The Maintenance of Single-Locus Polymorphism. I. Numerical Studies of a Viability Selection Model

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ABSTRACT

The ability of viability selection to maintain single-locus polymorphism is investigated with two models in which the population is bombarded with a series of mutations with random fitnesses. In the first model, the population is allowed to reach equilibrium before mutation resumes; in the second the iterations and mutation occur simultaneously. Monte Carlo simulations of these models show that viability selection is easily able to maintain stable 6- or 7-allele polymorphisms and that monomorphisms and diallelic polymorphisms are uncommon. The question of how monomorphisms arise is also discussed.

HOW large amounts of genetic variation are preserved in populations has been a recurring question in theoretical population genetics since the advent of electrophoresis in the late 1960s revealed that such variation was widespread [see LEWONTIN (1974) for a discussion]. However, most of the theoretical models so far examined suggest that multiallele (one-locus) polymorphisms are extremely difficult to construct. LEWONTIN, GINZBURG and TULJAPURKAR (1978) showed that under constant viability selection the proportion of randomly generated fitness matrices that lead to stable, feasible polymorphisms for more than five alleles was vanishingly small (see also GILLESPIE 1977). They also looked at the cases in which the loci were pairwise heterotic (*i.e.*, each heterozygote had greater viability than both the corresponding homozygotes) and totally heterotic (*i.e.*, all heterozygotes were fitter than the fittest homozygote). Again they found that the chances of stable feasible polymorphisms were miniscule.

In a study of structured fitness matrices, KARLIN (1981) showed that the probability of a (globally) stable equilibrium was greater than in the purely random case. For example, in the "generalized dominance fitness model" (in which the alleles have a dominance ordering $A_1 < A_2 < \ldots < A_k$ and the fitness of $A_i A_j$ is given by a_j for $i < j$ and that of $A_j A_j$ by b_j) the probability of a stable 5-allele polymorphism is about 0.0062, about 100 times the probability for a "random" matrix. When the a_j and b_j are ordered ($a_i < a_j$ and $b_i < b_j$ for all $i < j$) then the probability increases to about 0.1113. This latter model also maintains a fairly large number of alleles at equilibrium (given a larger number in the initial frequency distribution) (KARLIN and FELDMAN 1981). For example, when starting with eight alleles, the average number at equilibrium was 3.17 compared to 1.68 in the random case.

CLARK and FELDMAN (1986) found no qualitative difference between random single-locus fertility and random viability models in their ability to maintain large levels of polymorphism.

The theoretical population genetics problem of how alleles are maintained is analogous to the stability *vs.* complexity problem in theoretical ecology. The greater the number of species present in a community the smaller is the proportion of the ecological parameter space that permits all the species to coexist (MAY 1974). One approach to the ecological problem has been to change the question from "Are stable multispecies communities rare in parameter space?" to "Are multispecies communities hard to construct?" (TAYLOR 1985). TAYLOR has shown that by introducing species one at a time to an already stable multispecies community, the number of species present can be increased to quite high levels. Sometimes the introduction of the new species can trigger a partial collapse of the system, but over time the number of species will increase. Hence, although multispecies communities are rare in the total parameter space, they may not be hard to reach.

The analogous approach has been used here to see if multiallele polymorphisms are hard to construct.

DYNAMICS OF VIABILITY SELECTION AND MUTATION

Given a stable n-allele polymorphism, a new (mutant) allele A_{n+1} will invade if its marginal fitness is

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greater than the mean fitness of the population at the equilibrium, *i.e.*, $w_{n+1}, . w_{n+1}, . > \bar{w}$ (KINGMAN 1961). If it does invade then the changes in allele frequencies will be governed by

$$p_i' = w_i , . wi, . pi\ p_i/\bar{w}, \quad \text{for}$$

$$i = 1, 2, \ldots, n + 1 \quad (1)$$

in which p_i is the frequency of the ith allele at generation t,

p_i' is the frequency at generation $t + 1$,

$w_{i.} = \sum w_{ij} p_j$ is the marginal fitness of the ith allele at generation t,

$w_{i,j}$ is the viability of an individual with genotype A_iA_j and

$\bar{w} = \sum \sum w_{i,j}p_ip_j$ is the mean fitness of the population at generation t.

