Frequency-Dependent Selection: The High Potential for Permanent Genetic Variation in the Diallelic, Pairwise Interaction Model

Marjorie A. Asmussen*,† and Eraj Basnayake†

**Department of Genetics and †Department of Mathematics, University of Georgia, Athens, Georgia 30602*

Manuscript received August 15, 1989
Accepted for publication January 17, 1990

ABSTRACT

A detailed analytic and numerical study is made of the potential for permanent genetic variation in frequency-dependent models based on pairwise interactions among genotypes at a single diallelic locus. The full equilibrium structure and qualitative gene-frequency dynamics are derived analytically for a symmetric model, in which pairwise fitnesses are chiefly determined by the genetic similarity of the individuals involved. This is supplemented by an extensive numerical investigation of the general model, the symmetric model, and nine other special cases. Together the results show that there is a high potential for permanent genetic diversity in the pairwise interaction model, and provide insight into the extent to which various forms of genotypic interactions enhance or reduce this potential. Technically, although two stable polymorphic equilibria are possible, the increased likelihood of maintaining both alleles, and the poor performance of protected polymorphism conditions as a measure of this likelihood, are primarily due to a greater variety and frequency of equilibrium patterns with one stable polymorphic equilibrium, in conjunction with a disproportionately large domain of attraction for stable internal equilibria.

FREQUENCY-dependent selection has been widely cited as a potentially important mechanism for the preservation of genetic diversity in natural populations. Under this type of selection the fitness of a genotype depends on the genetic composition of the population in which it is found. For example, many general population studies have demonstrated negative frequency dependence, in which the fitness of a genotype is highest when rare (*e.g.*, TEISSIER 1954; PETIT 1966; SNYDER and AYALA 1979; ANDERSON *et al.* 1986). A low frequency advantage may also arise in a variety of special situations, such as rare male mating advantage, in which minority genotypes participate in mating in greater numbers than expected based on their frequencies in the population (*e.g.*, PETIT and EHRMAN 1969; SPEISS 1987; PARTRIDGE 1988); minority advantage in predation, in which a rare form may be overlooked when predators concentrate on one or only a few common prey varieties (*e.g.*, ALLEN and CLARKE 1968); and in the classic operation of Batesian mimicry where palatable individuals can avoid predation by mimicking other, unpalatable prey, provided such mimics are rare (*e.g.*, SHEPPARD 1959). The opposite phenomenon of positive frequency dependence has also been reported, in which common genotypes are favored. Causative factors include predation when prey density is high (ALLEN 1988), as well as selection based on the production of toxins and allelopathic agents in bacteria (LEVIN 1988) and other forms of intraspecific competition (ANTONOVICS and KAREIVA 1988).

More generally, a particular genotype may be favored in the presence of certain genotypes but be at a disadvantage in the presence of others (LEVENE, PAVLOVSKY and DOBZHANSKY 1954, 1958; DOBZHANSKY 1957; SAKAI 1961; KOJIMA and YARBROUGH 1967; KOJIMA and TOBARI 1969a, b; HUANG, SINGH and KOJIMA 1971; PRICE and WASER 1982). This is particularly true in plants, where the performance of an individual is often affected by its neighbors (ALLARD and ADAMS 1969a, b; ANTONOVICS and ELLSTRAND 1984). A common, but not ubiquitious finding is that individuals are least fit when in association with others of the same, or similar, genotype. Further examples of frequency-dependent selection can be found in reviews by AYALA and CAMPBELL (1974) and CLARKE and PARTRIDGE (1988).

Together these abundant experimental findings provide strong evidence that intergenotypic interactions may be an important evolutionary force. This conclusion has in turn motivated a number of theoretical studies of frequency-dependent selection. Some of these models assume that genotypic fitnesses are direct functions of the gene frequencies in the population (*e.g.*, WRIGHT 1955; LEWONTIN 1958; RAVEH and RITTE 1976; CURTSINGER 1984). Other models focus on the evidence for negative frequency dependence, assuming each genotype's fitness is a decreasing function of the genotype's frequency in

the population (*e.g.*, CLARKE and O'DONALD 1964). Considerable attention has also been paid to a general class of models in which genotypic fitnesses are determined by pairwise interactions among the individuals in the population (see, *e.g.*, SCHUTZ, BRIM and USANIS 1968; ALLARD and ADAMS 1969a; COCKERHAM and BURROWS 1971; HUANG, SINGH and KOJIMA 1971; HEDRICK 1972, 1973; COCKERHAM *et al.* 1972). The latter includes subclasses of negative and positive frequency-dependent models as special cases.

These theoretical investigations have provided further evidence that frequency-dependent selection can facilitate the preservation of genetic variation by showing that, in contrast to the classical, diallelic selection model in which genotypic fitnesses are constant through time, (i) genetic variation can be maintained without heterozygote advantage; and (ii) multiple stable polymorphic equilibria are possible, in which genetic diversity is preserved. These results give no indication, however, of how much genotypic interactions increase the likelihood of preserving genetic variation, or even whether this increase is significant. Here we formally address this issue within the class of diallelic, pairwise interaction models. We first present a complete analytic description of the equilibrium structure and the qualitative gene frequency dynamics under a new, symmetric model. This is supplemented by a Monte Carlo simulation which provides a quantitative assessment of the potential for genetic variation in this and other special cases, as well as under the general pairwise interaction model. As a by-product, our analysis shows that this potential can be vastly underestimated by the rough estimate based on conditions for a protected polymorphism.

GENERAL FREQUENCY-DEPENDENT FORMULATION

We are concerned with the genetic composition at a diploid autosomal locus with two alleles, A_1 (with frequency p) and A_2 (with frequency $q = 1 - p$), subject to the following assumptions: (i) a large (effectively infinite), randomly mating population with discrete non-overlapping generations; (ii) identical selection in the two sexes, which acts only through viability differences; and (iii) the net fitness of each genotype A_iA_j is a differentiable function of the gene frequency, p, denoted by $W_{ij} = W_{ij}(p)$ for $i, j = 1, 2$.

The adult gene frequency (p) is then governed by the transformation

$$p' = f(p) = \frac{pW_1(p)}{\bar{W}(p)} \tag{1}$$

where $'$ denotes the value after one generation,

$$W_1(p) = pW_{11}(p) + (1 - p)W_{12}(p) \tag{2}$$

is the marginal fitness of allele A_1, and

$$\bar{W}(p) = p^2W_{11}(p) + 2p(1 - p)W_{12}(p) + (1 - p)^2W_{22}(p) \tag{3}$$

TABLE 1

Local stability criteria for general frequency-dependent fitnesses

Equilibrium	Local stability criterion
$\hat{p} = 0$	$W_{12}(0) < W_{22}(0)$
$\hat{p} = 1$	$W_{12}(1) < W_{11}(1)$
$\hat{p} \in (0,1)$	$-2 < \frac{\hat{p}(1 - \hat{p})[W_1'(\hat{p}) - W_2'(\hat{p})]}{\bar{W}(\hat{p})} < 0$

is the mean fitness in the population. The change in gene frequency from one generation to the next is given by

$$\Delta p = p' - p = p(1 - p)\frac{[W_1(p) - W_2(p)]}{\bar{W}(p)} \tag{4}$$

where

$$W_2(p) = pW_{12}(p) + (1 - p)W_{22}(p) \tag{5}$$

is the marginal fitness of allele A_2.

The population is at *gene frequency equilibrium* if and only if $\Delta p = 0$. In addition to the two boundary (or fixation) equilibria, $\hat{p} = 0$ and $\hat{p} = 1$, there may be polymorphic (internal) equilibria, with $0 < \hat{p} < 1$, given by the solutions to the equation $W_1(p) = W_2(p)$. The exact number of polymorphic equilibria (if any) depends on the functional form of the fitnesses.

An equilibrium frequency, $\hat{p}$, is called *locally stable* if the infinite sequence of gene frequencies determined by recursion (1), $\{p_0, p_1 = f(p_0), p_2 = f(p_1), \ldots\}$, converges to $\hat{p}$ for all initial gene frequencies, p_0, sufficiently close to $\hat{p}$. This definition leads to the functional local stability criterion,

$$-1 < f'(\hat{p}) < 1 \tag{6}$$

(or equivalently, $-2 < \frac{d\Delta p}{dp} < 0$ or $-2 < \frac{d\Delta q}{dq} < 0$)

where

$$f'(p) = \frac{W_1(p)}{\bar{W}(p)} + \frac{p[\bar{W}(p)W_1'(p) - W_1(p)\bar{W}'(p)]}{\bar{W}^2(p)} \tag{7}$$

with $'$ here denoting the first derivative with respect to p (see (*e.g.*, EDELSTEIN-KESHET 1988). The values of $f'(p)$ are given in APPENDIX A, from which we obtain the general local stability criteria in Table 1. Equilibria which fail (6) are classified as neutrally stable ($|f'(\hat{p})| = 1$) or unstable ($|f'(\hat{p})| > 1$).

CLASSICAL SELECTION MODEL

The basis of comparison in the subsequent analysis is the classical selection model, in which the genotypic fitnesses are independent of gene frequency and constant over time (*i.e.*, $W_{ij}(p) = W_{ij}$ where W_{ij} is a constant which can be normalized to lie in [0, 1]). This model's salient features are summarized in Table 2 where it is

TABLE 2

Equilibrium patterns and dynamical behavior of the gene frequency, p_t, in each generation $t \geq 0$ under the classical selection model

Fitness condition	Equilibrium pattern[a]	P (pattern)	Initial frequency[b]	Trajectory[c]
$W_{11} \leq W_{12} \leq W_{22}$[d]	SU	$\frac{1}{6}$	$0 < p_0 < 1$	$p_t \downarrow 0$
$W_{22} \leq W_{12} \leq W_{11}$[d]	US	$\frac{1}{6}$	$0 < p_0 < 1$	$p_t \uparrow 1$
$W_{12} < W_{11}, W_{22}$	SUS	$\frac{1}{3}$	$0 < p_0 < \hat{p}$	$p_t \downarrow 0$
			$\hat{p} < p_0 < 1$	$p_t \uparrow 1$
$W_{12} > W_{11}, W_{22}$	USU	$\frac{1}{3}$	$0 < p_0 < \hat{p}$	$p_t \uparrow \hat{p}$
			$\hat{p} < p_0 < 1$	$p_t \downarrow \hat{p}$

[a] The leftmost entry indicates the stability of $\hat{p} = 0$ (U = unstable, S = locally stable), while the rightmost entry indicates the stability of $\hat{p} = 1$. The intermediate entry indicates the stability of the polymorphic equilibrium, when it exists.

[b] $\hat{p} = \dfrac{W_{12} - W_{22}}{2W_{12} - W_{11} - W_{22}}$ is the unique polymorphic equilibrium.

