



Review

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Evolutionary rescue and the limits of adaptation

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Populations subject to severe stress may be rescued by natural selection, but its operation is restricted by ecological and genetic constraints. The cost of natural selection expresses the limited capacity of a population to sustain the load of mortality or sterility required for effective selection. Genostasis expresses the lack of variation that prevents many populations from adapting to stress. While the role of relative fitness in adaptation is well understood, evolutionary rescue emphasizes the need to recognize explicitly the importance of absolute fitness. Permanent adaptation requires a range of genetic variation in absolute fitness that is broad enough to provide a few extreme types capable of sustained growth under a stress that would cause extinction if they were not present. This principle implies that population size is an important determinant of rescue. The overall number of individuals exposed to selection will be greater when the population declines gradually under a constant stress, or is progressively challenged by gradually increasing stress. In gradually deteriorating environments, survival at lethal stress may be procured by prior adaptation to sublethal stress through genetic correlation. Neither the standing genetic variation of small populations nor the mutation supply of large populations, however, may be sufficient to provide evolutionary rescue for most populations.

1. Eco-evolutionary dynamics

The gradualist view of evolution is that natural selection is almost always very weak, causing very gradual change over long periods of time. It follows that field and laboratory studies of selection are likely to be fruitless, and very few were attempted for the first hundred years of evolutionary biology. More fundamentally, extreme gradualism uncouples evolution from ecology. It implies that ecological processes can be studied without reference to natural selection, at least to a good approximation, because genetic variation is inadequate to fuel appreciable change in the short term of a few dozen generations. Any species can then be regarded as having a fixed set of attributes during the period of an ecological study. At the same time, evolutionary theory was often almost devoid of ecological context. In particular, the dynamics of allele frequency under selection were conventionally analysed by assuming that the population size is fixed (or infinite), implying that agents of selection have no appreciable effect on abundance.

The removal of evolution from ecology, and ecology from evolution, were useful simplifying devices that made it possible to lay out distinct foundations for both fields. The success of field studies of natural selection subsequent to the 1950s, however, made it clear that selection was often much stronger than had been expected, and could cause rapid modification in response to environmental change [1,2]. That is, the genetic variance of fitness uncovered by selection greatly exceeds that estimated from screens. This has been amply confirmed in the past decade by reports of rapid evolution in a broad range of organisms [3,4]. In many cases, therefore, the dynamics of a population exposed to a stress, or a stimulus, will have both ecological and evolutionary components: an overall shift in abundance and a change in composition. Evolutionary change may be modulated by a trend in abundance, whereas ecological change may respond to a trend in mean character state.

Eco-evolutionary dynamics have two principal consequences. The first is that natural selection may act to modify characters and yet have no permanent result because the population becomes extinct. A population may well become steadily better adapted to a deteriorating environment while irreversibly declining in abundance. The second is that populations may adapt to conditions that would have been lethal to their ancestors, allowing the population to persist when in the absence of genetic variation it would have become extinct. This is the phenomenon of evolutionary rescue.

The interplay of ecological and evolutionary processes is not a new observation, of course: it has been appreciated for as long as the two fields have existed [5]. It has become more prominent in the past few years, however, and has attracted a growing body of theory and experiment, reviewed in the other articles in this volume. In particular, the potential of evolutionary rescue to mitigate the effects of anthropogenic stress has been widely discussed. Again, the idea is by no means new: the evolution of antibiotic resistance by bacteria is an excellent example of evolutionary rescue, although the term was rarely used in this context. Rather, the generality of the process is being investigated with renewed vigour, perhaps in the hope that it may help to moderate the wave of extinction predicted by some to follow global environmental change [6].

Whether the balance tips towards rescue or extinction for a population exposed to a stress depends primarily on the state of the environment, and in particular on the rate and severity of deterioration, and on the state of the population, and in particular on the availability of genetic variation in growth. These are strongly related—whether resistant types exist depends on the severity of the stress that is applied to a population—but ecological and genetic factors are usually treated separately.