An equilibrium is reached when $p_i' = p_i$ for all $i = 1, 2, \ldots, n + 1$. For the one locus viability model KINGMAN (1961) has shown that at most one $(n + 1)$-allele polymorphism is stable for a given set of $w_{i,j}$ values and that it is globally stable. Hence it will be reached irrespective of the value of the n-allele polymorphism. Of course, the successful invasion of the $(n + 1)$th allele may not result in a stable $(n + 1)$-allele polymorphism, but instead in the extinction of one or more of the alleles present in the n-allele polymorphism.

AOKI (1980) used this dynamic to see how often a stable $n + 1$ allele polymorphism was reached after an unbroken run of n successful increasing invasions. (By an increasing invasion we mean an invasion leading from a stable n-allele polymorphism to a stable $(n + 1)$-allele polymorphism. By contrast, a decreasing invasion leads to a decrease in the number of alleles present at the new equilibrium, while in a replacement invasion the invading allele drives one other to extinction leaving the system with an n-allele polymorphism.) AOKI looked at the stability of the new system in which the fitnesses of the mutant (*i.e.*, the $w_{i,n+1}$'s $i = 1, 2, \ldots, n + 1$) were drawn from the uniform distribution on (0, 1). His results indicated that the most likely outcome was the repulsion of the invading allele, *i.e.*, it did not successfully invade. The next most likely was a replacement or a decreasing invasion, and always the least likely was an increasing invasion. Moreover, the probability of an increasing invasion given that there was an invasion was a decreasing function of n. These results held for $n = 2$, 3, 4 and 5 and when the $w_{i,n+1}$'s were drawn from a β (3, 3) distribution. Furthermore, the probability of successful invasion decreased as the number of alleles increased, but this is confounded by the fact that $\bar{w}$ increases monotonically over time and the greater $\bar{w}$ the harder it is for a mutant to invade, everything else being equal (see below).

AOKI also conducted two runs in which he looked at all systems, not just those with unbroken runs of increasing invasions. If the mutant invaded successfully he iterated Equation 1 to equilibrium and found that some polymorphisms were remarkably stable to invasion, one run maintaining a seven-allele polymorphism in the face of 94,266 mutations. The other run, however, was unable to sustain more than two alleles, although it ran for only 36 mutations.

MODEL 1—MUTATION WITH INTERVENING EQUILIBRATION

This first model was very similar to AOKI's latter model. The initial system consisted of one allele with $w_{1,1} = 0.5$ and was bombarded with new mutants (potential second alleles), the $w_{i,2}$ $(i = 1, 2)$ being drawn from the uniform distribution on (0, 1). If the marginal fitness of a new mutant was greater than the mean fitness, *i.e.*, $w_2 , . w_2 > \bar{w}$ $(w_{1,2} > w_{1,1})$ we had a successful invasion and Equation 1 was iterated to equilibrium. The invading allele was given an initial frequency of 10^{-6}, an allele was considered extinct if its frequency fell below 5×10^{-8} and equilibrium was defined as the point at which the maximum change in allele frequency in one generation was less than 5×10^{-8}. This sequential invasion process was repeated until the required number of invasions had occurred. The simulations were written in Pascal, compiled with the TURBO-87 compiler and performed on an IBM-XT microcomputer. The (pseudo)random numbers came from a lagged Fibonacci generator (KNUTH 1981), as the TURBO generator does not correctly supply a uniform distribution.

MODEL 1—RESULTS

The levels of polymorphism for seven replicate runs (runs 1.1–1.7) are shown in Figure 1 and Table 1. Run 1.4 had 25 invasions, run 1.7 28 and the rest 40. Clearly the number of alleles maintained under this scheme is much larger than might be expected from a naive reading of LEWONTIN, GINZBURG and TULJAPURKAR's (1978) results. The minimum number of alleles after 10^4 mutations (which was about the length of time until the system settled down) was 4, and it was not unusual to observe 7 or 8. This was also true if we restrict ourselves to "common" alleles, by which we mean those with frequencies of 0.01 or greater.

