Convergence of multilocus systems under weak epistasis or weak selection

Thomas Nagylaki[1], Josef Hofbauer[2], Pavol Brunovský[3]

[1] Department of Ecology and Evolution, The University of Chicago,
1101 East 57th Street, Chicago, Illinois 60637-1573, USA
[2] Institute of Mathematics, University Vienna, Strudlhofgasse 4, A-1090 Wien, Austria
[3] Institute of Applied Mathematics, Comenius University, Mlýnska Dolina,
84215 Bratislava, Slovakia

Dedicated to the memory of Charles Conley

Abstract. The convergence of multilocus systems under viability selection with constant fitnesses is investigated. Generations are discrete and nonoverlapping; the monoecious population mates at random. The number of multiallelic loci, the linkage map, dominance, and epistasis are arbitrary. It is proved that if epistasis or selection is sufficiently weak (and satisfies a certain nondegeneracy assumption whose genericity we establish), then there is always convergence to some equilibrium *point*. In particular, cycling cannot occur. The behavior of the mean fitness and some other aspects of the dynamics are also analyzed.

1 Introduction

In a recent paper (Nagylaki 1993), the evolution of multilocus systems under selection was discussed and the case of weak selection was analyzed. In this paper, we shall focus on one interesting aspect of multilocus dynamics: the (non)existence of cycling. The existence of stable cycling in two-locus models of selection was established for continuous time in Akin (1979, 1982, 1983, 1987) and Hofbauer (1985), and for discrete time in Hastings (1981) and Hofbauer and Iooss (1984). Here, we shall prove for an arbitrary number of loci that if epistasis or

selection is sufficiently weak (and satisfies a certain nondegeneracy assumption whose genericity we establish), then there is always convergence to some equilibrium *point*. For weak epistasis, the proof is based on perturbation results for the set of chain-recurrent points, which we show to coincide with the set of equilibria. In the case of weak selection, the proof comprises two steps: The theory of normally hyperbolic manifolds implies the existence of a *quasi-linkage-equilibrium manifold* that attracts all solutions of the system; and on that invariant manifold, the dynamics is a small perturbation of a system that possesses a Lyapunov function, i.e., the mean fitness increases 'almost' everywhere on that manifold.

We assume that generations are discrete and nonoverlapping; the monoecious population mates at random. The number of multiallellic loci, the linkage map, dominance, and epistasis are arbitrary. There are no fertility differences, and the viabilities are constant. Essentially, we follow Nagylaki's (1993) description and notation.

Suppose there are n loci and m_k alleles $A_{i_k}^{(k)}$ (with $i_k = 1, \ldots, m_k$) at locus k. We use the multi-index $i = (i_1, \ldots, i_n)$ as an abbreviation for the gamete $A_{i_1}^{(1)} A_{i_2}^{(2)} \ldots A_{i_n}^{(n)}$, whose frequency we denote by p_i. Collectively, these form the vector $\boldsymbol{p}$, a probability vector in the simplex $S_{m_1 \cdots m_n}$. The frequency of $A_{i_k}^{(k)}$ in gametes is

$$p_{i_k}^{(k)} = \sum_i{}^{(k)} p_i, \tag{1.1}$$

where the sum runs over all multi-indices i with the k-th component fixed as i_k. Let $\boldsymbol{\rho} = (\boldsymbol{p}^{(1)}, \boldsymbol{p}^{(2)}, \ldots, \boldsymbol{p}^{(n)}) \in S_{m_1} \times \cdots \times S_{m_n}$ represent the $(m_1 + m_2 + \cdots + m_n)$-dimensional vector of all the gene frequencies.

We signify the fitness of genotype ij by W_{ij} ($W_{ij} = W_{ji}$), which we assume to be nonnegative and constant; the fitness of gamete i by

$$W_i(\boldsymbol{p}) = \sum_j W_{ij} p_j; \tag{1.2}$$

and the mean fitness of the population by

$$\bar{W}(\boldsymbol{p}) = \sum_{i,j} W_{ij} p_i p_j. \tag{1.3}$$

Let I, J be a nontrivial decomposition of the set of loci $N = \{1, 2, \ldots, n\}$, i.e., $I \cup J = N$ and $I \cap J = \emptyset$, normalized by $1 \in I$. We designate by c_I the probability of reassociation of the genes at the loci in I, inherited from one parent, with the genes at the loci in J, inherited from the other.

The gametic frequencies in the next generation are determined by the recurrence relation

$$p_i' = p_i \frac{W_i}{\bar{W}} - D_i, \tag{1.4}$$

where

$$D_i = \frac{1}{\bar{W}} \sum_j \sum_I c_I (W_{ij} p_i p_j - W_{i_I j_J, j_I i_J} p_{i_I j_J} p_{j_I i_J}) \tag{1.5}$$

represents a measure of the linkage disequilibrium in gamete i. (Here, $i_I j_J$ signifies the vector with k-th component i_k if $k \in I$ and j_k if $k \in J$.)

To demonstrate that the simplex $S_{m_1 \cdots m_n}$ is forward invariant, sum (1.4) over i and use (1.2), (1.3), and (1.5). This yields immediately

$$\sum_i p_i' = 1. \tag{1.6}$$

Let

$$c_{\text{tot}} = \sum_I c_I \tag{1.7}$$

denote the total recombination frequency. Then

$$\gamma_N = 1 - c_{\text{tot}} \tag{1.8}$$

is the probability that there is no recombination. Invoking (1.2), (1.5), (1.7), and (1.8), we cast (1.4) into the form

$$p_i' = \gamma_N p_i \frac{W_i}{\bar{W}} + \frac{1}{\bar{W}} \sum_j \sum_I c_I W_{i_I j_J, j_I i_J} p_{i_I j_J} p_{j_I i_J}. \tag{1.9}$$

Therefore, if $p_i \geqq 0$ for every i, then $p_i' \geqq 0$ for every i. If all the fitnesses are positive ($W_{ij} > 0$ for every i and j), then the interior of the simplex is also forward invariant: if $p_i > 0$ for every i, then $p_i' > 0$ for every i.

The gene frequencies in the next generation are

$$p_{i_k}^{(k)'} = p_{i_k}^{(k)} W_{i_k}^{(k)} / \bar{W}, \tag{1.10}$$

where the fitness $W_{i_k}^{(k)}$ of the allele $A_{i_k}^{(k)}$ is defined by

$$p_{i_k}^{(k)} W_{i_k}^{(k)} = \sum_i^{(k)} p_i W_i. \tag{1.11}$$

The *linkage-equilibrium manifold* (also called the Wright manifold; see Akin 1979; Shahshahani 1979) is defined as

$$\Lambda_0 = \{ \boldsymbol{p} \colon p_i = p_{i_1}^{(1)} p_{i_2}^{(2)} \ldots p_{i_n}^{(n)} \text{ for every } i \}. \tag{1.12}$$

Linkage equilibrium is sometimes called Robbins equilibrium. This manifold is diffeomorphic to $S_{m_1} \times \cdots \times S_{m_n}$. A point $\boldsymbol{p}$ on Λ_0 is

uniquely determined by the vector of gene frequencies $\boldsymbol{\rho}$. If

$$W_{ij} = W_{i,j,,j,i,} \tag{1.13}$$

for every i, j, and I, we say that there is no position effect. In this case, $D_i = 0$ for every i for every $\boldsymbol{p} \in \Lambda_0$, so

$$\Lambda_0 \subseteq \{\boldsymbol{p}: \boldsymbol{D} = \boldsymbol{0}\} \equiv \Delta_0, \tag{1.14}$$

where $\boldsymbol{D}$ is the vector with components D_i.

Let $c_{k\ell}$ designate the recombination frequency between loci k and ℓ, ordered so that $k < \ell$. To express $c_{k\ell}$ in terms of the linkage map $\{c_I\}$, define the set of sets of loci

$$N_{k\ell} = \{I: k \in I \text{ and } \ell \in J, \text{ or } k \in J \text{ and } \ell \in I\}. \tag{1.15}$$

Then we have

$$c_{k\ell} = \sum_{I:I \in N_{k\ell}} c_I. \tag{1.16}$$

An important parameter is the smallest two-locus recombination frequency

$$c_{\min} = \min c_{k\ell}, \tag{1.17}$$

in which the minimum is over every k, $\ell \in N$ such that $k < \ell$. If $c_{k\ell} = 0$ for some k and ℓ, then we combine loci k and ℓ. Therefore, without loss of generality, we assume henceforth that $c_{\min} > 0$.

If there is no selection, we may choose $W_{ij} = 1$ for every i and j. Then not only does (1.13) hold trivially, but also $\Lambda_0 = \Delta_0$. To see this, note first that, by (1.4), if $\boldsymbol{p} \in \Delta_0$, then $\boldsymbol{p}$ is an equilibrium. Consequently, $\boldsymbol{p} \in \Lambda_0$ (Lyubich 1992, Theorem 6.3.1), whence $\Delta_0 \subseteq \Lambda_0$. Because of (1.14), we conclude that $\Lambda_0 = \Delta_0$.

2 Weak epistasis

Weak epistasis means that the fitness scheme has the form

$$W_{ij} = \sum_{k=1}^{n} \alpha_{i_k J_k}^{(k)} + \varepsilon r_{ij}, \tag{2.1}$$

where ε, the strength of epistasis, is sufficiently small. We assume $\alpha_{i_k J_k}^{(k)} > 0$. See Hastings (1985, 1986) for some investigations under this hypothesis.

If $\varepsilon = 0$ in (2.1), then there is no (additive) epistasis. We start with a review and analysis of that case. Note that (1.13) and therefore (1.14)

hold. The mean fitness is the sum of its one-locus contributions:

$$\bar{W} = \sum_{i,j} \sum_k \alpha^{(k)}_{i_k j_k} p_i p_j = \sum_k \sum_{i_k, j_k} \alpha^{(k)}_{i_k j_k} p^{(k)}_{i_k} p^{(k)}_{j_k} = \sum_k \bar{\alpha}^{(k)}, \qquad (2.2)$$

where

$$\bar{\alpha}^{(k)} = \sum_{i_k, j_k} \alpha^{(k)}_{i_k j_k} p^{(k)}_{i_k} p^{(k)}_{j_k} \qquad (2.3)$$

denotes the contribution of locus k to the mean fitness.

