"Haldane's Dilemma" and the Rate of Evolution

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A recent estimate of the maximum rate of evolution by natural selection may be too low, based as it is on a maxim that seems to be erroneous.

KIMURA[1] has recently argued that the rate of evolution at the molecular level is greater than can be accounted for by natural selection, so that a large part of the observed molecular changes must be selectively almost neutral, and be established by drift.

I do not want to query the conclusion that drift has been important, but Kimura's conclusion that the rate of evolution is too great to be explained by natural selection can be queried on two grounds. First, his estimate of the rate of molecular evolution may be too high. It is based on the assumption that the whole haploid complement of DNA in man (4×10^9 nucleotide pairs) codes for proteins the rate of amino-acid substitution of which has been the same as the average for three proteins (haemoglobin, cytochrome *c*, triosephosphate dehydrogenase) for which estimates can be made. This assumption may be seriously wrong; for example, it would overestimate the rate of amino-acid substitution by several orders of magnitude if the "master–slave" hypothesis of Callan[2] and Whitehouse[3] is correct. It is difficult, however, to see what other assumption could be made at the present time, and it will not be criticized further here.

The chief intention of this article is to argue that Kimura's estimate of the maximum rate of evolution may be too low by several orders of magnitude.

The Argument from the Cost of Natural Selection

Kimura's estimate is based essentially on an argument first put forward by Haldane[4]; it is this argument which I believe to be erroneous. Haldane bases his argument on the idea of the "cost" of natural selection. The unit step in evolution is the substitution of one allele, say A, for another, a, in a population. This happens because individuals carrying the gene a are killed selectively or because they have a lower fertility. The larger the number of selective deaths, the more rapidly will gene frequencies change. Haldane estimated the total number of selective deaths (that is, deaths of individuals who would have survived had they had the optimum genotype) required to substitute one allele for another. He concluded that, for a diploid population with moderate selective advantage, the total "cost" of selection would be between 10 and 100 times the population size, per gene substitution. Now there is an upper limit to the number of selective deaths which can occur in one generation. Thus if, for example, a population consisting wholly of individuals of optimal genotype could in favourable circumstances increase by a factor R, then the fraction of selective deaths cannot be greater than $(R-1)/R$ per generation. This places an upper limit on the rate of evolution.

Thus for simplicity consider a haploid population. (I shall confine myself to the evolution of haploids, because I am concerned only with the assumptions behind the mathematics, which can be illustrated quite well by considering haploids, and not with algebraic details.)

Suppose: (i) the average "cost" per gene substitution is 30 times the population size, and (ii) a number of loci are selected simultaneously. At the ith locus the alleles A and a have fitnesses 1 and $1-k$, and frequencies p and q, respectively.

If in the next generation the frequency of A is p', then

$$p' = \frac{p}{p+q(1-k)} \simeq p(1+qk)$$

if k is small. Hence the change in p per generation

$$\Delta p = p' - p = pqk \qquad (1)$$

Now the presence of allele a causes a fraction of selective deaths $\delta_i = qk$.

Hence the fitness of the population is $\Pi(1-\delta_i) \simeq \exp(-\Sigma\delta_i)$, as compared with a fitness of unity for the optimal population.

Now the average number of loci changed per generation is equal to the cost per generation divided by the total cost per gene substitution; that is, it is $\Sigma\delta_i/30$. Hence, if N is the average number of generations per gene substitution, $\Sigma\delta_i = 30/N$, so that the fitness of the population is $e^{-30N^{-1}}$.

Thus if when a population moves into a new environment its reproductive capacity is half that obtainable when selection has run its course, then $N = 43$; that is, if in each generation half the population were killed selectively, there would be one gene substitution per forty-three generations. Haldane suggests that this represents rather intense selection, and that a more typical figure during evolution for the total intensity of selection at all loci might be 10 per cent selective deaths per generation, giving one gene substitution per 300 generations.

It is this estimate of 300 generations per gene substitution which Kimura finds to be incompatible with the observed rate of molecular evolution. It follows directly from the assumption of 10 per cent of selective deaths per generation and the estimate of the cost of one gene substitution as thirty times the population size.

An Alternative Model for Selection

Haldane's conclusion depends critically on the way in which selection at different loci is supposed to act. Thus for a single locus, to increase the frequency of the favourable allele from, say, 1 to 2 per cent in a single generation would require selective deaths amounting to 50 per cent of the population. Haldane assumed that if favourable alleles at several loci are to increase in frequency from 1 to 2 per cent, the total cost will be the sum of the costs for each allele separately; that is, for n loci it would be $0{\cdot}5n$ times the population size. This may be true but it need not be. Thus if selective deaths were confined to individuals with none of the favourable alleles, it would be possible to increase the frequency of fifty separate alleles from 1 to 2 per cent in one generation for the same cost as would be required to change the frequency of a single allele (actually, more than fifty alleles could be changed in

frequency, because some individuals would have more than one favourable allele).