[c] $\uparrow$ ($\downarrow$) denotes a monotone increasing (decreasing) sequence.

[d] With at least one inequality strict.

seen that (i) there are only four possible equilibrium patterns, in terms of the number and stability characteristics of the equilibria present; (ii) there is at most one internal equilibrium; (iii) whenever $W_{12} > W_{11}$, W_{22} there is a stable polymorphic equilibrium which is converged to monotonically from all initial (polymorphic) gene frequencies; and (iv) under all other fitness conditions, the gene frequency monotonically converges to one of the fixation states, 0 or 1. (Note that our discussion excludes the degenerate case with $W_{11} = W_{12} = W_{22}$ for which $p_t \equiv p_0$ for all $t \geq 0$.)

These properties in turn imply three final key features of the classical constant viability selection model: the "probability" that there is a locally stable polymorphic equilibrium, the probability that the gene frequency converges to a polymorphic equilibrium, and the probability that genetic variation is maintained in the population are all 1/3. Paralleling other studies of constant viability and fertility models (*e.g.*, KARLIN and CARMELLI 1975; LEWONTIN, GINZBURG, and TULJAPURKAR 1978; KARLIN 1981; KARLIN and FELDMAN 1981; CLARK and FELDMAN 1986), these probabilities are based on the assumption that the three genotypic fitnesses are independent and uniformly distributed on [0, 1]. They therefore do not necessarily reflect the true probabilities in natural populations, for these depend on the actual distribution of the fitness values in nature, of which we have no *a priori* knowledge. Rather the probabilities here measure the proportion of three-genotype-fitness arrays which give rise to each of the events above, and thereby represent the potential for the preservation of genetic variation under the classical selection model. A similar approach is used in our analysis of the frequency-dependent models below.

TABLE 3

Genotypic viabilities in pairwise association or competition

Genotype	Competing with A_1A_1	A_1A_2	A_2A_2	Net fitness
A_1A_1	$W_{11,11}$	$W_{11,12}$	$W_{11,22}$	$W_{11}(p)$
A_1A_2	$W_{12,11}$	$W_{12,12}$	$W_{12,22}$	$W_{12}(p)$
A_2A_2	$W_{22,11}$	$W_{22,12}$	$W_{22,22}$	$W_{22}(p)$

PAIRWISE INTERACTION MODEL

Consider now the general class of frequency-dependent selection models in which genotypic fitnesses are based on pairwise interactions between the various individuals in the population (*e.g.*, HUANG, SINGH and KOJIMA 1971; COCKERHAM *et al.* 1972). Under this selection scheme the net fitness of an A_iA_j individual is the weighted average of its fitness taken across all pairwise associations, with

$$\begin{aligned} W_{11}(p) &= p^2W_{11,11} + 2p(1-p)W_{11,12} \\ &\quad + (1-p)^2W_{11,22} \\ W_{12}(p) &= p^2W_{12,11} + 2p(1-p)W_{12,12} \\ &\quad + (1-p)^2W_{12,22} \\ W_{22}(p) &= p^2W_{22,11} + 2p(1-p)W_{22,12} \\ &\quad + (1-p)^2W_{22,22} \end{aligned} \tag{8}$$

where in the present notation, $W_{ij,kl}$ (Table 3) is the (constant) viability of genotype A_iA_j in the presence of genotype A_kA_l. Since the gene frequency dynamics in (1) are unchanged if the pairwise fitness parameters $W_{ij,kl}$ are each multiplied (or divided) by the same constant factor, we assume without loss of generality that the fitnesses are normalized so that each $W_{ij,kl}$ lies in [0, 1].

Note that the pairwise interaction model includes the classical selection model as a special case, since if fitnesses are independent of interactions (*i.e.*, for each genotype A_iA_j, $W_{ij,kl} \equiv W_{ij}$ for $k, l = 1, 2$, where W_{ij} is a constant) the net fitnesses reduce to $W_{ij}(p) = W_{ij}$. The fitness scheme in (8) also subsumes cases of negative frequency dependence. For example, taking $W_{ij,ij} = W_{ij}(1 - s_{ij})$ and $W_{ij,kl} = W_{ij}$ for $k, l \neq i, j$ where $0 < s_{ij} \leq 1$, leads to the net fitnesses $W_{11}(p) = W_{11}(1 - s_{11}p^2)$, $W_{12}(p) = W_{12}[1 - 2s_{12}p(1-p)]$, and $W_{22}(p) = W_{22}[1 - s_{22}(1-p)^2]$, each of which is a decreasing function of the corresponding genotypic frequency. The same example with s_{ij} replaced by $-s_{ij}$ in the definition of $W_{ij,ij}$ similarly shows that (8) also includes cases of positive frequency dependence.

TABLE 4

Standard equilibrium patterns for the pairwise interaction model

No. of polymorphic equilibria	Equilibrium stability pattern[a]
0	SU
	US
1	SUS
	USU
2	SUSU
	USUS
3	SUSUS
	USUSU

[a] The end entries indicate the stability of $\hat{p} = 0$ and $\hat{p} = 1$ (U = unstable, S = locally stable), while the intermediate entries (if any) refer to the stability of polymorphic equilibria.

Applying the general equilibrium analysis to the pairwise interaction model (8), we find that the internal equilibria are here roots of a complicated cubic equation (APPENDIX B). It is therefore possible to have either 0, 1, 2, or 3 distinct, polymorphic equilibria in (0, 1). Although the exact number is still difficult to predict in general, some additive × dominance or dominance × dominance effects are necessary for the existence of multiple internal equilibria (COCKERHAM *et al.* 1972). The derivatives comprising the local stability criterion for polymorphic equilibria (Table 1) are complex and can be found in APPENDIX B. The local stability criterion for the fixation states (Table 1) are quite simple for this model, however, with $\hat{p} = 0$ locally stable whenever $W_{12,22} < W_{22,22}$ and $\hat{p} = 1$ locally stable whenever $W_{12,11} < W_{11,11}$. In order to have a "protected polymorphism" in which neither allele can be lost, it is thus sufficient that each homozygote have a lower fitness in the presence of its own genotype than do heterozygotes in the presence of that homozygote. More precise, necessary and sufficient conditions can be found in COCKERHAM *et al.* (1972). As we shall see later, however, protected polymorphism conditions greatly underestimate this model's potential for the maintenance of genetic variation.

The complexity of the frequency-dependent fitnesses in (8) precludes a full analytic characterization of the gene frequency dynamics through time. Even the equilibrium structure is complex and difficult to predict, with eight standard equilibrium patterns theoretically possible, in which stable and unstable states alternate along the line from $p = 0$ to $p = 1$ (Table 4). Many other, nonstandard patterns could conceivably arise, however, including ones in which none of the equilibria are stable, if damped or permanent gene frequency oscillations occur. [See MAY (1974) and ASMUSSEN (1986) for ecological and ecological genetic examples of the latter situation.]

Note that again our classification extends to the complete equilibrium set (compare Table 2), including both fixation and (any) polymorphic equilibria. The notation in Table 4 therefore differs from that in COCKERHAM *et al.* (1972) in that the end entries always denote the stability of $\hat{p} = 0$ and $\hat{p} = 1$, and the intermediate entries focus simply on the distinct internal equilibria. Their original analysis of a subclass of general dominance models suggests that all the standard patterns shown for polymorphic equilibria can indeed be realized, but gives no indication of their relative frequency in the fitness space nor of the likelihood of convergence to a polymorphic equilibrium.

TABLE 5

Pairwise fitnesses under the symmetric model

	Competing with			
Genotype	A_1A_1	A_1A_2	A_2A_2	Net fitness
A_1A_1	a	b	c	$W_{11}(p) = (a + c - 2b)p^2 + 2(b - c)p + c$
A_1A_2	b	d	b	$W_{12}(p) = 2(d - b)p(1 - p) + b$
A_2A_2	c	b	a	$W_{22}(p) = (a + c - 2b)p^2 + 2(b - a)p + a$

Greater insight into the potential for genetic polymorphism under the pairwise interaction model is obtained in the next sections through a complete analytic investigation of a new, symmetric version. This analytic study is augmented by an extensive numerical analysis of the symmetric model, the general dominance model of COCKERHAM *et al.* (1972), and other special cases of particular biological interest, in addition to the general case (Table 3). Together the results help determine when and how often the various equilibrium patterns arise, together with the likelihood of permanent genetic variation under frequency-dependent selection generated by pairwise interactions.

SYMMETRIC PAIRWISE INTERACTION MODEL

We introduce here a symmetric model in which the pairwise fitnesses are principally determined by the degree of genetic similarity of the individuals involved (Table 5). This formulation has some empirical justification (*e.g.*, HUANG, SINGH and KOJIMA 1971) and is reminiscent of the classical two-locus symmetric viability model in which fitnesses are based on the genotype's heterozygosity (see *e.g.*, KARLIN 1975). The nine pairwise fitness parameters in the general case (Table 3) are here reduced to four, reflecting the following classes of interactions: homozygote × like-homozygote (a), homozygote × heterozygote (b), homozygote × unlike-homozygote (c), and heterozygote × heterozygote (d). Under this formulation, both interacting individuals have the same fitness, and the separate parameters a and d partition the effects of

like × like interactions between homozygotes and heterozygotes.

The potential internal equilibria are easily derived from the general equilibrium equation (B1), which here reduces to

$$(2p - 1)[(4b - a - 2d - c)p(1 - p) + a - b] = 0. \quad (9)$$

Clearly $\hat{p} = \frac{1}{2}$ is always a solution of (9). Further inspection reveals that the symmetric model has either a single polymorphic equilibrium ($\hat{p} = \frac{1}{2}$) *or* three polymorphic equilibria ($0 < \hat{p}_1 < \hat{p}_2 = \frac{1}{2} < \hat{p}_3 < 1$), where

$$\hat{p}_1, \hat{p}_3 = \frac{1}{2} \mp \frac{1}{2}\sqrt{\frac{c + 2d - 3a}{a + 2d + c - 4b}}. \quad (10)$$

Three internal solutions arise if and only if $b < a < (c + 2d)/3$ or $b > a > (c + 2d)/3$, in which case the two outer polymorphic equilibria, $\hat{p}_1$ and $\hat{p}_3$, are symmetrically located about the central equilibrium $\hat{p}_2 = \frac{1}{2}$. Observe from Table 5 that these existence conditions (for multiple internal equilibria) are equivalent to the requirement that the homozygote × like-homozygote fitness (a) be intermediate between the homozygote × heterozygote fitness (b), and a weighted average of homozygote × unlike-homozygote (c) and heterozygote × heterozygote fitnesses (d), in which the latter interactions are given double weight.

