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Long-term Response: 2. Finite Population Size and Mutation

Adaptation depends on how the various evolutionary processes shape variation in populations
— Barton and Partridge (2000)

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As we saw in Chapter 18, drift has significant short-term consequences, generating variance around the expected response. Over longer time scales, drift has considerable importance in allele frequency change in most artificial selection experiments, which tend to have small effective population sizes. Drift also has important implications on the nature of response in even very large natural populations (e.g., Chapters 8, 10). This chapter examines its implications for long-term response, considering how drift interacts with selection to change allele frequencies and how new mutations contribute to response. Throughout, we restrict attention to directional selection, considering stabilizing selection in Chapter 27. Given that both initial variation and new mutation can contribute, we use **long-term response** to refer to the gain from the variation in the population at the start of selection. Eventually, all this initial variation is exhausted and response from this component reaches a selection limit. The actual response, however, can continue past this limit due to the input from new mutation, eventually (under constant selection) approaching an **asymptotic response**, wherein the contribution to σ_A^2 from new mutation is balanced by its removal by drift and selection.

Much of the material here builds on results from Chapter 7 on the interaction between selection and drift, and it may prove useful for the reader to review those sections before proceeding. This chapter is organized as follows. First, we briefly review a few key results from Chapter 7 and then expand on our brief discussion from Chapter 3 on the subtle (but important) effect of selection in decreasing the effective population size (over that expected from the same number of reproducing individuals in a nonselected population). With selection on a heritable character, a few families (and their relatives) make most of the contribution to the total response. Individuals surviving selection are thus closer relatives than expected by chance, increasing the rate of inbreeding.

The effects of drift and mutation are examined next. Long-term response theory initially considered only the effects of drift, but was later augmented to include the role of new mutation. Our discussion follows this same historical development by first considering Robertson's theory for the expected response in the presence of drift using only the initial variation. Two important results emerge. First, a *simple upper bound* of $2N_eR(1)$, twice the effective population size times the response in generation one, on the selection limit. This simple result is in sharp contrast to the complete lack of such a bound under completely deterministic theory (Chapter 25). Second, there is an *optimal selection intensity*. With a fixed number of measured individuals, as we increase the selection intensity (and hence the short-term response), we do so at the expense of reducing the effective population size, reducing long-term response. We conclude our discussion of Robertson's theory by considering extensions to allow for linkage and various aspects of population structure (such as family

selection, drift in the base population, and selection in a subdivided population). Next, we consider the effects of new mutations, both in terms of their (generally) minor role at the start of selection (except for rare mutations of large effect) and their growing role as drift and selection erode the initial variance, eventually leading to an asymptotic rate of response. Finally, the joint interactions of drift, mutation, and selection are critical to understanding how adaptation proceeds in nature. We started this discussion in Chapters 8 and 10 by focusing on molecular evolution and conclude this chapter by examining the theory of adaptive walks (the pattern of substitutions) during adaptation. There are two general frameworks for examining walks, Fisher's geometric model and Gillespie's mutational landscape model, the former focusing on the phenotypic effects of adaptive substitutions, the later on fitness effects of substitutions. We show how these models are connected and examine their joint implications for the native of adaptive substitutions.

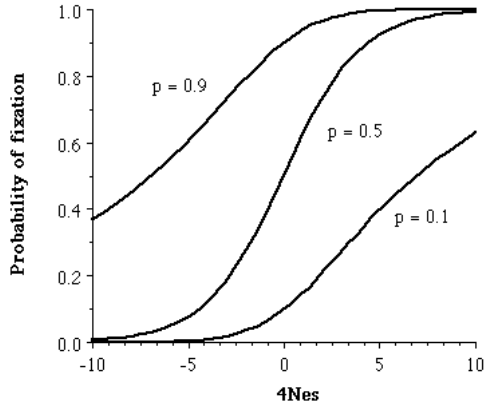

Figure 26.1. Probability of fixation of an additive allele ($h = 0$) as a function of $N_e s$ and initial allele frequency p (using Equation 26.2a).

THE POPULATION GENETICS OF SELECTION AND DRIFT

Chapter 7 examined the interaction of selection and drift at a single locus, and we briefly review a few of the key results here. With finite population size, a favorable allele may become lost, and hence our interest is on u, the probability that an allele is fixed. In an infinite population, $u = 1$ for an allele favored by selection (provided it is not overdominant). In a finite population, $u < 1$ and depends on (among other things) its initial frequency p_0 and the effective population size N_e. Let $u(p_0)$ denote the probability that an allele starting at initial frequency p_0 becomes fixed. The fixation probability of a neutral allele depends only on its initial frequency,

$$u(p_0) = p_0 \tag{26.1}$$

being independent of population size. This is not the case for an allele under selection. For additive selection (fitnesses of $0 : s : 2s$),

$$u(p_0) \simeq \frac{1 - e^{-4N_e s p_0}}{1 - e^{-4N_e s}} \tag{26.2a}$$

$$\simeq p_0 + 2N_e s p_0(1 - p_0) \qquad \text{when } 2N_e|s| \leq 1 \tag{26.2b}$$

Equation 26.2a, due to Kimura (1957), is derived using diffusion theory in Appendix 1 and values are plotted in Figure 26.1. Equation 26.2b, due to Robertson (1960), uses the approximation $e^{-x} \simeq 1 - x + x^2/2$ for $|x| \ll 1$ to further simplify Kimura's result. Finally, note that Equation 26.2b implies

$$u(p_0) \simeq p_0 \qquad \text{if} \qquad 2N_e|\,s\,| \ll 1 \tag{26.2c}$$

Comparing this result to Equation 26.1 shows that such an allele behaves as if were neutral over all allele frequencies. Alleles with $s \neq 0$, but $2N_e|\,s\,| \ll 1$, are called **effectively neutral** to reflect this fact. Chapter 7 gives corresponding expressions for the probability of fixation when dominance is present (Equations 7.18 – 7.20).

Even when an allele is strongly selected, drift is important when its frequency is near zero or one. Equation 26.2b implies that the probability of fixation starting with a single copy ($p_0 = 1/[2N]$) of an advantageous allele is approximately $2s\,(N_e/N)$ when $4N_e s \gg 1$. Hence, a favored allele introduced as a single copy is usually lost by drift. Conversely, when the frequency of a favored allele becomes sufficiently large, fixation is almost certain. If $p_0 \geq 1/(2N_e s)$, Equation 26.2a shows that the probability of fixation exceeds 0.70, while if $p_0 \geq 1/(N_e s)$, the probability of fixation exceeds 0.93 (Robertson 1960). If **A** initially increases by drift, it reaches a threshold frequency above which deterministic selection takes over, rapidly increasing its frequency towards one. Near frequency one, drift again takes over, fixing the allele much more rapidly than expected under deterministic selection (Example 8.1).

Fixation Probabilities for Alleles at a QTL

We can translate the above results (and those from Chapter 7) for the fixation probability of an allele given its additive (s) and dominance (h) effects on *fitness* into the fixation probability for a favorable QTL allele as a function of its additive (a) and dominance (k) effects on the *trait* under selection. When the locus has only a small effect on the character, the fitnesses $s = \overline{\imath}\, a/\sigma_z, h = k$ for a QTL under directional selection (Equation 25.4) can be used in conjunction with Equation 7.18a to obtain fixation probabilities. If the allele displays no dominance in the character ($k = 0$), then our previous results imply that its probability of fixation exceeds 0.7 when

$$N_e\, s\, p = N_e\, \overline{\imath}\; p\, \frac{a}{\sigma_z} \geq 1/2 \tag{26.3a}$$

Expressed in terms of a critical allele frequency for the fixation probability to exceed 0.7,

$$p > \frac{\sigma_z}{a\, 2N_e\, \overline{\imath}} \tag{26.3b}$$

The fixation probability exceeds 93% when $4N_e sp > 1$, or a critical allele frequency of twice that given by Equation 26.3b,

$$p > \frac{\sigma_z}{a\, N_e\, \overline{\imath}} \tag{26.3c}$$

Hence, if the product of initial allele frequency and the standardized allelic effect $p|a|/\sigma_z$ is sufficiently small, drift dominates even if selection ($\overline{\imath}$) on the character is strong. With small values of $N_e\overline{\imath}$, only alleles of large effect and/or at moderate to high frequency are likely to be fixed by selection. As $N_e\overline{\imath}$ increases, favored alleles with smaller effects and/or lower frequencies are increasingly more likely to become fixed. Finally, the careful reader might recall from Chapter 14 that with truncation selection in a finite population, sampling causes fluctuations in $\overline{\imath}$. This additional complication need not overly concern us, as Hill (1969a, 1985) and Kojima (1961) show that the error introduced by assuming a constant $\overline{\imath}$ is small.

The Cohan Effect: Increased Divergence Under Uniform Selection

Selection is generally considered to increase the determinism of a system, but selection can actually *increase* between-line divergence relative to drift (Example 7.3), a point with implications for replicated selection lines. Suppose two replicate populations are segregating alleles **A** and **a** at a particular locus with $p = \text{freq}(\mathbf{A}) = 0.25$. Under pure drift, Equation 26.1 implies that the probability replicate one is fixed for **A** and replicate two for **a** is $0.25 \times (1 - 0.25) = 0.1875$, with the same probability for the alleles being fixed in the opposite pattern. The resulting probability that two replicate lines are fixed for alternate alleles becomes 0.375. Now suppose that **A** is favored by selection. Cohan (1984b) showed that when selection is weak to moderate the probability of divergence between replicate populations often *increases* relative to pure drift. For example, if $N_e s = 1/2$, Equation 26.2a gives the fixation probability of **A** as 0.46, implying the probability of fixing alternate alleles is $2 \cdot 0.46 \cdot 0.54 = 0.496$. Divergence in this case is *increased* by the interaction between selection and drift. We refer to this as the **Cohan effect**, and this has some bearing the expected gain in response when crossing replicate selected lines (see below).

In general, the probability of fixing alternate alleles in two replicates is $2u(p)\,[\,1 - u(p)\,]$. Under pure drift, $u(p) = p$, giving $2p(1-p)$, which is maximized when $p = 1/2$. Thus the probability of divergence is increased by selection if $u(p)$ is closer to $1/2$ than p, which can be formally stated as

$$|\,u(p) - 1/2\,| < |\,p - 1/2\,| \tag{26.4}$$

Figure 7.3 shows that under additive selection the conditions for this to occur are not very restrictive.

