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The cost of natural selection revisited

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In a constantly changing environment, organisms must continuously adapt or face extinction. J. B. S. Haldane argued that the "cost of natural selection" (also called the cost of substitution) puts an upper limit on the rate of adaptation, and showed that the cost (C) was a decreasing function of the initial frequency of the beneficial alleles. Based on mutation-selection balance and 10% selective mortality, he suggested that the limit to adaptive evolution was about one allelic substitution per 300 generations. I have tested Haldane's results using simulations of a population limited by density-dependent regulation and subject to a constantly changing environment that affects n (= 1–7) independent survival traits, each controlled by a single locus. I investigated the influence of carrying capacity (K), mutation rate (u), number of beneficial mutations per generation (approximated by $M = 2Ku$) and net reproductive rate (R). Of these, M has the predominant influence. The effect of large changes in R was relatively small. The cost of selection (C) was measured as the shortest number of generations between an allelic substitution at all loci under selection that was consistent with population persistence. The results differed from Haldane's solution. Across a range of conditions, the cost of simultaneous selection at n loci was determined by the linear relationship $C = C_0(M) + nC_1(M)$, where $C_0(M)$ is the intercept and $C_1(M)$ is the slope of the linear regression of C on n, for a given M. The intercept defined a positive fixed cost of substitution, that appears to reflect genetic deaths occurring during the stochastic phase when the beneficial alleles are rare. For $M > 1/2$, the cost of natural selection is substantially less than Haldane's estimate; however, when $M < 1/2$, the cost (and particularly the fixed cost) increases in an accelerating fashion as M is lowered. This result has important implications for conserved populations, since for $u \approx 5 \times 10^{-6}$ the carrying capacity of the population must be 50 000 for $M = 1/2$. To avoid low M, smaller populations should be linked together into a large metapopulation whenever possible. This large unit would be capable of adapting when the isolated parts could not. It also suggests that if $M << 1$, small gains in K through increases in habitat can have a very large positive influence on the future survival of the population in a changing environment.

Introduction

In his seminal paper entitled "the cost of natural selection", Haldane (1957) showed that the rate of adaptive evolution was limited by the number of selective deaths that had to occur during the replacement of one allele by another. His calculations suggested that the long-term rate of allelic substitution was unlikely to exceed 1 per 300 generations. If correct, this result has far-reaching consequences, both for the interpretation of molecular data (Kimura 1968) and for expectations regarding the survival of populations exposed to long-term environmental change. In a changing environment, it defines the upper limit to evolution driven by natural selection, and predicts that if this rate is insufficient to maintain adaptation, then the population will go extinct.

The problem of adaptation to continuous environmental change has been studied from a quantitative genetic perspective. Pease *et al.* (1989) considered the important problem of how movement and adaptation interact in determining the range and persistence of a population along an environmental gradient that is undergoing directional change. Unfortunately, in our increasingly fragmented environment, population movement is becoming less of an option for populations responding to environmental change. It is thus important to model the response of populations to directional environmental change given the constraint that they are unable to move. Addressing this problem, Lynch and Lande (1993) concluded that the maximum rate of long-term evolution in a trait would generally be much less than the phenotypic standard deviation per generation. Burger and Lynch (1995) cut this estimate by about a factor of ten.

The quantitative genetic models assume that a large number of loci (generally tens or more) determine the trait under selection. Here I concentrate on adaptation involving fewer than ten loci, and focus specifically on the problem posed by Haldane (1957). He showed that the cost of selection (also called the cost of substitution) was determined by the initial frequency of a beneficial allele destined to spread to fixation and not by the strength of selection. This means that the number of selective deaths is relatively constant on a per locus basis, and predicts that a specific adaptation involving several loci requires more selective death than the same adaptation involving a single locus. Haldane's (1957) calculations made important predictions about the limits placed on the rate of adaptation.