2. An environmental constraint: the cost of selection

The conditions of growth change on all time-scales, from minutes to millennia. The most general description of the state of the environment is that the variance of physical factors such as temperature increases over time as a power law with a small exponent [7,8], and abundance follows a similar rule [9,10]. Hence, organisms encounter steadily more extreme conditions as time goes on. Over short periods of time (within a single generation), they cope by plastic modification of phenotype or behaviour, and this may be the over-riding determinant of survival [11]. Over longer periods of time (between generations), however, selection may drive heritable change in mean phenotype. Purifying selection routinely restores mean fitness in the face of mutation, immigration and fluctuating conditions. This seems to involve an increase in mean fitness of a few per cent between offspring and adults in the few cases that have been carefully investigated [12]. Over longer periods of time, there may be persistent trends in conditions. Change is usually for the worse, because any population is likely to be better adapted to the conditions it has experienced in the past than to the new and therefore stressful conditions of the future. Directional selection will then act to restore adaptedness through the proliferation of lineages resistant to the stress. Whether or not selection is effective depends on a host of constraints, however, including the availability

of superior types, the existence of a chain of intermediate forms, the load of deleterious mutations and so forth (reviewed by Barton & Partridge [13]).

The first systematic investigation of the demographic constraints that limit the rate of adaptation was based on Haldane's notion of a 'cost of natural selection' [14]. The passage of a beneficial allele from mutation–selection balance to quasi-fixation, following a change in conditions, is brought about by the death (or sterility) of poorly adapted individuals in the population. The strain that is put on the ability of the population to persist is proportional to the number of genetic deaths—the cost of selection—incurred during the process of adaptation. Haldane came to three main conclusions. First, the cost is independent of the intensity of selection, and thus of the rate of deterioration of the environment. Second, the cost is proportional to the initial frequency p_0 of the allele; for a dominant allele, for example, the number of deaths required is approximately equal to $-\ln p_0$. Third, the number of loci experiencing intense selection at any one time must be small, because the costs are additive over loci with independent effects on fitness. Overall, Haldane estimated that the number of genetic deaths required for the fixation of a single favourable allele would amount to 10–30 times the size of the population at any one time. Hence, selection is likely to be slowed down by the limited capacity of the population to replace the missing individuals.

The demographic consequences of selection are only implicit in this argument: it is assumed that populations might be extinguished by the high death rate of juveniles required for allele fixation at several loci simultaneously. Population size does not appear directly as a consequence of environmental deterioration, however, which is why the cost is found to be independent of the rate of deterioration—it is assumed that the allele does indeed become fixed, rather than the population becoming extinct, because the cost is calculated on that basis. Population regulation is likewise ignored, although density-regulated populations may be able to sustain very high rates of juvenile mortality without damage (as Haldane was well aware; see Nunney [15]). Nevertheless, the concept of a cost of selection provided a clear link between the capacity to reproduce and the capacity to evolve.

3. A genetic constraint: genostasis

The second quantity that influences the likelihood of rescue is the amount of appropriate genetic variation. This is simply the reverse of the coin: the quantity of variation will be inversely proportional to the rate and severity of deterioration. In most contexts, it is genetic variation in relative fitness that fuels adaptation. For a population experiencing lethal stress, however, genetic variance in absolute fitness is critically important, because adaptation will not be permanent unless the most fit genotype has a positive rate of growth in the new conditions of growth.

One of the classic case studies in evolutionary biology is the evolution of heavy metal tolerance by grasses living on the spoil heaps of abandoned mines. Nevertheless, Bradshaw [16,17] emphasized that only a few species have this ability. Most species never evolve appreciable levels of tolerance, and are absent from the polluted sites. By surveying populations of several species, it could be shown that the species

which evolved tolerance often had substantial genetic variance for tolerance in populations growing at unpolluted sites, whereas species that failed to evolve tolerance had no such reservoir of variation. The ability to evolve tolerance thus depended on pre-existing genetic variation in the source populations. Without this resource, species exposed to the stress never became adapted, even though many millions of individuals had been exposed for many generations. Bradshaw called this evolutionary inertia, brought about by the lack of appropriate genetic variation, ‘genostasis’.

Bradshaw also pointed out that genostasis could dissolve when a new source of genetic variation becomes available. The example he gives involves grasses in the genus *Spartina* that grow in salt marshes on both sides of the North Atlantic [18]. *Spartina maritima* is found in western Europe and *Spartina alterniflora* in eastern North America; both are fertile diploids with $2n = 60$ and 62 , respectively. They also both grow only in the upper zone of the marsh, where salt concentration is relatively low: although large populations have lived for thousands of years a few metres away from fully marine conditions, neither species became adapted to life in the lower region of the marsh. The American species was accidentally introduced into British harbours around 1820. By 1870, hybrid plants, named *Spartina × townsendii*, had appeared, and invaded the lower marsh. This form is diploid but sexually sterile. About 20 years later, however, a new species, *Spartina anglica*, had arisen through chromosome doubling. It is a fertile tetraploid and thrives in the lower marsh. Hence, a long-lasting genetic constraint can be overcome in exceptional circumstances when genomes are remodelled.

