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Isolation, Gene Flow, and Genetic Differentiation Among Populations

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ISOLATION, GENE FLOW, AND GENETIC DIFFERENTIATION AMONG POPULATIONS

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ORIGINAL REPORT

(For Duplication Only)

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INTRODUCTION

The genetic resources of a species exist at two fundamental levels: genetic differences between individuals within local populations and genetic differences between different populations. Population genetic theory, developed principally by Sewall Wright (1943, 1951, and 1969), has long emphasized the evolutionary importance of the genetic structure of populations. However, it has only been in the last 15 years, through the electrophoretic detection of genetic variation at many protein loci, that it has been possible to describe the amounts and distribution of genetic variation in natural populations (Nei, 1975).

Efforts to preserve genetic resources must take into account both the within and between population components of genetic variation. Management plans must consider the expected effects of human actions on the amount and distribution of genetic variation.

The pattern of genetic diversity in a species is determined by the effects of three fundamental evolutionary forces: genetic drift, migration (gene flow), and natural selection (Slatkin, 1980, 1981, and 1982). We therefore need a good understanding of the effects of these three forces on genetic diversity in natural populations. The purpose of this paper is an analysis of the action of these forces on the distribution of genetic variation in natural populations. I also consider the implications of these results on the problem of maintaining genetic diversity in natural and manipulated populations of plants and animals. This is accomplished using population genetics theory and a series of

computer simulations.

THE MODEL

The simulation program is an extension of that described by Allendorf and Phelps (1981). Consider a locus with two alleles in a diploid species composed of 20 local random mating groups (demes or subpopulations), each with a population size of N. Each generation an individual has a probability of m of breeding in a deme other than that of his birth. An emigrant is equally likely to immigrate into any of the other demes; this is known as the 'island model' of migration. Three different modes of natural selection are considered: (1) selective neutrality, (2) heterozygous advantage, and (3) opposing directional selection in different demes.

Changes in allele frequencies are simulated using Monte Carlo simulations. Uniformly distributed (0-1) pseudorandom numbers are used to select each zygote. The first pseudorandom number determines whether the parent comes from the local deme or is an immigrant. The second number determines if the parent survives to reproductive age. The third number determines the allele transmitted by the parent. This process is then repeated to form a zygote. This is completed for N new zygotes for the next generation. The initial allele frequency in each deme is 0.5. This model does not include the effects of mutation.

Rationale for the Model

There are four primary variables that we must consider to

understand the distribution of genetic diversity: population size, migration rates, and the mode and intensity of natural selection.

Genetic drift is chance changes in allele frequencies as a result of random sampling among gametes from generation to generation (p. 142, Hartl, 1980). Because small samples are frequently not representative, genetic drift is particularly important in small populations. The effects of genetic drift are taken into account in this model by changes in population size (N) of the 20 demes that comprise the species.

Migration is the exchange of reproductively successful individuals among demes (p. 189, Hartl, 1980). In this model, migration is equally likely to occur among all 20 demes at a rate of m, as defined above. This pattern of migration (i.e., the island model) was chosen because of its simplicity which allows greater generality and mathematical tractability.

Natural selection is the differential success of genotypes in contributing to the next generation (p. 63, Hartl, 1980). In this model natural selection occurs by differential survival probabilities. Three different patterns of natural selection are used: (1) selective neutrality, where all genotypes have equal probability of survival; (2) heterozygous advantage, where heterozygotes have a survival probability of one but the survival probability of both homozygotes is reduced by a value s; and (3) differential directional selection, where one allele is favored by directional selection in ten of the demes and the other allele is favored in the other ten demes by the same intensity of directional selection in the opposite direction. With this mode

of selection, the survival probability of the deleterious homozygous genotype is reduced by a value of t and heterozygotes have a survival probability of $(1-0.5t)$ in all demes.

These three patterns of natural selection were chosen because they represent extremes in the effects of natural selection on divergence among demes. This pattern of heterozygous advantage will act to maintain a stable equilibrium at an allele frequency of 0.5 and therefore will restrict divergence among demes in comparison to the amount of divergence expected with selective neutrality. Differential directional selection will have the opposite effect. That is, directional selection favoring different alleles in different demes will increase the amount of divergence among demes in comparison with that expected with selective neutrality. A comparison of the amount of divergence with these three patterns of selection for the same values of m and N will allow us to determine the potential effects of natural selection on genetic divergence among natural populations.

Simulations

The following parameters were specified for each simulation:

(1) the population size of each deme, N;

(2) the migration rate, m; and

(3) the mode and intensity of natural selection.

The standard measure of divergence at individual loci, F[ST] as defined by Wright (1943), was used to estimate the amount of allele frequency divergence among demes

$$(1) \quad F[ST] = \frac{\sigma_q^2}{\bar{q}(1 - \bar{q})}$$

where $\underline{q}$ and σ_q^2 are the mean and variance of allele frequencies among demes. Lower values of F[ST] indicate less genetic divergence. Wright (1969) has shown that at equilibrium with the island model of migration and an infinite number of demes that

$$(2) \quad F[ST] = (1 - m)^2/[2N - (2N - 1)\ (1 - m)^2]$$

If $\underline{m}$ is small this approaches the more familiar

$$(3) \quad F[ST] = 1/(4Nm + 1)$$

Nei and Chakravarti (1977) have shown that with a finite number of demes that F[ST] will eventually become 0 because all demes will eventually become fixed for the same allele. We ignore this effect, however, assuming that in nature some migrants will be entering our 'closed' system from the outside. In the finite deme model, F[ST] will reach some steady-state decay distribution (Nei et al., 1977). The decay to F[ST]=0 will be extremely slow in these simulations because the total population size is 500-2000. The rate of approach to steady-state values depends upon both $\underline{m}$ and $\underline{N}$ (Wright, 1951). Values of F[ST] were estimated in these simulations after sufficient number of generations to ensure that steady-state

values had been reached; this is described in more detail in Allendorf and Phelps (1981).

