AN n LOCUS MULTIALLELE MODEL FOR GENE SUBSTITUTION

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ABSTRACT

We discuss the conceptual conflict between a slow series of gene substitutions as the mechanism of evolutionary change, and the apparent need for rapid and coordinated changes at many loci simultaneously in producing complex adaptations. To improve on the limitations of classical theory and accommodate the enormous amount of variability disclosed by electrophoretic studies, we develop a model that can deal with gene substitution at n loci, with numerous alleles at each locus. Fitness is treated somewhat differently from the usual way by allowing it to vary between zero and the number of offspring an individual of a particular species can produce. As maximum fitnesses, we chose five as typical of large mammals, 100 for insects like Drosophila, and 1000 for very prolific species. When our model is applied to the classical problem of determining the number of generations required to change the gene frequency from 0.0001 to 0.9999 (but for 100 loci rather than one), we find that it requires 22,899 generations when maximum fitness is five, 7,984 generations when maximum fitness is 100 and 5,333 generations when it is 1000. This is something of an improvement over the 300,000 generations calculated by HALDANE (1957). By allowing the fitnesses in our model to be explicitly frequency dependent, these results are reduced considerably. In addition, allowing varying proportions of the population to inbreed reduces the number of generations required for the classical problem by as much as 50%. We also point out that, given the large amount of observed genetic variation, evolutionary change may not be so much a matter of classical gene substitution as it is of changing from one array of alleles to another. With our model, the array (0.5, 0.15, 0.2, 0.1, 0.05) can be changed to (0.03, 0.1, 0.2, 0.17, 0.5) at 1000 loci in 6,043, 2,108, or 1,408 generations, depending on whether the maximum fitness is five, 100, or 1000. Finally, we note that it is possible to substitute one array for another while continuously favoring heterozygotes.

FROM the time of Charles Darwin to the present, evolution has been considered by most evolutionists to be a slow, gradual process. When the neo-Darwinian view that evolutionary change involves a series of gene substitutions became generally accepted, the concept that it is a slow process remained unaltered. HALDANE’s (1957) classic paper on the cost of natural selection is widely cited and generally concurred with. He concluded that the average rate of gene substitution is only one per 300 generations and that the number of deaths required is 30 times the population size. Nevertheless, in recent years there has been an increasing awareness that some major difficulties are posed by this view. A number of cases have been documented in which extensive changes have occurred...

in a much shorter period of time than would be conceivable with Haldane’s limitation (Mayr 1975). The observed rate of amino acid substitution in several proteins is in direct conflict with Haldane’s calculations (Kimura 1968). Furthermore, it has become increasingly obvious that the origin of complex characters and complex adaptations require delicately balanced interactions of batteries of genes that are hard to understand in terms of simple gene substitution.

Models based on the classical concept of multiplicative fitnesses can neither explain the amount of heterozygosity apparently present in natural populations nor allow for rapid gene substitution. In the classical problem where rare alleles are to be substituted for abundant ones, the major difficulty is that the reproductive rates of organisms are not great enough to offset the extremely low chance for an offspring simultaneously to transmit many of its rare alleles. However, the fact that there may be many alleles present at each locus may change the magnitude of the problem. Gene substitution may no longer mean replacing a gene that makes up 99.99% of the gene pool with one that constitutes only 0.01%. Instead, it is necessary to talk about replacing one distribution or array of alleles \((p_A, p_B, \ldots, p_T)\) with a different distribution or array of alleles \((p'_A, p'_B, \ldots, p'_T)\). Such changes can take place more easily than classical gene substitution and have the property of maintaining heterozygosity. When dealing with many loci, this is similar to the shifting balance theory of Wright (1931, 1970).

In this paper, we consider a multilocus, multiallele model and discuss the substitution of one array for another. We also consider the classical model and make modest improvements on it by taking into account the reproductive rates of various organisms, as well as inbreeding.

**The Model**

We consider \(n\) independent loci where for the \(i\)th locus there are several alleles, \(A_i, B_i, \ldots, T_i\). Our approach to fitness is somewhat classical. We shall assume that a proportion of each genotype will suffer random deaths that are independent of the genotype and, therefore, nonselective. In addition, there will be selective deaths that are genotype dependent. These involve the ability of the individual to cope with the physical and climatic features of its environment, to compete with individuals of other species that may utilize a common resource, and to compete with other conspecific individuals of different genotype at this locus. We allow the population size to vary, but we place an upper limit on its size corresponding to the carrying capacity of the environment. Consequently, the fitnesses will be both genotype and frequency dependent. We assume that generations are nonoverlapping.

