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MODULARITY AND THE COST OF COMPLEXITY

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Abstract.—In this work we consider the geometrical model of R. A. Fisher, in which individuals are characterized by a number of phenotypic characters under optimizing selection. Recent work on this model by H. A. Orr has demonstrated that as the number of characters increases, there is a significant reduction in the rate of adaptation. Orr has dubbed this a ''cost of complexity.'' Although there is little evidence as to whether such a cost applies in the natural world, we suggest that the prediction is surprising, at least naively. With this in mind, we examine the robustness of Orr's prediction by modifiying the model in various ways that might reduce or remove the cost. In particular, we explore the suggestion that modular pleiotropy, in which mutations affect only a subset of the traits, could play an important role. We conclude that although modifications of the model can mitigate the cost to a limited extent, Orr's finding is robust.

Key words.—Adaptation, evolutionary rates, Fisher's geometrical model, modularity, pleiotropy.

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What factors determine the rate of adaptive evolution? Suggested answers to this question have emerged from within theoretical population genetics (e.g., Maynard Smith 1976; Barton and Partridge 2000), evolutionary ecology (e.g., Resnick and Ghalamber 2001), and evolutionary developmental biology (e.g., Raff and Raff 2000). In an important recent paper a new factor has been identified. Orr (2000) investigated a theoretical model of multiple quantitative characters under optimizing selection. He showed that as the number of phenotypic characters under selection increases, there is a dramatic slow-down in the population's rate of adaptation, as measured for example by its expected increase in fitness over time. Orr dubbed this slow-down the ''cost of complexity.'' Throughout this work, we follow Orr and use the term ''complexity'' to correspond to the number of traits under selection. Thus, with this usage, organisms with a few traits under selection are less complex than organisms with a larger number of traits under selection.

Orr's (2000) paper makes use of the geometrical model introduced by Fisher (1930, ch. 2) and described fully below. Fisher's model has been used elsewhere in a series of key papers investigating such topics as the genetics of adaptation (Hartl and Taubes 1998; Orr 1998, 1999), hybridization (Barton 2001), and drift load (Hartl and Taubes 1996; Peck et al. 1997; Poon and Otto 2000). Furthermore, the basic picture of selection is familiar from numerous theoretical quantitative genetic studies—the key differences being the rate of mutations and their distribution of effects (Barton 2001). To the extent that this much-used model makes a strong prediction, it is important to ask whether the cost of complexity applies in the natural world. Unfortunately, we have little evidence to guide us here. Relating Fisher's model to empirically measurable quantities is problematic (Barton 1998), and all definitions of phenotypic complexity are contentious (Bonner 1988; Valentine 2000 and references therein). The range of studies on contemporary microevolution available (Hendry and Kinnison 1999; Bone and Farres 2001; Kinnison and Hendry 2001) does not allow us to begin to ask the question in a rigorous manner. However, naively, it is surprising that such a substantial cost should be predicted. For example, in their review of empirical studies of rapid adaptive evolution in natural populations Resnick and Ghalamber (2001) note that the majority of their examples involve complex characters and express surprise at this given Orr's (2000) finding. Indeed if a substantial cost does exist, then the very existence of phenotypic complexity in the world seems puzzling, particularly given the key role of rapid evolution in preventing population extinction (e.g., Lynch and Lande 1993).

In this study we further explore Fisher's model and its extension by Orr, with particular regard to the cost of complexity. In particular, we make three advances. First, we test the extent to which the cost is a robust feature of the model; we do this by varying the original treatment with some alternative, biologically reasonable assumptions. Second, we examine the claim that the rate of evolution of complex phenotypes could be accelerated through some sort of phenotypic modularity. Finally, we ask if there might be key features of the natural world absent from Fisher's model that might scale in a consistent way with phenotypic complexity. All three of these advances follow up on suggestions in Orr (2000). We begin by presenting a general framework for the investigations.

SINGLE-MUTANT ADAPTIVE WALKS

In this paper, we consider the process of adaptation as a single-mutant adaptive walk in a population of haploids. Time is measured in events, where an event is the fixation or loss of a newly arisen mutation, and we assume that at any instant there is, at most, one mutation segregating in the population. This approach, related to the strong-selection-weak-mutation approximation of Gillespie (1983, 1991), is common to most of the recent work on Fisher's model and other unrelated work (e.g., Maynard Smith 1970; Kauffman and Levin 1987; Metz et al. 1996; Orr 2002). We use the approach to remove the influence of mutation rate, levels of dominance, population size, and reproductive mode, all of which influence the rate of adaptation, but are not the focus here (Maynard Smith 1976;

Barton 2001). Results can be easily modified to apply to diploids when dominance is intermediate and are qualitatively unaltered. The mutation arising at time t has a selection coefficient, s_t, that is defined in the usual way for multiplicative models:

$$s_t = \frac{W_t'}{W_t} - 1, \tag{1}$$

where W_t' (W_t) is the fitness of a mutated (nonmutated) individual. Under these assumptions, it is clear that if a mutation reaches fixation, then the population's fitness becomes $W_{t+1} = (1 + s_t)W_t$. The probability that a mutation with selection coefficient s fixes is denoted by $\Pi(s)$. In a multiplicative fitness model, it is natural to express the dynamics in terms of the natural logarithm of fitness. The expected change in log fitness, from event t to event $t + 1$ is then

$$\begin{aligned} E[\ln W_{t+1} - \ln W_t] &\equiv E[\Delta \ln W_t] \\ &= E[\ln (1 + s_t)\Pi(s_t)] \qquad (2) \\ &\equiv \int_{-1}^{\infty} \phi_t(s)\ln(1 + s)\Pi(s)\, ds. \qquad (3) \end{aligned}$$

Here, $\phi_t(s)$ denotes the probability distribution of selection coefficients at time t. Note that the expectation, $E[\ldots]$ above, is taken over replicate populations, each of which is identical at time $t = 0$, and monomorphic during the majority of time when no mutation is segregating. However, different replicate populations will have different evolutionary histories due to the stochastic appearance, fitness effects, and loss of new mutations by genetic drift. For completeness we give details, in Appendix 1, of the full stochastic process underlying equations (2) and (3).

Again, following Orr (2000), we restrict ourselves to a population sufficiently large that only beneficial mutations, that is, those with $s > 0$, can reach fixation. In this case Haldane (1927) showed that when offspring number is Poisson-distributed and selection coefficients are small, the fixation probability is given by the approximation

$$\Pi(s) \simeq \begin{cases} 0, & s \le 0 \\ 2s, & s > 0. \end{cases} \tag{4}$$

Additionally, small s allows us to use $s \approx \ln(1 + s)$, thereby allowing equation (3) to be written in the useful approximate form

$$E[\Delta \ln W_t] \simeq 2 \int_0^{\infty} \phi_t(s)[\ln(1 + s)]^2\, ds. \tag{5}$$

We now turn to an examination of Fisher's model.

Fisher's Geometrical Model

Under Fisher's model an organism is uniquely characterized by the values of n quantitative characters. When a mutation occurs, it generally changes all n traits, thus the model exhibits universal pleiotropy. We collect the n trait values and the n changes due to mutation into n-dimensional vectors, which we denote $\mathbf{z}(t)$ and $\Delta\mathbf{z}(t)$:

$$\mathbf{z}(t) = [z_1(t), z_2(t), \ldots, z_n(t)] \quad \text{and} \tag{6}$$

$$\Delta\mathbf{z}(t) = [\Delta z_1(t), \Delta z_2(t), \ldots, \Delta z_n(t)]. \tag{7}$$

It is this picture of the phenotypic state of an organism as a point in an n-dimensional space and a mutation as a vector of change in that space that makes the model geometrical.