RESULTS AND DISCUSSION

Selective Neutrality

In the absence of natural selection, the amount of genetic divergence among demes is a function of the absolute number of migrants exchanged (mN) and not the proportion of exchange among demes (m). Thus, a given number of migrants will result in the same amount of allele frequency divergence regardless of the population size of the local demes (Table 1). For example, we expect to find the same amount of genetic divergence among demes of size 1000 with an m of 2.5% as with demes of size 50 with an m of 50%. The dependence of divergence on the number of migrants, rather than on the proportion of migrants, may at first seem counter-intuitive. The rate of divergence, however, results from the opposing forces of migration and genetic drift. The larger the demes are, the slower they diverge through drift; thus, proportionally fewer migrants will counteract the effects of drift. Small demes will diverge rapidly through drift and thus proportionally more migrants are required to counteract drift.

Low amounts of exchange (approximately one individual per generation) will maintain the presence of the same alleles in all demes (p. 122, Kimura and Ohta, 1971). Nevertheless, in contrast to what has been suggested by some authors (e.g., Spieth, 1974; p. 128, Frankel and Soule, 1980), substantial allelic divergence is often present even when there is large amount of exchange among demes. For example, an exchange rate of 10 individuals per

generation almost always results in significant divergence among the 20 demes in the present model (Allendorf and Phelps, 1981). Thus, low amounts of exchange will maintain 'qualitative' similarity among demes but large amounts of exchange are needed to maintain 'quantitative' similarity among demes.

Heterozygous Advantage

As expected, this pattern of selection acts to maintain similar allele frequencies in different demes (Table 1). That is, for a given amount of genetic exchange, there is less allelic divergence among demes in comparison to the neutral model. The amount of divergence is not simply a function of the absolute number of migrants with this model of selection. There is less divergence for a given number of migrants with increasing population size. This is because the effect of genetic drift is less in larger populations and natural selection is more effective in maintaining the same equilibrium frequency in all demes.

This effect can be seen by considering the two possible extremes. With a deterministic model, assuming N is infinite, any value of s greater than zero will maintain an allele frequency of 0.5 in every deme, even in the complete absence of genetic exchange among demes. In the other extreme, if s is 1.0 (homozygous lethality), then every deme will maintain an allele frequency of 0.5, irrespective of m and N. Thus, heterozygous advantage will significantly reduce the amount of genetic divergence among demes when there is either strong selection or large demes.

Heterozygous advantage is effective in reducing divergence among demes under a wide range of conditions (Table 1). For example, the amount of divergence with one migrant individual per generation and N=100 with a 5% heterozygous advantage is reduced by approximately 67% in comparison to the neutral model (F[ST]=0.0661 versus 0.2000). The effect on the distribution of allele frequencies of this intensity of selection can be seen in Figure 1.

Figures 2 and 3 display the interaction among the intensity of selection, migration rate, and deme size. Figure 2A shows the effect of variable mN with an s of 0.05 on all three deme sizes. There is a significant reduction in divergence for all three deme sizes for an mN of two or less. With an mN of five, however, there is very little effect with an N of 25. And with an mN of 25, there is no detectable effect even with an N of 100.

Figure 3A shows the effects of variable selection intensity with an mN of 5 on all three deme sizes. With an N of 25, not even an s of 0.10 has an appreciable effect on divergence. With an N of 100, there is a reduction in divergence even with weak selection, s=0.01.

These results can be generalized somewhat by comparing the relative magnitudes of s and m. In general, heterozygous advantage has no detectable effect on reducing divergence among demes when the quantity s/m is less than one (Table 1). The effectiveness of this pattern of selection increases as this quantity becomes increasingly greater than one. For example, when mN is one, m is equal to 0.04, 0.02, and 0.01, for deme sizes of 25, 50, and 100, respectively. Therefore, with deme

sizes of 25 and an mN of 1, s must be approximately 0.05 or greater to be effective.

Differential Directional Selection

This pattern of selection acts to maintain allele frequency divergence among demes so that large differences in allele frequencies can be maintained even with extensive genetic exchange. As with heterozygous advantage, this pattern of selection is more effective with larger populations (Table 2). Figures 2B and 3B show the effectiveness of this mode of selection in increasing divergence under different conditions. For example, a selection intensity of t=0.05 has no detectable effect with an N of 25 or with an mN of 10, irrespective of N (Figure 2B). As with heterozygous advantage, these results can also be generalized by using the quantity s/m. A detectable increase in divergence occurs only when this quantity is greater than one (Table 2).

IMPLICATIONS

Natural Populations

How can an analysis of the amount and pattern of allelic divergence among natural populations be used to estimate the amount of gene flow occurring between demes? The present model can be used to estimate gene flow only if its assumptions are realistic. One primary assumption is the island model pattern of gene flow. This model assumes equal amounts of immigration and emigration for all demes and that there is no 'structure' to the pattern of gene flow. That is, an emigrant from a particular

deme is equally likely to migrate into any of the other demes.

