

On fitness and the cost of natural selection

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1. INTRODUCTION

In genetic experiments the population size is normally not a biologically important variable but is determined by extraneous conditions or laboratory facilities; the same is true in sampling natural populations as well as in breeding experiments. The geneticist is therefore compelled to think in terms of relative frequencies of gene variants rather than in absolute numbers of their carriers. Accordingly, the mathematical formulas used by geneticists usually refer only to relative frequencies and relative fitnesses. They describe the structural changes in a population satisfactorily as long as the total population size remains constant. This condition is usually inconsequential because in practice population sizes remain nearly constant over moderate periods of observation. A novel situation confronts us in evolutionary theory when one considers developments over extremely long periods. The familiar formulas then introduce an error which is negligible over moderate time-intervals, but whose cumulative effect may be so great that the whole picture changes when absolute population sizes are taken into account. This seems to be true in particular for the calculation of the cost of natural selection, for problems of survival of genes and for the notion of an unstable equilibrium.

This paper is written by a mathematician, and accordingly no new biological models or hypotheses are advanced. The models we study are the familiar ones obtained by applying the Mendelian laws to a single isolated locus. Obviously such a model is too crude to reflect the deeper problems currently exciting geneticists. In fact, a one-locus Mendelian population is a mathematical fiction in the sense that it cannot be observed in nature whereas it could be simulated on a computer. Despite all this the model continues to be used for purposes of orientation, and certain purely mathematical deductions from it (such as the notion of equilibrium and the tendency to it) continue to play a fruitful role in genetical thinking. It may be useful therefore to present the theoretical conclusions from this model when proper account is taken of the fluctuations in the population size. The point is that (save in certain exceptional configurations) a Mendelian population cannot have a constant rate of increase, that is, it cannot be Malthusian. Given the various fitnesses, it is possible to calculate the size N_n of the n th generation; if only the relative fitnesses are known, the size N_n can be calculated up to a factor μ^n where μ is the maximal absolute fitness. When this is done there seems to be more room and flexibility for evolutionary processes than is sometimes supposed.

For clarity we begin with a review of some fairly obvious facts concerning

Malthusian populations and the notion of environment. Next we turn to the main topic of this paper, namely, an analysis of the calculation of the cost of natural selection made by J. B. S. Haldane and M. Kimura (Haldane, 1957, 1960; Kimura, 1960, 1961). The problem is roughly to estimate the effect on the ultimate population size of a depression in fitness at one particular locus due to an assumed change of the prevailing conditions. The loss in population size is called selective death by Haldane, and substitutional (or evolutionary) load by Kimura. This loss was found to be practically independent of the amount of depression (as long as the latter is small) and so enormous as to lead to the conclusion that simultaneous selection at several loci cannot proceed at a reasonable rate. The present scrutiny of these calculations was undertaken at the suggestion of Th. Dobzhansky who commented on the paradoxical nature of Haldane's result and its grave consequences. Other evolutionists were worried by Haldane's conclusions and it was hoped that a revision of the observational data may lead to a more acceptable result (Brues, 1964; Mayr, 1963).*

Haldane calculated the cost of selection for various types of organism, but since the basic principle remains the same it will suffice to analyze in detail only the case of haploid organisms, which is mathematically by far the simplest. Indeed, in this special case no problem arises when one considers the population size. In sections 4–5 we analyze Haldane's definition and the possibility of alternative models assuming constant population size.

Next we consider the selection at an autosomal locus in a sexually reproducing diploid without mutations. The (rather unexciting) result of the formal calculation of the cost of natural selection is presented in a companion paper (Feller, 1966) but here we discuss some noteworthy features requiring only a minimum of mathematics.

In section 6 we indicate how the true population size can be calculated. In section 7 it is shown that the so-called state of *unstable* equilibrium is easily misinterpreted: under the usual assumptions the population is destined to die out rather than to be maintained at an equilibrium.

In section 8 we turn to the problem of survival of a gene, which cannot be treated without reference to absolute population size because the fact that the frequency q_n of the a -gene tends to zero does not necessarily imply the disappearance of this gene. Indeed, when $q_n \rightarrow 0$ the absolute number of a -genes may increase from generation to generation at a geometric rate. Even if the total population is kept at a fixed level, the process of elimination of the a -genes may be so slow that these genes are not in practice eliminated from the evolutionary process. The examples of sections 9 and 10 will clarify this point.

2. MALTHUSIAN POPULATIONS AND CONSTANT ENVIRONMENT

Consider a uniform population with non-overlapping generations in which each individual gives rise to a random number of direct descendants. If μ is the expected

* After completion of this paper and the publication of the companion paper (Feller, 1966) I became the grateful recipient of letters with references to other pertinent papers.

number of such descendants and the parental population consists of N_0 individuals, the expected size of the next generation is $N_1 = N_0\mu$. The actual size is a random variable but for large populations the true size is likely to be close to the expected size and it is therefore usual to treat N_1 as if it were the actual size. Assuming unchanged conditions we get for the expected size of the next generation $N_2 = N_1\mu = N_0\mu^2$, and generally $N_n = N_0\mu^n$. This is the well-known Malthusian model for population growth.

