THE FUNDAMENTAL THEOREM OF NATURAL SELECTION: RECONSIDERED

Dr. James F. Crow
Professor of Genetics, University of Wisconsin
Madison, Wisconsin 53700
THE FUNDAMENTAL THEOREM OF NATURAL SELECTION RECONSIDERED

In 1930 R. A. Fisher stated the "Fundamental Theorem of Natural Selection" (Fisher always capitalized Natural Selection, as theologians capitalize God):

The rate of increase in fitness of any organism at any time is equal to its genetic variance in fitness at that time.

By genetic variance, Fisher meant the genic or additive genetic variance. He regarded this theorem as a law holding "the supreme position among the biological sciences." Whether we assign the principle to this exalted position or not, it must, I think, be admitted that the statement does compress a great deal of information into a few words and that this and similar rules form much of the foundation for evolution and for quantitative animal and plant breeding.

In symbols,

$$\frac{d\bar{m}}{dt} = V_G$$

when the genotypic fitness values are constants. Formulae that apply when these are not constant have been given by Wright (1955), Crow and Kimura (1955), and Kimura (1958).

Wright (most recently in 1967) has considered a related problem -- the way in which the fitness of a population changes -- by following the trajectory of the mean fitness as this moves during the course of gene frequency change. He uses the metaphor of an adaptive surface, each point of which corresponds to the average fitness of a population with a specified array of gene frequencies.

Recently, both of these concepts have come in for a spate of criticism. Most of it, I think, is irrelevant to the considerations that I am interested in.
in this paper. For example, Li (1967) has pointed out that the Fisher theorem is not exact for a population with dominance when the generations are discrete. But Fisher made no claim that his formulation applied exactly to a discrete generation model. Similarly, Moran (1964) noted that under some circumstances in the Wright picture the fitness does not follow an upward gradiant on the adaptive surface. For example, a population out of linkage equilibrium may even change to a lower fitness because of changed linkage relations. For this reason he concludes that adaptive surfaces are "nonexistent". However, Wright (1967) has shown that the path followed by the population is little changed by linkage and epistasis unless linkage is tight. He has been interested mainly in genes with relatively small effect and, of course, most pairs of genes in most organisms are not closely linked.

It is good, of course, to have the mathematical theory as general and rigorous as possible, and exact formulations are preferable to approximations when this is feasible and when they are equally informative. The circumstances under which the Fisher theorem holds exactly are not, I think, completely understood (not by me, in any case). One approach, suggested by Fisher, is by weighting each individual in the population by its reproductive value to get around the problem of nonequilibrium age distributions, but this has not been worked out in detail for Mendelian populations.

But, I am here interested in Fisher's theorem as a statement that may or may not be exact, or may be exact only under a very restricted model, but which is a satisfactory approximation under a variety of circumstances that correspond to what often happens in nature. So, for the purposes of this discussion, I am concerned
with the reasonableness of the model and the accuracy of the approximation rather
than with exactness and rigor, or with precise specification of the model.

Henceforth I shall assume that the population is changing continuously
and in such a way that equations of the general form

$$\frac{dp}{dt} = p(m - \bar{m})$$

are applicable (Fisher, 1958; Wright, 1967). In this equation, p is the
frequency of the gene or chromosome and m is the average fitness of this gene
or chromosome measured in Malthusian parameters.

The rate of change in fitness will be given by the genic variance, provided
that the genotypic fitnesses are constant and that there is a constant level of
departure from random mating proportions. The appropriate measure of departure
has been given by Fisher (1934), Crow and Kimura (1955), and Kimura (1958). And,
of course, as a special case, the theorem applies with random mating.

However, it would appear that linkage and epistasis would complicate the
situation and make the theorem no longer applicable even with random mating. For,
Cockerham (1954) and Kempthorne (1957) have shown that the regression of offspring
on midparent involves epistatic terms, even when the population is in gametic
phase (linkage) equilibrium. More specifically, twice the covariance of parent
and offspring is

$$2 \text{Cov}_{po} = V_G + \frac{1}{2} V_{AA} + \ldots$$

So we might expect that the genic variance would be insufficient to describe the
rate of fitness change where epistasis is involved, and that additive by additive
epistatic terms would need to be included.
On the other hand, it is well known that with linkage and epistasis the population may remain permanently out of gametic phase equilibrium. This is true even for genes with recombination frequency 1/2, that is, unlinked.