Lemma 2.1. *In the case of no epistasis, a point p is an equilibrium point of (1.4) if and only if it is both a selection equilibrium for each locus and it is in linkage equilibrium.*

Proof. If p is an equilibrium, then $p \in \Lambda_0$ (Lyubich 1992, Theorem 9.6.13). We show that on Λ_0 equilibrium is equivalent to

$$p^{(k)}_{i_k} = 0 \quad \text{or} \quad \alpha^{(k)}_{i_k} = \bar{\alpha}^{(k)} \qquad (2.4)$$

for every k and i_k, where

$$\alpha^{(k)}_{i_k} = \sum_{j_k} \alpha^{(k)}_{i_k j_k} p^{(k)}_{j_k}. \qquad (2.5)$$

From Nagylaki (1989a, Eq. 23) we have

$$p^{(k)}_{i_k} W^{(k)}_{i_k} = \alpha^{(k)}_{i_k} p^{(k)}_{i_k} + \sum_{l:l \neq k} \sum_{i_l} \alpha^{(l)}_{i_l} p^{(kl)}_{i_k i_l}, \qquad (2.6)$$

where $p^{(kl)}_{i_k i_l}$ is the frequency of the gamete $A^{(k)}_{i_k} A^{(l)}_{i_l}$. Since $p \in \Lambda_0$, therefore $p^{(kl)}_{i_k i_l} = p^{(k)}_{i_k} p^{(l)}_{i_l}$, so (2.6) becomes

$$W^{(k)}_{i_k} = \alpha^{(k)}_{i_k} + \sum_{l:\, l \neq k} \bar{\alpha}^{(l)} \quad \text{if } p^{(k)}_{i_k} \neq 0. \qquad (2.7)$$

Since the gene frequencies do not change at equilibrium, from (1.10) we obtain (Ewens 1976; Ewens and Thomson 1977; Nagylaki 1989a, Eq. 16)

$$p^{(k)}_{i_k} = 0 \quad \text{or} \quad W^{(k)}_{i_k} = \bar{W}. \qquad (2.8)$$

From (2.2) and (2.7) we see that on Λ_0 (2.8) is equivalent to (2.4). $\quad\square$

Ewens (1969a,b) has demonstrated that the mean fitness $\bar{W}$ is nondecreasing if there is no epistasis. (The reason is that, by (2.2) and (2.3), $\bar{W}$ depends only on the gene-frequency vector ρ. Given the gametic frequencies p, the gene frequencies ρ' in the next generation do not depend on the recombination frequencies c_I. Hence, we can compute $\bar{W}'$ as if there were no recombination.) Therefore, $\Delta\bar{W} \equiv \bar{W}' - \bar{W} \geqq 0$, with equality if and only if

$$p_i(W_i - \bar{W}) = 0 \quad \text{for every } i \qquad (2.9)$$

(Lyubich 1992, Theorem 9.5.4). Let $\mathscr{F}$ denote the set of points $\boldsymbol{p}$ that satisfy (2.9). At these points, the selection part of (1.4) is in equilibrium, and the mean fitness is the same in the next generation.

Hence (by what is sometimes called the LaSalle invariance principle, Theorem C(a), stated below), every limit point of a trajectory of (1.4) is contained in $\mathscr{F}$. Using properties of the entropy (see (2.21) and (2.22) below), Kun and Lyubich (1979, 1980; see also Lyubich 1992) show further that every limit point is an equilibrium. Our objective is to extend this statement to the case of weak epistasis. However, limit sets need not change continuously under small perturbations of the dynamics: they can 'explode'. What has good behavior under perturbations is the set of chain-recurrent[1] points, introduced by Conley (1978), which contains the limit sets of all orbits. Therefore, we have to strengthen the convergence result of Kun and Lyubich for $\varepsilon = 0$ to a statement on the chain-recurrent set (see Lemma 2.2 below).

Before doing so, we discuss the structure of the set $\mathscr{F}$ in more detail. In general, points in $\mathscr{F}$ are not isolated, because $\det W = 0$ for nonepistatic selection. This follows at once from the observation that (Lyubich 1992, p. 332)

$$W_{ij} + W_{kj} = W_{i_k k_j, j} + W_{k_i i_j, j}, \qquad (2.10)$$

i.e., the sum of the row vectors on the left equals that of those on the right. In fact, either (2.9) has no internal ($p_i > 0$ for every i) solution or it has uncountably many (Hughes and Seneta 1975).

From (1.2), (2.1), (1.1), and (2.5) we obtain

$$W_i = \sum_k \alpha_{i_k}^{(k)}; \qquad (2.11)$$

combining this with (2.2) yields

$$W_i - \bar{W} = \sum_k (\alpha_{i_k}^{(k)} - \bar{\alpha}^{(k)}). \qquad (2.12)$$

Since $p_i \leqq p_{i_k}^{(k)}$ for every i and k, we infer from (2.12) that (2.4) implies (2.9), i.e., $\boldsymbol{p} \in \mathscr{F}$. Thus, if each locus is at equilibrium under selection, then $\Delta p_{i_k}^{(k)} = 0$ by (1.10) and (1.11), and $\Delta \bar{W} = 0$. Of course, (2.9) does not imply that the gametic frequencies $\boldsymbol{p}$ are at equilibrium; this holds only if additionally $\boldsymbol{p} \in \Lambda_0$.

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[1] Let X be a compact set with a metric d and let $f: X \to X$ be a continuous map. A point $x \in X$ is called *chain recurrent* (with respect to f) if, for every $\delta > 0$, there exists a finite sequence $x_0 = x, x_1, \ldots, x_{r-1}, x_r = x$ (often called a δ-pseudo-orbit) such that $d(f(x_m), x_{m+1}) < \delta$ for $m = 0, 1, \ldots, r - 1$.

We proceed to discuss the forward-invariance properties of $\mathscr{F}$. By Lemma 2.1 and the last paragraph, for every equilibrium $\hat{p}$, the set

$$\mathscr{G}(\hat{\rho}) = \{p: \rho = \hat{\rho}\} \tag{2.13}$$

satisfies $\mathscr{G}(\hat{\rho}) \subseteq \mathscr{F}$ and is forward invariant. Therefore,

$$\Gamma \equiv \bigcup_{\hat{\rho}} \mathscr{G}(\hat{\rho}) \subseteq \mathscr{F}, \tag{2.14}$$

and Γ is forward invariant. Since, by (2.2) and (2.3), the mean fitness depends only on ρ, it is constant on each set $\mathscr{G}(\hat{\rho})$.

Next, we show that the subset of $\mathscr{F}$ in the interior of the simplex,

$$\mathscr{F}^* \equiv \mathscr{F} \cap \operatorname{int} S_{m_1 \cdots m_n} = \{p: p \in \mathscr{F} \text{ and } p_i > 0 \text{ for every } i\}, \tag{2.15}$$

is forward invariant. For $p \in \mathscr{F}$, from (1.10), (1.11), and (2.9) we conclude that

$$\rho' = \rho. \tag{2.16}$$

Then (2.11), (2.5), (2.2), and (2.3) give

$$W_i' = W_i \quad \text{and} \quad \bar{W}' = \bar{W} \tag{2.17}$$

for every i. But (2.9) informs us that $W_i = \bar{W}$ for every i if $p \in \mathscr{F}^*$. Consequently, $W_i' = \bar{W}'$ for every i, so $p' \in \mathscr{F}$. In Sect. 1, we proved that $\operatorname{int} S_{m_1 \cdots m_n}$ is forward invariant, which demonstrates that $p' \in \mathscr{F}^*$.

We now establish that

$$\mathscr{F}^* \subseteq \Gamma. \tag{2.18}$$

Suppose $p^* \in \mathscr{F}^*$ and consider the solution $p(t) \in \mathscr{F}^*$ ($t = 0,1,2,\dots$) of (1.4) such that $p(0) = p^*$. From (2.16) we infer

$$\lim_{t \to \infty} \rho(t) = \rho^*, \tag{2.19}$$

and hence ρ^* must satisfy the gene-frequency equilibrium condition (2.4), which proves that

$$p^* \in \mathscr{G}(\rho^*) \subseteq \Gamma. \tag{2.20}$$

In the highly symmetric example in Remark 2.4 below, $\mathscr{F}$ is forward invariant. Together with the forward invariance of Γ, this might suggest that $\mathscr{F}$ is always forward invariant. The example in Remark 2.5 disposes of this idea.

Lemma 2.2. *In the case of no epistasis, the only chain-recurrent points of (1.4) are its equilibria.*

Proof. On $\mathscr{F}$, the mean fitness $\bar{W}$ takes only finitely many values. This follows from the well-known facts that for one-locus systems, the equilibria are either isolated or a part of linear manifolds, and that the mean fitness is constant along such continua of equilibria (see, e.g., Lyubich 1992, Sect. 9.1).

By Theorem C(b),[2] this implies that not only the ω-limit set of each orbit, but even each chain-recurrent point is contained in $\mathscr{F}$.

It remains to consider the dynamics on $\mathscr{F}$. From (2.16) we have $\rho' = \rho$ for $p \in \mathscr{F}$. This implies that Lemma 9.6.8 and Theorem 9.6.10 of Lyubich (1992) on the behavior of the entropy $H(p) = -\sum_i p_i \log p_i$ remain valid for $p \in \mathscr{F}$:

$$\text{if } p \in \mathscr{F}, \quad \text{then } H(p') \geqq H(p), \tag{2.21}$$

and equality holds if and only if p is an equilibrium point of (1.4), i.e.,

$$\text{if } p \in \mathscr{F}, \quad \text{then } H(p') = H(p) \Leftrightarrow p \in \Lambda_0. \tag{2.22}$$

To conclude the proof, it suffices to show that the maximal invariant set in $\mathscr{F}$ (which obviously contains the set of chain-recurrent points) coincides with the set of equilibria $\mathscr{F} \cap \Lambda_0$.[3] Suppose it does not. Then there exists a full orbit $\{p(t): t \in \mathbf{Z}\}$ such that $p(t) \in \mathscr{F}$, $p(t)$ is mapped under (1.4) to $p(t+1)$, and $H(p(t+1)) > H(p(t))$ for each integer $t \leqq 0$. Consider α-limit and ω-limit points p_- and p_+ of this orbit. Since $\mathscr{F}$ is closed, we have $p_-, p_+ \in \mathscr{F}$, and from Theorem C(a) it follows that $H(p'_-) = H(p_-)$ and $H(p'_+) = H(p_+)$. By (2.22), both p_- and p_+ are equilibria, and are therefore contained in Λ_0. By (2.16), the gene frequencies are constant along the orbit, including the limiting points, so we conclude that $p_- = p_+$, which contradicts the inequalities $H(p_-) < H(p(0)) < H(p_+)$. $\qquad\square$

Theorem 2.3. *If for $\varepsilon = 0$, each equilibrium of (1.4) is hyperbolic, then for sufficiently small ε, each trajectory of (1.4) converges to an equilibrium point.*

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[2] **Theorem C.** *Let the continuous function $V: X \to \mathbb{R}$ be a Lyapunov function for the map $f: X \to X$, i.e., $V(f(x)) \geq V(x)$ for all $x \in X$. Consider the set $\mathscr{F} = \{x: V(f(x)) = V(x)\}$.*

(a) *Then $\mathscr{F}$ contains all ω-limit points and α-limit points of orbits in X.*

(b) *If V takes only finitely many values on the set $\mathscr{F}$, then every chain–recurrent point is contained in $\mathscr{F}$.*

Part (a) is due to LaSalle; part (b) is a special case of Conley (1978, Theorem II.6.4.C), or in discrete time rather of Akin (1993, Theorem 3.16).

[3] If there are only finitely many equilibria, then we can again use Theorem C(b), now with the Lyapunov function H.