When $\mu = 1$ the expected population size remains constant. A large population may be expected to remain constant over a number of generations, but the cumulative effect of chance fluctuations will grow more pronounced and ultimately a *Malthusian population with fitness $\mu = 1$ is bound to die out.** A similar remark applies to Mendelian populations and shows that caution is indicated in dealing with very large time intervals and with assumed states of equilibrium.

Obviously evolution could not occur without some species having fertilities exceeding 1, and then the Malthusian model breaks down for a different reason. With increasing density the population is bound to affect the environment, and hence the assumption of constant external conditions becomes biologically untenable. To take this into account one assumes that the fertility μ depends on the population density in such a manner that the expected population size will tend to a maximum value N_∞ . Over reasonably short observational periods the fertility will not change appreciably, and over such periods the population will appear as practically Malthusian. However, when the model of density-dependent fertilities is accepted, the observed fertilities at any time cannot be used to predict the ultimate population size: of two populations the one with lower fertility may tend to a higher plateau.

Another limitation of the long-run significance of the Malthusian parameter (and of fitness in general) is inherent in the relativity of the notion of environment. To explain this by a simple example, consider a population which in two separated geographic regions R_1 and R_2 has different fertilities μ_1 and μ_2 . We suppose positive migration probabilities s_1 and s_2 with the effect that an offspring of an individual in R_1 may serve as a parent in either R_1 or R_2 , with corresponding probabilities $1 - s_1$ and s_1 . Initially the population may be distributed in an arbitrary manner, for example, be concentrated in region R_1 . Assuming constant conditions the two regional subpopulations in R_1 and R_2 tend to become practically Malthusian with the same fertility rate μ which is a complicated average† of μ_1 and μ_2 . Thus the effective long-run fertility μ depends on the migration probabilities between the two regions, however small these probabilities may be. To an observer in R_1 one

* This is a basic result of the Galton-Fisher theory of branching processes which applies to Malthusian populations. Readers puzzled by the phenomenon that a population with fixed expected size can be condemned to extinction may consider a hypothetical population as follows: the n th generation consists with probability $1/n$ of n individuals, and with probability $1 - 1/n$ of 0 individuals. The expected size of the n th generation equals 1, but the probability that the population survives n generations is only $1/n$ and tends to zero.

† Letting $a_j = \mu_j(1 - s_j)$ one gets (using the theory of Markov chains)

$$2\mu = a_1 + a_2 + \sqrt{(a_1 - a_2)^2 + 4\mu_1\mu_2s_1s_2}$$

population may appear less fit than another, and yet it will ultimately grow faster. This is so because the whole biological environment contains both R_1 and R_2 while any given observer sees only one region and the corresponding fertility. In the long run the hidden parameters turn out to be crucial. With obvious verbal changes this model applies also to temporal chance fluctuations within the same region.

3. HAPLOID ORGANISMS AND MIXED MALTHUSIAN POPULATIONS

The theory of selection in haploid, clonal, or self-fertilizing organisms is concerned with a gene pool of two kinds of genes A and A' . Assuming constant external conditions and disregarding possible mutations one is led to a model in which there is no interaction between the genes. Mathematically the nature of the genes is then irrelevant and in effect we are dealing with a composite (mixed) population consisting of two Malthusian components. To fix ideas, denote fertilities in the two components (or the fitnesses of the A - and A' -genes) by μ and μ' , so that the ratio

$$\frac{\mu'}{\mu} = 1 - k \quad (3.1)$$

represents the relative fitness of A' . The sizes N_n and N'_n of the two components in the n th generation are given by the geometric progressions

$$N_n = N_0 \mu^n, \quad N'_n = N'_0 \mu'^n \quad (3.2)$$

and the total population size equals $N_n + N'_n$. As usual we denote the relative frequencies of A and A' by p_n and q_n , so that

$$p_n = \frac{N_n}{N_n + N'_n}, \quad q_n = \frac{N'_n}{N_n + N'_n} \quad (3.3)$$

Since A and A' are representative in the proportion $p_n : q_n$ the average rate of increase* μ_n of the n th generation is given by

$$\mu_n = p_n \mu + q_n \mu' = \mu(1 - kq_n) \quad (3.4)$$

This rate of increase varies from generation to generation except in the trite case $k=0$ when A and A' have the same fertility. Accordingly, a mixture of two Malthusian populations is *not* Malthusian, and the expected population size remains constant only in the trite case $\mu = \mu' = 1$. On the other hand, if k is positive, the frequency q_n tends to zero, and from (3.4) it is seen that the effective fertility μ_n tends to μ . This means that after a sufficiently long time the population will be practically Malthusian with a rate of increase μ . It should be noticed, however, that it may take an exceedingly long time to complete this process.