A deeper insight into this situation came with Kimura's discovery of "quasi-equilibrium," whereby with loose linkage and weak epistasis the population tends toward a state of relatively constant departure from linkage equilibrium. When the departure is constant the epistatic variance component and the component from linkage disequilibrium cancel each other and the rate of fitness change is given by the genic variance.

It is necessary to show that a population mating at random does, in fact, tend to approach such a state of relative constancy. But it turns out to be necessary to measure linkage disequilibrium in an appropriate way: by the ratio of the coupling to the repulsion double heterozygotes, rather than by their difference. Constancy for the ratio leads to the Fisher theorem, but constancy for the difference does not (but cf. Li, 1967a, p. 467).

This, then, is the purpose of my paper. I have nothing new to report, but I think I have made some slight improvements in the clarity of Kimura's argument and perhaps made it more convincing. It seems to me to be indeed remarkable that natural selection seems to operate so as to generate just enough linkage disequilibrium that the rate of fitness change is given by the genic variance.
The Rate of Change in Chromosome Frequencies

Assume that there are two loci, each with two alleles, and with frequencies and fitnesses as follows:

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>ab</th>
<th>Ab</th>
<th>aB</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>$P_1$</td>
<td>$P_2$</td>
<td>$P_3$</td>
<td>$P_4$</td>
</tr>
<tr>
<td>Average fitness</td>
<td>$m_1$</td>
<td>$m_2$</td>
<td>$m_3$</td>
<td>$m_4$</td>
</tr>
</tbody>
</table>

I adopt a continuous model and measure fitness in malthusian parameters. Then $m_1$ is the average fitness of chromosome $ab$, the average being taken over all genotypes containing this chromosome and weighted by the genotype frequency and the number of $ab$ chromosomes.

Let $d_{12}$ be the death rate of genotype $ab/AB$ and $b_{12}$ be the rate at which it gives birth. Thus, during the interval $\Delta t$, the excess of births over deaths per individual of this genotype is $(b_{12} - d_{12})\Delta t = m_{12}\Delta t$. The fitnesses and frequencies of the zygotic combinations are given in Table 1.

Assume that selection is slow enough that the gene frequency change is given satisfactorily by

$$\frac{dp_1}{dt} = p_1 (m_1 - \bar{m})$$  \hspace{1cm} (1)

where, as given in Table 1,

$$m_1 = \sum_j p_j m_{ij}$$  \hspace{1cm} (2)

and

$$\bar{m} = \sum_{ij} p_i p_j m_{ij} = \sum_i p_i m_i$$  \hspace{1cm} (3a)
Table 1

Frequencies and fitnesses of the various zygotic combinations of two linked loci. The gametic values are given along the margins, and the zygotic values in the main body of the table.

<table>
<thead>
<tr>
<th></th>
<th>ab</th>
<th>Ab</th>
<th>aB</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Frequency</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fitness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Totals</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Averages</td>
</tr>
</tbody>
</table>

\[ \bar{m} = \sum_{i,j} p_{i} p_{j} m_{ij} = \sum_{i} p_{i} m_{i} \]

\[ m_{i} = \sum_{j} p_{j} m_{ij} \]

\[ m_{ij} = m_{ji} \]

\[ P_{A} = p_{2} + p_{4}, \quad P_{B} = p_{3} + p_{4} \quad \text{(gene frequencies)} \]

\[ D = p_{1} p_{4} - p_{2} p_{3}, \quad z = p_{1} p_{4} / p_{2} p_{3} \quad \text{(measures of gametic unbalance)} \]
If there is recombination between the $A$ and $B$ loci the formulae are modified (Kimura, 1956). Letting $r$ be the recombination fraction, we have

