J. Math. Biol. (2009) 58:939–978
DOI 10.1007/s00285-008-0236-5

Mathematical Biology

Multilocus selection in subdivided populations I. Convergence properties for weak or strong migration

Reinhard Bürger

Abstract The dynamics and equilibrium structure of a deterministic population-genetic model of migration and selection acting on multiple multiallelic loci is studied. A large population of diploid individuals is distributed over finitely many demes connected by migration. Generations are discrete and nonoverlapping, migration is irreducible and aperiodic, all pairwise recombination rates are positive, and selection may vary across demes. It is proved that, in the absence of selection, all trajectories converge at a geometric rate to a manifold on which global linkage equilibrium holds and allele frequencies are identical across demes. Various limiting cases are derived in which one or more of the three evolutionary forces, selection, migration, and recombination, are weak relative to the others. Two are particularly interesting. If migration and recombination are strong relative to selection, the dynamics can be conceived as a perturbation of the so-called weak-selection limit, a simple dynamical system for suitably averaged allele frequencies. Under nondegeneracy assumptions on this weak-selection limit which are generic, every equilibrium of the full dynamics is a perturbation of an equilibrium of the weak-selection limit and has the same stability properties. The number of equilibria is the same in both systems, equilibria in the full (perturbed) system are in quasi-linkage equilibrium, and differences among allele frequencies across demes are small. If migration is weak relative to recombination and epistasis is also weak, then every equilibrium is a perturbation of an equilibrium of the corresponding system without migration, has the same stability properties, and is in quasi-linkage equilibrium. In both cases, every trajectory converges to an equilibrium, thus no cycling or complicated dynamics can occur.

R. Bürger (✉)
Department of Mathematics, University of Vienna,
Nordbergstrasse 15, 1090 Vienna, Austria
e-mail: reinhard.buerger@univie.ac.at

Keywords Selection · Migration · Recombination · Linkage equilibrium · Quasi-linkage equilibrium · Equilibrium structure · Multiple alleles · Epistasis · Discrete demes · Geographic structure · Dispersal

Mathematics Subject Classification (2000) 92D10 · 92D15 · 34D05 · 37N25

1 Introduction

Many natural populations are geographically structured and selection varies spatially due to heterogeneity in the environment. Dispersal of individuals is usually modeled in one of two alternative ways, either by diffusion in space or by migration between discrete colonies, or demes. If population size is sufficiently large, so that random genetic drift can be ignored, then the first kind of model leads to partial differential equations [19,34] and is a natural choice for the study of clines, i.e., the gradual change of phenotype or genotype frequencies along an environmental gradient [25]. This is a wide and fruitful area, but here we will not be concerned with it and instead refer to Barton [4] and Nagylaki and Lou [49] for recent theoretical developments and references.

Models of selection and migration between discrete demes originated from the work of Haldane [24] and Wright [54]. Most of the existing theory is devoted to study selection on a single diallelic locus in populations with discrete, nonoverlapping generations that mate randomly within demes. A central focus of research has been the derivation of conditions for a protected polymorphism, i.e., for protecting both alleles from eventual loss (e.g., [6,30,50], [42, Chap. 6]).

An important special case is the commonly studied Levene [37] model, in which individuals disperse independently of their deme of origin. It is much easier to analyze than other models because after one generation of migration, allele frequencies are equalized across demes. However, even in the Levene model with a single diallelic locus, many open problems remain. For instance, the maximum number of coexisting polymorphic (internal) equilibria is unknown. The theoretical upper bound is $2\Gamma - 1$, where Γ is the number of demes. Numerical searches suggest that it is not achieved if $\Gamma \geq 3$, and that the maximum number of equilibria increases very slowly with Γ. No cases with more than two stable (and one unstable) polymorphic equilibria have been detected, and this can occur already with two demes. With seven demes, a fitness scheme yielding two stable polymorphic together with two stable boundary equilibria (and three unstable polymorphic equilibria) has been found [29]. However, there are results that establish simple dynamic behavior. For instance, sufficient conditions for the existence of a unique, globally stable equilibrium in the Levene model have been derived (Bürger, unpublished manuscript; [29], [49, Sect. 4.2.4]). For two alleles, all trajectories converge to some equilibrium because of monotonicity. For multiple alleles, the existence of a Lyapunov function ensures at least generic convergence [8,38], [42, Chap. 6.3].

For arbitrary migration between two diallelic demes, trajectories converge to an equilibrium in continuous time [49, Section 4.3.2]. With three demes, unstable limit cycles may occur (Akin, personal communication). In discrete time, convergence has not even be proved for two diallelic demes. It can be shown, however, that convergence occurs if in both demes fitnesses are submultiplicative, which notably includes no dominance, complete dominance of the fitter allele, and overdominance (Karlin and Campbell [31]; the proofs of their Results III and IV can be rectified). For arbitrary migration between multiple demes, convergence is unresolved even for multiplicative fitnesses, i.e., haploid selection.

In a recent series of papers, Nagylaki and Lou [44,46–48] performed an extensive study of migration-selection models for a single multiallelic locus. Among others, they derived conditions for global fixation of an allele, for global loss of an allele, and they studied how many alleles can be maintained under various assumptions on selection or dominance, especially, in relation to the number of demes. In addition, when migration is either sufficiently weak or sufficiently strong relative to selection, the equilibria are described and convergence of the gene frequencies to an equilibrium point is demonstrated. Similar results are provided if selection is the same in every deme. For a succinct review (see [49, Sect. 4.2]). It seems worth noting that these results for strong and weak migration, and for a homogeneous environment, have been derived by resorting to analyses of and results on single-locus selection models.

Whereas the theory of migration-selection models for a single locus is fairly well developed, notwithstanding the many unresolved problems, this is not at all the case for multiple loci. This lack of theory is likely due to the daunting complexity of multilocus systems that is apparent already in the absence of migration (e.g., [7]). Some brave attempts have been made, however. For instance, the existence of clines has been studied for two [53] and for multiple loci [36]. With discrete demes and two diallelic loci, Christiansen and Feldman [11] derived sufficient conditions for the protection of gametes for the so-called Deakin [13] model, which were later generalized to multiple diallelic loci [10, p. 277]. Christiansen [10, Chap. 5] also studied linkage disequilibria generated by population (ad)mixture in versions of the continent-island model, as well as various aspects of migration and selection (see below).

Li and Nei [39] showed that despite absence of epistasis, linkage disequilibrium can be maintained at migration-selection balance (see also [11]). This is an interesting phenomenon that cannot occur without migration, because then, for nonepistatic selection and any number of loci and alleles, every trajectory converges to an equilibrium point that is in linkage equilibrium [35,41]. The identification of conditions under which linkage equilibrium or near (quasi) linkage equilibrium is approached is of considerable theoretical interest because it tremendously simplifies the mathematical analysis and opens the route to obtaining more insight.

This paper is the first in a series in which a mathematical theory of multiallelic multilocus migration-selection models is developed and applied to specific biological problems, such as the role of population subdivision in maintaining genetic variation. It was inspired by numerous discussions with Thomas Nagylaki, who also shared extensive unpublished results. After setting up the general model, migration and recombination in the absence of selection are studied in Sect. 3. It is proved that if migration is ergodic, i.e., irreducible and aperiodic, then all trajectories converge at a geometric rate to a manifold on which global linkage equilibrium holds and allele frequencies are identical across demes (Theorem 3.1). This generalizes a classical result valid in the absence of migration (Remark 3.2).

Section 4 is devoted to the study of strong migration, whereas selection or recombination may be weak. Because constant backward migration rates are assumed, the results mainly apply to soft selection, i.e., population regulation within niches. The main and most interesting result is Theorem 4.3 which establishes the equilibrium structure and convergence of trajectories to an equilibrium point if selection is sufficiently weak relative to migration and recombination. In this case, the full dynamics can be conceived as a perturbation of the so-called weak-selection limit. This is a rather simple system of differential equations, closely related to the multiallelic single-locus selection dynamics, in which fitnesses are appropriate averages over demes. Under nondegeneracy hypotheses on the weak-selection limit, which are satisfied generically, it is proved that every equilibrium is a perturbation of a corresponding equilibrium of the weak-selection limit and has the same stability properties. In particular, after an evolutionary short time, quasi-linkage equilibrium is approached, allele frequencies become nearly deme independent, and all trajectories converge. This generalizes previous results by Nagylaki et al. [45] for multilocus systems with no migration, and by Nagylaki and Lou [48] for a single locus with migration. As an application, the increase of mean fitness is studied in Sect. 4.1.2. The other important limiting case occurs if migration is strong relative to selection *and* recombination. It leads to more complicated dynamics, closely related to that of multilocus selection-recombination systems and is treated in Sect. 4.2.

In Sect. 5, weak migration is explored, whereas other evolutionary forces may be weak or strong. The main result (Theorem 5.4 in Sect. 5.2) establishes the equilibrium structure if migration and epistasis are both weak, but not necessarily equally weak, and recombination and nonepistatic selection are strong. Under a generic assumption about hyperbolicity of equilibria, it is established that every equilibrium is a perturbation of a corresponding equilibrium of the much simpler system in which there is no migration and selection within each deme is purely nonepistatic. Each equilibrium has the same stability properties as its corresponding equilibrium in the absence of migration. Again, convergence of trajectories is established. The limiting cases of weak migration and weak selection (Sect. 5.1) and when all evolutionary forces are weak (Sect. 5.3) may lead to more complicated dynamics, hence weaker perturbation results are obtained. The Appendix contains a glossary of symbols.

The results derived here about the dynamical and equilibrium properties of multilocus migration-selection models will be useful for a number of applications. First, they establish scenarios, the weak-selection and the weak-migration case, for which perturbation techniques can be applied to obtain specific results for special models. They also justify the use of (quasi-) linkage-equilibrium approximations in such cases. These are important tools in the study of multilocus systems because they greatly simplify mathematical analysis. In the companion paper, part II, we apply the present results to study the maintenance of multilocus polymorphism under weak or strong migration.

2 Notation and model

We consider a diploid population with discrete, nonoverlapping generations, in which the two sexes need not be distinguished. The population is subdivided into $\Gamma \geq 1$

panmictic colonies (demes) that exchange adult migrants independently of genotype. In each of the demes, selection acts through differential viabilities, which are time and frequency independent. Mutation and random genetic drift are ignored.

The genetic system consists of $L \geq 1$ loci and $I_n \geq 2$ alleles, $\mathcal{A}_{i_n}^{(n)}$ ($i_n = 1, \ldots, I_n$), at locus n. We use the multi-index $i = (i_1, \ldots, i_L)$ as an abbreviation for the gamete $\mathcal{A}_{i_1}^{(1)} \ldots \mathcal{A}_{i_L}^{(L)}$. We designate the set of all demes by $\mathsf{G} = \{1, \ldots, \Gamma\}$, the set of all loci by $\mathsf{L} = \{1, \ldots, L\}$, the set of all alleles at locus n by $\mathsf{I}_n = \{1, \ldots, I_n\}$, and the set of all gametes by I. The number of gametes is $I = |\mathsf{I}| = \prod_n I_n$, the total number of genes (alleles at all loci) is $I_1 + \cdots + I_L$. We use letters $i, j, \ell \in \mathsf{I}$ for gametes, $k, n \in \mathsf{L}$ for loci, and $\alpha, \beta \in \mathsf{G}$ for demes. Sums or products without ranges indicate summation over all admissible indices, e.g., $\sum_n = \sum_{n \in \mathsf{L}}$, $\sum_\alpha = \sum_{\alpha \in \mathsf{G}}$, $\sum_i = \sum_{i \in \mathsf{I}}$, $\sum_{i_n} = \sum_{i_n \in \mathsf{I}_n}$. We denote the simplex by

$$\Delta_I = \left\{ z \in \mathbb{R}^I : z_i \geq 0 \text{ for every } i \in \mathsf{I}, \sum_i z_i = 1 \right\}, \tag{2.1}$$

and the Γ-fold cartesian product by Δ_I^Γ.

Let $p_{i,\alpha} = p_{i,\alpha}(t)$ represent the frequency of gamete i among zygotes in deme α in generation t. We define the following column vectors (the superscript ^{T} indicates transposition):

$$p_i = (p_{i,1}, \ldots, p_{i,\Gamma})^T \in \mathbb{R}^\Gamma, \tag{2.2a}$$

$$p_{(\alpha)} = (p_{1,\alpha}, \ldots, p_{I,\alpha})^T \in \Delta_I, \tag{2.2b}$$

$$p = \left(p_{(1)}^T, \ldots, p_{(\Gamma)}^T\right)^T \in \Delta_I^\Gamma. \tag{2.2c}$$

Here, p_i, $p_{(\alpha)}$, and p signify the frequency of gamete i in each deme, the gamete frequencies in deme α, and all gamete frequencies, respectively. We will use analogous notation for other quantities, e.g., for $D_{i,\alpha}$.

The frequency of allele $\mathcal{A}_{i_k}^{(k)}$ among gametes in deme α is

$$p_{i_k,\alpha}^{(k)} = \sum_{i|i_k} p_{i,\alpha}, \tag{2.3}$$

where the sum runs over all multi-indices i with the kth component fixed as i_k. The marginal frequency of the gamete with components i_k for the loci $k \in \mathsf{K}$ is

$$p_{i_\mathsf{K},\alpha}^{(\mathsf{K})} = \sum_{i|i_\mathsf{K}} p_{i,\alpha}, \tag{2.4}$$

where $\sum_{i|i_\mathsf{K}}$ runs over all multi-indices i with the components in K fixed as i_K. We write

$$p_{i_k}^{(k)} = \left(p_{i_k,1}^{(k)}, \ldots, p_{i_k,\Gamma}^{(k)}\right)^T \in \mathbb{R}^\Gamma \tag{2.5a}$$

for the vector of frequencies of allele $\mathcal{A}_{i_k}^{(k)}$ in each deme, and similarly,

$$p_{i_{\mathsf{K}}}^{(\mathsf{K})} = \left(p_{i_{\mathsf{K}},1}^{(\mathsf{K})}, \dots, p_{i_{\mathsf{K}},\Gamma}^{(\mathsf{K})}\right)^T \in \mathbb{R}^\Gamma. \tag{2.5b}$$

Let $x_{ij,\alpha}$ and $w_{ij,\alpha}$ denote the frequency and fitness of genotype ij in deme α, respectively. We designate the marginal fitness of gamete i in deme α and the mean fitness of the population in deme α by

$$w_{i,\alpha} = w_{i,\alpha}(p_{(\alpha)}) = \sum_j w_{ij,\alpha} p_{j,\alpha} \tag{2.6a}$$

and

$$\bar{w}_\alpha = \bar{w}_\alpha(p_{(\alpha)}) = \sum_{i,j} w_{ij,\alpha} p_{i,\alpha} p_{j,\alpha}, \tag{2.6b}$$

respectively.

Let $m_{\alpha\beta}$ be the probability that an adult individual in deme α migrated from deme β. Then, the $\Gamma \times \Gamma$ backward migration matrix $M = (m_{\alpha\beta})$ is stochastic, i.e., it satisfies

$$m_{\alpha\beta} \geq 0 \text{ for every } \alpha, \beta \in \mathsf{G} \quad \text{and} \quad \sum_\beta m_{\alpha\beta} = 1 \text{ for every } \alpha. \tag{2.7}$$

We assume that M is constant, as it is the case for soft selection [9,14], [42, p. 135].

Our life cycle starts with zygotes in Hardy–Weinberg proportions. Selection acts in each deme on the newly born offspring. Adults migrate, then recombination and random mating occur in each deme. This life cycle extends that of Nagylaki [42, p. 133]. To deduce the general multilocus migration-selection dynamics (Nagylaki, personal communication), let

$$x_{ij,\alpha}^* = p_{i,\alpha} p_{j,\alpha} w_{ij,\alpha} / \bar{w}_\alpha \tag{2.8a}$$

be the frequency of genotype ij in deme α after selection, and

$$x_{ij,\alpha}^{**} = \sum_\beta m_{\alpha\beta} x_{ij,\beta}^* \tag{2.8b}$$

its frequency in deme α after selection and migration. Then, the frequency of gamete i in deme α in the next generation, i.e., after recombination, is

$$p_{i,\alpha}' = \sum_{j,\ell} R_{i,j\ell} x_{j\ell,\alpha}^{**}, \tag{2.8c}$$

where $R_{i,j\ell}$ is the probability that during gametogenesis, paternal haplotypes j and ℓ produce a gamete i by recombination. We leave it to the reader to check the obvious fact that the processes of migration and recombination commute. Thus, instead of (2.8b) and (2.8c), we can write

$$p'_{i,\alpha} = \sum_{\beta} m_{\alpha\beta} p^{\#}_{i,\beta}, \tag{2.9a}$$

where

$$p^{\#}_{i,\alpha} = \sum_{j,\ell} R_{i,j\ell} x^{*}_{j\ell,\alpha} \tag{2.9b}$$

describes selection and recombination in deme α. We shall view (2.8) or, equivalently, (2.9) as a dynamical system on Δ_I^{Γ}.

