

Chapter 5

Optimality and Evolutionary Stability under Short-Term and Long-Term Selection

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The theory of long-term selection was originally suggested as a means of closing the gap between the phenotypic and the genotypic approaches to natural selection (Eshel and Feldman 1984; Eshel 1991; see also Eshel 1996; Hammerstein 1996; Matessi and Di Pasquale 1996). The objective was to incorporate aspects of the dynamical theory of selection on genotypes, sometimes called the *population genetic* approach to evolution, into the population game theory of evolution, which is widely used in ecology, especially behavioral ecology. The latter theory usually seeks some specific value of the behavior under study, a value that can be regarded as optimal with respect to some array of alternatives. For this reason, the game-theoretic or phenotypic approaches are subsumed under the title "optimality models." They generally involve implicit assumptions about the genotypic basis for the phenotypic variation, assumptions that are often regarded as unrealistic by population geneticists. In this chapter we discuss these two approaches and explain how they are related. In particular, we are interested in the genetic conditions under which the results of optimality models coincide with those of explicit population genetic models.

We start by distinguishing two sorts of population dynamics. Each one is characteristic of the process of biological evolution, but each is appropriate for a different time scale.

We call *short-term evolution* the dynamics of the relative frequencies of a finite, fixed set of genotypes, usually those that exist in the population at a given time but that may also include mutation from among a finite set of alleles. Short-term evolution proceeds by changes in the frequencies of genotypes represented in the population. For most of these genotypic dynamical systems, the

vector of genotype frequencies proceeds either toward a stable fixed point at which all frequencies are positive (called an *interior equilibrium*) or toward one at which some frequencies are zero (called a *boundary equilibrium*). For a given set of genotypes, there may be many equilibria that are stable for the same set of evolutionary parameters, fitness values, mutation rates, migration rates, recombination fractions, and so on. This kind of stability entails that from a starting set of frequencies close to the equilibrium, evolution will take the population ever closer to the equilibrium.

Long-term evolution refers to the process, popularly termed "trial and error," whereby mutation continuously introduces into the population new genotypes that are then subject to the forces of natural selection, sexual selection, recombination, and the like. Each new type may either be eliminated or become established within the population. The successful establishment of any new mutation initiates a new process of short-term evolution toward a new (short-term) stable equilibrium, possibly with the extinction of one or more genotypes that were originally in the population. Thus, long-term evolution proceeds by an infinite sequence of transitions from one fixed set of genotypes to another fixed set of genotypes, with each of these sets subject to short-term evolution toward a new equilibrium characteristic of its fixed set of genotypes. We will restrict our study of long-term evolution to those mutations that result in changes of phenotypes that are involved in a specific game or conflict.

This transition between short-term processes requires that mutation changes the set of genotypes involved in each of the short-term processes. Because we are concerned with mutations affecting phenotypes that are involved in a specific game or conflict, it is reasonable to assume that the rate is sufficiently low that after the occurrence of (and invasion by) a mutation, the subsequent short-term process has sufficient time to approach its equilibrium before transition to another short-term process occurs. Because we are interested in the random occurrence of mutations that affect the phenotypes under study, the process of sampling induced by finiteness of the population is ignored. Randomness enters only through the order in which mutations appear. The order of appearance of mutations in the initial stages can determine different (hence random) future paths of the long-term process.

Analysis of the dynamics of genetic systems – that is, population-genetic theory – has traditionally concentrated on the short-term process. It is the short-term process that one might observe directly in a population, subject to an immediate selection pressure. On the other hand, verbal discussions of the theory of evolution are often couched (even if implicitly) in terms of the long-term process. Note, however, that short-term and long-term evolution do not correspond to any specific, absolute time scale. Indeed, long-term evolution in bacteria may be faster than short-term evolution in mammals.

The two processes are often confused, but it is important to distinguish between the two kinds of evolutionary processes because it can be shown that they obey radically different quantitative rules. Thus, terms such as *unbeatable strategy* (Hamilton 1967) or *evolutionarily stable strategy* (ESS) (Maynard Smith and Price 1973), which concern immunity of a system to the introduction of *any* new mutation (perhaps from a biologically restricted but still infinite set of potential mutations), correspond to the long-term process of evolution as defined here. Yet whenever these criteria have been compared with specific population dynamics, it has invariably been in terms of dynamics of changes in genotype frequencies, namely short-term evolution. It is therefore not surprising that in reasonably complex genetic systems (e.g., those with linkage and epistasis among multiple loci) – except in special cases, such as additivity among the genotypic effects (e.g., Hines and Turelli 1997) – an ESS is not stable in the basic, Liapunov sense. This is why the concept of ESS has generally been used either in a dynamics-free context (e.g., in economics) or in connection with simple, asexual dynamics (Hofbauer and Sigmund 1988), where the effects of sex and recombination are dismissed as a sort of white noise superimposed on the “descent” process of evolution.

Since the time of Fisher, an implicit working assumption in the quantitative study of evolutionary dynamics is that qualitative laws governing long-term evolution can be extrapolated from results obtained for the short-term process. We maintain that this extrapolation is not accurate. The two processes are qualitatively different from each other. One obvious difference is that the mutational changes that cause the transition between one set of genotype frequencies, close to its short-term equilibrium, and the

next set are random even in large populations. In the present discussion we concentrate on another important difference: the *adaptability and tendency to an optimum* of complex genetical systems.

Fisher's Fundamental Theorem of Natural Selection (Fisher 1930) guarantees that, under certain conditions, the average fitness of a population subject to frequency-independent viability selection will increase over time until the population approaches a stable equilibrium. A stable equilibrium is, then, a local maximum of the population's mean fitness. The theorem, which is immediate for an asexual population (e.g., for replicator dynamics), was proved by Kingman (1961) for diploid sexual populations undergoing random mating, provided that the viability of the individual is determined by alleles at one locus. The theorem has been extended (e.g., Ewens 1969) to some special multilocus systems.

Unfortunately, Fisher's fundamental law does not generally hold for multilocus systems, even with random mating and frequency-independent viability selection. The first counterexample was suggested by Moran (1964) and has been extended since then by many authors. Moreover, extensive further investigations (e.g., Karlin 1975 and references therein) have established that Fisher's law appears to be a property of only a small subset of multilocus viability systems, a subset that includes the additive systems (but not the multiplicative viability systems; see also Hines and Turelli 1997). Quite generally, the frequencies of genotypes within a multilocus genetic system do not approach an equilibrium that determines an optimal fitness distribution of phenotypes under frequency-independent selection. It might therefore be predicted that the introduction of frequency-dependent selection would only exacerbate matters so that the distribution of phenotypes would not be likely to converge to an ESS. We shall see that this prediction is not always borne out.

The situation is different in the case of a long-term process of evolution. In this chapter, we discuss one important example, namely, that of a diploid, random-mating population subject to multilocus viability selection. We discuss two kinds of selection processes.

1. *Frequency-independent selection.* Consider a phenotypic trait that can be measured in terms of a parameter γ (one- or multidimensional). The fitness of an individual with phenotype γ is $w(\gamma)$, and

$w(\gamma)$ attains a unique strict maximum at the value γ^* , which is called the *optimal value* of the phenotype.

The phenotype is determined by the individual's multilocus genotype. When there is no danger of confusion, we can write the fitness of genotype G as $w(G)$ where actually

$$w(G) = w[\gamma(G)]$$

with $\gamma(G)$ the phenotype generated by G .

It is known that with fitness determined by two or more loci, short-term selection, characterized by changes in genotypic frequencies, does not in general produce convergence to the optimal phenotypic value, even if this value is in the range of phenotypes produced by the genotypes present in the population (Moran 1964; Karlin 1975; Ewens 1969).

2. *Frequency-dependent selection.* Here we treat the simplest case of a two-strategy random-encounter population game in which (as in the case of frequency-independence) an individual's strategy p is determined by its multilocus genotype G . If the distribution of genotypes in the population is F , then the fitness of an individual of genotype G will be written as

$$w(G, F) = V[p(G), q(F)]$$

where $p(G)$ is the strategy associated with genotype G , and $q(F)$ is the population strategy phenotypically generated by the distribution of genotypes, F . Here, $V[p, q]$ denotes the payoff to a player playing strategy p against an opponent playing q in a two-strategy random-encounter game.

