

The Maintenance of Single-locus Polymorphism. V. Sex-dependent Viabilities

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Since natural selection requires variation to act, the amount of genetic variation in a given population is of central theoretical and experimental importance. This amount is estimated by the genetic variation present in current populations. Electrophoretic studies of natural populations reveal that ten to twenty percent of all loci have multiple alleles. These multi-allelic loci may be the result of the accumulation of unselected mutations (neutral theory) or of balancing selection (selectionist theory). The neutral theory views selection as primarily eliminating variation, whereas the selectionist theory views selection as often maintaining variation. Therefore, our view of selection and evolution depends upon the question of how multiple allelic systems evolve.

To address whether balancing selection increases genetic variation, we examined Owen's model in which selection varies in the two sexes (sex-dependent model) and compared it to a model in which selection is constant across the two sexes (sex-independent model). We explored these models for a single multi-allelic locus to explore more generally the effect of balancing selection on the maintenance and construction of multi-allelic systems. To do so, we constructed two computer models. The "fitness-space" approach examines the proportion of all possible fitnesses capable of maintaining different sized allelic systems. The proportion of possible fitnesses is greater in balancing selection models. The "constructionist" approach examines the ease in reaching this portion of possible fitnesses. The ease in reaching fitnesses is less in balancing selection models. Thus, in contrast to previous hypotheses, our research suggests that balancing selection may not increase the amount of variation present in natural populations.

Keywords: Balancing selection, neutralist theory, maintenance and construction of polymorphism

1. Introduction

The history of population genetics has often been characterized as a struggle to understand variation (e.g. Lewontin, 1974). A considerable body of theoretical work – building simple models of Mendelian segregation, mutation, migration, drift, inbreeding, and many patterns of selection – addresses this question of variation. In particular, microevolutionary discussions of the maintenance of genetic variation have been dominated by the well-known result that polymorphism can be maintained by heterozygote advantage in fitness. But this specific result is not particularly robust. The analytical conditions for the maintenance of three or more alleles as the result of

selection alone are quite a bit more complicated than those for two alleles (Kimura, 1956; Mandel, 1959; see Hartl and Clark, 1989, pp. 168–177 for a summary). Though for any particular pattern of allele frequencies it is possible to construct a fitness set that has those frequencies as its equilibrium solution (Marks and Spencer, 1991), the relationship between the fitnesses and the equilibrium allele frequencies are substantially more constrained for multiple alleles than in the two allele result. These difficulties raise the theoretical question of whether a simple model of viability selection is a likely explanation for loci with large numbers of alleles in nature.

This theoretical question has been explored in two different ways. The first of these measures the volume of the fitness space in which a fully polymorphic equilibrium (i.e. one with all alleles present) will be obtained. This approach was followed by Gillespie (1977) and Lewontin et al. (1978)

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studying the standard multiple-allele constant-viability model. The somewhat surprising result of these studies is that the fraction of the fitness space that supports a fully polymorphic equilibrium becomes vanishingly small for even a moderate number of alleles.

But this static measure of the fitness space ignores the evolutionary dynamic of the process in nature. The standing crop of alleles in a population is the result of, at a minimum, mutation and selection. As Ginzburg (1979) has pointed out, alleles that persist are not a randomly selected sample from within a fitness space, but rather the result of a historical process. That is, the alleles that are found in a population are the result of an evolutionary process, and so their fitnesses are an evolutionary outcome as well.

With this critique in mind, earlier papers in this series (Spencer and Marks, 1988, 1992; Marks and Spencer, 1991) have been directed at the basic question in a second way. Rather than ask about the size of fully polymorphic regions of the fitness space, they ask instead whether a simple process of recurrent mutation and selection would find such regions, regardless of their size. The general result from these "constructionist" studies is that more alleles could be maintained than might have been predicted from considerations of the fitness space volume alone. That simple result is fairly robust with respect to assumptions about the distribution of the fitnesses of new alleles. Indeed, with some simple assumptions about the relationship between the fitnesses of genotypes formed by a new mutation and the related genotypes of the parent, the number of alleles that could be supported is quite large (Spencer and Marks, 1992).

The literature of population genetics is rich with examples of two allele models that have been advanced as potential explanations for allelic variation. With simple relaxation of some key assumptions, many have richer equilibrium behavior than a simple two allele model. For example, Owen (1953) demonstrates that a model with sex-dependent fitnesses can produce two stable feasible equilibria for two alleles (i.e. equilibrium allele frequencies between 0 and 1). The behavior of this sex-dependent model has been explored further by several authors (Haldane, 1962; Li, 1963; Bodmer, 1965; Mérat, 1969; Kidwell et al., 1977; Selgrade and Ziehe, 1987). This work has largely been directed at char-

acterizing the behavior of equilibria for two alleles. Prout (1971) points out that a genotype that affects the reproductive component of fitness will almost certainly have effects that are sex-dependent.

The rich behavior of the sex-dependent model in the two allele case suggests that it might be another factor in the explanation of multiple allele polymorphisms. Indeed, Hartl and Clark (1989), looking at one sufficient (but not necessary) condition for the existence of a nontrivial equilibrium in this sex-dependent model, find that the fraction of the two allele fitness space (6 fitnesses; three each for males and females) in which both alleles will be maintained is at least 42%, substantially larger than the 33% for the simple viability model. The model is also of interest since it is a special case of the more general fertility selection model, in which the fertility of a mating pair is simply the product of constant fitness parameters for male and female (Bodmer, 1965). Clark and Feldman (1986) take the same approach as Lewontin et al. (1978) in an examination of fertility selection. They find that fertility models appear to be no more capable than viability models in explaining highly polymorphic equilibria (see also Hartl and Clark, 1989, p. 190). Though the monstrous intractability of multiple allele fertility models makes a constructionist examination of the general case difficult, a constructionist examination of sex-dependent selection may give us some insight into the behavior of fertility models.

