Published in final edited form as:
Nat Rev Genet. 2009 August ; 10(8): 531–539. doi:10.1038/nrg2603.

Fitness and its role in evolutionary genetics

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Abstract

Although the operation of natural selection requires that genotypes differ in fitness, for some geneticists it seems easier to understand natural selection than fitness. Partly this reflects the fact that the word “fitness” has been used to mean subtly different things. Here I distinguish among these meanings (e.g., individual versus absolute versus relative fitness) and explain how evolutionary geneticists use fitness to predict changes in the genetic composition of populations through time. I also review the empirical study of fitness, emphasizing approaches that take advantage of recent genetic and genomic data. Finally, I highlight important unresolved problems.

Without differences in fitness natural selection cannot act and adaptation cannot occur. Given its central role in evolutionary biology, one might expect the idea of fitness to be both straightforward and widely understood among geneticists. Unfortunately, this may not be the case; although evolutionary biologists have a clear understanding of fitness, the idea is sometimes misunderstood among general geneticists.

Here I discuss a number of conceptual and empirical aspects of fitness. Throughout this review, I emphasize two points. First, it is often easier to perform experiments on fitness than to think clearly about it. Our difficulties are, in other words, more often conceptual than empirical. For this reason, I devote more space to theoretical than experimental issues. Second, much of this confusion can be eliminated by keeping a simple distinction clear: that between fitness as the phenotype of an individual and fitness as a summary statistic.

I do not attempt mathematical rigor here. My aim is to introduce — and hopefully demystify — a large literature for the general geneticist and my approach is sometimes intuitive or heuristic. I also do not attempt to navigate the large philosophical literature that has grown up around fitness [1–5]. This does not reflect my assessment of the significance of this work, but the constraints of space and expertise.

I first consider conceptual issues both from the perspectives of population genetics and quantitative genetics and then turn to empirical studies.

Conceptual issues

Although biologists have offered a staggering number of definitions of fitness [6], they agree broadly on the essence of the idea. In the crudest terms, fitness involves the ability of organisms — or, more rarely, populations or species— to survive and reproduce in the environment in which they find themselves [6–9]. The consequence of this survival and reproduction is that organisms contribute genes to the next generation. To get any further, we need to analyze these ideas into sharper ones. Fitness is commonly analyzed in two ways. One involves the actual “components” that give rise to differences in fitness among organisms and the other involves mathematical measures of fitness.

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Components of fitness

Consider a species that has a simple life cycle. Zygotes are produced and either survive to adulthood or do not. If they do, adults attempt to court and mate. If all goes well, these adults produce some number of offspring and the cycle begins anew. Differences in fitness among individuals can arise from differences in "performance" at any of these stages. Each of these "fitness components"— in this case, viability, mating success, fecundity— can contribute to differences in total fitness among individuals, i.e., can cause different individuals to leave different numbers of progeny.

While simple and useful, this way of partitioning fitness has some drawbacks. First, the nature of fitness components is not universal but can differ across taxa: an asexual bacterium has no mating success while a bear does. Second, fitness components can be subdivided arbitrarily. Differences in survival in insects, for example, can be divided into survival at the embryonic stage, larval stage, pupal stage, and adult stage. Larval survival, in turn, can be subdivided into that at the first, second, etc. instar. Where we terminate this process is largely a matter of convenience or convention. While these shortcomings cause no problems in practice, they suggest that this way of analyzing fitness may not carve nature at a joint.

Mathematical measures of fitness

Another way to think about fitness involves various mathematical measures. To simplify matters, I will focus on differences in fitness that arise from differences in survival, assuming all else equal. While this represents a considerable (and, in some ways, consequential) simplification, it at least lets us capture much of what is interesting about the mathematics of fitness without becoming mired in technicalities.

Much confusion can be avoided by distinguishing between the fitness of particular individuals and fitness as a summary statistic. To see the distinction, again consider viability selection acting on zygotes. Each zygote can be assigned a viability: the first zygote might survive, the second might not, and so on. Fitness (viability) here is a trait and the trait is sometimes called "individual fitness" (e.g., Ref. 10). With viability selection alone, individual fitness is binary [10]: an individual either survives (1) or it does not (0) (Ref. 10, p. 64). In the language of probability theory, viability is a Bernoulli random variable. As with any random variable, we can calculate various summary statistics. We can, for instance, calculate the mean individual fitness. If a proportion P of zygotes survives, the mean individual fitness (viability) is $P(1)+(1-P)(0) = P$[10]. Similarly, we can calculate the variance in individual fitness (viability), which can be shown to equal $P(1-P)$.

Importantly, we have assumed nothing so far about genetics. We have not specified the genotype of any individual nor even whether any genetic variation segregates in the population. Indeed our population might be composed of a single genotype and all of the above would remain true: among genetically identical individuals, survival would be due to chance with a proportion P surviving. Although such a scenario involves differences in individual fitness, no Darwinian evolution is possible. Response to natural selection requires that some of the differences in fitness have a genetic basis, i.e., fitness must be at least partly heritable. Given this, it is convenient to introduce two new summary statistics, ones that play far larger roles in the evolutionary literature: absolute and relative fitness.

Absolute fitness is a statistic that is usually assigned to a genotype and it typically refers to a genotype's expected total fitness, that complex mix of viability, mating success, fecundity, etc. As such, absolute fitness, symbolized W, is a quantity that can be greater than or equal to zero[11]. But if we continue to restrict attention to viability selection with all else equal,

individuals of a given genotype have some probability of surviving. We can think of this probability as the absolute viability of the genotype.

