

Limits to natural selection

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Summary

We review the various factors that limit adaptation by natural selection. Recent discussion of constraints on selection and, conversely, of the factors that enhance “evolvability”, have concentrated on the kinds of variation that can be produced. Here, we emphasise that adaptation depends on how the various evolutionary processes shape variation in populations. We survey the limits that population genetics places on adaptive evolution, and discuss the relationship between disparate literatures. *BioEssays* 22:1075–1084, 2000.

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Introduction

Natural selection follows inevitably from inherited variation in the ability to reproduce. The systematic accumulation of chance variations is the only process that can lead to biological adaptations, and has produced impressive results: organisms that can live in extreme environments and on diverse energy sources,⁽¹⁾ finely honed organs such as the ribosome, the eye or the human brain, and developmental programs that can reliably construct such organs from the limited information encoded in the genome. Over much shorter times, artificial selection has dramatically increased yields from domesticated plants and animals; applied to populations of RNA molecules *in vitro*, it has produced novel catalytic activities (e.g. Ref.2).

In this essay, we consider what limits the power of selection to produce such adaptations. We can ask how rapidly populations respond to selection and what limits the rate of response, whether any absolute limit is reached, and, if so, what determines it. These are practical questions for the design of artificial selection schemes, either *in vivo* or *in vitro*. When applied to natural evolution, we may also ask whether actual rates of adaptation are close to any limit, and whether actual genetic systems have evolved so as to improve the response to selection. This last question is especially delicate, since species do not in general evolve so as to optimise their own evolvability. In order to show that populations have

evolved so as to facilitate further evolution, one would need to show either that selection within populations favours individual alleles that modify the genetic system appropriately, or that selection between groups can overcome the intrinsically stronger force of selection between individuals. Such arguments require the greatest care.⁽³⁾

There have been recurrent arguments that straightforward natural selection is in some way unable to explain various features of evolution. Following Darwin and Wallace's proposal of adaptation by natural selection, it was argued that there had not been enough time since the formation of the earth for natural selection to act (Ref. 4 p206), and that sexual reproduction and blending inheritance would eliminate the variation on which selection depends.⁽⁵⁾ These doubts were settled at the turn of the century by the discovery of radioactive decay, which established the antiquity of the earth, and by the rediscovery of Mendelian heredity, which maintains variation from generation to generation. The early Mendelian geneticists argued that natural selection could not generate novelty, since it could only sift amongst genotypes that already existed in the population (Ref. 4, p238). However, selection does not occur in a single step: it is the accumulation of successive favourable variants that produces genotypes that are, overall, exceedingly improbable.⁽⁶⁾ Wright⁽⁷⁾ emphasised that selection on a single population cannot establish variants that are favourable in combination, but individually deleterious. He proposed that this limitation could be circumvented by a “shifting balance”, involving selection among populations carrying different gene combinations. The discovery in mid-century of extensive variation in protein and DNA sequence, both within and between species, stimulated Kimura⁽⁸⁾ to propose that most of this variation has no effect on fitness, on the grounds that it could not all be maintained by selection. Finally, the striking stasis of species both across wide geographic regions, and over long geological timespans, has suggested that special mechanisms such as founder events are required for new species to form,⁽⁹⁾ and that macroevolution is uncoupled from microevolution.⁽¹⁰⁾

Here, we try to make sense of these disparate arguments by classifying and clarifying the various kinds of limits to selection. We consider (1) constraints on variation that arise from limitations on what can be built, (2) lack of a chain of fit transitional forms leading to an optimal phenotype, (3) limits inherent in the process of selection, set by the number of selective deaths and by interference between linked variants, (4) limits due to all the other evolutionary processes, which

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necessarily tend to oppose adaptation by natural selection, and (5) limits caused by conflicting natural selection.

Most discussion has tended to be of the first kind of limit: throughout the history of evolutionary biology, there has been a tension over whether the course of evolution is determined primarily by selection among slight variants, or by constraints on the kinds of major variant that can be produced. This is apparent in Jenkin's⁽⁵⁾ concerns over blending inheritance, in the bitter conflict between biometricians and Mendelians at the turn of the century, and on through to current debates over the evolutionary consequences of developmental and genetic mechanisms. "Developmental constraints" have been much discussed elsewhere (e.g. Refs 3,11,12) and we do not discuss these further. In this article, we take a population-genetic view, and survey a variety of limits on the evolution of whole populations. Selection acts on variation that has accumulated in populations and that is influenced by a variety of processes: it is not simply a matter of whether or not a particular favourable variant can be produced.

