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GENETIC POLYMORPHISM IN HETEROGENEOUS ENVIRONMENTS: A DECADE LATER

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INTRODUCTION

Ten years ago, Joseph Felsenstein (35) and I (56) both wrote reviews discussing the maintenance of genetic polymorphisms in heterogeneous environments. I addressed the question of the importance in maintaining genetic variation of diversifying selection (sometimes called the niche-variation hypothesis), i.e. selection for different alleles in different environments. My focus was on the evidence and theory supporting the connection of a variable environment with genetic variation, particularly as an explanation for the large amounts of allozymic variation. At that time, the empirical evidence suggesting a genetic-environment connection for allozymic variation was mostly correlative and not in general experimentally based. Theory suggested, however, that polymorphism maintenance was possible in a variable environment; it was most likely when there was variable selection in space and limited gene flow and/or habitat selection. The purpose of this review is to evaluate the research of the intervening decade on genetic polymorphism in variable environments.

The topics of this review are divided in a fashion similar to that of the earlier review. First, I mention some recent work in which there has been detailed investigation of the relationship of different environments and the maintenance of genetic variation. Second, I review the theoretical developments in the past decade. Finally, I discuss recent experimental work in some detail. An emphasis in the review is to evaluate these experimental studies, a number of which were designed specifically to determine the importance of heterogeneous environments in maintaining genetic variation.

GENETIC-ENVIRONMENT ASSOCIATIONS

An association between aspects of the environment and particular genotypes may suggest a genetic-environment relationship, but without further investigation, other factors such as gene flow, genetic drift, historical events, or the effects of other loci cannot be eliminated as important influences on the patterns of genetic variation. In fact, where such information is available, the spatial and temporal patterns of genetic variation may be consistent with a nonselective model (e.g. 38, 95, 146). There are recent comprehensive reviews relating genetic variation to heterogeneous environments in plants (33), cactophilic *Drosophila* (9), melanic insects (84), and *Cepaea* (73).

General Examples

Some of the better examples of variable environments affecting genetic variation involve genes that confer resistance to human-related changes in the environment (e.g. 14). In many cases, the effects resulting from application of pesticides, use of antibiotics, or environmental pollution are so strong that selection is readily observed. For example, norway rats have developed resistance to the rodenticide warfarin primarily because dominant alleles alter the anticoagulant effects of warfarin. The maintenance of the polymorphism appears to result from a high vitamin K requirement for resistant homozygotes and from gene flow between areas baited with warfarin and areas not baited (see, e.g., 13). However, detailed examination of melanism in *Biston betularia* in recent years has shown that gene flow and visual selection related to the presence or absence of pollution do not completely explain the patterns of allelic frequency; this suggests that other factors besides predation are important in viability selection (26, 92; see also 24).

Although the development of crop varieties resistant to particular diseases or pests reduces chemical use, it also results in strong selection pressures on pathogens and pests to become virulent to the resistant variety. A classic study of such an effect is the interaction over many decades of wheat and the hessian fly, a pest of wheat. Introduction of new resistant varieties of wheat has been closely followed by the evolution of new virulent biotypes of the hessian fly, resulting in what appears to be a gene-for-gene evolutionary response (39). However, the genetic basis of virulence in many pest species and some pathogen species and resistance in many host species may not always follow this simple pattern (12, 31). On related topics, Futuyma & Peterson (37) have reviewed the evidence for genetic variation in resource use by insects, and Lenski & Levin (85) present a comprehensive introductive to the coevolution of bacteria and virulent phage.

There has long been speculation that the diversity of genetic types in the major histocompatibility complex (MHC) is the result of past selection for

resistance to different diseases (e.g. 15, 16). The even distribution of the large number of alleles at the *HLA* genes (human MHC) as well as consideration of other evolutionary factors suggests the importance of some sort of balancing selection for these loci (58, 59). Recent support for this hypothesis comes from the accidental introduction of a feline virus into a colony of cheetahs (*Acinoryx jubatus*). Cheetahs appear to have little or no genetic variation, and all of those tested appear to have identical MHC types (112). The virus was lethal to nearly 50% of the cheetah colony, while none of the resident lions or several purposely exposed house cat kittens were affected.

Polymorphism of the *abnormal abdomen* allele, a temperature-sensitive variant caused by an insertion into the 28S rRNA gene, appears to be maintained by environmental heterogeneity in a Hawaiian population of *Drosophila mercatorum* (137, 138). This variant results in both an increase in egg production and a decrease in adult survival. Thus, in dry habitats where adult mortality is high, the allele appears to exist at a frequency higher than in other areas because of its fecundity advantage. Furthermore, a drought in 1981 resulted in a twofold increase in the frequency of the *abnormal abdomen* allele at one site, giving evidence for strong natural selection.

A number of surveys of genetic variation have shown clinal variation that appears to be related to the environment. For example, a latitudinal cline in the frequency of *Ldh* alleles of the killifish, *Fundulus heteroclitus,* along the Atlantic coast of the United States is associated with the catalytic efficiencies and oxygen affinities of the different allozymes and the swimming speed of different genotypes at different temperatures (e.g. 30). An altitudinal cline in the frequency of different α-hemoglobin haplotypes in the deer mouse, *Peromyscus maniculatus,* is associated with differences with oxygen affinity and oxygen consumption during exercise and cold (19). Both of these cases (see also 11) provide a substantial biochemical and physiological basis for the maintenance of the polymorphisms.

The observation of a cline need not be the result of selection acting on the loci examined. For example, Hamrick & Allard (47) found different multilocus allozymic genotypes of the annual slender wild oat, *Avena barbata,* in xeric and mesic sites on a hillside. However, because *A. barbata* reproduces largely (98%) by self-fertilization and has only been in California since the eighteenth century, the differences are explainable by diversifying selection at an unlinked locus and consequent genetic hitchhiking at the allozymic loci (57). Figure 1 gives these simulation results in which allele A_1 is favored in one niche and A_2 in another, with the *A* locus *unlinked* to neutral loci *B* and *C* (the allelic frequencies in niche 2 are the complements of those shown). Note that the theoretical disequilibrium values between loci *B* and *C* are consistent with the observed values for electrophoretic variants (open circles) at a time between 100 and 200 generations after a founding event.

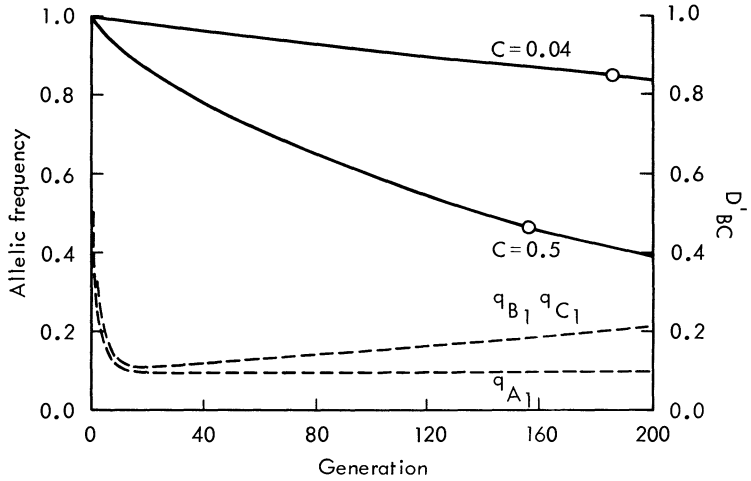

Figure 1 The changes in allelic frequency (broken lines) and within-niche gametic disequilibrium (solid lines) for a two-niche simulation model, used to mimic possible changes in a population of *Avena barbata* (from 57). The open circles indicate the values of D' observed in the *Avena* population.

