or} \\ \text{(A.25b) and } \rho < \tilde{\rho}^{\mathsf{M}_4} \text{ and } \phi^{\mathsf{B}} < \phi < \phi^{\mathsf{M}_4}, \text{or} \\ \text{(A.25b) and } \tilde{\rho}^{\mathsf{M}_4} < \rho < \alpha_1 \text{ and } \tilde{\phi}^{\mathsf{M}_4} < \phi < \phi^{\mathsf{M}_4}, \text{or} \\ \text{(A.25b) and } \alpha_1 < \rho < \beta_1 \text{ and } \tilde{\phi}^{\mathsf{M}_4} < \phi, \end{cases} \tag{A.35b}$$

$$0 < m^{\mathsf{M}_4} < m^{\mathsf{A}} < m^{\mathsf{B}} \iff$$

$$\begin{cases} \tilde{\rho}^{\mathsf{M}_4} < \rho < \beta_1 \text{ and } \phi^{\mathsf{B}} < \phi < \tilde{\phi}^{\mathsf{M}_4}, \text{or} \\ \beta_1 < \rho \text{ and } \phi^{\mathsf{B}} < \phi. \end{cases} \tag{A.35c}$$

From (A.18f) it follows that

$$0 < m^{\mathsf{B}} < m^{\mathsf{A}} < m^{\mathsf{M}_4} \text{ occurs never if } \alpha_1 < \beta_1, \tag{A.36a}$$

$$0 < m^{\mathsf{B}} < m^{\mathsf{M}_4} < m^{\mathsf{A}} \text{ occurs never if } \alpha_1 < \beta_1, \tag{A.36b}$$

$$0 < m^{\mathsf{M}_4} < m^{\mathsf{B}} < m^{\mathsf{A}} \text{ occurs never if } \alpha_1 < \beta_1. \tag{A.36c}$$

If $\phi < \phi^{\mathsf{A}}$ or $\phi > \phi^{\mathsf{B}}$, the relations involving m^{F_0}, m^{A} and m^{B} follow immediately by (4.10), i.e., by setting $\rho = 0$ in the relevant formulas in (A.32)-(A.35). The remaining cases where $\phi^{\mathsf{A}} < \phi < \phi^{\mathsf{B}}$ can be calculated easily using $\tilde{\theta} = \alpha_1\alpha_2 - \beta_1\beta_2$, (4.5), (4.15), and (A.18). Then, all admissible relations are:

$$0 < -m^{\mathsf{A}} < -m^{\mathsf{B}} < -m^{\mathsf{F}_0} \iff \alpha_2 > \beta_2 \text{ and } \phi < \tilde{\phi}^{\mathsf{AB}}, \tag{A.37a}$$

$$0 < -m^{\mathsf{B}} < -m^{\mathsf{A}} < -m^{\mathsf{F}_0} \iff \begin{cases} \alpha_2 > \beta_2 \text{ and } \tilde{\phi}^{\mathsf{AB}} < \phi < \phi^{\mathsf{M}_1}, \text{or} \\ \alpha_2 \le \beta_2 \text{ and } \phi < \phi^{\mathsf{M}_1}, \end{cases} \tag{A.37b}$$

$$0 < m^{\mathsf{A}} < -m^{\mathsf{B}} < -m^{\mathsf{F}_0} \iff \tilde{\theta} > 0 \text{ and } \phi^{\mathsf{AB}} < \phi < \phi^{\mathsf{F}_0}, \tag{A.37c}$$

$$0 < -m^{\mathsf{B}} < m^{\mathsf{A}} < -m^{\mathsf{F}_0} \iff \begin{cases} \tilde{\theta} < 0 \text{ and } \phi^{\mathsf{AF}_0} < \phi < \phi^{\mathsf{F}_0}, \text{or} \\ \tilde{\theta} \ge 0 \text{ and } \phi^{\mathsf{AF}_0} < \phi < \phi^{\mathsf{AB}}, \end{cases} \tag{A.37d}$$

$$0 < m^{\mathsf{A}} < -m^{\mathsf{B}} < m^{\mathsf{F}_0} \iff \begin{cases} \tilde{\theta} < 0 \text{ and } \phi^{\mathsf{AB}} < \phi < \phi^{\mathsf{BF}_0}, \text{or} \\ \tilde{\theta} \ge 0 \text{ and } \phi^{\mathsf{F}_0} < \phi < \phi^{\mathsf{BF}_0}, \end{cases} \tag{A.37e}$$

$$0 < -m^{\mathsf{B}} < m^{\mathsf{A}} < m^{\mathsf{F}_0} \iff \tilde{\theta} < 0 \text{ and } \phi^{\mathsf{F}_0} < \phi < \phi^{\mathsf{AB}}, \tag{A.37f}$$

$$0 < m^{\mathsf{A}} < m^{\mathsf{B}} < m^{\mathsf{F}_0} \iff \phi^{\mathsf{M}_4}(\rho = 0) < \phi, \tag{A.37g}$$

$$0 < -m^{\mathsf{B}} < -m^{\mathsf{F}_0} < -m^{\mathsf{A}} \iff \phi^{\mathsf{M}_1}(\rho = 0) < \phi < \phi^{\mathsf{A}}, \tag{A.37h}$$

$$0 < -m^{\mathsf{B}} < -m^{\mathsf{F}_0} < m^{\mathsf{A}} \iff \phi^{\mathsf{A}} < \phi < \phi^{\mathsf{AF}_0}, \tag{A.37i}$$

$$0 < m^{\mathsf{A}} < m^{\mathsf{F}_0} < -m^{\mathsf{B}} \iff \phi^{\mathsf{BF}_0} < \phi < \phi^{\mathsf{B}}, \tag{A.37j}$$

$$0 < m^{\mathsf{A}} < m^{\mathsf{F}_0} < m^{\mathsf{B}} \iff \phi^{\mathsf{B}} < \phi < \phi^{\mathsf{M}_4}(\rho = 0). \tag{A.37k}$$

Because other strict inequalities between m^{A}, m^{B}, and m^{F_0} do not occur, we infer

$$\min\{|m^{\mathsf{A}}|, |m^{\mathsf{B}}|\} \leq |m^{\mathsf{F}_0}|. \tag{A.38}$$

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A. TEMME'S CONTRIBUTION: I derived the equilibrium and stability configurations for most of the limiting cases in Section 3, the bifurcation patterns and the maximum migration rate admitting polymorphism in Section 4, and the effective migration rate in Section 8. I investigated F_{ST} averaged over the loci. This analysis is not included in the manuscript but was a preliminary to our investigation of F_{ST}^{X} in Section 6. As a preliminary I also investigated the invasion of a beneficial mutant (Section 7).

The consequences of dominance and gene flow for local adaptation and differentiation at two linked loci

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ABSTRACT. *We study a population subdivided into two demes connected by migration in which selection acts in opposite directions. We assume two linked diallelic loci with intermediate dominance (i.e., no over- or underdominance) but no epistasis. Generations are discrete and nonoverlapping. We explore the effects of dominance, recombination, and migration on multilocus polymorphism, local adaptation, and differentiation. For weak migration, as well as for weak selection, we derive the equilibrium and stability configuration explicitly. As a special case, we analyze a continent-island model in continuous time (CI model). For the CI model we obtain the equilibrium and stability configuration explicitly for weak migration, for independent loci, and for complete linkage. For independent loci we obtain the possible bifurcation pattern as a function of the migration rate. This pattern depends strongly on the degree of dominance. We determine the effects of dominance, linkage, and migration on the amount of linkage disequilibrium (LD) and on local adaptation. We obtain explicit formulas of* D $(= x_1x_4 - x_2x_3)$ *and* r^2 *(the squared correlation in allelic state), and show that dominant island alleles increase* D *and decrease* r^2*. Local adaptation is elevated by dominant island alleles. In addition, we investigate the effective migration rate at a linked neutral locus and show that linkage to highly dominant island alleles does not decrease the effective migration rate significantly below the actual one. Finally, we study differentiation of a quantitative trait subject to diversifying selection. We obtain explicit expressions for* Q_{ST} *and two types of* F_{ST} *at equilibrium.*

1. Introduction

Despite extensive treatment in the literature, the interplay of the evolutionary forces selection, recombination, and migration is far from being well understood. When it comes to local adaptation and its conceptual issues, the examination of these interactions is inevitable (Lenormand, 2002; Kawecki and Ebert, 2004). Also, the exploding amount of data obtained by genome-wide sequencing of individuals from different geographical regions cannot be assessed properly without comprehending the effects of selection and migration on multilocus variation and the effects of genetic architecture (Charlesworth et al., 1997; Nordborg and Tavaré, 2002; Slatkin, 2008).

For one-locus models, both general theory and the study of numerous particular models have provided considerable insight into the evolutionary consequences of the interaction between migration and selection (reviewed by Karlin, 1982; Lenormand, 2002; Nagylaki and Lou, 2008). Several one-locus models incorporating selection and migration investigate the effect of dominance on the maintenance of polymorphisms (Prout, 1968; Nagylaki and Lou, 2001, 2007; Nagylaki 2009; Peischl 2010). In these models dominance is intermediate. In structured populations, intermediate dominance is of particular interest as stable polymorphisms can be maintained. With panmixia, stable polymorphisms are admissible if and only if alleles exhibit overdominance.

Recent years showed some progress in the study of the joint evolutionary effect of migration, selection and linkage. Due to the increased complexity by considering several evolutionary forces simultaneously, the theory of multilocus migration-selection models focuses on limiting or special cases. These include weak or strong migration (Bürger 2009a, b) or the Levene model (Nagylaki 2009; Bürger 2009c, 2010; Barton 2010). In all of these cases, linkage disequilibrium (LD) is weak or absent.

Recently, simple but informative migration models have been studied where high levels of LD may be maintained. These include the continent-island model (Bürger and Akerman, 2011; henceforth cited as BA11) and the two-deme model with forward and backward migration (Akerman and Bürger, 2013) where genic selection is assumed (i.e., absence of dominance and epistasis). Ignoring dominance, Bank et al. (2012) investigated the continent-island model with epistasis. In these works, the effects of gene flow on local adaptation, on differentiation, and on the maintenance of polymorphism at two linked diallelic loci in the absence of dominance were investigated. They obtained analytical characterizations of the possible equilibrium configurations and bifurcation patterns for wide ranges of parameter combinations. In particular, explicit formulas were derived for the maximum migration rate below which a fully polymorphic equilibrium can be maintained.

Only few multilocus migration-selection models investigate the evolutionary consequences of dominance, as it leads to substantial mathematical complications (Bürger 2009a, b, c, 2010; Nagylaki 2009; Chasnov 2012). With this work, we want to shape our intuition about the interplay of migration and linkage on multilocus variation exhibiting dominance. The main goal of this paper is to explore and quantify the role of intermediate dominance on linked loci for local adaptation in the presence of maladaptive gene flow. For simplicity, we study a population inhabiting two demes interchanging migrants. We consider two diallelic loci A and B, where alleles A_1 and B_1 are favored in deme 1 and alleles A_2 and B_2 are favored in deme 2. Recombination between the loci is arbitrary. We assume that dominance is intermediate (no over- or underdominance) and

assume absence of epistasis. Mutation and random drift are neglected. Generations are discrete and nonoverlapping.

We introduce the model in Section 2. In Section 3, we derive the equilibrium and stability structure for two important special cases: weak migration and weak selection. In Section 4, we study the limiting case where selection, recombination, and migration are weak, and where migration is in one direction only. Under these assumptions, the continuous-time continent-island model (CI model) is obtained from the discrete-time two-deme model. For the CI model, we investigate several special cases: weak migration, independent loci (linkage equilibrium; LE), and complete linkage. For these cases, we derive the possible equilibrium structure and the bifurcation patterns. We show that the equilibrium and stability structure maintained in the population depends crucially on the degree of dominance, in particular if linkage is loose. One explanation may be that strong recombination facilitates the formation of heterozygotes, where dominance becomes evident only. We relegate several purely technical proofs of results derived in Sections 3 and 4 to the Appendix.

In Section 5 we treat several applications of the results obtained in Sections 3 and 4.

In Section 5.1 we investigate how two widely used measures of LD, D and r^2, depend on the amount of dominance and on linkage. We show that D is elevated and r^2 is reduced if the locally adaptive alleles are dominant. In Section 5.2, we use the migration load to quantify the dependence of local adaptation on the recombination rate and the degree of dominance. Our analysis shows that elevated levels of local adaptation are to be expected if the locally adaptive alleles are dominant.

In Section 5.3, we study the strength of barriers to gene flow at neutral sites linked to the selected loci by deriving an explicit approximation for the effective migration rate at a linked neutral site. We show that gene flow at the neutral locus experiences the strongest barrier if the locally adaptive alleles are recessive or if there is no dominance. If the locally adaptive alleles are completely dominant, linkage has (almost) no effect on the effective migration rate and gene flow at the neutral locus is not significantly reduced.

In Section 5.4, we investigate a quantitative trait subject to diversifying selection. Our main focus lies on determining the amount of differentiation under maladaptive gene flow. To this aim, we analyze three different measures of differentiation known from the literature: (i) $\bar{F}_{ST}$, which is F_{ST} averaged over the two loci, (ii) F_{ST}^X, a multilocus F_{ST} introduced in Akerman and Bürger (2013), and (iii) Q_{ST}, which measures differentiation of the trait. We derive informative explicit approximations of these measures and their relations. Using these, we determine the effect of the parameters, especially dominance and linkage, on the differentiation of the measured trait and of the genotypes.

2. The model

In the following we introduce the discrete-time two-deme migration-selection model for two diallelic loci. Throughout the paper we ignore mutation, stochastic effects, and epistasis. The population is assumed to be diploid, monoecious, and infinitely large. Generations are discrete and nonoverlapping. The population is subdivided into two discrete demes (throughout denoted by $k = 1, 2$) wherein random mating occurs. Therefore, offspring are in Hardy-Weinberg proportions.

Alleles are denoted by A_1, A_2 at locus A and by B_1, B_2 at locus B. The frequencies of the four gametes A_1B_1, A_1B_2, A_2B_1, and A_2B_2 in deme $k = 1, 2$ are designated by $x_{1,k}$, $x_{2,k}$, $x_{3,k}$, and $x_{4,k}$, respectively. For every deme the state space is given by the probability simplex S_4, where $S_4 = \left\{(x_1, x_2, x_3, x_4) : \ x_i \geq 0 \ \text{ and } \ \sum_{i=1}^{4} x_i = 1\right\}$. The complete state space is $S_4 \times S_4$.

As we neglect epistasis we can assign fitness to each locus independently of the other locus. Assuming absence of position effects, the fitness matrix in deme $k = 1, 2$ is given by

$$\begin{array}{c} \\ A_1A_1 \\ A_1A_2 \\ A_2A_2 \end{array} \begin{array}{c} \begin{array}{ccc} B_1B_1 & B_1B_2 & B_2B_2 \end{array} \\ \begin{pmatrix} 1 + a_k + b_k & 1 + a_k + \sigma_k b_k & 1 + a_k - b_k \\ 1 + \vartheta_k a_k + b_k & 1 + \vartheta_k a_k + \sigma_k b_k & 1 + \vartheta_k a_k - b_k \\ 1 - a_k + b_k & 1 - a_k + \sigma_k b_k & 1 - a_k - b_k \end{pmatrix} \end{array}, \tag{2.1}$$

where $a_k \neq 0$ and $b_k \neq 0$ are the selection coefficients at locus A and locus B in deme $k = 1, 2$, respectively. Dominance coefficients are denoted by ϑ_k and σ_k and fulfill

$$|\vartheta_k| \leq 1 \ \text{ and } \ |\sigma_k| \leq 1 \quad (k = 1, 2), \tag{2.2}$$

i.e., we ignore over- and underdominance. There is no dominance if

$$\vartheta_k = \sigma_k = 0 \quad \text{ for } k = 1, 2, \tag{2.3}$$

and there is deme-independent degree of dominance (DIDID) if

$$\vartheta_1 = \vartheta_2 = \vartheta \quad \text{ and } \quad \sigma_1 = \sigma_2 = \sigma; \tag{2.4}$$

see Nagylaki (2009). For definiteness

$$|a_k| + |b_k| < 1 \tag{2.5}$$

is assumed. Without loss of generality, we assume

$$a_1 > 0 > a_2 \ \text{ and } \ b_1 > 0 > b_2. \tag{2.6}$$

Let $r \in [0, \frac{1}{2}]$ denote the recombination probability between the two loci, where $r = 0$ corresponds to complete linkage and $r = \frac{1}{2}$ to free recombination. The probability that an individual in deme 1 (deme 2) immigrated from deme 2 (deme 1) is denoted by m_1 (m_2). We assume $0 \leq m_k < \frac{1}{2}$ for $k = 1, 2$.

We denote the marginal fitness of gamete $i = 1, 2, 3, 4$ and the mean fitness in deme $k = 1, 2$ by $W_{i,k}$ and $\bar{W}_k$, respectively. Let $W_{14,k} = 1 + \vartheta_k \alpha_k + \sigma_k \beta_k$ in deme $k = 1, 2$ and $\eta_1 = \eta_4 = -\eta_2 = -\eta_3 = 1$. Then the frequency of gamete $i = 1, 2, 3, 4$ in deme $k = 1, 2$ after selection and recombination ($x^*_{i,k}$) and after migration ($x'_{i,k}$) is given by

$$x^*_{i,k} = \frac{x_{i,k} W_{i,k} - \eta_i r D_k W_{14,k}}{\bar{W}_k}, \tag{2.7a}$$

and

$$x'_{i,1} = (1 - m_1) x^*_{i,1} + m_1 x^*_{i,2} \quad \text{and} \quad x'_{i,2} = m_2 x^*_{i,1} + (1 - m_2) x^*_{i,2}, \tag{2.7b}$$

where

$$D_k = x_{1,k} x_{4,k} - x_{2,k} x_{3,k} \tag{2.8}$$

is the measure of LD in deme $k = 1, 2$. If $D_k = 0$ ($k = 1, 2$), we speak of LE.

Instead of gamete frequencies it is often more convenient to use the allele frequencies of A_1 and B_1,

$$p_k = x_{1,k} + x_{2,k} \quad \text{and} \quad q_k = x_{1,k} + x_{3,k}, \tag{2.9}$$

respectively, and the measure D_k of LD in deme $k = 1, 2$. Then the gamete frequencies $x_{i,k}$ are obtained from p_k, q_k, and D_k by

$$x_{1,k} = p_k q_k + D_k, \qquad x_{2,k} = p_k (1 - q_k) - D_k, \tag{2.10a}$$

$$x_{3,k} = (1 - p_k) q_k - D_k, \quad x_{4,k} = (1 - p_k)(1 - q_k) + D_k\,. \tag{2.10b}$$

The constraints $x_{i,k} \geq 0$ and $\sum_{i=1}^{4} x_{i,k} = 1$ for $i = 1, 2, 3, 4$, and $k = 1, 2$ transform into

$$0 \leq p_k \leq 1 \;\text{ and }\; 0 \leq q_k \leq 1 \tag{2.11a}$$

and

$$-\min\{p_k q_k, (1 - p_k)(1 - q_k)\} \leq D_k \leq \min\{p_k (1 - q_k), (1 - p_k) q_k\}\,. \tag{2.11b}$$

The mean fitness is given by

$$\bar{W}_k = 1 - \alpha_k (1 - 2p_k - 2p_k (1 - p_k) \vartheta_k) - \beta_k (1 - 2q_k - 2q_k (1 - q_k) \sigma_k). \tag{2.12}$$

Applying the transformations in (2.10) to $x^*_{i,k}$ given in (2.7a), the allele frequencies of A_1 and B_1 in deme $k = 1, 2$ after selection and recombination are

$$p^*_k = x^*_{1,k} + x^*_{2,k} \quad \text{and} \quad q^*_k = x^*_{1,k} + x^*_{3,k}, \tag{2.13a}$$

and the measure of LD in deme $k = 1, 2$ after selection and recombination is

$$D_k^* = x_{1,k}^* x_{4,k}^* - x_{2,k}^* x_{3,k}^*. \tag{2.13b}$$

The allele frequencies and LD in deme $k = 1, 2$ after migration are

$$p_1' = (1 - m_1)p_1^* + m_1 p_2^*, \quad p_2' = m_2 p_1^* + (1 - m_2)p_2^*, \tag{2.14a}$$

$$q_1' = (1 - m_1)q_1^* + m_1 q_2^*, \quad q_2' = m_2 q_1^* + (1 - m_2)q_2^*, \tag{2.14b}$$

$$D_1' = (1 - m_1)D_1^* + m_1 D_2^* + m_1(1 - m_1)(p_1^* - p_2^*)(q_1^* - q_2^*), \tag{2.14c}$$

$$D_2' = m_2 D_1^* + (1 - m_2)D_2^* + m_2(1 - m_2)(p_1^* - p_2^*)(q_1^* - q_2^*), \tag{2.14d}$$

where the equations for D_k' were derived in Li and Nei (1974).

3. Equilibria

Equilibria of (2.14) satisfy $p_k' = p_k$, $q_k' = q_k$, and $D_k' = D_k$ for $k = 1, 2$. Three types of equilibria can be characterized: (i) monomorphisms, (ii) single-locus polymorphisms, and (iii) two-locus (full) polymorphisms. Monomorphisms and single-locus polymorphisms are in LE, i.e., they are located at the boundary of the state space where $D_k = 0$ for $k = 1, 2$. At a monomorphism both loci are fixed for one allele throughout the population. Single-locus polymorphisms are defined as polymorphisms where at one locus one allele is fixed and at the other locus two alleles are segregating. Full polymorphisms are equilibria where all alleles are present with positive frequency.

There are four monomorphisms, which are given by

$$\mathsf{M}_1\ (A_1B_1 \text{ fixed}): \quad \hat{p}_k = 1, \ \hat{q}_k = 1, \ \hat{D}_k = 0 \ \text{ for } \ k = 1, 2, \tag{3.1a}$$

$$\mathsf{M}_2\ (A_1B_2 \text{ fixed}): \quad \hat{p}_k = 1, \ \hat{q}_k = 0, \ \hat{D}_k = 0 \ \text{ for } \ k = 1, 2, \tag{3.1b}$$

$$\mathsf{M}_3\ (A_2B_1 \text{ fixed}): \quad \hat{p}_k = 0, \ \hat{q}_k = 1, \ \hat{D}_k = 0 \ \text{ for } \ k = 1, 2, \tag{3.1c}$$

$$\mathsf{M}_4\ (A_2B_2 \text{ fixed}): \quad \hat{p}_k = 0, \ \hat{q}_k = 0, \ \hat{D}_k = 0 \ \text{ for } \ k = 1, 2, \tag{3.1d}$$

where a $\hat{}$ signifies an equilibrium.

On the marginal one-locus systems, the stability of the monomorphisms is known from the theory of protected polymorphisms (Maynard-Smith 1970; Bulmer 1972; Nagylaki 1992). If a (single-locus) polymorphism is protected, the two neighboring monomorphisms are unstable. The local stability of the monomorphisms with respect to the interior of the state space can be derived, but the explicit formulas of the eigenvalues pointing inwards the state space (which depend on the recombination probability r) are complicated and uninformative. We refrain from presenting them.

If there is migration in both directions between the demes and if dominance is absent (2.3), the equilibrium frequencies of the single-locus polymorphisms can be calculated

explicitly (formulas not shown). In this case, generically, at most one single-locus polymorphism is admissible at each one-locus system.

If there is arbitrary dominance, the explicit frequencies at the single-locus polymorphisms and at the full polymorphisms cannot be calculated, as this would require solving polynomial equations of order higher than three. In the following sections, we study several informative special cases where we derive the possible equilibrium and stability structure explicitly. We investigate the limiting case of weak migration in Section 3.1, and of weak selection in Section 3.2, respectively. In Section 4 we analyze a continuous-time continent-island model (CI model) with dominance. This system can be obtained from the discrete-time model (2.7) if selection, recombination, and migration are weak and migration is in one direction only. We study the CI model for weak migration (Section 4.3), for LE (Section 4.4), for complete linkage (Section 4.5), and for completely dominant island alleles (Section 4.6).

The maximum number of admissible full polymorphisms derived by the subsequent analysis and encountered in numerical simulations which supplement our analysis (details not shown) was four.

3.1. Weak migration. In the absence of migration, $m_1 = m_2 = 0$, the dynamics in the two demes are decoupled. If there is intermediate or complete dominance (2.2), the fittest haplotype is fixed in the respective deme. Considering the two demes together, the globally asymptotically stable equilibrium in the absence of migration is given by

$$\mathsf{F}_0: \quad \hat{p}_1 = \hat{q}_1 = 1, \quad \hat{p}_2 = \hat{q}_2 = 0, \quad \hat{D}_1 = \hat{D}_2 = 0. \tag{3.2}$$

F_0 is globally asymptotically stable as mean fitness increases in every deme if fitnesses are additive (Ewens, 1969). The eigenvalues at F_0 are given by

$$\lambda_1^{\mathsf{F}_0} = \frac{1+\vartheta_1 a_1 + b_1}{1+a_1+b_1}, \quad \lambda_2^{\mathsf{F}_0} = \frac{1+a_1+\sigma_1 b_1}{1+a_1+b_1}, \quad \lambda_3^{\mathsf{F}_0} = (1-r)\frac{1+\vartheta_1 a_1+\sigma_1 b_1}{1+a_1+b_1}, \tag{3.3}$$

$$\lambda_4^{\mathsf{F}_0} = \frac{1+\vartheta_2 a_2 - b_2}{1-a_2-b_2}, \quad \lambda_5^{\mathsf{F}_0} = \frac{1-a_2+\sigma_2 b_2}{1-a_2-b_2}, \quad \lambda_6^{\mathsf{F}_0} = (1-r)\frac{1+\vartheta_2 a_2+\sigma_2 b_2}{1-a_2-b_2}. \tag{3.4}$$

All eigenvalues are real and positive. From the assumptions (2.2) and $0 \le r \le \frac{1}{2}$, the relations $\lambda_3^{\mathsf{F}_0} \neq 1$ and $\lambda_6^{\mathsf{F}_0} \neq 1$ follow. F_0 is hyperbolic (i.e., no eigenvalue lies on the unit circle) if and only if the dominance coefficients satisfy

$$\vartheta_1 \neq 1 \ \text{ or } \ \sigma_1 \neq 1 \ \text{ or } \ \vartheta_2 \neq -1 \ \text{ or } \ \sigma_2 \neq -1. \tag{3.5}$$

Beside F_0 (3.2), other equilibria are admissible if $m_1 = m_2 = 0$: The monomorphisms M_i ($i = 1, 2, 3, 4$) (3.1), eight single-locus polymorphisms, and three other (unstable) full polymorphisms exist; see Appendix A.1 for details. The monomorphisms and the single-locus polymorphisms are unstable with respect to the complete state space. The unstable

full polymorphisms are located at the boundary of $S_4 \times S_4$ in LE. Under complete linkage, $r = 0$, and in the absence of migration an unstable full polymorphism in LD may be admissible (not shown). It is located on the boundary connecting $x_{2,k} = 1$ (A_1B_2 fixed) and $x_{3,k} = 1$ (A_2B_1 fixed) for deme $k = 1, 2$. This full polymorphism is not of interest, as it leaves the state space under positive migration rates. If $r > 0$, equilibria in LD are not admissible (see Bürger 2000, Section II.1).