Let $\{\mathsf{K}, \mathsf{N}\}$ be a nontrivial decomposition of L, i.e., K and its complement $\mathsf{N} = \mathsf{L} \backslash \mathsf{K}$ are each proper subsets of L and, therefore, contain at least one locus. (The decompositions $\{\mathsf{K}, \mathsf{N}\}$ and $\{\mathsf{N}, \mathsf{K}\}$ are identified.) We designate by c_{K} the probability of reassociation of the genes at the loci in K, inherited from one parent, with the genes at the loci in N, inherited from the other. Let

$$c_{\text{tot}} = \sum_{\mathsf{K}} c_{\mathsf{K}}, \tag{2.10}$$

where $\sum_{\mathsf{K}}$ runs over all (different) decompositions $\{\mathsf{K}, \mathsf{N}\}$ of L, denote the total recombination frequency. We designate the recombination frequency between loci k and n, such that $k < n$, by c_{kn}. It is given by

$$c_{kn} = \sum_{\mathsf{K} \in \mathsf{L}_{kn}} c_{\mathsf{K}}, \tag{2.11}$$

where $\mathsf{L}_{kn} = \{\mathsf{K} : k \in \mathsf{K} \text{ and } n \in \mathsf{N}\}$ [7, p. 55]. Throughout this paper, we assume that all pairwise recombination rates c_{kn} are positive. Hence,

$$c_{\min} = \min_{k<n} c_{kn} > 0. \tag{2.12}$$

We define

$$D_{i,\alpha} = \frac{1}{\bar{w}_\alpha} \sum_j \sum_{\mathsf{K}} c_{\mathsf{K}} \left(w_{ij,\alpha}\, p_{i,\alpha} p_{j,\alpha} - w_{i_{\mathsf{K}} j_{\mathsf{N}}, j_{\mathsf{K}} i_{\mathsf{N}},\alpha}\, p_{i_{\mathsf{K}} j_{\mathsf{N}},\alpha}\, p_{j_{\mathsf{K}} i_{\mathsf{N}},\alpha} \right). \tag{2.13}$$

This is a measure of linkage disequilibrium in gamete i in deme α. Therefore ([7, p. 56], [43]), we obtain

$$p^{\#}_{i,\alpha} = p_{i,\alpha} \frac{w_{i,\alpha}}{\bar{w}_\alpha} - D_{i,\alpha}. \tag{2.14}$$

It seems worth noting that the full dynamics, (2.8) or (2.9), does not depend on linkage disequilibria between demes.

Let

$$\Lambda_{0,\alpha} = \left\{ p_{(\alpha)} : p_{i,\alpha} = p^{(1)}_{i_1,\alpha} \cdot \cdots \cdot p^{(L)}_{i_L,\alpha} \right\} \subseteq \Delta_I \tag{2.15}$$

denote the *linkage-equilibrium manifold* (also called the Wright manifold) in deme α, and let

$$\Lambda_0 = \Lambda_{0,1} \times \cdots \times \Lambda_{0,\Gamma} \subseteq \Delta_I^\Gamma. \tag{2.16}$$

If there is no position effect, i.e., if

$$w_{ij,\alpha} = w_{i_\mathsf{K} j_\mathsf{N}, j_\mathsf{K} i_\mathsf{N};\alpha}$$

for every i, j, and K, then $D_{i,\alpha} = 0$ for every $p_{(\alpha)} \in \Lambda_{0,\alpha}$. Hence,

$$\Lambda_{0,\alpha} \subseteq \{p_{(\alpha)} : D_{(\alpha)} = 0\}, \tag{2.17}$$

where $D_{(\alpha)}$ is defined in analogy to (2.2b). In the absence of selection, equality holds in (2.17).

We posit that

The backward migration matrix M is ergodic, i.e., irreducible and aperiodic. (E)

Given irreducibility, the biologically trivial condition that individuals have positive probability of remaining in some deme, i.e., $m_{\alpha\alpha} > 0$ for some α, suffices for aperiodicity [17, p. 426].

By (E), there exists a principal left eigenvector $\mu \in \mathrm{int}\Delta_\Gamma$ such that

$$\mu^T M = \mu^T. \tag{2.18}$$

The corresponding principal eigenvalue 1 of M is simple and exceeds every other eigenvalue in modulus [20, p. 53, 80]. The principal eigenvector μ is the unique stationary distribution of the Markov chain with transition matrix M. The vector μ depends only on the relative migration rates [48, p. 29]. For $z \in \mathbb{R}^\Gamma$ we define its norm $\|z\| = \max_\alpha |z_\alpha|$. Moreover, we write

$$e = (1, \ldots, 1)^T \in \mathbb{R}^\Gamma. \tag{2.19}$$

Let λ_1 denote the nonunit eigenvalue of M with largest modulus. Then, the convergence theorem for ergodic, or stochastic and primitive, matrices [17, p. 393], [52, p. 9] implies that for every κ with

$$|\lambda_1| < \kappa < 1, \tag{2.20}$$

we have

$$\left\| M^t z - e\mu^T z \right\| \leq c_z \kappa^t, \tag{2.21}$$

where c_z is independent of t. If λ_1 is a simple eigenvalue (which it is generically), we can take $\kappa = |\lambda_1|$.

For $y, z \in \mathbb{R}^\Gamma$, we denote the Schur, i.e., componentwise, product of y and z by

$$y \circ z = (y_1 z_1, \ldots, y_\Gamma z_\Gamma)^T. \tag{2.22}$$

We average $p_{i,\alpha}$ with respect to μ,

$$P_i = \mu^T p_i, \quad P = (P_1, \ldots, P_I)^T \in \Delta_I, \tag{2.23}$$

and define the gamete-frequency deviations q from the average gamete frequency P:

$$q_{i,\alpha} = p_{i,\alpha} - P_i, \tag{2.24a}$$

$$q_i = p_i - P_i e \in \mathbb{R}^\Gamma, \tag{2.24b}$$

$$q_{(\alpha)} = p_{(\alpha)} - P \in \mathbb{R}^I, \tag{2.24c}$$

$$q = (q_{(1)}^T, \ldots, q_{(\Gamma)}^T)^T \in \mathbb{R}^{I\Gamma}. \tag{2.24d}$$

Therefore, q measures spatial heterogeneity or diversity. If $q = 0$, the gametic distribution is spatially homogeneous.

3 Migration and recombination

We study migration and recombination in the absence of selection. Our aim is to prove that if migration is ergodic and all pairwise recombination rates are positive, then after a sufficiently long time all gamete and allele frequencies become deme independent and global linkage equilibrium is approached. This generalizes the well known fact that in multilocus systems in which recombination is the only evolutionary force, linkage disequilibria decay to zero at a geometric rate (see Remark 3.2).

In the absence of selection, i.e., if $w_{ij,\alpha} = 1$ for every i, j, α, the dynamics (2.8) reduces to

$$p'_{i,\alpha} = \sum_\beta m_{\alpha\beta}(p_{i,\beta} - D_{i,\beta}), \tag{3.1}$$

where [43, eq. 32]

$$D_{i,\beta} = \sum_{\mathsf{K}} c_{\mathsf{K}} \left(p_{i,\beta} - p^{(\mathsf{K})}_{i_{\mathsf{K}},\beta} p^{(\mathsf{N})}_{i_{\mathsf{N}},\beta} \right) \tag{3.2}$$

and $\{\mathsf{K},\mathsf{N}\}$ as above (2.10). In vector form, i.e., with the notation (2.2a), (3.1) becomes

$$p_i' = M(p_i - D_i). \tag{3.3}$$

Using the vector notation (2.5b) and (2.22), we define the vector of linkage disequilibria

$$D_{i_\mathsf{K}}^{(\mathsf{K})} = \sum_{i|i_\mathsf{K}} D_i = \sum_\mathsf{S} c_\mathsf{S}^{(\mathsf{K})} \left[p_{i_\mathsf{K}}^{(\mathsf{K})} - p_{i_\mathsf{S}}^{(\mathsf{S})} \circ p_{i_\mathsf{T}}^{(\mathsf{T})} \right] \in \mathbb{R}^\Gamma, \tag{3.4}$$

where $\{\mathsf{S},\mathsf{T}\}$ is a nontrivial decomposition of K, i.e., S and $\mathsf{T} = \mathsf{K}\backslash\mathsf{S}$ are each proper subsets of K, and $c_\mathsf{S}^{(\mathsf{K})}$ designates the probability of reassociation of the genes at the loci in S, inherited from one parent, with the genes at the loci in T, inherited from the other.

Summing (3.3) over all multi-indices i with the components in K fixed as i_K and using the linearity of M, we obtain the recursion

$$p_{i_\mathsf{K}}^{(\mathsf{K})\prime} = M\left(p_{i_\mathsf{K}}^{(\mathsf{K})} - D_{i_\mathsf{K}}^{(\mathsf{K})}\right) \tag{3.5}$$

for the gametic frequencies of loci in K. For allele frequencies, (3.5) reduces to

$$p_{i_k}^{(k)\prime} = M p_{i_k}^{(k)}. \tag{3.6}$$

In analogy to (2.23), we define the average allele frequency of $\mathcal{A}_{i_k}^{(k)}$ by

$$P_{i_k}^{(k)} = \mu^T p_{i_k}^{(k)} \in \mathbb{R} \tag{3.7}$$

and observe that, by (2.18), $P_{i_k}^{(k)\prime} = P_{i_k}^{(k)}$. Therefore, in the absence of selection, the average allele frequencies $P_{i_k}^{(k)}(t)$ are constant, and we write

$$P_{i_k}^{(k)} = P_{i_k}^{(k)}(t) = P_{i_k}^{(k)}(0). \tag{3.8}$$

Let $q_{i_k}^{(k)} = \sum_{i|i_k} q_i \in \mathbb{R}^\Gamma$. Then,

$$q_{i_k}^{(k)}(t) = p_{i_k}^{(k)}(t) - P_{i_k}^{(k)} e, \tag{3.9}$$

and, from (3.6) and (3.7),

$$q_{i_k}^{(k)}(t) = M^t p_{i_k}^{(k)}(0) - e\mu^T p_{i_k}^{(k)}(0).$$

Hence, applying (2.21) to $z = p_{i_k}^{(k)}(0)$, we obtain

$$\left\| q_{i_k}^{(k)}(t) \right\| \leq a_{i_k}^{(k)} \kappa^t \tag{3.10}$$

for every k and every i_k, where the $a_{i_k}^{(k)}$ are appropriate constants. Therefore, every allele-frequency vector $p_{i_k}^{(k)}(t)$ converges geometrically at least as fast as κ^t to the constant and uniform vector $P_{i_k}^{(k)}e$. For reasons that will become clear in (3.25), we choose κ such that, in addition to (2.20), it satisfies

$$\kappa \neq 1 - c_{kn} \tag{3.11}$$

for every two-locus recombination rate c_{kn}.

If $\mathsf{K} \subseteq \mathsf{L}$, $\mathsf{K} \neq \emptyset$, we write

$$\prod_{k\in\mathsf{K}} p_{i_k}^{(k)} = \left(\prod_{k\in\mathsf{K}} p_{i_k,1}^{(k)}, \ldots, \prod_{k\in\mathsf{K}} p_{i_k,\Gamma}^{(k)}\right)^T \in \mathbb{R}^\Gamma \tag{3.12}$$

and similarly for other vectors in $\mathbb{R}^\Gamma$. According to our general convention for sums and products, we simply write $\prod_k p_{i_k}^{(k)}$ if $\mathsf{K} = \mathsf{L}$. Moreover, we shall use the abbreviations

$$\tilde{P}_{i_\mathsf{K}}^{(\mathsf{K})} = \prod_{k\in\mathsf{K}} P_{i_k}^{(k)} \in \mathbb{R} \quad \text{and} \quad \tilde{P}_i = \prod_{k\in\mathsf{L}} P_{i_k}^{(k)} \in \mathbb{R}. \tag{3.13}$$

Theorem 3.1 *Suppose that* (3.3) *and* (E) *hold. Then, the manifold*

$$\Psi_0 = \left\{p \in \Delta_I^\Gamma : p_i = \tilde{P}_i e\right\} = \left\{p \in \Delta_I^\Gamma : D = 0 \text{ and } q = 0\right\} \tag{3.14}$$

is invariant under (3.3) *and globally attracting at a uniform geometric rate. Furthermore, every point on* Ψ_0 *is an equilibrium point. Thus, linkage equilibrium and spatial homogeneity are quickly approached under recombination and* (*ergodic*) *migration.*

Remark 3.2 (i) In the absence of migration, this theorem is well known [5], [7, pp. 56–57], [23,40], [41, pp. 248–251 and 265–266], [43,51].

(ii) Another representation of Ψ_0 is

$$\Psi_0 = \left\{ p \in \Delta_I^\Gamma : p_i = \prod_k p_{i_k}^{(k)} \text{ and } q_{i_k}^{(k)} = 0 \text{ for every } k \text{ and } i_k \right\}.$$

The equivalence of $p_i = \prod_k p_{i_k}^{(k)}$ for every i and $D_i = 0$ for every i is readily checked and well known (e.g., [45, p. 114]). Clearly, $q = 0$ implies $q_{i_k}^{(k)} = 0$. If $q_{i_k}^{(k)} = 0$ for every k and i_k, and $p_i = \prod_k p_{i_k}^{(k)}$, hence $D = 0$, we obtain $q_i = p_i - P_i e = \prod_k p_{i_k}^{(k)} - \tilde{P}_i e = 0$.

Remark 3.3 As pointed out by T. Nagylaki, this theorem does not hold if the migration matrix is reducible or periodic. If, for instance, $M = \begin{pmatrix} 1 & 0 \\ \frac{1}{2} & \frac{1}{2} \end{pmatrix}$, then an allele that is initially absent in the second deme will be also absent at equilibrium, whereas its frequency can be positive in the first deme. If $M = \begin{pmatrix} 0 & 1 \\ 1 & 0 \end{pmatrix}$, then each generation the gamete frequencies are swapped between the demes. In both cases, convergence to $q = 0$ will in general not occur.

Proof of Theorem 3.1 First, we show equivalence of the two representations in (3.14). If $p_i = \tilde{P}_i e$, then $P_i = \mu^T p_i = \tilde{P}_i$, hence $q = 0$. Moreover, $p_{i_k}^{(k)} = P_{i_k}^{(k)} e$, hence $p_i = \prod_k p_{i_k}^{(k)}$ which implies $D_i = 0$. The other inclusion is even more obvious.

If $p \in \Psi_0$, then (3.3) implies $p_i' = M p_i$. Because $q = 0$, we have $p_i = P_i e$ and $p_i' = M P_i e = P_i e = p_i$. This proves that every point is an equilibrium, hence invariance of Ψ_0.

The proof of convergence is inspired by that of Nagylaki [43, pp. 634–635] for the decay of linkage disequilibria under recombination and weak selection. We will use induction and proceed in five steps.