The second primary assumption is the mode and intensity of natural selection. It has been notoriously difficult to estimate the effects of natural selection on genotypes at individual loci in natural populations (p. 236, Lewontin, 1974). In fact, it is still under much debate whether the allelic variation of proteins detected with electrophoresis results from the action of natural selection or selectively neutral mutations and genetic drift.

We have only considered three basic possible modes of natural selection. The simplest mode of selection is neutrality; this model is attractive for several reasons. First, it is falsifiable. The breeding structure (migration rates and local population sizes) is the same for all loci (Cavalli-Sforza, 1966). With selective neutrality, all loci are expected to show approximately the same pattern of allelic divergence. Statistical tests have been developed to determine if selective neutrality can account for the observed distributions of allelic frequencies at many loci in the same populations (Lewontin and Krakauer, 1973; see also Nei and Maruyama, 1975, and Robertson, 1975). Natural selection, however, is not falsifiable. There are an infinite number of models of natural selection that can be assumed to explain any set of data.

A second attractive feature of selective neutrality is its simplicity. In order to apply a model including selective differences among genotypes, it is necessary to make many assumptions about the mode and intensity of selection in each deme.

Thus, in analysing allelic divergence in natural populations

it is appropriate to consider selective neutrality as the null hypothesis. This hypothesis should be rejected only if there is evidence of significant differences in the distribution of allele frequencies at different loci or some other evidence for the action of natural selection.

I have applied this analysis to data of Ryman and Ståhl (1981) that describes allelic divergence at three loci among five local demes of brown trout (Salmo trutta) spawning in tributary streams of Lake Lulejaure, a large Swedish mountain lake (Table 3). There is significant allele frequency heterogeneity at all three loci. There is no geographical pattern to the distribution of allele frequencies; that is, geographically close demes are not more similar than distant demes. Thus, the island model of migration seems appropriate for these demes.

The mean F[ST] for the three loci is 0.069. Using formula (3), this estimates 3.4 migrant individuals among demes each generation. Are the differences in divergence for the three loci compatible with selective neutrality? I have tested this using repeated simulations with an mN value of 3.4 among ten demes, assuming an N of 50 (Figure 4). The patterns of divergence at all three loci are compatible with this breeding structure; 41% of the simulated F[ST] values are less than the F[ST] for Mdh2, and 17% are greater than the F[ST] for Ldh5.

Thus, the observed patterns of allelic divergence are compatible with an average of 3.4 migrants per generation with selective neutrality under an island model of migration. This estimate of 3.4 migrants will be conservative if there is some tendency for increased exchange between adjacent demes

('isolation by distance'). In this case, a migrant is less effective in retarding divergence because it has a higher probability of reproducing in a deme that is similar to the one from which it emigrated.

The importance of examining many polymorphic loci can be seen from this example. A single estimate of F[ST] would be compatible with an extremely wide range of migration rates. As each additonal locus and estimate of F[ST] are added, the possible range of compatible migration rates is narrowed.

Manipulated Populations

These results can also be applied to design appropriate breeding structure for populations that are controlled by the action of humans, e.g., populations in nature reserves or zoos. Franklin (1980) has argued that an effective population size of at least 500 is needed to preserve useful genetic variation within a species. How should this population be subdivided? We should try to maximize both the 'adaptedness' of individual demes to local conditions and the evolutionary potential of the species. To do this we should try to maintain a high amount of genetic variation both between individuals within demes and between different demes.

We are likely to be limited by habitat or financial restraints as to the number and size of demes to be maintained. Therefore, the major aspect of the breeding structure that can be easily controlled is the amount of exchange among demes. There are two ways to approach this question; we can either base our choice on the particular genetic characteristics of individual

species or we can try to develop a general rule of thumb (p. 90, Frankel and Soule, 1981). I am in complete agreement with Franklin (1980) that our theoretical and empirical understanding of the action of natural selection is currently insufficient to serve as a basis for application to individual species.

We should therefore identify the 'ideal' amount of exchange among demes that can be generally applicable. An average exchange of one reproductively successful migrant individual ($mN=1$) among demes would be preferred for a variety of reasons. First, this amount of exchange is sufficient to avoid the loss of alleles in local demes due to genetic drift in the absence of natural selection. Such losses occur with F[ST] values of 0.33 or larger ($mN=0.5$) (p. 122, Kimura and Ohta, 1971). Second, this amount of exchange is not sufficient to influence the frequencies of alleles in local demes under natural selection. Thus, one migrant individual among demes per generation would ensure that all of the genetic variation of a species is present in all local demes but would allow genetic differentiation among demes in response to local selective pressures.

SUMMARY

The interaction among genetic drift, gene flow, and natural selection in determining patterns of allele frequency divergence among a series of semi-isolated local demes is examined using population genetics theory and a series of computer simulations. With selective neutrality, the amount of divergence among demes is a function of the number of migrants, and not the proportion

of individuals exchanged. Therefore, some knowledge of effective local population sizes is needed to estimate the degree of reproductive isolation from allele frequency data. In addition, contrary to some previous claims, significant allele frequency divergence is expected to be present even when there is substantial exchange among populations. An average exchange of one migrant individual per generation will maintain the same alleles in all demes, but much larger amounts of exchange are required to maintain similar allele frequencies among demes.

Heterozygous advantage reduces the divergence among demes; that is, for a given amount of gene flow, there is less divergence in comparison with the absence of natural selection. The amount of divergence is not simply a function of the number of migrants with this mode of selection because natural selection is more effective in larger demes because of reduced genetic drift. Heterozygous advantage significantly reduces allelic divergence among demes when there is strong selection or large demes. In general, heterozygous advantage will be effective when the selection coefficient is greater than the migration rate.