These predictions can be ranked from the general to the specific. First, he noted that the mortality cost of substituting one allele for another was independent of the strength of selection, and that the cost was additive across loci. Second, he calculated that the cost per substitution was determined by the initial frequency of the beneficial allele. Third, he showed that the cost was defined by:

$$C_1 = -2\ln(p_0) \tag{1}$$

for an autosomal diploid locus with additive allelic effects, where the cost for a single locus (C_1) is measured as the number of genetic deaths in units of N, the population size. Thus the cost of simultaneously selecting on n loci (C) is predicted to be:

$$C = -2n \times \ln(p_n) = nC_1 \tag{2}$$

assuming, for simplicity, that p_0 is the same across loci. From Eq. 1, Haldane (1957) estimated that a typical allelic substitution required about 30N genetic deaths. However, he believed that, in general, only about 10% of the overall mortality would be related to genotype, leading to a total mortality of 300N per substitution.

Haldane (1957) recognized that his cost translated directly to a maximum rate of evolutionary change. The cost of natural selection can be defined as the number of deaths (in units of N) required for an allelic substitution, or as the minimum time (in generations) between allelic substitutions that is compatible with population persistence. Using Haldane's (1957) approximation that the cost of substituting one allele for another was about 300N deaths, then the maximum rate of evolution was one substitution per 300 generations, since no more than N deaths could occur per generation. It is the link between the number of genetic deaths per substitution and evolutionary rate that makes quantifying the cost of natural selection so important.

It is self evident that the organisms that persist today have been able to respond to environmental change in the past. As noted above, the response of a species is frequently a shift in range that minimizes the environmental change; however, if movement is precluded, then the response must be adaptation through natural selection. Under these conditions, the cost of natural selection is crucial in determining whether or not a population is capable of adapting to long-term environmental change. If the long-term rate of allelic substitution needed to track environmental change is faster than the cost, then the population will be unable to adapt, leading to its extinction. Note that under these conditions, the problem is not the availability of appropriate allelic variation. The problem is spreading rare beneficial alleles through the population.

Haldane's conclusion that the cost of allelic substitution placed a restrictive upper limit on the rate of adaptive change was strongly criticized (*see* Mather 1973). Haldane's calculation ignored density-dependent effects, and density-dependence is relevant in two ways: first, due to potential cost reduction resulting from density-dependent "soft" selection, and second, due to the low-density increase in absolute fitness. The primary argument that has been used against the relevance of Haldane's cost to adaptive evolutionary change concerns the relative importance of hard vs. soft selection. In population genetic models, we generally assume that the relative fitness of genotypes is independent of density. This defines hard selection. In contrast, under soft selection, relative fitness of a genotype is a function of the size and composition of its "proximity group" (defined as the individuals with which it interacts; Nunney 2002). In particular, fitness differences may only become apparent in a highly competitive high-density environment (Wallace 1970). Soft selection provides a buffer against extinction, since all genotypes survive relatively equally if population size decreases. As a result, soft selection inevitably reduces or eliminates the cost of substitution. However, given directional environmental change, it is likely that hard selection will dominate the adaptive process (*see* Discussion). It is certainly unrealistic to assume that, as a general rule, an arbitrarily maladapted genotype will flourish under low-density conditions.

Density-dependence is also important for a second reason that is generally overlooked. Haldane (1957) assumed that only about 10% of the overall mortality in a population would be determined by genotype. In reality, this percentage is likely to vary with the population density. At low density, overall survival is expected to be relatively high, so that a high percentage of this minimal mortality may be genetic in origin. In contrast, at high density, the overall survival will be lower and the same amount of genetic death will represent a much smaller percentage of the total mortality. The same argument also applies if the increased loss is due to a density-dependent drop in fecundity. Such density dependence results in the absolute (Malthusian) fitness of individuals increasing with decreasing density, and this increase may help to buffer a population against extinction since beneficial genotypes exhibit high rates of increase at low population density.

It certainly seems probable that the "excess" reproductive potential present in all species can permit evolutionary rates faster than those suggested by Haldane (1957). But how much faster? On the other hand, we expect small populations to be restricted in their ability to adapt to environmental change. Haldane (1957) implicitly assumed a large population, by assuming that all the required adaptive mutations were present in the population at mutation-selection balance. What is the cost in small populations, and what defines "small"? The answer to these questions is of fundamental importance in understanding the persistence of populations confronted by environmental change. I investigated the question using computer simulations of a population subjected to a directional change in the environment. This change imposed hard selection acting on multiple traits, each determined by a single locus. This is the genetic model assumed by Haldane (1957). He began his paper by noting that "It is well known that breeders find difficulty in selecting for all of the qualities desired in a stock" (p. 511), so that it was clear he was concerned with the problem of natural selection acting simultaneously on more than one trait.