(i) *Recursion relations for the linkage disequilibria.* We introduce the linkage disequilibria

$$d_{i,\alpha} = p_{i,\alpha} - \prod_k p_{i_k,\alpha}^{(k)}. \tag{3.15}$$

Then, for every nonempty subset $\mathsf{K} \subseteq \mathsf{L}$, we have

$$d_{i_\mathsf{K},\alpha}^{(\mathsf{K})} = \sum_{i | i_\mathsf{K}} d_{i,\alpha} = p_{i_\mathsf{K},\alpha}^{(\mathsf{K})} - \prod_{k \in \mathsf{K}} p_{i_k,\alpha}^{(k)}, \tag{3.16}$$

where $p_{i_\mathsf{L},\alpha}^{(\mathsf{L})} = p_{i,\alpha}$ and $d_{i_\mathsf{L},\alpha}^{(\mathsf{L})} = d_{i,\alpha}$. In analogy to (2.2a) and (2.5b), we use the vector notation d_i and $d_{i_\mathsf{K}}^{(\mathsf{K})}$. Then, (3.16) takes the form

$$d_{i_\mathsf{K}}^{(\mathsf{K})} = p_{i_\mathsf{K}}^{(\mathsf{K})} - \prod_{k \in \mathsf{K}} p_{i_k}^{(k)}. \tag{3.17}$$

The following relation between $D_{i_\mathsf{K}}^{(\mathsf{K})}$ and $d_{i_\mathsf{K}}^{(\mathsf{K})}$ is immediately obtained from (3.4) and (3.17):

$$D_{i_\mathsf{K}}^{(\mathsf{K})} = c^{(\mathsf{K})} d_{i_\mathsf{K}}^{(\mathsf{K})} - g_{i_\mathsf{K}}^{(\mathsf{K})} \left(p_{i_\mathsf{K}}^{(\mathsf{K})} \right). \tag{3.18}$$

Here, $c^{(\mathsf{K})} = \sum_\mathsf{S} c_\mathsf{S}^{(\mathsf{K})}$ denotes the probability of a recombination event in K, S is a nonempty proper subset of K, and

$$g_{i_\mathsf{K}}^{(\mathsf{K})}(p_{i_\mathsf{K}}^{(\mathsf{K})}) = \sum_\mathsf{S} c_\mathsf{S}^{(\mathsf{K})} \left[d_{i_\mathsf{S}}^{(\mathsf{S})} \circ d_{i_\mathsf{T}}^{(\mathsf{T})} + d_{i_\mathsf{S}}^{(\mathsf{S})} \circ \prod_{n \in \mathsf{T}} p_{i_n}^{(n)} + d_{i_\mathsf{T}}^{(\mathsf{T})} \circ \prod_{n \in \mathsf{S}} p_{i_n}^{(n)} \right], \tag{3.19}$$

where $\mathsf{T} = \mathsf{K} \backslash \mathsf{S}$ and the circle denotes the Schur product, (2.22). From (3.17), we deduce the recursion relation for $d_{i_\mathsf{K}}^{(\mathsf{K})}$ by employing successively (3.5) and (3.6), (3.17) and (3.18), and collecting terms:

$$\begin{aligned} d_{i_{\mathsf{K}}}^{(\mathsf{K})\prime} &= p_{i_{\mathsf{K}}}^{(\mathsf{K})\prime} - \prod_{k\in\mathsf{K}} p_{i_k}^{(k)\prime} \\ &= Mp_{i_{\mathsf{K}}}^{(\mathsf{K})} - MD_{i_{\mathsf{K}}}^{(\mathsf{K})} - \prod_{k\in\mathsf{K}} Mp_{i_k}^{(k)} \\ &= Md_{i_{\mathsf{K}}}^{(\mathsf{K})} + M\prod_{k\in\mathsf{K}} p_{i_k}^{(k)} - c^{(\mathsf{K})}Md_{i_{\mathsf{K}}}^{(\mathsf{K})} + Mg_{i_{\mathsf{K}}}^{(\mathsf{K})}(p_{i_{\mathsf{K}}}^{(\mathsf{K})}) - \prod_{k\in\mathsf{K}} Mp_{i_k}^{(k)} \\ &= \chi_{\mathsf{K}} Md_{i_{\mathsf{K}}}^{(\mathsf{K})} + M\prod_{k\in\mathsf{K}} p_{i_k}^{(k)} - \prod_{k\in\mathsf{K}} Mp_{i_k}^{(k)} + Mg_{i_{\mathsf{K}}}^{(\mathsf{K})}(p_{i_{\mathsf{K}}}^{(\mathsf{K})}), \end{aligned} \tag{3.20}$$

where $\chi_{\mathsf{K}} = 1 - c^{(\mathsf{K})}$ is the probability that there is no recombination event in K.

(ii) *A convergence property under migration.* Our aim is to prove

$$\left\| M\prod_{k\in\mathsf{K}} p_{i_k}^{(k)}(t) - \prod_{k\in\mathsf{K}} Mp_{i_k}^{(k)}(t) \right\| \le b_{i_{\mathsf{K}}}^{(\mathsf{K})} \kappa^t \tag{3.21}$$

for some constant $b_{i_{\mathsf{K}}}^{(\mathsf{K})}$ independent of κ. Using (3.9) and expanding, we obtain

$$\begin{aligned} \prod_{k\in\mathsf{K}} p_{i_k}^{(k)}(t) &= \prod_{k\in\mathsf{K}} \left(q_{i_k}^{(k)}(t) + P_{i_k}^{(k)} e \right) \\ &= \sum_{\mathsf{S}} \left(\prod_{n\in\mathsf{S}} q_{i_n}^{(n)}(t) \circ \left(\tilde{P}_{i_{\mathsf{T}}}^{(\mathsf{T})} e \right) \right) + \tilde{P}_{i_{\mathsf{K}}}^{(\mathsf{K})} e, \end{aligned} \tag{3.22}$$

where $\sum_{\mathsf{S}}$ is over all nonempty subsets $\mathsf{S} \subseteq \mathsf{K}$ and $\mathsf{T} = \mathsf{K} \setminus \mathsf{S}$. Using $Mp_{i_k}^{(k)}(t) = p_{i_k}^{(k)}(t+1)$ and applying (3.22) twice, we get

$$\begin{aligned} &M\prod_{k\in\mathsf{K}} p_{i_k}^{(k)}(t) - \prod_{k\in\mathsf{K}} Mp_{i_k}^{(k)}(t) \\ &= M\left[\sum_{\mathsf{S}} \left(\prod_{n\in\mathsf{S}} q_{i_n}^{(n)}(t) \circ \left(\tilde{P}_{i_{\mathsf{T}}}^{(\mathsf{T})} e \right) \right) + \tilde{P}_{i_{\mathsf{K}}}^{(\mathsf{K})} e \right] \\ &\quad - \sum_{\mathsf{S}} \left(\prod_{n\in\mathsf{S}} q_{i_n}^{(n)}(t+1) \circ \left(\tilde{P}_{i_{\mathsf{T}}}^{(\mathsf{T})} e \right) \right) - \tilde{P}_{i_{\mathsf{K}}}^{(\mathsf{K})} e \\ &= M\left[\sum_{\mathsf{S}} \left(\tilde{P}_{i_{\mathsf{T}}}^{(\mathsf{T})} \prod_{n\in\mathsf{S}} q_{i_n}^{(n)}(t) \right) \right] - \sum_{\mathsf{S}} \left(\tilde{P}_{i_{\mathsf{T}}}^{(\mathsf{T})} \prod_{n\in\mathsf{S}} q_{i_n}^{(n)}(t+1) \right), \end{aligned}$$

where we have used $M\left(\tilde{P}_{i_{\mathsf{K}}}^{(\mathsf{K})}e\right) = \tilde{P}_{i_{\mathsf{K}}}^{(\mathsf{K})}Me = \tilde{P}_{i_{\mathsf{K}}}^{(\mathsf{K})}e$. Applying the obvious estimates $\|Mz\| \le \|z\|$ and $P_{i_k}^{(k)} \le 1$, as well as (3.10), we arrive at the desired estimate:

$$\begin{aligned}
&\left\| M\prod_{k\in\mathsf{K}} p_{i_k}^{(k)}(t) - \prod_{k\in\mathsf{K}} Mp_{i_k}^{(k)}(t)\right\| \\
&\quad\le \sum_{\mathsf{S}}\left(\prod_{n\in\mathsf{S}}\left\|q_{i_n}^{(n)}(t)\right\| \tilde{P}_{i_{\mathsf{T}}}^{(\mathsf{T})}\right) + \sum_{\mathsf{S}}\left(\prod_{n\in\mathsf{S}}\left\|q_{i_n}^{(n)}(t+1)\right\| \tilde{P}_{i_{\mathsf{T}}}^{(\mathsf{T})}\right) \\
&\quad\le \sum_{\mathsf{S}}\prod_{n\in\mathsf{S}}\left(a_{i_n}^{(n)}\kappa^t\right) + \sum_{\mathsf{S}}\prod_{n\in\mathsf{S}}\left(a_{i_n}^{(n)}\kappa^{t+1}\right) \le b_{i_{\mathsf{K}}}^{(\mathsf{K})}\kappa^t.
\end{aligned}$$

The leading term κ^t on the right-hand side results from sets S with a single element. The constant $b_{i_{\mathsf{K}}}^{(\mathsf{K})}$ can be chosen such that $b_{i_{\mathsf{K}}}^{(\mathsf{K})} < 2\sum_{\mathsf{S}}\prod_{n\in\mathsf{S}} a_{i_n}^{(n)}$.

(iii) *Decay of the linkage disequilibria for two embedded loci.* Let us assume that K contains only two loci. Then, $d_{i_k}^{(k)} = 0$ for every k and i_k. Therefore, $g_{i_{\mathsf{K}}}^{(\mathsf{K})}(p_{i_{\mathsf{K}}}^{(\mathsf{K})}) = 0$ and (3.20) simplifies to

$$d_{i_{\mathsf{K}}}^{(\mathsf{K})\prime} = \chi_{\mathsf{K}} M d_{i_{\mathsf{K}}}^{(\mathsf{K})} + M\prod_{k\in\mathsf{K}} p_{i_k}^{(k)} - \prod_{k\in\mathsf{K}} Mp_{i_k}^{(k)}. \tag{3.23}$$

We prove that the $d_{i_{\mathsf{K}}}^{(\mathsf{K})}$ decay geometrically at rate

$$\lambda_{\mathsf{K}} = \max(\kappa, \chi_{\mathsf{K}}). \tag{3.24}$$

From (3.23) and (3.21), we infer

$$\left\|d_{i_{\mathsf{K}}}^{(\mathsf{K})}(t+1)\right\| \le \chi_{\mathsf{K}}\left\|d_{i_{\mathsf{K}}}^{(\mathsf{K})}(t)\right\| + b_{i_{\mathsf{K}}}^{(\mathsf{K})}\kappa^t.$$

By iteration, we obtain

$$\begin{aligned}
\left\|d_{i_{\mathsf{K}}}^{(\mathsf{K})}(t)\right\| &\le \chi_{\mathsf{K}}^t\left\|d_{i_{\mathsf{K}}}^{(\mathsf{K})}(0)\right\| + b_{i_{\mathsf{K}}}^{(\mathsf{K})}\sum_{\tau=0}^{t-1}\chi_{\mathsf{K}}^{\tau}\kappa^{t-\tau} \\
&\le \chi_{\mathsf{K}}^t\left\|d_{i_{\mathsf{K}}}^{(\mathsf{K})}(0)\right\| + b_{i_{\mathsf{K}}}^{(\mathsf{K})}\frac{\lambda_{\mathsf{K}}^t}{\lambda_{\mathsf{K}} - \min(\kappa, \chi_{\mathsf{K}})} \\
&\le A_{i_{\mathsf{K}}}^{(\mathsf{K})}\lambda_{\mathsf{K}}^t,
\end{aligned} \tag{3.25}$$

where the constant $A_{i_{\mathsf{K}}}^{(\mathsf{K})}$ can be chosen such that

$$A_{i_{\mathsf{K}}}^{(\mathsf{K})} \le \left\|d_{i_{\mathsf{K}}}^{(\mathsf{K})}(0)\right\| + \frac{b_{i_{\mathsf{K}}}^{(\mathsf{K})}}{\lambda_{\mathsf{K}} - \min(\kappa, \chi_{\mathsf{K}})},$$

and (3.11) guarantees that $\lambda_{\mathsf{K}} - \min(\kappa, \chi_{\mathsf{K}}) = \max(\kappa, \chi_{\mathsf{K}}) - \min(\kappa, \chi_{\mathsf{K}}) > 0$. This implies that for every subset $\mathsf{K} \subseteq \mathsf{L}$ consisting of two loci, the linkage disequilibria $D_{i_{\mathsf{K}}}^{(\mathsf{K})}$ tend to zero geometrically at rate λ_{K} because for two loci we have $D_{i_{\mathsf{K}}}^{(\mathsf{K})} = c^{(\mathsf{K})} d_{i_k}^{(k)}$; cf. (3.18).

(iv) *Decay of the linkage disequilibria for multiple loci.* We extend the definition (3.24) to sets K containing more than two loci by setting

$$\lambda_K = \max\left(\kappa, 1 - c_{\min}^{(\mathsf{K})}\right), \tag{3.26}$$

where $c_{\min}^{(\mathsf{K})}$ denotes the smallest two-locus recombination rate in K. We now show that if (3.25) holds for every proper subset $\mathsf{K} \subset \mathsf{L}$, then it holds for L with

$$\lambda = \lambda_{\mathsf{L}} = \max(\kappa, 1 - c_{\min}). \tag{3.27}$$

Clearly, $\chi_K \le \lambda_{\mathsf{K}} \le \lambda$ for every $\mathsf{K} \subset \mathsf{L}$, and $\lambda < 1$ by (2.12) and (2.20).

First, we estimate $g_i(p_i) = g_{i_{\mathsf{L}}}^{(\mathsf{L})}\left(p_{i_{\mathsf{L}}}^{(\mathsf{L})}\right)$. If we set $\mathsf{K} = \mathsf{L}$ in (3.19) and observe $\left\| p_{i_k}^{(k)} \right\| \le 1$ and $\left\| d_{i_k}^{(k)} \right\| \le 1$, the induction hypothesis yields

$$\|g_i(p_i)\| \le \sum_{\mathsf{S}} c_{\mathsf{S}}^{(\mathsf{K})} \left(2 \left\| d_{i_{\mathsf{S}}}^{(\mathsf{S})} \right\| + \left\| d_{i_{\mathsf{T}}}^{(\mathsf{T})} \right\|\right) \le A_i \lambda^t, \tag{3.28}$$

with S and T as in (3.19) and $A_i = \sum_{\mathsf{S}} c_{\mathsf{S}}^{(\mathsf{K})} \left(2A_{i_{\mathsf{S}}}^{(\mathsf{S})} + A_{i_{\mathsf{T}}}^{(\mathsf{T})}\right)$. Therefore, (3.20), (3.21), and (3.28) imply

$$\|d_i(t+1)\| \le \chi_{\mathsf{L}} \|d_i(t)\| + b_i \kappa^t + A_i \lambda^t \le \chi_{\mathsf{L}} \|d_i(t)\| + (b_i + A_i)\lambda^t,$$

where $\chi_{\mathsf{L}} = 1 - c^{(\mathsf{L})} = 1 - c_{\text{tot}} \le \lambda$. As in (3.25), we infer

$$\|d_i(t)\| \le B_i \lambda^t, \tag{3.29}$$

for an appropriate constant B_i. This completes the induction argument and shows that $d_{i_{\mathsf{K}}}^{(\mathsf{K})}$ decays to zero geometrically at rate λ for every nonempty subset $\mathsf{K} \subseteq \mathsf{L}$.

