



Polymorphism in the two-locus Levene model with nonepistatic directional selection

Reinhard Bürger*

Department of Mathematics, University of Vienna, Austria

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ABSTRACT

For the Levene model with soft selection in two demes, the maintenance of polymorphism at two diallelic loci is studied. Selection is nonepistatic and dominance is intermediate. Thus, there is directional selection in every deme and at every locus. We assume that selection is in opposite directions in the two demes because otherwise no polymorphism is possible. If at one locus there is no dominance, then a complete analysis of the dynamical and equilibrium properties is performed. In particular, a simple necessary and sufficient condition for the existence of an internal equilibrium and sufficient conditions for global asymptotic stability are obtained. These results are extended to deme-independent degree of dominance at one locus. A perturbation analysis establishes structural stability within the full parameter space. In the absence of genotype-environment interaction, which requires deme-independent dominance at both loci, nongeneric equilibrium behavior occurs, and the introduction of arbitrarily small genotype-environment interaction changes the equilibrium structure and may destroy stable polymorphism. The volume of the parameter space for which a (stable) two-locus polymorphism is maintained is computed numerically. It is investigated how this volume depends on the strength of selection and on the dominance relations. If the favorable allele is (partially) dominant in its deme, more than 20% of all parameter combinations lead to a globally asymptotically stable, fully polymorphic equilibrium.

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1. Introduction

Understanding the consequences of spatially varying selection on the maintenance of genetic variation in subdivided populations has been one of the main research themes in population genetics. Numerous modeling approaches for studying the interaction of migration and selection have been undertaken. Probably the simplest and best investigated model incorporating dispersal and selection is the Levene (1953) model. It assumes a finite number of niches, or demes, selection within demes, and individuals dispersing independently of their deme of origin. As a consequence, there is no population structure despite geographically variable selection. Nevertheless, at a single diallelic locus a stable polymorphism can be maintained under conditions when this is impossible in a panmictic population. In particular, stable polymorphism can occur in the absence of overdominance (Levene, 1953; Prout, 1968; Karlin, 1977). Despite the fact that geometric mean fitness is a Lyapunov function (Li, 1955; Cannings, 1971; Nagylaki, 1992), a number of interesting problems remains unresolved, even for the diallelic case.

For instance, no necessary and sufficient condition for the existence of a unique internal equilibrium is known, and it is unknown how the maximum number of possible equilibria depends on the number of demes (Karlin, 1977).

An important question concerns the relation between the number of demes and the number of alleles that can be maintained at a locus in the absence of overdominance or underdominance. For a haploid population, Strobeck (1979) showed that the number of demes provides a generic upper bound on the number of alleles that can be maintained at equilibrium. If an internal equilibrium exists (point or manifold), it is unique and globally asymptotically stable. The diploid multiallelic Levene model was studied only much more recently. Among other results, Nagylaki and Lou (2001) derived sufficient conditions for the existence of a globally asymptotically stable equilibrium. One of them is absence of dominance in each deme. Then, as with haploid selection, generically, no more alleles can be maintained as there are demes, and an internal equilibrium is globally asymptotically stable if it exists. Nagylaki (2009a) extended these results by showing that the qualitative behavior of solutions is the same as without dominance if the degree of dominance is intermediate and deme independent. For a recent review of the single-locus theory of migration and selection, we refer to Nagylaki and Lou (2008).

Since many biologically relevant traits are determined by more than one locus, it seems desirable to investigate the maintenance

* Corresponding address: Institut für Mathematik, Universität Wien, Nordbergstraße 15, A-1090, Wien, Austria.

E-mail address: reinhard.buerger@univie.ac.at.

of multilocus polymorphism in subdivided populations. A number of general results about the dynamics and equilibrium properties, especially for weak and for strong migration, was derived in Bürger (2009a,b). In particular, scenarios were identified when arbitrarily many recombining loci can be maintained polymorphic if epistasis is absent or weak and dominance is intermediate. In a panmictic population, polymorphism is impossible under these conditions (Bürger, 2009b, Proposition 3.2 and Corollary 3.4).

Nagylaki (2009b) performed a detailed study of the Levene model with multiple multiallelic loci. For additive fitnesses (no dominance and no epistasis), he proved generic convergence to linkage equilibrium. With no epistasis but dominance, this is true at least for two loci. By contrast, for general migration, stable linkage disequilibrium can be maintained under additive fitnesses in diallelic two-locus models (Li and Nei, 1974; Christiansen and Feldman, 1975). In the Levene model, stable linkage disequilibrium can be maintained by simple forms of epistasis (Wiehe and Slatkin, 1998).

The Levene model harbors the potential for extensive multilocus polymorphism. Bürger (2009b, Theorem 2.2 and Remark 2.4) showed that arbitrarily many nonepistatic loci can be maintained polymorphic for an open set of parameters exhibiting intermediate dominance. However, if in addition the degree of dominance is deme independent at every locus and loci are diallelic, generically, a fully polymorphic equilibrium does not exist unless the number of demes exceeds the number loci (Nagylaki, 2009b).

It is the purpose of this paper to explore the conditions for maintaining genetic variation at two diallelic loci in the Levene model. Because in a panmictic population polymorphic equilibria do not exist in the absence of epistasis and of overdominance and underdominance, throughout we assume no epistasis and an intermediate degree of dominance. We choose the simplest possible setting by assuming two demes with directional selection in opposite directions. Then surprisingly concrete results can be obtained that nicely complement the general results discussed above.

In Section 2, we introduce the multilocus Levene model and summarize the results that will be needed later. Section 3 reviews the basic single-locus theory, presents a new sufficient condition for global convergence, and reformulates well known results in an alternative way, suitable for the subsequent two-locus analysis.

The equilibrium and stability properties of the two-locus model with intermediate dominance are investigated in Section 4. With no dominance at one locus (Section 4.1), a complete analysis is performed. It yields a simple necessary and sufficient condition for the existence of an internal equilibrium which is unique. In Section 4.2, these results are extended to the case when at one locus the degree of dominance is deme independent. By perturbation methods it is shown that these results are structurally stable (Section 4.3). For comparison, the weak-selection limit is treated in Section 4.4.

In Section 5, the equilibrium properties are derived if at both loci there is no dominance or, more generally, if the degree of dominance is deme independent. This case turns out to have nongeneric properties if genotype-environment interaction is absent. Section 6 is concerned with the role of genotype-environment interaction, especially in the context of linear selection in each deme on a quantitative trait. In Section 7, a numerical analysis is performed to estimate the volume of the parameter space in which a fully polymorphic equilibrium exists or is stable. It is investigated how this volume depends on the strength of selection and the pattern of dominance. If the favorable allele is (partially) dominant in its deme, then, depending on the strength of selection, between 22% and 37% of all parameter combinations lead to a globally asymptotically stable and fully polymorphic equilibrium. The paper closes with a brief discussion.

2. The multilocus Levene model

Recently, Nagylaki (2009b) introduced the multilocus Levene model and derived several important properties. Here, we briefly present the model for diallelic loci and summarize the results that will be needed.

We assume $\Gamma \geq 1$ demes and denote the relative size of deme α by $c_\alpha > 0$, so that $\sum_\alpha c_\alpha = 1$.¹ We consider $L \geq 1$ diploid, diallelic loci. The linkage map is arbitrary. Because there is no population structure in the Levene model, gamete and gene frequencies are deme independent. We denote the frequency of (the multilocus) gamete i by p_i and the fitness of the diploid genotype ij in deme α by $w_{ij,\alpha}$. Then the marginal fitness of gamete i and the mean fitness of the population in deme α are

$$w_{i,\alpha} = \sum_j p_j w_{ij,\alpha} \quad \text{and} \quad \bar{w}_\alpha = \sum_{i,j} p_i p_j w_{ij,\alpha}. \quad (2.1)$$

Further, let $R_{i,jk}$ denote the probability that a parent of genotype jk produces a gamete i during meiosis. Assuming soft selection, adult dispersal, and random mating within demes, the gamete frequencies evolve according to Nagylaki (2009b, Eq. (2.42))

$$p'_i = \sum_{j,k,\alpha} R_{i,jk} p_j p_k c_\alpha w_{jk,\alpha} / \bar{w}_\alpha. \quad (2.2)$$

The state space is the simplex $\Delta_J \subseteq \mathbb{R}^J$, where $J = 2^L$ is the number of gametes. We write $p = (p_1, \dots, p_L)^T \in \Delta_J$ for the vector of gametic frequencies. A prime, ', denotes the next generation.

For the rest of this paper we assume *absence of epistasis*. Therefore, we can assign fitness contributions to single-locus genotypes and denote the contributions at locus n in niche α by $u_{i_n j_n, \alpha}^{(n)}$, where $i_n, j_n \in \{1, 2\}$ refer to the alleles carried by the genotype ij at locus n . Thus, we assume throughout that the fitness of genotype ij is given by

$$w_{ij,\alpha} = \sum_n u_{i_n j_n, \alpha}^{(n)}. \quad (2.3)$$

We denote the frequency of the 'first' allele at locus n by $p^{(n)}$, and we write

$$\rho = (p^{(1)}, \dots, p^{(L)}) \in \Omega = [0, 1]^L \quad (2.4)$$

for the vector of gene frequencies. Then the fitness contributions of the two alleles at locus n in deme α are

$$u_{1,\alpha}^{(n)}(p^{(n)}) = p^{(n)} u_{11,\alpha}^{(n)} + (1 - p^{(n)}) u_{12,\alpha}^{(n)} \quad (2.5a)$$

and

$$u_{2,\alpha}^{(n)}(p^{(n)}) = p^{(n)} u_{12,\alpha}^{(n)} + (1 - p^{(n)}) u_{22,\alpha}^{(n)}, \quad (2.5b)$$

and the mean fitness contribution of locus n in deme α is

$$\bar{u}_\alpha^{(n)}(p^{(n)}) = p^{(n)} u_{1,\alpha}^{(n)}(p^{(n)}) + (1 - p^{(n)}) u_{2,\alpha}^{(n)}(p^{(n)}) \quad (2.6a)$$

$$= (p^{(n)})^2 u_{11,\alpha}^{(n)} + 2p^{(n)}(1 - p^{(n)}) u_{12,\alpha}^{(n)} \\ + (1 - p^{(n)})^2 u_{22,\alpha}^{(n)}. \quad (2.6b)$$

The mean fitness in deme α is

$$\bar{w}_\alpha(\rho) = \sum_n \bar{u}_\alpha^{(n)}(p^{(n)}). \quad (2.7)$$

Importantly, \bar{w}_α depends only on the vector ρ of gene frequencies, but not on the vector p of gamete frequencies.

The dynamics of gene frequencies is given by (Nagylaki, 2009b, Eq. (2.48))

¹ If in a sum or product no range is indicated, then it is assumed to be over all admissible values.

$$p^{(n)'} = \sum_{\alpha} \frac{c_{\alpha}}{\bar{w}_{\alpha}} \left(p^{(n)} u_{1,\alpha}^{(n)} + \sum_{\ell:\ell \neq n} (p_{11}^{(\ell n)} u_{1,\alpha}^{(\ell)} + p_{21}^{(\ell n)} u_{2,\alpha}^{(\ell)}) \right), \quad (2.8)$$

where $p_{j1}^{(\ell n)}$ is the frequency of gametes with alleles j and 1 at loci ℓ and n , respectively. In general, this is not a self-contained system of recursion relations but it is independent of the recombination map.

We define

$$\Lambda = \{p \in \Delta_J : \rho' = \rho\} \quad (2.9)$$

as the set of gametic frequencies at gene-frequency equilibrium, or the set of gene-frequency equilibria for short, and

$$\mathcal{E} = \{p \in \Delta_J : p_i = p_{i_1}^{(1)} \cdots p_{i_L}^{(L)} \text{ for every } i \in J\} \quad (2.10)$$

as the linkage-equilibrium manifold, where $p_{i_n}^{(n)}$ denotes the frequency of allele i_n at locus $n = 1, \dots, L$.

The following results concern the evolution of gamete frequencies, (2.2), under nonepistatic selection, (2.3). They will play an important role.

Result 2.1 (Nagylaki, 2009b, Theorem 3.1 and Remark 3.2).

(a) The geometric mean fitness

$$\tilde{w}(\rho) = \prod_{\alpha} [\bar{w}_{\alpha}(\rho)]^{c_{\alpha}} \quad (2.11)$$

satisfies $\Delta \tilde{w}(\rho) = \tilde{w}(\rho') - \tilde{w}(\rho) \geq 0$, and $\Delta \tilde{w}(\rho) = 0$ if and only if $\rho = \rho'$.

(b) The set Λ of gene-frequency equilibria is globally attracting, i.e., every $p(t) \rightarrow \Lambda$ as $t \rightarrow \infty$.

(c) If every equilibrium $\hat{\rho}$ is isolated in the gene-frequency space Ω , as is generic, then every $\rho(t)$ converges as $t \rightarrow \infty$ to some $\hat{\rho} \in \Omega$.

Instead of $\tilde{w}(\rho)$, it is often more convenient to work with

$$F(\rho) = \ln \tilde{w}(\rho) = \sum_{\alpha} c_{\alpha} \ln \bar{w}_{\alpha}(\rho). \quad (2.12)$$

Result 2.1 implies that F is also a Lyapunov function for the gene-frequency dynamics.

Result 2.2 (Nagylaki, 2009b, Corollary 3.8 and the subsequent remark). If $F(\rho)$ is concave, then there exists exactly one stable gene-frequency equilibrium (point or manifold), and it is globally attracting. If an internal gene-frequency equilibrium exists, it is globally asymptotically stable.

Result 2.1 generalizes a well known one-locus result (Li, 1955; Cannings, 1971; Nagylaki, 1992), and Result 2.2 extends Theorem 3.6 in Nagylaki and Lou (2001) to multiple loci. In particular, it applies if there is no dominance (Nagylaki, 2009b).