Differential directional selection acts to maintain allelic divergence among demes even when there is a large amount of gene flow. As with heterozygous advantage, selection is effective when the selection coefficient is greater than the migration rate. Thus, for a given number of migrant individuals, this mode of selection is more effective with larger local deme sizes.

These results are considered with respect to the design of appropriate breeding structures for populations that are controlled by human actions. An average exchange rate of one

reproductively successful migrant individual among demes is desirable. This amount of exchange is sufficient to avoid the loss of alleles in local demes due to genetic drift but will allow the allele frequency in individual demes to respond to local selective pressures.

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TABLE 1. Simulation results of steady-state F(ST) values with 20 subpopulations and heterozygous advantage in which both homozygous phenotypes have a reduction in fitness of s. The first, second, and third values for each value of s represent population sizes of 25, 50, and 100, respectively. Each value is the mean of 20 repeats.

	mN					
s	0.5	1	2	5	10	25
[1/(4mN+1)]	0.3333	0.2000	0.1111	0.0476	0.0244	0.0099
0.00	0.3070	0.2043	0.1245	0.0418	0.0198	-
	0.3350	0.1826	0.1077	0.0484	0.0264	0.0120
	0.3216	0.1884	0.1061	0.0437	0.0251	0.0095
0.01	0.2826	0.1640	0.0666	0.0499	0.0220	-
	0.2431	0.1534	0.0824	0.0406	0.0232	0.0117
	0.1782	0.1236	0.0930	0.0383	0.0355	0.0109
0.05	0.1930	0.1259	0.0714	0.0441	0.0237	-
	0.1327	0.1072	0.0620	0.0341	0.0238	0.0092
	0.0827	0.0661	0.0432	0.0242	0.0185	0.0110
0.10	0.1217	0.1039	0.0533	0.0429	0.0216	-
	0.0938	0.0763	0.0503	0.0307	0.0207	0.0087
	0.0410	0.0290	0.0317	0.0217	0.0103	0.0070

TABLE 2. Simulation results of steady-state F(ST) values for 20 subpopulations with differential directional selection. One homozygous genotype has a reduction in fitness of t in ten subpopulations; the other homozygous genotypes has the same reduction in fitness in the ten other subpopulations. Heterozygotes have a reduction in fitness of one-half t in all subpopulations. The first, second, and third values below each value of t represent subpopulation sizes of 25, 50, and 100, respectively. Each values is the mean of 20 repeats.

	mN					
t	0.5	1	2	5	10	25
[1/(4mN+1)]	0.3333	0.2000	0.1111	0.0476	0.0244	0.0099
0.01	0.3343	0.1703	0.1070	0.0556	0.0220	-
	0.2979	0.1192	0.1000	0.0381	0.0256	0.0099
	0.2997	0.1850	0.1146	0.0354	0.0229	0.0105
0.05	0.3560	0.1857	0.1204	0.0497	0.0217	-
	0.4618	0.2679	0.1489	0.0550	0.0265	0.0113
	0.5950	0.4230	0.1982	0.0632	0.0207	0.0118
0.10	0.4700	0.2446	0.1632	0.0473	0.0289	-
	0.6242	0.3653	0.2611	0.0771	0.0356	0.0128
	0.8054	0.6575	0.4432	0.1589	0.0632	0.0193

TABLE 3. Allele frequency divergence among five demes of brown trout spawning in tributaries of Lake Lulejaure, Sweden (Ryman and Ståhl, 1981). There are two alleles at each locus; the frequency presented is that of the common allele.

Sample	Agp-2	Ldh-5	Mdh-2
Ruoktojokok	0.962	0.691	0.938
Såkasjokk (upper)	0.827	0.877	0.865
Såkasjokk (lower)	1.000	0.800	0.865
Tjegnaljokk	0.860	0.529	0.980
Appakisjokk	0.988	0.835	1.000
F[ST]	0.074	0.082	0.052