\[
\begin{align*}
\frac{dp_1}{dt} &= p_1 (m_1 - \bar{m}) - rbD \\
\frac{dp_2}{dt} &= p_2 (m_2 - \bar{m}) + rbD \\
\frac{dp_3}{dt} &= p_3 (m_3 - \bar{m}) + rbD \\
\frac{dp_4}{dt} &= p_4 (m_4 - \bar{m}) - rbD
\end{align*}
\]

where $b$ is the birth rate of the double heterozygote; i.e. $b = b_{14} = b_{23}$. $D$ is a measure of gametic unbalance (linkage disequilibrium),

\[
D = P_1P_4 - P_2P_3.
\]

For our purposes it is more useful to measure gametic unbalance in another way,

\[
z = \frac{P_1P_4}{P_2P_3},
\]

as has been done by Kimura (1965) and Felsenstein (1965). Felsenstein's $Z$ is $\log e z$. The relation between $D$ and $z$ is given by

\[
D = P_2P_3 (z - 1).
\]

To understand the change of $z$ we differentiate $\log e z$, giving

\[
\frac{d \log e z}{dt} = \frac{1}{z} \frac{dz}{dt} = \frac{1}{P_1} \frac{dp_1}{dt} - \frac{1}{P_2} \frac{dp_2}{dt} - \frac{1}{P_3} \frac{dp_3}{dt} + \frac{1}{P_4} \frac{dp_4}{dt}.
\]

Substituting from (4) gives

\[
\frac{1}{z} \frac{dz}{dt} = E - rbDP
\]
where

\[ E = m_1 - m_2 - m_3 + m_4 \]  \hspace{1cm} (10)

and

\[ p = \frac{1}{p_1} + \frac{1}{p_2} + \frac{1}{p_3} + \frac{1}{p_4} \]  \hspace{1cm} (11)

(Felsenstein, 1965).

**The Rate of Change in Fitness**

We obtain the rate of change in the average fitness by differentiating (3) and then using (2)

\[
\frac{dm}{dt} = \sum_{ij} m_{ij} \left( \frac{dp_i}{dt} + \frac{dp_j}{dt} \right)
\]

\[
= \sum_j \frac{dp_j}{dt} \sum_i p_{ij} m_{ij} + \sum_i \frac{dp_i}{dt} \sum_j p_{ij} m_{ij}
\]

\[
= \sum_j \frac{dp_j}{dt} \sum_i m_i + \sum_i \frac{dp_i}{dt} \sum_j m_j
\]

\[
= 2 \sum_i m_i \frac{dp_i}{dt}
\]

Substituting from (4) and then using (3a)

\[
\frac{1}{2} \frac{dm}{dt} = \sum_{i} p_i m_i^2 - \bar{m} \sum p_i m_i - rbDE
\]

\[
= \sum p_i m_i^2 - \bar{m}^2 - rbDE
\]

However, \( \sum p_i m_i^2 - \bar{m}^2 \) is the variance of the \( m_i \)'s, or the variance of the margin (see the totals and averages at the bottom of Table 1).
I shall call this the gametic variance, $V_{gam}$. It is half the chromosomal variance of Kimura (1965). This includes components from epistasis, but not from dominance. Thus (13) can be written

$$\frac{d\bar{m}}{dt} = 2(V_{gam} - rbDE) = V_G + \frac{1}{2} V_{AA} - 2rbDE$$  \hspace{1cm} (14)$$

We now make use of the familiar least squares technique to estimate the additive component of the gametic variance. From Table 1, the quantity to be minimized is

$$Q = p_1(m_1 - m)^2 + p_2(m_2 - m - \alpha)^2 + p_3(m_3 - m - \beta)^2$$

$$+ p_4(m_4 - m - \alpha - \beta)^2$$  \hspace{1cm} (15)$$

Taking derivatives and equating to zero gives

(1) \[ \frac{1}{2} \frac{\partial Q}{\partial m} = -p_1(m_1 - m) - p_2(m_2 - m - \alpha) - p_3(m_3 - m - \beta) - p_4(m_4 - m - \alpha - \beta) = 0 \]