The simulated population exhibited density-dependent population regulation, so that the absolute fitness of genotypes varied with density (but their relative fitness was density independent). I examined how the cost of substitution was influenced by the number of genes (and hence traits) involved in the adaptation, the mutation rate, the net reproductive rate, and the carrying capacity of the population.

The cost of natural selection can be measured in two ways. It can be measured directly by summing the loss of fitness due to the adaptive process. This was the approach used by Haldane (1957); however, this summation is complicated in the presence of density-dependent population regulation. Alternatively, as noted earlier, the cost of natural selection can be measured indirectly as the rate of allelic substitution consistent with population persistence. This measure has the advantage of integrating all of the demographic and genetic complexities into a criterion that has profound biological implications: whether or not a population can survive in the face of environmental change.

Simulation model

The simulation model has four components: environmental change, the relationship between genotypic fitness and the environment, density-dependent female fecundity, and genetic transmission, which includes Mendelian inheritance and mutation. The environment was assumed to change at a constant rate, and the optimal adaptive response required an allelic substitution every T generations at all loci under selection. Thus decreasing T corresponds to increasing the rate of environmental change.

Female fecundity (f) was defined by a logistic-like density-dependent function and was assumed to be independent of genotype:

$$f = 2\exp\left\{r\left[1-\left(\frac{N}{K}\right)^{1/r}\right]\right\} \tag{3}$$

where r is the intrinsic growth rate of the population and K is the carrying capacity. Thus the net reproductive rate (R, the maximum fecundity per female) is defined as:

$$R = 2\exp(r) \tag{4}$$

and is realized when $N \approx 0$. The fecundity function (Eq. 3) eliminates the oscillatory and chaotic dynamic behavior characteristic of the logistic function given realistic values of a female's potential fecundity. Dynamic behavior close to the carrying capacity (K) is stable and independent of r.

The relationship between genotypic fitness and the environment was defined by a multilocus model, in which the different (unlinked) loci acted independently on survival, i.e. each gene determined a different survival trait. Fitness was defined by a normally distributed fitness function according to the following rules. The possible alleles at each locus were numbered in integers $A = 0,1,2\ldots$, so that the name of each allele was also its value (A). The maximum fitness benefit of allele A occurred at time AT, so the survival probability of genotype i was:

$$w_i = \exp\left\{-\frac{r}{n}\sum\left[Av_{ij}-\left(\frac{t}{T}\right)\right]^2\right\} \tag{5}$$

where Av_{ij} is the allelic value of locus j of genotype i averaged across its two alleles, and the summation is over all n loci. It is important to note that as the number of loci is increased, the effect of each locus on fitness is reduced, so that the net effect of the environmental change on fitness is independent of the number of loci.

The simulations were initiated at time $t = -T/2$, with the population fixed for allele 0. The first $T/2$ generations were included to permit the appearance of new mutations prior to the 00 genotype reaching its highest fitness ($w = 1$) at $t = 0$. In most of the simulations it was assumed that the fitness peaks were the same across all loci (e.g. allele 1 had its maximum fitness benefit at time T for all loci); however, simulations with the fitness peaks of the loci spaced evenly across T generations were also run to confirm that this assumption had no effect on the results.

The three components of the simulation model, environmental change, fitness, and density-dependent population regulation, ensure that a population fixed for allele A in its optimum environment ($t = AT$) can increase from low density ($N \approx 0$) at a rate R, since $w = 1$ (*see* Eqs. 3–5). However, the genetically identical population in an environment more than T generations away from its optimum environment (i.e. $t > AT + T$) will decline to extinction. This decline is inevitable because when $t > AT + T$, the productivity of a female ($f \times w$; Eqs. 3 and 5) can never exceed the replacement rate of two, since $w < \exp(-r) = 2/R$. The population will only persist if the alleles 0, 1, 2 etc. are sequentially substituted in the population as time progresses.