Increased Recombination Rates Following Selection

We have extensively reviewed the Hill-Robertson effect (Chapters 3, 7, 8), wherein the effective population size is reduced in regions linked at a selected site. Otto and Barton (1997) showed that alleles at modifier loci which increase the recombination rate also increase the probability of fixation of favored alleles at a linked locus under selection (also see Felsenstein 1974; Felsenstein and Yokoyama 1976). This can result in these recombination modifiers hitchhiking along to fixation with the favored mutations. Such modifiers are favored because under low recombination, the selection coefficient on a particular mutation affecting a character under selection also depends on the selection coefficients at linked loci (e.g., Equation 7.42). Thus, the fate of a particular mutant is highly dependent upon the background in which it arose. As recombination increases, the fate of a mutation becomes increasingly uncoupled from the fate of its initial background. Rice and Chippendale (2001) experimentally demonstrate this by showing that the fixation probability of a mutation favored by artificial selection (white eye color in *Drosophilia*) increases with the recombination rate. Otto and Barton suggest this provides an explanation for the evolution of increased recombination frequencies (and hence the evolution of sex). Otto and Barton's theory makes the prediction that recombination rates may increase in selected populations relative to unselected controls.

Example 26.1. Korol and Iliadi (1994) subjected a *Drosophila melanogaster* population to divergent selection for positive and negative geotaxis (positive geotaxis flies have an increased tendency to fly up, negative geotaxis flies to fly down). Recombination frequencies were scored on the unselected controls and the positively (geo^+) and negatively (geo^-) selected lines, with chromosomes II, III, and X scored after 36, 40, and 44 generations of selection (respectively). Over the scored regions (roughly 220 cM in the control), the map distance in the geo^+ line increased by a total of 78 cM (35%), while the geo^- line increased by 66 cM (30%). Presumably these increases result from the increased probability of fixation of favorable

mutations that are linked to modifiers increasing recombination frequencies. Other artifical selection experiments in *Drosophila* also showed an increase in the recombination frequency following either directional or stabilizing selection (e.g., Thoday et al. 1964; Flexon and Rodell 1982; Zhuchenko et al. 1985; Rodell et al. 2004). Similarly, Morran et al. (2009) found that a collection of wild-type populations of the nematode *C. elegans* exposed to a bacterial pathogen had elevated rates of outcrossing compared with a set of controls that were not exposed.

THE EFFECT OF SELECTION ON EFFECTIVE POPULATION SIZE

The simple act of selecting a trait reduces the effective population size. Part of this is obvious, in that if a fraction p of T scored individuals are allowed to reproduce, the number of parents becomes $N = pT$, so that stronger selection picks fewer parents, decreasing N_e. There is second, and much more subtle, effect that further reduces the N_e for a selected population below that of an unselected control population with the same number of parents (so that $N_e < Tp$). This phenomenon is often attributed to Morley (1954), who noted in sheep flocks exposed to selection that "the genetically superior individuals will tend to be most inbred". However, Lush (1946) very clearly understood this process, noting the "correlation between the fates of relatives" under selection and how this is expected to inflate the variance in offspring number.

To see how selection reduces N_e, recall from Chapter 3 that one of the assumptions of an ideal population (where the actual size N equals the effective size N_e) is that all parents have an equal chance of contributing offspring. With a character under selection this is no longer true, as superior families contribute more offspring to the next generation than inferior families, inflating the offspring variance and reducing N_e. This follows since $N_e = (N-1/2)/(\sigma_k^2/4+1/2)$, where σ_k^2 is the variance in offspring number (Equation 3.4). If the number of offspring follows a Poisson distribution, then $\sigma_k^2 = 2$ and $N_e = N - 1/2 \simeq N$. However, if some parents contribute a disproportionate number of offspring, $\sigma_k^2 > 2$ and $N_e < N$. The more disproportionate the contribution from some families, the larger the variance and the smaller N_e. Thus, a single generation of selection reduces N_e by inflating σ_k^2 over that for an unselected population. A second factor, and the major complication in computing N_e for a population under selection, is that continued selection has a *cumulative* effect in reducing the variance beyond the single-generation effect. This occurs because parents pass on some of their ability to have an increased contribution (preferred values for the selected trait) to their offspring, inflating σ_k^2 further, leading to a greater reduction in N_e. This reduction becomes more pronounced as either heritability and/or selection intensity increases.

The Expected Reduction in N_e from Directional Selection

While the effective population size due to artificial selection can easily be retrospectively computed from either pedigree information or from the sampling variance in marker allele frequencies (see Chapter 4), predicting the reduction of N_e *in advance* is more difficult. The exact value of N_e/N depends on a variety of assumptions about both the family and population structure and on the underlying genetical model (the infinitesimal is typically assumed). Theoretical investigations of the effects of selection on reducing N_e were initiated by Robertson (1961), who gave simple approximations for both the single generation change in N_e and the asymptotic change following many generations of selection. Two different approaches have been used to examine the reduction in N_e — computing the expected variance in gene frequency for an unselected locus in a population under selection (Robertson 1961;

Nei and Murata 1966; Caballero 1994; Santiago and Caballero 1995) and computing the rate of inbreeding from the number of ancestors (Burrows 1984a,b; Wolliams 1989; Verrier et al. 1990; Wray and Thompson 1990; Wray et al. 1990, 1994; Wolliams et al. 1994). The former corresponds to the variance effective population size, the latter to the inbreeding effective population size. Strictly speaking, diffusion theory results require usage of the variance effective size (as diffusion approximations use the sample variance in allele frequency). However, as discussed in Chapter 3, inbreeding and variance size are usually equivalent unless the population size is changing over time. While these treatments consider the effective population size on a neutral locus unlinked to loci influencing the traits(s) under selection, the results should be very similar for selected loci under the infinitesimal model, as in this case drift (rather than selection) provides the major impetus for allele frequency change.

Our treatment follows Santiago and Caballero (1995), who give a general expression for N_e under selection allowing for nonrandom mating. Assuming random mating, their expression for N_e after τ generations of selection is

$$\frac{N_{e,\tau}}{N} = \left[\frac{1-\alpha_1}{2} + \left(\frac{\sigma_k^2}{4} + Q_\tau^2 C^2 \right) (1+\alpha_1) \right]^{-1} \tag{26.6a}$$

where σ_k^2 is the sampling variance in offspring number in the absence of selection, $\alpha_1 = -1/(N-1)$ is a measure of the departure from Hardy-Weinberg due to finite population size, Q_τ accounts for the cumulative effects of τ generations of selection, and C^2 is the variance in selective advantage among families. For a single generation of selection, $Q_1 = 1$, implying that $\sigma_k^2/4 + C^2$ is the effect of selection in the current generation, while $(Q_\tau^2 - 1)C^2$ is the cumulative effect of selection in previous generations. As shown below, both Q and C^2 are functions of the selection intensity, heritability, and intraclass correlation of sibs. Assuming that N is large (so that $\alpha_1 \simeq 0$), and a Poisson distribution of offspring in the absence of selection ($\sigma_k^2 = 2$), Equation 26.6a reduces to

$$\frac{N_{e,\tau}}{N} = \frac{1}{1 + Q_\tau^2 C^2} \tag{26.6b}$$

Robertson (1961) and Milkman (1978) show that $C^2 \simeq \bar{i}^2\, t$ where $t = \mathrm{Cov}(FS)/\sigma_z^2$ is the intraclass correlation of full sibs (LW Equation 17.3).

Obtaining the value of t requires a little care, as selection changes the genetics variances, and hence t. Under the infinitesimal model (Chapters 16, 24) all the change in genetic variances are due to selection-induced linkage disequilibrium. In this case, the additive genetic variance $\sigma_A^2 = \sigma_a^2 + d$, where σ_a^2 (the additive genic variance) is the additive genetic variance in the absence of disequilibrium (the additive genetic variance in the base population) and d is the disequilibrium. Recall (Chapter 16) that under the infinitesimal model, the within- and between-family contributions to the additive genetic variance differ, as the within-family contribution ($\sigma_a^2/2$) is not influenced by disequilibrium, while the between-family variance ($\sigma_a^2/2 + d$) is. Assuming (for now) the absence of dominance and shared sib environmental effects, the intraclass correlation becomes

$$\begin{aligned} t &= \frac{\sigma_a^2/2 + d}{\sigma_A^2 + \sigma_E^2} = \frac{\sigma_a^2/2 + d}{\sigma_a^2 + d + \sigma_E^2} = \frac{h_0^2/2 + d/\sigma_{z(0)}^2}{h_0^2 + d/\sigma_{z(0)}^2 + (1 - h_0^2)} \\ &= \frac{h_0^2/2 + d/\sigma_{z(0)}^2}{1 + d/\sigma_{z(0)}^2} \end{aligned} \tag{26.7a}$$

where h_0^2 and $\sigma_{z(0)}^2$ are the heritability and phenotypic variance in the unselected base population. The last equality in the first line of Equation 26.7a follows by dividing through by

$\sigma^2_{z(0)}$ (the phenotypic variance in the base population) and noting that $\sigma^2_E/\sigma^2_{z(0)} = (1 - h^2_0)$, where σ^2_E includes all sources of variation besides the additive genetic variance. Thus, the larger $\bar{\imath}^2$ and/or h^2, the larger C^2 and the smaller N_e becomes. When dominance and/or shared environmental effects are present, t is also a function of σ^2_D and $\sigma^2_{Ec(FS)}$ (Table 25.1).

We now have all the results needed to compute the single-generation reduction in N_e. Defining $(1-\kappa) = \sigma^2_{z*}/\sigma^2_z$ as the reduction in the phenotypic variance in the selected parents, (Equation 16.10a), Equation 16.7a gives $d(1)/\sigma^2_{z(0)} = -\kappa\, h^4_0/2$. Substituting into Equation 26.7a gives

$$t(1) = \frac{h^2_0(1 - \kappa h^2_0)/2}{1 - \kappa h^4_0/2} \tag{26.7b}$$

Recalling that $Q_1 = 1$ gives the reduction in N_e from a single generation of selection as approximately

$$N_{e,1} \simeq N \left(1 + \bar{\imath}^2 \, \frac{(h^2_0/2)(1 - \kappa h^2_0)}{1 - \kappa h^4_0}\right)^{-1} \tag{26.8}$$

This result was first obtained by Robertson (1961), who did not include the $(1 - \kappa h^4_0/2)$ term, and corrected by Wray and Thompson (1990).