Many multiallele polymorphisms were resistant to invasion. The most resistant was run 1.4, in which a 7-allele polymorphism repulsed 4,210,363 mutants. The vulnerability of a polymorphism to invasion is a function of $\bar{w}$ and the number and frequencies of those alleles present. Clearly, if $\bar{w}$ increases then, if the number and frequencies of the alleles in the polymorphism remain the same, the invadability of the polymorphism decreases. The distribution of alleles in the polymorphism affects the invadability in a more

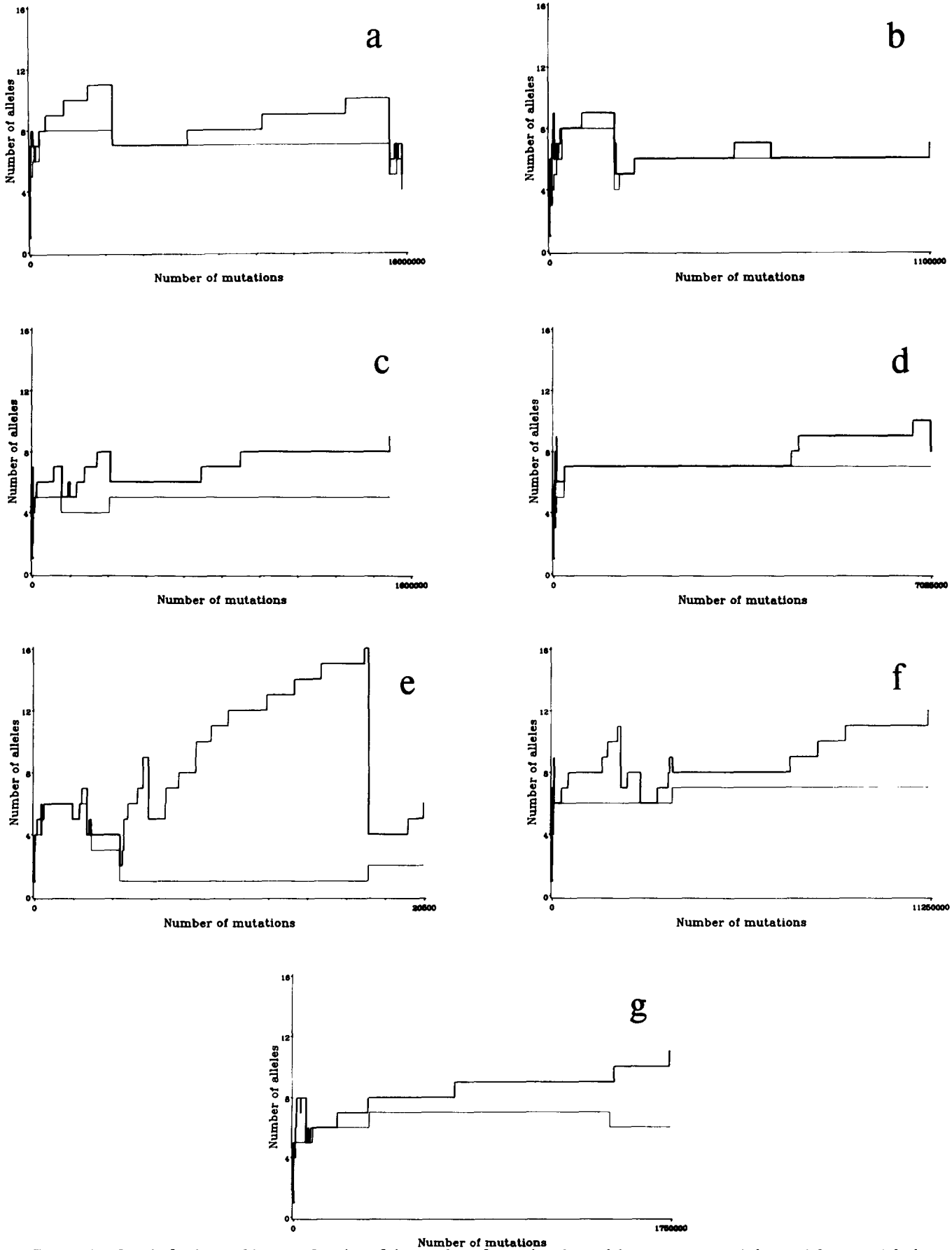

FIGURE 1.—Level of polymorphism as a function of the number of mutations in model 1 runs: a, run 1.1; b, run 1.2; c, run 1.3; d, run 1.4; e, run 1.5; f, run 1.6; g, run 1.7. Heavy (upper) lines indicate the total number of alleles, light (lower) indicate the number of common alleles.