Proceeding to the stability analysis, we find that the general local stability conditions in Table 1 and APPENDIX B here reduce to (i) $b < a$ for both $\hat{p} = 0$ and $\hat{p} = 1$; (ii) $a < (c + 2d)/3$ for $\hat{p} = \frac{1}{2}$; and (iii) $(c + 2d)/3 < a < b$ for both $\hat{p}_1$ and $\hat{p}_3$. Note that the outlying internal equilibria, $\hat{p}_1$ and $\hat{p}_3$, are either both locally stable *or* both locally unstable, whenever they exist. Moreover, the equilibrium structure of the symmetric model depends solely on the relative magnitudes of the three quantities a, b, and $(c + 2d)/3$, with only four distinct equilibrium patterns possible (Table 6), corresponding to the standard patterns expected with either one or three polymorphic equilibria.

In addition to allowing a complete equilibrium analysis, the prevailing symmetry makes this model, like the classical model, one of the few nonlinear systems for which a complete analytic characterization can be made of the qualitative gene frequency trajectory through time. The full behavior is derived in APPENDIX C and summarized in Table 6. Three immediate observations from this detailed analysis are that, paralleling the classical model, (i) the gene frequency always converges *monotonically* to a locally stable equilibrium, with no overshooting possible; (ii) the range of initial frequencies (domain of attraction) leading to a locally stable fixation equilibrium ($\hat{p} = 0$ or $\hat{p} = 1$) extends to the nearest unstable (polymorphic) equilibrium; and (iii) the domain of attraction of a given locally stable polymorphic equilibrium extends to the nearest unstable equilibrium on either side.

TABLE 6

Equilibrium patterns and dynamical behavior under the symmetric model

Fitness condition	Equilibrium pattern	P (pattern)	Initial frequency[a]	Trajectory[b]
$a \geq b, \frac{c + 2d}{3}$[c]	SUS	0.352	$0 < p_0 < \frac{1}{2}$	$p_t \downarrow 0$
			$\frac{1}{2} < p_0 < 1$	$p_t \uparrow 1$
$a \leq b, \frac{c + 2d}{3}$[c]	USU	0.352	$0 < p_0 < \frac{1}{2}$	$p_t \uparrow \frac{1}{2}$
			$\frac{1}{2} < p_0 < 1$	$p_t \downarrow \frac{1}{2}$
$b < a < \frac{c + 2d}{3}$	SUSUS	0.148	$0 < p_0 < \hat{p}_1$	$p_t \downarrow 0$
			$\hat{p}_1 < p_0 < \frac{1}{2}$	$p_t \uparrow \frac{1}{2}$
			$\frac{1}{2} < p_0 < \hat{p}_3$	$p_t \downarrow \frac{1}{2}$
			$\hat{p}_3 < p_0 < 1$	$p_t \uparrow 1$
$b > a > \frac{c + 2d}{3}$	USUSU	0.148	$0 < p_0 < \hat{p}_1$	$p_t \uparrow \hat{p}_1$
			$\hat{p}_1 < p_0 < \frac{1}{2}$	$p_t \downarrow \hat{p}_1$
			$\frac{1}{2} < p_0 < \hat{p}_3$	$p_t \uparrow \hat{p}_3$
			$\hat{p}_3 < p_0 < 1$	$p_t \downarrow \hat{p}_3$

[a] $\hat{p}_1$, $\hat{p}_3$ are defined in Equation 10.
[b] $\uparrow$ ($\downarrow$) denotes a monotonically increasing (decreasing) sequence.
[c] With at least one inequality strict.

Further key observations are evident from the pattern probabilities shown in Table 6. These are derived analytically in APPENDIX D assuming, in analogy to the classical model above, that the four fitness parameters (Table 5) are independent and uniformly distributed on [0, 1]. From the pattern frequencies we conclude that the symmetric model has the potential to produce (i) three internal equilibria (SUSUS, USUSU) 30% of the time; (ii) two stable internal equilibria (USUSU) 15% of the time; and (iii) one stable internal equilibrium (USU, SUSUS) 50% of the time. This is in strong contrast to the classical model (Table 2) for which the corresponding percentages are 0,0, and 33.

Even more importantly, there is at least one stable polymorphic equilibrium as long as the homozygote × like-homozygote fitness (a) is less than either the homozygote × heterozygote fitness (b) *or* the weighted average, $(c + 2d)/3$, of the homozygote × unlike-homozygote and heterozygote × heterozygote fitnesses. This means that genetic variation can be preserved under 65% of the symmetric pairwise fitness space, which is almost double the corresponding fraction for the classical selection model. Furthermore, permanent genetic diversity is guaranteed in 50% of the fitness space, since the gene frequency necessarily converges to a polymorphic equilibrium if the homozygote × like-homozygote fitness is less that in homozygote × heterozygote interactions (*i.e.*, $a < b$).

These computations provide our first quantitative measure of when and how much pairwise interactions

enhance the likelihood of permanent genetic variation. They also suggest that the simple protected polymorphism condition ($a < b$) may seriously underestimate the potential for permanent genetic diversity in this system. In particular, although both alleles are always maintained by the fitness sets producing a protected polymorphism (USU, USUSU), these underestimate by 23% the fitness sets under which a permanent genetic polymorphism is possible (50% *vs.* 65%).

Similar results hold for the fully symmetric model in which fitnesses are completely determined by the degree of genetic similarity of the interacting individuals (*i.e.*, $d = a$). In this case the equilibrium structure and dynamical behavior simply depend on the relative magnitudes of the three pairwise fitnesses corresponding to like × like (a), homozygote × heterozygote (b), and homozygote × unlike-homozygote (c) interactions. Many of the results above consequently have a more straightforward interpretation, because all conditions involving the weighted average, $(c + 2d)/3$, reduce to equivalent conditions on the single fitness, c. The quantitative statements are only slightly altered by the change in the pattern probabilities in Table 6 to 1/3, 1/3, 1/6, and 1/6.

The analytic investigation of the symmetric models demonstrates that frequency-dependent selection based on pairwise interactions can significantly facilitate the maintenance of genetic variation (relative to the classical, constant fitness regime). The equilibrium pattern probabilities on which these comparisons have been made, however, do not fully measure the potential for permanent genetic variation in frequency-dependent systems, due to the uncertain outcome under patterns where fixation and polymorphic equilibria are simultaneously stable (*e.g.*, SUSUS). In such cases, not all gene frequency trajectories will converge to the stable polymorphic value, since under some initial frequencies the trajectory will converge to 0 or 1. Thus, in contrast to the classical model, the existence of a locally stable polymorphic equilibrium does *not* generally guarantee that genetic variation will be maintained in the population.

To properly ascertain the potential for the maintenance of genetic variation under frequency-dependent models, and others where boundary and internal equilibria can be simultaneously stable, we must also compute the average proportion of initial gene frequencies that lead to a polymorphic equilibrium. These expected values are difficult to determine analytically, for even in the fully symmetric case the delimiting frequencies, $\hat{p}_1$ and $\hat{p}_3$, defined in (10) have complex functional forms. The following sections formally address this issue through an extensive numerical investigation of symmetric and other special forms of pairwise interactions, as well as of the general case in Table 3.

NUMERICAL STUDY

Twelve different pairwise fitness schemes were analyzed numerically. These include

1. *General pairwise interaction model*: All 9 pairwise fitnesses (Table 3) are independently generated by a random number generator with a uniform distribution on [0, 1].

2. *Symmetric pairwise interaction models*: The four fitness parameters (Table 5) are randomly generated from [0, 1], or just three in the fully symmetric case with $d = a$.

3. *General dominance model* (COCKERHAM *et al.* 1972): The dominance parameters, h and k, and the four homozygote × homozygote fitnesses ($W_{ii,jj}$ for i, $j = 1, 2$) are randomly generated from [0, 1] and the remaining fitnesses computed by

$$W_{ij,12} = (1 - k)W_{ij,11} + kW_{ij,22} \qquad i, j = 1, 2$$

and

$$W_{12,ij} = (1 - h)W_{11,ij} + hW_{22,ij} \qquad i, j = 1, 2.$$

4. *Negatively ordered model* (generalization of negative frequency dependence, where individuals are least fit when interacting with others of the same genotype): All 9 pairwise fitnesses (Table 3) are randomly generated from [0, 1] and rearranged, if necessary, so that for each genotype A_iA_j

$$W_{ij,ij} < W_{ij,kl} \quad \text{for} \quad k, l \neq i, j.$$

5. *Fully negatively ordered model* (negatively ordered fitnesses where additionally each homozygote's pairwise fitnesses decrease with increasing genetic similarity of the interacting individuals): All 9 pairwise fitnesses (Table 3) are randomly generated from [0, 1] and rearranged, if necessary, so that

$$W_{ii,ii} < W_{ii,12} < W_{ii,jj} \qquad i, j = 1, 2 \quad \text{with} \quad i \neq j,$$

and

$$W_{12,12} < W_{12,ii} \qquad i = 1, 2.$$

6. *Positively ordered model* (generalization of positive frequency dependence where individuals are most fit when interacting with others of the same genotype): All 9 pairwise fitnesses (Table 3) are randomly generated from [0, 1] and rearranged, if necessary, so that for each genotype A_iA_j

$$W_{ij,ij} > W_{ij,kl} \quad \text{for} \quad k, l \neq i, j.$$

7. *Fixed maximum interaction models* (where a given genotypic interaction has maximum fitness): One pairwise fitness ($W_{ij,kl}$) is fixed at 1 and the remaining 8 fitnesses are randomly generated from [0, 1].

Numerical methods: In each case the random fit-

ness parameters ($W_{ij,kl}$) were produced by the uniform random number generator (UNIFORM) proposed by L'ECUYER (1988) for 32-bit computers. This algorithm was selected because of its high periodicity (2.30584×10^{18}), uniformity, and randomness. We independently verified the latter two properties by a series of four basic tests (APPENDIX E). Two to five replicate runs, each with at least 20,000 fitness sets (with a maximum of 80,000), were analyzed for each model.

Each fitness scheme was investigated through the four-step procedure outlined below. (Verification of the numerical protocol can be found in APPENDIX E.)

Step 1. Iterate to assess likelihood of genetic variation: This step was used to identify stable equilibria, the extent of the domains of attraction of all internal equilibria, and any limit cycles or nonmonotonic trajectories. Recursion (1) is iterated from $p_0 = 0.01, \ldots, 0.99$ (or in the symmetric cases $p_0 = 1/99, \ldots, 98/99$) until convergence ($|\Delta p_t| < 10^{-8}$) or 10,000 generations, whichever comes first. If $\{p_t\}$ converges for a given p_0, the final iterate is saved as a stable equilibrium value ($\hat{p}$), and counters updated for (i) the number of sequences (*i.e.*, initial p_0 values) that converged to a polymorphic equilibrium; and (ii) the number of distinct, stable polymorphic equilibria found for that fitness set. Although iteration cannot locate unstable internal equilibria, a fixation equilibrium is considered unstable at the end of this step if no sequences converged to it. In order to detect the potential for limit cycles and nonmonotonic trajectories, a fitness set is stored for individual investigation and an error signaled if, for any initial p_0, convergence is not attained in 10,000 generations or the sign of Δp_t changes at any iterate.

