Genetica Vol. 48, 3: 161-168, 1978

CYCLICAL SELECTION IN SMALL POPULATIONS

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Received October 13, 1977/Accepted December 13, 1977

A theoretical analysis is made of a cyclical selection model exhibiting 'marginal overdominance' (in the sense of geometric mean overdominance) in small populations. When the fitnesses are additive, geometric mean overdominance produces similar results as constant overdominance: fixation is retarded most effectively at central equilibrium gene frequencies and can be accelerated (as compared to the neutral case) at extreme equilibrium frequencies (Robertson, 1962). However, with increasing degree of dominance with respect to fitness, the maximal retardation of fixation is shifted towards low equilibrium frequencies of the 'recessive' allele. From a comparison between the cyclical selection models and appropriate constant selection models it is concluded that for low equilibrium gene frequencies and (some degree of) dominance, geometric mean overdominance resulting from cyclical selection is more effective in maintaining genetic variation than constant overdominance, while at intermediate equilibrium frequencies the reverse holds. The results are discussed in relation to the idea of using theoretical distribution patterns of heterozygosity under various assumptions in order to discriminate among different hypotheses on the maintenance of enzyme polymorphisms.

Introduction

During the last decade the problem of explanation of the large amounts of electrophoretic genetic variation has received wide attention. As a result there has been a growing interest in the effects of environmental heterogeneity on the evolution of populations. Restricting attention to temporal heterogeneity, theoretical work on systematic temporal variation in selection intensities has been published by Dempster (1955), Haldane & Jayakar (1963), Hedrick (1974, 1976), Hoekstra (1975), and others.

Exact conditions for a stable non-trivial gene frequency equilibrium in an infinite diploid population subjected to cyclical selection were first given by Haldane & Jayakar (1963), and extended by Karlin & Lieberman (1974) and Hoekstra (1975). The most important condition requires 'geometric mean overdominance', which means that the geometric mean fitness of the heterozygote must be greater than the geometric mean fitnesses of both homozygotes. In finite populations the environmental pattern has a great influence on the maintenance of genetic variation, the maintenance being highest when there is a strict alternation every generation of two environments with selection in opposite directions (Hedrick, 1974, 1976).

Karlin & Levikson (1974) showed, using a random temporal selection model, that variance in selection coefficients reduces the mean selective effects; for example, the probability of fixation of the abundant allele is smaller with randomly varying selection than with constant selection.

In this paper the effect of geometric mean overdominance in a cyclical selection model in small populations is studied. The investigation has been designed in such a way that among other things a comparison can be made with the results of Robertson (1962) on the effect of overdominance with constant selection in small populations.

The model will have relevance to species living in a seasonal environment and having a generation-time equal to or shorter than the duration of a season.

Methods

The genetic model used in this study is formulated as follows: consider a monoecious diploid population having in each generation N individuals characterized by their genotype with respect to an autosomal locus with two alleles, A_1 and A_2; reproduction occurs in discrete generations by random mating. The population is subjected to cyclical selection with a cycle-length of two generations (alternating selection), which means that the relative fitnesses of the three genotypes A_1A_1, A_1A_2 and A_2A_2 in generation t are w_1, 1, v_1 for t = 1,3,5,... and w_2, 1, v_2 for t = 2,4,6,... . More specifically, the fitnesses will be specified as follows in terms of selection coefficients s_1, s_2 and degree of dominance d:

	A_1A_1	A_1A_2	A_2A_2
environment 1	$w_1 = 1 + s_1$	1	$v_1 = 1 - (1 - d)s_1$
environment 2	$w_2 = 1 - s_2$	1	$v_2 = 1 + (1 - d)s_2$

(1)