2. Methods

The model is based upon the standard population genetics model of selection and thus makes the same assumptions. It differs in that the selection coefficients for a given genotype differ between the two sexes, rather than being equal for males and females. Thus, the recursion for the frequency of allele A_i in females is given by

$$f'_i = \frac{\frac{1}{2} \sum_j u_{ij} [f_i \cdot m_j + m_i \cdot f_j]}{\sum_i \sum_j u_{ij} \cdot f_i \cdot m_j}$$

in which f_i is the frequency in the current generation of the i th allele in females, m_i is the frequency in the current generation of the i th allele in males, and u_{ij} is

the fitness associated with genotype $A_i A_j$ in females. Similarly, the recursion for males is

$$m'_i = \frac{\frac{1}{2} \sum_j v_{ij} [f_i \cdot m_j + m_i \cdot f_j]}{\sum_i \sum_j v_{ij} \cdot f_i \cdot m_j}$$

in which v_{ij} is the fitness associated with the genotype $A_i A_j$ in males. Note that u_{ij} and v_{ij} are viabilities the other components of fitness are assumed to be the same across all genotypes within a sex.

We take two approaches to the study of this model. The first parallels the work of Gillespie (1977), Lewontin et al. (1978), and Clark and Feldman (1986) and measures the volume of the n -allele fitness space in which fully polymorphic equilibria are found. The second follows the approach of Spencer and Marks (1988) in which a population evolves under a simple process of recurrent mutation and selection, to address the question of how likely it is that selection will cause the population to reach those regions of the fitness space that support complete polymorphism. We will refer to the former as the “fitness space” approach. Spencer and Marks (1993) have suggested the latter be referred to as the “constructionist” approach. For both approaches, as a check of our computer programs, we also run the special case of sex-independent fitnesses for direct comparison to earlier work.

2.1. Fitness space approach

For a given number of alleles (n), 100,000 sets of the appropriate number of viabilities ($n[n+1]/2$ for each gender) are chosen from uniform distribution on $[0,1)$. Initial allele frequencies are generated using a broken stick process: $n-1$ uniform random numbers are used to divide the interval $[0,1)$ line into n pieces with the size of each piece giving one allele frequency. For each of $10n$ randomly selected initial allele frequencies (these same frequencies are used for all 100,000 replicates), the recursions are iterated until the sum of the squares of the differences in allele frequencies from one generation to the next is less than $1.0 \cdot 10^{-17}$, or until one allele frequency falls below $1.0 \cdot 10^{-5}$ in both sexes. $10n$ initial allele frequencies are used not only to examine the possibility of two internal equilibria (Owen, 1953), but also to compensate for the possibility of an internal

as well as external stable equilibrium (Selgrade and Ziehe, 1987). For a given fitness set, two equilibria are considered distinct if the frequency for any allele differs by more than $1.0 \cdot 10^{-4}$ between the two. The proportion of the initial 100,000 fitness sets that have at least one internal fully polymorphic equilibrium quantifies the fraction of the fitness space for nontrivial stable equilibria. When fully polymorphic internal equilibria are achieved, the fitness set and the equilibrium allele frequencies are recorded. The simulations continue with increasing numbers of alleles until two successive numbers of alleles generate no fully polymorphic equilibria.

2.2. Constructionist approach

The constructionist model is begun with one allele for which the homozygote viabilities in the two sexes are each set to values chosen from $U[0,1)$. In each generation, a new allele is generated with an initial allele frequency of $1.0 \cdot 10^{-5}$ in one sex chosen at random. An existing allele in one sex is randomly chosen (with probability equal to its frequency) as the source of this new mutant; the allele frequency of this source is decremented by $1.0 \cdot 10^{-5}$. Viabilities for genotypes involving the new allele (as a homozygote and as heterozygote in combination with all other current alleles) are randomly generated from $U[0,1)$, independently for each sex. In each generation, following iteration of the recursion, any alleles whose average frequency across the sexes falls below $1.0 \cdot 10^{-5}$ are considered to have gone extinct and are removed. This invasion and extinction scheme was chosen, in part, to avoid mutations that invade only for one generation. Since these mutations are transient, they are not salient to the questions addressed here. To characterize individual iterations, 12 replicates are run for 1,000,000 generations. For the production runs, 25,000 replicates are run for 25,000 generations. At the end of this process the final allele frequencies, final fitness sets, and age of each surviving allele are recorded. For Figures 7–9, replicates are run for 75,000 generations.

The random numbers used in the simulations are drawn from a uniform $[0,1)$ using a lagged Fibonacci generator (Marsaglia et al., 1990). Each of us independently wrote all programs. Any differences in outcomes (due to errors in the code or differences

in coding decisions) were traced to their source and reconciled before the experimental runs reported here were made.

3. Results

3.1. Fitness space approach

In Table 1 are shown the fraction of times that at least one of the $10n$ initial conditions led to a fully polymorphic equilibrium. The results in the first column (sex-independent selection) replicate the results of Lewontin et al. (1978, their Table 2, third column). For sex-dependent selection the area of the fitness space that leads to a fully polymorphic equilibrium is larger than that for the sex-independent selection in every case in which fully polymorphic equilibria are reached. However, as with sex-independent selection, for sex-dependent selection the size of the fully polymorphic regions of the fitness space for 6 alleles or more is less than 10^{-5} .