The effective size (N_e) of the simulated population was close to its actual size. Mate choice was by lottery polygyny (Nunney 1993): each female mated only once, but the male population was sampled randomly by each female for her mate. This has the effect of lowering the effective population size. However, female fecundity was equal across females, and when the population was close to the carrying capacity, female fecundity was close to 2. This pattern of low and equal fecundity increases N_e (Nunney 1991). The two effects precisely cancel each other, so that, ignoring selection and any associated population declines, $N_e \approx N$.

The simulations were stochastic, and each simulation lasted $8T$ generations, so that a population completed eight cycles of allelic substitution at each locus under selection. As T was reduced (i.e. as the rate of environmental change was increased), there was a transition from successful long-term adaptation, to the failure of long-term adaptation (marked by extinction). However, the stochasticity of the simulations ensured that the cost of natural selection (C), defined as the value of T marking the transition from guaranteed persistence to occasional extinction, was not a clear threshold. It was necessary to define a criterion to recognize this threshold. The initial criterion for $T = C$ was the lowest value of T for which no extinction was observed in 20 simulations. This value was deemed the threshold C if (i) the approach to C was from below (i.e a lower threshold was already excluded), and (ii) $1.02C$, $1.05C$, and $1.10C$ showed no extinction (each in 20 simulations). If more than one of the higher values showed extinction, then the threshold was moved up. If only one showed extinction, then this value was retested. If the retested value still showed extinction then the threshold was moved up.

Results

Number of loci

Simulations changing only the number of loci involved in adaptation (n), showed a positive linear relationship between n and the cost of substitution (C), measured by the minimum interval between allelic substitutions consistent with persistence (Fig. 1). For each set of simulations, n was varied from 1 to 7 loci, while carrying capacity (K), net reproductive rate (R), and mutation rate (u) were held constant. Different sets of simulations used different mutation rates ($u = 10^{-3} - 5 \times 10^{-6}$), using a constant carrying capacity ($K = 5000$), and net reproductive rate ($R = 10$). The slope and elevation of these regressions increased with decreasing mutation rate.

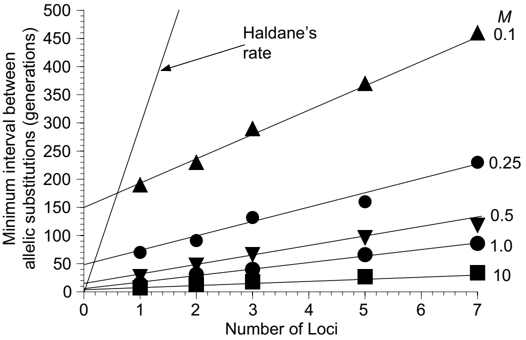

Fig. 1. The cost of natural selection, measured as the minimum interval between allelic substitutions consistent with population persistence, increases linearly with the number of loci being simultaneously selected, even though the total strength of selection is unaltered. The different lines define the fitted regression for each of the values of $M = 2Ku$, the number of new mutations per generation. The simulations were carried out as described in the test, with K (carrying capacity) = 5000, R (net reproductive rate) = 10, and the mutation rate (u) varied appropriately. The maximum rate of long-term substitution suggested by Haldane (1957) (300 generations/locus) is shown.

None of these regressions linking n and C passed through the origin (Fig. 1 and Table 1) and were thus inconsistent with Haldane's (1957) result (Eq. 2). The intercept was positive in all cases, showing that the cost of simultaneously selecting on several traits is less than the summed cost of selecting on each trait separately in different generations. For simplicity, we can consider the slope of the regressions as the per locus cost of natural selection (C_1) and the intercept as a "fixed" cost (C_0) not identified by Haldane (1957). The minimum cost is incurred when a single locus is selected ($C = C_0 + C_1$), meaning that the fastest environmental change can be tolerated when the adaptive response is to replace alleles at a single locus. Obviously, this partition is meaningless for the case of $n < 1$ traits (there is no “fixed” cost of selecting on zero traits!). More generally, the simultaneous selection of n traits incurs a cost equal to a fixed cost plus n-times the per-locus cost. Thus the cost per locus decreases with n, since it is defined by $(C_0/n) + C_1$. As a result, the maximum rate of evolution is reduced when the adaptive response is spread across several loci; however, it is reduced much less than expected based on Haldane’s (1957) result (Fig. 1).