The change in the number of A_1-genes over successive generations is described with the well-known Wright-Fisher Markov chain formulation: let $X(t)$ denote the number of A_1-genes in generation t. Then the distribution of $X(t + 1)$ is binomial with parameters $(2N, p_{t+1})$, where p_{t+1} denotes the expected frequency of A_1-genes in generation $t + 1$. Thus, the conditional probability that there will be j A_1-genes in generation $t + 1$, given that there are i A_1-genes in generation t (and assuming that the relative fitnesses of A_1A_1, A_1A_2 and A_2A_2 in generation t are given by $w_t, 1, v_t$) is

$$\text{prob}\{X(t+1) = j \mid X(t) = i\} = \binom{2N}{j} p_{t+1}^{j} (1 - p_{t+1})^{2N-j} \qquad (2)$$

where

$$p_{t+1} = \{w_t i^2 + i(2N - i)\} / \{w_t i^2 + 2i(2N - i) + v_t (2N - i)^2\}.$$

With each of the two environments in the alternating selection model there is associated a transition probability matrix as specified by (2). Denote by P_1 and P_2 the transition matrices associated with the first and the second environment in the cycle. Then the matrix product $P = P_1P_2$ is the appropriate transition probability matrix if a cycle instead of a generation is taken as the time-unit of the process. Now the process of selection and drift over a cycle can be represented by the multiplication of the transition matrix P by a vector y_t having $2N + 1$ elements corresponding with the $2N + 1$ possible values of the gene frequency at the start of cycle t:

$$y_{t+1} = P y_t \qquad (3)$$

Because exact results are very difficult to obtain from this model, we have resorted to the method of iterating equation (3). This method is indicated in Crow & Kimura (1970:407) and is used in a similar context by Hedrick (1974, 1976).

It is a well-known property of this model that the probability distribution of the unfixed gene frequency classes finally reaches a state of constant proportional decline, the so-called state of steady decay. In the absence of selection the unfixed gene frequency classes are in this state declining by a constant fraction $1/2N$ each generation. It is easy to see that if one takes a cycle of two generations as the time-unit, the rate of steady decay per cycle in the neutral case is equal to

$$1 - (1 - 1/2N)^2 = (4N - 1) / (4N^2) \qquad (4)$$

The behaviour of the selection model in small populations will be characterized by the retardation factor R_c, which is equal to the ratio between the rates of steady decay in the neutral case and in the selection case (see Robertson, 1962). From (4) it follows that

$$R_c = \frac{4N - 1}{4N^2 \lambda_c},$$

where λ_c denotes the rate of steady decay per cycle in the particular selection model considered. As pointed out above, λ_c is obtained by iteration of the appropriate equation (3).

Results

The selection models in this study are fully specified by four parameters; the population size N, the mean deterministic equilibrium gene frequency $\bar{p} = (\hat{p}_1 + \hat{p}_2)/2$ (where $\hat{p}_1$ and $\hat{p}_2$ are the gene frequency

equilibria in the alternating selection model), the mean selection coefficient $\bar{s} = (s_1 + s_2)/2$, and the degree of dominance d. The following parameter values were used: N = 10,30,50; $\bar{p}$ = .05,.1,.2,.3,.4,.5,.7,.9; $\bar{s}$ = .1,.2,.3,.4; d = 0,.25,.5,.75,1.

For any given combination of $\bar{p}$, d and $\bar{s}$, the values of s_1 and s_2 are uniquely determined. They were obtained analytically in the case of additive fitnesses ($d = 0$), and by a numerical procedure for the other levels of dominance. The retardation factor was computed for all combinations of the parameter values.

Figure 1 shows the retardation factor plotted as a function of the mean deterministic equilibrium gene frequency for the combinations of the following parameter values: N = 10, 30, 50; d = 0, 0.5, 1; $\bar{s}$ = 0.2,0.4. These retardation factors differ much less from unity than in the case of constant overdominance with selection coefficients of the same order of magnitude because the net selective effect per cycle is much smaller than in the generations separately; for instance, constant heterosis with mean selection coefficient of 0.4 in a population of $N = 30$ gives a maximal retardation factor which is about ten times greater than in the cyclical model with $N = 30$ and $\bar{s} = 0.4$, while the minimal retardation factor in the constant overdominance model is two times smaller than with cyclical selection. This phenomenon is most marked when there is a complete dominance ($d = 1$) (see Fig. 2). Thus, the effect of geometric mean overdominance in the cyclical selection model varies less with the deterministic equilibrium gene frequency with increasing dominance.