Throughout this paper we impose the assumption

$$\text{For every } n \text{ there exists an } \alpha \text{ such that } u_{12,\alpha}^{(n)} > 0. \quad (2.13)$$

It excludes heterozygous genotypes that are lethal in every environment.

A central result of Nagylaki (2009b, Theorem 4.6) shows that if there are two recombining loci, (2.13) holds, and if the equilibria $\hat{\rho}$ of $\rho(t)$ are isolated, then $d(t) \rightarrow 0$ globally as $t \rightarrow \infty$. As shown below, an important consequence is that, under mild conditions, it is sufficient to investigate existence and stability of equilibria on the linkage-equilibrium manifold \mathcal{E} .

For arbitrary $L \geq 1$ and assuming linkage equilibrium, the gene-frequency dynamics (2.8) becomes the closed system

$$\Delta p^{(n)} = p^{(n)}(1-p^{(n)}) \sum_{\alpha} \frac{c_{\alpha}}{\bar{w}_{\alpha}} [u_{1,\alpha}^{(n)} - u_{2,\alpha}^{(n)}], \quad (2.14a)$$

$$= \frac{1}{2} p^{(n)}(1-p^{(n)}) \frac{\partial F(\rho)}{\partial p^{(n)}}, \quad n = 1, \dots, L, \quad (2.14b)$$

where (2.14a) follows from (2.8) by using

$$\sum_{\ell:\ell \neq n} (p_{11}^{(\ell n)} u_{1,\alpha}^{(\ell)} + p_{21}^{(\ell n)} u_{2,\alpha}^{(\ell)}) = p^{(n)} \sum_{\ell:\ell \neq n} \bar{u}_{\alpha}^{(\ell)} = p^{(n)} (\bar{w}_{\alpha} - \bar{u}_{\alpha}^{(n)})$$

and (2.6a); (2.14b) is a straightforward consequence of (2.12), (2.7) and (2.6). Although (2.14) is a closed system on Ω , it should be noted that \mathcal{E} is not invariant under the full dynamics (2.2), as this is not even the case in a panmictic population.

Remark 2.3. $F(\rho)$ and $\tilde{w}(\rho)$ are Lyapunov functions for (2.14). Therefore, asymptotically stable equilibria of (2.14) are the local maxima of $F(\rho)$. The internal equilibria of (2.14) are exactly the internal critical points of $F(\rho)$, or of $\tilde{w}(\rho)$, and this holds for every lower-dimensional subsystem. They are the solutions of

$$\sum_{\alpha} \frac{c_{\alpha}}{\bar{w}_{\alpha}} [u_{1,\alpha}^{(n)} - u_{2,\alpha}^{(n)}] = 0, \quad n = 1, \dots, L \quad (2.15)$$

(cf. Theorem 3.3 in Nagylaki, 2009b). Consequently, $\hat{\rho}$ is an equilibrium of (2.14) if and only if it gives rise to a gene-frequency equilibrium of (2.2). In addition, the stability properties correspond and the conclusions of Results 2.1 and 2.2 apply to (2.14).

In analogy to Karlin's (1977) definition of submultiplicative fitnesses, see (3.9), we call the fitness contributions of locus n *sublinear* if in every deme the contribution of the heterozygote is as least as high as the arithmetic mean of the two homozygous contributions, i.e., if

$$u_{12,\alpha}^{(n)} \geq \frac{1}{2} (u_{11,\alpha}^{(n)} + u_{22,\alpha}^{(n)}) \quad \text{for every } \alpha. \quad (2.16)$$

Thus, the inferior allele is not (partially) dominant.

We will often write

$$p = (\rho, d), \quad (2.17)$$

where d denotes the vector of linkage disequilibria. Thus, $d = 0$ signifies linkage equilibrium. If $L = 2$, then $d \in [-\frac{1}{4}, \frac{1}{4}]$ is the usual measure of linkage disequilibrium. The following theorem summarizes the results that form the basis for our analysis of the two-locus Levene model.

Theorem 2.4. Suppose $L = 2$ and the recombination rate is positive. Then the following hold:

- (a) $\hat{\rho} = (\hat{\rho}, \hat{d})$ is an equilibrium of (2.2) if and only if $\hat{\rho}$ is an equilibrium of (2.14) and $\hat{d} = 0$.
- (b) $\hat{\rho}$ is an asymptotically stable equilibrium of (2.2) if and only if $\hat{\rho}$ is an asymptotically stable equilibrium of (2.14). This equivalence also holds for globally asymptotically stable equilibrium points.
- (c) If every equilibrium of (2.14) is isolated, then the (finite) set $\Lambda \cap \mathcal{E}$ is the global attractor for solutions of (2.2).
- (d) If $F(\rho)$ is concave and $\hat{\rho}$ is an isolated equilibrium of (2.14) that is either stable or internal, then $(\hat{\rho}, 0)$ is the globally asymptotically stable equilibrium of (2.2).
- (e) If fitness contributions of every locus are sublinear, then (d) applies.

Proof. (a) $p = (\rho, d)$ is an equilibrium of (2.2) if and only if $\rho' = \rho$ and $d' = d$. Nagylaki's (2009b) Eq. (4.38) applies to every internal $\hat{\rho}$, and his Remark 4.4 yields $d' = d$ if and only if $d = 0$. If ρ is not internal, then $d = 0$ because $L = 2$.

(b) We recall the conclusions of Remark 2.3. Obviously, asymptotic stability of $\hat{\rho}$ implies asymptotic stability of $\hat{\rho}$. If $\hat{\rho}$ is asymptotically stable, it is necessarily isolated and a strict local maximum of $F(\rho)$. Therefore, and because $L = 2$, Proposition 4.10 of Nagylaki (2009b) yields asymptotic stability of $\hat{\rho}$. Because $L = 2$, Eq. (4.44) in the proof of this proposition reduces to his (4.38), from which we infer $d(t) \rightarrow 0$ for every admissible $d(0)$. Thus, if the region of attraction of $\hat{\rho}$ with respect to (2.14) is \hat{A} , the region of

attraction of \hat{p} with respect to (2.2) is $\{p \in \Delta_I : \rho \in \hat{A}\}$. This implies the statement on global asymptotic stability.

(c) In view of Remark 2.3, this is equivalent to Theorem 4.6 in Nagylaki (2009b).

(d) This is an immediate consequence of Result 2.2, Remark 2.3, and statement (b).

(e) Differentiating $\bar{u}_\alpha^{(n)}$ (2.6b) twice, we see that $\bar{u}_\alpha^{(n)}$ is concave if and only if (2.16) holds. Since we require this for every locus, Lemma 3.2 of Nagylaki and Lou (2001) implies concavity of F . \square

For an arbitrary number of loci, Nagylaki (2009b, Theorem 4.14) proved global convergence to linkage equilibrium if there is no dominance. Otherwise, only local convergence was demonstrated (Nagylaki, 2009b, Theorem 4.13). Nevertheless, Theorem 2.4 can be generalized to $L \geq 2$ diallelic loci because Bürger (unpublished) proved that then global convergence to linkage equilibrium occurs (cf. Remark 4.16 in Nagylaki, 2009b).

3. One-locus results

Here, we collect a number of results about the Levene model when selection acts on a single diallelic locus. Most, but not all of them, are well known or are simple consequences of well known results. An introductory treatment to the basic theory can be found in Nagylaki (1992, Chap. 6).

We denote the alleles at our locus by A and a , and write p for the frequency of A . We assume that the fitnesses of genotypes are scaled as follows:

$$\begin{array}{ccc} AA & Aa & aa \\ x_\alpha = 1 + s_\alpha & 1 & y_\alpha = 1 - t_\alpha, \end{array} \quad (3.1a)$$

where $x_\alpha, y_\alpha > 0$, hence

$$s_\alpha > -1 \text{ and } t_\alpha < 1. \quad (3.1b)$$

We use either representation, whichever is more convenient. Throughout, we exclude the trivial case of no selection, i.e., $x_\alpha = y_\alpha = 1$ for every α . With $u_{11,\alpha}^{(1)} = x_\alpha$, $u_{12,\alpha}^{(1)} = 1$, and $u_{22,\alpha}^{(1)} = y_\alpha$, the single-locus dynamics is given by (2.14), where $n = L = 1$.

An important concept, especially for a diallelic locus, is the concept of a protected polymorphism (Prout, 1968), meaning that, whatever the initial state, the population cannot lose any of its alleles. It is well known that allele A is protected from loss if the harmonic mean of the y_α is less than one, i.e., if (Levene, 1953)

$$y^* = \left(\sum_\alpha \frac{c_\alpha}{y_\alpha} \right)^{-1} < 1. \quad (3.2a)$$

Analogously, allele a is protected if

$$x^* = \left(\sum_\alpha \frac{c_\alpha}{x_\alpha} \right)^{-1} < 1. \quad (3.2b)$$

If A is recessive everywhere ($y_\alpha = 1$ for every α), then it is protected if (Prout, 1968)

$$\bar{x} = \sum_\alpha c_\alpha x_\alpha > 1. \quad (3.3)$$

Jointly, (3.2a) and (3.2b) provide a sufficient condition for a protected polymorphism. If $y^* > 1$ or $x^* > 1$, then A or a , respectively, is lost if initially rare. This precludes the existence of a protected polymorphism. If A is recessive everywhere, then (3.2a) cannot be fulfilled and a sufficient condition for a protected polymorphism is

$$x^* < 1 < \bar{x}. \quad (3.4)$$

Of course, if $\bar{x} < 1$, then A will be lost if rare. Analogous conditions hold if a is recessive.

The conditions (3.2) show that if one or more of the x_α or y_α is decreased, then a protected polymorphism persists. Hence, if there is intermediate dominance, then an increased degree of dominance of the advantageous allele favors a protected polymorphism.

Remark 3.1. Because geometric mean fitness \tilde{w} and $F = \ln \tilde{w}$ are Lyapunov functions, in the Levene model the existence of a protected polymorphism implies the existence of a locally stable internal equilibrium. The converse is not true because already with two diallelic demes, a monomorphic equilibrium can be simultaneously stable with an internal equilibrium (Karlin, 1977, Result II and Appendix C). Nagylaki (2009a, Theorem 3.11) shows that this can occur even with an intermediate degree of dominance.

Remark 3.2. In the following cases one gets global convergence to a unique, stable equilibrium: (i) in every deme there is no dominance; (ii) fitnesses are multiplicative everywhere or, equivalently, selection acts on haploids; (iii) there is overdominance in every deme; (iv) if without migration, i.e., with the same fitness assignments but isolated demes, a globally attracting internal equilibrium exists. For (i), (iii), and (iv), see Nagylaki and Lou (2001, Theorem 3.4 and Remark 3.7); for (ii), see Nagylaki (2009a, Section 3.1).

The next result is an application of Theorem 3.6 in Nagylaki and Lou (2001) and extends the list in Remark 3.2.

Theorem 3.3. For every α , let the fitnesses in (3.1a) satisfy

$$x_\alpha y_\alpha \leq 1 + (1 - y_\alpha)^2 \text{ and } y_\alpha \leq 1 \quad (3.5a)$$

or

$$x_\alpha y_\alpha \leq 1 + (1 - x_\alpha)^2 \text{ and } x_\alpha \leq 1. \quad (3.5b)$$

Then F is concave on $[0, 1]$. Hence, there exists at most one internal equilibrium. If an internal equilibrium exists, it is globally asymptotically stable. If a monomorphic equilibrium is stable, then it is globally asymptotically stable.

Proof. We first prove that $\ln \tilde{w}_\alpha$ is concave if and only if (3.5) is fulfilled. We have $\tilde{w}_\alpha(p) = x_\alpha p^2 + 2p(1-p) + y_\alpha(1-p)^2$. Therefore, the second derivative of $\ln \tilde{w}_\alpha$ is

$$\frac{d^2 \ln \tilde{w}_\alpha(p)}{dp^2} = \frac{-2g_\alpha(p)}{\tilde{w}_\alpha(p)^2}, \quad (3.6)$$

where

$$g_\alpha(p) = [1 - y_\alpha + p(x_\alpha + y_\alpha - 2)]^2 + 1 - x_\alpha y_\alpha. \quad (3.7)$$

Obviously, we have $g_\alpha(p) \geq 0$ for every p if $x_\alpha y_\alpha \leq 1$. Hence, $\ln \tilde{w}_\alpha$ is concave if $x_\alpha y_\alpha \leq 1$, which is definitely the case if $x_\alpha + y_\alpha \leq 2$.

If $x_\alpha \geq 1$ and $y_\alpha \geq 1$ (and not both equal to 1), then $\ln \tilde{w}_\alpha$ is not concave. Indeed, if $x_\alpha \geq y_\alpha$, then $x_\alpha y_\alpha \geq y_\alpha^2 \geq 1 + (1 - y_\alpha)^2$ and at least one of the inequalities is strict because $x_\alpha > y_\alpha$ or $y_\alpha > 1$. Hence, we have $g_\alpha(0) = (1 - y_\alpha)^2 + 1 - x_\alpha y_\alpha < 0$. If $y_\alpha \geq x_\alpha$, we obtain $g_\alpha(1) < 0$. In both cases, $\ln \tilde{w}_\alpha$ is not concave.

Therefore, we can assume $x_\alpha + y_\alpha > 2$ and, without loss of generality, $y_\alpha \leq 1$. This implies that g_α is increasing on $[0, 1]$ because

$$\frac{dg_\alpha(p)}{dp} = 2(x_\alpha + y_\alpha - 2)[1 - y_\alpha + p(x_\alpha + y_\alpha - 2)] \geq 0, \quad (3.8)$$

where equality can hold only if $p = 0$. Thus, $g_\alpha(p) \geq 0$ on $[0, 1]$ if and only if $g_\alpha(0) \geq 0$. The latter, however, holds if and only if (3.5a) is satisfied. If $x_\alpha \leq 1$, then $g_\alpha(p) \geq 0$ on $[0, 1]$ if and only if (3.5b) holds.