Just as we can calculate a mean individual fitness, so we can calculate a mean absolute fitness. If only two genotypes segregate in a haploid population, mean absolute fitness is $\bar{W} = pW_1 + qW_2$, where p is the frequency of genotype 1, q is the frequency of genotype 2 ($p + q = 1$), and W_1 and W_2 are, respectively, the absolute fitnesses of genotypes 1 and 2. It is easy to show mathematically that mean absolute fitness equals mean individual fitness. This is also easy to see intuitively. The mean absolute viability is the chance that an individual having a randomly chosen genotype survives; but this must be the same as the probability that a randomly chosen individual survives, regardless of information on genotype. We can also calculate the variance in absolute fitness. This quantity is less than or equal to the variance in individual fitness. The reason is that the variance in absolute fitness takes into account only variation in fitness due to differences in genotype, whereas the variance in individual fitness takes into account variation in fitness due to genotype and to chance differences in the environment.

Although absolute fitness is easy to think about, evolutionary geneticists almost always use a different summary statistic, relative fitness. The relative fitness of a genotype, symbolized w, equals its absolute fitness normalized in some way. In the most common normalization, the absolute fitness of each genotype is divided by the absolute fitness of the fittest genotype [11], such that the fittest genotype has a relative fitness of one. We can also define a selection coefficient, a measure of how much worse the A_2 allele is than A_1. Mathematically, $w_2 = 1 - s$. Just as before, we can calculate various statistics characterizing relative fitness. We can, for instance, find the mean relative fitness ($\bar{w} = pw_1 + qw_2$), as well as the variance in relative fitness.

Although the definition of relative fitness is simple, the mathematical relationship between absolute and relative fitness is subtle [12–14]. In particular, there is a curve of diminishing returns between the two quantities: increasing the absolute fitness of a genotype by some amount has less effect on relative fitness (compared to the mean relative fitness) than does decreasing the relative fitness of the genotype by the same amount. This surprising relationship has some consequences in population genetic theory but, given their subtlety, we omit discussion of them here (see Ref. 14).

It is the relative fitness of a genotype that almost always matters in evolutionary genetics. The reason is simple. Natural selection is a differential process: there are winners and losers. It is, therefore, the difference in fitness that typically matters.

Selection equations

Evolutionary biologists have introduced various measures of fitness for good reason: fitness does work for us. In particular, only by defining fitness mathematically can we construct selection equations, equations that allow us to predict how rapidly allele frequencies will change under natural selection. To see this, consider again a haploid species with two alleles, A_1 and A_2. If $W_1 > W_2$, A_1 will become relatively more common through time and A_2 will become relatively less common. To say anything further, however, requires mathematics. Fortunately the necessary mathematics is straightforward.

As zygotes attempt to mature, selection acts, killing some. Because a proportion W_1 of A_1 individuals and W_2 of A_2 individuals survives, the proportion of individuals that carry A_1 after selection acts is $pW_1/(pW_1 + qW_2)$. As Box 1 shows, it follows that selection will increase the frequency of the fit A_1 allele from one generation to the next by

$$\Delta p = \frac{pqs}{1 - qs}. \quad \text{(Eq. 1)}$$

We conclude, therefore, that change in allele frequency by natural selection depends only on the difference in relative fitness between two alleles (and starting allele frequency). The absolute magnitudes of W_1 and W_2 are irrelevant. If we iterate Eq. 1 over many generations, the difference in fitness lets us predict how A_1 will increase from an initial low frequency to higher frequencies. As Figure 1 shows, the path of allele frequency through time is sigmoidal.

The result given in Eq. 1, which holds for a single generation of selection in haploids, has been generalized by population geneticists for diploids (with any pattern of dominance at a locus) and for any number of generations of selection. Indeed these various cases constitute a considerable part of the classical population genetic literature [11, 15]. Although we have considered species that have discrete generations, population geneticists have also generalized measures of fitness and have derived selection equations for the case in which populations or genotypes grow continuously through time (see Box 2).

Variation in fitness

Alleles almost surely do not enjoy constant fitness through time. Instead the fitness, either absolute or relative, of most alleles likely fluctuates through time in response to physical and biological changes in the environment.

The consequences of temporal fluctuations in fitness have been well studied [12,16–20] and the results are surprising. In particular, one might guess that the allele with the highest average fitness through time would ultimately predominate in a population. This turns out not to be right.

To see why, consider again the simple case of two alleles in a haploid. We now let the fitness of each allele to vary randomly through time (with no autocorrelation). In particular, in each generation, the fitness of each allele is drawn from a probability distribution: $W_{1,t}$ (where the subscript denotes allele 1 in generation t) is drawn from the distribution $f(W_1)$ and $W_{2,t}$ is drawn from $f(W_2)$. Analysis shows that the allele that ultimately predominates in a population is the one with the highest geometric mean fitness through time[12,16–20]. The geometric mean is given by the t-th root of t terms in a product[11]: $G_1 = (W_{1,1}\, W_{1,2}\, W_{1,3} \ldots W_{1,t})^{1/t}$.

This role for the geometric mean fitness makes some intuitive sense: selection over many generations is a multiplicative process and, when considering multiplicative processes, the geometric mean provides a more natural metric than does the arithmetic mean (Ref. 17, p. 147). As Box 3 explains, this role of the geometric mean also implies that, all else equal, natural selection favors alleles with a smaller variance in fitness through time.

Population geneticists have also considered the effects of spatial variation in fitness [21–23]. A genotype might, within a generation, enjoy one fitness value if it lives in one part of a population's geographic range but another fitness value if it lives in another part of the range. Box 4 provides a brief introduction to this topic, as well as to the related ideas of "hard" and "soft" selection.

The quantitative genetic view

Our discussion of fitness so far has been population genetic. A somewhat different view emerges from the quantitative genetic tradition, a tradition that focuses on the evolution of traits that are genetically complex. The difference is, however, mostly one of emphasis.

