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The evolutionary genetics of adaptation: a simulation study

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Summary

It is now clear that the genetic basis of adaptation does not resemble that assumed by the infinitesimal model. Instead, adaptation often involves a modest number of factors of large effect and a greater number of factors of smaller effect. After reviewing relevant experimental studies, I consider recent theoretical attempts to predict the genetic architecture of adaptation from first principles. In particular, I review the history of work on Fisher's geometric model of adaptation, including recent studies which suggest that adaptation should be characterized by exponential distributions of gene effects. I also present the results of new simulation studies that test the robustness of this finding. I explore the effects of changes in the distribution of mutational effects (absolute versus relative) as well as in the nature of the character studied (total phenotypic effect versus single characters). The results show that adaptation towards a fixed optimum is generally characterized by an exponential effects trend.

> The situation to which these studies point is not one of a large number of genes all with more or less equal effect. It seems, rather, that a small number of genes with large effects are responsible for most of the response, the remainder of the response being due to a larger number of loci with small effects.
>
> D. S. Falconer (1981)

1. Introduction

The history of quantitative genetics has been characterized by a curious tension. On the one hand, theorists since Fisher (1930) have typically maintained that response to selection in general – and adaptation in particular – involves many genes of small phenotypic effect each. Taken to its logical conclusion, this view gets formalized in the infinitesimal model: phenotypic variation and hence response to selection is underlaid by a nearly infinite number of loci of infinitesimally small effect each. On the other hand, virtually all textbook examples of adaptation in nature appear to involve a modest number of genes – often one – of quite large effect. The litany of such cases is familiar, including industrial melanism (Lees, 1981), heavy metal tolerance in plants (Macnair, 1987) and Batesian and Mullerian mimicry (Turner, 1977).

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More recent work has confirmed these classic findings from ecological genetics. ffrench-Constant (1994), for instance, has shown that insecticide (cyclodiene) resistance in the wild among at least three orders of insects involves the same amino acid substitution (Ala → Ser) in the same single gene (*Rdl*, *resistance to dieldrin*, which encodes a subunit of a GABA-gated chloride ion channel). Indeed cyclodiene resistance routinely involves the same *nucleotide* substitution in all orders studied, a result that is as inconsistent with the infinitesimal view as logically possible. (See also Roush & McKenzie (1987).)

Empirical evidence against the infinitesimal view has also come from artificial selection experiments. The relevant findings fall into two classes. First, certain statistical inferences from responses to selection cast doubt on the 'micromutational' view. Falconer (1981; see especially his table 12.2), for instance, appreciated early on that half-lives for *Drosophila* and mouse artificial selection lines taken to selection limits were often much shorter than predicted under the infinitesimal model. (Robertson's (1960) theory of selection limits shows that 1·4 N_e generations are required to proceed to half the selection limit under the infinitesimal model; with major factors, the half-life is reached more quickly (Hill & Caballero, 1992).) Although such patterns do not readily allow

firm conclusions – as Falconer himself was quick to emphasize – they suggest, at the very least, that the infinitesimal assumption deserves closer scrutiny.

Such scrutiny is provided by the second line of evidence from artificial selection: the direct mapping of factors underlying response to selection, typically by quantitative trait locus (QTL) analysis. The genetic basis of response to artificial selection has been analysed in a fair number of cases, including experiments in *Drosophila* (Shrimpton & Robertson 1988*a*, *b*; Long *et al*., 1995; Frey *et al*., 1995) mice (Keightley *et al*., 1996) and several crop species (Paterson *et al*., 1991; Edwards *et al*., 1992; Tanksley 1993; Paterson *et al*., 1995). Analysis by Doebley and colleagues (Doebley & Stec, 1991; Doebley & Wang, 1997) of the profound phenotypic differences distinguishing maize from its wild ancestor, teosinte, represents perhaps the most impressive example of such an analysis to date. Remarkably, Doebley's group found that the maize–teosinte differences involve as few as five QTL. Indeed one morphological difference, in lateral branching patterns, appears due to a single gene, *teosinte branched-1* (*tb1*). *Tb1*'s role has been confirmed in a critical complementation test and the gene has been cloned (Doebley & Wang, 1997). Indeed very recent work suggests that *tb1*'s morphological effect may map to a small non-transcribed regulatory region of the gene (Wang *et al*., 1999).