Limits to variation

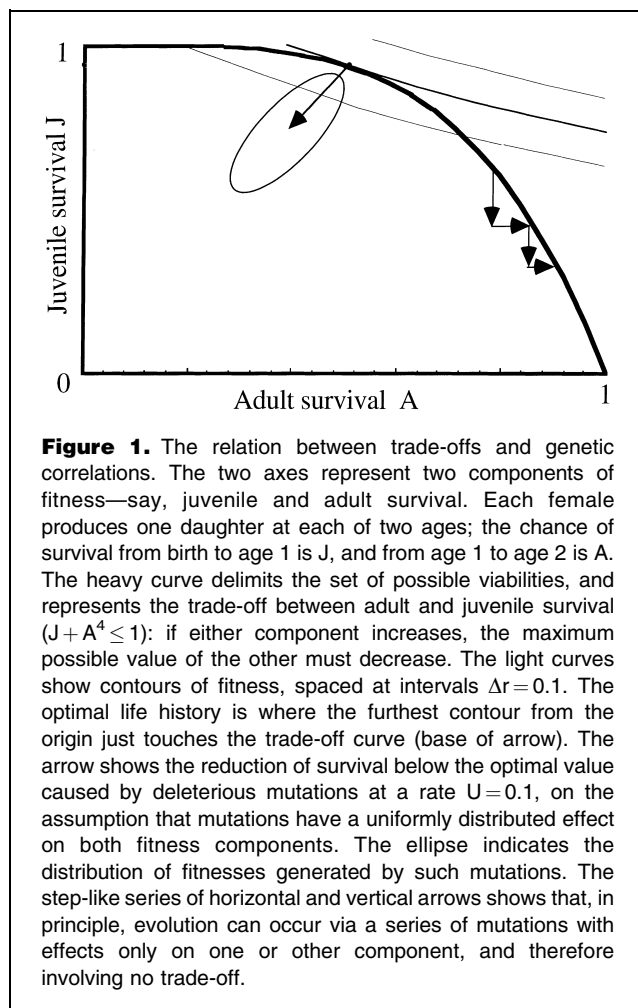
The most obvious limit to natural selection is that suitable variation may not be available. This may be because certain phenotypes cannot be built, being ruled out either by physical law or by the properties of biological materials. Some examples of such limitations are: (1) enzyme catalysis by the rate of diffusion of substrates to the active site, (2) mutation rate by the thermodynamics of base pairing, (3) reaction times by the speed of propagation of nerve impulses, and (4) the acuity of the eye by spherical aberration. These limits depend on assumptions about what is possible, and may be circumvented by the ingenuity of natural selection. For example, (1) sparse molecules diffusing in three dimensions may be concentrated by absorption onto two- or one-dimensional surfaces, as on a moth's antenna,⁽¹³⁾ (2) mutation rates may be reduced by successive proof-reading mechanisms,⁽¹⁴⁾ and (3) spherical aberration can be abolished by a pupil that closes down to the diffraction limit. Nevertheless, we can suppose that there is a set of possible phenotypes, while bearing in mind that this set occupies a space with more dimensions than we can imagine. There is necessarily no variation across the boundary of this set, and hence no response to selection for phenotypes that cannot be realised (Ref. 3 Chapters 6,11).

Long-term artificial selection is a powerful way of exploring the space of possible phenotypes. Darwin's strongest evidence for the power of natural selection was by analogy with the dramatic success of artificial selection,^(Ref. 15, Chapter 1) and studies since Darwin's time have confirmed his view. What is remarkable is that almost all traits respond to selection, and that selection on large sexual populations causes a sustained response over many generations.^(16,17) For example, Weber⁽¹⁸⁾ selected on the angle between two wing veins in *Drosophila melanogaster* for 20 generations, and achieved

divergence of 20 phenotypic standard deviations. There was no sign of a decrease in response over time, suggesting that the response is due to variants of slight effect. Such sustained responses conflict with the frequent identification of major "quantitative trait loci" (QTL) responsible for divergence. However, statistical bias leads QTL effects to be over-estimated, and so there may well be no conflict between these different lines of evidence.⁽¹⁹⁾ Artificial selection on growth rate has been continued for over 20,000 generations on large asexual populations of bacteria, and has led to a plateau.⁽²⁰⁾ This may reflect a genuine limit to selection. However, these results cannot be compared directly with those from sexual populations, which respond much more effectively to selection (see below).

