MULTILOCUS BEHAVIOR IN RANDOM ENVIRONMENTS
I. RANDOM LEVENE MODELS

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Manuscript received January 27, 1975
Revised copy received August 18, 1975

ABSTRACT

In this paper the consequences of natural selection acting on several loci simultaneously in a spatially fluctuating environment are described. The fitnesses of the genotypes are assumed to be additive both within and between loci. The environment is assumed to be made up of a very large (effectively infinite) number of patches in which fitnesses are assigned at random. The resulting deterministic model is called a Random Levene Model and its properties are approximated by a system of differential equations. The main equilibrium properties are that (1) the linkage disequilibrium is zero and (2) the correlations in fitnesses between alleles at different loci are the principal determinants of the dynamic inter-locus interactions. Although there is no epistasis as conventionally defined, the equilibrium state at the two loci are highly interdependent, the governing principle being that two alleles at different loci whose fitnesses are negatively correlated across environments have a higher overall fitness due to the reduction in their variance in fitness through the negative correlation. When a large number of loci are considered, they naturally fall into correlation groupings which lead to an enhanced likelihood for polymorphism over that predicted by single-locus theory.

In a recent review article, LEWONTIN (1973) wrote, “The current and future genetic composition of populations is certainly the result of the evolution of coupled systems of genes in a fluctuating environment, and these interactions and temporal instabilities are first order phenomena, not simply minor modifications of an otherwise simple and constant process.” We have examined some multi-locus models in fluctuating environments and have discovered that LEWONTIN’S prediction is quite accurate. The “first order phenomena” involve, in the simplest cases, the correlations in fitness between different genotypes as their fitnesses change randomly in space and time. Our results indicate that these correlations are as important as the effects of epistasis and should thus be a major target for work on the co-adaptation of genotypes.

In this paper we begin by formally defining a class of models of selection in stochastic, spatially varying environments. These models will be called Random Levene Models (RLM’s) since they begin with LEVENE’S (1953) description of the progress of selection in a multiple-niche environment. We will consider only additive models. We have argued previously for the relevance of additivity across

alleles (Gillespie and Langley 1974) and will, in a future paper, argue for the biological relevance of approximate additivity across loci. In this paper, however, we will concentrate on describing the consequences of the additive assumption on the progress of natural selection.

ONE-LOCUS RANDOM LEVENE MODELS

Much of the mathematical theory of population genetics is concerned with the changes in the frequency of a genotype in a uniform environment. In 1953 Howard Levene significantly extended these models by considering the way genotype frequencies behave in environments that are subdivided into distinct patches. The particular model explored by Levene assumes that the individuals of the population are distributed at random into the patches, that they undergo natural selection within the patches, and that density regulation occurs within the patches. Once these processes are completed, the individuals from the different patches assemble into a large random-mating pool, the individuals from the $i^{th}$ patch making up a fraction $C_{iM}$ of this pool. After mating, the individuals distribute themselves at random to the patches and the process begins anew. If natural selection changes the frequency of an allele in the $i^{th}$ patch by an amount $\Delta p_i$, then Levene showed that, for $M$ total patches, the allele frequency in the entire population changes by an amount

$$\Delta p = \sum_{i=1}^{M} C_{iM} \Delta p_i$$

(1)

In the case of a diploid locus with two alleles with fitnesses for the genotypes $AIAI$, $AIA2$ and $AIA2$ of $W_{11}(i)$, $W_{12}(i)$, and $W_{22}(i)$ in the $i^{th}$ patch:

$$\Delta p_i = \frac{p(1-p)[p(W_{11}(i)-W_{12}(i))-(1-p)(W_{22}(i)-W_{12}(i))]}{p^2W_{11}(i)+2p(1-p)W_{12}(i)+(1-p)^2W_{22}(i)}$$

(2)

As it stands, there is a tremendous latitude in the behavior of (1) which can be uncovered by assigning various values to the parameters and watching the behavior of $p$ through time. Much of the work on (1) has been geared toward understanding what behavior is possible given certain fitnesses and patch sizes. As dramatically shown by Li (1955), for certain parametric values the behavior of $p$ can be quite complex. However, we are concerned here not with the possible behavior of $p$, but with the probable behavior. If the fitnesses are assigned according to some probability law, rather than arbitrarily, the probable behavior of $p$ becomes open to investigation. This tactic also fits more closely with our ideas of environmental variation. Just as the environment is frequently viewed as changing at random through time, it can also be viewed as changing at random through space. When this change conforms to some stochastic model, those unusual fitness combinations, which make $p$ behave peculiarly, happen so infrequently that they contribute little to the overall change in the allele frequency. These ideas will be made precise in the following definition of the Random Levene Model.
The definition of the Random Levene Model will involve the following two assumptions:

1. The vectors \([W_{11}(i), W_{12}(i), W_{22}(i)], i = 1, 2, \ldots, M\) are independent, identically distributed random vectors. That is, the fitnesses in each patch are assigned independently from those in other patches, but the same probability law governs all patches. While this assumption is stronger than it need be, it emphasizes the fact that in the Levene Model there is no hierarchical spatial structure analogous to that of the stepping-stone models. The environment is viewed as divided into a large number of patches, but the patches are independent from each other.