When there is additivity with respect to fitness ($d = 0$) there is agreement with the findings of Robertson (1962) for constant heterozygote advantage: the retardation of fixation is greatest at $\bar{p} = 0.5$, becoming less for more extreme equilibrium frequencies. Increasing N or $\bar{s}$ results in greater retardation and when the equilibrium frequency is extreme even in acceleration of fixation. In the models with partial dominance ($d = 0.5$) and in those with complete dominance ($d = 1$) increase in N or $\bar{s}$ has in principle a similar effect, but this is interfering with an asymmetry of the retardation factor with respect to the equilibrium frequencies. The asymmetry increases with increasing d and is greatest for small N and $\bar{s}$. This phenomenon can be explained by the fact that dominance ($d > 0$) causes the deterministic gene frequency change per cycle Δp to be asymmetric around $p = 0.5$ (Hedrick, 1974).

The retardation factor implies a comparison of a model population undergoing cyclical selection with a

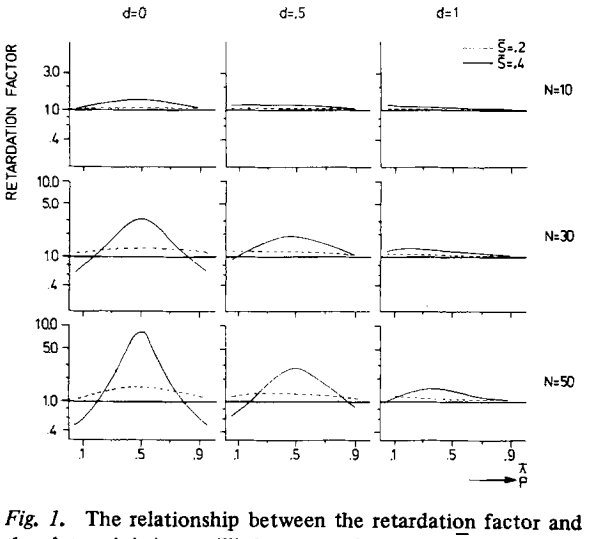

Fig. 1. The relationship between the retardation factor and the deterministic equilibrium gene frequency $\bar{p}$ for various different parameter combinations of the cyclical selection model.

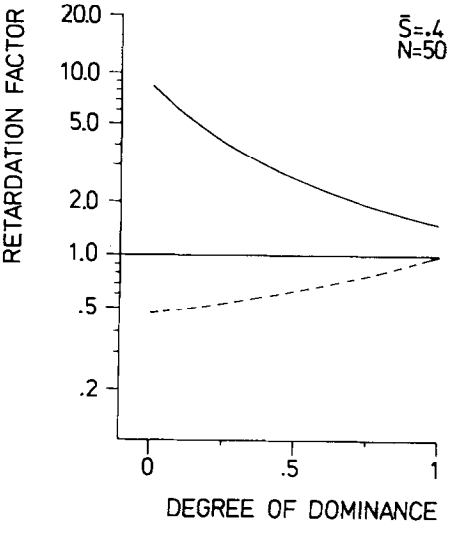

Fig. 2. The maximal (solid line) and the minimal (broken line) value of the calculated retardation factors at different levels of dominance in a model population of size $N = 50$ with mean selection coefficient $\bar{s} = 0.4$.

model population of the same size in which differential selection is absent and the gene frequency is influenced by genetic drift only. In addition, when considering questions concerning the adaptive significance of particular responses to a variable environment, one would like to compare the effect of cyclical selection with that of constant selection. To this end the cyclical model will be compared with a corresponding constant selection model, which is defined as that constant selection model having (i) a deterministic gene frequency equilibrium equal to the mean equilibrium frequency of the cyclical model and (ii) an area between the Δp curve and the p-axis (on the interval [0,1]) equal to the mean area between the p-axis and the two Δp curves (resulting from the two different sequences of the two environments of the cyclical model). Here Δp denotes the deterministic gene frequency change per cycle of two generations. Thus defined, the corresponding constant selection model can be regarded as that constant selection model which approximates best the behaviour of the cyclical model in a very large population.