Unfortunately, the above lines of evidence all involve human intervention, in the form of either environmental disturbance or direct artificial selection. Because such cases typically involve strong – and perhaps unnaturally harsh – selection, it has often been argued that they are potentially misleading (e.g. Lande, 1983). Thus 'natural adaptations', those *not* involving human intervention, might well still have a polygenic basis.

This argument has not aged well. Although we still suffer from an appalling shortage of rigorous genetic analysis of natural adaptations, the data we do possess provide little comfort to micromutationism. Orr & Irving (1997), for instance, found that differences between natural populations of *Drosophila melanogaster* in ability to overcome parasitism by the common parasitoid wasp *Asobara tabida* involve factor(s) restricted to the second chromosome and probably to the centromeric region of this chromosome: at least 60% of the genome thus plays no role. Similar results have been obtained for *D. melanogaster*'*s* resistance to another parasitic wasp, *Leptopilina boulardi* (Carton & Nappi, 1997). Several more recent and powerful QTL analyses also provide evidence against micromutationism. Jones (1998) genetically dissected *D. sechellia*'s resistance to the normally toxic effects of its host fruit, *Morinda citrifolia*. Using 15 markers scattered throughout the genome, he showed that resistance appears oligogenic. While at least five factors underlie adult resistance, large chromosome regions of no effect are also common. Similarly, preliminary data show that *D. sechellia*'s behavioural preference for ovipositing on *Morinda* has a fairly simple genetic basis. Although several factors are involved, large regions of the genome, including the entire X chromosome – which represents 20% of the genome – play no role (C. D. Jones, personal communication). (The significance of such negative results has not been widely appreciated. While the QTL community has been largely concerned with the precision of QTL map positions, demonstration that whole chromosomes have *no* effect may be of considerably more evolutionary import.) Finally, Bradshaw *et al*. (1998) performed QTL analysis of a suite of 12 floral characters distinguishing two species of the monkeyflower, *Mimulus*. Their results also suggest an oligogenic basis: much of the observed phenotypic difference appears due to a few factors of large effect, although an appreciable number of factors of small effect probably also exist. Although QTL analyses tend systematically to overestimate QTL effects when sample sizes are small (Beavis, 1994), this problem would not appear serious in the above studies: the *Drosophila* work involves thousands of genotyped individuals, while the *Mimulus* work involves approximately 500 individuals genotyped at 66 RAPD markers.

These observations highlight the poverty of our theoretical understanding of adaptation. There is an undeniable and deep gulf between the known genetical facts and traditional micromutational theory. Indeed the problem is not merely that classical quantitative and population genetic theory fail to explain the observed genetic architecture of adaptation; the deeper problem is that they do not *attempt* to explain the observed architecture. The infinitesimal model does not, after all, represent the endpoint of some extended theoretical argument. There is no principled reason *why* the genetics of character evolution should have such a basis. Instead (and obviously) the infinitesimal view represents an assumption made for its undeniable mathematical convenience. Given this – and given micromutationism's empirical inadequacy – it seems worth asking whether the enterprise can be profitably stood on its head. Can one, starting from first principles, make any non-trivial predictions about the genetics of adaptation? Can one make any theoretical claims about what the genetic architecture of adaptation *should* look like?

Recently, I suggested that at least one such prediction was possible. Phenotypic effects among genes fixed during adaptation should be exponentially distributed (Orr, 1998). This finding, which follows from Fisher's (1930) model of adaptation (see below), supports Robertson's (1967) precocious insight into the genetics of phenotypic evolution and provides a

heuristic expectation about the genetics of adaptation as seen in QTL, associational and experimental evolution studies.

The remainder of this paper has two goals. First, I will briefly review Fisher's model of adaptation and the history of recent work on it, including the finding of exponential gene effects. Secondly, I will examine the generality of this result, asking how robust this trend is to changes in the distribution of mutational effects as well as to changes in the nature of the character studied. The results will show that the exponential trend is surprisingly robust. Under a remarkably wide variety of circumstances, adaptation towards a fixed optimum is characterized by exponential distributions of gene effects.

