EVOLUTION IN POPULATIONS IN APPROXIMATE EQUILIBRIUM.

By SEWALL WRIGHT.

(*Department of Zoology, The University of Chicago.*)

CONTENTS.

Introduction.

This paper is concerned with the evolutionary processes in populations in which the selective values of different grades of a character depend on the (squared) deviations of the latter, from an optimum. It is assumed that the effects of different genes on the character combine additively (no epistasis). The cases of no dominance and of complete dominance in these primary effects will be treated in succession. A preceding paper (1934) dealt with the analysis of variability and the correlations between relatives with respect to squared deviations from the optimum. The same symbols will be used here. Equation numbers from the preceding paper will be referred to in square brackets.

Case of no dominance on primary scale.

The nature of the evolutionary processes under the conditions described may be visualised by treating the population at a given moment as located at a point in a multidimensional space defined by the set of gene frequencies ($q_1, \ldots q_n$) pertaining to the *plus* members ($A_1, \ldots A_n$) of gene pairs affecting the character (cf. Haldane, 1931). Ordinates are to be erected measuring the average adaptive value ($\bar{H}$) of the character. The signs of $\bar{H}$ and γ_i (net effect of substitution of A_i for a_i on adaptive value in the population in question) are taken so as to make the high points correspond to optimal values. The effect of substitution of A_i for a_i on the *primary character* is represented by α_i. The position of the optimum on this primary scale is represented by O and that of the mean by M ($=2\Sigma\alpha q$):

$$\bar{H} = -2\Sigma\alpha^2 q\,(1-q) - (M-O)^2, \quad \ldots\ldots(1)\ (=[16])$$

$$\gamma_i = \alpha_i\,[\alpha_i(2q_i - 1) - 2(M-O)]. \quad \ldots\ldots(2)\ (=[19])$$

The rate at which the mean of a character changes in relation to changes in the frequency (q_i) of one of the genes must equal twice the net effect of a single gene substitution:

$$\frac{\partial H}{\partial q_i} = 2\gamma_i. \qquad \text{.....(3) (=[18])}$$

The rate of change of gene frequency per generation in the case of no dominance is well known to be $\Delta q = sq\,(1-q)$, where s measures the selective disadvantage of one allelomorph (Fisher, 1922). In the general case, the selective disadvantage must be proportional to the momentary net effect of gene replacement on adaptive value:

$$\Delta q_i = s\gamma_i q_i (1-q_i). \qquad \text{.....(4)}$$

The rate of change of the mean adaptive level of the population per generation can be written

$$\Delta \bar{H} = \sum_{i=1}^{n} \frac{\partial \bar{H}}{\partial q_i}\,\Delta q_i = 2s\Sigma\gamma^2 q\,(1-q). \qquad \text{.....(5)}$$

The right-hand member of this equation is proportional to the general formula for the portion of the variance of H which can be attributed to additive gene effects [20].

$$\Delta \bar{H} = s\sigma_G^2. \qquad \text{.....(6)}$$

This principle was arrived at in a different way by Fisher (1930). He enunciated it as the "fundamental theorem of natural selection." "The rate of increase in fitness of an organism at any time is equal to its genetic[1] variance at that time."

I have criticised this application of it on the ground that it measures merely the *tendency* toward increase in fitness due to selection. Other evolutionary factors such as recurrent mutation, immigration and the effects of sampling in populations of limited size must also be considered. There must ordinarily be an approximate balancing of these *first* order pressures so that evolutionary change is a *second* order resultant (Wright, 1930).

From the formula as given, $\Delta \bar{H}$ cannot be negative as is of course to be expected. In the absence of other factors, evolutionary change ceases whenever $\Delta \bar{H} = 0$. This occurs at any point at which each q has one of the three values 0, 1 or such a value that $\gamma = 0$.