2. \(C_{iM} = 0\left(\frac{1}{M}\right)\) as \(M \to \infty\) for all \(i\). We will let the number of patches increase while the contribution to the whole population of any single patch decreases. By doing this, the random fluctuations are smoothed out and the moments of the process dominate.

With these assumptions, as \(M \to \infty\), the law of large numbers applied to (1) gives

\[ \Delta p \to E\Delta p_i \] \hspace{1cm} (3)

In other words, the change in \(p\) for the population approaches the expected change in any one of the separate patches. The limiting process obtained as \(M \to \infty\) is the deterministic process

\[ \Delta p = E\Delta p_i \] \hspace{1cm} (4)

and will define an RLM. This limiting model was given for the special case \(C_{iM} = \frac{1}{M}\) in Gillespie and Langley (1974) and some of its properties were investigated.

In general the expectation in (4) is extremely difficult to evaluate, so some form of approximation is necessary. If selection is very weak, it is natural to approximate the behavior of (4) by an ordinary differential equation. We will do this only for the special case of additivity:

\[ W_{11}(i) = 1 + U_{A_1}(i), W_{12}(i) = 1 + \frac{1}{2}(U_{A_1}(i) + U_{A_2}(i)), W_{22}(i) = 1 + U_{A_2}(i). \] \hspace{1cm} (5)

Assume that the time between generations is \(\tau\), and that the first- and second-order moments of \((U_{A_1}(i), U_{A_2}(i))\) are all \(0(\tau)\) as \(\tau \to 0\) and that the higher order moments are all of order \(\tau^2\) or smaller. For concreteness write

\[ EU_{A_1} = \mu_{A_1}\tau \]

\[ \text{Var}U_{A_1} = \sigma_{A_1}^2\tau \]

\[ \text{Cov}(U_{A_1}, U_{A_2}) = \sigma_{A_1A_2}\tau \]

\[ \alpha = \frac{\sigma_{A_1A_2}}{\sigma_{A_1}\sigma_{A_2}}. \] \hspace{1cm} (6)
Then it is easily shown that
\[ p(t+\tau) - p(t) = \frac{p(1-p)}{2} \left[ \Delta \Gamma_A + \sigma_A^2 \left( \frac{1}{2} - p \right) \right] \tau + o(\tau^2) \] (7)

where
\[
\Delta \Gamma_A = \mu_A - \frac{1}{2} \sigma_A^2 - (\mu_A - \frac{1}{2} \sigma_A^2) \\
\sigma_A^2 = \sigma_A^2 + \sigma_A^2 - 2\sigma_A A \frac{1}{2} . \tag{8}
\]

As \( \tau \to 0 \), we get
\[
\dot{p} = \frac{1}{2} p(1-p) \left[ \Delta \Gamma_A + \sigma_A^2 \left( \frac{1}{2} - p \right) \right] . \tag{9}
\]

Clearly a stable polymorphism will occur if and only if
\[
|\Delta \Gamma_A| < \frac{\sigma_A^2}{2} . \tag{10}
\]

In a symmetric case where \( \sigma_A^2 = \sigma_A^2 = \sigma^2 \) we can write (10) as
\[
|\Delta \Gamma_A| < \sigma^2 (1 - \alpha_A) . \tag{11}
\]

This is the form for the conditions which will be most useful in contrasting multi-locus results.

The equilibrium allele frequency when (11) is satisfied is
\[
\hat{p} = \frac{1}{2} + \frac{\Delta \Gamma}{2 \sigma^2 (1 - \alpha_A)} . \tag{12}
\]

Notice that \( \hat{p} > 0.5 \) if and only if \( \Delta \Gamma > 0 \). We will loosely say that allele \( A_i \) has an average advantage over \( A_s \) in this instance. What actually occurs when \( \Delta \Gamma > 0 \) is that the geometric mean of \( U_{A_i} \) is greater than geometric mean of \( U_{A_s} \). To the order of approximation being used in this paper, the geometric mean of \( U_{A_i} \) is
\[ 1 + (\mu_{A_i} - \frac{1}{2} \sigma_{A_i}^2) \tau. \]