Now the conclusion follows from Theorem 3.6 in Nagylaki and Lou (2001) because F is concave if every $\ln \tilde{w}_\alpha$ is concave. \square

Theorem 3.3 generalizes Result I in [Karlin \(1977\)](#), who proved uniqueness of an internal equilibrium and global convergence under the assumption of *submultiplicative fitnesses*, i.e., if

$$x_\alpha y_\alpha \leq 1 \quad (3.9)$$

holds for every α . His proof was based on a different method. (Another proof can be found in Appendix 2 of [Kisdi and Geritz, 1999](#). In addition, examples (i) and (iii) in [Remark 3.2](#) satisfy (3.5), as do sublinear fitnesses, (2.16). A partial converse to [Theorem 3.3](#) is Result IA in [Karlin \(1977\)](#).

In terms of s_α and t_α , condition (3.5) becomes

$$0 \leq s_\alpha \leq t_\alpha \frac{1+t_\alpha}{1-t_\alpha}, \quad (3.10a)$$

or

$$0 \geq t_\alpha \geq s_\alpha \frac{1-s_\alpha}{1+s_\alpha}. \quad (3.10b)$$

This is satisfied not only in the cases listed in [Remark 3.2](#), but in particular whenever there is partial or complete dominance of the fitter allele ($0 \leq s_\alpha \leq t_\alpha$ or $s_\alpha \leq t_\alpha \leq 0$).

Sometimes, fitnesses are scaled such that

$$\begin{array}{lll} AA & Aa & aa \\ 1 + \tau_\alpha & 1 + \delta_\alpha \tau_\alpha & 1 - \tau_\alpha, \end{array} \quad (3.11)$$

where δ_α measures the degree of dominance. Then condition (3.5) becomes

$$\delta_\alpha \geq \frac{\sqrt{1+2\tau_\alpha-3\tau_\alpha^2}-1+\tau_\alpha}{2\tau_\alpha} \quad \text{if } \tau_\alpha \geq 0, \quad (3.12a)$$

or

$$\delta_\alpha \leq \frac{1-\tau_\alpha-\sqrt{1-2\tau_\alpha-3\tau_\alpha^2}}{-2\tau_\alpha} \quad \text{if } \tau_\alpha \leq 0. \quad (3.12b)$$

This can be satisfied if the fitter allele is slightly recessive. For instance, if $\tau_\alpha = 0.1$, then $\delta_\alpha \geq -0.092$ must hold. The fitnesses (3.11) are submultiplicative if $\delta_\alpha \geq -(1 - \sqrt{1 - \tau_\alpha^2})/\tau_\alpha$. If $\tau_\alpha = 0.1$, this requires $\delta_\alpha \geq -0.050$.

We say there is *deme-independent degree of intermediate dominance* (DIDID) if, with fitnesses as in (3.11), for every α

$$\delta_\alpha = \delta \quad \text{and} \quad |\delta| \leq 1 \quad (3.13)$$

holds. Obviously, DIDID covers complete dominance or recessiveness, and no dominance, but not multiplicativity.

Remark 3.4. As (3.12) shows, with DIDID, (3.5) is generally not satisfied and F is not necessarily concave. Nevertheless, the other conclusions of [Theorem 3.3](#) remain valid, even for an arbitrary number of alleles ([Nagylaki, 2009a](#), Theorem 3.2 and Remark 3.3).

We say, there is *directional selection* in every deme if $s_\alpha t_\alpha \geq 0$ for every α and either $s_\alpha \neq 0$ or $t_\alpha \neq 0$. This is equivalent to intermediate dominance in every deme, and it is the case we are mainly interested in. It is an easy exercise to show that then a protected polymorphism is possible only if there are at least two demes, α and β , such that $s_\alpha \geq 0$, $t_\alpha \geq 0$, $s_\beta \leq 0$, and $t_\beta \leq 0$. Thus, selection must be in opposite directions in at least two demes.

3.1. Two demes

For the rest of this section, we assume that there are two demes and, to avoid pathologies, that selection acts in both demes, i.e., for every $\alpha = 1, 2$ at least one of s_α or t_α does not vanish. We assume opposite directional selection in the two demes. To achieve definiteness, we posit without loss of generality

$$\begin{aligned} s_1 \geq 0, t_1 \geq 0, s_2 \leq 0, t_2 \leq 0, \quad &\text{and} \\ s_1 + t_1 > 0, s_2 + t_2 < 0. \end{aligned} \quad (3.14)$$

If (3.5), or equivalently (3.10), holds, then (3.14) can be strengthened to

$$s_1 \geq 0, t_1 > 0, \quad s_2 < 0, t_2 \leq 0, \quad (3.15)$$

which excludes that an advantageous allele is recessive or an allele is recessive everywhere.

Rearrangement of (3.2) shows that a protected polymorphism exists if

$$t_1 t_2 < c_1 t_1 + c_2 t_2 \quad \text{and} \quad c_1 s_1 + c_2 s_2 < -s_1 s_2. \quad (3.16)$$

It follows immediately that stronger selection, i.e., multiplication of the t_α or s_α by the same constant greater than unity, facilitates the maintenance of a protected polymorphism. If there is no dominance ($s_1 = t_1$ and $s_2 = t_2$), (3.16) simplifies to

$$s_1 s_2 < c_1 s_1 + c_2 s_2 < -s_1 s_2. \quad (3.17)$$

If A is recessive everywhere ($t_1 = t_2 = 0$), then a protected polymorphism exists if

$$0 < c_1 s_1 + c_2 s_2 < -s_1 s_2. \quad (3.18)$$

It will often be convenient to use the single parameter $c = c_1$ instead of c_1 and $c_2 = 1 - c_1$. [Corollary 3.5](#), and its repeated application, motivates the following definitions:

$$c^- = \begin{cases} \frac{t_2(1-t_1)}{t_2-t_1} & \text{if } t_1 > 0 \text{ or } t_2 < 0, \\ \frac{s_2}{s_2-s_1} & \text{if } t_1 = t_2 = 0, \end{cases} \quad (3.19a)$$

$$c^+ = \begin{cases} \frac{s_2(1+s_1)}{s_2-s_1} & \text{if } s_1 > 0 \text{ or } s_2 < 0, \\ \frac{t_2}{t_2-t_1} & \text{if } s_1 = s_2 = 0. \end{cases} \quad (3.19b)$$

By virtue of (3.1b) and (3.14), we observe that $c^- < 0$ and $c^+ < 1$.

Corollary 3.5. Suppose (3.14).

(a) There is a protected polymorphism if

$$c^- < c < c^+. \quad (3.20)$$

(b) If condition (3.5) holds, then there exists a unique internal equilibrium if and only if (3.20) is satisfied. This equilibrium is globally asymptotically stable.

(c) If there is DIDID, then there exists a unique internal equilibrium if and only if (3.20) is satisfied. This equilibrium is globally asymptotically stable.

Proof. (a) Given (3.1b), (3.14) and (3.19), the equivalence of (3.16) and (3.20), or (3.18) if A is recessive, follows by straightforward rearrangement.

(b) By [Theorem 3.3](#), at most one internal equilibrium exists if (3.5) holds. Therefore, and by (a), it suffices to prove the ‘only if’ statement. We know that there is no protected polymorphism if one of the inequalities in (3.2), or (3.16), is reversed. Therefore, it is sufficient to exclude the existence of an internal equilibrium if either $c = c^-$ or $c = c^+$. Simple calculations show that if $c = c^-$, then $p = 0$ is a critical point of F and, because F is concave (and not constant), it is the only critical point. If $c = c^+$, then $p = 1$ is the only critical point. The statement about stability follows from [Theorem 3.3](#).

(c) Lemma 3.1 and [Theorem 3.2](#) in [Nagylaki \(2009a\)](#) show that with DIDID, the dynamics is homeomorphic to that with no dominance. For the latter, the assertion follows from (b). \square

Remark 3.6. (a) There are parameter combinations (s_1, s_2, t_1, t_2) such that $c^- > c^+$, and hence condition (3.20) is not realizable. This is best seen by fixing, for instance, s_1 , t_1 , and t_2 , and letting $s_2 \uparrow 0$.

(b) We note that $c^- < c$ is equivalent to (3.2a), and $c < c^+$ is equivalent to (3.2b).

(c) If (3.5) is not fulfilled, then the ‘only if’ part of statement (b) may be false. To see this, choose $s_1 > 0, s_2 < -s_1/(1+2s_1), t_2 < 0, t_1 = t_2/(2t_2 - 1)$, and $c = \frac{1}{2}$. Then $c^- = \frac{1}{2}, y^* = 1$, and $p = 1$ is repelling because $x^* > 1$. Therefore, the fixation equilibrium $p = 0$ has an eigenvalue 1, but is repelling, as is easily shown. Hence, there is a protected polymorphism if $c = c^- = \frac{1}{2}$. Choosing $s_1 = 1, s_2 = -\frac{1}{2}, t_2 = -1$, hence $t_1 = \frac{1}{3}$, we obtain

$$F'(p) = \frac{p(1-4p)}{2(2-p)(1+p+p^2)}, \quad (3.21)$$

which has the zeros $p = 0$ and $p = \frac{1}{4}$, and a local maximum in between. Therefore, $p = \frac{1}{4}$ is globally asymptotically stable. Clearly, F is not concave on $[0, 1]$ and (3.10), hence (3.5), is violated for $\alpha = 1$ because $1 = s_1 > t_1(1+t_1)/(1-t_1) = \frac{2}{3}$.

To understand this example intuitively, we note that if $0.325 \approx -6 + 2\sqrt{10} < t_1 < \frac{1}{3}$, a second internal equilibrium exists which is unstable. At $t_1 = \frac{1}{3}$ it bifurcates through $p = 0$; cf. Remark 3.1.

Remark 3.7. Karlin (1977, Appendix A) showed that up to five equilibria, three of them internal, can exist. In such a case, the two fixation states and the middle of the three internal equilibria are locally asymptotically stable. This can occur with opposite directional selection, but requires very extreme fitness differences, which, of course, do not satisfy (3.5).

4. Two loci with intermediate dominance

We now investigate the equilibrium and stability structure of the diallelic two-locus Levene model with two demes, intermediate dominance, and absence of epistasis. In particular, we shall derive sufficient conditions for the maintenance of an asymptotically stable, fully polymorphic equilibrium. As already noted in the introduction, in a panmictic population only monomorphic equilibria can be stable under such conditions.

We specify the fitness contributions of the single-locus genotypes as follows:

$$u_{11,\alpha}^{(1)} = \frac{1}{2} + a_\alpha, \quad u_{12,\alpha}^{(1)} = \frac{1}{2} + \vartheta_\alpha a_\alpha, \quad u_{22,\alpha}^{(1)} = \frac{1}{2} - a_\alpha, \quad (4.1a)$$

$$u_{11,\alpha}^{(2)} = \frac{1}{2} + b_\alpha, \quad u_{12,\alpha}^{(2)} = \frac{1}{2} + \sigma_\alpha b_\alpha, \quad u_{22,\alpha}^{(2)} = \frac{1}{2} - b_\alpha. \quad (4.1b)$$

The parameters ϑ_α and σ_α measure the degree of dominance. Although there are only eight parameters in (4.1), this is the most general model. Indeed, for two demes, two loci, and three genotypes per locus, the general model has $2 \times 2 \times 3 = 12$ parameters. However, two can be removed by shifting fitnesses between loci and, because we assume soft selection, another two can be removed by scaling fitnesses in each deme.

Denoting the alleles at the first locus by A_1 and A_2 , and those at the second locus by B_1 and B_2 , the fitnesses of genotypes in deme α are given by the following matrix:

$$\begin{matrix} & B_1B_1 & B_1B_2 & B_2B_2 \\ A_1A_1 & 1 + a_\alpha + b_\alpha & 1 + a_\alpha + \sigma_\alpha b_\alpha & 1 + a_\alpha - b_\alpha \\ A_1A_2 & 1 + \vartheta_\alpha a_\alpha + b_\alpha & 1 + \vartheta_\alpha a_\alpha + \sigma_\alpha b_\alpha & 1 + \vartheta_\alpha a_\alpha - b_\alpha \\ A_2A_2 & 1 - a_\alpha + b_\alpha & 1 - a_\alpha + \sigma_\alpha b_\alpha & 1 - a_\alpha - b_\alpha \end{matrix}. \quad (4.2a)$$

Because fitnesses need to be nonnegative and to avoid degeneracy, we assume

$$a_\alpha \neq 0, \quad b_\alpha \neq 0, \quad \text{and} \quad |a_\alpha| + |b_\alpha| < 1 \quad (4.2b)$$

for every α . Thus, (2.13) is always satisfied. Throughout, we restrict attention to intermediate dominance at both loci and in every deme, i.e.,

$$-1 \leq \vartheta_\alpha, \sigma_\alpha \leq 1. \quad (4.2c)$$

This corresponds to directional selection on every locus and in every deme.

