Limitations of Darwinian selection in a finite population

(substitution load/neutral theory/natural selection/cost of natural selection)

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ABSTRACT   In a finite population, the rate at which favorable mutations at several loci can evolve simultaneously is limited by the reproductive capacity of the species and the effective population number. The number of such loci is given by $n < -(N_e/2) \ln(1 - L_T)$, in which N_e is the effective population number and L_T is the "substitution load" (roughly, the reproductive excess available for positive selection). If $L_T = 0.1$, as seems reasonable for large mammals, $n < 0.05 N_e$.

It seems to be widely accepted among biologists that Darwinian selection can act almost without limit as to the number of loci or sites that are simultaneously substituting advantageous alleles. Yet reproductive capacity must somehow be limiting.

In this regard, Haldane (1) proposed, in one of his pioneering papers, a concept that he called "cost of natural selection" and that I later termed "substitutional load." For details, see Kimura and Ohta (2). The main point of this concept is that even the substitution of advantageous mutants entails a reproductive cost or genetic load. This is because the substitution of a favorable mutant requires elimination of its less advantageous alleles, and this requires sufficient reproductive excess to balance the loss. Haldane showed that, assuming a model of infinite population size, for mammalian species (including the human) whose reproductive capacity is low the rate of substitution of advantageous mutants cannot greatly exceed one per 300 generations.

Here I intend to show that the effectiveness of positive natural selection is nullified by random genetic drift if the effective population number (roughly, the number of breeding adults) is the same order of magnitude or smaller than the number of loci at which advantageous alleles are being substituted.

Consider a randomly mating population of effective number N_e. Let n be the number of loci at which advantageous mutants are in the process of substitution. I shall denote a pair of alleles at the ith locus by A_i and A_i', in which A_i' represents the advantageous mutant ($i = 1, 2, \ldots, n$). To simplify the treatment, I assume that there is no dominance and that the selection coefficient, s_i, is the same for all loci ($s_i \equiv s$ for all i). This means that the relative fitnesses of A_iA_i, A_iA_i', and $A_i'A_i'$ are $1 - 2s$, $1 - s$, and 1 for all loci ($s > 0$). Thus, for a locus at which an advantageous allele is segregating, the amount of selective elimination or the load is $2sx^2 + 2sx(1 - x)$, or $2sx$, where x is the frequency of A_i.

If we denote by L_T the total amount of selective elimination over all the segregating loci, we have

$$L_T = 1 - (1 - 2sx)^n$$

or

$$\ln(1 - L_T) = n \ln(1 - 2sx) \approx -2nsx,$$

assuming that s is much smaller than unity ($s \ll 1$).

To simplify the treatment again, I assume that frequencies of advantageous mutations are distributed uniformly among the loci. Thus, we get

$$\ln(1 - L_T) = -\int_0^1 2nsx \, dx = -ns. \qquad [1]$$

We now consider the probability of fixation of a single mutant gene in a finite population of size N, ignoring for the moment the distinction between actual and effective population numbers. The probability of fixation of a mutant with selective advantage s ($s > 0$) is

$$u = \frac{1 - e^{-2s}}{1 - e^{-4Ns}} \approx \frac{2s}{1 - e^{-4Ns}}$$

for small s. Furthermore, if $|4Ns| \ll 1$, $u \approx 1/(2N)$, so the mutant behaves as if selectively neutral. On the other hand, if $Ns \geq 2$, $u \approx 2s$, and the process is dominated by natural selection.

As a criterion for Darwinian selection to prevail over random drift acting on neutral mutations, I use the condition

$$N_e s > 2. \qquad [2]$$

Combining Eqs. 1 and 2, we obtain

$$s = -\ln(1 - L_T)/n > 2/N_e,$$

so that

$$n < -(N_e/2)\ln(1 - L_T). \qquad [3]$$

This has the pleasing property, as does Haldane's principle, of being independent of s, but it is more realistic in taking population size into account and not being dependent on the initial mutant frequency.

For example, if the amount of selective elimination, or roughly the reproductive excess available for natural selection, is 10% ($L_T = 0.1$), we have approximately $n < 0.05 N_e$. More generally, if L_T is small, $n < N_e(L_T/2)$. On the other hand, if $L_T = 0.5$, $n < 0.35 N_e$ approximately. For mammalian species with large body size, L_T is not likely to exceed 0.1. This means that Darwinian natural selection cannot act effectively if the number of loci or sites segregating for advantageous mutants is >5% of the effective population size.

Furthermore, deleterious mutants occur much more frequently than those that are advantageous. Thus, even if the genetic load due to elimination of deleterious mutants is individually much smaller than that due to advantageous ones, a considerable fraction of L_T in Eq. 3 may be consumed by elimination of deleterious mutants, and the remainder available for positive selection becomes correspondingly <0.1.

In mammals, including man, the total number of nucleotide sites per genome is about 3 billion, and two randomly chosen haploid sets differ in several million sites. At the same time, the effective population number of most wild mammalian species is probably of the order of hundreds of thousands or less. This means that the

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majority of nucleotide substitutions in the course of evolution are propelled by mutation and random genetic drift, as is the case for selectively neutral mutants. This indirectly supports my neutral theory of molecular evolution (3), which claims that the great majority of evolutionary changes at the molecular level are driven by mutation and random genetic drift. For details and more recent data supporting the theory, see refs. 4 and 5.

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3. Kimura, M. (1968) *Nature (London)* **217,** 624–626.
4. Kimura, M. (1983) *The Neutral Theory of Molecular Evolution* (Cambridge Univ. Press, Cambridge, U.K.).
5. Kimura, M. (1991) *Jpn. J. Genet.* **66,** 367–386.