When the genotype involves a single locus, if there is convergence under short-term selection, the limit must be an ESS. If the selection is sufficiently weak, then if an ESS exists, the system must converge to it (Eshel 1982; Hines 1982; see also Thomas 1985a,b; Cressman and Hines 1984; Hines and Bishop 1984a,b). This is generally not true for a multilocus system. It might be predicted that this failure for frequency-independent selection can be exacerbated only under (short-term) frequency-dependent selection. We shall see, however, that the process of long-term selection in both cases is most likely to produce convergence to an ESS.

LONG-TERM SELECTION AND TWO-LOCUS
POPULATION GENETICS

Consider a two-locus random-mating diploid genetic system with alleles A_1, A_2, \dots, A_n at one locus and B_1, B_2, \dots, B_m at the other and recombination rate $R(0 < R \leq 1/2)$ between the loci. (See Eshel and Feldman [1984] for further details and Liberman [1988] for a generalization to multiple loci.) The viability of genotype $A_i B_k / A_j B_l$ is w_{ijkl} ($i, j = 1, 2, \dots, n; k, l = 1, 2, \dots, m$) with

$$w_{ijkl} = w_{jikl} = w_{ijlk} = w_{jilk} \quad (1)$$

Here, w_{ijkl} may be either frequency-dependent or -independent.

Denote by x_{ik} the frequency of the chromosome $A_i B_k$ after selection and recombination. Under random mating, the average viability of newborn offspring is

$$\bar{w} = \sum_{ijkl} w_{ijkl} x_{ik} x_{jl} \quad (2)$$

After random mating, selection, and recombination, the frequency of $A_i B_k$ in the next generation is

$$x'_{ik} = (\bar{w})^{-1} \left\{ R \sum_{jl} w_{ijkl} x_{il} x_{jk} + (1-R) \sum_{jl} w_{ijkl} x_{ik} x_{jl} \right\} \quad (3)$$

Equilibrium frequencies of $\{A_i B_k\}$ will be denoted by $\{x_{ik}^*\}$, where $\{x_{ik}^*\}$ solves Equation 3 with the prime removed from the left side.

Now assume that viability mutations occur at random at each of the loci. We make no specific assumption about the distribution of effects of a single mutation on the phenotype of its carriers. We assume only the following:

- A(i) All mutations that affect the phenotype under study are possible in the long run.
- A(ii) The rate of mutation (at least of successful mutations, i.e., those that invade the population) is low enough to guarantee that after an advantageous mutation arises, short-term convergence occurs to a small neighborhood of a stable equilibrium before a new, advantageous mutation arises.

In what follows, the second assumption enables us to ignore the extremely unlikely occurrence of favorable double mutations. We

therefore suppose that a new allele A_{n+1} appears at a low frequency near the equilibrium $\{x_{ik}^*\}$. Denote $x_{n+1,k}$ by ε_k ($k = 1, 2, \dots, m$), where $\sum_k \varepsilon_k = \varepsilon > 0$ and $|x_{ik} - x_{ik}^*| < \varepsilon$ for $i = 1, 2, \dots, n$.

We are interested first in necessary and sufficient conditions for the initial success of the new mutant allele. Note that such an allele introduces m^2n new genotypes $A_iB_l/A_{n+1}B_k$, each of which in general has a different viability. The frequencies of these genotypes (even after random mating) will depend on both the resident frequencies $\{x_{ik}^*\}$ and the relative frequencies $\varepsilon_1, \varepsilon_2, \dots, \varepsilon_m$ of the mutant chromosomes $A_{n+1}B_k$ upon their introduction. We can, however, use the Hardy-Weinberg law to calculate the average viability of an offspring that carries the mutant chromosome $A_{n+1}B_k$. Neglecting terms of smaller order than ε , this will be

$$\bar{w}_{n+1,k}^* = \sum_{jl} w_{n+1,jkl}^* x_{jl}^* \quad (4)$$

where, in the frequency-dependent case, $w_{n+1,jkl}^*$ is evaluated at $\{x_{ik}^*\}$, that is, with respect to the resident frequencies. With frequency-independent selection, $w_{ijkl}^* = w_{ijkl}$. The marginal fitness of the mutant chromosome $A_{n+1}B_k$ is therefore uniquely determined by the distribution of resident chromosomes $\{x_{ij}^*\}$. This is not true for the average fitness of all mutant genotypes, which is

$$\bar{w}_{n+1}^* = \sum_k \frac{\varepsilon_k}{\varepsilon} \bar{w}_{n+1,k}^* = \sum_{k=1}^m \frac{\varepsilon_k}{\varepsilon} \sum_{j=1}^n \sum_{l=1}^m w_{n+1,jkl}^* x_{jl}^* = \bar{w}_{n+1}^*(\varepsilon) \quad (5)$$

Average fitness obviously depends on the relative frequencies at which the mutant chromosomes are introduced.

Now use Equation 3 with $n + 1$ alleles at the A locus and neglect terms of smaller order than ε . We have for all $k = 1, 2, \dots, m$,

$$\begin{aligned} \varepsilon'_k = x'_{n+1,k} = (\bar{w}^*)^{-1} & \left\{ \varepsilon_k \sum_{j=1}^n \sum_{l=1}^m w_{n+1,jkl}^* x_{jl}^* \right. \\ & \left. + R \sum_{j=1}^n \sum_{l=1}^m w_{n+1,jkl}^* (\varepsilon_l x_{jk}^* - \varepsilon_k x_{jl}^*) \right\} \end{aligned} \quad (6)$$

If λ is the leading eigenvalue of the local stability matrix from Equation 6, with $\mathbf{u} = (u_1, u_2, \dots, u_m)$, the associated right eigenvector, normalized to $\sum u_i = 1$, then we show in Appendix 1 that

$$\lambda = (\bar{w}^*)^{-1} \sum_{k=1}^m u_k \sum_{j=1}^n \sum_{l=1}^m w_{n+1,jkl}^* x_{jl}^* = \frac{w_{n+1}^*(\mathbf{u})}{\bar{w}^*} \quad (7)$$

This allows us to state the following:

Proposition 1 (Eshel and Feldman 1984). A necessary condition for the initial increase of the rare mutant allele A_{n+1} introduced at the A locus is

$$\bar{w}_{n+1}^*(\mathbf{u}) \geq \bar{w}^* \quad (8)$$

A sufficient condition for the invasion by a rare mutant allele is that Equation 8 hold as a strict inequality.

Note that because \mathbf{A} is a positive matrix, for any vector $\varepsilon = (\varepsilon_1, \varepsilon_2, \dots, \varepsilon_m) \geq 0$ with $\sum_{k=1}^m \varepsilon_k > 0$,

$$\lim_{t \rightarrow \infty} \frac{\mathbf{A}^t \varepsilon}{\|\mathbf{A}^t \varepsilon\|} = \mathbf{u}$$

where the norm $\|\mathbf{z}\|$ is defined as $\sum_k |z_k|$ (e.g., Karlin and Taylor 1975). Thus, the biological interpretation of Proposition 1 is that if the initial frequency of A_{n+1} , namely ε , is small enough, then the normalized vector of frequencies of $A_{n+1}B_k$ will remain as close as we wish to the vector \mathbf{u} for as long as we wish. With this in mind, we first present details of the consequences of frequency-independent selection and follow this with some analysis of frequency dependence.

LONG-TERM FREQUENCY-INDEPENDENT SELECTION

With frequency-independent selection, $w_{ijkl}^* = w_{ijkl}$. In this case, as defined in Equation 5, $\bar{w}_{n+1}^*(\mathbf{u})$ is the average fitness of all the genotypes that contain the mutant allele, where the relative frequencies of the mutant chromosomes are u_1, u_2, \dots, u_m . But if the initial frequency of the mutant is low enough, the relative frequencies of these chromosomes will remain arbitrarily close to u_1, u_2, \dots, u_m . Then Proposition 1 can be interpreted as follows:

Result 1. In a two-locus genetic model with frequency-independent viability selection and random mating, except for the case of unit eigenvalue, a newly introduced mutant allele at one of the loci will

invade the population if and only if it initially increases the average viability of the population.