We denote the frequency of the alleles A_1 and B_1 by $p^{(1)}$ and $p^{(2)}$, respectively. Then their dynamics on the linkage-equilibrium manifold \mathcal{E} is governed by (2.14). In the following, however, it will be more convenient to use the variables

$$x = 2p^{(1)} - 1 \quad \text{and} \quad y = 2p^{(2)} - 1 \quad (4.3)$$

instead of the gene frequencies. Then the dynamics on \mathcal{E} can be formulated in terms of

$$(x, y) \in \mathcal{I} = [-1, 1] \times [-1, 1]. \quad (4.4)$$

Substituting (4.1) into (2.5), (2.6), and (2.7), we obtain

$$u_{1,\alpha}^{(1)} = \frac{1}{2} + \vartheta_\alpha a_\alpha + p^{(1)} a_\alpha (1 - \vartheta_\alpha), \quad (4.5a)$$

$$u_{2,\alpha}^{(1)} = \frac{1}{2} - a_\alpha + p^{(1)} a_\alpha (1 + \vartheta_\alpha), \quad (4.5b)$$

$$u_{1,\alpha}^{(1)} - u_{2,\alpha}^{(1)} = a_\alpha (1 - \vartheta_\alpha x), \quad (4.5c)$$

$$u_{1,\alpha}^{(2)} - u_{2,\alpha}^{(2)} = b_\alpha (1 - \sigma_\alpha y), \quad (4.5d)$$

$$\bar{u}_\alpha^{(1)} = \frac{1}{2} [1 + 2a_\alpha x + a_\alpha \vartheta_\alpha (1 - x^2)], \quad (4.5e)$$

$$\bar{u}_\alpha^{(2)} = \frac{1}{2} [1 + 2b_\alpha y + b_\alpha \sigma_\alpha (1 - y^2)], \quad (4.5f)$$

$$\bar{w}_\alpha = 1 + a_\alpha x + b_\alpha y + \frac{1}{2} a_\alpha \vartheta_\alpha (1 - x^2) + \frac{1}{2} b_\alpha \sigma_\alpha (1 - y^2). \quad (4.5g)$$

On \mathcal{I} , the gene-frequency dynamics (2.14) can then be written as

$$\Delta x = \frac{1-x^2}{4\bar{w}_1\bar{w}_2} [ca_1(1-\vartheta_1x)\bar{w}_2 + (1-c)a_2(1-\vartheta_2x)\bar{w}_1], \quad (4.6a)$$

$$\Delta y = \frac{1-y^2}{4\bar{w}_1\bar{w}_2} [cb_1(1-\sigma_1y)\bar{w}_2 + (1-c)b_2(1-\sigma_2y)\bar{w}_1], \quad (4.6b)$$

where throughout we use c and $1 - c$ instead of c_1 and c_2 . By Theorem 2.4, this is the system of recursion relations we will have to analyze.

It follows immediately that $\Delta x > 0$ for $x \in (-1, 1)$ if $a_1 > 0$ and $a_2 > 0$, and $\Delta x < 0$ if $a_1 < 0$ and $a_2 < 0$. An analogous statement holds for Δy . Therefore, an internal equilibrium can exist only if $a_1 a_2 < 0$ and $b_1 b_2 < 0$.

For definiteness, throughout the rest of this paper we assume that in addition to (4.2),

$$a_1 > 0 > a_2 \quad \text{and} \quad b_1 > 0 > b_2 \quad (4.7)$$

holds. We point out that whereas most results below concern the (full) gamete-frequency dynamics (2.2), some concern the gene-frequency dynamics (4.6).

For the gene-frequency dynamics (4.6), the following three classes of equilibria may exist:

- (i) Four monomorphic equilibria, M_i , where i indicates fixation of gamete i . They exist always.
- (ii) Single-locus polymorphisms. On each of the four edges of \mathcal{I} , $x = 1, x = -1, y = 1, y = -1$, up to three internal equilibria may exist (Remark 3.7). We label these edges $j = 1, 2, 3, 4$, respectively.
- (iii) Internal equilibria. If they are isolated, up to nine internal equilibria are feasible theoretically. A general treatment seems difficult. Below, detailed results for important special cases are obtained.

Without further simplification, only little analytical progress can be made because the terms in brackets in (4.6) are polynomials in two variables of degree three. Thus, in general, even the single-locus polymorphisms cannot be expressed in simple form. However, it is straightforward to determine the conditions for the existence of single-locus polymorphisms by using the single-locus theory about the protection of alleles. Consider for instance fixation of B_1 ($y = 1$). To study the existence of a polymorphism in A_1 and A_2 , we write

Genotypes:	$A_1A_1B_1B_1$	$A_1A_2B_1B_1$	$A_2A_2B_1B_1$
Fitnesses:	$1 + a_\alpha + b_\alpha$	$1 + \vartheta_\alpha a_\alpha + b_\alpha$	$1 - a_\alpha + b_\alpha$
Rescaled Fit.:	$1 + s_\alpha$	1	$1 - t_\alpha$

(4.8)

where

$$s_\alpha = \frac{(1 - \vartheta_\alpha)a_\alpha}{1 + \vartheta_\alpha a_\alpha + b_\alpha} \quad \text{and} \quad t_\alpha = \frac{(1 + \vartheta_\alpha)a_\alpha}{1 + \vartheta_\alpha a_\alpha + b_\alpha}. \quad (4.9)$$

Because assumptions (4.7) and (4.2) imply (3.14), Corollary 3.5 shows that a protected polymorphism exists in this marginal single-locus system if $c_3^- < c < c_3^+$, where evaluation of (3.19) yields

$$c_3^- = \left(1 - \frac{a_1(1 + \vartheta_1)(1 - a_2 + b_2)}{a_2(1 + \vartheta_2)(1 - a_1 + b_1)}\right)^{-1}, \quad (4.10a)$$

$$c_3^+ = \left(1 - \frac{a_1(1 - \vartheta_1)(1 + a_2 + b_2)}{a_2(1 - \vartheta_2)(1 + a_1 + b_1)}\right)^{-1}. \quad (4.10b)$$

It is interesting to note that the existence of this polymorphism depends on the second locus, even if the background is fixed both genetically and geographically ($b_1 = b_2$).

Analogously, a protected polymorphism exists in the marginal one-locus system on edge j if $c_j^- < c < c_j^+$. If $j = 4$, i.e., if B_2 is fixed ($y = -1$), then

$$c_4^- = \left(1 - \frac{a_1(1 + \vartheta_1)(1 - a_2 - b_2)}{a_2(1 + \vartheta_2)(1 - a_1 - b_1)}\right)^{-1}, \quad (4.11a)$$

$$c_4^+ = \left(1 - \frac{a_1(1 - \vartheta_1)(1 + a_2 - b_2)}{a_2(1 - \vartheta_2)(1 + a_1 - b_1)}\right)^{-1}. \quad (4.11b)$$

We do not present the analogous expressions for the edges $j = 1, 2$ because they will be needed only in a special case.

If we restrict attention to parameters satisfying the condition (3.5), then at most one internal equilibrium point, P_j , exists in the marginal system on edge j and, if it exists, it is globally asymptotically stable in this subsystem (Corollary 3.5). In general, its coordinate is not given by a simple expression.

The following result settles local stability of the monomorphic equilibria.

Proposition 4.1. Suppose (2.2). Then

- (a) M_1 is asymptotically stable if $\max(c_1^+, c_3^+) < c \leq 1$.
- (b) M_2 is asymptotically stable if $c_4^+ < c < c_1^-$.
- (c) M_3 is asymptotically stable if $c_2^+ < c < c_3^-$.
- (d) M_4 is asymptotically stable if $0 \leq c < \min(c_2^-, c_4^+)$.

If one of the inequalities is reversed, the corresponding monomorphism is unstable.

Proof. First consider (4.6). Because M_i is asymptotically stable if the two alleles not constituting gamete i are lost if rare, the statements follow immediately from (3.2), or (3.3), and Remark 3.6 (b). Theorem 2.4 yields the assertions for (2.2). \square

We note that if fitnesses are as in (4.2a) and satisfy (4.7), then the contributions of locus A are sublinear if and only if

$$\vartheta_1 \geq 0 \quad \text{and} \quad \vartheta_2 \leq 0, \quad (4.12)$$

and analogously for locus B .

4.1. No dominance at one locus

To make further analytical progress, throughout this subsection we assume absence of dominance at locus B , i.e.,

$$\sigma_1 = \sigma_2 = 0. \quad (4.13)$$

Then mean fitness in deme α simplifies to

$$\bar{w}_\alpha = 1 + a_\alpha x + b_\alpha y + \frac{1}{2}a_\alpha \vartheta_\alpha(1 - x^2), \quad (4.14)$$

and the terms in brackets in (4.6) become linear in y (but remain cubic in x). As a consequence, at most one polymorphic equilibrium with either fixation of A_1 ($x = 1$) or of A_2 ($x = -1$) can exist (Theorem 3.3 or Remark 3.4), and they can be calculated explicitly. We call them P_1 and P_2 . Simple calculations show that they are given by

$$P_1 : x = 1, \quad y = \xi_1 = -\left(c \frac{1 + a_2}{b_2} + (1 - c) \frac{1 + a_1}{b_1}\right), \quad (4.15a)$$

$$P_2 : x = -1, \quad y = \xi_2 = -\left(c \frac{1 - a_2}{b_2} + (1 - c) \frac{1 - a_1}{b_1}\right). \quad (4.15b)$$

Corollary 3.5 yields the following bounds on c for admissibility of the equilibria P_1 and P_2 :

$$c_1^- = \frac{b_2(1 + a_1 - b_1)}{b_2 - b_1 + \theta}, \quad c_1^+ = \frac{b_2(1 + a_1 + b_1)}{b_2 - b_1 + \theta}, \quad (4.16a)$$

$$c_2^- = \frac{b_2(1 - a_1 - b_1)}{b_2 - b_1 - \theta}, \quad c_2^+ = \frac{b_2(1 - a_1 + b_1)}{b_2 - b_1 - \theta}, \quad (4.16b)$$

where

$$\theta = a_1 b_2 - a_2 b_1 \quad (4.17)$$

will play an important role. From (3.19) we obtain immediately $c_j^+ < 1$ and $c_j^- > 0$. Therefore,

$$b_2 - b_1 + |\theta| < 0, \quad (4.18)$$

which together with (4.7) implies $c_j^- < c_j^+$ and shows that for given a_α and b_α the intervals of existence of P_1 and P_2 are nonempty.

We note that if only one of σ_1 or σ_2 is zero, then ξ_1 and ξ_2 are the solutions of a quadratic equation.

From the considerations above, we obtain the following conditions for admissibility of equilibria with a single polymorphic locus.

Proposition 4.2. Suppose (4.6).

- (a) There is a protected polymorphism on edge j if

$$c_j^- < c < c_j^+. \quad (4.19)$$

- (b) If $j = 1$ or 2 , then (4.19) is a necessary and sufficient condition for the admissibility of the equilibria P_1 and P_2 . Each of P_1 and P_2 is unique and globally asymptotically stable within its marginal one-locus system.

- (c) If the fitness contributions at locus B satisfy (3.5), then (4.19) is a necessary and sufficient condition for the existence of a unique internal equilibrium, P_3 or P_4 , on the edges 3 or 4. Each equilibrium is globally asymptotically stable within its marginal one-locus system.

We define

$$\theta^* = \vartheta_1 a_1 b_2 - \vartheta_2 a_2 b_1. \quad (4.20)$$

Our next theorem settles the existence and stability of internal equilibria.

Theorem 4.3. Suppose (2.2) and $\theta^* \neq 0$.

- (a) The following internal equilibrium point, denoted by $E = (\hat{x}, \hat{y}, \hat{d})$, may exist:

$$\hat{x} = \theta/\theta^*, \quad (4.21a)$$

$$\begin{aligned} \hat{y} &= -\frac{c_1}{b_2} \left[1 + a_2 \hat{x} + \frac{1}{2} a_2 \vartheta_2 (1 - \hat{x}^2) \right] \\ &\quad - \frac{(1-c)}{b_1} \left[1 + a_1 \hat{x} + \frac{1}{2} a_1 \vartheta_1 (1 - \hat{x}^2) \right], \end{aligned} \quad (4.21b)$$

$$\hat{d} = 0. \quad (4.21c)$$

If E exists, i.e., if it is admissible, then it is the unique internal equilibrium.

(b) E is admissible if and only if

$$|\theta| < |\theta^*|$$

and

$$c_{\min} < c < c_{\max},$$

where

$$c_{\min} = \frac{2b_2(1 + a_1[\frac{1}{2}\vartheta_1(1 - \hat{x}^2) + \hat{x}] - b_1)}{2(b_2 - b_1) + \theta^* + \theta\hat{x}}, \quad (4.22a)$$

$$c_{\max} = \frac{2b_2(1 + a_1[\frac{1}{2}\vartheta_1(1 - \hat{x}^2) + \hat{x}] + b_1)}{2(b_2 - b_1) + \theta^* + \theta\hat{x}}. \quad (4.22b)$$

(c) For every parameter combination $(a_1, a_2, b_1, b_2, \vartheta_1, \vartheta_2)$, the interval (4.22b) of existence of E is a nonempty subset of $(0, 1)$. Therefore, (4.22a) is necessary and sufficient for the existence of E for some values c .

(d) If the fitness contributions of locus A are sublinear, i.e., satisfy (4.12), and either $\vartheta_1 > 0$ or $\vartheta_2 < 0$, then E is globally asymptotically stable whenever it exists.

Proof. Theorem 2.4 shows that it is sufficient to prove the statements for (4.6).

(a) By (4.6), we have to solve

$$ca_1(1 - \vartheta_1 x)\bar{w}_2 + (1 - c)a_2(1 - \vartheta_2 x)\bar{w}_1 = 0, \quad (4.23a)$$

$$cb_1\bar{w}_2 + (1 - c)b_2\bar{w}_1 = 0. \quad (4.23b)$$

The substitution $(1 - c)\bar{w}_1 = -cb_1\bar{w}_2/b_2$ transforms (4.23a) into

$$\begin{aligned} \frac{c\bar{w}_2}{b_2} [a_1b_2(1 - \vartheta_1 x) - a_2b_1(1 - \vartheta_2 x)] &= \frac{c\bar{w}_2}{b_2} (\theta - \theta^*x) \\ &= 0. \end{aligned} \quad (4.24)$$

If $\theta^* \neq 0$, we obtain (4.21a). If $\theta^* = 0$ and $\theta \neq 0$, then no solution exists. If $\theta^* = \theta = 0$, then every x is a solution of (4.24).

For given x , (4.23b) is linear in y and has the unique solution

$$\begin{aligned} y &= -\frac{c}{b_2} \left[1 + a_2x + \frac{1}{2} a_2 \vartheta_2 (1 - x^2) \right] \\ &\quad - \frac{(1-c)}{b_1} \left[1 + a_1x + \frac{1}{2} a_1 \vartheta_1 (1 - x^2) \right]. \end{aligned} \quad (4.25)$$

If $\theta^* \neq 0$, this yields a unique solution of (4.23), which is given by (4.21a) and (4.21b). If $\theta^* = \theta = 0$, then a linear manifold of equilibria may exist.