4. The importance of extremes

It is well known that adaptation requires genetic variation in relative fitness, whereas absolute fitness, under certain assumptions, can be ignored. Genostasis and the cost of selection, on the other hand, express how adaptation is constrained by the genetic and demographic capacity of populations. Variation in relative fitness is not sufficient to ensure permanent adaptation; there must also be enough variation in absolute fitness to encompass at least one viable type within a population. The fundamental theorem states that the rate of change of mean fitness is equal to the additive genetic variance of fitness [19], with the implicit assumption that the population continues to exist. We also require a principle that would state in its most general form that permanent adaptation requires an adequate quantity of genetic variation in absolute fitness. The amount of genetic variation required increases with the rate and severity of environmental change. I believe this argument will be widely accepted—perhaps regarded as obvious—and indeed has been established by the theory of evolutionary rescue and selection in fluctuating environments that has been developed recently. The eco-evolutionary dynamics of populations in deteriorating or fluctuating environments, with respect to the maximum rate of change that can be withstood, have been discussed by Lynch & Lande [20], Burger & Lynch [21], Gomulkiewicz & Holt [22], Orr & Unckless [23] and others. Gomulkiewicz & Houle [24] have synthesized this literature and derived expressions for the critical level of heritability required for evolutionary rescue following abrupt or gradual environmental deterioration.

When conditions change, the members of the population will vary in growth rate. We are concerned with the case of severe degradation, in which most types have negative growth. The entire distribution of the finite rate of growth among types is unknown, but the fate of the population depends only on the extreme right-hand tail of this distribution, which for a large class of distributions, including the negative exponential and normal distributions, decays exponentially or faster (alternatives are analysed by Beisel *et al.* [25]). Estimates of fitness often follow some such distribution. The fitness of rare beneficial mutations arising in laboratory populations of *Pseudomonas* is exponentially distributed [26]. This becomes approximately normal for fixed beneficial mutations [27], with an exponential-like right tail of extremely high values. The viability of chromosomal homozygotes and heterozygotes in *Drosophila* [28] and the growth of deletion strains of yeast [29] likewise have exponential-like right tails. This also characterizes fitness and lifetime reproductive success in natural populations of annual plants and birds [30–32], although in field studies much of the variation is environmental.

The alleles responsible for adaptation are likely to be rare when altered conditions require different attributes, and those ultimately responsible for renewed adaptation will confer exceptionally high fitness. This was recognized by Gillespie [33], who developed a theory of adaptation based on the distribution of extreme values of fitness among alleles. This theory was extended by Orr [34] to describe the successive substitution of beneficial alleles in a population adapting to novel conditions of growth. A catastrophic event that threatens the survival of a population is likely to occur only at long intervals, but when it does occur, it will have a decisive effect on the subsequent history of that population, because the resistant types that survive may have previously been very rare. Thus, the long-term fate of a population will often be governed by the extreme values of environmental and genetic variation. This suggests that current population genetic theory needs to be supplemented by explicit consideration of the distribution of absolute fitness. Variation in relative fitness alone is sufficient for adaptation to occur, but sufficient variation in absolute fitness, such that types with positive rates of growth exist or will arise in the population, is necessary for permanent adaptation to evolve. The extreme-value theory that has been successful as an account of adaptation might also furnish the supplementary principle that is required as a genetic interpretation of evolutionary rescue.

The importance of extremes emphasizes population size as a crucial factor in adaptation, because for any given level of variation larger populations are more likely to contain extreme individuals. In experimental populations of yeast subjected to salt stress, the minimal population size for consistent rescue was that at which the number of resistant cells in the ancestral population was estimated to be one or two [35], in conformity with an extreme-value interpretation. Most natural systems will be more complicated, of course. The population will be successfully propagated, for example, only if stress resistance is heritable, such that the rate of growth refers to the distribution of breeding values [36]. The very small population comprising a single survivor, or a few survivors, may soon become extinct, despite its resistance, through demographic stochasticity [37]. If individuals are able to survive and produce offspring, albeit at less than replacement rate, the

population will gradually dwindle in numbers rather than disappearing abruptly, so that new variation may appear before extinction through mutation or recombination [22,38]. All of these considerations require a more sophisticated analysis, such as that given by Gomulkiewicz & Houle [24]. The extreme-value approach suggested here merely serves to stress the importance of absolute rather than relative fitness, and to show how the range rather than the variance determines the outcome of selection in extreme circumstances.