TABLE 1

Model 1—levels of polymorphism

Run	No. invasion attempts	No. successful	No. of alleles: Total	No. of alleles: Common	$\bar{w}$
1.1	15,814,342	40	5	4	0.9718
1.2	1,098,893	40	7	6	0.9672
1.3	1,506,796	40	9	5	0.9785
1.4	7,006,429	25	8	7	0.9703
1.5	20,446	40	6	2	0.9940
1.6	11,161,155	40	12	7	0.9704
1.7	1,742,571	28	11	6	0.9624

TABLE 2

Model 1—measures of evenness for three 7-allele polymorphisms

Measure[a]	Theoretical minimum/maximum	Run 1.2	Run 1.3	Run 1.4
σ^2	0.00000	0.02718	0.04178	0.02533
H	0.8571	0.6669	0.5647	0.6799
E	1.9459	1.3649	1.0500	1.3662
$\bar{w}$	1.0000	0.96564	0.97851	0.96963
No. mutations repulsed		105,650	164,013	4,210,363

[a] σ^2 = variance = $\sum(p_i - \bar{p})^2/n$, where of course $n = 7$ and $\bar{p} = 1/7$; H = heterozygosity = $1 - \sum p_i^2$; E = entropy = $-\sum p_i \ln p_i$.

TABLE 3

Model 1—No. of transitions from i-allele polymorphisms to j-allele polymorphisms, given a successful invasion

i	j	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1			2	7													
			26	10													
2				7	12												
		1	14	10													
3			1	12	14												
		1		26	15												
4			1	1	5	21											
			2	4	34	13	1										
5			2		5	8	26										
		1		1	3	23	11	1									
6				1	1	5	5	29									
				1	2	1	28	2	2								
7			1		2	5	5	3	19								
						1	1	12									
8				1		1	2	2	3	14							
					1			1	4								
9						1	4		1	1	7						
10						1			1			5					
11								2					2				
12														1			
13															1		
14																1	
15																	1
16					1												

The first (or only) line of numbers is the number of transitions between polymorphisms counting all alleles; the second counts only common ones. Blanks indicate zeros.

complex way: more even allelic distributions are more resistant to invasion. This is because more of the $w_{i,n+1}$'s matter in the calculation of w_{n+1},. . If, for example, allele k is rare, then it is irrelevant what $w_{k,n+1}$ is—it contributes very little to w_{n+1},. . The success of the mutant thus depends on the $w_{i,n+1}$'s in which allele i is common, and the fewer of these the greater the chance of success. This boils down to the probability that the weighted sum of n uniform random numbers on (0, 1) will exceed $\bar{w}$, a constant ($>1/2$). In general the weighted sum has mean $1/2$ and variance $\sum p_i^2/12$. For an absolutely even distribution the weights (*i.e.*, the p_i's) are all $1/n$ and so the variance is $1/(12n)$. As n becomes larger, the distribution of the weighted sums becomes bell-shaped (*cf.* the central limit theorem). At the other extreme, a very uneven distribution has $n - 1$ of the p_i's close to 0.0 and one 1.0, and so the variance is $1/12$, much larger than before. The larger the variance the greater the probability that a particular sum will exceed the $\bar{w}$ threshold. Thus the variance of the allele frequencies is the best measure of the invadability of a polymorphism. Increasing the number of alleles in a polymorphism often, but not always, increases the evenness of the allelic distribution and if it does so will also increase the polymorphism's stability to invasion. Various measures of evenness for three actual 7-alleles polymorphisms are shown in Table 2. These all show that the more even the allelic distribution, the more resistant to invasions the polymorphism was, allowing for the differences in $\bar{w}$.

The numbers of transitions between levels of polymorphism in runs 1.1–1.7 are shown in Table 3. The elements on the diagonal represent replacement invasions, those below it decreasing invasions and those above increasing invasions. Inspection of Table 3 and Figure 1 reveals that decreasing invasions often led to extinction of more than one allele. This was in part a consequence of a quasi-equilibrium being reached in which the frequencies of rare transient alleles change very slowly before extinction (which looks like a true equilibrium to the program) and hence some of the levels of polymorphism are inflated. The same pattern was observed, however, with the common alleles. Table 3 shows that for common alleles the transition from n to $n - 1$ alleles occurred eleven times and that from n to $n - 2$ or less, ten. This is not surprising given the nature of the equilibria: if the maintenance of an allele is thought of as being partitioned among the alleles, then because alleles mutually maintain each other, the extinction of one allele may easily remove the main support of another, driving the latter to extinction.

Run 1.5 (Figure 1e) showed the most extreme quasi-equilibria. Only at the two major extinctions, when the number of alleles fell from 9 to 5 and 16 to 4, respectively, were there more than 30 iterations of

Equation 1 and so the true levels of polymorphism were probably in the vicinity of 4 or 5 alleles for most of this history. Note that at the latter extinction the number of common alleles increased. An increase in the number of common alleles at the same time as a decrease in the total number of alleles as the system moved to a true equilibrium was not uncommon.