Proof. By Lemma 2.2, for $\varepsilon = 0$, the chain-recurrent set consists of finitely many hyperbolic equilibria. This property is robust against small C^1 perturbations of the dynamics (see, e.g., Akin 1993, p. 244). Indeed, as an immediate consequence of the definition of chain recurrence, it follows that the chain-recurrent set of (1.4) changes in an upper semicontinuous way with ε. In particular, the chain-recurrent set for $\varepsilon > 0$ is contained in the union of the δ-neighborhoods of the equilibria for $\varepsilon = 0$, with $\delta \to 0$ for $\varepsilon \to 0$. By the implicit function theorem and the openness of hyperbolicity (Hartman–Grobman theorem), if $\varepsilon > 0$ is small, then the maximal invariant sets in those neighborhoods are hyperbolic equilibria. Hence, for small ε, the chain-recurrent set consists only of finitely many equilibria, which implies convergence of all trajetories.   □

Remark 2.1. Lemma 2.2 implies that each orbit has its ω-limit in Λ_0. But it says more, viz., that the orbits can be of three types only:

  (i) equilibria;
  (ii) complete orbits $p(t)$, defined for all times $-\infty < t < \infty$;
  (iii) incomplete orbits $p(t)$, which cannot be defined for all times because some of their points have no pre-image $p(t - 1)$ with all non-negative components.

From Theorem C(b) and the proof of Lemma 2.2, it follows that orbits of type (ii) converge to equilibria for both $t \to \infty$ and $t \to -\infty$, and that the mean fitnesses at those two equilibria are different. In particular, homoclinic orbits are excluded. An orbit of type (ii) exists if (1.4) admits at least one unstable equilibrium.

Remark 2.2. In Appendix A, we establish the genericity of the hypothesis in Theorem 2.3, i.e., we prove that for almost all nonepistatic fitness matrices $W = (W_{ij})$, each equilibrium of (1.4) is hyperbolic. For internal equilibria, we use the eigenvalues derived by Karlin and Liberman (1979); for boundary equilibria, we evaluate all the eigenvalues in terms of the linkage map and the eigenvalues for selection at each locus (see (A44)). The eigenvalues at the boundary equilibria are of independent interest because they determine whether new mutants spread or are lost.

Remark 2.3. Suppose each equilibrium of (1.4) is hyperbolic for $\varepsilon = 0$. Then for $\varepsilon > 0$, each equilibrium of (1.4) is within $O(\varepsilon)$ of the corresponding equilibrium with $\varepsilon = 0$ and has the same stability properties. In particular, at equilibrium, $\boldsymbol{D} = O(\varepsilon)$ and $\bar{W}$ differs by $O(\varepsilon)$ from its value without epistasis.

This is an immediate consequence of the inverse function theorem and the Hartman–Grobman theorem. One must prove only that the

equilibria remain feasible (i.e., nonnegative) when epistasis is switched on (which need not be true when recombination is switched on). This follows from the explicit characterization (2.4) of the equilibria for $\varepsilon = 0$: For some equilibrium $\boldsymbol{p}$, let $I_k = \{i_k\colon p_{i_k}^{(k)} > 0\}$ denote the set of alleles present at locus k. The face of $S_{m_1 \cdots m_n}$ determined by $p_i = 0$ for $i \notin \prod_k I_k$ is invariant under (1.4) (for each value of ε), and hence the equilibrium $\boldsymbol{p}$, which is hyperbolic for $\varepsilon = 0$, persists in this face for $\varepsilon > 0$.

See Hastings (1985, 1986) for some perturbation calculations.

Remark 2.4. Here, we discuss the behavior of the mean fitness $\bar{W}$ for weak epistasis.

As we saw above, if there is no epistasis, then the continuous function $\Delta \bar{W}(\boldsymbol{p}) \geqq 0$, with equality if and only if $\boldsymbol{p} \in \mathscr{F}$. Therefore, we conclude that $\Delta \bar{W} > 0$ for weak epistasis if $\boldsymbol{p}$ is bounded away from the set $\mathscr{F}$. For $\boldsymbol{p}$ in or close to $\mathscr{F}$, however, $\Delta \bar{W} < 0$ can occur for arbitrarily small $\varepsilon > 0$, as illustrated by the following example.

We examine two diallelic loci, in the usual simplified notation (see, e.g., Nagylaki 1992, p. 185). Let the alleles be A and a at the first locus and B and b at the second. We denote the frequencies of the gametes AB, Ab, aB, and ab by p_1, p_2, p_3, and p_4, respectively. Then

$$W_i = \sum_{j=1}^{4} W_{ij} p_j, \qquad \bar{W} = \sum_{i,j=1}^{4} W_{ij} p_i p_j. \tag{2.23}$$

The recurrence relations (1.4) reduce to

$$p_i' = \frac{1}{\bar{W}}(W_i p_i - \eta_i c D), \tag{2.24}$$

where c $(0 \leqq c \leqq \frac{1}{2})$ designates the recombination rate; $\eta_1 = \eta_4 = 1$ and $\eta_2 = \eta_3 = -1$; and

$$D = W_{14} p_1 p_4 - W_{23} p_2 p_3 \tag{2.25}$$

signifies the linkage disequilibrium.

We now take $c = \frac{1}{2}$ (unlinked loci) and

$$W = \begin{pmatrix} 0 & 1-\varepsilon & 1-\varepsilon & 2 \\ 1-\varepsilon & 0 & 2 & 1-\varepsilon \\ 1-\varepsilon & 2 & 0 & 1-\varepsilon \\ 2 & 1-\varepsilon & 1-\varepsilon & 0 \end{pmatrix}, \tag{2.26}$$

where $0 \leqq \varepsilon \leqq 1$. Since $W_{14} = W_{23}$, there is no position effect. If $\varepsilon = 0$, homozygous loci do not contribute to W and each heterozygous locus contributes 1. We choose

$$p_2 = p_3 = \kappa, \qquad p_1 = p_4 = \tfrac{1}{2} - \kappa, \tag{2.27}$$

with $0 \leqq \kappa \leqq \frac{1}{2}$. (This is a subset of $\mathcal{F}$ for this example; its complement in $\mathcal{F}$ consists of equilibria with at most one locus segregating.) An easy calculation gives $p_i' = \frac{1}{4}$ for every i and

$$\Delta \bar{W} = - \tfrac{1}{2}\varepsilon(4\kappa - 1)^2 \leqq 0, \tag{2.28}$$

with equality if and only if $\varepsilon = 0$ (no epistasis) or $\kappa = \frac{1}{4}$ (equilibrium).

Remark 2.5. We end this section by exhibiting the forward-invariant and -noninvariant subsets of $\mathcal{F}$ in an example. Consider two diallelic loci without epistasis, in the notation of Remark 2.4. Suppose AA, Aa, aa, BB, Bb, and bb contribute 0, 1, 0, 2, 3, and 0 to fitness, respectively, so that

$$W = \begin{pmatrix} 2 & 3 & 3 & 4 \\ 3 & 0 & 4 & 1 \\ 3 & 4 & 2 & 3 \\ 4 & 1 & 3 & 0 \end{pmatrix}. \tag{2.29}$$

Then at equilibrium, the frequencies of A and B are $\frac{1}{2}$ and $\frac{3}{4}$, respectively. We assume that $0 < c \leqq \frac{1}{2}$.

From (2.9) we deduce

$$\mathcal{F} = \Theta \cup \Gamma, \tag{2.30}$$

where

$$\Theta = (0, \tfrac{1}{3}, \tfrac{2}{3}, 0) \cup (\tfrac{2}{3}, 0, 0, \tfrac{1}{3}), \tag{2.31a}$$

$$\Gamma = \{(\mu, \tfrac{1}{2} - \mu, \tfrac{3}{4} - \mu, \mu - \tfrac{1}{4}): \tfrac{1}{4} \leqq \mu \leqq \tfrac{1}{2}\}$$

$$\cup (0, 0, \tfrac{3}{4}, \tfrac{1}{4}) \cup (0, \tfrac{1}{2}, 0, \tfrac{1}{2}) \cup (\tfrac{1}{2}, 0, \tfrac{1}{2}, 0) \cup (\tfrac{3}{4}, \tfrac{1}{4}, 0, 0,)$$

$$\cup (1, 0, 0, 0) \cup (0, 1, 0, 0) \cup (0, 0, 1, 0) \cup (0, 0, 0, 1). \tag{2.31b}$$

At the two points in Θ, both loci are polymorphic and $D \neq 0$. This subset is not forward invariant: if $\boldsymbol{p} \in \Theta$, then $\boldsymbol{p}' \notin \mathcal{F}$. The first subset displayed in Γ is a line; for $\frac{1}{4} < \mu < \frac{1}{2}$, this is the forward-invariant set $\mathcal{F}^*$. Both loci are polymorphic even if $\mu = \frac{1}{4}$ or $\frac{1}{2}$. The second line in (2.31b) comprises four equilibrium points, each with a single polymorphic locus; the third line comprises four equilibria, at each of which a single gamete is fixed.

3 Weak selection

Now let $W_{ij} = 1 + s r_{ij}$, with $|r_{ij}| \leqq 1$, so that s is a measure of the *selection intensity*. If s is small compared with $c_{\min}$, where $c_{\min} > 0$

denotes the smallest two-locus recombination frequency (see (1.17)), then we speak of *weak selection*, or loose linkage.

We first review the known results in the case of no selection, $s = 0$. Here, the map (1.4) simplifies to

$$p_i' = p_i - D_i. \tag{3.1}$$

Now D_i tends to zero at a geometric rate (Nagylaki 1993, pp. 634–635 and references therein). Hence, the linkage-equilibrium manifold

$$\Lambda_0 = \{\boldsymbol{p}: p_i = p_{i_1}^{(1)} p_{i_2}^{(2)} \cdots p_{i_n}^{(n)} \text{ for every } i\} = \{\boldsymbol{p}: \boldsymbol{D} = \boldsymbol{0}\} \tag{3.2}$$

is invariant and globally attracting at a uniform geometric rate. All points on Λ_0 are fixed points under (3.1). The rates of approach, i.e., the eigenvalues transverse to Λ_0, were evaluated explicitly by Lyubich (1971; 1992, pp. 252–255). One can derive them easily by linearizing Eq. ($*$) of Nagylaki (1993, p. 634) and reading the eigenvalues off recursively, starting with two loci. They are given by the $2^n - n - 1$ numbers γ_Q, where Q denotes a subset with at least two elements of the set N of loci, and γ_Q designates the probability that there is no recombination in Q. In terms of the linkage map c_I, we have $\gamma_Q = 1 - c_{\text{tot}}^{(Q)}$, in which

$$c_{\text{tot}}^{(Q)} = \sum_{I:\, \emptyset \neq I \cap Q \neq Q} c_I \tag{3.3}$$

represents the total probability of recombination among the loci in Q. These eigenvalues must also be a special case of (A3). Hence, for generic initial conditions, the rate of approach, i.e., the largest eigenvalue, is given by max $\gamma_Q = 1 - c_{\text{min}}$.