Perhaps the most studied electrophoretic polymorphism is the *Adh* locus variation in *D. melanogaster* (see 144 for a review). The two major alleles are similarly associated with latitude on three continents, Australia, Europe, and North America, with the *F* allele in higher frequency in colder areas (109). However, latitudinal changes also occur in the frequency of an inversion on the same chromosome; whether the *Adh* geographic patterns are caused by these inversion differences is not clear (e.g. 66, 109). In any case, frequency changes in electrophoretic variants and inversions may be strongly associated. Figure 2 gives the frequencies of *Adh-S* and *αGpd-S* over time for three different temperatures (145). At the highest temperature, the *Adh-S* allele increased and an inversion on the same chromosome reached a frequency of 24.5%, while at the two lower temperatures, *Adh-S* declined and the inversion disappeared.

Given extensive allelic frequency data over time or over space, what can be concluded about the existence or type of selection? The statistical test suggested by Lewontin & Krakauer (88) seems appropriate to differentiate selective versus nonselective causes for temporal data (e.g., 38); several other approaches may also be appropriate (8a, 101, 123). Recently, Mueller et al (102) proposed a technique based on time-series statistics that examines the joint temporal change of a pair of alleles at different loci that may identify alleles associated with temporal selective changes.

Construction of tests of spatial data that exclude the effects of geographic

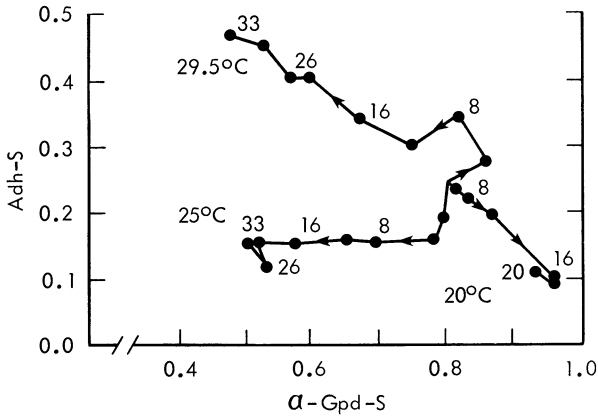

Figure 2 Changes in *Adh-S* and *α-Gpd-S* allele frequencies in three populations kept at 20°, 25°, and 29.5°C, respectively. Numbers indicate generations (from 145).

structure is even more difficult (36). However, examination of spatial patterns of genetic variation using autocorrelation analyses may indicate the relative importance of different evolutionary factors, particularly when some historical information is available. These techniques have recently been applied to cactophilic *D. buzzatii* populations in Australia [*D. buzzatii* is an immigrant in the last 50 years from Argentina (127)], and to the Yanomama Indians of the Amazon basin (128). From these studies Sokal and his colleagues concluded, based on demographic information, that stochastic factors were important in determining the pattern of genetic variation in the Yanomama, while in *D. buzzatii,* "mainly because of the large numbers of generations (roughly 300) since establishment, selection at different spatial scales plays an important role."

Statistical Associations

As a first step in identifying a genotype-environment association, a search for a statistical association of allelic frequencies with environmental variables is appropriate. Such an analysis may identify patterns too subtle ordinarily to be noticed. In Hedrick et al (56) there is a fairly extensive discussion of the appropriate statistical techniques and their application. Mulley et al (103) examined these different procedures using electrophoretic and environmental data from *D. buzzatii* populations throughout eastern Australia, and Manly (93) discussed several techniques and their application to the association of the habitat and morph frequencies in *Cepaea*. Mulley et al compared four different multivariate techniques: canonical correlation, multiple regression, principal components, and factor analysis. Although the different analyses

were generally consistent in their conclusions, they recommend "that canonical correlation and multiple regression would be sufficient in future studies of this nature."

A number of workers have used this correlative approach to investigate the association of electrophoretic variation with various ecological measures in particular groups of organisms, such as crustacea (106), higher plants (48), or mycophagous *Drosophila* (81). For a very cautious interpretation of such data, see the review by Schnell & Selander (125) on genetic variation in mammals. Using data from a questionnaire, Nevo et al (107) examined the correlation of electrophoretic variation with ecological, demographic, and life-history variables (largely nonquantitative values) in 815 species. As might be expected by combining data from such a large array of species, only 20% of the genetic variation over all species was explained by these variables, with the highest proportion explicable through ecological measures. It seems that such studies limited to particular groups of organisms may provide clues to relevant environmental variables or organisms in which environmental variation is quite important. As Nevo et al conclude, however, "the establishment of *direct* cause-effect relationships . . . is a future challenge at both the protein and DNA levels."

Biochemical Associations

Because of space limitation and the availability of a number of recent reviews on the association of biochemical characteristics and environmental factors (80, 144, 148), I mention this topic only briefly (however, see the brief discussion of 19 and 30). Understanding the mechanism maintaining a protein polymorphism is the evolutionary goal for examination of in vitro biochemical properties of different allozymes. However, in some cases it appears that what were once relatively clear biochemical explanations become more complicated with further research. Perhaps this is to be expected because of the many genetic factors that can affect enzyme activity (82, 83), i.e. the potential importance of regulatory factors in evolution (94), and the uncertain meaning of in vitro measures for adaptation.

THEORETICAL MODELS

It has often been suggested that variable selection over space or time may be responsible for the maintenance of extensive genetic variation. Indeed, the conditions placed on the relative fitness values that will result in a stable polymorphism in a variable environment are generally less restrictive than those in a constant environment. However, variation in fitness associated with different environments does not necessarily result in a stable genetic polymorphism (54, 56). In fact, the conditions for a stable polymorphism are fairly restrictive in many situations (61, 96). Summarizing from my previous

review, it appears that "temporal variation in selection may be of limited importance in maintaining genetic polymorphism, while spatial variation in selection may play a much more significant role in maintaining genetic polymorphism. Single locus theory indicates that selection acting differentially in space coupled with limited migration and/or habitat selection will maintain a substantial amount of polymorphism." Because of space limitation, I discuss only two specific theoretical areas, namely, the assumptions of Gillespie's SAS-CFF model and models of habitat selection, and I make only general reference to much of the remaining extensive theoretical literature of the last decade.

Gillespie's SAS-CFF Model

Maynard Smith & Hoekstra (96) in their review of theoretical work on heterogenous environments concluded that "unless the selective advantages per locus are large, protected polymorphism requires that the relative niche sizes lie in a narrow range . . . the only models which may escape this criticism are diploid models . . . such as one proposed by Gillespie, in which in all niches the fitness of heterozygotes is higher than the arithmetic mean of the homozygotes." Let us examine the two-niche version of Gillespie's model because it has been suggested as a reasonable alternative to heterozygous advantage, as an explanation for the extensive genetic variation found by electrophoresis (87).