(2) \[ \frac{1}{2} \frac{\partial Q}{\partial \alpha} = -p_2(m_2 - m - \alpha) - p_4(m_4 - m - \alpha - \beta) = 0 \]

(3) \[ \frac{1}{2} \frac{\partial Q}{\partial \beta} = -p_3(m_3 - m - \beta) - p_4(m_4 - m - \alpha - \beta) = 0 \]

To solve these, I follow Kimura and let

$$p_1(m_1 - m) = K \hspace{1cm} .$$

Then, after subtracting (3) from (1)

$$-p_2(m_2 - m - \alpha) = K \hspace{1cm} .$$

Likewise, subtracting (2) from (1)

$$-p_3(m_3 - m - \beta) = K \hspace{1cm} ,$$

and finally

$$p_4(m_4 - m - \alpha - \beta) = K \hspace{1cm} .$$
Dividing these four equations by \( p_1, p_2, p_3 \) and \( p_4 \) respectively, and adding, we obtain

\[
\begin{align*}
\frac{1}{p_1} m_1 - \frac{1}{p_2} m_2 - \frac{1}{p_3} m_3 + \frac{1}{p_4} m_4 &= K \left( \frac{1}{p_1} + \frac{1}{p_2} + \frac{1}{p_3} + \frac{1}{p_4} \right) \\
&= K \frac{1}{p} \\
\end{align*}
\]

or

\[ E = KP \]  

(16)

Q is the nonadditive component of the gametic variance. Substituting into (15) gives

\[ Q = K^2 \left( \frac{1}{p_1} + \frac{1}{p_2} + \frac{1}{p_3} + \frac{1}{p_4} \right) \]

\[ = K^2 P \]  

(16a)

Thus, \( V_{\text{gam}} = V_a + K^2 P \), where \( V_a \) is the additive component of the gametic variance. Substituting into (14) yields

\[ \frac{d \bar{m}}{dt} = 2 (V_a + K^2 P - rbDE) \]

\[ = 2 (V_a + \frac{E^2}{P} - rbDE) \quad \text{from (16)} \]

\[ = 2 (V_a + \frac{E}{P} \frac{dz}{dt}) \quad \text{from (9)} \]  

(17)

With random mating the zygotic additive variance or genic variance is simply twice the gametic additive variance so we finally obtain

\[ \frac{d \bar{m}}{dt} = V_G + \frac{2E}{P} \frac{dz}{dt} \quad \text{(18)} \]

This shows that when \( z \) is constant the Fisher Fundamental Theorem is appropriate. Similar formulae were obtained by Kimura (1958).

Formulation in this manner shows the desirability of measuring gametic unbalance by \( z \) (or log \( z \)) rather than \( D \). Only when \( z \) is constant does the
the Fisher principle work.

We therefore want to see whether $z$ is anywhere near constant. The next section will show, as Kimura (1965) first did, that with weak epistasis and loose linkage this is true.

"Quasi Linkage Equilibrium"

We start by writing (9) and substituting from (7), to give

$$
\frac{dz}{dt} = Ez + rba (1-z) p_2 p_3 P
$$

$$
= Ez + rb (1-z) - rb (1-z)^2 (p_2 + p_3)
$$

(19)

Since $0 < p_2 + p_3 < 1$ we can write

$$
\frac{dz}{dt} < Ez + rb (1-z)
$$

(20a)

$$
\frac{dz}{dt} > Ez + rb (1-z) - rb (1-z)^2 = Ez + rbz (1-z)
$$

(20b)

Consider first a haploid model, in which case the $m_1$'s, and therefore $E$, are constants. We then integrate 20a and b to obtain

$$
z < \frac{rb}{rb-E} (1 + K_1 e^{-(rb-E)t}), K_1 = z_0 \frac{rb-E}{rb} - 1
$$

(21a)

$$
z > \frac{E+rb}{rb} \left( \frac{1}{1 + K_2 e^{-(E+rb)t}} \right), K_2 = \frac{E+rb}{rbz_0} - 1
$$

(21b)

Consider first that recombination is large relative to the epistasis, as measured by $E$. The value of $b$ will ordinarily be close to 1. If $rb > |E|$, then as $t$ gets large the value of $z$ is given by

$$
\frac{E+rb}{rb} < z < \frac{rb}{rb-E}
$$

(22)
or, if \( R = E / rb \),

\[
1 + R < z < \frac{1}{1 - R} \quad (22a)
\]

For example, if \( r = 10E \) and \( b = 1 \), \( z \) comes to lie between 11/10 and 10/9.