2. Fisher's model of adaptation

To Fisher (1930), the essence of adaptation is that organisms must conform to the environment in many different ways. He further suggested that this conformity could be captured in a simple geometric model. Because organisms must simultaneously optimize a large number of independent characters, adaptation can be pictured as movement towards an optimum in an n-dimensional phenotypic space. If an organism were comprised of just two characters, phenotypic evolution could be tracked in a Cartesian coordinate system, where each axis represents a trait, the optimal combination of trait values sits at the origin, and fitness falls off as a Gaussian function of distance from the optimum. But because real organisms are very complex, Fisher argued that we must consider adaptation in the case where the number of dimensions is large.

Beginning some distance from the optimum, organisms adapt via production of random mutations, where a mutation's phenotypic effect is represented by a vector of some magnitude but having random direction in phenotypic space. A mutation is favourable if it takes the population closer to the optimum and deleterious if it takes the population further from the optimum.

Fisher used this model to find the probability that random mutations of a given size would be favourable. Beginning with a population residing a distance, $d/2$, from the optimum, he calculated the probability that random mutations of magnitude r would move an organism nearer the optimum. He famously showed that, while small mutations have a good chance of being favourable, larger ones suffer a rapidly decreasing probability. He thus concluded that small mutations are the stuff of adaptation, a claim which laid the intellectual foundation for micromutationism and which was repeatedly cited by the founders of the modern synthesis (see reviews by Turner, 1985; Orr & Coyne, 1992).

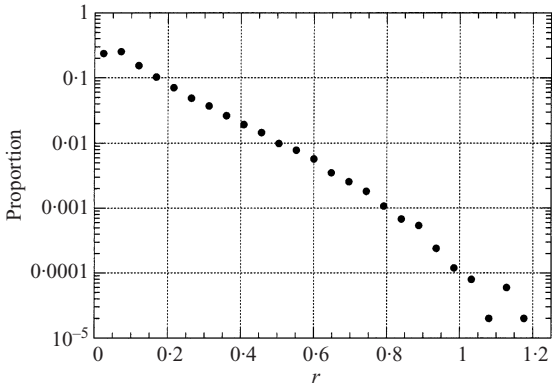

Fig. 1. The distribution of factors fixed during adaptation in Fisher's model (semilog plot). Mutations were uniformly distributed and simulations were performed at $n = 25$ dimensions. Data derive from 50000 substitutions over many walks to the optimum.

Fifty years later, however, Kimura (1983) pointed out that Fisher's conclusion is seriously compromised by considerations of probability of fixation. For although smaller mutations are more likely to be favourable, larger ones are more likely to escape stochastic loss when favourable – a point neglected by Fisher. Taking both factors into account, Kimura argued that Fisher's micromutational conclusion was in error and derived a corrected distribution of gene effects fixed in adaptation. In particular, Kimura showed that adaptation will typically involve mutations of *intermediate* size.

While bringing us one step closer to the distribution of factors underlying adaptation, one problem remained with Kimura's analysis. In experimental, e.g. QTL or experimental evolution, analyses we study the results of an entire – and perhaps extended – bout of evolution. Following an environmental change, a population substitutes a favourable allele and so moves closer to the phenotypic optimum. But the population then likely substitutes another and, on average, smaller mutation, moving again closer to the optimum. Such an 'adaptive walk' to the optimum might involve many steps. What we would most like to known, then, is the distribution of effects among factors fixed *summing over the entire walk to the optimum*.

Derivation of this distribution requires knowing the mean distance travelled to the optimum by favourable mutations – a quantity derived by Hartl & Taubes (1996) – as well as the mean distance travelled to the optimum by those favourable mutations that actually get fixed – derived by Orr (1998, 1999). Knowing these quantities, one can obtain an approximate solution to the distribution of factors fixed over the walk to the optimum (Orr, 1998). In all cases studied, this distribution was found to be nearly exponential, i.e. different from either Fisher's or Kimura's distribution (see Fig. 1 for an example). Theory and

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simulations further showed that the largest factor fixed during such an adaptive walk to the optimum is on average far larger than Fisher's argument implied.

Because this exponential result appears to offer a heuristic expectation about the results of QTL and experimental evolution studies, it is of some importance to test its generality. I turn now therefore to an examination of the robustness of this trend.