Run 1.5 also illustrates one reason that monomorphism may be hard to reach. The early polymorphism with three common alleles at 2991 to 4489 mutations had a mean fitness of 0.93859, while after the successful invasion that brought the system to monomorphism (with respect to common alleles) $\bar{w}$ was 0.99388. For an invasion leading to monomorphism to occur the new mutation must have most $w_{i,n+1}$ ($i \neq n + 1$) less than $w_{n+1,n+1}$. Since $w_{n+1,n+1}$ is irrelevant to the calculation of $w_{n+1,}$ and hence the success of the invasion itself, mutations with low $w_{n+1,n+1}$ values are not selected out, at least not until they are common. The method of generating the $w_{i,n+1}$'s in the simulation may appear to exacerbate this feature: because the maximum value of any $w_{i,n+1}$ is 1, the $w_{i,n+1}$ ($i \neq n + 1$) of successful invaders will become closer and closer to 1 as the simulation proceeds and yet the $w_{n+1,n+1}$ will continue to range from 0 to 1. However, drawing the $w_{i,n+1}$ from an unbounded distribution (say a normal) may not make much difference because the $w_{n+1,n+1}$ are irrelevant to the success of the invasion and will often be less than most if not all the $w_{i,n+1}$ ($i \neq n + 1$). Studies of this modification to the model are underway.

The distributions of the alleles during the runs showed a wide range of forms. Some polymorphisms had J-shaped distributions: one allele would be by far the commonest with the remainder less than 10%, *e.g.*, in run 1.2, the 8-allele polymorphism lasting from mutations 35524 to 93083 had one allele at a frequency of 0.7736, the others being at 0.0623, 0.0581, 0.0292, 0.0262, 0.0261, 0.0125 and 0.0120. Later in the same run, the 6-allele polymorphism lasting from mutations 638,938 to 1,098,893 had a more even distribution, the frequencies being 0.4828, 0.1462, 0.1418, 0.1028, 0.0782 and 0.0483. The final equilibrium in run 1.1 showed no predominant allele—the frequencies here were 0.3539, 0.3403, 0.1614, 0.1443 and 0.0001.

The form of some of the $w_{i,j}$ matrices was also investigated. Of the six matrices examined one showed total heterosis, four were pairwise heterotic, and one had a heterozygote less fit than one of its (two) corresponding homozygotes. In this last case the distribution was noticeably J-shaped, one allele accounting for 0.7749 of the frequency distribution. Its homozygote fitness was greater than 13 of the 21 heterozygote fitnesses (there were 7 alleles present at equilibrium), but not one of the 13 involved that allele. The heterozygotic fitness (0.6318) that was lower than its corresponding homozygotic fitness (0.6693), involved one extremely rare allele (with homozygotic fitness 0.4001), so that the frequency of the heterozygote involved would have been $2pqw_{p,q}/\bar{w} = 5.7 \times 10^{-8}$.

MODEL 2—MUTATION WITH SIMULTANEOUS EQUILIBRATION

Model 1 assumes that equilibrium will always be reached before a new mutant can invade the population. To see what effect this had on the results above and to get around the quasi-equilibrium problem, the model was altered so that new mutants arose while Equation 1 was still being iterated. The number of mutations occurs according to a poisson distribution with mean m mutants per generation (*i.e.*, per iteration). Simulations were run for 10^6 generations.

MODEL 2—RESULTS

The levels of polymorphism in four replicate runs (runs 2.1–2.4) with $m = 1.0$ are shown in Figure 2, a–d, and four with $m = 0.1$ (runs 2.5–2.8) in Figure 2, e–h. Table 4 shows the number of successful invasions, as well as the means and variances of the homozygote and heterozygote fitnesses at the ends of the runs. As with model 1, the results of model 2 show that polymorphisms with four to six common alleles are the norm, that monomorphism is extremely difficult to attain (perhaps even more than in model 1), that multiallele polymorphisms are often extremely resistant to invasion, that decreasing invasions often lead to the extinction of several alleles and that extinctions and invasions often occur together in bursts.