If \( E \) is negative then \( z \) becomes less than 1. For example with \( r = -10E \), \( z \) comes to lie between 9/10 and 10/11.

This is equivalent to Felsenstein's (1965) statement that \( D \) becomes the same sign as \( E \). We can say that \( \log z \) becomes the same sign as \( E \). Of course, if the selection is intense and \( y \) and \( E \) are small, the gene frequency change may be so rapid that the whole process is over (or nearly over) before the conditions of (22) are reached.

Alternatively, if \( rb < |E| \) there is not necessarily any quasi-stable value of \( z \). When \( t \) gets large

\[
1 + R < z \quad , \quad R > 1 \quad (23)
\]

\[
0 < z < \frac{1}{1 - R} \quad , \quad R < -1 \quad (24)
\]

with no upper limit in the first case and no positive lower limit in the second.

We are especially interested in the case where \( r \) is large relative to \( E \) and where the \( m \)'s are not far from zero, a condition that must often be true for pairs of loci that are components of a quantitative trait or of fitness.

How fast is quasi-equilibrium attained?

If \( \hat{z} \) is the quasi-equilibrium value, and \( z \) is initially greater than \( \hat{z} \), then for \( |R| < 1 \), from (20b)

\[
\frac{dz}{dt} \frac{1}{z - \hat{z}} > \frac{Ez + rbz (1 - z)}{z - \hat{z}} = \frac{rbz (R + 1 - z)}{z - \hat{z}}
\]

But \( \hat{z} > R + 1 \), so

\[
- \frac{dz}{dt} \cdot \frac{1}{z - \hat{z}} < rbz \frac{z - R - 1}{z - R - 1} = rbz
\]
Also, from (20a)

\[
\frac{dz}{dt} \cdot \frac{1}{z} < \frac{Ez + rb(1-z)}{z-\hat{z}} = rb\left[\frac{Rz+1-z}{z-\hat{z}}\right]
\]

But \( \hat{z} < \frac{1}{1-R} \), so

\[
- \frac{dz}{dt} \cdot \frac{z}{z-\hat{z}} > rb\left[\frac{z-1-Rz}{z(1-R)}\right] = rb(1-R)
\]

Thus, for \( z > \hat{z} \)

\[
rb(1-R) < \frac{-dz}{(z-\hat{z})dt} < rbz
\]

Likewise, for \( z < \hat{z} \)

\[
rbz < \frac{dz}{(z-\hat{z})dt} < rb(1-R)
\]  \hspace{1cm} (26)

Therefore, if the population starts near \( z = 1 \), \( b \) is nearly 1, and \( R \) is small, the rate of approach to quasi-equilibrium, expressed as a fraction of the degree of departure, is approximately equal to the recombination fraction. This means, for example, that unlinked genes go about half of the distance to equilibrium each generation.

**Diploid Populations**

Table 2 gives the Malthusian parameter for all genotypes in slightly different form and defines four epistatic parameters. These were first introduced by Fisher and have been used by Kojima and Kelleher (1961) and by Felsentein (1965).