Paralleling other iterative studies (*e.g.*, CLARK and FELDMAN 1986) this step rests on the following practical principle: Two limiting values, $\hat{p}_i$ and $\hat{p}_j$, are considered equivalent if $|\hat{p}_i - \hat{p}_j| < 10^{-4}$. This assumption further implies that any value less than 10^{-4} is treated as 0, any value greater than 0.9999 is treated as 1, and any value in [0.0001, 0.9999] is classified as polymorphic. While this convention may fail to distinguish between nearby, distinct equilibria, the risk is apparently small, since no nonstandard equilibrium patterns (*i.e.*, not in Table 4) were detected.

Step 2. Identify the equilibrium pattern for the fitness set: This step was used to identify all equilibria, both stable and unstable, and as a by-product provided an independent check of whether all stable equilibria were found by iteration. The internal equilibria are obtained by first finding all real-valued solutions of the equilibrium equation (B1) via the cubic-equation-solving-method presented in PRESS *et al.* (1986). Roots classified as polymorphic by the convention outlined in Step 1 are then substituted back into (B1) and judged valid if the absolute value of (B1) is less than 10^{-8}. (This test was always satisfied in our runs.)

The stability of the equilibria are then determined by evaluating (A1) at $\hat{p} = 0$ and $\hat{p} = 1$, and (A2) at all internal equilibria, where in deference to possible roundoff error an equilibrium is considered neutrally stable if $1 \leq |f'(\hat{p})| < 1.0001$. Neutrally stable points are then reclassified as stable if they were identified as stable equilibria in Step 1, and otherwise recorded as unstable.

The results are then compared to those from Step 1 with respect to the number of stable polymorphic equilibria, the values of the stable polymorphic equilibria (for agreement to within 10^{-4}), and the stability of the fixation states, 0 and 1. In cases where a boundary equilibrium is judged stable by (A1) but unstable by Step 1 (*e.g.*, $|f'(0)| < 1$ but no trajectories converged to $p = 0$) the program attempts to resolve the discrepancy by performing an additional iteration from $p_0 = 0.0001$ for $p = 0$, or $p_0 = 0.9999$ for $p = 1$.

If there is no discrepancy, the equilibrium pattern is classified and the following 19 statistics updated: (1–3) N_i: the number of fitness sets with $i = 1$, 2, or 3 distinct, polymorphic equilibria; (4–6) N_{ip}: the number of initial frequencies that converge to a polymorphic equilibrium, for those fitness sets with exactly $i = 1$, 2, or 3 stable polymorphic equilibria; (7–14) Num_*pattern*: total number of fitness sets with the observed equilibrium pattern (*pattern*) found in Table 4; (15–18) P_*pattern*: total number of initial frequencies that converge to a polymorphic equilibrium, if the equilibrium pattern (*pattern*) is USU, SUSU, USUS, or SUSUS; and (19) FITSETS: the number of fitness sets with no errors.

A fitness set is stored for individual investigation and an error signaled if either the results from the two steps disagree or the observed pattern is not shown in Table 4.

Step 3. Calculate measures of genetic variation: After each 10,000 fitness sets the following 20 probability statistics are calculated, based on the cumulative error free fitness sets (where n = total number of initial frequencies used for iterating each fitness set): (1–8) P(*pattern*) = (Num_*pattern*)/FITSETS, for each equilibrium pattern in Table 4; (9–11) P(exactly i stable polymorphic equilibria) = N_i/FITSETS, for $i = 1$, 2, and 3; (12–14) P(converge to a polymorphic equilibrium given there are i stable internal equilibria) = $N_{ip}/[N_i \times n]$, for $i = 1$, 2, and 3; (15) P(converge to a polymorphic equilibrium) = $\sum_{i=1}^{3} N_{ip}/[\text{FITSETS} \times n]$; (16) P(protected polymorphism) = P(USU) + P(USUSU); and (17–20) P(converge to a polymorphic equilibrium given the equilibrium pattern) = *P_pattern*/[Num_*pattern* $\times$ n] for the equilibrium pat-

TABLE 7

Summary probabilities for pairwise interaction models

Fitness scheme	At least 1 stable internal equilibrium	Converge to a polymorphic equilibrium	Protected polymorphism
General	0.506	0.433	0.250
Negatively ordered	0.842	0.814	0.774
Fully negatively ordered	0.826	0.808	0.772
Symmetric	0.648[a]	0.594	0.500[a]
Fully symmetric	0.662[a]	0.578	0.498[a]
General dominance	0.248	0.248	0.248
Positively ordered	0.125	0.099	0.020
Classical	0.333	0.333	0.333
$W_{11,11} = 1$	0.191	0.117	0.000
$W_{11,12} = 1$	0.511	0.423	0.249
$W_{11,22} = 1$	0.512	0.447	0.246
$W_{12,12} = 1$	0.579	0.524	0.252
$W_{12,22} = 1$	0.767	0.694	0.499

[a] Note close agreement to analytic values in Table 6 and text.

terns with exactly one stable polymorphic equilibrium (*i.e.*, USU, SUSU, USUS, SUSUS).

A model's run is terminated after 100,000 fitness sets, or if the following 14 statistics agree to within 5×10^{-3} of their values after the last 10,000 sets: the probabilities in (1–8) corresponding to patterns with exactly one stable polymorphic equilibrium, and all probabilities in (9–14) and (17–20).

Step 4. Individually examine all fitness sets which signal errors: All fitness sets/limiting values saved because of nonmonotonic trajectories, nonconvergence after 10,000 generations, a discrepancy between steps 1 and 2, or a nonstandard equilibrium pattern are individually investigated with the aid of a special program which implements Steps 1–3. No more than 109 (with an average of 20) of the 20,000–80,000 fitness sets on a run fell in this category.

Numerical results: The numerical results are summarized in Tables 7–9, where in each case the values shown represent the average across 2 to 5 replicate runs. Key features of this analysis are highlighted below.

1. Probability of at least one stable internal equilibrium: The summary statistics in Table 7 confirm that genotypic interactions can greatly facilitate the maintenance of genetic variation. In the general model 51% of the pairwise fitness space produces at least one stable polymorphic equilibrium as opposed to 33% of the fitness space for the classical model and 65–66% of the fitness space for the symmetric models. This probability has a remarkable maximum of 84% in the negatively ordered model, where individuals are least fit when interacting with another of their own genotype. Interestingly, this value is slightly lower (83%) in the fully negatively ordered case, where additionally each homozygote's pairwise fitnesses decrease with increasing genetic similarity of the interacting individuals. In contrast, a stable polymorphic equilibrium exists for only 25% of the general dominance fitnesses (COCKERHAM *et al.* 1972), and, in keeping with the analytical results for the symmetric model (Table 6), is least likely (13%) in the positively ordered case.

The fixed maximum interaction models provide further insight into the types of interactions which increase or decrease the likelihood of a stable polymorphic equilibrium. On average, this likelihood is lowest (19%) when a homozygote × like-homozygote interaction fitness is highest ($W_{11,11} = 1$), and greatest (77%) when a heterozygote × homozygote fitness is highest ($W_{12,22} = 1$). The two extreme values thus correspond to the two fitness schemes which respectively insure the stability or instability of one of the fixation states (see Table 1). In the other three cases, where a homozygote × heterozygote fitness is maximal ($W_{11,12} = 1$), a homozygote × unlike-homozygote fitness is maximal ($W_{11,22} = 1$), or the heterozygote × heterozygote fitness is maximal ($W_{12,12} = 1$) the boundary equilibria may be either stable or unstable. For the first two of these, the likelihood of a stable polymorphic equilibrium is equivalent to that for the general model (51%), and interestingly is only slightly higher (58%) in the third ($W_{12,12} = 1$), which could be viewed as the heterotic, pairwise fitness scheme.

2. Probability of converging to a polymorphic equilibrium: A more precise measure of the potential for permanent genetic variation is provided by the overall fraction of initial gene frequencies which lead to a polymorphic equilibrium. This statistic exhibits the same relative ordering as the probability of having at least one stable internal equilibrium, and is in fact only slightly reduced by the possible simultaneous stability of one or both fixation equilibria. For the basic models in Table 7 (*i.e.*, not fixed-maximum), the probability of converging to a polymorphic equilibrium is again only less than the classical value (33%) in the general dominance (25%) and positively ordered (10%) models. On average, a polymorphic equilibrium is reached for 43% of the fitness space/initial frequencies in the general case and for 81% in the negatively ordered models. This value is intermediate (58–59%) for the symmetric models.

In the fixed maximum interaction models, the likelihood of converging to an internal equilibrium ranged from a minimum average value of 12% when a homozygote × like-homozygote fitness is highest ($W_{11,11} = 1$), to a maximum average value of 69% when a heterozygote × homozygote fitness is highest ($W_{12,22} = 1$). In the other three cases, this probability is similar to that in the general model (43%), with a notable difference only in the heterotic scheme ($W_{12,12} = 1$) where the value is increased to 52%.

3. Probability of a protected polymorphism as an esti-

TABLE 8

Pattern and conditional convergence probabilities

Pattern	General	Negatively ordered[a]	Symmetric[b]	General dominance	Positively ordered	Classical
SU	0.127 (0.000)	0.074 (0.000)	0.000 (—)	0.251 (0.000)	0.057 (0.000)	0.167 (0.000)
US	0.128 (0.000)	0.063 (0.000)	0.000 (—)	0.253 (0.000)	0.084 (0.000)	0.167 (0.000)
SUS	0.239 (0.000)	0.020 (0.000)	0.352 (0.000)	0.247 (0.000)	0.734 (0.000)	0.333 (0.000)
USU	0.238 (1.000)	0.736 (1.000)	0.352 (1.000)	0.248 (1.000)	0.020 (1.000)	0.333 (1.000)
SUSU	0.124 (0.718)	0.039 (0.585)	0.000 (—)	0.000 (—)	0.022 (0.817)	0.000 (—)
USUS	0.120 (0.715)	0.029 (0.582)	0.000 (—)	0.000 (—)	0.046 (0.800)	0.000 (—)
SUSUS	0.013 (0.712)	0.000[c] (—)	0.147 (0.632)	0.000 (—)	0.037 (0.656)	0.000 (—)
USUSU	0.012 (1.000)	0.038 (1.000)	0.148 (1.000)	0.000 (—)	0.000[c] (—)	0.000 (—)
1 Stable polymorphic equilibrium	0.494 (0.853)	0.804 (0.965)	0.499 (0.891)	0.248 (1.000)	0.125 (0.792)	0.333 (1.000)
2 Stable polymorphic equilibria	0.012 (1.000)	0.038 (1.000)	0.148 (1.000)	0.000 (—)	0.000[c] (—)	0.000 (—)
At least 1 stable polymorphism	0.506 (0.856)	0.842 (0.967)	0.648 (0.916)	0.248 (1.000)	0.125 (0.792)	0.333 (1.000)

Pattern probabilities followed by P(converge to polymorphic equilibrium | pattern) in parentheses for each pattern with frequency of at least 5×10^{-4}.