(b) The first admissibility condition, (4.22a), is obvious. To derive (4.22b), we calculate the derivative of \hat{y} with respect to c :

$$\frac{\partial \hat{y}}{\partial c} = \frac{\zeta}{2b_1b_2}, \quad (4.26)$$

where, using (4.21a),

$$\begin{aligned} \zeta &= 2(b_2 - b_1) + 2\theta\hat{x} + \theta^*(1 - \hat{x}^2) \\ &= 2(b_2 - b_1) + \theta^* + \theta\hat{x}. \end{aligned} \quad (4.27)$$

Because we have $|\hat{x}| < 1$ and the estimates

$$|\theta| \leq |a_1||b_2| + |a_2||b_1| \leq |b_1| + |b_2| = b_1 - b_2 \quad (4.28)$$

and

$$|\theta^*| \leq |\vartheta_1||a_1||b_2| + |\vartheta_2||a_2||b_1| \leq |b_1| + |b_2| = b_1 - b_2, \quad (4.29)$$

which are based on (4.2b), (4.7), and $|\vartheta_\alpha| \leq 1$, we obtain $\zeta < 0$. Therefore, $\partial\hat{y}/\partial c > 0$, and c_{\min} and c_{\max} are obtained as the unique solutions of $\hat{y} = -1$ and $\hat{y} = 1$, respectively.

(c) First, we prove $c_{\min} > 0$ and $c_{\max} < 1$. We can write

$$c_{\min} = 2(b_2/\zeta) \left(1 + a_1 \left[\frac{1}{2} \vartheta_1 (1 - \hat{x}^2) + \hat{x} \right] - b_1 \right), \quad (4.30)$$

where $b_2/\zeta > 0$. By (4.2b), it is sufficient to show $|\frac{1}{2}\vartheta_1(1 - \hat{x}^2) + \hat{x}| \leq 1$. This, however, holds because

$$\begin{aligned} -1 &\leq -\frac{1}{2}(1 - \hat{x}^2) + \hat{x} \leq \frac{1}{2}\vartheta_1(1 - \hat{x}^2) + \hat{x} \\ &\leq \frac{1}{2}(1 - \hat{x}^2) + \hat{x} \leq 1 \end{aligned} \quad (4.31)$$

if $\vartheta_1 \in [-1, 1]$ and $\hat{x} \in [-1, 1]$. Further, it is not difficult to check that

$$(1 - c_{\max})(-\zeta) = 2b_1 \left(1 + a_2 \left[\frac{1}{2} \vartheta_2 (1 - \hat{x}^2) + \hat{x} \right] + b_2 \right), \quad (4.32)$$

and this is positive by (4.31) applied to ϑ_2 , (4.2b) and (4.7). Finally, we observe that

$$c_{\max} - c_{\min} = \frac{4b_1b_2}{\zeta} > 0. \quad (4.33)$$

(d) This follows from Theorem 2.4 (e) ($\theta^* \neq 0$ requires $\vartheta_1 > 0$ or $\vartheta_2 < 0$). \square

Remark 4.4. (a) If $\vartheta_1 = \vartheta_2 = \vartheta$, so that the degree of dominance is deme independent, then $\theta^* = \vartheta\theta$ and the internal equilibrium (4.21) does not exist if $\theta \neq 0$ because $|\vartheta| \leq 1$ by assumption. This is in accordance with Nagylaki's (2009b) Proposition 3.18, which states that with DIDID, generically, no internal gene-frequency equilibrium exists if the number of demes is less than or equal the number of loci.

(b) In the proof of Theorem 4.3 (a) it is shown that if $\theta = \theta^* = 0$, then a linear manifold of equilibria may exist; it is given by (4.25). The determination of its admissibility conditions is left to the reader. The special case of no dominance and $\theta = 0$ is treated in detail in Section 5.2.

(c) It is straightforward, and also left to the reader, to express (4.22a) in terms of bounds on ϑ_1 or ϑ_2 . It is obvious that for given a_α , b_α , and $\theta \neq 0$, not both ϑ_1 and ϑ_2 can be arbitrarily close to zero.

Remark 4.5. (a) With weaker selection, the length of the interval $[c_{\min}, c_{\max}]$, in which a fully polymorphic equilibrium exists, shrinks. This is readily seen from (4.33) by setting $\tilde{a}_i = \kappa a_i$ and $\tilde{b}_i = \kappa b_i$. Thus, as expected, stronger selection favors stable multilocus polymorphism.

(b) It is straightforward to check that E coincides with P_3 if $c = c_{\max}$ and E coincides with P_4 if $c = c_{\min}$.

Remark 4.6. (a) We have not proved that the internal equilibrium is the global attractor if fitness contributions are not sublinear, because this is not the case. However, we have proved uniqueness.

(b) Numerical results show that if $\vartheta_2 = 0$, then the internal equilibrium is unstable if $\vartheta_1 < 0$. In the special case $a_1 = b_1 = -a_2 = -b_2 = a$ and $c = \frac{1}{2}$, when $\hat{x} = 0$ and $\hat{y} = -\frac{1}{4}\vartheta_1$,

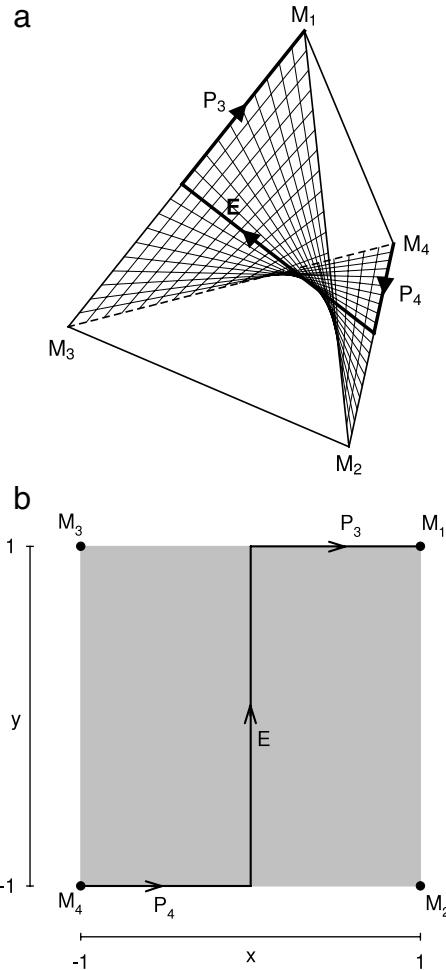


Fig. 1. (a) Stable equilibria as a function of c with no dominance at locus B . The linkage-equilibrium manifold is indicated by hatching. The bold line indicates the track of the globally stable equilibrium as c increases from 0 to 1. A simple example for this behavior is obtained if $a_1 = -a_2 = a > 0$, $b_1 = -b_2 = b > 0$, $\vartheta_1 > 0$, and $\vartheta_2 = 0$, when $\hat{x} = \theta = 0$, $\theta^* = \vartheta_1 a_1 b_2$, and $0 < c_4^- < c_2^- < c_{\min} < c_{\max} < c_1^+ < c_3^+ < 1$. Then M_1 is stable if and only if $c \geq c_3^+$. P_3 is admissible if and only if $c_3^- < c < c_3^+$, and it is stable if and only if $c_{\max} < c < c_3^+$. The internal equilibrium, E , exists and is stable if and only if $c_{\min} < c < c_{\max}$. P_4 is admissible if and only if $c_4^- < c < c_4^+$, and it is stable if and only if $c_4^- < c < c_{\min}$. M_4 is stable if and only if $0 \leq c \leq c_4^-$. The numerical example shown has $a = 0.1$, $b = 0.15$, $\vartheta_1 = 0.5$. Then $c_3^+ = 0.769$, $c_{\max} = 0.580$, $c_{\min} = 0.432$, $c_4^- = 0.286$. By Theorem 2.4, in every case ‘stable’ implies ‘globally asymptotically stable’. (b) As in (a), but here only the linkage-equilibrium manifold in its parameterization $(x, y) \in \mathcal{I}$ is shown.

this follows immediately from the characteristic polynomial of the Jacobian.

Because (4.22) determines whether or not an internal equilibrium can exist, it is instructive to consider the equilibrium structure as a function of c . This is illustrated in Fig. 1 for a special case with sublinear fitness contributions. Then Theorem 2.4 (e) shows that every asymptotically stable equilibrium is globally attracting. Therefore, Proposition 4.1 informs us that the monomorphic equilibrium M_1 , or M_4 , is globally asymptotically stable if c is sufficiently large, or small, respectively. For intermediate c , either a single-locus polymorphism or the fully polymorphic equilibrium is globally asymptotically stable.

4.2. Deme-independent degree of dominance at one locus

Most results of the previous section can be extended to deme-independent degree of dominance at locus B . Therefore, through-

out this subsection we assume

$$\sigma_1 = \sigma_2 = \sigma \quad (4.34)$$

and $|\sigma| \leq 1$ (cf. Remark 3.4). The basis for this extension is a result by Nagylaki (2009a) showing that, for a single locus, the qualitative dynamics with DIDID is the same as without dominance. Since we consider a diallelic locus, his multiallelic results simplify greatly. With fitnesses scaled as in (3.1), we have DIDID if there exists $\delta \in [0, 1]$ such that $1 = \delta(1 + s_\alpha) + (1 - \delta)(1 - t_\alpha)$ for every α . Hence,

$$\delta = \frac{t_\alpha}{s_\alpha + t_\alpha}, \quad (4.35)$$

and the transformation

$$z = \varphi(p) = 2\delta p(1 - p) + p^2 \quad (4.36)$$

is a homeomorphism from $[0, 1]$ onto itself that linearizes the single-locus mean fitness $\bar{w}_\alpha(p)$ for every α , i.e.,

$$\bar{w}_\alpha(p) = \bar{w}_\alpha(z) = \begin{cases} 1 - t_\alpha + (t_\alpha/\delta)z, & \text{if } \delta > 0, \\ 1 + s_\alpha z, & \text{if } \delta = 0 \end{cases} \quad (4.37)$$

(cf. Lemma 3.1 in Nagylaki, 2009a). As a consequence (Theorem 3.2 in Nagylaki, 2009a), the evolution of $p(t)$ with DIDID is qualitatively the same as without dominance.

We apply this reasoning to locus B , and we continue to use the coordinates (x, y) instead of $(p^{(1)}, p^{(2)})$. If we set

$$\delta = \frac{1}{2}(1 + \sigma), \quad (4.38)$$

then a simple calculation involving (4.36) shows that the desired homeomorphism $\psi : \mathcal{I} \rightarrow \mathcal{I}$ is given by

$$(x, z) = \psi(x, y) = \left(x, y + \frac{1}{2}\sigma(1 - y^2) \right). \quad (4.39)$$

As in (4.14), mean fitness in deme α is then linear in z ,

$$\bar{W}_\alpha(x, z) = \bar{w}_\alpha(x, y) = 1 + a_\alpha x + b_\alpha z + \frac{1}{2}a_\alpha \vartheta_\alpha(1 - x^2), \quad (4.40)$$

and independent of σ . However, the recursion relations for $(x(t), z(t))$ are much more complicated than for $(x(t), y(t))$ and are not needed.

Theorem 4.7. Suppose (2.2) and $\theta^* \neq 0$.

(a) There may exist an internal equilibrium point $E = (\hat{x}, \hat{y}, \hat{d})$, where

$$\hat{x} = \theta/\theta^*, \quad (4.41)$$

\hat{y} is the solution in $(-1, 1)$ of a quadratic equation, (4.44), and $\hat{d} = 0$. If E is admissible, then it is the unique internal equilibrium.

(b) E is admissible if and only if the conditions (4.22a) and (4.22b) in Theorem 4.3 are satisfied, where c_{\min} and c_{\max} remain unchanged. Therefore, admissibility of E is independent of σ .

(c) For every parameter combination $(a_1, a_2, b_1, b_2, \vartheta_1, \vartheta_2, \sigma)$, the interval (4.22b) of existence of E is a nonempty subset of $(0, 1)$. Therefore, (4.22a) is necessary and sufficient for the existence of E for some values c .

(d) If fitness contributions of locus A are sublinear and either $\vartheta_1 > 0$ or $\vartheta_2 < 0$, then E is globally asymptotically stable whenever it exists.

Proof. Assertions (a)–(c) follow as in the proof of Theorem 4.3 by using the coordinates (x, z) instead of (x, y) .

However, there is also a simple explicit way to derive these statements. As in the proof of Theorem 4.3, we obtain the equilibrium condition (4.23), because the factor $1 - \sigma y$ arising from (4.6) cancels since we have $|\sigma| \leq 1$ and restrict attention to $|y| < 1$. Therefore, (4.24) and (4.21a) are obtained. Instead of (4.25) we get

$$h(x) + b_1 b_2 g(y) = 0, \quad (4.42)$$

where

$$h(x) = cb_1 \left[1 + a_2x + \frac{1}{2}a_2\vartheta_2(1-x^2) \right] \\ + (1-c)b_2 \left[1 + a_1x + \frac{1}{2}a_1\vartheta_1(1-x^2) \right], \quad (4.43a)$$

and

$$g(y) = y + \frac{1}{2}\sigma(1-y^2). \quad (4.43b)$$

Then $g(-1) = -1$, $g(1) = 1$, and g is strictly monotone increasing on $[-1, 1]$ because $|\sigma| \leq 1$. Therefore, $g(y) = 0$ has a unique solution in $[-1, 1]$. Hence,

$$h(\hat{x}) + b_1b_2g(y) = 0 \quad (4.44)$$

has a solution $y \in (-1, 1)$ if and only if $|h(\hat{x})| < -b_1b_2$. Solving $|h(\hat{x})| = -b_1b_2$ for c , we obtain c_{\min} and c_{\max} for every $\sigma \in [0, 1]$.