**TWO-LOCUS RLM'S**

The techniques and definitions of the previous section carry over completely for two-locus RLM's. Consider a diploid population with gametes \( A_iB_i, A_iB_s, A_sB_i, \) and \( A_sB_s \) in the relative frequencies \( x_1, x_2, x_3, \) and \( x_4 \). In analogy with the one-locus RLM, we shall assign the fitnesses for the nine zygotic types at random in each of the patches. Rather than displaying this in full generality, we will restrict the development to the additive model. Let the random vectors \([U_{A_i}(j), U_{A_s}(j), U_{A_s}(j), U_{B_i}(j), U_{B_s}(j)]\), \( j = 1, 2, \ldots \), be independent and identically distributed, with the argument \( j \) referring to the \( j \)th patch. Using these vectors, the fitnesses
of the nine zygotic types under the assumption of complete additivity of gene action may be written:

\[
\begin{align*}
A_1A_1 & \quad A_1A_2 & \quad A_2A_2 \\
B_1B_1 & = 1 + U_{A_1} + U_{B_1} & = 1 + \frac{1}{2}(U_{A_1} + U_{A_2}) + U_{B_1} & = 1 + U_{A_2} + U_{B_1} \\
B_1B_2 & = 1 + U_{A_1} + \frac{1}{2}(U_{B_1} + U_{B_2}) & = 1 + \frac{1}{2}(U_{A_1} + U_{A_2}) + \frac{1}{2}(U_{B_1} + U_{B_2}) & = 1 + U_{A_2} + \frac{1}{2}(U_{B_1} + U_{B_2}) \\
B_2B_2 & = 1 + U_{A_1} + U_{B_2} & = 1 + \frac{1}{2}(U_{A_1} + U_{A_2}) + U_{B_2} & = 1 + U_{A_2} + U_{B_2}
\end{align*}
\] (13)

These fitnesses determine the change in the frequency of the \(i\)th gamete in the \(j\)th patch, \(\Delta x_{ij}\). The overall change in the \(x_i\), according to the assumptions of the RLM, is the expected change in any single patch:

\[
\Delta x_i = E_j \Delta x_{ij}
\] (14)

As before, assume the mean, variances, and covariances of the \(UA_i\) and \(UB_i\) are of order \(\tau\). For concreteness write the means as:

\[
EU_{A_i} = \mu_{A_i}\tau \quad \quad EU_{B_i} = \mu_{B_i}\tau
\] (15)

and the covariance matrix for the random vector \((U_{A_1}, U_{A_2}, U_{B_1}, U_{B_2})\) as:

\[
\begin{bmatrix}
\sigma_{A_1}^2 & \sigma_{A_1}A_2 & \sigma_{A_1}B_1 & \sigma_{A_1}B_2 \\
\sigma_{A_1}A_2 & \sigma_{A_2}^2 & \sigma_{A_2}B_1 & \sigma_{A_2}B_2 \\
\sigma_{A_1}B_1 & \sigma_{A_2}B_1 & \sigma_{B_1}^2 & \sigma_{B_1}B_2 \\
\sigma_{A_1}B_2 & \sigma_{A_2}B_2 & \sigma_{B_1}B_2 & \sigma_{B_2}^2
\end{bmatrix} = \tau
\] (16)

Assume also that higher-order moments are of order \(\tau^n\) or smaller.

In order to obtain a limiting system of differential equations, some assumption about the order of magnitude of \(R\) (the probability of a recombination between the \(A\) and \(B\) loci) must be introduced. The most informative assumption is to let \(R=0(\tau)\) as \(\tau \to 0\). Introduce the new parameter \(r\) by

\[
R = r\tau,
\]

then, as \(\tau \to 0\), the system of difference equations (13) approaches the system of differential equations

\[
\begin{align*}
\dot{x}_1 &= \frac{1}{2}x_1 (q_1\phi_A + q_2\phi_B) - rD \\
\dot{x}_2 &= \frac{1}{2}x_2 (q_1\phi_A - p_2\phi_B) + rD \\
\dot{x}_3 &= \frac{1}{2}x_3 (-p_1\phi_A + q_2\phi_B) + rD \\
\dot{x}_4 &= \frac{1}{2}x_4 (-p_1\phi_A - p_2\phi_B) - rD
\end{align*}
\] (17)
where
\[ \phi_A = \Delta \Gamma_A + \sigma_A^2 \left( \frac{1}{2} - p_1 \right) - p_2 \left( \sigma_{A_1B_1} - \sigma_{A_2B_1} \right) + q_2 \left( \sigma_{A_2B_2} - \sigma_{A_1B_2} \right) \]
\[ \phi_B = \Delta \Gamma_B + \sigma_B^2 \left( \frac{1}{2} - p_2 \right) - p_1 \left( \sigma_{A_1B_1} - \sigma_{A_1B_2} \right) + q_2 \left( \sigma_{A_2B_2} - \sigma_{A_2B_1} \right) \]
\[ \Delta \Gamma_A = (\mu_{A_1} - \frac{1}{2} \sigma_A^2) - (\mu_{A_2} - \frac{1}{2} \sigma_A^2) \]
\[ \Delta \Gamma_B = (\mu_{B_1} - \frac{1}{2} \sigma_B^2) - (\mu_{B_2} - \frac{1}{2} \sigma_B^2) \]
\[ \sigma_A^2 = \sigma_{A_1}^2 + \sigma_{A_2}^2 - 2 \sigma_{A_1A_2} \]
\[ \sigma_B^2 = \sigma_{B_1}^2 + \sigma_{B_2}^2 - 2 \sigma_{B_1B_2} \]
\[ p_1 = (1 - q_1) = x_1 + x_2 \]
\[ p_2 = (v - q_2) = x_1 + x_3 \]
\[ D = x_1x_4 - x_5x_3 \]