For two alleles, sex-dependent viabilities can generate two simultaneous stable internal equilibria (Owen, 1953; Kidwell et al., 1977). Table 1 also shows the fraction of replicates from our simulations for which two different fully polymorphic equilibria exist simultaneously. This behavior is, however, rare, never occurring in more than 2% of the cases for which a stable internal equilibrium exists.

As important as the number of alleles that can be maintained by this process is the distribution of these alleles. Lewontin et al. (1978) suggests using

$$I = \left(p_i - \frac{1}{n} \right)^2$$

TABLE 1

The proportion of runs (out of 100,000) for which at least one initial condition leads to a fully polymorphic equilibrium in the fitness space study

No. of alleles	Proportion with fully polymorphic equilibria		
	Sex-independent selection	Sex-dependent selection	Fraction of replicates with two equilibria
2	0.33174	0.46602	0.00584
3	0.04363	0.06672	0.00032
4	0.00237	0.00346	0.00002
5	0.00003	0.00010	0
6	0	0	0

For comparison, the results for the sex-independent control model are shown.

(n times the variance in allele frequency) as a measure of unevenness of allele frequency distribution. A value of I close to zero indicates that all alleles are approximately equally frequent; a value of I far from zero indicates that alleles have very different frequencies. The distributions of I for all fully polymorphic equilibria are shown in Figure 1. Also shown in Figure 1 are distributions of I in the frequency space that would be expected if points representing n -allele polymorphisms are chosen from a uniform distribution on $[0,1)$ within the space. These distributions are generated using the broken stick method as described in Marks and Spencer (1991). The allele frequencies from the internal equilibria appear to be slightly less variable than uniformly distributed allele frequencies. That is, the stable feasible equilibria are somewhat more concentrated near the centroid of the space.

We also compare the fitnesses that result in stable feasible equilibria in this system with the conventional views regarding heterosis. This comparison is

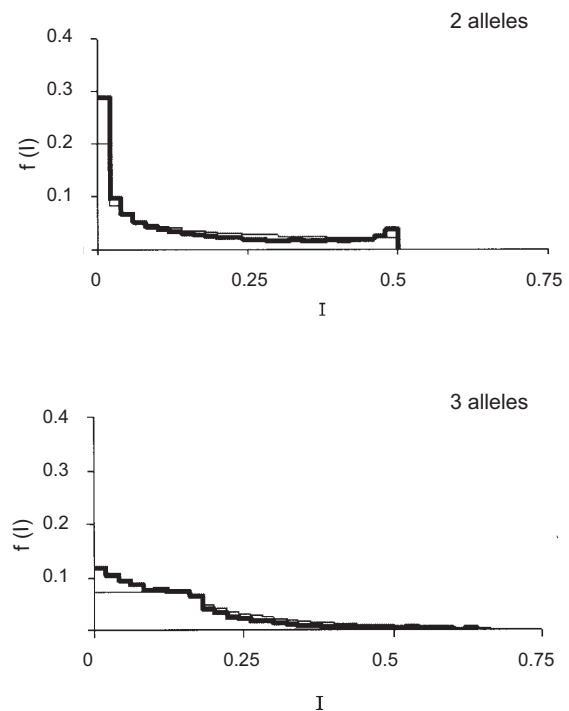


FIG. 1. Distribution of I for fitness space approach. The heavy line is the observed distribution. The light line is what is expected if frequency arrays are chosen uniformly. The same patterns are seen in the plot for 4 alleles. (The blip at 0.5 for two alleles does not seem to be an artifact of lack of convergence.)

TABLE 2
Classification of stable, feasible equilibria
by the patterns of fitnesses in males and females
from the fitness space approach

2 alleles:		Female		
		heterosis	pairwise heterosis	no heterosis
Male	heterosis	0.2390		0.3193
	pairwise heterosis			
	no heterosis	0.3182		0.1236
3 alleles:		Female		
		total heterosis	pairwise heterosis	no heterosis
Male	total heterosis	0.0303	0.0070	0.2358
	pairwise heterosis	0.0115	0.0030	0.0378
	no heterosis	0.2308	0.0358	0.4062

Following Lewontin et al. (1978), each fitness set was classified as "total heterosis" if every heterozygote was fitter than every homozygote, "pairwise heterosis" if every heterozygote was fitter than the two associated homozygotes, and "no heterosis" if at least one heterozygote was less fit than one of the associated homozygotes. For 4 alleles, the same pattern shown here is observed.

not entirely straightforward since each genotype has a fitness in both males and females. We report the fraction of fitness sets classified according to the simultaneous fitness patterns in males and females in Table 2. The marginal classifications are the same as those of Lewontin et al. (1978). Even for the two allele case, at least one parent has nonheterotic fitnesses in the majority of cases. For more alleles, an increasing fraction of equilibria are obtained in which there is no form of heterosis in either sex.

The relationship between the fitnesses of individual genotypes in males and females is examined in Figure 2. The figure shows a scatterplot of male and female fitnesses from the first 1,000 replicates. Heterozygote fitness tends to be higher than homozygote fitness (since heterozygote fitness spreads out from the top left corner and homozygote fitness spreads out from the bottom right corner) even though both were drawn initially from the same distribution. Thus, even though an increasing number of fitness sets do not exhibit total or pairwise heterosis, heterosis of some sort appears to be an important criteria for fitness sets to maintain all initial alleles. Furthermore, male and female fitnesses are negatively correlated for both homozygotes and heterozygotes.