First, Gillespie assumes that enzyme activity for different alleles is additive in nature or scale (see Table 1). If the environment varies randomly, then the enzyme activity becomes a stochastic additive scale (SAS). Second, he

Table 1 The SAS-CFF model of Gillespie and that of Levene for two niches

	A_1A_1	A_1A_2	A_2A_2
Gillespie			
Enzyme Activity	x_1	$\frac{x_1 + x_2}{2}$	x_2
Fitness			
General	$\phi(x_1)$	$\phi\left(\frac{x_1 + x_2}{2}\right)$	$\phi(x_2)$
Niche 1	1	$1 - ks$	$1 - s$
Niche 2	$1 - s$	$1 - ks$	1
Levene			
Niche 1	1	$1 - ks$	$1 - s$
Niche 2	$1 - s$	$1 - (1 - k)s$	1

assumes that the enzyme activity maps in a concave manner onto the fitness function, called the concave fitness function (CFF). If we assume that there are only two niches, one in which A_1A_1 has the highest fitness and one in which A_2A_2 has an equivalent advantage, then the fitnesses for this symmetrical case are given in Table 1 (40, 96).

To digress for a moment, Gillespie (40) shows that the level of dominance here is $k = \alpha/(2\alpha + s)$. Solving for the parameter α, then $\alpha = sk/(1 - 2k)$. From data for newly arisen lethals ($s = 1.0$) in which k was estimated, Gillespie suggests that α is approximately 0.05. The formula above implies that as s increases, the level of dominance increases, making the heterozygotes closer and closer in fitness to the favorable homozygote. Note that this model assumes a reversal of dominance—in different niches, different homozygotes are favored, and the heterozygote is always closest in fitness to the favorable one. Although it is not clear how common such reversals of dominance are in nature, Gillespie & Langley (44), Hedrick (50), and Hoekstra et al (61) give some possible situations; T. Yamazaki (unpublished) has found variable dominance for amylase activity in *D. melanogaster;* and Hartl et al (49) discuss concave fitness functions in terms of saturation kinetics in metabolic pathways.

Using the two-niche model in Table 1 where c is the proportion of niche 1 ($1 - c$ in niche 2), the range of c for which there is a stable polymorphism for different selection coefficients is given in Figure 3 (between the broken lines). As a comparison, the range of c for the soft selection, Levene (86) model—where the heterozygote is exactly intermediate in fitness to the two homozygotes (constant dominance, see Table 1)—is also given (between the solid lines). For low values of s, the SAS-CFF model is stable for a wide range of c, while the Levene model results in a polymorphism for only a very narrow range of niche size. The difference is not surprising because scaling fitness in a concave manner as Gillespies does results in the harmonic mean of the heterozygote remaining larger than that of the homozygotes for a much wider range of c (for an extensive review of this model see 41).

Habitat Selection

Habitat selection is often suggested as a factor that may result in broadened conditions for a polymorphism. Habitat selection may take several different conceptual forms; for example, it may or may not be genotypic specific, or it may be only in females or in both sexes. For example, the model of habitat selection used by Hoekstra et al (61) is limited to females and is independent of genotype, based only on conditioning or the homing tendency of individuals; in this way the model is similar to restricted gene flow between niches. In this case, the parameter h measures the extent of habitat selection so that, for example, a female raised in habitat 1 lays a fraction $[c + h(1 -$

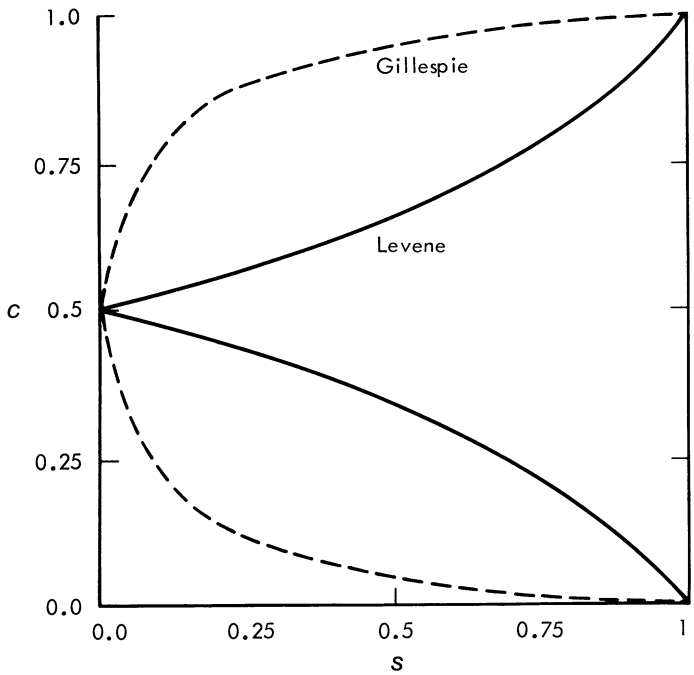

Figure 3 The proportion of niche 1, c, for which polymorphism is stable as a function of the selection coefficient, s, where the region between the solid lines is stable for the Levene model (constant dominance) and the region between the broken lines is stable for Gillespie's SAS-CCF model (reversal of dominance).

c)] of her eggs in habitat 1 and $[1 - c - h(1 - c)]$ in habitat 2 ($h = 0$ indicates no habitat selection, and $h = 1$ complete habitat selection). Using this model and assuming constant dominance, I give the region for which there is a stable polymorphism in Figure 4. This assumes $k = \frac{1}{2}$ when there is no habitat selection (region between solid lines) and that $h = \frac{1}{2}$ (region between broken lines) (after 61). The region of stability for a given s value is only slightly increased from the Levene model with no habitat selection. This slight increase is surprising, until one realizes that there is global random mating. If random mating is assumed to take place within each niche, then the conditions for a polymorphism are less stringent and are given for $h = \frac{1}{2}$ in Figure 4 (between the dotted lines). This region is somewhat larger than for habitat selection with global random mating. However, note that when s is low and mating occurs within each niche, the relative niche sizes must still lie in a narrow range if a stable polymorphism is to exist.