This system may be transformed into one \( P_1, P_2, \) and \( D \) as follows:
\[ \dot{p}_1 = \frac{1}{2} p_2 q_1 \phi_A + \frac{1}{2} D \phi_B \]
\[ \dot{p}_2 = \frac{1}{2} p_2 q_2 \phi_B + \frac{1}{2} D \phi_A \]
\[ \dot{D} = \frac{1}{2} D \left[ (q_1 - p_1) \phi_A + (q_2 - p_2) \phi_B - 2r \right] . \]

The major points of this paper may be illustrated most simply by a special case involving a high degree of symmetry in the second-order moments. Let
\[ \sigma_{A_1}^2 = \sigma_{A_2}^2 = \sigma_{B_1}^2 = \sigma_{B_2}^2 = \sigma^2 \]
\[ \sigma_{A_1A_2} = \sigma_{B_1B_2} = \rho \sigma^2 \]
\[ \sigma_{A_1B_1} = \sigma_{A_2B_2} = \sigma_{A_1B_2} = \sigma_{A_2B_1} = \rho \sigma^2 . \]

For these parameters the covariance matrix will be positive definite if and only if
\[ |\alpha| < 1 \]
\[ |\rho| < \frac{|1 - \alpha|}{2} . \]

(See Appendix II.)
The functions $\phi_A$ and $\phi_B$ may now be written in a more informative fashion:

$$\phi_A = \Delta \Gamma_A + 2\sigma^2(1-\alpha) \left( \frac{1}{2} - p_1 \right) + 4\sigma^2 \rho \left( \frac{1}{2} - p_2 \right)$$

$$\phi_B = \Delta \Gamma_B + 2\sigma^2(1-\alpha) \left( \frac{1}{2} - p_2 \right) + 4\sigma^2 \rho \left( \frac{1}{2} - p_1 \right)$$

(22)

The role of the correlation between loci, $\rho$, can be most dramatically illustrated by considering a case where the $A$, allele is fixed due to a tremendous selective advantage over $A,$ and the random variables $U_{B_1}$ and $U_{B_2}$ have the same geometric means. That is, let

$$\Delta \Gamma_A \rightarrow \infty$$

$$\Delta \Gamma_B = 0 \quad \alpha = 0$$

(23)

Then, at equilibrium

$$\hat{p}_1 = 1, \quad D = 0$$

$$\hat{p}_2 = \frac{1}{2} - \rho$$

(24)

Clearly (21) assures that $0 < p_2 < 1$. It is easy to verify that this equilibrium is stable. Obviously, if $\rho$ is positive, allele $B_2$ has an advantage over $B_1$ in the sense that $\hat{p}_2 < \frac{1}{2}$. If $\rho < 0$, the opposite is true. The reason for this is simple but fundamental to the rest of this paper. By fixing $A_1$, the problem is reduced to one of a single segregating locus with a specified "genetic background", $A,A,,$. The variance in fitness of the $B_1B_1$ homozygote is, therefore, $2\sigma^2(1+\rho)$ which increases as $\rho$ increases while that of $B_2B_2$ is $2\sigma^2(1-\rho)$ which clearly decreases with $\rho$. In random-environment models, increasing the variance in fitness across environments lowers the overall fitness of a genotype (e.g., GILLESPIE and LANGLEY 1974). This explains the reduction of $\hat{p}_2$ with increasing $\rho$. This interaction between the loci is due to the correlations of fitness between alleles over patches; thus it is quite different from epistasis as it is conventionally defined. We have here an entirely new principle for understanding the integration and coadaptation of genotypes, one that is only present if environments fluctuate, but one that of necessity will occur if they do fluctuate.

Returning to the system (22), one internal equilibrium, if it exists, may be written

$$\hat{p}_1 = \frac{1}{2} + \frac{\Delta \Gamma_A(1-\alpha) - 2\rho \Delta \Gamma_B}{2\sigma^2(1-\alpha)^2 - 8\sigma^2 \rho^2}$$

$$\hat{p}_2 = \frac{1}{2} + \frac{\Delta \Gamma_B(1-\alpha) - 2\rho \Delta \Gamma_A}{2\sigma^2(1-\alpha)^2 - 8\sigma^2 \rho^2}$$

$$\hat{D} = 0$$

(25)
We will examine in detail only the case where $\Delta \Gamma_A = \Delta \Gamma_B$, in which case the corresponding internal symmetric equilibrium exists if and only if

$$|\Delta \Gamma| < \sigma^2 [(1-\alpha) + 2\rho]$$

where

$$\Delta \Gamma_A = \Delta \Gamma_B = \Delta \Gamma$$

This equilibrium may be written

$$\dot{\hat{\rho}} = \hat{\rho}_1 = \hat{\rho}_2 = \frac{1}{2} + \frac{\Delta \Gamma}{2\sigma^2 [(1-\alpha) + 2\rho]}$$