Therefore, setting $\mathsf{K} = \mathsf{L}$ in (3.18) and (3.19), (3.28) and (3.29) imply that

$$D(t) \to 0 \text{ as } t \to \infty \text{ at the geometric rate } \lambda. \tag{3.30}$$

(v) *Decay of the spatial heterogeneity, q.* By (2.23) and (3.15), we can write

$$P_i = \mu^T p_i = \mu^T d_i + \mu^T \prod_k p_{i_k}^{(k)}.$$

This together with (2.24b) and (3.15) shows that

$$\begin{aligned}\|q_i(t)\| &= \|p_i(t) - P_i(t)e\| \\ &= \left\| d_i(t) + \prod_k p_{i_k}^{(k)} - e\mu^T d_i(t) - e\mu^T \prod_k p_{i_k}^{(k)} \right\| \\ &\le 2\,\|d_i(t)\| + \left\| \prod_k p_{i_k}^{(k)} - e\mu^T \prod_k p_{i_k}^{(k)} \right\|, \end{aligned} \tag{3.31}$$

where we have used $\left\| e\mu^T \right\| \le 1$. Using (3.9) and expanding, we get

$$\begin{aligned} &\prod_k p_{i_k}^{(k)} - e\mu^T \prod_k p_{i_k}^{(k)} \\ &= \prod_k \left(q_{i_k}^{(k)} + P_{i_k}^{(k)} e \right) - e\mu^T \prod_k \left(q_{i_k}^{(k)} + P_{i_k}^{(k)} e \right) \\ &= \sum_{\mathsf{K}:\mathsf{K}\neq\emptyset} \left(\prod_{k\in\mathsf{K}} q_{i_k}^{(k)} \circ \left(\tilde{P}_{i_\mathsf{N}}^{(\mathsf{N})} e \right) \right) + \tilde{P}_i e \\ &\quad - e\mu^T \left[\sum_{\mathsf{K}:\mathsf{K}\neq\emptyset} \left(\prod_{k\in\mathsf{K}} q_{i_k}^{(k)} \circ \left(\tilde{P}_{i_\mathsf{N}}^{(\mathsf{N})} e \right) \right) + \tilde{P}_i e \right] \\ &= \sum_{\mathsf{K}:\mathsf{K}\neq\emptyset} \left(\tilde{P}_{i_\mathsf{N}}^{(\mathsf{N})} \prod_{k\in\mathsf{K}} q_{i_k}^{(k)} \right) - e\mu^T \left[\sum_{\mathsf{K}:\mathsf{K}\neq\emptyset} \left(\tilde{P}_{i_\mathsf{N}}^{(\mathsf{N})} \prod_{k\in\mathsf{K}} q_{i_k}^{(k)} \right) \right], \end{aligned} \tag{3.32}$$

where $\sum_{\mathsf{K}:\mathsf{K}\neq\emptyset}$ runs over all nonempty subsets of L, $\mathsf{N} = \mathsf{L}\setminus\mathsf{K}$, and $\tilde{P}_{i_\mathsf{N}}^{(\mathsf{N})} = 1$ if $N = \emptyset$. From (3.32), $P_{i_k}^{(k)} \le 1$, and (3.10), we obtain

$$\begin{aligned} \left\| \prod_k p_{i_k}^{(k)}(t) - e\mu^T \prod_k p_{i_k}^{(k)}(t) \right\| &\le 2 \sum_{\mathsf{K}:\mathsf{K}\neq\emptyset} \prod_{k\in\mathsf{K}} \left\| q_{i_k}^{(k)}(t) \right\| \\ &\le 2 \sum_{\mathsf{K}:\mathsf{K}\neq\emptyset} \prod_{k\in\mathsf{K}} \left(a_{i_k}^{(k)} \kappa^t \right) \le a_i \kappa^t \end{aligned} \tag{3.33}$$

for some constant a_i. Therefore, employing (3.29) and (3.33), (3.31) yields

$$\|q_i(t)\| \le 2B_i\lambda^t + a_i\kappa^t \le (2B_i + a_i)\lambda^t.$$

Hence

$$q(t) \to 0 \text{ as } t \to \infty \text{ at the geometric rate } \lambda. \tag{3.34}$$

This finishes the proof of Theorem 3.1. □

Remark 3.4 If, as is generically the case, the nonunit eigenvalue of M of largest modulus, λ_1, is simple and $|\lambda_1| \neq 1 - c_{\min}$, then the rate of convergence to Ψ_0 is $\lambda = \max(|\lambda_1|, 1 - c_{\min})$. Otherwise, any λ with $\max(|\lambda_1|, 1 - c_{\min}) < \lambda < 1$ can be chosen.

4 Strong migration

We assume that migration is strong, whereas other evolutionary forces may be weak. The most interesting case arises if migration and recombination are both strong and selection is weak. We treat it first. In Sect. 4.1.1, we prove that all trajectories converge to an invariant manifold Ψ_ϵ close to Ψ_0 (3.14) on which there is linkage equilibrium and allele frequencies are deme independent. On Ψ_ϵ, the dynamics can be described by a small perturbation of a system that has a Lyapunov function. In particular, this implies that all trajectories converge, i.e., no cycling can occur, and the equilibrium structure can be inferred. As an application, we study the increase of mean fitness in Sect. 4.1.2. A further application, the maintenance of polymorphism under strong migration, is treated in the subsequent paper. The second case, investigated in Sect. 4.2, is that of weak selection and weak recombination. Then, the limiting dynamics is equivalent to that of a panmictic population under selection and recombination. Since, in general, the latter admits richer dynamics and is not fully understood, only weaker conclusions can be drawn.

Throughout this section, we assume (E), i.e., the backward migration matrix is ergodic.

4.1 Weak selection

To investigate weak selection we follow Nagylaki et al. [45], Sect. 3, and set

$$w_{ij,\alpha} = 1 + \epsilon r_{ij,\alpha}, \tag{4.1}$$

where $\epsilon \geq 0$ is sufficiently small and $\left|r_{ij}\right| \leq 1$. We assume fixed migration and recombination rates, $m_{\alpha\beta}$ and c_{K}, so that fitness differences are small compared with them. From (2.6) and (4.1), we deduce

$$w_{i,\alpha}(p_{(\alpha)}) = 1 + \epsilon r_{i,\alpha}(p_{(\alpha)}), \quad \bar{w}_\alpha(p_{(\alpha)}) = 1 + \epsilon \bar{r}_\alpha(p_{(\alpha)}), \tag{4.2}$$

in which

$$r_{i,\alpha}(p_{(\alpha)}) = \sum_j r_{ij,\alpha} p_{j,\alpha}, \quad \bar{r}_\alpha(p_{(\alpha)}) = \sum_{i,j} r_{ij,\alpha} p_{i,\alpha} p_{j,\alpha}. \tag{4.3}$$

4.1.1 Equilibrium structure and convergence

When selection is dominated by migration and recombination, we expect that linkage disequilibria within demes as well as gamete- and gene-frequency differences between demes decay rapidly to small quantities. In particular, we expect approximately panmictic evolution of suitably averaged gamete frequencies in quasi-linkage equilibrium. We also show that all trajectories converge to an equilibrium point, i.e., no complicated dynamics, such as cycling, can occur. In the absence of migration, this was proved by Nagylaki et al. [45] (Theorem 3.1). For a single locus under selection and strong migration, this is the content of Theorem 4.5 in Nagylaki and Lou [48]. The following Theorem 4.3 and its proof combine and extend these results as well as the underlying ideas and methods.

To formulate and prove this theorem, we define the vector

$$\rho_\alpha = \left(p^{(1)}_{1,\alpha}, \dots, p^{(1)}_{I_1,\alpha}, \dots, p^{(L)}_{1,\alpha}, \dots, p^{(L)}_{I_L,\alpha}\right)^T \in \Delta_{I_1} \times \cdots \times \Delta_{I_L} \tag{4.4}$$

of all allele frequencies at every locus in deme α, and the vector

$$\pi = \left(P^{(1)}_{1}, \dots, P^{(1)}_{I_1}, \dots, P^{(L)}_{1}, \dots, P^{(L)}_{I_L}\right)^T \in \Delta_{I_1} \times \cdots \times \Delta_{I_L} \tag{4.5}$$

of all averaged allele frequencies at every locus. We note that in the presence of selection the $P^{(k)}_{i_k}$, hence π, are time dependent. Instead of p, we will use π, D, and q to analyze (2.8), and occasionally write $p = (\pi, D, q)$.

On the linkage-equilibrium manifold $\Lambda_{0,\alpha}$ (2.15), which is characterized by the ρ_α ($\alpha \in \mathsf{G}$), the selection coefficients of gamete i, allele i_n at locus n, and of the entire population are

$$r_{i,\alpha}(\rho_\alpha) = \sum_j r_{ij,\alpha} \prod_k p^{(k)}_{j_k,\alpha}, \tag{4.6a}$$

$$r^{(n)}_{i_n,\alpha}(\rho_\alpha) = \sum_{i|i_n} r_{i,\alpha}(\rho_\alpha) \prod_{k:k\neq n} p^{(k)}_{i_k,\alpha}, \tag{4.6b}$$

$$\bar{r}_\alpha(\rho_\alpha) = \sum_i r_{i,\alpha}(\rho_\alpha) \prod_k p^{(k)}_{i_k}, \tag{4.6c}$$

cf. (4.3). As in (2.18), let μ denote the principal left eigenvector of M. We introduce the average selection coefficients of genotype ij, gamete i, allele i_n at locus n, and of the entire population:

$$\omega_{ij} = \sum_\alpha \mu_\alpha r_{ij,\alpha}, \tag{4.7a}$$

$$\omega_i(\pi) = \sum_j \omega_{ij} \prod_k P^{(k)}_{j_k} = \sum_\alpha \mu_\alpha r_{i,\alpha}(\pi), \tag{4.7b}$$

$$\omega^{(n)}_{i_n}(\pi) = \sum_{i|i_n} \omega_i(\pi) \prod_{k\neq n} P^{(k)}_{i_k} = \sum_\alpha \mu_\alpha r^{(n)}_{i_n,\alpha}(\pi), \tag{4.7c}$$

$$\bar{\omega}(\pi) = \sum_i \omega_i(\pi) \prod_k P^{(k)}_{i_k} = \sum_\alpha \mu_\alpha \bar{r}_\alpha(\pi). \tag{4.7d}$$

For $\bar{\omega}$, we obtain the alternative representations

$$\bar{\omega}(\pi) = \sum_n \sum_{i_n} \omega_{i_n}^{(n)} P_{i_n}^{(n)} \tag{4.7e}$$

$$= \sum_{i,j} \omega_{ij} \left(\prod_n P_{i_n}^{(n)} \right) \left(\prod_k P_{j_k}^{(k)} \right), \tag{4.7f}$$

and

$$\frac{d\bar{\omega}(\pi)}{dP_{i_n}^{(n)}} = 2\omega_{i_n}^{(n)}(\pi). \tag{4.8}$$

For reasons that will be justified by the following theorem, we call the differential equation

$$\frac{dP_{i_n}^{(n)}}{dt} = P_{i_n}^{(n)} \left[\omega_{i_n}^{(n)}(\pi) - \bar{\omega}(\pi) \right], \tag{4.9a}$$

$$D = 0, \quad q = 0 \tag{4.9b}$$

on Δ_I^Γ the *weak-selection limit* of (2.8). In view of the following theorem, it is more convenient to consider (4.9a) and (4.9b) on Δ_I^Γ instead of (4.9a) on $\Delta_{I_1} \times \cdots \times \Delta_{I_L}$. The differential equation (4.9a) is a Svirezhev–Shashahani gradient ([7, p. 42], [45, p. 16]) with potential function $\bar{\omega}$. In particular, $\bar{\omega}$ increases strictly along nonconstant solutions of (4.9a) because

$$\frac{d\bar{\omega}}{dt} = 2 \sum_n \sum_{i_n} P_{i_n}^{(n)} \left[\omega_{i_n}^{(n)}(\pi) - \bar{\omega}(\pi) \right]^2 \geq 0. \tag{4.10}$$

We shall also need the assumption:

$$\text{All equilibria of (4.9a) are hyperbolic.} \tag{H.1}$$

Remark 4.1 An equilibrium of a system of differential equations is *hyperbolic* if the Jacobian matrix at that equilibrium has no eigenvalues on the imaginary axis. For systems of difference equations, hyperbolicity means that no eigenvalue has modulus one. A hyperbolic equilibrium is always an equilibrium point, and in a compact set there can be at most finitely many hyperbolic equilibria. Hyperbolicity is a generic property for systems of the form (4.9a) (see [45, Appendix B]). We call a property *generic* if it holds in an open dense set of full measure.

Remark 4.2 The proofs of the theorems below are based on the notion of a *chain-recurrent point* [12]. Let X be a compact set with metric d and let $f : X \to X$ be a continuous map. A point $x \in X$ is called *chain recurrent* (with respect to f) if, for every $\delta > 0$, there exists a finite sequence $x_0 = x, x_1, \ldots, x_{r-1}, x_r = x$ (often called a δ-pseudo-orbit) such that $d(f(x_m), x_{m+1}) < \delta$ for $m = 0, 1, \ldots, r-1$. The set of chain-recurrent points contains the limit sets of all orbits. In contrast to these limit sets, which need not change continuously under small perturbations (they can 'explode'), the set of chain-recurrent points has good properties under perturbations [3, p. 244].

Theorem 4.3 *Suppose that* (2.8), (4.1), (E) *and* (H.1) *hold, the backward migration matrix* M *and all recombination rates* c_{K} *are fixed, and* $\epsilon > 0$ *is sufficiently small.*

(a) *The set of equilibria* $\Xi_0 \subset \Delta_I^\Gamma$ *of* (4.9) *contains only isolated points, as does the set of equilibria* $\Xi_\epsilon \subset \Delta_I^\Gamma$ *of* (2.8)*. As* $\epsilon \to 0$*, each equilibrium in* Ξ_ϵ *converges to the corresponding equilibrium in* Ξ_0*.*

(b) *In the neighborhood of each equilibrium in* Ξ_0*, there exists exactly one equilibrium point in* Ξ_ϵ*. The stability of each equilibrium in* Ξ_ϵ *is the same as that of the corresponding equilibrium in* Ξ_0*; i.e., each pair is either asymptotically stable or unstable.*

(c) *Every solution* $p(t)$ *of* (2.8) *converges to one of the equilibrium points in* Ξ_ϵ*.*

Proof In view of Theorem 3.1 and the theory of normally hyperbolic manifolds [18,27], for sufficiently small ϵ there exists a smooth invariant manifold Ψ_ϵ close to Ψ_0, and Ψ_ϵ is globally attracting at a geometric rate for (2.8) [45, p. 114]. The manifold Ψ_ϵ is characterized by an equation of the form

$$(D, q) = \epsilon\psi(\pi, \epsilon), \tag{4.11}$$

where ψ is a smooth function of π. Thus, on Ψ_ϵ, and more generally, for any initial values, after a long time,

$$D(t) = O(\epsilon) \quad \text{and} \quad q(t) = O(\epsilon). \tag{4.12a}$$

Plugging (4.1) into (2.13) shows that, for given p, linkage disequilibrium D in the presence of selection differs from D in the absence of selection only by terms of order ϵ. Therefore, (3.18) and (3.19) imply that $D(t) = O(\epsilon)$ is equivalent to

$$d(t) = O(\epsilon), \tag{4.12b}$$

where $d = \left(d_{(1)}^T, \ldots, d_{(\Gamma)}^T\right)^T \in \mathbb{R}^{I\Gamma}$.