5. Progressive adaptation in deteriorating environments

The number of individuals that are exposed to selection may exceed the current population size for two reasons. The first is that there will be more opportunity for resistant types to arise by mutation or recombination in slowly declining populations. The number of individuals liable to mutation itself depends on the rate of deterioration. If a population of size N_0 has an exponential rate of increase $r_0 < 0$ following environmental deterioration, it will become extinct at time $t = -(\ln N_0)/r_0$, while the total number of individuals that have lived during this period is $-N_0/r_0$. Any particular realization will vary around these values through demographic stochasticity. Suppose that rescue mutations with $r_1 > 0$ are a fraction ϕ of the overall genomic rate of mutation U . The probability that a new rescue mutation will spread is about $2r_1$ and the expected number of rescue mutations that become fixed before extinction is then $B = 2N_0U\phi r_1/|r_0|$, and the Poisson probability that at least one will spread is $P = 1 - \exp(-B)$ [23,39; see 40]. This may generate a substantial probability of rescue, although unfortunately we have few reliable estimates of ϕ and little understanding of how it is related to r_0 , which expresses the level of stress.

Second, the conditions of growth will often deteriorate over a more or less protracted period of time rather than abruptly collapsing. The population is more likely to survive because it can adapt gradually to the gradually increasing stress. This common situation has been modelled as a moving optimal phenotype that the population tracks by virtue of a constant stock of additive genetic variation [21,24,41]. In more mechanistic terms, adaptation to a deteriorating environment may arise from the positive genetic correlation between growth rates at different levels of stress.

In the initial phase of deterioration, the population may readily adapt to mildly stressful conditions. The allele or alleles responsible will spread to high frequency, provided that deterioration is sufficiently slow. They are unlikely to be precisely specific to a given level of stress, and are likely to confer some protection at somewhat higher levels of stress; that is, there will be a genetic correlation between growth at current mild stress and growth at the more severe stress that will be experienced in the near future. Consequently, when the more severe stress is imposed, the population can persist by virtue of alleles that have previously spread in response to milder stress. These, in turn, provide a basis for further mutations that are beneficial in the new regime, but which likewise have somewhat enhanced ability to grow in the even more severe stress of the next phase of deterioration. In this way, the limit of tolerance advances in step with the direct response to selection in current conditions. The rate of advance depends on two

quantities: the rate at which beneficial mutations are substituted, which is governed by the waiting time before the appearance of a successful mutation and the passage time required for its spread through the population, and the genetic correlation of growth under the conditions when it first appears and those when it has spread. If this exceeds the rate of deterioration of the environment then the population will persist.

The rate of substitution depends on the mutation supply rate, through its effect on waiting time, and thereby increases with population size. This can be demonstrated by propagating experimental populations with a continually increasing level of stress and periodically testing them for survival at a level lethal to the ancestor. Larger populations adapt to lethal stress more rapidly and by mutations of larger effect [42]. In principle, this effect is attenuated in large populations by clonal interference [43], but in practice, the rate of adaptation is a power function of population size over a very broad range. A similar pattern occurs in artificial selection experiments, where the advance in character value is related to the extent of the experiment (log of number of individuals selected multiplied by number of generations) [44, fig. 6.8]. Hence, it is likely that the frequency of rescue will increase with population size in deteriorating environments, as it does when a stress is applied suddenly.

The genetic correlation of growth in two environments depends on their disparity, either in physical units or in terms of the difference in average growth. In two experiments with *Chlamydomonas*, the genetic correlation of vegetative growth fell linearly from nearly +1 for pairs of environments with very similar characteristics to about zero for comparisons of permissive and highly stressful environments [45,46]. Hence, there is substantial genetic correlation between rather dissimilar levels of stress, which favours the evolution of resistance to lethal stress via the indirect effects of alleles adapted to successively higher levels of stress in a gradually deteriorating environment.

It appears that large populations experiencing slowly deteriorating environments should often succeed in adapting to lethal conditions. There is some experimental evidence that rescue is more frequent [47] and adaptation more precise [48] when conditions deteriorate more slowly (see also Gonzalez & Bell [49]), presumably because this gives more time for beneficial alleles to spread in sublethal conditions.