3. Absolute distributions of mutational effects

The distribution of factors fixed during adaptation, $\psi(r)$, must to some extent depend on the distribution of mutational effects provided to natural selection, $m(r)$, where r is the magnitude of a displacement in Fisher's n-character space and mutations appear at many loci. (Note that the 'size' of a mutation reflects its phenotypic effects over all characters.) Previous work considered two classes of mutational distributions: uniform ones (following Kimura, 1983) and those in which small mutations are more common than large. In both cases, the distribution of factors fixed in adaptation is nearly exponential, where we assume that evolution involves substitution of unique mutations (Orr, 1998).

For reasons of mathematical tractability, however, attention was restricted in the second case to 'relative' distributions of mutational effects, i.e. to cases in which the magnitude of mutant effects scales with an organism's present phenotype (Distance from the optimum, z). This assumption greatly simplifies the analysis: the population faces the same problem and attempts the same solution at each step in the walk to the optimum and adaptation merely involves repeated changes of scale (i.e. is self-similar). Unfortunately, this assumption may be biologically unrealistic for many characters. It is thus important to characterize the distribution of factors fixed during adaptation when mutational effects are 'absolute', i.e. unchanging over the walk to the optimum.

The shift to absolute effects requires that we abandon analytical treatment. Instead, I use computer simulations. These simulations, which are exact, are identical to those in Orr (1998) except for the manner in which mutations are produced. In particular, we now draw a mutation of magnitude r from a distribution, $m(r)$, where r is measured on the same 'raw' scale as Euclidean distance from the optimum, not on Fisher's standardized x scale. Because small mutations appear to be more common than large (Kimura, 1983), we restrict our attention to leptokurtic distributions in which mutations with effects near zero are most common. For convenience, we assume that the population begins unit distance from the optimum and focus on the $n = 25$ dimensions case.

First consider the case in which mutational effects are exponentially distributed ($m(r) = (1/\bar{r})\exp(-r/\bar{r})$)

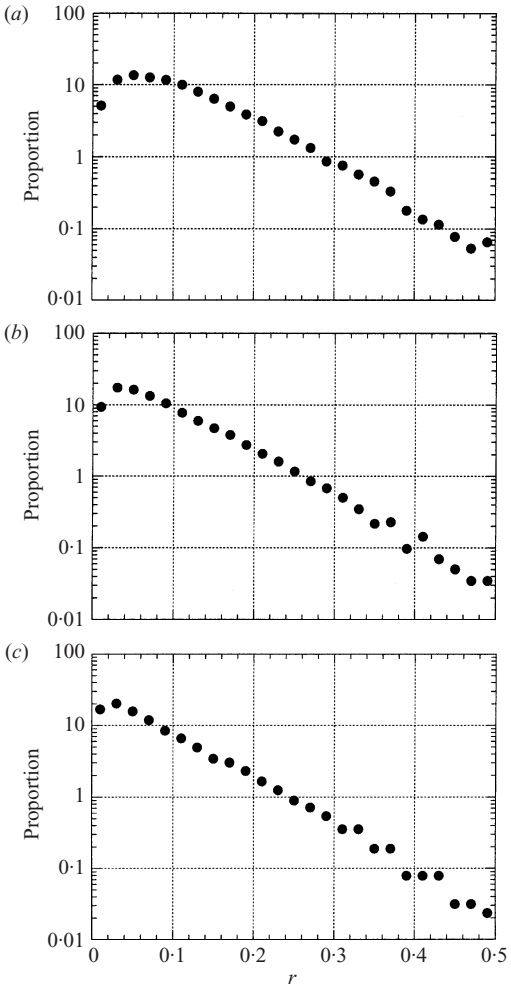

Fig. 2. The distribution of factors fixed given absolute mutational effects that were exponentially distributed with $\bar{r} = 0{\cdot}1$ (semilog plots). Plots correspond to populations that have travelled (*a*) 75%; (*b*) 90%, and (*c*) 95% of the distance to the optimum. In all cases, more than 12000 substitutions were sampled over 200–500 replicate walks to the optimum at $n = 25$ dimensions.

and let $\bar{r} = 0{\cdot}1$ (10% of the distance to the optimum). Fig. 2 shows the resulting distribution of factors fixed during adaptation, $\psi(r)$. Remarkably, $\psi(r)$ remains nearly exponential even under absolute mutational effects. Moreover, this result is roughly independent of when during adaptation the population is analysed. As Fig. 2 shows, $\psi(r)$ is nearly exponential whether we study the population after it has traversed 75%, 90% or 95% of the distance to the optimum (in all cases, over 12000 substitutions were sampled in 200–500 replicate walks to the optimum). Essentially identical results were obtained for other dimensions and for other exponential $m(r)$ having various small means (results not shown).