It could be argued that artificial selection is successful because it is strong. If alleles that influence the selected trait have deleterious side-effects on fitness, then selection on the trait may need to be above some threshold for there to be any response (see below). However, selection in nature is also intense,^(21,22) and so the ready response of domesticated and laboratory populations remains the strongest evidence for the power of natural selection.

The limited set of feasible phenotypes could imply that there are "trade-offs" between different components of fitness; the constraint on the phenotype would then arise from constraints on trait combinations, rather than on single traits. One of the most frequently observed trade-offs is that between reproductive rate and survival—the "cost of reproduction".⁽²³⁾ Imagine that each phenotype is described by components of fitness, for example, survival, mating success and fecundity, measured across various ages and environments. If one component increases then, if trade-offs are present, the maximum possible contribution of other components must necessarily decrease (Fig. 1). This has spawned a research program that measures genetic correlations between fitness components, and infers a trade-off, and hence a constraint, if such correlations are negative. However, there are two problems with this approach.^(23–25) First, a negative genetic correlation does not necessarily imply an absolute constraint: the response to selection may be reduced by the conflict between different components, but not eliminated. No empirical measurements can establish that there is absolutely no variation in the desired direction. Second, a trade-off only describes variation along the boundary of feasible phenotypes. Mutations may in principle affect only single traits, and involve no trade-off. In addition, standing variation may lie inside the feasible set, and involve primarily positive correlations among fitness components (Fig. 1). The genetic correlation does predict the immediate direction in which a population will respond to selection, but cannot safely be extrapolated over evolutionary timespans.⁽²⁶⁾ The response to artificial selection, this time on combinations of traits, therefore, gives a better indication of the presence of trade-offs.



The evidence from artificial selection, then, suggests that most (but not all) traits are capable of responding to artificial selection, but that limits on trait combinations may be important in limiting the response to selection.

Rates of evolution

Almost all populations contain abundant genetic variation, at all levels: DNA sequence, protein sequence, and phenotypic traits. Thus, at least the initial response to selection may depend on standing variation, rather than new mutations. If, on one hand, this standing variation is mainly due to what were originally neutral or deleterious mutations (the “classical” view of genetic variation, in which standing genetic variation is maintained by mutation, in opposition to drift or selection), then, in theory, the longer-term rate of evolution will still be proportional to mutation rate. If, on the other hand, most standing variation is due to balancing selection on different alleles (either heterozygote advantage, or, more likely, some kind of frequency-dependent selection that favours rare variants), then long-term rates of evolution need not depend

strongly on mutation rates. Instead, the response will be limited by a conflict between directional selection on the trait of interest, and whatever form of balancing selection maintains variation. Despite considerable efforts, we do not at present know if the “classical” or the “balance” view is more nearly correct. Discriminating tests have proved hard to devise.

Are observed rates of evolution limited by rates of environmental change, or by levels of genetic variability? If the latter, is the immediate limitation set by mutation rate? First, consider morphological change. Average rates of change seen in the fossil record are extremely slow, and even the fastest are easily explained by the levels of standing variation seen in present-day populations: genetic variability does not seem limiting.^(22,27) In artificially selected populations, genetic variation necessarily determines the initial rate of response. However, the increase in additive genetic variance due to mutation is $\sim 10^{-3}$ of the standing variation, which makes a significant contribution after ~ 50 generations of selection.^(19,28)

Any one gene mutates much more rarely: $\mu \sim 10^{-9}$ per base per generation, say.⁽²⁹⁾ Nevertheless, in a large population of $N > 10^9$ diploid individuals, any favourable single base change will be established quickly: a mutation with selective advantage s has a chance $2s$ of being established,⁽³⁰⁾ and so the net rate of substitution is $2N \cdot 2s \cdot \mu = 4N\mu s$. This is reflected in the rapid evolution of pesticide and antibiotic resistance, and by the frequent multiple mutational origin of such adaptations. Genetic variation and, more specifically, lack of mutations should not and, it seems, does not limit at least straightforward selection response.