6. Uncertainty of rescue

Whether or not a population adapts to lethal stress may depend on phenotypic variation, heritability, the pattern of genetic correlation, breeding system, demographic stochasticity, the rate of environmental deterioration, the complexity of stressors, the rate of beneficial mutation, dispersal and other factors. It is correspondingly difficult to formulate a brief precise condition for the likelihood of rescue; and in any case, many of the quantities involved are very difficult to estimate in natural populations. Population size is relatively easy to estimate (at least relatively), however, and plays a part in any realistic scenario. This is a little unusual: both purifying selection and directional selection are traditionally described in terms of gene frequencies and relative fitness, with population size playing only a minor role, if any. Mutation–selection equilibrium, balanced

polymorphism, the probability of establishment of a novel mutation and many other staple topics can all be analysed, at least to a good approximation, without reference to the number of individuals involved. Population size usually becomes a major player in evolutionary theory only for neutral processes of genetic drift, where selection is excluded or ineffective. One distinctive feature of evolutionary rescue is that it brings population size back as an essential element in the dynamics of adaptation.

Adaptation in animals and plants with relatively small populations will often depend on the quantity of standing genetic variation [50]. The crucial criterion for evolutionary rescue is then the range of breeding values for fitness, which will depend on both genetic variation and population size. Examples of genostasis suggest that this may often be an onerous requirement. In a prescient article on adaptation to global climate change, Bradshaw & McNeilly [51, p. 12] wrote:

Although, therefore, there is a range of good evidence that evolution can and does take place in relation to climate, we must beware of assuming that its power is unlimited. A fair assessment might be to suggest that some evolution is likely to occur in relation to global climatic change in some species, but that, despite the evidence of long-term evolution, in most cases this is likely to be insufficient to mitigate completely the effects of the climatic change expected in the next 200 years.

It is difficult to improve on this statement 20 years later.

Adaptation in microbes will often depend on the quantity of novel genetic variation. The crucial criterion for evolutionary rescue is then the mutation supply rate for fitness, such that in the simplest case the product of a beneficial mutation rate and the population size must at least exceed unity. Large populations of bacteria, microbes or fungi are sometimes regarded as being almost completely immune from extinction because of the buffering effect of their huge populations. It is clear that they are more likely than larger organisms with smaller populations to adapt permanently to severe physical stress, and there are clear demonstrations of rescue in experimental microbial systems. Nevertheless, however large a population might be, all its members are affected immediately and equally by environmental change, and rescue is by no means guaranteed even for very large populations. Laboratory populations of *Escherichia coli* readily adapt to elevated temperatures, for example, and lines cultured at

32°C can be rescued by the spread of beneficial mutations when transferred to 42°C [52; see fig. 8]. Neither these lines nor lines propagated at 42°C for 2000 generations were able to grow consistently at 44°C, however, although they often show some degree of increased survival up to 50°C [53]. Evidently, there are hard limits to the level of a given stress to which a given organism can adapt that often lead to extinction even when some billions of individuals are exposed to a slightly lower level for thousand of generations.

Microbial populations may fail to adapt even when the environment deteriorates slowly over the course of many generations. The phytoplankton communities of many Canadian lakes, for example, were exposed to acidification and elevated metal concentration through pollution by the plume of the nickel smelter at Sudbury [54; see 39]. A drop from pH 7 to pH 5 reduced algal diversity from about 55 to 34 species; after a further drop to pH 4.5, only 12 species remained; and at pH 4, only a sparse population of resistant *Chlorella* persisted. This was not owing to the replacement of some species by others: overall abundance decreased faster than species diversity. Some species evolved tolerance to low pH and elevated metal concentrations and were able to persist as a result. Most did not, however, despite populations of the order of 10^{10} cells per lake being exposed to a slowly increasing stress for about 20 years. In the most severely affected lakes, only a very small fraction of the community evolved sufficient tolerance to survive.

The initial enthusiasm for evolutionary rescue as a route to survival for stressed populations has, perhaps, moderated more recently, to be replaced by a more sceptical outlook and a greater role for plasticity. The most realistic prediction might be that there will be many species, especially very abundant species, that will successfully adapt to a gradually deteriorating environment, but there will be many more that will not. We have scarcely begun to investigate the evolutionary dynamics of populations adapting to deteriorating environments, however, and what we have found out so far only serves to stimulate a renewed programme of laboratory and field experimentation.

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