Fitness is determined by the distance of each of the characters from its optimal value. Each trait is taken to be under independent selection, so its optimal value is a feature of the environment and does not depend on the state of the other traits. Without loss of generality, we set the optimal value of all traits to be zero. We take a Gaussian scheme of selection, where all traits are subject to the same intensity of selection. Here, for simplicity and following Orr (2000), we take this intensity to be one; this has no effect on our conclusions concerning the cost of complexity, as shown in Appendix 4. With these assumptions, the fitness of the population prior to mutation, W_t, and the fitness of a mutated individual, W_t', are given by

$$W_t = \exp\left[-\frac{1}{2}\|\mathbf{z}(t)\|^2\right] \quad \text{and} \tag{8a}$$

$$W_t' = \exp\left[-\frac{1}{2}\|\mathbf{z}(t) + \Delta\mathbf{z}(t)\|^2\right], \tag{8b}$$

where double vertical bars denote the Euclidean length of the vector: $\|\mathbf{z}\| = \sqrt{z_1^2 + z_2^2 \cdots + z_n^2}$. An explicit form for the quantity $\ln(1 + s_t)$ appearing in equation (2) follows from equations (1) and (8):

$$\begin{aligned} \ln(1 + s_t) = \ln\left(\frac{W_t'}{W_t}\right) &= \frac{1}{2}[\|\mathbf{z}(t)\|^2 - \|\mathbf{z}(t) + \Delta\mathbf{z}(t)\|^2] \\ &= -\mathbf{z}(t)\cdot\Delta\mathbf{z}(t) - \frac{\|\Delta\mathbf{z}(t)\|^2}{2} \\ &= -\|\mathbf{z}(t)\| r \cos\theta - \frac{r^2}{2} \qquad (9) \end{aligned}$$

where $\mathbf{z}(t)\cdot\Delta\mathbf{z}(t)$ is the scalar (or dot) product of the vectors $\mathbf{z}(t)$ and $\Delta\mathbf{z}(t)$, θ is the angle between $\mathbf{z}(t)$ and $\Delta\mathbf{z}(t)$ and $r = \|\Delta\mathbf{z}(t)\|$ is the magnitude of the change associated with a mutation. It is clear from equation (9), that the selection coefficient is a function of the three variables, $\|\mathbf{z}(t)\|$, θ, and r. Figure 1 shows a graphical representation of Fisher's model with these three quantities labeled. It is also clear that the all-important distribution of selection coefficients, $\phi_t(s)$ of equation (3), must be derived from the distributions of these three variables. The first two variables present few problems. First, it will shortly be evident that only the mean value of $\|\mathbf{z}(t)\|^2 = -2\ln(W_t)$ will be necessary for our calculations, and second, the distribution of the angle, θ, can be found from geometric considerations under the assumption that mutations are equally likely in all ''directions'' (see Fig. 1 and Appendix 2 for full details).

We discuss the third variable, r, at greater length, because it marks our first departure from Orr (2000). This variable is the overall magnitude of mutational change across all phenotypic traits, and we denote its distribution by $p(r)$. Orr (2000) treats r as fixed parameter, so all mutations have the same magnitude, but it seems more realistic to allow some

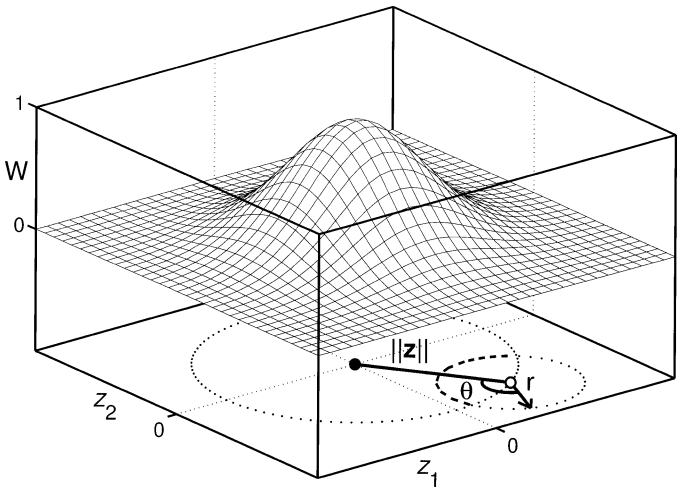

FIG. 1. A graphical representation of Fisher's geometrical model is shown for the case of two traits, $n = 2$. In the upper half of the plot the fitness, W, is plotted as a function of the two trait values z_1 and z_2. The fitness landscape is seen to decline smoothly with distance from the phenotypic optimum, which lies at $(z_1, z_2) = (0, 0)$. In the lower half of the plot, this optimum is represented by a filled dot. The unfilled dot represents the current state of a population and the arrow stemming from this point represents a mutational change, Δz. The labels show the three quantities that appear in equation (9), namely $\|\mathbf{z}\|$, the distance of the population from the optimum; r, the magnitude of the mutational change, and θ, the angle between z and Δz. The two dotted circles demonstrate the isotropy of the model. As regards fitness, any population lying on the circle with radius $\|\mathbf{z}\|$ will have the same fitness as the population shown. As regards mutation, all points on the circle with radius r are equally likely to be reached by a single mutation. The dashed arc shows the proportion of those mutations that are closer to the optimum than the parental population and are thus beneficial (with $s > 0$).

variation, as Orr himself does in a different context (Orr 1998, 1999). The distribution $p(r)$ must simply be specified as part of the model, and in the absence of much empirical evidence, different authors have made different choices (see below). For these reasons we present results that apply to a broad class of distributions of mutation magnitudes. This class of distributions will be characterized by two important parameters. The first is a single length parameter, denoted ρ, and taken to be the mean value of the distribution. The second is a shape parameter, denoted a, that describes how the distribution behaves for very small r. We define these parameters via

$$E[r] \equiv \rho \quad \text{and} \tag{10}$$

$$p(r) \propto r^{(a-1)}, \tag{11}$$

for $r \to 0$, where $a > 0$.

The condition $a > 0$ ensures the distribution $p(r)$ is normalizable. In Appendix 4, we specify the full class of $p(r)$ considered in this work, but note that the class includes almost all of the distributions considered previously for Fisher's model. These distributions include the uniform distribution (Kimura 1983; Orr 1999) and the exponential distribution (Orr 1999; Poon and Otto 2000; Barton 2001) for both of which $a = 1$; as well as the more general family of gamma distributions (see eq. (A3) in Appendix 3) and other power law distributions (Orr 1999). Our results also apply to the special case of fixed-magnitude mutations (Orr 2000), which can be treated as a form of the gamma distribution for which $a \to \infty$ (see Appendix 3).

Although we have little evidence to guide us on the exact form of the distribution of mutation magnitudes, $p(r)$, we do have empirical measurements of the effects of mutations on single traits, and, to a lesser extent, of their fitness effects, both of which are distributions that are related to $p(r)$. Our choice of $p(r)$ should be consistent with the available data on these distributions, in particular, the finding that the distribution of mutation effects on single traits tends to be leptokurtic (e.g., Keightley and Ohnishi 1998; Garcia-Dorado et al. 1999; Welch and Waxman 2002) and the existence of a large class mutations with very small fitness effects (e.g. Kimura 1983; Davies et al. 1999). As set out in Appendix 3, both lines of evidence suggest that $a \ll n$ might be appropriate but offer little guidance beyond this. As such, we keep the results in the text general. However, to give an indication of how $p(r)$ can influence the distribution of selection coefficients, $\phi_t(s)$, Figure 2 shows $\phi_t(s)$ for fixed, uniformly distributed, and gamma-distributed mutation lengths.

Figure 2 shows clearly that changing the distribution of mutation magnitudes, $p(r)$, is not merely a cosmetic change to the model. Different $p(r)$ values lead to qualitatively different distributions of selection coefficients, $\phi_t(s)$, the distribution that governs the rate of adaptation; see equation (3). Figure 2a, shows that with fixed-length mutations, the distribution $\phi_t(s)$ is maximized for quite large negative selection coefficients (see Appendix 3). By contrast, Figure 2b shows that uniformly distributed mutation magnitudes yield a $\phi_t(s)$ that is singular (with an infinite spike) in the vicinity of $s = 0$. Figure 2c shows that for gamma-distributed mutation magnitudes with a large shape parameter ($a = 4$), this spike is lost, but there is, nevertheless, a concentration of very small-effect mutations. We also note another difference between fixed and variable magnitude mutations. With fixed magnitude mutations (Fig. 2a), adaptation can only continue until the population lies at a certain distance from the optimum, until $\|\mathbf{z}(t)\| < \rho/2$. After this, no beneficial mutations can be generated (see Fig. 1). By contrast, with continuous magnitude mutations (Figs. 2b, 2c), adaptation can continue indefinitely because arbitrarily small effect mutations can be produced. As such, only variable-magnitude mutations allow us to examine the cost of complexity for a population that is well adapted.