Mutation rate and carrying capacity

In Haldane’s (1957) formulation, the cost of natural selection is dependent upon the initial frequency of beneficial alleles (Eq. 2). This initial frequency (p_0) is affected by changes in the mutation rate (u). Decreasing the mutation rate inevitably decreases the initial frequency of the beneficial alleles (p_0), which predicts an increased cost. This prediction is supported: the cost of natural selection increased with decreasing mutation rate (Fig. 1, where $u \propto M$).

The effect of increasing carrying capacity (K) on p_0 is less easy to predict. In populations at mutation-selection balance, we expect the initial frequency to be independent of K. However, if new mutations are limiting, the initial frequency of a single new mutation increases with decreasing K, resulting in a lowered cost. The simulations showed that decreasing K (while holding the mutation rate constant) increases the cost (Table 1: e.g. compare $K = 5000$, $M = 10$ to $K = 500$, $M = 1.0$), a result not predicted by Eq. 2.

The number of new mutations

The observation that decreasing K increased the minimum interval between allelic substitutions was unexpected. Decreasing K results in fewer new mutations, M ($\approx 2Ku$) per generation. This parameter was not a component of Haldane’s (1957) model and I tested the hypothesis that the number of new, potentially beneficial, mutations per generation is an important but unrecognized determinant of the cost of natural selection. Paired simulations using $K = 5000$ and $K = 500$ over a range of M (0.05–10), showed that M is indeed the primary determinant of the cost of natural selection (Table 1 and Fig. 2). Both the intercept (fixed cost) and the slope (cost per locus) for a given M were similar across the two carrying capacities. Indeed, the costs were frequently statistically indistinguishable despite the 10-fold difference in the K and u (*see* Table 1).

These simulations were also used to confirm that the results were not dependent upon a particular feature of the simulations: the synchronization of the fitness peaks of alleles across loci. As noted in the model description, allele A (where $A = 0,1,2\ldots$) at any locus contributed its greatest fitness benefit at generation AT (where T is the number of generations between fitness peaks). It was important to determine if the results were the same if the fitness peaks for the alleles at different loci were offset, by being spaced evenly across the T generations. It was found that the correspondence of the two kinds of simulation was extremely high. Two comparsions are shown in Fig. 2a for $K = 500$. The simulations with evenly spaced fitness peaks

Table 1. The dependence of the two components of the cost of substitution, the fixed cost and per-locus cost, on the number of new mutations per generation, M (= $2Ku$), where K is the carrying capacity and u is the mutation rate. The values of the fixed and per-locus costs (± standard error) correspond to the intercept and slope of the regression of cost on the number of loci (*see* Eq. 6) using data from simulations.

M	Fixed cost		Additional cost/Locus	
	$K = 5000$	$K = 500$	$K = 5000$	$K = 500$
0.05	429.0 ± 20.6	400.6 ± 39.4	68.6 ± 4.9	72.9 ± 9.4
0.1	150.2 ± 4.3	167.6 ± 8.7	44.4 ± 1.0	40.9 ± 2.1
0.25	43.6 ± 9.2	55.8 ± 7.1	25.8 ± 2.2	18.7 ± 1.7
1.0	4.8 ± 2.3	9.6 ± 2.4	11.8 ± 0.5	8.4 ± 0.6
10.0	3.7 ± 1.0	3.4 ± 0.7	4.5 ± 0.2	2.4 ± 0.2