In the model of habitat selection above, all genotypes, whether their viability is high or low in a particular habitat, have the same extent of

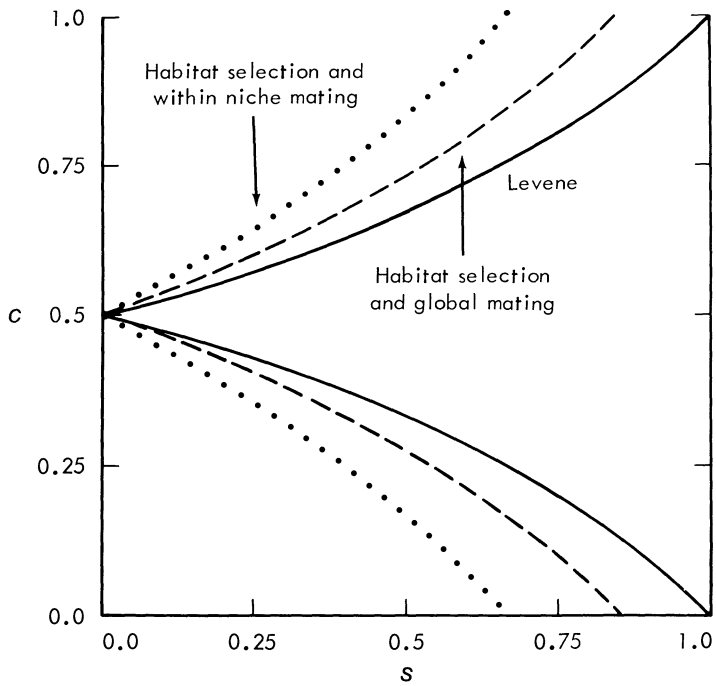

Figure 4 The proportion of niche 1, c, for which polymorphism is stable as a function of s where the region between the solid lines is stable for the Levene model; the region between the broken lines stable with habitat selection (h = ½) and global random mating; and the region between the dotted lines stable with habitat selection (h = ½) and mating within niches.

conditioning. Let us examine the two-niche case of the model of Templeton & Rothman (139) in which habitat selection is specific to particular genotypes and there is global random mating. [For a model of habitat selection in a continuous environment, see (134) or (135). For one with fecundity selection, see (119), and for the parallel theory of species habitat selection, see (121)]. Table 2 gives two arrays of habitat selection: (*a*) assumes that habitat selection is directly related to the relative fitness of a genotype in the two niches (see here the Levene fitness values in Table 1), and (*b*) assumes h_1, $h_2 > ½$, so that the genotypes prefer the niches in which they are favored by a constant amount. Figure 5 gives the region for polymorphism for the Levene model and these two models of habitat selection. Notice that the first model has only a slightly larger stability region than the Levene model. However, in the second model, the region is much larger—for example, when $h_1 = h_2 = ¾$, as in Figure 5. In fact, in this case the polymorphism can be maintained by habitat selection alone, with no differential viability ($s = 0$) (119); it can be maintained even when there is a fitness disadvantage (139). Of course these

Table 2 Genotypic-specific habitat selection models used in Figure 5 where in (*a*) it is a function of fitness difference of the genotypes in the two niches and in (*b*) a constant for each genotype

		A_1A_1	A_1A_2	A_2A_2
(*a*)	1	$\frac{1}{2 - s}$	$\frac{1 - ks}{2 - s}$	$\frac{1 - s}{2 - s}$
	2	$\frac{1 - s}{2 - s}$	$\frac{1 - (1 - k)s}{2 - s}$	$\frac{1}{2 - s}$
(*b*)	1	h_1	½	$1 - h_2$
	2	$1 - h_1$	½	h_2

models generally only maintain genetic variation at loci directly involved in habitat selection but may broaden somewhat the conditions for a polymorphism at a tightly linked locus with selection that is environmentally dependent (P. W. Hedrick, unpublished).

Other Theoretical Considerations

That the conditions for a protected polymorphism under soft selection [constant-fertile-adult-number hypothesis (86)] are less stringent than for hard selection [constant-zygote-number-hypothesis (29)] is a dogma that has been challenged (77, 147). Walsh (147) points out that "hard protection is usually less stringent than soft protection if those demes where allele *A* is favored when rare have higher fitnesses than those demes where *A* is at a disadvantage." However, one should be aware that a consequence is that the conditions for protection of the other allele are less stringent for soft protection (excluding fitness arrays with either heterozygote advantage or disadvantage).

An aspect of variable selection that has been mentioned by Nei & Graur (105) is that some models will reduce genetic variation compared to neutrality. One problem with pure neutrality theory (and the SAS-CFF model) is that the predicted amount of genetic variation is much higher than that actually observed. This may make some variable selection models in finite populations (43, 50, 133) or perhaps in infinite populations (42) important in lowering the genetic variation.

A number of recent treatments of heterogeneous environments are important extensions of previous work. These include examinations of ecological

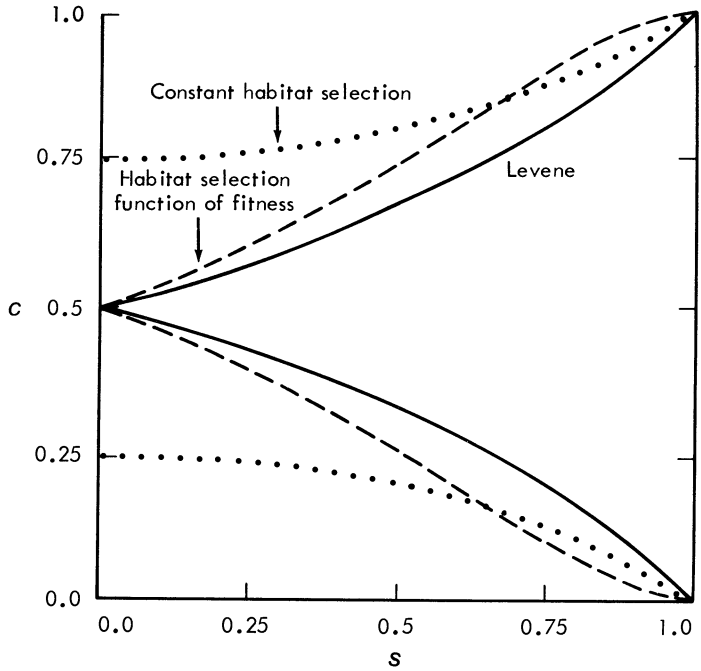

Figure 5 The proportion of niche 1, c, for which polymorphism is stable as a function of s where the region between the solid lines is stable for the Levene model; the region between the broken lines stable with genotypic habitat selection as a function of fitnesses and $k = ½$ (Table 2a); and the region between the dotted lines stable with constant genotypic specific habitat selection ($h_1 = h_2 = ¾$ in Table 2b).

aspects, such as intraspecific competitive differences (3, 22, 23, 89, 149), or of life-history characteristics (4, 113, 138). In addition, models that assume differential gene flow of male and female gametes (45, 104), maternal effects (152), or inbreeding, (55) can result in broader conditions for a polymorphism. The conditions for a polymorphisms are also somewhat broader when there is both temporal and spatial variation in fitness (34, 60, 61; see also 20). The extensive work by Karlin and his coworkers (76) explored the joint effect of population structures and variable selection on the conditions for protected polymorphism. Turelli (142) has shown that the conditions for a multiple allele polymorphism in a temporal SAS-CFF model are closely related to the conditions in a constant environment for the geometric mean of the variable fitnesses. Strobeck (131) gave the conditions for polymorphism of multiple alleles for a haploid, Levene model. Finally, as previous discussion (51, 56) suggested, conclusions from analysis of infinite populations may be misleading when applied to finite populations [see (6, 7, 62) for other finite population studies].

EXPERIMENTAL STUDIES

The statistical and biochemical associations between environmental parameters and genotypes discussed above suggest that environmental variation may result in variable selection pressures. However, often other nonselective explanations for such patterns are not easy to exclude, and the demonstration of a cause-effect relationship may be difficult. Experimental studies in which either environmental or genetic components are perturbed can produce evidence consistent with an environment-genotype connection. Most of the recent relevant experiments have involved artificial manipulation of the environment or measurement of the extent of habitat fidelity. As discussion above and in the previous review would indicate, it is often difficult to determine the exact impact of an environmental difference on the organism, and the genotypic background may cause particular genetic changes through genetic hitchhiking (53, 140). Evaluation of the studies below makes it obvious that the problems of designing critical experiments in this area of research (sensu 114) are substantial.

