Long-Term Evolution, Short-Term Evolution, and Population Genetic Theory

Ilan Eshel
Marcus W. Feldman
Aviv Bergman

SFI WORKING PAPER: 1997-05-045

SFI Working Papers contain accounts of scientific work of the author(s) and do not necessarily represent the views of the Santa Fe Institute. We accept papers intended for publication in peer-reviewed journals or proceedings volumes, but not papers that have already appeared in print. Except for papers by our external faculty, papers must be based on work done at SFI, inspired by an invited visit to or collaboration at SFI, or funded by an SFI grant.

©NOTICE: This working paper is included by permission of the contributing author(s) as a means to ensure timely distribution of the scholarly and technical work on a non-commercial basis. Copyright and all rights therein are maintained by the author(s). It is understood that all persons copying this information will adhere to the terms and constraints invoked by each author's copyright. These works may be reposted only with the explicit permission of the copyright holder.

www.santafe.edu
Long-term evolution, short-term evolution, and population genetic theory

Ilan Eshel*, Marcus W. Feldman†, & Aviv Bergman‡

*Department of Statistics, Tel Aviv University, Tel Aviv 69 978, Israel
†Department of Biological Sciences, Stanford University, Stanford, California 94305-5020
‡Interval Research Corporation, 1801 Page Mill Rd. Bldg. C, Palo Alto, California 94304

Key words: Games and dynamics, ESS, Multiple loci, Epistasis, Local stability
This note is intended to reconcile the two most widely used approaches to quantitative evolutionary theory: exact population genetic analysis and purely phenotypic analysis commonly cast in terms of population game theory or evolutionary stable strategies (ESS). To this end, we introduce a dichotomy between long- and short-term evolution. The latter is the domain of most population genetic theory while the former provides a paradigm to connect population genetics with population game theory. Convergence to an ESS in multilocus genetic in systems is discussed in terms of long-term evolution.

An ESS has been defined in two ways: First, by Maynard Smith and Price\(^1\) and later by Maynard Smith\(^2\), following Hamilton\(^3\), as a strategy (e.g., a distribution of phenotypes) which, once fixed in the population, is immune to invasion by any alternative strategy. Second, by Bishop and Cannings\(^4\) and by Maynard Smith\(^5\) in the more familiar game-theory form, as a strategy \(\hat{p}\) such that for any alternative strategy \(p\), the two following conditions are satisfied:

\[
A(i) \quad V(\hat{p}, \hat{p}) \geq V(p, \hat{p})
\]

and in case of equality in \(A(i)\):

\[
A(ii) \quad V(\hat{p}, p) > V(p, p),
\]

where \(V(x, y)\) is some evolutionarily relevant payoff (e.g., fitness or inclusive fitness) accruing to an individual of strategy \(x\) in a population with a mean strategy \(y\).

In the case of a random-encounter population game, \(A(i)\) and \(A(ii)\) together are equivalent to the requirement that for any strategy \(p\) alternative to \(\hat{p}\), there is a positive value \(\varepsilon > 0\) such that if at least a fraction \(1 - \varepsilon\) of the population chooses the strategy \(\hat{p}\) and the rest of the population chooses the mutant strategy \(p\), then the average payoff to the resident \(\hat{p}\)-players is strictly higher than that to
the mutant $p$-player individuals. Thus, in using conditions A(i) and A(ii) there is a tacit assumption that natural selection operates at each generation to increase the relative frequency of any strategy which yields a payoff $V$ higher than the average of the population at that generation.

Unfortunately, for complex genetic systems, that is, those involving multiple loci with epistasis and recombination, this is not true even when the payoff is measured in terms of individual viability. In fact, even under frequency-independent selection in a multilocus system with recombination, the average viability of the population does not necessarily increase\(^6\), and it might be suspected that frequency-dependent selection would only aggravate the situation.

It has been suggested elsewhere\(^7\)–\(^14\), that the appropriate dynamics relevant for the concept of ESS as a strategy immune to all possible mutations is that of “trial and error,” in which the population is carried from one short-term stable state to another as a result of new mutations being introduced into the system. We call this process \textit{long-term evolution}, to distinguish it from the well-studied process of changes in the genotype frequencies of a given finite set of genotypes, which we refer to as \textit{short-term evolution}. Long-term evolution is a process whereby successful mutations invade the population, renewing the process of short-term evolution towards a new stable equilibrium, cycle or state of chaos. When the short-term dynamics result in a stable equilibrium, and if successful mutations are rare relative to the time it takes to reach equilibrium, we may postulate that new mutations occur near the stable equilibria of the short-term process.

