THE GENETIC THEORY OF ADAPTATION: A BRIEF HISTORY

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Abstract | Theoretical studies of adaptation have exploded over the past decade. This work has been inspired by recent, surprising findings in the experimental study of adaptation. For example, morphological evolution sometimes involves a modest number of genetic changes, with some individual changes having a large effect on the phenotype or fitness. Here I survey the history of adaptation theory, focusing on the rise and fall of various views over the past century and the reasons for the slow development of a mature theory of adaptation. I also discuss the challenges that face contemporary theories of adaptation.

STANDING GENETIC VARIATION
Allelic variation that is currently segregating within a population; as opposed to alleles that appear by new mutation events.

FITNESS
A quantity that is proportional to the mean number of viable, fertile progeny produced by a genotype.

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doi:10.1038/nrg1523

Adaptation is not natural selection. As Ronald A. Fisher[1] emphasized in 1930, adaptation is characterized by the movement of a population towards a phenotype that best fits the present environment. The result is an often astonishingly precise match between an organism and the world in which it lives. But as Fisher also emphasized, the steady increase in the frequency of an allele under selection need not invariably result in "the adaptive modification of specific forms". Competition among 'selfish genes', for instance, can change a population's sex ratio but we have no reason to expect any improved fit between an organism and its environment.

To an evolutionary geneticist, there is another, simpler way of distinguishing between selection and adaptation: we know a lot about the former but little about the latter. Many important questions about the genetic basis of adaptation remain unanswered. Do most adaptations involve new mutations or STANDING GENETIC VARIATION? Do most adaptations involve single genes of large phenotypic effect ('major' genes)? If so, can we say anything about the expected effect of this major gene? Can we describe the distribution of phenotypic effects among the mutations that are substituted during a typical bout of adaptation? How does FITNESS change as a population approaches an optimum? For example, do populations evolve quickly at first and then more slowly? Because random mutations are more likely to be deleterious in complex organisms than in simple organisms, do complex organisms adapt more slowly than simple ones?

These questions have two things in common. First, they are important; indeed they are among the simplest and most obvious questions that can be asked about the changes underlying Darwinian evolution. Second, they are not answered by traditional evolutionary theory. In fact, the deeper problem is that they are not even asked by traditional evolutionary theory.

Despite this near theoretical void, experimental evolutionary geneticists have begun to address several of the above questions. These studies — and the sometimes surprising answers that they have provided — have reinvigorated attempts to elaborate a mathematical theory of adaptation. Here I survey these attempts. My approach is historical, considering the rise and fall of various views on the genetic basis of adaptation, the reasons a mature theory has been slow to develop and the prospects and problems facing current theory.

As we will see, recent models of adaptation seem to successfully explain certain qualitative patterns that characterize morphological evolution in animals and plants, as well as patterns that characterize fitness increase in microbes. Although this success is encouraging — and long overdue — future work must determine whether present theory can explain the genetic data quantitatively.

Micromutationism: its rise and fall

The theory. The earliest view of the genetic basis of adaptation was pre-Mendelian. This view, which emphasized the extreme gradualness of phenotypic evolution, began

Box 1 | Experimental studies of adaptive evolution

Genetic analyses of phenotypic differences between species or populations often reveal major quantitative trait loci (QTL). A recent burst of work, for instance, has focused on the genetic basis of armour-plate reduction and pelvic reduction in postglacial-lake forms of the threespine stickleback, *Gasterosteus aculeatus*. Although marine forms of this species are heavily armoured, lake populations (which are recently derived from the marine form) are not. Instead, lake forms have repeatedly and independently evolved reduced armour-plate and pelvic structures, leaving little doubt that these morphological changes are adaptive. QTL and developmental genetic studies indicate that this adaptive evolution sometimes involves the same genes[97–99]. A strong candidate gene, *Pitx1*, has been identified that has a major effect on pelvic reduction; the Pitx1 protein sequence is identical between marine and lake forms, indicating that this case of morphological change involved regulatory evolution[99].

Similarly, Sucena and Stern[100] showed that a qualitative difference in larval morphology (the presence or absence of a lawn of fine hairs) between two species of *Drosophila* (*Drosophila simulans* and *Drosophila sechellia*) is due to a single gene. Through DEFICIENCY MAPPING and COMPLEMENTATION TESTS, they showed that the relevant gene is *ovo/shaven-baby*, which resides on the X chromosome.

Evidence for major genes is not limited to animals. Work in the 1990s showed, for example, that the evolution of maize from its wild ancestor teosinte involved the substitution of a QTL that had large effects on morphology (for example, *tb1*, which affects lateral-branching pattern[101,102] and *tga1*, which affects kernel architecture[101,103]). Although the evolution of maize involved human intervention, QTL studies of two wild species of *Mimulus* yielded qualitatively similar results. *Mimulus lewisii* is primarily bee-pollinated, whereas *Mimulus cardinalis* is primarily pollinated by hummingbirds; not surprisingly, the flowers of the two species differ markedly. In a QTL analysis of a suite of floral characters that distinguish these species, Bradshaw *et al.*[104,105] found that one to six QTL underlie each of the 12 floral traits analysed. For 9 of these 12 traits, at least one QTL explains 25% or more of the species difference. Indeed, a single QTL at the *yup* locus qualitatively affects carotenoid concentration between the species. Recent work further shows that replacement of chromosomal material at the *yup* region from one species with that from the other has a large effect on pollinator visitation[106].