We can now write equation (5), the rate of change of log fitness, in a form that applies specifically to Fisher's geometrical model. The derivation is set out in full in Appendix 4, and yields a simple difference equation for $E[\ln W_t]$:

$$E[\Delta \ln W_t] \simeq \frac{-4E[\ln W_t]\rho^2}{n} \times F\left(\frac{-4E[\ln W_t]}{n\rho^2}\right). \tag{12}$$

Here $F(\cdot)$ is function whose exact form is determined by the distribution of the mutation magnitudes, $p(r)$. However, in Appendix 4, we show that, for the broad class of $p(r)$ described above, $F(x)$ is an increasing function of x. This means that any decrease of the argument of F in equation (12) will always decrease the value of F and hence decrease the rate

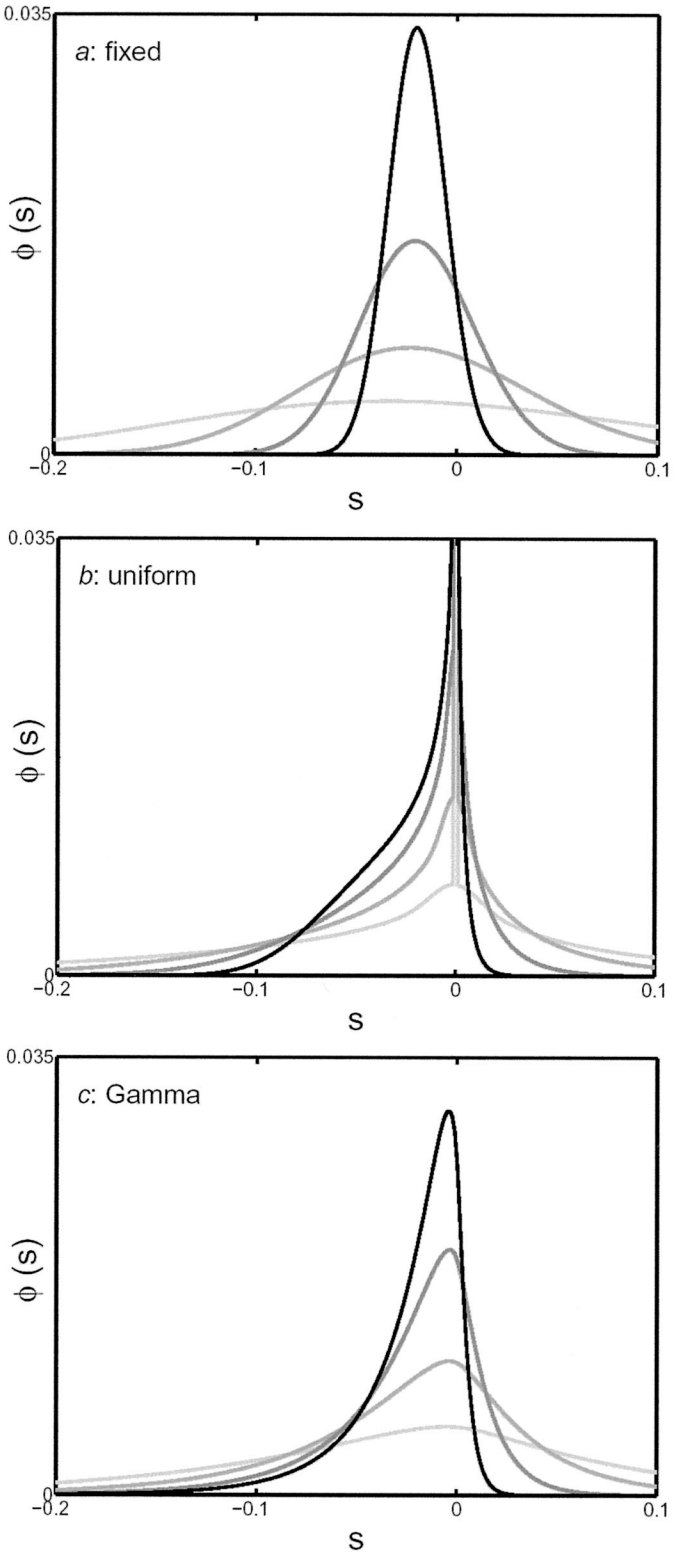

FIG. 2. The distribution of selection coefficients, $\phi_t(s)$, is plotted for three different distributions of overall mutation magnitudes, $p(r)$. (a) shows $\phi_t(s)$ for fixed-magnitude mutations, where all mutations have magnitude ρ. (b) shows $\phi_t(s)$for mutation magnitudes that are uniformly distributed on the range [0, 2ρ]. In (c), mutation magnitudes are gamma distributed (see eq. A3). Each plot shows four different values of the distance, $\|\mathbf{z}\|$, of the population from the optimum, with the population becoming more adapted as the curves become darker. From light to dark, the plots show $\|\mathbf{z}\| = 2$, 1, 0.5, and 0.25. All plots take the same number of traits: $n = 12$, and the same mean magnitude of a mutation: $\rho = 0.2$. In (c) the shape parameter is taken as $a = 4$. In (a, b) it implicitly takes the values $a = \infty$ and $a = 1$, respectively (see Appendix 3).

of adaptation. When the magnitude of mutations is fixed, equation (12) is equivalent to Orr's (2000) equation (7b). Indeed, examining equation (12) allows us to draw a number of conclusions that were all noted by Orr (2000) for the case of fixed-length mutations and are here shown to hold also in the case of variable length mutations. The conclusions follow by noting where the quantities ln W_t, ρ, and n, appear in the right of equation (12).

First, as mean fitness increases, $-E[\ln W_t]$ decreases, and this will always decrease the rate of adaptation. Second, because ρ appears in the numerator of the first factor of equation (12), but in the denominator of the argument of F, an intermediate mean length of mutation, balancing these two factors, will maximize the rate of adaptation. This was the insight of Kimura (1983), who pointed out that while the very smallest mutations have the highest probability of being beneficial (Fisher 1930) they are subject to the weakest selection, and as such, have little chance fixing. We show in Appendix 4 that the balance will hold for the broad class of $p(r)$.

Third, and most importantly for this paper, the number of traits, n, appears in the denominator in both factors on the right side of equation (12), and so increasing n will always decrease the rate of adaptation. Furthermore, it is clear that the decrease in the rate of adaptation will generally be greater than n^{-1} because the first factor alone shows this rate of decline. This observation, that the higher the value of n, the slower the rate of adaptation, embodies the cost of complexity demonstrated by Orr (2000).

Although the minimum cost of complexity follows directly from examining equation (12) as Orr (2000) pointed out, the cost can be much greater. To quantify this, we need to examine the function $F(x)$. In Figure 3 we show the form of $F(x)$ for the three choices of $p(r)$ used in Figure 2 above. The first thing to notice is how remarkably similar the three curves are over this range, despite their very different distributions of selection coefficients (Fig. 2). Because the gradients displayed in the figure are substantial, it is clear that the function F can affect the cost of complexity. To see this in detail, consider what happens when the argument to F is very small or very large: see Appendix 4 for full details. We find

$$F\left(\frac{2\|\mathbf{z}\|^2}{n\rho^2}\right) \propto n^{-(1+a/2)}, \qquad \text{for } \frac{2\|\mathbf{z}\|^2}{n\rho^2} \ll 1 \quad \text{and} \tag{13}$$

$$F\left(\frac{2\|\mathbf{z}\|^2}{n\rho^2}\right) \simeq \frac{1}{2}[\mathrm{CV}^2(r) + 1], \quad \text{for } \frac{2\|\mathbf{z}\|^2}{n\rho^2} \gg 1, \tag{14}$$

where CV(r) is the coefficient of variation (standard deviation divided by mean) of the distribution of mutation magnitudes, $p(r)$. These approximations yield interesting insights. Equation (13) will apply whenever the population is well adapted or when the distance from the optimum is small compared with the mean magnitude of a mutation ($\|\mathbf{z}\|/\rho \ll 1$). In this regime the cost of complexity is substantially more than the