For weak selection, the theory of normally hyperbolic manifolds (see Fenichel 1971; or Hirsch et al. 1977) implies the existence of a smooth invariant manifold Λ_s close to Λ_0, which is globally attracting at a geometric rate for (1.4).[4]

For small s, this manifold Λ_s is characterized by equations of the form

$$D_i = s\psi_i(\boldsymbol{\rho}, s), \tag{3.4}$$

where the ψ_i are smooth functions of the vector of gene frequencies $\boldsymbol{\rho}$. Thus, on Λ_s, and more generally, for any initial values, after a long time, the linkage disequilibria D_i are $O(s)$. (For a direct proof, see

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[4] In the continuous-time model, this observation is due to Charles Conley (see Shah-shahani 1979, p. 29). See also Passekov (1984).

Nagylaki 1993, pp. 634–635.) This implies that the recursion relations for the gene frequencies on the invariant manifold Λ_s can be written as (Nagylaki 1993, Eq. 56)

$$p_{i_m}^{(m)\prime} = F_{i_m}^{(m)}(\boldsymbol{\rho}) + O(s^2). \tag{3.5}$$

The leading term in (3.5), the *weak–selection approximation*, is given by the map $\boldsymbol{\rho} \mapsto F(\boldsymbol{\rho})\colon S_{m_1} \times \cdots \times S_{m_n} \to S_{m_1} \times \cdots \times S_{m_n}$ (see Nagylaki 1989b, 1993)

$$p_{i_m}^{(m)\prime} = F_{i_m}^{(m)}(\boldsymbol{\rho}) = p_{i_m}^{(m)} \sum_i{}^{(m)} \sum_j W_{ij} \left(\prod_{k:\, k \neq m} p_{i_k}^{(k)} \right) \left(\prod_l p_{j_l}^{(l)} \right) \Big/ \bar{W}, \tag{3.6}$$

with

$$\bar{W} = \sum_{i,j} W_{ij} \left(\prod_k p_{i_k}^{(k)} \right) \left(\prod_l p_{j_l}^{(l)} \right). \tag{3.7}$$

Denote $\bar{w}(\boldsymbol{\rho}) = \bar{W}(\boldsymbol{p})$ for $\boldsymbol{p} \in \Lambda_0$. Then (3.6) can be expressed also in the form

$$p_{i_m}^{(m)\prime} = \frac{p_{i_m}^{(m)}}{2\bar{w}} \frac{\partial \bar{w}}{\partial p_{i_m}^{(m)}} = \frac{1}{2} p_{i_m}^{(m)} \frac{\partial}{\partial p_{i_m}^{(m)}} \log \bar{w},$$

which is equivalent to Wright's (1935; 1937; 1969, pp. 65–66) and Barton and Turelli's (1987) expressions for gene-frequency change. From (3.7) we see that $\bar{w}(\boldsymbol{\rho})$ is homogeneous and quadratic in the gene frequencies $\boldsymbol{p}^{(m)}$ at each locus, so

$$\sum_{i_m} p_{i_m}^{(m)} \frac{\partial \bar{w}}{\partial p_{i_m}^{(m)}} = 2\bar{w}$$

by Euler's theorem on homogeneous functions. Therefore, we can recast our recursion relation to exhibit the normalization of the gene frequencies:

$$p_{i_m}^{(m)\prime} = p_{i_m}^{(m)} \frac{\partial \bar{w}}{\partial p_{i_m}^{(m)}} \Big/ \sum_{j_m} p_{j_m}^{(m)} \frac{\partial \bar{w}}{\partial p_{j_m}^{(m)}}. \tag{3.8}$$

Baum and Eagon's (1967) theorem implies that the mean fitness $\bar{w}$ is nondecreasing for (3.8). More precisely, for (3.8) we have (Nagylaki 1989b, p. 236)

$$\bar{w}(\boldsymbol{\rho}') > \bar{w}(\boldsymbol{\rho}) \quad \text{unless } \boldsymbol{\rho}' = \boldsymbol{\rho}. \tag{3.9}$$

This shows that the approximate dynamics (3.8) on the linkage-equilibrium manifold Λ_0 is gradient-like. We wish to extend this result here to the exact system (1.4), which has the form (3.5) on Λ_s.

Since $W_{ij} = 1 + sr_{ij}$, (3.5) can be rewritten as

$$p_{i_m}^{(m)\prime} = p_{i_m}^{(m)} + sp_{i_m}^{(m)} \frac{u_{i_m}^{(m)}(\boldsymbol{\rho})}{\bar{w}(\boldsymbol{\rho})} + O(s^2), \tag{3.10}$$

where we have defined

$$r_i = \sum_j r_{ij}\left(\prod_k p_{j_k}^{(k)} \right), \qquad r_{i_m}^{(m)} = \sum_i^{(m)} r_i \left(\prod_{k:\, k \neq m} p_{i_k}^{(k)} \right), \tag{3.11}$$

$$\bar{r} = \sum_i r_i \left(\prod_k p_{i_k}^{(k)} \right), \qquad u_{i_m}^{(m)} = r_{i_m}^{(m)} - \bar{r}. \tag{3.12}$$

Thus, $u_{i_m}^{(m)}$ depends only on r_{ij}, but not on s. Note that (3.10) holds not only on Λ_s but in an $O(s)$ neighborhood of Λ_0 (Nagylaki 1993, Eq. 56). Rescaling time $t\, (= 0, 1, 2, \dots)$ in generations as $\tau = st$, we see at least formally that as $s \to 0$, the difference equation (3.10) approaches the differential equation

$$\dot{p}_{i_m}^{(m)} = p_{i_m}^{(m)} u_{i_m}^{(m)}(\boldsymbol{\rho}) \tag{3.13}$$

on $S_{m_1} \times \cdots \times S_{m_n}$, where the superior dot signifies $\partial/\partial\tau$. Note that the fixed points of (3.10) coincide with the equilibria of (3.13). We shall refer to (3.13) as the *weak-selection limit* of (1.4). As we shall see below, the continuous-time system (3.13) may be more convenient for describing the dynamics for small s than the discrete-time system (3.6).

Comparison with (3.8) shows that (3.13) is the Shahshahani gradient vector field of the potential function $\bar{r}$. In particular, and in analogy to (3.9), $\bar{r}$ increases strictly along nonconstant solutions of (3.13):

$$\dot{\bar{r}} = 2\sum_k \sum_{i_k} p_{i_k}^{(k)}[u_{i_k}^{(k)}(\boldsymbol{\rho})]^2 \geqq 0. \tag{3.14}$$

Now we posit hyperbolicity for the weak-selection limit (3.13):

$$\text{all equilibria of (3.13) are hyperbolic.} \qquad (\mathscr{H})$$

Since (3.13) is a gradient system, all eigenvalues of the Jacobian are real. Hence, $(\mathscr{H})$ is equivalent to regularity (nondegeneracy) of all equilibria of (3.13), i.e., 0 must not be an eigenvalue. Obviously, the eigenvalues λ of (3.13) correspond to the eigenvalues $1 + \frac{s\lambda}{\bar{w}}$ of (3.10), in which $\hat{\bar{w}}$ is evaluated at equilibrium. Therefore, $(\mathscr{H})$ is equivalent to the hypothesis that (3.10) has no fixed point with an eigenvalue 1, or to the hyperbolicity of fixed points of (3.5) or (3.6) for small s.

Now we can formulate our main result, which shows that there is no cycling or more complicated dynamics possible under weak selection.

Theorem 3.1. *If s is sufficiently small and the hyperbolicity condition* ($\mathscr{H}$) *is satisfied, then each solution* $\boldsymbol{p}(t)$ *of* (1.4) *converges to a fixed point of* (1.4) *as* $t \to \infty$.

Proof. Since solutions are in phase with solutions on the invariant manifold Λ_s (see Fenichel 1971; or Hirsch et al. 1977), it is sufficient to prove convergence for initial conditions $\boldsymbol{p} \in \Lambda_s$. The estimate (3.5) implies that (1.4) restricted to Λ_s, and expressed in the coordinates $\boldsymbol{\rho} \in S_{m_1} \times \cdots \times S_{m_n}$, behaves like a first-order numerical discretization procedure for the differential equation (3.13), with step size s, whereas (3.6) or (3.10) is essentially the Euler scheme for (3.13). Hence, we can apply general results from the qualitative theory of numerical approximations (see, e.g., Garay 1993, 1996) to relate the dynamical behavior of (3.5) and (3.6) to that of (3.13). Under assumption ($\mathscr{H}$), the weak-selection limit (3.13) has only finitely many equilibria, all of which are hyperbolic. By Corollary 2.3 of Garay (1993), which is an extension of the Hartman–Grobman theorem, there exists a $\delta > 0$ such that for sufficiently small s, the recursion relation (3.5) has a single hyperbolic fixed point as the only invariant set in the δ-neighborhood of each of the equilibria of (3.13). Since (3.13) is gradient-like by (3.14), its chain-recurrent set (Conley 1978; Akin 1993) consists only of these finitely many equilibria. As shown in Garay and Hofbauer (1997), the robustness argument of the proof of Theorem 2.3 extends to the singular δ-perturbation of (3.13) to either (3.10) or (3.5). □

Remark 3.1. The fact that the chain-recurrent set of (3.5) is contained in neighborhoods of the set of equilibria of (3.13) follows essentially from the result that the Lyapunov function $\bar{r}$ for (3.13) is also a Lyapunov function for (3.5) outside these neighborhoods of the equilibria. To verify this explicitly in our case, we first define

$$v_{i_m}^{(m)} = p_{i_m}^{(m)} u_{i_m}^{(m)} / \bar{w}. \tag{3.15}$$

On Λ_s, we obtain from (3.5), (3.6), (3.10), (3.12), and (3.15)

$$\bar{r}(\boldsymbol{\rho}') = \bar{r}(\boldsymbol{\rho} + s\boldsymbol{v} + O(s^2))$$

$$= \bar{r}(\boldsymbol{\rho}) + s\boldsymbol{v} \cdot \partial_\rho \bar{r} + O(s^2)$$

$$= \bar{r}(\boldsymbol{\rho}) + 2s \sum_k \sum_{i_k} p_{i_k}^{(k)} [u_{i_k}^{(k)}(\boldsymbol{\rho})]^2 + O(s^2). \tag{3.16}$$

Therefore, $\bar{r}(\boldsymbol{\rho}') > \bar{r}(\boldsymbol{\rho})$ for sufficiently small s whenever $\boldsymbol{\rho}$ is bounded away from the equilibria of (3.13). The same result holds for $\bar{w} = 1 + s\bar{r}$.

Remark 3.2. In Appendix B, we show that the hyperbolicity assumption ($\mathscr{H}$) is a generic property, i.e., that for almost every fitness matrix

$W = (W_{ij})$ the elements of which are sufficiently close to 1, i.e., for almost all matrices $R = (r_{ij})$, all the equilibria of the selection equation (3.13) are hyperbolic.