With selection on a heritable character, gene frequency changes between generations are correlated. As a consequence, the simple sampling variance correction $C^2 = \bar{\imath}^2\, t$ is not sufficient to account for the effects of selection as it ignores the cumulative effects (Q_τ) of these correlations over τ prior generations of selection. Santiago and Caballero (1995) show that the cumulative effect Q_τ is given by

$$Q_\tau = 1 + \frac{G}{2}(1 + r) + \cdots + \left[\frac{G}{2}(1 + r)\right]^\tau = \sum_{i=0}^{\tau} \left[\frac{G}{2}(1 + r)\right]^i \tag{26.9a}$$

G is the fraction of genetic variance remaining after selection and r is the correlation between the selective values of mates ($r = -1/[N - 1]$ under random matting). Since (under the infinitesimal model) $G = 1 - \kappa\, h^2$, it is potentially changing each generation. However, recalling from Chapter 16 that h^2 quickly (2-3 generations) reaches its equilibrium value, we typically take $G = 1 - \kappa\, \widehat{h^2}$, a function of the equilibrium heritability under the effects of selection and disequilibrium alone. In the limit ($\tau \to \infty$), this sum converges to

$$Q = \frac{2}{2 - G(1 + r)} \tag{26.9b}$$

Robertson assumed that the limiting value of Q is 2, but Equation 26.9b shows that this is an overestimate, and hence N_e is underestimated.

Example 26.2. Consider directional truncation selection on a normally-distributed character by selecting the uppermost 20 percent of the population ($p = 0.2$). From Example 16.2, this gives a selection intensity of $\bar{\imath} = 1.40$ and a reduction in variance of $\kappa = 0.781$. Assuming initial (before selection) values of $h^2_0 = 0.5$ and $\sigma^2_{z(0)} = 100$, Example 16.2 gives (under the infinitesimal model) equilibrium values of $\widehat{h}^2 = 0.428$ and $\widehat{d} = -12.59$. Hence,

$$G = 1 - \kappa\, \widehat{h}^2 = 1 - 0.781 \cdot 0.428 = 0.666$$

and

$$\widehat{t} = \frac{h^2_0/2 + \widehat{d}/\sigma^2_{z(0)}}{1 + \widehat{d}/\sigma^2_{z(0)}} = \frac{0.5/2 - 12.59/100}{1 - 12.59/100} = 0.14$$

Hence, $\widehat{C}^2 = \overline{i}^2 \cdot \widehat{t} = 1.4^2 \cdot 0.14 = 0.278$ while (assuming $r \simeq 0$)

$$Q = \frac{2}{2 - G} = \frac{2}{2 - 0.666} = 1.499,$$

giving the equilibrium reduction in N_e as

$$N_e = \frac{N}{1 + Q_\tau^2 \widehat{C}^2} = 0.615\, N$$

Robertson's approximation ($Q = 2$) gives $N_e = 0.473\, N$.

Similar calculations using other p values (smaller p equals stronger selection) gives

p	κ	$\widehat{d}$	$\widehat{t}$	G	$\widehat{C}^2$	Q	Ne/N
0.50	0.64	-10.96	0.16	0.72	0.10	1.56	0.80
0.10	0.83	-13.04	0.14	0.65	0.42	1.48	0.52
0.05	0.86	-13.34	0.13	0.64	0.57	1.47	0.45
0.01	0.90	-13.73	0.13	0.62	0.93	1.45	0.34

The general prediction that effective population size decreases in selected populations has been examined in a number of *Drosophila* experiments, where inbreeding is estimated directly from parental pedigrees. This prediction has generally been confirmed, with a reasonable fit to Robertson's theory (McBride and Robertson 1963; Jones 1969a,b; López-Fanjul 1989). As expected from Equation 26.8, N_e is lowest in lines showing the greatest response to selection, as these lines have the highest realized heritabilities. Gallego and López-Fanjul (1983) tested a second prediction using selection on sternopleural bristles: since the reduction in N_e occurs because of between-family selection (inflating the between-family variance σ_k^2), no reduction in N_e is expected under within-full-sib family selection. In accordance with theory, no reduction was observed.

As reviewed in Chapter 25, reproductive fitness often declines during long-term selection experiments. This can result in a further increases the variance in fitness among individuals, which in turn further increases the variance in offspring number contributed by each parent. This increased variance can significantly decrease the effective population size below that predicted by Equation 26.8, which assumes only the variance effects associated with artificial selection. Yoo (1980c) found that differences in fertility were more important in reducing effective population size than the effects of artificial selection during a long-term selection experiment for increased abdominal bristle number in *Drosophila*.

Example 26.3. Cohan and Hoffmann (1986) examined the divergence between replicate lines of *Drosophila melanogaster* selected for increased resistance to ethanol. The selected lines had a higher between-line variance for characters associated with increased resistance than did the unselected control replicates. This could be explained by a reduction in effective population size due to selection and/or by the Cohan effect. The reduction in effective population size, by increasing drift, is expected to increase the between-line variance in any character, selected or unselected. Conversely, the Cohan effect predicts that only characters under selection, or characters controlled by loci tightly linked to these selected characters, should show increased divergence. To distinguish between these, Cohan and Hoffmann examined three unselected

characters, and found no differences between the selected and control lines, suggesting the main cause of increased divergence was due to the Cohan effect.

DRIFT AND LONG-TERM SELECTION RESPONSE

Recall that we make a distinction between long-term and asymptotic response. The former is the response attributable to the existing variation at the start of selection, while later is the expected eventual rate of response due to the input of new mutation. When the effective population size is small, essentially all of the observed response is due to the initial variation, with the population reaching an apparent selection limit until the appearance of new mutations allows further response. In larger populations, these two components of response become more difficult to separate, and no selection limit may be observed when in fact all of the initial variation has become exhausted. Much of the theory of long-term response has ignored mutation and we examine this first. Even thought this theory is unrealistic over long time scales, it often provides a good description of how the population exhausts its initial variation.

Basic Theory

We expect response to selection in very small populations to be significantly influenced by drift, showing less total response than expected in larger populations starting with the same initial genetic variance. A fairly extensive theory examining the effects of drift on long-term response (the utilization of the existing genetic variation) has been developed, starting with the extremely influential paper of Robertson (1960). Most of this theory is based on summing over single-locus results, and we continue approach unless stated otherwise (this assumes that epistasis and linkage effects can be ignored). As before, we first consider a single diallelic locus (indexed by i) where the genotypes $\mathbf{aa} : \mathbf{Aa} : \mathbf{AA}$ have genotypic values (for the character under selection) of $0 : a(1+k) : 2a$. Let p_t denote the frequency of $\mathbf{A}$ at this locus at generation t, $\Delta_i(t)$ be the contribution to total response from this locus in generation t, and $u_i(p_0)$ the probability that $\mathbf{A}$ is ultimately fixed at this locus given it starts at frequency p_0. The total response is given by summing over all loci, $R(t) = \sum_i \Delta_i(t)$. Under drift, both p_t and $\Delta_i(t)$ are random variables and (assuming genotypes are in Hardy-Weinberg proportions) are related by

$$\begin{aligned}\Delta_i(t) &= m_i(p_t) - m_i(p_0) \\ &= 2a\Big[\, p_t - p_0 + k\Big(p_t(1-p_t) - p_0(1-p_0)\Big)\,\Big] \end{aligned} \tag{26.10a}$$

where $m_i(p)$ is given by Equation 25.1a. The expected contribution (at generation t) from this locus is

$$E[\,\Delta_i(t)\,] = 2a\left[\, E(\,p_t\,) - p_0 + k\Big(E[\,p_t(1-p_t)\,] - p_0(1-p_0)\Big)\,\right] \tag{26.10b}$$

Since $\mathbf{A}$ is ultimately either fixed ($p_\infty = 1$) or lost ($p_\infty = 0$), $E(\,p_t\,)$ converges to

$$1 \cdot u_i(p_0) + 0 \cdot [\,1 - u_i(p_0)\,] = u_i(p_0)$$

while $E\,[\,p_t(1-p_t)\,]$ converges to zero. Thus, the limiting expected contribution from locus i is

$$E[\,\Delta_i(\infty)\,] = 2a\Big[u_i(p_0) - p_0 - k\Big(p_0(1-p_0)\Big)\,\Big] \tag{26.11a}$$

Two cases of special interest are when **A** is additive ($k = 0$),

$$E[\,\Delta_i(\infty)\,] = 2a\,[u_i(p_0) - p_0] \tag{26.11b}$$

and when **A** is recessive ($k = -1$),

$$E[\,\Delta_i(\infty)\,] = 2a\,\left[u_i(p_0) - p_0^2\,\right] \tag{26.11c}$$

The variance (and indeed all higher moments) of the total response at the selection limit are easily computed, as $\Delta_i(\infty)$ takes on only two values,

$$\begin{aligned} \Delta_i(\infty) &= 2a - m_i(p_0) \quad \text{with probability } u_i(p_0) \\ &= \;\; 0 - m_i(p_0) \quad \text{with probability } 1 - u_i(p_0) \end{aligned} \tag{26.12}$$

In particular, the variance in the contribution from this locus over replicate selected lines is

$$\begin{aligned} \sigma^2\,[\,\Delta_i(\infty)\,] &= E\left[\,\Delta_i^2(\infty)\,\right] - \Big(E\,[\,\Delta_i(\infty)\,]\Big)^2 \\ &= 4a^2 u_i(p_0)\,[1 - u_i(p_0)] \end{aligned} \tag{26.13a}$$

With weak selection, $u_i(p) \simeq p$ (i.e., the allelic dynamics are governed by drift), implying

$$\sigma^2\,[\,R(\infty)\,] \simeq 4\sum a^2 p_0(1 - p_0) \tag{26.13b}$$

If all loci are additive, this is simply $2\sigma_A^2(0)$, the expected between-line divergence under pure drift (Chapter 11). Under sufficiently strong selection, almost all favorable alleles are fixed and the variance is close to zero as $u_i(p) \simeq 1$. When selection is moderate to weak, Equation 26.4 shows that loci for which $u_i(p)[\,1 - u_i(p)\,] > p(1-p)$ show a Cohan effect. If such loci are sufficiently frequent, selection *increases* the between-line variance relative to drift. This requires both weak selection and that most favored alleles are rare. The variance in response at the selection limit is considered in more detail by Hill and Rasbash (1986), Zeng and Cockerham (1990), and Zhang and Hill (2005).