The evidence that, in the short term, the direction and rate of evolution are not limited by mutation must be reconciled with other evidence that, over the longer term, evolution may be limited by lack of the appropriate variability. On the broadest scale, the contrast between the metabolic diversity of prokaryotes and the morphological diversity of the eukaryotes, presumably reflects fundamental constraints on the type of variation that can arise in these groups (perhaps due to the mechanism of replication, or the structure of the cell wall).⁽¹⁾ Dramatic adaptive radiations (for example, of metazoans at the beginning of the Cambrian or of *Drosophila* on the Hawaiian islands) involve the diversification of a single lineage into very different morphologies and behaviours. However, none of the suggestions for the limiting factors—from the wait for a single appropriate variant, as was supposed by the mutationist theories from de Vries and Bateson, through to recent suggestions that multiple duplications of the Hox genes triggered vertebrate evolution (for review see Ref. 31)—are satisfactory. There are two more plausible explanations. The radiation may simply have awaited an appropriate environment,^(32,33) for example, rising oxygen levels in the Precambrian,⁽¹⁾ or an island lacking competitors.⁽³⁴⁾ Alternatively, major shifts may await a combination or sequence of histori-

cal circumstances (including a sequence of mutations and appropriate environments). In the next section, we consider obstacles to the assembly of multiple evolutionary changes.

Absence of fit intermediates

“If it could be demonstrated that any complex organ existed, which could not possibly have been formed by numerous, successive, slight modifications” then Darwin’s theory of evolution by natural selection “would absolutely break down” (Ref. 15, Chapter 6). The difficulty in establishing multiple changes, all of which are apparently required to give a selective advantage, has long been seen as a key objection to adaptation by simple natural selection, and has stimulated elaborate alternative explanations. For an asexual organism, the problem can be seen as one of lack of variation: the probability that two or more specific mutations occur in the same individual is extremely low, and so individual favourable mutations must be established in sequence.^(35,36) In a sexual species, recombination breaks up adaptive gene combinations even if they do arise at low frequency, and again prevents establishment of all but immediately favourable variants.

Darwin’s response to this difficulty remains convincing: some sequence of changes, each individually advantageous, can always be found. Only a single sequence of ancestral forms, each fit in at least some environment, is needed. The existence of such a sequence is more plausible when one realises the very large number of directions in which a population might evolve. To take Darwin’s original example, eyes capable of focusing an image have evolved independently at least 15 times, through a series of gradations ranging up from single photoreceptive cells.⁽³⁷⁾ Plausible assumptions about genetic variation in each component part lead to reasonably rapid evolution of the whole system.⁽³⁸⁾ The requirement that natural selection can only produce changes that each give an immediate fitness advantage has been termed a “selective constraint”, in contrast with “developmental constraints”, which limit what kind of organisms can be produced.⁽¹¹⁾

Selective constraints are most easily satisfied if an organism evolves through a series of slight adjustments. Fisher⁽³⁵⁾ proposed a simple quantitative model of Darwin’s gradualist argument. He assumed that fitness depends on a large number, n , of continuously varying traits, and increases towards some optimal combination of phenotype. Mutations of small effect have roughly equal chances of taking the population towards the optimum or away from it, whereas mutations of large effect are certainly deleterious. (Imagine a population lying at a point in n dimensional space, some distance r from the optimum; mutations of effect larger than $2r$ must take it further from the optimum). Kimura (Ref. 39, Chapter 6) extended this argument to allow for the greater chance that a strongly selected allele will be fixed, and

Orr^(40,41) further extended Fisher’s model to follow a sequence of substitutions with additive effects, which take the population closer and closer to the optimum. Orr showed that regardless of the distribution of mutational effects, the distribution of effects of the substitutions that actually occur is exponential, with mean inversely proportional to \sqrt{n} . The initial substitution can be quite large, relative to the distance from the optimum, and tends to have deleterious side effects. Later substitutions tend to have smaller effects, which compensate for the deleterious side-effects of the earlier mutations. (Such compensation for the deleterious consequences of major mutations is seen in the evolution of antibiotic and pesticide resistance, Refs. 42,43).

The Fisher/Orr model suggests that adaptation of complex organs (i.e., of high dimension, n) is likely to be slow, and to depend on predominantly minor variations. (We consider below how the effective dimensionality of an organism affects its evolvability). It is much oversimplified, in that it supposes that evolution is based on a sequence of allelic substitutions at single genes, rather than on standing variation at multiple loci, and in that it assumes a smooth “fitness landscape”. If there are many fitness peaks, then the population will be trapped at the nearest. In a broad sense, this is clearly why different lineages are constrained to particular ways of life: almost all of the multiple changes needed to allow a pig to fly would be deleterious. However, there is a sequence of ancestral phenotypes that connects pigs with bats and birds, and a combination of appropriate environments and appropriate genetic variability has taken organisms along this path.