Example. In his calculations of the cost of natural selection Haldane assumes that prior to a sudden change in the environment the A genes had been at a disadvantage, and hence their frequency p_0 in the parental generation is exceedingly

* That is, the ratio of the expected sizes of two successive generations.

small. The following calculations are based on the value of $p_0 = 10^{-4}$ which Haldane quotes repeatedly as relatively large. It is assumed that k is positive, but small. The A' -genes are then at a disadvantage and their relative frequency q_n decreases steadily from the initial value $q_0 = 0.9999$ to 0. Table 1 shows how many generations it takes to reduce the frequency q_n to 0.99, 0.9, and so on. The values are calculated from (3.5) and do not depend on the absolute fitness μ . When $k = 0.01$ it takes some 460 generations to reduce the frequency q_n to 0.99 and some 1000 generations to reduce it to 0.3. The average fitness of the whole population equals initially 0.99001μ ; eventually the population is homozygous with fitness μ . Natural selection increases the fitness by 1%, but after 460 generations it is still only 0.9901μ and after 1000 generations only 0.997μ . In other words, 1000 generations cover only seven-tenths of the whole selection process. It is true that for $k = 0.1$ the process is slightly more than 10 times faster, but for smaller k it is incredibly slow. In the extreme example, $k = 10^{-3}$, 1000 generations will reduce q_n only to 0.99973 and the total fitness is increased only by 0.0000003μ .

Table 1. Number n of generations required to reduce the initial frequency $q_0 = 0.9999$ of the A' -gene to the given value q

$q =$	0.99	0.9	0.7	0.5	0.3	0.1
Assuming:						
$k = 0.01$	459	698	832	917	1000	1135
$k = 0.1$	44	67	79	87	95	109

Returning to the general situation note that the sizes of the A - and A' -components are given by (3.2) whence

$$q_n = \frac{q_0(1-k)^n}{p_0 + q_0(1-k)^n} \tag{3.5}$$

When $k > 0$ one has $q_n \rightarrow 0$. This means that the relative size of the A' -component tends to zero, but this is not necessarily true of the absolute size. Several situations are possible.

Case (i). If $\mu > \mu' > 1$ each of the two components increases at a geometric rate. (Biologically this model ultimately breaks down for the reasons discussed in the preceding section.)

Case (ii). If $\mu > 1 > \mu'$ the expected size of the A' -component decreases geometrically, but the total population size exhibits in the long run a geometric increase.

Case (iii). If $\mu = 1 > \mu'$ the A' -component dies out geometrically. The expected size of the A -component remains constant (namely N_0), but because of chance fluctuations even the A -component is bound to die out ultimately (see footnote, page 3). Within the deterministic approximation which equates actual population size with its expected value one would say that the ultimate population size equals N_0 : the A -component remains constant while the A' -component dies out.

4. HALDANE'S SELECTIVE DEATHS

Haldane calculated the cost of natural selection for various Mendelian populations, but the simplest case appears under the heading 'selection in haploid, clonal, or self-fertilizing organisms' (Haldane, 1957, 1960). The other cases present greater biological interest, but require deeper mathematical techniques. The basic principle being the same in all cases, we shall discuss in detail only the simplest case. As Haldane remarks, low mutation rates do not affect the general picture and are therefore disregarded. We are then concerned with the simple model of the preceding section: there are two types of gene, A and A' , with fertilities (absolute fitnesses) μ and $\mu' = 1 - k$. The genes do not interact in any way. In the n th generation their expected numbers are N_n and N'_n , respectively, and they appear in the proportion $p_n : q_n$ [see (3.2) and (3.3)]. To comply with the general usage (and Haldane's notation) we put* $\mu = 1$ and $\mu' = 1 - k$. The expected size of the A -component then remains for all times equal to N_0 , while the number of A' -genes decreases geometrically. The loss in the n th generation equals $N'_n - N'_{n+1}$, and these losses add up to

$$(N'_0 - N'_1) + (N'_1 - N'_2) + \dots = N'_0 \quad (4.1)$$

This is intuitively obvious seeing that the total population size decreases from $N_0 + N'_0$ to N_0 .

It may now be best to analyze Haldane's notion of selective deaths formally before considering its biological background and motivation. Using the size $N_0 + N'_0$ of the parental generation as unit of measurement Haldane defines as selective deaths in the n th generation the quantity $d_n = kq_n$; the sum $D = d_0 + d_1 + \dots$ then represents the total of selective deaths.† The q_n are given by formula (3.5), and from it Haldane obtains an approximation to the sum D using a subtle and original approach.