Contrary to an implicit working assumption dating back to Fisher\(^{18}\), and tacitly adopted without examination by mainstream students of qualitative evolution, the laws governing long-term evolution cannot possibly be extrapolated from
results obtained for the short-term process: The two processes are qualitatively
different from one another. One difference between short-term and long-term evolu-
tion, which is the subject of the present article, concerns the tendency of a
multilocus genetic system in the long-term process, but not in the short-term,
to approach a phenotypic optimum under the operation of frequency-independent
selection and an ESS (when it exists) under frequency-dependent selection.

In principle, if the distribution of mutations were known, then 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 evolu-
tion 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 generally not known. However, under deterministic short-term evolu-
tion, knowledge of the genetic structure and the selection parameters is sufficient
to determine which mutations cannot succeed in the long-term sense; these de-
termine zero-probability transitions. Surprisingly, this information is sufficient to
obtain quite strong results concerning the limiting behavior of long-term evolu-
tion. In order to characterise this limiting behaviour we first introduce some useful
stability criteria.

**Long-Term Evolution, Long-Term Stability, External Stability and Phenotypic Sta-
bility**

The following definitions are used throughout the discussion.

**Definition 1.** (Ref. 9) A set $\Gamma$ of short-term stable genetic equilibria is said to be
externally stable if, starting from any genetic equilibrium in $\Gamma$, the long-term
process of evolution allows passage only to another state in $\Gamma$. 
Recall that the long-term process of evolution can be defined as a Markovian stochastic process over the set of all short-term stable genetic equilibria. Hence we state

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

**Definition 2.** (Ref 10, following Ref 3) A phenotype or a distribution of phenotypes $F$ is called a **phenotypically stable strategy** if there is an externally stable set of genetic equilibria, 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 state within a given absorbing set of states for the process of long term evolution.

Note, however, that unlike in a finite-state Markovian process, the attainable sample space of the process we are dealing with (say, all short-term stable genetic equilibria) does not guarantee convergence to an absorbing set. Thus, an asexual evolutionary model has recently been constructed$^{15}$, in which all ESS’s are phenotypically stable strategies but only those which satisfy some additional criteria (i.e., continuous stability) are attainable with positive probability from states in their vicinity (in which case, convergence occurs in probability 1). We are, therefore, interested mainly in the following property:
Definition 3. A strategy \( p \) is said to be long-term stable if for any vicinity \( S \) of \( p \), starting from any genetic equilibrium that phenotypically generates a population strategy close enough to \( p \), the long-term process will not leave \( S \) and, moreover, will converge to \( p \) with probability one.

Long-Term Selection and Two-Locus Population Genetics

Consider a two-locus random mating diploid genetic system with alleles \( A_1, A_2, \ldots, A_n \) at one locus and \( B_1, B_2, \ldots, B_m \) at the other and recombination rate \( R(0 < R \leq 1/2) \) between the loci. (A generalization to multiple loci was made by Liberman.) Assume now that the various genotypes in the population differ from each other only in their probabilities of choosing the pure strategies \( \alpha_1, \ldots, \alpha_r \) in an \( r \times r \) random-encounter population game (the case \( r = 1 \) standing for frequency-independent selection over a single phenotype). Let \( p^{(ij\ell)} \) be the strategy vector of the genotype \( A_iB_k/A_jB_\ell \) \( p^{(ijk\ell)} = p^{(ij\ell)} = p^{(i\ell k)} = p^{(j\ell k)} \). That is, genotype \( A_iB_k/A_jB_\ell \) chooses strategy \( \alpha_r \) with probability \( p_r(ij\ell) \). Also let the payoff to a \( p \) player when encountering a \( q \) player be a positive bi-linear function \( V(p, q) \). Denote by \( x = (x_{ik}) \) the vector of frequencies of the chromosomes \( A_iB_k \) after selection and recombination. Using the Hardy-Weinberg Law we know that the mean population strategy of newborn offspring will be

\[
p = \sum_{ij\ell} p^{(ij\ell)} x_{ik} x_{j\ell}, \tag{1}
\]

and the viability of the genotype \( A_iB_k/A_jB_\ell \) will then be

\[
w_{ijk\ell} = w_{ijk\ell}(x) = V(p^{(ij\ell)}, p). \tag{2}
\]