Despite these findings, there can be no doubt that many QTL of small effect also contribute to adaptation. As experimental sample sizes and therefore statistical power increase, more of these small-effect QTL will surely be found.

with Charles Darwin himself, who argued that "natural selection can act only by taking advantage of slight successive variations; she can never take a leap, but must advance by the shortest and slowest steps"[2]. Although Darwin had no clear understanding of the nature of inheritance (or more exactly, had an incorrect understanding of it[3]), he concluded that the heritable basis of adaptive evolution was extremely fine-grained. After all, precise adaptation is possible only if organisms can come to fit their environments by many minute adjustments (see also REF. 4). This 'micromutational' view of adaptation proved extraordinarily influential, laying the foundation for the British BIOMETRIC school of evolution led by Karl Pearson and Walter Weldon. The biometricians used newly invented statistical tools, such as regression, to analyse the inheritance of CONTINUOUS CHARACTERS, as well as the evolutionary response to selection[5,6]. (See William B. Provine's[7] classic history of this period, including the formation of the influential Royal Society Committee on Biometrics.)

This micromutational view of adaptation was vigorously challenged by the rising Mendelian school of genetics[7–11]. William Bateson, for example — the brashest and most articulate of the Mendelians — argued that the popularity of micromutationism merely reflected the light demands it placed on naturalists. "By suggesting that the steps through which an adaptive mechanism arises are indefinite and insensible, all further trouble is spared. While it could be said that species arise by an insensible and imperceptible process of variation, there was clearly no use in tiring ourselves by trying to perceive that process. This labor-saving counsel found great favor"[12].

Despite such opposition — and despite the larger victory of Mendelism — the micromutationist view won out among evolutionists by about 1930. To a considerable extent, this victory reflected the efforts of Fisher, a founding father of population genetics and a tireless champion of Darwinian gradualism. Fisher successfully fused micromutationism with Mendelism[13], producing a mathematical framework known as the infinitesimal model. Response to selection, he argued, could be analysed through a kind of statistical mechanics: instead of following the effects of individual genes on a selected phenotype, one could calculate their aggregate effects under the assumption that a character is underlaid by an infinite number of genes, each unlinked to all others, each having no EPISTATIC INTERACTIONS with the others, and each having an infinitesimally small effect on the character[3,14]. Although modern evolutionists treat the infinitesimal model as little more than a mathematical convenience[15] (the model has many attractive properties, including constant ADDITIVE GENETIC VARIANCE under selection), there is some evidence that Fisher went further and considered the infinitesimal view a reasonable approximation to biological reality[16] (see especially Fisher's role in the debate over the genetic basis of mimicry[11]).

The data. Early empiricists, including Theodosius Dobzhansky[17], Hermann J. Muller[18–20], Kenneth Mather[21,22] and Julian Huxley[23,24], claimed that there was considerable empirical support for micromutationism. For example, Huxley argued that "selective advantages so small as to be undetectable in any one generation, are capable … of producing all the observed phenomena of biological evolution…. Evolutionary change is almost always gradual"[23]. Despite such confident statements, the case studies to which these early workers pointed were uniformly (and in retrospect, appallingly) weak[11,25]. Rigorous data bearing on micromutationism did not appear until remarkably recently, in the 1980s. Although this delay partly reflected certain technical difficulties — such as the development of dense linkage maps — part of the problem was inherent in the micromutational view itself. Although all scientific views are simplifications of nature, the micromutational view had the unfortunate effect of excluding entire classes of questions from empirical study. There is little reason, after all, to ask non-trivial questions about the genes that underlie adaptation if one assumes that there are thousands of them, each with small and interchangeable effects on the phenotype.

DEFICIENCY MAPPING
A type of genetic mapping that uses chromosomal deletions to 'uncover' recessive alleles that affect a trait.

COMPLEMENTATION TESTS
The use of genetically defined knockout mutations to identify loci that affect a trait.

BIOMETRIC
An approach to the study of phenotypes that emphasizes quantitative measurements (such as of body size) and statistical analysis.

CONTINUOUS CHARACTER
A trait (such as body size) that varies smoothly (continuously) in magnitude; as opposed to discrete characters.

In the 1980s, two new experimental approaches were developed that finally allowed the collection of rigorous data on the genetics of adaptation — QUANTITATIVE TRAIT LOCUS (QTL) analysis and MICROBIAL EXPERIMENTAL EVOLUTION. In QTL analysis, the genetic basis of phenotypic differences between populations or species can be analysed using a large suite of mapped molecular markers. In microbial evolution work, microbes are introduced into a new environment and their adaptation to this environment is allowed; genetic and molecular tools then allow the identification of some or all of the genetic changes that underlie this adaptation. The results of both approaches were surprising: evolution often involved genetic changes of relatively large effect and, at least in some cases, the total number of changes seemed to be modest. As this empirical literature has been well reviewed[26–30], I devote little space to it here. However, BOX 1 describes several classical studies, including those that analyse the evolution of reduced body armour or pelvic structure in lake stickleback, the loss of larval trichomes (fine 'hairs') in *Drosophila* species, and the evolution of new morphologies in maize and the monkeyflower *Mimulus* spp. Microbial studies further revealed that genetic changes occurring early in adaptation often have larger fitness effects than those that occur later[31], and that parallel adaptive evolution is surprisingly common[32–35].