Consider first the case in which there is complete homozygosis (all q's either 0 or 1). Whether there is stability in the face of low rates of mutation or immigration depends on the gradient. If $q_1 = 0$ and $\frac{\partial \bar{H}}{\partial q_1} > 0$,

[1] Fisher explicitly includes in "genetic variance" only that portion of the variance which can be attributed to additive gene effects.

the homozygote a_1a_1 is unstable, since $\bar{H}$ increases with mutation of a to A. Similarly if $q_1=1$ and $\frac{\partial \bar{H}}{\partial q_1}<0$, A_1A_1 is unstable. These conditions for instability may be written as follows from (3) and (2):

$$(M-O)<-\frac{\alpha_1}{2}, \quad (q_1=0) \qquad \ldots\ldots(7)$$

$$(M-O)>\frac{\alpha_1}{2}. \quad (q_1=1) \qquad \ldots\ldots(8)$$

Thus if the mean of the character is below the optimum by more than half the effect of a gene which is fixed in the minus phase, this fixation is unstable, or if the mean is above the optimum by more than half the effect of a fixed plus factor, minus mutations will tend to accumulate.

Since the effect of replacing a_1a_1 by A_1A_1 is to increase the mean by $2\alpha_1$, it is possible for both homogenic populations to be unstable. There is stable equilibrium at the point $q_1=\frac{1}{2}+\frac{M-O}{\alpha_1}$ if all other genes are fixed.

The condition when the population is heterogenic in more than one respect requires further consideration. The condition that the γ's for all unfixed genes be zero is that for each of them

$$q_1=\tfrac{1}{2}+\frac{M-O}{\alpha_1}. \qquad \ldots\ldots(9)$$

Thus all of the q's (frequencies of plus genes) must be less than $\frac{1}{2}$, all equal to $\frac{1}{2}$ (mean and optimum coincide at the mid-point of the scale where $M=\Sigma\alpha$), or all greater than $\frac{1}{2}$. Those with the same effect (α) must have the same gene frequency at equilibrium. The limiting case for small values of all q's, all α's the same, occurs with the optimum at $\frac{\alpha}{2}$. The other limiting case (all q's close to 1) occurs with the optimum at $2n\alpha-\frac{\alpha}{2}$. Thus no equilibrium of 2 or more unfixed factors is possible unless the optimum is more than half a gene effect within the limits of variation. With unequal gene effects, the possible range of location of the optimum is less.

As to the stability of these equilibria, consider the way in which the γ's vary:

$$\frac{\partial \gamma_i}{\partial q_j}=-4\alpha_i\alpha_j, \qquad \ldots\ldots(10)$$

unless $i=j$, when

$$\frac{\partial \gamma_i}{\partial q_i}=-2{\alpha_i}^2.$$

$$\partial\gamma_i=\sum_{j=1}^{n}\frac{\partial \gamma_i}{\partial q_j}\delta q_j=2\alpha_i\left[\alpha_i\delta q_i-\delta M\right]. \qquad \ldots\ldots(11)$$

The expression $\delta M (= 2\Sigma\alpha\delta q)$ is the deviation of the mean of the character from its value at equilibrium, brought about by the deviations of the q's from their values at equilibrium. If all $\delta\gamma$'s are opposite in sign to the corresponding δq's (as is obviously the case when all δq's are of the same sign) all q's tend to return to equilibrium. If, on the other hand, all $\delta\gamma$'s are of the same sign as the corresponding δq's (as is obviously the case when the signs of the δq's are so balanced that there is no change of mean ($\delta M = 0$)), *all* q's tend to depart farther from equilibrium. In intermediate cases, some q's may go toward equilibrium, others go farther away. Clearly there can be no stable equilibrium (under selection alone) when more than one factor is unfixed. The points at which $\Delta H = 0$ and more than one gene is unfixed are of the nature of saddles in our multidimensional space.

With n factors affecting the character, there may be any number from 1 to $\frac{\lfloor n}{(\lfloor n/2)^2}$ "peaks," stable to small displacements, relative to adaptive value H. As shown above, there is either fixation of all loci or of all but one, at each peak. The number of such peaks depends on the position of the optimum and the relative magnitudes of the gene effects.

While the number of peaks is in general large (if n is large), the total number of stationary points ($\Delta\bar{H} = 0$) is much larger. These are of the two sorts already discussed. All of the 2^n points at which all genes are fixed, minus those which are peaks, are stable only in the absence of mutation or immigration. In addition are the usually numerous 2 to n-dimensional "saddles."

For further discussion it will be convenient to restrict attention to the case in which all genes have the same effect on the character.