The variance in the selection limit across replicate lines has a direct bearing on whether further response can occur by crossing plateaued lines and then reselecting. If drift has played a significant role in response, a line formed by crossing replicate plateaued lines should show further response to selection, as each line should be fixed for a considerable number of unfavorable alleles. Further, with weakly-selected loci, the Cohan effect can occur, segregating favorable variation over replicated lines.

Replicate lines at their selection limits usually show considerable genetic differences (reviewed by Cohan 1984a,b). For example, Scowcroft (1965) used chromosomal analysis to show that three replicate *Drosophila* lines selected for increased scutellar bristles differed considerably in the amount of response attributable to each chromosome and the nature of interactions between chromosomes. Synthetic lines formed by crossing either replicate (Frankham et al. 1968, Eisen 1975, Frankham 1980) or unrelated (Falconer and King 1953, Roberts 1967) plateaued lines generally respond to selection. An interesting exception was that of Gallego and López-Fanjul (1983), who selected sternopleural bristle number in *Drosophila*. Replicate lines showed a very rapid exhaustion of response, and crosses between lines did not result in further response. The authors interpret these results as being consistent with a few major alleles of large effect at intermediate frequency — these alleles rapidly go to fixation, with all lines being fixed for the same major alleles. Similarly, Skibinski and Shereif (1989) found that the between-line variance of lines selected for sternopleural bristle number decreased

over time. The between-line variance is expected to increase over time if drift dominates (e.g., Equation 11.1b) or with weak selection on the underlying loci, but decrease if the lines are fixed for the same few major genes.

Robertson's Theory of Selection Limits

Equations 26.10-26.13 are fairly general, assuming only Hardy-Weinberg, no epistasis, and that single-locus results can be added across loci. To proceed further, we need explicit expressions for $u_i(p)$ to describe the limit and for both $E(\,p_t\,)$ and $E[\,p_t(1-p_t)\,]$ to describe the dynamics. The most complete description, due to Robertson (1960), is for additive alleles, where $E[\,\Delta_i(t)\,] = 2a[\,E(\,p_t\,) - p_0)\,]$. Recalling (Equation 7.28a) that

$$E(p_t) \;\simeq p_0 + 2N_e\left(1 - e^{-t/2N_e}\right) s\, p_0(1-p_0)$$

is an approximate expression for the expected allele frequency under the assumption that the allele has a small effect (i.e., the infinitesimal model). For notational ease, we will drop the expectation notation, but the reader should keep in mind that we are examining the expected response. Recalling from Equation 25.4 that $s = a\bar{\imath}/\sigma_z = aS/\sigma_z^2$, substitution into Equation 7.28a gives the expected response from locus i after t generations of selection as

$$\Delta_i(t) = 2a[\,E(\,p_t\,) - p_0)\,] \simeq 2N_e\left(1 - e^{-t/2N_e}\right)\left(\frac{aS}{\sigma_z^2}\right) 2a\, p_0(1-p_0) \tag{26.14a}$$

This can by simplified further by noting that $2a^2p_0(1-p_0)$ is the initial additive variance contributed by the locus. Since we assumed no epistasis and no linkage disequilibrium, summing over all loci gives the cumulative response at generation t as

$$R(t) \simeq 2N_e\left(1 - e^{-t/2N_e}\right)\frac{S\sigma_A^2(0)}{\sigma_z^2} \tag{26.14b}$$

Note that $S\,\sigma_A^2(0)/\,\sigma_z^2 = S\,h^2(0) = R(1)$ is the expected response in the first generation, provided that the conditions for the breeder's equation hold. Thus,

$$R(t) \simeq 2N_e\left(1 - e^{-t/2N_e}\right) R(1) \tag{26.15a}$$

giving an expected limiting total response of

$$R(\infty) \simeq 2N_e\, R(1) \tag{26.15b}$$

Since $R(1)/\sigma_z = h^2\, S/\sigma_z = h^2\,\bar{\imath}$, the expected limiting response in terms of phenotypic standard deviations is

$$R(\infty)/\sigma_z \simeq h^2(2N_e\,\bar{\imath}\,) \tag{26.15c}$$

Note that Equation 26.15a motivates use of exponential regressions in Chapter 25 to estimate selection limits (Equation 25.10). The careful reader will note that we assumed the phenotypic variance remains relatively constant over time, as would occur if h^2 is small (Chapter 25). Provided this assumption holds, the total expected response is simply $2N_e$ times the initial response, as first suggested by Dempster (1955) and formally derived by Robertson (1960). An alternative derivation of Equation 26.15a is as follows. Assuming the main force for allele frequency change is drift, Equation 10.2 implies $\sigma_A^2(t) \simeq \sigma_A^2(0)[1 - 1/(2N_e)]^t$. Writing the response in generation t as $h^2(t)S = \sigma_A^2(t)\,\bar{\imath}/\sigma_z$, summing over generations and applying Equation 7.28b recovers Equation 26.15a.

Equation 26.15b is an *upper limit* for total response, which may seem somewhat counter-intuitive since it was derived by assuming weak selection. The key is that (everything else being equal) the initial response $R(1)$ when selection dominates is much larger than when drift dominates, so that $2N_e$ times the initial response overestimates the total response when selection dominates.

To see this point, consider the maximal contribution $\Delta_i^{max} = 2a(1-p_0)$ from a locus (which occurs when the favored allele is fixed) relative to the predicted contribution $\Delta_i(\infty)$. From Equation 26.14a, it follows that $\Delta_i(\infty) = 2N_e\, 2a^2 p_0(1-p_0)S/\sigma_z^2$, giving the ratio of maximal to expected contribution as

$$\frac{\Delta_i^{max}}{\Delta_i(\infty)} = \frac{1}{2N_e}\,\frac{2a(1-p_0)}{2a^2 p_0(1-p_0)\,\overline{\imath}/\sigma_z} = \frac{\sigma_z}{2N_e\,\overline{\imath}\,a\,p_0} \tag{26.16a}$$

Thus, when

$$2N_e\,\overline{\imath}\,a\,p_0 > \sigma_z \tag{26.16b}$$

it follows that $\Delta_i^{max} < \Delta_i(\infty)$ and hence $2N_eR(1)$ overestimates the ultimate limit. Recalling Equation 26.3b, the probability of fixation is greater then 70% when Equation 26.16 is satisfied. Further increases in effective population size much above this threshold do not have a significant effect on increasing the selection limit as $\mu_i(p) \simeq 1$ and hence the contribution from the ith locus is Δ_i^{max}. Alternatively, when the inequality given by Equation 26.16b fails, $\Delta_i^{max} > \Delta_i(\infty)$. However, in this case drift is expected to dominate (see Equation 26.3a), so that we do not expect the maximal possible response from each locus, as many favored loci will be lost, rather than fixed.

Another quantity of interest is the expected half-life of response, $t_{1/2}$, the time required to obtain half the final response. Recalling Equation 26.14a and solving $1 - e^{-t_{1/2}/2N_e} = 1/2$ gives the expected half-life as

$$t_{1/2} = N_e\,\ln 2 \simeq 1.4N_e \tag{26.17}$$

Again, this is an *upper limit* with the half-life decreasing as the product $N_e\overline{\imath}$ increases. An observed half-life considerably below that predicted by Equation 26.17 suggests that a large portion of the response is due to fixation of favorable alleles by selection, as selection (when it dominates) changes allele frequencies much faster than drift.

Equations 26.14-17 rely on a number of assumptions besides additivity: no opposing natural selection, no linkage effects, two alleles per locus, and weak selection. Several authors have examined how well these results hold up when these assumptions are relaxed. Hill and Rasbash (1986) found for diallelic loci that the distribution of allelic effects is relatively unimportant, but differences in allele frequencies can be critical. In particular, increasing effective population size has much more of an effect on the selection limit when favored alleles are rare. This is expected, as common alleles are often over the threshold frequency where their dynamics are largely determined by drift (Equation 26.3b). Increasing population size lowers this threshold, eventually capturing even rare alleles (Zhang and Hill 2005). Latter and Novitski (1969) and Zeng and Cockerham (1990) examined the effects of multiple alleles, finding that the expected limit and half-life results given by Equations 26.15b and 26.17 are reasonable when selection is weak. As $N_e\overline{\imath}$ increases, $R(\infty)\,/\,R(1)$ becomes highly dependent on the number and frequencies of alleles at each locus (Chapter 25). In general, it increases as the number of alleles increases, decreases as $N_e\overline{\imath}$ increases, all the while remaining bounded by $2N_e$. Likewise, $t_{1/2}$ decreases as $N_e\overline{\imath}$ increases, but is rather insensitive to the number of alleles.

With dominance, analytic results for the limit and half-life ($R(\infty)$ and $t_{1/2}$) are more complicated. Strictly recessive alleles have received the most study. In this case, the selection limit can considerably exceed $2N_e$ times the initial response when the character is controlled

by a large number of rare recessives (Robertson 1960). Additive genetic variance increases, often considerably, as these recessives increase in frequency, so this result should not be surprising (Chapter 25). With weak selection, the half-life varies from approximately N_e when $p \simeq 1$ to approximately $2N_e$ when $p \simeq 0$ (Robertson 1960). Again, as $N_e\,\overline{\imath}$ increases, half-life decreases. Even with strictly additive loci, an temporary increase in the genetic variance (even in the face of genetic drift) can occur if there are a number of rare, but favored, alleles (Chapter 25). As these increase in frequency, the additive variance also increases. If genetic drift strictly governs the dynamics of the variance, these rare alleles have only a small chance of increasing and do not significantly (on average) inflate the variance. However, if selection is of even modest importance on the dynamics at any particular locus, as Chapter 25 highlights, the single-generation response is a very poor predictor the long-term response.

James (1962), Verghese (1974), and Nicholas and Robertson (1980) extended Robertson's theory for various models of natural selection opposing artificial selection. Not surprisingly, the selection limit is reduced by the presence of opposing natural selection. None of these models retains genetic variability, as drift eventually fixes all loci, even those overdominant in fitness.

TESTS OF ROBERTSON'S THEORY OF SELECTION LIMITS

Robertson's theory applies to the expected response from the existing variation in the base population at the start of selection. Eventually, mutational input becomes important and will ultimately dominate the long-term response, a point we will develop in detail shortly. In the very small population sizes common in many selection experiments, the distinction between exhaustion of the initial variation and the additional response due to new mutation can be fairly clear, as the latter takes many more generations to become apparent than it takes to remove existing variation. For larger population sizes, the two sources of response become increasingly blurred. Hence, most tests of Robertson's theory use very small populations.