These experimental findings posed — and continue to pose — a considerable challenge to evolutionary geneticists: to bridge the gap between adaptation data and theory. Evolutionary geneticists find themselves in a decidedly awkward position. On the one hand, we can point to a rich and formidable body of mathematical theory on phenotypic evolution, built largely on an infinitesimal foundation. On the other hand, we can point to a large and growing body of data on the genetic basis of adaptation. The problem, of course, is that the formidable theory says little or nothing about the formidable data. To ask what might seem an obvious question, where is the theory that tells us what we should find in QTL or microbial evolution experiments?

More precisely, recent empirical findings force us to confront two questions. Can we construct a theory of adaptive evolution that speaks in the same terms as the data; that is, in terms of individual mutations that have individual effects? And if so, can this theory account for the observed phenomena?

Several attempts to construct such a theory have been made throughout the history of evolutionary genetics. Although my survey of these attempts is far from exhaustive, I consider each of the two main classes of adaptation model — those that are phenotype-based and those that are DNA-sequence based.

Phenotypic evolution

Given his role as father of the infinitesimal model, it is surprising to learn that Fisher also presented the first model of adaptation that allowed individual mutations to have different-sized phenotypic effects. In *The Genetical Theory of Natural Selection*, Fisher offered his so-called

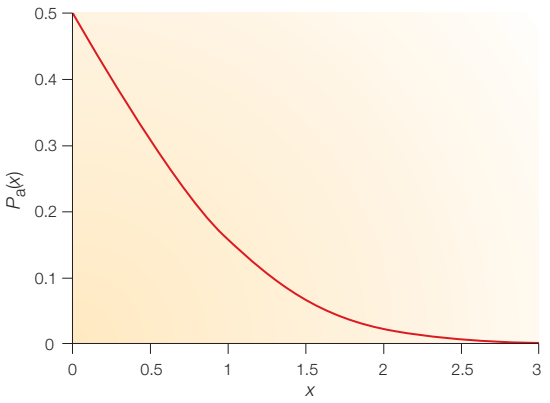
EPISTATIC INTERACTION
Any non-additive interaction between two or more mutations at different loci, such that their combined effect on a phenotype deviates from the sum of their individual effects.

ADDITIVE GENETIC VARIANCE
The part of the total genetic variation that is due to the main (or additive) effects of alleles on a phenotype; as opposed to the dominance and epistatic variances. The additive variance determines the degree of resemblance between relatives and therefore the response to selection.

QUANTITATIVE TRAIT LOCUS (QTL)
A mapped chromosomal region that has a detectable effect on a phenotypic difference between two populations or species. A QTL does not necessarily correspond to a single gene, but can reflect several linked genes.

MICROBIAL EXPERIMENTAL EVOLUTION
An experimental approach that involves the 'real time' adaptation of microbes (typically bacteria, phage or yeast) to defined laboratory conditions.

Box 2 | Fisher's geometric model of adaptation



Ronald A. Fisher argued that his geometric model captures the statistical essence of adaptation — the fact that "one thing [the organism] is made to conform to another [the environment] in a large number of different respects"[1]. Fisher represented each character of an organism as an axis in a Cartesian coordinate system. The optimal combination of trait values is represented by the origin of this coordinate system (see FIG. 1). Because of a recent environmental change, the population no longer resides at the optimum. As in actual Darwinian evolution, Fisher's model has three features. First, that populations must adapt by using mutations that are random with respect to the needs of organisms (that is, that are random in phenotypic direction, pointing away from the optimum at least as often as towards). Second, that mutations have different phenotypic 'sizes' (that is, some mutations are vectors of large magnitude and others are vectors of small magnitude). Third, that populations must adapt in the face of pleiotropy (that is, a mutation affects many characters and, although improving one character, might worsen many others).

Fisher showed that the probability, $P_a(x)$, that a random mutation of a given phenotypic size, r, is favourable is $1 - \Phi(x)$, where Φ is the cumulative distribution function of a standard normal random variable and x is a standardized mutational size, $x = r\sqrt{n}/(2z)$, where n is the number of characters and z is the distance to the optimum. This probability, which is plotted in the figure, falls rapidly with mutational size. This famous plot from Fisher's *The Genetical Theory of Natural Selection*[1] shows that infinitesimally small mutations enjoy a 50% chance of being favourable but that this probability falls rapidly for progressively larger mutations. Although Fisher presented no derivation of his famous probability, it has since been re-derived by Leigh[107], and Hartl and Taubes[44].