The cost of natural selection

Natural selection establishes fitter genes because those genes reproduced, whilst others did not. Haldane⁽⁴⁴⁾ argued that selection is therefore costly, relative to the ideal alternative in which all genes are instantaneously changed to the currently optimal allele. For example, suppose that conditions change suddenly, so that most genes have viability $1 - s$, whilst a rare allele at frequency p_0 is certain to survive. That allele will take $\sim (1/s)\ln(1/p_0)$ generations to reach appreciable frequency. During each of those generations, a fraction $\sim s$ of the population dies because it does not carry the optimal allele-, and, overall, a total of $\ln(1/p_0)$ selective deaths are required, per head of population. This “substitution load” is twice as great for a diploid population, if heterozygotes have intermediate viability. A single substitution requires at least $\ln(1/p_0)$ selective deaths; unlike other arguments based on “genetic load”, this is true even if fitnesses vary over time, or depend on gene frequency,⁽⁴⁵⁾ and even if selection is “soft” (i.e., does not influence population size). There have been on average ~ 1.3 amino-acid substitutions per generation since humans diverged from chimpanzees.⁽⁴⁶⁾ Haldane’s argument implies that no more than a small fraction of these could have been established by selection.

The cost of natural selection can be seen as limiting the rate of accumulation of genetic information. An allele with no effect on fitness has a chance of eventually fixing in the population, which is just equal to its initial frequency. Natural selection makes this unlikely event certain (at least, provided that the initial frequency is high enough for random drift to be negligible). The information added by some signal is defined as the log of the ratio between the probability of events, given the signal, and the probability without it: it is a measure of the concentration of probability around certain outcomes. Thus, the information added by natural selection in this example is $\log(1/p_0)$, and can be no greater than the number of selective deaths that occurred. Kimura⁽⁴⁷⁾ argued that only a limited amount of genetic information could have been accumulated by natural selection in any one lineage since the Cambrian. Gene duplication complicates matters, since it increases genome size for the same cost as substitution of a single base pair. A duplication in itself, however, increases genetic information by a small amount: it is the subsequent divergence of the duplicate gene that requires an additional cost. More selective deaths, however, are presumably due to fluctuating selection rather than to substitutions; the former does not increase the amount of functional genetic information. While it is not easy to define the amount of information in the genome, Kimura's argument does seem to put a strong upper bound on the size of the functional genome.

The most serious difficulty with Haldane's argument is that the effects of different loci are assumed to be independent. In contrast, if just those individuals with the largest number of favourable alleles reproduce, then very many more alleles can be substituted for the same reduction in mean fitness.^(48,49) This can be demonstrated very simply. Most of the substitution load accrues while favourable alleles are rare, and in different individuals. If a fraction $w < 1$ of the population survives in each generation, and if this fraction includes all those individuals that carry rare favourable alleles, then the frequency of each such allele increases by $1/w$. Hence, each takes $\sim \log(1/p_0)/\log(1/w)$ generations to become common, and the overall mean log fitness is $\sim \log(1/p_0)$. On this argument, alleles at any number of loci can be substituted with the same fitness loss as at one. Of course, these theoretical arguments leave open two questions: whether interactions between genes are in fact such as to reduce the "cost of natural selection", and if so, why interactions have evolved to be of this form (Refs 3,39,Chapter 2). We return to this issue below.

Mutation

Natural selection apart, all evolutionary processes are random with respect to adaptation, and therefore tend to degrade it. The other three evolutionary forces, mutation, genetic drift and gene flow can all work against adaptation by natural selection. The most important of these is mutation, which is the inevitable consequence of imperfect replication. In a large population, a

balance is reached between selection and deleterious mutation, which reduces mean fitness. This limits the net mutation rate, and hence the size of functional genome that can be maintained by selection. With asexual reproduction, a simple argument shows that deleterious mutation reduces mean fitness by a factor e^{-U} , where U is the genomic deleterious mutation rate. The population can only sustain itself if those fittest individuals, which carry no deleterious mutations, produce the same number of intact offspring. Since the chance that an offspring escapes mutation is e^{-U} (assuming a Poisson distribution of mutant number), the fittest class must reproduce at a rate e^U faster than the average. With sexual reproduction, the fittest class can be regenerated by recombination between genomes carrying different mutations; the load can be greatly reduced if there is "negative epistasis", such that fitness decreases faster than multiplicatively with number of mutations^(50,51) (Fig. 2). In asexual bacteria, mutation rates are low enough that the mutation load is negligible, even in absence of recombination.^(14,29) In contrast, RNA viruses are close to the maximum mutation limit,⁽⁵²⁾ and in vitro replication experiments show that genome size is limited by the mutation load. In eukaryotes, genomic mutation rates are not well known, but may be high enough to require that negative epistasis and recombination combine to alleviate the load.⁽⁵³⁾ In particular, examination of sequence conservation between humans and primates implies that $\sim 38\%$ of coding sites are maintained by selection, and that the net mutation rate is high: $U \sim 4.2$ per generation.⁽⁴⁶⁾ At present, it is not understood whether or how genome size might evolve so as to approach the upper limit set by mutation load: presumably, there is a balance between the evolution of novel gene function, and loss of existing functions under mutation pressure.