Noting from (2) that

\[
m_i = \sum_j p_j m_{ij}
\]
Table 2

Fitnesses of the various genotypes and definitions of the epistatic parameters

<table>
<thead>
<tr>
<th></th>
<th>aa</th>
<th>Aa</th>
<th>AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>bb</td>
<td>$m_{11}$</td>
<td>$m_{12}$</td>
<td>$m_{22}$</td>
</tr>
<tr>
<td></td>
<td>$E_1$</td>
<td>$E_2$</td>
<td></td>
</tr>
<tr>
<td>Bb</td>
<td>$m_{13}$</td>
<td>$m_{14} = m_{23}$</td>
<td>$m_{24}$</td>
</tr>
<tr>
<td></td>
<td>$E_3$</td>
<td>$E_4$</td>
<td></td>
</tr>
<tr>
<td>BB</td>
<td>$m_{33}$</td>
<td>$m_{34}$</td>
<td>$m_{44}$</td>
</tr>
</tbody>
</table>

$E_1 = m_{11} - m_{12} - m_{13} + m_{14}$

$E_2 = m_{21} - m_{22} - m_{23} + m_{24}$

$E_3 = m_{31} - m_{32} - m_{33} + m_{34}$

$E_4 = m_{41} - m_{42} - m_{43} + m_{44}$
we substitute these into equations (4). These in turn are substituted for \( dp_i/dt \) in (8), which leads - after some algebra - to

\[
\frac{1}{z} \frac{dz}{dt} = \bar{E} - rbDP
\]

where

\[
\bar{E} = p_1E_1 + p_2E_2 + p_3E_3 + p_4E_4
\]

We cannot proceed directly with (27) as we did with equations (19-21) because \( \bar{E} \) is a function of the \( p_i \)'s rather than a constant.

However, we can obtain useful but less precise limits when all \( E_i \)'s are less than \( rb \) in absolute value, by writing in analogy with (22)

\[
\min \frac{E_{\min} + rb}{rb} < z < \max \frac{rb}{rb - E_{\max}} , \quad |E_i| < rb
\]

where \( E_{\min} \) and \( E_{\max} \) are the smallest and largest values of the \( E_i \)'s.

Thus, as in the haploid model, if \( r \) is large relative to the absolute values of the \( E_i \)'s the value of \( z \) eventually comes to lie within specified limits and the conditions for quasi-equilibrium are met. If the selective differences are small and \( r \) large the quasi-equilibrium is attained rapidly and the Fisher theorem is a good approximation throughout most of the time when the gene frequencies are changing.

On the other hand, with closely linked genes and strong epistasis (\( |E| > rb \)), there may not be any quasi-equilibrium. One can understand this intuitively by noting that with \( |E| << r \) the two loci behave nearly independently and the fitness change is given by the additive variance. With close linkage the chromosome acts more as a unit and the gametic variance is more appropriate. Kimura (1965) has given numerical illustrations for both situations.
The Limiting Value of $z$ with Directional Selection

The limits set on the value of $z$ when quasi-linkage equilibrium is attained are appropriate, regardless of the direction that selection is going. It may be approaching an equilibrium with some intermediate gene frequencies, as with heterosis, in which case these limits hold during the process. However, if the population is going toward fixation of one chromosomal type, one can be more precise.

If one chromosome type (or pair of genes, if these are on independent chromosomes) is ultimately to be fixed, we can ask about the asymptotic behavior of $z$. Assume, to be concrete, that $E$ is positive and that the $ab$ or $AB$ chromosome is favored by selection and will eventually be fixed. As this stage is neared, $p_2 + p_3$ approaches 0, and (20a) and (21a) become equalities rather than inequalities. Thus, we would expect for this situation that the limiting value of $z$ is given by

$$z_\infty = \frac{cb}{cb - E}.$$  \hspace{1cm} (30)

If $Ab$ or $aB$ is eventually fixed, (20b) and (21b) are appropriate and

$$z_\infty = \frac{E + cb}{cb}.$$  \hspace{1cm} (31)

On the other hand, if $|E| > cb$ these equations do not have obvious limits and a more careful treatment is needed.

Some Examples

Equations (25) and (26) showed that the rate of approach to quasi-equilibrium is approximately equal to the recombination value. So we would expect that independent loci would go 50% of the way toward equilibrium each generation and would be very close within a few generations. In all these cases $b$ is taken to be one,
This is illustrated in Figure 1. The model is haploid, for simplicity, but is adequate for illustration. Three starting populations are assumed, one at linkage equilibrium, one with large positive departure, and one with a large negative departure. In this case \( E = m_1 - m_2 - m_3 + m_4 = 0.1 \) and \( r = 0.5 \). Therefore, from (22) we would expect the value of \( z \) to quickly come to a value between 1.20 and 1.25 and to remain there during the remainder of the selection process. Since the AB type will ultimately be fixed in each of these examples, the final value is 1.25, as indicated by the arrow in the figure.