Proposition 1 and Result 1, which have been generalized by Liberman (1988) to include mutations at one of any number of loci, may provide a weaker, long-term counterpart to the short-term Fundamental Theorem of Natural Selection, which is false for multilocus genetic systems.

Result 1 has an immediate application to the important case of multilocus genetic determination of a quantitative phenotype γ that achieves a strict global maximum at $\gamma = \gamma^*$ (i.e., $w(\gamma^*) > w(\gamma)$ for all $\gamma \neq \gamma^*$). In this case, the only fixed points of the long-term process are those (phenotypically equivalent) genotypic equilibria that determine γ^* . Specifically, we have the following:

Result 2. Suppose that the viability w of an individual in a large (i.e., infinite) population is determined by its phenotype γ , and suppose $w(\gamma)$ attains a global maximum at $\gamma = \gamma^*$. Let an individual's phenotype γ be determined by its genotype G at a given set of loci. Then

- i. The only genotypes that are stable to invasion by any mutation that affects the genotype are those that determine γ^* .
- ii. The set Γ of genotypes that determine the optimal phenotype γ^* is stable to invasion by any mutation that affects the phenotype.

The proofs of both parts of Result 2 are given as Appendix 2.

EXTERNAL STABILITY, PHENOTYPICALLY STABLE STRATEGIES, AND LONG-TERM STABILITY

The concept of a phenotypically stable strategy is an extension of Hamilton's concept of an unbeatable strategy, namely a strategy p that, once fixed in the population, is immune to (say, short-term stable against) any invading mutant strategy (Hamilton 1967). The motivation for this extension (Hammerstein and Selten 1994) stems from the finding that the strict requirement for unbeatability is too strong to be generally satisfied by the ESS even under haploid asexual dynamics (see also Weissing 1996). This is because a set of genotypes may determine the same phenotype, but some (or even all) of these geno-

types may disappear following mutation. If, however, the mutation does not change the phenotype, then that phenotype can still be regarded as stable relative to the mutation. In this sense, genotypic stability is a stronger concept than phenotypic stability. The weaker concept of phenotypic stability, however, retains the spirit of unbeatability in the sense that it allows the population to be "trapped" in a set of states that determine the phenotypically stable strategy. It is worthwhile to formalize this brief discussion using the following definitions.

Definition 1. An absorbing set of states for the stochastic process of long-term evolution is said to be an externally stable set.

In other words (see also Lessard 1990; Eshel 1996), a set Γ of short-term stable genetic equilibria is said to be externally stable if, starting from any genetic equilibrium in Γ , the long-term process of evolution allows passage only to another state in Γ .

Definition 2 (after Hammerstein and Selten 1994). A phenotype or a distribution of phenotypes F (a strategy, say) is said to be phenotypically stable if there is an externally stable set of genotypes, each of which phenotypically generates F as a population strategy.

Equivalently,

Definition 2'. A strategy p is said to be phenotypically stable if it is phenotypically determined by each genotypic state within a given absorbing set of states for the process of long-term evolution.

Result 2 asserts that in a random-mating population with frequency-independent viabilities, a phenotypic optimum and only a phenotypic optimum is a phenotypically stable strategy with respect to single-locus mutations, regardless of the number of loci involved. This is not a trivial statement because the short-term process of natural selection does not generally converge to a genetic equilibrium that phenotypically generates the optimal phenotype. On the contrary, a stable genetic equilibrium may determine a phenotypic distribution that is not even the closest possible (given the available genotypes) to the optimum.

The preceding remark leads us to ask whether Results 1 and 2 guarantee that the long-term process actually converges, or at least converges with positive probability, to a genetic equilibrium that produces the optimal phenotypic value when it exists.

By definition, a phenotypically stable strategy p is the phenotypic result of an absorbing set of states in the long-term evolutionary stochastic process. Moreover, in the case treated here (and all others with which we are familiar), this absorbing set is attainable from all other states. However, if the sample space of the long-term process (all short-term equilibria) is not finite, it does not guarantee long-term convergence to the absorbing set, and the probability of this event may be zero. Thus, in a recent paper, Eshel et al. (1997) address long-term asexual selection with a population game structure having a continuum of types. They show that the phenotypically stable strategies of the long-term process are exactly the ESSs of the population game. However, starting from a distribution of strategies close enough to an ESS, convergence with probability 1 to the ESS is guaranteed only under specific additional conditions (namely, continuous stability; Eshel and Motro 1980). If these conditions are not met, the probability of long-term convergence to the absorbing ESS is zero! For this reason, we need the following definition:

Definition 3. A strategy p is said to be long-term stable if for any $\varepsilon > 0$ there is a neighborhood of p such that starting from this neighborhood, the long-term process will converge to p with probability greater than $1 - \varepsilon$.

Of course, the exact transition law of the long-term process is determined by the distribution of the mutations, and this generally is not known. However, the form of the selection matrix, in combination with the genetic structure of the population, tells us which transitions have zero density. It is somewhat surprising that in many cases, this is sufficient to prove either long-term convergence or nonconvergence. Theorem 1 implies that in a two-locus random-mating genetic system with frequency-independent selection, a new mutation will invade if it initially brings the phenotypic value of its carriers closer to the optimum, at least with respect to the weighting used in Equation 7. When a new mutation invades, however, our analysis is not informative as to whether the *final* state to which the subsequent short-term process moves must produce a distribution of phenotypes whose average fitness is greater than that of the initial population. When true, this is a very strong result. It would entail that even though the long-term process is essentially random (because each realization of the ordering of mutations introduced is the result of a stochastic process) the average

fitness of the population should increase from one equilibrium state to the next. Thus, in the vicinity of a phenotypically stable strategy, the population should converge to it with probability 1, regardless of the distribution of the mutations, given only the general assumptions A(i) and A(ii) earlier.

Simple structural assumptions on the parameters of the evolutionary system may guarantee this property and, therefore, convergence with probability 1 to a phenotypic value that is at least a local optimum. To see this, consider two loci with a recombination rate $R > 0$. Suppose that the effect of the phenotype in question on the overall viability of the individual is small. In this case, the fitness differences among all genotypes are sufficiently small relative to R , and we know that the linkage disequilibrium for all chromosomes is small, even relative to the selection forces, and short-term selection will eventually lead to an increase in the mean fitness of the population (Nagylaki 1976, 1992). Under these conditions, if the successive mutations are also of sufficiently small effect, then the long-term process should behave like a one-locus genetic system, converging monotonically with probability 1 to a local optimum, which is then long-term strictly stable.

It is interesting, and somewhat surprising, that this result is not generally true. Bergman et al. (1997) have recently shown by numerical simulation that the initial increase of the average fitness of the population that occurs with the establishment of a new mutation, may be followed by a decrease of the average fitness to less than its initial value. However, this appears to occur in a rather small fraction of cases. With randomly chosen fitnesses for the carriers of the mutation (see Bergman et al. [1997] for details), we conjecture that the *expected* change in average fitness from one equilibrium to the next should be positive. If this is the case, the stochastic long-term process must approach the vicinity of the phenotypic optimum, if it exists. The optimum would then still be long-term stable.

An interesting case would take the phenotypic effects of all single mutations from some distribution with a small variance so that with some nonzero probability a mutation would have a large effect on all its carriers, although for the large majority of mutations, the average fitness of the population would increase from one (short-term) stable genetic equilibrium to the next. In this case, therefore, most of the time the system would be close to the local optimum, although in a small fraction of that small fraction of

mutations with large effects, the system may depart further from the optimum. Because this rare event involves mutations of relatively large effect, given that the system departs from the optimum, it is likely to move relatively far from it. In this event, the long-term process is likely to take the population near a new local optimum in whose vicinity it should stay for a long time. This pattern of evolution would be reflected in the phenotypic distribution (although not, of course, if the genetics is one-locus) behaving as a punctuated process in which most of the time, but not always, the system moves toward a higher optimum.