For one locus, we use the following notation:

- \(p_A, p_B, \ldots, p_T\) are the proportion of alleles \(A, B, \ldots, T\), respectively;
- \(N\) is the population size;
- \(R\) is the number of offspring per individual;
- \(1-E\) is the proportion of offspring surviving (to reproduction) nonselective deaths; and
- \(1-S_x\) is the proportion of the offspring that are of genotype \(x\) that survive (to reproduction) selective deaths. (Here, \(x\) can be any of the genotypes, \(AA, AB, \ldots, TT\).)
Then, \((1-E)(1-S_x)\) is the proportion of those offspring of genotype \(x\) that survive to reproduction, that is, the relative fitness of genotype \(x\). If we multiply this by \(R\), the number of offspring per individual, we get \(W_x = R(1-E)(1-S_x)\), the absolute fitness of genotype \(x\), which is the average number of offspring (per individual) of genotype \(x\) that survive to reproduction. The average fitness of the population is:

\[
\bar{W} = p^2_A W_{AA} + \ldots + p^2_T W_{TT} + 2p_A p_B W_{AB} + \ldots + 2 p_s p_T W_{ST}.
\]  

(1)

Using this notation, we can describe the population changes from one generation to the next. If the present population changes from \(N\) to \(N'\) in the next generation, we shall write \(N \rightarrow N'\). As a result we have:

\[
N \rightarrow N \bar{W}.
\]  

(2)

We assume that if the population size approaches a value \(M\), which is the maximum size the environment can support, the proportion of nonselective deaths will increase to the point where \(\bar{W} = 1\).

To keep track of how the genotypic structure changes from generation to generation, we use the gene frequency ratios

\[
\lambda_A = \frac{p_A}{p_T}, \quad \lambda_B = \frac{p_B}{p_T}, \ldots, \quad \lambda_s = \frac{p_s}{p_T}.
\]

(These ratios generalize the usual gene frequency ratio \(\lambda = \frac{p_A}{q} \). Here \(p_A = \frac{\lambda_A}{\lambda_A + \ldots + \lambda_s + 1}\), \(\ldots, p_s = \frac{\lambda_s}{\lambda_A + \ldots + \lambda_s + 1}\), and \(p_T = \frac{1}{\lambda_A + \ldots + \lambda_s + 1}\), so that knowing \(\lambda_A, \ldots, \lambda_s\) is sufficient.) We are interested in how long it takes for a given initial array of gene frequency ratios \((\lambda_A, \ldots, \lambda_s)\) to change to a different array \((\lambda_A', \ldots, \lambda_s')\). In the \(n\)-locus case, there will be an array for each locus.

The proportion of each allele changes from one generation to the next as follows:

\[
p_A \rightarrow p_A' = \frac{(W_{AA} p^2_A + W_{AB} p_A p_B + \ldots + W_{AT} p_A p_T) / \bar{W}}{W}
\]

\[
p_T \rightarrow p_T' = \frac{(W_{AT} p_A p_T + \ldots + W_{TT} p_s p_T + W_{TT} p_T^3) / \bar{W}}{W}.
\]

If we now express these changes in terms of the gene frequency ratios, we obtain:

\[
\lambda_A \rightarrow \lambda_A' = \frac{p_A'}{p_T'} = \lambda_A \left[ \frac{\lambda_A W_{AA} + \lambda_B W_{AB} + \ldots + \lambda_s W_{AS} + W_{AT}}{\lambda_A W_{AT} + \lambda_B W_{BT} + \ldots + \lambda_s W_{ST} + W_{TT}} \right], \quad (3A)
\]

\[
\lambda_s \rightarrow \lambda_s' = \frac{p_s'}{p_T'} = \lambda_s \left[ \frac{\lambda_A W_{AS} + \lambda_B W_{BS} + \ldots + \lambda_s W_{SS} + W_{ST}}{\lambda_A W_{AT} + \lambda_B W_{BT} + \ldots + \lambda_s W_{ST} + W_{TT}} \right]. \quad (3S)
\]

In the \(n\)-locus case, there will be a set of these equations for each locus.
In order to continue with the analysis, we must make some assumptions about the fitnesses, \( W_x \). The simplest assumption is that the fitnesses are multiplicative. That is, at each locus there are numbers, \( \beta, \gamma, \ldots, \sigma, \tau \), that compare the fitness of each genotype with \( W_{AA} \), the fitness of \( AA \). For the heterozygous genotypes \( AB, AC, \ldots, AT \), we assume \( W_{AB} = \beta W_{AA}, \ldots, W_{AT} = \tau W_{AA} \). For the other heterozygotes, \( W_{BC} = \beta \gamma W_{AA}, W_{BD} = \beta \delta W_{AA}, \ldots, W_{BT} = \sigma \tau W_{AA} \). And for the homozygotes, \( BB, \ldots, TT \), we assume \( W_{BB} = \beta^2 W_{AA}, \ldots, W_{TT} = \tau^2 W_{AA} \). The fitnesses at each locus are then multiplied together to produce the absolute fitness of each genotype.