The stability of the model 2 system implies that model 1 is often a fairly good approximation to the more realistic model 2. Usually equilibrium had been reached before a successful invasion occurred, the two important exceptions being near the start of the simulations and when the number of alleles had recently been reduced by more than one. Even in run 2.6 where one rare allele took 197,833 generations to become extinct no new mutation invaded until after that allele's demise. The exceptions to this arise for similar reasons. At the beginning of the process, it was relatively easy for a mutant to invade successfully and because the system took several generations to reach equilibrium, further mutants also invaded what was essentially a monomorphism. This led to extremely large numbers of alleles in the population in the first 200 or so generations for runs with $m = 1.0$. For example, in run 2.3 the maximum number of alleles was 21, occurring at generations 39, 40 and 41, but only 3 of these were ever common. By generation 173 $\bar{w}$ had increased to 0.8749 and the system had settled down to 4 common alleles only. When m

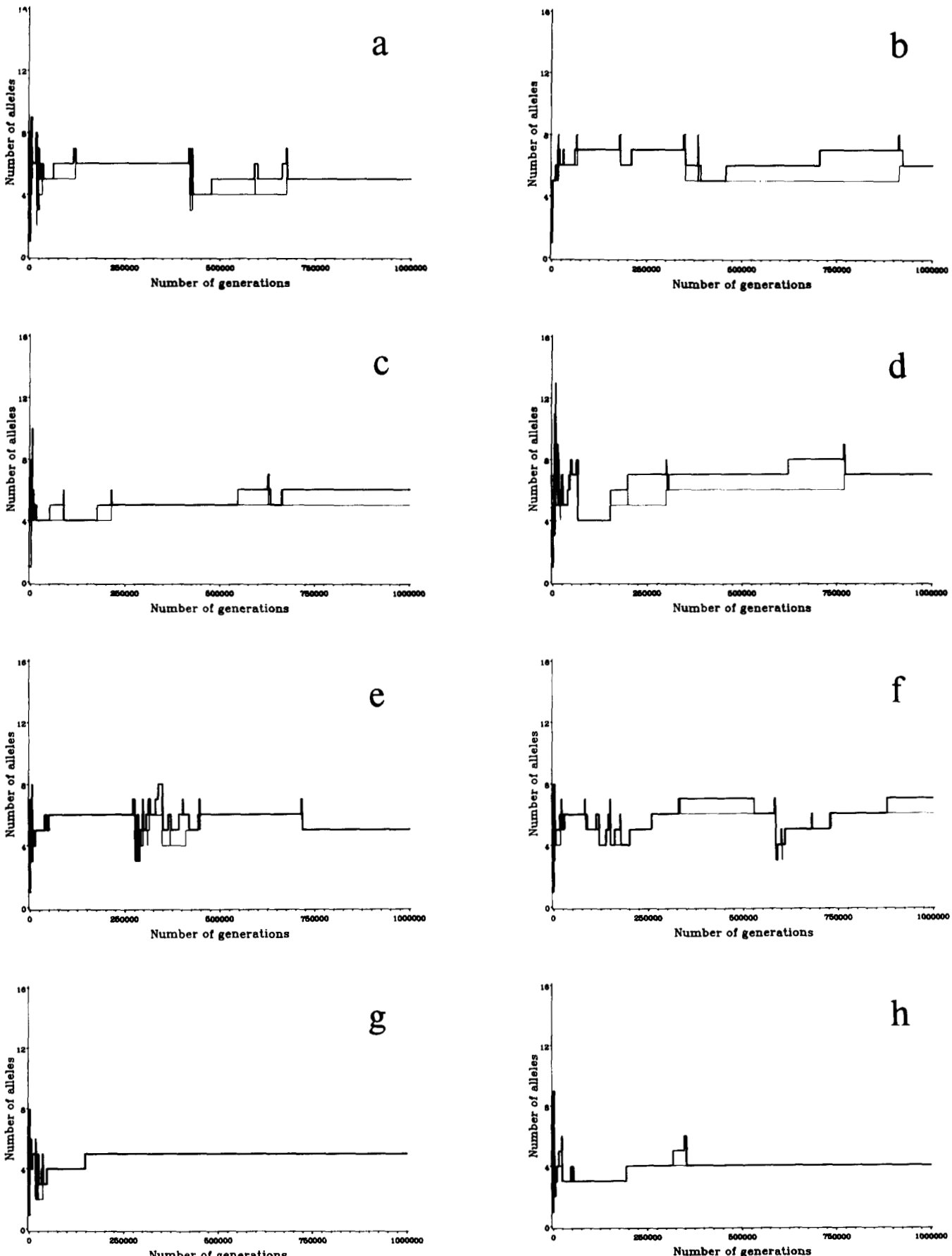

FIGURE 2.—Level of polymorphism as a function of the number of generations in model 2 runs: a, run 2.1; b, run 2.2; c, run 2.3; d, run 2.4; e, run 2.5; f, run 2.6; g, run 2.7; h, run 2.8. Heavy (upper) lines indicate the total number of alleles, light (lower) lines indicate the number of common alleles.