If dominance coefficients satisfy

$$-1 < \vartheta_k < 1 \quad \text{and} \quad -1 < \sigma_k < 1 \quad \text{for deme} \quad k = 1, 2, \tag{3.6}$$

generically, all equilibria are hyperbolic in the absence of migration (not shown). For sufficiently weak migration, Theorem 5.4 in Bürger (2009a) guarantees that the perturbation of F_0 for small $m_1 > 0$ and $m_2 > 0$ is admissible in a sufficiently small neighborhood of the unperturbed equilibrium F_0. Moreover, its stability is preserved, i.e., it is globally asymptotically stable. We note that the results by Karlin and McGregor (1972) imply only asymptotic stability.

A straightforward calculation using series expansion gives the equilibrium, which we denote by F_m, up to first order in m_1 and m_2:

$$\hat{p}_1 = 1 - m_1 \frac{1 + a_1 + b_1}{a_1(1 - \vartheta_1)} \frac{a_1(1 - \vartheta_1) + r(1 + \vartheta_1 a_1 + \sigma_1 b_1)}{a_1(1 - \vartheta_1) + b_1(1 - \sigma_1) + r(1 + \vartheta_1 a_1 + \sigma_1 b_1)}, \tag{3.7a}$$

$$\hat{q}_1 = 1 - m_1 \frac{1 + a_1 + b_1}{b_1(1 - \sigma_1)} \frac{b_1(1 - \sigma_1) + r(1 + \vartheta_1 a_1 + \sigma_1 b_1)}{a_1(1 - \vartheta_1) + b_1(1 - \sigma_1) + r(1 + \vartheta_1 a_1 + \sigma_1 b_1)}, \tag{3.7b}$$

$$\hat{D}_1 = m_1 \frac{1 + a_1 + b_1}{a_1(1 - \vartheta_1) + b_1(1 - \sigma_1) + r(1 + \vartheta_1 a_1 + \sigma_1 b_1)}, \tag{3.7c}$$

$$\hat{p}_2 = m_2 \frac{1 - a_2 - b_2}{-a_2(1 + \vartheta_2)} \frac{-a_2(1 + \vartheta_2) + r(1 + \vartheta_2 a_2 + \sigma_2 b_2)}{-a_2(1 + \vartheta_2) - b_2(1 + \sigma_2) + r(1 + \vartheta_2 a_2 + \sigma_2 b_2)}, \tag{3.7d}$$

$$\hat{q}_2 = m_2 \frac{1 - a_2 - b_2}{-b_2(1 + \sigma_2)} \frac{-b_2(1 + \sigma_2) + r(1 + \vartheta_2 a_2 + \sigma_2 b_2)}{-a_2(1 + \vartheta_2) - b_2(1 + \sigma_2) + r(1 + \vartheta_2 a_2 + \sigma_2 b_2)}, \tag{3.7e}$$

$$\hat{D}_2 = m_2 \frac{1 - a_2 - b_2}{-a_2(1 + \vartheta_2) - b_2(1 + \sigma_2) + r(1 + \vartheta_2 a_2 + \sigma_2 b_2)}. \tag{3.7f}$$

If dominance coefficients satisfy (3.6), F_m is unique, i.e., the three unstable full polymorphisms that exist if $m_1 = m_2 = 0$ leave the state space if $m_1 > 0$ and $m_2 > 0$ are sufficiently small. The proof is given in Appendix A.1. If dominance coefficients satisfy $\vartheta_1 = -1$, $\sigma_1 = -1$, $\vartheta_2 = 1$, or $\sigma_2 = 1$, the weak-migration approximation (3.7) of the asymptotically stable full polymorphism F_m applies, but F_m may not be unique: Whenever $|\vartheta_1| = 1$, $|\sigma_1| = 1$, $|\vartheta_2| = 1$, or $|\sigma_2| = 1$, there exist boundary equilibria of the dynamics (2.7) in the absence of migration which are not hyperbolic if $m_1 = m_2 = 0$. Under weak migration, these equilibria may give rise to additional full polymorphisms (details not shown).

By (3.7), it follows that up to first order in m_1, m_2 the allele frequencies p_k and q_k and the measure D_k of LD in deme $k = 1, 2$ at F_m depend only on the amount of selection (and dominance) in deme k.

From our assumptions on the selection coefficients (2.5) and (2.6), and on the dominance coefficients (2.2) it follows that F_m exhibits positive LD. Tighter linkage leads to larger LD and elevates the equilibrium frequency of the locally adaptive alleles within the respective deme because

$$\frac{\partial \hat{D}_1}{\partial r} < 0, \quad \frac{\partial \hat{D}_2}{\partial r} < 0, \quad \text{and} \tag{3.8a}$$

$$\frac{\partial \hat{p}_1}{\partial r} < 0, \quad \frac{\partial \hat{q}_1}{\partial r} < 0, \quad \frac{\partial \hat{p}_2}{\partial r} > 0, \quad \frac{\partial \hat{q}_2}{\partial r} > 0. \tag{3.8b}$$

Next, we study how the equilibrium frequencies and the amount of LD at F_m depend on the degree of dominance. It can easily be checked that

$$\frac{\partial \hat{p}_k}{\partial \vartheta_k} < 0, \quad \frac{\partial \hat{p}_k}{\partial \sigma_k} < 0, \quad \frac{\partial \hat{q}_k}{\partial \vartheta_k} < 0, \quad \frac{\partial \hat{q}_k}{\partial \sigma_k} < 0 \quad \text{for} \quad k = 1, 2. \tag{3.9a}$$

This means that if for example in deme 1 the locally adaptive allele A_1 is partially dominant, i.e., $0 < \vartheta_1 < 1$, the frequency of A_2 in deme 1, $1 - \hat{p}_1$, is elevated compared to the case where dominance at locus A is absent. The reason is that in this case the fitness of heterozygotes is similar to the fitness of the adapted genotype and A_2 is masked in heterozygotes.

Moreover,

$$\frac{\partial \hat{D}_1}{\partial \vartheta_1} > 0, \quad \frac{\partial \hat{D}_1}{\partial \sigma_1} > 0, \quad \frac{\partial \hat{D}_2}{\partial \vartheta_2} < 0, \quad \frac{\hat{D}_2}{\partial \sigma_2} < 0, \tag{3.9b}$$

such that in deme 1

$$\frac{\partial \hat{x}_{i,1}}{\partial \vartheta_1} > 0 \quad \text{for} \quad i = 2, 3, 4, \quad \text{and} \quad \frac{\partial \hat{x}_{1,1}}{\partial \vartheta_1} < 0 \tag{3.9c}$$

hold, and in deme 2

$$\frac{\partial \hat{x}_{i,2}}{\partial \vartheta_2} < 0 \quad \text{for} \quad i = 1, 2, 3, \quad \text{and} \quad \frac{\partial \hat{x}_{4,2}}{\partial \vartheta_2} > 0. \tag{3.9d}$$

Analogous relations to (3.9c) or (3.9d) hold for σ_1 or σ_2, respectively. It follows from (3.9b) that partially dominant adaptive alleles (i.e., $0 < \vartheta_1 < 1, 0 < \sigma_1 < 1, -1 < \vartheta_2 < 0$, or $-1 < \sigma_2 < 0$ hold) elevate the amount of LD in their respective deme. By (3.9c) and (3.9d), this elevation mainly results from an increase of the frequency of the maladapted, homozygote haplotype (i.e., $\hat{x}_{4,1}$ in deme 1 or $\hat{x}_{4,2}$ in deme 2).

Completely dominant adaptive alleles. Note that if (3.5) would not hold, i.e., $\vartheta_1 = 1$, $\sigma_1 = 1$, $\vartheta_2 = -1$, or $\sigma_2 = -1$, some denominators in (3.7) would be zero. In this case, the approximation (3.7) of F_m is not admissible. In the following, we briefly analyze a

special case where dominance coefficients satisfy

$$\vartheta_1 = \sigma_1 = -\vartheta_2 = -\sigma_2 = 1. \tag{3.10}$$

In this case, F_0 (3.2) is not hyperbolic; cf. (3.5). Assuming a positive recombination probability ($0 < r \leq \frac{1}{2}$) and (3.10), we obtain the approximation of F_m by performing a nonregular perturbation of F_0 for weak migration. It is given by

$$\hat{p}_1 = 1 - \sqrt{m_1 \frac{1 + a_1 + b_1}{2a_1}} + \sqrt{m_1 m_2 \frac{(1 + a_1 + b_1)(1 - a_2 - b_2)}{-2a_1 a_2}} + \frac{m_1}{2r}\sqrt{\frac{b_1}{a_1}}, \tag{3.11a}$$

$$\hat{q}_1 = 1 - \sqrt{m_1 \frac{1 + a_1 + b_1}{2b_1}} + \sqrt{m_1 m_2 \frac{(1 + a_1 + b_1)(1 - a_2 - b_2)}{-2b_1 b_2}} + \frac{m_1}{2r}\sqrt{\frac{a_1}{b_1}}, \tag{3.11b}$$

$$\hat{D}_1 = \frac{m_1}{r}, \tag{3.11c}$$

$$\hat{p}_2 = \sqrt{m_2 \frac{1 - a_2 - b_2}{-2a_2}} + \sqrt{m_1 m_2 \frac{(1 + a_1 + b_1)(1 - a_2 - b_2)}{-2a_1 a_2}} - \frac{m_2}{2r}\sqrt{\frac{b_2}{a_2}}, \tag{3.11d}$$

$$\hat{q}_2 = \sqrt{m_2 \frac{1 - a_2 - b_2}{-2b_2}} + \sqrt{m_1 m_2 \frac{(1 + a_1 + b_1)(1 - a_2 - b_2)}{-2b_1 b_2}} - \frac{m_2}{2r}\sqrt{\frac{a_2}{b_2}}, \tag{3.11e}$$

$$\hat{D}_2 = \frac{m_2}{r}. \tag{3.11f}$$

Interestingly, the amount of LD in deme $k = 1, 2$ is independent of selection up to first order in m_k. Provided that $r > 0$, the formulas of D_k in (3.11) are equal to those of D_k in (3.7) if the dominance coefficients satisfy (3.10).

If linkage is tight ($r = 0$), F_m is approximated by

$$\hat{p}_1 = \hat{q}_1 = 1 - \sqrt{m_1 \frac{1 + a_1 + b_1}{2(a_1 + b_1)}}, \quad \hat{D}_1 = \hat{p}_1(1 - \hat{p}_1), \tag{3.12a}$$

$$\hat{p}_2 = \hat{q}_2 = \sqrt{m_2 \frac{1 - a_2 - b_2}{-2(a_2 + b_2)}}, \quad \hat{D}_2 = \hat{p}_2(1 - \hat{p}_2). \tag{3.12b}$$

At this equilibrium, $\hat{x}_{2,k} = \hat{x}_{3,k} = 0$ ($k = 1, 2$) and strong LD is maintained.

In summary, if dominance coefficients satisfy (3.10), F_m is approximated by (3.11) if $r > 0$ or by (3.12) if $r = 0$, respectively. From arguments in the paragraph below formula (3.7) it follows that if (3.10) holds, F_m may not be the only admissible full polymorphism. This contrasts the case where dominance coefficients satisfy (3.6): In this case F_m is unique.

3.2. Weak selection. Bürger (2009a, Section 4.1) showed that if selection is sufficiently weak relative to migration and recombination, the discrete-time dynamics (2.7) can be approximated by a system of ordinary differential equations for the allele frequencies in LE averaged over the demes. This continuous-time system is much easier to

study. Generically, equilibria of the discrete-time model can be obtained by perturbing the equilibria of the continuous-time system. In the following, we derive this system for our model.

For the following, we assume that selection is weak relative to migration and recombination, i.e., we can rewrite the selection coefficients as

$$a_k = \epsilon\alpha_k \quad \text{and} \quad b_k = \epsilon\beta_k \quad \text{for } k = 1, 2 \tag{3.13}$$

where $\epsilon > 0$ is sufficiently small and $\alpha_1 > 0 > \alpha_2$ and $\beta_1 > 0 > \beta_2$, such that $\max\{|a_k|, |b_k|\} \ll \min\{m_k, r\}$.

We define the ratio

$$\phi = \frac{m_1}{m_1 + m_2}, \tag{3.14}$$

where $(1-\phi, \phi)$ is the maximal left eigenvector of the backward migration matrix (which has the diagonal elements $1 - m_1$ and $1 - m_2$). We assume that migration occurs in both directions, i.e., $0 < \phi < 1$. Using ϕ, we define the averaged allele frequencies by

$$\bar{p} = (1-\phi)p_1 + \phi p_2 \quad \text{and} \quad \bar{q} = (1-\phi)q_1 + \phi q_2. \tag{3.15}$$

The averaged selection coefficients are given by

$$\bar{\alpha} = (1-\phi)\alpha_1 + \phi\alpha_2 \quad \text{and} \quad \bar{\beta} = (1-\phi)\beta_1 + \phi\beta_2, \tag{3.16}$$

and the average effects of the heterozygotes by

$$\overline{\vartheta\alpha} = (1-\phi)\vartheta_1\alpha_1 + \phi\vartheta_2\alpha_2 \quad \text{and} \quad \overline{\sigma\beta} = (1-\phi)\sigma_1\beta_1 + \phi\sigma_2\beta_2. \tag{3.17}$$

If there is no dominance at locus A, we obtain $\overline{\vartheta\alpha} = 0$, and if there is DIDID at locus A ($\vartheta_1 = \vartheta_2 = \vartheta$), then $\overline{\vartheta\alpha} = \vartheta\bar{\alpha}$ (analogously for locus B).

For our subsequent analysis we assume (w.l.o.g.) that $\bar{\alpha} > 0$ and $\bar{\beta} > 0$ (we treat the degenerate cases $\bar{\alpha} = 0$ and $\bar{\beta} = 0$ separately in the end of this section). We rewrite the averaged Malthusian fitnesses of A_1A_1, A_1A_2, and A_2A_2 (i.e., $\bar{\alpha}$, $\overline{\vartheta\alpha}$, and $-\bar{\alpha}$) as 0, $-h_\mathsf{A}s_\mathsf{A}$, and $-s_\mathsf{A}$ via the transformation

$$s_\mathsf{A} = 2\bar{\alpha} \quad \text{and} \quad h_\mathsf{A} = \frac{\bar{\alpha} - \overline{\vartheta\alpha}}{2\bar{\alpha}}. \tag{3.18a}$$

Using an analogous argument for locus B, we define

$$s_\mathsf{B} = 2\bar{\beta} \quad \text{and} \quad h_\mathsf{B} = \frac{\bar{\beta} - \overline{\sigma\beta}}{2\bar{\beta}}. \tag{3.18b}$$

The parameters h_A and h_B determine the degree of dominance at locus A and B, respectively. There is (on average) intermediate dominance at locus A if and only if $0 \leq h_\mathsf{A} \leq 1$, where $h_\mathsf{A} = \frac{1}{2}$ corresponds to absence of dominance, and $0 \leq h_\mathsf{A} < \frac{1}{2}$ or $\frac{1}{2} < h_\mathsf{A} \leq 1$ to

partial dominance or recessiveness, respectively. (On average) overdominance at locus A corresponds to $h_{\mathsf{A}} < 0$, and (on average) underdominance to $1 < h_{\mathsf{A}}$. Analogous formulas (h_{B} instead of h_{A}) apply for locus B.

The weak-selection limit is given by a system of two decoupled ordinary differential equations for the averaged allele frequencies:

$$\dot{\bar{p}} = \frac{d\bar{p}}{dt} = \bar{p}(1-\bar{p})s_{\mathsf{A}}\left[1 - h_{\mathsf{A}} - \bar{p}(1-2h_{\mathsf{A}})\right], \tag{3.19a}$$

$$\dot{\bar{q}} = \frac{d\bar{q}}{dt} = \bar{q}(1-\bar{q})s_{\mathsf{B}}\left[1 - h_{\mathsf{B}} - \bar{q}(1-2h_{\mathsf{B}})\right], \tag{3.19b}$$

$$D_1 = D_2 = 0. \tag{3.19c}$$

It can be obtained from the dynamics (2.14) if (3.13) holds and $\epsilon \to 0$. The system obtained in (3.19) is on $[0,1]^2$ and much easier to study than the full system (2.7) on $S_4 \times S_4$. Note that the dynamics in (3.19) is decoupled, i.e., the loci can be studied independently. For each one-locus system, generically, we can apply results from the well-developed theory of a diallelic locus exhibiting dominance in a panmictic population, which applies to each of (3.19a) and (3.19b) (e.g.; Bürger 2000, Section I.9.3). In the following, we derive all possible equilibrium and stability configurations of (3.19) by the Cartesian product of the dynamics at the two independent loci A and B. Therefore, in the absence of epistasis this approach can be extended to more than two loci.

Define

$$\bar{p}^* = \frac{1-h_{\mathsf{A}}}{1-2h_{\mathsf{A}}} \quad \text{and} \quad \bar{q}^* = \frac{1-h_{\mathsf{B}}}{1-2h_{\mathsf{B}}}. \tag{3.20}$$

For the following, we summarize the results from Bürger (2000, Section I.9.3), which are relevant to our subsequent analysis: At locus A, no polymorphism is admissible if and only if $0 \le h_{\mathsf{A}} \le 1$ holds. In this case $\hat{\bar{p}} = 1$ is globally asymptotically stable and $\hat{\bar{p}} = 0$ is unstable (as we assumed $\bar{\alpha} > 0$). If there is overdominance at locus A, i.e., $h_{\mathsf{A}} < 0$ holds, there exists a unique polymorphism at locus A given by $\hat{\bar{p}} = \bar{p}^*$. It is globally asymptotically stable and $\hat{\bar{p}} = 1$ and $\hat{\bar{p}} = 0$ are unstable. If there is underdominance at locus A, i.e., $h_{\mathsf{A}} > 1$ holds, the unique polymorphism $\hat{\bar{p}} = \bar{p}^*$ is admissible but unstable. Both $\hat{\bar{p}} = 1$ and $\hat{\bar{p}} = 0$ are stable. Analogous results apply to locus B, where the polymorphism is given by $\hat{\bar{q}} = \bar{q}^*$ if admissible (the details are left to the reader).

The Cartesian product of the equilibria derived separately for the two loci yield the equilibria of the complete system (3.19). We define the admissible single-locus polymorphisms at locus A by

$$\mathsf{P}_1^{\mathsf{A}}: \ \hat{\bar{p}} = \bar{p}^* \text{ and } \hat{\bar{q}} = 1, \tag{3.21a}$$

$$\mathsf{P}_0^{\mathsf{A}}: \ \hat{\bar{p}} = \bar{p}^* \text{ and } \hat{\bar{q}} = 0, \tag{3.21b}$$

and at locus B by

$$\mathsf{P}_1^{\mathsf{B}}: \ \hat{\bar{p}} = 1 \text{ and } \hat{\bar{q}} = \bar{q}^*, \tag{3.22a}$$

$$\mathsf{P}_0^{\mathsf{B}}: \ \hat{\bar{p}} = 0 \text{ and } \hat{\bar{q}} = \bar{q}^*, \tag{3.22b}$$

where $\bar{p}^*$ and $\bar{q}^*$ are defined in (3.20). A unique full polymorphism may be admissible. Its equilibrium frequency is given by

$$\mathsf{F}: \ \hat{\bar{p}} = \bar{p}^* \ \text{ and } \ \hat{\bar{q}} = \bar{q}^*. \tag{3.23}$$

As (3.19) is a Cartesian product of two one-locus systems, it follows that F (3.23) is globally asymptotically stable if and only if both loci exhibit overdominance (see arguments below equation (3.20)). Global stability follows from the following argument: Bürger (2009a) showed that the dynamics (3.19) is a Svirezhev-Shashahani gradient with a potential function which increases strictly along nonconstant solutions of (3.19). In our model, we define the potential function V by

$$\dot{V} = \bar{p}(1-\bar{p})s_{\mathsf{A}}^2\left[1-h_{\mathsf{A}}-\bar{p}(1-2h_{\mathsf{A}})\right]^2 + \bar{q}(1-\bar{q})s_{\mathsf{B}}^2\left[1-h_{\mathsf{B}}-\bar{q}(1-2h_{\mathsf{B}})\right]^2 \geq 0. \tag{3.24}$$

Thus, complicated dynamical behavior of (3.19) does not occur. Whenever only one equilibrium is asymptotically stable (and the others are unstable), it is globally stable.

The following proposition is an immediate consequence of one-locus theory, as the equilibrium and stability configuration of the full system (3.19) is derived from the Cartesian product of the equilibrium and stability structure at two independent, panmictic one-locus systems with dominance:

PROPOSITION 3.1. *Assume* (3.19) *holds. The following equilibrium and stability structure of* (3.19) *can be distinguished according to the degree of dominance:*

(i) *Average overdominance at both loci:* F *is admissible and globally asymptotically stable. The monomorphisms and all single-locus polymorphisms are admissible and unstable.*

(ii) *Average overdominance at one locus, average underdominance at the second locus:* F *is admissible and unstable. All single-locus polymorphisms are admissible. The two single-locus polymorphisms where the locus exhibiting overdominance is segregating are asymptotically stable. The two remaining single-locus polymorphisms and the monomorphisms are unstable.*

(iii) *Average underdominance at both loci:* F *and the four single-locus polymorphisms are admissible and unstable. All monomorphisms are locally asymptotically stable.*

(iv) *Average overdominance at one locus, on average intermediate or no dominance at the second locus:* F *is not admissible. Two single-locus polymorphisms where the locus exhibiting overdominance is segregating are admissible. One single-locus polymorphism is globally asymptotically stable, one is unstable. The monomorphisms are unstable.*

(v) *Average underdominance at one locus, on average intermediate or no dominance at the second locus:* F *is not admissible. Two single-locus polymorphisms where the locus exhibiting underdominance is segregating are admissible and both are unstable. Two monomorphisms are locally asymptotically stable, two monomorphisms are unstable.*

(vi) *On average intermediate or no dominance at both loci:* F *and the single-locus polymorphisms are not admissible. One monomorphism is globally asymptotically stable, all other monomorphisms are unstable.*

We note that the cases (ii), (iii), (v) correspond to bistability. In cases (i), (iv), and (vi) there exists a unique globally asymptotic stable equilibrium.

All equilibria of (3.19) are hyperbolic if $\bar{\alpha} \neq 0$ and $\bar{\beta} \neq 0$. In this generic case, Theorem 4.3 in Bürger (2009a) applies. Provided selection is weak relative to recombination and migration, Theorem 4.3 in Bürger (2009a) guarantees the existence of one equilibrium of the discrete-time model (2.7) in a sufficiently small neighborhood of an equilibrium derived in (3.19), with the same local stability behavior.

Case (vi) of Theorem 3.1 shows that in the absence of dominance or under average intermediate dominance at both loci (including DIDID (2.4)), no polymorphisms can be maintained and one monomorphism is globally asymptotically stable. This result corresponds to Proposition 2.6 in Bürger (2009b), where he showed that for multiple loci with two or more alleles under genic selection, generically, one globally asymptotically stable monomorphism exists.

Finally, we treat the degenerate case where there is (on average) no dominance and no selection at least at one locus, i.e., $\bar{\alpha} = 0$ or $\bar{\beta} = 0$ holds. If $\bar{\alpha} = 0$ ($\bar{\beta} = 0$) holds, then the transformation yielding h_{A} (h_{B}) (3.18) is not admissible (division by zero) and our results obtained above do not hold. We leave the detailed analysis of the degenerate system on $[0, 1]^2$ to the interested reader and summarize the relevant results in the subsequent paragraph.

If either $\bar{\alpha} = 0$ or $\bar{\beta} = 0$ holds, no full polymorphism is maintained. If both $\bar{\alpha} = 0$ and $\bar{\beta} = 0$ hold, the following scenarios are possible: (i) If both $\overline{\vartheta\alpha} \neq 0$ and $\overline{\sigma\beta} \neq 0$, one full polymorphism is admissible. It is given by $\hat{\bar{p}} = \hat{\bar{q}} = \frac{1}{2}$ and it is globally stable if and only if $\overline{\vartheta\alpha} > 0$ and $\overline{\sigma\beta} > 0$. It is unstable otherwise. (ii) If $\overline{\vartheta\alpha} = 0$ or $\overline{\sigma\beta} = 0$, there

exists a manifold of full polymorphisms. In this case, no equilibrium is hyperbolic and Theorem 4.3 in Bürger (2009a) does not apply.

4. Continent-island model

If migration is in one direction only, i.e., if either $m_1 = 0$ or $m_2 = 0$ holds, the continent-island model (CI model) is obtained. For the following, we assume that $m_2 = 0$ in (2.14). In the CI model, maladapted individuals from a continent (corresponding to deme 2, where the alleles A_2 and B_2 are fixed) migrate to an island (deme 1) where the locally adaptive alleles A_1 and B_1 are established. As one needs to keep track only of the frequencies on the island (deme 1), the CI model is much easier to study. The state space is S_4. For simplicity, we omit the index for deme 1, i.e., $a = a_1$ etc.

For one diallelic locus with dominance and discrete, nonoverlapping generations, the CI model was analyzed by Nagylaki (1992, Section 6.1). Nagylaki derived the possible equilibrium and stability structure explicitly. He showed that up to two (one-locus) polymorphisms are admissible.

In our model, Nagylaki's results apply to the marginal one-locus systems. It is easy to show that single-locus polymorphisms are admissible only on the marginal one-locus systems where A_2 is fixed and locus B is polymorphic, or B_2 is fixed and locus A is polymorphic, respectively. In total, up to four single-locus polymorphisms may be admissible. Stability of the single-locus polymorphisms within their one-locus system follows directly from Nagylaki (1992). The stability with respect to the interior of S_4 is difficult to derive. Also, the equilibrium frequency of full polymorphisms cannot be calculated explicitly, as this would require solving polynomial equations of high order.

In the following, we study an informative special case, where we assume that selection, recombination, and migration are weak. Under this assumption, we rescale the selection coefficients as in (3.13), the recombination probability, and the migration rate as

$$r = \epsilon\rho \tag{4.1}$$

and

$$m = \epsilon m, \tag{4.2}$$

with $\epsilon > 0$ sufficiently small, $m \geq 0$ and the recombination rate $\rho \geq 0$.