After random mating, selection and recombination, the frequency of \( A_iB_k \) in the
next generation is
\[ x'_{ik} = (\bar{w})^{-1} \left\{ R \sum_{j \neq k} w_{ij \ell} x_{i \ell} x_{jk} + (1 - R) \sum_{j \neq k} w_{ij \ell} x_{ik} x_{j \ell} \right\}, \]  
where
\[ \bar{w} = \sum_{i \neq k} w_{i j k} x_{ik} x_{j k} = V(p, p). \]
Equilibrium frequencies of \( \{A_i B_k\} \) will be denoted by \( \{x^*_{ik}\} \), where \( \{x^*_{ik}\} \) solves eqn [3] with the prime removed from the left side.

Now assume that 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 and assume only:

B(i) Mutations having any effect on a resident genotype are possible in the long run.
B(ii) The rate of mutation to alleles 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 there is a new advantageous mutation.

We suppose that a new allele \( A_{n+1} \) appears at a low frequency near the equilibrium \( \{x^*_{ik}\} \). Denote \( x_{n+1,k} \) by \( \varepsilon_k \) (\( k = 1, 2, \ldots, m \)), with \( \varepsilon = (\varepsilon_1, \varepsilon_2, \ldots, \varepsilon_m) \), \( \sum_k \varepsilon_k = \varepsilon > 0 \), and \( |x_{ik} - x^*_{ik}| < \varepsilon \) for \( i = 1, 2, \ldots, n \). From eqn [3] with \( n + 1 \) alleles at the \( A \) locus, and neglecting terms of smaller order than \( \varepsilon \), we have
\[ \varepsilon' = A \varepsilon, \]
where \( A = \|\partial \varepsilon'_k / \partial \varepsilon_\ell\| \) with
\[ \frac{\partial \varepsilon'_k}{\partial \varepsilon_\ell} = (\bar{w}^*)^{-1} R \sum_{j} w^*_{n+1,j \ell} x^*_{jk} \quad \text{for} \quad k \neq \ell \]  
and
\[ 7 \]
\[
\frac{\partial \varepsilon_k'}{\partial \varepsilon_k} = (\bar{w}^*)^{-1} \left\{ R \sum_j w_{n+1,jkk}^* x_{jk}^* + (1 - R) \sum_{j\ell} w_{n+1,jkk\ell}^* x_{j\ell}^* \right\}, \tag{5b}
\]

where \( w_{n+1,jkk\ell}^* \) is calculated at \( \{x_{ik}\}^* \); i.e., \( w_{n+1,jkk\ell}^* = V(p^{(n+1,jkk\ell)}, p^*) \).

Denote by \( \lambda \) the leading eigenvalue of \( A \), with \( u = (u_1, u_2, \ldots, u_m) \) the corresponding right eigenvector normalized to \( \sum u_i = 1 \). Note that for any positive vector \( \varepsilon \geq 0 \),

\[
\lim_{t \to \infty} \frac{A^t \varepsilon}{\|A^t \varepsilon\|} \to u
\]

(e.g. ref. 17). Thus, starting from vectors \( \varepsilon \) close enough to \( 0 \), the distribution of the mutant chromosomes will be as close to \( u \) as we wish, and for as long as we wish. Since \( A \) is a positive matrix, the Perron-Frobenius theorem ensures that \( \lambda \) is a positive real number and \( u \) is a unique positive vector. It follows that

\[
\lambda = \frac{w_{n+1}^*(u)}{\bar{w}^*}, \tag{6}
\]

\[
w_{n+1}^*(u) = \sum_{k=1}^{m} u_k \sum_{j=1}^{n} \sum_{\ell=1}^{m} w_{n+1,jkk\ell} x_{j\ell}^* = V(p^{(n+1)}, p^*) \tag{7},
\]

and \( p^{(n+1)} \) is the mean strategy of a random mutant after the distribution of the mutant chromosomes has reached the limit \( u \). Indeed, \( \bar{w}^* = V(p^*, p^*) \) and we therefore have

\[
\text{Proposition 1} \quad \text{A necessary condition for the initial increase of allele } A_{n+1} \text{ is that the mean strategy } p^{(n+1)} \text{ of the rare mutant genotypes be at least as good as the population average strategy } p^* \text{ when playing against } p^*. \text{ That is}
\]

\[
V(p^{(n+1)}, p^*) \geq V(p^*, p^*). \tag{8}
\]

A sufficient condition for initial increase of \( A_{n+1} \) is that [8] holds as a strict inequality.
As a special case, we get

**Proposition 2** A sufficient condition for the initial increase of allele $A_{n+1}$ under frequency-independent selection is that $A_{n+1}$ initially increases the population's average fitness. A necessary condition is that it does not decrease it.