The assumption of multiplicative fitnesses is mathematically convenient and considerably simplifies the analysis. Moreover, any set of measured fitnesses can be adjusted to be multiplicative by reducing the fitnesses of some genotypes. Our results (see Examples 1, 2 and 5) can thus be regarded as upper limits for a wide variety of nonmultiplicative situations. In addition, we do obtain numerical results directly with nonmultiplicative fitnesses (see Examples 3 and 4).

Using these assumptions about fitnesses, equation (1) becomes:

\[
\bar{W} = p_A^2 W_{AA} + p_B^2 \beta^2 W_{AA} + \ldots + p_T^2 \tau^2 W_{AA} + 2p_A p_B \beta W_{AA} + \ldots + 2p_A p_T \tau W_{AA},
\]

or

\[
\bar{W} = (p_A + \beta p_B + \ldots + \tau p_T)^2 W_{AA}. \tag{4}
\]

In the \( n \)-locus case, there is one of these terms for each locus, so that equation (1) becomes

\[
\bar{W} = \left( p_{A_1} + \beta_1 p_{B_1} + \ldots + \tau_1 p_{T_1} \right)^2 \ldots \left( p_{A_n} + \beta_n p_{B_n} + \ldots + \tau_n p_{T_n} \right)^2 \times W_{A_1 A_1} \times \ldots \times A_n A_n. \tag{5}
\]

Equation (3A) becomes

\[
\lambda_A \rightarrow \frac{\lambda_A \left( W_{AA} + \lambda_B \beta W_{AA} + \ldots + \lambda_S \sigma W_{AA} + \tau W_{AA} \right)}{\lambda_A \left( W_{AA} + \lambda_B \beta W_{AA} + \ldots + \lambda_S \sigma W_{AA} + \tau W_{AA} \right)}. \tag{6A}
\]

We can factor out a \( \tau \) from each term in the denominator. The remaining denominator will cancel with the numerator. In this way we get

\[
\lambda_A \rightarrow \frac{1}{\tau} \lambda_A. \tag{6A}
\]

Similarly,

\[
\lambda_B \rightarrow \frac{\beta}{\tau} \lambda_B. \tag{6B}
\]

\[
\lambda_S \rightarrow \frac{\sigma}{\tau} \lambda_S. \tag{6S}
\]

In the \( n \)-locus case, the gene frequency ratios will satisfy equations like this at each locus.
First, we consider the generalization of the classical gene substitution problem. We consider a population where at each locus the distribution of alleles is given by \((p_A, p_B, \ldots, p_T)\). For simplicity, we consider this distribution to be the same at each locus. We suppose some change in the environment has caused fitnesses to change and, in turn, the distribution of alleles will change from its present status to a different distribution \((p_A', p_B', \ldots, p_T')\). Equivalently, we assume the present distribution of gene frequency ratios is changing from \((\lambda_A, \ldots, \lambda_S)\) to \((\lambda_A', \ldots, \lambda_S')\). We wish to show that there are values of \(\beta, \gamma, \ldots, \sigma, \tau\) that will allow this to happen.

We assume that currently \(A_i\) is the most abundant allele at each locus, while \(T_i\) eventually will be. Therefore, \(A_1A_1 \times \ldots \times A_nA_n\) is the least fit genotype and \(T_1T_1 \times \ldots \times T_nT_n\) is the most fit. We require that the average absolute fitness is at least one in order to insure the continued existence of the population. Therefore, according to (5),

\[
W = (p_A + \beta p_B + \ldots + \sigma p_T + \tau p_T) \cdot W_{A_1A_1} \times \ldots \times A_nA_n = 1 .
\]

Thus, the fitness of the least fit will be

\[
W_{A_1A_1} \times \ldots \times A_nA_n = \frac{1}{(p_A + \beta p_B + \ldots + \tau p_T)^2} ,
\]

and the fitness of the most fit is

\[
W_{T_1T_1} \times \ldots \times T_nT_n = \frac{\tau^{2n}}{(p_A + \beta p_B + \ldots + \tau p_T)^2} .
\]

Clearly, now, the fitness of the most fit genotype cannot exceed the reproductive capacity of the organism. Thus,

\[
W_{T_1T_1} \times \ldots \times T_nT_n = \frac{\tau^{2n}}{(p_A + \beta p_B + \ldots + \tau p_T)^2} \leq R ,
\]

where \(R\) is the number of offspring per individual.