What is the maximum rate at which gene substitution can be made if 50 per cent of the population is killed selectively in each generation? As before, consider a haploid population. At each of n loci let there be two alleles with frequencies p and q and fitnesses 1 and $1-k$. Then the average number of favourable alleles per individual is np, and the standard deviation of the number $\sqrt{npq}$.

If 50 per cent are selected each generation, the most efficient procedure, as judged by the rate of gene substitution, is to select those with the largest number of favourable alleles. This will be termed "threshold selection", because all those with more than a threshold number of favourable alleles survive. In the subsequent discussion the term "threshold selection" will be used for patterns of selection which approximate to this, even if the threshold is not a precise one. It is worth noting that artificial selection typically operates by threshold selection.

Table 1. NUMBER OF LOCI AT WHICH SELECTION CAN ACT SIMULTANEOUSLY WITH A SELECTIVE ADVANTAGE OF 1 PER CENT AT EACH LOCUS, WHEN 50 PER CENT OF THE POPULATION ARE SELECTED EACH GENERATION, ACCORDING TO TWO ASSUMPTIONS

Frequency of less favourable allele	Multiplicative fitness	Threshold selection
0·5	138	25,500
0·9	77	71,000

The figures are for a haploid population: for a diploid population with a 1 per cent difference in fitness between the homozygotes, with the heterozygotes intermediate, the numbers for multiplicative fitness are unaltered, and for threshold selection should be doubled.

If n is large the number of favourable alleles will be normally distributed, and the 50 per cent of the population selected will have a mean number of favourable alleles equal to $np+\sqrt{2npq/\pi}$. Thus at each of n loci the frequency of the favourable allele in the next generation is

$$p' = \frac{np+\sqrt{2npq/\pi}}{n} = p+\sqrt{2pq/n\pi}$$

so that

$$\Delta p = \sqrt{2pq/n\pi} \quad (2)$$

Combining this with equation (1) gives

$$n = 2/pqk^2\pi \quad (3)$$

The comparable formula on Haldane's assumptions can be obtained as follows. With 50 per cent selection, $\Sigma\delta_i = \ln 2 = 0{\cdot}69$. If the frequencies and selection pressures are the same at all loci, $\Sigma\delta_i = nkq$.

Hence

$$n = 0{\cdot}69/kq \quad (4)$$

Estimates (3) and (4) are compared in Table 1. They differ by several orders of magnitude. Which set of assumptions comes closest to reality?

Comparison of the Two Models of Selection

There are two related differences between the assumptions underlying these models.

First, Haldane assumes multiplicative fitnesses. Thus if the relative fitnesses of alleles A and a are $1:1-k$, and of B and b are $1:1-l$, the relative fitnesses of AB, Ab, aB and ab are $1:1-l:1-k:(1-l)(1-k)$. In contrast, the threshold assumption implies a "law of diminishing returns", as the number of favourable alleles increases. This multiplicative assumption will be true if selection acts independently on the two loci; for example, if selection acts first on A versus a, ignoring B, and then on B versus b, ignoring A. The lower efficiency arises because in selecting A versus a some B genotypes will be eliminated, and in selecting B versus b some A genotypes will be eliminated, whereas in threshold selection, provided A and B are not too frequent, no A, B or AB genotypes would be eliminated.

The second assumption made by Haldane is that the relative fitnesses of genotypes can be used to tell us something about the reproductive capacity of populations composed of such genotypes. Thus a population consisting wholly of ab individuals is assumed to have a reproductive capacity lower, by a factor $(1-k)(1-l)$, than a population of AB individuals. This assumption is necessary to his argument, for on it is based his estimate of the permissible number of selective deaths. The threshold assumption says nothing explicitly about the fitness of populations, but it assumes tacitly that populations consisting of any of the genotypes under consideration could reproduce themselves.

The relevance of this difference is as follows. I have argued that threshold selection, by culling 50 per cent, could increase the frequency of favourable alleles at more than fifty loci from 1 to 2 per cent in one generation. On Haldane's assumptions this could not happen, because the initial population could never have existed. Thus if at each of fifty loci there is a two-fold difference in the fitness of two alleles, a population consisting principally of individuals with the unfavourable allele at all fifty loci would have a reproductive capacity lower by a factor of 2^{50} than would a population with the optimal genotype, which is absurd.

Thus whether the advantages, in terms of rapid evolution, of the threshold type of selection are realized in practice depends on the answers to two questions. First, does selection operate on different loci independently, or do the different loci interact so as to produce a phenotype which survives if it is better adapted than other phenotypes? Second, can a population exist and reproduce in nature, in which a number of favourable gene substitutions could be made, the selective advantage of the favourable over the unfavourable allele at the ith locus being $1+k_i:1$, such that $\Pi(1+k_i)$ is a large number? Thus Haldane assumes that $\Pi(1+k_i)$ even with intense selection would not be greater than 2, and typically would be nearer 1·1, whereas with threshold selection $\Pi(1+k_i)$ could be as large as 10 or even 100.

I shall consider these questions in turn.

Does Selection act on Different Loci Independently?

The general answer to this question is obviously no. Yet there will be cases in which selection at different loci is effectively independent. Suppose, for example, that in an insect A confers resistance to a viral disease of the larvae to which a individuals are susceptible, and B camouflages the adult against a predator. In such a case fitnesses would be multiplicative.