The quantitative genetic view begins by emphasizing, as above, that fitness is a trait. It further emphasizes, however, that this trait is special. Of the potentially infinite number of traits that make up an organism, one trait— fitness— is unique in that it is the only trait that allows us to predict how much any other trait will change under natural selection from one generation to the next. This idea is captured in a result that was derived surprisingly late in the history of evolutionary biology. In late 1960s and early 1970s, Alan Robertson [24] and George Price [25] independently showed that the amount by which any trait, *X*, changes from one generation to the next is given by the genetic covariance between the trait and relative fitness. (The relevant covariance here is the "additive genetic covariance," a statistic that disentangles the additive from dominance and epistatic effects of alleles [26]) If a trait strongly covaries with relative fitness, it will change a good deal from one generation to the next; if not, not. This result is now known as the Secondary Theorem of Natural Selection [27, 28].

If the trait, *X*, is relative fitness itself, the additive genetic covariance between *X* and fitness collapses into the additive genetic variance in relative fitness, $V_{A\,(w)}$. Theory allows us to predict, therefore, how much the average relative fitness of a population will change from one generation to the next under selection: it will change by $V_{A\,(w)}$. Because a variance cannot be negative, the mean relative fitness of a population either increases or does not change under natural selection (the latter possibility could occur if, for instance, the population harbors no genetic variation). This finding, the Fundamental Theorem of Natural Selection, was first derived by Ronald A. Fisher [29] early in the history of evolutionary genetics. Despite the misleading nomenclature, the Fundamental Theorem is clearly a special case of the Secondary Theorem. It is the Secondary Theorem that is more fundamental.

The Secondary Theorem of Natural Selection is loosely associated with a particular way of thinking about fitness and natural selection, a way described by both Alan Robertson [30–32] and Douglas Falconer [26]. According to this view, "the 'character' that natural selection selects for is fitness" (Ref. 26, p. 301). Fitness, in other words, is the trait that natural selection "sees" and other traits change only because they are associated genetically with fitness and so get dragged along with the response to selection on fitness itself. This view is at first counterintuitive and perhaps paradoxical. After all, individuals differ in fitness because of their traits— height, weight, resistance to disease, etc. Biologically, then, trait differences cause fitness differences. But, under the Robertson-Falconer view, when looking across generations, it is useful to turn the relationship around: response to natural selection on fitness causes evolutionary responses at other traits. However paradoxical the Robertson-Falconer "inversion" might seem, it provides a powerful mathematical approach to the action of natural (or artificial) selection.

The evolution of mean fitness

The Fundamental Theorem of Natural Selection implies that the mean relative fitness, $\bar{w}$ of a population generally increases through time and specifies the amount by which it will increase per small unit of time. This suggests a tempting way to think about natural selection: it is a process that increases mean relative fitness.

While attractive and often powerful, it should be emphasized that— surprisingly— the mean fitness of a population does not always increase under natural selection. Population geneticists have identified a number of scenarios in which selection acts but $\bar{w}$ does not increase. These include frequency dependent selection (wherein the fitness of a genotype depends on its

frequency in a population) and, in sexual species, certain forms of epistasis (wherein the fitness of a genotype depends on non-additive effects over multiple loci). Put differently, these findings show that the Fundamental Theorem of Natural Selection does not invariably hold. This perplexing conclusion has given rise to a mathematical literature devoted to discerning whether an unorthodox interpretation of fitness (and its additive genetic variance) is available under which the Fundamental Theorem does hold strictly. The answer appears to be yes, although the relevant literature is forbidding [27, 33–37]. Fortunately, the distinctions involved rarely arise outside of consideration of the Fundamental Theorem.

Fitness landscapes

Many recent discussions of molecular evolution by natural selection have focused on evolution on so-called fitness landscapes [17, 38–40]. At least two types of landscapes have been described.

The first was introduced by Sewall Wright in the early 1930s [41, 42]; indeed Wright's imagery of an adaptive landscape has proved one of the most popular in the history of biology. Wright's landscape is easily pictured in three dimensions (Figure 2). The two axes that form the "floor" of the graph each represent allele frequency at a locus: the x axis gives allele frequency at locus 1 and the y axis gives allele frequency at locus 2 (it is generally assumed that allele frequencies at the two loci are independent and that fitness is not frequency-dependent). The third (z) axis rising above the floor of the graph represents the mean fitness of a population having a combination of allele frequencies at the two loci. The result is a surface of mean fitnesses corresponding to the range of allele frequencies at the two loci. A peak represents a high mean fitness population and a valley represents a low mean fitness population. Any fitness landscape for any real species must, of course, involve many more than two loci: real fitness landscapes are high dimensional.

Wright's interest in fitness landscapes centered on a constraint that confronts adaptation. Because selection often can be viewed as increasing the mean fitness of a population, selection can be thought of as a hill-climbing process. Given a population's starting position on a landscape, selection will move the population uphill, to a higher mean fitness. The difficulty arises when a landscape features multiple peaks (Figure 2). Then, selection will typically push a population to the top of the nearest fitness peak. But, at that point, selection is stuck. Any further evolution would require moving downhill on the landscape, which selection disallows. Because the local peak may not represent the highest peak, i.e., the global peak, natural selection would seem to have a hard time ascending global fitness peaks.

Wright's attempted solution to this problem involved his "shifting balance theory" of evolution [41–43]. Briefly, Wright maintained that species find and ascend global peaks because evolution involves two additional processes: genetic drift (random change in allele frequency in finite populations) and inter-demic selection (wherein some local populations perform better, and so presumably produce more migrants, than do others). Wright's shifting balance theory is extremely controversial (see Ref. 44).