[a] For the fully negatively ordered model, the pattern probabilities are within 0.03 of the entries for the negatively ordered model; the conditional convergence probabilities differ only for SUSU (0.667), USUS (0.659), and for 1 and at least 1 stable polymorphism (0.978).

[b] For the fully symmetric model, the pattern probabilities are within 0.03 of those for the symmetric model; the conditional convergence probabilities differ only for SUSUS (0.492) and for 1 stable (0.830) and at least 1 stable (0.874) polymorphism.

[c] Pattern occurred in only 1–2 fitness sets, with frequency of 5×10^{-4} or less.

TABLE 9

Pattern and conditional convergence probabilities for the fixed maximum interaction models

Pattern	$W_{11,11} = 1$	$W_{11,12} = 1$	$W_{11,22} = 1$	$W_{12,12} = 1$	$W_{12,22} = 1$
SU	0.000 (—)	0.030 (0.000)	0.084 (0.000)	0.108 (0.000)	0.000 (—)
US	0.318 (0.000)	0.208 (0.000)	0.171 (0.000)	0.112 (0.000)	0.233 (0.000)
SUS	0.491 (0.000)	0.251 (0.000)	0.233 (0.000)	0.201 (0.000)	0.000 (—)
USU	0.000 (—)	0.224 (1.000)	0.240 (1.000)	0.252 (1.000)	0.476 (1.000)
SUSU	0.000 (—)	0.220 (0.702)	0.167 (0.769)	0.141 (0.847)	0.000 (—)
USUS	0.180 (0.614)	0.042 (0.461)	0.080 (0.739)	0.140 (0.848)	0.269 (0.727)
SUSUS	0.010 (0.655)	0.001 (0.678)	0.018 (0.726)	0.046 (0.730)	0.000 (—)
USUSU	0.000 (—)	0.025 (1.000)	0.006 (1.000)	0.000 (—)	0.023 (1.000)
1 Stable polymorphic equilibrium	0.191 (0.616)	0.486 (0.818)	0.506 (0.872)	0.579 (0.905)	0.744 (0.902)
2 Stable polymorphic equilibria	0.000 (—)	0.025 (1.000)	0.006 (1.000)	0.000 (—)	0.023 (1.000)
At least 1 stable polymorphism	0.191 (0.616)	0.511 (0.827)	0.512 (0.874)	0.579 (0.905)	0.767 (0.905)

Pattern probabilities followed by P(converge to a polymorphic equilibrium | pattern) for each pattern with frequency of at least 5×10^{-4}.

mate of the potential for permanent genetic variation: It is clear from Table 7 that the probability of a protected polymorphism (*i.e.*, $\hat{p} = 0$ and $\hat{p} = 1$ both unstable) is usually a poor estimate of the full potential for permanent genetic variation. For the general model this probability underestimates the likelihood of having a stable internal equilibrium by 51%, and the probability of actually converging to a polymorphic equilibrium by 42%. The same is true for the three middle fixed maximum models in which a homozygote × unlike-type or heterozygote × heterozygote fitness is maximal. The discrepancies are somewhat less in the other special cases, with the exception of the two fitness schemes with the lowest potential for permanent genetic variation. For the positively ordered model, the protected polymorphism condition underestimates the more precise measures of genetic variation by 5- to 6-fold. The worst discrepancy occurs under the fixed maximum interaction model where a homozygote × like-homozygote fitness is maximal ($W_{11,11} = 1$). In this case there is never a protected polymorphism, yet there is a stable internal equilibrium 19% of the time and one is reached 12% of the time. Interestingly, the protected polymorphism conditions appear to be perfect predictors of the maintenance of genetic variation in the general dominance model just as in the classical model (see pattern probability discussion below).

4. Pattern probabilities: Further general observations are evident from the individual pattern probabilities in Tables 8 and 9: (i) Only the 8 standard equilibrium patterns (Table 4) were ever detected. (ii) Pattern frequencies strongly depend on the pairwise fitness regime. The full range of patterns was only found in the general case and in the two fixed maximum models in which a homozygote × unlike-type fitness is maximal. All but one pattern was found for negatively or positively ordered fitnesses (see last footnote to Table 8), and for fixed maximum fitnesses in which the heterozygote × heterozygote fitness is max-

imal. At the opposite extreme, only four patterns were found for the classical, general dominance, and symmetric models, as well as for the fixed maximum models where a homozygote × like-homozygote or heterozygote × homozygote fitness is maximal. (iii) For some models, the missing patterns may be completely excluded by the fitness regime. Such is the case for the classical model, the symmetric models, and the fixed maximum models in which $W_{ii,ii} = 1$ or $W_{12,ii} = 1$ for i = 1 or 2. In other models, the missing patterns may be theoretically possible but restricted to such a small range of their fitness space that they were not encountered. This seems the most likely explanation of the results for the general dominance model, since although its stability analysis (COCKERHAM *et al.* 1972) appears to have been based on an analog of the insufficient condition, $f'(\hat{p}) < 1$, rather than the full stability criterion in (6), the model did not produce any nonmonotonic trajectories (which should occur whenever $f'(\hat{p}) < 0$). (iv) With the slight exception of the general dominance case, the two equilibrium patterns with one internal equilibrium (SUS, USU) are together the most frequent. In the general case these constitute almost half the total distribution, with the twin patterns with zero or two internal equilibria each occurring in 24–25% of the fitness space, and the two patterns with three internal equilibria occurring in less than 3% of the fitness space. (Note the symmetric frequencies for each pair of patterns with the same number of internal equilibria.) (v) Although it is possible to have two stable polymorphic equilibria, this evidently only occurs in a small subset of the total fitness space. The associated pattern (USUSU) was only produced by ~1% of the general pairwise interaction fitness space and by less than 4% of the fitness space for all the special cases except the two symmetric models. It was never encountered in the general dominance model or in the fixed maximum models where a like × like fitness is maximal, and occurred only twice in the positively ordered model. Note that the latter findings are consistent with the analytic results for the symmetric model (Table 6). (vi) Each pattern probability obtained under the negatively ordered model is close to that for the "complementary" pattern (*i.e.*, the pattern obtained by replacing every "U" by "S" and every "S" by "U") in the positively ordered model.

5. *Probability of converging to a polymorphic equilibrium given the equilibrium pattern*: The conditional probabilities in Tables 8 and 9 show that genetic variation is very likely to be maintained in all cases where there is a stable polymorphic equilibrium (USU, SUSU, USUS, SUSUS, USUSU). In the general model, the gene frequency converges to a polymorphic value 86% of the time that at least one stable polymorphic equilibrium exists. Although this always occurs when both fixation states are unstable (USU, USUSU), a stable polymorphic equilibrium is even reached (on average) from over 71% of the initial frequencies when one or both fixation states are also stable.

The various special models are also very apt to maintain both alleles whenever there is at least one stable polymorphic equilibrium. The likelihood is lowest, but still fairly high (62%), for the fixed maximum model where a homozygote × like-homozygote fitness is maximal, and highest (97%) for the negatively ordered model. The values in the other cases range from 79 to 92%. With a single exception (USUS pattern when $W_{11,12} = 1$) the probability of converging to a polymorphic value exceeds, and often greatly so, the fraction of stable equilibria that are polymorphic. (The classical and general dominance models are omitted from this discussion because both fixation states are, or were found to be, unstable whenever a stable internal equilibrium exists.) The surprisingly high probabilities of converging to a stable polymorphic equilibrium in the presence of one or more stable fixation equilibria (*i.e.*, for SUSU, USUS, and SUSUS patterns) further account for the generally high likelihood of maintaining genetic variation in the pairwise interaction model, as well as for the often poor performance of protected polymorphism conditions as a measure of this potential.

6. *Nonmonotonic trajectories/limit cycles*: In contrast to the symmetric model, fitness sets with nonmonotonic gene frequency trajectories are possible under other pairwise fitness schemes. Such behavior is rare, however, and was found only in runs for the general pairwise interaction model, the negatively ordered model, and the fixed maximum model with a homozygote × unlike-homozygote fitness maximal. In all nonmonotonic trajectories the gene frequency overshot the ultimate equilibrium in the first generation, with the subsequent trajectory generally converging very quickly, either monotonically or with further oscillations.

Most fitness sets with errors were so identified because of nonconvergence in the allotted 10,000 generations. All such cases were found upon individual investigation to be converging to an equilibrium frequency, albeit very slowly, without any cyclical behavior. Since there is no evidence of limit cycles, the statistics concerning polymorphic equilibria suffice to assess the potential for genetic variation in this class of models.

DISCUSSION

The present study of frequency-dependent, pairwise interaction models joins a growing series of quantitative assessments of the potential for permanent genetic variation under various forms of natural selec-

tion (*e.g.*, KARLIN and CARMELLI 1975; LEWONTIN, GINZBURG and TULJAPURKAR 1978; KARLIN 1981; KARLIN and FELDMAN 1981; CLARK and FELDMAN 1986). The results from such studies provide a novel perspective on the biological conditions which enhance or reduce this potential, as well as on the relative strengths of their effects. Here, the primary measures of genetic variability are (i) the fraction of pairwise fitness sets which produce at least one stable polymorphic equilibrium; and (ii) the overall fraction of initial gene frequencies, averaged across all possible fitness sets, which converge to an internal equilibrium, calculated under the assumption that the pairwise fitnesses are independently and uniformly distributed on [0, 1].

Our first step involved a complete analytic description of the equilibrium structure and dynamical behavior under a symmetric model, in which the pairwise fitnesses depend on the genetic similarity of the individuals involved. This was supplemented by an extensive numerical investigation of the equilibrium patterns and gene frequency dynamics under the general pairwise interaction model, as well as under the symmetric model and other special cases. A key aspect of the numerical study was an assessment of the combined domains of attraction of stable polymorphic equilibria.