This gives the simplification that at stationary points all unfixed genes have the same value of q. Assume that at a stationary point ($\Delta\bar{H} = 0$) there are n_1 genes in which the plus phase is fixed ($q = 1$), n_0 in which the minus phase is fixed ($q = 0$) and n_x which are unfixed ($q = q_x$). Let $O = k\alpha$ be the optimum.

$$q_x = \frac{k - 2n_1 - \frac{1}{2}}{2n_x - 1}, \qquad \text{.....(12)}$$

from (9).

There is, of course, a stationary point only if the values of n_1, n_0 and n_x are such that q_x falls between 0 and 1. The number of combinations with the same values of n_1, n_0 and n_x is $\frac{\lfloor n}{\lfloor n_1 \lfloor n_0 \lfloor n_x}$. All of these are stationary

points with the same adaptive value, if any one is. The adaptive value $\bar{H}$ reduces to the following expression:

$$\bar{H} = -\left[\frac{n_x\alpha^2}{2} - (M-O)^2\,(2n_x-1)\right], \qquad \text{.....(13)}$$

where $$(M-O) = \left(\frac{k-2n_1-n_x}{2n_x-1}\right)\alpha.$$

The points which are stationary merely because all factors are fixed ($n_x=0$) have, of course, the mean adaptive value

$$\bar{H} = -(M-O)^2 = -(k-2n_1)^2\alpha^2.$$

This may range from 0 to very large negative values. On the other hand, a stationary population with even a large number of unfixed factors is not handicapped very much if its mean is at the optimum. In this case, $\bar{H} = -\frac{n_x}{2}\alpha^2$.

For example, with n factors with unit effects and optimum at the mid-point of the range ($k=n$), the adaptive values of completely fixed combinations may be as low as $-n^2$ while a population in which no factors are fixed, all values of q being $\frac{1}{2}$, would have a value of $\bar{H}$ only $\frac{n}{2}$ points below that of the optimal fixed combination. This is the greatest depression for any "saddle," since the term $(M-O)^2\,(2n_x-1)$ is necessarily positive for all values of n_x except 0. Thus the population can pass from one peak to any other of the $\frac{\lfloor n}{(\lfloor n/2)^2}$ "peaks" without crossing any but very shallow valleys.

COMPLETE DOMINANCE.

It is important to compare the preceding results with those found where there is complete dominance of gene effects on the primary character. Using p_i for the frequency of a recessive gene and α_i for the effect of the corresponding dominant gene (whether plus or minus), the mean adaptive value $\bar{H}$ of the population and γ_i the momentary net effect on adaptive value of replacing a_i by A_i, are as follows:

$$\bar{H} = -\Sigma\alpha^2p^2(1-p^2) - (M-O)^2, \qquad \text{.....(14) [=69]}$$

where $M = \Sigma\alpha\,(1-p^2)$,

$$\gamma_i = -\alpha_i p_i[\alpha_i(2p_i^2-1) + 2(M-O)]. \qquad \text{.....(15) [=70]}$$

As before (equation 5), $\Delta\bar{H}=0$ if each p_i is 0, 1 or such a value that $\gamma_i=0$. In this case if $p_i=0$, $\gamma_i=0$. There is instability of a fixed dominant

($p_i=0$) in the face of occasional mutation if $\gamma_i<0$, which occurs if the mean exceeds the optimum by more than half the effect of a dominant plus gene or is below the optimum by more than half the effect of a dominant minus gene. The value of γ_i is of course exceedingly small in either case.

If $p_i=1$ (fixation of recessive), dominant mutations will tend to accumulate if $\gamma_i>0$. This occurs if $(M-O)<-\frac{\alpha_i}{2}$, where the mutation has a plus effect, and if $(M-O)>\frac{(-\alpha_i)}{2}$ if α_i is negative.

As the effect of replacing a_ia_i by A_iA_i is to change the mean by α_i, one or the other homogenic population must be stable against rare mutations. It is, however, possible for $\overline{H}$ to remain unchanged for all frequencies of one gene.

The condition that the γ's for all unfixed gene pairs be zero is that for each of them

$$p_i^2=\tfrac{1}{2}-\frac{M-O}{\alpha_i}. \qquad \text{.....(16)}$$

But as $M=\Sigma\alpha\,(1-p^2)$, p_i^2 drops out. Thus the value of the character $\overline{H}$ at any of these equilibrium points remains unchanged by change in any one of the gene frequencies. But change of any one at such a point will change the γ's of all others. Thus these points are all of the nature of "saddles." This agrees with conclusions of Fisher (1930) and of Haldane (1932) reached by different methods.