(d) By Remark 2.3, \tilde{w} is a Lyapunov function of (2.14) and, therefore, of (4.6). As a consequence,

$$\tilde{W}(x, z) = \prod_{\alpha} [\tilde{W}_{\alpha}(x, z)]^{c_{\alpha}} = \tilde{w}(x, y) = \tilde{w}(p^{(1)}, p^{(2)}) \quad (4.45)$$

satisfies $\Delta\tilde{W} \geq 0$ with equality only at equilibrium. Now statement (d) of Theorem 4.3 applies to the coordinates (x, z) and, therefore, the assertion follows from the properties of ψ and Theorem 2.4(b). \square

4.3. General intermediate dominance at both loci

If there is general intermediate dominance at both loci, internal equilibria cannot usually be computed explicitly. However, existence can be proved for an open set of parameters by applying the Implicit Function Theorem to Theorem 4.3 or 4.7.

Theorem 4.8. Assume (2.2) and let $a_{\alpha}, b_{\alpha}, \vartheta_{\alpha}, \sigma$, and c_{α} ($\alpha = 1, 2$) be such that the internal equilibrium $E = (\hat{x}, \hat{y}, 0)$ in Theorem 4.7 is admissible. Furthermore, let $\hat{y} \neq 0$. Then for sufficiently small deviations σ_1 and σ_2 from σ , there exists an isolated internal equilibrium E' , which is close to E and in linkage equilibrium. If E is asymptotically stable, then E' is asymptotically stable.

Proof. By Theorem 2.4, it is sufficient to study (4.6). We define the map $G(x, y, \sigma_1, \sigma_2) = (G_1(x, y, \sigma_1, \sigma_2), G_2(x, y, \sigma_1, \sigma_2))$ by

$$G_1(x, y, \sigma_1, \sigma_2) = ca_1(1-\vartheta_1x)\bar{w}_2 + (1-c)a_2(1-\vartheta_2x)\bar{w}_1, \quad (4.46a)$$

$$G_2(x, y, \sigma_1, \sigma_2) = cb_1(1-\sigma_1y)\bar{w}_2 + (1-c)b_2(1-\sigma_2y)\bar{w}_1. \quad (4.46b)$$

We know from Theorem 4.3 that $G(\hat{x}, \hat{y}, \sigma, \sigma) = 0$, where (\hat{x}, \hat{y}) is the internal equilibrium given by (4.21). We seek $(x, y) = f(\sigma_1, \sigma_2)$ such that $G(x, y, \sigma_1, \sigma_2) = 0$. By the Implicit Function Theorem, such a function f exists on a (small) neighborhood of (σ, σ) if the derivative of G with respect to (σ_1, σ_2) and evaluated at $(\hat{x}, \hat{y}, \sigma, \sigma)$,

$$DG(\hat{x}, \hat{y}, \sigma, \sigma) = \begin{pmatrix} \frac{\partial G_1}{\partial \sigma_1}(\hat{x}, \hat{y}, \sigma, \sigma) & \frac{\partial G_1}{\partial \sigma_2}(\hat{x}, \hat{y}, \sigma, \sigma) \\ \frac{\partial G_2}{\partial \sigma_1}(\hat{x}, \hat{y}, \sigma, \sigma) & \frac{\partial G_2}{\partial \sigma_2}(\hat{x}, \hat{y}, \sigma, \sigma) \end{pmatrix} \quad (4.47)$$

is invertible. This is the case if and only if its determinant $\det(DG(\hat{x}, \hat{y}, \sigma, \sigma))$ does not vanish. Straightforward calculations yield

$$\det(DG(x, y, \sigma, \sigma)) = \frac{1}{4}b_1b_2(1-y^2)\kappa, \quad (4.48)$$

where

$$\kappa = \{(1-c)a_2(1-\vartheta_2x)[cb_1(1-y^2)(1-\sigma y) - 2(1-c)\bar{w}_1y] \\ - ca_1(1-\vartheta_1x)[(1-c)b_2(1-y^2)(1-\sigma y) - 2c\bar{w}_2y]\}. \quad (4.49)$$

Further simplification is obtained by making use of the fact that we need to evaluate this determinant at $(x, y) = (\hat{x}, \hat{y})$. We already know from Theorem 4.7 that (\hat{x}, \hat{y}) is the solution of (4.23). Writing this in the form

$$(1-c)a_2(1-\vartheta_2x)\bar{w}_1 = -ca_1(1-\vartheta_1x)\bar{w}_2 \quad (4.50a)$$

and

$$c\bar{w}_2 = -(1-c)b_2\bar{w}_1/b_1, \quad (4.50b)$$

we obtain by simple rearrangement

$$\kappa = c(1-c) \left[(1-\hat{y}^2)(1-\sigma\hat{y})(\theta^*\hat{x} - \theta) \right. \\ \left. + 2\frac{a_1}{b_1}(1-\vartheta_1\hat{x})\hat{y}(b_1\bar{w}_2 - b_2\bar{w}_1) \right]. \quad (4.51)$$

Clearly, $\theta^*\hat{x} - \theta = 0$. Moreover, (4.23b) gives $b_1\bar{w}_2 - b_2\bar{w}_1 = -b_2\bar{w}_1/c$. Putting all this together, we finally arrive at

$$\det(DG(\hat{x}, \hat{y}, \sigma, \sigma)) = -\frac{1}{2}(1-c)a_1b_2^2\bar{w}_1(1-\vartheta_1\hat{x})\hat{y}(1-\hat{y}^2), \quad (4.52)$$

where \bar{w}_1 is evaluated at $(\hat{x}, \hat{y}, \sigma, \sigma)$. This expression vanishes if and only if $\hat{x} = 1/\vartheta_1$, $|\hat{y}| = 1$, or if $\hat{y} = 0$. The first two cases cannot occur because they do not admit an internal equilibrium, and the third case has been excluded by assumption. This establishes existence of the (one-to-one) function $f(\sigma_1, \sigma_2) = (x, y)$, hence of a perturbed equilibrium, E' . By Theorem 2.4, E' is in linkage equilibrium. Theorem 9.1 in LaSalle (1977) yields the statement about asymptotic stability. \square

If fitness contributions of both loci and in every deme are multiplicative, then Result 2.2 does not apply because $\log(\sum_n \bar{u}_{\alpha}^{(n)})$ is not necessarily concave if $L > 1$. Indeed, numerical results suggest that if an internal equilibrium exists for multiplicative fitness contributions, it is unstable and two monomorphic equilibria are stable. We do not know if, in this case, an internal equilibrium is always unstable. In view of Remark 4.6, this would not be surprising.

Numerically, we found up to three internal equilibria for general intermediate dominance. All of them were unstable. These examples involve near recessivity of the favored alleles and extreme fitness differences (the dominant allele is nearly lethal). We do not know if two stable internal equilibria can exist with intermediate dominance.

4.4. The weak-selection limit

It is instructive to consider the weak-selection limit, which has been shown to be equivalent to panmixia with averaged fitnesses (Nagylaki, 2009b, Proposition 2.2). Let

$$a_{\alpha} = \epsilon\tilde{a}_{\alpha} \quad \text{and} \quad b_{\alpha} = \epsilon\tilde{b}_{\alpha} \quad (\alpha = 1, 2). \quad (4.53)$$

Then $\bar{w}_{\alpha} \rightarrow 1$ as $\epsilon \rightarrow 0$, and (4.6) simplifies greatly. An internal equilibrium has to satisfy

$$x = \frac{c\tilde{a}_1 + (1-c)\tilde{a}_2}{c\tilde{a}_1\vartheta_1 + (1-c)\tilde{a}_2\vartheta_2} \quad \text{and} \quad y = \frac{c\tilde{b}_1 + (1-c)\tilde{b}_2}{c\tilde{b}_1\sigma_1 + (1-c)\tilde{b}_2\sigma_2}. \quad (4.54)$$

This equilibrium is admissible if and only if there is average overdominance or average underdominance at every locus, i.e., if and only if $|c\tilde{a}_1\vartheta_1 + (1 - c)\tilde{a}_2\vartheta_2| > |c\tilde{a}_1 + (1 - c)\tilde{a}_2|$ and, analogously, for the second locus. This internal equilibrium is (globally) asymptotically stable if and only if there is average overdominance at both loci. For locus A this means $c\tilde{a}_1\vartheta_1 + (1 - c)\tilde{a}_2\vartheta_2 > |c\tilde{a}_1 + (1 - c)\tilde{a}_2|$.

5. Two loci with no dominance

If there is no dominance or, more generally, DIDID, then Proposition 3.18 in Nagylaki (2009b) informs us that generically no internal (gene-frequency) equilibrium exists if $L \leq \Gamma$. Indeed, without dominance the conditions for the existence of an internal equilibrium in Theorem 4.3 or Theorem 4.7 are not satisfied because $\theta^* = 0$. In the following, we study this special case, which will be relevant for the quantitative-genetic application in the next section. Thus, in addition to (4.2) and (4.7), we assume the absence of dominance, i.e.,

$$\vartheta_1 = \vartheta_2 = \sigma_1 = \sigma_2 = 0. \quad (5.1)$$

Hence, fitnesses are additive within and between loci. This is equivalent to assigning fitness contributions to alleles as follows:

$$\begin{array}{lll} \text{Alleles:} & A_1 & A_2 \\ \text{Fitnesses: } v_{1,\alpha}^{(1)} = & \frac{1}{4} + \frac{1}{2}a_\alpha & \frac{1}{4} - \frac{1}{2}a_\alpha \\ v_{2,\alpha}^{(1)} = & \frac{1}{4} + \frac{1}{2}b_\alpha & \frac{1}{4} - \frac{1}{2}b_\alpha \end{array} \quad (5.2)$$

For the mean fitness in deme α , we obtain from (4.5g)

$$\bar{w}_\alpha(x, y) = 1 + a_\alpha x + b_\alpha y. \quad (5.3)$$

From (4.6), the dynamics of allele frequencies on the linkage-equilibrium manifold can be written as

$$\begin{aligned} \Delta x = & \frac{1 - x^2}{4\bar{w}_1\bar{w}_2} [ca_1(1 + a_2x + b_2y) \\ & + (1 - c)a_2(1 + a_1x + b_1y)], \end{aligned} \quad (5.4a)$$

$$\begin{aligned} \Delta y = & \frac{1 - y^2}{4\bar{w}_1\bar{w}_2} [cb_1(1 + a_2x + b_2y) \\ & + (1 - c)b_2(1 + a_1x + b_1y)], \end{aligned} \quad (5.4b)$$

where $(x, y) \in \mathcal{I}$. Unless a manifold of equilibria exists, and statements (b)–(e) of Theorem 2.4 do not apply, it is sufficient to restrict further analysis to the study of the system (5.4).

Again three classes of equilibria may exist. Clearly, the monomorphic equilibria M_i always exist. Because there is no dominance, all single-locus polymorphisms P_i are uniquely determined if they exist. P_1 and P_2 are given by (4.15), and P_3 and P_4 are given by

$$P_3 : y = 1, \quad x = \xi_3 = -\left(c\frac{1 + b_2}{a_2} + (1 - c)\frac{1 + b_1}{a_1}\right), \quad (5.5a)$$

$$P_4 : y = -1, \quad x = \xi_4 = -\left(c\frac{1 - b_2}{a_2} + (1 - c)\frac{1 - b_1}{a_1}\right). \quad (5.5b)$$

Equilibrium P_i is admissible if and only if $|\xi_i| < 1$. In addition to (4.16), we obtain

$$c_3^- = \frac{a_2(1 - a_1 + b_1)}{a_2 - a_1 - \theta}, \quad c_3^+ = \frac{a_2(1 + a_1 + b_1)}{a_2 - a_1 - \theta}, \quad (5.6a)$$

$$c_4^- = \frac{a_2(1 - a_1 - b_1)}{a_2 - a_1 + \theta}, \quad c_4^+ = \frac{a_2(1 + a_1 - b_1)}{a_2 - a_1 + \theta}. \quad (5.6b)$$

Therefore, Corollary 3.5 implies

Proposition 5.1. *The single-locus polymorphism P_i is admissible if and only if (4.19) holds. Then P_i is globally asymptotically stable within its (marginal) one-locus system.*

Because there is no dominance, we have $\theta^* = 0$ and Remark 4.4 informs us that an internal equilibrium can exist only if $\theta = 0$ (cf. Example 3.22 in Nagylaki, 2009b). We will treat this case separately in Section 5.2.

5.1. The case $\theta \neq 0$

Because $F(\rho)$ is concave if there is no dominance, and because there are at most eight equilibria ($M_i, P_i, i = 1, 2, 3, 4$), Theorem 2.4(d) proves that there exists exactly one stable equilibrium and it is globally attracting. The stability properties of the monomorphic equilibria were settled by Proposition 4.1. In particular, a monomorphic equilibrium can never be stable if a single-locus polymorphism exists on one of the edges connecting to it.

Next, we treat stability of the single-locus polymorphisms.

Proposition 5.2. *Suppose (2.2) and $\theta \neq 0$.*

- (a) *If P_1 or P_4 is admissible, then it is asymptotically stable if and only if $\theta < 0$.*
- (b) *If P_2 or P_3 is admissible, then it is asymptotically stable if and only if $\theta > 0$.*

Proof. It is sufficient to consider (5.4). We prove statement (a) for P_1 . The other statements follow analogously. By Proposition 5.1, it is sufficient to check the stability with respect to the interior of \mathcal{I} . This can be done by calculating the eigenvalue of the Jacobian at P_1 pertaining to the ‘direction’ x or by calculating the partial derivative of F with respect to x at P_1 .