Random drift

Since different genes produce different numbers of offspring by chance, allele frequencies inevitably fluctuate. This process of random genetic drift interferes with selection in several ways. Even in a large population, most favourable mutations are lost: the chance of a single copy fixing in the population is only twice its selective advantage.⁽³⁰⁾ This fixation probability is further reduced by selection on linked loci, which in effect amplifies the random influence of genetic drift.⁽⁵⁴⁾ In the extreme case of an asexual population, favourable mutations that occur in different lineages cannot be brought together in one individual. Thus, a slightly favourable allele can only be fixed if it arises in a genetic background that is free of deleterious mutations.⁽³⁵⁾ Such perfect backgrounds may be extremely rare.

Even in a sexual population, selection at one locus is impeded by any kind of selection at linked loci. Weakly selected alleles are especially sensitive: an allele that increases fitness by less than some critical value, proportional to the rate of selective sweeps per map unit, has essentially no

place. Such spatially varying selection is common, as a result of changes in the physical and biological environment. Allele frequency can track changing conditions only over distances greater than $\sim \sigma/\sqrt{s}$, where σ is the distance moved by a gene in each generation, and s is the selection coefficient.⁽⁶⁴⁾ Quantitative traits subject to stabilising selection of strength s towards an optimum can track changes in the optimum over distances greater than $\sim \sigma/\sqrt{sV_a}$.⁽⁶⁵⁾ In many organisms, dispersal ranges are short, so that genetic divergence can occur over short distances if selection is sufficiently strong. A classic example is the adaptation of the grass *Agrostis tenuis* to tolerate heavy metals concentrated in mine waste only a few tens of metres across.⁽⁶⁶⁾ Burt⁽⁶⁷⁾ pointed out that the overall degree of local adaptation can be measured by finding how much mean fitness is reduced when individuals are transplanted by one dispersal range. The limited data available from plant populations suggest that selection must raise mean fitness by a few percent each generation in order to counter immigration.⁽⁶⁷⁾

Fluctuating selection

Selection pressures can vary greatly with time, so that the phenotype favoured by natural selection changes. Even within a species held under apparently constant conditions, genetic conflicts can lead to varying selection and continuing evolution (Ref. 68 and see below). A single gene can only respond to selection over time scales inversely proportional to the selection coefficient, or longer if genetic variation is limiting: this leads to a “lag load”, equivalent to the “cost of natural selection” discussed above.⁽⁶⁹⁾ Similarly, selection can change a quantitative trait at a rate proportional to its additive genetic variance, V_a . In principle, arbitrarily rapid fluctuations can be tracked, provided that V_a is large enough. However, quantitative traits are usually subject to selection against extreme phenotypes (“stabilising selection”), and so high genetic variance reduces fitness. There is an optimal value of genetic variance, set by a trade-off between directional and stabilising selection. Even with this optimal variance, a population will go extinct if selection fluctuates too much.⁽⁷⁰⁾

Conflicts between levels of selection

Any entity that has the capacity for replication and variation can be subject to natural selection. Because more than one kind of such an entity can be present simultaneously, conflicting selection can occur. Such conflicts are most obvious in interactions between species, but also occur between genes that are carried within one organism, but are inherited in different ways.

Selection can act at different levels. Transposable genetic elements, present in the genomes of most living organisms, often behave as genomic parasites. By replicative transposition, they disobey Mendel's laws, and both increase their own

rate of reproduction and disrupt the genome of their host.⁽⁷¹⁾ There is therefore conflicting selection on transposition rate, with the transposable element selected to increase its own reproductive rate and the genes of the host selected to suppress the element. Several cellular processes can be understood as host adaptations of this kind.^(68,72,73) Sexual reproduction and outbreeding by the host exacerbate this kind of conflict, because in an asexual organism the transposable elements cannot disobey Mendel's laws, their own evolutionary future becomes identical with that of their host clone, and conflicting selection ceases. To the extent that transposition is a cause of mutation, we might therefore expect to find variation in mutation rate between organisms with different kinds of breeding system. The data are at present too sparse for any conclusion to be reached.