Essentially all studies of adaptation in Fisher's geometric model assume that adaptation involves the appearance and substitution of new mutations (not standing genetic variation) and that the optimum does not move during the bout of adaptation that is studied (but see REF. 108). Results might well differ under other scenarios[92].

geometric model as an explicit attempt to capture the "statistical requirements of the situation" of adaptation[1]. In this model, an organism is represented as a set of phenotypic characters, each measured on a Cartesian axis and each having an optimal value in the present environment (BOX 2; FIG. 1). Because of a recent environmental change, the population has fallen off the optimum; the problem for adaptation is to return to the optimum. The essence of Darwinian evolution is that populations must attempt this return by producing mutations that are random with respect to the organism's need, that is those that have random direction in phenotypic space. Crucially, some of these mutations might be larger than others.

Fisher used his geometric model to ask a simple question — what is the probability that a random mutation of a given phenotypic size will be beneficial? He showed that, although infinitesimally small mutations enjoy a 50% chance of being beneficial, this probability falls to "exceedingly small values" with increasing mutational size (see figure in BOX 1). Fisher therefore concluded that very small mutations are the genetic basis of adaptation — a conclusion that was extraordinarily influential and that was cited by nearly all the founders of the modern synthesis (reviewed in REF. 25). Interestingly, although Fisher published his calculations only in 1930, brief comments in previous publications[36] reveal that he had arrived at his micromutational conclusion far earlier and for essentially the same reasons as he emphasized in 1930.

Ironically, although Fisher offered the first sensible model of adaptation, the sole question he asked of it suppressed all further interest in the model. His answer, after all, suggested that micromutationism is plausible and that one could, therefore, study adaptation through infinitesimally based quantitative genetics. To make it doubly ironic, Fisher erred here and his conclusion (although not his calculation) was flawed. Unfortunately, his error was only detected half a century later, by Motoo Kimura[37]. Kimura pointed out that to contribute to adaptation, mutations must do more than be beneficial — they must escape accidental loss when rare — and mutations of larger effect are more likely to escape such loss. Taking both factors into account, Kimura concluded that mutations of intermediate size are the most likely to contribute to adaptation, a conclusion that did curiously little to curb enthusiasm for micromutationism.

In the late 1990s, however, it became clear that Kimura's conclusion was also not what it first seemed. Although Kimura derived the distribution of sizes among mutations that are used at a particular step in adaptation this is not the same as the distribution of mutations that are substituted throughout an entire bout of adaptation, a bout that might involve many steps (FIG. 1). Using a combination of analytical theory and computer simulation, it has been shown[38,39] that the size distribution of mutations that are substituted over entire bouts of adaptation is nearly exponential. Adaptation in Fisher's model therefore involves a few mutations of relatively large phenotypic effect and many of relatively small effect. This work further showed that the mean sizes of mutations substituted at the first versus the second substitution, and so on

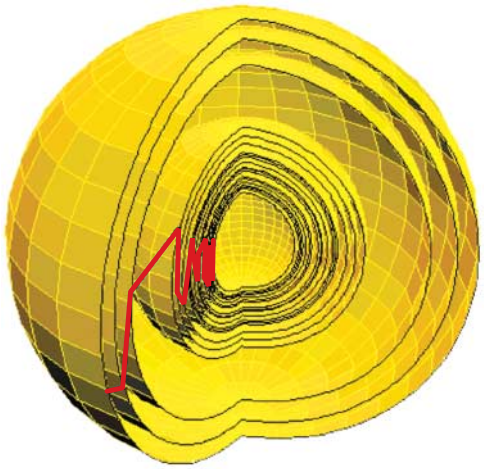


Figure. 1 | **Adaptation in Fisher's geometric model.** A bout of adaptation in Ronald A. Fisher's geometric model is shown. For simplicity, the organism that is considered comprises only three characters. The population begins on the surface of the sphere and, by substituting beneficial mutations (red vectors), evolves towards the phenotypic optimum at the centre of the sphere. The mutations that are substituted become smaller on average as the population nears the optimum. Modified, with permission, from REF. 41 © (2002) Macmillan Magazines Ltd.

for subsequent substitutions, fall off by an almost constant proportion; that is, as an approximate geometric sequence. Adaptation is therefore characterized by a pattern of diminishing returns — larger-effect mutations are typically substituted early on and smaller-effect ones later[38–41]. These results appear to be reasonably robust to assumptions about the precise shape of the fitness function and the distribution of mutational sizes provided to natural selection[38,39].

Although Fisher's model has recently been used to study the evolution of sex[42], the evolution of development[43], COMPENSATORY EVOLUTION[44], the distribution of phenotypes under mutation–selection-drift balance[45], MUTATION LOAD in finite populations[46] and the effects of species hybridization[47], some of the most surprising findings concern the so-called cost of complexity. Analysis of Fisher's model shows that complex species (those having many characters) typically show slower increases in fitness during adaptation than do simple species[48]. Part of the reason is that the distance travelled to the optimum by a beneficial mutation is smaller in a complex than a simple species (this distance decreases with the square root of the number of characters)[48]. Recent work by Welch and Waxman[49] indicates that this cost of complexity might be a general feature of adaptation; indeed, this cost may be little affected by the degree of organismal MODULARITY.

Sequence evolution

Maynard Smith and sequence spaces. Although Fisher's model takes into account the Mendelian nature of mutation, it does not reflect the molecular basis of inheritance; that is, the fact that DNA is a linear sequence of nucleotides that, among other things, encodes a linear sequence of amino acids. In the early 1960s, however,

COMPENSATORY EVOLUTION
Evolution in which a second substitution compensates for the deleterious effects of an earlier substitution.