If (3.13), (4.1), and (4.2) hold, the continuous-time CI model is obtained from the discrete-time CI model (with $m_2 = 0$ and $\hat{p}_2 = \hat{q}_2 = \hat{D}_2 = 0$ in (2.14)) if $\epsilon \to 0$. Its dynamics is given by

$$\dot{p} = \frac{dp}{dt} = \alpha p(1-p)(1+\vartheta(1-2p)) + \beta D(1+\sigma(1-2q)) - mp, \tag{4.3a}$$

$$\dot{q} = \frac{dq}{dt} = \beta q(1-q)(1+\sigma(1-2q)) + \alpha D(1+\vartheta(1-2p)) - mq, \tag{4.3b}$$

$$\dot{D} = \frac{dD}{dt} = D\left[\alpha(1-2p)(1+\vartheta(1-2p)) + \beta(1-2q)(1+\sigma(1-2q))\right] - \rho D + m(pq - D). \tag{4.3c}$$

Because we are treating a continuous-time model, the parameters α, β, ρ, and m are rates (of growth, recombination, and migration), whence they can be arbitrarily large. Their magnitude is determined by the time scale. By rescaling time, for instance to units of ρ or m, the number of independent parameters could be reduced by one without changing the equilibrium properties. We refrain from doing so because in our applications it will be illuminating to use either ρ or m as an independent parameter.

Instead of the dynamics (4.3) of the allele frequencies p, q and the measure D of LD, the dynamics of the gamete frequencies x_i ($i = 1, 2, 3, 4$) can be used. It is given by formula (A.8) in the Appendix and needed in the proof of Theorem 4.2 below.

The dynamics (4.3) is much easier to study than to the discrete-time model, and several explicit results can be derived. The continuous-time CI model for one diallelic locus exhibiting (arbitrary) dominance is fully understood; see Nagylaki (1975) for the explicit derivation of the possible equilibrium and stability configurations. Recently, several results were obtained for the dynamics at two recombining loci in the continuous-time CI model under genic selection (BA11) and under epistasis (Bank et al., 2012).

In the following sections, we derive approximations of the equilibrium frequencies at the full polymorphism under weak migration (Section 4.3) and the explicit equilibrium frequencies of the full polymorphisms under LE (Section 4.4), and complete linkage (Section 4.5), respectively.

For the following we define some critical migration rates which will be needed in the subsequent sections:

$$m_1^{\mathsf{A}} = \alpha(1+\vartheta), \tag{4.4a}$$

$$m_1^{\mathsf{B}} = \beta(1+\sigma), \tag{4.4b}$$

$$m_2^{\mathsf{A}} = -\frac{\alpha(1-\vartheta)^2}{8\vartheta}, \tag{4.4c}$$

$$m_2^{\mathsf{B}} = -\frac{\beta(1-\sigma)^2}{8\sigma}, \tag{4.4d}$$

$$m^{\mathsf{M}} = \alpha(1+\vartheta) + \beta(1+\sigma) - \rho. \tag{4.4e}$$

The following relations apply:

$$m_1^{\mathsf{A}} > 0 \text{ and } m_1^{\mathsf{B}} > 0 \text{ always}, \tag{4.5a}$$

$$m_2^{\mathsf{A}} > 0 \iff -1 < \vartheta < 0, \tag{4.5b}$$

$$m_2^{\mathsf{B}} > 0 \iff -1 < \sigma < 0, \tag{4.5c}$$

$$m^{\mathsf{M}} > 0 \iff 0 \le \rho < \alpha(1+\vartheta) + \beta(1+\sigma). \tag{4.5d}$$

The relations between the critical migration rates defined in (4.4) are derived in Appendix A.3.

4.1. The monomorphic equilibrium. There exists one monomorphic equilibrium of (4.3), given by

$$\mathsf{M}: \quad \hat{p} = 0, \quad \hat{q} = 0, \quad \hat{D} = 0. \tag{4.6}$$

The eigenvalues at M are real and given by

$$\alpha(1+\vartheta) - m, \quad \beta(1+\vartheta) - m, \quad \alpha(1+\vartheta) + \beta(1+\sigma) - \rho - m. \tag{4.7}$$

Then,

$$\mathsf{M} \text{ is asymptotically stable} \iff m > \max\{m_1^{\mathsf{A}}, m_1^{\mathsf{B}}, m^{\mathsf{M}}\}, \tag{4.8}$$

where m_1^{A}, m_1^{B}, and m^{M} satisfy the relations given in (A.11). M is not hyperbolic (i.e., no eigenvalue is zero) if and only if $m = m_1^{\mathsf{A}}$, $m = m_1^{\mathsf{B}}$, or $m = m^{\mathsf{M}}$ holds.

In the following, we prove global convergence to M if $m > 2(\alpha+\beta)$ for arbitrary dominance. Our proof is analogous to that for the continuous-time CI model with genic selection (in Section 3.4.3 of BA11). Bürger and Akerman proved that if $\vartheta = \sigma = 0$, the monomorphic equilibrium on the island is globally asymptotically stable if $m > \alpha + \beta$.

Because $0 \le 1 + \vartheta(1-2p) \le 2$ or $0 \le 1 + \sigma(1-2q) \le 2$ hold by $-1 \le \vartheta \le 1$ or $-1 \le \sigma \le 1$, respectively, and as $D \le p(1-q)$, we obtain from (4.3) that

$$\dot{p} \le p[2(\alpha+\beta) - m - 2(\alpha p + \beta q)] \le 0 \tag{4.9}$$

if $m > 2(\alpha+\beta)$ with equality if and only if $\hat{p} = 0$. A similar argument using $D \le q(1-p)$ follows for $\dot{q}$. Thus, there exist two global Lyapunov functions, and all trajectories must converge to M (LaSalle, 1976). If the island alleles are completely dominant ($\vartheta = \sigma = 1$) and recombination is tight ($\rho = 0$) the bound $2(\alpha+\beta)$ is best possible as it is equal to m^{M}; cf. (4.8) and (A.11c) and (A.11f).

4.2. The single-locus polymorphisms. Up to four single-locus polymorphisms of (4.3) are admissible. Their equilibrium frequencies and their stability within the one-locus system is known from one-locus theory; see equation (25) and the paragraph below in Nagylaki (1975). Using the notation

$$p_\pm = \frac{1 + 3\vartheta \pm \sqrt{(1-\vartheta)^2 + \frac{8m\vartheta}{\alpha}}}{4\vartheta}, \tag{4.10a}$$

$$q_{\pm} = \frac{1 + 3\sigma \pm \sqrt{(1-\sigma)^2 + \frac{8m\sigma}{\beta}}}{4\sigma}, \tag{4.10b}$$

the equilibrium frequencies of the four single-locus polymorphisms are given by

$$\mathsf{E}_{\mathsf{A},1}: \quad \hat{p} = p_-, \quad \hat{q} = 0, \quad \hat{D} = 0, \tag{4.11a}$$

$$\mathsf{E}_{\mathsf{A},2}: \quad \hat{p} = p_+, \quad \hat{q} = 0, \quad \hat{D} = 0, \tag{4.11b}$$

$$\mathsf{E}_{\mathsf{B},1}: \quad \hat{p} = 0, \quad \hat{q} = q_-, \quad \hat{D} = 0, \tag{4.11c}$$

$$\mathsf{E}_{\mathsf{B},2}: \quad \hat{p} = 0, \quad \hat{q} = q_+, \quad \hat{D} = 0. \tag{4.11d}$$

$\mathsf{E}_{\mathsf{A},1}$ and $\mathsf{E}_{\mathsf{A},2}$ are located on the edge of the LE manifold connecting $x_2 = 1$ (A_1B_2 fixed) and $x_4 = 1$ (A_2B_2 fixed), and $\mathsf{E}_{\mathsf{B},1}$ and $\mathsf{E}_{\mathsf{B},2}$ are located on the edge of the LE manifold connecting $x_3 = 1$ (A_2B_1 fixed) and $x_4 = 1$ (A_2B_2 fixed).

$\mathsf{E}_{\mathsf{A},1}$ is in the state space if and only if one of the following two conditions holds

$$-\frac{1}{3} \le \vartheta < 1 \quad \text{and} \quad 0 \le m \le m_1^{\mathsf{A}}, \text{ or} \tag{4.12a}$$

$$-1 < \vartheta < -\frac{1}{3} \quad \text{and} \quad 0 \le m \le m_2^{\mathsf{A}}. \tag{4.12b}$$

$\mathsf{E}_{\mathsf{A},2}$ is in the state space if and only if

$$-1 < \vartheta < -\frac{1}{3} \quad \text{and} \quad m_1^{\mathsf{A}} \le m \le m_2^{\mathsf{A}} \tag{4.13}$$

holds, where

$$\mathsf{E}_{\mathsf{A},2} = \mathsf{M} \iff m = m_1^{\mathsf{A}}. \tag{4.14}$$

If (4.13) holds, $\mathsf{E}_{\mathsf{A},1}$ and $\mathsf{E}_{\mathsf{A},2}$ are simultaneously admissible. For increasing migration $\mathsf{E}_{\mathsf{A},1}$ and $\mathsf{E}_{\mathsf{A},2}$ leave the state space according to the following relations:

$$-\frac{1}{3} \le \vartheta < 1 \quad \text{and} \quad m \uparrow m_1^{\mathsf{A}} \iff \mathsf{E}_{\mathsf{A},1} \to \mathsf{M}, \tag{4.15a}$$

$$-1 < \vartheta < -\frac{1}{3} \quad \text{and} \quad m \uparrow m_2^{\mathsf{A}} \iff \mathsf{E}_{\mathsf{A},1} \to \mathsf{E}_{\mathsf{A},2}. \tag{4.15b}$$

$\mathsf{E}_{\mathsf{B},1}$ is in the state space if and only if one of the following two conditions holds

$$-\frac{1}{3} \le \sigma < 1 \quad \text{and} \quad 0 \le m \le m_1^{\mathsf{B}}, \text{ or} \tag{4.16a}$$

$$-1 < \sigma < -\frac{1}{3} \quad \text{and} \quad 0 \le m \le m_2^{\mathsf{B}}. \tag{4.16b}$$

$\mathsf{E}_{\mathsf{B},2}$ is in the state space if and only if

$$-1 < \sigma < -\frac{1}{3} \quad \text{and} \quad m_1^{\mathsf{B}} \le m \le m_2^{\mathsf{B}} \tag{4.17}$$

holds, where

$$\mathsf{E}_{\mathsf{B},2} = \mathsf{M} \iff m = m_1^{\mathsf{B}}. \tag{4.18}$$

$\mathsf{E}_{\mathsf{B},1}$ and $\mathsf{E}_{\mathsf{B},2}$ leave the state space according to the following relations:

$$-\frac{1}{3} \le \sigma < 1 \quad \text{and} \quad m \uparrow m_1^{\mathsf{B}} \iff \mathsf{E}_{\mathsf{B},1} \to \mathsf{M}, \tag{4.19a}$$

$$-1 < \sigma < -\frac{1}{3} \quad \text{and} \quad m \uparrow m_2^{\mathsf{B}} \iff \mathsf{E}_{\mathsf{B},1} \to \mathsf{E}_{\mathsf{B},2}. \tag{4.19b}$$

The stability of the single-locus polymorphisms with respect to their one-locus system follows immediately from Nagylaki (1975). Within their respective one-locus systems, $\mathsf{E}_{\mathsf{A},1}$ and $\mathsf{E}_{\mathsf{B},1}$ are asymptotically stable whenever admissible. $\mathsf{E}_{\mathsf{A},2}$ and $\mathsf{E}_{\mathsf{B},2}$ are always unstable.

Although the eigenvalues at the single-locus polymorphisms with respect to the complete state space S_4 can be determined explicitly, the general stability conditions are too complicated and not informative. We refrain from presenting them and derive their stability only in the special cases below.

4.3. Weak migration. In this section, we assume that migration is weak relative to selection and recombination, i.e., $m \ll \min\{\alpha, \beta, \rho\}$. From similar arguments as in Section 3.1 and from Appendix A.4 it follows that, generically, a unique, globally asymptotically stable full polymorphism F_{m} exists if

$$-1 < \vartheta < 1 \quad \text{and} \quad -1 < \sigma < 1 \tag{4.20}$$

hold. Up to first order in m, its coordinates are given by

$$\hat{p} = 1 - \frac{m}{\alpha(1-\vartheta)} \frac{\alpha(1-\vartheta) + \rho}{\alpha(1-\vartheta) + \beta(1-\sigma) + \rho}, \tag{4.21a}$$

$$\hat{q} = 1 - \frac{m}{\beta(1-\sigma)} \frac{\beta(1-\sigma) + \rho}{\alpha(1-\vartheta) + \beta(1-\sigma) + \rho}, \tag{4.21b}$$

$$\hat{D} = \frac{m}{\alpha(1-\vartheta) + \beta(1-\sigma) + \rho}. \tag{4.21c}$$

In the absence of dominance ($\vartheta = \sigma = 0$), the approximation given in (4.21) was obtained in BA11 or can be derived from Barton (1983) if selection acts equally strong on both loci, i.e., $\alpha = \beta$.

If $\rho = 0$, a second full polymorphism may exist on the edge $x_1 = x_4 = 0$ if $m = 0$. It is unstable and leaves the state space for positive migration rates (details not shown).

Note that the equations in (4.21) are not admissible if $\vartheta = 1$ or $\sigma = 1$, i.e., if the island alleles are completely dominant. If $\vartheta = -1$ or $\sigma = -1$, F_{m} is admissible and asymptotically stable (with its approximation given in (4.21)), but it is not unique in general. Up to two additional full polymorphisms (if either $\vartheta = -1$ or $\sigma = -1$) or up

to three additional full polymorphisms (if $\vartheta = \sigma = -1$) may enter the state space under weak migration; see Appendix A.4.

By (4.21) it follows that F_m exhibits positive LD, where tighter linkage leads to increased levels of D. Tighter linkage also increases the equilibrium frequencies of A_1 and B_1, $\hat{p}$ and $\hat{q}$, respectively.

The following relations with respect to dominance hold:

$$\frac{\partial \hat{p}}{\partial \vartheta} < 0, \quad \frac{\partial \hat{p}}{\partial \sigma} < 0, \quad \frac{\partial \hat{q}}{\partial \vartheta} < 0, \quad \frac{\partial \hat{q}}{\partial \sigma} < 0, \tag{4.22a}$$

$$\frac{\partial \hat{D}}{\partial \vartheta} > 0, \quad \frac{\partial \hat{D}}{\partial \sigma} > 0, \tag{4.22b}$$

$$\frac{\partial \hat{x}_1}{\partial \vartheta} < 0, \quad \frac{\partial \hat{x}_1}{\partial \sigma} < 0, \quad \frac{\partial \hat{x}_i}{\partial \sigma} > 0, \quad \text{and} \quad \frac{\partial \hat{x}_i}{\partial \vartheta} > 0 \quad \text{for} \quad i = 2, 3, 4. \tag{4.22c}$$

By (4.22b), D increases monotonically with increasing dominance of the island alleles.

The special case where the island alleles are completely dominant ($\vartheta = \sigma = 1$) is treated separately in Section 4.6. The weak-migration approximation of F_m for this special case in derived therein.

4.4. Linkage equilibrium. If recombination is strong relative to selection and migration, $\rho \gg \max\{\alpha, \beta, m\}$, the dynamics in (4.3) can be approximated by a dynamical system in LE given by

$$\dot{p} = \alpha p(1-p)(1 + \vartheta(1-2p)) - mp, \tag{4.23a}$$

$$\dot{q} = \beta q(1-q)(1 + \sigma(1-2q)) - mq, \tag{4.23b}$$

$$D = 0. \tag{4.23c}$$

This is a system on $[0,1]^2$. Due to absence of epistasis the system in (4.23) is decoupled and the dynamics for locus A and locus B can be studied separately. The continuous-time CI dynamics of a diallelic locus exhibiting dominance is fully understood (Nagylaki, 1975). The dynamics of the full system (4.23) is then obtained from the Cartesian product of the dynamics at locus A and B.

Beside the monomorphism and the four single-locus polymorphism, up to four full polymorphisms may exist. Their equilibrium frequencies are given by

$$\mathsf{F}_1: \quad \hat{p} = p_-, \quad \hat{q} = q_-, \tag{4.24a}$$

$$\mathsf{F}_2: \quad \hat{p} = p_-, \quad \hat{q} = q_+, \tag{4.24b}$$

$$\mathsf{F}_3: \quad \hat{p} = p_+, \quad \hat{q} = q_-, \tag{4.24c}$$

$$\mathsf{F}_4: \quad \hat{p} = p_+, \quad \hat{q} = q_+, \tag{4.24d}$$

where $p_\pm$ and $q_\pm$ are defined in (4.10), and

$$\mathsf{F}_1 \text{ is admissible} \iff \text{(4.12) and (4.16) hold,} \tag{4.25a}$$

$$\mathsf{F}_2 \text{ is admissible} \iff \text{(4.12) and (4.17) hold,} \tag{4.25b}$$

$$\mathsf{F}_3 \text{ is admissible} \iff \text{(4.13) and (4.16) hold,} \tag{4.25c}$$

$$\mathsf{F}_4 \text{ is admissible} \iff \text{(4.13) and (4.17) hold.} \tag{4.25d}$$

As F_1 is the Cartesian product of two asymptotically stable equilibria of the respective single-locus dynamics, it follows that

$$\mathsf{F}_1 \text{ is asymptotically stable whenever admissible.} \tag{4.26}$$

From a similar argument it follows that

$$\mathsf{F}_i \ (i = 2, 3, 4) \text{ is unstable whenever admissible.} \tag{4.27}$$

In the following theorem, we present all qualitatively possible equilibrium and stability configurations of (4.23) derived as a Cartesian product of two independent one-locus dynamics. For an efficient subsequent presentation of our results, we define

$$\zeta_1 = \frac{1+\sigma}{1+\vartheta}, \tag{4.28a}$$

$$\zeta_2 = \frac{\vartheta}{\sigma}\frac{(1-\sigma)^2}{(1-\vartheta)^2}, \tag{4.28b}$$

$$\zeta_3 = -8\vartheta\frac{1+\sigma}{(1-\vartheta)^2}, \tag{4.28c}$$

where dominance is intermediate such that (4.20) holds, and we assume w.l.o.g. that

$$0 < \alpha < \zeta_1\beta. \tag{4.29}$$

The remaining case $\alpha > \zeta_1\beta > 0$ can be obtained by exchanging the loci, i.e., by the transformation $\alpha \leftrightarrow \beta$, $\vartheta \leftrightarrow \sigma$, $\mathsf{E}_{\mathsf{A},1} \leftrightarrow \mathsf{E}_{\mathsf{B},1}$ etc.

THEOREM 4.1. *Assume* (4.23) *and* (4.29) *hold. Figure 1 shows all possible bifurcation diagrams which occur for an open set of parameters* $(\alpha, \beta, \vartheta, \sigma, \rho)$*, where m is the bifurcation parameter.*

(i) *Diagram (a) in Figure 1 applies if and only if*

$$-\frac{1}{3} < \vartheta < 1 \quad \textit{and} \quad -\frac{1}{3} < \sigma < 1 \tag{4.30}$$

hold.

(ii) *Diagram (b) in Figure 1 applies if and only if*

$$-1 < \vartheta < -\frac{1}{3} \quad \textit{and} \quad -\frac{1}{3} < \sigma < 1 \quad \textit{and} \quad 0 < \alpha < \zeta_3\beta \tag{4.31}$$

hold.

(iii) *Diagram (c) in Figure 1 applies if and only if*

$$-1 < \vartheta < -\frac{1}{3} \quad \textit{and} \quad -\frac{1}{3} < \sigma < 1 \quad \textit{and} \quad \zeta_3\beta < \alpha < \zeta_1\beta \tag{4.32}$$

hold.

(iv) *Diagram (d) in Figure 1 applies if and only if*

$$-\frac{1}{3} < \vartheta < 1 \quad \textit{and} \quad -1 < \sigma < -\frac{1}{3} \tag{4.33}$$

hold.

(v) *Diagram (e) in Figure 1 applies if and only if*

$$-1 < \vartheta < -\frac{1}{3} \quad \textit{and} \quad -1 < \sigma < -\frac{1}{3} \quad \textit{and} \quad 0 < \alpha < \zeta_3\beta \tag{4.34}$$

hold.

(vi) *Diagram (f) in Figure 1 applies if and only if either*

$$-1 < \sigma \leq \vartheta < -\frac{1}{3} \quad \textit{and} \quad \zeta_3\beta < \alpha < \zeta_1\beta, \tag{4.35}$$

or

$$-1 < \vartheta < \sigma < -\frac{1}{3} \quad \textit{and} \quad \zeta_3\beta < \alpha < \zeta_2\beta \tag{4.36}$$

hold.

(vii) *Diagram (g) in Figure 1 applies if and only if*

$$-1 < \vartheta < \sigma < -\frac{1}{3} \quad \textit{and} \quad \zeta_2\beta < \alpha < \zeta_1\beta \tag{4.37}$$

hold.

Proof. Assume (4.23) holds. As the dynamics at locus A and locus B in (4.23) is decoupled, the equilibrium frequencies of (4.23) and their stability are obtained straightforwardly from the Cartesian product of the respective single-locus equilibria known from Nagylaki (1975). The derivation of the relations of the critical migration rates at which equilibria collide (as shown in Figure 1) and of the conditions on the selection and dominance coefficients determining the different scenarios in Theorem 4.1 is lengthy (but straightforward). We have therefore relegated this to Appendix A.5. □

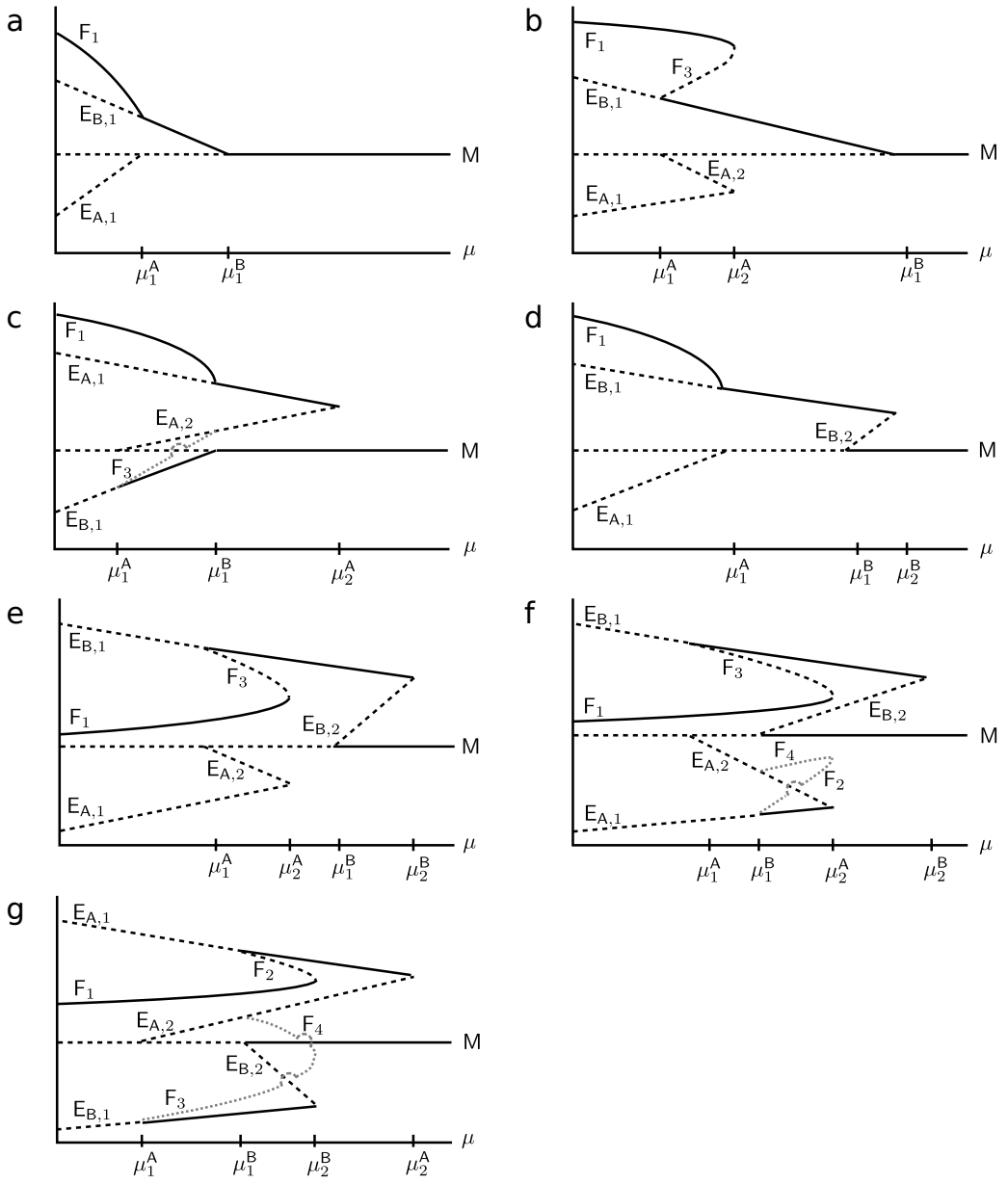

FIGURE 1. Bifurcation diagrams for the CI model under linkage equilibrium. Diagrams (a)–(g) represent all possible equilibrium configurations, corresponding to the cases (i)–(vii) in Theorem 4.1. Each diagram displays the possible equilibria as a function of the migration rate m. Each line indicates one equilibrium. The lines are drawn such that intersections of lines occur if and only if the corresponding equilibria bifurcate (note that the gray lines in diagrams (c), (f), and (g) intersect only at their origin and their end). Solid lines represent asymptotically stable equilibria, dashed lines unstable equilibria. Equilibria are shown if and only if they are admissible.

Note that case (i) in Theorem 4.1 is the only case where only one equilibrium is asymptotically stable at a fixed but arbitrary migration rate. In all other cases, if migration is intermediate two equilibria (cases (ii)-cases (iv) of Theorem 4.1) or four equilibria (cases (v) and (vi) of Theorem 4.1) are asymptotically stable.

The case where dominance is absent ($\vartheta = \sigma = 0$) corresponds to case (i) in Theorem 4.1. This special case was already derived for the CI model with genic selection in BA11. Whereas in the absence of dominance only one, simple bifurcation scenario occurs in the limiting case of LE (or sufficiently strong recombination) (see diagram (a) of Figure 1), this is in general not the case if alleles exhibit dominance (see diagrams (b)–(g) of Figure 1).

Theorem 4.1 shows that the bifurcation pattern for the continuous-time CI model under LE (4.23) depends significantly on the degree of dominance. The effect of dominance becomes evident only in heterozygotes. The stronger recombination, the more likely it is that heterozygotes are produced. Thus it is not surprising that under LE we observe several bifurcation patterns if the two loci exhibit dominance in comparison to no dominance.

Theorem 4.1 presents all possible bifurcation patterns for generic selection rates and dominance coefficients. We refrain from presenting the nongeneric cases as they are not needed here.

4.5. No recombination. In the following section we study the dynamics of the CI model in the special case of complete linkage. For this aim we set $\rho = 0$ in (4.3).