TABLE 4

Model 2—levels of polymorphism and statistics of fitnesses

Run	m	No. Successful Invasions	No. of Alleles		$\bar{w}$	$w_{i,i}$		$w_{i,j}$		No. $W_{i,j}<$ Max $w_{i,i}$
			Total	Common		Mean	Variance	Mean	Variance	
2.1	1.0	56	5	5	0.9787	0.8850	0.0057	0.9815	4.5336×10^{-4}	1
2.2	1.0	39	6	6	0.9573	0.7409	0.0304	0.9701	9.9482×10^{-4}	2
2.3[a]	1.0	45	6	5	0.9707	0.7485	0.0580	0.9550	8.2991×10^{-3}	1
2.4	1.0	66	7	7	0.9596	0.7335	0.0218	0.9719	9.3715×10^{-4}	1
2.5	0.1	36	5	5	0.9568	0.7090	0.0505	0.9743	2.0490×10^{-4}	0
2.6[a]	0.1	43	7	6	0.9488	0.5638	0.0670	0.9219	1.4294×10^{-2}	5
2.7	0.1	21	5	5	0.9802	0.7587	0.0348	0.9780	1.0943×10^{-3}	3
2.8	0.1	26	4	4	0.9810	0.9202	0.0018	0.9921	2.4799×10^{-5}	0
[a] with common alleles only										
2.3						0.8453	0.0135	0.9796	8.4844×10^{-4}	1
2.6						0.6108	0.0628	0.9236	1.7541×10^{-2}	0

was 0.1 this was not nearly so apparent: the longer intervals between invasions allowed more equilibration and extinction. Also, when the number of alleles had recently been reduced a rapid series of invasions could occur. This is because the system is effectively unchanged after a successful invasion and invasion can occur easily because the number of alleles is small.

The difference in initial behavior between runs with different m values suggests that m is an important parameter in a system with few alleles. Suppose that m was large enough so that several mutants invaded before equilibrium was reached. If these same mutations arose but at a different rate (*i.e.*, m was different), then the subsequent polymorphism could well be different. This is because the success of a mutant may well depend on the $w_{i,n+1}$ of the ith allele (say) which would have been extinct or rare and hence irrelevant to the mutation's success if the mutation had arisen later. Thus not only is the order of events important in evolution (see, *e.g.*, LEWONTIN 1967), but so is the rate at which they occur.

The main difference between the results of models 1 and 2 is in the number of rare alleles present. As was noted above, the quasi-equilibrium problem of model 1 means that the levels of polymorphism for the total number of alleles is probably inflated. In model 2 this problem is removed and although the number of common alleles does not appear to be different, the number of rare alleles is not usually greater than one. When more than one rare allele is present, it is most frequently immediately after an invasion and the system is probably not at equilibrium.

The forms of the distributions of alleles were similar to those in model 1, with some J-shaped (*e.g.*, the end of run 2.7) and others very even (*e.g.*, the end of run 2.4) and most in between. The final 8 $w_{i,j}$ matrices showed two cases of total heterosis (runs 2.5 and 2.8) and 6 of pairwise heterosis. Note that the two runs that resulted in total heterosis had the two lowest levels of polymorphism (5 and 4 alleles, respectively) and neither had any rare alleles. In contrast, the furthest departure from total heterosis, run 2.6, had 2 homozygotes fitter than 5 heterozygotes and another homozygote fitter than 3 (of the same) heterozygotes and maintained 7 alleles, 6 of which were common. A more detailed investigation of a much larger sample of such matrices may be found in MARKS and SPENCER (1989).

The differences and similarities between runs with $m = 1.0$ and those with $m = 0.1$ are interesting. There was no significant difference in $\bar{w}$ at either 10^5 or 10^6 generations (indeed at the latter the mean of the $\bar{w}$'s was greater for $m = 0.1$!). The number of successful invaders, however, was different ($t = 3.598$, $P < 0.02$ and $t = 2.593$, $P < 0.05$ at 10^5 and 10^6 generations respectively), those runs with $m = 1.0$ having about 2.05 (10^5 generations) and 1.65 (10^6 generations), times the number of successful invasions as those with $m = 0.1$.