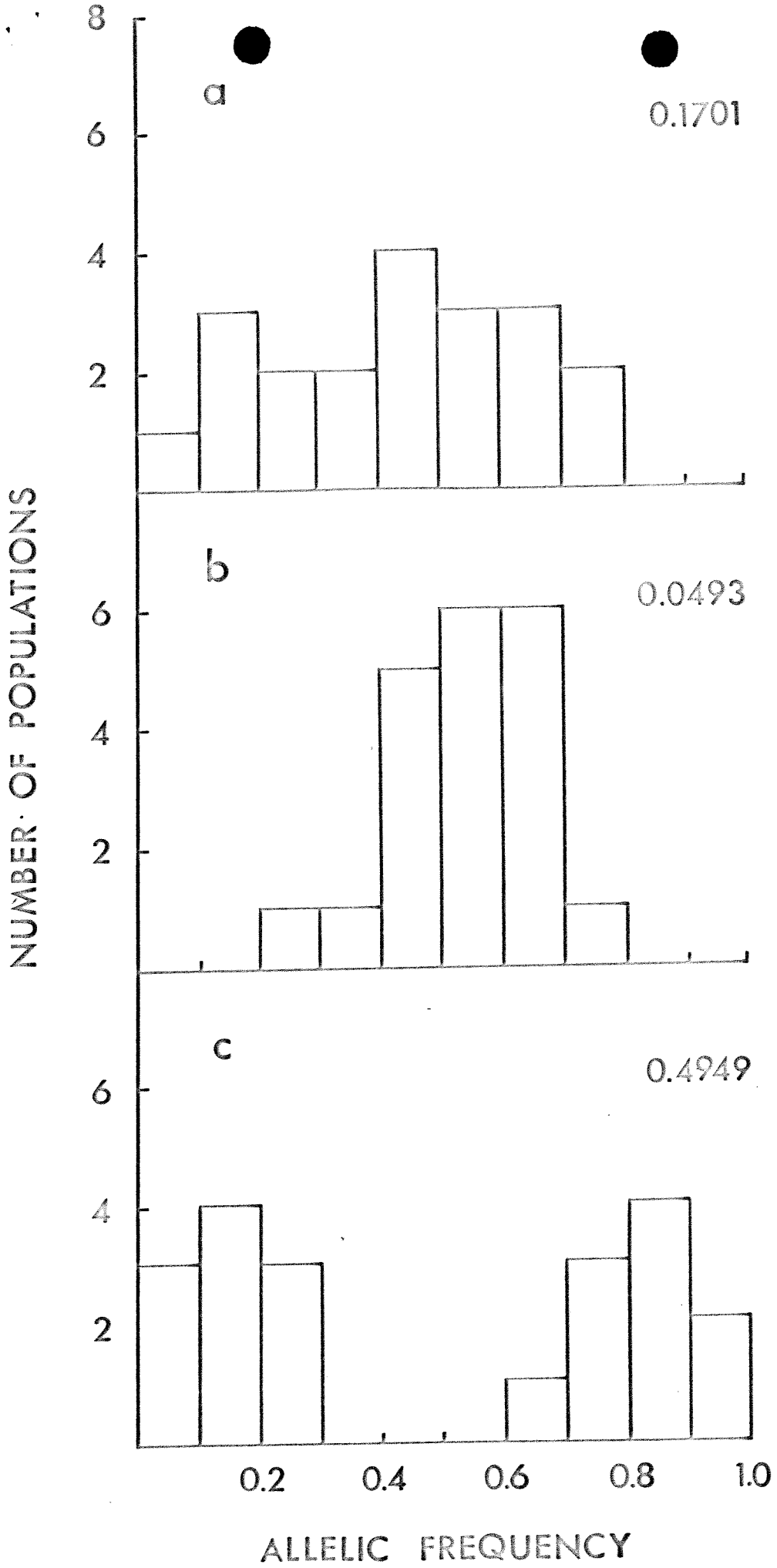
LEGENDS

FIG. 1. Simulation results showing distribution of allele frequencies in 20 demes with different modes of natural selection. In all cases N=100 and m=0.01 (mN=1). (a) selective neutrality; (b) heterozygous advantage with s=0.05; and (c) differential directional selection with t=0.05.

FIG.2. Simulation results showing the effects of variable mN on the relative amount of divergence with natural selection. The relative divergence is the observed F[ST] divided by the F[ST] expected with selective neutrality. Three different deme sizes are shown: 25 (circles), 50 (triangles), and 100 (squares). (A) Heterozygous advantage, s=0.05; (B) Differential directional selection, t=0.05.

FIG. 3. Simulation results showing the effects of variable intensity of selection on the relative amount of divergence with an mN of 5. (See Fig. 2 for explanation of symbols.) (A) Heterozygous advantage; (B) Differential directional selection.