Figure 2 shows an example that is the same in every regard except that the genes are linked, with \( r = 0.2 \). In this case the quasi-equilibrium value lies between 1.5 and 2.0 with an eventual value of 2.0. Again the three populations converge to quasi-equilibrium within the assigned limits, but the approach to this quasi-limit is slower because of less recombination.

Figure 3 shows a diploid example. As shown in the lower right part of the figure the double recessive is favored while each of the single recessives is deleterious. The starting population was at linkage equilibrium with chromosome frequencies \( p_1 = p_2 = 0.2 \) and \( p_3 = p_4 = 0.3 \). In this graph the time scale is much longer. As before, with free recombination the quasi-equilibrium is approximated within half a dozen generations. Then, \( z \) gradually changes, always staying between 1.0 and 1.099, as given by (29), and finally approaching 1.099. The example is from Kimura (1965) who also gives other examples. The calculations in the graph are made from a discrete model, but the agreement is good, as can be seen. Finally, Figure 4 shows for the same data the rate of change in fitness.
The upper dotted line is the genic variance plus half the additive x additive epistasis. The lower line is the genic variance. The solid line shows the increment in fitness in one generation. Initially this is given by $V_G + \frac{1}{2} V_{AA}$, as would be expected with linkage equilibrium. But the quasi-equilibrium is quickly attained, as shown in Figure 3, and when this is true the rate of fitness increase is given solely by the genic variance. The fitness change and the genic variance are so close after the first few generations that the two lines are superimposable on the graph. Also shown on the abscissa is the frequency of the favored chromosome, $p_4$.

In all these examples the absolute value of $E$ is considerably less than $br$. When $|E| > rb$ the population may never attain quasi-equilibrium; the value may increase or decrease indefinitely. Also, under such circumstances the fitness may decrease, or may change directions. Kimura's paper gives examples of such situations.

In physics, electromagnetic radiation of very high energy is conveniently described as particulate; that of low energy is more easily thought of by means of wave theory. In evolution, when the recombination is very small relative to $E$, the chromosome acts as a unit and the gametic variance is more relevant than the additive portion thereof. When recombination is free the genes behave more or less independently, and the genic variance is the relevant measure. For intermediate situations where $E$ is of the same rough magnitude as $rb$ the situation is difficult to analyze, and it is necessary to compute individual cases by equation (13).
Summary

When a pair of loci are independent or loosely linked and epistasis is not great, the population attains a state of "quasi-linkage equilibrium." When the population is in such a state the rate of change in fitness is given approximately by the additive genetic variance, as foreshadowed by Fisher and shown explicitly by Kimura.

More specifically, quasi-equilibrium is attained when $|E| < br$, where $E$ is the epistatic parameter (the excess in average fitness of coupling chromosomes over that of repulsion chromosomes), $b$ is the birth rate of double heterozygotes (usually near 1), and $r$ is the amount of recombination between the loci. Under such circumstances the population attains a degree of linkage disequilibrium just large enough that this balances the epistatic variance and the rate of change in fitness is given by the additive genetic variance.
References


Genetics 52:349-363.


Kojima, K., and T. Kelleher. 1961. Changes of mean fitness in random mating populations when epistasis and linkage are present.

Genetics 46:527-540.


$Z_0 > Z > 1.25$

$E = 0.01$

| A | 0.02 | B | 0.06 |

$\mathcal{N} = 5.5$

$Z_0 = 3.3$

$Z = 2.8$
GORDON DICKERSON: (1) Parent x offspring or half-sib estimates of heritability include some add. x add. epistasis. Does this mean that use of such estimates would lead to overestimation of the response to selection where the same type of selection is continued for a long time?