LONG-TERM FREQUENCY-DEPENDENT SELECTION

We discuss a random-encounter population game with r pure strategies $\alpha_1, \alpha_2, \dots, \alpha_r$. Let v_{ij} be the viability of an α_i -player who encounters an α_j -player; $i, j = 1, 2, \dots, r$. In reality, most individuals are unlikely to play a pure strategy. The payoff function for a player who chooses a mixed strategy \mathbf{p} (i.e., a player who plays strategy α_i with probability p_i) when encountering a \mathbf{q} -strategist is

$$V(\mathbf{p}, \mathbf{q}) = \sum_{ij=1}^r p_i v_{ij} q_j \quad (9)$$

Different genotypes are assumed to have different distributions of the propensities to play the different strategies. To be precise, assume that the individuals in the population have genotypes defined at two loci, with genotype $A_i B_k / A_j B_l$ choosing the strategy (or having the distribution of phenotypes) $\mathbf{p}^{(ijkl)}$ where

$$\mathbf{p}^{(ijkl)} = \mathbf{p}^{(ijlk)} = \mathbf{p}^{(jilk)} = \mathbf{p}^{(jilk)}$$

If x_{ik} is the frequency of chromosome $A_i B_k$ in the population after selection and recombination, then the average strategy of a newborn offspring, namely the population strategy, will be

$$\mathbf{p} = \mathbf{p}(\mathbf{x}) = \sum_{ijkl} \mathbf{p}^{(ijkl)} x_{ik} x_{jl} \quad (10)$$

(In other words, the probability that a newborn offspring will choose the strategy α_s is $p_s = \sum_{ijkl} p_s^{(ijkl)} x_{ik} x_{jl}$). The viability of genotype $A_i B_k / A_j B_l$ is therefore

$$w_{ijkl} = w_{ijkl}(\mathbf{x}) = V(\mathbf{p}^{(ijkl)}, \mathbf{p})$$

Recall that the (short-term) equilibrium frequencies $\{x_{ik}^*\}$ of chromosomes $\{A_i B_k\}$ are the solutions of Equation 3 with the primes removed from the left-hand sides, regardless of whether the selection is or is not a function of the frequencies.

Suppose now that a new mutant allele A_{n+1} occurs at the A-locus. We know that in this case Proposition 1 still holds; that is, A_{n+1} will become established in the population if Equation 8 holds as a strict inequality. The viability $w_{n+1,jkl}^*$ of the mutant genotype $A_{n+1}B_k/A_jB_l$, when it is rare, is computed at the equilibrium point $\{x_{ik}^*\}$, and for the population game, is interpreted as

$$w_{n+1,jkl}^* = V(\mathbf{p}^{(n+1,jkl)}, \mathbf{p}^*) \quad (11)$$

where

$$\mathbf{p}^* = \mathbf{p}(x^*) = \sum_{ijkl} \mathbf{p}^{(ijkl)} x_{ik}^* x_{jl}^* \quad (12)$$

is the population strategy at equilibrium.

Assume now that the vector $(\varepsilon_1, \varepsilon_2, \dots, \varepsilon_m)$ of frequencies of the mutant chromosomes is close to the right eigenvector \mathbf{u} used in Equation 7. The mean strategy of an individual carrying the mutant chromosome $A_{n+1}B_k$ is

$$\mathbf{p}^{(n+1,k)} = \sum_{jl} \mathbf{p}^{(n+1,jkl)} x_{jl}^*$$

Hence, the mean strategy of a random mutant individual in the population is

$$\mathbf{p}^{(n+1)} = \mathbf{p}^{(n+1)}(\mathbf{u}) = \sum_k u_k \mathbf{p}^{(n+1,k)} = \sum_{jkl} u_k \mathbf{p}^{(n+1,jkl)} x_{jl}^* \quad (13)$$

When we combine Equations 5, 11, and 13, one has

$$\bar{w}_{n+1}^* = V(\mathbf{p}^{(n+1)}, \mathbf{p}^*) \quad (14)$$

This is the payoff to a random mutant upon encountering a nonmutant individual. In the same way, the residents' mean strategy is

$$\begin{aligned} w^* &= \sum_{ijkl} w_{ijkl}^* x_{ik}^* x_{jl}^* = \sum_{ijkl} V(\mathbf{p}^{(ijkl)}, \mathbf{p}^*) x_{ik}^* x_{jl}^* \\ &= V\left(\sum_{ijkl} \mathbf{p}^{(ijkl)} x_{ik}^* x_{jl}^*, \mathbf{p}^*\right) = V(\mathbf{p}^*, \mathbf{p}^*) \end{aligned} \quad (15)$$

We can therefore write Proposition 1 in this case as follows:

Proposition 2 (Eshel and Feldman 1984). A necessary condition for the initial increase of allele A_{n+1} is that the mean strategy $\mathbf{p}^{(n+1)}$ of the rare mutant genotypes be at least as good as the population average strategy \mathbf{p}^* when playing against \mathbf{p}^* . That is,

$$V(\mathbf{p}^{(n+1)}, \mathbf{p}^*) \geq V(\mathbf{p}^*, \mathbf{p}^*) \quad (16)$$

A sufficient condition for initial increase of A_{n+1} is that Equation 16 hold as a strict inequality.

A phenotypically stable strategy, if it exists, must be a best response against itself. This is so because if the population mean strategy \mathbf{p}^* were not a best response to \mathbf{p}^* in the phenotypic game, then another strategy, \mathbf{s} , must exist such that $V(\mathbf{s}, \mathbf{p}^*) > V(\mathbf{p}^*, \mathbf{p}^*)$. In that case, it follows from Proposition 2 that a mutant determining the strategy \mathbf{s} will initially increase in the population.

Suppose the population mean strategy \mathbf{p}^* is a best response to \mathbf{p}^* and is not an ESS in the phenotypic game. It follows from the definition of ESS that another strategy \mathbf{s} must exist such that $V(\mathbf{s}, \mathbf{s}) \geq V(\mathbf{p}^*, \mathbf{s})$ (see Hofbauer and Sigmund 1988, 121). In such a case, the frequency of a dominant mutation A_{n+1} that (monomorphically) generates the strategy \mathbf{s} , regardless of the alleles in the other locus, can become established in the population and \mathbf{p}^* cannot possibly be phenotypically stable. Thus, we have the following (see also Hammerstein 1996):

Result 3. Any phenotypically stable strategy for the two-locus population game is an ESS.

LONG-TERM STABILITY OF AN ESS

An important question still to be addressed concerns whether the long-term process, once in the vicinity of an ESS $\hat{\mathbf{p}}$, will converge to $\hat{\mathbf{p}}$. Let us distinguish two cases:

Case I. $\hat{\mathbf{p}}$ is a strict best response against itself; that is, for all $\mathbf{p} \neq \hat{\mathbf{p}}$, $V(\mathbf{p}, \hat{\mathbf{p}}) < V(\hat{\mathbf{p}}, \hat{\mathbf{p}})$.

Case II. $\hat{\mathbf{p}}$ is a weak best response against itself; that is, for some $\mathbf{p} \neq \hat{\mathbf{p}}$, $V(\mathbf{p}, \hat{\mathbf{p}}) = V(\hat{\mathbf{p}}, \hat{\mathbf{p}})$, in which case we know that $V(\mathbf{p}, \mathbf{p}) < V(\hat{\mathbf{p}}, \mathbf{p})$.