FIG. 4. Simulation results showing distribution of F[ST] values in 200 repeats for N=50 and m=0.068 with 10 demes. The dotted lines show the F[ST] values actually estimated by Ryman and Ståhl (1981) for three loci in brown trout from tributaries to Lake Lulejaure.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b
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c
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8
6
4
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NUMBER OF POPULATIONS
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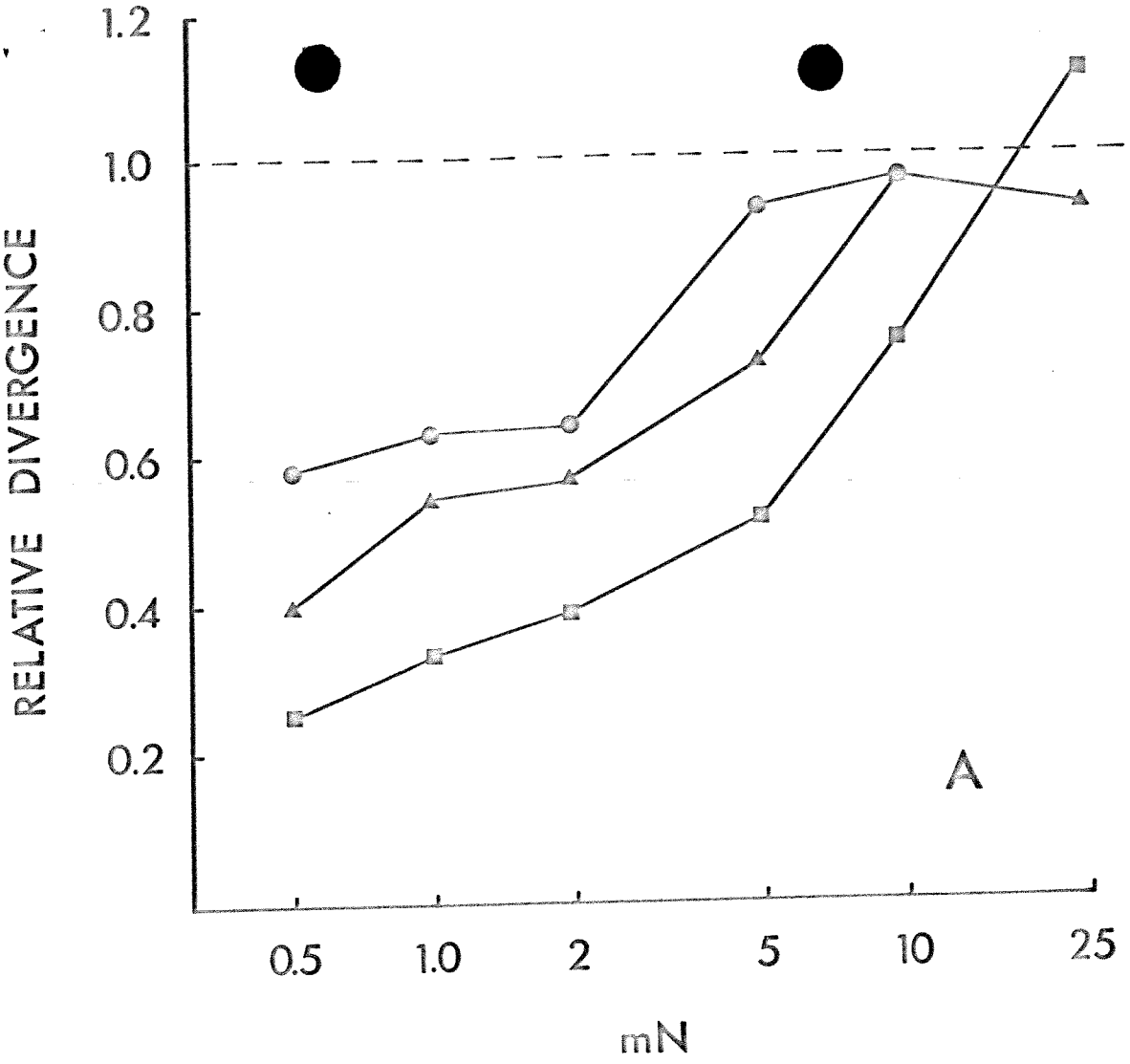
0.4
0.6
0.8
1.0
ALLELIC FREQUENCY

Fig. 1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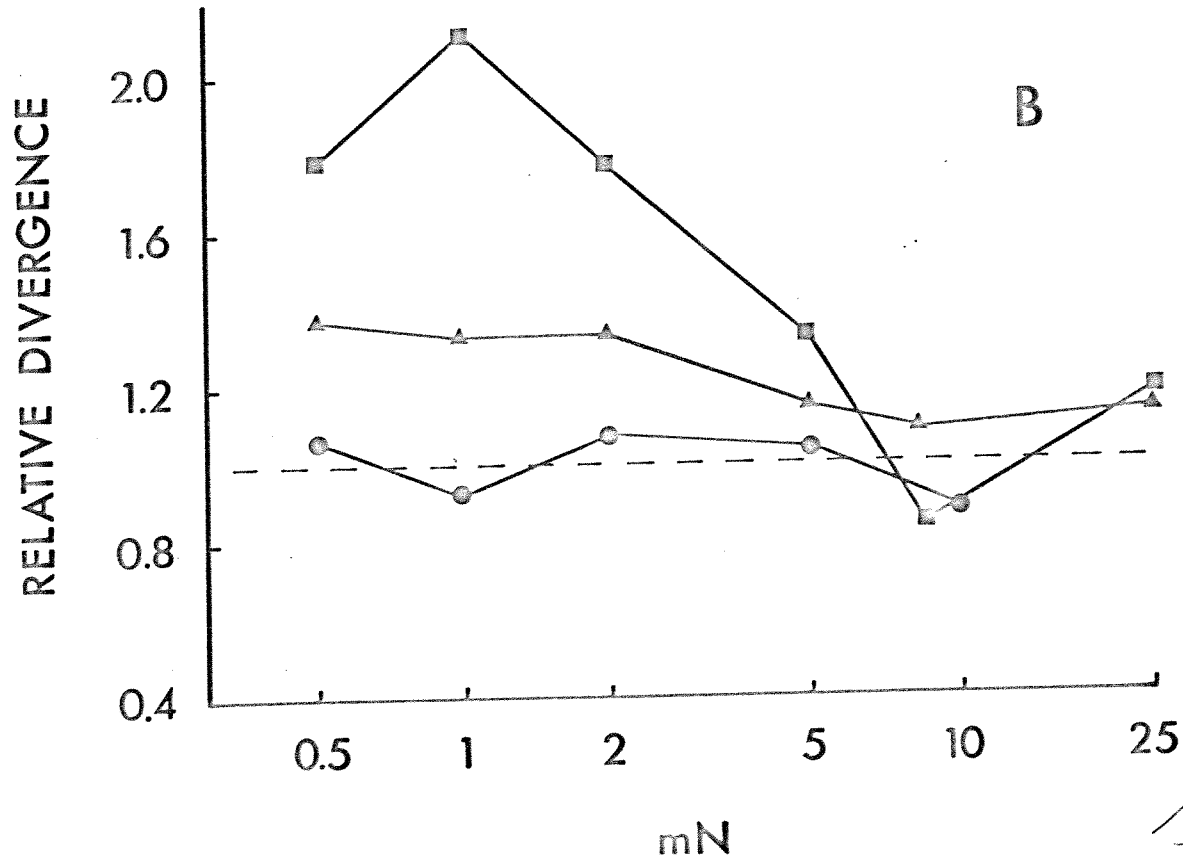
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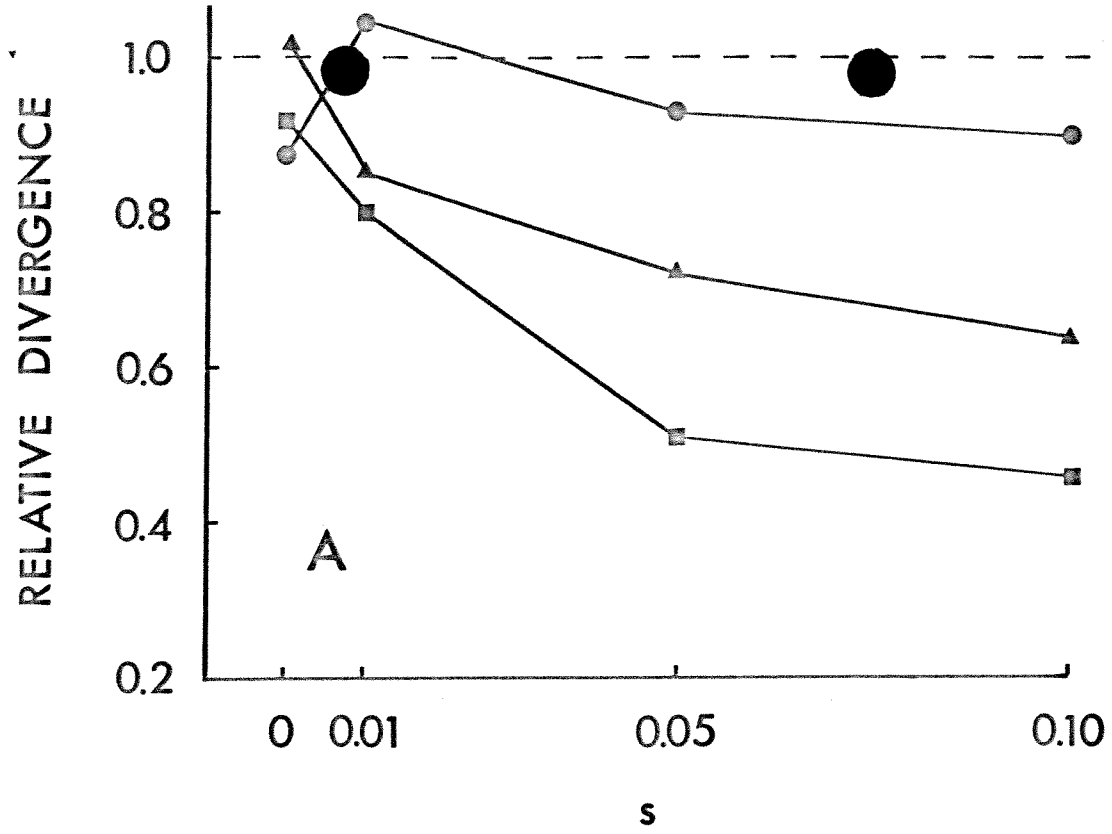
Fig 2