(2) What happens to mean fitness when selection is relaxed? (That is, as gametic disequilibrium declines or Z approaches 1)

CROW: (1) I think it might. If the prediction formula included additive by additive variance components and the population were at or near quasi-equilibrium, the rate of selection progress would be overestimated. However, the point about which I'm not sure is the extent to which the correlations used to measure the heritability are also altered by the same considerations, perhaps in the same direction so that the predictions might not be so bad.

(2) It seems to me that the population would regress toward the old value that it had before selection because the linkage equilibrium that has been generated is in the direction of favorable linked combinations. Relaxation of selection would tend to restore the original combinations.

RALPH COMSTOCK: In Fisher's presentation of the Fundamental Theorem he defined genetic variance in a special way. Do you know whether, in the presence of epistasis, genetic variance as defined by Fisher is equal to additive genetic variance as defined by Kempthorne or Cockerham?

CROW: I think that Fisher's definition of genetic variance is the same as the additive genetic variance of Kempthorne and Cockerham, using the same least squares definition.
JOHN GILL: Can you relate the change from adequacy of \((V_G + \frac{1}{2}V_{AA})\) to adequacy of \(V_G\) to Griffing's model, which includes \(V_{AA}\) and \(r\)?

CROW: Unfortunately I am not as well acquainted with Griffing's work as I should like to be and should be; nor am I as well acquainted with John Gill's work as I would like to be, either. I know that Griffing considered the effect of epistasis in generating linkage disequilibrium with truncation selection, but I don't know whether anything like quasi-linkage equilibrium appears in his formulae.

GORDON DICKERSON: Recognizing the relatively large proportion of the epistatic superiority due to gametic disequilibrium that is lost in the first generation of relaxed selection, can we visualize a portion of the selection applied in each generation of continued selection as necessary to offset recombination loss of epistatic superiority which would occur each generation if selection were not continuous.

CROW: Yes, this seems correct to me. A certain amount of the selection each generation is devoted to maintaining the level of linkage disequilibrium against the randomizing effects of recombination.

G. B. HAVENSTEIN: If one were to start a selection experiment using a population known to have been under recent selection as the base, should one allow several generations of random mating in both groups before starting? Or what are the consequences of relaxed selection using an offshoot of a selected line as a control?

CROW: I suppose this depends on the purpose of the experiment. It might be good to have a few generations of unselected random mating so you know where you are starting from in terms of linkage parameters.
A. W. NORDSKOG: How far can we extrapolate from natural selection to "Domestic" selection? Under "Domestic selection genetic gain = \( h^2 \times \text{sel. diff.} \) but Haldane (1958) points out that this does not apply to natural selection - that its measurement is a function of the ratio of variances in the selected and non-selected generations.

CROW: Strict truncation selection as practiced in principle by the animal breeder is of course different from natural selection where the contribution of each genotype is proportional to its fitness. However, I should think that with relatively slow selection and with several genes involved, the consequences ought to be roughly the same. I want to emphasize, as this question brings out, that all my discussion applies strictly only to fitness; if the trait of interest is only partially correlated with fitness, then the conclusions are to this extent non-applicable.

J. L. LUSH: Does the "fitness" in Fisher's Theorem (and your formulae) wholly concern intrademe variance? In this case intrademe fitness could rise and, at the same time, the deme could become less and less fit relative to other demes.

CROW: Yes, indeed. I am talking about intrademe variance. I think I mean the same thing as Wright's internal fitness. In any case we are measuring the change in fitness that would result from this particular change in gene frequency if the individual genotypic fitnesses did not change during the process. It is course possible for natural selection to produce a change in the population so that it becomes steadily less fit -- as for example selection of genes that helped their carriers at the expense of the population. If there is selection both
within and between demes, the relevant interdemic term, I think, is the total variance of the differences among the deme means.

L. P. JONES: How serious is the possible bias in your calculations if fitness of one genotype is a function of other genotypes in the population.

CROW: The calculations apply, of course, to constant fitness coefficients. If the fitness of a genotype depends on which other genotypes are present, or for any reason is not constant, then one would have to know the ways in which fitness changes with other genotypes in order to make any reasonable predictions.