Observed limits and half-lives are usually considerably below the values predicted from Robertson's theory (reviewed in Roberts 1966; Kress 1975; Eisen 1980; Falconer and Mackay 1996). Table 26.1 gives various results from experiments with mice. These discrepancies between observation and theory are not unexpected. Robertson's theory assumes that the limit is reached as genetic variance is exhausted by fixation at all loci. As noted in Chapter 25, selection limits can occur in spite of significant additive genetic variance, often because natural and artificial selection are in conflict. Further, as we have stressed, the selection limit of $2N_eR(1)$ and half-life of $1.4N_e$ are expected *upper* limits and require that drift largely dominates. An additional complication is that the effective population size is overestimated by taking the number of parents as N_e (Chapter 3). For example, variation in male mating success in *Drosophila* can decrease the effective population size to less than half of the number of male parents (Crow and Morton 1955). Further, most experiments have not corrected for the expected reduction in N_e from the cumulative effects of selection (Equation 26.6b).

A more direct test of Robertson's theory is that the selection limit should increase, and half-life should decrease, as $N_e\overline{\imath}$ increases. In general, both these predictions hold. For example, the estimated effective population sizes of lines M4, M8, and M16 in Table 26.1 are 7.7, 18.6, and 40.9, while each line experiences essentially the same value of $\overline{\imath}$. (Eisen 1975). For this data set, half-life decreases as $N_e\,\overline{\imath}$ increases as predicted by theory. In a more extensive experiment, Jones et al. (1968) examined the effects of changing N_e and/or $\overline{\imath}$ on otherwise replicate lines of *Drosophila melanogaster*. Since all of their populations were still responding at the end of the experiment (50 generations), they did not estimate the limit or half-lives (although one could use their data with Equation 25.10 to do so). Nevertheless, the data (Table 26.2) are consistent with Robertson's qualitative predictions, as long-term

response increases with $N_e\bar{\imath}$ (Figure 26.2).

Table 26.1. Observed and predicted selection limits (scaled in terms of base-population phenotypic standard deviations) and half-lives (scaled in terms of N_e) for a variety of characters in laboratory populations of mice. From Falconer (1977), Eisen (1975), and Hanrahan et al. (1973).

Character Selected	Direction of Selection	Total Response			
		Observed	Predicted	Ratio	Half-life
Weight					
Strain N	Up	3.4	7.2	0.47	0.6
	Down	5.6	15.9	0.35	0.6
Strain Q	Up	3.9	15.8	0.27	0.2
	Down	3.6	9.6	0.38	0.4
Growth	Up	2.0	7.4	0.27	0.3
	Down	4.5	13.7	0.33	0.5
Litter Size	Up	1.2	2.3	0.52	0.5
	Down	0.5	7.7	0.06	0.5
Postweaning weight gain					
Line M4	Up	1.5	5.4	0.27	0.9
Line M8	Up	2.0	10.0	0.20	0.5
Line M16	Up	4.3	45.0	0.10	0.3

Table 26.2. The cumulative response after 50 generations of selection for increased abdominal bristle number in *Drosophila melanogaster* as a function of effective population size and selection intensity. N_e is estimated as half the number of parents. None of the lines showed an apparent plateau, but the experiment was stopped after 50 generations. Notice that, for fixed N_e that response increases with $\bar{\imath}$ (compare entries within a column), while for fixed $\bar{\imath}$, response increases with N_e (compare across a row). After Jones et al. (1968).

N_e	$\bar{\imath}$	$R(50)$	N_e	$\bar{\imath}$	$R(50)$	N_e	$\bar{\imath}$	$R(50)$
10	1.6	16.3	20	1.7	20.3	40	1.7	31.7
10	1.3	11.2	20	1.4	14.7	40	1.4	18.8
10	0.9	8.1	20	1.0	12.2	40	1.0	16.4

Robertson's theory further predicts that when the effective population is sufficiently large, further increases in N_e should not change the limit (provided mutational input can be ignored), as all favorable alleles initially present become fixed. This has yet to be observed, which is perhaps not surprising given that most experiments have N_e below 50. By designing ingenious devices to facilitate mass selection in *Drosophila melanogaster*, Weber and colleagues (Weber 1990, 1996, 2004; Weber and Diggins 1990) have been able to examine the consequences of larger population sizes. Selection experiments on wing-tip height (Weber 1990) and ethanol tolerance (Weber and Diggins 1990) had effective population sizes on the order of $N_e \simeq 200$–400. Both characters showed an increased response with increasing N_e. The data for wing-tip height are given in Figure 26.3A. Figure 26.3B summarizes the

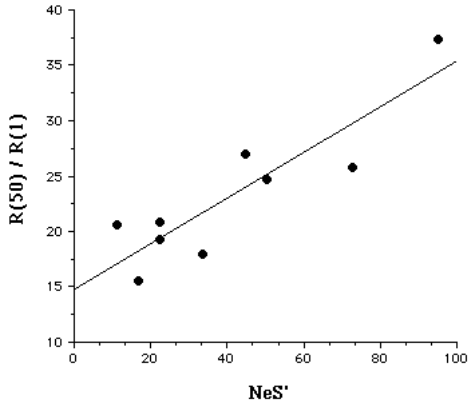

Figure 26.2. Cumulative response at generation 50 as a function of $N_e\overline{i}$ for selection on increased abdominal bristle number is *Drosophila melanogaster*. After Jones et al. (1968).

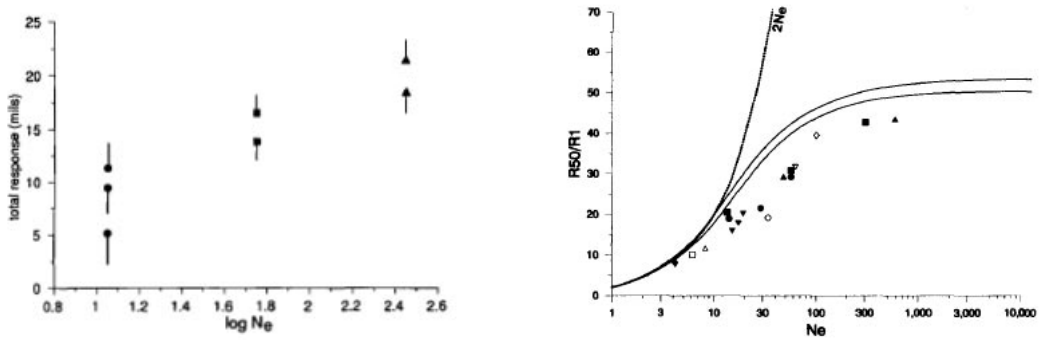

Figure 26.3. **A** (Left): Selection for wing-tip height in *Drosophila melanogaster*. Three replicated selection lines (left to right) with estimated population sizes of 11 (3 replicates), 56 (2 replicates) and 280 (2 replicates) were used. Note that the response increases with N_e. From Weber (1990). **B** (Right): The ratio of cumulative selection response at generation 50 to response in the first generation as a function of effective population size, for nine different experiments. The lower sigmoidal curve is the prediction using Equation 26.15a, the upper sigmoidal curve the prediction given by Equation 26.30c which allows for response from new mutations (assuming $\sigma_m^2/\sigma_E^2 = 0.001$). The dashed curve (marked $2N_e$) is the expected limit under Robertson's additive model (Equation 26.15b). From Weber and Diggins (1990).

results of nine other experiments from previous studies, showing the ratio of response after 50 generations to the initial response. As predicted, this ratio generally increases with N_e. The implication is that there is additional "useable" genetic variation present in the base population that can be exploited by increasing the scaled strength of selection ($N_e\,\overline{i}$). In very small populations, only major alleles are influenced by selection (Equation 26.3). That response continues to increase with N_e suggests that there is a large pool of loci of smaller effects. As $N_e\,\overline{i}$ increases, favorable alleles at these loci are more likely to become fixed, increasing response. Larger populations also provide a greater chance for recombination to remove deleterious linked combinations, which might be fixed in smaller populations, further increasing the potential for response. One complication is that as population size increases, the contribution from mutational input becomes increasingly important over the

time scales it takes to remove the initial variation. We will address this point shortly. A second complication is that when the character value is influenced by inbreeding depression (as would occur if directional dominance is present), its effects are more dramatic is smaller populations. One test for whether inbreeding depression is reducing response is to cross divergently selected lines and look for significant changes in the mean in the resulting F_1 population (e.g., Eisen 1975; Kownacki 1979).

Weber's Selection Experiment on *Drosophila* Flight Speed

Perhaps the largest long-term artificial selection experiment (in terms of effective population size) is the heroic effort of Weber, introduced in Chapter 25. Weber (1996) scored a total of over 9,000,000 *Drosophila* for flight speed in two replicate lines subjected to 100 generations of selection (Figure 25.8). The resulting N_e was in the 500-1000 range, with a percent selected of $p = 0.045$ (for a selection intensity of $\overline{i} = 2.11$). The average speed before selection was around 2 cm/second, while the mean speed at generation 100 was 170 cm/sec. As shown in Figure 25.8, response continued in both lines for 100 generations, but was diminishing with time, as indicated by a significant quadratic component in the response curve. Figure 26.3A shows the results for over 320 generations of selection from Weber (2004). As of this writing, the experiment is over 650 generations, with a diminishing response still occurring (Weber, pers. comm.).

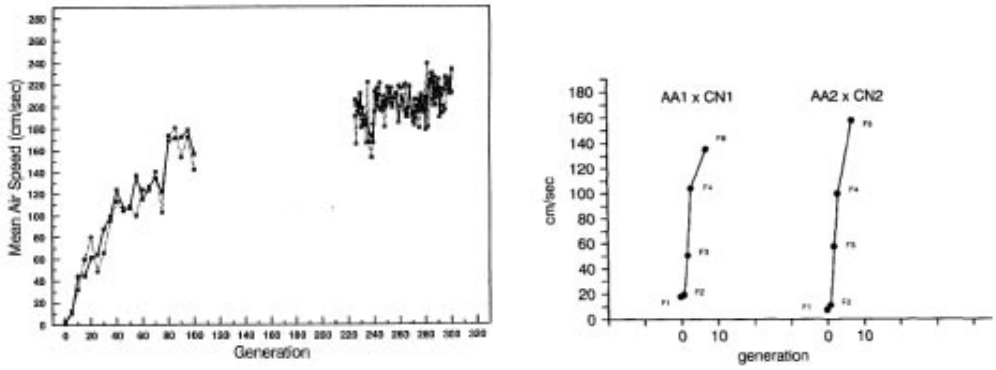

Figure 26.4. Weber's selection experiments for increased flight speed in *Drosophila*. **A** (Left): Results of 320 generations of selection in two replicate lines (open circles and squares), also see Figure 25.8 for the first 100 generations (after Weber 2004). **B** (Right): Response to selection in hybrid sublines formed by crossing generation 75 selection lines back to controls. Selection started on the F_3 lines, with only six generations of selection (the F_8 lines) required to recover essentially all of the initial response. After Weber (1996).