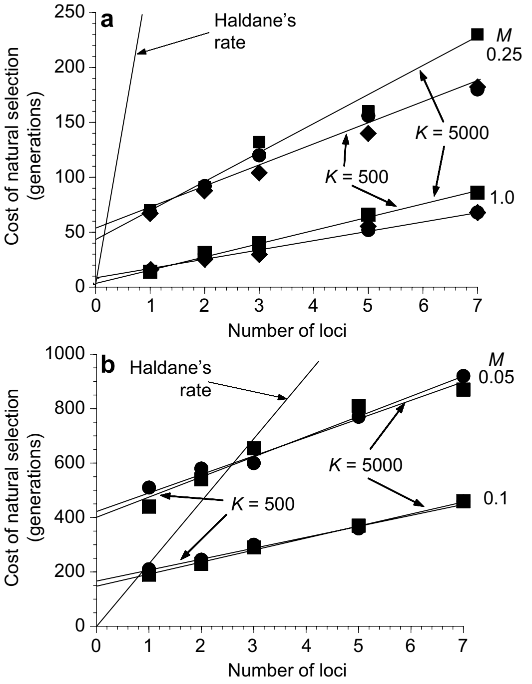

Fig. 2. The effect of carrying capacity (*K*) on the cost of natural selection (the minimum interval between allelic substitutions). The regressions of cost on the number of loci are little influenced by a ten-fold change in carrying capacity (*K* = 500 and *K* = 5000), for a given value of *M* (= 2*Ku*). — **a**: *M* = 1.0 and 0.25. The diamond symbols were derived from a set of simulations (*K* = 500) in which the fitness peaks of the different loci were evenly distributed across the time between single locus peaks (*see* text). For the other simulations, the peaks were synchronized across loci. — **b**: *M* = 0.1 and 0.05. For other details *see* Fig. 1.

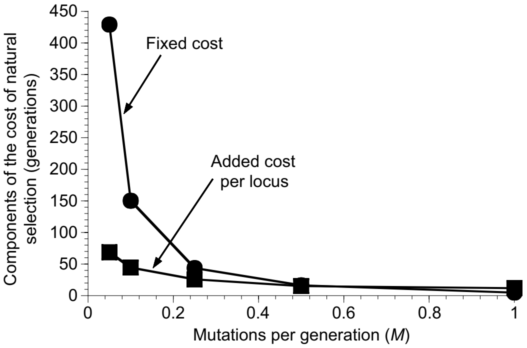

Fig. 3. The two components of the cost of natural selection, the fixed cost and per-locus cost, as functions of the number of new mutations per generation (*M* = 2*Ku*). The costs are the intercept and slope of the regressions of cost on the number of loci (*see* Table 1). For other details and parameter values, *see* Fig. 1.

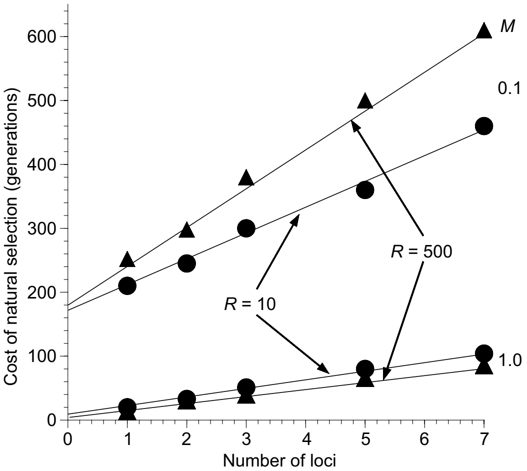

Fig. 4. The effect of net reproductive rate (*R*) on the cost of natural selection (the minimum interval between allelic substitutions). The regressions of cost on the number of loci are little influenced by a fifty-fold change in net reproductive rate (*R* = 10 and *R* = 500), for a given value of *M* (= 2*Ku*). For other details *see* Fig. 1.

(diamond symbols) followed the same regression as the simulations with synchronized fitness peaks (circles).

From the patterns shown in Figs. 1 and 2, we can conclude that under a wide range of conditions, the cost of natural selection is well approximated by:

$$C = C_0(M) + nC_1(M) \qquad (6)$$

where both $C_0(M)$ and $C_1(M)$ are decreasing functions of M (Fig. 3 and Table 1). The fixed cost was very large for small M (< 1/2), but decreased to a negligible level when $M \geq 1$. The per-locus cost showed a similar pattern of increase for $M \ll 1$.

Net reproductive rate

The net reproductive rate (R) is the maximum fecundity of females at low population density (Eq. 4). Increasing R might be predicted to decrease the cost of selection, based on the expectation that a high fecundity population can withstand higher levels of genetic death, however, no consistent pattern was seen (Fig. 4). I compared populations with $R = 10$ and $R = 500$, for both $M = 1.0$ and 0.1 ($K = 5000$ and $K = 500$, respectively). The fixed cost of selection was largely unaffected by the large change in R. The per locus cost was decreased by increasing R for $M = 1.0$, but was increased by increasing R for $M = 0.1$.