For the subsequent presentation of our results, and assuming $(\alpha\vartheta + \beta\sigma) \neq 0$, it will be useful to define

$$\varphi_{\pm}^{(1)} = \frac{\alpha(1+3\vartheta)+\beta(1+3\sigma)}{4(\alpha\vartheta+\beta\sigma)} \tag{4.38a}$$

$$\pm \frac{\sqrt{(\alpha(1+3\vartheta)+\beta(1+3\sigma))^2 - 8(\alpha\vartheta+\beta\sigma)(\alpha(1+3\vartheta)+\beta(1+3\sigma)-m)}}{4(\alpha\vartheta+\beta\sigma)}, \tag{4.38b}$$

$$\varphi_{\pm}^{(2)} = \frac{\alpha[2\alpha\vartheta(1+\vartheta)+\beta(\sigma-\vartheta+2\vartheta\sigma)] \pm \sqrt{\alpha^2\beta^2(\sigma+\vartheta)^2 + 8\alpha\vartheta\beta\sigma m(\alpha\vartheta+\beta\sigma)}}{4\alpha\vartheta(\alpha\vartheta+\beta\sigma)}, \tag{4.38c}$$

$$\varphi_{\pm}^{(3)} = \frac{\beta[2\beta\sigma(1+\sigma)+\alpha(\vartheta-\sigma+2\vartheta\sigma)] \pm \sqrt{\alpha^2\beta^2(\sigma+\vartheta)^2 + 8\alpha\vartheta\beta\sigma m(\alpha\vartheta+\beta\sigma)}}{4\beta\sigma(\alpha\vartheta+\beta\sigma)}. \tag{4.38d}$$

The following theorem describes the possible equilibrium and stability configurations under complete linkage:

THEOREM 4.2. *Assume* (4.3) *with* $\rho = 0$ *holds, and dominance coefficients satisfy* (4.20).

(i) *In the generic case*

$$\alpha\vartheta + \beta\sigma \neq 0, \tag{4.39}$$

up to four full polymorphisms are admissible. Their equilibrium frequencies are

$$\mathsf{F}_{\rho,1}: \quad \hat{p} = \hat{q} = \varphi_-^{(1)}, \quad \hat{D} = \hat{p}(1-\hat{p}), \tag{4.40a}$$

$$\mathsf{F}_{\rho,2}: \quad \hat{p} = \hat{q} = \varphi_+^{(1)}, \quad \hat{D} = \hat{p}(1-\hat{p}), \tag{4.40b}$$

$$\mathsf{F}_{\rho,3}: \quad \hat{p} = \varphi_-^{(2)}, \quad \hat{q} = \varphi_-^{(3)}, \quad \hat{D} = -\hat{p}\hat{q}, \tag{4.40c}$$

$$\mathsf{F}_{\rho,4}: \quad \hat{p} = \varphi_+^{(2)}, \quad \hat{q} = \varphi_+^{(3)}, \quad \hat{D} = -\hat{p}\hat{q}. \tag{4.40d}$$

$\mathsf{F}_{\rho,1}$ *is asymptotically stable whenever admissible, whereas* $\mathsf{F}_{\rho,i}$ *(*$i = 2, 3, 4$*) are unstable. If admissible,* $\mathsf{F}_{\rho,1}$ *is either globally asymptotically stable or simultaneously asymptotically stable with* M*. In the subsequent proof, we derive the parameter sets explicitly that determine these two scenarios.*

(ii) *In the degenerate case*

$$\alpha\vartheta + \beta\sigma = 0, \tag{4.41}$$

up to two full polymorphisms are admissible. Their equilibrium frequencies are

$$\tilde{\mathsf{F}}_{\rho,1}: \quad \hat{p} = \hat{q} = 1 - \frac{m}{\alpha+\beta}, \quad \hat{D} = \hat{p}(1-\hat{p}), \tag{4.42a}$$

$$\tilde{\mathsf{F}}_{\rho,2}: \quad \hat{p} = \frac{1}{2}\left(1 + \frac{2m}{\alpha-\beta} + \frac{1}{\vartheta}\right), \quad \hat{q} = \frac{1}{2}\left(1 - \frac{2m}{\alpha-\beta} - \frac{\beta}{\alpha\vartheta}\right), \quad \hat{D} = -\hat{p}\hat{q}. \tag{4.42b}$$

$\tilde{\mathsf{F}}_{\rho,1}$ *is globally asymptotically stable whenever admissible, whereas* $\tilde{\mathsf{F}}_{\rho,2}$ *is unstable.*

In both cases, the full polymorphisms are located on the boundary of S_4*, thus no internal full polymorphism exists. Moreover,* M *is globally asymptotically stable if migration is sufficiently large.*

PROOF. In the first part of the proof, we derive some general properties which hold in both cases of the theorem.

M is asymptotically stable if and only if (4.8) holds. It follows from the relations of the critical migration rates m_1^{A}, m_1^{B}, and m^{M} derived in (A.11c) and (A.11f) in the Appendix that under complete linkage ($\rho = 0$), M is asymptotically stable if and only if $m > m^{\mathsf{M}}$, where m^{M} is defined in (4.4e). Global stability for sufficiently strong migration follows from the arguments surrounding equation (4.9).

Although the eigenvalues at the single-locus polymorphisms can be determined explicitly, their formulas are complicated in most of the cases. Instead, we derive the following result about convergence in the interior of S_4: Given $x_1 > 0$, we obtain that

$$\frac{d}{dt}\left(\frac{x_2}{x_1}\right) = -\beta x_2 \frac{1 + \sigma(1 - 2(x_1 + x_3))}{x_1} \leq 0, \tag{4.43a}$$

$$\frac{d}{dt}\left(\frac{x_3}{x_1}\right) = -\alpha x_3 \frac{1 + \vartheta(1 - 2(x_1 + x_2))}{x_1} \leq 0, \tag{4.43b}$$

where the inequalities in (4.43) follow from $(x_1, x_2, x_3, x_4) \in S_4$, and because $1 + \vartheta(1 - 2(x_1 + x_2)) > 0$ and $1 + \sigma(1 - 2(x_1 + x_3)) > 0$ if (4.20) holds. Equality in (4.43) holds if and only if $x_2 = 0$ (4.43a), or $x_3 = 0$ (4.43b), respectively. Thus, we infer that the ω-limit of every trajectory with $x_1 > 0$ is contained in the invariant edge $x_2 = x_3 = 0$ (LaSalle, 1976). On this edge, single-locus theory applies, where A_1B_1 and A_2B_2 correspond to 'alleles' at a diallelic locus as $\rho = 0$. From the arguments above it follows that all single-locus polymorphisms are unstable whenever admissible.

In the following, we derive the equilibrium and stability configuration for the nondegenerate case (i), i.e., assume (4.39) holds. In this case, up to four full polymorphisms may exist, with their equilibrium frequencies given in (4.40). The derivation of their equilibrium frequencies is technical and therefore relegated to Appendix A.6. There, we also show that no internal full polymorphism exists, i.e., equilibria where $0 < \hat{x}_i < 1$ for $i = 1, 2, 3, 4$ are not admissible. All full polymorphisms are on the boundary of S_4. $\mathsf{F}_{\rho,1}$ and $\mathsf{F}_{\rho,2}$ are on the edge $x_2 = x_3 = 0$ of S_4, and $\mathsf{F}_{\rho,3}$ and $\mathsf{F}_{\rho,4}$ are on the boundary $x_1 = 0$ of S_4. If admissible, $\mathsf{F}_{\rho,1}$ and $\mathsf{F}_{\rho,2}$ exhibit positive LD, and $\mathsf{F}_{\rho,3}$ and $\mathsf{F}_{\rho,4}$ exhibit negative LD. If migration is weak, $\mathsf{F}_{\rho,1}$ is given by (4.21) up to first order in m, i.e., $\mathsf{F}_{\rho,1} = \mathsf{F}_{\mathsf{m}}$.

Assuming $\vartheta \neq -\frac{1}{3}$, we define

$$\zeta_5 = -\frac{1 + 3\sigma}{1 + 3\vartheta}, \tag{4.44}$$

and decompose the set (4.20) into:

$$-\frac{1}{3} < \vartheta < 1 \quad \text{and} \quad -\frac{1}{3} \leq \sigma < 1, \tag{4.45a}$$

$$-\frac{1}{3} < \vartheta < 1 \quad \text{and} \quad -1 < \sigma < -\frac{1}{3} \quad \text{and} \quad \alpha \geq \zeta_5\beta, \tag{4.45b}$$

$$-\frac{1}{3} < \vartheta < 1 \quad \text{and} \quad -1 < \sigma < -\frac{1}{3} \quad \text{and} \quad \alpha < \zeta_5\beta, \tag{4.45c}$$

$$-1 < \vartheta < -\frac{1}{3} \quad \text{and} \quad -\frac{1}{3} < \sigma < 1 \quad \text{and} \quad \alpha \leq \zeta_5\beta, \tag{4.45d}$$

$$-1 < \vartheta < -\frac{1}{3} \quad \text{and} \quad -\frac{1}{3} < \sigma < 1 \quad \text{and} \quad \alpha > \zeta_5\beta, \tag{4.45e}$$

$$-1 < \vartheta < -\frac{1}{3} \quad \text{and} \quad -1 < \sigma \leq -\frac{1}{3}. \tag{4.45f}$$

By symmetry, the case $\vartheta = -\frac{1}{3}$ can be obtained analogously to the considerations above and is left to the interested reader (assume $\sigma \neq -\frac{1}{3}$). Assuming (4.39), we define

$$m^* = -\frac{(\alpha(1-\vartheta) + \beta(1-\sigma))^2}{8(\alpha\vartheta + \beta\sigma)}. \tag{4.46}$$

$\mathsf{F}_{\rho,1}$ is admissible if and only if one of the following two conditions holds:

$$m < m^{\mathsf{M}} \quad \text{and either} \quad (4.45a) \quad \text{or} \quad (4.45b) \quad \text{or} \quad (4.45d) \quad \text{holds , or} \tag{4.47a}$$

$$m < m^* \quad \text{and either} \quad (4.45c) \quad \text{or} \quad (4.45e) \quad \text{or} \quad (4.45f) \quad \text{holds.} \tag{4.47b}$$

$\mathsf{F}_{\rho,2}$ is admissible if and only if

$$m^{\mathsf{M}} < m < m^* \quad \text{and either} \quad (4.45c) \quad \text{or} \quad (4.45e) \quad \text{or} \quad (4.45f) \quad \text{holds,} \tag{4.48}$$

where $\mathsf{F}_{\rho,2} = \mathsf{M}$ if and only if $m = m^{\mathsf{M}}$. If one of the cases (4.45a), (4.45b), or (4.45d) holds,

$$\mathsf{F}_{\rho,1} \to \mathsf{M} \iff m \uparrow m^{\mathsf{M}}. \tag{4.49}$$

If one of the cases (4.45c), (4.45e), or (4.45f) holds,

$$\mathsf{F}_{\rho,1} \to \mathsf{F}_{\rho,2} \iff m \uparrow m^*. \tag{4.50}$$

From one-locus theory it follows that $\mathsf{F}_{\rho,1}$ is asymptotically stable within the system where only A_1B_1 and A_2B_2 are present ($x_2 = x_3 = 0$), and $\mathsf{F}_{\rho,2}$ is always unstable. Thus, if one of the cases in (4.45) holds, $\mathsf{F}_{\rho,1}$ is globally asymptotically if $m < m^{\mathsf{M}}$ (where the argument of global stability follows from (4.43)). Therefore, if one of the cases (4.45a), (4.45b), or (4.45d) holds, $\mathsf{F}_{\rho,1}$ is globally asymptotically stable whenever admissible. If one of the cases (4.45c), (4.45e), or (4.45f) holds, $\mathsf{F}_{\rho,1}$ is simultaneously asymptotically stable with M if $m^{\mathsf{M}} < m < m^*$.

Although the conditions for admissibility of $\mathsf{F}_{\rho,3}$ and $\mathsf{F}_{\rho,4}$ can be derived explicitly, they are of complicated form and not so informative, as $\mathsf{F}_{\rho,3}$ and $\mathsf{F}_{\rho,4}$ are unstable (with respect to S_4) whenever admissible. We refrain from presenting their explicit admissibility conditions.

In the final part of the proof, we consider the degenerate case where (4.41) holds. We leave the derivation of the possible equilibria to the interested reader as it is similar to that for case (4.39), which is presented in Appendix A.6. Up to two full polymorphisms are admissible, given by $\tilde{F}_{\rho,1}$ and $\tilde{F}_{\rho,2}$ in (4.42a) and (4.42b), respectively.

The equilibrium frequency at $\tilde{F}_{\rho,1}$ is equivalent to the equilibrium frequency at the full polymorphism maintained in the continuous-time CI model with genic selection (i.e.,

$\vartheta = \sigma = 0$) under complete linkage; see equation (3.14) in BA11. $\tilde{F}_{\rho,1}$ is located on the edge $x_2 = x_3 = 0$ of S_4. It is admissible if and only if

$$m < \alpha + \beta, \tag{4.51}$$

where $\alpha + \beta = m^{\mathsf{M}}$ if (4.41) holds. The eigenvalues at $\tilde{F}_{\rho,1}$ are real and given by

$$-\alpha - \beta - m, \quad -\alpha + \alpha\vartheta\frac{\alpha + \beta - 2m}{\alpha + \beta}, \quad -\beta - \alpha\vartheta\frac{\alpha + \beta - 2m}{\alpha + \beta}. \tag{4.52}$$

Whenever $\tilde{F}_{\rho,1}$ is admissible (4.51), it is asymptotically stable (details not shown). Therefore, it is globally asymptotically stable whenever admissible (see arguments below formula (4.43)).

$\tilde{F}_{\rho,2}$ is located on the surface $x_1 = 0$ of S_4. It is unstable whenever admissible. We refrain from presenting the admissibility conditions of $\tilde{F}_{\rho,2}$ as these are not of interested to our analysis. If dominance is absent ($\vartheta = \sigma = 0$), a case which is included in (4.41), $\tilde{F}_{\rho,2}$ is not admissible. In this case, $\tilde{F}_{\rho,1}$ is unique; see also Theorem 2 in BA11. □

Theorem 4.2 shows that the effect of dominance on the stability and on the (significant) bifurcation pattern of the dynamics (4.3) for completely linked loci is not as pronounced as in the case of LE; cf. Theorem 4.1. An explanation for this might be that heterozygotes cannot be formed by recombination if the loci are completely linked, and that the effects of dominance are evident in heterozygotes only.

4.6. Completely dominant island alleles. In the following section we briefly analyze the CI model with completely dominant island alleles, i.e., $\vartheta = \sigma = 1$.

In Section 4.3, we derived an approximation of the full polymorphism F_{m} under weak migration under the condition that both $1 \leq \vartheta < 1$ and $1 \leq \sigma < 1$ hold. Note that if $\vartheta = \sigma = 1$, the denominators in (4.21) are zero, thus the approximation is not admissible in this case. Assuming $\vartheta = \sigma = 1$, a nonregular perturbation of the globally asymptotically stable equilibrium under no migration, ($\hat{p} = \hat{q} = 1$ and $\hat{D} = 0$), gives the following weak-migration approximation of the equilibrium frequencies:

$$\hat{p} = 1 - \sqrt{\frac{m}{2\alpha}} + \frac{m}{2\rho}\sqrt{\frac{\beta}{\alpha}} - \frac{m}{4\rho^2}\sqrt{\frac{m}{2\alpha}}(3\beta + 2\rho + 6\sqrt{\alpha\beta}) + O(m^2), \tag{4.53a}$$

$$\hat{q} = 1 - \sqrt{\frac{m}{2\beta}} + \frac{m}{2\rho}\sqrt{\frac{\alpha}{\beta}} - \frac{m}{4\rho^2}\sqrt{\frac{m}{2\beta}}(3\alpha + 2\rho + 6\sqrt{\alpha\beta}) + O(m^2), \tag{4.53b}$$

$$\hat{D} = \frac{m}{\rho} - \frac{m}{\rho^2}\sqrt{\frac{m}{2\alpha\beta}}(\sqrt{\alpha} + \sqrt{\beta})(\rho + 2\sqrt{\alpha\beta}) + O(m^2), \tag{4.53c}$$

(higher order terms are needed in several applications of Section 5.3). The approximation (4.53) is valid if and only if $\rho > 0$, i.e., if linkage is not complete.

From arguments in Appendix A.4 it follows that F_m is not necessarily unique: If $\vartheta = \sigma = 1$ holds, up to two additional full polymorphisms may enter the state space under weak migration. In the following we show that at least in the limiting case of LE, F_m is unique for sufficiently weak migration. For complete linkage and sufficiently weak migration, we show that F_m is not unique.

The derivations of the equilibria under LE and under complete linkage in Sections 4.4 and 4.5 remain valid if $\vartheta = \sigma = 1$.

Under LE, if both $\vartheta \to 1$ and $\sigma \to 1$, the full polymorphism F_1 (4.24a) becomes

$$\mathsf{F}_1 : \quad \hat{p} = 1 - \sqrt{\frac{m}{2\alpha}}, \quad \hat{q} = 1 - \sqrt{\frac{m}{2\beta}}, \quad \hat{D} = 0, \tag{4.54}$$

(cf. also $\rho \to \infty$ in (4.53)). Case (i) in Theorem 4.1 can easily be extended to the case where $\vartheta = \sigma = 1$. Therefore, F_1 (4.54) is globally stable whenever admissible, i.e., if and only if $m < 2\min\{\alpha,\beta\}$. As F_1 is the only admissible full polymorphism (see diagram (a) of Figure 1) it follows that $\mathsf{F}_1 = \mathsf{F}_\mathsf{m}$ if migration is weak, and F_m is unique.

Under complete linkage and if $\vartheta \to 1$ and $\sigma \to 1$ hold, the equilibrium $\mathsf{F}_{\rho,1}$ (4.40a) is given by

$$\mathsf{F}_{\rho,1} : \quad \hat{p} = \hat{q} = 1 - \sqrt{\frac{m}{2(\alpha+\beta)}}, \quad \hat{D} = \sqrt{\frac{m}{2(\alpha+\beta)}}\left(1 - \sqrt{\frac{m}{2(\alpha+\beta)}}\right). \tag{4.55}$$

The argument in (4.47a) can easily be extended to $\vartheta = \sigma = 1$, i.e., $\mathsf{F}_{\rho,1}$ is globally asymptotically stable whenever admissible, i.e., if and only if $m < 2(\alpha+\beta) = m^\mathsf{M}$. If migration is weak, $\mathsf{F}_{\rho,1}$ is not the only admissible full polymorphism. In this case, $\mathsf{F}_{\rho,1} = \mathsf{F}_\mathsf{m}$ is simultaneously admissible with the unstable full polymorphism $\mathsf{F}_{\rho,3}$ (4.40c) (details not shown).

5. Applications

5.1. Linkage disequilibrium. In the following, we study the effect of dominance and linkage on the amount of LD in the continuous-time CI model of Section 4. We measure LD by $D = x_1x_4 - x_2x_3$ (as already used above) or by r^2, which is used for statistical purposes (e.g., Nordborg and Tavaré, 2002; Slatkin, 2008):

$$r^2 = \frac{D^2}{p(1-p)q(1-q)}. \tag{5.1}$$

The latter can be interpreted as the squared correlation in allelic state between the two loci.

Bürger and Akerman (2011) showed that in the continuous-time CI model without dominance ($\vartheta = \sigma = 0$), r^2 and D show a different behavior with respect to migration m. If migration is weak, D increases with increasing migration rate whereas r^2 is monotone

decreasing in m (see their Figure 3). In the following, we examine if these results extend to the CI model with dominance. To this aim, we analyze D and r^2 exhibited at the full polymorphism F_m if migration is weak.

From the approximations (4.21c) and (4.53c), and from the assumptions on the parameters it follows that the amount of LD measured by D at F_m increases with increasing migration rate m (provided migration is sufficiently weak), for arbitrary degree of dominance. Next, we calculate r^2 at F_m.

Intermediate dominance. First, we assume $-1 \leq \vartheta < 1$ and $-1 \leq \sigma < 1$. We assume that migration is weak and approximate F_m up to second order in m (details not shown; the approximation up to first order in m is given in (4.21)). We use this approximation to obtain the weak-migration approximation of r^2 at F_m:

$$\begin{aligned}\hat{r}^2 = {} & \frac{\alpha(1-\vartheta)\beta(1-\sigma)}{[\alpha(1-\vartheta)+\rho][\beta(1-\sigma)+\rho]} - \frac{m\rho}{(1-\vartheta)(1-\sigma)[\alpha(1-\vartheta)+\rho]^2[\beta(1-\sigma)+\rho]^2}\cdot \\ & \left(\frac{\alpha\rho(1-\vartheta)^2(1-3\sigma)[\alpha(1-\vartheta)+\rho]+\beta\rho(1-\sigma)^2(1-3\vartheta)[\beta(1-\sigma)+\rho]}{\alpha(1-\vartheta)+\beta(1-\sigma)+\rho}\right. \\ & \left. -2\alpha(1-\vartheta)\beta(1-\sigma)\frac{\alpha\sigma(1-\vartheta)^2+\beta\vartheta(1-\sigma)^2+\rho[\sigma(1-\vartheta)+\vartheta(1-\sigma)]}{\alpha(1-\vartheta)+\beta(1-\sigma)+\rho}\right). \qquad (5.2)\end{aligned}$$

By setting $\vartheta = \sigma = 0$, we obtain $\hat{r}^2$ as given by equation (4.9) in BA11 for no dominance. The equation (5.2) for arbitrary dominance is of complicated form. With the help of *Mathematica* we can show that if $-1 \leq \vartheta \leq 0$ and $-1 \leq \sigma \leq 0$, then $\hat{r}^2$ is monotonically decreasing in m. If $\frac{1}{3} \leq \vartheta < 1$ and $\frac{1}{3} \leq \sigma < 1$, then $\hat{r}^2$ is monotonically increasing in m. If ϑ and σ satisfy other relations than stated above, the effect of gene flow on $\hat{r}^2$ depends heavily on the strength of selection and on the relation between recombination and selection. Although the conditions that determine when $\hat{r}^2$ is monotonically increasing in m can be derived explicitly we refrain from presenting them as these are of very complicated form and we do not gain much insight from them.

In the subsequent paragraph, we study the effect of linkage and dominance on $\hat{D}$ and $\hat{r}^2$. Tighter linkage increases both $\hat{D}$ (4.21c) and $\hat{r}^2$ (5.2), as

$$\frac{\partial \hat{D}}{\partial \rho} < 0 \quad \text{and} \quad \frac{\partial \hat{r}^2}{\partial \rho} < 0. \qquad (5.3)$$

From (5.2) we also derive that

$$\frac{\partial \hat{r}^2}{\partial \vartheta} < 0 \ \text{ and } \ \frac{\partial \hat{r}^2}{\partial \sigma} < 0. \qquad (5.4)$$

Note that by (4.22b), dominance has opposite effects on $\hat{r}^2$ and $\hat{D}$: Whereas dominant island alleles increase the amount of LD measured by $\hat{D}$, they decrease the level of $\hat{r}^2$.

The lower $\hat{r}^2$ the less statistically associated are the alleles. If the island alleles are partially dominant (i.e., $0 < \vartheta < 1$ or $0 < \sigma < 1$ hold), the fitness of heterozygotes is similar to that of adapted homozygotes and the frequency of maladapted haplotypes increases; cf. (4.22c). Therefore, the adaptive alleles are expected to be associated to maladaptive alleles more often compared to the case where at least one island allele is recessive. This may be one explanation why we expect decreased levels of $\hat{r}^2$ if the island alleles are dominant.

We illustrate the effects of linkage and the distinct effect of dominance on $\hat{r}^2$ and $\hat{D}$ in Figure 2 by comparing $\hat{r}^2$ and $\hat{D}$ at F_m for different dominance coefficients as functions of the recombination rate ρ.

Completely dominant island alleles. If the island alleles are completely dominant ($\vartheta = \sigma = 1$), we use the approximation (4.53) of F_m to obtain the approximate r^2 at F_m for $\rho > 0$. It is given by

$$\hat{r}^2 = 2m\frac{\sqrt{\alpha\beta}}{\rho^2}. \tag{5.5}$$

Consequently, $\hat{r}^2$ increases with increasing m. Reduced recombination has a much more pronounced effect on $\hat{r}^2$ than increased selection has. Equation (5.5) shows that with completely dominant island alleles, $\hat{r}^2$ decreases remarkably rapidly as ρ increases.

5.2. Local adaptation and migration load. In this section, we study the joint effects of migration, recombination, and dominance on local adaptation. Immigration of maladapted individuals may severely reduce the mean fitness of a population. This reduction is defined as the migration load. We use the migration load as a measure of local adaptation. For simplicity, we consider one-way migration only, i.e., the CI model.

In the continuous-time CI model (4.3), the mean fitness on the island is given by

$$\bar{w} = \alpha(2p + 2p(1-p)\vartheta - 1) + \beta(2q + 2q(1-q)\sigma - 1). \tag{5.6}$$

Mean fitness is maximized or minimized if the island haplotype ($\hat{p} = \hat{q} = 1$ and $\hat{D} = 0$) or the continental type ($\hat{p} = \hat{q} = 0$ and $\hat{D} = 0$), respectively, is fixed on the island.

Intermediate dominance. If migration is sufficiently weak and dominance parameters satisfy $-1 \le \vartheta < 1$ and $-1 \le \sigma < 1$, (4.21) approximates the asymptotically stable full polymorphism F_m. Inserting its coordinates into (5.6), we obtain the mean fitness at F_m by series expansion. It is given by

$$\hat{\bar{w}} = \alpha + \beta - 2m\left(1 + \frac{\rho}{\alpha(1-\vartheta) + \beta(1-\sigma) + \rho}\right) + O(m^2). \tag{5.7}$$

In the absence of dominance ($\vartheta = \sigma = 0$), equation (5.7) was obtained in BA11; see their equation (4.19b). By $\frac{\partial \hat{\bar{w}}}{\partial \rho} < 0$ it follows that tighter linkage facilitates local adaptation.