$$D = 0$$

As far as we have been able to determine, this is the only internal equilibrium, although others might exist. The eigenvalues for the matrix arising from the linear approximation of (22) near the equilibrium are

$$\lambda_1 = -\hat{\rho} (1-\hat{\rho}) \sigma^2 [(1-\alpha) - 2\rho]$$

$$\lambda_2 = -\hat{\rho} (1-\hat{\rho}) \sigma^2 [(1-\alpha) - 2\rho]$$

$$\lambda_3 = -\rho$$

The condition for positive definiteness of the covariance matrix assures that all three eigenvalues are negative and thus the equilibrium is stable. All of the fixed points involving fixation of one or both alleles in this model are unstable if condition (26) is satisfied. For the case $\Delta \Gamma_A = \Delta \Gamma_B$, therefore, both loci will segregate or fix depending on the values of the parameters. In no case will there be a stable point involving one fixed and one segregating locus.

This result shows the irrelevance of linkage to the steady state. This is not surprising since the basic model is additive. Linkage will affect the rate of approach to equilibrium, however, as shown by $\lambda^3 = -\rho$.

The interaction of $\Delta \Gamma$, $\rho$, and $\alpha$ may be visualized more easily by referring to the following diagram of the correlations:

![Diagram of correlations]

Suppose, for the sake of argument, that $\Delta \Gamma > 0$. Then loosely speaking, alleles $A_1$ and $B_1$ have an average advantage and, in the absence of inter-locus correlations (i.e., $\rho = 0$), will be more frequent at equilibrium than $A_2$ and $B_2$. If, however, we introduce a small positive inter-locus correlation (i.e., let $\rho > 0$), we are increasing the variance of the fitness of the $A_1A_1B_1B_1$ homozygote across environments and thus lowering its overall fitness. Since, before introducing the correlation this genotype was composed of the alleles with the higher overall fitnesses, the effect of the new correlation is to make polymorphism more likely. Conversely, if $\rho$ is made negative, the variance of $A_1A_1B_1B_1$ decreases relatively and its fitness is enhanced. This encourages monomorphism.
In the next section, we will be examining the extension of the symmetric case to an arbitrary number of loci. To set the stage for this, consider two contrasting cases for the two-locus model. If we group the alleles, one from each locus, in such a way that those within each group are mutually positively correlated, and those between groups are mutually negatively correlated, we get two such groupings:

\[ \{A_1, B_1\} \text{ vs. } \{A_2, B_2\} \]

and

\[ \{A_1, B_2\} \text{ vs. } \{A_2, B_1\} \]

In the first case, the two alleles with the highest overall fitness are together. In the second, they are in opposite groups. Assuming that all intragroup correlations are equal to \( \rho > 0 \), and all intergroup correlations are \(-\rho \) (thus, \( \alpha = -\rho \)), then the first grouping, diagrammed as

\[
\begin{array}{c}
A_1 \\
\downarrow \rho \\
A_2 \\
\uparrow \rho
\end{array}
\begin{array}{c}
B_1 \\
\downarrow -\rho \\
B_2 \\
\uparrow -\rho
\end{array}
\]

will be polymorphic providing

\[
|\Delta \Gamma| < \sigma^2 [1 + 3\rho]
\] (29)

while the second grouping,

\[
\begin{array}{c}
A_1 \\
\downarrow -\rho \\
A_2 \\
\uparrow -\rho
\end{array}
\begin{array}{c}
B_1 \\
\downarrow \rho \\
B_2 \\
\uparrow \rho
\end{array}
\]

will be polymorphic if

\[
|\Delta \Gamma| < \sigma^2 [1 - \rho]
\] (30)

Polymorphism is easier in the first case—easier, in fact, than if there were no correlation between loci, but an interallelic correlation of \( \alpha = -\rho \). Thus the effect of adding loci when the fitnesses of the alleles with the “higher average fitnesses” are positively correlated is to make polymorphism more likely. Conversely, if the alleles with the “higher average fitnesses” are negatively correlated, their advantages are enhanced and they are more likely to take over in the population. An interesting consideration arises, however, if we extend this observation to more loci. It becomes impossible to have a large number of alleles whose fitnesses are all mutually negatively correlated and to simultaneously have the correlations remain appreciable. On the other hand, it is natural to think that the alleles may fall into two groups, those within each group being mutually negatively correlated. The consequences of this will be examined next.
MORE LOCI

The differential equations for a large number of loci are very complex with a high dimensionality. However, the two-locus case shows the irrelevance of linkage disequilibrium and linkage to the final equilibrium state; so we can safely assume that in multi-locus extensions with moderate linkage the disequilibria for all combinations of loci will be zero at equilibrium. In fact, we can obtain a zero disequilibrium system of differential equations as a bone fide limit from the RLM difference equation if, instead of assuming \( R = 0(\tau) \), we keep \( R \) a fixed constant as \( \tau \to 0 \). This corresponds to the biologically reasonable case of moderate linkage (\( R = 0.01 \) - 0.1) and weak selection (\( \approx 0.001 \) - 0.01).