In any case, Wright's mean fitness landscape plays a diminished role in current studies of fitness landscapes. In lieu of a continuous landscape underlain by continuous allele frequencies, evolutionists now often focus on a discrete fitness landscape underlain by discrete DNA or protein sequences. Evolution, in other words, is modeled as movement through a series of related sequences. If, for simplicity, we consider a gene that is only 7 base pairs long, we could assign fitness values to the 4^7 sequences possible at this gene. The result is a discrete surface of fitness values corresponding to the various possible sequences. From any starting sequence, natural selection would then try to move the gene uphill to a similar but fitter sequence: AATGCCG (having some fitness) might get replaced by AAAGCCG (having higher fitness), which in turn might get replaced by AAAGCTG (having yet higher fitness). It is generally

assumed that evolution can effectively see only one mutational step away, i.e., sequences can change only at one site at a time. Again, populations can become stuck on a local adaptive peak that does not represent the global adaptive peak. This problem will obviously be serious on rugged fitness landscapes (those featuring many local optima) but less serious on smoother landscapes (those featuring fewer local optima). Just how rugged actual fitness landscapes are remains a largely unsolved empirical problem (see below).

While discrete versions of fitness landscapes were discussed by Wright, the molecular version of the model just described was introduced by Maynard Smith [45, 46], who considered the evolution of protein sequences. Subsequent work has focused on DNA sequences. This work has involved generalizations by Gillespie (who introduced the so-called molecular landscape model [17,47,48]), Kauffman (who introduced the NK model, in which the ruggedness vs. ruggedness of a fitness landscape can be tuned [38,49,50]), Macken and Perelson (who considered another type of tunably-rugged fitness landscape [51–53]), Orr and colleagues (who extended Gillespie's use of extreme value theory in such models [40,54–57]), and many others.

Although this literature has received a great deal of attention, Gillespie [17], echoing Fisher [29], has emphasized an important concern: fitness landscape models generally assume that landscapes remain unchanged over vast stretches of time. But if the fitness of various sequences changes at least as fast as evolution occurs (due to changes in the abiotic and biotic environments), these models are potentially misleading. Real evolution may look less like an attempt to evolve uphill on a static landscape and more like an attempt to keep one's footing on an ever-morphing landscape.

Empirical issues: measuring fitness in contemporary populations

Turning to empirical issues, we confront a large and diffuse literature and can hope to do no more than highlight important parts of it. Experimental studies of fitness generally take one of three approaches: *i*) measuring fitness differences among genotypes that currently segregate in a population; *ii*) inferring past increases in fitness from DNA sequence data; or *iii*) watching fitness evolve in real time.

Although natural populations harbor considerable genetic variation in fitness [58, 59], measuring the fitness of particular genotypes is often difficult. Different approaches have been taken when considering particular components of fitness *versus* total lifetime fitness. Hedrick (Ref. 60, chapter 5; see also Ref. 61) provides an excellent introduction. As noted there, the effects of, say, viability fitness differences among genotypes can be assessed directly by comparing the frequencies of genotypes at the beginning of a life cycle (zygotes or seedlings) with frequencies in adults (after viability selection has acted). Christiansen and Frydenberg[62] and Bundgaard and Christiansen [63] further describe methods that allow assessment of whether selection acts at various stage in the life cycle. Chromosome extraction techniques also allow estimates of viability among chromosomes sampled from natural populations, at least in those species that possess the required genetic tools, e.g., balancer chromosomes. The classical population genetic literature, particularly that of Dobzhansky and colleagues [58] was largely concerned with such work, particularly in *Drosophila pseudoobscura,* though the approach necessarily yields estimates of the fitness effects of whole chromosomes or large chromosome regions, not individual loci (reviewed in Ref. 59).

It is worth noting that some seemingly obvious approaches to detecting selection on fitness components may not work. One might guess, for example, that differences in survival among alleles at a locus could be inferred from observed deviations in a diploid population from random-mating Hardy-Weinberg proportions among adults, i.e., after selection has acted. Surprisingly, however, Lewontin and Cockerham [64] showed that adults can remain in Hardy-Weinberg proportions even given large fitness differences among genotypes (though the

required conditions are strict). Finally, it must be emphasized that a particular fitness component need not map onto total fitness in a simple way. Empirical assays could reveal, for example, that a genotype has high viability although it actually suffers low (or even zero) total fitness because the genotype is, say, partially or completely sterile.

Measurements of total lifetime fitness are even harder to come by and are also susceptible to counterintuitive complications. For example, it might be thought that the magnitude of genotype frequency changes from one generation to the next would allow reliable inference of the relative fitnesses of genotypes, especially when genotypes are counted at the same stage in the life cycle each generation. But the approach may not work. Prout [65, 66] showed that genotype frequency shifts alone do not guarantee correct estimation of the fitnesses of homozygotes and heterozygotes: if lifetime selection is not complete at the stage in the life-cycle at which genotypes are counted, the approach can fail. Perhaps most surprising, Denniston and Crow [67] showed that even a complete history of allele frequency change over many generations does not allow unique determination of genotypic fitnesses. For any trajectory of allele frequencies through time an infinite number of different fitness models is formally possible, though nearly all involve complex schemes of frequency dependent selection.

Last but not least, attempts to estimate fitness differences among genotypes in natural populations face a difficulty famously emphasized by Lewontin[59]: positive natural selection likely often operates on variants that have small effects on fitness (selection can detect mutations having effects as small as the reciprocal of population size). Experiments, however, can usually hope to detect only pronounced differences in fitness, differences that may often reflect genetic pathologies— not the material of future adaptive evolution.

Given these difficulties, it is perhaps unsurprising that attempts to measure fitness differences among genotypes segregating in natural populations are rarer today than several decades ago. Interest has instead shifted to two other approaches: inferring a history of positive selection from genome sequence data and watching fitness evolve in real time.