MUTATION LOAD
The decrease in population fitness below its ideal value owing to recurrent deleterious mutation.

MODULARITY
The idea that organisms are broken developmentally into roughly independent modules, such that mutations affecting traits in one module do not affect traits in other modules.

theorists began to develop models of adaptation that were sequence-based. As with so many innovative ideas in late twentieth-century evolutionary genetics, the key insight was that of John Maynard Smith[50]. Maynard Smith[50,51] emphasized what would become a dominant theme in the theory of adaptation — real adaptation occurs in a sequence space that, unlike the phenotypic space considered above, is discrete. He also emphasized that this discreteness imposes certain constraints on adaptation. For example, the number of possible sequences at a gene is limited — given a gene that is L base-pairs long, only 4^L different sequences are possible. The constraints on adaptation are, however, far more severe than this number implies. Because the per site mutation rate is low ($\sim 10^{-9}$ per base pair), Maynard Smith argued that multiple (for example, double or triple) mutations are "probably too rare to be important in evolution"[51]. Instead, natural selection is constrained to surveying sequences that differ from the wild type at a single site. There are only $3L$ such one-mutational step sequences; a finite number indeed.

Maynard Smith also emphasized that adaptation involves what came to be called 'adaptive walks' through sequence space: "if evolution by natural selection is to occur, functional proteins [or DNA sequences] must form a continuous network which can be traversed by unit mutational steps without passing through non-functional intermediates"[51]. In particular, if a wild-type sequence can mutate to one or more fitter sequences, natural selection will ultimately substitute one of these beneficial alleles; this new wild-type sequence will in turn produce its own suite of one-mutational step sequences and, if any is fitter than the current wild-type, selection will again substitute one of these beneficial alleles. This adaptive walk ends only when the population arrives at a wild-type sequence that is fitter than all of its $3L$ one-mutational-step neighbours. At that point, the population has arrived at a local optimum.

Although Maynard Smith's work appeared early in the molecular revolution, his ideas on adaptive walks were almost entirely ignored for two decades. The cause of this neglect seems clear: the rise of the neutral theory of molecular evolution. Throughout the 1960s and 1970s, evolutionary geneticists grew increasingly convinced that much, if not most, molecular evolution reflects the substitution of neutral[52,53] or nearly neutral[37,54–56] mutations, not beneficial ones. Throughout much of this period, the study of adaptation itself grew intellectually suspect[57] and the theoretical study of molecular adaptation essentially ceased.

Kauffman and NK models. In the 1980s, theoretical study of adaptation at the sequence level finally resumed. One of the best known of these new efforts involved so-called NK models. This work, launched by Kauffman and Levin[58], ultimately grew into a large and sophisticated body of mathematical and computational literature[59–69]. Arguing that evolutionary geneticists possess "essentially no theory of adaptation", Kauffman and colleagues[58] set out to discover the laws, if any, that describe adaptation through sequence space.

Their approach emphasized the idea that different sequence spaces might feature different numbers of local optima. This is most easily seen by picturing a 'fitness landscape'. Fitness, or adaptive landscapes were introduced by Sewall Wright[70,71] in his studies of the SHIFTING BALANCE THEORY of evolution (for an excellent review of landscape types and theory, see REF. 72). Wright's landscapes typically plotted the fitnesses of different combinations of genotypes across multiple loci (Wright spoke of a "field of possible gene combinations"). The fitness landscapes considered by NK theorists were similar, except that each 'locus' was typically taken to represent a particular site in a DNA sequence. To see this, imagine all possible DNA sequences at a gene as points on a grid (FIG. 2); sequences that differ slightly from each other reside near each other on this grid, whereas sequences that differ more substantially reside farther apart; the fitness of each sequence is then plotted as its height above this grid. The resulting picture of hills and valleys represents a fitness landscape. The key point is that fitness landscapes can differ in their ruggedness. The smoothest possible landscape features a single optimum and all adaptation necessarily involves walks up this single peak; the most rugged landscape possible features many local optima and adaptation involves walks up the nearest optimum. The NK model allows one to 'tune' the ruggedness of fitness landscapes between these extremes by varying two mathematical parameters (N and K), allowing the analysis of adaptation for many families of landscapes.

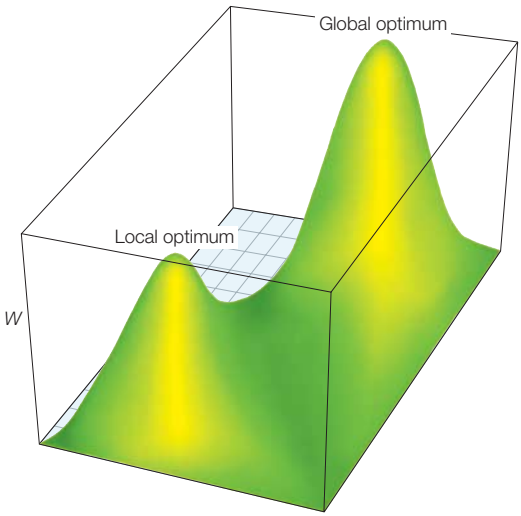


Figure 2 | **A fitness landscape.** The underlying grid represents a DNA sequence space. Although such a space cannot actually be represented in two dimensions (and instead must be depicted as a high dimensional hypercube), we can loosely imagine that alleles that are similar in sequence sit near each other on the grid shown, whereas alleles that are different in sequence sit farther apart. Allelic fitnesses (W) are plotted above the grid. Adaptation in a large population will involve adaptive walks up the nearest fitness peak. Because natural selection will not allow a population to descend into an adaptive valley, adaptation drives a population to a local optimum, which might or might not correspond to the global optimum. Modified, with permission, from REF. 111 © (2004) Sinauer Associates Inc.