The results from both phases of the study provide concrete evidence that models which incorporate the frequency-dependent effects of pairwise interactions have a high potential for permanent genetic variation. For general pairwise fitnesses, the probabilities of producing at least one stable internal equilibrium and of actually converging to a polymorphic frequency are respectively 51% and 43%, versus 33% for the classical, constant viability selection model. These probabilities are both highest (84% and 81%) when like × unlike interactions are beneficial with respect to those between like types (negatively ordered fitnesses), and lowest (13% and 10%) when like × unlike interactions are detrimental (positively ordered fitnesses). In the symmetric models these two conditions respectively insure and preclude the maintenance of genetic variation. The potential for permanent genetic variation is only reduced below that in the classical model when each individual's fitness is highest in association with like genotypes (positively ordered model), a homozygote × like-homozygote fitness is maximal, or fitnesses satisfy the conditions of the general dominance model (COCKERHAM *et al.* 1972).

These results are consistent with qualitative predictions on biological grounds, as well as with theoretical demonstrations of an increased retardation of fixation in finite populations under certain pairwise fitness arrays (HEDRICK 1972, 1973). What is perhaps surprising, however, is the actual extent to which intergenotypic interactions can enhance or reduce genetic variability. Our quantitative results also provide a number of other useful insights into this class of models. For instance, the numerical analyses of the negative and fully negatively ordered models show that the likelihood of maintaining genetic variation is not increased if in addition to having each genotype's fitness lowest in association with another of the same genotype, each homozygote's pairwise fitnesses are decreasing functions of the genetic similarity of the interacting individuals.

Another important point, from the numerical investigation of the set of fixed maximum models, is that it is the homozygote × like-homozygote and heterozygote × homozygote fitnesses which, presumably because they determine the stability of the fixation states, have the greatest impact on the likelihood of genetic diversity. Interestingly, the "heterotic" pairwise fitness scheme, in which the heterozygote × heterozygote fitness is maximal, is only slightly more likely to preserve both alleles than is the "average" pairwise fitness scheme. In the same vein, the heterozygote × heterozygote fitness only affects the outcome under the symmetric model as part of a weighted average including the homozygote × unlike-homozygote fitness. Although the stability of the boundary equilibria strongly influences the likelihood of stable polymorphic equilibria and of ultimately converging to a polymorphic frequency, the conditions for a protected polymorphism, which ensure genetic variability through the instability of both fixation states, underestimate by an average of 50% the full potential for permanent genetic variation.

The increased likelihood of maintaining both alleles, and the poor performance of a protected polymorphism as a measure of this likelihood, are caused primarily by a greater variety and frequency of equilibrium patterns with *one* stable polymorphic equilibrium, in conjunction with a large domain of attraction for stable internal equilibria. For instance, on average, the gene frequency converges to a polymorphic value 86% of the time that a stable internal equilibrium exists, and even does so over 71% of the time if one or both fixation states are simultaneously stable. The existence of multiple, stable internal equilibria, on the other hand, does not contribute significantly to the increased potential for genetic variation in these models since, although it is possible to have two stable internal equilibria, this situation is highly unlikely except in the symmetric models, where it occurs in 15–17% of the fitness space. In all other cases considered, multiple, stable polymorphisms were generated in less than 4% of the fitness space, and did not arise at all (or with negligible frequency) when like × like fitnesses are maximal (positively ordered model, symmetric models, or fixed maximum schemes with a

homozygote × like-homozygote or the heterozygote × heterozygote fitness maximal).

Two further points should be borne in mind when interpreting the numerical results from this and similar studies. First, the statistics are based on a uniform distribution of initial frequencies (as well as the unconstrained pairwise fitnesses), whereas the initial frequencies in actual populations are perhaps more apt to be near 0 or 1, due to the recent appearance of a new mutant. Moreover, in such cases random genetic drift may critically influence the ultimate outcome. Second, in addition to trajectories which converge to an internal equilibrium, genetic variation can also in principle be preserved through regular or chaotic limit cycles (see *e.g.*, ASMUSSEN 1979, 1983, 1986). In fact, at least in density-regulated systems, the potential for permanent genetic diversity may be significantly greater when the conditions producing limit cycles are taken into account. A number of previous theoretical studies of frequency-dependent selection (LEWONTIN 1958; CLARKE and O'DONALD 1964; COCKERHAM *et al.* 1972; ENDLER 1988), as well as a recent population genetics textbook (HARTL and CLARK, 1989 pp. 159–161), have referred to the insufficient local stability criterion $d\Delta q/dq < 0$, or equivalently $f'(\hat{p}) < 1$, rather than the full condition in (6). By failing to check that $f'(\hat{p}) > -1$, a stability analysis may not only be invalid, it misses the potential for limit cycles. Our detailed study shows, nonetheless, that limit cycles evidently do not play a role in maintaining genetic variation in the pairwise interaction model.

In conclusion, this investigation sheds considerable insight into the potential for permanent genetic variation in deterministic, frequency-dependent selection models based on pairwise interactions among the genotypes at a single diallelic locus. Important further steps will be to determine the extent to which the present results extend to pairwise interactions at multiallelic loci and other forms of frequency-dependent selection, as well to stochastic models incorporating the effects of drift.

This research was supported in part by National Science Foundation grants BSR-8420803 and BSR 88-19482. We thank WYATT W. ANDERSON, JANIS ANTONOVICS, LISA BROOKS, ANDREW G. CLARK, MICHAEL T. CLEGG, and BRUCE S. WEIR for helpful discussions, and FRANK LETHER and PAUL WENSTON for critically reading an earlier draft. Special thanks are due ANDREW SCHNABEL for his invaluable assistance through all stages of this project.

LITERATURE CITED

ALLARD, R. W., and J. ADAMS, 1969a The role of intergenotypic interactions in plant breeding. Proc. XII Int. Congr. Genet. **3:** 349–370.

ALLARD, R. W., and J. ADAMS, 1969b Population studies in predominantly self-pollinating species. XIII. Intergenotypic competition and population structure in barley and wheat. Am. Nat. **103:** 621–645.

ALLEN, J. A., 1988 Frequency-dependent selection by predators, pp 27–45 in *Frequency-Dependent Selection*, edited by B. C. CLARKE and L. PARTRIDGE. The Royal Society, London.

ALLEN, J. A., and B. CLARKE, 1968 Evidence for apostatic selection by wild passerines. Nature **220:** 501–502.

ANDERSON, W. W., J. ARNOLD, S. A. SAMMONS and D. G. YARDLEY 1986 Frequency-dependent viabilities of *Drosophila pseudoobscura* karyotypes. Heredity **56:** 7–17.

ANTONOVICS, J., and N. C. ELLSTRAND, 1984 Experimental studies of the evolutionary significance of sexual reproduction. I. A test of the frequency-dependent selection hypothesis. Evol. **38:** 103–115.

ANTONOVICS, J., and P. KAREIVA, 1988 Frequency-dependent selection and competition: empirical approaches, pp. 143–155 in *Frequency-Dependent Selection*, edited by B. C. CLARKE and L. PARTRIDGE. The Royal Society, London.

ASMUSSEN, M. A., 1979 Regular and chaotic cycling in models of ecological genetics. Theor. Popul. Biol. **16:** 172–190.

ASMUSSEN, M. A., 1983 Density-dependent selection incorporating intraspecific competition. II. A diploid model. Genetics **103:** 335–350.

ASMUSSEN, M. A., 1986 Regular and chaotic cycling in models from population and ecological genetics, pp. 243–262 in *Chaotic Dynamics and Fractals*, edited by M. BARNSLEY and S. G. DEMKO. Academic Press, Orlando, Fla.

AYALA, F. J., and C. A. CAMPBELL, 1974 Frequency-dependent selection. Annu. Rev. Ecol. Syst. **5,** 115–138.

BUCK, R. C., 1978 *Advanced Calculus*, Ed. 3. McGraw-Hill, New York.

CLARK, A. G., and M. W. FELDMAN, 1986 A numerical simulation of the one-locus multiple-allele fertility model. Genetics **113:** 161–176.

CLARKE, B., and P. O'DONALD, 1964 Frequency-dependent selection. Heredity **19:** 201–206.

CLARKE, B. C., and L. PARTRIDGE (Editors), 1988 *Frequency-Dependent Selection.* The Royal Society, London.

COCKERHAM, C. C., and P. M. BURROWS, 1971 Populations of interacting autogenous components. Am. Nat. **105:** 13–29.

COCKERHAM, C. C., P. M. BURROWS, S. S. YOUNG and T. PROUT, 1972 Frequency-dependent selection in randomly mating populations. Am. Nat. **106:** 493–515.

CODY, W. J., and W. WAIT, 1980 *Software Manual for the Elementary Functions.* Prentice-Hall, Englewood Cliffs, N.J.

CURTSINGER, J. W., 1984 Evolutionary principles for polynomial models of frequency-dependent selection. Proc. Natl. Acad. Sci. USA **81:** 2840–2842.

DOBZHANSKY, T., 1957 Mendelian populations as genetic systems. Cold Spring Harbor Symp. Quant. Biol., **22:** 385–393.

EDELSTEIN-KESHET, L., 1988 *Mathematical Models in Biology.* Random House, New York.

ENDLER, J. A., 1988 Frequency-dependent predation, crypsis, and aposematic coloration, pp. 47–65 in *Frequency-Dependent Selection*, edited by B. C. CLARKE and L. PARTRIDGE. The Royal Society, London.

FREUND, J. E., 1988 *Modern Elementary Statistics*, Ed. 7. Prentice-Hall, Englewood Cliffs, N.J.

HARTL, D. L., and A. G. CLARK, 1989 *Principles of Population Genetics*, Ed. 2. Sinauer Associates, Sunderland, Mass.

HEDRICK, P. W., 1972 Maintenance of genetic variation with a frequency dependent selection model as compared to the overdominant model. Genetics **72:** 771–775.

HEDRICK, P. W., 1973 Genetic variation and the generalized frequency-dependent model. Am. Nat. **107:** 800–802.

HUANG, S. L., M. SINGH and K. KOJIMA, 1971 A study of frequency-dependent selection observed in the esterase-6 locus of *Drosophila melanogaster* using a conditioned media method. Genetics **68:** 97–104.

KARLIN, S., 1975 General two-locus selection models: Some ob-

jectives, results and interpretations. Theor. Popul. Biol. **7:** 364–398.

KARLIN, S., 1981 Some natural viability systems for a multiallelic locus: a theoretical study. Genetics **97:** 457–473.

KARLIN, S., and D. CARMELLI, 1975 Numerical studies on two-loci selection models with general viabilities. Theor. Popul. Biol. **7:** 399–421.

KARLIN, S., and M. W. FELDMAN, 1981 A theoretical and numerical assessment of genetic variability. Genetics **97,** 475–493.