Next, we derive the recursion relations in an $O(\epsilon)$ neighborhood of Ψ_0 which, in particular, contains Ψ_ϵ. Equation (3.10) in Nagylaki et al. [45] shows that in an $O(\epsilon)$ neighborhood of Ψ_0 we have

$$p_{i_n,\alpha}^{(n)\,\#} = p_{i_n,\alpha}^{(n)} + \epsilon p_{i_n,\alpha}^{(n)} \frac{r_{i_n,\alpha}^{(n)}(\rho_\alpha) - \bar{r}_\alpha(\rho_\alpha)}{\bar{w}_\alpha(\rho_\alpha)} + O(\epsilon^2) \tag{4.13}$$

for every $\alpha \in \mathsf{G}$. From (4.6b) and (3.9), (4.7b) and (4.12a), and (4.7c), we obtain

$$\begin{aligned}\sum_\alpha \mu_\alpha r^{(n)}_{i_n,\alpha}(\rho_\alpha) &= \sum_\alpha \sum_{i|i_n} \mu_\alpha r_{i,\alpha}(\rho_\alpha) \prod_{k:k\neq n} \left(P^{(k)}_{i_k} + q^{(k)}_{i_k,\alpha}\right) \\ &= \sum_{i|i_n} \omega_i(\pi) \prod_{k:k\neq n} P^{(k)}_{i_k} + O(\epsilon) \\ &= \omega^{(n)}_{i_n}(\pi) + O(\epsilon). \end{aligned} \tag{4.14}$$

Furthermore, (4.6c) and (3.9), as well as (4.7b), (4.7d), and (4.12a) yield

$$\sum_\alpha \mu_\alpha \bar{r}_\alpha(\rho_\alpha) = \sum_\alpha \sum_i \mu_\alpha r_{i,\alpha}(\rho_\alpha) \prod_k \left(P^{(k)}_{i_k} + q^{(k)}_{i_k,\alpha}\right) = \bar{\omega}(\pi) + O(\epsilon). \tag{4.15}$$

From (4.14), (4.15), and (4.2), we conclude

$$\sum_\alpha \mu_\alpha \frac{r^{(n)}_{i_n,\alpha}(\rho_\alpha) - \bar{r}_\alpha(\rho_\alpha)}{\bar{w}_\alpha(\rho_\alpha)} = \omega^{(n)}_{i_n}(\pi) - \bar{\omega}(\pi) + O(\epsilon). \tag{4.16}$$

Therefore, we obtain from (3.7); (2.9a); (2.18); (4.13) and (3.9); (3.7), (4.16) and (4.12a):

$$\begin{aligned} P^{(n)\prime}_{i_n} &= \mu^T p^{(n)\prime}_{i_n} = \mu^T M p^{(n)\#}_{i_n} = \mu^T p^{(n)\#}_{i_n} \\ &= \mu^T p^{(n)}_{i_n} + \epsilon \sum_\alpha \mu_\alpha \left(P^{(n)}_{i_n} + q^{(n)}_{i_n,\alpha}\right) \frac{r^{(n)}_{i_n,\alpha}(\rho_\alpha) - \bar{r}_\alpha(\rho_\alpha)}{\bar{w}_\alpha(\rho_\alpha)} + O(\epsilon^2) \\ &= P^{(n)}_{i_n} + \epsilon P^{(n)}_{i_n} \left[\omega^{(n)}_{i_n}(\pi) - \bar{\omega}(\pi)\right] + O(\epsilon^2). \end{aligned} \tag{4.17}$$

The leading term in (4.17),

$$P^{(n)\prime}_{i_n} = P^{(n)}_{i_n} + \epsilon P^{(n)}_{i_n} \left[\omega^{(n)}_{i_n}(\pi) - \bar{\omega}(\pi)\right], \tag{4.18}$$

is the weak-selection approximation of (2.8). Because this is exactly the approximate dynamics under panmixia, i.e., (3.6) in Nagylaki et al. [45], we have $\bar{\omega}(\pi') > \bar{\omega}(\pi)$ unless $\pi' = \pi$. In particular, the dynamics (4.18) on Ψ_0 is gradient like.

Rescaling time t in generations as $\tau = \epsilon t$, we see at least formally that as $\epsilon \to 0$, the difference equation (4.17) approaches the differential equation (4.9a). Both have the same equilibria. The latter is a Svirezhev–Shahsahani gradient [7, p. 42–43]. In particular, (4.10) shows that $\bar{\omega}$ increases strictly along nonconstant solutions of (4.9a). The eigenvalues ν of (4.9a) correspond to the eigenvalues $1 + \epsilon\nu + O(\epsilon^2)$ of (4.17). Since (4.9a) is a gradient system, all eigenvalues of the Jacobian are real. As in Nagylaki et al. [45] (p. 116, below their assumption $\mathcal{H}$), it follows that (H.1) is equivalent to the hypothesis that (4.17) has no equilibria with an eigenvalue 1, or to hyperbolicity of equilibria of (4.18) for small ϵ.

Now the proof of Theorem 3.1 in Nagylaki et al. [45] yields all statements of Theorem 4.3 except the first in (b), where instead of 'exactly one' only 'at most one' follows because, in principle, the perturbed equilibrium may lie outside the simplex if the unperturbed is unstable. It remains to show that this cannot happen in the present case. The reason is that at every boundary equilibrium $\hat{p} = (\hat{\pi}, 0, 0)$ of (4.9), a subset of alleles is absent from the population because $\hat{P}_{i_n}^{(n)} = 0$ implies $\hat{p}_{i_n,\alpha}^{(n)} = 0$ for every α. Of course, if $P_{i_n}^{(n)} = 0$ for some n and i_n, then $P_{i_n}^{(n)\prime} = 0$ for any migration, selection, or recombination scheme. Hence, the condition $\hat{P}_{i_n}^{(n)} = 0$ is preserved under perturbations. Because all pairwise recombination rates are positive and gamete frequencies are equalized among demes, the frequencies of exactly those gametes are positive at equilibrium in one and, hence, every deme that carry none of the absent alleles. The positive gamete frequencies can change under perturbations, but will remain positive (and ≤ 1) under sufficiently small perturbations. Since the proof of Theorem 3.1 in Nagylaki et al. [45] demonstrates that a unique perturbed equilibrium exists in a small neighborhood of $(\hat{\pi}, 0, 0)$, it must be the one with the same subset of alleles absent as at the unperturbed equilibrium, and with the positive gamete frequencies slightly perturbed. Hence, it is again at the boundary of Δ_I^Γ. □

Remark 4.4 For applications, the essence of the above theorem is that the exact dynamics for weak selection can be perceived as a perturbation of the weak-selection limit. This is much easier to study because of linkage equilibrium and deme-independent allele frequencies. Under weak selection, the exact dynamics quickly leads to quasi-linkage equilibrium and spatial quasi-homogeneity (cf. Remark 4.9).

Remark 4.5 (i) To apply the proof of Theorem 3.1 in Nagylaki et al. [45], the references in [45] to Eqs. (3.6), (3.10), (3.13), and (3.14) have to be replaced by references to the present equations (4.18), (4.17), (4.9a), and (4.10). Their (3.5) is not needed here because it is equivalent to their (3.10), which corresponds to our (4.17).

(ii) The proof of Theorem 3.1 in Nagylaki et al. [45] shows in particular that, for sufficiently small ϵ, the number of chain-recurrent points of (4.9a) is finite. It is this property which implies convergence of trajectories of the perturbed dynamics (2.8); see [22] and Remark 3.1 in [45], which applies unaltered here.

(iii) Remark 3.4 in [45] suggests that the hyperbolicity condition (H.1) can be weakened, i.e., it is sufficient to assume that if an eigenvalue 0 occurs at any equilibrium of (4.9a), it has algebraic multiplicity 1.

(iv) By assuming $\pi - \rho_\alpha = O(\epsilon)$ for every α, Christiansen [10, p. 295], showed that for multiple diallelic loci and weak selection, linkage disequilibria decay to order $O(\epsilon)$.

Remark 4.6 We can easily estimate the time $\tilde{t}_1$ required to reach (4.12a). By Remark 3.4 and because the rate of approach to Ψ_ϵ is of order $\lambda + O(\epsilon)$, we can take $(\lambda + O(\epsilon))^{\tilde{t}_1} = \epsilon$, so that (4.12a) holds for

$$t \geq \tilde{t}_1 = \frac{\ln \epsilon}{\ln(\lambda + O(\epsilon))} = \frac{\ln \epsilon}{\ln \lambda} + O(\epsilon) \tag{4.19}$$

(cf. [43] for multiple loci without migration; and [48] for a single locus with migration). The time $\tilde{t}_1$ is evolutionary short unless selection or migration are very weak or linkage is very tight.

4.1.2 Increase of mean fitness

We study properties of mean fitness and generalize results of Nagylaki [43] and Nagylaki et al. [45] for multiple loci without migration and of Nagylaki and Lou [48] for a single locus with migration.

Remark 4.7 Suppose the assumptions of Theorem 4.3 apply. If (4.12a) holds and π is bounded away from the equilibria of (4.9a), then $\Delta\bar{\omega}(\pi) = \bar{\omega}(\pi') - \bar{\omega}(\pi) > 0$.

To prove this statement, we designate by $\varphi \in \mathbb{R}^{(I_1+\cdots+I_L)}$ the vector that has the components $P_{i_n}^{(n)}\left[\omega_{i_n}^{(n)}(\pi) - \bar{\omega}(\pi)\right]$ for all n and i_n. Further, we denote the scalar product of two vectors y, z of the same length by $\langle y, z\rangle = \sum_j y_j z_j$. Then, we obtain from (4.17), Taylor's theorem, and (for the last equality) (4.8) and (4.7e):

$$\begin{aligned}
\bar{\omega}(\pi') &= \bar{\omega}(\pi + \epsilon\varphi + O(\epsilon^2)) \\
&= \bar{\omega}(\pi) + \epsilon\langle\varphi, \nabla_\pi\bar{\omega}(\pi)\rangle + O(\epsilon^2) \\
&= \bar{\omega}(\pi) + \epsilon\sum_n\sum_{i_n} P_{i_n}^{(n)}\left[\omega_{i_n}^{(n)}(\pi) - \bar{\omega}(\pi)\right]\frac{d\bar{\omega}(\pi)}{dP_{i_n}^{(n)}} + O(\epsilon^2) \\
&= \bar{\omega}(\pi) + 2\epsilon\sum_n\sum_{i_n} P_{i_n}^{(n)}\left[\omega_{i_n}^{(n)}(\pi) - \bar{\omega}(\pi)\right]^2 + O(\epsilon^2).
\end{aligned} \tag{4.20}$$

This implies $\bar{\omega}(\pi') > \bar{\omega}(\pi)$ if π is bounded away from the equilibria and $\epsilon > 0$ is sufficiently small.

Next, we prove a deeper result for the average of the (exact) mean fitnesses over demes:

$$\bar{w}(p) = \sum_\alpha \mu_\alpha \bar{w}_\alpha(p_{(\alpha)}). \tag{4.21}$$

Theorem 4.8 *Suppose the assumptions of Theorem 4.3 apply. If (4.12a) holds, π is bounded away from the equilibria of (4.9a), and p is within $O(\epsilon^2)$ of Ψ_ϵ, then $\Delta\bar{w}(p) > 0$.*

Proof The proof is an adaptation of that in Remark 3.7 of Nagylaki et al. [45]; see also Theorem 4.12 of Nagylaki and Lou [48]. First, we prove that our assumptions imply

$$(D', q') - (D, q) = O(\epsilon^2). \tag{4.22}$$

Writing the exact recursion for (D, q) as

$$(D', q') = f(\pi, (D, q), \epsilon), \tag{4.23}$$

where f is a smooth function of π and (D, q), we infer from (4.11) that

$$\epsilon\psi(\pi', \epsilon) = f(\pi, \epsilon\psi(\pi, \epsilon), \epsilon). \tag{4.24}$$

By assumption, we have

$$(D, q) = \epsilon\psi(\pi, \epsilon) + O(\epsilon^2). \tag{4.25}$$

Appealing successively to (4.23) and (4.25), Taylor's theorem, (4.24), Taylor's theorem again and (4.17), and (4.11), we obtain

$$\begin{aligned}(D', q') &= f(\pi, \epsilon\psi(\pi, \epsilon) + O(\epsilon^2), \epsilon) = f(\pi, \epsilon\psi(\pi, \epsilon), \epsilon) + O(\epsilon^2)\\ &= \epsilon\psi(\pi', \epsilon) + O(\epsilon^2) = \epsilon\psi(\pi, \epsilon) + O(\epsilon^2)\\ &= (D, q) + O(\epsilon^2),\end{aligned}$$

which is precisely (4.22).

The averaged mean fitness can be written as

$$\bar{w}(p) = 1 + \epsilon\bar{r}(\pi, (D, q)), \tag{4.26}$$

where $\bar{r}(\pi, (D, q)) = \sum_\alpha \mu_\alpha \bar{r}_\alpha(p_{(\alpha)})$. On Ψ_0 this gives, by employing (3.14), (4.3), and (4.7d),

$$\bar{r}(\pi, (0, 0)) = \sum_\alpha \mu_\alpha \bar{r}_\alpha(\pi) = \bar{\omega}(\pi). \tag{4.27}$$

Finally, we obtain by invoking successively (4.17) and (4.22), Taylor's theorem, again Taylor's theorem and (4.11), (4.27) and (4.20),

$$\begin{aligned}\bar{r}(\pi', (D', q')) &= \bar{r}(\pi + \epsilon\varphi + O(\epsilon^2), (D, q) + O(\epsilon^2))\\ &= \bar{r}(\pi, (D, q)) + \epsilon\langle\varphi, \nabla_\pi \bar{r}(\pi, (D, q))\rangle + O(\epsilon^2)\\ &= \bar{r}(\pi, (D, q)) + \epsilon\langle\varphi, \nabla_\pi \bar{r}(\pi, (0, 0))\rangle + O(\epsilon^2)\\ &= \bar{r}(\pi, (D, q)) + 2\epsilon \sum_n \sum_{i_n} P_{i_n}^{(n)} \left[\omega_{i_n}^{(n)}(\pi) - \bar{\omega}(\pi)\right]^2 + O(\epsilon^2).\end{aligned} \tag{4.28}$$

Therefore, the assertion of the theorem follows from (4.26). □

Remark 4.9 Equation (4.22) shows that linkage disequilibria and the measure q of spatial diversity change very slowly on Ψ_ϵ. It justifies to call states on Ψ_ϵ spatially quasi-homogeneous and to be in quasi-linkage equilibrium.

4.2 Weak selection and weak recombination

Here, we derive the strong-migration, weak-selection weak-recombination limit. In addition to (4.1), we posit

$$c_{\mathsf{K}} = \epsilon\gamma_{\mathsf{K}}, \quad \mathsf{K} \subseteq \mathsf{L}, \tag{4.29}$$

where $\epsilon \geq 0$ is sufficiently small and γ_{K} is defined by this relation. We assume fixed $m_{\alpha\beta}$ and let $\epsilon \to 0$ in (4.1) and in (4.29). Then, migration is the only strong evolutionary force, and selection and recombination are 'equally' weak.

In the absence of selection and recombination ($\epsilon = 0$), the system (2.8) reduces to

$$p_i' = Mp_i \tag{4.30}$$

for every $i \in \mathsf{I}$. Repeating the calculations that led from (3.6) to (3.10), we find $P_i' = P_i$ and

$$q(t) \to 0 \tag{4.31}$$

as $t \to 0$ at the geometric rate κ; cf. (2.20). In particular,

$$p_i(t) \to P_i(0)e, \tag{4.32}$$

so that the gamete frequencies become deme independent.

Therefore, the manifold

$$\Pi_0 = \left\{p \in \Delta_I^\Gamma : q = 0\right\} \tag{4.33}$$

is invariant under (4.30) and globally attracting at the uniform geometric rate κ. Furthermore, every point on Π_0 is an equilibrium of (4.30).

For sufficiently small ϵ, there exists a smooth invariant manifold Π_ϵ close to Π_0, and Π_ϵ is globally attracting at a geometric rate for (2.8) [45, p. 114]). The manifold Π_ϵ is characterized by an equation of the form [45, p. 114]

$$q = \epsilon\sigma(P, \epsilon), \tag{4.34}$$

where σ is a smooth function of P. Thus, on Π_ϵ, and more generally for any initial values after a long time,

$$q(t) = O(\epsilon), \tag{4.35}$$

i.e., on Π_ϵ the distribution of gamete frequencies is spatially quasi-homogeneous.