With Mathematica it is easy to check that the eigenvalues at P_1 can be written as

$$\lambda_1 = 1 + \frac{1}{4}b_1b_2(1 - \xi_1^2), \quad (5.7a)$$

$$\lambda_2 = 1 + c_1c_2\theta\alpha_1, \quad (5.7b)$$

where

$$\alpha_1 = \frac{b_2 - b_1 + \theta}{b_1b_2} = \frac{1 + a_1}{b_1} - \frac{1 + a_2}{b_2} > 0. \quad (5.8)$$

The first eigenvalue determines stability within the edge $x = 1$. Because P_1 is admissible if and only if $|\xi_1| < 1$, and because we have $b_1b_2 < 0$, we obtain $0 < \lambda_1 < 1$, as it must be.

In addition, we have $0 < \lambda_2 < 1$, hence asymptotic stability of P_1 , if and only if $\theta\alpha_1 < 0$. Because $\alpha_1 > 0$, we must have $\theta < 0$. \square

It is instructive to study the existence and stability of equilibria as a function of c . The most interesting cases occur if every single-locus polymorphism can exist for some c . For definiteness, we posit $\theta < 0$. \square

We want to show that if c increases from 0 to 1, equilibria are stable in the order $M_4 \rightarrow P_4 \rightarrow M_2 \rightarrow P_1 \rightarrow M_1$. More precisely, we prove the following:

Theorem 5.3. *Suppose (2.2) and (5.9). Then*

$$0 < c_4^- < c_4^+ < c_1^- < c_1^+ < 1 \quad (5.10)$$

and

- (a) *M_4 is stable if and only if $0 \leq c \leq c_4^-$.*
- (b) *P_4 exists and is stable if and only if $c_4^- < c < c_4^+$.*
- (c) *M_2 is stable if and only if $c_4^+ \leq c \leq c_1^-$.*
- (d) *P_1 exists and is stable if and only if $c_1^- < c < c_1^+$.*
- (e) *M_1 is stable if and only if $c_1^+ \leq c \leq 1$.*

In all cases, ‘stable’ is equivalent to ‘globally asymptotically stable’.

Proof. The inequalities (5.10) follow straightforwardly from (4.7), (5.9), (4.15) and (5.5). The stability of the monomorphic equilibria

was settled in [Proposition 4.1](#). [Propositions 5.1](#) and [5.2](#) yield the assertions about existence and asymptotic stability of P_1 and P_4 . The statement about global asymptotic stability follows from [Theorem 2.4](#) because F is concave. \square

Together with simple geometric considerations, the above theorem shows that as c increases from c_4^- to c_4^+ , P_4 moves along the edge $y = -1$ and hits M_2 if $c = c_4^+$. At this value, M_2 becomes stable. If $c = c_1^-$, then M_2 becomes unstable and P_1 bifurcates through M_2 into existence. It remains stable until it hits M_1 if $c = c_1^+$.

We have DIDID at both loci if

$$\vartheta_1 = \vartheta_2 \quad \text{and} \quad \sigma_1 = \sigma_2. \quad (5.11)$$

Corollary 5.4. *Theorem 5.3 holds without change if (5.1) is generalized to (5.11). The critical values c_i^- and c_i^+ remain unchanged and existence of equilibria is independent of the dominance parameters at the two loci.*

The proof is analogous to that of statement (d) in [Theorem 4.7](#). The nonlinear transformation (4.36) has to be applied to both loci.

5.2. The case $\theta = 0$

With $\theta = 0$, we obtain from (4.10), (4.11) and (4.16):

$$c_1^+ = c_3^+ = \frac{1 + a_1 + b_1}{1 - a_1/a_2}, \quad (5.12a)$$

$$c_1^- = c_4^+ = \frac{1 + a_1 - b_1}{1 - a_1/a_2}, \quad (5.12b)$$

$$c_2^+ = c_3^- = \frac{1 - a_1 + b_1}{1 - a_1/a_2}, \quad (5.12c)$$

$$c_2^- = c_4^- = \frac{1 - a_1 - b_1}{1 - a_1/a_2}. \quad (5.12d)$$

As shown in the proof of [Theorem 4.3](#), Eq. (4.25), if $\theta = 0$, the linear manifold

$$y = -\left(c \frac{1 + xa_2}{b_2} + (1 - c) \frac{1 + xa_1}{b_1}\right) \quad (5.13)$$

of equilibria may exist. Because we have $a_1/b_1 = a_2/b_2$, we can rewrite (5.13) as

$$y = -x \frac{a_1}{b_1} - \frac{1}{b_1} + c \left(\frac{1}{b_1} - \frac{1}{b_2}\right). \quad (5.14)$$

It is instructive to consider this as a straight line in the full plane \mathbb{R}^2 , and not just restricted to the square \mathcal{I} . By (4.7), its slope is negative and the intercept with the y -axis increases with c . A simple calculation shows that all four points, P_1 – P_4 , are on this line, i.e., if $x = 1$ then $y = \xi_1$, etc. Admissible equilibria emerge if and only if this line passes through \mathcal{I} . Then the line segment contained in \mathcal{I} yields a manifold of equilibria. This occurs if and only if

$$c_4^- < c < c_1^+, \quad (5.15)$$

because by [Theorem 5.3](#) the line (5.14) passes through M_1 if and only if $c = c_1^+$ and through M_4 if and only if $c = c_4^-$.

We obtain the following theorem. For an illustration, see Fig. 2.

Theorem 5.5. *Suppose (2.2), $\theta = 0$, and $a_1/b_1 > 1$. Then*

$$0 < c_4^- < c_2^+ < c_1^- < c_1^+ < 1, \quad (5.16)$$

and the existence and stability of equilibria are as follows:

- (a) M_4 is globally asymptotically stable if and only if $0 \leq c \leq c_4^-$.
- (b) A line of internal equilibria connects

P_2 and P_4 if and only if $c_4^- < c < c_2^+$.

M_3 and P_4 if and only if $c = c_2^+$.

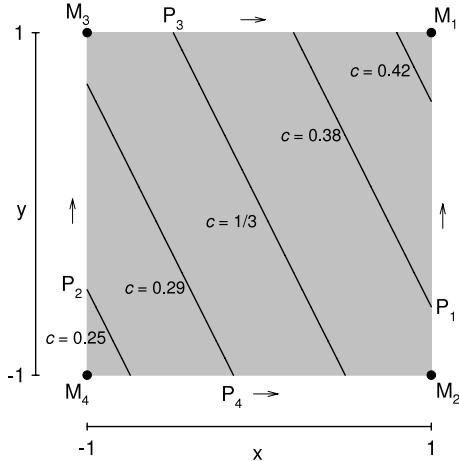


Fig. 2. Internal equilibria in the absence of genotype environment interaction, i.e., no dominance and $\theta = 0$. Then an internal equilibrium consists of a line of equilibrium points. The figure shows these lines in \mathcal{I} for various values of c . The parameters are $a_1 = 0.2$, $a_2 = -0.1$, $b_1 = 0.1$, $b_2 = -0.05$. Therefore, $c_{\min} = 7/30 \approx 0.233$ and $c_{\max} = 13/30 \approx 0.433$.

P_3 and P_4 if and only if $c_2^+ < c < c_1^-$.

M_2 and P_3 if and only if $c = c_1^-$.

P_1 and P_3 if and only if $c_1^- < c < c_1^+$.

- (c) M_1 is globally asymptotically stable if and only if $c_1^+ \leq c \leq 1$.

Proof. The inequalities not covered by (5.10), $c_4^- < c_2^+ < c_1^-$, follow readily from (5.12). [Proposition 4.1](#) yields the conditions for asymptotic stability of the monomorphic equilibria, and [Proposition 5.1](#) yields the conditions for admissibility of the single-locus polymorphisms. [Proposition 5.2](#) on their asymptotic stability is no longer applicable because $\theta = 0$. Indeed, (5.7) shows that if a single-locus polymorphism is admissible, then the eigenvalue corresponding to internal stability is zero.

Global asymptotic stability of the M_1 and M_4 is a consequence of [Theorem 2.4](#). The assertions in (b) follow from the considerations above. \square

If there is a manifold of gene-frequency equilibria, as in statement (b) above, then the decay of linkage disequilibrium seems likely but has not been established rigorously. In fact, Nagylaki (2009b, Theorem 4.6) assumed that all gene-frequency equilibria are isolated. Additional arguments are required to relax this (generic) assumption. [Theorem 2.4](#) (a) shows that every equilibrium has to be in linkage equilibrium; thus, no other equilibria than those found above can exist. However, it does not exclude more complicated limit sets.

Corollary 5.6. *Theorem 5.5 holds without change if (5.1) is generalized to (5.11). The critical values c_i^- and c_i^+ remain unchanged and existence of equilibria is independent of the dominance parameters at the two loci.*

The proof is essentially the same as that of statement (d) of [Theorem 4.7](#) if the transformation (4.36) is applied to both loci.

6. Linear selection on a quantitative trait and $G \times E$ interaction

Assume that selection acts on a quantitative trait that is controlled by two diallelic, nonepistatic loci. Let the contributions of A_1 , A_2 , B_1 , and B_2 to the genotypic value G be $-\frac{1}{2}\gamma_1$, $\frac{1}{2}\gamma_1$, $-\frac{1}{2}\gamma_2$, and $\frac{1}{2}\gamma_2$. Thus, there is no allele-environment interaction. Because we admit deme-independent degree of dominance at both loci, the contributions of the single-locus genotypes A_1A_1 , A_1A_2 , A_2A_2 , and B_1B_1 , B_1B_2 , B_2B_2 are $-\gamma_1$, $-\vartheta\gamma_1$, γ_1 , and $-\gamma_2$, $-\sigma\gamma_2$, γ_2 , respectively. Since we assume absence of epistasis, the genotypic values G in every deme are given by the matrix

$$\begin{array}{l} B_1B_1 \quad B_1B_2 \quad B_2B_2 \\ A_1A_1 \left(\begin{array}{ccc} -\gamma_1 - \gamma_2 & -\gamma_1 - \sigma\gamma_2 & -\gamma_1 + \gamma_2 \\ -\vartheta\gamma_1 - \gamma_2 & -\vartheta\gamma_1 - \sigma\gamma_2 & -\vartheta\gamma_1 + \gamma_2 \\ \gamma_1 - \gamma_2 & \gamma_1 - \sigma\gamma_2 & \gamma_1 + \gamma_2 \end{array} \right). \end{array} \quad (6.1)$$

We restrict our attention to intermediate dominance, i.e., $|\vartheta| \leq 1$ and $|\sigma| \leq 1$. For definiteness, we assume $\gamma_1 \geq \gamma_2 > 0$ and refer to these loci as major and minor, respectively. We call γ_1 and γ_2 the effects of the loci. It is easy to see that (6.1) is the most general model with absence of epistasis and of genotype-environment interaction.

We study linear directional selection on the trait in every deme, i.e.,

$$W_\alpha(G) = 1 - s_\alpha G, \quad (6.2)$$

where we require $s_\alpha < (\gamma_1 + \gamma_2)^{-1}$ for every α , so that fitnesses are always positive. Using the notation of (4.2a), we obtain by simple calculations

$$a_\alpha = s_\alpha \gamma_1, \quad b_\alpha = s_\alpha \gamma_2, \quad \vartheta_\alpha = \vartheta, \quad \sigma_\alpha = \sigma \quad (6.3)$$

for $\alpha = 1, 2$. Hence, we have DIDID at both loci, and

$$\frac{a_\alpha}{a_\beta} = \frac{b_\alpha}{b_\beta} \quad (6.4)$$

holds for every α and β . For two demes, this is exactly the condition $\theta = 0$ (4.17).

If we assume two demes and

$$s_1 > 0 \text{ and } s_2 < 0, \quad (6.5)$$

we obtain $a_1 > 0 > a_2$ and $b_1 > 0 > b_2$, and Corollary 5.6 applies, where the c_i^- and c_i^+ are calculated from (5.12). Therefore, on \mathcal{I} a globally attracting line of internal equilibria exists whenever $c_4^- < c < c_1^+$.

In terms of the model of Section 4, absence of genotype-environment interaction can be defined by requiring that phenotypes (fitnesses) in the different demes differ only by a linear transformation, i.e., for every α and β there are parameters $\mu_{\alpha\beta}$ and $\nu_{\alpha\beta}$, such that $w_{ij,\alpha} = \mu_{\alpha\beta} + \nu_{\alpha\beta} w_{ij,\beta}$. Then it is an easy exercise to show that with $w_{ij,\alpha}$ given by (4.2a), $\vartheta_\alpha = \vartheta_\beta$, $\sigma_\alpha = \sigma_\beta$, and $a_\alpha/a_\beta = b_\alpha/b_\beta$ hold; hence we have DIDID at both loci and $\theta = 0$.

Let us assume that there is no $G \times E$ interaction and an internal line of equilibria exists. We investigate the effects of small perturbations, i.e., the introduction of weak $G \times E$ interaction. In the unperturbed state, indicated by the subscript 0, we have $\theta_0 = 0$ and $\theta_0^* = \vartheta_0 \theta_0 = 0$. If one of the allelic effects ($a_{\alpha,0}, b_{\alpha,0}$) is perturbed, then $\theta \neq 0$, hence $|\theta^*| = |\vartheta_0| |\theta| \leq |\theta|$ and, by Theorem 4.7, an internal equilibrium can not exist. If instead the degree of dominance changes in one of the demes, e.g., $\vartheta_1 \neq \vartheta_2 = \vartheta_0$, then we still have $\theta = \theta_0 = 0$, but $\theta^* \neq 0$. Hence, there will exist an isolated internal equilibrium. However, this equilibrium may be asymptotically stable or unstable, depending on the choice of ϑ_1 and ϑ_2 .

In summary, absence of genotype-environment interaction leads to nongeneric dynamic and equilibrium properties in the Levene model: if a full polymorphism exists, then it is a line of (internal) equilibria that is stable and globally attracting (provided linkage disequilibria decay also in this case). The smallest deviation from $G \times E$ interaction may lead to complete loss of an internal equilibrium, or to an unstable or an asymptotically stable internal equilibrium point.