We now wish to find fitness coefficients \(\beta, \gamma, \ldots, \sigma, \tau\) and the number of generations, \(m\), needed to produce a change from \((\lambda_A, \ldots, \lambda_S)\) to \((\lambda_A', \ldots, \lambda_S')\). According to equations (6), the distribution of gene frequency ratios changes from generation to generation according to:

\[
(\lambda_A, \lambda_B ; \ldots, \lambda_S) \rightarrow \left(\frac{1}{\tau} \lambda_A, \frac{\beta}{\tau} \lambda_B, \ldots, \frac{\sigma}{\tau} \lambda_S\right) .
\]

Therefore, after \(m\) generations, the distribution will be:

\[
(\lambda_A', \lambda_B', \ldots, \lambda_S') = \left[\left(\frac{1}{\tau}\right)^m \lambda_A, \left(\frac{\beta}{\tau}\right)^m \lambda_B, \ldots, \left(\frac{\sigma}{\tau}\right)^m \lambda_S\right] .
\]

We first use (8) to find a \(\tau\) such that \(W_{T_1T_1} \times \ldots \times T_nT_n\) is no greater than
To make this possible, we replace $\beta, \ldots, \sigma$ by 1, thus increasing the value of the fraction and solve:

$$
\frac{\tau^{2n}}{(p_A + p_B + \ldots + p_S + \tau p_T)^{2n}} = R.
$$

The solution is:

$$
\tau = \frac{(p_A + \ldots + p_S) R^{1/2n}}{1 - p_T R^{1/2n}}.
$$

(If $p_T R^{1/2n} \geq 1$, there are alternative ways of determining $\tau$.)

We can now solve (9) for $m$, the number of generations required to change the distribution. The solution is:

$$
m = \log_e \left( \frac{\lambda_A'}{\lambda_A} \right) / \log_e \left( \frac{1}{\tau} \right).
$$

The other parts of (9) can now be solved for $\beta$, $\ldots$, $\sigma$.

$$
\beta = \tau \exp \left( \frac{1}{m} \log_e \left( \frac{\lambda_B'}{\lambda_B} \right) \right),
$$

(12B)

$$
\sigma = \tau \exp \left( \frac{1}{m} \log_e \left( \frac{\lambda_T'}{\lambda_T} \right) \right).
$$

(12S)

**Example 1—Classical two-allele model:** We first consider the classical problem in which the distribution $(p_A = 0.9999, p_T = 0.0001)$ is replaced by the distribution $(p_A' = 0.0001, p_T' = 0.9999)$ at 1000 loci. We consider three different values of $R$, the reproductive capacity. They are: $R = 5$ (humans), $R = 100$ (certain species of Drosophila) and $R = 1000$ (very prolific species). The results are displayed in Table 1 and somewhat improve traditional estimates. Note the very small “fitness differentials” $\tau$. For example, when the reproductive capacity is five, the value $\tau = 1.000805$ indicates that, for any two genotypes differing by a single allele, one will only be 0.08% more fit than the other. It is also of interest to compute the “expected fitness differential,” which is the average fitness differential between any two genotypes selected at random during the process of substitution. These values—1.182 when $R = 5$, 1.841 when $R = 100$ and 2.953 when $R = 1000$—show that, on the average, fitness differentials between any two members of the population are nowhere near the reproductive capacities.

**Table 1**

<table>
<thead>
<tr>
<th>$R$</th>
<th>$\tau$</th>
<th>$m$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>1.000805</td>
<td>22,889</td>
</tr>
<tr>
<td>100</td>
<td>1.00231</td>
<td>7,984</td>
</tr>
<tr>
<td>1000</td>
<td>1.00346</td>
<td>5,333</td>
</tr>
</tbody>
</table>
Example 2—Multiallele model; multiplicative fitness: We next consider the problem of changing one multiallele array to another. We begin with the distribution \((p_A = 0.5, p_B = 0.15, p_C = 0.2, p_D = 0.1, p_T = 0.05)\) at 1000 loci, and calculate the fitnesses and time required to change to the distribution \((p_A' = 0.03, p_B' = 0.1, p_C' = 0.2, p_D' = 0.17, p_T = 0.5)\).

The results are displayed in Table 2. Clearly, the number of generations required for such a change of distribution is considerably reduced.