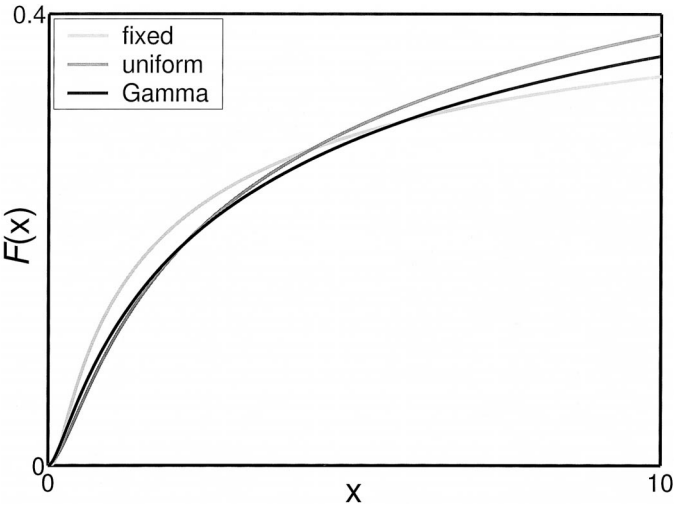

FIG. 3. The function $F(x)$, appearing in equation (12), is plotted as a function of x. The three forms of $F(x)$ plotted correspond to the three different distributions of mutation magnitudes, $p(r)$, as used in Figure 2 (see Fig. 2 caption). Using these distributions of mutation magnitudes, $F(x)$ can be found in terms of standard functions. The values of x plotted cover a plausible range of values of the argument of F (see the discussion in the text), and over this range, the three distributions of mutation magnitudes yield surprisingly similar curves. For (perhaps implausibly) large arguments of F, the curves asymptotically approach widely different values that can be found from eq. (14). The definition of F is given in equation (A19) and uses equations (A2) and (A16).

minimum cost, which arises from just the first factor on the right side of equation (12). Combining the contributions from the two factors on the right side of equation (12), yields a cost proportional to $n^{-1} \times n^{-(1+a/2)} = n^{-(2+a/2)}$. By contrast, when the argument to F is large, the function reaches a constant value given by equation (14), that shows no dependence on n (perhaps less obviously, this quantity will also be independent of ρ). In this regime, where the population's distance from the optimum is large compared with the mean magnitude of a mutation, the minimum cost of complexity, n^{-1}, is paid. We note, however, that the convergence to equation (14) is in general slow and even if mutations are very small ($\rho^2 n \sim 1$), to have a $\|\mathbf{z}\|$ of sufficient magnitude for this regime to apply implies an enormous genetic load. We will consider both regimes—small argument, and large argument—in what follows, but we expect the former to be the most relevant.

The main conclusion of this section is that the cost of complexity is robust to the inclusion of variable length mutations. This was not obvious considering that continuously distributed mutation lengths make qualitative differences to the distribution of selection coefficients, $\phi_t(s)$ (see Fig. 1). We now discuss further alterations to the assumptions of the model.

Constant Mean Mutational Change Per Trait

The result of equation (12) depends strongly on the assumption that the mean overall magnitude of a mutation, $\rho = E[r]$, remains constant for all levels of complexity, that is, for all n. This has the consequence that the average mutational change per trait declines rapidly with n. This follows because $\|\mathbf{z}(t)\|^2$ suffers a mutational change of r^2, so the mean square change in any single trait is $E[r^2]/n \propto \rho^2/n$ for the class of $p(r)$ considered (also see Orr 1998, 1999). It is not clear that this decline with n is the most biologically reasonable assumption, and so we examine the alternative assumption: that the average mutational change per trait remains independent of n. We achieve this by allowing ρ to vary with n, such that the mean square change in any single trait remains constant across all levels of complexity. With this end, we introduce an n-independent constant, ρ^* via

$$\rho \equiv \rho(n) = \rho^* \sqrt{n}. \tag{15}$$

With this alternative assumption about mutation we find

$$E[\Delta \ln W_t] \simeq -4E[\ln W(t)]\rho^{*2} \times F\left\{\frac{-4E[\ln W(t)]}{n^2\rho^{*2}}\right\}. \tag{16}$$

Note that the first factor on the right side of this equation is now independent of n, and so part of the cost of complexity has vanished. Indeed when, the argument of F is large and the approximation of equation (14) applies, no cost applies at all. However, the inclusion of n^{-2} rather than n^{-1} in the argument of F makes the attainment of the large argument regime even less plausible. On the contrary, when the argument is small, a state that becomes more likely due to the n^{-2}, we have, by extension from equation (13),

$$F\left(\frac{2\|\mathbf{z}\|^2}{n^2\rho^{*2}}\right) \propto n^{-(2+a)}, \qquad \frac{2\|\mathbf{z}\|^2}{n^2\rho^{*2}} \ll 1. \tag{17}$$

So here, when the argument of F is small, the total cost of complexity is $n^{-(2+a)}$. Comparing this with the result for unscaled mutation, $n^{-(2+a/2)}$, it is clear that the cost can be more severe with scaled mutation—and significantly more with high a.

We conclude that holding the mean mutational change per trait constant as the number of traits increases can lead to a situation where the rate of adaptation too is independent of the number of traits, thus removing the cost of complexity. However, such a situation is unlikely, and under plausible conditions, when a population is close to its phenotypic optimum, the cost is more severe. Again, Orr's observation is robust to a change in assumptions.

Modularity

Given that the cost of complexity is a robust phenomena, Orr's (2000) identification of an important evolutionary advantage to reducing the number of effectively independent characters comprising an organism, remains compelling. He suggests that this might be achieved by developmentally ''bundling'' characters, and relates this to the notion of ''modularity'' as present in the work of Wagner and others (Wagner 1996; Wagner and Altenberg 1996; Baatz and Wagner 1997). Barton and Partridge (2000) make a similar claim, suggesting that many of the regulatory processes listed by Kirschner and Gerhart (1998) as facilitating the evolvability of metazoans, could be modeled as a reduction in the dimensionality of Fisher's model. The notion that features of the developmental system act to somehow facilitate adaptive evolution, or to increase ''evolvability,'' has been a much