We will only display these differential equations for certain symmetric additive models. Consider a case with \( m \) loci, each with two alleles. The alleles will be notated \( A_{ij} \), \( i = 1, 2; j = 1, 2, \ldots, m \); referring to the \( i \)th allele at the \( j \)th locus. The random variable giving the contribution of the \( i \)th allele at the \( j \)th locus to the fitness of the genotype \( n \)th patch will be notated \( U_{ij}(n) \). The same sort of assumptions about the order of magnitudes of the first two moments of the \( U_{ij}(n) \) will be made as in the previous section. If the correlation of \( U_{ik} \) and \( U_{il} \) is \( p \) (this having the form \( p_{alleles}^{\text{alleles}} \)) the assumption of fixed \( R \) as \( \tau \to 0 \) takes the RLM difference equations into the system of differential equations

\[
\dot{p}_i = \frac{1}{2} p_i q_i \left[ \Delta \Gamma_i + 2\sigma^2 (1-\alpha_i) \left( \frac{1}{2} - p_i \right) - \sigma^2 \sum_{j \neq i}^m [p_j (\rho_{ij}^{11} - \rho_{ij}^{21}) - q_j (\rho_{ij}^{22} - \rho_{ij}^{12})] \right]
\]

if

\[ \text{Var} \ U_{ij}(n) = \sigma^2 \tau \text{ for all } i, j. \]

The cases of immediate interest are those patterns of correlations which lead to groupings of alleles into mutually positively correlated sets—the motivation of this grouping coming from the notion that there may be a few environmental variables such as temperature, pH, etc., which affect the alleles at a large number of loci. If, for example, all the \( A_{ij} \) alleles do better in warmer temperatures, and all the \( A_{ij} \) alleles do better in colder temperatures, then \( U_{ik} \) and \( U_{jl} \) will be positively correlated and \( U_{ik} \) and \( U_{jl} \), \( i \neq j \), will be negatively correlated. This grouping may be written

\[
\{A_{11}, A_{12}, A_{13}, \ldots\} \text{ vs. } \{A_{21}, A_{22}, A_{23}, \ldots\}.
\]

If we assume that the within-group correlations are all the same and equal to \( \rho \), and that the between-group correlations are all equal and equal to \( -\rho \), then (31) becomes

\[
\dot{p}_i = p_i q_i \left[ \Delta \Gamma_i + 2\sigma^2 (1+\rho) \left( \frac{1}{2} - p_i \right) + 4\sigma^2 \rho \sum_{j \neq i}^m \left( \frac{1}{2} - p_j \right) \right].
\]

The remaining problem is to assign the \( \Delta \Gamma_i \) for the various loci. This will be easier if we assume that \( |\Delta \Gamma_i| = \Delta \Gamma \) for all \( i \). This imposes another partitioning of the alleles into those with an “average selective advantage” (i.e., \( \Delta \Gamma > 0 \)) and those with an “average disadvantage” (i.e., \( \Delta \Gamma < 0 \)). Since linkage plays no role
in this development, we can assume, without loss of generality, that $\Delta \Gamma_i = \Delta \Gamma > 0$ for $i=1,2, \ldots, k$, and $\Delta \Gamma_i = -\Delta \Gamma$ for $i=k+1, k+2, \ldots m$. Then, at equilibrium the following pair of equations will be satisfied.

$$\Delta \Gamma + 2\sigma^2 (1+\rho) \left( \frac{1}{2} - \hat{\rho} \right) + 4\sigma^2 \rho (k-1) \left( \frac{1}{2} - \hat{\rho} \right) + 4\sigma^2 \rho (m-k) \left( \frac{1}{2} - \hat{\rho^*} \right) = 0$$

$$-\Delta \Gamma + 2\sigma^2 (1+\rho) \left( \frac{1}{2} - \hat{\rho^*} \right) + 4\sigma^2 \rho k \left( \frac{1}{2} - \hat{\rho} \right) + 4\sigma^2 \rho (m-k-1) \left( \frac{1}{2} - \hat{\rho^*} \right) = 0,$$

(33)

where, at equilibrium

$$p_i = \hat{\rho} \quad i = 1, 2, \ldots, k$$

$$p_i = \hat{\rho^*} \quad i = k+1, \ldots, m$$

(34)

The solution is

$$\hat{\rho} = \frac{1}{2} + \Delta \Gamma \frac{(1-\rho) + 4\rho (m-k)}{2\sigma^2(1-\rho) [(1-\rho) + 2\rho m]} > \frac{1}{2}$$

$$\hat{\rho^*} = \frac{1}{2} + \Delta \Gamma \frac{(1-\rho) + 4\rho k}{2\sigma^2(1-\rho) [(1-\rho) + 2\rho m]} < \frac{1}{2}.$$  

(35)

If, for some reason, $k=m$, then all of the $A_{ij}$ alleles will have a mean advantage, and

$$\hat{\rho} = \frac{1}{2} + \Delta \Gamma \frac{\sigma^2}{2\sigma^2 [(1-\rho) + 2\rho m]}$$