It will be noticed that (using the original population size $N_0 + N'_0$ as unit) one has $N'_0 = q_0$, and so $kq_0 = (1 - \mu')N'_0 = N'_0 - N'_1$. For the parental population therefore the selective deaths d_0 are the same as the decrement in population size $N'_0 - N'_1$, and this interpretation agrees with Haldane's general explanations. But since every generation can be taken as parental it follows that the number of selective deaths in the n th generation should equal $N'_n - N'_{n+1}$ which is *not* the same as Haldane's $d_n = kq_n$ because the population size has decreased from $N_0 + N'_0 = 1$ to $N_n + N'_n < 1$. Now Haldane was interested only in approximations, and since k is small, the effective population size does remain approximately constant over rather long periods of time. It seems therefore obvious that conceptually Haldane's selective deaths are identical with the true decrements $N'_n - N'_{n+1}$, but that in his

* There is no serious restriction in this convention. With an arbitrary μ it suffices to measure the size of the n th generation in units μ^n to reduce the general model to $\mu = 1$. It must be noted, however, that μ is the fertility of the A -component and not of the whole population. As was remarked above, the fertility of the latter varies from generation to generation.

† Kimura's substitutional (or evolutionary) load differs from Haldane's d_n by an adjustment factor α^n to which the remark of the preceding footnote applies.

calculation he used the standard mathematical approximation familiar to geneticists and applicable as long as the population size remains nearly unchanged.*

In other words, Haldane actually defines the selective deaths in a given generation as the loss $N'_n - N'_{n+1}$ in population size. The total selective deaths then amount to the number of A' -genes originally present, in accordance with the fact that the A' -component is ultimately lost. The formula $d_n = kq_n$ expresses the number of selective deaths in units of the population size of the n th generation, and the calculations neglect the effect of the changes in this size. The cumulative effect of this approximation is disastrous. In fact, Haldane concluded that (as long as k is small) the total of selective deaths is practically independent of k and given by

$$D = \log \frac{1}{p_0} \tag{4.2}$$

(in units of the size of the parental population). For reasons discussed in the next section we are interested only in situations where p_0 is small, and hence D large. Indeed, Haldane considers $p_0 = 10^{-4}$ as rather large, and with it $D = 9.2$. Haldane's general conclusion is that the selective deaths involve 'a number of deaths equal to about 10 or 20 times the number in a generation, always exceeding this number, and perhaps rarely being 100 times this number. To allow for occasional high values I take 30 as a mean'.

To appreciate the magnitude of this estimate it should be remembered that the deaths are due solely to the disability of the A' -genes and that the total of A' -genes ever to be born equals

$$N'_0 + N'_1 + N'_2 + \dots = N'_0(1 + (1 - k) + (1 - k)^2 + \dots) = N'_0/k$$

In extreme cases the number D of presumed selective deaths may exceed the number of A' -genes ever to be born.

5. DISCUSSION OF THE MODEL

As we have seen, assuming strictly constant conditions, the expected total population size cannot remain constant except when $\mu = \mu' = 1$. Given a fixed relative fitness $(\mu'/\mu) = 1 - k < 1$ it is possible to obtain a constant population size either by postulating that the fertility μ is an appropriate function of the population size, or else by assuming the existence of external forces ensuring the desired stability. One may suspect that Haldane had some such model in mind, in particular since the quoted sentence refers to the number 'in a generation' rather than in the parental generation. It seems to me that Haldane's discussion leaves no doubt that he was thinking in terms of our model with constant environment and constant fertilities, and that notions of steady state and constant populations enter

* The reader may wonder why Haldane should have resorted to subtle approximations when the exact result can be written down in the simple form (4.1). The answer is that Haldane was interested in more general situations which admit of no simple solution. In other words, the general problem did require a new approach, and no general method is universally the best in every special case.

the discussion merely as an unintended byproduct of the routine mathematical formulas to which geneticists are used. It is my impression that similar unwarranted extrapolations in evolutionary theory are accepted as unavoidable mathematical truths and render biological thinking more difficult. It may therefore be useful to discuss the alternative models in some detail. However, the following discussion has no bearing on the subsequent sections. Let us consider the following extreme possibilities:

(a) The absolute fitnesses are constant, but the environmental conditions are such as to maintain a constant population size (say by immigration or emigration). It suffices to consider the simple case $\mu = 1$, $\mu' = 1 - k < 1$. The loss caused by the disadvantage of the A' -genes must be replaced by immigration or some other method. The cost of natural selection is not borne by the population as such, but by the assumed mechanism of replacement. This cost depends on the method of replacement. The most economical method consists in replacing each A' -gene that is lost by a superior A -gene. The replacements may occur at various times, but each A' -gene in the parental population will ultimately cost exactly one replacement, and the total number of replacements equals the number N'_0 of A' -genes originally present. The least economical way consists in replacing each A' -gene lost by another A' -gene. With this system the composition of the population remains unchanged, and each generation requires the same number of replacements (namely $q_0 N'_0$). Among the infinity of intermediate procedures there is one whose total cost is given by Haldane's expression $D = k(q_0 + q_1 + \dots)$. It consists in adding to the n th generation A - and A' -genes in the proportion $p_n : q_n$ so as not to upset the proportions observed. Under no conditions does the population itself bear any load, and the number of replacements is a measure of the efficiency of the mechanism of replacements rather than of the cost of selection.