Unlike most other selection experiments, there was little slippage upon relaxation of selection and only a minimal loss in fitness relative to the control populations (fitness decreases of six and seven percent at generations 50 and 85, respectively). Weber attributes this to the larger effective population size which both reduces the level of inbreeding and allows for more efficient selection on modifiers. The later potentially allows for reducing any deleterious pleiotropic effects that accompany major alleles improving flight speed, as the weak second-order effects on modifiers are much easier to select in larger populations. Larger population sizes also allows recombination to be more efficient, reducing the effects deleterious alleles linked to alleles improving flight speed.

Weber gained some insight into the genetic nature of the response by examining the se-

lection response in hybrid lines formed by crossing each replicate selection line at generation 75 (lines AA1 and AA2) back to control lines (CN1 and CN2). As Figure 26.4B shows, both the F_1 and F_2 were close to the control line values, indicating very strong dominance for reduced flight speed. Evidence for epistasis was more equivocal. From the theory of line cross analysis (LW Chapter 9), an estimate of composite epistatic effects is provided by the linear contrast of means of the parental and first two filal populations, $4\,\overline{z}_{F_2} - 2\,\overline{z}_{F_1} - \overline{z}_{P_1} - \overline{z}_{P_2}$, but the resulting value was not significantly different from zero (-38.5 ± 37.5). Selection on both resulting F_2 lines required only six generations to recover essentially all of the response seen in the parental (75-generation) lines.

EFFECTS OF LINKAGE ON THE SELECTION LIMIT

When QTLs are linked, we expect some reduction in the limit as selection at linked loci reduces the fixation probabilities of beneficial alleles (Hill and Robertson 1966; Birky and Walsh 1988; Barton 1995). Simulation studies (Fraser 1957; Latter 1965, 1966a,b; Gill 1965a,b,c; Qureshi and Kempthorne 1968; Qureshi et al. 1968; Qureshi 1968) show that linkage has only a small effect unless loci are very close (less that 5 map units). As mentioned in Chapter 7, most of these studies inflate the importance of linkage by assuming that all loci have equal effects. Simulation studies by McClosky and Tanksley (2013) found only a modest gains ($\simeq 10\%$) in short-term (less than 20 generations) response between populations with normal versus fully-unconstrained levels of recombination.

An approximate analytic treatment of linkage was offered by Robertson (1970a, 1977) (and later by Hospital and Chevalet 1993, 1996; Zhang and Hill 2005), who relied on certain normality assumptions. In the absence of recombination, selection acts on an entire chromosome, and Robertson framed his results in terms of the response contributed by a single chromosome. Robertson considered three different limits, corresponding to different amounts of recombination: L_f, the chromosomal limit with free recombination between all loci; L_0, the limit under complete linkage; and L_ℓ, the limit when the map length of the chromosome is ℓ — if n loci occur on this chromosome, the recombination rate between adjacent pairs is approximately ℓ/n.

As before, the completely additive model is assumed, and loci are assumed to start in gametic-phase equilibrium. Let $\sigma^2_{A^*}$ be the initial additive genetic variance contributed by the focal chromosome and define $(h^*)^2 = \sigma^2_{A^*}/\sigma^2_z$ as the initial fraction of phenotypic variance attributable to this chromosome. The expected contribution from this chromosome following a single generation of selection is $S\sigma^2_{A^*}/\sigma^2_z = \overline{\imath}\, h^* \sigma_{A^*}$. When $N_e \overline{\imath}\, h^*$ is small, the expected limit for a chromosome with freely recombining loci is $2N_e$ times the initial response, giving $L_f \simeq 2N_e\, \overline{\imath}\, h^* \sigma_{A^*}$. Assuming weak selection, Robertson (1970a) found that the ratio of the free-recombination limit to the complete-linkage limit is approximately

$$\frac{L_f}{L_0} \simeq 1 + \frac{2}{3}(N_e \overline{\imath}\, h^*)^2 \qquad \text{when } 2N_e\, \overline{\imath}\, h^* < 1 \tag{26.18}$$

Hence, for weak selection, complete linkage has only a trivial effect when the chromosome contains a large number of QTLs.

When selection is strong ($N_e\, \overline{\imath}\, h^* \gg 1$), the results are more complicated. Robertson assumes that there are n underlying loci, each with frequency p of the favored allele, which increases the character by $2a$ (the difference between the homozygotes). Under these assumptions, the additive variance contributed by this chromosome is $\sigma^2_{A*} = 2na^2p(1-p)$. If selection is sufficiently strong, under free recombination all favored alleles are fixed, and the total response becomes $L_f = 2na(1-p)$. Noting that $a = \sigma_{A*}\,/\sqrt{2np(1-p)}$, this can also be

restated as

$$L_f = 2na(1-p) = \sigma_{A*}\sqrt{\frac{2n(1-p)}{p}} \tag{26.19}$$

On the other hand, with complete linkage the limit approaches twice the value of the best of the initial $2N$ chromosomes sampled (as this chromosome is ultimate fixed). The expected value for the best chromosome is given by the expected value largest order statistic (Example 6 in LW Chapter 9). For a unit normal, this is expressed in terms of standard deviations (here σ_{A*}) above the mean, so that if x_{2N} is the standardized largest order statistic in a sample of $2N$ chromosomes, the limit is given by

$$L_0 = (x_{2N}\sqrt{2})\,\sigma_{A*} \tag{26.20a}$$

Robertson (1970a) showed for $10 < N < 40$ that $x_{2N}\sqrt{2} \simeq 3$, so that that $L_0/\sigma^2_{A^*} \simeq 3$. Hence, for these values of N,

$$\frac{L_f}{L_0} \simeq \frac{1}{3}\sqrt{\frac{2n(1-p)}{p}} \tag{26.20a}$$

The factor of 3 increases to 3.8 when $N = 80$ and to 4.6 when $N = 500$. For larger values of N, using the asymptotic approximation for the largest order statistic given by Kendall and Stuart (1977), the factor of 3 is replaced by

$$x_{2N}\sqrt{2} \simeq \frac{0.577}{\sqrt{\ln(2N)}} + 2\sqrt{\ln(2N)} \tag{26.20b}$$

Note that the increase in the selection limit is only weakly dependent on N, as the largest order statistic scales as $\sqrt{2\,\ln(2N)}$. For example, for $N = 10^9$, it is $\simeq 9.4$.

As the number of loci n increases, Robertson suggested that the limit under free recombination approaches a limit independent of n and p, namely the infinitesimal limit $L_f = 2N_eR(1) = 2N_e\bar{\imath}\,h^*\sigma_{A*}$, so that with strong selection and a large number of loci

$$L_f/L_0 \simeq \left(\frac{2}{x_{2n}\sqrt{2}}\right) N_e\bar{\imath}\,h^* \qquad \text{when} \;\; N_e\,\bar{\imath}\,h^* > 5 \tag{26.20c}$$

Robertson also observed that for large values of $N_e\bar{\imath}\,h^*$ (> 5), the half-life with no recombination is approximately $t_{1/2} \simeq 2/(\bar{\imath}\,h^*)$ generations, and that differences in response (relative to free recombination) only become apparent after this number of generations have passed.

Allowing for some recombination, Robertson found that the limit for a chromosome of length ℓ is

$$L_\ell/L_0 \simeq 1 + N_e\,\ell/3 \qquad \text{when} \;\; N_e\ell \ll 1 \tag{26.21a}$$

To a poorer approximation, over the entire range of $N_e\,\ell$,

$$L_\ell/L_0 \simeq 1 + \frac{KN_e\,\ell/3}{N_e\,\ell/3 + K} \tag{26.21b}$$

where $K = L_f/L_0$. Thus L_ℓ/L_0 approaches L_f/L_0 as $N_e\ell$ increases. Provided $L_f \gg L_0$, L_ℓ is halfway between L_f and L_0 when $N_e\,\ell = 3L_f/L_0$. Assuming moderate to large values of N_e, this result (together with Equation 26.20c) implies that if $\ell > 2\,\bar{\imath}\,h^*$, response will be at least half that expected for free recombination. The above expressions are approximate and assume that each locus has equal effect. Any variation between loci in allelic effects reduces the effect of linkage (Hill and Robertson 1966; Robertson 1970a).

Experimental results generally confirm that suppression of recombination has only a modest effect on the selection limit (Example 26.4). This is a bit at odds with the often dramatic increase in recombination rates seen during some aritifical selection experiments (Example 26.1).

Example 26.4. By using the inversions *Curly* and *Moiré*, McPhee and Robertson (1970) were able to select for sternopleural bristles in *Drosophila* under conditions of suppressed recombination on chromosomes II and III. From previous work, h^2 = 0.4, with these chromosomes accounting for 1/3 and 1/2 (respectively) of the genetic variation in bristle number (the X chromosome accounts for the remaining 1/6). In lines suppressed for recombination at both chromosomes, the limit (on a transformed scale) was 0.166 $\pm$ 0.014 in up-selected lines and -0.134 ± 0.009 in down-selected lines, reductions of 28 $\pm$ 8% and 22 $\pm$ 7% relative to the limit obtained when normal recombination was allowed. For these studies, $N_e \simeq 10$ and $\overline{\imath} \simeq 1$, while $h^*_{II} = \sqrt{0.4/3} \simeq 0.37$ and $h^*_{III} = \sqrt{0.4/2} \simeq 0.45$. Thus, selection is strong on both chromosomes as $N_e\,\overline{\imath}\,h^*_{II} \simeq 3.7$ and $N_e\,\overline{\imath}\,h^*_{III} \simeq 4.5$. Under these conditions, Robertson's theory predicts that the limiting contribution from each (recombination-suppressed) chromosome will be approximately $3\sigma_{A^*}$. Given $\sigma_z = 0.059$, $\sigma_{A^*} = 0.059 \cdot h^*$ and the expected contributions from chromosomes II and III are 3· 0.059· 0.37 $\simeq$ 0.065 and 3·0.059·0.45 $\simeq$ 0.080, for a total absolute contribution of 0.145, consistent with the observed limits. Robertson's theory further predicts that the half-life in recombinationally suppressed lines is roughly $2/(\overline{\imath}\,h^*)$ generations, or $2/0.37 \simeq 5.4$ and $2/0.45 \simeq 4.4$ for chromosomes II and III, respectively, consistent with the observed half-life of 5 generations.