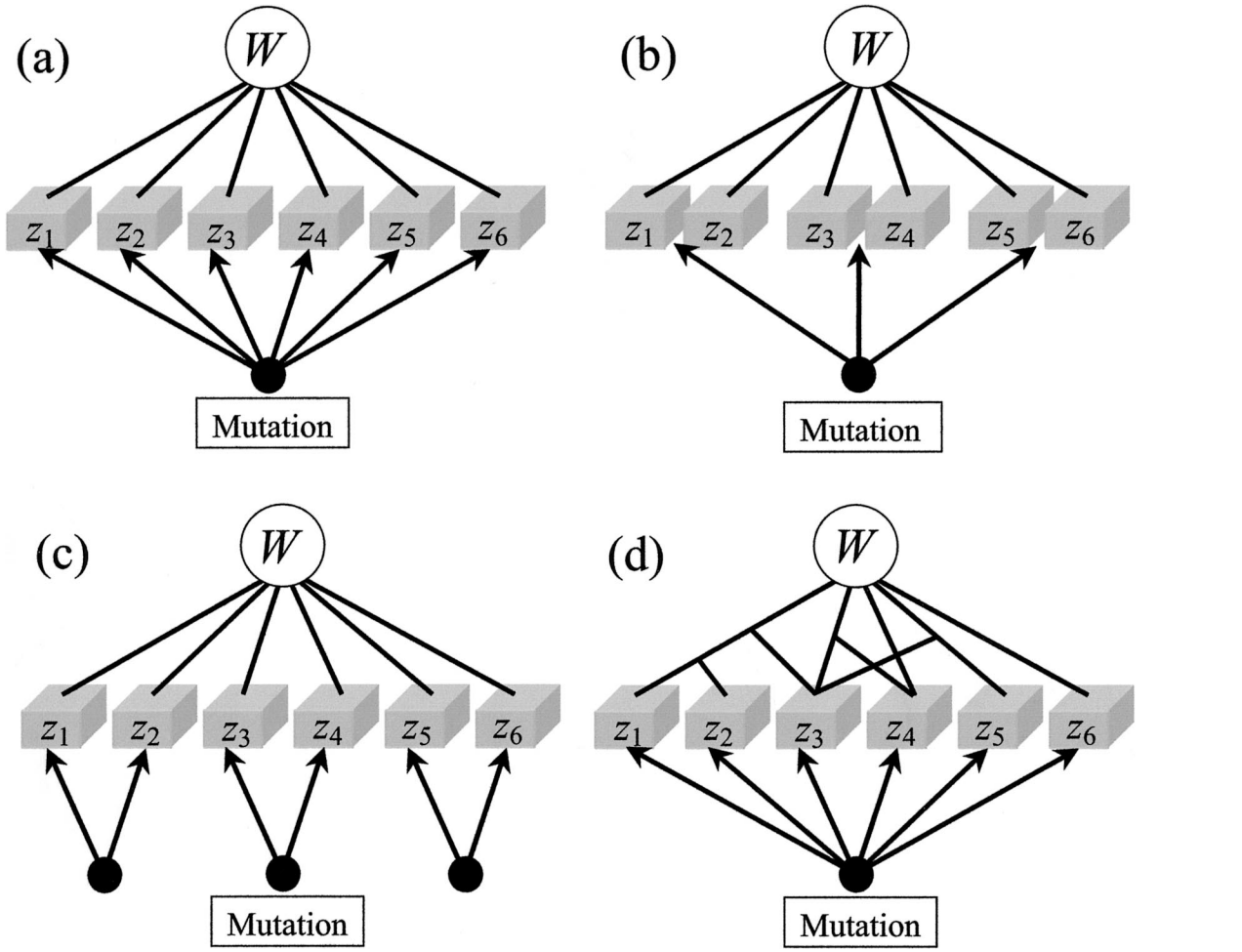

FIG. 4. The interactions between mutations, traits, and fitness, *W*, are depicted for four variations on Fisher's geometrical model, each with six traits, $n = 6$. (a) shows the original model without modularity. Pleiotropy is universal in that each mutation affects all traits, but the mutational change in each trait is independent of the changes to other traits, such that the expected genetic correlation between any two traits is zero. (b) represents one possible interpretation of modularity. Pleiotropy is still universal, but pairs of traits are subject to the same mutational effect. This reduces the dimensionality of the phenotypic space in which the population can move from 6 to 3. However, as the top half of the diagram shows, each trait still alters fitness independently (see text). (c) represents another interpretation of modularity and the model examined in this paper (e.g., eq. 19). Groups of traits are parceled through a restriction of the pleiotropic effect of mutations into $m = 3$ modules. (d) represents a particular case of fitness interactions among a set of traits, with the phenotypic state of certain traits altering selection on other traits. This is a characteristic of the evolutionary process absent from Fisher's model (see Discussion).

discussed topic within evolutionary developmental biology (Wagner and Altenberg 1996; Kirschner and Gerhart 1998; Raff and Raff 2000; Barton and Partridge 2000) and modularity has been a central concern. Though modularity (like complexity) is a slippery concept, the key idea is that further adaptation should not undo adaptation previously achieved, that a change to one part should not disrupt the whole system (Barton and Partridge 2000).

We would suggest that this notion is not well captured by a reduction in the dimensionality of the phenotypic space in which the population can evolve. The bundling of two characters, in this particular sense, would not mean that a change in other characters would leave them undisturbed—universal pleiotropy ensures that they probably would be altered. Rather, it would prevent either of the characters from evolving independently; a change in one character would imply a change in a given direction in the other. Figure 4b depicts this kind of modularity, and Figure 4a shows Fisher's original model for comparison. The kind of bundling shown in Figure 4b relates to the notion of genetic correlation, much discussed in the quantitative genetics literature, and it would be equivalent to setting the genetic correlation of a pair of characters close to one. Such correlations are normally discussed in the context of evolutionary constraint, their presence evidence of reduced rather than enhanced evolvability (Maynard Smith et al. 1985; for an example in a natural setting see Grant and Grant 1995). The reason for this is clear: as Figure 4b shows, each trait still affects fitness independently, and this is a property of the world not under genetic control. As such, if an environmental change were to shift the optimal value of one, but not the other bundled trait or were to shift both in different directions, or to greatly different extents, then their

inability to evolve independently would greatly hinder the population's ability to respond; only if environmental change typically shifted the optima of the two traits in a way that mirrored their genetic correlation would the correlation enhance the rate of adaptation. The evolution of genetic correlations is an exciting and largely unexplored field both theoretically and empirically (see Stephen et al. 2002 and references therein), and we note that such correlations could enhance evolvability, but that, at least naively, this seems unlikely. Either way, Figure 4b could not be modeled by a simple reduction of n in equation (12).

Despite this, it is clear that modularity can be easily incorporated into Fisher's model, not through a reduction in the number of traits that comprise an organism, but by a reduction in the number of traits that a single mutation can affect; in other words, by a restriction of the degree of pleiotropy. Such a situation is depicted in Figure 4c. Wagner has suggested that a key way in which the developmental system might become modular is through the ''parcellation'' of the pleiotropic effects of genes such that the set of genes controlling one group of traits have little or no influence on another group of traits (Wagner 1996; Wagner and Altenberg 1996). Note that although genetic correlations may indicate the existence of pleiotropy (although linkage disequilibrium is another possible explanation), pleiotropy need not imply genetic correlation. A pair of traits may be pleiotropically bundled, in the sense that the same set of genes affect both, and yet the set of alleles present might mean that positive and negative correlations cancel, resulting in zero genetic correlation overall (Cheverud 1984; Baatz and Wagner 1997). Baatz and Wagner call this ''hidden pleiotropy.''

The Fisher model in its original formulation included universal pleiotropy. Some authors have considered Fisher's model with no pleiotropy in the context of drift load (Peck et al. 1997; Poon and Otto 2000), but to our knowledge there have been no considerations of immediate levels of pleiotropy in this model. Here, we introduce modular pleiotropy, as depicted in Figure 4c, to determine the extent to which it might reduce the cost of complexity. We consider the case where the n traits are divided into a series of m equally sized modules, each containing n/m traits and labeled $1, 2, \ldots, m$ (Fig. 4c depicts a case where $m = 3$). Thus, $\|\mathbf{z}(t)\|^2$ decomposes into a sum of m contributions from the m modules

$$\|\mathbf{z}(t)\|^2 = \sum_{i=1}^{m} \|\mathbf{z}_i(t)\|^2, \tag{18}$$

where $\|\mathbf{z}_i(t)\|$ is the Euclidean distance of the ith module from its optimal value. The appropriate generalization of equation (12) to incorporate modularity is

$$E[\Delta \ln W_t] \simeq \frac{1}{m} \sum_{i=1}^{m} \frac{2E[\|\mathbf{z}_i(t)\|^2]\rho^2}{n/m} F\left\{\frac{2E[\|\mathbf{z}_i(t)\|^2]}{\rho^2 n/m}\right\}. \tag{19}$$

The factor $1/m$ appears in equation (19) because a mutation may occur with equal probability in any of the m modules. Note that when $m = 1$ and there is no modularity, the result reduces to the universally pleiotropic formula given in equation (12).

All Groups of Traits Equally Maladapted

In the case where all modules of traits are equally distant from the optimum, we have from equation (18), $\|\mathbf{z}_i(t)\|^2 = \|\mathbf{z}(t)\|^2/m$. Substituting this into equation (19) yields the universally pleiotropic result of equation (12). Thus, under the approximations adopted, the rate of adaptation is entirely independent of the degree of modularity (but see Appendix 2).

When the mean mutational change is held fixed per trait, the situation is different. We note that any single mutation affects only one module and hence only changes n/m traits. Thus, analogous to equation (15), we introduce ρ^* a fixed constant (independent of n and m) and set

$$\rho = \rho^* \sqrt{n/m} \tag{20}$$

and obtain

$$E[\Delta \log W_t] \simeq -\frac{4E[\log W_t]\rho^{*2}}{m} F\left\{-\frac{4mE[\log W_t]}{n^2\rho^{*2}}\right\}. \tag{21}$$

This presents an interesting picture. When the argument of F is large and the function reaches a constant value, modularity will decrease the rate of adaptation (featuring only in the first factor of equation 21). When the argument of F is small, the total cost is found to be $m^{a/2}n^{-(2+a)}$. Here, modularity may help to alleviate the cost, but the extent is rather small, particularly, when a is small.

So far, this analysis suggests little advantage to modularity—indeed a disadvantage is predicted under certain circumstances. However, the situation where all traits are equally maladapted is not the situation where we might expect modularity to be favored. Modular architectures are thought to be favored when some traits are maladapted but others are not; modularity then allows adaptation to take place without undoing the adaptation achieved elsewhere (Wagner 1996). With this in mind, we examine the other extreme case, where a single trait is maladapted and all of the others are at their optimal values.