The corresponding constant selection models are of the overdominance type with selection coefficients 5 to 20 times smaller than in the cyclical models, the latter phenomenon being caused by the fact noted before, that the net selective effect over a cycle is much smaller than in the separate generations. The difference between a cyclical selection model and the corresponding constant model in their behaviour in small populations will be measured by the difference between the retardation factors of the two models expressed as a percentage of the retardation factor of the constant selection model:

$$\Delta R = \frac{R_c - R_{\text{const}}}{R_{\text{const}}} \times 100\%$$

where R_c and R_{const} denote the retardation factor of respectively a cyclical selection model and the corresponding constant selection model.

A positive value of ΔR therefore indicates that the cyclical model is more effective in maintaining genetic variation in a small population than the corresponding constant model, while with a negative value of ΔR the reverse holds.

Figure 3 shows ΔR as a function of $\bar{p}$ at three different levels of dominance with $N = 50$ and $\bar{s} = 0.4$. In the additivity case ($d = 0$) the plot of ΔR is symmetrical around $\bar{p} = 0.5$, while for $d > 0$ the curve is asymmetrical. Furthermore, it is clear that the cyclical model can better retain genetic variation than the constant selection model when the deterministic equilibrium gene freqeuncy is small (especially with high levels of dominance), while at intermediate and high equilibrium frequencies the constant selection model maintains genetic variation more effectively than the cyclical model. These results can be understood by noting that the ΔR curves are the outcome of two different effects. First, although the average gene frequency change per cycle in both the cyclical and the corresponding constant model is the same, there is in the cyclical model a fluctuation of the gene frequency within a cycle from generation to generation, which is (in the neighbourhood of the equilibrium frequency) greatest for $\bar{p} = 0.50$ and smallest for the most extreme equilibrium frequencies. The fluctuation in gene frequency within a cycle causes a dispersion in the gene frequency distribution towards more extreme values, thus increasing the rate of fixation. This effect is illustrated clearly in the ΔR curve for $d = 0$ (Fig. 3). The second effect (which modifies the first) causes the ΔR curve to be asymmetrical

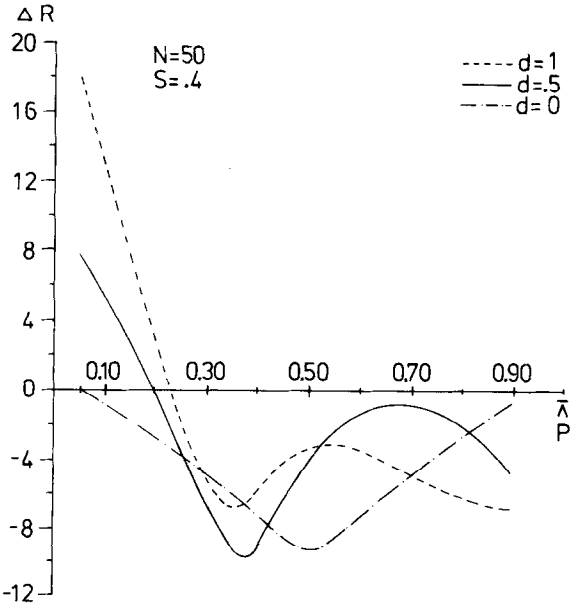

Fig. 3. The percent difference between the retardation factors of the cyclical and the corresponding constant selection model ΔR at three levels of dominance in a model population of size $N = 50$ with mean selection coefficient $\bar{s} = 0.4$.

when there is (some) dominance: in the absence of dominance ($d = 0$) the Δp curves of the cyclical and the corresponding constant model coincide, but with increasing degree of dominance these curves increasingly differ in form. A qualitative picture of this difference is presented in Figure 4. When the equilibrium frequency is small the approach (from above) towards equilibrium is much slower in the cyclical model than in the corresponding constant model, which results in a lower rate of fixation in small populations. Here the second effect dominates the opposing first effect and causes ΔR to be greater than zero for small equilibrium frequencies. At high equilibrium frequencies the difference between the Δp curves of the two models is reversed, and here the two effects reinforce each other causing lower values of ΔR for increasing levels of dominance.