Genetic Perturbations

In the past decade, several genetic perturbation studies in natural populations have attempted to detect selection. Experiments in *Cepaea* and *D. pseudoobscura* were unsuccessful in detecting selection (74), although Halkka et al (46) suggested selection was important in maintaining a color polymorphism in the spittlebug, *Philaenus spumarius*. (Some recent laboratory experiments are 98, 110, 111, and 150.)

Barker & East (8) perturbed the frequency of alleles at three electrophoretic loci on different chromosomes in cactophilic *D. buzzatii* by releasing adults and injecting larvae into cactus rots. The perturbation site consisted of some 40 large cactus plants 3 km from other cacti. The released individuals were homozygous for three alleles, two of which had natural frequencies less than 0.2. As can be seen in Figure 6, the release resulted in a large increase of the three alleles; when the release was completed, the allelic frequencies quickly decreased to preexperimental levels. To determine whether the changes were repeatable and to obtain estimates of short distance gene flow, J. S. F. Barker, F. B. Christiansen, and P. D. East (unpublished) carried out a similar experiment elsewhere with two sites 100 m apart. Although they observed significant gene flow in this second experiment, it was substantially less than that needed to explain the observed change in allelic frequencies. Therefore, it seems quite likely that selection was responsible for these results, either because diversifying selection maintained the monitored alleles at a given frequency or perhaps because selection was against the introduced chromosomes that had been maintained in the laboratory for a number of generations (a genetic hitchhiking explanation).

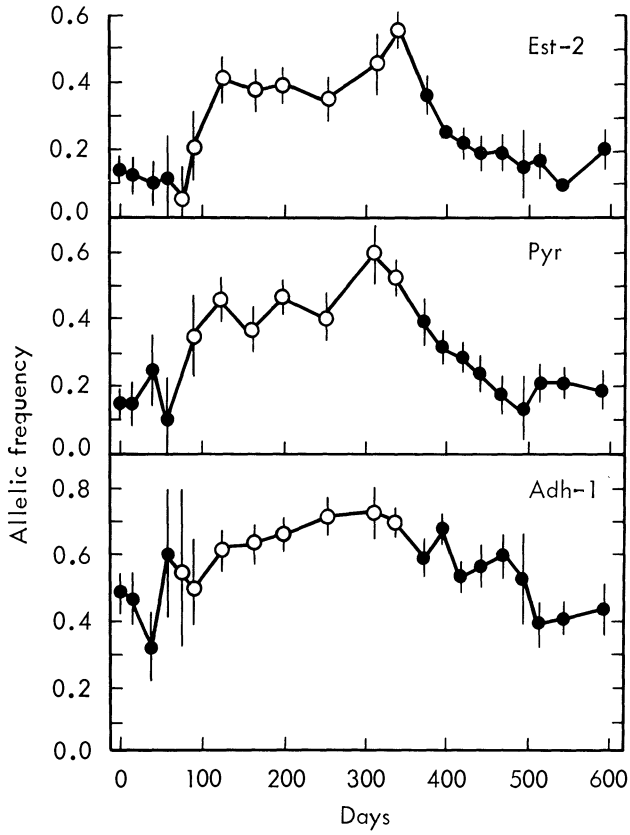

Figure 6 The allelic frequencies at three loci in a *D. buzzatii* population before, during, and after a genetic perturbation. The open circles indicate the frequencies during the release of flies (from 8).

Environmental Perturbations

A number of recent experiments have attempted to examine the relationship between environmental heterogeneity and genetic variation by varying environmental parameters. The majority of these experiments have been conducted in *Drosophila* using electrophoretic variation as an indicator of genetic variation. Before we discuss the results of these experiments, let us examine the different experimental designs used in order to better compare and evaluate them (Table 3). First, notice that the populations differ in their initiation characteristics. For example, the number of initial isofemale lines was highest in the experiments of McDonald & Ayala (97) and Yamazaki et al (151). The stock used by Yamazaki et al was in culture for six years, much longer than that of McDonald & Ayala, Powell & Wistrand (118), or Haley & Birley

Table 3 Characteristics of the six experiments discussed in Table 4[1]

Reference	Species	Initial Population		Environmental Factors
		Number	Time in Culture	
McDonald & Ayala (97)	*D. pseudoobscura*	141 isofemale lines	3 months	food (S) light (T?) temperature (T?) yeast (S)
Powell & Wistrand (118)	*D. pseudoobscura*	23 isofemale lines	2 to 4 generations	food (S) *D. persimilis* (S) temperature (T)
Minawa & Birley (100)	*D. melanogaster*	30 isofemale lines	130 generations	food (S) temperature (T)
Oakeshott (108)	*D. melanogaster*	?	?	alcohol (T,S) temperature (T) yeast (T,S)
Yamazaki et al (151)	*D. melanogaster*	400 isofemale lines	6 years	food (T*) light (T*) temperature (T*)
Haley & Birley (53a)	*D. melanogaster*	100 isofemale lines	3 generations	food (S)

[1]S, spatial variation; T, temporal variation; T*, coarse-grained temporal

(45a). One might expect from these differences that the most disequilibrium would have been between loci (say between electrophoretic loci and other loci undergoing selection) and that the potential for the influence of the genetic background would be highest in Powell & Wistrand's or in Haley & Birley's experiments, and the least in Yamazaki et al.

Second, the environmental regime used differs among the experiments (Table 3). If we use the general conclusions from theoretical models discussed in the previous review, a locus the fitness of which is affected by environmental differences would most likely be maintained when the environment varies spatially in a coarse-grained fashion and least likely, when it varies in a fine-grained manner. However, in all these experiments except Haley & Birley, the environments appear to be varied either in a spatial, fine-grained manner or a temporal, coarse-grained manner. From a theoretical perspective then, one might expect the most maintenance of genetic variation in the experiments of Haley & Birley, McDonald & Ayala, or Powell & Wistrand and the least in Yamazaki et al.

The mean heterozygosities for these experiments are given in Table 4 [the

Table 4 The mean heterozygosity in six different experiments in which the environment was varied

Reference	Time	Number heterogeneous environmental factors				
		0	1	2	3	4
McDonald & Ayala (97)	0	0.212				
	12 mo	0.146	0.186	0.201	0.208	0.186
	12 mo	0.254	0.297	0.326	0.338	—
Powell & Wistrand (118)	18 mo	0.236	0.291	0.322	0.333	—
	24 mo	0.220	0.288	0.318	0.337	—
Minawa & Birley (100)	0	0.293				
	6 mo	0.271	—[a]	0.284	—	—
	18 mo	0.248	—	0.262	—	—
Oakeshott (108)	0	0.338				
	20 gns	0.288	0.297	0.308	0.274	—
Yamazaki et al (151)	0	0.333				
	12 mo	0.332	0.343	0.343	0.331	—
	24 mo	0.346	0.355	0.353	0.343	—
Haley & Birley (53a)	0	0.333				
	11 mo	0.345	0.332	—	—	—
	22 mo	0.342	0.339	—	—	—

[a]—, not done

data from Powell (115) are not presented because of the many inversions in the species he used, *D. willistoni]*. Note that in all of the experiments, there is a small decline in heterozygosity over time, or there may be virtually no change, as in Yamazaki et al, Haley & Birley, and Powell & Wistrand. However, note that there is no initial estimate of genetic variation in the experiment of Powell & Wistrand (none until after 12 months); this leaves open the possibility that the differences observed were the result of unknown factors in the early generations and unrelated to the environmental regime. Thus, the general impression is that environmental heterogeneity may slightly reduce the rate of decay of genetic variation but that it does not seem to increase the amount of heterozygosity. The small difference between the experiments could be accounted for by the influence of the experimental design on the extent of disequilibrium and the potential for effective variable selection, as discussed above.