A Single Maladapted Trait

In this case all but one of the $\|\mathbf{z}_i(t)\|$ in equation (19) are zero and the remaining maladapted $\|\mathbf{z}_i(t)\|$ completely determines fitness. Thus,

$$E[\Delta \log W_t] \simeq -\frac{4E[\log W_t]\rho^2}{n} F\left\{-\frac{4mE[\log W_t]}{n\rho^2}\right\}. \tag{22}$$

In this case, the degree of modularity appears only in the second factor on the right-side, and so it can alleviate the cost of complexity only when the argument of F is not too large. Significant alleviation, but not elimination, of the cost takes place when the argument is small. The cost is then $m^{(1+a/2)}n^{-(2+a/2)} \equiv (m/n)^{(1+a/2)}n^{-1}$. Note, however, that the minimum cost, of n^{-1}, will always apply.

When the mutation magnitude per trait is held constant, $\rho = \rho^*\sqrt{n/m}$, we have

$$E[\Delta \log W_t] \simeq -\frac{4E[\log W_t]\rho^{*2}}{m} F\left\{-\frac{4m^2E[\log W_t]}{n^2\rho^{*2}}\right\}. \tag{23}$$

The pattern here is the similar to that with all traits mal-

adapted. Modularity will retard adaptation when the argument of F is large, and when it is small, the cost is $m^{1+a}n^{-(2+a)} \equiv (m/n)^{(1+a)}n^{-1}$. Again, a minimum cost of n^{-1} will always apply. Comparing equations (22) and (23) with the cases in which all traits are equally maladapted, equations (12) and (21), it is clear that, as expected, a higher level of modularity will be favored when only a single trait is maladapted, but it is also clear that the cost of complexity cannot be eliminated with modular pleiotropy, a minimum cost of n^{-1} always applies. Furthermore, under some conditions, modularity can retard the rate of adaptation (although not all of these are plausible).

Note that the case considered here is very similar to the mosaic and corridor models of quantitative trait evolution examined by Wagner and others (Wagner 1988; Zeng 1988; Baatz and Wagner 1997) in which directional selection on one trait is affected by stabilizing selection on pleiotropically linked traits. Our findings are consistent with those of Baatz and Wagner (1997), who showed that hidden pleiotropic effects, in absence of genetic correlations, could lead to a reduced rate of adaptation.

Discussion

In this paper, we have shown that Orr's (2000) cost of complexity is a robust phenomenon. Neither altered assumptions about mutation nor phenotypic modularity, in the sense of parcellated pleiotropy, can remove the cost, although both can reduce it significantly under some circumstances. Altering the structure of genetic correlations (the **G**-matrix in quantitative genetic parlance) could reduce the cost but under quite restrictive circumstances; in general we expect such correlations to act as a constraint. Our results do depend on the assumption of a single-mutant adaptive walk, which may be restrictive (Barton 2001). In particular, the restriction that only one mutation is allowed to segregate in a single timestep leads to the factor $1/m$ in equation (19), and this of course effects all the subsequent results. To address this we have carried out a number of explicit population simulations in which multiple mutations can segregate. Initial results suggest that the findings obtained here may be robust at least in some regions of parameter space, but the question remains open.

There is, as we have said, little evidence as to whether phenotypic complexity, in any measurable sense, is associated with a reduced rate of adaptation in the world. The robustness of Orr's finding adds confidence to the assertion that such a cost is important, but there remains the strong possibility that the model is in some way inadequate. Fisher's model is of course a gross simplification of the way selection acts on phenotypes. The question is whether it really captures, in Fisher's words (1930, ch. 2), ''the statistical requirements of the situation,'' or whether it is lacking some essential features. By ''essential,'' we mean features that might be expected to vary systematically with phenotypic complexity. Phenomena such as balancing selection, hitchhiking, or nonadditive genetics, although important in the world, might not be expected to so vary, and so have not been considered here. Discussions related to the following are found in Leigh (1987) and Orr (2000), and we draw on them both here.

A fundamental assumption of Fisher's model is that the optimal value of each trait is independent of the phenotypic state of all the other traits. This, quite clearly, is likely to be the exception rather than the rule when it comes to selection on real phenotypes. The situation in the world might be represented by Figure 4d, where the state of certain traits provides part of the selective context for other traits. Such a notion is central to the literature on modularity, where a module is often assumed to comprise a functionally integrated sets of traits (Bonner 1988; Cheverud 1996; Wagner 1996), rather than an essentially random set, as here (Fig. 4c). The point is interesting in light of the fact that Fisher spoke of his model as pertaining to a single complex organ, such as the vertebrate eye (Fisher 1930; Orr 1999). It is also clear that fitness interactions between traits need not reflect an obvious functional or developmental connection. It has been suggested by many authors, for example, that behavioral complexity can increase the rate at which new niches are colonized, altering the selective forces and thus the rate of evolution, for other, quite distinct traits (West-Eberhard 1987; Bateson 1988; Gittleman et al. 1996 and references therein; Orr 2000; Resnick and Ghalamber 2001).

A second feature absent from Fisher's model is closely related to trait interactions. Fisher's model posits a single optimal point in n-dimensional space. Despite the difficulties in testing this assumption (Whitlock et al. 1995), some lines of experimental evidence suggest that it may be questionable and that alternative phenotypic optima may be accessible from identical initial conditions. For example, Lenski and Trevisiano (1994) showed that genetically identical populations of bacteria subject to identical selection regimes evolved to seemingly optimal states that were phenotypically as well as genetically distinct. The importance of results such as these is not clear. The findings could be exceptional or misleading (with the eventual phenotypic diversity reflecting chance variation in neutral traits rather than true alternative phenotypic optima, for example). However, it is clear that fitness interactions between traits, as depicted in Figure 4d, could easily lead to such a state of affairs. If this situation is widespread, then we would need to replace the smooth single peak in Figure 1 with an alternative fitness landscape. Such a landscape would be more-or-less rugged, containing multiple peaks, and ridges of near-neutrality (e.g., Kauffman and Levin 1987; Whitlock et al. 1995; Gavrilets 1999). Indeed it is this ruggedness that is often meant by the term ''complexity'' in discussions of biological evolution (e.g., Kauffman and Levin 1987), rather than the dimensionality of the landscape, as used here.

The related phenomena of trait interactions and rugged or holely adaptive landscapes would almost certainly affect the conclusions reached here. If multiple optima are important, for example, we can surely expect their number and availability to vary (and possibly increase) with the number of phenotypic traits under selection. Furthermore, in a rugged or holey fitness landscape, a population trapped at a local fitness optimum in n-dimensional space might find that the addition of extra dimensions enabled further adaptive evolution along those dimensions. This could increase the rate of evolution for organisms characterized by more phenotypic dimensions (higher n).

Multiple optima can be easily incorporated into Fisher's geometrical model (e.g., Barton 2001) and into related multivariate quantitative genetics. However, to answer questions about the cost of complexity would require knowledge of how the relevant properties of the fitness surface might vary with increasing phenotypic complexity. There is no empirical guidance on this point, and no obvious way to incorporate such variation mathematically.

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Appendix 1

In this appendix, we give details of the full stochastic process underlying equation (2) of the main text.

Consider a population of identical individuals that all, at time t, have fitness W_t. A new mutation is assumed to arise and to have fitness W_t'. The value of W_t' has a random component but does, generally, also depend on the state of the population at time t. The selection coefficient associated with the mutation, s_t, is given by $s_t = (W_t'/W_t) - 1$. We introduce the probability of fixation, $\Pi(s)$, using another independent random variable $\eta(s)$, which is 1 (0) with probability $\Pi(s)$ $[1 - \Pi(s)]$. One possible representation of $\eta(s)$ is as $\Theta[\Pi(s) - \xi]$, where $\Theta(\cdot)$ denotes Heaviside's step function and ξ is an independent, uniformly distributed random variable over [0,1]. When $\eta(s)$ is 1 (0), fixation (loss) of a mutant with selection coefficient s occurs.

Loss or fixation of a mutant corresponds to an event, and the fitness at time $t + 1$ is $W_{t+1} = W_t^{1-\eta(s_t)}(W_t')^{\eta(s_t)} \equiv W_t^{1-\eta(s_t)} \times [W_t \times (1 + s_t)^{\eta(s_t)} = W_t \times (1 + s_t)^{\eta(s_t)}$. Thus, $\Delta \log W_t \equiv \log W_{t+1} - \log W_t = \eta(s_t)\log(1 + s_t)$. Taking an expectation of this equation and explicitly carrying out this expectation with respect to ξ yields equation (2).