Other *Drosophila* experiments examined the consequences of suppressed recombination on selection response. Both Markow (1975) and Thompson (1977) used stocks with inversions while selecting for increased/decreased phototactic behavior. While Markow observed that suppression reduced the limit, Thompson observed no differences. Markow did not use replicate lines, so the statistical significance of her results are unclear. However, she observed that the most recombinationally-suppressed lines had the most reduced response, consistent with theory. In Thompson's experiments, $N_e \simeq 50$, $\overline{\imath} \simeq 1$, and $h^* \simeq 0.1$ (for both autosomes), giving an expected half-life of $2/(\overline{\imath}\,h^*) = 20$ generations (López-Fanjul 1989). Given that Thompson's experiments were stopped at generation 21, it is not surprising that he found no difference as the effects of linkage on total response are not readily apparent until after the half-life. Bourguet et al. (2003) comment that there is a slightly flaw in all of these *Drosophilia* experiments in that balancer chromosomes are used to suppress recombination, which may have different levels of variation from the base population. Using a more careful approach to suppress recombination, they observed no difference in the response after 38 generation of selection for geotaxis between normal and recombinationally-suppressed lines. However, they noted that their experiment, and likely most others, suffer from low power.

Finally, Morran et al. (2009) contrasted the response of obligate outcrosses versus obligate selfing populations of *Caenorhabditis elegans* to a bacterial pathogen. After 40 generations of exposure, outcrossing populations adapted t the pathogen whereas the obligate selfers did not.

Robertson's result largely focused on the ultimate selection limit, while Hospital and Chevalet (1993, 1996) considered the dynamics of approach to this limit. In particular, Hospital and Chevalet (1996) explicitly considered the effects of gametic-phase disequilibrium (also see Zhang and Hill 2005). Initially, selection generates negative gametic-phase disequilibrium, reducing the initial additive variance and decreasing response. The tighter the linkage, the more pronounced this effect (Chapters 16, 24). Surprisingly, Hospital and Chevalet (and

Zhang and Hill) showed that linkage can often result in an *increase* in the additive variation in later generations of selection. This seemingly counterintuitive result arises because (under strong selection and tight linkage), selection increases the frequency of those gametes carrying the most favored alleles. Any linked alleles decreasing the trait are also dragged along. This increases the probability of fixation of some unfavorable alleles and hence reduces the ultimate selection limit. On the other hand, rare recombination events among such gametes can result in the creation of new, more favored gametes. As these sweep through the population, an increase in the additive variance results. Thus the negative gametic-phase disequilibrium that suppresses the early response stores up some genetic variation that can become released in later generations. This effect is most pronounced in larger populations, as in small population gametes will become fixed before any such recombination events occur.

OPTIMAL SELECTION INTENSITY FOR MAXIMIZING LONG-TERM RESPONSE

When a fixed number M of individuals are scored, there is a tradeoff between the intensity of selection ($\overline{\imath}$) and the amount of drift (N_e). If N individuals are allowed to reproduce (giving $p = N/M$ as the fraction saved), decreasing N (and hence p) increases $\overline{\imath}$ but decreases N_e. Recalling Equation 26.15b, Robertson's selection limit can be expressed as

$$2N_e R(1) = N_e\,\overline{\imath}\,\left(\frac{2\sigma_A^2(0)}{\sigma_z^2}\right) \tag{26.22}$$

showing that the ultimate response (from the initial variation) depends on the product of N_e and $\overline{\imath}$. While decreasing p results in a larger short-term response due to increased $\overline{\imath}$, it also can result in a decreased long-term response by decreasing N_e, as $N_e\,\overline{\imath}$ decreases for sufficiently large or small values of p. Table 26.3 and Figure 26.5B both illustrate, this tradeoff. For example, while the single-generation response using $p = 50\%$ is less than half that for $p = 10\%$, it gives a selection limit over twice as large.

Table 26.3. Differences in short-term versus long-term response as a function of the number of adults saved N when $M = 50$. Initially $h^2 = 0.5$, $\sigma_z^2 = 100$. The infinitesimal model is assumed and we further assume $N_e = N$. The selection intensity $\overline{\imath}$ is obtained using Equation 14.3a (corrected for finite population size). From Equation 13.6b, $R(1) = 5\,\overline{\imath}$, while from Equation 26.15b, $R(\infty) = 2N\,R(1)$.

N	p	$\overline{\imath}$	$R(1)$	$R(\infty)$
25	0.5	0.8	4.0	200
10	0.2	1.4	7.0	140
5	0.1	1.8	9.0	90

Robertson (1960), supporting an earlier conjecture of Dempster (1955), found (for additive loci and normally-distributed phenotypes) that the intensity of selection giving the largest total response is $p = 50\%$, as $N_e\,\overline{\imath}$ is maximized for fixed M when half the population is saved. This can be seen directly for truncation selection on a normally-distributed character. Recall from Equation 14.3a that $\overline{\imath} = \varphi(x_{[1-p]})/p$ (ignoring the correction for finite population size) where x_p satisfies $\Pr(\,U < x_{[p]}\,) = p$ for a unit normal U and $\varphi(x)$ is the unit normal density function. Since the number saved $N = Mp$, we have (following Hospital

and Chevalet 1993),

$$R(t) \simeq Mp\left(1 - e^{-t/2N_e}\right) \frac{\varphi(x_{[1-p]})\sigma_A^2(0)}{p\sigma_z}$$
$$= \varphi(x_{[1-p]}) \left[\frac{M\sigma_A^2(0)}{\sigma_z}\left(1 - e^{-t/2N_e}\right)\right] \quad (26.23)$$

Since the term in brackets is independent of p, response (as a function of p) is maximized at the maximum value of $\varphi(x_{[1-p]})$, which occurs at $x = 0$, or a p value of 0.5.

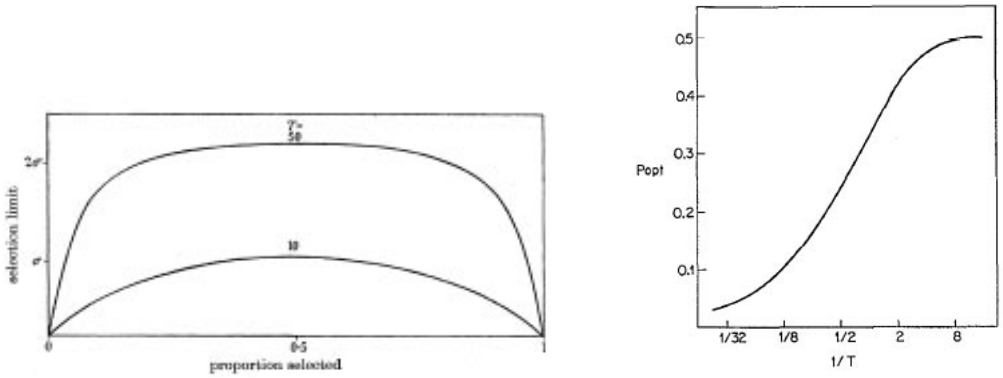

Figure 26.5. **A** (Left): The selection limit as a function of the proportion selected (percent of the population allowed to reproduce) for 10 and 50 individuals scored. From Robertson (1960). **B** (Right): The optimal proportion p_{opt} of individuals selected each generation to maximize the selection advance over t generations, as a function of t/M. From Robertson (1970b).

As Figure 26.5A illustrates, the selection limit as a function of p becomes extremely flat-topped as M increases, so even fairly large deviations from $p = 50\%$ give essentially the same limit. Cockerham and Burrows (1980), relaxing the assumption of normality, found that the optimal proportion for truncation selection is still near 50%, unless the phenotypic distribution is extremely skewed. Hill and Robertson (1966), Robertson (1970a), and Hospital and Chevalet (1993) found that the optimal proportion increases to above $p = 50\%$ when linkage is important.

Robertson's prediction of the optimal selection intensity for long-term response is supported experimentally. For example, Madalena and Robertson (1975) selected for decreased sternopleural bristle number in *Drosophila*. When the best 5 of 25 were chosen, the limit was 17.98 bristles, less extreme than the limit of 17.08 when the best 10 of 25 were chosen. Similar results were seen for increased abdominal bristle number in *Drosophila* (Jones et al. 1968), increased egg-laying in *Tribolium castaneum* (Ruano et al. 1975), and increased post-weaning weight in mice (Hanrahan et al. 1973).

While N places an upper limit on N_e, it often severely overestimates it (Chapter 3), especially since N_e/N decreases as selection intensity increases (Equation 26.6). Hence, increasing selection intensity increases drift by both reducing N and by further reducing the ratio of N_e/N. Table 26.4 illustrates this effect using the same parameters as Table 26.3. Without incorporating this further reduction in N_e, the ratio of expected limits when $p = 50\%$ versus $p = 10\%$ is $200/90 = 2.2$. When this reduction in N_e due to selection is accounted for, this increases to $161/41 = 3.9$.

Table 26.4. As selection intensity increases, N_e is increasingly less than the actual number of parents, further increasing drift. The reduction in effective population size due to selection is computed using Equation 26.6b. Parameters and assumptions are as in Table 26.3 ($M = 50$, $h^2 = 0.5$).

N	$\overline{i}$	N_e	N_e/N	$2N_e\,R(1)$
25	0.8	20.2	0.81	161
10	1.4	5.8	0.58	81
5	1.8	2.3	0.47	41

More generally, Robertson (1970b) obtained the optimal selection intensity when the goal is to maximize the total response (from the initial variation in the base population) at generation t. Robertson's derivation follows using Equation 26.15a. As Figure 26.5B shows, the optimal proportion is function of t/M. Robertson assumed the infinitesimal model and equal contributions from each sex. Jódar and López-Fanjul (1977) extend these results to unequal sex ratios, finding that the maximal response occurs when the number of individuals scored and the proportions selected are the same in each sex. This follows since effective population size is reduced as the sex ratio deviates from one-to-one (Equation 3.12), increasing the effects of drift. Hospital and Chevalet (1993) examined the effects of linkage, finding that the amount by which the optimal p exceeds the predicted value increases with population size. In small populations, the value predicted from drift (for any particular t/M value) is close to the optimal value, while in larger populations Robertson's value seriously underestimates the optimal p value.