A number of other possible considerations are important to the evaluation of these results. First, maybe only a few loci, marking only a small proportion of the genome, are affected by these environmental factors, and the effects of these loci are diluted by that of others at which there may be little or no environmental effect. Second, the time scale may be too short to pick up selective differences, i.e. if we are comparing the relative effect of genetic drift on neutral versus marginally selected loci in relatively large populations such as these, then many generations may be necessary to tell the difference. If a locus were maintained by diversifying selection and if its equilibrium in the laboratory environment were near the initial frequency, then differences between this locus and a neutral locus resulting from genetic drift would be difficult to detect. Third, the optimum environmental regime for maintaining genetic variation—a spatial, coarse-grained environment with opportunity for habitat fidelity or selection—was not present. In fact, generally the environmental regime used was one in which retention of genetic variation for selected loci should be only slightly higher than neutrality. Apparently, T. Yamazaki et al (personal communication) deliberately picked such an environmental scheme so that their experiment would not favor diversifying selection.

If one believes that these experiments demonstrate a connection between environmental and genetic variation, even this does not have to be the result of diversifying selection. Jaenike (67) suggests, using a quantitative genetics, near-neutrality model, that increasing the environmental variation results in an increase in the proportion of loci that are effectively neutral. In other words, the slightly higher retention of genetic variation in some of the experiments summarized in Table 4 could result from greater selective elimination of variants in more homogeneous environments. His model is a nonequilibrium one in terms of particular alleles and would not predict a

short-term increase in variation in more heterogeneous environments from a low initial level. These are aspects that would allow it to be falsified in properly designed experiments.

Three sets of experiments have examined the effect of environmental variation on quantitative traits. MacKay (90, 91) varied the amount of ethanol (0% or 15%) spatially and temporally and then determined the effect of heritability and additive genetic variance on two bristle traits and body weight in *D. melanogaster*. She observed that the heritability (and additive genetic variance) was much larger in the variable environments than in the controlled (Table 5). However, upon close examination these results are somewhat puzzling and raise several questions. For example, the heritability was not always the highest in the spatial, coarse-grained environment, as expected from one-locus theory; the heritability decreased over time for abdominal bristles in the variable environments; there was no alcohol control to determine whether high alcohol by itself affects heritability; and there were no values from the initiation of the experiment for comparison.

The second set of experiments examined the effect of variation in flour over a 10-yr period on various components of fitness and growth in *Tribolium castaneum* and *T. confusum*. The first experiments examined populations grown on corn flour, on wheat flour, or on corn and wheat flour alternated each generation (153). In this case, additive genetic variance for pupal weight was greatest on wheat flour, half as much on the corn/wheat, and again much less on corn, suggesting that one type of homogeneous environment results in more genetic variation than does a heterogeneous environment. However, there were no initial estimates, and these final estimates were carried out on wheat flour only. The second comparison was for various mixtures of flour versus homogeneous corn, wheat, rye, or barley flour (28, 120). In these experiments, there was no support for the hypothesis that genetic variation was maintained by environmental variation. The authors suggest that pleiotropy of genes affecting metabolism may inhibit such responses; however, it

Table 5 The heritability of three traits in experiments in which ethanol was present or absent (From Ref. 91)

Traits		Control	Temporal		Spatial
			Short-term	Long-term	
Sternopleural bristle	12 mo	0.400	0.615	0.628	0.626
	24 mo	0.387	0.758	0.805	0.706
Abdominal bristle	12 mo	0.505	0.534	0.394	0.558
	24 mo	0.470	0.460	0.363	0.455
Body weight	24 mo	0.197	0.644	0.612	0.453

seems that the spatial, fine-grained nature of the heterogeneous environment may have made diversifying selection or habitat fidelity unlikely.

The third study, by Tachida & Mukai (132), was to determine the cause of genetic variation in viability of *D. melanogaster*. They raised strains made homozygous or heterozygous for different wild second chromosomes in nine different environments, all combinations of three different yeasts and three types of media. Using an analysis of variance approach, they found that the genotype-environment interaction component was significantly larger for homozygotes than for heterozygotes. Another way of understanding this effect is to examine the distribution of genotype-environment interaction, which as given in Figure 7 illustrates that there is a broader distribution for homozygotes than for heterozygotes. Separating out the components of genotype-interaction variance, Tachida & Mukai found that the component that could be related to diversifying selection was the largest. As a result, they suggest that these results are consistent with a hypothesis that genetic variation in viability is in part maintained by diversifying selection (see also 133a). However, it is possible that much of this effect may result from a net effect on whole chromosomes that have gametic disequilibrium among viability genes; it may not be true for single genes.

Habitat Fidelity or Choice

Following Hoffmann & Turelli (65), I will use the term "habitat choice" judiciously because it implies that the organism weighs the value of alterna-

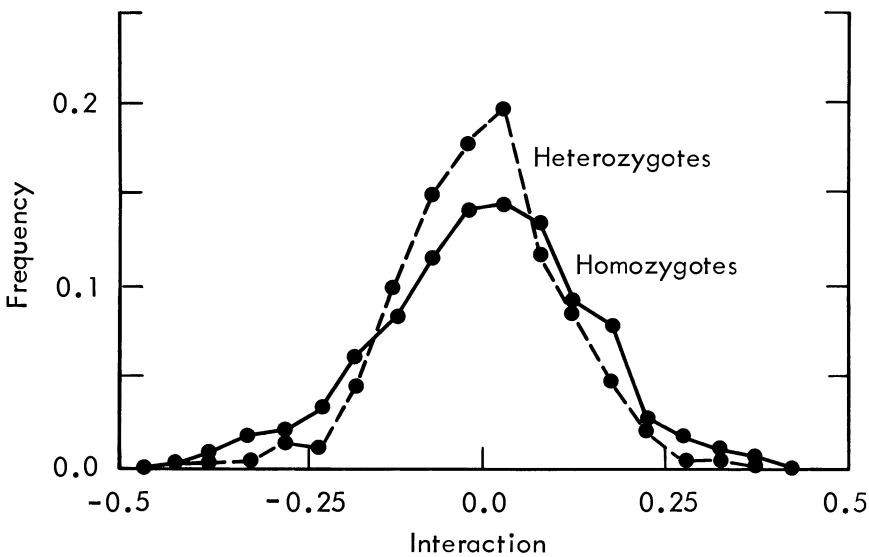

Figure 7 The frequency distribution of the genotype-environment interactions for viability for chromosomal homozygotes and heterozygotes (from 132).

tive resources. For example, in insects such a response mechanism may not be important (99), and the term "habitat fidelity" is more appropriate. A number of reports of an association of genetic variants with different habitats suggest the existence of habitat choice or fidelity; these include reports of chromosomal variants (25, 130), morphological differences (79, 124; see also 32) electrophoretic variants (10, 17, 18, 21) and plant clones (122).