Proposition 2 may be interpreted as a somewhat weaker long-term version of Fisher’s fundamental theorem\(^{18}\), which holds in this case for multilocus genetic systems. As an immediate result of Proposition 1, we obtain (see also ref 12).

**Theorem 1.** Any phenotypically stable strategy for the two-locus population game is an ESS.

**Proof.** First we see that a phenotypically stable strategy, if it exists, must be a best response against itself. This is so because if the population mean strategy $p^*$ were not a best response to $p^*$ in the phenotypic game, then another strategy, $s$, must exist such that $V(s, p^*) > V(p^*, p^*)$, in which case it follows from Proposition 1 that a mutant determining the strategy $s$ will initially increase in the population.

But if the population mean strategy $p^*$ is a best response to $p^*$ and is not an ESS in the phenotypic game, it follows from the definition of ESS that another strategy $s$ must exist such that $V(s, s) \geq V(p^*, s)$. In such a case, a dominant mutation $A_{n+1}$ which (monomorphically) generates the strategy $s$, regardless of the alleles at the other locus, can become established in the population and $p^*$ cannot possibly be phenotypically stable.

For the case of frequency-independent selection, it immediately follows, that a necessary as well as sufficient condition for a phenotype to be phenotypically
stable is that it brings the fitness of its carrier to an optimum.

*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 \( \mathbf{p} \), will converge to \( \mathbf{p} \). Here we focus on two cases: a two strategy population game and frequency-independent selection. The problem of long-term stability of the ESS when more than two strategies are involved remains open even for the case of asexual population dynamics.

For a two strategy population game, we know that an ESS \( \mathbf{p} \) either (Case I) is a strict best response against itself or (Case II) it satisfies the equality \( V(\mathbf{p}, \mathbf{p}) = V(\mathbf{p}, \mathbf{p}) \) for all \( \mathbf{p} \neq \mathbf{p} \), in which case it must satisfy also the inequality \( V(\mathbf{p}, \mathbf{p}) < V(\mathbf{p}, \mathbf{p}) \). We start with Case II which is possibly more interesting because it always applies when \( \mathbf{p} \) is a mixed strategy. It was also conjectured\(^{10}\) to be the more difficult case for which to prove stability. Surprisingly, the opposite is true, and long-term stability of the so called weak ESS is always guaranteed. This is because in case II, the selection forces operating on the population can be chosen as weak as one wishes, provided the population is sufficiently close to the ESS.

We apply results of Nagylaki\(^{19,20}\) to the effect that for any positive recombination rate, as the maximum selection differential approaches zero, short-term selection will take the linkage disequilibrium to the order of the square of the selection differentials. Further, Nagylaki has shown that for any fixed set of \( w_{ijk\ell} \) (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,

\[
\sum_{ijk\ell} w_{ijk\ell} x'_{ik} x'_{j\ell} > \sum_{ijk\ell} w_{ijk\ell} x_{ik} x_{j\ell}.
\]  

[9]
where the $x'_{ik}$ are defined in eqn [3].

Inequality [9] is true as a mathematical statement regardless of how \( \{w_{ij\ell} \} \) are interpreted. In Nagylaki’s analysis, \( w_{ij\ell} \) were understood as fixed fitnesses so that [9] was interpreted in the sense that the average fitness must increase over time. But [9] remains mathematically valid for any choice of \( w_{ij\ell} \), in particular, if we choose the fixed values \( w_{ij\ell} = w_{ij\ell}(p) \), where \( p \) is the population strategy before selection, recombination and random mating. In this case, employing [2] and [3], [9] immediately becomes

\[
V(p', p) > V(p, p),
\]

where

\[
p' = \sum_{ij\ell} x'_{ik} x'_{j\ell} p^{(ij\ell)}
\]

is the population strategy after selection, recombination and random mating. This can be summarized as