RELATIVE DIVERGENCE
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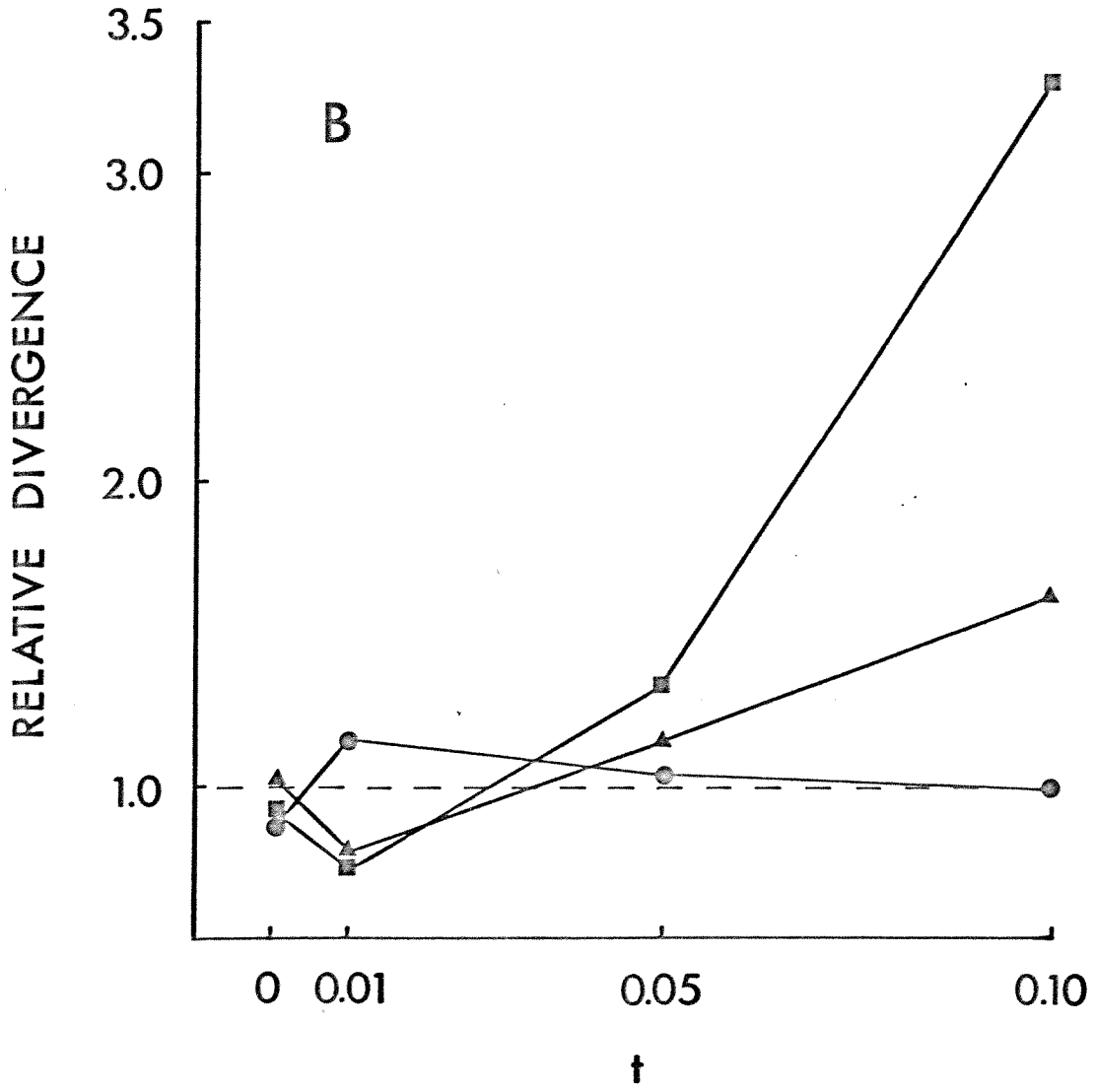
RELATIVE DIVERGENCE
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Fig. 3