Case I

Note that this case is possible only if $\hat{\mathbf{p}}$ is a pure strategy. In such a case, when the population strategy is close to $\hat{\mathbf{p}}$, the viabilities of the genotypes $w_{ijkl} = V(\mathbf{p}^{(ijkl)}, \mathbf{p})$ can be estimated well by the fixed values $\hat{w}_{ijkl} = V(\mathbf{p}^{(ijkl)}, \hat{\mathbf{p}})$. We therefore expect (and simulations done in collaboration with A. Bergman offer some support for this conjecture) that the conditions for long-term convergence to the ESS should be very similar to those for convergence to a local optimum under frequency-independent selection. This tends to occur with a probability that approaches 1 when the population strategy is chosen initially to be arbitrarily close to the ESS. It might be conjectured, however, that with some positive probability a single mutation of large effect may perturb the population sufficiently far from the ESS that convergence to another ESS, if one exists, might ensue.

This would be impossible in a one-locus genetic system, and, as shown for the case of frequency-independent selection, it would also be impossible in a multilocus system under selection that is an order of magnitude weaker than the rate of recombination. In a population game, however, the viabilities of the genotypes are always bounded from below and from above by the minimal and maximal payoff functions, respectively. We can then state the following:

Proposition 3. If the ratio between the maximal and minimal payoff function of the population game, measured in terms of viability, is sufficiently close to 1, then for any ESS that is a strict best response against itself there is a neighborhood of it from which the long-term process converges to the ESS with probability 1. The optimum is then long-term stable.

Case II

This involves convergence to an ESS that is not a *strict* best response against itself. This is always the case when the ESS is mixed. Here we concentrate, for simplicity, on the case of a fully mixed ESS. That is, $\hat{p}_i \neq 0, 1$ for all $i = 1, 2, \dots, r$. It is surprising that convergence to this "weaker" ESS is more easily guaranteed than in the "stronger" Case I. To see this, recall that for a mixed ESS, $\hat{\mathbf{p}}$, $V(\mathbf{p}, \hat{\mathbf{p}}) = V(\hat{\mathbf{p}}, \hat{\mathbf{p}})$ for all \mathbf{p} . Hence, at the ESS, the viabilities $w_{ijkl}(\hat{\mathbf{p}}) = V(\hat{\mathbf{p}}^{(ijkl)}, \hat{\mathbf{p}})$ are all equal. By continuity, it follows that the viabilities

$w_{ijkl}(\mathbf{p})$ can be guaranteed to be arbitrarily close to each other provided that \mathbf{p} is close enough to the ESS $\hat{\mathbf{p}}$. Hence, the selection operating on the population may be chosen to be weak as we wish by choosing the population strategy sufficiently close to $\hat{\mathbf{p}}$. Note that this does not depend on any specific assumptions about the phenotypic effect of a single mutation, in contrast to what we saw for frequency-independent selection: even large changes in an individual's strategy will be only weakly selected for or against.

Now for any positive recombination rate, as the maximum selection differential approaches zero, short-term selection will take the linkage disequilibrium (i.e., the covariances between allelic frequencies at the two loci) to the order of the square of the selection differentials (Nagylaki 1976, 1992). This must be true for frequency-dependent selection as well as for frequency-independent selection, because the only assumption made is that selection differentials are sufficiently weak relative to the recombination rate. Furthermore, Nagylaki has shown that for any fixed set of w_{ijkl} (e.g., for frequency-independent selection), if the linkage disequilibrium is small enough, then for chromosome frequencies $\{x_{ik}\}$ in one generation and $\{x'_{ik}\}$ in the next generation,

$$\sum_{ijkl} w_{ijkl} x'_{ik} x'_{jl} > \sum_{ijkl} w_{ijkl} x_{ik} x_{jl} \quad (17)$$

as in Equation 3.

Equation 17 is true, then, as a mathematical statement regardless of how $\{w_{ijkl}\}$ are interpreted. In Nagylaki's analysis, w_{ijkl} were understood as fixed fitnesses so that Equation 17 was interpreted in the sense that the average fitness must increase over time. But Equation 17 remains mathematically valid for any choice of w_{ijkl} and, in particular, if we choose $w_{ijkl} = w_{ijkl}(\mathbf{p})$, where \mathbf{p} is the population strategy before selection, recombination, and random mating. In this case, the meaning of Equation 17 will be different. On one hand, it follows from Equation 10 that

$$\begin{aligned} \sum_{ijkl} w_{ijkl} x_{ik} x_{jl} &= \sum_{ijkl} V(\mathbf{p}^{(ijkl)}, \mathbf{p}) x_{ik} x_{jl} \\ &= V\left(\sum_{ijkl} x_{ik} x_{jl} \mathbf{p}^{(ijkl)}, \mathbf{p}\right) = V(\mathbf{p}, \mathbf{p}) \end{aligned} \quad (18)$$

On the other hand, the same argument gives

$$\begin{aligned}\sum_{ijkl} w_{ijkl} x'_{ik} x'_{jl} &= V\left(\sum_{ijkl} x'_{ik} x'_{jl} \mathbf{p}^{(ijkl)}, \mathbf{p}\right) \\ &= V(\mathbf{p}', \mathbf{p})\end{aligned}\tag{19}$$

where

$$\mathbf{p}' = \sum_{ijkl} x'_{ik} x'_{jl} \mathbf{p}^{(ijkl)}$$

is the population strategy after selection, recombination, and random mating. We therefore have the following:

Result 4. If $\hat{\mathbf{p}}$ is a mixed ESS (or, more generally, any ESS that is not a strict best response against itself) and if the population strategy \mathbf{p} determined by the two-locus genetic model is sufficiently close to $\hat{\mathbf{p}}$, then after one generation the population strategy \mathbf{p}' is a better response against \mathbf{p} than \mathbf{p} ; that is,

$$V(\mathbf{p}', \mathbf{p}) > V(\mathbf{p}, \mathbf{p})\tag{20}$$

Remark. This result holds for any distribution \mathbf{p} of genotypes in a one-locus genetic system (Eshel 1982) but not in general for a two-locus system with recombination and selection unless \mathbf{p} is close to the ESS.

For a population game with two pure strategies, Eshel (1982) further proved that whenever a system satisfies Equation 20, it also satisfies the following two conditions:

- a. If the ESS $\hat{\mathbf{p}}$ is within the range of all genetically available vectors \mathbf{p} – that is, vectors $\mathbf{p} = \mathbf{p}(\mathbf{x})$ obtained for some chromosome distribution $\{x_{ik}\}$ on the right-hand side of Equation 10 – then short-term selection will result in convergence to a stable genetic equilibrium \mathbf{x} that phenotypically generates the ESS $\hat{\mathbf{p}}$.
- b. If $\hat{\mathbf{p}}$ is not in the interval of available genetic values of \mathbf{p} , then short-term selection will result in convergence to a stable equilibrium \mathbf{x}^* such that $\mathbf{p}'(\mathbf{x}^*)$ is the closest possible to $\hat{\mathbf{p}}$. We then have

Result 5. If a two-strategy mixed ESS exists, it is phenotypically stable and strictly long-term stable in a two-locus genetic system with selection and random mating.

Proof. Phenotypic stability is an immediate result of condition a of a system satisfying Equation 20. Indeed, the ESS is genetically

available within a genetic system in which it existed prior to the introduction of a new mutation. Hence, after the introduction of the new mutation, short-term selection must move the population to a genetic equilibrium, possibly a different one from the original one prior to the appearance of the mutation but one that again phenotypically generates the ESS. Condition b associated with Equation 20 guarantees that no mutation that invades can take the population further from the ESS, but any mutation that increases the genetic availability in the direction of the ESS will result in a stable population strategy that is closer to the ESS. Moreover, condition a guarantees that when the population reaches the vicinity of the ESS, the exact ESS will be attained after a finite number of steps. Hence, the ESS is globally and strictly long-term stable in this case.

More can be proved for the two-strategy case. For a mixed ESS in a two-strategy population game, the long-term process will converge with probability 1 to the ESS. This is true because no other state is long-term stable, and from any state there is a positive probability that the system reaches a vicinity of the ESS within a finite number of steps, and from here we have proved that there is convergence to the ESS with probability 1.