**Theorem 2.** If \( \hat{p} \) is an ESS which is not a strict best response against itself, and if the population strategy \( p \) determined by the two locus genetic model is sufficiently close to \( \hat{p} \), then after one generation the population strategy \( p' \) is a better response against \( p \) than \( p \); i.e.,

\[
V(p', p) > V(p, p). \tag{10}
\]

But for a population game with two pure strategies if its dynamic satisfies [10], then starting from a population strategy close to an ESS, short-term dynamics will eventually bring the population to the ESS, if genetically available, or to a strategy which is the closest possible genetically available to the ESS\(^2\). As a result, we have
Theorem 3. If a two-strategy ESS exists, which is not strictly a best response against itself, it is phenotypically stable and long-term stable in a two-locus genetic system with selection and random mating.

Surprisingly, the situation is more complicated in Case I, namely that of an ESS (inevitably pure) which is strictly a best response against itself or equivalently a strict optimum under frequency-independent selection. From Proposition 1, it then follows that in a two-locus random mating genetic system, a new mutation will invade if it initially brings the phenotypic value of its carriers closer to the optimum or to the ESS respectively. Once 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 which is actually closer to the ESS (or to the optimum). If true, this result would entail that starting from the vicinity of an ESS, the long-term process should converge monotonically to the ESS with probability one, regardless of the distribution of the mutations (given only the general assumptions A(i) and A(ii) above).

This result holds under weak selection on the phenotypic trait or in the population game in question. For a fixed positive rate of recombination, the argument goes straightforwardly as just employed.

It is somewhat surprising that with strong selection, this result is not generally true. Recent numerical simulations have shown that that even under frequency-independent selection, initial increase of the average fitness of the population, concomitant with the establishment of a new mutation, may be followed by a decrease of the average fitness below its initial value. However, this appears to occur in a rather small fraction of cases, and, with a random choice of the
effect of the mutation we conjecture that the expected change in fitness from one equilibrium to the other tends to be always positive. If this is the case, with probability one the stochastic long-term process must always approach an arbitrarily small neighborhood of the phenotypic optimum, if it exists. Whether the same results hold for the case of a strict pure ESS is under investigation. For example, in the coordination game, it appears that near a pure strategy, the fitness difference between the mean strategy and a mutant may be sufficiently great to cause further departure of the population strategy from the ESS.

*Phenotypic Stability of the ESS with Multiple Loci and with any Number of Strategies*

If the ESS is strictly the best response against itself, then it immediately follows from Proposition 1 that the set of genetic equilibria that phenotypically determine the ESS is externally stable. Note, however, that only a pure strategy can be a strict best response against itself. Weissing (personal communication) has shown 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\textsuperscript{10} and later Hammerstein\textsuperscript{12} 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 above, the ESS would indeed be phenotypically stable). Besides some problems with Hammerstein and Selten’s proof, Hammerstein’s later mathematical statement was much weaker than this, and actually claims that the set of all phenotypically monomorphic equilibria that generate the ESS is stable against
some, but by no means all, mutations that can shift the population out of this set. Instead, we prove

**Theorem 4.** Let \( \hat{p} \) be a fully mixed ESS with any number of pure strategies. Then

(i) The set \( \Gamma \) of all genetic equilibria that phenotypically generate the ESS \( \hat{p} \) as a population strategy, each of which includes at least one double homozygote that phenotypically generates \( \hat{p} \) as its own strategy, is externally stable.

(ii) The mixed ESS \( \hat{p} \) is, therefore, phenotypically stable.

**Proof.** Let \( G \) be any genetic equilibrium that phenotypically generates \( \hat{p} \) as a mean population strategy including a positive frequency \( x_{1111} \) of the double homozygote \( A_1B_1/A_1B_1 \) which, 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, since \( \hat{p} \) is an ESS, \( V(p, p) < V(\hat{p}, p) \). But \( V(p, p) \) is the new average fitness of the population, while \( V(\hat{p}, p) \) 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, since \( p \) is arbitrarily close to \( \hat{p} \), the selection forces can be as weak as we wish, in which due to recombination, any linkage disequilibrium will be arbitrarily small relative to the selection differentials. In particular, 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 one, or reach another positive limit as the population strategy tends to the ESS.
References


Correspondence and requests for materials should be addressed to M.W.F. (e-mail: marc@charles.stanford.edu).