Inferring past selection from genomic data

A suite of molecular population genetic approaches attempts to use DNA sequence data to infer increases in fitness that occurred in the evolutionary past. The literature here is vast and well reviewed [68–72] but key approaches can be sketched briefly.

To determine if mutations that increased fitness swept through a species in the past, one can perform a so-called McDonald-Kreitman test [73]. Formally, this statistical test asks whether a gene has evolved neutrally, i.e., by mutation and genetic drift alone. But certain departures from the null hypothesis of neutrality suggest a history of adaptive evolution (see Box 5).

The McDonald-Kreitman test has been generalized in several ways. For one thing, the test has now been performed not only on individual genes but on entire genomes. Begun et al. [74] recently performed McDonald-Kreitman tests using data from approximately 6000 genes in the closely related species *Drosophila simulans* and *D. melanogaster* (polymorphism data are available from *D. simulans*). Begun et al. were able to reject the null hypothesis of neutral evolution at 19% of these genes, i.e., many loci evolved adaptively since the species split.

Furthermore, Eyre-Walker and colleagues [71, 75] have shown how data employed in the McDonald-Kreitman test can be used to estimate the proportion, α, of amino acid substitutions driven by positive natural selection, i.e., the proportion that caused an increase in fitness. (The approach takes advantage of the fact that beneficial mutations that change an amino acid will contribute to the number of diverged amino acid sites between two species but not to the number

of amino acid polymorphisms segregating within species: beneficial mutations generally sweep through species too rapidly to contribute to within-species standing genetic variation.) This inference represents one of the most elegant and profound in recent population genetics. Analyses of data from *Drosophila* suggest that approximately half of all replacement substitutions (those that change an amino acid) were driven by positive natural selection, a surprisingly high value (reviewed in Ref. 71). Even more surprisingly, similar studies suggest that adaptive evolution may be common in non-coding DNA. Andolfatto [76] has argued that, in Drosophila, roughly 20% of substitutions in introns and perhaps 60% in untranslated regions may be adaptive.

Finally, DNA polymorphism data alone can be used to infer the genomic location of adaptive substitutions and the magnitudes of the fitness increases involved, though the approach may be less powerful than the above ones. The key idea is that the sweep from low to high frequency of a beneficial mutation wipes out sequence polymorphism at flanking nucleotide sites. As this effect is attenuated by recombination, sites that are loosely linked to the one under selection may show normal levels of variation while those that are tightly linked may show little variation. Such valleys in polymorphism can allow inference of both the likely location of a beneficial mutation and the magnitude of its fitness advantage [77, 78].

Microbial experimental evolution

In lieu of statistical inferences about past increases in fitness, one can attempt to watch the evolution of fitness in real time. To do so, clonal populations of microbes are typically placed in a novel environment to which the organism must adapt, usually via substitution of new mutations. The growth rate of the population, a good proxy for total fitness, is then assessed periodically. The results of such experiments— which are now routinely performed in bacteria and viruses (e.g., Ref.s 79–89)— are reasonably consistent. Fitness typically rises rapidly at the start of the experiments and then plateaus as the population nears a new (local) optimal genotype and phenotype.

Whole genome sequencing can then allow identification of the particular mutations that underlay the increase in fitness seen in these experiments. Some such analyses focus only on the first step in adaptation (BOX 6), while others focus on entire bouts of evolution. By competing or measuring growth rates among samples that carry 0 vs. 1, or 1 vs. 2, etc., substitutions, one can estimate directly the fitness effect of each substitution. The results of such experiments are again fairly consistent (e.g., Ref.s 82, 89): adaptation typically involves a modest number of substitutions, which are usually non-synonymous, not synonymous (consistent with their presumed role in adaptation). Furthermore, earlier substitutions typically have larger positive effects on fitness— often very large ones— than do later substitutions [82, 89].

The fitness effects of new mutations

While we have considered mutations that segregate in natural populations or that swept to fixation (either historically or in the course of microbial evolution studies), we have not asked: What is the distribution of fitness effects among new mutations and, especially, among new beneficial mutations? Although this represents one of the simplest questions one can ask about the evolutionary genetics of fitness, we can provide no confident answer to it.

The problem is simple: mutations are rare and beneficial mutations are extremely rare. Consequently, experimental attempts to determine the distribution of fitness effects among new beneficial mutations are notoriously difficult. Though theory suggests that beneficial effects should often be approximately exponentially distributed [48, 55]— with many small-effect mutations and fewer large-effect ones— this prediction rests upon mathematical assumptions

that, while reasonable, could prove false. If so, further theory shows that the distribution of fitness effects among new beneficial mutations could assume non-exponential shapes [40].

Unfortunately, the few available data are mixed. While several studies in microbes have shown that beneficial fitness effects are at least roughly exponential, recent data from viruses suggest that they may sometimes be more nearly uniform (reviewed in Ref. 40). Worse, many of these studies, though heroically difficult, suffer technical shortcomings. In the end, then, we are left with no clear answer.

Conclusions and Future Prospects

Although Darwinian evolution is founded on the idea that some genotypes have higher fitness than others, the idea of fitness itself is fairly subtle. Fortunately, some, though not all, of the confusion can be cleared by distinguishing between fitness as a phenotype assigned to individuals and fitness as a summary statistic, e.g., absolute fitness, relative fitness, mean fitness, geometric mean fitness, etc. Fitness as a phenotype is generally unproblematic and confusion typically arises only when attempting to determine which summary statistic is most appropriate given a certain evolutionary scenario.