Remark 3.3. Without the nondegeneracy hypotheses, Theorem 3.1 would be a consequence of Theorem 2.3 because neutrality ($s = 0$) is trivially nonepistatic. The nondegeneracy hypotheses make the results different, though. Indeed, neutrality is obviously degenerate for the purpose of Theorem 2.3, and therefore the latter does not apply. In fact, the nondegeneracy hypotheses of Theorems 2.3 and 3.1 differ in character. In Theorem 2.3, the hypothesis is imposed on the unperturbed system. Since the unperturbed system is always degenerate in Theorem 3.1, nondegeneracy can be introduced only by the perturbation. Therefore, in this case, the nondegeneracy hypothesis refers to the perturbation.

Remark 3.4. The hyperbolicity condition ($\mathscr{H}$) could be weakened: It is sufficient to assume that if an eigenvalue 0 occurs at any equilibrium of (3.13), it has algebraic multiplicity 1. Then a reduction to the resulting one-dimensional center manifolds yields the same convergence result as above. Only if the weak-selection limit (3.13) has at least a doubly degenerate fixed point, might cycling occur in the exact dynamics (1.4) for arbitrarily small s. It would be interesting to construct such examples.

Remark 3.5. If, in addition to the above hyperbolicity condition ($\mathscr{H}$), the usual transversality condition, i.e., that the stable and unstable manifolds of any two fixed points intersect transversally, is satisfied for the weak-selection limit (3.13), then the dynamics of (3.13) is structurally stable. By another result of Garay (1995), this structural stability extends to the discrete-time systems (3.5) and (3.6). Hence, for small s, the phase portrait of the exact equations (1.4) on the quasi-linkage manifold and that of the weak-selection approximation (3.6) are both the same as that of the time-s map of (3.13). Therefore, under these assumptions, it is sufficient to analyse the weak-selection limit (3.13). However, in contrast to ($\mathscr{H}$), these transversality conditions often cannot be checked in practice. If the transversality conditions are not satisfied, then the basins of attraction of the fixed points of (3.13), (3.6), and (3.5) might differ drastically. We expect that this occurs only for nongeneric sets of fitness parameters.

Remark 3.6. Theorem 3.1 holds also for the continuous–time version of the multilocus selection equation. The proof is much easier, since it does not require the reference to discretization procedures.

Remark 3.7. Here, we discuss the behavior of the mean fitness $\bar{W}$ for weak selection. The mean fitness may decrease during the short period, of order $\log(1/s)$ generations, of approach to the quasi-linkage-equilibrium manifold Λ_s (Moran 1964; Kimura 1965; Nagylaki 1977, 1993). The mean fitness may also decrease close to equilibrium, generically after a long time of order $1/s$ generations (Nagylaki 1977, 1993). For intermediate times, $\bar{W}$ must increase. More precisely, we prove below that $\bar{W}$ increases for sufficiently small s if $\boldsymbol{\rho}$ is bounded away from the equilibria of (3.13) on Λ_0 and if $\boldsymbol{p}$ is within $O(s^2)$ of Λ_s.

First, we prove that our assumptions imply (cf. Nagylaki 1993, Eq. (70))

$$\varDelta\boldsymbol{D} \equiv \boldsymbol{D}' - \boldsymbol{D} = O(s^2). \tag{3.17}$$

Writing the exact recurrence relation for $\boldsymbol{D}$ as

$$\boldsymbol{D}' = \boldsymbol{g}(\boldsymbol{\rho}, \boldsymbol{D}, s), \tag{3.18}$$

where $\boldsymbol{g}$ is a smooth function of $\boldsymbol{\rho}$ and $\boldsymbol{D}$, from (3.4) we infer that

$$s\boldsymbol{\psi}(\boldsymbol{\rho}', s) = \boldsymbol{g}[\boldsymbol{\rho}, s\boldsymbol{\psi}(\boldsymbol{\rho}, s), s]. \tag{3.19}$$

By assumption, we have

$$\boldsymbol{D} = s\boldsymbol{\psi}(\boldsymbol{\rho}, s) + O(s^2). \tag{3.20}$$

Appealing successively to (3.18) and (3.20); Taylor's theorem; (3.19); Taylor's theorem again and (3.10); and (3.4), we obtain

$$\begin{aligned}
\boldsymbol{D}' &= \boldsymbol{g}[\boldsymbol{\rho}, s\boldsymbol{\psi}(\boldsymbol{\rho}, s) + O(s^2), s] \\
&= \boldsymbol{g}[\boldsymbol{\rho}, s\boldsymbol{\psi}(\boldsymbol{\rho}, s), s] + O(s^2) \\
&= s\boldsymbol{\psi}(\boldsymbol{\rho}', s) + O(s^2) \\
&= s\boldsymbol{\psi}(\boldsymbol{\rho}, s) + O(s^2) \\
&= \boldsymbol{D} + O(s^2),
\end{aligned} \tag{3.21}$$

which establishes (3.17).

Now the mean fitness is given by

$$\bar{W}(\boldsymbol{p}) = 1 + s\bar{R}(\boldsymbol{\rho}, \boldsymbol{D}), \tag{3.22}$$

where

$$\bar{R}(\boldsymbol{\rho}, \boldsymbol{D}) = \sum_{i,j} r_{ij} p_i p_j. \tag{3.23}$$

We complete our proof by invoking successively (3.5), (3.10), (3.15), and (3.21); Taylor's theorem; again Taylor's theorem and (3.20); and (3.16):

$$
\begin{aligned}
\bar{R}(\boldsymbol{\rho}', \boldsymbol{D}') &= \bar{R}[\boldsymbol{\rho} + s\boldsymbol{v} + O(s^2), \boldsymbol{D} + O(s^2)] \\
&= \bar{R}(\boldsymbol{\rho}, \boldsymbol{D}) + s\boldsymbol{v} \cdot \partial_\rho \bar{R}(\boldsymbol{\rho}, \boldsymbol{D}) + O(s^2) \\
&= \bar{R}(\boldsymbol{\rho}, \boldsymbol{D}) + s\boldsymbol{v} \cdot \partial_\rho \bar{R}(\boldsymbol{\rho}, \boldsymbol{0}) + O(s^2) \\
&= \bar{R}(\boldsymbol{\rho}, \boldsymbol{D}) + 2s \sum_k \sum_{i_k} p_{i_k}^{(k)}[u_{i_k}^{(k)}]^2 + O(s^2).
\end{aligned}
\tag{3.24}
$$

In fact, our conclusion can be strengthened. If $\boldsymbol{p}$ is within $o(s)$ of Λ_s, the error terms in (3.17), (3.20), (3.21), and (3.24) become $o(s)$, but $\bar{W}(\boldsymbol{p})$ must still increase for sufficiently small s when $\boldsymbol{\rho}$ is bounded away from the equilibria of (3.13) on Λ_0.

Appendix A. Generic hyperbolicity for nonepistatic selection

Let $\mathscr{W}$ represent the set of all nonepistatic fitness matrices $W = (W_{ij})$. We shall prove that hyperbolicity of equilibria is generic in $\mathscr{W}$. We treat internal and boundary equilibria separately.

A.1. Internal equilibria

The eigenvalues of the linearization at an interior equilibrium of (1.4) for nonepistatic selection ($\varepsilon = 0$) have been computed explicitly by Karlin and Liberman (1978, p. 208, for two loci; 1979, p. 367, for n loci). Let $\boldsymbol{\rho}$ denote the gene frequencies at an equilibrium (see (2.4)), and for each $k = 1, \ldots, n$, let λ_{k,i_k} ($i_k = 1, \ldots, m_k$) designate the eigenvalues of the positive matrix $(p_{i_k}^{(k)} \alpha_{i_k j_k}^{(k)} / \bar{\alpha}^{(k)})_{1 \le i_k, j_k \le m_k}$. These eigenvalues are real (Kingman 1961) because this matrix is similar to a symmetric matrix. The maximal eigenvalue is obviously $\lambda_{k,1} = 1$, and hence, by the Perron–Frobenius theorem, $|\lambda_{k,i_k}| < 1$ for $i_k = 2, \ldots, m_k$. The eigenvalues of the corresponding one–locus selection dynamics close to $\boldsymbol{p}^{(k)}$ are given by $1 + \lambda_{k,i_k}$ for $i_k = 2, \ldots, m_k$. In the full system (1.4) without epistasis, these give rise to the $\sum_{k=1}^{n} (m_k - 1)$ positive eigenvalues

$$
1 + \lambda_{k,i_k} \frac{\bar{\alpha}^{(k)}}{\bar{W}} \quad \text{for } i_k = 2, \ldots, m_k,
\tag{A1}
$$

with eigendirections tangent to Λ_0. The remaining $\prod_{k=1}^{n} m_k - \sum_{k=1}^{n} m_k + n - 1$ eigenvalues, corresponding to eigendirections parallel to the linear invariant manifold $\mathcal{G}(\boldsymbol{\rho})$ (and hence transverse to Λ_0), are given by

$$\frac{1}{\bar{W}}((1-c)\bar{W} + c(\lambda_{1,i_1}\bar{\alpha}^{(1)} + \lambda_{2,i_2}\bar{\alpha}^{(2)})), \quad i_1, i_2 \geqq 2, \qquad \text{(A2)}$$

for two loci with recombination fraction c, and in the general case by

$$\frac{1}{\bar{W}}\left(\gamma_N \bar{W} + \sum_{I:I \subsetneqq N} \sum_{k=1}^{n} c_I \bar{\alpha}^{(k)} \Gamma_{k,i}(I)\right), \qquad \text{(A3)}$$

where i denotes a multi–index with at least two components i_k not equal to 1, and $\Gamma_{k,i}(I) = 0, 1,$ or λ_{k,i_k}. For each i, there exist k and I such that $\Gamma_{k,i}(I) = 0$. The eigenvalues (A2) are all positive.

Because of (1.7), (1.8) and (2.2), each transverse eigenvalue (A3) is a weighted average of numbers in $(-1,1]$, and hence is itself in $(-1,1)$, exhibiting the geometric rate of convergence in $\mathcal{G}(\boldsymbol{\rho})$ toward Λ_0. The eigenvalues (A1) are different from 1 if and only if each $\lambda_{k,i_k} \neq 0$. Therefore, an interior equilibrium of (1.4) with no epistasis is hyperbolic if and only if it is hyperbolic in each one-locus system. For one-locus systems, hyperbolicity can be characterized explicitly by well-known determinant conditions. These conditions are obviously satisfied for generic (= an open, dense set of full measure of) fitness schemes (Lyubich 1992, Theorem 9.4.15).

A.2. Boundary equilibria

Consider a boundary equilibrium $\hat{\boldsymbol{p}}$ with $\hat{m}_k$ ($\leqq m_k$) alleles present at locus k. Without loss of generality, we suppose

$$\hat{p}_{i_k}^{(k)} > 0 \quad \text{for } i_k = 1, 2, \ldots, \hat{m}_k; \qquad \text{(A4a)}$$

$$\hat{p}_{i_k}^{(k)} = 0 \quad \text{for } i_k = \hat{m}_k + 1, \ldots, m_k. \qquad \text{(A4b)}$$

We choose a subset of loci $K \subseteq N$ and analyze locally the frequencies p_i of gametes i that satisfy

$$i_k \leqq \hat{m}_k \quad \text{if} \quad k \in K, \quad \text{and} \quad i_k > \hat{m}_k \quad \text{if} \quad k \notin K. \qquad \text{(A5)}$$

Our analysis will establish and use the block triangular structure of the Jacobian matrix. Our main result is (A44). We separate the three cases (i) $K = N$, (ii) $K = \emptyset$, and (iii) $K \neq \emptyset, N$.