Figure 5 shows the parameter combinations for which the cyclical and the corresponding constant selection model have the same retardation factor ($\Delta R = 0$). They were obtained by extrapolation from the calculated ΔR values at $\bar{p} = 0.05,0.1,0.2,0.3,\ldots$. For parameter combinations represented in the diagram below the appropriate line the cyclical model is more effective in maintaining genetic variation ($\Delta R > 0$), while for parameter combinations represented by points above the line the corresponding constant model has a better maintenance of variation ($\Delta R < 0$). The results presented in Figure 5 suggest that for a given value of $\bar{s}$ there exist optimum values for d and N such that both smaller and larger values result in a decrease of the 'critical' value of $\bar{p}$ at which $\Delta R = 0$.

The results on the comparison between the cyclical selection models and the corresponding constant selection models are summarized in the form of phase-diagrams (Fig. 6). They allow the following conclusions:

(1) The difference between the retardation factors of the two models increases with increasing $\bar{s}$ and N.

(2) This difference varies with equilibrium frequency $\bar{p}$ and with degree of dominance d in the following way:

– when $\bar{p}$ is low (less than .2) ΔR is positive and increases with decreasing $\bar{p}$ and with increasing d;

– when $\bar{p}$ is high (greater than .8) ΔR is increasingly negative with increasing $\bar{p}$ and d.

– when $\bar{p}$ is intermediate (between .2 and .8) ΔR is negative in most cases, showing an increasing asymmetry around $\bar{p} = .5$ with increasing dominance (cf. Fig. 3).

(3) The transition between a positive and a negative value of ΔR, considered as a function of the equili-

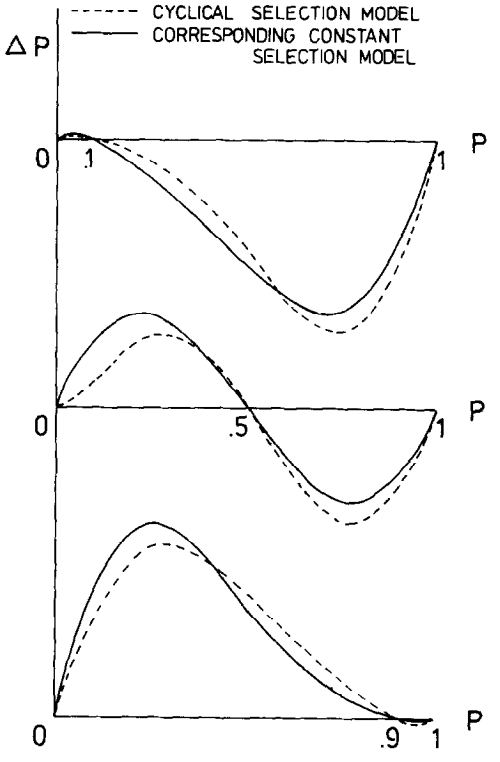

Fig. 4. The deterministic mean gene frequency change per cycle Δp as a function of the gene frequency p in the cyclical selection model (broken lines) and in the corresponding constant selection model (solid lines).

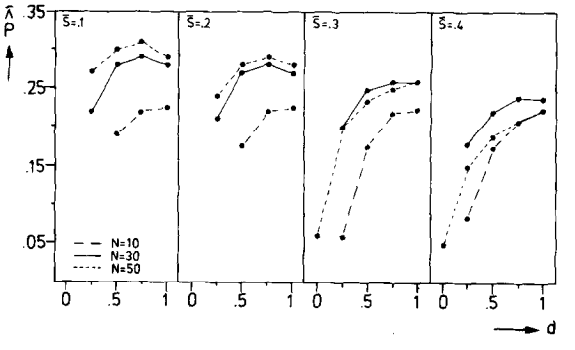

Fig. 5. Parameter combinations for which the cyclical selection model has the same retardation factor as the corresponding constant selection model.