(36)

providing

$$|\Delta \Gamma| < \sigma^2 (1-\rho) + 2\rho m.$$  

(37)

Obviously, as loci are added the affect of inter-locus correlations is to make polymorphism more likely, and to make the allele frequencies adhere closely to $1/2$. The same occurs if $k=0$. These cases may not be entirely unrealistic. If, for example, the $A_{ij}$ alleles are all better in warmer temperatures, and if the $A_{ij}$ are better in colder temperatures (thus assuring $\rho>0$), then a slight mean shift up in temperature may give all the $A_{ij}$ an average advantage, and thus lead to the situation above. This is the most favorable for polymorphism since the advantages of a positive $\Delta \Gamma$ for the $A_{ij}$ alleles are countered by the disadvantage of their fitnesses being positively correlated.

If $k=m/2$

$$\hat{\rho} = \frac{1}{2} + \Delta \Gamma \frac{\sigma^2}{2\sigma^2 (1-\rho)}$$

(38)

providing

$$|\Delta \Gamma| < \sigma^2 (1-\rho).$$  

(39)

corresponding exactly to (30) of the previous section. This is the least favorable condition for polymorphism and remarkably in this case the conditions stay the same no matter how many loci are added.
The cases \( k=0, m/2 \) and \( m \) suggest that polymorphism is least likely when \( k=m/2 \), and increases in likelihood as \( k \) deviates from \( m/2 \). This can be easily shown if we assume \( m, k, \) and \( m-k \) are all very large but finite. In this case (35) becomes approximately

\[
\hat{\rho} \approx \frac{1}{2} + \frac{\Delta \Gamma}{\sigma^2(1-\rho)} \left( \frac{m-k}{m} \right)
\]

\[
\hat{\rho}^* \approx \frac{1}{2} - \frac{\Delta \Gamma}{\sigma^2(1-\rho)} \left( \frac{k}{m} \right)
\]

This can be easily shown if we assume \( m, k, \) and \( m-k \) are all very large but finite. In this case (35) becomes approximately

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\]

\[
\hat{\rho}^* \approx \frac{1}{2} - \frac{\Delta \Gamma}{\sigma^2(1-\rho)} \left( \frac{k}{m} \right)
\]

corresponding to an average heterozygosity of

\[
\bar{H} = \frac{k}{m} 2\hat{\rho} (1-\hat{\rho}) + \frac{m-k}{m} 2\hat{\rho}^* (1-\hat{\rho}^*)
\]

\[
= \frac{1}{2} - \left[ \frac{\Delta \Gamma}{\sigma^2(1-\rho)} \right]^2 \frac{k}{m} \left( 1-\frac{k}{m} \right)
\]

Obviously \( \bar{H} \) increases with \( |k - \frac{m}{2}| \).

**DISCUSSION**

The most exciting aspect of the results reported here concerns the role of the correlations in fitness between alleles at different loci in the final genetic makeup of the population. To put the results in the context of previous studies, it is important to note that the work on constant fitness models has led to a belief that in additive models two things invariably hold: (1) there is zero linkage disequilibrium at the dynamic equilibrium and (2) the equilibria at the separate loci are exactly those predicted from single-locus considerations.

Our model is also additive, and in common with the constant fitness model \( D=0 \) at equilibrium. But unlike the constant fitness model, the final genetic makeup depends on a complex multi-locus behavior which is caused by the correlations in fitnesses across environments. Surprisingly, the ultimate (i.e., equilibrium) expression of this complex behavior is not in the non-random association of alleles on chromosomes, but rather in the allele frequencies. This is most dramatically illustrated in (24).

The principle operating in this model is a simple one: if two alleles at two different loci have fitnesses \( U_{ij}(n) \) which are negatively correlated across patches, their overall fitnesses will be enhanced over what they would be if there were no such correlation. The enhancement comes from the reduction in the variance in fitness of these two alleles across environments. It is natural to inquire whether these postulated correlations exist in natural populations. Many lines of thought all point to their probable existence, if environmental fluctuations do, in fact, affect fitnesses. The simplest instances involve any environmental parameter which is likely to affect a broad category of enzymes. Temperature, humidity, mineral and hydrogen ion concentrations, etc., all have a
potential differential affect on different alleles at all loci and will lead naturally to a high correlation between loci due to the ordered nature of the parameters. Less obvious are factors which may affect enzymes participating in a single pathway. For example, in the oxidation of alcohols it is easy to envision that one allele in an alcohol dehydrogenase may work on one category of alcohols, the other allele on another category. The same may be true for an aldehyde oxidase which works on the product of the alcohol dehydrogenase reaction with the same categorization of compounds. Thus fluctuations in the qualitative nature of alcohols in the environment will lead to highly correlated fluctuations in fitnesses of the alleles at the two loci. Similar reasoning will lead to many other ways in which the correlations could crop up. The two cases mentioned, however, illustrate two extreme situations—one where we would expect a very large number of loci to be involved, the other a very few. The former case has a greater consequence in the genetic structure of populations since it leads to the categorization of alleles into sets of alleles within which the fitnesses are positively correlated and between which they are negatively correlated. Using the results of the previous section, we could then characterize the polymorphic state in this situation as one where the more common alleles are more likely to be positively correlated in their fitnesses than the less common alleles. This prediction is certainly open to experimental verification if the relevant environmental parameter can be identified.