These results are *not* an artefact of assuming that $m(r)$ is itself exponential. Fig. 3 shows the distribution of factors fixed with mutations are gamma distributed with shape parameter $\beta = 0{\cdot}5$ and the mean muta-

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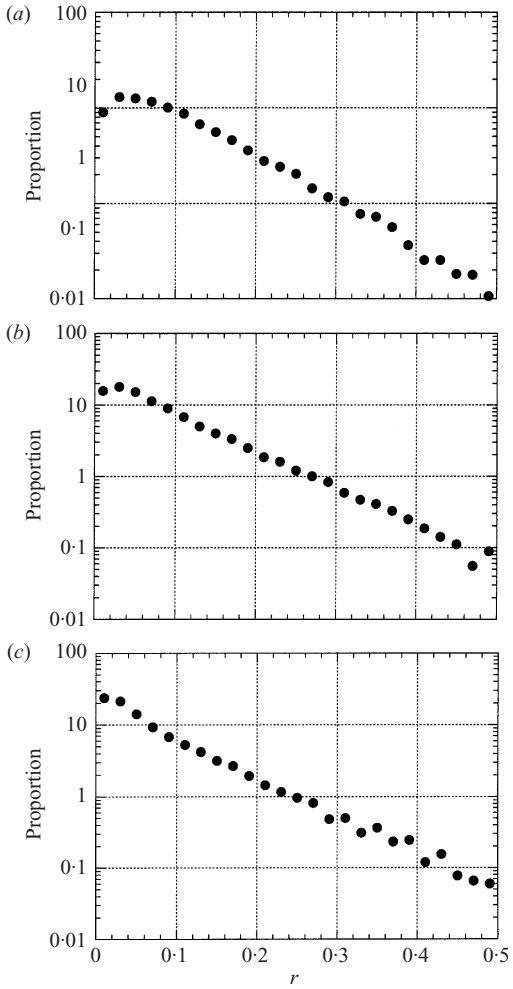

Fig. 3. The distribution of factors fixed given absolute mutational effects that were gamma distributed with shape parameter $\beta = 0{\cdot}5$ and scale parameter $\alpha = 5$ (thus $\bar{r} = 0{\cdot}1$). In all cases, over 16000 substitutions were sampled over 250–750 replicate walks to the optimum at $n = 25$ dimensions.

tional effect remains $\bar{r} = 0{\cdot}1$. Once again, $\psi(r)$ is exponential and, once again, this result is roughly independent of distance to the optimum travelled (in all cases, over 16000 substitutions were sampled in 250–750 replicate walks to the optimum).

Analysis of many different absolute mutational distributions with many different means reveals that $\psi(r)$ remains nearly exponential whenever: (1) small mutations are more common than large; and (2) the mean mutation is small relative to the starting distance from the optimum. The precise shape of $m(r)$ and the precise distance to the optimum travelled are of little significance, as long as the latter is reasonably large. Fortunately, these conditions correspond to the biologically relevant ones: small mutations are almost certainly more common than large and genetic analysis is only performed when the phenotypic difference between taxa is large – far larger than the effect of the average random mutation. (In Bradshaw *et al.*'s (1998) study, for instance, the *Mimulus* species analysed differed by more than 7 phenotypic standard deviation units at 8 of 12 traits.)

It is also worth noting that the previously curious finding that $\psi(r)$ is exponential even when $m(r)$ is uniform (i.e. even when small mutations are *not* more common than large) has a simple explanation. The uniform distribution – like any power law distribution – is scale-free. This property ensures that adaptation remains self-similar throughout a walk to the optimum. Extensive simulations (not shown) confirm that $\psi(r)$ remains exponential under *any* reasonable power law distribution of mutational effects, e.g. when $m(r)$ varies as r^{-2}, r^{-1}, $r^{-1/2}$ or r^{0}.