Next, we derive the recursion relations in an $O(\epsilon)$ neighborhood of Π_0 which, in particular, contains Π_ϵ. Substituting (2.24a) and (4.34) into (4.3), we obtain

$$r_{i,\alpha}(p_{(\alpha)}) = r_{i,\alpha}(P) + O(\epsilon), \quad \bar{r}_\alpha(p_{(\alpha)}) = \bar{r}_\alpha(P) + O(\epsilon). \tag{4.36}$$

Consequently, (4.2) yields

$$w_{i,\alpha}(p_{(\alpha)}) = 1 + \epsilon r_{i,\alpha}(P) + O(\epsilon^2), \tag{4.37a}$$

$$\bar{w}_\alpha(p_{(\alpha)}) = 1 + \epsilon \bar{r}_\alpha(P) + O(\epsilon^2). \tag{4.37b}$$

For the linkage disequilibria we obtain from (2.13) by invoking (4.1), (4.29), and (4.37b):

$$\begin{aligned} D_{i,\alpha} &= \frac{1}{1+O(\epsilon)} \sum_j \sum_{\mathsf{K}} \epsilon \gamma_{\mathsf{K}} \left\{ [1+O(\epsilon)] p_{i,\alpha} p_{j,\alpha} - [1+O(\epsilon)] p_{i_{\mathsf{K}} j_{\mathsf{N}},\alpha}\, p_{j_{\mathsf{K}} i_{\mathsf{N}},\alpha} \right\} \\ &= \epsilon \Theta_{i,\alpha} + O(\epsilon^2), \end{aligned} \tag{4.38}$$

where $\mathsf{N} = \mathsf{L} \backslash \mathsf{K}$ and

$$\Theta_{i,\alpha} = \sum_j \sum_{\mathsf{K}} \gamma_{\mathsf{K}} (p_{i,\alpha} p_{j,\alpha} - p_{i_{\mathsf{K}} j_{\mathsf{N}},\alpha}\, p_{j_{\mathsf{K}} i_{\mathsf{N}},\alpha}) = \sum_{\mathsf{K}} \gamma_{\mathsf{K}} \left(p_{i,\alpha} - p^{(\mathsf{K})}_{i_{\mathsf{K}},\alpha} p^{(\mathsf{N})}_{i_{\mathsf{N}},\alpha} \right), \tag{4.39}$$

cf. (3.2). Inserting (4.37) and (4.38) into (2.9a) and using (2.14), we obtain

$$p'_{i,\alpha} = \sum_\beta m_{\alpha\beta} \left\{ p_{i,\beta}[1 + \epsilon(r_{i,\beta}(P) - \bar{r}_\beta(P))] - \epsilon \Theta_{i,\beta} \right\} + O(\epsilon^2). \tag{4.40}$$

We multiply (4.40) by μ_α, sum over α, use (2.23), (2.18), (2.24a), (4.38) and (4.39), and, for the second equality, (4.35) to infer

$$\begin{aligned} P'_i &= P_i + \epsilon \sum_\beta \mu_\beta (P_i + q_{i,\beta})[r_{i,\beta}(P) - \bar{r}_\beta(P)] \\ &\quad - \epsilon \sum_{\mathsf{K}} \gamma_{\mathsf{K}} \sum_\beta \mu_\beta \left[p_{i,\beta} - \left(P^{(\mathsf{K})}_{i_{\mathsf{K}}} + q^{(\mathsf{K})}_{i_{\mathsf{K}},\beta} \right) \left(P^{(\mathsf{N})}_{i_{\mathsf{N}}} + q^{(\mathsf{N})}_{i_{\mathsf{N}},\beta} \right) \right] + O(\epsilon^2) \\ &= P_i + \epsilon P_i \sum_\beta \mu_\beta [r_{i,\beta}(P) - \bar{r}_\beta(P)] - \epsilon \sum_{\mathsf{K}} \gamma_{\mathsf{K}} \left[P_i - P^{(\mathsf{K})}_{i_{\mathsf{K}}} P^{(\mathsf{N})}_{i_{\mathsf{N}}} \right] + O(\epsilon^2), \end{aligned} \tag{4.41}$$

where $P^{(\mathsf{K})}_{i_{\mathsf{K}}} = \mu^T p^{(\mathsf{K})}_{i_{\mathsf{K}}}$ and $q^{(\mathsf{K})}_{i_{\mathsf{K}}}$ is defined in analogy to (2.5b). In analogy to (4.7), we define the average selection coefficients of gamete i and the entire population by

$$\omega_i(P) = \sum_j \omega_{ij} P_j = \sum_\alpha \mu_\alpha r_{i,\alpha}(P), \tag{4.42a}$$

$$\bar{\omega}(P) = \sum_{i,j} \omega_{ij} P_i P_j = \sum_\alpha \mu_\alpha \bar{r}_\alpha(P). \tag{4.42b}$$

Setting

$$h_i(P) = P_i[\omega_i(P) - \bar{\omega}(P)] + \sum_{\mathsf{K}} \gamma_{\mathsf{K}} \left(P_i - P_{i_{\mathsf{K}}}^{(\mathsf{K})} P_{i_{\mathsf{N}}}^{(\mathsf{N})} \right), \tag{4.43a}$$

(4.41) simplifies to

$$P_i' = P_i + \epsilon h_i(P) + O(\epsilon^2). \tag{4.43b}$$

Hence, we can express the *strong-migration approximation* in (4.43b) as

$$P' = P + \epsilon h(P), \quad h = h(P) = (h_1(P), \dots, h_I(P))^T \in \mathbb{R}^I. \tag{4.44}$$

This is equivalent to the dynamics for panmixia with L recombining loci, fitnesses $1 + \epsilon\omega_{ij}$ and recombination rates $\epsilon\gamma_{\mathsf{K}}$. We note that (4.44) holds not only on Π_ϵ, but also in an $O(\epsilon)$ neighborhood of Π_0 because in its derivation we used (4.35) rather than (4.34).

If we scale time in generations as $\tau = \epsilon t$, we see at least formally that as $\epsilon \to 0$, the difference equation (4.43b) converges to the differential equation

$$\frac{dP_i}{d\tau} = h_i(P) = P_i[\omega_i(P) - \bar{\omega}(P)] - \sum_{\mathsf{K}} \gamma_{\mathsf{K}} \left[P_i - P_{i_{\mathsf{K}}}^{(\mathsf{K})} P_{i_{\mathsf{N}}}^{(\mathsf{N})} \right], \tag{4.45a}$$

which we augment with

$$q = 0. \tag{4.45b}$$

We call (4.45) the *strong-migration limit* of (2.8). Clearly, (4.44) and (4.45a) have the same equilibria. The eigenvalues ν of (4.45a) correspond to the eigenvalues $1 + \epsilon\nu$ of (4.44).

In general, it cannot be expected that the asymptotic behavior of solutions of (2.8) under strong migration is governed by (4.45) because its chain-recurrent set does not always consist of finitely many hyperbolic equilibria. Akin [1,2] proved that (4.45) may exhibit stable cycling. Therefore, under strong migration and if selection and recombination are about equally weak, convergence of trajectories of (2.8) will not generally occur. The dynamics (4.43b) and (4.45) become simple, for instance, if there is no epistasis (cf. [16,41,45]). Then, mean fitness is a Lyapunov function, all equilibria are in linkage equilibrium, and a special case of Theorem 4.3, which does not assume weak nonepistatic selection, is recovered.

Instead of Theorem 4.3, the following considerably weaker result can be proved.

Proposition 4.10 *Suppose that* (4.1), (4.29) *and* (E) *hold, the backward migration matrix M is fixed and $\epsilon > 0$ is sufficiently small.*

(a) *Every solution $p(t)$ of* (2.8) *converges to the manifold Π_ϵ given by* (4.34)*, i.e., after a sufficiently long time gamete frequencies between demes differ by at most $O(\epsilon)$.*

(b) *In the neighborhood of each hyperbolic equilibrium of* (4.45)*, there exists exactly one equilibrium point of* (2.8)*. The stability properties of the two equilibria are the same.*

Proof (a) has been shown above.

(b) follows from an adaptation of (part of) the proof of Theorem 3.1 in Nagylaki et al. [45]. The estimates (4.41) and (4.43b) imply that (2.8) restricted to Π_ϵ, and expressed in the coordinates $P \in \Delta_I$, behaves like a first-order numerical discretization procedure for the differential equation (4.45a), with step size ϵ, whereas (4.44) is essentially the Euler scheme for (4.45a). By Corollary 2.3 of Garay [21], which is an extension of the Hartman–Grobman theorem, there exists a $\delta > 0$ such that for sufficiently small ϵ, the recursion relation (4.41) has a single hyperbolic fixed point as the only invariant set in the δ-neighborhood of each of the equilibria of (4.45a). Unstable boundary equilibria cannot move out of the simplex by the same reasoning as at the end of the proof of Theorem 4.3. □

Remark 4.11 An argument as in Remark 4.6 shows that after an evolutionary short time, $\tilde{t}_2$, deviations from the manifold Π_0 are of order $O(\epsilon)$. After this time span, the population evolves approximately as if it were panmictic. More precisely, let $p(t)$ denote a solution of the full dynamics (2.8) and let $P(t)$ be a solution of the much simpler strong-migration approximation (4.44) such that

$$P_i(\tilde{t}_2) = \mu^T p_i(\tilde{t}_2) \tag{4.46}$$

for every $i \in \mathsf{I}$. Then,

$$p_i(t) = \check{p}_i(t) + O(\epsilon), \quad \tilde{t}_2 \le t \le K_1/\epsilon, \tag{4.47}$$

as $\epsilon \to 0$, where K_1 denotes a constant and $\check{p}_{i,\alpha} = P_i$ for every $\alpha \in \mathsf{G}$. The proof is analogous to that of Eq. (53) in Nagylaki [43] and is omitted.

If $P(t)$ does not convergence to some equilibrium point or if $P(\tilde{t}_2)$ is on the stable manifold of an unstable equilibrium, the restriction $t \le K_1/\epsilon$ may become necessary.

Remark 4.12 Assume (4.1) and (4.29), and let $P^{(\epsilon)}(t)$ and $P(\tau)$, where $\tau = \epsilon t$, denote solutions of (4.44) and (4.45), respectively, satisfying $P^{(\epsilon)}(0) = P(0)$. Then, classical results on numerical discretization show that there exists a constant K_2 such that

$$P(\tau) = P^{(\epsilon)}(t) + O(\epsilon), \quad 0 \le \tau \le K_2. \tag{4.48}$$

Thus, the solutions remain close together for a time interval of length $O(1)$, i.e., for $O(1/\epsilon)$ generations. The reason is that the discretization (4.44) is the Euler method, hence has consistency order one [15, Theorem 4.10 and Example 4.11]. Clearly, in the range of attraction of an asymptotically stable equilibrium, these solutions remain close together for all times.

Combining this remark with that above shows that after an evolutionary short time, $\tilde{t}_2$, solutions of (2.8) can be approximated by solutions of the strong-migration limit (4.45) for an evolutionary long time.

Similar remarks apply to the weak-selection approximation (4.18). There, however, every solution converges to an equilibrium. Hence, the constraint $t \leq K_2/\epsilon$ is needed only in the nongeneric case in which a solution is started on the stable manifold of an unstable equilibrium.

4.3 Weak recombination

If recombination is weak relative to migration and selection, the limiting dynamics becomes formally equivalent to a single-locus migration-selection model. Such models have been treated in considerable detail by Nagylaki and Lou [46–49], and are not further considered here.

5 Weak migration

The second interesting limiting case that admits a fairly general analytical study is that of weak migration. Selection and recombination may be weak or strong. The equilibrium structure as well as convergence of trajectories to an equilibrium point can be established for strong recombination and selection if epistasis is weak (Sect. 5.2). The limiting cases in which migration and selection are weak (Sect. 5.1) or when all evolutionary forces are weak (Sect. 5.3) do, in general, not yield simple dynamics. An application, the maintenance of multilocus polymorphism under weak migration, weak epistasis, and in the absence of overdominance and underdominance will be studied in the companion paper.

In the absence of migration, the dynamics (2.8) reduces to $p'_{i,\alpha} = p^{\#}_{i,\alpha}$, which can be written in the form

$$p'_{i,\alpha} = p_{i,\alpha} \frac{w_{i,\alpha}}{\bar{w}_\alpha} - D_{i,\alpha} \tag{5.1}$$

for every $i \in I$ and every $\alpha \in \mathsf{G}$; see (2.14). Therefore, we have Γ decoupled multilocus selection dynamics, one for each deme. For a single deme, (5.1) is well known. Although many special cases have been studied, in part in considerable detail (e.g., [7, Chapter 2]), no general results are available. In particular, trajectories of (5.1) do not necessarily converge to an equilibrium. For two diallelic loci, the occurrence of stable cycling in (5.1) has been established [26,28].

To investigate weak migration, we follow Nagylaki and Lou [48] and set

$$m_{\alpha\beta} = \delta_{\alpha\beta} + \epsilon a_{\alpha\beta}, \tag{5.2}$$

where $\epsilon \geq 0$ measures the strength of migration. Because M is a stochastic matrix, we have

$$a_{\alpha\beta} \geq 0 \ \text{ for every } \ \beta \neq \alpha, \quad \text{and} \quad \sum_\beta a_{\alpha\beta} = 0 \ \text{ for every } \ \alpha. \tag{5.3}$$

If $\epsilon = 0$, there is no migration and the dynamics is given by (5.1). In this section, we do not assume ergodicity (nor irreducibility) of the backward migration matrix M.

Convergence of trajectories of (2.8) does occur under sufficiently weak migration and arbitrary selection if every equilibrium of (5.1) is hyperbolic, whence there are only finitely many equilibria, and the only chain-recurrent points of (5.1) are its equilibria. This follows immediately from the results on the perturbation properties of chain-recurrent sets [3, p. 244]. In general, however, it is difficult to characterize the set of chain-recurrent points.

5.1 Weak selection

In the absence of migration and selection, the linkage-equilibrium manifold Λ_0 (2.16) is invariant and globally attracting at a uniform geometric rate (Remark 3.2(i) or Theorem 3.1). For weak migration and selection, i.e., for sufficiently small ϵ, the theory of normally hyperbolic manifolds [18,27] implies the existence of a smooth invariant manifold Λ_ϵ close to Λ_0, which is globally attracting at a geometric rate for (2.8) [45, p. 114]. The manifold Λ_ϵ is characterized by an equation of the form

$$D = \epsilon\zeta(\rho, \epsilon), \tag{5.4}$$

where ζ is a smooth function of ρ. Thus, on Λ_ϵ, and more generally, for any initial values, after a long time,

$$D(t) = O(\epsilon). \tag{5.5}$$

It follows that on Λ_ϵ, linkage disequilibria are of order ϵ and, in fact, change very slowly, i.e., $\Delta D(t) = O(\epsilon^2)$; cf. [43] and (4.22). Therefore, Λ_ϵ can be called the quasi-linkage equilibrium manifold [45]. Clearly, $\Lambda_\epsilon \supseteq \Psi_\epsilon$; cf. Remark 4.9.

From (2.9) and (2.14) we obtain by invoking (5.2) and (4.1):

$$p'_{i,\alpha} = p_{i,\alpha}[1 + \epsilon(r_{i,\alpha} - \bar{r}_\alpha)] - D_{i,\alpha} + \epsilon\sum_\beta a_{\alpha\beta}p_{i,\beta} - \epsilon\sum_\beta a_{\alpha\beta}D_{i,\beta} + O(\epsilon^2). \tag{5.6}$$

By summing (5.6) over all multi-indices i with i_n fixed and using $\sum_{i|i_n} D_{i,\alpha} = 0$ [7, p. 72], we obtain in an $O(\epsilon)$ neighborhood of Λ_0, in which $r^{(n)}_{i_n,\alpha}(p_{(\alpha)}) = r^{(n)}_{i_n,\alpha}(\rho_\alpha) + O(\epsilon)$ and $\bar{r}_\alpha(p_{(\alpha)}) = \bar{r}_\alpha(\rho_\alpha) + O(\epsilon)$ hold:

$$p^{(n)\,\prime}_{i_n,\alpha} = p^{(n)}_{i_n,\alpha} + \epsilon p^{(n)}_{i_n,\alpha}\left[r^{(n)}_{i_n,\alpha}(\rho_\alpha) - \bar{r}_\alpha(\rho_\alpha)\right] + \epsilon\sum_\beta a_{\alpha\beta}p^{(n)}_{i_n,\beta} + O(\epsilon^2). \tag{5.7}$$

Therefore, the limiting dynamics on Δ_I^Γ is given by

$$\frac{dp^{(n)}_{i_n,\alpha}}{dt} = p^{(n)}_{i_n,\alpha}\left[r^{(n)}_{i_n,\alpha}(\rho_\alpha) - \bar{r}_\alpha(\rho_\alpha)\right] + \sum_\beta a_{\alpha\beta}p^{(n)}_{i_n,\beta}, \tag{5.8a}$$

$$D = 0. \tag{5.8b}$$

Equation (5.8a) is formally equivalent to the slow evolution limit for a single locus in Nagylaki and Lou [48, Eq. (2.20)].

In general, convergence of trajectories in (5.8a) does not occur. Akin (personal communication) has established for three diallelic demes that Hopf bifurcations can produce unstable limit cycles. This result precludes global convergence, though not generic convergence. No general results concerning (5.8) are available. For some special cases, such as two alleles or uniform selection in all demes, see [48,49].

The following result is proved in essentially the same way as Proposition 4.10.

Proposition 5.1 *Suppose that* (4.1) *and* (5.2) *hold, the backward migration matrix* M *and the recombination rates* c_{K} *are fixed, and* $\epsilon > 0$ *is sufficiently small.*

(a) *Every solution* $p(t)$ *of* (2.8) *converges to the manifold* Λ_ϵ *given by* (5.4)*, i.e., after a sufficiently long time quasi-linkage equilibrium is approached.*

(b) *In the neighborhood of each hyperbolic, asymptotically stable equilibrium of* (4.45)*, there exists exactly one equilibrium point of* (2.8)*, and it is asymptotically stable. In the neighborhood of each hyperbolic, unstable internal equilibrium of* (4.45)*, there exists exactly one equilibrium point of* (2.8)*, and it is unstable. In the neighborhood of each hyperbolic, unstable boundary equilibrium of* (4.45)*, there exists at most one equilibrium point of* (2.8)*, and if it exists, it is unstable.*

Analogs of Remarks 4.11 and 4.12 apply.