There has been a series of field experiments, apparently stimulated by the initial positive findings of Taylor and Powell (136), to determine whether there is habitat fidelity in *Drosophila*. A measure suggested by Turelli et al (143) that is useful in determining the extent of habitat fidelity is based on the probability of recapture in a given habitat x, given that the first capture was in habitat x or another habitat y. Specifically, the measure is the difference $\Delta = Pr(x \cdot x) - Pr(x \cdot y)$, where $Pr(x \cdot y)$ is the probability of recapture in habitat x given that the individual was first captured in habitat y. The range of this index is -1 to 1, with an expectation of zero if there is no habitat fidelity or aversion. Positive values indicate that individuals tend to return to the habitat type in which they were first caught.

The habitat fidelity values from six different studies are given in Table 6; a majority of these suggest positive habitat fidelity. For example, Jaenike (68) observed that flies raised in the laboratory on tomatoes or mushrooms tended to be captured on their natal food, but it was statistically significant only in the females of one strain. In addition, the strains showed differential association with the two resources independent of experience. This strain difference and the observation that F_2 progeny from these strains had nearly intermediate association suggests a genetic basis for the behavior involved. In addition, oviposition site association in the lab for the two strains was the reverse of that found for habitat fidelity. Recently, Jaenike (70) has shown that oviposition behavior and habitat fidelity appear to be determined by different genes in disequilibrium in these strains.

Some of the cases that did not show positive habitat fidelity are noteworthy. Taylor & Powell did not observe significant positive fidelity on a rainy day; this implies that light or moisture cues were important for the flies to distinguish habitats. Taylor & Powell also did not observe fidelity in laboratory-raised flies, and this suggests that the fidelity being measured was not genetically based or that laboratory-raised flies had not learned relevant cues in nature. In addition, the experiments of Turelli et al (143) were carried out in orchards that had an abundance of rotting fruit on which the flies were breeding; this made it unlikely that the flies were starved (see discussion below).

Although laboratory evidence relates behavioral genetic variation to resource utilization in *Drosophila* (65, 68), determination of resource utilization is apparently complex and depends upon which behavior is investigated and

which assay of that behavior is used (63). In addition, Jaenike (69) discusses some of the major weaknesses of these mark-recapture studies and documents that males and females may have quite different fidelity behaviors. This may lead to positive fidelity values when the sexes are lumped, and fidelity may appear to be only a very short-term effect (cf his results for *D. melanogaster,* given in Table 6). Hoffman & Turelli (64) suggest that the positive habitat fidelity observed in the experiments in Table 6 may be a result of a combination of experience and the physiological state of the individuals. They conjecture and experimentally support the notion that physiologically stressed individuals will be less discriminating in their habitat choice.

To illustrate their experiments, Table 7 displays data from release 2, which used apples and oranges as baits; the data are summarized as the mean over three days of capture. The top half of the table gives the probabilities of capture on orange conditioned on whether the flies had experienced apples or oranges and/or starvation. For example, $Pr(o \cdot a,s)$ indicates the proportion of flies captured on oranges that had experienced apples and starvation. First, notice that experience, measured by Δ as given in Table 6, gives insignificant values. Second, starvation after experience on apples results in relative aversion to oranges—$\Pr(o \cdot a,s)$ values. The net effect of both starvation and experience is given in the last column on the bottom of the table, in which there are positive values or habitat fidelity. Hoffman & Turelli's explanation for this effect is that when resources differ in quality (orange is the better resource in this case), the starved flies will differentially prefer resources. In this case, the flies that were apple experienced and then starved are recaptured on apple in relatively high proportions, even though it is the poorer resource.

What is the evidence that genotypes select specific habitats? A good demonstration of the potential for environmental heterogeneity to maintain a polymorphism in a coarse-grained spatial environment dependent on habitat selection is the experiment conducted by Jones & Probert (75) using white-eye (*w*) mutants in *D. simulans*. In a uniform habitat of either normal or dim red light, the *w* mutant is lost; it went from 0.5 to 0.01 in normal light and 0.5 to 0.06 in dim red light in 30 weeks. [In trying to develop an experimental system for heterogeneous environments using *w* mutants in *D. melanogaster,* Hedrick (52) found that the *w* frequency went from 0.95 to 0.00 in 26 weeks in the light and 0.95 to 0.19 in 40 weeks in the dark.] However, in a population cage split so that half the flies had normal light and half had dim red light, the frequency of *w* after 30 weeks was still 0.32 (average of 5 replicates). In addition, the frequency of *w* was quite different between the two halves of the cage—much higher in the dim-red-light sector (Figure 8). Because in the control experiments *w* was always lost, this experiment indicates that heterogeneity in the environment is necessary for the maintenance of a polymorphism. The apparent basis for the polymorphism is habitat

Table 6 The extent of habitat fidelity in a series of experiments in different species of *Drosophila*

	Species	Environments	Comments	Δ
Taylor & Powell (136)	*D. pseudoobscura/D. persimilis*	dry vs moist woods	—	0.306 ± 0.066**
			—	0.236 ± 0.061**
			—	0.284 ± 0.106*
			—	0.185 ± 0.078*
			rainy day	0.043 ± 0.089
			F_1	-0.044 ± 0.064
Turelli et al (143)	*D. pseudoobscura/D. persimilis*	fig vs peach	—	-0.239 ± 0.083**
			—	-0.297 ± 0.197
Atkinson & Miller (5)	*D. subobscura*	dark vs light	—	0.003 ± 0.072
			—	-0.216 ± 0.102*
Kekic et al (78)	*D. subobscura*	shade vs open	—	0.332 ± 0.097*
Shorrocks & Nigro (126)	*D. subobscura*	dry and dark vs wet and light	—	0.219 ± 0.066**
			—	0.154 ± 0.069*
Turelli et al (143)	*D. melanogaster/D. simulans*	fig vs peach	—	0.087 ± 0.022**
			—	0.087 ± 0.065
			—	0.009 ± 0.039
Jaenike (69)	*D. melanogaster*	tomatoes vs grapes	♂♂, 1 hour	0.13 ± 0.04**
			♀♀, 1 hour	0.10 ± 0.04**
			♂♂, 12 hours	0.05 ± 0.03
			♀♀, 12 hours	0.04 ± 0.04

Jaenike (68)	*D. tripunctata*	tomatoes vs mushrooms	♂♂, S64	0.069 ± 0.083
			♂♂, S74	0.032 ± 0.076
			♀♀, S64	0.301 ± 0.079**
			♀♀, S74	0.141 ± 0.070
Jaenike (69)	*D. tripunctata*	tomatoes vs mushrooms	—	0.15 ± 0.06*
			—	0.41 ± 0.12**
Jaenike (70)	*D. putrida*	tomatoes vs mushrooms	—	0.08 ± 0.07
			—	0.07 ± 0.07

*$P < 0.05$, **$P < 0.01$

Table 7 Probability of capture (*a*) and the average measure of habitat fidelity (*b*) due to experience, Δ, starvation after experience on orange, $\Delta s(\cdot o)$ or apples, $\Delta s(\cdot a)$ or both due to experience and starvation, $\Delta(e,s)$ (Hoffmann and Turelli, 64).