Evolutionary conflict can occur between sex chromosomes and autosomes, nuclear and cytoplasmic genes, females and males and between individual and group interests.⁽⁶⁸⁾ Long-term persistence of populations or of whole species may be best served by reproductive restraint of individuals, if exhaustion of local food supplies can lead to extinction. However, genes increasing reproductive success of individuals are under selection to increase within local groups. Which side in such an evolutionary conflict will win? In general, selection acts more strongly at lower levels.⁽³⁾ Selection on genes increasing reproductive success of individuals within groups is stronger than selection for individual restraint as a result of extinction of whole groups. The reason is that, for a system of reproductive restraint to be evolutionarily stable, every allele that increases individual reproductive success that is established by mutation or immigration must be balanced by one group extinction.

Arguments that characteristics of organisms have evolved “for the good of the species” should therefore be treated with scepticism. It has, for instance, recently been argued (but echoing back to a much earlier debate, Ref. 74), that ageing has evolved to allow faster turnaround of generations and hence evolution, because this is good for the persistence of species on the long term. Such an argument overlooks the much stronger force of natural selection on individuals to maintain survival and reproduction so as to maximise lifetime reproduction.⁽³⁾ Recent suggestions that mutases⁽⁷⁵⁾ and systems for co-ordinate expression of groups of genes⁽⁷⁶⁾ have evolved because they increase the potential rate of evolution suffer from a similar difficulty (see Ref. 14).

Evolvability

We have discussed a variety of limits to natural selection, arising from (1) what organisms can be constructed, (2) the fitness of those organisms and the lineages that connect them, (3) the nature of selection itself, (4) the interaction between selection and other evolutionary processes, and (5) conflicting selection. We now reverse the question: instead of asking what limits evolution, we ask what features of life have

facilitated its extraordinary diversification, and why those features are as they are.

Recent interest in “evolvability” began in computer science, where genetic algorithms are designed to evolve efficiently towards some optimum⁽⁷⁷⁾ The term has a technical meaning in evolutionary biology, as a dimensionless measure of quantitative genetic variance.⁽⁷⁸⁾ However, it is now used in a broader sense by molecular and developmental biologists. Kirschner and Gerhart⁽¹²⁾ define “evolvability” as “the capacity to generate heritable, selectable phenotypic variation”, a definition that relates to both “selective” and “developmental” constraints (see Refs. 11,79).

Kirschner and Gerhart⁽¹²⁾ discuss several features of life that facilitate the generation of variation that can be the basis of adaptive evolution. A key requirement is that a change to one part should not disrupt the whole system. This is achieved by the following: (1) versatile proteins, which contain several functional sites connected by allosteric regulation, and which can bind to a variety of targets,⁽⁸⁰⁾ (2) the division of the embryo into separate compartments, each with independent patterns of gene expression, (3) “weak linkage” of regulatory networks (for example, where gene expression depends on subtle interactions among many transcription factors), and (4) “exploratory mechanisms” which adapt to circumstances rather than following a predetermined program (for example, in growth of neurons towards their targets, foraging behaviour of ants, or generation of diversity by the vertebrate immune system). It is this issue that is addressed by Fisher’s geometrical argument: one can see many of these features as reducing the effective dimensionality of the organism, allowing evolution by a wider range of larger steps.

Discussions of “evolvability” concentrate on limits on the production of “selectable variation”.⁽⁷⁹⁾ Since adaptation involves the accumulation of variations in populations, the factors identified by Kirschner and Gerhart⁽¹²⁾ influence the long-term fate of variants, as well as their initial production and selective advantage. In addition, many other factors are important: effective population size, breeding system, recombination rate, and so on. There is a substantial population genetic literature on the evolution of genetic systems, which is essentially concerned with “evolvability”, but which is not usually associated with that term (e.g. Ref. 81). For example, Maynard Smith and Szathmari⁽⁸²⁾ demonstrate the importance of discrete and unlimited heredity, such as that allowed by DNA sequence and by human language in allowing continued biological or cultural evolution. Maynard Smith and Szathmari⁽⁸²⁾ also emphasise the importance of factors that suppress conflicts between different replicators, which has allowed cooperation of genes within cells, and of cells within organisms.