If $K = N$, we assume that no rare alleles are present: for every k, we take $p_{j_k}^{(k)} = 0$ if $j_k > \hat{m}_k$. Then we have simply the interior problem in Subsect. A.1 with m_k replaced by $\hat{m}_k$. Therefore, the

$$\left(\prod_{k=1}^{n} \hat{m}_k \right) - 1 \tag{A6}$$

eigenvalues corresponding to eigenvectors parallel to the boundary at $\hat{p}$ are given by (A1) and (A3) with carets on m_k, $\bar{\alpha}^{(k)}$, and $\bar{W}$.

Henceforth, we consider only gametes that carry at least one rare allele: $K \subset N$. In that case, linearizing the first term in (1.9) yields

$$p_i' \sim \gamma_N p_i \frac{\hat{W}_i}{\hat{\bar{W}}} + G_i, \tag{A7a}$$

where

$$G_i = \frac{1}{\bar{W}} \sum_j \sum_I c_I W_{i,j,,j,i,} p_{i,j,} p_{j,i,}, \tag{A7b}$$

and the notation $(\sim)$ in (A7a) signifies the omission of higher-order terms in the small gametic frequencies. In the absence of epistasis, from (2.11), (2.2), (2.5), and (2.3) we obtain

$$\hat{W}_i = \sum_{k=1}^{n} \hat{\alpha}_{i_k}^{(k)}, \qquad \hat{\bar{W}} = \sum_{k=1}^{n} \hat{\bar{\alpha}}^{(k)}, \tag{A8a}$$

$$\hat{\alpha}_{i_k}^{(k)} = \sum_{j_k=1}^{\hat{m}_k} \alpha_{i_k j_k}^{(k)} \hat{p}_{j_k}^{(k)}, \qquad \hat{\bar{\alpha}}^{(k)} = \sum_{i_k=1}^{\hat{m}_k} \sum_{j_k=1}^{\hat{m}_k} \alpha_{i_k j_k}^{(k)} \hat{p}_{i_k}^{(k)} \hat{p}_{j_k}^{(k)}. \tag{A8b}$$

If the gamete i carries only rare alleles, i.e., $K = \emptyset$, then (A7b) shows that G_i is second order, so for arbitrary fitnesses W_{ij}, (A7a) yields the eigenvalues

$$v_i = \gamma_N \hat{W}_i / \hat{\bar{W}}. \tag{A9}$$

The interpretation of (A9) is that if $A_{i_k}^{(k)}$ is rare for every k, then (to first order) recombination can eliminate but not produce gamete i, so the growth rate $\hat{W}_i / \hat{\bar{W}}$ is reduced by a fraction c_{tot}.

That the positive eigenvalues v_i differ generically from 1 is clear because the linkage and selection factors (γ_N and $\hat{W}_i / \hat{\bar{W}}$, respectively) are mutually independent. Furthermore, $\hat{W}_i$ depends on $\alpha_{i_k j_k}^{(k)}$ with $i_k > \hat{m}_k$ for every k, whereas $\hat{\bar{W}}$ does not.

Evidently, there are

$$\prod_{k=1}^{n} (m_k - \hat{m}_k) \tag{A10}$$

eigenvalues of the form (A9).

Now we turn to the much more difficult case $K \neq \emptyset, N$. First, we simplify G_i for additive loci. Substituting

$$W_{i_I j_I, j_I i_J} = W_{ij} = \sum_k \alpha_{i_k j_k}^{(k)} \tag{A11}$$

into (A7b) gives

$$G_i = \frac{1}{\bar{W}} \sum_k \left(\sum_{I:\, k \in I} + \sum_{I:\, k \in J} \right) \sum_j c_I \alpha_{i_k j_k}^{(k)} p_{i_I j_I} p_{j_I i_J}. \tag{A12}$$

We introduce complementary subsets S and T such that $S \subseteq N$ and $T = N - S$. Then the gametic frequencies for loci in S are

$$p_{i_S}^{(S)} = \sum_{i_T} p_i. \tag{A13}$$

Using (A13) in (A12), we find

$$G_i = \frac{1}{\bar{W}} \sum_k \left(\sum_{I:\, k \in I} \sum_{j_k} c_I \alpha_{i_k j_k}^{(k)} p_{i_I}^{(I)} p_{j_k i_J}^{(k,J)} + \sum_{I:\, k \in J} \sum_{j_k} c_I \alpha_{i_k j_k}^{(k)} p_{j_k i_I}^{(k,I)} p_{i_J}^{(J)} \right). \tag{A14}$$

Recall that $I \neq \emptyset, N$ and $1 \in I$. We define S without the last condition: $S \neq \emptyset, N$, but $1 \in S$ or $1 \in T$. Since $c_S = c_T$, we reduce (A14) to

$$G_i = \frac{1}{\bar{W}} \sum_{k=1}^n \sum_{S:\, k \in S} \sum_{j_k=1}^{m_k} c_S \alpha_{i_k j_k}^{(k)} p_{i_S}^{(S)} p_{j_k i_T}^{(k,T)}. \tag{A15}$$

Next, we linearize (A15). The contribution of locus k to G_i is second order unless either $S \subseteq K$, or $j_k \leq \hat{m}_k$ and $T \subseteq K$, so

$$G_i \sim \tilde{G}_i = \frac{1}{\hat{\bar{W}}} \sum_k \left(\sum_{S:\, k \in S \subseteq K} \sum_{j_k=1}^{m_k} c_S \alpha_{i_k j_k}^{(k)} \hat{p}_{i_S}^{(S)} p_{j_k i_T}^{(k,T)} \right.$$
$$\left. + \sum_{S:\, k \in S,\, T \subseteq K} \sum_{j_k=1}^{\hat{m}_k} c_S \alpha_{i_k j_k}^{(k)} p_{i_S}^{(S)} \hat{p}_{j_k i_T}^{(k,T)} \right). \tag{A16}$$

By Lemma 2.1,

$$\hat{p}_{i_S}^{(S)} = \prod_{k:\, k \in S} \hat{p}_{i_k}^{(k)}; \tag{A17}$$

in particular, $\hat{p}_{j_k i_T}^{(k,T)} = \hat{p}_{j_k}^{(k)} \hat{p}_{i_T}^{(T)}$, and with the aid of (A8b), this enables us to sum over j_k in the second term in (A16). We now assume that there are no rare alleles at loci in K, i.e., for every $k \in K$, we take $p_{j_k}^{(k)} = 0$ if $j_k > \hat{m}_k$. This restriction replaces the upper summation limit m_k in the first term in (A16) by $\hat{m}_k$. Therefore, we have the linear approximation

$$\tilde{G}_i = \frac{1}{\hat{\bar{W}}} \sum_{k=1}^n \left(\sum_{S:\, k \in S \subseteq K} \sum_{j_k=1}^{\hat{m}_k} c_S \alpha_{i_k j_k}^{(k)} \hat{p}_{i_S}^{(S)} p_{j_k i_T}^{(k,T)} + \sum_{S:\, k \in S,\, T \subseteq K} c_S \hat{\alpha}_{i_k}^{(k)} \hat{p}_{i_T}^{(T)} p_{i_S}^{(S)} \right). \tag{A18}$$

Let $L = N - K$. The only allelic summation in (A18) is over j_k for $k \in K$. Hence, i_L is fixed in (A18), which we can study by varying only i_K, so that $i_k = 1, \ldots, \hat{m}_k$ for every $k \in K$. We suppress i_L and write

$$x_{i_K}^{(K)} = p_i = p_{i_K i_L}. \tag{A19}$$

In the first sum in (A18), since $k \in S \subseteq K$, we get

$$T = N - S = K \cup L - S = (K - S) \cup L, \tag{A20}$$

whence

$$p_{j_k i_T}^{(k,T)} = p_{j_k i_{K-S} i_L}^{(k,T)} = x_{j_k i_{K-S}}^{(k,K-S)}. \tag{A21}$$

From (A13) we see that

$$x_{j_k i_{K-S}}^{(k,K-S)} = \sum_{i_{S-\{k\}}} x_{j_k i_{K-\{k\}}}^{(K)}. \tag{A22}$$

In the second sum in (A18), $k \in S$ and $T \subseteq K$, which implies

$$S = N - T = K \cup L - T = (K - T) \cup L, \tag{A23}$$

whence

$$p_{i_S}^{(S)} = p_{i_{K-T} i_L}^{(S)} = x_{i_{K-T}}^{(K-T)}. \tag{A24}$$

Now (A13) reveals that

$$x_{i_{K-T}}^{(K-T)} = \sum_{i_T} x_{i_K}^{(K)}. \tag{A25}$$

Inserting (A21) and (A24) into (A18) yields

$$\tilde{G}_i = \frac{1}{\hat{\bar{W}}} \sum_{k=1}^{n} \left(\sum_{S:\, k \in S \subseteq K} \sum_{j_k=1}^{\hat{m}_k} c_S \alpha_{i_k j_k}^{(k)} \hat{p}_{i_S}^{(S)} x_{j_k i_{K-S}}^{(k,K-S)} + \sum_{S:\, k \in S,\; T \subseteq K} c_S \hat{\alpha}_{i_k}^{(k)} \hat{p}_{i_T}^{(T)} x_{i_{K-T}}^{(K-T)} \right). \tag{A26}$$

Guided by the work of Karlin and Liberman (1979), we are now prepared to find the desired eigenvalues. For each locus k, we define the elements of the positive matrix $B^{(k)}$ by (cf. Subsect. A.1)

$$b_{i_k j_k}^{(k)} = \hat{p}_{i_k}^{(k)} \alpha_{i_k j_k}^{(k)} / \hat{\bar{\alpha}}^{(k)}, \tag{A27}$$

where $i_k, j_k = 1, 2, \ldots, \hat{m}_k$. By (2.4), the maximal eigenvalue of $B^{(k)}$ is 1, and the corresponding right and left eigenvectors are $\hat{p}^{(k)}$ and $\mathbf{1}^{(k)}$, respectively, where $\mathbf{1}^{(k)^T} = (1, 1, \ldots, 1)$ has $\hat{m}_k$ components:

$$\mathbf{1}^{(k)^T} B^{(k)} = \mathbf{1}^{(k)^T}, \qquad B^{(k)} \hat{p}^{(k)} = \hat{p}^{(k)}. \tag{A28}$$

Consequently, the other $\hat{m}_k - 1$ eigenvalues λ_k and right eigenvectors $\xi^{(k)}$ satisfy $|\lambda_k| < 1$ and

$$\mathbf{1}^{(k)} \cdot \xi^{(k)} = 0, \qquad B^{(k)} \xi^{(k)} = \lambda_k \xi^{(k)}. \tag{A29}$$

Recall that the eigenvalues λ_k are real (Kingman 1961).