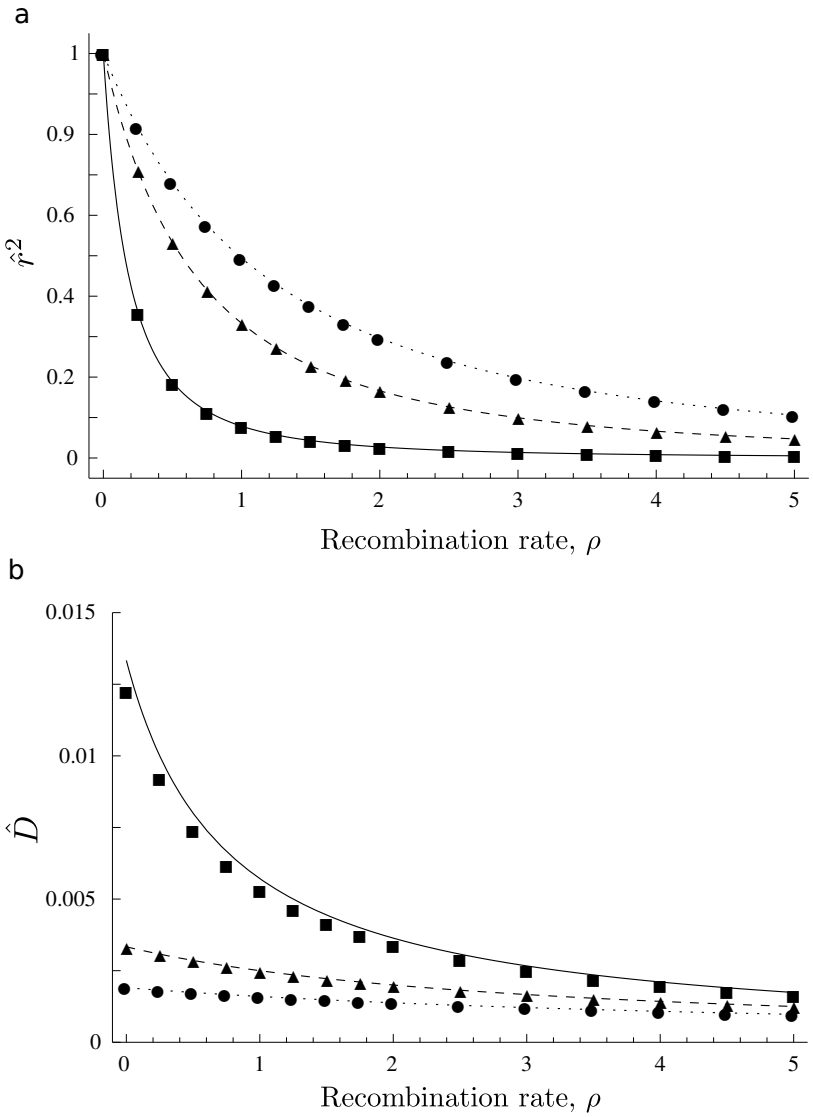

FIGURE 2. The amount of LD exhibited at the fully polymorphic equilibrium F_m in the CI model (4.3). In diagram (a) and (b) we present the LD measure $\hat{r}^2$ and $\hat{D}$ at F_m as a function of ρ, respectively. The lines in diagram (a) show the approximation (5.2) of $\hat{r}^2$. The squares, triangles, and circles correspond to values of $\hat{r}^2$ which were obtained numerically from (4.3). The lines in diagram (b) show the approximation (4.21c) of $\hat{D}$. The squares, triangles, and circles correspond to values of $\hat{D}$ which were obtained numerically from (4.3). In both diagrams we assume $\alpha = 2\beta = 1$, $m = 0.01$, and $\vartheta = \sigma$. The solid line and the squares correspond to $\vartheta = \frac{3}{4}$ (dominant island alleles). The dashed line and the triangles correspond to $\vartheta = 0$ (no dominance). The dotted line and the circles correspond to $\vartheta = -\frac{3}{4}$ (recessive island alleles).

Under LE, mean fitness (5.7) at the asymptotically stable full polymorphism F_1 (4.24a) simplifies to

$$\hat{\bar{w}} = \alpha + \beta - 4m + O(m^2). \tag{5.8a}$$

For complete linkage, mean fitness (5.7) at the asymptotically stable full polymorphism $\mathsf{F}_{\rho,1}$ (4.40a) simplifies to

$$\hat{\bar{w}} = \alpha + \beta - 2m + O(m^2). \tag{5.8b}$$

The approximations of the mean fitness given in (5.8a) and (5.8b) correspond to the exact mean fitnesses at equilibrium in the absence of dominance under LE or complete linkage, respectively; see paragraph below formula (4.19b) in BA11. Thus if $-1 \leq \vartheta < 1$ and $-1 \leq \sigma < 1$ hold, (intermediate) dominance has no effect on the mean fitness on the island up to first order in m if there is LE or complete linkage.

Completely dominant island alleles. For completely dominant island alleles ($\vartheta = \sigma = 1$) and if $\rho > 0$, we derive the mean fitness at F_m using the approximation (4.53). It is given by

$$\hat{\bar{w}} = \alpha + \beta - 2m + \frac{m\sqrt{2m}}{\rho}(\sqrt{\alpha} + \sqrt{\beta}) + O(m^2). \tag{5.9}$$

The migration load increases with increasing recombination rate ρ. In the limit of LE ($\rho \to \infty$), the mean fitness at F_1 (4.54) is

$$\hat{\bar{w}} = \alpha + \beta - 2m. \tag{5.10a}$$

Under complete linkage ($\rho = 0$), the mean fitness at $\mathsf{F}_{\rho,1}$ (4.55) is

$$\hat{\bar{w}} = \alpha + \beta - m. \tag{5.10b}$$

The equations for the mean fitness given in (5.10) are exact, as we derived the exact equilibrium frequencies in these two limiting cases.

From comparison of equations (5.8) – (5.10) it follows that local adaptation is best if linkage is tight ($\rho = 0$) and if the adaptive island alleles are completely dominant ($\vartheta = \sigma = 1$).

We note that for complete linkage such that, effectively, the dynamics (4.3) describes the evolution of one locus with four 'alleles', the load introduced by migration is of similar form to that introduced by mutation: Assume that only mutations of one type appear, for our particular case, only the deleterious mutant A_2B_2 arises on the island with a sufficiently weak mutation rate $\nu > 0$. Then the introduced mutation load is approximately equal to the load that is introduced under weak migration if $\nu = m$. This follows from comparing (5.8b) with the mutation load introduced by A_2B_2 if there is intermediate dominance (then, the mutation load is 2ν), and from comparing (5.10b) with the load introduced if the island alleles are completely dominant (or equivalently,

if the mutant 'allele' A_2B_2 is completely recessive) which is given by ν; see Section 3 in Bürger (2000).

In addition to the analogy of the mutation and migration load we observe that the equilibrium frequencies at the full polymorphism contain square roots of the ratio between the migration rate and the selection coefficient if $\vartheta = \sigma = 1$; see equations (4.53)–(4.55). Similarly, in the continuous-time mutation-selection model the frequency of the completely recessive maladaptive mutant allele is the square root of the ratio between the mutation rate and the selection coefficient.

5.3. Effective migration rate. In this section, we consider a neutral locus, N, located between the two loci under selection, A and B. Recently, the effective migration rate at the neutral locus (introduced by Petry, 1983; Bengtsson, 1985; Barton and Bengtsson, 1986) was studied for the continuous-time CI model (BA11), and for the continuous-time two-deme model (Akerman and Bürger, 2013) for genic selection. Here, we derive an explicit expression for the effective migration rate at the neutral locus N for the continuous-time CI model with dominance.

Recombination between locus A (B) and the neutral locus occurs with rate ρ_1 (ρ_1) such that $\rho = \rho_1 + \rho_2$. Thus, only one crossover event occurs in a sufficiently small time interval. We assume that ρ_1 and ρ_2 are positive, i.e., the neutral locus is not completely linked to a selected site. We consider two variants at the neutral locus, N_1 and N_2, where we denote the frequency of N_1 on the island by n and on the continent by n_c.

We model evolution at the three loci by a system of seven ordinary differential equations for the allele frequencies and linkage disequilibria (p, q, D_{AB}, n, D_{AN}, D_{NB}, D_{ANB}). The equations for the change of p, q, and D_{AB} are given by (4.3). The equations for the allele frequencies at the neutral locus and the associated linkage disequilibria are given in equations (A.32) in the Appendix. The system has an equilibrium with $n = n_c$ and $D_{\mathsf{AN}} = D_{\mathsf{NB}} = D_{\mathsf{ANB}} = 0$. If migration is weak, the population is maintained at F_m. At this globally stable full polymorphism, the Jacobian has block structure,

$$J = \begin{pmatrix} J_\mathsf{S} & 0 \\ 0 & J_\mathsf{N} \end{pmatrix}, \tag{5.11}$$

where J_S is the Jacobian describing convergence of (p, q, D_{AB}) to F_m (4.21), and J_N is the Jacobian describing convergence of $(n, D_{\mathsf{AN}}, D_{\mathsf{NB}}, D_{\mathsf{ANB}})$ to $(n_c, 0, 0, 0)$.

The rate of convergence to equilibrium at the neutral locus is determined by the leading eigenvalue of J_N. In the limit of weak migration, we derived an approximation for this leading eigenvalue λ_N (details not shown; a *Mathematica* notebook is available on request). We define the effective migration rate by $m_{\text{eff}} = -\lambda_\mathsf{N}$ (Bengtsson, 1985; Kobayashi et al., 2008).

Intermediate dominance. First, we assume $-1 \le \vartheta < 1$ and $-1 \le \sigma < 1$. Then, using the approximation (4.21) of F_m, we obtain that up to first order in m the effective migration rate under weak migration is given by

$$m_{\text{eff}} = m\frac{\rho_1}{\rho_1 + \alpha(1-\vartheta)}\frac{\rho_2}{\rho_2 + \beta(1-\sigma)}. \tag{5.12}$$

In the absence of dominance (2.3), equation (5.12) has been derived in BA11. Equation (5.12) shows that if the island alleles are recessive ($-1 \le \vartheta < 0$ and $-1 \le \sigma < 0$), the largest reduction of the effective migration rate occurs.

Completely dominant island alleles. In the limit $\vartheta \uparrow 1$ and $\sigma \uparrow 1$, (5.12) is not admissible because the weak-migration approximation (4.21) of F_m is not admissible. If we use the weak-migration approximation (4.53) of F_m for completely dominant island alleles ($\vartheta = \sigma = 1$) to derive the effective migration rate, we obtain

$$m_{\text{eff}} = m - m\sqrt{2m}\left(\frac{\sqrt{\alpha}}{\rho_1} + \frac{\sqrt{\beta}}{\rho_2}\right). \tag{5.13}$$

As we assume weak migration, $m \ll \{\alpha, \beta, \rho(=\rho_1+\rho_2)\}$, up to first order in m, $m_{\text{eff}} \approx m$ holds. Thus if both island alleles are completely dominant, we do not expect a significant effect of linkage on the effective migration rate of a linked neutral marker allele.

5.4. Differentiation of a quantitative trait. In this section we investigate a quantitative trait that is subject to directional selection. We study how differentiation is affected by dominance and by linkage if the population inhabits two demes and migrants are exchanged at a sufficiently small rate. For this aim, we compare three different measures of differentiation used in the literature (Q_{ST} and two measures of F_{ST}).

The trait is determined by two diallelic, nonepistatic loci. The genotypic values (also called allelic effects) of the alleles A_1, A_2, B_1, and B_2 are $-\frac{1}{2}\gamma_1$, $\frac{1}{2}\gamma_1$, $-\frac{1}{2}\gamma_2$, and $\frac{1}{2}\gamma_2$, respectively, where γ_1 and γ_2 are positive and fixed.

The coefficients of dominance are denoted as ϑ_k and σ_k for deme $k = 1, 2$, where (2.2) holds. If $\vartheta_k = \vartheta$ and $\sigma_k = \sigma$ for $k = 1, 2$, there is no genotype-environment interaction (or DIDID). The matrix G_k of genotypic values in deme $k = 1, 2$ is given by

$$\begin{array}{c} \\ A_1A_1 \\ A_1A_2 \\ A_2A_2 \end{array} \begin{array}{c} \begin{array}{ccc} B_1B_1 & B_1B_2 & B_2B_2 \end{array} \\ \begin{pmatrix} -\gamma_1 - \gamma_2 & -\gamma_1 - \sigma_k\gamma_2 & -\gamma_1 + \gamma_2 \\ -\vartheta_k\gamma_1 - \gamma_2 & -\vartheta_k\gamma_1 - \sigma_k\gamma_2 & -\vartheta_k\gamma_1 + \gamma_2 \\ \gamma_1 - \gamma_2 & \gamma_1 - \sigma_k\gamma_2 & \gamma_1 + \gamma_2 \end{pmatrix} \end{array}. \tag{5.14}$$

$G_{ij,k}$ is the genotypic value of a genotype formed by gametes i and j ($i, j \in \{1,2,3,4\}$) in deme $k = 1, 2$. Without loss of generality, we normalize the allelic effects such that

$$\gamma_1 + \gamma_2 = 1. \tag{5.15}$$

Let s_k be the selection coefficient in deme $k = 1, 2$ acting on the quantitative trait. We assume without loss of generality that $s_1 > 0 > s_2$ and for definiteness $|s_k| \leq 1$ for $k = 1, 2$. The relationship between fitness and genotypic value is given by

$$W_{ij,k} = 1 - s_k G_{ij,k}, \tag{5.16}$$

i.e., $a_k = s_k\gamma_1$, $b_k = s_k\gamma_2$ for $k = 1, 2$ in (2.1). Using (5.16), we obtain that the dynamics of the alleles and LD determining the trait in the two demes is given by (2.14).

Next, we introduce three different measures of differentiation known from the literature that we will use in our subsequent analysis.

Estimators of multilocus F_{ST} are usually defined as weighted averages of one-locus F_{ST} estimators (e.g., Weir and Cockerham 1984; Leviyang and Hamilton, 2011). In our two-locus model, we denote this measure by

$$\bar{F}_{ST} = \frac{1}{2}\left(F^A_{ST} + F^B_{ST}\right), \tag{5.17}$$

where $F^A_{ST} = \frac{\mathrm{Var}(p)}{\bar{p}(1-\bar{p})}$ is the classical differentiation measure at the diallelic locus A (analogously for F^B_{ST} with q instead of p). Using the migration ratio ϕ (3.14), the allele frequencies are averaged according to $\bar{p} = (1-\phi)p_1 + \phi p_2$ (for simplicity, we assume that deme proportions c_1, c_2 are equal to the migration ratios, i.e., $c_1 = 1-\phi$ and $c_2 = \phi$).

In Akerman and Bürger (2013), a new multilocus measure of F_{ST} was defined as a two-locus extension of a fixation index defined by Nagylaki (1998). It is a genuine multilocus version of F_{ST} that measures the covariance of the frequencies of (multilocus) haplotypes. In our diallelic model, it is given by

$$F^X_{ST} = \frac{1}{\sum_i \bar{x}_i(1-\bar{x}_i)} \sum_i \bar{x}_i(1-\bar{x}_i)F^{x_i}_{ST}, \tag{5.18}$$

where

$$F^{x_i}_{ST} = \frac{\mathrm{Var}(x_i)}{\bar{x}_i(1-\bar{x}_i)} \tag{5.19}$$

for $i = 1, 2, 3, 4$. The mean frequency $\bar{x}_i$ of the haplotype i is obtained by averaging according to $\bar{x}_i = (1-\phi)x_{i,1} + \phi x_{i,2}$.

In many applications, Q_{ST} is used as a measure of differentiation of a quantitative trait (Lande 1992; Spitze 1993). It is given by

$$Q_{ST} = \frac{\mathrm{Var}_T(G)}{\mathrm{Var}_T(G) + 2\mathrm{Var}_S(G)}. \tag{5.20}$$

$\mathrm{Var}_S(G)$ is the average genotypic variance within demes, and $\mathrm{Var}_T(G)$ is the genotypic variance among subpopulations (the subscript S denotes subpopulation and T denotes total population). Using ϕ (3.14), these are given by

$$\mathrm{Var}_S(G) = (1-\phi)\mathrm{Var}(G_1) + \phi\mathrm{Var}(G_2), \quad \text{and} \tag{5.21a}$$

$$\mathrm{Var}_T(G) = (1-\phi)\left(\bar{G}_1 - \bar{G}\right)^2 + \phi\left(\bar{G}_2 - \bar{G}\right)^2 = (1-\phi)\phi\left(\bar{G}_1 - \bar{G}_2\right)^2, \tag{5.21b}$$

where

$$\bar{G}_k = \sum_{i,j} G_{ij,k} x_{i,k} x_{j,k}, \tag{5.22a}$$

$$\mathrm{Var}(G_k) = \sum_{i,j} (G_{ij,k} - \bar{G}_k)^2 x_{i,k} x_{j,k}, \tag{5.22b}$$

is the mean genotypic value and the genetic variance within deme $k = 1, 2$, respectively, and

$$\bar{G} = (1-\phi)\bar{G}_1 + \phi\bar{G}_2 \tag{5.22c}$$

is the average genotypic value of the metapopulation. Explicitly, the mean genotypic value in deme $k = 1, 2$ is given by

$$\bar{G}_k = \gamma_1\left[1 - 2p_k(1 + \vartheta_k(1-p_k))\right] + \gamma_2\left[1 - 2q_k(1 + \sigma_k(1-q_k))\right]. \tag{5.23}$$

The genetic variance within deme $k = 1, 2$, $\mathrm{Var}(G_k)$, was derived by Avery and Hill (1978). It can be decomposed into an additive and a dominance component of the variance, $\mathrm{Var}_{\mathrm{add}}(G_k)$ and $\mathrm{Var}_{\mathrm{dom}}(G_k)$. The additive variance itself can be decomposed into the independent contributions of the two loci and an interaction part due to linkage disequilibrium:

$$\mathrm{Var}_{\mathrm{add}}(G_k) = 2\gamma_1^2 p_k(1-p_k) + 2\gamma_2^2 q_k(1-q_k) + 4\gamma_1\gamma_2 D_k. \tag{5.24}$$

The part due to dominance is of more complicated form:

$$\begin{aligned}\mathrm{Var}_{\mathrm{dom}}(G_k) = {} & 2\gamma_1^2\vartheta_k p_k(1-p_k)[2(1-2p_k) + \vartheta_k(1-2p_k(1-p_k))] \\ & + 2\gamma_2^2\sigma_k q_k(1-q_k)[2(1-2q_k) + \sigma_k(1-2q_k(1-g_k))] \\ & + 4\gamma_1\gamma_2 D_k[\vartheta_k(1-2p_k) + \sigma_k(1-2q_k) + \vartheta_k\sigma_k((1-2p_k)(1-2q_k) + 2D_k)].\end{aligned} \tag{5.25}$$

Whenever $\bar{F}_{ST}$, F_{ST}^X, or Q_{ST} attain the value one or zero we speak of complete differentiation or of no differentiation, respectively.

In the following, we present explicit formulas for F_{ST}^X, $\bar{F}_{ST}$, and Q_{ST} at the full polymorphism under weak migration F_{m} (a *Mathematica* notebook with detailed derivations

is available on request). For an easier presentation of our results, we define the total migration rate by $m = m_1 + m_2$ such that $\phi = m_1/m$ in (3.14).

Intermediate dominance. If dominance coefficients satisfy (2.2) and (3.5), the full polymorphism F_m is admissible for weak migration with approximate equilibrium frequencies given in (3.7). It is unique and globally asymptotically stable if (3.6) holds.

If total migration m is sufficiently weak, F_{ST}^A at F_m is given by,

$$\begin{aligned} F_{ST}^A \approx 1 - \frac{m}{\gamma_1}\Bigg(&\frac{1+s_1}{s_1(1-\vartheta_1)}\,\frac{s_1\gamma_1(1-\vartheta_1)+r(1+s_1\vartheta_1\gamma_1+s_1\sigma_1\gamma_2)}{s_1(1-\vartheta_1\gamma_1-\sigma_1\gamma_2)+r(1+s_1\vartheta_1\gamma_1+s_1\sigma_1\gamma_2)} \\ &+\frac{1-s_2}{s_2(1+\vartheta_2)}\,\frac{s_2\gamma_1(1+\vartheta_2)-r(1+s_2\vartheta_2\gamma_1+s_2\sigma_2\gamma_2)}{-s_2(1+\vartheta_2\gamma_1+\sigma_2\gamma_2)+r(1+s_2\vartheta_2\gamma_1+s_2\sigma_2\gamma_2)}\Bigg). \end{aligned} \tag{5.26}$$

The formula for F_{ST}^B is of similar form, which by (5.17) together with (5.26) yields the approximation of $\bar{F}_{ST}$ up to first order in m

$$\begin{aligned} \bar{F}_{ST} \approx 1 &- \frac{m}{2\gamma_1}\Bigg(\frac{1+s_1}{s_1(1-\vartheta_1)}\,\frac{s_1\gamma_1(1-\vartheta_1)+r(1+s_1\vartheta_1\gamma_1+s_1\sigma_1\gamma_2)}{s_1(1-\vartheta_1\gamma_1-\sigma_1\gamma_2)+r(1+s_1\vartheta_1\gamma_1+s_1\sigma_1\gamma_2)} \\ &+\frac{1-s_2}{s_2(1+\vartheta_2)}\,\frac{s_2\gamma_1(1+\vartheta_2)-r(1+s_2\vartheta_2\gamma_1+s_2\sigma_2\gamma_2)}{-s_2(1+\vartheta_2\gamma_1+\sigma_2\gamma_2)+r(1+s_2\vartheta_2\gamma_1+s_2\sigma_2\gamma_2)}\Bigg) \\ &- \frac{m}{2\gamma_2}\Bigg(\frac{1+s_1}{s_1(1-\sigma_1)}\,\frac{s_1\gamma_2(1-\sigma_1)+r(1+s_1\vartheta_1\gamma_1+s_1\sigma_1\gamma_2)}{s_1(1-\vartheta_1\gamma_1-\sigma_1\gamma_2)+r(1+s_1\vartheta_1\gamma_1+s_1\sigma_1\gamma_2)} \\ &+\frac{1-s_2}{s_2(1+\sigma_2)}\,\frac{s_2\gamma_2(1+\sigma_2)-r(1+s_2\vartheta_2\gamma_1+s_2\sigma_2\gamma_2)}{-s_2(1+\vartheta_2\gamma_1+\sigma_2\gamma_2)+r(1+s_2\vartheta_2\gamma_1+s_2\sigma_2\gamma_2)}\Bigg). \end{aligned} \tag{5.27}$$

Recall the definition of F_{ST}^X (5.18). Under sufficiently weak migration, F_{ST}^X at F_m is approximately given by

$$\begin{aligned} F_{ST}^X \approx 1 - \frac{m}{\gamma_1\gamma_2}\Bigg(&\frac{1+s_1}{s_1(1-\vartheta_1)(1-\sigma_1)}\cdot \\ &\frac{s_1\gamma_1\gamma_2(1-\vartheta_1)(1-\sigma_1)+r(1-\vartheta_1\gamma_1-\sigma_1\gamma_2)(1+s_1\vartheta_1\gamma_1+s_1\sigma_1\gamma_2)}{s_1(1-\vartheta_1\gamma_1-\sigma_1\gamma_2)+r(1+s_1\vartheta_1\gamma_1+s_1\sigma_1\gamma_2)} \\ &+\frac{(1-s_2)}{-s_2(1+\vartheta_2)(1+\sigma_2)}\cdot \\ &\frac{-s_2\gamma_1\gamma_2(1+\vartheta_2)(1+\sigma_2)+r(1+\vartheta_2\gamma_1+\sigma_2\gamma_2)(1+s_2\vartheta_2\gamma_1+s_2\sigma_2\gamma_2)}{-s_2(1+\vartheta_2\gamma_1+\sigma_2\gamma_2)+r(1+s_2\vartheta_2\gamma_1+s_2\sigma_2\gamma_2)}\Bigg). \end{aligned} \tag{5.28}$$

Both $\bar{F}_{ST}$ and F_{ST}^X increase with decreasing recombination probability r, i.e., for fixed s_k, ϑ_k, σ_k, m_k ($k = 1, 2$) and fixed allelic effects $\gamma_1, \gamma_2 = 1 - \gamma_1$, differentiation is maximized under complete linkage ($r = 0$) und minimized under free recombination ($r = 1/2$). Under sufficiently weak migration, the difference $F_{ST}^X - \bar{F}_{ST}$ is approximately given by

$$-\frac{mr}{2\gamma_1\gamma_2}\Bigg(\frac{1+s_1}{s_1(1-\vartheta_1)(1-\sigma_1)}\,\frac{(1-\vartheta_1\gamma_1-\sigma_1\gamma_2)(1+s_1\vartheta_1\gamma_1+s_1\sigma_1\gamma_2)}{s_1(1-\vartheta_1\gamma_1-\sigma_1\gamma_2)+r(1+s_1\vartheta_1\gamma_1+s_1\sigma_1\gamma_2)}$$

$$+\frac{1-s_2}{-s_2(1+\sigma_2)(1+\vartheta_2)}\,\frac{(1+\vartheta_2\gamma_1+\sigma_2\gamma_2)(1+\vartheta_2\sigma_2\gamma_1+s_2\sigma_2\gamma_2)}{-s_2(1+\vartheta_2\gamma_1+\sigma_2\gamma_2)+r(1+s_2\vartheta_2\gamma_1+s_2\sigma_2\gamma_2)}\Bigg). \tag{5.29}$$

As the term in bracket is positive, $F_{ST}^X < \bar{F}_{ST}$ if and only if $r > 0$ (with the largest difference obtained if $r = 1/2$). In the absence of dominance ($\vartheta_k = \sigma_k = 0$ for $k = 1, 2$), the difference is given by

$$F_{ST}^X - \bar{F}_{ST} \approx -\frac{mr}{2\gamma_1\gamma_2}\left(\frac{1+s_1}{s_1(r+s_1)} + \frac{1-s_2}{-s_2(r-s_2)}\right), \tag{5.30}$$

and

$$F_{ST}^X \approx 1 - \frac{m}{\gamma_1\gamma_2}\left(\frac{(r+s_1\gamma_1\gamma_2)(1+s_1)}{s_1(r+s_1)} + \frac{(r-s_2\gamma_1\gamma_2)(1-s_2)}{-s_2(r-s_2)}\right). \tag{5.31}$$

Under complete linkage ($r = 0$), (5.29) yields $F_{ST}^X = \bar{F}_{ST}$ and (5.28) produces

$$F_{ST}^X = \bar{F}_{ST} \approx 1 - m\left(2 + \frac{1}{s_1} - \frac{1}{s_2}\right). \tag{5.32}$$

In this special case, $F_{ST}^X (= \bar{F}_{ST})$ is independent of the magnitude of allelic effects.

If $r = 0$ and under dominance such that (3.5) holds, we obtain

$$F_{ST}^X = \bar{F}_{ST} \approx 1 - m\left[\frac{1}{1-\vartheta_1\gamma_1-\sigma_1\gamma_2}\left(1+\frac{1}{s_1}\right) + \frac{1}{1+\gamma_1\vartheta_2+\gamma_2\sigma_2}\left(1-\frac{1}{s_2}\right)\right]. \tag{5.33}$$

Next, we investigate the effects of selection and of dominance on F_{ST}^X and $\bar{F}_{ST}$. For simplicity, we assume that only one locus exhibits dominance (locus A). Setting $\sigma_1 = \sigma_2 = 0$ in the respective formulas of $\bar{F}_{ST}$ (5.27) and F_{ST}^X (5.28), we obtain that independent of the degree of dominance ϑ_k ($k = 1, 2$), both $\bar{F}_{ST}$ and F_{ST}^X increase with increasing selection strength s_1 (and $-s_2$ respectively). As expected, stronger diversifying selection leads to increased population differentiation.

Dominance has qualitatively equal effects on F_{ST}^X and $\bar{F}_{ST}$: With the help of *Mathematica* it is easy to show that if ϑ_1 and ϑ_2 are varied independently,

$$\frac{\partial F_{ST}^X}{\partial\vartheta_1} < 0 \text{ and } \frac{\partial\bar{F}_{ST}}{\partial\vartheta_1} < 0, \text{ and } \frac{\partial F_{ST}^X}{\partial\vartheta_2} > 0 \text{ and } \frac{\partial\bar{F}_{ST}}{\partial\vartheta_2} > 0 \tag{5.34}$$

hold for fixed but arbitrary selection coefficients and recombination probabilities. This implies that locally adaptive recessive alleles (i.e., A_1 in deme 1 if $\vartheta_1 < 0$ and A_2 in deme 2 if $\vartheta_2 > 0$) may elevate population differentiation (measured by F_{ST}^X and $\bar{F}_{ST}$).