(b) At the other extreme one may assume a constant environment and a fertility μ depending on the actual population size so as to ensure a steady state. In other words, it is assumed that the population size will change from the original size, say unity, to a steady-state level $N_\infty \leq 1$. If $N_\infty = 1$ there is no drop in population size, and hence no cost of natural selection. Otherwise the variable size of the initial generations must be taken into account, and our argument is not affected by the new model. Furthermore, the cost of selection now depends on the manner in which μ depends on the population size; this presents a biological rather than a mathematical problem.

The biologist may think of a variety of conditions producing a nearly constant population size, but mathematically it will lead to a combination of our two extreme situations.* The question of the cost of natural selection appears in a new light in each case.

Finally a word concerning the biological background of the problem which may

* This conclusion may conflict with biological facts and intuition. If it is untenable, so is the basic assumption of the model that the gene pair (A, a) may be treated independently of others. (It must be borne in mind that two strongly interacting species cannot be treated separately as Malthusian populations.)

be described very roughly as follows. It is supposed that originally the population was in a near equilibrium with fertility rates α and α' . At a time when the population size is N_0 and the two genes stand in the proportion $p_0:q_0$ the external conditions are changed with the effect that from now on the fertilities are μ and μ' . It is assumed that the change has a negative effect on the population size and the problem is to find the anticipated new level of equilibrium. Before the change the A' -genes had been at an advantage, and hence the A -genes were maintained at a low level by mutation. This explains the assumed low values for p_0 . Note that the development of our population is independent of the fertilities α and α' before the change to the new fertility rates μ and μ' , but without keeping the original situation in mind one would obviously never speak of selective *deaths*. Haldane had, of course, good reasons to *assume* an actual depression in the fertility of the A' type. This does not change the fact that his arguments in no way depend on this assumption; and the results should apply for all past fitnesses α and α' , and hence *both* fertilities have *increased*. To give an extreme example, the change from $\alpha = \alpha' = \frac{1}{2}$ to $\mu = 1$ and $\mu' = 0.99$ would be called a 'depression' merely because a *relative* fitness is decreased. But how can a doubling of fertilities in Malthusian populations lead to deaths? The whole problem is affected by the habitual reliance on relative fitnesses as if they had an objective meaning.

6. DIPLOID POPULATIONS

Haldane's theory applies to arbitrary Mendelian populations, and although the calculations are more intricate, the principle is the same. We shall therefore be satisfied with an indication of the solution of his problem when absolute population sizes and fitnesses are taken into account.

Consider then a random-mating population with non-overlapping generations and an autosomal pair of alleles A and a not subject to mutations. We wish to study the development of the absolute population size and associate with the three genotypes AA , Aa , aa fixed *absolute* fitnesses w_1 , w_2 , w_3 . In other words, w_1 is the expected number of offspring (counted at an appropriate stage of development) resulting from a pairing of two A -genes. As usual we denote the two gene frequencies in the n th generation by p_n and q_n . We have then the familiar relations

$$p_{n+1} = \frac{p_n(w_1 p_n + w_2 q_n)}{w(p_n)}, \quad q_{n+1} = \frac{q_n(w_2 p_n + w_3 q_n)}{w(p_n)} \tag{6.1}$$

where

$$w(p_n) = w_1 p_n^2 + 2w_2 p_n q_n + w_3 q_n^2 \tag{6.2}$$

is the average fitness of the n th generation. If N_0 is the size of the parental population then the expected sizes N_n of the successive generations can be calculated recursively from the relation

$$N_{n+1} = w(p_n) \cdot N_n \tag{6.3}$$

Our problem is to find out how the choice of the initial frequencies (p_0, q_0) affects the ultimate population size. The principle of the calculations may be illustrated by an example.

Example. Let $w_1 = 0.36$, $w_2 = 1.16$, and $w_3 = 0.96$. For convenience we take the initial population size as unit, that is, we put $N_0 = 1$. For the initial gene frequencies we take $p_0 = 0.8$ and $q_0 = 0.2$. From (6.2) one gets $w(p_0) = 0.64$. The frequencies p_1 and q_1 in the first generation can now be calculated from (6.1), and the population size N_1 is obtained from (6.3). Proceeding in this manner we get the development summarized in Table 2.