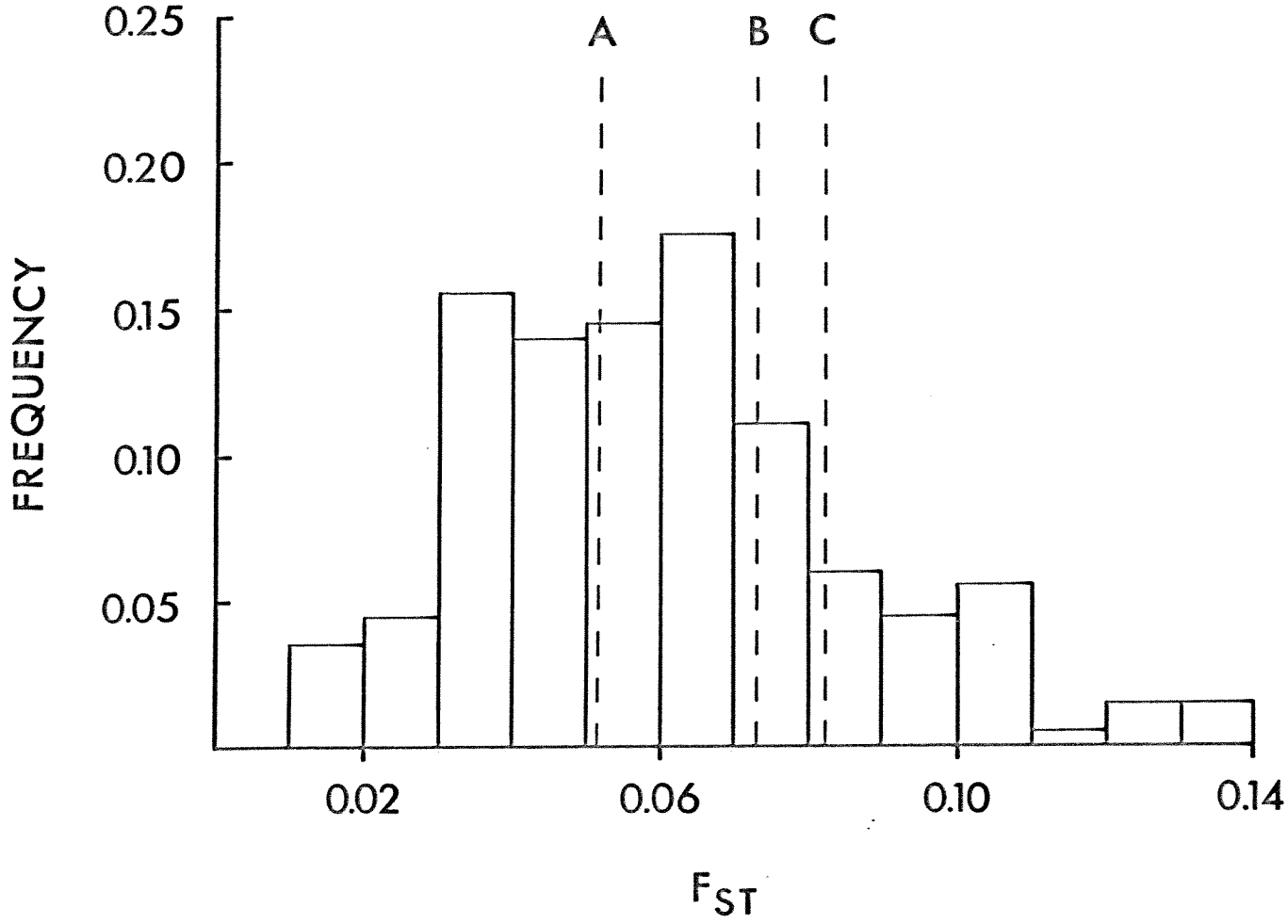

Fig. 4