Let $K^* \subseteq K$; we allow $K^* = \emptyset$ and put $K^{**} = K - K^*$. We demonstrate that $\boldsymbol{x}^{(K)}$, with components

$$x_{i_K}^{(K)} = \left(\prod_{\ell: \, \ell \in K^*} \hat{p}_{i_\ell}^{(\ell)} \right) \left(\prod_{r: \, r \in K^{**}} \xi_{i_r}^{(r)} \right), \tag{A30}$$

is an eigenvector of the matrix defined by (A26). In the first sum in (A26), from (A22), (A30), and (A29) we see that

$$x_{j_k i_{K-S}}^{(k, K-S)} = 0 \quad \text{unless } S - \{k\} \subseteq K^*. \tag{A31a}$$

Similarly, in the second sum,

$$x_{i_{K-T}}^{(K-T)} = 0 \quad \text{unless } T \subseteq K^*. \tag{A31b}$$

We introduce the indicator function

$$\theta_{\{k \in K^*\}} = \begin{cases} 1 & \text{if } k \in K^*, \\ 0 & \text{if } k \notin K^*. \end{cases} \tag{A32}$$

Using (A31), (A32), (A17), and (A27) in (A26) leads to

$$\tilde{G}_i = \frac{1}{\hat{\bar{W}}} \sum_k \left[\sum_{\substack{S: \, k \in S \subseteq K, \\ S - \{k\} \subseteq K^*}} c_S \hat{\bar{\alpha}}^{(k)} b_{i_k j_k}^{(k)} \hat{p}_{i_{S-\{k\}}}^{(S-\{k\})} (\theta_{\{k \in K^*\}} \hat{p}_{j_k}^{(k)} + \theta_{\{k \in K^{**}\}} \xi_{j_k}^{(k)}) y_{i,S} \right.$$

$$\left. + \sum_{S: \, k \in S, \, T \subseteq K^*} c_S \hat{\alpha}_{i_k}^{(k)} \hat{p}_{i_T}^{(T)} y_{i,T} \right], \tag{A33a}$$

where

$$y_{i,S} = \left(\prod_{q: \, q \in K^* \cap (K-S)} \hat{p}_{i_q}^{(q)} \right) \left(\prod_{r: \, r \in K^{**} \cap (K-S)} \xi_{i_r}^{(r)} \right). \tag{A33b}$$

We now invoke (A28) to (A30) and simplify:

$$\tilde{G}_i = \frac{1}{\hat{\bar{W}}} \left\{ \sum_k \left[\sum_{\substack{S: \, k \in S \subseteq K, \\ S - \{k\} \subseteq K^*}} c_S \hat{\bar{\alpha}}^{(k)} (\theta_{\{k \in K^*\}} + \lambda_k \theta_{\{k \in K^{**}\}}) \right. \right.$$

$$\left. \left. + \sum_{S: \, k \in S, \, T \subseteq K^*} c_S \hat{\alpha}_{i_k}^{(k)} \right] \right\} x_{i_K}^{(K)}. \tag{A34}$$

Recalling (A7a), we obtain the eigenvalues

$$v_{i_L}^{(L)} = \frac{1}{\hat{\bar{W}}} \left(\gamma_N \hat{W}_i + \sum_{k: \, k \in K^*} \sum_{S: \, k \in S \subseteq K^*} c_S \hat{\bar{\alpha}}^{(k)} + \sum_{k: \, k \in K^{**}} \sum_{S: \, k \in S \subseteq K^* \cup \{k\}} c_S \hat{\bar{\alpha}}^{(k)} \lambda_k \right.$$

$$\left. + \sum_{k=1}^n \sum_{S: \, k \in S, \, T \subseteq K^*} c_S \hat{\alpha}_{i_k}^{(k)} \right). \tag{A35}$$

To reduce (A35), note first from (2.4) that

$$\hat{\alpha}_{i_k}^{(k)} = \hat{\bar{\alpha}}^{(k)} \quad \text{if } k \in K. \tag{A36}$$

Hence, we can rewrite the sum of the first, second, and fourth terms in the parentheses as

$$\sigma_{i_L} = \gamma_N \hat{W}_i + \sum_{k=1}^{n} \left(\sum_{S:\, k\in S \subseteq K^*} + \sum_{S:\, k\in S,\ T \subseteq K^*} \right) c_S \hat{\alpha}_{i_k}^{(k)}$$

$$= \gamma_N \hat{W}_i + \sum_{k=1}^{n} \left(\sum_{S:\, k\in S} - \sum_{S:\, k\in S;\ S,T \nsubseteq K^*} \right) c_S \hat{\alpha}_{i_k}^{(k)}. \tag{A37}$$

By (1.7),

$$c_{\text{tot}} = \sum_{S:\, k\in S} c_S \tag{A38}$$

for each k; together with (A8a), this shows that the second term in (A37) is $c_{\text{tot}} \hat{W}_i$. Appealing to (1.8), we find

$$\sigma_{i_L} = \hat{W}_i - \sum_{k=1}^{n} a_k \hat{\alpha}_{i_k}^{(k)}, \tag{A39a}$$

where

$$a_k = \sum_{S:\, k\in S;\ S,T \nsubseteq K^*} c_S. \tag{A39b}$$

Now relabel (A39b) by interchanging S and T; since $c_S = c_T$, we get

$$a_k = \sum_{S:\, k\in T;\ S,T \nsubseteq K^*} c_S. \tag{A40}$$

Adding (A40) to (A39b) gives

$$2a_k = \sum_{S:\, S,T \nsubseteq K^*} c_S, \tag{A41}$$

whence $(1 \in I)$

$$a_k = \sum_{I:\, I,J \nsubseteq K^*} c_I, \tag{A42}$$

independent of k. Consequently, (A39a) becomes

$$\sigma_{i_L} = \hat{W}_i \left(1 - \sum_{I:\, I,J \nsubseteq K^*} c_I \right), \tag{A43}$$

and substituting this into (A35) yields our main result, the eigenvalues

$$v_{i_L}^{(L)} = \frac{1}{\hat{\bar{W}}} \left[\left(1 - \sum_{I:\, I,J \nsubseteq K^*} c_I \right) \hat{W}_i + \sum_{k:\, k\in K^{**}} \sum_{S:\, k\in S \subseteq K^* \cup \{k\}} c_S \hat{\bar{\alpha}}^{(k)} \lambda_k \right]. \tag{A44}$$

That $v_{i_L}^{(L)}$ is really independent of i_K follows from (A8a) and (A36).

There are

$$\sum_{K: K \neq \emptyset, N} \left[\prod_{k: k \in K} \hat{m}_k \right] \left[\prod_{\ell: \ell \in L} (m_\ell - \hat{m}_\ell) \right] \tag{A45}$$

eigenvalues of the form (A44). Adding (A6) and (A10) to (A45) leads to precisely the required number of eigenvalues:

$$\sum_K \left[\prod_{k: k \in K} \hat{m}_k \right] \left[\prod_{\ell: \ell \in L} (m_\ell - \hat{m}_\ell) \right] - 1 = \prod_k [\hat{m}_k + (m_k - \hat{m}_k)] - 1$$

$$= \left(\prod_{k=1}^n m_k \right) - 1. \tag{A46}$$

To establish generic hyperbolicity, fix the recombination frequencies c_S. Then the double sum in (A44) depends only on the fitnesses $\alpha_{i_k j_k}^{(k)}$ with $i_k, j_k \leqq \hat{m}_k$ for every k. Since $L \neq \emptyset$, there exists some $\ell \in L$; the coefficient of $\hat{\alpha}_{i_\ell}^{(\ell)}$ in $\hat{W}_i$ depends only on $\{c_S\}$ and is at least as great as $\gamma_N > 0$. Therefore, if a (real) eigenvalue $v_{i_L}^{(L)}$ happens to be ± 1, it can be shifted away from that value by perturbing $\alpha_{i_\ell j_\ell}^{(\ell)}$ for $i_\ell > \hat{m}_\ell$ and $j_\ell \leqq \hat{m}_\ell$. (Of course, such a perturbation does not change the location of the equilibrium.)

In the following remarks, we discuss special cases of (A44) that are instructive and provide checks.

Remark A.1. Although we derived (A44) under the assumption that $K \neq \emptyset$, setting $K = \emptyset$ immediately reduces (A44) to (A9).

Remark A.2. For each $K \neq \emptyset, N$ and i_L, the maximal eigenvalue is obtained by setting $K^* = K$ because that corresponds to a positive eigenvector $\hat{p}^{(K)}$. This reduces (A44) to

$$v_{i_L}^{(L)} = \frac{\hat{W}_i}{\hat{\bar{W}}} \left(1 - \sum_{I: I, J \nsubseteq K} c_I \right). \tag{A47}$$

Remark A.3. The eigenvalues at a corner equilibrium can be derived for arbitrary fitnesses W_{ij}. Choose the corner at $i = u^T = (1, 1, \ldots, 1)$, where u has n components. If the gametes are ordered lexicographically, the Jacobian matrix turns out to be upper triangular; its diagonal elements are the eigenvalues

$$\frac{W_{ui}}{W_{uu}} \left(1 - \sum_{I: I, J \nsubseteq K} c_I \right), \tag{A48}$$

in which K is defined by (A5) with $\hat{m}_k = 1$ for every k. Thus, for nonepistatic selection, (A47) is a generalization of (A48).

Remark A.4. The eigenvalues associated with gene-frequency change can be calculated *ab initio* from the following lemmas.

a) Suppose that (i) $p_{i_k}^{(k)} \alpha_{i_k}^{(k)} = p_{i_k}^{(k)} \bar{\alpha}^{(k)}$ for every i_k and every $k \neq \ell$, for some ℓ, and that (ii) $\boldsymbol{p} \in \Lambda_0$. Then (i) $\boldsymbol{p}^{(k)'} = \boldsymbol{p}^{(k)}$ for every $k \neq \ell$ and (ii) $\boldsymbol{p}' \in \Lambda_0$, i.e., every locus except ℓ is at equilibrium, and linkage equilibrium is preserved.

To prove result i, we use successively (2.6), assumptions (ii) and (i), and (2.2):

$$p_{i_k}^{(k)} W_{i_k}^{(k)} = p_{i_k}^{(k)} \left(\alpha_{i_k}^{(k)} + \sum_{m:\, m \neq k} \bar{\alpha}^{(m)} \right) \tag{A49}$$

$$= p_{i_k}^{(k)} \sum_m \bar{\alpha}^{(m)} = p_{i_k}^{(k)} \bar{W}, \tag{A50}$$

where (A50) holds for every i_k and every $k \neq \ell$. The conclusion follows from (1.10) and (A50).