KOJIMA, K., and Y. N. TOBARI, 1969a The pattern of viability changes associated with genotypic frequency at the alcohol dehydrogenase locus in a population of *Drosophila melanogaster*. Genetics **61:** 201–209.

KOJIMA, K., and Y. N. TOBARI, 1969b Selective modes associated with karyotype in *Drosophila ananassae*. II. Heterosis and frequency-dependent selection. Genetics **63:** 639–651.

KOJIMA, K., and K. M. YARBROUGH, 1967 Frequency-dependent selection at the esterase-6 locus in *Drosophila melanogaster*. Proc. Natl. Acad. Sci. USA **57:** 645–649.

L'ECUYER, P., 1988 Efficient and portable combined random number generators. Commun. ACM **31:** 742–749.

LEVENE, H., O. PAVLOVSKY and T. DOBZHANSKY, 1954 Interaction of the adaptive values in polymorphic experimental populations of *Drosophila pseudoobscura*. Evolution **8:** 335–349.

LEVENE, H., O. PAVLOVSKY and T. DOBZHANSKY, 1958 Dependence of the adaptive values of certain genotypes in *Drosophila pseudoobscura* on the composition of the gene pool. Evolution **12:** 18–23.

LEVIN, B. R., 1988 Frequency-dependent selection in bacterial populations, pp. 1–14 in *Frequency-Dependent Selection*, edited by B. C. CLARKE and L. PARTRIDGE. The Royal Society, London.

LEWONTIN, R. C., 1958 A general method for investigating the equilibrium of gene frequency in a population. Genetics **43:** 419–434.

LEWONTIN, R. C., L. R. GINZBURG and S. D. TULJAPURKAR, 1978 Heterosis as an explanation for large amounts of genic polymorphism. Genetics **88:** 149–170.

MAY, R. M., 1974 Biological populations with nonoverlapping generations: stable points, stable cycles, and chaos. Science **186:** 645–647.

PARTRIDGE, L., 1988 The rare-male effect: what is its evolutionary significance? pp 67–81 in *Frequency-Dependent Selection*, edited by B. C. CLARKE and L. PARTRIDGE. The Royal Society, London.

PETIT, C., 1966 La concurrence larvaire et le maintien du polymorphisme. C. R. Acad. Sci. **263:** 1262–1265.

PETIT, C., and L. EHRMAN, 1969 Sexual selection in *Drosophila* pp. 177–223, in *Evolutionary Biology*, edited by TH. DOBZHANSKY, M. K. HECHT and W. C. STEERE. Plenum Press, New York.

PRESS, W. H., B. P. FLANNERY, S. A. TEUKOLSKY and W. T. VETTERLING, 1986 *Numerical Recipes, the Art of Scientific Computing*. Cambridge University Press, New York.

PRICE, M. V., and N. M. WASER, 1982 Population structure, frequency-dependent selection, and the maintenance of sexual reproduction. Evolution **36:** 35–43.

RAVEH, A., and U. RITTE, 1976 Frequency-dependence and stability. Math. Biosci. **30:** 371–374.

ROSS, S., 1988 *A First Course in Probability*, Ed. 3. Macmillan, New York.

SAKAI, K. J., 1961 Competitive ability in plants: its inheritance and some related problems. Symp. Soc. Exp. Biol. **15:** 245–263.

SCHEFLER, W. C., 1988 *Statistics Concepts and Applications*. Benjamin/Cummings, Menlo Park, CA.

SCHUTZ, W. M., C. A. BRIM and S. A. USANIS, 1968 Intergenotypic competition in plant populations. I Feedback systems with stable equilibria in populations of autogamous homozygous lines. Crop. Sci. **8:** 61–66.

SHEPPARD, P. M., 1959 The evolution of mimicry: a problem in ecology and genetics. Cold Spring Harbor Symp. Quant. Biol. **24:** 131–40.

SNYDER, T. P., and F. J. AYALA, 1979 Frequency-dependent selection at the PGM-1 locus of *Drosophila pseudoobscura*. Genetics **92:** 995–1003.

SPIESS, E. B., 1987 Discrimination among prospective mates in *Drosophila*, pp. 75–119 in *Kin Recognition in Animals*, edited by D. J. C. FLETCHER and C. D. MICHENER. Wiley, New York.

TEISSIER, G., 1954 Conditions d'équilibre d'un couple d'alléles et supèrvité des hétérozygotes. C. R. Acad. Sci. **238:** 621–623.

WRIGHT, S., 1955 Classification of the factors of evolution. Cold Spring Harbor Symp. Quant. Biol. **20:** 16–24

Communicating editor: A. G. CLARK

APPENDIX A

Local stability eigenvalues for frequency-dependent fitnesses: At the fixation equilibria, $\hat{p} = 0$ and $\hat{p} = 1$, (7) reduces to

$$f'(0) = \frac{W_{12}(0)}{W_{22}(0)} \quad \text{and} \quad f'(1) = \frac{W_{12}(1)}{W_{11}(1)}, \qquad \text{(A1)}$$

while at polymorphic equilibria ($0 < \hat{p} < 1$),

$$f'(\hat{p}) = 1 + \frac{\hat{p}(1-\hat{p})[W_1'(\hat{p}) - W_2'(\hat{p})]}{\bar{W}(\hat{p})}. \qquad \text{(A2)}$$

where

$$W_1'(p) = W_{11}(p) - W_{12}(p) + pW_{11}'(p) + (1-p)W_{12}'(p)$$

$$W_2'(p) = W_{12}(p) - W_{22}(p) + pW_{12}'(p) + (1-p)W_{22}'(p).$$

APPENDIX B

Internal equilibrium equation and local stability derivatives under the pairwise interaction model: Substituting (8) into the internal equilibrium equation, $W_1(p) = W_2(p)$, shows that the polymorphic equilibria are the roots (if any) on (0, 1) of the cubic

$$C_3p^3 + C_2p^2 + C_1p + C_0 = 0 \qquad \text{(B1)}$$

where

$$C_3 = W_{11,11} - 2W_{11,12} + W_{11,22} - 2W_{12,11} + 4W_{12,12} - 2W_{12,22} + W_{22,11} - 2W_{22,12} + W_{22,22}$$

$$C_2 = 2W_{11,12} - 2W_{11,22} - 6W_{12,12} + 5W_{12,22} + 4W_{22,12} - 3W_{22,22} + W_{12,11} - W_{22,11}$$

$$C_1 = W_{11,22} - 4W_{12,22} + 3W_{22,22} + 2W_{12,12} + 2W_{22,12}$$

$$C_0 = W_{12,22} - W_{22,22}.$$

Local stability of each polymorphic equilibrium $\hat{p}$ is

determined by applying the criterion in (6) to (A2), where from (8)

$$W'_{ij}(p) = 2(W_{ij,11} + W_{ij,22} - 2W_{ij,12})p + 2(W_{ij,12} - W_{ij,22}) \quad \text{for} \quad i, j, = 1, 2.$$

APPENDIX C

Proof of monotonic convergence under the symmetric pairwise interaction model: For this model Δp_t given by (4) can be written as

$$\Delta p_t = \frac{2p_t(1 - p_t)}{\bar{W}(p_t)} g(p_t)(p_t - \tfrac{1}{2}) \tag{C1}$$

where

$$g(p_t) = (4b - a - 2d - c)p_t(1 - p_t) + a - b \tag{C2}$$

and

$$\bar{W}(p_t) = k_4 p_t^4 + k_3 p_t^3 + k_2 p_t^2 + k_1 p_t + k_0 \tag{C3}$$

with coefficients

$$k_4 = 2(a + 2d + c - 4b)$$
$$k_3 = -4(a + 2d + c - 4b)$$
$$k_2 = 2(3a + 2d + c - 6b)$$
$$k_1 = 4(b - a)$$
$$k_0 = a.$$

The proof is divided into four parts depending on the relative order of a, b, and $(c + 2d)/3$.

Case 1. $b > a > (c + 2d)/3$ (USUSU): Under this condition $g(p_t)$ in (C2) can be factored as

$$g(p_t) = (a + 2d + c - 4b)(p_t - \hat{p}_1)(p_t - \hat{p}_3) \tag{C4}$$

where $\hat{p}_1$ and $\hat{p}_3$ are the internal equilibria defined in (10). It follows that

$$\Delta p_t \begin{cases} > 0 & \text{if } 0 < p_t < \hat{p}_1 \\ < 0 & \text{if } \hat{p}_1 < p_t < \tfrac{1}{2} \\ > 0 & \text{if } \tfrac{1}{2} < p_t < \hat{p}_3 \\ < 0 & \text{if } \hat{p}_3 < p_t < 1. \end{cases} \tag{C5}$$

To prove monotonicity we must rule out overshooting by showing that

$$0 < p_t < \tfrac{1}{2} \quad \text{implies} \quad |\Delta p_t| < |p_t - \hat{p}_1|, \tag{C6}$$

and

$$\tfrac{1}{2} < p_t < 1 \quad \text{implies} \quad |\Delta p_t| < |p_t - \hat{p}_3|. \tag{C7}$$

Observe that the implication (C6) holds if and only if

$$\frac{2p_t(1 - p_t)(\hat{p}_3 - p_t)(\tfrac{1}{2} - p_t)(4b - a - 2d - c)}{\bar{W}(p_t)} \tag{C8}$$

less than 1.

To establish (C8) it suffices to show that

$$2p_t(1 - p_t)^2(\tfrac{1}{2} - p_t)(4b - a - 2d - c) < \bar{W}(p_t)$$

which from (C3) reduces to

$$-(4b - a - 2d - c)p_t^2(1 - p_t) - (3a - 2d - c) \cdot [\tfrac{1}{4} - p_t(1 - p_t)] - (a + 2d + c)/4 < 0,$$

which clearly holds under the prevailing pairwise fitness relations.