While considerable progress has been made in the experimental study of fitness, some major problems remain poorly resolved. It remains difficult, for example, to estimate the fitnesses of genotypes segregating in natural populations of many species. Worse, we know little about the ruggedness of biological fitness landscapes. While the phenomena of hybrid sterility and inviability show that landscapes are not perfectly smooth (as hybrids clearly fall into fitness valleys), the existence of many small-effect, and probably neutral, mutations suggests that landscapes are not maximally rugged (as the fitnesses of sequences that differ by a single change are, on a completely rugged landscape, uncorrelated). But we do not know where biological reality falls between these extremes. Also, we know little about the types of molecular changes that give rise to most beneficial mutations in nature. Are these mutations, for example, often *cis*-regulatory (as several evo-devo workers have suggested [90]) or are they often coding [91]? Finally, we can say little with confidence about the distribution of fitness effects among new beneficial mutations.

There is a reason, of course, why these problems remain unresolved: they are formidable. But the approaches required for resolution are reasonably clear: except for the problem of the fitnesses of genotypes in natural populations, most can be settled by labor-intensive but straightforward microbial experimental evolution studies or by the (similarly labor-intensive) genetic mapping and characterization of alleles underlying derived, adaptive phenotypes. While theoretical problems with fitness largely reflect conceptual subtleties, our empirical problems generally do not; instead, they reflect the sheer arduousness of the required experiments.

Box 1. A simple selection equation

Viability selection acts as zygotes attempt to mature into adults, killing some: a proportion W_1 of A_1 individuals and W_2 of A_2 individuals survives. The proportion of individuals that carry A_1 after selection acts is thus $pW_1/(pW_1 + qW_2)$. Dividing numerator and denominator by W_1, and recalling that $w_1 = W_1/W_1 = 1$ and $w_2 = W_2/W_1 = 1 - s$, we get $p/(1 - qs)$. Because surviving adults produce a new generation of zygotes, with A_1 adults producing A_1 zygotes and A_2 adults producing A_2 zygotes, the frequency of A_1 among the new zygotes is also $p/(1 - qs)$.

Natural selection thus changes allele frequency in a single generation by $\Delta p = p/(1 - qs) - p$, which, re-arranging, is

$$\Delta p = \frac{pqs}{1 - qs}.$$

The denominator of the above equation equals the mean relative fitness of the population: $\bar{w} = P(1) + q(1 - s) = 1 - qs$. We can thus re-write the equation as $\Delta p = pqs/\bar{w}$.

Considering the more general case of diploids, with any number of alleles segregating at a locus, and with any pattern of dominance, it can be shown that

$$\Delta p_i = \frac{p_i(1 - p_i)}{2\overline{w}} \frac{\partial \overline{w}}{\partial p_i},$$

where p_i is the frequency of the i-th allele and ($\partial \bar{w}/\partial p_i$ gives the change in mean relative fitness that results from a change in p_i, holding all else constant.

Box 2. Fitness in continuously growing populations

While we have focused on the case of a species that has discrete generations, we can also define fitness for a species that shows continuous growth through time. In this case, fitness is typically measured using a growth rate or "malthusian fitness," symbolized m. Because a population (or genotype) that has a constant growth rate *per capita* will increase in numbers exponentially, we have $N_t = N_0 \exp[m\, t]$, where t is time, N_0 is the initial number of individuals, and N_t is the number of individuals after time t [11, 15]. When $m > 0$, the number of individuals increases through time. If we compare two genotypes, the ratio of their numbers after time t is just $N_{1,t}/N_{2,t} = \exp[m_1\, t]/\exp[m_2\, t] = \exp[(m_1 - m_2)t]$. In words, it is the difference in malthusian fitnesses that determines the ratio of numbers of individuals. Mathematically, malthusian fitness can be thought of as a logarithmic transformation of the more common measure of fitness [11]: $m = \mathrm{Log}(W)$.

Box 3. Why the variance in fitness matters

When fitness fluctuates through time and the fluctuations are modest, the geometric mean fitness of an allele is $G_1 \approx \overline{W}_1 - \sigma_1^2/(2\overline{W}_1)$, where $\bar{W}_1$ is the arithmetic mean fitness through time and σ_1^2 is the variance in fitness through time. Surprisingly, then, the identity of the allele that predominates in a population depends on both the mean *and* the variance in fitness. Consequently, if two alleles have the same (arithmetic) mean fitness through time, the allele that "wins" is the one with the smaller variance in fitness.

While first surprising, this role for the variance has a simple explanation. When we multiply a set of numbers (e.g., values of W_1 through time), small values depress the final product more than large values boost it. (To see this, consider the extreme case in which one term in a product equals zero.) Given this, it pays for alleles to avoid large fluctuations in fitness.

Note also that, when there are no fluctuations in fitness through time, $G_1 \approx \overline{W}_1 - \sigma_1^2/(2\overline{W}_1)$ collapses to the arithmetic mean fitness: $G_1 = \bar{W}_1$. A reasonable case can, therefore, be made that the geometric mean represents a more appropriate measure of allelic fitness. The case of constant fitness is a special case that is still captured mathematically by the geometric mean.

Box 4. Spatial variation in fitness

A genotype's fitness might vary spatially. Within a generation, a genotype might enjoy high fitness if it resides in one region but lower fitness if it resides in other regions. In diploids, spatial variation in fitness can, under certain conditions, maintain genetic variation in a population, a form of so-called balancing selection. The conditions required depend on the precise way in which natural selection acts.

In one scenario, different regions, following viability selection, contribute a fixed proportion of adults to a large random-mating population. This scenario involves "soft selection": selection acts in a way that changes genotype frequencies within a region but that does not affect the number of adults produced by the region. Under this scenario, genetic variation at a locus is maintained if the harmonic mean fitness of a heterozygote averaged over regions is greater than that of both homozygotes [21]. (The harmonic mean equals the reciprocal of the mean of reciprocals.)