Example 3—Multiallele model; nonmultiplicative fitnesses: There are other possible methods for assigning fitnesses that will accomplish the substitution of one distribution for another. As an example, consider a single locus where we wish to substitute \((p_A', p_B', p_C') = (0.1, 0.4, 0.5)\) for \((p_A, p_B, p_C) = (0.5, 0.4, 0.1)\).

By taking the fitnesses \(W_{AA} = 0.62, W_{BB} = 0.33, W_{CC} = 0.70, W_{AB} = 1.41, W_{AC} = 1.95, W_{BC} = 2.65\), the substitution can be accomplished in approximately 30 generations. The interesting point about this substitution is accomplished under conditions in which selection is for the heterozygotes and in which the limiting distribution is the equilibrium distribution for the population with the given fitness.

Example 4—Two-allele model; nonmultiplicative fitnesses: It is apparent that even though small fitness differentials led to some improvements in the length of time required for gene substitution, in the final analysis it is the magnitude of these differentials that plays a major role in evolution. Furthermore, the reproductive rate of the organism determines the maximum fitness differential that can exist between the most fit and the least fit genotypes. The use of multiplicative fitnesses, together with a large number of loci, results in small fitness differentials for “adjacent genotypes” (differing by a single allele). An alternative is to use nonmultiplicative frequency-dependent fitnesses that provide for relatively large differentials between abundant genotypes and small differentials among the others. During the process of gene substitution, such fitnesses produce a “logistic type fitness wave,” as illustrated for two loci in Table 3. These fitnesses in the \(3 \times 3\) fitness matrix were generated by the formula

\[
W(i, j) = 5 
\frac{4p_x^i p_y^j}{p_x^i p_y^j + 1} \quad \text{where} \quad 1 \leq i, j \leq 3.
\]

In order to insure that the appropriate fitness differentials are large enough,
Mix non multiplicatives and distributions of genotypes

**TABLE 3**

<table>
<thead>
<tr>
<th>Distribution</th>
<th>( A_1A_1 )</th>
<th>( A_1T_1 )</th>
<th>( T_1T_1 )</th>
<th>( A_1A_1 )</th>
<th>( A_2T_2 )</th>
<th>( T_2T_2 )</th>
<th>( A_1A_1 )</th>
<th>( A_1T_1 )</th>
<th>( T_1T_1 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitnesses</td>
<td>0.998</td>
<td>0.001</td>
<td>0.000</td>
<td>0.024</td>
<td>0.081</td>
<td>0.061</td>
<td>0.000</td>
<td>0.000</td>
<td>0.003</td>
</tr>
<tr>
<td>( A_1A_1 )</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.081</td>
<td>0.244</td>
<td>0.163</td>
<td>0.000</td>
<td>0.010</td>
<td>0.050</td>
</tr>
<tr>
<td>( A_1T_1 )</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.061</td>
<td>0.163</td>
<td>0.122</td>
<td>0.003</td>
<td>0.050</td>
<td>0.883</td>
</tr>
<tr>
<td>( T_1T_1 )</td>
<td>1.000</td>
<td>4.998</td>
<td>5.000</td>
<td>1.000</td>
<td>1.667</td>
<td>2.500</td>
<td>1.000</td>
<td>1.087</td>
<td>1.179</td>
</tr>
<tr>
<td>( A_1A_1 )</td>
<td>4.998</td>
<td>5.000</td>
<td>5.000</td>
<td>1.667</td>
<td>2.500</td>
<td>3.333</td>
<td>1.087</td>
<td>1.179</td>
<td>1.277</td>
</tr>
<tr>
<td>( A_1T_1 )</td>
<td>5.000</td>
<td>5.000</td>
<td>5.000</td>
<td>2.500</td>
<td>3.333</td>
<td>5.000</td>
<td>1.179</td>
<td>1.277</td>
<td>5.000</td>
</tr>
</tbody>
</table>

It is necessary to limit the number of loci. When the reproductive rate is five, the optimal number of loci is four. The fitnesses are given by the formula

\[
W(i, j, k, l) = \frac{5}{4p_T^i p_T^j p_T^k p_T^l + 1}, \quad \text{where} \quad 1 \leq i, j, k, l \leq 3.
\]

Using these, it is possible to carry out the classical gene substitution at all four loci in 31 generations. At this rate, the substitution could be carried out at 1000 loci in 7,750 generations, one-third the time required with multiplicative fitnesses. Similar improvements are possible for other reproductive rates.