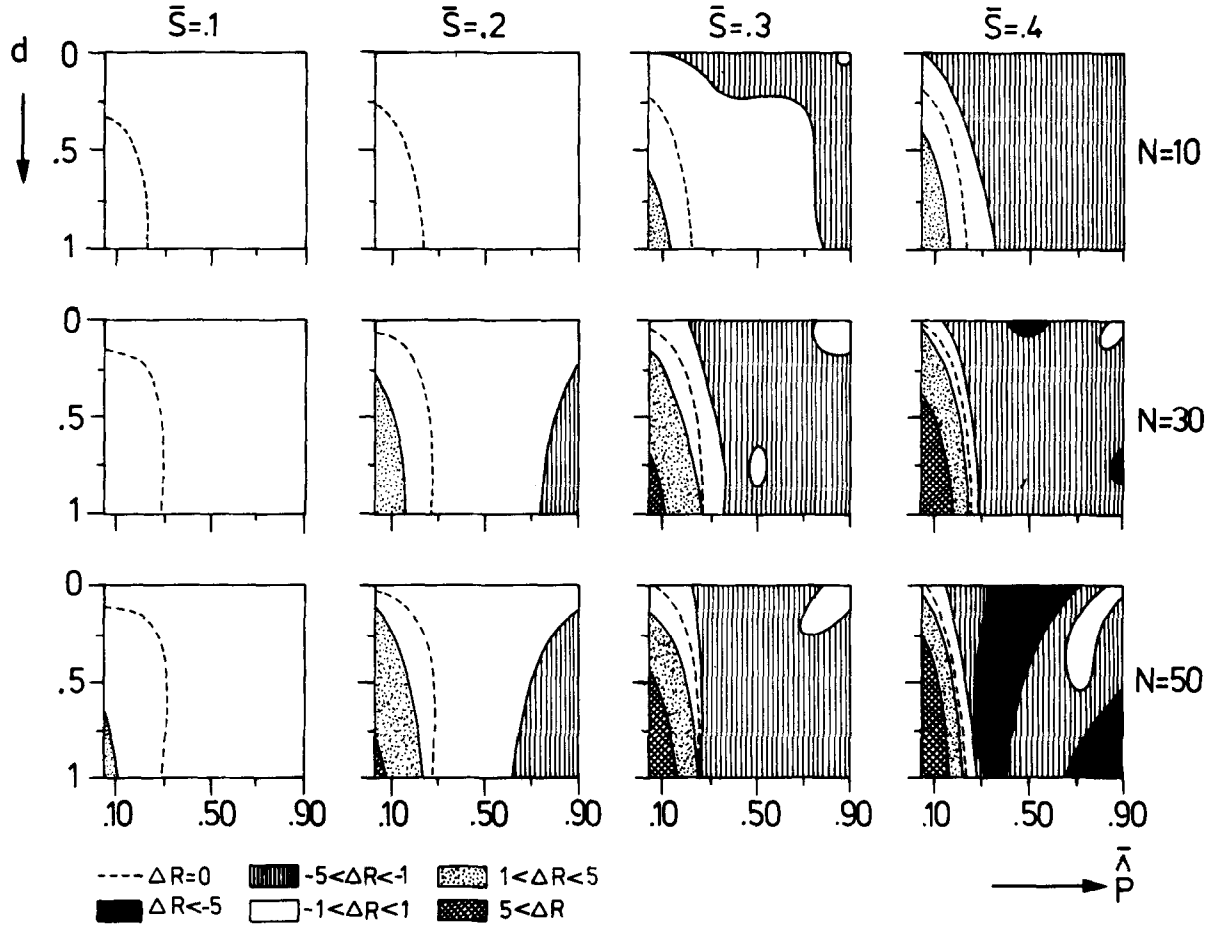

Fig. 6. Phase diagrams of the results on the comparison between the cyclical selection models and the corresponding constant selection models, expressed in the percent difference of the respective retardation factors ΔR. In each diagram the ordinate represents the level of dominance and the abscissa the deterministic equilibrium frequency. The broken line represents the parameter combinations for which $\Delta R = 0$.

brium frequency, is becoming sharper with increasing N, $\bar{s}$ and d.