Diagram (a) of Figure 3 shows one representative example of the effect of dominance on $\bar{F}_{ST}$ and F_{ST}^X in which we assume $\vartheta_1 = -\vartheta_2$. By (5.34), both $\bar{F}_{ST}$ and F_{ST}^X decrease with increasing ϑ_1. Population differentiation (measured by $\bar{F}_{ST}$ or F_{ST}^X) is largest if $\vartheta_1 = -\vartheta_2 = -1$.

If there is DIDID, i.e., $\vartheta_1 = \vartheta_2 = \vartheta$, F_{ST}^X and $\bar{F}_{ST}$ are not monotone in ϑ. Numerical calculations suggest that F_{ST}^X and $\bar{F}_{ST}$ are always concave with respect to ϑ, with their maximum at intermediate values of ϑ. Unfortunately, no general proof is available.

In diagram (b) of Figure 3 we assume DIDID ($\vartheta_1 = \vartheta_2$) and illustrate the effect of the degree of dominance on F_{ST}^X and $\bar{F}_{ST}$. Due to the symmetry assumptions on selection, F_{ST}^X and $\bar{F}_{ST}$ attain their maximum at $\vartheta_1 = \vartheta_2 = 0$.

Subsequently, we investigate the effects of linkage, selection, and dominance on the third differentiation measure, Q_{ST}, defined in (5.20). Under sufficiently weak migration, Q_{ST} at $\mathsf{F_m}$ is given by

$$Q_{ST} \approx 1 - m\left[(1 - \gamma_1\vartheta_1 - \gamma_2\sigma_1)\left(1 + \frac{1}{s_1}\right) + (1 + \gamma_1\vartheta_2 + \gamma_2\sigma_2)\left(1 - \frac{1}{s_2}\right)\right]. \tag{5.35}$$

From (5.35), we note that under sufficiently weak migration, Q_{ST} is independent of the recombination probability r up to first order in m. Supplemental numerical investigations (not shown) confirm that Q_{ST} is not very sensitive to varying recombination probabilities if migration is weak. However, in contrast to $\bar{F}_{ST}$ and F_{ST}^X (see above), $Q_{ST}(r = 0) < Q_{ST}(r = 1/2)$ may occur (though the difference is very small).

By our assumption on the selection coefficients and allelic effects, the term in brackets in (5.35) is positive, and it increases with increasing selection strength $|s_k|$ ($k = 1, 2$). Thus, the stronger selection the more trait differentiation occurs.

If ϑ_1 and ϑ_2 vary independently, the effect of dominance on Q_{ST} is given by

$$\frac{\partial Q_{ST}}{\partial \vartheta_1} > 0 \quad \text{and} \quad \frac{\partial Q_{ST}}{\partial \vartheta_2} < 0 \tag{5.36}$$

(analogous formulas hold for locus B with σ_1 and σ_2). Thus, differentiation Q_{ST} of the trait is elevated if the locally adaptive alleles are dominant compared with the case where the adaptive alleles are recessive (e.g., trait differentiation will be larger if A_1 is dominant in deme 1, $\vartheta_1 > 0$, and if A_2 is dominant in deme 2, $\vartheta_2 < 0$).

Dominance may have opposite effects on the differentiation of the population (measured by difference in haplotypes, F_{ST}^X, or alleles, $\bar{F}_{ST}$) and on the differentiation of the trait (measured by Q_{ST}). This is illustrated by diagram (a) of Figure 3 which assumes $\vartheta_1 = -\vartheta_2$. There, Q_{ST} increases in ϑ_1, whereas both F_{ST}^X and $\bar{F}_{ST}$ decrease; cf. (5.34) and (5.36).

If there is DIDID, we obtain that

$$\frac{\partial Q_{ST}}{\partial \vartheta} < 0 \iff s_1 > -s_2. \tag{5.37}$$

In diagram (b) of Figure 3, where DIDID is assumed ($\vartheta_1 = \vartheta_2$), Q_{ST} is independent of the degree of dominance because $s_1 = -s_2$ in our example. We note also that under DIDID, Q_{ST} may show a different dependence on dominance than F_{ST}^X and $\bar{F}_{ST}$.

We obtain that $Q_{ST} = F_{ST}^X = \bar{F}_{ST}$ if and only if linkage is complete ($r = 0$) and dominance is absent ($\vartheta_k = \sigma_k = 0$ for $k = 1, 2$); cf. (5.33) and (5.35). The explicit formula is given in (5.32). In the absence of dominance ($\vartheta_k = \sigma_k = 0$ for $k = 1, 2$) it follows from $\frac{\partial F_{ST}^X}{\partial r} < 0$ and $\frac{\partial \bar{F}_{ST}}{\partial r} < 0$, and from Q_{ST} being independent of r (5.35) that

$$F_{ST}^X \leq \bar{F}_{ST} \leq Q_{ST} \tag{5.38}$$

under sufficiently weak migration, where equality holds if and only if $r = 0$.

With dominance, (5.38) does not hold in general. We investigated several numerical examples, which showed that $Q_{ST} < F_{ST}^X$ or $Q_{ST} < \bar{F}_{ST}$ may hold (one example is shown in diagram (a) of Figure 3, where $Q_{ST} < F_{ST}^X < \bar{F}_{ST}$ if $\vartheta_1 = -\vartheta_2 < -\frac{1}{4}$). In Figure 3, the relation given in (5.38) is observed if $\vartheta_1 = 0$ (= ϑ_2, and $\sigma_1 = \sigma_2 = 0$).

In summary, the measures of population differentiation $\bar{F}_{ST}$ and F_{ST}^X (based on differences in alleles or haplotypes) show a qualitatively different behavior with respect to dominance than Q_{ST} (which measures differentiation with respect to the trait).

Completely dominant locally adaptive alleles. If the locally adaptive alleles are completely dominant in their respective deme (3.10), the approximation (3.11) or (3.12) of F_m applies instead of (3.7) if $r > 0$ or $r = 0$, respectively. We will use these approximations in the following to obtain $\bar{F}_{ST}$, F_{ST}^X, and Q_{ST} assuming dominance satisfies (3.10).

If (3.10), we obtain for $r > 0$ the following approximation for F_{ST}^X:

$$F_{ST}^X \approx 1 - \sqrt{\frac{m}{2}}\left(\frac{1}{\sqrt{\gamma_1}} + \frac{1}{\sqrt{\gamma_2}}\right)\left(\sqrt{\frac{1+s_1}{s_1\phi}} + \sqrt{\frac{1-s_2}{-s_2(1-\phi)}}\right), \tag{5.39}$$

and for $r = 0$:

$$F_{ST}^X \approx 1 - \sqrt{\frac{m}{2}}\left(\sqrt{\frac{1+s_1}{s_1\phi}} + \sqrt{\frac{1-s_2}{-s_2(1-\phi)}}\right). \tag{5.40}$$

Thus if $r = 0$, F_{ST}^X is independent of the allelic effects γ_1, γ_2 up to first oder in $\sqrt{m}$. Independently of the recombination probability, we obtain that if dominance coefficients satisfy (3.10) then

$$\bar{F}_{ST} \approx \frac{1}{2}\left(1 + F_{ST}^X\right), \tag{5.41}$$

holds, such that $F_{ST}^X \leq \bar{F}_{ST}$. We note that if $r > 0$, F_{ST}^X and $\bar{F}_{ST}$ are independent of the recombination probability up to first order in $\sqrt{m}$.

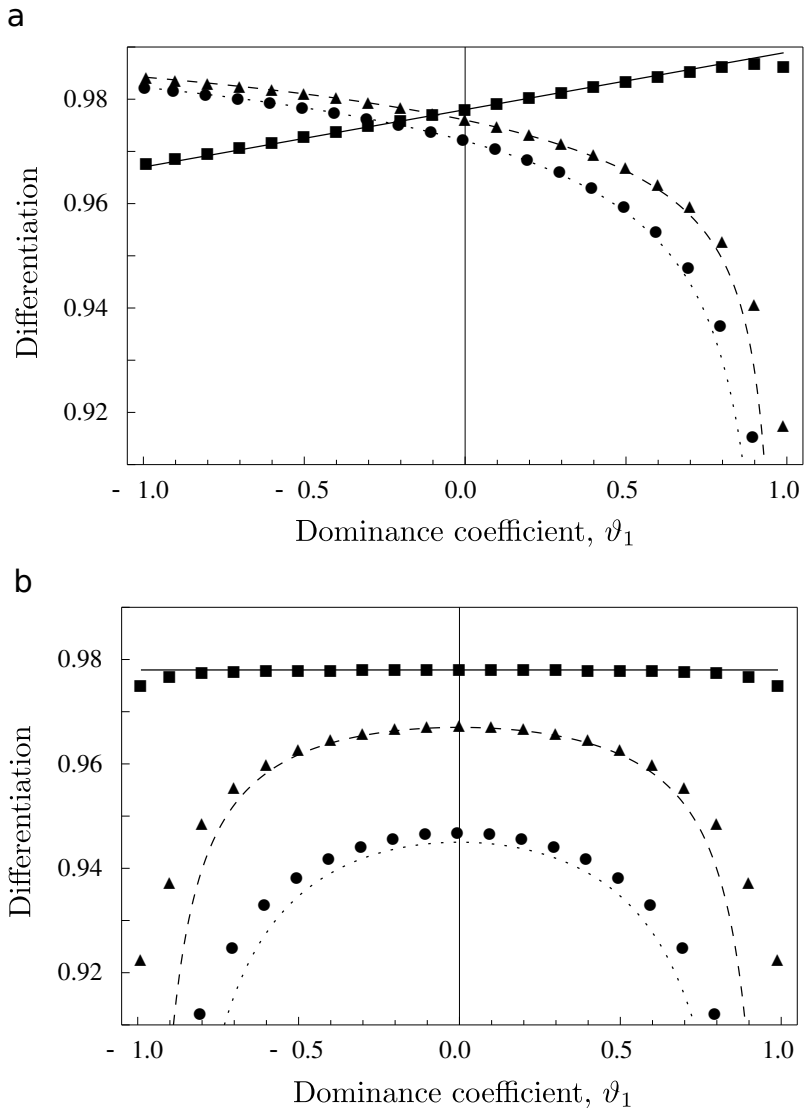

FIGURE 3. Differentiation of a quantitative trait. Diagrams (a) and (b) show F_{ST}^X, $\bar{F}_{ST}$, and Q_{ST} at F_m in the two-deme model (2.7) as functions of the dominance coefficient ϑ_1. In both diagrams we assume $s_1 = -s_2 = 0.1$, $\gamma_1 = \gamma_2 = \frac{1}{2}$, $m = 0.001$, $\phi = \frac{1}{2}$, and $\sigma_1 = \sigma_2 = 0$. Diagram (a) corresponds to the case where $\vartheta_1 = -\vartheta_2$. Diagram (b) corresponds to the case where $\vartheta_1 = \vartheta_2$ (DIDID). In both diagrams, the solid line, the dashed line, and the dotted line correspond to the approximation of Q_{ST} given in (5.35), of $\bar{F}_{ST}$ given in (5.27), and of F_{ST}^X given in (5.28), respectively. Squares, triangles, and circles correspond to values of Q_{ST}, $\bar{F}_{ST}$, and F_{ST}^X at F_m, respectively. They are obtained by calculating the internal equilibrium numerically from (2.7).

Q_{ST} at F_m is given by

$$Q_{ST} \approx 1 - m\left(2 + \frac{1}{s_1} - \frac{1}{s_2}\right). \tag{5.42}$$

Q_{ST} is independent of the recombination probability r and of the allelic effects γ_1, γ_2 up to first order in m. Interestingly, the value of Q_{ST} assumed at F_m for complete dominance (3.10) is equal to the value of Q_{ST} at F_m assumed if dominance is absent (up to first order in m); cf. (5.35) with $\vartheta_1 = \sigma_1 = \vartheta_2 = \sigma_2 = 0$.

6. Discussion

The purpose of our analysis was to determine the combined effects of gene flow, linkage, and dominance on the maintenance of polymorphism, on the amount of LD, and on the degree of local adaptation and of differentiation in a subdivided population inhabiting a heterogeneous environment. To this aim, we studied a diallelic two-locus two-deme model with dominance but no epistasis.

The first part of our analysis focused on the existence and the stability of polymorphic equilibria and on the dependence of the equilibrium configurations on migration, selection, dominance, and recombination. From these results, we derived for the CI model informative approximations for the LD measures D and r^2, the migration load, and the effective migration rate of a linked neutral marker locus. We also studied differentiation at a quantitative trait where migrants are exchanged between two demes in which selection acts in opposite directions. We derived informative approximations of and relations between Q_{ST} and two different measures of F_{ST}.

In Section 2, we introduced the two-deme selection-migration model for two linked diallelic loci exhibiting intermediate dominance, given in (2.7). We assumed discrete and nonoverlapping generations, and ignored epistasis and drift.

In Section 3.1 we assumed that migration is weak. We derived the approximate coordinates (3.7) of the asymptotically stable full polymorphism F_m under the assumption that dominance is intermediate such that (2.2) and (3.5) hold. We showed that, generically, F_m is unique and globally asymptotically stable if dominance coefficients satisfy (3.6). Using (3.7), we analyzed how local allele frequencies, the amount of LD, and the frequency of haplotypes at F_m depend on the degree of dominance; see (3.9). Up to first order in the migration rates m_1 and m_2, the approximation of the equilibrium frequencies and LD (3.7) can be studied separately for each deme. Our results show that if the locally adaptive alleles are dominant within their respective deme, the equilibrium frequencies of the locally adaptive alleles, as well as the equilibrium frequency of the adaptive haplotype is reduced in that deme, whereas the measure of LD in that deme is elevated; cf. (3.9). By (3.8), tighter linkage leads to elevated levels of LD and increases the equilibrium frequency of the locally adaptive alleles within each deme.

We studied the weak-migration dynamics of (2.7) for the special case that the locally adaptive alleles are completely dominant in their respective deme (3.10) in Section 3.1.

The approximation (3.11) of F_m reveals that if the recombination probability is nonnegative, the measure of LD is independent of selection up to first order in the migration rate m_k (for deme $k = 1, 2$) and is approximately the ratio between immigration rate and recombination probability.

In Section 3.2, we analyzed the dynamics (2.7) under weak selection. In this case, the dynamics are approximated by the Cartesian product of two independent loci exhibiting dominance. This system is given in (3.19). This approach can be extended to an arbitrary number of diallelic loci provided epistasis is absent. We derived all possible stability and equilibrium configurations explicitly. In total, six distinct, nondegenerate scenarios can be distinguished; see Proposition 3.1. Only in one generic scenario (where there is average overdominance at both loci) or in the degenerate case of super-symmetric demes, a unique, fully polymorphic equilibrium can be maintained in the population. We identified two scenarios where there exists a unique but unstable full polymorphism, and three remaining cases where no full polymorphism is admissible. Whenever at least one locus exhibits average underdominance (which applies to three of the six possible nondegenerate cases), the dynamics (3.19) shows bistability, i.e., up to four boundary equilibria may be simultaneously asymptotically stable.

In Section 4 we derived the continuous-time continent-island model (CI model) in (4.3) from the discrete-time two-deme migration-selection model (2.7) in the limit of weak selection, weak recombination, and weak migration. Recently, several results were derived for the CI model under genic selection (BA11), and under epistasis in the absence of dominance (Bank et al, 2012). In BA11 the complete equilibrium structure at two recombining diallelic loci in the absence of dominance was derived explicitly for arbitrary strength of selection, recombination, and immigration from the continent. Their results show that tight linkage may act as a strong barrier to maladaptive gene flow. Moreover, they showed that more complicated dynamical behavior (including bistability) may occur if recombination is intermediate (with respect to selection). In contrast to intermediate recombination, in the limiting case of LE or of complete linkage, qualitatively simple bifurcation pattern (where the migration rate m is the bifurcation parameter) are obtained; see Figure 1 in BA11. We complemented their results under no dominance ($\vartheta = \sigma = 0$) by admitting intermediate dominance (2.2) and by deriving the possible equilibrium and stability patterns in the limiting cases of weak migration (Section 4.3), LE (Section 4.4), and complete linkage (Section 4.5).

We derived the approximation (4.21) of the full polymorphism F_m for weak migration. We showed that linkage increases the frequency of the island alleles and the amount of LD. LD is also elevated if the island alleles are dominant.

The dynamics in the absence of dominance and under LE exhibits a single bifurcation pattern with respect to the bifurcation parameter m: Three critical migration rates m°, $m^\bullet$, and $m^\diamond$ exist (which can be calculated explicitly) such that $m^\circ < m^\bullet < m^\diamond$. A unique, globally asymptotically stable full polymorphism is admissible if and only if migration satisfies $m < m^\circ$. If $m^\circ < m < m^\bullet$, the full polymorphism is not admissible and a single-locus polymorphism is globally asymptotically stable. If $m > m^\diamond$, no island allele is maintained. Our results suggest that the degree of dominance has a large effect on the possible equilibrium and stability behavior of the dynamics (4.3) under strong recombination. We identified seven qualitatively different bifurcation patterns for the special case of LE in Theorem 4.1 and Figure 1 for intermediate dominance, i.e., $-1 < \vartheta < 1$ and $-1 < \sigma < 1$. If the dominance coefficients satisfy (4.30), i.e., if the island alleles are dominant or not 'too much' recessive, the bifurcation diagram is qualitatively the same as that under no dominance; see diagram (g) of Figure 1 in BA11 and digram (a) of Figure 1. Whenever the island alleles are sufficiently recessive, the bifurcation diagrams reveal complicated behavior and bistability; see diagrams (b)–(g) of Figure 1. If the island alleles are sufficiently recessive such that either diagram (f) or diagram (g) of Figure 1 applies, four equilibria are simultaneously stable at intermediate migration rates m: one full polymorphism, two single-locus polymorphisms, and the monomorphism.

In Section 4.5, we derived the possible equilibrium and stability configurations of the dynamics (4.3) for complete linkage. In Theorem 4.2, we showed that no internal full polymorphisms exist and that all internal haplotype frequencies converge to the edge $x_2 = x_3 = 0$, so that only the specialist haplotypes A_1B_1 and A_2B_2 remain in the population. We determined the possible equilibrium and stability configurations on this edge, which are qualitatively similar to one diallelic locus exhibiting dominance: If the 'allele' A_1B_1 is dominant, weakly recessive, or if dominance is absent, the full polymorphism is unique on the edge $x_2 = x_3 = 0$, and globally asymptotically stable whenever admissible, i.e., if $m < m^{\mathsf{M}}$ (with m^{M} given in (4.5d)). If the 'allele' A_1B_1 is sufficiently recessive, one full polymorphism is admissible on the edge $x_2 = x_3 = 0$ if $m < m^{\mathsf{M}}$. If $m^{\mathsf{M}} < m < m^*$ (with m^* given in (4.46)), two full polymorphism are admissible, and one full polymorphism is simultaneously asymptotically stable with the monomorphism. The second full polymorphism is unstable. The monomorphism is globally asymptotically stable for sufficiently strong migration.

Compared to the results for no dominance in BA11, our results from Section 4.4 and Section 4.5 show that dominance may increase the number of qualitatively different equilibrium and stability configurations in the two limiting cases of LE or complete linkage. Under complete linkage, the number of different bifurcation scenarios with respect to the degree of dominance is seven, and under LE is two (if only bifurcations

of the asymptotically stable equilibria are considered and unstable ones are neglected). An explanation why dominance elevates the number of bifurcation scenarios for the dynamics in particular under strong recombination may be that recombination facilitates the formation of heterozygotes, in which the effects of dominance become evident only.

Another distinct feature of the CI model with dominance is that bistability may occur (at least) under LE or complete linkage if migration is intermediate. This is not the case in the CI model with genic selection. There, bistability occurs if and only if recombination is intermediate (i.e., of similar strength as selection). Whereas in the CI model with genic selection at most two equilibria are simultaneously asymptotically stable, up to four equilibria may be simultaneously asymptotically stable if the loci exhibit dominance. In particular, this occurs if the island alleles are sufficiently recessive; see Theorem 4.1.

In Section 4.6, we briefly discussed the CI model with completely dominant island alleles ($\vartheta = \sigma = 1$). We derived the approximate coordinates of the full polymorphism under weak migration (4.53), and the explicit coordinates of the full polymorphism under LE (4.54) and under complete linkage (4.55). In all cases, the coordinates depend on the square root of the ratio between migration rate and selection coefficients. This is similar to mutation-selection models with completely recessive deleterious mutants, where the equilibrium frequency at the polymorphism depends on the square root of the ratio between mutation rate and selection coefficient.

Section 5 was devoted to various applications.

In Section 5.1, we studied the amount of LD exhibited at the full polymorphism under weak migration F_m in the CI model. We compared two measures of LD: The classical population-genetic measure D ($= x_1x_4 - x_2x_3$), and r^2 (5.1) which is often used for statistical purposes. Increased levels of ϑ (or σ) result in an increased D, whereas r^2 decreases; see Figure 2. We showed that independently of the degree of dominance, D increases monotonically with increasing migration. In contrast, the measure r^2 may increase or decrease with increasing m. This depends strongly on the values of ϑ and σ. Both D and r^2 increase with increasing linkage.

In Section 5.2, we analyzed the effects of dominance and linkage on population adaptation on the island. To this aim, we calculated explicitly the load on the island introduced by immigration from the continent of the maladaptive type (A_2B_2) if the island population is maintained at the globally asymptotically stable full polymorphism under weak migration F_m. We derived equation (5.7) for the migration load for $-1 \leq \vartheta < 1$ and $-1 \leq \sigma < 1$, and equation (5.9) for completely dominant island alleles ($\vartheta = \sigma = 1$). Our results suggest that independently of the degree of dominance, the migration load is twice as high if the two loci are in LE compared to the case where the loci are completely

linked (up to first order in m); cf. (5.8) and (5.10). If recombination is intermediate, migration load increases with decreasing ϑ or σ. Reduced adaptation is expected if the adaptive island alleles are recessive. In general, migration load decreases with decreasing recombination rate ρ. The smallest decay in mean fitness is expected if the island alleles are completely dominant ($\vartheta = \sigma = 1$) and completely linked ($\rho = 0$). In this case, the migration load is approximately the migration rate m; see (5.10b).

In Section 5.3, we derived the approximation (5.12) for the effective migration rate, m_{eff}, at a linked neutral locus that is located between two selected loci exhibiting dominance in the continuous-time CI model. Our results extend the approximation of the effective migration rate derived in BA11 for the absence of dominance. We proved that gene flow at neutral sites may be severely reduced if the island alleles are recessive or if dominance is absent ($\vartheta \leq 0$, $\sigma \leq 0$). Dominant island alleles ($\vartheta > 0$, $\sigma > 0$) act as much weaker barriers to neutral gene flow than recessive island alleles or as alleles in the absence of dominance. In the limiting case of completely dominant island alleles ($\vartheta = 1$, $\sigma = 1$), we proved that $m_{\text{eff}} \approx m$, i.e., linkage to loci where the adaptive island alleles are completely dominant does not alter the migration rate at neutral sites significantly. Thus, neutral differentiation and effective gene flow at neutral sites heavily depend on the dominance pattern exhibited at the selected loci. Future work will have to study the actual amount and pattern of neutral diversity at such sites in finite populations. Although our analysis of the effective migration rate at a linked marker locus is confined to a continuous-time CI model, we expect an extension to a two deme-model (with weak migration in both directions) to be straightforward and of similar form as already derived by Akerman and Bürger (2013).

In Section 5.4, we studied the evolution of a quantitative trait determined by two diallelic loci exhibiting dominance. We used the discrete-time two-deme model (2.7) and assumed that migration between the two demes is sufficiently weak, such that the (generically unique) globally asymptotically stable full polymorphism F_m is maintained in the population with approximate equilibrium frequencies given in (3.7). Our analysis focused on determining the amount of differentiation in the population. To this aim, we used and compared three distinct measures of differentiation: (i) F_{ST} averaged over the two loci, denoted by $\bar{F}_{ST}$ (5.17), and measuring differentiation of alleles in the population, (ii) A multilocus version of F_{ST}, denoted by F_{ST}^X (5.18), which measures differentiation of haplotypes in the population, (iii) Q_{ST} (5.20), a measure of differentiation of the quantitative trait. For sufficiently weak migration, we derived approximations for $\bar{F}_{ST}$ (5.27), F_{ST}^X (5.28), and Q_{ST} (5.35) at F_m. Our results demonstrate that F_{ST}^X and $\bar{F}_{ST}$ show qualitatively the same behavior with respect to selection, recombination, and the

degree of dominance. Elevated values of F_{ST}^X and $\bar{F}_{ST}$ are expected if the locally adaptive alleles are recessive in their respective deme; see (5.34). This is in contrast to Q_{ST}, which decreases with increasing recessiveness of the locally adaptive alleles (and vice versa); see (5.36). $\bar{F}_{ST}$, F_{ST}^X, and Q_{ST} all increase with decreasing recombination or with increasing strength of selection on the trait. In the absence of dominance, we derived the relation between all three measures in (5.38). In the presence of dominance, (5.38) does not hold in general. Whereas we proved that $F_{ST}^X < \bar{F}_{ST}$ holds for arbitrary dominance (under weak migration), numerical investigations complementing our explicit analysis showed that $Q_{ST} < \bar{F}_{ST}$ and $Q_{ST} < F_{ST}^X$ may occur. In addition, we derived approximations of F_{ST}^X, $\bar{F}_{ST}$, and Q_{ST} for completely dominant island alleles ($\vartheta = \sigma = 1$) in equations (5.39)–(5.42).

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A. Appendix

A.1. Two-deme model: Weak migration. In the absence of migration ($m_1 = m_2 = 0$) and if considering the complete state space $S_4 \times S_4$ there exist four full polymorphisms. Beside F_0 defined in (3.2), the three remaining full polymorphisms (located on the boundary of $S_4 \times S_4$) are given by:

$$\mathsf{F}_0{}^{(2)}: \quad \hat{p}_1 = \hat{q}_1 = 0, \quad \hat{p}_2 = \hat{q}_2 = 1, \quad \hat{D}_1 = \hat{D}_2 = 0, \tag{A.1a}$$

$$\mathsf{F}_0{}^{(3)}: \quad \hat{p}_1 = \hat{q}_2 = 1, \quad \hat{q}_1 = \hat{p}_2 = 0, \quad \hat{D}_1 = \hat{D}_2 = 0, \tag{A.1b}$$

$$\mathsf{F}_0{}^{(4)}: \quad \hat{p}_1 = \hat{q}_2 = 0, \quad \hat{q}_1 = \hat{p}_2 = 1, \quad \hat{D}_1 = \hat{D}_2 = 0. \tag{A.1c}$$

All $\mathsf{F}_0{}^{(i)}$ ($i = 2, 3, 4$) are unstable and generically hyperbolic. We show this for $\mathsf{F}_0{}^{(2)}$ explicitly, the remaining cases are left to the interested reader.