SHIFTING BALANCE THEORY
A largely verbal theory of evolution which maintains that the interaction between natural selection, genetic drift and migration is more important that the action of any single force. Sewall Wright argued that this theory helped to explain how species could effectively search for the global, and not merely local, optimum.

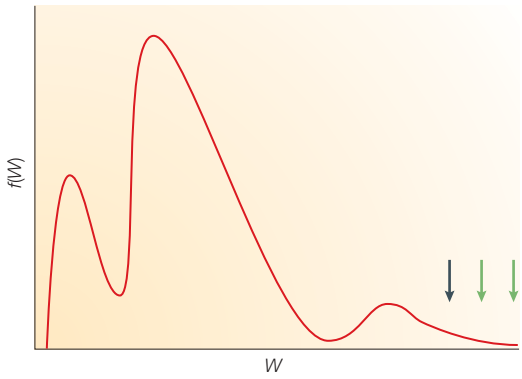


Figure 3 | **The distribution of fitnesses at a locus.** An arbitrary distribution of fitnesses among alleles at some gene is shown (*W*, fitness value; *f*(*W*), frequency of a certain fitness value). Although the precise shape of this distribution will, in reality, almost always be unknown, John Gillespie[75–77] emphasized that, in most cases, the wild-type allele will be highly fit; that is, drawn from the right-hand tail of the distribution (black arrow). Consequently, beneficial mutations represent even more extreme draws (green arrows). This implies that extreme value theory (EVT) can be used to study adaptation (see also BOX 3).

NK theorists derived several approximate results that characterize such landscapes. These included the probability that a sequence is a local optimum, the number of local optima, the proportion of local optima that can be reached from a given sequence and the average length of adaptive walks on landscapes of varying ruggedness (reviewed in REFS 60,69). NK and related models (such as the Block model[73]) were also applied to the study of AFFINITY MATURATION during immune response[58–60,64], genetic regulatory networks[58,60] and RNA folding[67].

Although NK models successfully explained certain features of affinity maturation[60] and received considerable attention in computer science and in physics (in which problems in SPIN GLASSES are similar[74]), it seems fair to say that these models ultimately had a lesser impact on evolutionary genetics where they began. In retrospect, two features of many NK studies were unbiological. The first involves the 'move rule' used to decide which of several beneficial mutant sequences a population will substitute at the next step in adaptation. The NK literature focused on two such rules: random, in which a beneficial sequence is randomly chosen from those available[58,61,63–67] and gradient, in which the fittest of available beneficial sequences is always chosen[58,63,67,68]. The problem is that natural selection uses neither of these rules (the correct move rule is described in the next section). Second, the NK literature typically considered adaptation from a random starting sequence or even from the worst possible sequence[58,62–64,66,67,69]. Real adaptation, however, often begins from a wild-type sequence of high fitness. The wild-type allele, after all, produces a functional protein and was, until a recent environmental change, the fittest sequence that was locally available. As we will see (and as Kauffman later acknowledged[60]), the simple fact that the wild-type allele is highly fit turns out to be of considerable importance.

AFFINITY MATURATION
An increase in the affinity of an antibody for an antigen which is seen as an immune response improves.

SPIN GLASSES
Magnetic objects that are disordered and in which adjacent dipoles can either 'point' in the same direction or in opposite directions.

Gillespie and the mutational landscape. How many sequences at a gene should be highly fit and how many lethal? Just what does the distribution of fitnesses look like on a fitness landscape? Unfortunately, we have almost no data relating to these questions. Given this situation, Ohta[54] and Kimura[55] suggested that we consider fitnesses as randomly drawn from a probability distribution. The question is, of course, which distribution? In the early 1980s, John Gillespie[75,76] surprisingly argued that it might not matter much. The reason unexpectedly follows from the point noted above — that adaptation typically begins from a high fitness sequence.

Gillespie's insight was that, although we do not know the detailed distribution of fitnesses at any gene, we do know two things: that the wild-type represents a draw from the right tail of the fitness distribution; and that beneficial mutations represent even more extreme draws from this tail (see FIG. 3). And this, Gillespie[75–77] argued, means that we can import extreme value theory (EVT) into the study of adaptation. EVT is a body of probability theory that is concerned with the properties of draws from the tails of distributions[78,79]. Remarkably, EVT shows that these draws have certain properties that are asymptotically independent of the (usually unknown) details of the distribution, a robustness that is reminiscent of the central limit theorem[79]. Although EVT is important in modern mathematical finance and risk analysis (extreme swings in security prices and insurance claims can have devastating effects on portfolios and insurance firms, respectively[80]), it had, until Gillespie's work, little role in evolutionary genetics. But Gillespie saw that, as most adaptation occurs in the right tail of fitness distributions, EVT might tell us a good deal about the adaptation of DNA sequences (BOX 3).