Appendix 2

In this appendix, we discuss the distribution of the variable θ, the angle between $\mathbf{z}(t)$ and $\Delta\mathbf{z}(t)$, that appears in equation (9). Following Leigh (1987), we derive the distribution of $y \equiv -\sqrt{n}\cos\theta$ (where n is the number of traits) because for large n, y has a distribution, denoted $f(y)$, that is independent of n. Formally, this distribution is given by $f(y) = \int \delta(y + \sqrt{n}\cos\theta)\, d\Omega / \int d\Omega$, where $d\Omega$ signifies the measure of angular integrals appropriate to a space of n dimensions and $\delta(\cdot)$ denotes a Dirac delta function. Here, and elsewhere in the appendices, integrals with unspecified limits cover the full range of $-\infty$ to ∞. It can be shown that all except one of the angular integrations cancel between numerator and denominator, so that all that remains is $f(y) = \int_0^\pi \delta(y + \sqrt{n}\cos\theta)\sin^{n-2}\theta\, d\theta / \int_0^\pi \sin^{n-2}\theta\, d\theta$. Evaluating the integrals yields

$$f(y) = \frac{\Gamma\left(\frac{n}{2}\right)}{\sqrt{n\pi}\,\Gamma\left(\frac{n-1}{2}\right)}\left(1 - \frac{y^2}{n}\right)^{(n-3)/2}\Theta\left(1 - \frac{y^2}{n}\right), \qquad \text{(A1)}$$

where $\Theta(\cdot)$ denotes Heaviside's step function and $\Gamma(\cdot)$ denotes Euler's gamma function.

Note that for $n \gg 3$, $f(y)$ becomes the standard normal distribution (Fisher 1930):

$$f(y) = \sqrt{\frac{1}{2\pi}}\exp\left(-\frac{y^2}{2}\right). \qquad \text{(A2)}$$

Although for most of this paper, including Figures 2 and 3, equation (A2) will be used, when we examine high levels of modular pleiotropy (e.g., equation 19), it may not apply, as a module may include a small number of traits. However, extensive numerical work and analysis of tractable cases using the exact form, equation (A1) suggest that the Gaussian approximation remains extremely accurate and that any correction will be in the direction of reducing the rate of adaptation.

Appendix 3

In this appendix, we relate properties of the distribution of magnitudes of mutations, $p(r)$, to the distribution of selection coefficients, $\phi_t(s)$, and the distribution of mutant effects on a single quantitative trait—both of which have been investigated empirically. At times, we will specialize to the prototypical case of the gamma distribution, parameterized to agree with definitions of ρ and a in the main text equations (10) and (11):

$$p(r) = \frac{a}{\rho\Gamma(a)}\left(\frac{ar}{\rho}\right)^{a-1} e^{-ar/\rho}. \qquad \text{(A3)}$$

This distribution is used in Figure 2c, and in the limit $a \to \infty$, it becomes the Dirac delta function $\delta(r - \rho)$, and so encompasses mutations of fixed magnitude as shown in Figure 2a. In addition, of course, the distribution is exponential when $a = 1$.

Initially, we focus on the distribution of selection coefficients, $\phi_t(s)$. As mentioned in the text, the issue is whether the existence of a large class of neutral or nearly neutral mutations places any constraints on the form of $p(r)$. We begin, assuming $\|\mathbf{z}(t)\|$ has a fixed value z. It then follows from equation (9) that the distribution of selection coefficients is

$$\begin{aligned}\phi_t(s) &= E(\delta\{s - [e^{-zr\cos\theta - (r^2/2)} - 1]\}) \\ &= \int_0^\infty dr\, p(r) \int_{-\infty}^\infty dy\, f(y)\delta\left(s - \exp\left\{\frac{zry}{\sqrt{n}} - \frac{r^2}{2}\right\} + 1\right) \qquad \text{(A4)}\end{aligned}$$

where y and $f(y)$ are as described in Appendix 2. Setting $y_0 \equiv y_0(r) = \sqrt{n}/zr[\ln(1 + s) + r^2/2]$ and using standard properties of a Dirac delta function allows us to write

$$\begin{aligned}\phi_t(s) &= \int_0^\infty dr\, p(r) \int_{-\infty}^\infty dy\, f(y)\frac{\delta(y - y_0)}{\frac{zr}{\sqrt{n}}(1 + s)} \\ &= \int_0^\infty dr\, p(r) f[y_0(r)]\frac{\sqrt{n}}{zr(1 + s)}. \qquad \text{(A5)}\end{aligned}$$

It is this function that is plotted in Figure 2, using the Gaussian form of $f(y)$, equation (A2). To examine the existence of small-effect mutations, we can characterize the behavior of this distribution in the vicinity of $s = 0$. First, we make a small s approximations: $(1 + s)^{-1} \simeq 1$ and $\ln(1 + s) \simeq s$ so

$$\phi_t(s) \simeq \frac{\sqrt{n}}{z}\int_0^\infty \frac{dr}{r} p(r) f\left(\frac{\sqrt{n}s}{zr} + \frac{\sqrt{n}r}{2z}\right). \qquad \text{(A6)}$$

Note that $\phi_t(s)$ has the potential to be singular in the vicinity of $s = 0$ because of the factor r^{-1} in the integrand. To investigate this, we consider the contribution to the integral for r in the range (0, ξ), where ξ is sufficiently small that $\xi \ll z/\sqrt{n}$ and $\xi \ll \sqrt{n}s/z$. In this range, the limiting form of $p(r)$, given in the text, is also assumed to apply, so $p(r) = p_0 r^{a-1}$, where p_0 is a constant. The contribution from r in the range (0, ξ) is approximately $(\sqrt{n}p_0/z)$ $\int_0^\xi r^{a-2} f(\sqrt{n}s/zr)\, dr = (\sqrt{n}/z)^a p_0 |s|^{a-1} \int_{\sqrt{n}|s|/(z\xi)}^\infty u^{-a} f(u)\, du$. Thus, in the vicinity of $s = 0$, $\phi_t(s)$ is singular for $a \leq 1$. In other words, for small a, a significant proportion of mutations will be neutral, with $s \simeq 0$. Specializing to the gamma distribution equation (A3), we find numerically, that, consistent with the above behavior, $\phi_t(s)$ contains a finite peak in the vicinity of $s = 0$ for $a > 1$ but that as a increases, the location of the peak moves to increasingly negative s. The location of the peak can be found exactly in the limit $a \to \infty$, when mutations have fixed magnitude, ρ. In this case, the modal value of the distribution is found to be

$$\text{mode}(s) = \exp\left(-\frac{(2z^2 + n)\rho^2}{2n}\right) - 1 \simeq -\frac{\rho^2}{2}, \qquad \text{(A7)}$$

where $z^2 \ll n$, $\rho \ll 1$. So for ρ not too large, the existence of a significant class of nearly neutral mutations seems consistent with

even the most extreme value of a. However, for large ρ, this will not be the case.

Let us now consider how the distribution of mutant effects of a single trait is affected by the precise form of $p(r)$. The key issue here is whether empirical evidence of leptokurtic distributions places any constraints on $p(r)$. A leptokurtic distribution has a kurtosis (fourth central moment divided by the squared variance) in excess of 3, the value associated with a Gaussian. The distribution of mutant effects on all n traits is assumed to depend on the mutational change in trait values, $\Delta\mathbf{z}$, only as a function of its magnitude, $\|\Delta\mathbf{z}\|$. We write this distribution as $M(\|\Delta\mathbf{z}\|)$ and the distribution of mutational magnitudes is given by $p(r) = \int \delta(r - \|\Delta\mathbf{z}\|)M(\|\Delta\mathbf{z}\|)\, d^n\Delta z$. This yields

$$p(r) = \Omega_n r^{n-1} M(r) \quad \text{and} \tag{A8a}$$

$$\Omega_n = \frac{2\pi^{n/2}}{\Gamma(n/2)}, \tag{A8b}$$

where Ω_n is the surface area of a unit radius sphere in n dimensional Euclidean space. The distribution of mutant effects on a single trait, say z_1, is given by