3.2. Constructionist approach

We began our exploration of the constructionist model by examining its long-term behavior, running replicates for 1,000,000 generations each. Figure 3 shows graphs of the total number of alleles and the number of "common" alleles, those alleles whose frequency exceeds 0.01, as a function of generation number for 2 of the 12 runs. Also plotted is the mean viability fitness for males and females over time. These graphs can be compared with those of Figure 1 in Spencer and Marks (1992). As in the sex-independent case, the process begins with a large number of substitutions and eventually settles down into a more stable long term behavior usually by 10,000 generations. Male and female mean viability fitness can be substantially different³; an increase in the mean fitness of one sex can be accompanied by a decrease in the mean fitness of the other sex. To characterize this typical behavior, we examined the dynamics of the process after generation 10,000 in the production runs.

The distribution of final numbers of alleles for the 25,000 runs of 25,000 generations each is shown in

TABLE 3
Final distribution of numbers of alleles for 25,000 replicates
of the 25,000 generation constructionist runs

No. of alleles	Sex-independent fitnesses	Sex-dependent fitnesses
1	0.00056	0.00064
2	0.01140	0.02424
3	0.07476	0.16036
4	0.20928	0.36576
5	0.30404	0.31040
6	0.23692	0.11636
7	0.11624	0.02048
8	0.03584	0.00160
9	0.00768	0.00016
10	0.00328	
Average	5.233	4.401

For comparison, the results for the sex-independent control model are shown.

³ In effect this results in differential fecundity in males and females. However, since the fecundity is not a function of genotype, the allele frequencies within males and females, which is what is modeled, are not affected by this differential fecundity. Another possibility is the sex ratio changes. Again the sex ratio does not affect allele frequencies within males and females. There is no mechanism within the model by which sex ratio could evolve.

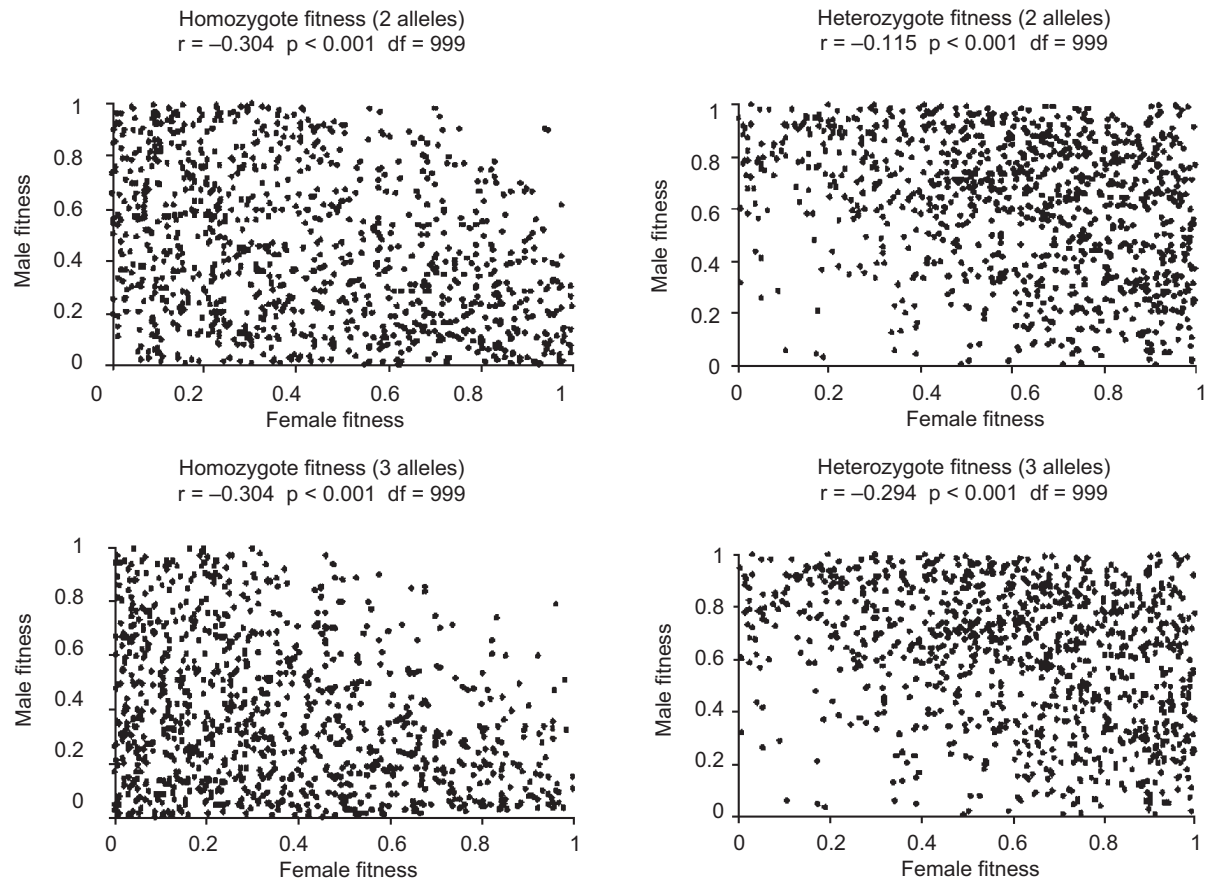


FIG. 2. Male fitness versus female fitness at equilibrium for the same genotype in the fitness space approach. The r value is Spearman's rank correlation between female and male fitness. The same patterns are seen in the plot for 4 alleles

Table 3. The Table also shows the distribution of the final numbers of alleles for the control runs with sex-independent fitnesses (as in Marks and Spencer, 1991; their Table 1, last column). The average level of polymorphism attained by the sex-dependent constructionist process is distinctly lower than that for sex-independent fitnesses. Although the fitness space approach leads to a larger region of the fitness space that supports fully polymorphic equilibria in the sex-dependent case than in the sex-independent case, the opposite is true for the constructionist approach.