Gillespie[75–77] used EVT to study adaptation over what he called the "mutational landscape". He was primarily concerned with evolution under strong selection–weak mutation (SSWM) conditions. His weak mutation assumption was essentially equivalent to that of Maynard Smith: mutation rates per site are sufficiently low for us to ignore double mutants; his strong selection assumption meant roughly that mutations are either definitely beneficial or deleterious (neutral mutations are not allowed). Under SSWM assumptions, a population is essentially fixed for a single wild-type sequence at any moment in time and this wild-type sequence recurrently mutates to $3L$ neighbouring sequences. Because the wild-type sequence enjoys high fitness, it is assumed that few, if any, of these $3L$ mutant sequences are beneficial. Each beneficial allele is likely to be lost accidentally each time it appears but, because mutation is recurrent, one will eventually be substituted; this completes one step in an adaptive walk. The new wild-type sequence now produces it own set of $3L$ mutants and the process is repeated. Gillespie assumed that mutant fitnesses are drawn from the same distribution throughout a (brief) adaptive walk; adaptation is therefore characterized by the movement of a population out along a tail of fitnesses.

MOLECULAR CLOCK
The empirical finding that a particular type of protein or DNA sequence evolves at a nearly constant rate through time.

POISSON PROCESS
A simple statistical process in which there is a small and constant probability of change during each short interval of time.

Gillespie[75–77] described several results that characterize adaptation over the mutational landscape. Perhaps most importantly, he calculated the 'move rule' that is used by positive natural selection. He showed that, when several beneficial mutations are available to a wild-type sequence, the probability that a population jumps to a beneficial allele j at the next step in evolution is, under SSWM conditions, $s_j/\Sigma s$, where s is the selective advantage of an allele, and the summation involves all available beneficial alleles. Explained in words, this formula means that the chance that a particular beneficial allele is the next substituted is proportional to the selective advantage of that allele. Beneficial mutations of greater effect are therefore more likely, although not guaranteed, to be the next substituted. This move rule differs from those used in NK studies (despite REF. 81).

Most of Gillespie's work focused on entire adaptive walks. He noted two key facts. First, because the fitness of wild-type sequences increases during adaptation, beneficial mutations become increasingly difficult to come by. The theory of records[82,83] shows that the cumulative number of alleles that break the previous 'fitness record' (that is, that are beneficial) only increases logarithmically during adaptive walks[84]. Second, Gillespie[77] showed that the mean number of steps taken during adaptive walks is small — typically two to five. Molecular evolution at a gene therefore occurs in small bursts of substitutions. Put differently, molecular evolution by natural selection leaves a signature that differs from that left by neutrality — whereas neutral evolution yields a simple MOLECULAR CLOCK (with substitutions that occur as a POISSON PROCESS), natural selection does not (the molecular clock is instead 'overdispersed'). Gillespie[77,85,86] argued that adaptation explained the existing molecular evolutionary data better than neutrality did (see also REF. 87).

Much of the recent work on adaptation theory has focused on Gillespie's mutational landscape model. Several results have been described over the past several years. Perhaps most surprising, two studies[88,89] showed that beneficial mutations should have exponentially distributed fitness effects that are independent of many biological details. Most recent analyses of the mutational landscape model, however, have focused on the unit event in adaptation — the substitution of a beneficial mutation. It has been shown[90] that, if the current wild-type sequence is the ith fittest allele (that is, $i-1$ beneficial mutations are available), the population will jump to a beneficial allele that has mean fitness rank $(i+2)/4$ at the next substitution. Adaptation is, therefore, characterized by surprisingly large jumps in fitness rank. If thirteen beneficial mutations are available to a wild-type sequence, populations will typically jump to the fourth best allele at the next step in adaptation. Adaptation therefore leap-frogs many moderately beneficial mutations, arriving at a strongly beneficial one. Recent work also shows that parallel evolution at the DNA sequence level is more common under natural selection than under neutrality. In fact, the probability of parallel evolution approximately doubles under positive selection[91]. Computer simulations of entire adaptive walks further show that at least half the total gain in fitness that occurs during adaptation is due to a single substitution[90]. Once again, therefore, adaptation features relatively large jumps. Indeed, adaptation seems to be characterized by a 'Pareto principle', in which the majority of an effect (increased fitness) is due to a minority of causes (one substitution). Finally, recent theory shows that, conditional on the substitutions occurring, the mean selection coefficient, s, among mutations that are fixed at subsequent steps in adaptation decreases as an approximate geometric sequence — again revealing a pattern of diminishing returns — and that the overall distribution of s among mutations that are substituted during adaptation is roughly exponential[90].

These results are obviously reminiscent of those from Fisher's geometric model — a similarity that is surprising given the fundamental differences between the older phenotypic and newer DNA sequence-based models[92]. This congruence represents one of the most tantalizing results to emerge from recent adaptation theory, indicating (although certainly not proving) that adaptation to a fixed optimum by new mutations may be characterized by certain robust patterns. Future work could of course show that different biological scenarios (for example, adaptation from the standing genetic variation) are characterized by different patterns.