**THE EFFECT OF INBREEDING**

We now wish to consider the effects of inbreeding on gene substitution. In a natural population, we would expect some proportion of the population to breed randomly, while the remaining fraction undergoes various degrees of inbreeding. In order to approximate this complex situation, we assume that a proportion \( 1 - \sigma \) of the population breeds randomly, and the remaining \( \sigma \) of the population self-fertilizes. Since self-fertilization is the most intense form of inbreeding, our results will be upper limits for other inbreeding schemes.

We first consider one locus with two alleles, \( A \) and \( B \). As before, we let \( W_x = R(1 - E)(1 - S_x) \) be absolute fitness of individuals of genotype \( x \).

Because, in this case, the population will not follow the Hardy-Weinberg Law, we must consider the frequencies of the genotypes. We let the initial frequencies of genotypes \( AA, AB \) and \( BB \) be \( f_{AA}, f_{AB} \) and \( f_{BB} \), respectively.

The fraction of the population that breeds randomly will follow the Hardy-Weinberg Law; the fraction that self-fertilizes will be equivalent to a haploid population.

Thus, the proportion of each genotype in the next generation will be:

\[
f_{AA} \rightarrow \frac{W_{AA}}{W} \left[ (1 - \sigma) \left( f_{AA}^2 + \frac{1}{4} f_{AB}^2 + f_{AA} f_{AB} \right) + \sigma (f_{AA} + \frac{1}{4} f_{AB}) \right]
\]

\[
f_{AB} \rightarrow \frac{W_{AB}}{W} \left[ (1 - \sigma) \left( \frac{1}{2} f_{AB}^2 + f_{AA} f_{AB} + 2f_{AA} f_{BB} + f_{AB} f_{BB} \right) + \frac{1}{2} \sigma f_{AB} \right]
\]
AN n LOcus MULTIALLELe MODEL

\[ f_{BB} \rightarrow \frac{W_{BB}}{\bar{W}} \left[ (1 - \sigma) \left( f_{BB}^2 + \frac{1}{4} f_{AB}^2 + f_{AB} f_{BB} \right) + \sigma (f_{BB} + \frac{1}{4} f_{AB}) \right] \] (13)

where \( \bar{W} \) is the average fitness of the population.

We can simplify equations (13) by rewriting them in terms of the gene ratio:

\[ \lambda = \frac{p_A}{p_B} = \frac{f_{AA} + \frac{1}{2} f_{AB}}{f_{BB} + \frac{1}{2} f_{AB}} \]

and the fixation index [WRIGHT]

\[ F = \frac{4f_{AA} f_{BB} - f_{AB}^z}{(2f_{AA} + f_{AB})(2f_{BB} + f_{AB})} . \]

The changes from one generation to the next can then be expressed by:

\[
\begin{align*}
(1 - \sigma) \left[ W_{AA} \lambda^2 + W_{AB} \lambda \right] + \sigma \left[ W_{AA} \lambda^2 + \frac{1}{2} (W_{AA} + W_{AB}) \lambda + \frac{1}{2} F (W_{AA} - W_{AB}) \lambda \right] \\
\lambda \rightarrow \left[ W_{BB} + W_{AB} \lambda \right] + \sigma \left[ W_{BB} + \frac{1}{2} (W_{BB} + W_{AB}) \lambda + \frac{1}{2} F (W_{BB} - W_{AB}) \lambda \right] \\
F \rightarrow \frac{2W_{AA} \lambda^2 + W_{AA} (1 + F) \sigma \lambda}{2W_{AA} \lambda^2 + 2W_{AB} \lambda + (W_{AA} - W_{AB}) (1 + F) \sigma \lambda} + \\
\frac{2W_{BB} + W_{BB} (1 + F) \sigma \lambda}{2W_{BB} + 2W_{AB} \lambda + (W_{BB} - W_{AB}) (1 + F) \sigma \lambda} - 1. \tag{14}
\end{align*}
\]

In order to generalize these expressions to more than one locus, we would like to simplify them. We see from Figure 1 that \( F \) changes rapidly at first, but soon approaches a stable equilibrium value. It is easy to calculate this value for the limit \( \lambda \rightarrow 0 \) (when the substitution is nearly complete).

\[ \lim_{\lambda \rightarrow 0} F = \frac{W_{AA} (1 + F) \sigma}{2W_{AB} + (W_{AA} - W_{AB}) (1 + F) \sigma} . \]

We now replace the variable \( F \) in equations (14) by the constant equilibrium value. The error in making this approximation is small.