An example that has received much recent attention in disparate literatures is the nature of gene interaction. A modular organisation may allow novel alleles to function in

different genetic backgrounds, reducing the constraints on selectable variation; conversely, the striking redundancy observed for most eukaryotic genes makes organisms robust to loss of function. This kind of gene interaction has important consequences at the population level. Both the mutation load, and the “cost of natural selection” may be unsupportable unless there is “synergistic epistasis”, such that the marginal effect of deleterious alleles increases with the number already present, and conversely, the benefits of favourable alleles decreases as they accumulate.⁽⁵¹⁾

Note that it is unlikely that any genes are strictly redundant: any gene that is not maintained by natural selection will be disabled by mutation and genetic drift. The pseudogenes found in eukaryotic genomes are presumably gene duplications that have suffered just this fate. On a larger scale, there is extensive loss of gene function following duplication of the entire genome by polyploidy.⁽⁸³⁾ The frequently undetectable effects of gene knockouts only imply that such genes are maintained by weak selection⁽⁸⁴⁾: even in microorganisms, no feasible experiments can detect fitness differences smaller than $\sim 0.5\%$.^(85,86) Moreover, absence of deleterious effects in the laboratory cannot necessarily be extrapolated to nature.

If it is the case that genes interact in such a way that genetic load is reduced, and the opportunity for future adaptation increased, we must ask why that should be. The simplest explanation is that evolvability is a simple side effect of selection for robustness of individuals to environmental or genetic perturbations. At the phenotypic level, selection reduces both environmental and genetic variation around the optimal phenotype (“genetic canalisation” Ref. 87). Extensive overlap in the function of genes can be maintained by selection if, for instance, the fidelity or reliability of a biological function is thereby enhanced.^(88,89) Genes that overlap in function are often the product of gene duplication and, in principle, genes with identical functions can be maintained, by selection for a functional copy of one in individuals that are mutant for the other.⁽⁹⁰⁾ However, such selection is weak (of order mutation rate) and, in yeast, gene duplicates are no more redundant than unique genes.⁽⁹¹⁾

Selection can also act on evolvability itself, if modifier alleles become associated with the favourable alleles that they produce. Evolution of mutation rates are the most straightforward example, at least theoretically.⁽¹⁴⁾ Rates of sex and recombination can also evolve in this way. For example, if a trait is under stabilising selection, then negative associations develop between the underlying genes (+ + - -, - + - + etc), which reduce the genetic variance. Sex and recombination break up these associations, and hence increase the genetic variance. With a constant optimum for the trait, recombination tends to decrease, but, with a moving optimum, alleles that increase recombination become associated with the favourable + + gene combinations which they generate.⁽⁹²⁾ Such mechanisms can generate short-term selection

for “evolvability”, and are supported by the observation of increased recombination in artificially selected populations.⁽⁹²⁾ However, recombination rates and genetic variance do not in general evolve to any optimal value, and selection on modifiers of the genetic system tends to be weak, and dependent on arbitrary factors such as the linkage relations of the modifying genes. While there is a good theoretical understanding of how selection may act on genetic systems, there is no consensus over the extent to which they have been shaped by adaptive selection.⁽⁸¹⁾

Conclusions

Although much of the emphasis in the recent literature has been on limits to selection set by the nature of the phenotypic variation that can be generated (“developmental constraints”), population genetic constraints may be just as, or even more, important. There is clear evidence that the rate and extent of evolutionary change can be constrained by (1) lack of fit intermediaries leading to an optimal phenotype, (2) limits inherent in the process of selection, set by the number of selective deaths and by interference between linked variants, (3) limits due to evolutionary forces such as drift, mutation and gene flow, and (4) limits caused by conflicting natural selection.

A particular kind of gene interaction is needed to allow species to counter the deleterious mutations that degrade large genomes, and to allow simultaneous adaptation of many genes; sex and recombination are needed to allow selection to act independently on separate functions; and strict genetic rules are required to prevent conflicts between different replicators.⁽⁸²⁾ In principle, such features can be selected because they facilitate evolution. However, such selection is weak, and the simpler alternative is that genetic systems are primarily determined by immediate functional requirements. These kinds of question cannot be resolved by either population genetics or molecular biology alone: the former merely calculates the consequences of specified fitness differences, while the latter specifies the components of life, without showing how or why they came to be as they are. A major challenge for the future is to bring together our detailed mechanistic knowledge of living organisms with an understanding of how they function as whole systems, and how they evolve in populations.

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