Box 3 | Adaptation and extreme value theory

Classical extreme value theory (EVT) emerged from early work by the biologist Ronald A. Fisher and the probabilists Richard von Mises and Boris V. Gnedenko, among others (reviewed in REFS 78,79,109). EVT is concerned with the asymptotic properties of the largest draws from a probability distribution, as the number of draws becomes large. The most fundamental, and best known result from EVT concerns the distribution of maxima. If many values from a given 'parent' distribution are drawn, the largest value saved, and then this process is repeated many times, the distribution of these maxima approaches the so-called extreme value distribution. There are in fact three extreme value distributions — one for 'ordinary' parent distributions (the Gumbel type), another for many parent distributions that are truncated on the right (the Weibull type) and a last for parent distributions that lack all or higher moments (the Fréchet type). The Gumbel type includes most ordinary distributions — for example, the normal, lognormal, gamma, exponential, Weibull and logistic — and was the focus of classical EVT. The Gumbel extreme value distribution is often referred to as 'the' extreme value distribution. The biologically important point is that extreme draws from a surprisingly wide array of parent distributions all converge to the same extreme value distribution. EVT is generally characterized by such robustness to distributional details, allowing conclusions to be made about adaptation that depend only weakly on the (generally unknown) distribution of fitnesses at a gene.

Gillespie[75–77] assumed that the distribution of fitnesses (see FIG. 3) belongs to the Gumbel type and subsequent work on the mutational landscape has followed suit. Recent work provides some support for this assumption. It can be shown, for example, that the distribution of mutational effects in Fisher's geometric model is of the Gumbel type (A.O., unpublished data). EVT describes not only the distribution of largest values from a parent distribution, but the distribution of the second, third, and so on, largest values[79]. EVT also describes the asymptotic distributions of the 'extreme spacings' between the largest and next-largest (and so on) draws — given a Gumbel-type parent distribution, these spacings are independent exponential random variables with averages that behave in a certain simple way[110]. This result has a fundamental role in recent theory of adaptation, as fitness differences among beneficial mutations represent extreme spacings. Recent work has begun to explore the consequences of non-Gumbel fitness distributions on adaptation over the mutational landscape (A.O., unpublished data).

Limitations and conclusions

The history of evolutionary genetics indicates that two main factors slowed the development of a mature theory of adaptation. The micromutational view of quantitative genetics and the neutral theory of population genetics. We cannot, after all, construct a meaningful theory of adaptation if we assume away the existence of mutations that have different-sized phenotypic effects or if we assume that substitutions at the DNA-sequence level have no effect on fitness. The fact that we possess little theory of adaptation went largely unnoticed until the 1980s, when QTL and microbial evolution approaches yielded abundant data that revealed a finite (and often modest) number of substitutions that have definite (and often different) effects on the phenotype or fitness.

In this article, I have emphasized that the appearance of such data forced evolutionary geneticists to confront two questions. First, can we construct a theory of adaptation that speaks in the same terms as the data? And, if so, can this theory actually account for the empirical phenomena observed? The answer to the first question is clearly yes. Evolutionists can and have built models of adaptation that speak in terms of individual mutations that have individual effects (whether phenotypic or fitness). The answer to the second question is less clear. Present theory appears to adequately explain certain qualitative patterns that characterize genetic data on adaptation. Four such patterns are: that there are more beneficial mutations of small than large effect[89,93,94]; that QTL studies reveal more substitutions of small than large effect[26,28,95]; that microbial studies show that early substitutions have larger fitness effects than later ones (that is, there is pattern of diminishing returns)[31]; and that parallel evolution is common at the DNA sequence level[32–35].

However, it is unclear whether current theory accomplishes much more than qualitative agreement with the data. There are in fact two problems. The first is that current theory is limited in several ways — all the models that have been mentioned rest on important assumptions and idealizations. Fisher himself noted such limitations in correspondence about his geometric model[96,92]. And the mutational landscape model assumes that adaptation occurs at a single gene (or small genome), that fitness distributions show certain tail behaviour, and that mutant fitnesses are taken from the same distribution throughout adaptation. Although they are reasonable starting points for theory, none of these assumptions is necessarily correct and changing any might well change our predictions (however, see BOX 3).

The second problem concerns testability. Although adaptation models have become more concrete and perhaps more realistic, it is not clear that they have become more testable. The difficulty is practical, not principled. Whereas current theory does make testable predictions, the effort required to perform these tests is often enormous (particularly as the theory is probabilistic, making predictions over many realizations of adaptation). Given, for example, the inevitable and often severe limits on replication in microbial evolution work, we can usually do no more than test qualitative predictions.

Despite such limitations, experiments to test the more tractable predictions of present theory (for example, those that focus on a single step in adaptation, where greater replication is possible) are important. The main reason is that the two problems noted above are related; only by testing present predictions can we determine which, if any, of the assumptions that underlie current theory are inappropriate. Only then will theorists know which assumptions to change, deriving new — and perhaps different — predictions and ultimately allowing the elaboration of a more realistic theory of adaptation.

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Acknowledgements

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

Competing interests statement

The author declares no competing financial interests.

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