The distributions of I are shown in Figure 4, along with the distribution that would result from points uniformly scattered in the frequency space. The evolved allele frequency sets are less centered about the centroid than uniformly generated frequencies. However, the evolved allele frequency sets are more centered about the centroid in the sex-dependent model than in the sex-independent

model (compare Figure 4 to Marks and Spencer, 1991; Figure 1).

We also want to examine whether in the constructionist runs the alleles that invade have differences in fitnesses between males and females. Figure 5 plots the genotype fitnesses of females and males separately for heterozygotes and homozygotes. Though heterozygotes are obviously more constrained than homozygotes, in both cases considerable variability between the sexes can and does evolve. Male and female heterozygote fitnesses are positively correlated, but there appears to be no correlation between male and female homozygote fitnesses.

We present the fraction of fitness sets exhibiting heterosis, classified according to the simultaneous fitness patterns in males and females in Table 4. The evolved fitness sets exhibit more heterosis than the fitness space fitness sets; over 60% of all fitness sets exhibit total heterosis for two alleles. However, as

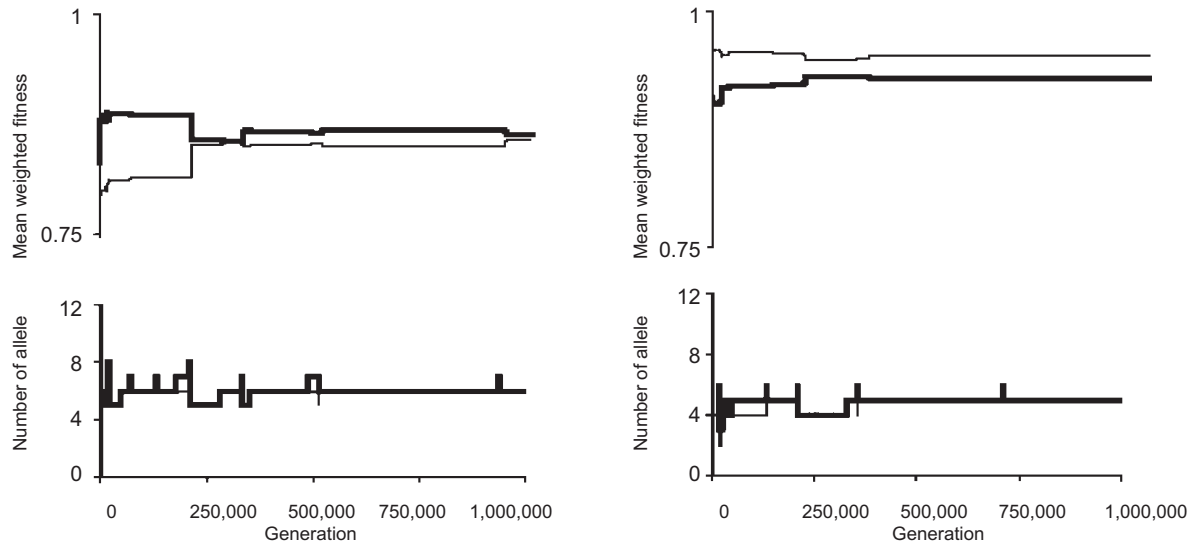


FIG. 3. In the bottom of each pair of graphs is the number of alleles over time for the constructionist approach. The heavy line is the total number of alleles. The light line is the number of common alleles (alleles whose average frequency in males and females is greater than 0.01). The top graph shows the associated mean viability fitness for females (heavy line) and males (light line) over time

the number of alleles increases, an increasing fraction of equilibria are again obtained in which there is no form of heterosis in either sex.

Mean weighted heterozygous and homozygous fitnesses over time for two individual runs are shown in Figure 6, with male and female fitness plotted separately. Fitness evolves over time, with mean heterozygous fitness usually exceeding mean homozygous fitness, especially initially. There can exist significant differences between female and male mean viability fitness.

Figure 7 displays some statistics about invading mutations. Between generation 10,000 and 25,000,

there are on average 2 successfully invading alleles (i.e. alleles persisting longer than one generation) out of 15,000 attempts. In the bottom graph is the number of generations these successfully invading alleles persist, for those alleles which have gone extinct by generation 75,000 (average persistence is 11,232 generations). We also examine the mean fitness of an allele weighted by its genotype frequencies upon invasion for alleles that invaded at generation 25,000. All alleles that invaded successfully had mean fitness greater than 0.80 for both male and female fitness, whereas the average fitness among those alleles that did not invade was 0.50 ($t = 56.9$ and $t_{crit} = 3.3$ for females and $t = 56.8$ and $t_{crit} = 3.4$ for males using Welch's approximate t -test for $n = 24999$, 51 and $p < 0.001$). However, this criterion of high fitness in both sexes for successful invasion is not sufficient, in that there are alleles that meet this condition and still fail to invade (Result 1).

The number of alleles present at generation 25,000 is 4.40, at 75,000 generations it is 4.57, and between 25,000 and 75,000 it is 5.39. Thus there is a slight increase in the mean number of alleles between 25,000 and 75,000 generations. Furthermore, the distribution of alleles immediately following the successful invasion of an allele is shifted up by slightly less than one allele ($F = 2205$, $p < 0.001$, $df = 2$, 74997; $LSD = 0.0002$, $p < 0.001$, $df = 74997$) (Result 2).