Thus, contrary to intuition, frequency-dependence does not exacerbate the analysis of convergence to a phenotypic optimum in a multilocus genetic system. In fact, we have just shown that with frequency-dependent selection, convergence occurs with probability 1 regardless of the distribution of the mutations, a stronger result than with frequency-independent selection. There is a simple reason for the stronger result with frequency-dependence. A multilocus system may react to natural selection by reducing the average fitness of the population, but this requires linkage disequilibrium. Recombination always reduces linkage disequilibrium, but epistatic selection can compensate for this. If the selection is weak enough, however, recombination will eventually render the linkage disequilibrium negligible (even compared to the selection differentials). With frequency-independent selection, the only way to reduce selection differentials is by reducing the phenotypic differences among the genotypes. But in the case of a mixed ESS with frequency-dependent selection, the differences in fitness among the genotypes tend to zero as the population strategy approaches the ESS, regardless of the phenotypic variation in the population. Thus, selection

tends to zero and recombination takes over and nullifies the effect of linkage disequilibrium.

Thus, for a general population game with any number of strategies, Equation 20 guarantees that the long-term process determined by a two-locus genetic system will behave like a one-locus system in the vicinity of an ESS. The question of long-term convergence to the ESS in this case remains open, even for an asexual population. We will see, however, that even under multilocus selection and recombination, the ESS is phenotypically stable in the sense that there exists an externally stable set of genetic equilibria such that each equilibrium in this set phenotypically generates the ESS as its mean strategy.

PHENOTYPIC STABILITY OF THE ESS WITH MULTIPLE LOCI

If the first ESS condition is satisfied as a strict inequality (i.e., if the ESS is strictly the best response against itself), then the set of genetic equilibria that phenotypically determine the ESS is externally stable. This follows from Proposition 2 in exactly the same way that Result 2 follows from Proposition 1. Consequently, we have the following:

Proposition 4. Any ESS that is a strict best response against itself is phenotypically stable.

Note, however, that only a pure strategy can be a strict best response against itself. Weissing (personal communication) showed that the set of all genetic equilibria that phenotypically determine the ESS is not always externally stable; with more than two strategies involved in the ESS, an invading mutant may shift the population to an ever-increasing cycle away from the ESS. Hammerstein and Selten (1994) and later Hammerstein (1996) suggested that the set of all phenotypically monomorphic genetic equilibria that phenotypically generate the ESS is actually externally stable (in which case, according to the definition given earlier, the ESS would indeed be unbeatable). The exact mathematical statement by Hammerstein (1996, Theorem 2) is, however, significantly weaker than this. This theorem claims only that "if p is an evolutionarily stable strategy of G , then the monomorphism is phenotypically stable and invasion stable (i.e., externally stable) against any mutant that cannot phenotypically generate p in heterozygous condition." From the proof (in particular, p. 525) it

appears that a "mutant allele that cannot phenotypically generate \mathbf{p} in heterozygous condition" means a mutant that does not include \mathbf{p} among the linear combinations of strategies generated by its heterozygotes. Unfortunately, stability of a set of states against such a restrictive set of mutations that take the population outside this set is meaningless; indeed, any set of states is stable against some class of mutations.

In fact, it is easy to find an example of a neutral invasion of the genotypes producing a phenotypically monomorphic ESS by a dominant mutation that, when associated with different alleles at another locus, phenotypically generates different strategies with the ESS as their average. If initially there is linkage equilibrium, neutrality is preserved regardless of the frequency of the mutant allele. A phenotypically nonmonomorphic equilibrium will then be attained. Moreover, it is not clear how the neutrally perturbed system will respond to a subsequent mutation.

Weissing (1996) suggested that if a two-locus double homozygote generates the ESS it will be externally stable. This seems actually to be a one-locus property and therefore standard except for neutral mutations that phenotypically generate the ESS as their mean strategy, thus again shifting the population to almost any mixture of phenotypically nonmonomorphic genotypes that on average phenotypically generate the ESS.

We have seen, however, that at least in the vicinity of a mixed ESS, short-term natural selection renders the effect of linkage disequilibrium negligible even relative to the weak selection operating on the population. Therefore, the multilocus system behaves as a one-locus system. For a one-locus system, Eshel and Sansone (1998) have recently proved the following:

Proposition 5. Let $\hat{\mathbf{p}}$ be an ESS of a population game (with any number of pure strategies) and let individual strategies be determined by a one-locus diploid genetic system with random mating. Then

- i. The set of all genetic equilibria that phenotypically generate the ESS $\hat{\mathbf{p}}$ as a population strategy, each including at least one homozygote with $\hat{\mathbf{p}}$ as its own strategy, is externally stable.
- ii. The ESS $\hat{\mathbf{p}}$ is therefore phenotypically stable in the one-locus system.

Following this result, we can now prove that in a multilocus genetic system, at least any mixed ESS is phenotypically stable. Here we state this for a two-locus system, and an analogous argument applies for any number of loci. The proof is included as Appendix 3.

Result 6. Let \hat{p} be a fully mixed ESS with any number of pure strategies. Then

- i. The set Γ of all genetic equilibria that phenotypically generate \hat{p} as a population strategy, each including at least one double homozygote that phenotypically generates \hat{p} exactly as its own strategy, is externally stable.
- ii. The mixed ESS \hat{p} is, therefore, phenotypically stable.

CONCLUSIONS

Our results indicate that in the debate about adaptation, adaptationism, and optimality (Maynard Smith 1978; Parker and Maynard Smith 1990; Orzack and Sober 1994, 1996; Brandon and Rausher 1996), a distinction should be made between short-term and long-term evolution. We call short-term evolution the process by which natural selection, combined with reproduction (including recombination in the multilocus context), changes the relative frequencies among a fixed set of genotypes, resulting in a stable equilibrium, a cycle, or even chaotic behavior. Long-term evolution is the process of trial and error whereby the mutations that occur are tested and, if successful, invade the population, renewing the process of short-term evolution toward a new stable equilibrium, cycle, or state of chaos. These two processes, even though tightly interconnected, are qualitatively different from each other.

In the debate about adaptationism the opposing arguments tacitly invoke different dynamic processes. Thus, the concept of evolutionary stability as immunity to *any* possible mutation (Hamilton 1967; Maynard Smith and Price 1973) corresponds naturally to the realm of long-term dynamics; yet, both the criticism and the defense of the relevance of this concept to population genetics have been by and large based on the analysis of short-term dynamic models (see Eshel 1991, 1996 for further discussion). Concerning short-term dynamic models, we have expressed our view elsewhere that convergence to individual local optima is likely to occur only

under the specific assumptions of often unrealistically simple models (Eshel 1991; Feldman et al. 1996). In this chapter we show that, quite surprisingly, this is not the case for long-term evolution. Phenotypic changes, when determined by long-term genetic dynamics, even with a multilocus genetic structure including recombination, tend to converge in the long term and, with probability 1, to local optima.

Does this mean that one can evaluate local optima without having to worry that they would rarely, if ever, be present because they are not dynamically accessible most of the time? The answer is only partly positive. Our results indicate that theories of local optima (e.g., population game theory) are by no means irrelevant to the theory of natural selection. Thus, local optima may be important. But arguments concerning such local optima cannot be indiscriminately employed for theoretical predictions. Although local optima are likely to be dynamically accessible for conflicts that persist for a long enough time under virtually the same conditions, they still might not be dynamically accessible most of the time under evolution in relatively new environments. In a different paper (Eshel 1991; see also Eshel and Matessi 1998), it was suggested that at least one role of sexual reproduction could be to prevent short-term optimal adaptation that removes heritable variation when environmental conditions change over time.

The model of long-term dynamics suggested here focuses on non-neutral, potentially successful mutations, chosen among those mutations that affect a specific phenotypic trait; this is a small fraction of a small fraction of all mutations that may occur at a few specific loci. Thus, it is assumed that the appearance of such a mutation is a rare event even in relatively large populations. A crucial question, then, is whether this assumption does not stand in contradiction to our deterministic treatment of the short-term stages of the dynamics. Deterministic short-term dynamics indeed correspond to the assumption of an infinite population size. But in an infinite population, the appearance of any possible mutation or, for that matter, a double or triple mutation, cannot possibly be a rare event; with probability 1, any such event must be instantaneous.