5.2 Weak epistasis

If migration and epistasis are weak relative to recombination and additive selection, then a much stronger result than Proposition 5.1 can be derived, namely Theorem 5.4. It is a twofold generalization of Theorem 2.3 of Nagylaki et al. [45], in which convergence of trajectories to equilibrium is proved in multilocus systems with weak epistasis. Here, we not only extend their theorem to weak migration, but also formulate a ‘uniform’ version as explained below. We shall need this stronger result for our application on the maintenance of polymorphism.

It will be convenient to collect fitness parameters in vectors. We write $W = (w_{ij,\alpha})$ for the collection of fitnesses of every genotype in each deme and view it as a vector, i.e., $W \in \mathbb{R}^{I^2\Gamma}$. In the absence of position effects, its dimension is $H\Gamma$, where $H = \prod_{n\in\mathsf{L}} \binom{I_n+1}{2}$. Similarly, we write $S = (s_{ij,\alpha})$ for the vector of epistasis parameters introduced below. S has the same length as W. Further, we need to assign additive fitness components $u^{(n)}_{i_nj_n,\alpha} > 0$ to single-locus genotypes. We collect them in the vector $U = (u^{(n)}_{i_nj_n,\alpha})$ of length $J\Gamma$, $J = \sum_{n\in\mathsf{L}} \binom{I_n+1}{2}$. Finally, we write $A = (a_{\alpha\beta})$ and consider it as a matrix of dimension $\Gamma \times \Gamma$. We define

$$\mathsf{S}_\eta = \{S = (s_{ij,\alpha}) : \left|s_{ij,\alpha}\right| \le \eta \text{ for every } i,\, j,\, \alpha\}, \tag{5.9a}$$

$$\mathsf{M}_{w,\epsilon} = \{A = (a_{\alpha\beta}) : A \text{ satisfies (5.3) and } \left|a_{\alpha\beta}\right| \le \epsilon \text{ for every } \alpha,\, \beta\}, \tag{5.9b}$$

$$\mathsf{U} = \{U = (u^{(n)}_{i_nj_n,\alpha}) : u^{(n)}_{i_nj_n,\alpha} > 0 \text{ for every } n,\, i_n,\, j_n,\, \alpha\}. \tag{5.9c}$$

To investigate weak migration and weak epistasis, we assume that the backward migration matrix is of the form

$$M = I + A, \tag{5.10}$$

where I is the $\Gamma \times \Gamma$ unity matrix and $A \in \mathsf{M}_{w,\epsilon}$, and

$$w_{ij,\alpha} = \sum_n u^{(n)}_{i_n j_n,\alpha} + s_{ij,\alpha}, \tag{5.11}$$

where $U \in \mathsf{U}$, $S \in \mathsf{S}_\eta$ and $\eta \geq 0$ measures the strength of epistasis. It is always assumed that η is small enough so that $w_{ij,\alpha} > 0$. Throughout the following, we posit

$$\eta = \eta(\epsilon), \tag{5.12}$$

where $\eta : [0, 1) \to [0, \infty)$ is C^1 and satisfies $\eta(0) = 0$. Therefore, migration and epistasis need not be 'equally' weak. In particular, the case $\eta \equiv 0$, i.e., no epistasis, is included.

In the absence of migration and of epistasis ($\epsilon = \eta = 0$), we have $\Delta \bar{w}_\alpha \geq 0$ within each deme, with equality if and only if

$$p_{i,\alpha}(w_{i,\alpha} - \bar{w}_\alpha) = 0 \;\text{ for every }\; i \in \mathsf{I}. \tag{5.13}$$

Let

$$\mathsf{F}_\alpha = \{p_{(\alpha)} : p_{i,\alpha}(w_{i,\alpha} - \bar{w}_\alpha) = 0 \;\text{ for every }\; i \in \mathsf{I}\} \subseteq \Delta_I \tag{5.14}$$

and let

$$\mathsf{F} = \mathsf{F}_1 \times \cdots \times \mathsf{F}_\Gamma \subseteq \Delta_I^\Gamma \tag{5.15}$$

be the cartesian product. We recall the definition of the linkage equilibrium manifold Λ_0 from (2.16).

Remark 5.2 Lemma 2.1 of Nagylaki et al. [45] implies that if $\epsilon = 0$, then the equilibria of (5.1) are exactly the points in $\mathsf{F} \cap \Lambda_0$. Thus, in the absence of epistasis and migration, p is an equilibrium point of (5.1) if and only if for every $\alpha \in \mathsf{G}$, $p_{(\alpha)}$ is both a selection equilibrium for each locus and is in linkage equilibrium.

We start by generalizing Lemma 2.2 of Nagylaki et al. [45].

Lemma 5.3 *If $\epsilon = \eta = 0$ in* (5.2) *and* (5.11)*, then the only chain-recurrent points of* (5.1) *are its equilibria.*

Proof Lemma 2.2 of Nagylaki et al. [45] shows that in every deme, i.e., for every fixed α, the only chain-recurrent points of (5.1) are its equilibria. Because, in the absence of migration, the dynamics in the demes are decoupled, a point p is chain recurrent if and only if every $p_{(\alpha)}$, $\alpha \in \mathsf{G}$, is chain recurrent for the dynamics restricted to deme α. Therefore, and by Remark 5.2, the chain-recurrent points of the (full) dynamics without migration are exactly the equilibria, $\mathsf{F} \cap \Lambda_0$. □

In Nagylaki et al. [45], it was shown that for given $U \in \mathsf{U}$ and $S \in \mathsf{S}_1$, an ϵ_0 exists such every trajectory of (2.8) converges if W is given by $w_{ij,\alpha} = \sum_n u^{(n)}_{i_n j_n,\alpha} + \epsilon s_{ij,\alpha}$, where $0 < \epsilon < \epsilon_0$. We observe that, infact, for given $U \in \mathsf{U}$ an $\epsilon > 0$ exists such that convergence of all trajectories occurs for every W satisfying (5.11) with $S \in \mathsf{S}_{\eta(\epsilon)}$. We shall need the following generic assumption (see [45, Appendix A], and Remark 4.1):

In the absence of epistasis, every equilibrium of (5.1) is hyperbolic. (H2)

Theorem 5.4 *Suppose that* (2.8) *holds,* $U \in \mathsf{U}$ *is such that* (H2) *holds, all recombination rates* c_{K} *are fixed, and* $\epsilon > 0$ *is sufficiently small. Then, for every parameter combination* (W, M) *satisfying* (5.10), (5.11), *and* (5.12), *the following holds*:

(a) *The set of equilibria* $\Sigma_0 \subset \Delta_I^\Gamma$ *of* (5.1) (*with* $\eta = 0$) *contains only isolated points, as does the set of equilibria* $\Sigma_{(W,M)} \subset \Delta_I^\Gamma$ *of* (2.8). *As* $\epsilon \to 0$ *in* (5.11), *each equilibrium in* $\Sigma_{(W,M)}$ *converges to the corresponding equilibrium in* Σ_0.

(b) *In the neighborhood of each asymptotically stable equilibrium in* Σ_0, *there exists exactly one equilibrium point in* $\Sigma_{(W,M)}$, *and it is asymptotically stable. In the neighborhood of each unstable internal equilibrium in* Σ_0, *there exists exactly one equilibrium point in* $\Sigma_{(W,M)}$, *and it is unstable. In the neighborhood of each unstable boundary equilibrium in* Σ_0, *there exists at most one equilibrium point in* $\Sigma_{(W,M)}$, *and if it exists, it is unstable.*

(c) *Every solution* $p(t)$ *of* (2.8) *converges to one of the equilibrium points in* $\Sigma_{(W,M)}$.

Proof By referring in the proof of Theorem 2.3 in Nagylaki et al. [45] to the above Lemma 5.3 instead of their Lemma 2.2, their proof of Theorem 2.3 applies unaltered because (5.10) together with (5.11) yields a small C^1 perturbation of the dynamics with $\epsilon = \eta = 0$. (Corollary 32 in [3] does not assume that the perturbation is caused by a single parameter. It holds for arbitrary, small C^1 perturbations.) □

Remark 5.5 (i) Parts (a) and (b) of the above theorem follow immediately from Theorem 4.4 of [33] which, essentially, is an application of the implicit function theorem. Part (c) is much stronger and relies, among others, on the notion of chain-recurrent points and their properties under perturbations of the dynamics. The reason is that hyperbolicity of all equilibria does not exclude the existence of limit cycles or of more complicated dynamics; cf. Remark 4.2.

(ii) In contrast to the case of weak selection (Theorem 4.3), unstable boundary equilibria can leave the state space under weak migration [32]. For an explicit example in a single-locus setting, see [48, Remark 4.2].

(iii) For the relation between Theorem 4.3 and Theorem 5.4, in particular, the different kinds of perturbations involved, we refer to Remark 3.3 in Nagylaki et al. [45].

(iv) If $\epsilon = 0$, then all equilibria are in Λ_0, i.e., there is linkage equilibrium within each deme, but not between demes. If $\epsilon > 0$ is sufficiently small, then there is weak linkage disequilibrium within each deme, i.e., $D_{i,\alpha} = O(\epsilon)$ for every i and every α; cf. Remark 2.3 in Nagylaki et al. [45].

5.3 Weak evolutionary forces

Finally, one can also consider the case when all evolutionary forces are weak, i.e., $\epsilon \to 0$ in (4.1), (4.29), and (5.2). Then the limiting dynamics on Δ_I^Γ becomes

$$\frac{dp_{i,\alpha}}{dt} = p_{i,\alpha}[r_{i,\alpha}(p_{(\alpha)}) - \bar{r}_\alpha(p_{(\alpha)})] - \Theta_{i,\alpha} + \sum_\beta a_{\alpha\beta} p_{i,\alpha}, \tag{5.16}$$

with Θ_{i_α} as in (4.39). Hence, selection, recombination, and migration are decoupled, and (5.16) may be viewed as the continuous-time version of (2.8). The dynamics (5.16) is neither fully understood if migration is absent nor if linkage disequilibria vanish.

Remark 5.6 If (5.16) is viewed as the continuous-time version of (2.8), then analogs of Theorem 4.3, Proposition 4.10, Proposition 5.1, and Theorem 5.4 apply. The proofs of the analogs of Theorem 4.3 and Proposition 4.10 are conceptually much easier because they do not require the reference to discretization procedures.

Acknowledgments The author is most grateful to Thomas Nagylaki for sharing unpublished results, numerous inspiring discussions, and helpful comments on the manuscript. The author also acknowledges helpful discussions with Josef Hofbauer and comments on the manuscript by Kristan Schneider and an anonymous referee. This work was supported by a grant of the Vienna Science and Technology Fund (WWTF). Part of this work was done while the author was a visiting researcher at the Program for Evolutionary Dynamics at Harvard University. Its hospitality is gratefully acknowledged.

Appendix

Table 1 Glossary of symbols. For both the Roman and Greek alphabets, uppercase letters precede lower case ones. For each uppercase or lowercase letter, listing is in order of appearance of the definition in the text. The references are to the equation closest to the definition of each symbol. Thus, (2.1), (2.1)+, (2.1)− refers to Eq. 2.1, the text below Eq. 2.1, the text above Eq. 2.1, respectively. Symbols that occur only in a single paragraph are not included

Symbol	Reference	Definition
$\mathcal{A}_{i_n,\alpha}^{(n)}$	(2.1)−	Allele i_n at locus n
$A_{i_\mathsf{K},\alpha}^{(\mathsf{K})}$	(3.25)	Constant
A_i	(3.28)	Constant
A	(5.9)−	Backward migration matrix with entries $a_{\alpha\beta}$
$a_{i_k}^{(k)}$	(3.10)	Constant
a_i	(3.33)	Constant
$a_{\alpha\beta}$	(5.2)	Backward migration rates
B_i	(3.29)	Constant

Table 1 continued

Symbol	Reference	Definition
$b_{i_{\mathsf{K}}}^{(\mathsf{K})}$	(3.21)	Constant
c_{K}	(2.10)−	Frequency of reassociation of the genes at the loci in K, inherited from one parent, with the genes at the loci in $\mathsf{L}\backslash\mathsf{K}$, inherited from the other
c_{tot}	(2.10)	Total frequency of recombination
c_{kn}	(2.11)	Recombination frequency between loci k and n with $k < n$
$c_{\min}$	(2.12)	The smallest two-locus recombination rate
$c_{\mathsf{S}}^{(\mathsf{K})}$	(3.4)+	Frequency of reassociation of the genes at the loci in S, inherited from one parent, with the genes at the loci in $\mathsf{K}\backslash\mathsf{S}$, inherited from the other
$c^{(K)}$	(3.18)+	Frequency of a recombination event in K
$c_{\min}^{(\mathsf{K})}$	(3.26)+	Smallest two-locus recombination rate in K
$D_{i,\alpha}$	(2.13)	L-locus linkage disequilibrium in deme α
$D_{(\alpha)}$	(2.2c)+	$(D_{1,\alpha}, \ldots, D_{I,\alpha})^T \in \mathbb{R}^I$
D_i	(2.2c)+	$(D_{i,1}, \ldots, D_{i,\Gamma})^T \in \mathbb{R}^\Gamma$
D	(2.2c)+	Vector in $\mathbb{R}^{I\Gamma}$ with components $D_{i,\alpha}$
$D_{i_{\mathsf{K}}}^{(\mathsf{K})}$	(3.4)	Vector in $\mathbb{R}^\Gamma$ of linkage disequilibria among all loci in K
$d_{i,\alpha}$	(3.15)	L-locus linkage disequilibrium in deme α
$d_{i_{\mathsf{K}},\alpha}^{(\mathsf{K})}$	(3.16)	Linkage disequilibrium in deme α among all loci in K
d_i	(3.17)−	$(d_{i,1}, \ldots, d_{i,\Gamma})^T \in \mathbb{R}^\Gamma$
$d_{i_{\mathsf{K}}}^{(\mathsf{K})}$	(3.17)	Vector in $\mathbb{R}^\Gamma$ of linkage disequilibria among all loci in K
d	(4.12b)+	Vector in $\mathbb{R}^{I\Gamma}$ with components $d_{i,\alpha}$
e	(2.19)	$(1, \ldots, 1)^T \in \mathbb{R}^\Gamma$
F_α	(5.14)	Set of equilibria under selection
F	(5.15)	$\mathsf{F}_1 \times \cdots \times \mathsf{F}_\Gamma$
G	(2.1)−	Set of all demes
$g_{i_{\mathsf{K}}}^{(\mathsf{K})}$	(3.19)	Recombination function
g_i	(3.28)−	Recombination function
H	(5.9)−	$\prod_{n\in\mathsf{L}} \binom{I_n+1}{2}$
h_i	(4.43a)	Selection function
h	(4.44)	Selection function
I_n	(2.1)−	Number of alleles at locus n
I_n	(2.1)−	Set of all alleles at locus n
I	(2.1)−	Set of all gametes
I	(2.1)−	Total number of gametes
i_n	(2.1)−	Allelic index at locus n
i	(2.1)−	Gametic index $(i_1, \ldots, i_L)$
i_{K}	(2.4)+	Vector with components i_k for every $k \in \mathsf{K}$
J	(5.9)−	$\sum_{n\in\mathsf{L}} \binom{I_n+1}{2}$