TABLE 4

Classification of final fitness sets for constructionist approach

2 alleles:		Female		
		heterosis	pairwise heterosis	no heterosis
Male	total heterosis	0.6205		0.1716
	pairwise heterosis			
	no heterosis	0.1832		0.0247
3 alleles:		Female		
		heterosis	pairwise heterosis	no heterosis
Male	total heterosis	0.1429	0.0531	0.2225
	pairwise heterosis	0.0506	0.0292	0.0696
	no heterosis	0.2255	0.0684	0.1382

Categories are those of Table 2 for fitness space approach. For 4–7 alleles, the same pattern shown here is observed.

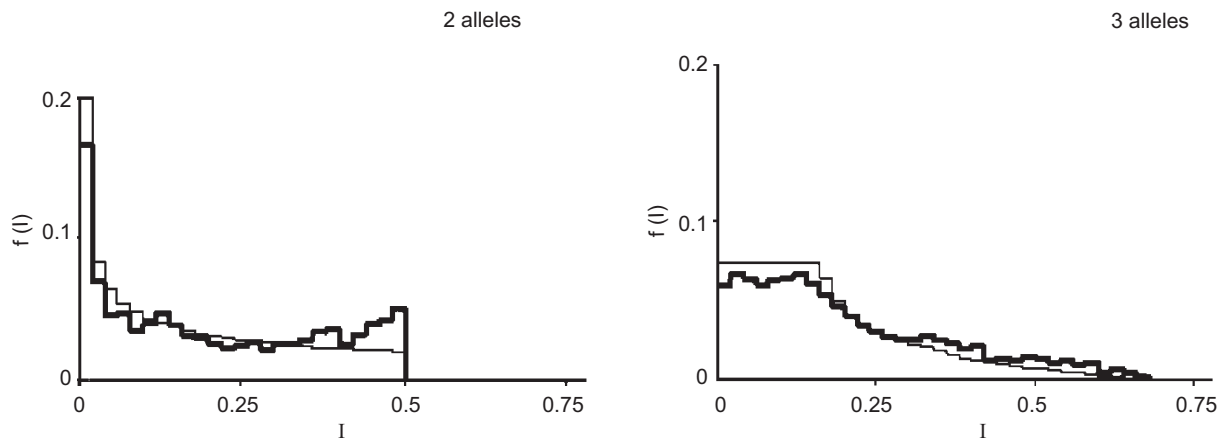


FIG. 4. Distribution of I for constructionist approach. The heavy line is the observed distribution. The light line is what is expected if frequency arrays are chosen uniformly. The same patterns are seen in the plots for 4–7 alleles

4. Discussion

One of the central issues in population genetics is the amount of genetic variation present in populations, which in natural populations is great. Some explanations for this diversity have centered on different modes of balancing selection, especially the role of heterosis (see Lewontin, 1974; Dobzhansky, 1955). To explore some of these explanations, we chose to examine the amount of variation maintained by Owen's model of sex-dependent selection. We conducted this examination in two ways. Following the work of Lewontin et al. (1978), we examined the proportion of the fitness space that can maintain all initial alleles (fitness space approach) and found that this proportion was higher in the sex-dependent model than in the sex-independent model. Then, following the work of Spencer and Marks (1988, 1991, 1992) we examined the number of alleles present in a system undergoing selection and recurrent mutation (constructionist approach), and found that the sex-dependent model resulted in fewer alleles present over time than the sex-independent model. These results suggest that differential fitness in the sexes is less likely to be a cause of polymorphism in nature than the same fitness in both sexes.

Explanations for the maintenance of variation have often centered on heterosis, since heterosis is a sufficient and necessary condition for stable polymorphism in the two-allele sex-independent model, for which one third of randomly generated fitness sets will result in polymorphisms. In the sex-depen-

dent model, a sufficient condition for protected polymorphism for two alleles is that

$$\frac{u_{ij}}{u_{ii}} + \frac{v_{ij}}{v_{ii}} > 2 \quad \text{and} \quad \frac{u_{ij}}{u_{jj}} + \frac{v_{ij}}{v_{jj}} > 2 \quad (\text{"ratio heterosis"})$$

(Kidwell et al., 1977). Forty-one percent of randomly generated fitness sets will exhibit this type of heterosis (Hartl and Clark, 1989). Thus, for two alleles, a higher proportion of randomly generated fitness sets will maintain all initial alleles in the sex-dependent model than in the sex-independent model. These conditions are neither sufficient nor necessary if the number of alleles exceeds two, although the existence of some sort of overall heterosis (Figure 2) suggests heterosis is important in some form. The probability of ratio heterosis continues to exceed the probability of classical heterosis as the number of alleles increases (Table 5). Thus in the fitness space approach, the higher levels of poly-

TABLE 5
The proportion (out of 500,000) of fitness sets randomly generated from a uniform distribution that exhibit pairwise heterosis

No. of alleles	Proportion exhibiting pairwise heterosis	
	Classical heterosis	Ratio heterosis
2	0.33281	0.41252
3	0.06720	0.12052
4	0.00954	0.02774
5	0.00108	0.00534
6	0.00009	0.00094
7	0.00002	0.00032
8	0.00001	0.00002
9	0	0