The exponential trend thus appears quite robust, arising under far broader conditions than considered before.

4. Single characters

We now turn to a subtler issue. By the 'magnitude' of a mutation, Fisher (1930) and Kimura (1983) meant its total phenotypic effect when summing over all characters. Similarly, the distribution of factors fixed discussed above concerns the total phenotypic effect of alleles. But in any real genetic analysis we cannot hope to measure the total phenotypic effect of a gene. We can only measure a QTL's effect on a *particular* character or on some small suite of characters. We are thus left with an important unresolved question: What is the distribution of phenotypic effects among factors fixed in adaptation when considering *single* characters? Is it also roughly exponential or does it assume some qualitatively different shape?

The answer will clearly depend on what we consider a 'character'. In some (fortunate) cases a character might well correspond to something approximating a mutation's total phenotypic effect. That is, if we consider some composite character, e.g. a complex organ, that is more or less independent of the remainder of the organism, Fisher's geometric model might sensibly pertain to this organ alone, not to the organism. (Indeed Fisher sometimes spoke as though his model referred to a single complex organ, e.g. the vertebrate eye.) For such a complex character we already know the distribution of phenotypic effects fixed during adaptation: it is exponential.

It seems more natural, however, to think of a measured character as corresponding to a single dimension in Fisher's model or perhaps to a linear combination of dimensions. We would like, therefore, to describe the distribution of gene effects arising during adaptation for such simple characters.

Some progress can be made analytically. It can be shown that the distribution of projections onto a single dimension, $f(r_i)$, given random mutations of constant total magnitude r is approximately normal

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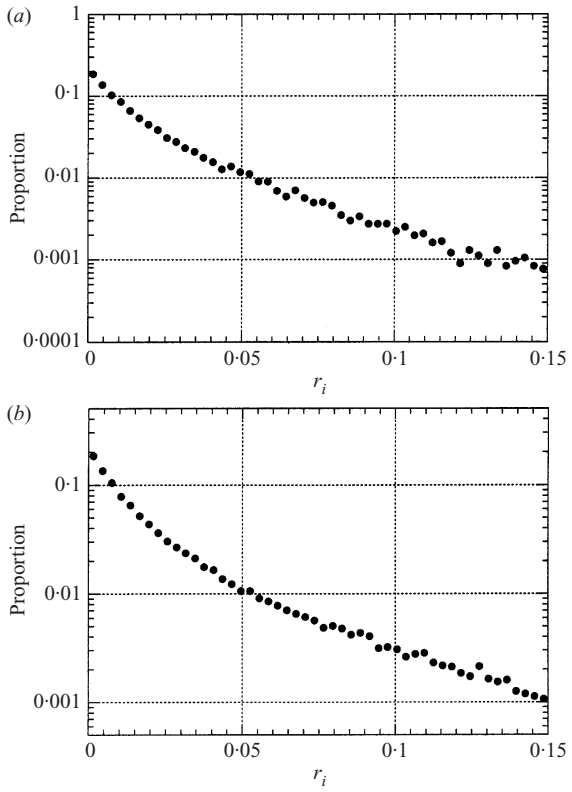

Fig. 4. The distribution of phenotypic effects for *single* characters among factors fixed during adaptation (semilog plots). (*a*) The case in which all n characters begin equally maladapted. Data derive over 32000 substitutions sampled in 1000 replicate walks to the optimum at $n = 25$. (*b*) The case in which characters begin *unequally* maladapted. Data correspond to the initially most maladapted character. Data derive over 32000 substitutions sampled in 1000 replicate walks to the optimum at $n = 25$.

($f(r_i) = (\sqrt{n}/\sqrt{2\pi}\, r) \exp[-nr_i^2/(2r^2)]$), with a mean per character (absolute) effect of

$$E[|r_i|] = \frac{2}{\pi}\frac{r}{\sqrt{n}}. \quad (1)$$

Because (1) is linear in r, it remains correct over an entire walk to the optimum, i.e. if we take r to refer to the mean mutation fixed during adaptation. Put differently, the mean gene effect on a single character equals the mean effect over all characters standardized by a factor of order $1/\sqrt{n}$, as claimed in Orr (1998).