Table 1 continued

Symbol	Reference	Definition
j	(2.1)−	Gametic index $(j_1, \ldots, j_L)$
k	(2.1)−	Locus index
K	(2.10)−	Subset of L
K_1	(4.47)	Constant
K_2	(4.48)	Constant
L	(2.1)−	Number of loci
L	(2.1)−	Set of all loci
L_{kn}	(2.11)+	$\{\mathsf{K} : k \in \mathsf{K} \text{ and } n \in \mathsf{N}\}$
ℓ	(2.1)−	Gametic index $(\ell_1, \ldots, \ell_L)$
M	(2.7)−	Backward migration matrix
$\mathsf{M}_{w,\epsilon}$	(5.9b)	Set of migration matrices
$m_{\alpha\beta}$	(2.7)−	Backward migration rate
N	(2.10)−	$\mathsf{L} \backslash \mathsf{K}$, complement of K in L
n	(2.1)−	Locus index
O	(4.12a)	Order symbol
P_i	(2.22)	Average frequency of gamete i
P	(2.22)	$(P_1, \ldots, P_I)^T \in \Delta_I$
$P_{i_k}^{(k)}$	(3.7)	Average frequency of allele $\mathcal{A}_{i_k}^{(k)}$
$P_{i_\mathsf{K}}^{(\mathsf{K})}$	(4.41)+	$\mu^T p_{i_\mathsf{K}}^{(\mathsf{K})} \in \mathbb{R}$
$\tilde{P}_{i_\mathsf{K}}^{(\mathsf{K})}$	(3.13)	$\prod_{k\in\mathsf{K}} P_{i_k}^{(k)} \in \mathbb{R}$
$\tilde{P}_i$	(3.13)	$\prod_{k\in\mathsf{L}} P_{i_k}^{(k)} \in \mathbb{R}$
$p_{i,\alpha}$	(2.2a)−	Frequency of gamete i in deme α
p_i	(2.2a)	$(p_{i,1}, \ldots, p_{i,\Gamma})^T \in \mathbb{R}^\Gamma$
$p_{(\alpha)}$	(2.2b)	$(p_{1,\alpha}, \ldots, p_{I,\alpha})^T \in \Delta_I$
p	(2.2c)	Vector in Δ_I^Γ with components $p_{i,\alpha}$
$p_{i_k,\alpha}^{(k)}$	(2.3)	Frequency of the allele $\mathcal{A}_{i_k}^{(k)}$ in deme α
$p_{i_\mathsf{K},\alpha}^{(\mathsf{K})}$	(2.4)	Gametic frequency for loci in K in deme α
$p_{i_k}^{(k)}$	(2.5a)	$\left(p_{i_k,1}^{(k)}, \ldots, p_{i_k,\Gamma}^{(k)}\right)^T \in \mathbb{R}^\Gamma$
$p_{i_\mathsf{K}}^{(\mathsf{K})}$	(2.5b)	$\left(p_{i_\mathsf{K},1}^{(\mathsf{K})}, \ldots, p_{i_\mathsf{K},\Gamma}^{(\mathsf{K})}\right)^T \in \mathbb{R}^\Gamma$
$q_{i,\alpha}$	(2.24a)	$p_{i,a} - P_i$
q_i	(2.24b)	$p_i - P_i e \in \mathbb{R}^\Gamma$
$q_{(\alpha)}$	(2.24c)	$p_{(\alpha)} - P \in \mathbb{R}^I$
q	(2.24d)	Vector in $\mathbb{R}^{I\Gamma}$ with components $q_{i,\alpha}$
$q_{i_k}^{(k)}$	(3.9)−	$\left(q_{i_k,1}^{(k)}, \ldots, q_{i_k,\Gamma}^{(k)}\right)^T \in \mathbb{R}^\Gamma$
$q_{i_\mathsf{K}}^{(\mathsf{K})}$	(4.41)+	$\left(q_{i_\mathsf{K},1}^{(\mathsf{K})}, \ldots, q_{i_\mathsf{K},\Gamma}^{(\mathsf{K})}\right)^T \in \mathbb{R}^\Gamma$
$\mathbb{R}^I$	(2.1)	I-dimensional Euclidean space
$R_{i,j\ell}$	(2.8c)+	Probability that haplotypes j and ℓ produce gamete i by recombination

Table 1 continued

Symbol	Reference	Definition
$r_{ij,\alpha}$	(4.1)	Selection coefficient of genotype ij in deme α
$r_{i,\alpha}(p_{(\alpha)})$	(4.3)	Selection coefficient of gamete i in deme α
$\bar{r}_\alpha(p_{(\alpha)})$	(4.3)	Mean selection coefficient in deme α
$r_{i,\alpha}(\rho_\alpha)$	(4.6a)	Selection coefficient of gamete i in deme α
$r^{(n)}_{i_n,\alpha}(\rho_\alpha)$	(4.6b)	Selection coefficient of allele $\mathcal{A}^{(n)}_{i_n}$ in deme α
$\bar{r}_\alpha(\rho_\alpha)$	(4.6c)	Mean selection coefficient in deme α
$\bar{r}$	(4.26)+	Average mean selection coefficient
$r^{(n)}_{i_n,\alpha}(p_{(\alpha)})$	(5.7)−	Selection coefficient of allele $\mathcal{A}^{(n)}_{i_n}$ in deme α
$\bar{r}_\alpha(p_{(\alpha)})$	(5.7)−	Mean selection coefficient in deme α
S	(3.4)+	Subset of K
S	(5.9)−	Vector in $\mathbb{R}^{I^2\Gamma}$ holding the epistasis parameters $r_{ij,\alpha}$
S_η	(5.9a)	Set of epistasis parameters
$s_{ij,\alpha}$	(5.11)	Epistasis parameters
T	(3.4)+	$\mathsf{K}\setminus\mathsf{S}$, complement of S in K
t	(2.2)−	Time in generations
$\tilde{t}_1$	(4.19)	Characteristic time to reach quasi-linkage equilibrium and spatial quasi-homogeneity
$\tilde{t}_2$	(4.46)−	Characteristic time to reach an $O(\epsilon)$ neighborhood of Π_0
U	(5.9)−	Vector in $\mathsf{R}^{J\Gamma}$ of additive fitness components $u^{(n)}_{i_nj_n,\alpha}$
U	(5.9c)	Set of vectors U
$u^{(n)}_{i_nj_n,\alpha}$	(5.11)	Additive fitness components
W	(5.9)−	Vector in $\mathsf{R}^{I^2\Gamma}$ of fitnesses $w_{ij,\alpha}$
$w_{ij,\alpha}$	(2.5b)+	Fitness of genotype ij in deme α
$w_{i,\alpha}$	(2.6a)	Marginal fitness of gamete i in deme α
$\bar{w}_\alpha$	(2.6b)	Mean fitness in deme α
$\bar{w}$	(4.21)	Average mean fitness
$x_{ij,\alpha}$	(2.5b)+	Frequency of genotype ij in deme α
y	(2.22)+	Vector in $\mathbb{R}^\Gamma$
z	(2.19)−	Vector in $\mathbb{R}^\Gamma$
α	(2.1)−	Deme index
β	(2.1)−	Deme index
Γ	(2.1)−	Number of demes
γ_{K}	(4.29)	Scaled recombination rate
Δ_I	(2.1)	Simplex in $\mathbb{R}^I$
Δ_I^Γ	(2.1)+	$(\Delta_I)^\Gamma$
ϵ	(4.1)	Small non-negative parameter
η	(5.12)	Smooth non-negative function of ϵ (or its value)
$\Theta_{i,\alpha}$	(4.39)	L-locus linkage disequilibrium in deme α in the absence of selection
κ	(2.20)	Number satisfying $\lvert\lambda_1\rvert \le \kappa < 1$

Table 1 continued

Symbol	Reference	Definition
$\Lambda_{0,\alpha}$	(2.15)	Linkage-equilibrium manifold for deme α
Λ_0	(2.16)	Linkage-equilibrium manifold
Λ_ϵ	(5.4)−	Quasi-linkage-equilibrium manifold
λ_1	(2.19)+	Nonunit eigenvalue of M with largest modulus
λ_K	(3.24)	$\max(\kappa, \chi_\mathsf{K})$
λ_K	(3.26)	$\max(\kappa, 1 - c_{\min}^{(\mathsf{K})})$
λ	(3.27)	$\max\,(\kappa, 1 - c_{\min})$
μ	(2.18)	Principal left eigenvector of M
Π_0	(4.33)	Invariant manifold under pure migration
Π_ϵ	(4.34)−	Invariant manifold under weak selection, weak recombination, and migration
π	(4.5)	Vector of averaged allele frequencies
p_α	(4.4)	Vector of allele frequencies in deme α
Σ_0	(5.15)+	Set of all equilibria of (5.1) with $\eta = 0$
$\Sigma_{(W,M)}$	(5.15)+	Set of all equilibria of (2.8) under weak migration and weak epistasis
τ	(4.18)+	Scaled time
Ξ_0	(4.11)−	Set of all equilibria of (4.9)
Ξ_ϵ	(4.11)−	Set of all equilibria of (2.8) under weak selection
χ_K	(3.20)+	Probability that there is no recombination event in K
Ψ_0	(3.14)	Invariant manifold under recombination and migration
Ψ_ϵ	(4.11)	Invariant manifold under recombination, migration and weak selection
ψ	(4.11)	Function characterizing Ψ_ϵ
ω_{ij}	(4.7a)	Average selection coefficient of genotype ij
$\omega_i(\pi)$	(4.7b)	Average selection coefficient of gamete i on Ψ_0
$\omega_{i_n}^{(n)}(\pi)$	(4.7c)	Average selection coefficient of allele $\mathcal{A}_{i_n}^{(n)}$ on Ψ_0
$\bar{\omega}(\pi)$	(4.7d)	Average mean selection coefficient on Ψ_0
$\omega_i(P)$	(4.42a)	Average selection coefficient of gamete i on Π_0
$\bar{\omega}(P)$	(4.42b)	Average mean selection coefficient on Π_0
^{T}	(2.2a)−	Transposition of a vector
*	(2.8a)	Value of quantity after selection
**	(2.8b)	Value of quantity after selection and migration
$'$	(2.8c)	Value of quantity in next generation
$^\#$	(2.9b)	Value of quantity after selection and recombination
$\hat{}$	(4.18)+	Indicates an equilibrium value
$\circ$	(2.21)	Schur product of vectors

References

1. Akin E (1979) The geometry of population genetics. Lecture Notes in Biomath, vol 31. Springer, Berlin
2. Akin E (1982) Cycling in simple genetic systems. J Math Biol 13:305–324
3. Akin E (1993) The general topology of dynamical systems. American Mathematical Society, Providence
4. Barton NH (1999) Clines in polygenic traits. Genet Res 74:223–236
5. Bennett JH (1954) On the theory of random mating. Ann Eugen 18:311–317
6. Bulmer MG (1972) Multiple niche polymorphism. Am Nat 106:254–257
7. Bürger R (2000) The mathematical theory of selection, recombination, and mutation. Wiley, Chichester
8. Cannings C (1971) Natural selection at a multiallelic autosomal locus with multiple niches. J Genet 60:255–259
9. Christiansen FB (1975) Hard and soft selection in a subdivided population. Am Nat 109:11–16
10. Christiansen FB (1999) Population genetics of multiple loci. Wiley, Chichester
11. Christiansen FB, Feldman M (1975) Subdivided populations: a review of the one- and two-locus deterministic theory. Theor Popul Biol 7:13–38
12. Conley C (1978) Isolated invariant sets and the Morse index. NSF CBMS Lecture Notes, vol 38. American Mathematical Society, Providence
13. Deakin MAB (1966) Sufficient conditions for genetic polymorphism. Am Nat 100:690–692
14. Dempster ER (1955) Maintenance of genetic heterogeneity. Cold Spring Harbor Symp Quant Biol 20:25–32
15. Deuflhard P, Bornemann F (1995) Numerical mathematics II. Integration of ordinary differential equations. de Gruyter, Berlin
16. Ewens WJ (1969) Mean fitness increases when fitnesses are additive. Nature 221:1076
17. Feller W (1968) An introduction to probability theory and its applications, vol I, 3rd edn. Wiley, New York
18. Fenichel N (1971) Persistence and smoothness of invariant manifolds for flows. Ind Univ Math J 21:193–226
19. Fisher RA (1937) The wave of advance of advantageous genes. Ann Eugen 7:355–369
20. Gantmacher FR (1959) The theory of matrices, vol II. Chelsea, New York
21. Garay BM (1993) Discretization and some qualitative properties of ordinary differential equations about equilibria. Acta Math Univ Comenianae 62:249–275
22. Garay BM, Hofbauer J (1997) Chain recurrence and discretization. Bull Austral Math Soc 55:63–71
23. Geiringer H (1944) On the probability theory of linkage in Mendelian heredity. Ann Math Stat 15:25–57
24. Haldane JBS (1930) A mathematical theory of natural and artificial selection Part VI. Isolation. Proc Camb Phil Soc 28:224–248
25. Haldane JBS (1948) The theory of a cline. J Genet 48:277–284
26. Hastings A (1981) Stable cycling in discrete-time genetic models. Proc Natl Acad Sci USA 78:7224–7225
27. Hirsch MW, Pugh C, Shub M (1977) Invariant Manifolds, Lecture Notes in Mathematics, vol 583. Springer, Berlin
28. Hofbauer J, Iooss G (1984) A Hopf bifurcation theorem of difference equations approximating a differential equation. Monatsh Math 98:99–113
29. Karlin S (1977) Gene frequency patterns in the Levene subdivided population model. Theor Popul Biol 11:356–385
30. Karlin S (1982) Classification of selection-migration structures and conditions for a protected polymorphism. Evol Biol 14:61–204
31. Karlin S, Campbell RB (1980) Selection-migration regimes characterized by a globally stable equilibrium. Genetics 94:1065–1084
32. Karlin S, McGregor J (1972a) Application of method of small parameters to multi-niche population genetics models. Theor Popul Biol 3:186–208
33. Karlin S, McGregor J (1972b) Polymorphism for genetic and ecological systems with weak coupling. Theor Popul Biol 3:210–238
34. Kolmogoroff A, Pretrovsky I, Piscounoff N (1937) Étude de l'équation de la diffusion avec croissance de la quantite de matiére et son application à un problème biologique. (French) Bull. Univ. Etat Moscou, Ser. Int., Sect. A, Math. et Mecan. 1, Fasc. 6:1–25

35. Kun LA, Lyubich YuI (1980) Convergence to equilibrium in a polylocus polyallele population with additive selection. Probl Inform Transmiss 16:152–161
36. Kruuk LEB, Baird SJE, Gale KS, Barton NH (1999) A comparison of multilocus clines maintained by environmental selection or by selection against hybrids. Genetics 153:1959–1971
37. Levene H (1953) Genetic equilibrium when more than one ecological niche is available. Am Nat 87:331–333
38. Li CC (1955) The stability of an equilibrium and the average fitness of a population. Am Nat 89:281–295
39. Li W-H, Nei M (1974) Stable linkage disequilibrium without epistasis in subdivided populations. Theor Popul Biol 6:173–183
40. Lyubich YuI (1971) Basic concepts and theorems of evolutionary genetics of free populations. Russ Math Surv 26:51–123
41. Lyubich YuI (1992) Mathematical structures in population genetics. Springer, Berlin
42. Nagylaki T (1992) Introduction to theoretical population genetics. Springer, Berlin
43. Nagylaki T (1993) The evolution of multilocus systems under weak selection. Genetics 134:627–647
44. Nagylaki T (2008) Polymorphism in multiallelic migration-selection models with dominance (submitted)
45. Nagylaki T, Hofbauer J, Brunovský P (1999) Convergence of multilocus systems under weak epistasis or weak selection. J Math Biol 38:103–133
46. Nagylaki T, Lou Y (2001) Patterns of multiallelic poylmorphism maintained by migration and selection. Theor Popul Biol 59:297–313
47. Nagylaki T, Lou Y (2006) Evolution under the multiallelic Levene model. Theor Popul Biol 70:401–411
48. Nagylaki T, Lou Y (2007) Evolution under multiallelic migration-selection models. Theor Popul Biol 72:21–40
49. Nagylaki T, Lou Y (2008) The dynamics of migration-selection models. In: Friedman A (ed) Tutorials in Mathematical Biosciences IV. Lecture Notes in Mathematics, vol 1922. Springer, Berlin, pp 119–172
50. Prout T (1968) Sufficient conditions for multiple niche polymorphism. Am Nat 102:493–496
51. Reiersøl O (1962) Genetic algebras studied recursively and by means of differential operators. Math Scand 10:25–44
52. Seneta E (1981) Non-negative matrices and Markov Chains. Springer, New York
53. Slatkin M (1975) Gene flow and selection in two-locus systems. Genetics 81:787–802
54. Wright S (1931) Evolution in Mendelian populations. Genetics 16:97–159