If $k = 1, 2$ the eigenvalues at $\mathsf{F}_0{}^{(2)}$ are given by

$$\lambda_{1,k} = \frac{1 - \alpha_k + \sigma_k\beta_k}{1 - \alpha_k - \beta_k}, \ \lambda_{2,k} = \frac{1 + \vartheta_k\alpha_k - \beta_k}{1 - \alpha_k - \beta_k}, \ \lambda_{3,k} = (1 - r)\frac{1 + \vartheta_k\alpha_k + \sigma_k\beta_k}{1 - \alpha_k - \beta_k}. \tag{A.2}$$

All eigenvalues are positive. $\mathsf{F}_0{}^{(2)}$ is hyperbolic if and only if $\vartheta_k \neq -1$, $\sigma_k \neq 1$ ($k = 1, 2$), or $r \neq \frac{\alpha_1(1+\vartheta_1)+\beta_1(1+\sigma_1)}{1+\vartheta_1\alpha_1+\sigma_1\beta_1} (\leq \frac{1}{2})$. As $\lambda_{1,1} \geq 1$ and $\lambda_{2,1} \geq 1$, $\mathsf{F}_0{}^{(2)}$ is unstable.

In the following we assume that (2.2) holds. Then F_0 is globally asymptotically stable. Provided all equilibria are hyperbolic (which is generically the case, but is not shown here), Theorem 5.4 in Bürger (2009a) can be applied. According to this theorem, unstable full polymorphisms located on the boundary of $S_4 \times S_4$ if $m_1 = m_2 = 0$ may leave the state space under small perturbations by positive migration. This is indeed the case for ${\mathsf{F}_0}^{(i)}$ ($i = 2, 3, 4$). For ${\mathsf{F}_0}^{(2)}$ we show this explicitly, the remaining full polymorphisms are left to the interested reader.

If migration is weak, the perturbation of ${\mathsf{F}_0}^{(2)}$ up to order m_1 and m_2 is given by

$$\hat{p}_1 = -m_1 \frac{(1-\alpha_1-\beta_1)}{\alpha_1(1+\vartheta_1)} \frac{r(1+\vartheta_1\alpha_1+\sigma_1\beta_1)-\alpha_1(1+\vartheta_1)}{r(1+\vartheta_1\alpha_1+\sigma_1\beta_1)-\alpha_1(1+\vartheta_1)-\beta_1(1+\sigma_1)}, \tag{A.3a}$$

$$\hat{q}_1 = -m_1 \frac{(1-\alpha_1-\beta_1)}{\beta_1(1+\sigma_1)} \frac{r(1+\vartheta_1\alpha_1+\sigma_1\beta_1)-\beta_1(1+\sigma_1)}{r(1+\vartheta_1\alpha_1+\sigma_1\beta_1)-\alpha_1(1+\vartheta_1)-\beta_1(1+\sigma_1)}, \tag{A.3b}$$

$$\hat{D}_1 = m_1 \frac{(1-\alpha_1-\beta_1)}{r(1+\vartheta_1\alpha_1+\sigma_1\beta_1)-\alpha_1(1+\vartheta_1)-\beta_1(1+\sigma_1)}, \tag{A.3c}$$

$$\hat{p}_2 = 1 - m_2 \frac{1+\alpha_2+\beta_2}{\alpha_2(1-\vartheta_2)} \frac{r(1+\vartheta_2\alpha_2+\sigma_2\beta_2)+\alpha_2(1-\vartheta_2)}{r(1+\vartheta_2\alpha_2+\sigma_2\beta_2)+\alpha_2(1-\vartheta_2)+\beta_2(1-\sigma_2)}, \tag{A.3d}$$

$$\hat{q}_2 = 1 - m_2 \frac{1+\alpha_2+\beta_2}{\beta_2(1-\sigma_2)} \frac{r(1+\vartheta_2\alpha_2+\sigma_2\beta_2)+\beta_2(1-\sigma_2)}{r(1+\vartheta_2\alpha_2+\sigma_2\beta_2)+\alpha_2(1-\vartheta_2)+\beta_2(1-\sigma_2)}, \tag{A.3e}$$

$$\hat{D}_2 = m_2 \frac{1+\alpha_2+\beta_2}{r(1+\vartheta_2\alpha_2+\sigma_2\beta_2)+\alpha_2(1-\vartheta_2)+\beta_2(1-\sigma_2)}. \tag{A.3f}$$

At this equilibrium, the constraint in (2.11b) in deme 1 is approximately

$$-\min\{0, 1-\hat{p}_1-\hat{q}_1\} = 0 < D_1 < \min\{\hat{p}_1, \hat{q}_1\} \tag{A.4}$$

if migration is sufficiently weak, where by (A.3b) the following relation holds:

$$\hat{D}_1 > 0 \iff r > \frac{\alpha_1(1+\vartheta_1)+\beta_1(1+\sigma_1)}{1+\vartheta_1\alpha_1+\sigma_1\beta_1}. \tag{A.5}$$

From (A.3a) and (A.3b) we note that

$$\hat{p}_1 = \hat{D}_1\left(1 - r\frac{1+\vartheta_1\alpha_1+\sigma_1\beta_1}{\alpha_1(1+\vartheta_1)}\right), \tag{A.6}$$

and obtain the following relation if $\hat{D}_1 > 0$:

$$\hat{p}_1 > 0 \iff r < \frac{\alpha_1(1+\vartheta_1)}{1+\vartheta_1\alpha_1+\sigma_1\beta_1}. \tag{A.7}$$

This is a contradiction to (A.5). Thus, the perturbation of ${\mathsf{F}_0}^{(2)}$ is not in the state space.

In the absence of migration, there exist eight single-locus polymorphisms. It can be shown that four single-locus polymorphisms are admissible under weak migration (one single-locus polymorphism at each marginal one-locus system). The remaining four

single-locus polymorphisms leave the state space under small perturbations. The details are not shown here and are left to the interested reader.

A.2. CI model: gamete dynamics. In Section 4, the dynamics in the continent-island model of the allele frequencies p, q and the measure of LD D is given in (4.3). For some derivations (e.g., in the proof of Theorem 4.2) it is more convenient to work with gamete frequencies x_i ($i = 1, 2, 3, 4$). Using the transformation (2.10) (where we omit the subscript k for the deme, as we keep track of the island types only), the dynamics (4.3) can be rewritten as

$$\dot{x}_1 = \frac{dx_1}{dt} = \alpha x_1(x_3 + x_4)[1 + \vartheta(1 - 2(x_1 + x_2))] \tag{A.8a}$$

$$+ \beta x_1(x_2 + x_4)[1 + \sigma(1 - 2(x_1 + x_3))] - \rho D - m x_1, \tag{A.8b}$$

$$\dot{x}_2 = \frac{dx_2}{dt} = \alpha x_2(x_3 + x_4)[1 + \vartheta(1 - 2(x_1 + x_2))] \tag{A.8c}$$

$$- \beta x_2(x_1 + x_3)[1 + \sigma(1 - 2(x_1 + x_3))] + \rho D - m x_2, \tag{A.8d}$$

$$\dot{x}_3 = \frac{dx_3}{dt} = -\alpha x_3(x_1 + x_2)[1 + \vartheta(1 - 2(x_1 + x_2))] \tag{A.8e}$$

$$+ \beta x_3(x_2 + x_4)[1 + \sigma(1 - 2(x_1 + x_3))] + \rho D - m x_3, \tag{A.8f}$$

$$\dot{x}_4 = \frac{dx_4}{dt} = -\alpha x_4(x_1 + x_2)[1 + \vartheta(1 - 2(x_1 + x_2))] \tag{A.8g}$$

$$- \beta x_4(x_1 + x_3)[1 + \sigma(1 - 2(x_1 + x_3))] - \rho D + m(1 - x_4). \tag{A.8h}$$

It is a system of ordinary differential equations where $(x_1, x_2, x_3, x_4) \in S_4$. In the absence of dominance $\vartheta = \sigma = 0$, (A.8) was derived in BA11.

A.3. CI model: important quantities. In the following section we derive several useful relations between the critical migration rates m_1^{A}, m_2^{A}, m_1^{B}, m_2^{B}, and m^{M} defined in (4.4). These are needed in the proofs of Theorem 4.1 and Theorem 4.2, respectively.

Recall the definitions of ζ_i ($i = 1, 2, 3$) given in (4.28) and define

$$\zeta_4 = -\frac{(1 - \sigma)^2}{8\sigma(1 + \vartheta)}. \tag{A.9}$$

The critical migration rates m_1^{A}, m_1^{B}, m_2^{A}, and m_2^{B} satisfy the following relations (which are independent of the recombination rate ρ): For any $-1 < \vartheta < 1$ and $-1 < \sigma < 1$,

$$0 < m_1^{\mathsf{A}} < m_1^{\mathsf{B}} \iff 0 < \alpha < \zeta_1\beta, \tag{A.10a}$$

$$0 < m_1^{\mathsf{B}} < m_1^{\mathsf{A}} \iff 0 < \zeta_1\beta < \alpha. \tag{A.10b}$$

If $-1 < \vartheta < -\frac{1}{3}$ and $-\frac{1}{3} \le \sigma < 1$ hold, the following relations hold:

$$0 < m_1^{\mathsf{A}} < m_2^{\mathsf{A}} < m_1^{\mathsf{B}} \iff \alpha < \zeta_3\beta, \tag{A.10c}$$

$$0 < m_1^{\mathsf{A}} < m_1^{\mathsf{B}} < m_2^{\mathsf{A}} \iff \zeta_3\beta < \alpha < \zeta_1\beta, \tag{A.10d}$$

$$0 < m_1^{\mathsf{B}} < m_1^{\mathsf{A}} < m_2^{\mathsf{A}} \iff \zeta_1\beta < \alpha. \tag{A.10e}$$

If $-\frac{1}{3} \le \vartheta < 1$ and $-1 < \sigma < -\frac{1}{3}$ hold, the following relations hold:

$$0 < m_1^{\mathsf{A}} < m_1^{\mathsf{B}} < m_2^{\mathsf{B}} \iff \alpha < \zeta_1\beta, \tag{A.10f}$$

$$0 < m_1^{\mathsf{B}} < m_1^{\mathsf{A}} < m_2^{\mathsf{B}} \iff \zeta_1\beta < \alpha < \zeta_4\beta, \tag{A.10g}$$

$$0 < m_1^{\mathsf{B}} < m_2^{\mathsf{B}} < m_1^{\mathsf{A}} \iff \zeta_4\beta < \alpha. \tag{A.10h}$$

If $-1 < \vartheta < -\frac{1}{3}$ and $-1 < \sigma < -\frac{1}{3}$ hold, the following relations hold:

$$0 < m_1^{\mathsf{A}} < m_2^{\mathsf{A}} < m_1^{\mathsf{B}} < m_2^{\mathsf{B}} \iff \alpha < \zeta_3\beta, \tag{A.10i}$$

$$0 < m_1^{\mathsf{A}} < m_1^{\mathsf{B}} < m_2^{\mathsf{A}} < m_2^{\mathsf{B}} \iff \text{either } \sigma \le \vartheta \text{ and } \zeta_3\beta < \alpha < \zeta_1\beta, \text{ or}$$
$$\vartheta < \sigma \text{ and } \zeta_3\beta < \alpha < \zeta_2\beta, \tag{A.10j}$$

$$0 < m_1^{\mathsf{A}} < m_1^{\mathsf{B}} < m_2^{\mathsf{B}} < m_2^{\mathsf{A}} \iff \vartheta < \sigma \text{ and } \zeta_2\beta < \alpha < \zeta_1\beta, \tag{A.10k}$$

$$0 < m_1^{\mathsf{B}} < m_2^{\mathsf{B}} < m_1^{\mathsf{A}} < m_2^{\mathsf{A}} \iff \zeta_4\beta < \alpha, \tag{A.10l}$$

$$0 < m_1^{\mathsf{B}} < m_1^{\mathsf{A}} < m_2^{\mathsf{B}} < m_2^{\mathsf{A}} \iff \text{either } \sigma \le \vartheta \text{ and } \zeta_2\beta < \alpha < \zeta_4\beta, \text{ or}$$
$$\vartheta < \sigma \text{ and } \zeta_1\beta < \alpha < \zeta_4\beta. \tag{A.10m}$$

The critical migration rates m_1^{A}, m_1^{B}, and m^{M} satisfy the following relations (which depend on the recombination rate ρ):

$$0 < m^{\mathsf{M}} < m_1^{\mathsf{A}} < m_1^{\mathsf{B}} \iff 0 < \alpha < \zeta_1\beta \text{ and } \beta(1+\sigma) < \rho < \alpha(1+\vartheta) + \beta(1+\sigma), \tag{A.11a}$$

$$0 < m_1^{\mathsf{A}} < m^{\mathsf{M}} < m_1^{\mathsf{B}} \iff 0 < \alpha < \zeta_1\beta \text{ and } \alpha(1+\vartheta) < \rho < \beta(1+\sigma), \tag{A.11b}$$

$$0 < m_1^{\mathsf{A}} < m_1^{\mathsf{B}} < m^{\mathsf{M}} \iff 0 < \alpha < \zeta_1\beta \text{ and } 0 \le \rho < \alpha(1+\vartheta), \tag{A.11c}$$

$$0 < m^{\mathsf{M}} < m_1^{\mathsf{B}} < m_1^{\mathsf{A}} \iff 0 < \zeta_1\beta < \alpha \text{ and } \alpha(1+\vartheta) < \rho < \alpha(1+\vartheta) + \beta(1+\sigma), \tag{A.11d}$$

$$0 < m_1^{\mathsf{B}} < m^{\mathsf{M}} < m_1^{\mathsf{A}} \iff 0 < \zeta_1\beta < \alpha \text{ and } \beta(1+\sigma) < \rho < \alpha(1+\vartheta), \tag{A.11e}$$

$$0 < m_1^{\mathsf{B}} < m_1^{\mathsf{A}} < m^{\mathsf{M}} \iff 0 < \zeta_1\beta < \alpha \text{ and } 0 \le \rho < \beta(1+\sigma). \tag{A.11f}$$

A.4. CI model: Weak migration. If $m = 0$ in (4.3), beside the globally asymptotically stable monomorphism $\hat{p} = \hat{q} = 1, \hat{D} = 0$ (we denote it in the following by $\mathsf{M}^{(1)}$) and the unstable monomorphism M (4.6) there exist two unstable ME given by

$$\mathsf{M}^{(2)}: \quad \hat{p} = 1,\ \hat{q} = 0,\ \hat{D} = 0, \text{ and} \tag{A.12}$$

$$\mathsf{M}^{(3)}: \quad \hat{p} = 0,\ \hat{q} = 1,\ \hat{D} = 0. \tag{A.13}$$

In the absence of migration, the eigenvalues at $\mathsf{M}^{(1)}$ are

$$-\alpha(1-\vartheta), \quad -\beta(1-\sigma), \quad -\rho-\alpha(1-\vartheta)-\beta(1-\sigma). \tag{A.14}$$

In this case, $\mathsf{M}^{(1)}$ is not hyperbolic if and only if $\vartheta = 1$, or $\sigma = 1$, or $\rho = 0$ and $\vartheta = \sigma = 1$. The eigenvalues at $\mathsf{M}^{(2)}$ if $m = 0$ are

$$-\alpha(1-\vartheta), \quad \beta(1+\sigma), \quad -\rho-\alpha(1-\vartheta)+\beta(1+\sigma), \tag{A.15}$$

where $\mathsf{M}^{(2)}$ is not hyperbolic if and only if $\vartheta = 1$, or $\sigma = -1$, or $\rho = -\alpha(1-\vartheta)+\beta(1+\sigma)$. The eigenvalues at $\mathsf{M}^{(3)}$ if $m = 0$ are

$$\alpha(1+\vartheta), \quad -\beta(1-\sigma), \quad -\rho+\alpha(1+\vartheta)-\beta(1-\sigma), \tag{A.16}$$

such that $\mathsf{M}^{(3)}$ is not hyperbolic if and only if $\vartheta = -1$, or $\sigma = 1$, or $\rho = \alpha(1+\vartheta)-\beta(1-\sigma)$. The eigenvalues at M if $m = 0$ are

$$\alpha(1+\vartheta), \quad \beta(1+\sigma), \quad -\rho+\alpha(1+\vartheta)+\beta(1+\sigma), \tag{A.17}$$

such that M is not hyperbolic if and only if $\vartheta = -1$, or $\sigma = -1$, or $\rho = \alpha(1+\vartheta)+\beta(1+\sigma)$.

If dominance coefficients satisfy $-1 < \vartheta < 1$ and $-1 < \sigma < 1$, generically, F_m (4.21) is the only full polymorphism entering the state space under weak migration. In the nongeneric cases where recombination is such that a monomorphism is not hyperbolic, an additional full polymorphism may enter the state space under weak migration.

In the following we treat the remaining cases where $|\vartheta| = |\sigma| = 1$. If only one locus is completely recessive, up to two three full polymorphisms may enter the state space under weak migration: F_m (4.21), one full polymorphism via M and either one full polymorphism which is a perturbation of $\mathsf{M}^{(3)}$ if $\vartheta = -1$ or one full polymorphism which is a perturbation of $\mathsf{M}^{(2)}$ if $\sigma = -1$. If both island alleles are recessive ($\vartheta = \sigma = -1$), beside F_m up to three additional full polymorphism may enter the state space under weak migration. If one locus is completely dominant, beside F_m (approximated by (4.53) if $\rho > 0$ or by (4.55) if $\rho = 0$, respectively) up to one additional full polymorphisms may enter the state space (if $\vartheta = 1$ or $\sigma = 1$ it is a perturbation of $\mathsf{M}^{(2)}$ or $\mathsf{M}^{(3)}$, respectively). If $\vartheta = \sigma = 1$, in total up to three full polymorphisms may enter the state space under weak migration.

A.5. CI model: Details of the proof of Theorem 4.1. In the following section, we complement the proof of Theorem 4.1. We assume that the two loci are in LE and that the dynamics are given by (4.23). As the dynamics at locus A and locus B in (4.23) are decoupled, the results in Theorem 4.1 are obtained straightforwardly from the Cartesian product of the respective single-locus dynamics known from Nagylaki (1975).

For sufficiently weak migration, only F_1 (4.24a) is admissible. Up to first order in m, it is given by (4.21). For sufficiently strong migration, F_i for $i = 2, 3, 4$ (4.24), may enter the state space. This occurs according to the following conditions given in equations (A.18):

$\mathsf{F}_2 = \mathsf{E}_{\mathsf{A},1}$ if and only if one of the following two conditions holds:

$$-\frac{1}{3} \leq \vartheta < 1 \text{ and } -1 < \sigma < -\frac{1}{3} \text{ and } m = m_1^{\mathsf{B}} < m_1^{\mathsf{A}}, \text{ or} \tag{A.18a}$$

$$-1 < \vartheta < -\frac{1}{3} \text{ and } -1 < \sigma < -\frac{1}{3} \text{ and } m = m_1^{\mathsf{B}} < m_2^{\mathsf{A}}. \tag{A.18b}$$

$\mathsf{F}_3 = \mathsf{E}_{\mathsf{B},1}$ if and only if one of the following two conditions holds:

$$-1 < \vartheta < -\frac{1}{3} \text{ and } -\frac{1}{3} \leq \sigma < 1 \text{ and } m = m_1^{\mathsf{A}} < m_1^{\mathsf{B}}, \text{ or} \tag{A.18c}$$

$$-1 < \vartheta < -\frac{1}{3} \text{ and } -1 < \sigma < -\frac{1}{3} \text{ and } m = m_1^{\mathsf{A}} < m_2^{\mathsf{B}}. \tag{A.18d}$$

$\mathsf{F}_4 = \mathsf{E}_{\mathsf{A},2}$ if and only if

$$-1 < \vartheta < -\frac{1}{3} \text{ and } -1 < \sigma < -\frac{1}{3} \text{ and } m_1^{\mathsf{A}} < m_1^{\mathsf{B}} < m_2^{\mathsf{A}} \text{ and } m = m_1^{\mathsf{B}}. \tag{A.18e}$$

$\mathsf{F}_4 = \mathsf{E}_{\mathsf{B},2}$ if and only if

$$-1 < \vartheta < -\frac{1}{3} \text{ and } -1 < \sigma < -\frac{1}{3} \text{ and } m_1^{\mathsf{B}} < m_1^{\mathsf{A}} < m_2^{\mathsf{B}} \text{ and } m = m_1^{\mathsf{A}}. \tag{A.18f}$$

$\mathsf{F}_4 = \mathsf{M}$ if and only if

$$-1 < \vartheta < -\frac{1}{3} \text{ and } -1 < \sigma < -\frac{1}{3} \text{ and } m = m_1^{\mathsf{A}} = m_1^{\mathsf{B}}. \tag{A.18g}$$

The following relations (A.19) describe the possible cases in which F_1 leaves the state space via collision with a boundary equilibrium:

$\mathsf{F}_1 \to \mathsf{E}_{\mathsf{A},1}$ if and only if one of the following two cases holds:

$$-\frac{1}{3} \leq \vartheta < 1 \text{ and } -\frac{1}{3} \leq \sigma < 1 \text{ and } m_1^{\mathsf{B}} < m_1^{\mathsf{A}} \text{ and } m \uparrow m_1^{\mathsf{B}}, \text{ or} \tag{A.19a}$$

$$-1 < \vartheta < -\frac{1}{3} \text{ and } -\frac{1}{3} \leq \sigma < 1 \text{ and } m_1^{\mathsf{B}} < m_2^{\mathsf{A}} \text{ and } m \uparrow m_1^{\mathsf{B}}. \tag{A.19b}$$

$\mathsf{F}_1 \to \mathsf{E}_{\mathsf{B},1}$ holds if and only if one of the following two cases holds:

$$-\frac{1}{3} \leq \vartheta < 1 \text{ and } -\frac{1}{3} \leq \sigma < 1 \text{ and } m_1^{\mathsf{A}} < m_1^{\mathsf{B}} \text{ and } m \uparrow m_1^{\mathsf{A}}, \text{ or} \tag{A.19c}$$

$$-\frac{1}{3} \leq \vartheta < 1 \text{ and } -1 < \sigma < -\frac{1}{3} \text{ and } m_1^{\mathsf{A}} < m_2^{\mathsf{B}} \text{ and } m \uparrow m_1^{\mathsf{A}}. \tag{A.19d}$$

$\mathsf{F}_1 \to \mathsf{M}$ if and only if one of the following conditions holds:

$$-\frac{1}{3} \leq \vartheta < 1 \text{ and } -\frac{1}{3} \leq \sigma < 1 \text{ and } m \uparrow m_1^{\mathsf{A}} = m_1^{\mathsf{B}}, \text{ or} \tag{A.19e}$$

$$-\frac{1}{3} \le \vartheta < 1 \text{ and } -1 < \sigma < -\frac{1}{3} \text{ and } m \uparrow m_1^{\mathsf{A}} = m_2^{\mathsf{B}}, \text{ or} \tag{A.19f}$$

$$-1 < \vartheta < -\frac{1}{3} \text{ and } -\frac{1}{3} \le \sigma < 1 \text{ and } m \uparrow m_2^{\mathsf{A}} = m_1^{\mathsf{B}}. \tag{A.19g}$$

F_1 never leaves the state space via $\mathsf{E}_{\mathsf{A},2}$ or $\mathsf{E}_{\mathsf{B},2}$.

Also, F_2 and F_3 may leave the state space via collision with a boundary equilibrium. This occurs in the following cases:

$\mathsf{F}_2 \to \mathsf{E}_{\mathsf{B},2}$ if and only if

$$-\frac{1}{3} \le \vartheta < 1 \text{ and } -1 < \sigma < -\frac{1}{3} \text{ and } m_1^{\mathsf{B}} < m_1^{\mathsf{A}} < m_2^{\mathsf{B}} \text{ and } m \uparrow m_1^{\mathsf{A}}. \tag{A.20a}$$

$\mathsf{F}_3 \to \mathsf{E}_{\mathsf{A},2}$ if and only if

$$-1 < \vartheta < -\frac{1}{3} \text{ and } -\frac{1}{3} \le \sigma < 1 \text{ and } m_1^{\mathsf{A}} < m_1^{\mathsf{B}} < m_2^{\mathsf{A}} \text{ and } m \uparrow m_1^{\mathsf{B}}. \tag{A.20b}$$

The following relations (A.21) describe the possible cases in which internal equilibria collide and annihilate each other:

$\mathsf{F}_1 \to \mathsf{F}_2$ if and only if one of the following two conditions holds:

$$-\frac{1}{3} \le \vartheta < 1 \text{ and } -1 < \sigma < -\frac{1}{3} \text{ and } m_2^{\mathsf{B}} < m_1^{\mathsf{A}} \text{ and } m \uparrow m_2^{\mathsf{B}}, \text{ or} \tag{A.21a}$$

$$-1 < \vartheta < -\frac{1}{3} \text{ and } -1 < \sigma < -\frac{1}{3} \text{ and } m_2^{\mathsf{B}} < m_2^{\mathsf{A}} \text{ and } m \uparrow m_2^{\mathsf{B}}. \tag{A.21b}$$

$\mathsf{F}_1 \to \mathsf{F}_3$ if and only if one of the following two conditions holds:

$$-1 < \vartheta < -\frac{1}{3} \text{ and } -\frac{1}{3} \le \sigma < 1 \text{ and } m_2^{\mathsf{A}} < m_1^{\mathsf{B}} \text{ and } m \uparrow m_2^{\mathsf{A}}, \text{ or} \tag{A.21c}$$

$$-1 < \vartheta < -\frac{1}{3} \text{ and } -1 < \sigma < -\frac{1}{3} \text{ and } m_2^{\mathsf{A}} < m_2^{\mathsf{B}} \text{ and } m \uparrow m_2^{\mathsf{A}}. \tag{A.21d}$$

$\mathsf{F}_4 \to \mathsf{F}_2$ if and only if

$$-1 < \vartheta < -\frac{1}{3} \text{ and } -1 < \sigma < -\frac{1}{3} \text{ and } \max\{m_1^{\mathsf{A}}, m_1^{\mathsf{B}}\} < m_2^{\mathsf{A}} < m_2^{\mathsf{B}} \text{ and } m \uparrow m_2^{\mathsf{A}}. \tag{A.21e}$$

$\mathsf{F}_4 \to \mathsf{F}_3$ if and only if

$$-1 < \vartheta < -\frac{1}{3} \text{ and } -1 < \sigma < -\frac{1}{3} \text{ and } \max\{m_1^{\mathsf{A}}, m_1^{\mathsf{B}}\} < m_2^{\mathsf{B}} < m_2^{\mathsf{A}} \text{ and } m \uparrow m_2^{\mathsf{B}}. \tag{A.21f}$$

If $-1 < \vartheta < -\frac{1}{3}$ and $-1 < \sigma < -\frac{1}{3}$ and $m_2^{\mathsf{A}} = m_2^{\mathsf{B}}$ hold, all internal equilibria F_i ($i = 1, 2, 3, 4$) collide and annihilate each other at $m \uparrow m_2^{\mathsf{A}} = m_2^{\mathsf{B}}$.