The condition for such a saddle is analogous to that in the case of no dominance. The range of variation of the primary character possible with a given set of equally effective unfixed factors, for n_x of which the plus phase is dominant (effect α) and for m_y of which the minus phase is dominant (effect $-\alpha$), is from $-m_y\alpha$ to $n_x\alpha$. The optimum must fall more than half a gene effect within these limits.

The nature of the "surface" of adaptive values ($\overline{H}$) is similar in many respects to that in the case of no dominance. Again assuming that the effects of all gene differences are the same in magnitude, but assuming that in n pairs the dominant has a plus effect while in m it has a minus effect, we may distinguish the following classes:

Dominant plus genes		Dominant minus genes	
p	No. loci	p	No. loci
0	n_0	0	m_0
1	n_1	1	m_1
$\sqrt{\frac{1}{2}-\frac{M-O}{\alpha}}$	n_x	$\sqrt{\frac{1}{2}+\frac{M-O}{\alpha}}$	m_y

The number of combinations with the same set of 6 numbers is

$$\frac{\lfloor n \quad \lfloor m}{\lfloor n_1 \lfloor n_0 \lfloor n_x \lfloor m_1 \lfloor m_0 \lfloor m_y}. \qquad \text{.....(17)}$$

All of these are stationary points if p_x and p_y for unfixed factors fall between 0 and 1. Assuming that the optimum is at $k\alpha$, we have

$$p_x^2 = \frac{n_x + n_0 - m_0 - k - \frac{1}{2}}{n_x + m_y - 1}, \quad p_y^2 = 1 - p_x^2, \qquad \text{.....(18)}$$

$$\bar{H} = -\left[\frac{(n_x + m_y)\alpha^2}{4} - (M - O)^2 (n_x + m_y - 1)\right]. \qquad \text{.....(19)}$$

For completely homogenic populations this, of course, reduces to $-(M-O)^2$ which may be a very large negative number. For "saddles" with mean at the optimum it reduces to $-\frac{(n_x + m_y)\alpha^2}{4}$ which is relatively small. Again we find that all peaks are connected by shallow saddles.

NATURE OF EVOLUTIONARY PROCESS.

If evolution were controlled only by selection, the locus of a population characterised by any given set of gene frequencies would move up the steepest gradient in the field, each gene frequency changing at the rate $\Delta q\ (= s\gamma q\,(1-q))$ and the mean adaptive value rising at the rate $\Delta \bar{H}\ (= s\Sigma\gamma^2 q\,(1-q) = s\sigma_G^2)$ per generation. This process, supplemented by the occurrence of wholly new mutations favourable from the first is that which has been investigated chiefly by Haldane in 1924 and later, and by Fisher (1930).

Having reached a "peak" at the optimum grade of the character in question such evolutionary change must cease until conditions change. Any new mutation must necessarily cause a shift from the optimum and therefore be injurious at its first appearance as Fisher (1930) has pointed out. Of course if the optimum is beyond the current limits of variation, there is the possibility of slow advance through utilisation of new mutations (each with chance of reaching fixation of $2s$ (Fisher, 1930)). But the process ceases with attainment of the optimum grade in all respects.

Indeed it may appear that there is no possibility of further advance by any mechanism. We have seen that with an intermediate optimum there is in general a very large number of separate peaks separated by shallow "saddles." But all of these peaks must be at the same or very nearly the same level, and even if the locus of the population could by some means be moved across a saddle to a new peak it would mean no advance.