However, to find the *distribution* of gene effects for a single character in a walk to the optimum we must turn to computer simulations. These simulations differ from those above only in that we now track projections onto all single dimensions. For simplicity, we consider Kimura's case of uniform mutational effects.

In the simplest scenario, all characters begin equally maladapted. Letting the population evolve 90% of the way to the optimum, Fig. 4*a* shows the resulting distribution of factors fixed for a single character. Although this distribution is clearly not perfectly exponential, it shows a strong exponential trend. (Indeed given the far from perfect resolution of real genetic analysis, it is difficult to believe that one could distinguish experimentally between a strictly exponential distribution and that in Fig. 4*a*). As expected, the mean gene effect on a single character is correctly predicted by (1).

We can also consider the more realistic case in which some characters begin far more maladapted than others. Fig. 4*b* shows the resulting distribution of gene effects in this case for an arbitrarily chosen character (see figure legend for details). Once again, the distribution of gene effects, while not perfectly exponential, shows a strong exponential trend. Analysis of many different characters, including ones that were initially very maladapted as well as ones that were initially well adapted reveals the same pattern. While the distribution of total phenotypic effects is almost perfectly exponential, that for single characters is roughly so.

Last, I considered the case in which the environment changes suddenly, throwing the population off the optimum in a random direction; the population is then allowed to walk adaptively back towards the optimum (in all cases the population begins unit distance from the optimum). The simulation results for single characters were indistinguishable from those in Fig. 4*a*, *b* (not shown).

Furthermore, in all the cases considered above, the distribution of gene effects for linear combinations of characters also shows a strong exponential trend.

The exponential trend thus seems to provide a robust (though approximate) expectation about the genetics of adaptation. Importantly, this pattern is roughly independent of the details of just how our measured character maps onto Fisher's model.

5. Concluding remarks

Our understanding of the genetics of adaptation remains appallingly weak. The problem involves both a shortage of rigorous genetic analyses of natural adaptations as well as a nearly complete absence of relevant theory. While early work by Robertson, Falconer and others suggested that the infinitesimal view of response to selection is incorrect (indeed Falconer & Mackay's (1996) latest text announces that 'the "infinitesimal" model … is clearly disproved'), evolutionists have been slow to consider theoretical alternatives. A number of authors, however, have recently suggested that Fisher's (1930) geometric model may allow considerable insight into adaptation (Rice, 1990; Hartl & Taubes, 1996, 1998; Orr, 1998). Although obviously an idealization – like

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the infinitesimal one before it – Fisher's model enjoys two strengths. First, by explicitly trading in mutations of measurable phenotypic effects, it provides a way of systematically mapping phenotypic effects onto fitness effects. As Barton (1998) and Harl & Taubes (1998) have emphasized, traditional population genetics sidesteps this problem by *beginning* with alleles of known selective advantage and makes no attempt to explain the origin of selection coefficients. (For this and other reasons, Hartl & Taubes (1998) conclude that 'classical population genetic models … are not well-suited to address the problems of the origin, progression, and limit of adaptation'.) Secondly, Fisher is surely right that, although idealized, his model captures the 'statistical requirements of the situation' of adaptation, namely that one complex system (the organism) must be made to conform to another (the environment).

By requiring that evolution in Fisher's model obey the laws of population genetics, e.g. probabilities of fixation, we can ask whether adaptation in this broadest sense of conformity shows any statistical regularities.

At least one such regularity has been identified. The factors fixed during adaptation show a nearly exponential distribution of phenotypic effects. Here I have explored the generality of this result, finding it to be reasonably robust to changes in both the distribution of mutational effects (absolute versus relative) and, to a lesser extent, the nature of the character analysed (total phenotypic effect versus single character versus linear combination of characters).

It would appear, then, that roughly exponential distributions of gene effects should characterize adaptation towards a fixed optimum. Although present genetic data are crudely consistent with this prediction (Orr, 1998), rigorous testing must obviously await far more powerful quantitative genetic analyses of natural adaptations. At the very least, it should be clear that such analyses need not proceed in a theoretical vacuum.

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