In another scenario, different regions, following viability selection, contribute variable proportions of adults to a large random-mating population, depending on the genotypes (and thus fitnesses) of individuals within a region. This scenario involves "hard selection": selection acts in a way that changes genotype frequencies within a region and affects the number of adults produced by the region. If the contribution of a region is proportional to the mean fitness of individuals from that region, genetic variation at a locus is maintained if the arithmetic mean fitness of a heterozygote averaged over regions is greater than that of both homozygotes [22].

Box 5. The McDonald-Kreitman test

We need not know anything about the traits a gene affects to infer whether the gene is evolving by natural selection. Instead, we can do so from DNA sequences alone. One of the simplest of the statistical tests devised by population geneticists is the McDonald-Kreitman test. Formally, this test asks whether a gene has evolved neutrally, that is, by mutation and random genetic drift alone. Certain patterns of departure from the neutral null hypothesis suggest a history of adaptive evolution.

The McDonald-Kreitman test requires DNA sequence data both from within species and between two species and the test takes advantage of the fact that DNA mutations within a gene can be either replacement or silent. The neutral theory of molecular evolution predicts that the ratio of replacement-to-silent mutations found segregating within a species should equal approximately the ratio of replacement-to-silent changes that distinguish two species, where all data derive from the same gene. These two ratios are compared statistically. So if— looking among individuals within a species— we observe, say, one replacement and 10 silent mutations, we would not be surprised— looking at sequence differences that distinguish two species— to observe two replacement and 20 silent differences. Such a result is consistent with neutrality. But population geneticists sometimes find far too many replacement differences between species to be consistent with neutrality, e.g., 21 replacement differences and 20 silent differences. Departures from the null hypothesis of neutrality in this direction— excess replacement site divergence— suggest that natural selection actively changed the protein encoded by the gene, i.e., the gene adapted under positive natural selection.

The McDonald-Kreitman test is clearly conservative. It can detect a pattern suggestive of adaptive evolution only if replacement substitutions occurred repeatedly at a gene since the two species diverged.

Box 6. Experimental evolution in a virus

Some microbial evolution experiments focus on the first step in adaptation: evolutionists allow a population to briefly adapt, generally by substituting single beneficial mutations. This process is repeated across many independent replicate populations, allowing one to ask: How many different mutations are used in the first step of adaptation? How often is the same mutation used? Rokyta et al. [92] performed such an experiment using the single-stranded DNA bacteriophage ID11. Selecting for rapid replication on a bacterial host, they followed 20 independently evolving populations. Sequencing the entire genome of each, they found that natural selection took advantage of nine different mutations during the first step of evolution. These mutations were not, however, used equally often. Instead, the same mutation was used in six populations and another mutation was used in five populations. Rokyta and colleagues further showed that the beneficial mutations used most often by natural selection were those that either had large positive effects on fitness or that simply appeared often by mutation (e.g., due to transition-trans version bias).

Acknowledgments

This work was supported by a grant from the U.S. National Institutes of Health.

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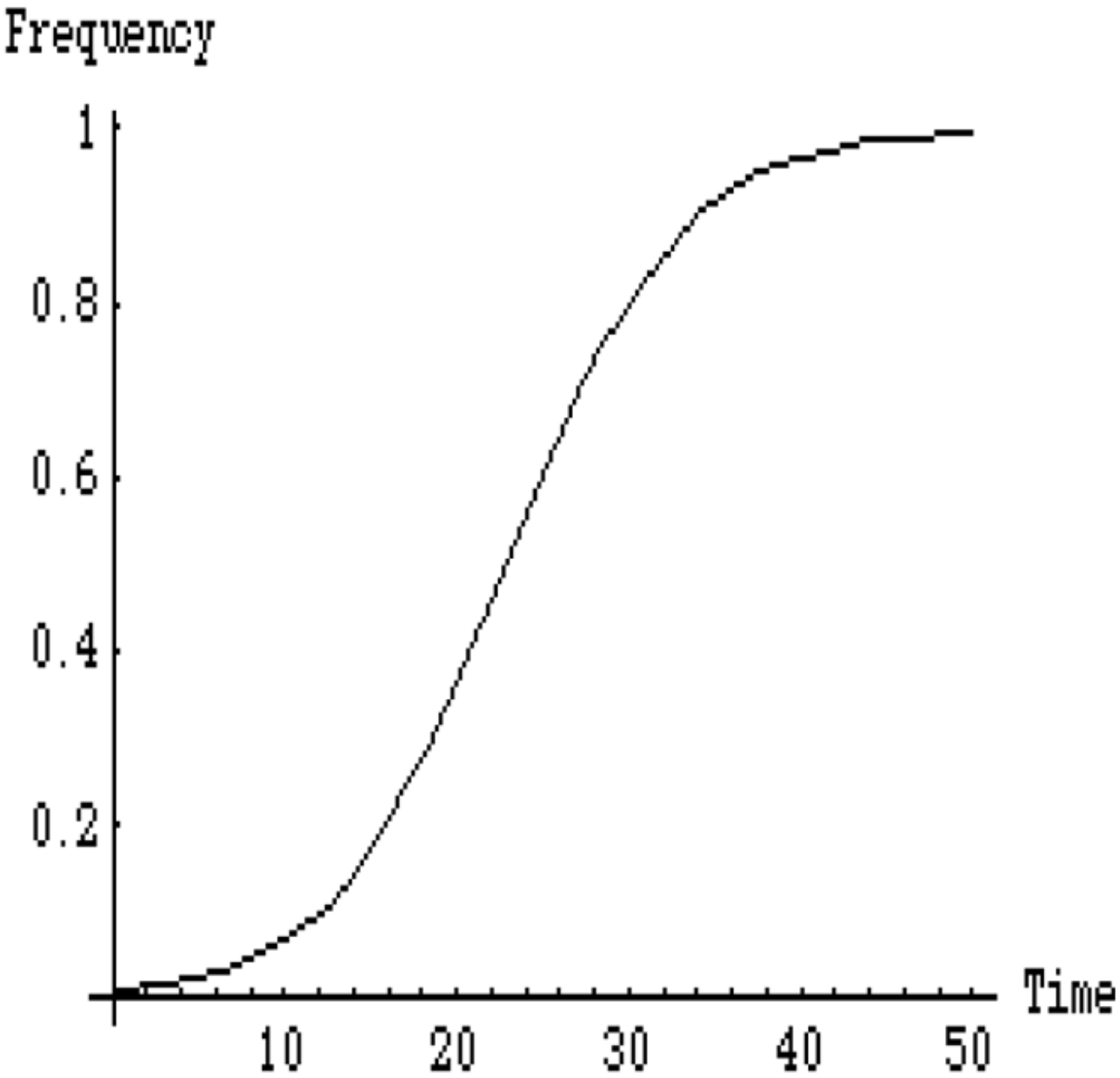