Discussion

Haldane (1957) ended his paper by noting "I am quite aware that my conclusions will probably need drastic revision. But I am convinced that quantitative arguments of the kind here put forward should play a part in all future discussions of evolution" (p. 523). The results presented here suggest that Haldane was correct that some revision of his conclusions is needed, but they also suggest that he was correct that the cost of natural selection is a real phenomenon that needs to be included in more discussions of adaptation in a changing environment. The concept is made even more relevant as we become increasingly aware of the potential for rapid environmental change, and as more and more natural populations become fragmented into many isolated units. These isolated populations are small and are generally unable to respond to environmental change by shifting their location, since they are surrounded by an inhospitable human environment.

The results of the simulations of a density-regulated population suggest that the cost of natural selection is an important factor driving populations to extinction in a rapidly changing environment. The cost of natural selection was measured as the minimum time between allelic substitutions compatible with population persistence. It was found that this cost increased rapidly when M ($= 2Ku$), the number of new mutations arising in the population per locus per generation, decreased below about 0.5, i.e. $4Ku < 1$ (*see* Fig. 3). At first sight, this inequality might appear to suggest that adaptive evolution is being limited by the availability of appropriate mutations. However, using the example of $M = 0.25$, beneficial mutations are appearing continuously through time, on average, one every four generations, and yet the cost of selection is about 70 generations (Table 1). Instead, the problem appears to be the persistence of beneficial mutations once they have entered the population. Genetic drift is very effective at overwhelming the selective advantage of the rare alleles, so that there is a high risk of loss (*see* Fisher 1930).

Haldane (1957) calculated the cost of natural selection by summing the genetic deaths per generation due to the lower of fitness of the suboptimal genotype. He assumed that each generation the frequency of the favored allele would increase, and so he did not incorporate the possibility that genetic deaths would occur without any increase in the frequency of the beneficial allele (due to the repeated loss of these rare mutants). Wright (1931) provided the theory that delimits regions of parameter space where random genetic drift drives genetic change, despite low levels of migration ($4Nm < 1$), weak selection ($2Ns < 1$), or mutation ($4Nu < 1$). Similarly, the inequality $4Ku < 1$ indicates the conditions under which new mutations are frequently eliminated by sampling.

Haldane (1957) assumed that the cost of natural selection was additive across loci, i.e. given a per-locus cost of C_1, then the cost of substitution at n loci would be nC_1. However, the simulations have shown that the cost can be divided into two components (*see* Eq. 6), a fixed cost (C_0) in addition to the per-locus cost. It is probable that the main factor contributing to the fixed cost is the average time that it takes for a beneficial allele to increase sufficiently in frequency to escape from the region dominated by genetic drift into the region dominated by selection.

The fixed cost indicates that simultaneous selection at n loci incurs less total cost than sequential selection involving the same loci (which would take n times longer). This possibility was not considered by Haldane (1957), who assumed that the cost would be the same whatever the temporal pattern of selection. However, selecting simultaneously across multiple loci is always more likely to lead to extinction than selecting at a single locus (i.e. the cost is higher). This is not because the selection intensity is stronger when multiple loci are involved, since in the simulations the selection intensity was independent of the number of loci (*see* Eq. 5).

In large populations, with more than one mutation per locus per generation ($M > 1$), the cost of substitution is low, even when multiple traits are selected simultaneously (Fig. 1). Thus, a simulated population with $M = 10$ can tolerate environmental change that requires allelic substitution at 7 loci (determining 7 independent traits) every 40 generations. With $M = 1$, change affecting so many traits would need to be almost 3 times slower for the population to survive; however, a single trait, determined by a single gene, could still undergo allelic turnover every 20 generations.

These limits are much lower than Haldane's (1957) suggested rate of 1 substitution every 300 generations (*see* Fig. 1). In large part the difference reflects the fact that in populations with density-dependent regulation, mortality (including unfulfilled fecundity) can shift from being primarily random to being primarily selective if the population begins to decline due to poor adaptation.