Discussion

In the cyclical selection model used in this study the selective forces in the two alternating environments are in opposite directions over the whole gene frequency range. As a consequence, the mean selective effect over a cycle of two generations is considerably smaller than the selective effects in the separate generations. This explains the result that the retardation factors in the cyclical selection models are much closer to unity than in constant overdominance models with the same population size and the same mean selection coefficient. Therefore, given a particular mean selection coefficient, constant overdominance can better maintain genetic variation in a small population than geometric mean overdominance resulting from cyclical selection when the deterministic equilibrium frequency is intermediate (between 0.2 and 0.8). However, when the equilibrium frequency is extreme (outside the range 0.2 to 0.8) cyclical selection is more effective in maintaining genetic variation – although not much more effective than when there is no selection. These effects are modified by (some degree of) dominance in the cyclical selection model: then at small equilibrium frequencies of the 'recessive' allele [the A_1 allele in

model (1)] the abovementioned difference in ability to maintain genetic variation between the two models is even greater.

Whereas with constant overdominance in small populations one would hardly expect to find equilibrium frequencies outside the range of 0.2 to 0.8 (Robertson, 1962), under cyclical selection (especially when there is dominance) extreme equilibrium frequencies should be relatively more common. This may have some bearing on the argument first developed by Yamazaki & Maruyama (1972), who use theoretical distribution patterns of heterozygosity under various assumptions in order to discriminate among the neutral hypothesis and selection hypotheses on the maintenance of protein polymorphisms.

Using all the data from polymorphism surveys published at the time, they found these data to be consistent with the neutral hypothesis. Latter (1975), using the same technique, showed that in the data on *Drosophila* species there are much more low frequency alleles than expected on the basis of the neutral hypothesis. Ohta (1975) reached the same conclusion for data on both *Drosophila* and man.

Latter (1975) explains this excess of low frequency alleles by selection for an optimum level of enzyme activity, Ohta (1975) explains the phenomenon with her hypothesis of slightly deleterious mutations, while Nei & Li (1976) remark that this excess also can be explained by the hypothesis of a recent bottleneck in numbers or population expansion, and also is expected to occur if the mutation rate varies from locus to locus.

The present study indicates that an excess of low frequency alleles also is expected in small populations undergoing cyclical selection, especially so when these alleles are recessive with respect to fitness. However, this effect is unlikely to be very important because the retardation factors in the cyclical selection model are rather small unless selection is very strong.

The question arises to what extent the results of the present study can be generalized to other types of cyclical selection. The results apply in a qualitative way also to longer cycles made up of two or more different environments. However, the ability to maintain genetic variation in small populations decreases with increasing fluctuations in gene frequency within a cycle; especially when the population is during several consecutive generations in the same environment, cyclical selection is not very effective in retarding fixation in small populations (Hedrick, 1976).

When there is a cyclical variation in environmental factors relevant to fitness, a population can adapt to this variation in a number of different ways, often termed 'strategies'. For example, a possible strategy is to track genetically the environment, i.e., different genotypes are selected in different environments, while another strategy is to create a single type (for example, in a one locus, two alleles situation, the heterozygote) which has the highest fitness in all environments. Which strategy is optimal in a given situation depends among other things on the environmental pattern and grain and on the biology of the organism (Levins, 1968).

Our results on the comparison between the cyclical models and the corresponding constant models suggest that genetic tracking of the environment will be advantageous when there is (some) dominance with respect to fitness and the deterministic equilibrium frequency of the 'recessive' allele is small, but that it will be disadvantageous when the equilibrium frequency is intermediate or high, or when the fitnesses are additive (see Fig. 3).

We thank Professor A.J. Stam, R. Bijlsma and P. Stam for discussion and comments.

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