The implication (C7) similarly holds if and only if

$$\frac{2p_t(1 - p_t)(p_t - \hat{p}_1)(p_t - \tfrac{1}{2}) \cdot (4b - a - 2d - c)}{\bar{W}(p_t)} < 1. \tag{C9}$$

To show (C9) it is sufficient to prove that

$$2p_t^2(1 - p_t)(p_t - \tfrac{1}{2})(4b - a - 2d - c) < \bar{W}(p_t) \tag{C10}$$

or, equivalently, that

$$4p_t(1 - p_t)^2(a - b) + a[3p_t^2(1 - p_t) - 1] - p_t^2(1 - p_t)(c + 2d) < 0$$

which is also true under the prevailing fitness relations. Since for every initial polymorphic gene frequency $0 < p_0 < 1$ the sequence $\{p_t\}$ is bounded within [0, 1] and monotonic, the sequence necessarily converges (Buck 1978, pp 47,57). In fact, from (C5) to (C7) we must have $\lim_{t\to\infty} p_t = \tilde{p}$ for some $\tilde{p} \in (0, 1)$. It remains to show that the limiting value $\tilde{p}$ is indeed $\hat{p}_1$ if $0 < p_0 < \tfrac{1}{2}$ and $\hat{p}_3$ if $\tfrac{1}{2} < p_0 < 1$. To prove this note first that

$$\lim_{t\to\infty} p_t = \tilde{p} \quad \text{trivially implies} \quad \lim_{t\to\infty} f(p_t) = \lim_{t\to\infty} p_{t+1} = \tilde{p}.$$

The continuity of the recursion function $f(\cdot)$ on [0, 1] in turn implies

$$\lim_{t\to\infty} f(p_t) = f\left[\lim_{t\to\infty} p_t\right] = f(\tilde{p})$$

(Buck 1978, p. 74). Since a converging sequence can only have 1 limit (Buck 1978, p. 47) we must have $\tilde{p} = f(\tilde{p})$, where $\tilde{p} \in (0, \tfrac{1}{2})$ if $0 < p_0 < \tfrac{1}{2}$, and $\tilde{p} \in (\tfrac{1}{2}, 1)$ if $\tfrac{1}{2} < p_0 < 1$. Since $\tilde{p}$ is thus an internal equilibrium, we conclude in the first case that $\tilde{p} = \hat{p}_1$, and in the second, that $\tilde{p} = \hat{p}_3$.

Case 2. $b < a < (c + 2d)/3$ (SUSUS): Δp_t is again given by (C1)–(C4), but the inequalities in (C5) are reversed. Arguments analogous to those given for case 1 can be invoked to show that here (i) $p_t \downarrow 0$ if $p_0 \in (0, \hat{p}_1)$, since $\hat{p} = 0$ is the only equilibrium below $\hat{p}_1$; and (ii) $p_t \uparrow 1$ if $p_0 \in (\hat{p}_3, 1)$, since $\hat{p} = 1$ is the only equilibrium above $\hat{p}_3$.

To prove monotone convergence to $\hat{p} = \tfrac{1}{2}$ from $\hat{p}_1 < p_0 < \hat{p}_3$ we have only to establish that $\hat{p}_1 < p_t < \hat{p}_3$ implies $|\Delta p_t| < |p_t - \tfrac{1}{2}|$. Using (C1)–(C4) we see that the desired implication holds if and only if

$$-2p_t(1 - p_t)g(p_t) < \bar{W}(p_t) \tag{C11}$$

or, equivalently,

$$2(b - a)p_t(1 - p_t) + a > 0. \quad \text{(C12)}$$

This is clearly the case since $p_t(1 - p_t) \leq 1/4$ on $[0, 1]$ implies that

$$2(b - a)p_t(1 - p_t) + a \geq \frac{b + a}{2} > 0.$$

Hence, by analogy to case 1 we conclude that $p_t \uparrow 1/2$ if $\hat{p}_1 < p_0 < 1/2$ and $p_t \downarrow 1/2$ if $1/2 < p_0 < \hat{p}_3$.

Case 3. $a \leq b$, $(c + 2d)/3$ with at least one inequality strict (USU): In this case $\hat{p} = 1/2$ is the only polymorphic equilibrium, and (C1)–(C3) imply that

$$\Delta p_t \begin{cases} > 0 & \text{if} \quad 0 < p_t < 1/2 \\ < 0 & \text{if} \quad 1/2 < p_t < 1. \end{cases} \quad \text{(C13)}$$

To prove monotonic convergence to $\hat{p} = 1/2$ we have only to show that $|\Delta p_t| < |p_t - 1/2|$ for all $0 < p_t < 1$. As in Case 2, this inequality reduces to (C11) and thence to (C12), which obviously holds under the current pairwise fitness relation. Hence, $p_t \uparrow 1/2$ if $0 < p_0 < 1/2$ and $p_t \downarrow 1/2$ if $1/2 < p_0 < 1$.

Case 4. $a \geq b$, $(c + 2d)/3$ with at least one inequality strict (SUS): Here the inequalities in (C13) are reversed. By analogy to Case 2 we conclude that $p_t \downarrow 0$ if $0 < p_0 < 1/2$ and $p_t \uparrow 1$ if $1/2 < p_0 < 1$.

APPENDIX D

Pattern probabilities for the symmetric pairwise interaction model: The probabilities in Table 6 assume that the pairwise fitness variables, a, b, c and d are independently and uniformly distributed on $[0, 1]$, with joint density function $f(a, b, c, d) = 1$ on $[0,1]\times[0,1]\times[0,1]\times[0,1]$ (Ross 1988, p. 203). Writing $e = (c + 2d)/3$, the probabilities for the patterns with three internal equilibria are found by straightforward integration to be

$$P(\text{USUSU}) = P(b > a > e) = \int_0^1 \int_0^1 \int_e^1 \int_e^b 1 \, da \, db \, dc \, dd = \frac{4}{27} \; (\approx 0.148)$$

and

$$P(\text{SUSUS}) = P(b < a < e) = \int_0^1 \int_0^1 \int_0^e \int_b^e 1 \, da \, db \, dc \, dd = \frac{4}{27} \; (\approx 0.148).$$

The probabilities for the two remaining patterns with one internal equilibrium can now be easily derived from the partitions

$$P(\text{USU}) = P(a \leq b, e) = P(a \leq b \leq e) + P(a \leq e \leq b) \quad \text{(D1)}$$

and

$$P(\text{SUS}) = P(a \geq b, e) = P(a \geq b \geq e) + P(a \geq e \geq b). \quad \text{(D2)}$$

By symmetry with respect to a and b, the last terms on the right-hand sides of (D1) and D2) are equivalent, the first right-hand term of (D1) is equivalent to $P(b < a < e) = 4/27$, and the first right-hand term of (D2) is equivalent to $P(b > a > e) = 4/27$. Since the USU and SUS patterns are equally likely and the four pattern probabilities must sum to 1, these two final patterns each have probability 19/54 (≈ 0.352).

APPENDIX E

Verification procedures for numerical methods: The programs to assess the relative frequencies of the various equilibrium patterns (Table 4) and the likelihood of permanent genetic variation were written in Turbo Pascal 4.0, and run in extended precision (19–20 significant digits) on an IBM PS/2 Model 80-111 with a 20 MHz 32-bit 80386 processor coupled with a 20 MHz 80387 coprocessor.

Because of its complexity, the general program was tested by (i) executing it for the classical and symmetric models, for which the equilibrium structure, pattern probabilities, and qualitative dynamics are known; and (ii) hand-calculating the output in small-scale runs with 100 random fitness sets iterated with up to 29 initial frequencies. The statistics for the general model were also checked against those predicted from the runs for the fixed-maximum models, assuming that each of the nine pairwise fitnesses is equally likely to be maximal. The predicted probability of a given event E under the general model can be simply calculated as $P(E) = \sum_{i=1}^{9} P(M_i)P(E \mid M_i)$, where M_i is the event that the ith pairwise fitness is maximal. The predicted value of each conditional convergence probability $P(C \mid E)$ can be calculated from standard conditional probability rules (Ross 1988) as

$$P(C \mid E) = \frac{\sum_{i=1}^{9} P(C \cap E \cap M_i)}{\sum_{i=1}^{9} P(E \cap M_i)} = \frac{\sum_{i=1}^{9} P(M_i)P(E \mid M_i)P(C \mid E \cap M_i)}{\sum_{i=1}^{9} P(M_i)P(E \mid M_i)}.$$

Similar methods were used to check for internal consistency among the summary statistics for individual models.

Two further technical issues involved in the numerical method are discussed below.

1. Random number generator (UNIFORM): UNIFORM's required twin seeds were generated from [0, 1] by the compiler's built-in random number generator and recorded in the output. In this way different seeds were used for replicate runs. As a safeguard, UNIFORM's uniformity and randomness (L'ECUYER 1988) were independently checked by the following tests. (a) Visual test: 100,000 ordered pairs (x_i, y_i) were obtained by generating the numbers x_i and y_i on [0, 1] using UNIFORM. The plotted points appear to be distributed evenly throughout the unit square, and no distinct pattern is evident. (b) Estimation of area under the curve $y = x^2$: 100,000 ordered pairs (x_i, y_i) were again generated on [0, 1] × [0, 1] using UNIFORM. The area under the graph $y = x^2$ was estimated by

$$\text{Area} = \frac{\text{number of } (x_i, y_i) \text{ points for which } y_i < x_i^2}{100{,}000}.$$

The resulting value was 0.33304 . . . which agrees to the third decimal place with the true area of ⅓. (c) Chi-square test: Three sets of 100,000 numbers were generated on [0, 1] using UNIFORM, and the counts of the numbers lying within each of n = 10 (or 101) equal subintervals were determined and tested for uniform distribution over those intervals via a chi-square test with 9 (or 100) degrees of freedom. This test was satisfied in all 6 cases at the 0.05 significance level (SCHEFLER 1988). (d) Serial correlation test: Three sets of 100,000 numbers were generated on [0, 1] by UNIFORM and their correlation coefficients (C) calculated and tested at the 0.05 significance level for the null hypothesis, H_0: no correlation exists between the data ($C = 0$), versus the alternative hypothesis, H_a: the numbers are correlated. Based on the resulting values for Fisher's test statistic, z, we conclude with 95% confidence that the null hypothesis H_0 holds, *i.e.*, the numbers generated by UNIFORM are uncorrelated (FREUND 1988).

2. Cubic-solver: A potential problem with the cubic-solver adopted from PRESS *et al.* (1986) is the need to evaluate the arccosine function ($\text{Cos}^{-1}(x)$). To overcome the potential error when $|x|$ is near 1, $\text{Cos}^{-1}(x)$ was set to 0 if $\sqrt{1 - x^2} < 10^{-18}$ and $x > 0$, set to Π if $\sqrt{1 - x^2} < 10^{-18}$ and $x < 0$, and otherwise evaluated by the basic identity

$$\text{Cos}^{-1}(x) = \frac{\Pi}{2} - \text{Tan}^{-1}\left(\frac{x}{\sqrt{1 - x^2}}\right)$$

using the compiler's built-in Tan^{-1} function.

In order to check this procedure, several relative error plots were made comparing this method and a polynomial approximation to $\text{Cos}^{-1}(x)$ presented by CODY and WAIT (1984). The results from the relative error curves for $x \in [0.95, 0.9995]$ and $[0.9999999998, 1.0)$ suggest that the relative error is no more than 10^{-10}. As a further check, the relative error between the two methods was also calculated during actual runs for the general pairwise interaction model, the symmetric pairwise interaction model, the general dominance model (COCKERHAM *et al.* 1972), the negatively ordered model, and other special cases (for a total of 280,000 comparisons). The relative error never exceeded 10^{-10}.