The application of such an argument to natural populations, however, should be made very cautiously. Natural populations are finite, even though sometimes large. Yet under most circumstances, deterministic dynamic models have proved quite satisfactory as

approximations for most aspects of (short-term) natural selection in populations that are not very small. More specifically, if the population is not too small and if the short-term deterministic dynamics of an infinite population results in a stable equilibrium, then the corresponding, finite population is likely to remain in the vicinity of this equilibrium. Moreover, in such a case, the only nonneutral mutations with a reasonable chance of successful establishment in the population are those that (when introduced close to the equilibrium in question) are initially successful in the deterministic model. It is therefore reasonable to expect that rare successful mutations in real populations are likely to occur quite close to stable equilibria of the deterministic version of the short-term process.

If the distribution of mutations were known then, in principle, the probability law governing the transition from one short-term equilibrium (or cycle or state of chaos) to the next could be deduced. From this perspective, long-term evolution is a stochastic process over the space of possible "states" to which short-term evolution carries the population. Unfortunately, the transition law governing this process is rarely known. However, knowledge of the genetic structure and the selection parameters is sufficient to determine the zero-probability transformations. Surprisingly, this information by itself is sufficient to obtain quite strong results concerning the limiting behavior of long-term evolution.

It is important that the asymptotic behavior of the long-term process may be very different from that of the more widely studied short-term process. Our focus here has been on long-term viability selection, either frequency-dependent or -independent, in multilocus genetic systems, where an increase in the average fitness of a population is not guaranteed even in the frequency-independent case. Moreover, a stable multilocus equilibrium may not correspond to a maximum of the population fitness over all possible distributions of genotypes. Furthermore, in the frequency-dependent case, a multilocus genetic system may support a stable genetic equilibrium that phenotypically determines a population strategy that is not an ESS, even if the ESS is genetically available (i.e., if it is phenotypically determined by some distribution of genotypes).

For the long-term process of evolution in a two-locus system with random mating and viability selection, we have shown that a strat-

egy (or a distribution of phenotypes) is phenotypically stable if and only if it is either an optimum (in the case of frequency-independent selection) or an ESS (in the case of frequency-dependent selection). This result and all others reported here can be generalized to any multilocus genetic system with random mating.

At least for a two-strategy population game, a mixed ESS is also long-term strictly stable and it also appears that any ESS is long-term stable. It is interesting that this result is independent of the distribution of mutations and requires only that the density of the distribution of the effect of a single mutation be positive in all directions.

Somewhat weaker results apply to a pure ESS in a frequency-dependent selection system and for a phenotypic optimum under frequency-independent selection. Although in these cases phenotypic stability is an immediate consequence of Proposition 1, long-term convergence (even though it appears to be likely) depends on plausible, although specific, assumptions (e.g., they should not be far from homogeneous or too biased in one direction). Convergence is not necessarily monotone, and in some cases a mutation can be established that causes the eventual population strategy to depart further from the ESS than the initial one.

Monotone convergence with probability 1 to either an optimum (under frequency-independent selection) or a pure ESS (in the case of frequency-dependent selection) is guaranteed only when the effect of natural selection via the phenotype is small relative to the rate of recombination. This is caused by the decline in the effect of linkage disequilibrium relative to selection differentials, as a consequence of which the system tends to behave as though only one locus were segregating. We have shown this to always be true near a mixed ESS, and that is why stronger results are available in this case.

The process defined here as long-term evolution involves only changes, due to mutation and selection, in the distribution of specific phenotypic traits – that is, an individual's strategy in a specific conflict. (Neither neutral mutations nor nonneutral mutations that affect other traits are considered in this process.) It is crucial for our analysis that such specific mutations are rare. A different model would apply if there were frequent relevant mutations for natural selection to act upon. In that case, the population might follow a so-called adaptive path (Hofbauer and Sigmund 1990). So far, however, this model has been developed only for asexual populations.

We make a stronger assumption concerning natural selection – namely, that the regime of selection acting on the trait under study remains invariant during the slow process of transitions between genetic equilibria. This is the kind of assumption relevant to Fisher's (1928) proposal for the evolution of dominance, but it may also be valid for long-lasting conflicts involving mate choice or predators and prey. Of course, each case requires its own specific model. For such cases (but by no means for all population games), the theory of long-term evolution predicts convergence to either an optimum or an ESS regardless of the genetic system.

For shorter-lived processes of conflict (e.g., in a newly colonized niche) we expect the population to be close to a short-term stable equilibrium, but not to one that is long-term stable. Sex and recombination are likely to cause deviations from either optimality or evolutionary stability.

Finally, if the environment changes frequently or continuously, convergence even to a short-term equilibrium is unlikely to occur. In such cases, unless the multilocus selection is strictly additive, the effects of sex and linkage may prevent the population not only from reaching an optimum (or an ESS) but also from attaining a locally adaptive trajectory.

APPENDIX 1: PROOF OF EQUATION 7

Rewrite Equation 6 in vector form as

$$\mathbf{e}' = \mathbf{A}\mathbf{e} \quad (\text{A1.1})$$

where $\mathbf{A} = \|\partial \mathbf{e}'_k / \partial \mathbf{e}_l\|$ with

$$\frac{\partial \mathbf{e}'_k}{\partial \mathbf{e}_l} = (\bar{w}^*)^{-1} R \sum_j w_{n+1,jkl}^* x_{jk}^* \quad \text{for } k \neq l \quad (\text{A1.2})$$

and

$$\frac{\partial \mathbf{e}'_k}{\partial \mathbf{e}_k} = (\bar{w}^*)^{-1} \left\{ R \sum_k w_{n+1,jkk}^* x_{jk}^* + (1-R) \sum_{kl} w_{n+1,jkl}^* x_{jl}^* \right\} \quad (\text{A1.3})$$

Denote by λ the leading eigenvalue of \mathbf{A} with $\mathbf{u} = (u_1, u_2, \dots, u_m)$ the corresponding right eigenvector normalized to $\sum u_i = 1$. Because \mathbf{A} is a positive matrix, it follows from the Perron-Frobenius theorem that λ is a positive real number and \mathbf{u} is a unique positive vector. Thus

$$\lambda u_k = \sum_{l=1}^m \frac{\partial \epsilon'_k}{\partial \epsilon_l} u_l \quad (\text{A1.4})$$

Inserting Equations A1.1, A1.2, and A1.3 into Equation A1.4 and summing over k we obtain

$$\lambda = (\bar{w}^*)^{-1} \left\{ (1-R) \sum_{j=1}^n \sum_{k=1}^m \sum_{l=1}^m u_k w_{n+1,jkl}^* x_{jl}^* + R \sum_{j=1}^n \sum_{k=1}^m \sum_{l=1}^m u_l w_{n+1,jkl}^* x_{jk}^* \right\} \quad (\text{A1.5})$$

Interchanging the indices k and l and using Equations 1 and 5, Equation A1.5 becomes

$$\lambda = (\bar{w}^*)^{-1} \sum_{k=1}^m u_k \sum_{j=1}^n \sum_{l=1}^m w_{n+1,jkl}^* x_{jl}^* = \frac{w_{n+1}^*(\mathbf{u})}{\bar{w}^*} \quad (\text{A1.6})$$

APPENDIX 2: PROOF OF RESULT 2

- i. We apply Result 1. Assume that the population is at a genotypic equilibrium Γ where at least some of the genotypes determine phenotypic values different from γ^* . The average viability of the population will then be smaller than the optimum $w(\gamma^*)$. It then follows from Result 1 that this equilibrium will be unstable with respect to any mutation that initially increases the average viability of its carriers. Such mutations must be possible; an example of a mutation of this kind is one that determines γ^* in all of its heterozygous carriers.
- ii. Assume that the population is at a phenotypically monomorphic genetic equilibrium Γ (i.e., Γ contains one genotype or is a set of equally fit genotypes) each of which produces the phenotype γ^* . Now consider a mutation that affects the phenotype of at least some of its carriers. Because γ^* is the optimum, the viabilities of all carriers of the mutation (either heterozygotes or homozygotes) that alter the phenotype will be lower than those of the genotypes in Γ . The viabilities of all other carriers of the mutation, if they exist, will equal those of the genotypes in Γ . Recombination will produce nonzero frequencies of the first kind of genotype so that the average fitness of carriers of the mutation will be less than that of the genotypes in Γ . As a result, the mutation will be selected against and cannot invade.