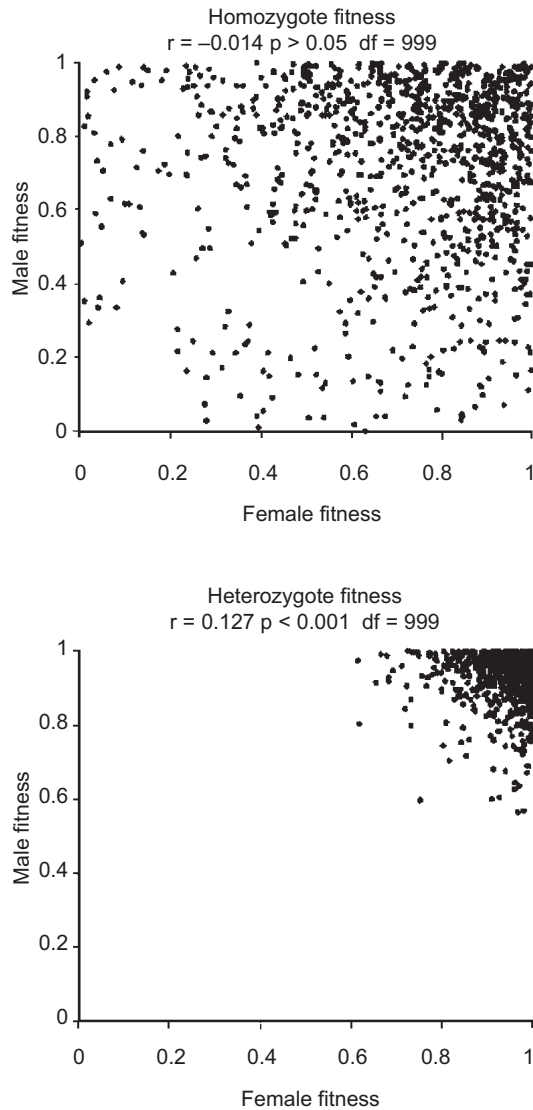


FIG. 5. Male fitness versus female fitness for the same genotype for constructionist approach. The r value is Spearman's rank correlation between female and male fitness

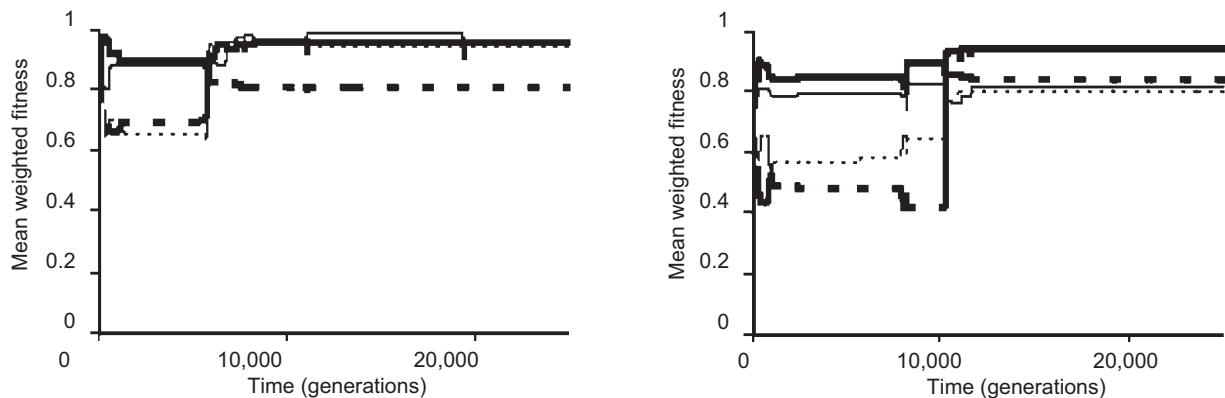


FIG. 6. Mean heterozygous and homozygous viability fitness over time weighted by genotype frequencies. The solid lines are heterozygous fitness, while the dashed lines are homozygous fitness. Thin lines are for male fitness, while thick lines are for female fitness

morphism seen in the sex-dependent model as compared to the sex-independent model may be a result of relaxed conditions for heterosis.

On the other hand, for the constructionist approach, variation is being continuously introduced into the population. Thus, alleles need to successfully invade as well as persist. Since the predominant factor in an invading allele's fitness is its fitness as a heterozygote, high heterozygote fitness evolves much faster than high homozygote fitness (Figures 4 and 6). As a result of these different rates of evolution in heterozygote and homozygote fitness, heterosis is being selected for and consequently is present in higher amounts in the constructionist approach than in the fitness space approach (compare Table 4 with Table 2, and Figure 5 with Figure 2).

Possibly the ease of reaching fitness sets with relatively large numbers of alleles (Table 3), despite the proportion of the fitness space that maintains these numbers becoming vanishingly small (Table 1), is a result of this culling process for invasibility. Fitness sets exhibiting some form of heterosis may be more likely to invade than those without some form of heterosis, since an allele needs to have high heterozygote fitness in order to invade but not a high homozygote fitness. Since heterosis seems to play a role in maintaining variation, the resulting fitness set may be more likely to persist and maintain a high number of alleles.