In contrast, if A and B affect the same phenotypic character, the threshold assumption will be nearer the truth. Even if A and B influence what to a human observer are different characters, the threshold assumption may still hold if both influence the probability of succumbing to the same mortality factor. Suppose, for example, that whether a bird survives the winter depends on its position in a peck order. This position could be influenced by genes affecting its behaviour, its physique, its disease resistance and so on, and if so, the threshold assumption would hold for all these genes.

Fitness of Populations

There are cases in which a number of gene substitutions $a\rightarrow A$, $b\rightarrow B$, $c\rightarrow C$, and so on, will be favoured by selection, and yet the final population $A\ B\ C\ \ldots$ will be little or no fitter than the initial one. This will be so if the genes influence success or failure in an intraspecific "conflict"[5] for a limiting resource such as food, space or cover. A conflict ensures that some members of a population acquire sufficient of a limiting resource to survive, whereas others acquire little or nothing and perish. It is quite possible that a large number of gene substitutions could increase the probability of success in such a conflict,

without altering the size or reproductive capacity of the population.

The same argument applies to genes influencing success in competition for mates.

It is more difficult to analyse the case in which a number of genes influence the probability of surviving some mortality factor which is not density dependent in its operation and in which intraspecific competition is not involved. Consider, for example, resistance to some physical factor, such as winter low temperatures (this probably depends in most cases on intraspecific competition for food and cover, but I shall ignore this). In such a case there is some plausibility in the argument that if $A\ B\ C\ \ldots\ N$ is the optimal genotype for survival, the selective advantages for each of the n loci being appreciable, then an initial population of $a\ b\ c\ \ldots\ n$ individuals could not have survived at all. But this argument applies only to an environment which is uniform in space. Given a spatially variable environment, it is possible that the initial $a\ b\ c\ \ldots\ n$ population could survive in the warmer part of the region, and that each gene substitution $a \rightarrow A$, $b \rightarrow B$, and so on, was favoured by selection because it increased the geographical range in which individuals could survive.

This argument from the variability of the environment refers not only to resistance to physical factors, but to non-density dependent mortality factors in general, in so far as they vary spatially.

The Rate of Evolution

The assumptions that underlie the "cost of natural selection" argument—that fitnesses are multiplicative and that the fitness of a population can be deduced from the relative fitnesses of its component genotypes—are true only in rather exceptional circumstances. Hence the conclusion that it will typically take 300 generations per gene substitution is unjustified; the rate of evolution could be greater than this by one or more orders of magnitude. Kimura's conclusion that a large proportion of amino-acid substitutions are selectively neutral and have occurred by drift, although it may be true, does not follow necessarily from the cost of selection argument.

This article is not the first to query Haldane's conclusions. His assumptions were queried by Van Valen[6], who argued that in the evolution of "general adaptations", there is "no necessary low limit on the number of genes which can be selected for simultaneously". I have never been able to follow his argument, but I do not think it is the same as that presented here.

Essentially the same argument that I have used has, however, been put forward before[7–9] in a slightly different context. It had been argued by Lewontin and Hubby[10], using the cost of selection approach, that the number of loci at which populations are heterozygous is probably too great to be explained by heterosis. This conclusion has been queried[7–9] on the grounds that fitnesses need not be multiplicative, and that selection may have a threshold character. I have tried here to bring out the importance of this argument for the rate of evolution, and to consider in more detail the circumstances in which one or other set of assumptions might be true.

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Genetics of the Human HL-A Transplantation System

by

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Genetic and statistical analyses indicate that the HL-A system contains two intimately related chromosome regions containing at least seven and eight alleles, respectively. The complex antibodies which these regions give rise to consist of a mixture of smaller components.

THERE has recently been rapid progress in the mapping of the HL-A system which seems to be important for human transplantation in the same way as the H2 locus in mice, the Ag-B locus in rats, and the B locus in chickens.

The greatest step forward was made at the Torino workshop on histocompatibility testing in June 1967. The data collected there[1] agreed with the idea that the genetic information determining the most important transplantation antigens is located in closely linked genetic elements on one pair of autosomal chromosomes constituting the HL-A system.

The transplantation antigens belonging to the HL-A system are present on leucocytes and platelets and can be determined by means of agglutinating and cytotoxic antibodies active against leucocytes, and complement-fixing antibodies active against platelets.

Leucocyte and platelet antigens which are independent of the HL-A system are known. The corresponding genetic elements are not linked with the HL-A system. These systems do not seem to be involved in transplantation. It is apparent from previous results[2–5] and from those of the Torino workshop[1] that the most important genetic information of the HL-A locus seems to be located in two separate units most frequently called the LA and 4-series. It is not known whether they are two separate loci or two subunits of one locus. If there are two separate loci they must be very close to each other, for no recombinants have been found in fairly comprehensive family studies.

During the Torino workshop, many teams could determine perfectly identical LA antigens with their reagents: LA1, LA2 and LA3 antigens and another antigen, LA4(?), determined by three of the teams with