Remark. Note that in Appendix 1, Result 1 was used only in the proof of part i of Result 2. No assumption about the leading eigenvalue was made in the proof of part ii of Result 2.

APPENDIX 3: PROOF OF RESULT 6

Let G be any genetic equilibrium that phenotypically generates \hat{p} as a mean population strategy, and let it include a positive frequency x_{III} of the double homozygote A_1B_1/A_1B_1 that, by itself, phenotypically generates \hat{p} . Now consider a mutant allele that when introduced into the population at low frequency shifts the average strategy away from \hat{p} . Let the population strategy after the introduction of the mutation be $p \neq \hat{p}$. We know $V(p, \hat{p}) = V(\hat{p}, \hat{p})$, and, because \hat{p} is an ESS, $V(p, p) < V(\hat{p}, p)$. But $V(p, p)$ is the new average fitness of the population, whereas $V(\hat{p}, p)$ is the fitness of A_1B_1/A_1B_1 in the perturbed population. Hence, whenever the population strategy is different from the ESS, the fitness of A_1B_1/A_1B_1 is greater than the average fitness of the population. Moreover, because p is arbitrarily close to \hat{p} , the selection forces are as weak as we wish, in which case, due to recombination, any linkage disequilibrium will be arbitrarily small relative to the selection differentials. In particular, the difference between the fitness of A_1B_1/A_1B_1 and the population mean fitness can be arbitrarily small. Hence, the frequency of A_1B_1/A_1B_1 should increase and therefore tend to a limit. It may either increase to 1 or reach another positive limit as the population strategy tends to the ESS.

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LITERATURE CITED

- Bergman, A., I. Eshel, and M. Feldman. 1997. Anomalous properties of long-term selection. Unpublished manuscript.
- Brandon, R. N., and M. D. Rausher. 1996. Testing adaptationism: A comment on Orzack and Sober. *American Naturalist* 148: 189–201.
- Cressman, R., and W. G. S. Hines. 1984. Evolutionarily stable strategies of diploid populations with semi-dominant inheritance patterns. *Journal of Applied Probability* 21: 1–9.

- Eshel, I. 1982. Evolutionarily stable strategies and viability selection in Mendelian populations. *Theoretical Population Biology* 22: 204-217.
- Eshel, I. 1991. Game theory and population dynamics in complex genetical systems: The role of sex in short-term and in long-term evolution. In *Game equilibrium models, Vol. I: Evolution and game dynamics*, ed., R. Selten, 6-28. Berlin: Springer-Verlag.
- Eshel, I. 1996. On the changing concept of evolutionary population stability as a reflection of a changing point of view in the quantitative theory of evolution. *Journal of Mathematical Biology* 34: 485-510.
- Eshel, I., and M. W. Feldman. 1984. Initial increase of new mutants and some continuity properties of ESS in two locus systems. *American Naturalist* 124: 631-640.
- Eshel, I., and C. Matessi. 1998. Canalisation, genetic assimilation and preadaptation: A quantitative genetic model. *Genetics* 149: 2119-2133.
- Eshel, I., and U. Motro. 1980. Kin selection and strong evolutionary stability of mutual help. *Theoretical Population Biology* 19: 420-433.
- Eshel, I., U. Motro, and E. Sansone. 1997. Continuous stability and long-term convergence. *Journal of Theoretical Biology* 185: 333-343.
- Eshel, I., and E. Sansone. 1998. ESS and unbeatability in sexual and asexual populations. Unpublished manuscript.
- Ewens, W. J. 1969. With additive fitness, the mean fitness increases. *Nature* 221: 1076.
- Feldman, M. W., S. P. Otto, and F. B. Christiansen. 1996. Population genetic perspectives on the evolution of recombination. *Annual Review of Genetics* 30: 261-295.
- Fisher, R. A. 1928. The possible modification of the response of the wild type to recurrent mutations. *American Naturalist* 62: 115-126.
- Fisher, R. A. 1930. *The genetical theory of natural selection*. Oxford: Clarendon Press.
- Hamilton, W. D. 1967. Extraordinary sex ratios. *Science* 156: 477-488.
- Hammerstein, P. 1996. Darwinian adaptation, population genetics and the streetcar theory of evolution. *Journal of Mathematical Biology* 34: 511-532.
- Hammerstein, P., and R. Selten. 1994. Game theory and evolutionary biology. In *Handbook of game theory with economic applications*, Vol. 2, ed. R. J. Aumann and S. Hart, 929-993. Amsterdam: Elsevier Science Publishers.
- Hines, W. G. S. 1982. Strategy stability in complex randomly mating diploid populations. *Journal of Applied Probability* 19: 653-659.
- Hines, W. G. S., and D. T. Bishop. 1984a. On the local stability of an evolutionarily stable strategy in a diploid population. *Journal of Applied Probability* 21(2): 215-224.
- Hines, W. G. S., and D. T. Bishop. 1984b. Can and will a sexual population attain an ESS? *Journal of Theoretical Biology* 111: 667-686.
- Hines, W. G. S., and M. Turelli. 1997. Multilocus evolutionarily stable strategy models: Additive effects. *Journal of Theoretical Biology* 187: 379-388.
- Hofbauer, J., and K. Sigmund. 1988. *The theory of evolution and dynamical systems*. Cambridge University Press.

- Hofbauer, J., and K. Sigmund. 1990. Adaptive dynamics and evolutionary stability. *Applied Mathematics Letters* 3(4): 75-79.
- Karlin, S. 1975. General two locus selection models: Some objectives, rules and interpretations. *Theoretical Population Biology* 7: 364-398.
- Karlin, S., and H. Taylor. 1975. *A first course in stochastic processes*, 2nd Ed. New York: Academic Press.
- Kingman, J. F. C. 1961. A mathematical problem in population genetics. *Proceedings of the Cambridge Philosophical Society* 57: 574-582.
- Lessard, S. 1990. Evolutionary stability: One concept, several meanings. *Theoretical Population Biology* 37: 159-170.
- Lieberman, U. 1988. External stability and ESS: Criteria for initial increase of new mutant allele. *Journal of Mathematical Biology* 26: 477-485.
- Matessi, C., and C. Di Pasquale. 1996. Long-term evolution of multilocus traits. *Journal of Mathematical Biology* 34: 613-653.
- Maynard Smith, J. 1978. Optimization theory in evolution. *Annual Review of Ecology and Systematics* 9: 31-56.
- Maynard Smith, and Price, G. R. 1973. The logic of animal conflict. *Nature* 246: 15-18.
- Moran, P. A. P. 1964. On the nonexistence of adaptive topographies. *Annals of Human Genetics* 27: 283-293.
- Nagylaki, T. 1976. The evolution of one and two locus systems. *Genetics* 83: 583-600.
- Nagylaki, T. 1992. *Introduction to theoretical population genetics*. Berlin: Springer-Verlag.
- Orzack, S. H., and E. Sober. 1994. Optimality models and the test of adaptationism. *American Naturalist* 143: 361-380.
- Orzack, S. H., and E. Sober. 1996. How to formulate and test adaptationism. *American Naturalist* 148: 202-210.
- Parker, G. A., and J. Maynard Smith. 1990. Optimality theory in evolutionary biology. *Nature* 348: 27-33.
- Thomas, B. 1985a. Genetical ESS-models. I. Concepts and basic model. *Theoretical Population Biology* 28: 18-32.
- Thomas, B. 1985b. Genetical ESS-models. II. Multi-strategy models and multiple alleles. *Theoretical Population Biology* 28: 33-49.
- Weissing, F. J. 1996. Genetic versus phenotypic models of selection: Can genetics be neglected in a long-term perspective? *Journal of Mathematical Biology* 34: 533-555.

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