Figure 1. Allele frequency versus time

The x-axis represents time in generations and the y-axis represents the frequency of the A_1 allele in a haploid species. A_1 is favored by natural selection: in the plot shown, $w_1 = 1$ and $w_2 = 0.8$. Given this fitness difference, natural selection will push A_1 to progressively higher frequencies. The curve shown is sigmoidal.

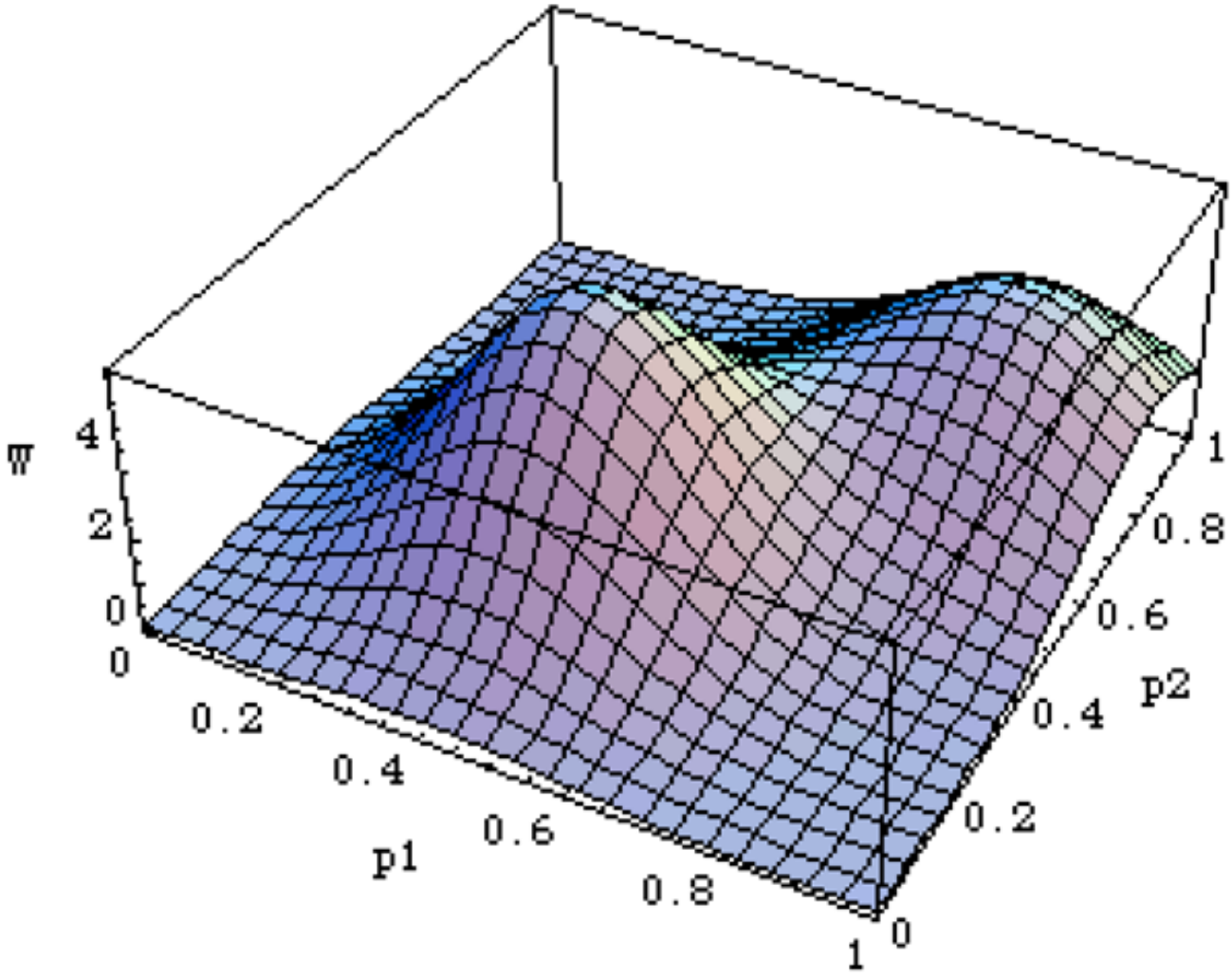

Figure 2. A three-dimensional Wrightian fitness landscape

The two axes making up the “floor” of the plot represent allele frequencies at two different loci and the z-axis rising out of the plot represents mean fitness. The fitness landscape shown has two peaks. As Wright emphasized, evolution by natural selection can get stuck on a local adaptive peak that may not represent the highest adaptive peak on the landscape.