To prove result (ii), define

$$q_i = \prod_k p_{i_k}^{(k)}, \qquad d_i = p_i - q_i. \tag{A51}$$

Now invoke successively (A51), (1.4), assumption (ii), (1.14), (1.10), result (i), (A51), (2.11), (A49), and assumption (i):

$$d_i' = q_i \frac{W_i}{\bar{W}} - p_{i_\ell}^{(\ell)} \frac{W_{i_\ell}^{(\ell)}}{\bar{W}} \prod_{k:\, k \neq \ell} p_{i_k}^{(k)}$$

$$= \frac{q_i}{\bar{W}} (W_i - W_{i_\ell}^{(\ell)})$$

$$= \frac{q_i}{\bar{W}} \left(\sum_k \alpha_{i_k}^{(k)} - \alpha_{i_\ell}^{(\ell)} - \sum_{k:\, k \neq \ell} \bar{\alpha}^{(k)} \right)$$

$$= \frac{q_i}{\bar{W}} \sum_{k:\, k \neq \ell} (\alpha_{i_k}^{(k)} - \bar{\alpha}^{(k)}) = 0.$$

b) Under the assumptions in part a, we can posit that $\boldsymbol{p} \in \Lambda_0$ and $\boldsymbol{p}^{(k)} = \hat{\boldsymbol{p}}^{(k)}$ for every $k \neq \ell$. Then

$$p_{i_\ell}^{(\ell)'} = p_{i_\ell}^{(\ell)} \alpha_{i_\ell}^{(\ell)*} / \bar{\alpha}^{(\ell)*}, \tag{A52a}$$

where the effective fitnesses at locus ℓ are

$$\alpha_{i_\ell j_\ell}^{(\ell)*} = \alpha_{i_\ell j_\ell}^{(\ell)} + \sum_{k:\, k \neq \ell} \hat{\bar{\alpha}}^{(k)}. \tag{A52b}$$

Result b follows immediately from (1.10), (A49), and (2.2). This result leads to an easy proof of (A1).

c) Suppose now that $p_{i_\ell}^{(\ell)} = 0$ at equilibrium for some ℓ and i_ℓ. Then (A52) demonstrates at once that the eigenvalue corresponding to $A_{i_\ell}^{(\ell)}$ is

$$\frac{\hat{\alpha}_{i_\ell}^{(\ell)*}}{\hat{\bar{\alpha}}^{(\ell)*}} = \frac{1}{\hat{\bar{W}}}\left(\hat{\alpha}_{i_\ell}^{(\ell)} + \sum_{k: k \neq \ell} \hat{\bar{\alpha}}^{(k)}\right). \tag{A53}$$

Setting $K = N - \{\ell\}$ in (A47) yields $\hat{W}_i/\hat{\bar{W}}$, in agreement with (A53).

Remark A.5. If $K^* = \emptyset$, then (A44) immediately reduces to

$$v_{i_L}^{(L)} = \frac{1}{\hat{\bar{W}}}\left(\gamma_N \hat{W}_i + \sum_{k: k \in K} c_{\{k\}}\hat{\bar{\alpha}}^{(k)}\lambda_k\right). \tag{A54}$$

Remark A.6. Finally, consider two multiallelic loci with recombination frequency c. If $K = \emptyset$, then (A9) gives the eigenvalues

$$v_i = (1 - c)\left[\frac{\hat{\alpha}_{i_1}^{(1)} + \hat{\alpha}_{i_2}^{(2)}}{\hat{\bar{\alpha}}^{(1)} + \hat{\bar{\alpha}}^{(2)}}\right]. \tag{A55}$$

Now suppose $K = \{1\}$. If $K^* = K$, from (A47) we obtain

$$v_{i_2}^{(2)} = \frac{\hat{\bar{\alpha}}^{(1)} + \hat{\alpha}_{i_2}^{(2)}}{\hat{\bar{\alpha}}^{(1)} + \hat{\bar{\alpha}}^{(2)}}. \tag{A56}$$

If $K^* = \emptyset$, then (A54) yields

$$v_{i_2}^{(2)} = \frac{(1 - c)(\hat{\bar{\alpha}}^{(1)} + \hat{\alpha}_{i_2}^{(2)}) + c\hat{\bar{\alpha}}^{(1)}\lambda_1}{\hat{\bar{\alpha}}^{(1)} + \hat{\bar{\alpha}}^{(2)}}. \tag{A57}$$

Since $\lambda_1 > -1$ and $c \leqq \frac{1}{2}$, we see at once that all the two-locus boundary eigenvalues are positive, as we noted for the two-locus internal eigenvalues.

If both loci are diallelic, the gametes AB and aB are segregating at equilibrium, and the allele b is introduced, then (A56) and (A57) can be simplified to

$$v_2^{(2)} = \frac{\hat{\bar{\alpha}}^{(1)} + \alpha_{12}^{(2)}}{\hat{\bar{\alpha}}^{(1)} + \alpha_{11}^{(2)}} \tag{A58a}$$

and

$$v_2^{(2)} = \frac{\hat{\bar{\alpha}}^{(1)} + \alpha_{12}^{(2)} - c(\alpha_{12}^{(1)} + \alpha_{12}^{(2)})}{\hat{\bar{\alpha}}^{(1)} + \alpha_{11}^{(2)}}, \tag{A58b}$$

respectively. The eigenvalues (A58) can also be deduced from Sect. 7 of Bodmer and Felsenstein (1967).

Appendix B. Generic hyperbolicity for weak selection

We denote by $\mathscr{R}$ the set of all matrices $R = (r_{ij})$ of scaled selection coefficients. We prove that the hyperbolicity assumption that

$$\text{all equilibria of (3.13) are hyperbolic} \qquad (\mathscr{H})$$

is generic in $\mathscr{R}$.

As usual, by saying that $(\mathscr{H})$ is generic we understand that the set of those R satisfying $(\mathscr{H})$ contains a residual subset of $\mathscr{R}$ (and, consequently, is dense in $\mathscr{R}$). Sometimes a generic property is said to hold almost everywhere in a topological sense. In this context, we endow the vector space $\mathscr{R}$ by its natural Euclidean metric.

As discussed in section 3 above, $(\mathscr{H})$ holds if and only if $\mathbf{0}$ is a regular value of the vector field $\boldsymbol{\rho} \mapsto \Phi(R, \boldsymbol{\rho})$ defined by

$$[\Phi(R, \boldsymbol{\rho})]_{i_m}^{(m)} = p_{i_m}^{(m)} u_{i_m}^{(m)}, \qquad (B1)$$

i.e., (3.13), on $S_{m_1} \times \cdots \times S_{m_n}$.

By the parametric Sard theorem (Chow and Hale 1982, Corollary 10.4), to prove that the set of those elements of $\mathscr{R}$ for which $\mathbf{0}$ is a regular value of $\Phi(R, \cdot)$ is residual, it suffices to show that if $\hat{\boldsymbol{\rho}}$ is an equilibrium, i.e., $\Phi(\hat{R}, \hat{\boldsymbol{\rho}}) = \mathbf{0}$ for some selection-coefficient matrix $\hat{R}$, then

$$\text{Range } \partial_R \Phi(\hat{R}, \hat{\boldsymbol{\rho}}) = T(S_{m_1} \times \cdots \times S_{m_n}),$$

where T denotes the tangent space, or, equivalently, that

$$\boldsymbol{q} \cdot \partial_R \Phi(\hat{R}, \hat{\boldsymbol{\rho}}) = 0 \quad \text{implies } \boldsymbol{q} \in (S_{m_1} \times \cdots \times S_{m_n})^{\perp}. \qquad (B2)$$

In order to prove (B2), we perturb the matrix $\hat{R}$ by considering selection–coefficient matrices of the form $R = \hat{R} + A$, where A is from the $(m_1 + \cdots + m_n)$-dimensional subspace of nonepistatic and underdominant selection–coefficient matrices with elements A_{ij} defined by

$$A_{ij} = \sum_{k=1}^{n} \beta_{i_k}^{(k)} \delta_{i_k j_k}.$$

We complete the proof by showing that if

$$\boldsymbol{q} \cdot (\partial / \partial \beta_{\mu_k}^{(k)}) \Phi(\hat{R}, \hat{\boldsymbol{\rho}}) = 0 \qquad (B3)$$

for each $k = 1, \ldots, n$ and $\mu_k = 1, \ldots, m_k$, then $\boldsymbol{q} \perp S_{m_1} \times \cdots \times S_{m_n}$, i.e.,

$$q_1^{(k)} = q_2^{(k)} = \cdots = q_{m_k}^{(k)} \qquad (B4)$$

for all $k = 1, \ldots, n$. Without loss of generality, we may assume that $0 < p_{i_k}^{(k)} < 1$ for all $k = 1, \ldots, n$, $i_k = 1, \ldots, m_k$: a similar argument holds

for all the faces of $S_{m_1} \times \cdots \times S_{m_n}$, and a finite intersection of residual sets is residual. Since

$$\bar{r}(\boldsymbol{\rho}) = \bar{\bar{r}} + \sum_{k=1}^{n} \sum_{\mu_k=1}^{m_k} \beta_{\mu_k}^{(k)} [p_{\mu_k}^{(k)}]^2, \tag{B5}$$

we have

$$\Phi_{i_m}^{(m)}(R, \boldsymbol{\rho}) = \Phi_{i_m}^{(m)}(\hat{R}, \boldsymbol{\rho}) + p_{i_m}^{(m)} \left[\beta_{i_m}^{(m)} p_{i_m}^{(m)} - \sum_{\mu_m} \beta_{\mu_m}^{(m)} [p_{\mu_m}^{(m)}]^2 \right]. \tag{B6}$$

This implies

$$\frac{\partial}{\partial \beta_{\mu_k}^{(k)}} \Phi_{i_m}^{(m)}(R, \boldsymbol{\rho}) = [p_{i_m}^{(m)}]^2 \delta_{mk} \delta_{i_m \mu_k} - \delta_{mk} p_{i_m}^{(m)} [p_{\mu_m}^{(m)}]^2$$

$$= \delta_{mk} [p_{\mu_k}^{(k)}]^2 [\delta_{i_m \mu_k} - p_{i_m}^{(m)}]. \tag{B7}$$

Consequently, if $\boldsymbol{q}$ satisfies (B3), we have

$$\sum_{i_k} q_{i_k}^{(k)} (\delta_{i_k \mu_k} - p_{i_k}^{(k)}) = 0, \tag{B8}$$

whence

$$q_{\mu_k}^{(k)} = \sum_{i_k} q_{i_k}^{(k)} p_{i_k}^{(k)} \tag{B9}$$

for all $\mu_k = 1, \ldots, m_k$. This implies (B4) and completes the proof.

For an interested reader, we note that $(\mathcal{H})$ is generic in a stronger sense: the set of fitness matrices for which it is satisfied is not only residual, but open dense, and even has full measure. This stronger result is a consequence of the fact that the equalities and inequalities characterizing a fitness matrix not satisfying $(\mathcal{H})$ are algebraic. Using arguments similar to those in the proof of Proposition 1 in Brunovský and Meravý (1984), one can show that the set of fitness matrices not satisfying $(\mathcal{H})$ is contained in a finite union of smooth manifolds of nonzero codimension, and therefore its complement contains an open dense subset of full measure of $\mathcal{R}$. As in our residuality proof, it is condition (B2) that has to be checked.

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