7. Numerical results

So far, we have obtained sufficient conditions for the existence and stability of a fully polymorphic equilibrium. Here, we complement them by numerical results about the volume of the parameters space that maintains an internal equilibrium or a stable

internal equilibrium. They were obtained by solving (4.6) numerically for internal equilibria, essentially by using the NSolve routine of *Mathematica*. Stability of internal equilibria was investigated by iterating (4.6) for 20 000 generations from 20 uniformly randomly drawn initial conditions in \mathcal{I} . This was sufficient for achieving convergence to equilibrium. Equilibria were classified as internal if both alleles at both loci had a frequency of at least 0.01.

As before, we assumed intermediate dominance and directional selection in opposite directions, i.e., (4.2) and (4.7). Three main scenarios were studied:

W. The weak-selection limit as defined in Section 4.4.

S1. Weak selection: $|a_\alpha| \leq 0.1$ and $|b_\alpha| \leq 0.1$ ($\alpha = 1, 2$).

S2. Strong selection: $|a_\alpha| \leq 0.5$ and $|b_\alpha| \leq 0.5$ ($\alpha = 1, 2$).

In each case, the following subscenarios were considered:

ad. Arbitrary intermediate dominance: (4.2c).

sl. Sublinear fitness contributions: $0 \leq \vartheta_1, \sigma_1 \leq 1$ and $-1 \leq \vartheta_2, \sigma_2 \leq 0$.

ss. The degree of dominance has the same sign in both demes: $\text{sign } \vartheta_1 = \text{sign } \vartheta_2$ and $\text{sign } \sigma_1 = \text{sign } \sigma_2$.

a|n. Arbitrary dominance at the first locus, no dominance at the second locus: $|\vartheta_\alpha| \leq 1$ ($\alpha = 1, 2$) and $\sigma_1 = \sigma_2 = 0$.

s|n. Sublinear fitness contributions of the first locus, no dominance at the second locus: $0 \leq \vartheta_1 \leq 1$, $-1 \leq \vartheta_2 \leq 0$, and $\sigma_1 = \sigma_2 = 0$.

nge. Absence of genotype-environment interaction: $\theta = 0$, $\vartheta_1 = \vartheta_2 = \vartheta$, $\sigma_1 = \sigma_2 = \sigma$.

For each scenario, 10 000 parameter combinations were drawn randomly from a uniform distribution subject to the above constraints. Table 1 reports the proportions of parameter combinations with at least one internal equilibrium (IE), with exactly two internal equilibria (TIE), and with a stable internal equilibrium (SIE).

For the subscenarios a|n and s|n, the proportion of parameter sets yielding an internal equilibrium are calculated from (4.22); for nge, this proportion is calculated as the length of the interval in (5.15). In subscenario nge, the internal equilibrium is in fact a line of equilibria (Theorem 5.5). For sublinear fitness contributions (scenarios sl, s|n, nge), Theorem 2.4 shows that every internal equilibrium is globally asymptotically stable, as confirmed by numerical iteration.

It is instructive to compare the weak and strong selection scenarios, S1 and S2, with the weak-selection limit from Section 4.4 (Table 1). For the latter, the proportion of internal (stable) equilibria can be calculated directly from the formulas in Section 4.4 by sampling the parameters from a uniform distribution and checking when a (stable) internal equilibrium results. For the three scenarios W.a|n, W.a|n, and W.nge, no two-locus polymorphism occurs because at the second locus average overdominance or underdominance is impossible.

As expected from single-locus theory (Section 3), stronger selection as well as sublinear fitness contributions facilitate the maintenance of polymorphism. In fact, although sublinear fitness contributions comprise only 1/16 of the full parameter space, i.e., of scenario ad, they contribute between 32% (for strong selection, S2) and 47% (for the weak-selection limit, W) of all stable, fully polymorphic equilibria. If the same allele is dominant in both niches but the degree of dominance varies (scenario ss), two-locus polymorphism is possible but rare. In the limiting case of DIDID at both loci, Proposition 3.18 in Nagylaki (2009b) shows that, generically, no two-locus polymorphism exists (therefore, this case is not included in the table). Particularly conspicuous is the disproportionate increase of (stable) internal equilibria with increasing selection strength for the nongeneric case of no genotype-environment interaction.

Table 1

Proportion of parameter combinations with at least one internal equilibrium (IE), with exactly two internal equilibria (TIE), and with an asymptotically stable internal equilibrium (SIE). Data from three main scenarios, the weak-selection limit (W), weak selection (S1), and strong selection (S2), are reported. Each is subdivided into six subscenarios, as described in the main text.

Scenario	IE	TIE	SIE
W.ad	0.118	0	0.029
W.sl	0.219	0	0.219
W.ss	0.047	0	0.013
W.a n	0	0	0
W.s n	0	0	0
W.ngc	0	0	0
S1.ad	0.119	0.001	0.037
S1.sl	0.256	0	0.256
S1.ss	0.049	0.001	0.018
S1.a n	0.017	0	0.009
S1.s n	0.023	0	0.023
S1.ngc	0.090	0	0.090
S2.ad	0.159	0.006	0.071
S2.sl	0.365	0	0.365
S2.ss	0.092	0.007	0.047
S2.a n	0.087	0	0.037
S2.s n	0.106	0	0.106
S2.ngc	0.427	0	0.427

The above random search never produced more than two internal equilibria. For extreme parameter combinations, three internal equilibria were found by a method inspired by Karlin (1977, p. 380). For parameter combinations admitting more than one internal equilibrium, all internal equilibria were unstable. In the above table, more than 99% of stable equilibria are globally stable in the sense that all 20 trajectories converged to the same equilibrium.

8. Discussion

The potential of the Levene model to maintain genetic polymorphism at a single locus in the absence of overdominance and of underdominance is relatively well studied (see Introduction and Section 3). For multiple loci little is known.

A general theorem for arbitrary migration establishes that if selection is sufficiently weak relative to migration and recombination, then at a stable equilibrium arbitrarily many loci can be maintained polymorphic for an open set of parameters that display no or weak epistasis and intermediate dominance (Bürger, 2009b, Theorem 2.2). Two demes are sufficient. This result applies also to the Levene model (Bürger, 2009b, Remark 2.4). Although it establishes structural stability, this results says nothing about the ‘likelihood’ of such a multilocus polymorphism. However, the conditions used in the constructive proof seem quite restrictive, especially if more than two alleles per locus shall be maintained.

The first systematic study of the multilocus Levene model was performed by Nagylaki (2009b). He derived important general results about the dynamics and provided necessary conditions and sufficient conditions for the maintenance of (stable) internal equilibria. We used some of these results to analyze the two-locus two-allele case with two demes. The detailed analysis here is made possible by the fact that Nagylaki proved global convergence to linkage equilibrium for two (multiallelic) loci. Hence, it is sufficient to study the dynamical and equilibrium behavior on the linkage-equilibrium manifold (Theorem 2.4).

Throughout, we assumed intermediate dominance and absence of epistasis because under these conditions no polymorphism is possible in a panmictic population (Bürger, 2009b). These conditions are equivalent to nonepistatic directional selection in the two demes. The most interesting case occurs if selection acts in opposite directions in the two demes. A useful sufficient condition for

the existence of a unique, globally asymptotically stable equilibrium is that fitness contributions of each locus and in every deme are sublinear (Theorem 2.4). This means that there is either no dominance or in every deme the allele with higher homozygous fitness is partially or completely dominant. For a relatively big subset of such parameter combinations, the unique stable equilibrium is fully polymorphic.

If there is no dominance at one locus, then a complete equilibrium analysis can be performed. The internal equilibrium and the conditions for its existence are determined explicitly in Theorem 4.3. Global asymptotic stability follows for sublinear fitness contributions. Theorem 4.7 extends this to the case when at one locus the degree of dominance is intermediate and deme independent (DIDID). In either case, generically, internal equilibria are unique and exist for an open subset of parameters. They persist under arbitrary but small perturbations of the parameters (Theorem 4.8).

A case of special interest arises if dominance is absent at both loci, or, more generally, if there is DIDID (cf. Nagylaki, 2009b). Then Theorems 5.3 and 5.5, and their corollaries, show that an internal equilibrium can exist only under the nongeneric symmetry assumption $\theta = 0$. If this equilibrium exists, then it is not an isolated point but a straight line of equilibria. Interestingly, this occurs if and only if there is no genotype-environment interaction, as is discussed in more detail in Section 6. In particular, slight perturbations from absence of $G \times E$ interaction can destroy polymorphism.

The numerical investigation in Section 7 quantifies the ‘likelihood’ of maintaining a fully polymorphic equilibrium, and how this depends on the dominance relations and the strength of selection. The results clearly support the notion that stronger selection facilitates polymorphism. Sublinear fitness contributions are particularly favorable for polymorphism since even in the weak-selection limit, more than 20% of all such parameter combinations yield a globally stable internal equilibrium; for strong selection, this fraction increases to about 37%. Although sublinear fitnesses comprise only 1/16 of the full parameter space, they contribute between 32% (strong selection) and 47% (weak-selection limit) of all stable, fully polymorphic equilibria. In contrast, if the same allele is dominant in both niches, and the degree of dominance varies, stable and fully polymorphic equilibria are possible but rare (less than 5%). In the limiting case of DIDID, generically, two-locus polymorphism cannot be maintained at all (see above). If there is no dominance at one locus, then the potential for maintaining both loci polymorphic is also reduced compared to arbitrary dominance.

Because in the Levene model gene flow is so high that population structure is prohibited, it appears much less favorable for the maintenance of genetic variation than other migration patterns that allow for population differentiation. Nevertheless, the present results show that, unless selection is very weak, the maintenance of a stable, fully polymorphic equilibrium in this two-locus Levene model is not unlikely. They highlight the importance of spatially varying dominance relations, which constitute one form of $G \times E$ interaction, in maintaining polymorphism. Interestingly, it has already been shown in the context of the Levene model that populations may evolve through sequential random substitutions into a parameter region where polymorphism is maintained (Kisdi and Geritz, 1999; van Doorn and Dieckmann, 2006; Star et al., 2007).

A number of questions for future study arise from this work and that of Nagylaki (2009b). For instance, it will be of interest to explore if the nongeneric equilibrium structure in the absence of $G \times E$ interaction is caused by the assumptions about selection, is a peculiarity of the Levene model, or else. A number of further unresolved issues revolves about the role of the number of demes in maintaining polymorphism with multiple alleles or multiple loci. To what extent does a greater number of demes facilitate

maintenance of polymorphism? Since in the Levene model there is no population structure, future work should extend this study to more general migration patterns that admit population differentiation. The analysis of such models is complicated by the fact that then convergence to linkage equilibrium will, in general, not occur. In some situations, however, quasi-linkage equilibrium can be expected (Bürger, 2009a,b) and this can simplify the analysis greatly.

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References

- Bürger, R., 2009a. Multilocus selection in subdivided populations I. Convergence properties for weak or strong migration. *J. Math. Biol.* 58, 939–978.
- Bürger, R., 2009b. Multilocus selection in subdivided populations II. Maintenance of polymorphism and weak or strong migration. *J. Math. Biol.* 58, 979–997.
- Cannings, C., 1971. Natural selection at a multiallelic autosomal locus with multiple niches. *J. Genetics* 60, 255–259.
- Christiansen, F.B., Feldman, M., 1975. Subdivided populations: A review of the one- and two-locus deterministic theory. *Theor. Popul. Biol.* 7, 13–38.
- Karlin, S., 1977. Gene frequency patterns in the Levene subdivided population model. *Theor. Popul. Biol.* 11, 356–385.
- Kisdi, E., Geritz, A.H., 1999. Adaptive dynamics in allele space: Evolution of genetic polymorphism by small mutations in a heterogeneous environment. *Evolution* 53, 993–1008.
- LaSalle, J.P., 1977. Stability theory for difference equations. In: Hale, J.K. (Ed.), *Studies in Ordinary Differential Equations*. In: *Studies in Mathematics*, vol. 14. Mathematical Association of America, Washington, DC, pp. 1–31.
- Levene, H., 1953. Genetic equilibrium when more than one ecological niche is available. *Amer. Natur.* 87, 331–333.
- Li, C.C., 1955. The stability of an equilibrium and the average fitness of a population. *Amer. Natur.* 89, 281–295.
- Li, W.-H., Nei, M., 1974. Stable linkage disequilibrium without epistasis in subdivided populations. *Theor. Popul. Biol.* 6, 173–183.
- Nagylaki, T., 1992. *Introduction to Theoretical Population Genetics*. Springer, Berlin.
- Nagylaki, T., 2009a. Polymorphism in multiallelic migration-selection models with dominance. *Theor. Popul. Biol.* 75, 239–259.
- Nagylaki, T., 2009b. Evolution under the multilocus Levene model without epistasis. *Theor. Popul. Biol.* 76, 197–213.
- Nagylaki, T., Lou, Y., 2001. Patterns of multiallelic polymorphism maintained by migration and selection. *Theor. Popul. Biol.* 59, 297–313.
- Nagylaki, T., Lou, Y., 2008. The dynamics of migration-selection models. In: Friedman, A. (Ed.), *Tutorials in Mathematical Biosciences IV*. In: *Lect. Notes Math.*, vol. 1922. Springer, Berlin Heidelberg New York, pp. 119–172.
- Prout, T., 1968. Sufficient conditions for multiple niche polymorphism. *Amer. Natur.* 102, 493–496.
- Star, B., Stoffels, R.J., Spencer, H.G., 2007. Evolution of fitnesses and allele frequencies in a population with spatially heterogeneous selection pressures. *Genetics* 177, 1743–1751.
- Strobeck, C., 1979. Haploid selection with n alleles in m niches. *Amer. Natur.* 113, 439–444.
- van Doorn, G.S., Dieckmann, U., 2006. The long-term evolution of multilocus traits under frequency-dependent disruptive selection. *Evolution* 60, 2226–2238.
- Wiehe, T., Slatkin, M., 1998. Epistatic selection in a multi-locus Levene model and implications for linkage disequilibrium. *Theor. Popul. Biol.* 53, 75–84.