LITERATURE CITED


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Corresponding editor: R. C. LEWONTIN

APPENDIX I

In this Appendix, we will sketch the derivation of the system of differential equations (17). Using the fitness matrix (13), we can immediately write down the expression for the change in the frequencies of the four gametes in the $j^{th}$ patch:

\[
\Delta x_{1j} = \frac{x_{1}[q_{1}A(j) + q_{2}B(j)] - 2RW_{22}(j)D}{2\bar{w}(j)}
\]

\[
\Delta x_{2j} = \frac{x_{2}[q_{1}A(j) - p_{2}B(j)] + 2RW_{22}(j)D}{2\bar{w}(j)}
\]

\[
\Delta x_{3j} = \frac{x_{3}[-p_{1}A(j) + q_{2}B(j)] + 2RW_{22}(j)D}{2\bar{w}(j)}
\]

\[
\Delta x_{4j} = \frac{x_{4}[-p_{1}A(j) - p_{2}B(j)] - 2RW_{22}(j)D}{2\bar{w}(j)}
\]  

(I-1)
The three ratios which appear repeatedly in these expressions are:

\[
\Phi_A = \frac{A(j)}{\bar{W}(j)}, \quad \Phi_B = \frac{B(j)}{\bar{W}(j)}, \quad \Phi_R = \frac{RW_{xx}(j)}{\bar{W}(j)} \tag{I-3}
\]

As an example of the expansions used, consider the ratio \( \Phi_A \). If \( \bar{W} \) is expanded as a geometric series, \( \Phi_A \) may be written

\[
\Phi_A = A(j) \left[ 1 - \delta + \delta^2 - \ldots \right]. \tag{I-4}
\]

The expectation of this over environments may be written

\[
E\Phi_A = \phi_A \tau + O(\tau^2) \tag{I-5}
\]

if the assumptions (15) are used. Since \( R = r \tau \),

\[
E\Phi_R = ERW_{xx}(j) \left[ 1 - \delta + \delta^2 - \ldots \right] = r\tau + O(\tau^2). \tag{I-6}
\]

As in the one-locus case, we can write (14) as

\[
\begin{align*}
x_1(t+\tau) - x_1(t) &= \frac{1}{2} [x_1(q_1\phi_A + q_2\phi_B) - 2rD]\tau + O(\tau^2) \\
x_2(t+\tau) - x_2(t) &= \frac{1}{2} [x_2(q_1\phi_B - p_2\phi_B) + 2rD]\tau + O(\tau^2) \\
x_3(t+\tau) - x_3(t) &= \frac{1}{2} [x_3(-p_1\phi_A + q_2\phi_B) + 2rD]\tau + O(\tau^2) \\
x_4(t+\tau) - x_4(t) &= \frac{1}{2} [x_4(-p_1\phi_B - p_2\phi_B) - 2rD]\tau + O(\tau^2)
\end{align*}
\]

which leads to (17) as \( \tau \to 0 \).

**APPENDIX II**

We wish to show that for the symmetrical parameters (20), the matrix \( C \) is positive definite if and only if the conditions (21) are met. The matrix \( C \) can be written

\[
\sigma^2 \begin{bmatrix}
1 & \alpha & \rho & -\rho \\
\alpha & 1 & -\rho & \rho \\
\rho & -\rho & 1 & \alpha \\
-\rho & \rho & \alpha & 1
\end{bmatrix} = \sigma^2 C^*. 
\]
C will be positive definite if and only if $C^*$ is positive definite. The usual criterion for positive definiteness is that the determinants of the leading principle minors be positive. For $C^*$ this gives

\[ D_1 = 1 > 0 \]  \hspace{1cm} (II-1)

\[ D_2 = \begin{vmatrix} 1 & \alpha \\ \alpha & 1 \end{vmatrix} = \alpha > 0 \]  \hspace{1cm} (II-2)

\[ D_3 = \begin{vmatrix} 1 & \alpha & -\rho \\ \alpha & 1 & -\rho \\ -\rho & -\rho & 1 \end{vmatrix} = (1+\alpha) (1-\alpha-2\rho^2) > 0 \]  \hspace{1cm} (II-4)

\[ D_4 = |C^*| = (1+\alpha)^2 \left[ (1-\alpha)^2 - 4\rho^2 \right] > 0 \]  \hspace{1cm} (II-4)

Obviously II-1 is satisfied. II-2 gives $|\alpha| < 1$, which is the first condition in (21). II-3 gives $\rho^2 < \frac{1-\alpha}{2}$, while II-4 gives $\rho^2 < \frac{(1-\alpha)^2}{4}$. If II-2 and II-4 hold, then so does II-3. Taking the positive square root of II-4 gives the second condition in (21).