The finding that natural selection can drive evolution much faster than suggested by Haldane's result only applies to large populations with $M \geq 1$. The situation changes rather dramatically for the worse as M declines below 1 (Fig. 3). In particular, below about 0.5, the effect of a decline in M results in a very rapid increase in the likelihood of population extinction in a changing environment. For example, a population of $K = 10\,000$, with a per-locus mutation rate of 5×10^{-6} per gamete, has a value of $M = 0.1$. This relatively large population will become extinct if the environmental change requires allelic substitution faster than about every 300 generations, i.e. at the rate suggested by Haldane (1957). Moreover, if the carrying capacity is reduced to 5000, the population could only tolerate an environment changing at less than half of this rate, i.e. about every 700 generations.

These results are very relevant to conservation planning. Early in the development of conservation biology, Gilpin and Soulé (1986) emphasized how any loss of genetic adaptation could feed back on demographic parameters, contributing to what they termed the extinction vortex. It is this feedback that is modeled in the simulations presented here: lack of adaptation leads to a lowered population size, and, in the absence of an adequate genetic response, extinction follows.

Demographic and genetic considerations suggest that, if possible, conserved populations should be maintained at a level of several thousand (Nunney & Campbell 1993). Lande (1995) argued that even larger populations ($N_e > 5000$) are necessary to maintain levels of additive genetic variation that approach those seen in natural populations, and that this is important to maintain the adaptive potential of the population. Lande's (1995) estimate was an order of magnitude higher than the rule-of-thumb proposed by Franklin (1980). Here we see that the cost of natural selection, acting on a limited number of multiplicative loci, leads to essentially the same conclusion as Lande's (1995) argument based on large numbers of additive loci. Assuming a typical per locus mutation rate of 5×10^{-6}, a multi-trait adaptive response in a rapidly changing environment is optimized only if the population size is greater than 10^5 (defining $M = 1$), and it is seriously compromised if the population size is less than 10^4 ($M < 0.1$). These values assume that the effective size and actual population size are not too different (as in the simulations). If the effective size is much smaller, then these guidelines for population size would need to be increased.

Many would rightly point out that in the face of economic pressures, conserving such large populations is difficult, if not impossible. However, two points should be emphasized. The first concerns linkages among populations to create a functioning metapopulation. Given low but significant levels of gene flow among populations, a metapopulation can have an effective size close to the sum of its parts (Whitlock & Barton 1997, Nunney 1999, 2000). It is likely that such a metapopulation could function as an effective adaptive unit. In contrast, if movement among populations is precluded then it is likely that, in the face of rapid environmental change, individually each population will fail to adapt leading to their sequential extinction. Under such circumstances, attempts at recolonization are unlikely to provide long term help due to the dramatic lowering of N_e that typically results from extinction-recolonization cycles (Gilpin 1991, Hedrick & Gilpin 1996, Whitlock & Barton 1997).

The second point to note is that small gains in population size can be very important. The steep decline in the fixed cost curve (Fig. 2) shows how a small increase in the carrying capacity of a small population can have a large effect on the likelihood of a population successfully responding to a changing environment.

It has long been argued that the cost natural selection can be ignored if soft selection prevails. The simulation model was a model of hard selection. It was assumed that juvenile survival was determined by Eq. 5, independent of population density. It is clear that soft selection, whereby all genotypes have equal fitness under low density, eliminates the cost of substitution (*see* Wallace 1970, Mather 1973). However, is it likely that most selection is of this type? If so, we can ignore the problem of the cost of natural selection. Unfortunately, soft selection is only important when natural selection is driven by intraspecific competition. While this is undoubtedly a large component of adaptation, interspecific effects (e.g. predation, interspecific competition) and abiotic factors have a very large role. In particular, it is likely that one of the major influences driving adaptation in the foreseeable future will be climate change. This will change both the abiotic norms and (probably) the interspecific interactions that populations will need to adapt to, unless, of course, they are able to move into refugia that maintain their original environment. Such challenges are unlikely to result in soft selection, and those species that cannot tolerate the cost of selection will go extinct.

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