We now assume that the fitnesses are of the form:

\[ W_{AB} = \tau W_{AA} \quad W_{BB} = \tau^2 W_{AA} . \]

We then have:

\[
\begin{align*}
\lambda \rightarrow \frac{\lambda \{(1 - \sigma) (\lambda + \tau) + \sigma [\lambda + \frac{1}{2} (1 + \tau) + \frac{1}{2} F (1 - \tau)]\}}{
\tau \{(1 - \sigma) (\lambda + \tau) + \sigma [\tau + \frac{1}{2} \lambda (1 + \tau) - \frac{1}{2} \lambda F (1 - \tau)]\}} . \tag{15}
\end{align*}
\]
This expression generalizes to more than one locus without difficulty. If we assume that the fitness of the organism increases by a factor of $\tau$ for every $B$ gene it possesses (at any locus), then:

$$
\lambda_i \rightarrow \lambda_i' \frac{(1 - \sigma)(\lambda_i + \tau) \prod_{j \neq i} (\lambda_j + \tau) + \sigma[\lambda_i + \frac{1}{2}(1 + \tau)] + \frac{1}{2}F(1 - \tau) \times (1 - \sigma)(\lambda_i + \tau) \prod_{j \neq i} (\lambda_j + \tau) + \sigma[\tau + \frac{1}{2}(1 + \tau)\lambda_i - \frac{1}{2}F(1 - \tau)\lambda_i]}{\prod_{j \neq i} [\lambda_j^2 + \frac{1}{2}\lambda_j(1 + \tau)^2 + \frac{1}{2}F\lambda_j(1 - \tau)^2]} \times \prod_{j \neq i} [\lambda_j^2 + \frac{1}{2}\lambda_j(1 + \tau)^2 + \frac{1}{2}F\lambda_j(1 - \tau)^2],
$$

where $\lambda_i$ is the gene ratio at the $i$th locus.

**Example 5—Classical two-allele model with inbreeding:** We calculated the number of generations necessary to change from $(p_A = 0.9999, p_B = 0.0001)$ to $(p_A' = 0.0001, p_B' = 0.9999)$ for 1000 loci. We used fitnesses identical to those in Example 1, and allowed various fractions of the population to inbreed. The results are displayed in Table 4. It is clear that taking account of inbreeding...
AN n LOCUS MULTIALLELE MODEL

significantly reduces the time necessary for gene substitution to occur. It is interesting to notice that the number of generations is reduced in a strikingly linear manner. Equation (11) gives us the number of generations necessary to shift the gene ratio with no inbreeding as:

\[ m = \log_e \left( \frac{\lambda'}{\lambda} \right) / \log_e \left( \frac{1}{\tau} \right) . \]

If we consider the case in which inbreeding is complete \((\sigma = 1, F = 1)\), equation (16) reduces to:

\[ \lambda' \rightarrow \frac{\lambda}{\tau} \left[ \frac{\lambda + 1}{\lambda \tau + 1} \right] = \frac{\lambda}{\tau^2} . \]

The number of generations necessary to shift the gene ratio from \(\lambda\) to \(\lambda'\) will now be

\[ m = \frac{1}{2} \log_e \left( \frac{\lambda'}{\lambda} \right) / \log_e \left( \frac{1}{\tau} \right) . \]

The linearity of the results for mixed random mating and inbreeding suggests that for \(0 \leq \sigma \leq 1\), it is a good approximation to take:

\[ m = (1 - \frac{1}{2} \sigma) \log_e \left( \frac{\lambda'}{\lambda} \right) / \log_e \left( \frac{1}{\tau} \right) . \]

### TABLE 4

Generations required for substitution of \((p_A' = 0.0001, p_B' = 0.9999)\) for \((p_A = 0.9999, p_B = 0.0001)\) at 1000 loci with various degrees of inbreeding

<table>
<thead>
<tr>
<th>(R)</th>
<th>(\tau)</th>
<th>(\sigma)</th>
<th>(m)</th>
<th>% of random ((\sigma = 0)) case</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>1.000805</td>
<td>0.00</td>
<td>22,889*</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.25</td>
<td>20,035</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.50</td>
<td>17,171</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.75</td>
<td>14,311</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.00</td>
<td>11,448</td>
<td>50</td>
</tr>
<tr>
<td>100</td>
<td>1.00231</td>
<td>0.00</td>
<td>7,984*</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.25</td>
<td>6,986</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.50</td>
<td>5,989</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.75</td>
<td>4,991</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.00</td>
<td>3,992</td>
<td>50</td>
</tr>
<tr>
<td>1000</td>
<td>1.00346</td>
<td>0.00</td>
<td>5,333*</td>
<td>100</td>
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<td></td>
<td></td>
<td>0.25</td>
<td>4,667</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.50</td>
<td>4,001</td>
<td>75</td>
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<tr>
<td></td>
<td></td>
<td>0.75</td>
<td>3,355</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.00</td>
<td>2,667</td>
<td>50</td>
</tr>
</tbody>
</table>