However, this phenomenon does not seem to translate into higher levels of variation being maintained for the model of sex-dependent selection than for the model of sex-independent selection. One problem may be that the invasion criteria have be-

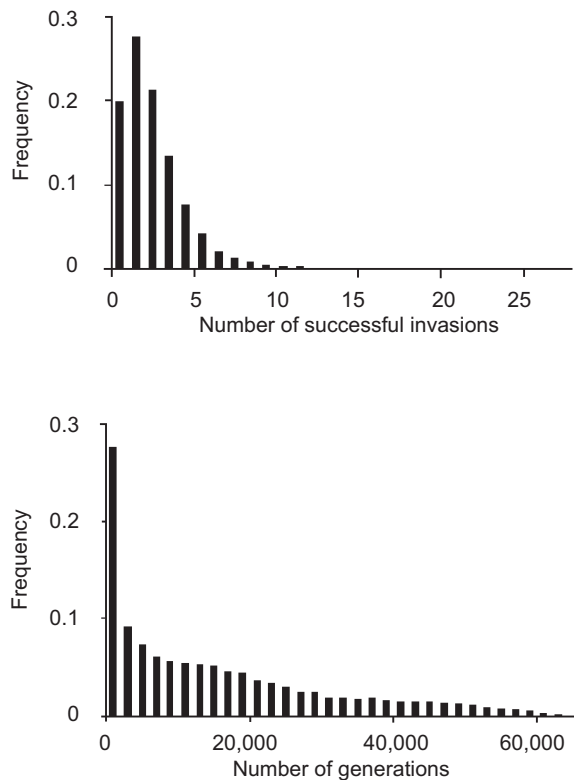


FIG. 7. Statistics about successfully invading alleles between generation 10,000 and 25,000. The top figure plots the distribution of the number of successful invading alleles between these generations ($n = 25,000$). The median is 2 alleles. This distribution differs from Poisson, mean 2.08 by having excessive occurrence of extreme values ($G_{\text{adj}} = 5433$, $p < 0.001$, $df = 10$). The bottom figure plots the average time these successfully invading alleles persist ($n = 25,000$) for those alleles which went extinct by generation 75,000. The median persistence time for these alleles is 11,232 generations. 43.2% of the original 25,000 alleles had not gone extinct by generation 75,000 and are not included in the plot.

come stricter. By 25,000 generations, most alleles present have high fitnesses in both sexes (Figures 3, 4, and 6). Thus, in order to invade, mutations need a high fitness in both sexes (Result 1). As a result, it is more difficult to invade in the sex-dependent model than in the sex-independent model. This difficulty will hold for any model where the fitnesses of both sexes are independently distributed, since it is more difficult to have high heterozygote fitness in both sexes than just one high heterozygote fitness overall. Thus, fewer alleles are expected to invade successfully and indeed, very few alleles are able to invade (Fig. 7). Presumably, as female and male fitnesses become increasingly correlated, the probability of high fitness in both sexes increases, and thus the number of successful invasions increases until, at a

correlation of 1.0, these numbers are equivalent to the sex-independent model.

Thus, the advantage of an increased probability of polymorphism under the weakened conditions of ratio heterosis is seemingly cancelled by the conditions for invasion in the constructionist approach. Although a new mutation does not need to have every heterozygote fitness greater than its respective homozygote fitnesses in order to reach a fully polymorphic equilibrium, it usually does in order to invade.

Furthermore, the system seems to reach a quasi-equilibrium by 10,000 generations, after which, in most cases, the mean weighted fitness does not appear to change greatly (Figures 3 and 6), nor does the number of alleles (Figure 3; Result 2). Even though there is a slight tendency for an increase in the number of alleles over time [since the mean number of alleles present at 75,000 generations is significantly, though slightly, greater than the mean number of alleles present at 25,000 generations (Result 2)], it appears that the increase is slightly more likely in runs which have fewer alleles present (since the mean number of alleles following the invasion of a successfully invading mutation is increased by fewer than one allele). Thus, this increase may not last. These results suggest that evolution, after some time, is largely replacement of one allele for another. Thus, the levels of diversity reached by the sex-dependent model may never reach those of the sex-independent model.

Besides heterosis, more general models of balancing selection have been advocated as a means to maintain diversity (see Lewontin, 1974; Dobzhansky, 1955). These more general models of balancing selection are characterized by fitness schemes in which, for a given allele, a low fitness under some circumstances is balanced by a high fitness under other circumstances. This can lead to higher levels of diversity in that alleles advantageous under different circumstances could all persist. Owen's model of differential selection in the sexes is an example of this possibility, since an allele can be disadvantageous in one sex, but advantageous in the other.

Evidence for this form of balancing selection can be seen in the results from the fitness space approach. Male and female fitnesses are on average negatively correlated both in homozygotes and in heterozygotes (Figure 2). This suggests that there

are many fitness sets in which an allele is advantageous only in one sex. However, this negative correlation is not seen in the constructionist approach; hetero-zygote fitnesses in males and females are positively correlated, whereas there appears to be no correlation between male and female homozygote fitness (Figure 4). This too may be the result of the conditions for invasion. Individuals need to have a high fitness in both sexes in order to invade (Result 1), thus one would expect male and female fitness to be positively correlated with respect to the mean fitness across iterations. Furthermore, since homozygote fitness is not selected for during invasion, there is much weaker selection on the relationship between male and female homozygote fitness and thus there is little or no correlation between these two. Here again the possible advantages gained by balancing selection as seen in the fitness space approach are counter to the requirements for successful invasion in the constructionist approach.

These same two approaches to the question of diversity maintenance have been applied to Haldane and Jayakar's (1962) model of cyclical variation in selection over time (Ptak and Marks, in prep.) and preliminarily to Levine's (1953) model of spatial variation in selection. The results in both models are very similar to the results presented here. All three of these models are (potential) examples of balancing selection, where the fitnesses could be high at some times or in some locations, but not others. The results presented here suggest that models of balancing selection may not explain the levels of variation found in natural populations (especially higher levels) as previously hypothesized. In these models, alleles that have high fitness in all circumstances predominate and this result seems to reduce the amount of variation present (possibly because such alleles are rare). If alleles with high but different fitnesses in the various circumstances are biologically infeasible, as a result of trade-offs for example, then maybe the expected elevated levels of allelic diversity could be seen.

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