Table 2

Generation	Frequency p_n	Fitness $w(p_n)$	Population size
0	0.80	0.64	1
1	0.65	0.80	0.64
2	0.52	0.90	0.51
3	0.43	0.95	0.46
4	0.37	0.97	0.44
5			0.42

The fitness $w(p_n)$ of the n th generation tends to 1, and the absolute population size N_n tends to a limit N_∞ which equals about 0.4. The true fitness varies from generation to generation, and our population is not Malthusian. Nevertheless, after a sufficient number of generations the fitness and the expected population size remain practically constant. The gene frequencies p_n and q_n converge to the stable equilibrium (\bar{p}, \bar{q}) given by $\bar{p} = 0.2$, $\bar{q} = 0.8$. If the population had started at this state of equilibrium all the gene frequencies p_n would have remained unchanged, and the population would have been maintained at the original level. The loss of some 60% of the original population is therefore attributable to the rather unfavourable initial gene frequencies $p_0 = 0.8$ and $q_0 = 0.2$. In this sense it represents the cost of natural selection (although Haldane preferred to exclude the case of a stable equilibrium).

The general case of a *stable* equilibrium can be treated in like manner, and the calculations will not be spelled out because the result is not exciting. Note, however, that the use of absolute fitness permits us to formulate various conclusions. For example, mutations do not affect the fitnesses w_1, w_2, w_3 but do change gene frequencies \bar{p}, \bar{q} in the state of equilibrium. Now the limit value \bar{p} is such that $w(\bar{p}) > w(p)$ for all p near \bar{p} . It follows unequivocally that small *mutation* rates always depress the ultimate fitness, and hence also the ultimate population size. As in Table 2 the fitnesses $w(p_n)$ and the population sizes N_n converge much faster than do the gene frequencies p_n .

7. THE SO-CALLED UNSTABLE EQUILIBRIUM

A more interesting situation is encountered when $w_1 > w_2 < w_3$, that is, when the heterozygotes are least fit. In this case there exists a critical point defined by the frequencies

$$\bar{p} = \frac{w_1 - w_2}{w_1 + w_3 - 2w_2}, \quad \bar{q} = \frac{w_3 - w_2}{w_1 + w_3 - 2w_2} \quad (7.1)$$

As is well known (and easily verified from (6.1)), the development now depends essentially on the initial gene frequencies p_0 and q_0 in the following way:

$$\text{If } \begin{matrix} q_0 < \bar{q} \\ q_0 > \bar{q} \end{matrix} \quad \text{then } \begin{matrix} q_n \rightarrow 0 \\ q_n \rightarrow 1 \end{matrix} \quad (7.2)$$

If $q_0 = \bar{q}$ then, theoretically, $q_0 = q_1 = q_2 = \dots$ and for this reason (7.1) is called a point of unstable equilibrium, but this term is apt to give an erroneous impression. Indeed, the chance fluctuations inherent in the Mendelian model are bound to bring the system off balance in the first generation with the effect that q_1 will not exactly equal \bar{q} . This means that an unstable equilibrium cannot be maintained but that always either $q_n \rightarrow 0$ or $q_n \rightarrow 1$. This result appears in a new light if the population size is taken into account. Only two essentially different cases are possible.

(a) Assume $w_1 = w_3 = 1$, but $w_2 < 1$. The so-called unstable equilibrium is represented by $\bar{p} = \bar{q} = \frac{1}{2}$. With any other initial frequencies (p_0, q_0) one has a tendency to homozygosity, but before this state is reached the total population size may have dwindled to a negligible fraction of its original size. Indeed, it can be shown that the expected size of the n th generation is given by*

$$N_n = \frac{p_0 - q_0}{p_n - q_n} \quad (7.3)$$

provided, of course, that $p_0 > q_0$ and the original population size N_0 is taken as unit. But then $p_n \rightarrow 1$ and $q_n \rightarrow 0$ so that the expected ultimate population size in the homozygous state equals $N_\infty = p_0 - q_0$. Thus if the initial gene distribution (p_0, q_0) is close to the so-called equilibrium ($\frac{1}{2}, \frac{1}{2}$) the expected population size dwindles to the small fraction $p_0 - q_0$. This is not quite what one expects from an equilibrium. In this special case the cost of natural selection is indeed exorbitant.

(b) Assume $w_1 > 1$ but $w_2 < w_3 < 1$. In the homozygous state aa the population decreases at the geometric rate w_3 , and hence it is bound to die out whenever $q_n \rightarrow 1$, that is, whenever the initial frequency q_0 exceeds the critical value \bar{q} . It is interesting that the elimination of the total population could have been avoided by making the homozygotes aa less fit than the heterozygote Aa , for in this case one would have $p_n \rightarrow 1$ and $q_n \rightarrow 0$. For our population with the initial gene distribution p_0, q_0 it would be preferable to have $w_3 = 0$ than $w_3 > w_2$: with a lethal in double dose the population would survive and, indeed, increase at the geometric rate w_1 .

* See Feller, 1966. The assertion can be proved by checking that

$$p_{n+1} - q_{n+1} = \frac{p_n - q_n}{w(p_n)}$$

and hence

$$N_{n+1} = \frac{p_n - q_n}{p_{n+1} - q_{n+1}} N_n$$

(see (6.1) and (6.3)). Use this relation with n replaced by $n-1, n-2, \dots, 0$ and multiply the resulting n equations. Most terms cancel, and one obtains (7.3).