* The results for \(\sigma = 0\) (no inbreeding) are identical with those of Table 1.
DISCUSSION

Many workers have discussed the problem of selectively maintaining many polymorphic loci and the effect of multiple heterozygosity on population fitness (Crow 1958; Kimura and Crow 1964; Lewontin and Hubby 1966; King 1967; Milkman 1967, 1973; Sved, Reed and Bodmer 1967; Wills 1978, to mention a few). This has led others to reconsider substitution rates, substitution costs and the reproductive excess required for gene substitution (Brues 1964; Sved 1968; Felsenstein 1971; and Nei 1971).

In this paper, we develop a model to deal with the problem of coordinated substitutions at many loci simultaneously where, at each locus, several alleles are present. Even though we have improved on Haldane’s (1957) rate calculations, we have not succeeded in refuting his basic assertion that gene substitution is a slow process for the classical case. In this regard, our results are in general agreement with Nei (1971), where he concludes, with a one-locus model, that Haldane was essentially correct. He also noted that competition automatically results in frequency-dependent selection, a point that we also make. However, we point out that considerable improvement can be accomplished by considering large fitness differentials and by taking inbreeding into account.

On the other hand, the observed presence of a great deal of heterozygosity in natural populations leads us to suggest that evolution may consist of the substitution of one heterozygous array for another. Under this hypothesis, evolution may take place considerably more rapidly than in the classical case because the presence of many alleles at each locus causes the gene-frequency ratio changes to be less drastic. In addition, such changes may be accomplished while continuously favoring heterozygotes.

Because of our simplifying assumption for fitnesses \( W_{AB} = \beta W_{AA} \) etc., the number of generations required for substitution is approximately linear with the number of loci. Thus, the number of generations required to change a smaller number of loci can be estimated by dividing the numbers in Tables 1 through 3 by an appropriate factor. For example, to change one heterozygous array to another at one hundred loci could be accomplished in 100 to 200 generations for intermediately and highly prolific species. We repeat that our simplifying assumption actually increased the time required.

Whether this solves the conflict between rapid and slow change is debatable. On the one hand, our model suggests rapid changes may occur. However, it puts us in the position of suggesting that changes can occur more easily in prolific species than in slowly reproducing ones, a position we are not prepared to take at this time. (Note that assuming fitness differentials could be greater in prolific species does not mean that in nature they actually are.)

In our model we have adopted the concept, similar to ones proposed by Brues (1964), Sved (1968) and Wallace (1975), that a given genotype is at a disadvantage only when a better genotype is physically present to take its place. Thus, its fitness depends on both the frequency and number of superior genotypes. As no one seems to have pointed out, this approach shifts the emphasis to a con-
Consideration of the proportion of the population that survives, rather than the proportion that fails to survive, as has been customary in the past. It is true, under these conditions, that substitution can occur at no cost whatever in terms of increased deaths over and above those that would occur anyway. However, our results indicate that, even when there is no cost, the substitution rate is nonetheless limited by the reproductive capacity of the species. This is in contrast to the conclusions of Sved (1968) that there is no obvious upper limit to the rate of gene substitution. Our model also requires multiplicative increases in fitness as the number of loci increases, but the fitness cannot exceed the reproductive capacity of the species. It should be pointed out that, in producing coordinated changes at many loci, it may be unreasonable to expect fitness to be multiplicative until the whole complex of favorable genes is intact.

We have not dealt with the problem of linkage or such possibilities as slowly building up small co-adapted complexes of closely linked genes and then quite rapidly substituting, say, ten of these as though each were a single gene. Also, we have not dealt with founder effects and the probability of success in very small marginal populations with intense inbreeding and intense selection. Even though this is a very attractive evolutionary mode, i.e., millions of expendable marginal populations under conditions potentially capable of producing radical change, the probabilities when very many loci are involved are discouragingly low.

Finally, we think the limits placed on substitution rates by the reproductive capacities of most organisms suggest the existence of other evolutionary modes. An obvious one would be changes in regulatory genes, but major duplications, changes in repetitive DNA sequences and frequencies, or other rare undiscovered reorganizational events cannot be ruled out. Thought of in this way, substitution may be viewed as a mechanism for improving the position of a species on an adaptive peak, while other modes are responsible for getting populations onto new peaks.

LITERATURE CITED


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