(*a*)	Pr(o·o)	Pr(o·a)	Pr(o·o,s)	Pr(o·a,s)
Males	0.72	0.74	0.70	0.62
Females	0.78	0.79	0.76	0.64
(*b*)	Δ	Δ(s·o)	Δ(s·a)	Δ(e,s)
Males	−0.02	-0.02^{1*}	-0.12^{1}	0.07^{1}
Females	−0.01	−0.02	-0.16^{3}	0.13^{2}

*The superscripts indicates the number out of three capture days in which the Δ was statistically significant from zero. $\Delta = Pr(o\cdot o) - Pr(o\cdot a)$, $\Delta(s\cdot o) = Pr(o\cdot o,s) - Pr(o\cdot o)$, $\Delta(s\cdot a) = Pr(o\cdot a,s) - P(o\cdot a)$, $\Delta(e,s) = Pr(o\cdot o,s) - Pr(o\cdot a,s)$.

preference; wild type flies are positively phototactic, and the white-eyed flies prefer (or perhaps are neutral to) the dim red light. The habitat selection model of Templeton & Rothman (139) predicts that a polymorphism can be maintained even in the face of a fitness disadvantage; this seems an appropriate theoretical explanation here.

Do phenotypes or genotypes choose the habitat in which they have the highest fitness? Sokolowski et al (129) found in *D. melanogaster* an association between the genetically different "rover" and "sitter" larvae and traits such as pupation site and survival in different soil moisture levels. They presented evidence that suggests that sitter larvae have a greater tendency to pupate on fruit and that there is higher pupal emergence on fruit when the soil moisture is low. Rover larvae have a tendency to pupate in the soil, and there is a higher emergence in soil when soil moisture is high. In addition, Taylor & Condra (135) found in longtime mutant strains of *D. pseudoobscura* a slight correlation between rate of development and larval habitat choice.

A good measure of habitat preference might be the total time spent in a habitat, although it is generally quite difficult to determine how much time a particular individual spends in a habitat. Jones (72) developed a technique using a paint that fades upon exposure to the sun, to determine the proportion of time snails *(Cepaea nemoralis)* spend in sunlight. He marked 20 yellow, unbanded snails and 20 yellow, five-banded snails in each of 10 natural populations, released them into field cages, and 60 days later, recaptured and measured them for extent of fading. In all 10 cages, the banded individuals appeared to spend more time in the sun; the explanation suggested was that the banded snails have less tolerance to heat and that lower positions on plants, near the soil, are hotter. As a result, the banded snails spent more time higher on the plants and were more exposed to the sun. Because in cages these

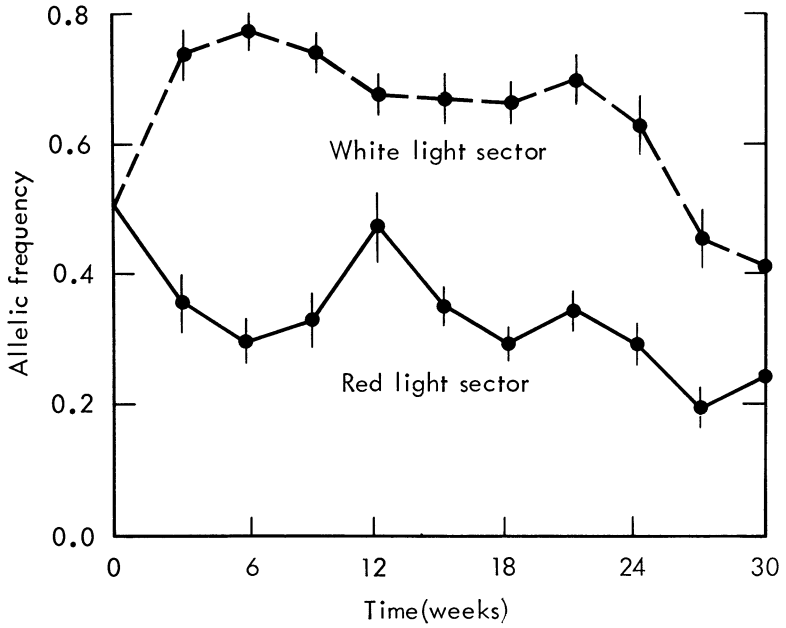

Figure 8 The average frequency of the *w* allele in *D. simulans* over five replicates in the red and white light sectors (from 75).

snails tend to spend much of the day buried, the differences between banded and unbanded snails may be due principally to their time of activity (J. S. Jones, personal communication). A possible interpretation is that the snails move until they are relatively "comfortable" and then tend to remain in this location. J. S. Jones (unpublished) has also shown that the behavior of snails can be changed by painting the shells. Using the same techniques in *Arianta arbustorum,* Abdel-Rahim (1) found in six different trials that brown snails spent less time in the sun than yellow snails. These results are consistent with the general physiological expectations that dark individuals spent less time in the sun than lighter individuals. It appears from these studies and others (2, 27, 71, 141) that explanation of such behavioral patterns requires a detailed knowledge of the ecology and physiology of the species examined.

CONCLUSIONS

Powell & Taylor (117) conclude that the large extent of genetic variation in natural populations occurs "because there are so many microhabitats in which different genotypes might be favored"; they emphasized the importance of habitat selection in the maintenance of polymorphism (see 116). However, theoretical considerations suggest that loci with differential habitat selection

may be maintained more easily than other loci but this maintenance is genotypic specific and probably does not generally result in the maintenance of loci not involved in habitat selection. In fact, the evidence for habitat fidelity is strongest in a few cases of single identifiable genes and is not as clear from the numerous capture-recapture studies in *Drosophila*. In addition, experiments developed to detect the importance of variable environments for electrophoretic variation have demonstrated only marginal effects, although these results are confounded with the design and the initiation characteristics of the experiments. In other words, variable environments may be important in affecting the amount of genetic variation, but present evidence appears to be inconclusive concerning their role in maintaining a large proportion of the variation in natural populations.

The relative stringency for maintenance of a polymorphism in many variable environment models (except for the model of genotypic habitat selection) has resulted in the advocacy of Gillespies' SAS-CFF model as one that would be important in explaining the large amounts of electrophoretic variation. However, this model is dependent on a reversal (or switching) of dominance in different environments such that the heterozygote is always closest in fitness to the favorable homozygote. Documentation of simultaneous reversals of selection and dominance in different environments would add credibility to the importance of the SAS-CCF model.

As one might expect, the last decade has both increased our understanding of the connection of variable environments and genetic variation and demonstrated the complexity of the case studies documenting this connection. Although it is still not clear what proportion of polymorphic loci are maintained by environmental heterogeneity, a number of instances now exist in which the support for such a relationship is relatively strong.

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