The subject presents a somewhat different aspect when we recall that genes in general have multiple effects. The system of peaks relative to one character is not independent of that relative to another. Moreover, it is the harmonious adjustment of all characteristics of the organism as a whole that is the object of selection, not the separate metrical "characters." It is estimated that there are many thousands of genes at least in higher organisms (about 15,000 in *Drosophila melanogaster*, according to Gowen and Gay), and each of these is probably capable of mutating through indefinitely extended series of multiple allelomorphs. No limit can be set to the number of possible combinations, and it seems safe to postulate an inconceivably great number of "peaks," many of them characterised by different harmonious combinations of characters (although many also for the same character). These may be at all levels and of all orders of dominance and subordination in relation to each other. It has seemed to me (1929 *et seq.*) that the central problem of evolution (as of live stock improvement (Wright, 1920, 1922)) is that of a trial and error mechanism by which the locus of a population may be carried across a saddle from one peak to another and perhaps higher one. This view contrasts with the conception of steady progress under natural selection developed in most extreme form by Fisher (1930). Haldane has taken to some extent an intermediate position. He notes (1931) that almost every species is to a first approximation in genetic equilibrium, and after treating mathematically the two-factor case of "metastable equilibrium" he suggests that in many cases "the process of species formation may be a rupture of the metastable equilibrium." The mathematical analysis in the present paper deals with a case in which there may be innumerable separate peaks though all at approximately the same level. It may be looked upon as a simplified model of the complex case in which adaptation of the organism as a whole replaces that of a single metrical character. Consideration of the means by which the locus of a population may be carried across a saddle may be of interest from this standpoint.

The rate of mutation of particular type genes has been found to be of the order of 10^{-5} or 10^{-6} per generation in *Drosophila* (Muller, 1928) and corn (Stadler, 1930). This is enough to prevent complete fixation of any genes in large populations. There may be special cases in which mutation pressure drives the locus of a population from one peak to another against the pressure of selection. In general, however, mutation pressure seems to be so low compared with selection pressure that the population would merely be held at a point a little below a particular peak. In the case of no dominance this point is approximately at the array of values typified

by $q_i = 1 - \frac{u_i}{s\alpha_i^2}$ [43] and in that of dominance by $p_i = \sqrt{\frac{u_i}{s\alpha_i^2}}$ (where u_i is the rate of mutation of gene A_i).

If the population is not indefinitely large, the accidents of sampling will cause independent fluctuations about this point of equilibrium in all of the gene frequencies. Each of these distributions is I-shaped if $4Nu$ and $4Ns$ are large (N effective size of breeding population) but J or U-shaped if $4Nu$ and $4Ns$ are less than 1 (Wright, 1931). While the rate of change per generation of gene frequency due to accidents of sampling is low (causing fixation at the rate of $1/2N$ per generation in the absence of selection and mutation) it is possible that in the course of time it may carry the system of gene frequencies across a shallow saddle to a new peak.

The effectiveness of this mechanism is enormously increased if the population is subdivided into many local groups which breed largely within themselves. The distribution of gene frequencies under random sampling is here determined by the relation between effective size of the local group and the cross breeding index. The rate of random drift of each gene frequency may be relatively rapid per generation. The shallow saddles would be crossed so easily that no local group would be expected to stay long at the same peak and no two sufficiently isolated local groups would occupy the same peak at a given time. As far as the metrical character in question is concerned there would be no appreciable changes. The average in all local groups would remain very close to the optimum even when the locus is crossing a saddle. But there would be a kaleidoscopic shifting among other characters, affected by the same genes, and at the time subject only to selection of second order importance. At any time combinations might be reached by chance, in particular local groups, with effects of the first order of importance, leading to expansion of such groups (intergroup selection). This process should be of much greater evolutionary significance if considered with respect to total adaptive value of the organism, instead of approach of a particular character to an optimum.

So far we have assumed that conditions are constant. A drastic change of conditions, resulting in a drastic shift in the position of the optimum, would be followed by steady evolutionary change of the type described by Haldane and Fisher until the lost ground is regained and the mean again coincides with the optimum. But minor changes of conditions, shifting the position of the optimum back and forth by no more than the effect of a single gene, will have evolutionary consequences of a different sort. With such a shift of the optimum, the old peak will be depressed and there will arise in general a large number of new peaks immediately about

it. To which of these the population moves will depend on the preceding accidents of sampling. If now the optimum shifts back to its original position, it will be very unlikely that the population will move back to the original peak. Thus trivial oscillations in conditions will be enough to carry the population to any peak in the system with similar consequences for other characters to those suggested above. Again the process will be enormously speeded up if there is local inbreeding and there are slight local differences in conditions.

The combination of the effects of inbreeding and of varying local conditions of selection provide a mechanism for the indefinitely continued process of trial and error among local populations with respect to gene *combinations* which is probably necessary for progressive evolution.

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