DISCUSSION

The above models show that viability selection is capable of maintaining as many as eight alleles in a population. This is in spite of the fact that random fitness matrices leading to stable feasible equilibria with five of more alleles are extremely rare (LEWONTIN, GINZBURG and TULJAPURKAR 1978). Even when the matrices are given some nonrandom structure, the probability of stability is still low (KARLIN 1981; KARLIN and FELDMAN 1981). The historical process of the models in this paper leads to greater levels of polymorphism for at least three reasons. First, the historical sampling of previous workers counts a system as stable only if all the alleles remain in the polymorphism. If, for example, one allele becomes extinct, then that system is not counted, whereas in our models such a system is still valid. Second, our models have no problems with feasibility—they simply

lose one or more alleles. Third, and most important, natural populations are more realistically thought of as being the results of a nonrandom selective process that weeds out unstable fitness matrices (and in particular the more pathological alleles) and leaves populations at stable polymorphisms. Furthermore, these stable polymorphisms are most unlikely to be the result of a series of monotonically increasing polymorphisms of lesser degree, as in AOKI's (1980) model. Rather, the periodic collapses of a polymorphism when a new mutant invades the population strengthen the resistance of the system to further invasions. It should be noted, however, that the models were unable to maintain an extremely large number of alleles, such as occurs at the esterase-5 locus in *Drosophila pseudoobscura* with at least 41 alleles (KEITH 1983).

The ability of viability selection to maintain polymorphisms and the speed with which new mutants invade after a collapse raise the question of how monomorphisms and diallelic polymorphisms arise. One possible answer is that the population sizes are smaller than in the models. In model 2, $m = 2N_e\mu$, where N_e is the effective population size and μ the mutation rate. Hence reducing N_e is tantamount to decreasing m and this does result in a decrease in n_e, the effective number of alleles in the population: at the end of runs 2.1–2.4 ($m = 1.0$) $n_e = 3.452$, whereas at the end of runs 2.5–2.8 ($m = 0.1$) $n_e = 2.5061$. A parallel argument holds for a reduction in the mutation rate μ. Incorporation of a finite population size also introduces the effect of drift which would eliminate some of the rare alleles. This is unlikely, however, to alter either the number of common alleles or n_e, unless the population size is quite small (less than 1000). We are currently investigating the effects of drift on these models.

The distributions of model 2 can be compared with those of the neutral infinite allele model [see EWENS (1979) for a complete description]. To see how close the distributions are we can ask what number of genes would need to be sampled from one of the final model 2 distributions in order to reject neutrality in favor of heterosis. We used a 5% significance level and assumed that the sample homozygosities are the same as those of the distributions from which they are sampled. From the table in Appendix C of EWENS (1979) we see that for all the distributions, except that of run 2.4, many more than 500 genes would need to be sampled. For run 2.7 it is unlikely that any sample size could distinguish the neutral and actual distributions. In run 2.4 a sample of at least 200 would be required. Because the fitnesses were drawn from a range with a upper bound of 1 and $\bar{w}$ is nondecreasing, over time more and more of the alleles present in the population have w_{ij} values very close to 1. This means that, not only does the invadability of the polymorphism decrease, but also the differences in heterozygote fitnesses become smaller. The model is slow to converge to a neutral one, however, since the homozygote fitnesses increase at a much slower rate (MARKS and SPENCER 1989).

One shortcoming of the above models is that they assume constant fitnesses for an inordinately long time. These simulations, however, could have been started at any point in their history and the same results obtained. Indeed, this rationale enables us to ignore the first 1000 or so generations of model 2 runs if we consider the low initial $\bar{w}$ unrealistic. Nevertheless, random fluctuations or small but persistent decreases in the fitnesses might be expected to lead to different levels of polymorphism. We are currently investigating models of this type. Note, however, that the rapid increase in the number of alleles at the start of every run suggests that such models will not show long periods of reduced variability.

One interesting extension of the models would be to change the way the $w_{i,n+1}$ are generated. It seems more probable that there would be some correlation between the values (including $w_{n+1,n+1}$) and this might make invasion easier. It is not clear what effect this would have on the level of polymorphism, but AOKI's (1980) results suggest that it might reduce it slightly.

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