8. SURVIVAL

So far we have considered diploid populations (without mutations) with fitnesses w_1, w_2, w_3 such that there exists a state of stable or unstable equilibrium. In all other cases the population will be ultimately homozygous, and we may suppose that the final state is AA . Then $q'_n \rightarrow 0$, but this does *not* imply that the a -genes die out. Indeed, the total number N'_n of a -genes depends ultimately only on w_2 , but not on w_1 or w_3 . When $w_2 > 1$ the numbers N'_n will ultimately increase at a geometric rate even though $q_n \rightarrow 0$.

To see this in detail we use the basic relations of section 6. Since we assume that $p_n \rightarrow 1$ and $q_n \rightarrow 0$ the (absolute) fitness $w(p_n)$ of the n th generation tends to the fitness w_1 of the AA type (see (6.2)). It follows that after a sufficiently large number of generations the population fitness is practically fixed at w_1 , which means that, as far as size is concerned, the population *ultimately* behaves like a Malthusian population with fertility w_1 . As we saw, the population is bound to extinction unless $w_1 > 1$.

The expected number N'_n of a -genes in the n th generation is given by $N'_n = N_n q_n$, where N_n is the expected population size. Thus

$$\frac{N'_{n+1}}{N'_n} = \frac{N_{n+1} q_{n+1}}{N_n q_n} = w(p_n) \frac{q_{n+1}}{q_n} \quad (8.1)$$

by the very definition of the fitness $w(p_n)$ (or by (6.3)). From the second relation in (6.1) it is seen that the right side in (8.1) equals $w_2 p_n + w_3 q_n$, which quantity tends to w_2 because $p_n \rightarrow 1$ and $q_n \rightarrow 0$. This means that after a sufficiently large number of generations the ratio N'_{n+1}/N'_n will be practically indistinguishable from w_2 . If $w_2 < 1$ the a -genes are doomed for extinction, but if $w_2 > 1$ this number will ultimately increase at a geometric rate. Of course, the total population size N_n increases at an even faster rate.

We have thus reached the interesting conclusion that *when the absolute fitness w_2 of the heterozygotes Aa exceeds 1, the number N'_n of a -genes will increase approximately as a geometric sequence with ratio w_2 even though $q_n \rightarrow 0$.*

It is surprising that the ultimate rate of increase of N'_n depends only on w_2 , *but not on the fitnesses of the homozygotes.** In particular, even when a is lethal in double dose the ultimate number of a -genes is the same as when the relative fitnesses of Aa and aa are the same.

It follows that a gene whose frequency q_n tends to 0 is not necessarily lost for the evolutionary process. We can go a step further. If $w_2 < 1$ the a -genes will be ultimately eliminated, but the process may be so slow that the genes survive for a period long enough to encounter changes of the environment which may modify the fitnesses. To judge the effect of the selection process we must solve two problems:

(a) Estimate the speed of the selection process, (b) estimate its cost, that is, the ratio of the ultimate population size in terms of what this size would be if the

* Under the present conditions, of course, $w_1 > w_2$ and $w_3 \leq w_2$.

population had been homozygous from the beginning. Such estimates are given in Feller, 1966, and we shall be satisfied here to give two instructive examples.

9. FIRST EXAMPLE

Assume $w_1 = w_2 > w_3$, that is, only the homozygotes *aa* have a disadvantage. As is well known, under these circumstances $p_n \rightarrow 1$ and $q_n \rightarrow 0$. It can be shown* that the expected size N_n of the *n*th generation tends to $N_0 p_0$. In other words, the ultimate population size is the same as if all *a*-genes had been removed from the parental population. The selection process in this case causes a loss of a fraction q_0 of the initial population as could be expected from the circumstance that in this example only *a*-genes are being eliminated.

This elimination process is exceedingly slow. Indeed, if $w_1 = w_2 = 1$ and $w_3 = 1 - k$ the gene frequency q_n is given approximately† by

$$q_n = \frac{q_0}{1 + kq_0 n} \tag{9.1}$$

at least when *n* is large. (Under all circumstances the right side underestimates the true value of q_n). The expected number N'_n of *a*-genes is therefore approximately

$$N'_n = \frac{N'_0 p_0}{1 + kq_0 n}$$

It seems that $k = 0.1$ would be generally considered a serious disadvantage, and yet it would take 1000 generations to reduce the initial frequency $q_0 = 0.01$ to half its value, that is, to eliminate one-half the *a*-genes. A 1000 generations should suffice for many changes in the environment but even if the assumption of constant conditions and fixed fitnesses is taken at face value it must be remembered that a population is spread over a great number of biological niches and that during a very slow process chance fluctuations are likely to produce a variety of results in different niches,