$$\begin{aligned} M_1(z_1) &= \int M(\sqrt{z_1^2 + z_2^2 + \cdots z_n^2})\, dz_2\, dz_3 \cdots dz_n \\ &= \frac{1}{\Omega_n} \int \frac{p(\sqrt{z_1^2 + z_2^2 + \cdots z_n^2})}{(z_1^2 + z_2^2 + \cdots z_n^2)^{(n-1)/2}}\, dz_2\, dz_3 \cdots dz_n \\ &= \frac{\Omega_{n-1}}{\Omega_n} \int_0^\infty \frac{p(\sqrt{z_1^2 + z^2})}{(z_1^2 + z^2)^{(n-1)/2}} z^{n-2}\, dz, \end{aligned} \tag{A9}$$

where in the last expression, we have used spherical polar coordinates in $n - 1$ spatial dimensions. The kurtosis of $M_1(z_1)$ can easily be found once the change of variable $z = |z_1|u$ is made:

$$\mathrm{kurt}(z_1) \equiv \frac{E[z_1^4]}{(E[z_1^2])^2} = \frac{3n}{n+2} \frac{E[r^4]}{(E[r^2])^2}, \tag{A10}$$

where $E[r^k] = \int_0^\infty r^k p(r)\, dr$. For large n the first factor on the right side is approximately 3, and the properties of moments tells us that the second factor is greater than or equal to unity. The distribution is unlikely then to be platykurtic (with a kurtosis less than 3), the only question is how readily will it become leptokurtic. Specializing again to the gamma distribution yields

$$\mathrm{kurt}(z_1) = \frac{3n}{n+2} \frac{(3+a)(2+a)}{(1+a)a}. \tag{A11}$$

The second factor is a decreasing function of a, so small a lead to the largest level of kurtosis. Although $\mathrm{kurt}(z_1) \approx 3$ only for $a \sim n$, much smaller values are required for substantial kurtosis. In the limit of large n, we find that $\mathrm{kurt}(z_1) = 4$ implies $a \simeq 12.45$ and $\mathrm{kurt}(z_1) = 6$ implies $a \simeq 4.37$.

Together, the results of this appendix allow us place surprisingly little restriction on the distribution of mutant effects. However, both lines of evidence suggest that, plausibly, $a \ll n$ should hold.

Appendix 4

In this appendix, we provide the mathematical details behind equation (12) and describe the broad class of $p(r)$ to which this equation applies.

We begin by writing equation (5) in terms of the distributions of $y = -\sqrt{n}\cos\theta$ and r, namely $f(y)$ and $p(r)$ (Appendices 2 and 3) and omit the time argument of $\|\mathbf{z}\|$ for brevity. Note that we do not need an explicit expression for $\phi_t(s)$ because it is fully equivalent to take the expectation with respect to the three variables that appear in equation (9), as long as we ensure that only positive selection coefficients, $s > 0$, contribute. We have

$$E[\Delta \ln W] = 2E\left[\int_0^\infty dr\, p(r) \int_{\sqrt{n}r/(2\|\mathbf{z}\|)}^\infty dy\, f(y)\left(\frac{\|\mathbf{z}\| ry}{\sqrt{n}} - \frac{r^2}{2}\right)^2\right], \tag{A12}$$

where the expectation on the right-side now refers only to $\|\mathbf{z}\|$. The lower limit of the y integral comes from the requirement that $s \geq 0$, and from equation (9), this requires $y = -\sqrt{n}\cos\theta > r\sqrt{n}/2\|\mathbf{z}\|$). We can write equation (A12) as

$$E[\Delta \ln W] = E\left[\frac{2\|\mathbf{z}\|^2}{n} \int_0^\infty dr\, r^2 p(r) K\left(\frac{2\|\mathbf{z}\|^2}{nr^2}\right)\right], \tag{A13}$$

where

$$K(x) = \int_{1/\sqrt{2x}}^\infty dy\, f(y)\left(y - \frac{1}{\sqrt{2x}}\right)^2. \tag{A14}$$

Let us note here, that including selection of arbitrary strength, σ, such that $W = \exp(-\sigma/2\|\mathbf{z}(t)\|^2)$ will simply multiply the right-side of equation (A13) by σ. Because σ, assuming it is independent of n, will be absent from the argument of K, its inclusion will have no effect on any conclusions about costs of complexity. Scaling σ with n would, of course, affect the cost. However, the only plausible scaling, such that σ decreases as n increases, would only make the cost of complexity more severe.

Note that $dK(x)/dx > 0$ for any $x < \infty$ because

$$\frac{dK(x)}{dx} = \left(\frac{x^{-3/2}}{\sqrt{2}}\right) \int_{1/\sqrt{2x}}^\infty dy\, f(y)\left(y - \frac{1}{\sqrt{2x}}\right)$$

and this is manifestly nonnegative. Also note that for large x, $K(x) \simeq \int_0^\infty dy\ f(y)y^2 = 1/2$. We assume the distribution of mutation magnitudes, $p(r)$, depends on a single length scale, ρ, and without loss of generality, this length scale can be taken as the mean value of r:

$$E[r] \equiv \int_0^\infty rp(r)\, dr = \rho. \tag{A15}$$

The assumption that $p(r)$ depends just on one length scale ρ means, without loss of generality, $p(r)$ can be written as

$$p(r) = \frac{q(r/\rho)}{\rho} \tag{A16}$$

for some function $q(x)$. Because $p(r) \geq 0$, $\int_0^\infty p(r)\, dr = 1$ and $\int_0^\infty rp(r)\, dr = \rho$ the function $q(x)$ must obey

$$q(x) \geq 0, \tag{A17a}$$

$$\int_0^\infty q(x)\, dx = 1, \quad \text{and} \tag{A17b}$$

$$\int_0^\infty xq(x)\, dx = 1. \tag{A17c}$$

Apart from these constraints, the function $q(x)$ is arbitrary, so a wide class of distribution functions, depending on shape parameters (but not other length scales), can be represented in the form of equation (A16). From the assumption in the text about $p(r)$, equation (11), it follows that for small u, $q(u) \simeq u^{(a-1)}q_0$, where $a > 0$ (as is required for normalizability of $q[u]$) and q_0 is a constant. If $q(u)$ is strictly zero for small u, we take $q_0 = 0$.

Using equations (A16) in (A13) quickly yields

$$E[\Delta \ln W] = E\left[\frac{2\|\mathbf{z}\|^2\rho^2}{n} F\left(\frac{2\|\mathbf{z}\|^2}{n\rho^2}\right)\right], \tag{A18}$$

where we have defined

$$F(x) = \int_0^\infty du\, u^2 q(u) K\left(\frac{x}{u^2}\right) = x^{3/2} \int_0^\infty du\, u^2 q(\sqrt{x}u) K\left(\frac{1}{u^2}\right). \tag{A19}$$

Equation (12) only follows from equation (A18) if the variance of $\|\mathbf{z}\|^2$ can be neglected. We have extensive numerical evidence that this variance always remains small and its neglect does not significantly influence the dynamical predictions for $E[\ln W(t)]$. We furthermore have analytical results indicating that when $\rho \ll \|\mathbf{z}(t)\|$, as may hold for a maladapted population, any variance of $\|\mathbf{z}(t)\|$ decreases with time. Overall, the neglect of the variance of $\|\mathbf{z}(t)\|$ appears to be a highly accurate approximation.

Some important properties of $F(x)$ follow immediately from its above definition equation (A19):

(1) $dF(x)/dx = \int_0^\infty du q(u)\, dK(y)/dy\big|_{y=x/u^2}$, and because $dK(y)/dy > 0$, it immediately follows that $dF(x)/dx > 0$;

(2) $\lim_{x\to 0} F(x)/x = 0$;

(3) $\lim_{x\to\infty} F(x)/x = 0$ when $\int_0^\infty du u^2 q(u) < \infty$;

(4) for small x, $F(x) \simeq x^{1+a/2} q_0 \times c$, where $c = \int_0^\infty du u^{a+1} K(1/u^2$ is a numerical constant, which for $a \leq 3$ is $O(1)$; and

(5) for large x, $F(x) \simeq \int_0^\infty du u^2 q(u)/2$, assuming $\int_0^\infty du u^2 q(u) < \infty$.

Property 1 shows that $F(x)$ is a monotonically increasing function of x. Properties 1–3, in conjunction with equation (12) shows that mutations of intermediate length will always maximize the rate of adaptation (Kimura 1983; Orr 2000). Properties 4 and 5 are the source of equations (13) and (14) and similar statements in the text. To derive the forms in the text requires equation (A16), remembering to use scalings such as equation (15) when appropriate.