The stability of the equilibria of the full system (4.23) is obtained as a Cartesian product of the stability of the equilibria in the two single-locus system derived in Nagylaki (1975). Whenever equilibria are admissible, they have real eigenvalues. As already stated in (4.26), F_1 is asymptotically stable whenever admissible. The remaining full

polymorphisms F_i ($i = 2, 3, 4$) are always unstable; cf. (4.27). $\mathsf{E}_{\mathsf{A},1}$ is asymptotically stable if and only if one of the following relations holds:

$$-\frac{1}{3} \leq \vartheta < 1 \text{ and } m_1^{\mathsf{B}} < m < m_1^{\mathsf{A}}, \text{ or} \tag{A.22a}$$

$$-1 < \vartheta < -\frac{1}{3} \text{ and } m_1^{\mathsf{B}} < m < m_2^{\mathsf{A}}, \tag{A.22b}$$

where $-1 < \sigma < 1$ is arbitrary. Analogously, $\mathsf{E}_{\mathsf{B},1}$ is asymptotically stable if and only if one of the following relations holds:

$$-\frac{1}{3} \leq \sigma < 1 \text{ and } m_1^{\mathsf{A}} < m < m_1^{\mathsf{B}}, \text{ or} \tag{A.23a}$$

$$-1 < \sigma < -\frac{1}{3} \text{ and } m_1^{\mathsf{A}} < m < m_2^{\mathsf{B}}, \tag{A.23b}$$

where $-1 < \vartheta < 1$ is arbitrary. As $\mathsf{E}_{\mathsf{A},2}$ and $\mathsf{E}_{\mathsf{B},2}$ arise from the Cartesian product of unstable equilibria in the one-locus model, they are always unstable within the full dynamics (4.23). From (4.8) and (4.5d) it follows that M is asymptotically stable if and only if

$$m > \max\{m_1^{\mathsf{A}}, m_1^{\mathsf{B}}\}. \tag{A.24}$$

Now we have all ingredients to finish the proof. In the following, we assume w.l.o.g. that (4.29) holds. Then, by (A.10a) we need to consider the case $m_1^{\mathsf{A}} < m_1^{\mathsf{B}}$ only.

Under the assumption of (4.29), by (A.24) and (A.10a) it follows that

$$\mathsf{M} \text{ is asymptotically stable} \iff m > m_1^{\mathsf{B}}. \tag{A.25}$$

Assume $-\frac{1}{3} < \vartheta < 1$ and $-\frac{1}{3} < \sigma < 1$ hold. $\mathsf{E}_{\mathsf{A},1}$ and $\mathsf{E}_{\mathsf{B},1}$ are admissible if and only if (4.12a) and (4.16a) holds, respectively. By (4.13) and (4.17), $\mathsf{E}_{\mathsf{A},2}$ and $\mathsf{E}_{\mathsf{B},2}$ are not admissible. By (4.25), F_1 is the only full polymorphism that may be admissible in this case. Applying (4.29) and (A.10a) to (4.15a) and (A.19c) it follows that $\mathsf{F}_1 \to \mathsf{E}_{\mathsf{B},1}$ and $\mathsf{E}_{\mathsf{A},1} \to \mathsf{M}$ if $m \uparrow m_1^{\mathsf{A}}$. By (A.23a), at collision, F_1 exchanges stability with $\mathsf{E}_{\mathsf{B},1}$. $\mathsf{E}_{\mathsf{B},1}$ leaves the state space via M if $m \uparrow m_1^{\mathsf{B}}$; cf. (4.19a). By (A.25), it exchanges stability with M. This gives (4.30) in case (i) of Theorem 4.1 and diagram (a) of Figure 1.

The remaining cases of Theorem 4.1 can be derived similarly. As their derivation is lengthy and as it mainly consists of combing the relations given in (A.10) with the results given in this proof above, we leave them to the interested reader.

A.6. CI model: Details of the proof of Theorem 4.2. In the following section, we complement the proof of Theorem 4.2 and derive the admissible full polymorphisms of

the continuous-time CI model in the absence of recombination, $\rho = 0$. The corresponding equations are obtained by setting $\rho = 0$ in (A.8):

$$\dot{x}_1 = x_1 \left[\alpha(x_3 + x_4)(1 + \vartheta(1 - 2(x_1 + x_2))) \right. \tag{A.26a}$$

$$\left. + \beta(x_2 + x_4)(1 + \sigma(1 - 2(x_1 + x_3))) - m\right], \tag{A.26b}$$

$$\dot{x}_2 = x_2 \left[\alpha(x_3 + x_4)(1 + \vartheta(1 - 2(x_1 + x_3))) \right. \tag{A.26c}$$

$$\left. + \beta(x_1 + x_3)(1 + \sigma(1 - 2(x_2 + x_4))) - m\right], \tag{A.26d}$$

$$\dot{x}_3 = x_3 \left[\alpha(x_1 + x_2)(1 + \vartheta(1 - 2(x_3 + x_4))) \right. \tag{A.26e}$$

$$\left. + \beta(x_2 + x_4)(1 + \sigma(1 - 2(x_1 + x_3))) - m\right], \tag{A.26f}$$

where $\dot{x}_4 = -(\dot{x}_1 + \dot{x}_2 + \dot{x}_3)$.

First we show that internal equilibria of (A.26) do not exist. Therefore, we set $x_4 = 1 - x_1 - x_2 - x_3$ in (A.26) and assume that $0 < x_i < 1$ for all $i = 1, 2, 3, 4$. Then, equilibria of (A.26) satisfy

$$\alpha(x_3 + x_4)[1 + \vartheta(1 - 2(x_1 + x_2))] + \beta(x_2 + x_4)[1 + \sigma(1 - 2(x_1 + x_3))] - m = 0, \tag{A.27a}$$

$$\alpha(x_3 + x_4)[1 + \vartheta(1 - 2(x_1 + x_3))] + \beta(x_1 + x_3)[1 + \sigma(1 - 2(x_2 + x_4))] - m = 0, \tag{A.27b}$$

$$\alpha(x_1 + x_2)[1 + \vartheta(1 - 2(x_3 + x_4))] + \beta(x_2 + x_4)[1 + \sigma(1 - 2(x_1 + x_3))] - m = 0. \tag{A.27c}$$

By expressing m from equation (A.27a) and inserting it into (A.27b) and (A.27c), these two equations transform into:

$$-\beta[1 + \sigma(1 - 2(x_1 + x_3))] = 0, \tag{A.28a}$$

$$-\alpha[1 + \vartheta(1 - 2(x_1 + x_2))] = 0. \tag{A.28b}$$

Solving this system of equations yields the manifold

$$\hat{x}_2 = \frac{1}{2}\left(1 + \frac{1}{\vartheta} - 2\hat{x}_1\right) \quad \text{and} \quad \hat{x}_3 = \frac{1}{2}\left(1 + \frac{1}{\sigma} - 2\hat{x}_1\right), \tag{A.29}$$

where $\hat{x}_1 \in [0, 1]$ and $\hat{x}_4 = 1 - \hat{x}_1 - \hat{x}_2 - \hat{x}_3$. Reinserting this solution into (A.27) we obtain that this manifold is a solution of (A.27) if and only if $m = 0$. Moreover, this solution is not in S_4. We leave this simple derivation to the interested reader. Thus we showed that solutions of (A.26) are not internal.

In the following we derive the full polymorphism on the boundary of S_4.

Setting $x_1 = 0$, we obtain from (A.26) the two full polymorphisms $\mathsf{F}_{\rho,3}$ (4.40c) and $\mathsf{F}_{\rho,4}$ (4.40d).

Setting $x_2 = 0$, (A.26) yields the full polymorphism $\mathsf{F}_{\rho,1}$ (4.40a) and $\mathsf{F}_{\rho,2}$ (4.40c), and two solutions

$$\hat{x}_3 = \frac{\beta\vartheta(\vartheta - \sigma(2-\vartheta)) \pm \sqrt{\beta\vartheta^4(\beta(1-\sigma)^2 + 8m\sigma)}}{4\beta\sigma\vartheta^2}, \quad \hat{x}_1 = \frac{1+\vartheta}{2\vartheta} \tag{A.30}$$

which are not in S_4 if the dominance coefficients satisfy (4.20).

Setting $x_3 = 0$, (A.26) yields the full polymorphism $\mathsf{F}_{\rho,1}$ and $\mathsf{F}_{\rho,2}$, and two solutions

$$\hat{x}_2 = \frac{\alpha\sigma(\sigma - \vartheta(2-\sigma)) \pm \sqrt{\alpha\sigma^4(\alpha(1-\vartheta)^2 + 8m\vartheta)}}{4\alpha\vartheta\sigma^2}, \quad \hat{x}_1 = \frac{1+\sigma}{2\sigma} \tag{A.31}$$

which are not in S_4 if the dominance coefficients satisfy (4.20).

No equilibria exist on the surface $x_4 = 0$.

A.7. The dynamics at a linked neutral locus. In Section 5.3, we derive the effective migration rate at a neutral locus N linked to the loci under selection. Recombination between locus A (B) and N occurs with rate ρ_1 (ρ_2), such that $\rho = \rho_1 + \rho_2$ is the recombination rate between locus A and B. Evolution at the three loci is described by a system of seven ordinary differential equations for the allele frequencies and linkage disequilibria (p, q, D_{AB}, n, D_{AN}, D_{NB}, D_{ANB}). The equations for the change of p, q, and D_{AB} are given by (4.3). The allele frequency of N_1 at the neutral locus evolves according to

$$\dot{n} = \alpha(1 + \vartheta(1-2p))D_{\mathsf{AN}} + \beta(1 + \sigma(1-2q))D_{\mathsf{NB}} + m(n_c - n), \tag{A.32a}$$

where n_c denotes the frequency of allele N_1 within immigrants. The rates of change of LD involving the neutral locus are given by

$$\begin{aligned}
\dot{D}_{\mathsf{AN}} =& -\rho_1 D_{\mathsf{AN}} + \alpha(1-2p)(1+\vartheta(1-2p))D_{\mathsf{AN}} + \beta(1+\sigma(1-2q))D_{\mathsf{ANB}} \\
&- mp(n_c - n), && \text{(A.32b)} \\
\dot{D}_{\mathsf{NB}} =& -\rho_2 D_{\mathsf{NB}} + \beta(1-2q)(1+\sigma(1-2q))D_{\mathsf{NB}} + \alpha(1+\vartheta(1-2q))D_{\mathsf{ANB}} \\
&- mq(n_c - n), && \text{(A.32c)} \\
\dot{D}_{\mathsf{ANB}} =& -\rho D_{\mathsf{ANB}} + [\alpha(1-2p)(1-\vartheta(1-2p)) + \beta(1-2q)(1+\sigma(1-2q))]D_{\mathsf{ANB}} \\
&- 2[\alpha(1+\vartheta(1-2p))D_{\mathsf{AN}} + \beta(1+\sigma(1-2q))D_{\mathsf{NB}}]D_{\mathsf{AB}} \\
&- m(D_{\mathsf{ANB}} - pD_{\mathsf{NB}} - qD_{\mathsf{AN}}) + m(pq - D_{\mathsf{AB}})(n_c - n). && \text{(A.32d)}
\end{aligned}$$

Genic selection is obtained if $\vartheta = \sigma = 0$, a case studied in BA11. The equations describing evolution at the neutral locus therein, i.e., equations (4.25), (4.26), and (4.28), contain errors. Instead of their equations (4.25) and (4.26), the correct dynamics are obtained from (A.32) with $\vartheta = \sigma = 0$. We point out that formula (4.30) in BA11 for the effective migration rate is not affected by these errors.

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References

Akerman, A. The consequences of dominance and gene flow for local adaptation and differentiation at two linked loci. Submitted

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Avery, P.J., Hill, W.G. 1978. The effect of linkage disequilibrium on the genetic variance of a quantitative trait. Advanc. in Appl. Prob. 10, 4-6.

Bank, C., Bürger, R., Hermisson, J. 2012. The limits to parapatric speciation: Dobzhansky-Muller incompatibilities in a continent-island model. Genetics 191, 845-865.

Barton, N.H. 1983. Multilocus clines. Evolution 37, 454-471.

Barton, N.H. 2010. What role does natural selection play in speciation? Phil. Trans. R. Soc. B. 365, 1825-1840.

Barton, N.H., Bengtsson, B.O. 1986. The barrier to genetic exchange between hybridising populations. Heredity 56, 357-376.

Bengtsson, B.O. 1985. The flow of genes through a genetic barrier. In: Evolution Essays in honour of John Maynard Smith, Greenwood, J.J., Harvey, P.H., and Slatkin, M. (eds), pp. 31-42. Cambridge: University Press.

Blanquart, F., Gandon, S., Nuismer, S.L. 2012. The effects of migration and drift on local adaptation to a heterogeneous environment. J. Evol. Biol. 25, 1351-1363.

Bulmer, M.G. 1972. Multiple Niche Polymorphism. Amer. Natur. 106, 254–257.

Bürger, R. 2000. The Mathematical Theory of Selection, Recombination, and Mutation. Wiley, Chichester.

Bürger, R. 2009a. Multilocus selection in subdivided populations I. Convergence properties for weak or strong migration. J. Math. Biol. 58, 939-978.

Bürger, R. 2009b. Multilocus selection in subdivided populations II. Maintenance of polymorphism under weak or strong migration. J. Math. Biol. 58, 979-997.

Bürger, R. 2009c. Polymorphism in the two-locus Levene model with nonepistatic directional selection. Theor. Popul. Biol. 76, 214-228.

Bürger, R. 2010. Evolution and polymorphism in the multilocus Levene model with no or weak epistasis. Theor. Popul. Biol. 78, 123-138.

Bürger, R., Akerman, A. 2011. The effects of linkage and gene flow on local adaptation: A two-locus continent-island model. Theor. Popul. Biol. 80, 272-288.

Charlesworth, B., Nordborg, M., Charlesworth, D. 1997. The effects of local selection, balanced polymorphism and background selection on equilibrium patterns of genetic diversity in subdivided populations. Genetical Research 70, 155-174.

Charlesworth, B., Charlesworth, D., 2010. Elements of Evolutionary Genetics. Roberts & Co., Greenwood Village, Colorado.

Charlesworth, D., Charlesworth, B. 1979. Selection on recombination in clines. Genetics 91, 581-589.

Chasnov, J.R. 2012. Equilibrium properties of a multi-locus, haploid-selection, symmetric-viability model. Theor. Popul. Biol. 81, 119-130.

Christiansen, F.B., Feldman, M. 1975. Subdivided populations: A review of the one- and two-locus deterministic theory. Theor. Popul. Biol. 7, 13-38.

Conley, C. 1978. Isolated invariant sets and the Morse index. NSF CBMS Lecture Notes 38. Providence, RI.: Amer. Math. Soc.

Conrad, D.F., Andrews, T.D., Carter, N.P., Hurles, M.E. and J.K. Pritchard 2006. A high-resolution survey of deletion polymorphism in the human genome. Nature Genet. 38, 7581.

Cutter, A.D., Baird, S.E., Charlesworth, D. 2006. High nucleotide polymorphism and rapid decay of linkage disequilibrium in wild populations of *Caenorhabditis remanei*. Genetics 174, 901913.

De, A., Durrett, R. 2007. Stepping-stone spatial structure causes slow decay of linkage disequilibrium and shifts the site frequency spectrum. Genetics 176, 969981.

Deakin, M.A.B. 1966. Sufficient conditions for genetic polymorphism. Amer. Natur. 100, 690-692.

Ewens, W.J. 1969. Mean fitness increases when fitnesses are additive. Nature 221, 1076.

Eyland, E.A. 1971. Moran's island migration model. Genetics 69, 399-403.

Feder, J.L., Gejji, R., Yeaman, S., Nosil, P. 2012. Establishment of new mutations under divergence and genome hitchhiking. Phil. Trans. R. Soc. B. 367, 461-474.

Fusco, D., Uyenoyama, M. 2011. Effects of polymorphism for locally adapted genes on rates of neutral introgression in structured populations. Theor. Popul. Biol. 80, 121-131.

Griswold, C.K. 2006. Gene flows effect on the genetic architecture of a local adaptation and its consequences for QTL analyses. Heredity 96, 445453.

Hadeler, K.P., Glas, D. 1983. Quasimonotone systems and convergence to equilibrium in a population genetic model. J. Math. Anal. Appl. 95, 297-303.

Haldane, J.B.S. 1930. A mathematical theory of natural and artificial selection. Part VI. Isolation. Proc. Camb. Phil. Soc. 26, 220-230.

Hernandez, R.D., Hubisz, M.J., Wheeler, D.A., et al. 2007. Demographic histories and patterns of linkage disequilibrium in Chinese and Indian Rhesus Macaques. Science 316, 240-243.

Karlin, S. 1982. Classification of selection-migration structures and conditions for a protected polymorphism. Evol. Biol. 14, 61-204.

Karlin, S., Feldman, M.W. 1970. Convergence to equilibrium of the two locus additive viability model. J. Appl. Prob. 7, 262-271.

Karlin, S., McGregor, J. 1972. Polymorphism for genetic and ecological systems with weak coupling. Theor. Popul. Biol. 3, 210-238.

Kawecki, T.J., Ebert, D. 2004. Conceptual issues in local adaptation. Ecology letters 7, 1225-1241.

Kimura, M. 1965. Attainment of quasi linkage equilibrium when gene frequencies are changing by natural selection. Genetics 52, 875-890.

King, R.B., Lawson, R. 1995. Color-pattern variation in Lake Erie Water snakes: The role of gene flow. Evolution 49, 885-896.

Kirkpatrick, M., Barton, N.H. 2006. Chromosome inversions, local adaptation and speciation. Genetics 173, 419-434.

Kobayashi, Y., Hammerstein, P., Telschow, A. 2008. The neutral effective migration rate in a mainland-island context. Theor. Popul. Biol. 74, 84-92.

Kobayashi, Y., Telschow, A. 2011. The concept of effective recombination rate and its application in speciation theory. Evolution 65, 617-628.

Kopp, M., Hermisson, J. 2006. The evolution of genetic architecture under frequency-dependent disruptive selection. Evolution 60, 15371550.

Lande, R. 1992. Neutral theory of quantitative genetic variance in an island model with local extinction and colonization. Evolution 46, 381-389.

LaSalle, J.P. 1976. The Stability of Dynamics Systems. SIAM, Philadelphia.

Lenormand, T. 2002. Gene flow and the limits to natural selection. Trends Ecol. Evol. 17, 183-189.

Lenormand, T., Otto, S.P. 2000. The evolution of recombination in a heterogeneous environment. Genetics 156, 423-438.

Leviyang, S., Hamilton, M.B. 2011. Properties of Weir and Cockerham's F_{ST} estimators and associated bootstrap confidence intervals. Theor. Popul. Biol. 79, 39-52.

Li, W.-H., Nei, M. 1974. Stable linkage disequilibrium without epistasis in subdivided populations. Theor. Popul. Biol. 6, 173-183.

Maynard Smith, J. 1970. Genetic polymorphism in a varied environment. Amer. Natur. 104, 487-490.

McVean, G.A.T. 2002. A genealogical interpretation of linkage disequilibrium. Genetics 162, 987-991.

Nagylaki, T. 1975. Conditions for the existence of clines. Genetics 80, 595-615.

Nagylaki, T. 1992. Introduction to Theoretical Population Genetics. Springer, Berlin Heidelberg

Nagylaki, T. 1998. Fixation indices in subdivided populations. Genetics 148, 1325-1332.

Nagylaki, T. 2009. Polymorphism in multiallelic migrationselection models with dominance. Theor. Popul. Biol. 75, 239-259.

Nagylaki, T. 2009. Evolution under the multilocus Levene model. Theor. Popul. Biol. 76, 197-213.

Nagylaki, T. 2011. The influence of partial panmixia on neutral models of spatial variation. Theor. Popul. Biol. 79, 19-38.

Nagylaki, T. 2012. Clines with partial panmixia in an unbounded unidimensional habitat. Theor. Popul. Biol. 82, 22-28.

Nagylaki, T., Hofbauer, J., Brunovský, P. 1999. Convergence of multilocus systems under weak epistasis or weak selection. J. Math. Biol. 38, 103-133.

Nagylaki, T., Lou, Y. 2001. Patterns of multiallelic polymorphism maintained by migration and selection. Theor. Popul. Biol. 59, 297-313.

Nagylaki, T., Lou, Y. 2007. Evolution under multiallelic migration-selection models. Theor. Popul. Biol. 72, 21-40.

Nagylaki, T., Lou, Y. 2008. The dynamics of migration-selection models. In: Friedman, A. (ed) Tutorials in Mathematical Biosciences IV. Lect. Notes Math. 1922, pp. 119 - 172. Springer, Berlin Heidelberg New York.

Nordborg, M., Tavaré, S. 2002. Linkage disequilibrium: what history has to tell us. Trends Genet. 18, 8390.

Ohta, T. 1982. Linkage disequilibrium with the island model. Genetics 101, 139-155.

Peischl, S. 2010. Dominance and the maintenance of polymorphism in multiallelic migration-selection models with two demes. Theor. Popul. Biol. 78, 12-25.

Petry, D. 1983. The effect on neutral gene flow of selection at a linked locus. Theor. Popul. Biol. 23, 300-313.

Prout, T. 1968. Sufficient conditions for multiple niche polymorphism. Amer. Natur. 102, 493-496.

Pylkov,K.V., Zhivotovsky, L.A., Feldman, M.W. 1998. Migration versus mutation in the evolution of recombination under multilocus selection. Genetical Research 71, 247-256.

Remington D.L., Thornsberry, J.M., Matsuoka Y., et al. 2001. Structure of linkage disequilibrium and phenotypic associations in the maize genome. Proc. Natl. Acad. Sci. 98, 11479-11484.

Schneider, K. 2007. Long-term evolution of polygenic traits under frequency-dependent intraspecific competition. Theor. Popul. Biol. 71, 342366.

Shahshahani, S. 1979. A new mathematical framework for the study of linkage and selection. Memoirs Amer. Math. Soc. 211. Providence, R.I.: Amer. Math. Soc.

Slatkin, M. 1975. Gene flow and selection in two-locus systems. Genetics 81, 787-802.

Slatkin, M. 2008. Linkage disequilibriumunderstanding the evolutionary past and mapping the medical future. Nat. Rev. Genet. 9, 477485.

Spichtig, M., Kawecki, T.J. 2004. The maintenance (or not) of polygenic variation by soft selection in heterogeneous environments. Amer. Natur. 164, 70-84.

Spitze, K. 1993. Population structure in Daphnia obtusa: quantitative genetic and allozymic variation. Genetics 135, 367-374.

Turelli, M., Barton, N.H. 1990. Dynamics of polygenic characters under selection. Theor. Pop. Biol. 38, 1-57.

van Doorn, G.S., Dieckmann, U. 2006. The long-term evolution of multilocus traits under frequency-dependent disruptive selection. Evolution 60, 2226-2238.

Wakeley, J., Lessard, S. 2003. Theory of the effects of population structure and sampling on patterns of linkage disequilibrium applied to genomic data from humans. Genetics 164, 1043-1053.

Weir, B., Cockerham, C. 1984. Estimating F statistics for the analysis of population structure. Evolution 38, 1358-1370.

Wu, C.-I., Ting, C.-T. 2004. Genes and speciation. Nat. Rev. Genet. 5, 114-122.

Yeaman, S., Otto, S.P. 2011. Establishment and maintenance of adaptive genetic divergence under migration, selection, and drift. Evolution 65, 2123-2129.

Yeaman, S., Whitlock, M. 2011. The genetic architecture of adaptation under migration-selection balance. Evolution 65, 1897-1911.

Zusammenfassung in deutscher Sprache

In dieser Dissertation präsentiere ich meine wissenschaftliche Arbeit im Bereich der mathematischen Populationsgenetik, welche im Rahmen meines Doktoratsstudiums der Mathematik durchgeführt wurde. Dabei steht das Zusammenspiel der evolutionären Kräfte Selektion, Rekombination und Migration sowie deren gemeinsame Wirkung auf die genetische Konstitution, auf das Ausmaß der lokalen Anpassung und auf den Grad der Differenzierung einer Population im Vordergrund. Alle hier präsentierten Arbeiten behandeln eine geografisch strukturierte Population mit zwei gekoppelten Genorten und jeweils zwei Allelen. Diese Genorte sind lokal unterschiedlicher Selektion ausgesetzt, wobei wir Interaktionen zwischen den Genorten (Epistasie) vernachlässigen.
Diese Dissertation besteht aus drei Abschnitten. Jeder Abschnitt entspricht einem publizierten oder eingereichten Manuskript (Stand September 2013).
Im ersten Teil (*The effects of linkage and gene flow on local adaptation: a two-locus continent-island model*) nehmen wir ein Kontinent-Insel-Modell an. Dies ist das einfachste Szenario um die evolutionäre Dynamik einer geografisch strukturierten Population zu studieren. Aus Gründen der Vereinfachung ignorieren wir in dieser Arbeit Dominanz und studieren ein zeitlich kontinuierliches Modell.
Im zweiten Teil (*The consequences of gene flow for local adaptation and differentiation: a two-locus two-deme model*) erweitern wir das Modell der ersten Arbeit indem wir eine Population betrachten die zwei Deme bevölkert. Diese sind durch Genfluss in beide Richtungen verbunden. Wie in der ersten Arbeit ist dieses Modell in kontinuierlicher Zeit und ignoriert Dominanz.
Im letzten Teil (*The consequences of dominance and gene flow for local adaptation and differentiation at two linked loci*) verallgemeinern wir einige Annahmen der ersten und zweiten Arbeit: Wir lassen Dominanz zu und gehen von diskreten, nicht überlappenden Generationen aus.
In der Einleitung motivieren und beschreiben wir die betrachteten Modelle und deren Zusammenhänge genauer. Dort diskutieren wir auch mögliche Konsequenzen welche sich aus den drei Arbeiten ableiten lassen.
Wie es die formalen Richtlinien einer kumulativen Dissertation erfordern, ist am Ende jeder Arbeit ein separater Abschnitt beigefügt welcher den Status der Einreichung (mit

Stand September 2013) und meine persönliche Leistung dokumentiert. Eine gemeinsame Bibliographie aller drei Arbeiten befindet sich am Ende dieser Dissertation.

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List of Publications

1. Akerman, A. The consequences of dominance and gene flow for local adaptation and differentiation at two linked loci. Submitted
2. Akerman, A., Bürger, R. 2013. The consequences of gene flow for local adaptation and differentiation: a two-locus two-deme model. J. Math. Biol. DOI: 10.1007/s00285-013-0660-z
3. Bürger, R., Akerman, A. 2011. The effects of linkage and gene flow on local adaptation: a two-locus continent-island model. Theor. Popul. Biol. 80, 272-288.

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