Anyhow, this discussion over-emphasizes one side of the picture in that we attributed fitness $w_1 = 1$ to the homozygotes *AA*, even though we saw in section 2 that a finite population with fitness 1 is bound for extinction. It is therefore necessary to assume that actually $w_1 > 1$, though the difference $w_1 - 1$ may be small. But then the number of *a*-genes will *increase* from generation to generation irrespective of the degree of disability of the *aa*-homozygotes. Assuming a rate of increase of 1% per generation, the size of the *n*th generation will be, approximately, $N_0 p_0 \mu^n$, where $\mu = 1.01$. The actual number of *a*-genes in the *n*th genera-

* From (6.1) one sees that $w(p_n) = p_n/p_{n+1}$, and hence $N_{n+1} = N_n p_n/p_{n+1}$. It follows by induction that $N_n = N_0 p_0/p_n$, and since $p_n \rightarrow 1$ the ultimate population size equals $N_0 p_0$.

† From the second relation in (6.1) we get

$$q_{n+1} = q_n \frac{1 - kq_n}{1 - kq_n^2} > q_n \frac{1}{1 + kq_n}$$

If the inequality $>$ were replaced by an equality sign formula (9.1) would represent the exact solution of the recurrence relation.

tion increases at a rate which is practically indistinguishable from an increase at the same rate μ . Even in the extreme case where a is lethal in double dose the actual number of a -genes in the n th generation increases *steadily* (and exceeds $N_0 p_0 q_0 \mu^n / (1 + q_0 n)$).

10. SECOND EXAMPLE

The preceding example is extreme in that the heterozygotes Aa have no disadvantage. As a fairly representative example we take $w_1 = 1$, $w_2 = \beta$, $w_3 = \beta^2$ where $\beta < 1$. For it exact formulas can be supplied.

The expected population size now tends* to $N_0 p_0^2$, which means that a fraction $N_0 q_0 (1 + p_0)$ of the original population is eliminated. In other words, each a -gene lost causes a loss of $p_0 q_0$ genes of the A -type, and so the process of selection is costlier than in the preceding example. The process itself proceeds faster, but for small $1 - \beta$ it is still exceedingly slow; the *exact*† expression for q_n is

$$q_n = \frac{q_0}{q_0 + p_0 \beta^{-n}}$$

SUMMARY

A Mendelian population without artificial external constraints does in general not increase at a constant rate. Formulas neglecting the changes in population size introduce an error which is negligible under ordinary circumstances but whose cumulative effect over long periods may be disastrous. Questions relating to the cost of natural selection, the nature of an unstable equilibrium, the survival of genes, etc. cannot be treated without regard to absolute population sizes. The limitation of the notion of relative fitnesses is illustrated by the fact that in some typical situations the survival of the a -gene depends only on the absolute fitness of the Aa -heterozygote, but not on the fitnesses of the homozygotes. Furthermore, a *decrease* of the (absolute or relative) fitness of one genotype may actually increase the viability of the population and its ultimate size.

Even when the relative frequency q_n of the a -gene tends to zero the absolute number of such genes may increase from generation to generation at a geometric rate. Therefore the circumstance that $q_n \rightarrow 0$ may be insignificant as compared to the fact that the earth cannot sustain an infinitely increasing population. Ultimately the population size is bound to influence the environment and so the fitnesses will change. Thus we must consider density-dependent fitnesses and then observed fitnesses cannot be used to predict the ultimate fate of a population. It is now known (Dobzhansky, 1965) that relative fitnesses are sometimes very sensitive

* The exact formula is now $N_n = N_0 p_n^2 / p_n^2$ as can be seen by induction from the fact that

$$w(p_n) = (p_n + \beta q_n)^2 = p_n^2 / p_{n+1}^2$$

† This can be verified from (6.1), but it is difficult to describe the method used to obtain the result.

to small changes in environment and that the same species may occupy a great variety of environmental niches. It is therefore quite likely that at least part of a population will find itself in a modified environment before too many generations have passed. For the evolution of a species and the development of new forms it is then not important that under fixed conditions the relative frequency q_n of the a -gene would tend to zero. The problem is whether the actual number of such genes will increase for a period sufficiently long to encounter changed conditions or to establish itself in new combinations. This question is significant because the convergence of the frequencies q_n to zero may be extremely slow. Thus even in a population of fixed size a disappearing gene could exist long enough to contribute to evolutionary processes.

Speaking generally, the thinking in terms of an assumed steady state and relative fitnesses seems to aggravate the problem of applying the wonderful results of modern genetics to the theory of evolution. For example, various mechanisms which are often considered as eliminating genetic variability may sometimes produce the opposite effect. The theory of evolution should distinguish between what the physicist would call macroscopic and microscopic equilibrium. Even if the world as we see it were in a perfect equilibrium this would not imply an approximate steady state for individual species, not to speak of genes. It is clear that an evolution to higher forms depends on a frequent decrease in fertility rates. If one considers slow changes rather than an unattainable steady state then a loss of fitness may be beneficial in the long run and contribute to genetic variety.

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