Ruano et al. (1975) and Frankham (1977) tested Robertson's predictions for the optimal response at a particular generation with selection experiments for egg-laying in *Tribolium* and abdominal bristle number in *Drosophila*, respectively. The theory holds up well for $t/M \leq 0.2$, but both authors found discrepancies between the observed and predicted rank order of lines subjected to different selection intensities for t/M values above this. One explanation of these discrepancies could be the presence of major alleles, resulting in additive variance declining more rapidly than expected under the infinitesimal model. This results in the optimal proportions being larger than those predicted from Figure 26.5B. Frankham (1977) also suggests that not correcting for the additional decrease in N_e with increased selection intensity (e.g., Table 26.4) results in incorrect values of N_e and hence incorrect optimal proportions. García-Dorado and López-Fanjul (1985) examined the consequences of unequal sex ratios using sternopleural bristle number in *Drosophila*. Equal sex ratios gave the highest response, and good agreement with the optimal values predicted by Jódar and López-Fanjul was seen with unequal sex ratios.

EFFECTS OF POPULATION STRUCTURE ON LONG-TERM RESPONSE

Our development of Robertson's theory of selection limits has made a two assumptions regarding population structure: selection occurs in a large panmictic population and the initial base population is infinite in size. This section relaxes these assumptions. We first examine the consequences of founder effects in the initial base population and of passing the population through bottlenecks during selection. We conclude by examining the expected limits when the population is subdivided and when selection is entirely within families.

Founder Effects and Population Bottlenecks

So far, we have been considering only the effects of drift due to selecting N adults each generation from an initial base population assumed to be infinite. Drift can occur prior to

selection if the base population is founded from only a few individuals. By altering the initial additive variance, this initial sampling can alter response. To distinguish between these different sources of drift, let N_0 denote the number of founders and N_e the effective population size during selection. Thus, if $\sigma_A^2(0)$ is the additive variance of the population from which the founders are drawn, then the expected initial additive variance (assuming no nonadditive effects) in the founder population is $[\,1 - 1/(2N_0)\,]\,\sigma_A^2(0)$.

Founder effects can have a significant effect on response. Robertson (1966), reporting on the unpublished thesis of Da Silva (1961), found that lines formed from a single parental pair had response decreased by roughly 30% relative to a non-bottlenecked line from the base population (Figure 26.6A). Lines formed from taking single parental pairs for three consecutive generations showed only a modest further reduction in response, suggesting that most of the founder effect occurred in the first generation. Robertson's interpretation was that response in this population was due largely to alleles at intermediate frequency, as alleles at low frequency are expected to be lost during the initial sampling. Segregating alleles present after this initial bottleneck of two individuals have intermediate frequencies ($1/4$, $1/2$, or $3/4$) and are thus somewhat resilient to further sampling events.

Using the above reasoning, Robertson (1960) predicted that the effect of restricting population size after several generations of selection is expected to be small, as favored alleles are expected to be at intermediate to high frequencies. Jones et al. (1968), however, found that even after many generations of selection such bottlenecks can have a large effect. Sublines formed by taking ten pairs of adults from a parental line selected for 16 generations showed reduced response relative to their parent lines (Figure 26.6B). One explanation is that there were still desirable alleles at low frequencies following 16 generations of selection. These alleles can be lost when the population passes through a bottleneck, reducing response. One source for these rare major alleles could be new mutations. Alternate explanations are considered by Frankham (1983b).

James (1970) examined the expected reduction in response due to founder effects. As before, results are developed for a single additive locus, and extended by assuming gametic-phase equilibrium and no epistasis. Since the initial additive variance in the founder population is $[\,1 - 1/(2N_0)]\,\sigma_A^2(0)$, the expected response for the first generation of selection from a bottlenecked population is $[\,1 - 1/(2N_0\,)]$ times the expected response for an initially infinite population. The long-term effects of an initial bottleneck are more unpredictable, depending on initial allele frequencies and the relative strength of selection. When selection is weak at all loci (the infinitesimal model), taking the initial additive variance as $[\,1 - 1/(2N_0)]\,\sigma_A^2(0)$ the arguments leading to Equation 26.15a give the expected response for a founder population at generation t as

$$R_{N_0}(t) = R(t)\,\left(1 - \frac{1}{2N_0}\right) \tag{26.24a}$$

where $R(t)$ is the response expected when the initial base population is infinite (Equation 26.15a). More generally, if two replicate populations of the same size are created using different numbers of founders (N_1, N_2) from a common large base population, the ratio of expected response at any generation is given by

$$\frac{R_{N_1}}{R_{N_2}} = \frac{1 - 1/(2N_1)}{1 - 1/(2N_2)} \tag{26.24b}$$

Thus, if selection at all loci is weak and all genetic variance is additive, the effect of a bottleneck depends only on N_0.

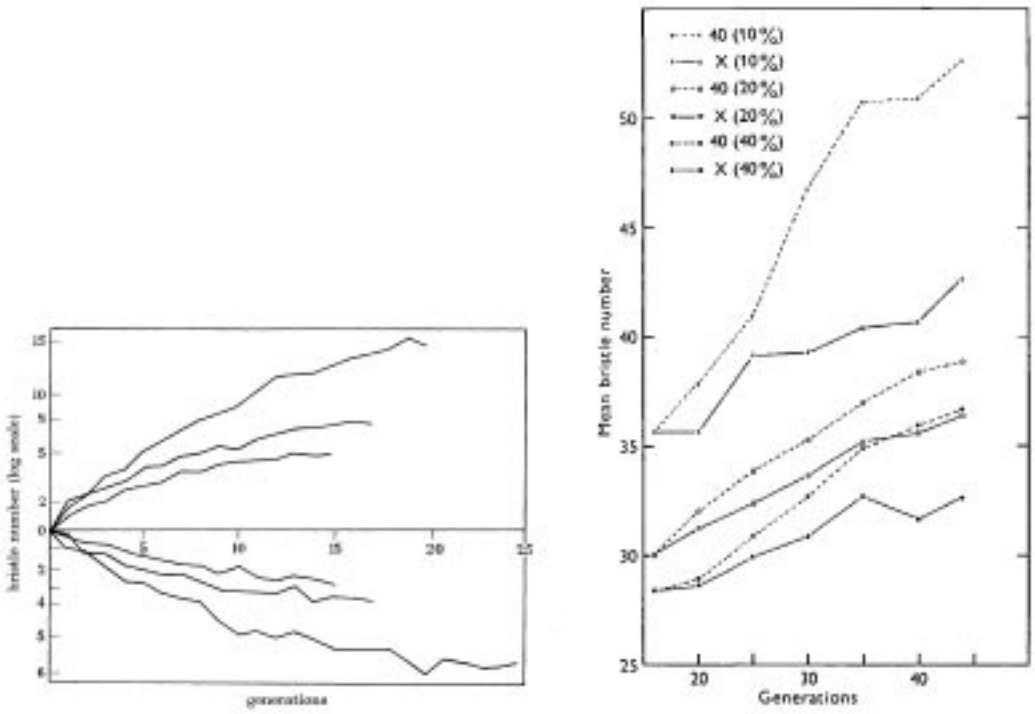

Figure 26.6. Effects of population bottlenecks on selection response. **A** (Left): Selection for sternopleural bristle number in *Drosophila melanogaster*, with the most extreme 10 pairs out of 25 scored pairs selected. The outer curves are the response using the base population. The middle curves are the response for sublines formed from a single parental pair, followed by six generations of random mating to build up population size prior to selection. The inner curves correspond to sublines formed by using a single parental pair for three consecutive generations prior to selection. From Robertson (1966). **B** (Right): Selection for abdominal bristle number in *Drosophila melanogaster*. The responses denoted by 40 (10%), 40 (20%), and 40 (40%) correspond to populations where the uppermost 40 pairs of adults are selected each generation, with different selection intensities. For example, 200 pairs are scored and the uppermost 40 chosen in the 40 (20%) population. Responses denoted by X (10%), X (20%), and X (40%) for X = 10 or 20 refer to lines split from the corresponding 40-pair lines after 16 generations of selection and selected thereafter at the same intensity with 10 pairs of parents per generation. From Jones et al. (1968).

Founder effects are most serious when rare favorable alleles of large effect are present, but predicting the magnitude of the effect in any given population is difficult. When selection on a locus is strong ($2N_e s \gg 1$), the probability that a selected line formed from a bottlenecked base population will eventually be fixed for the favored allele converges to

$$u_{N_0}(p_0) = 1 - (1 - p_0)^{2N_0} \tag{26.25a}$$

This follows since if selection is sufficiently strong, the favored allele will become fixed if it is found in the initial sample, which occurs with probability $1 - (1 - p_0)^{2N_0}$. The ratio of the expected limiting contribution from this locus to the expected contribution when the founding population is infinite is

$$\frac{u_{N_0}(p_0) - p_0}{u(p_0) - p_0} \simeq \frac{1 - (1 - p_0)^{2N_0} - p_0}{1 - p_0} = 1 - (1 - p_0)^{2N_0 - 1} \simeq 1 - e^{-p_o(2N_0 - 1)} \tag{26.25b}$$

Since the initial frequencies of major alleles are unknown, the long-term effects of a bottleneck, even when all genetic variance is additive, is unpredictable. To see this, suppose that a rare ($p \ll 0$), but favorable (a large), allele is initially present. Its contribution to the initial additive variance is $V = 2a^2p(1-p)$, while (if fixed), its contribution to the response is $R = 2a(1-p)$. Hence, $R = V/(ap)$ so that if $ap \ll 1$, but a large, it makes a large contribution if fixed, but only a small contribution to the initial variance. If $p \ll 0$, it could be easily lost by drift, with only a small effect on the additive variance, but a large potential loss of response. Further, as Zhang and Hill (2005) note, many artificial selection experiments examining the genetic architecture of a trait first start by breeding a wild-caught sample in the lab for many generations. This generates additional drift, and can result in rare (but important) alleles from the sampled population not being present at the start of artificial selection, and generating a selection response that is not different from that expected under an infinitesimal model.

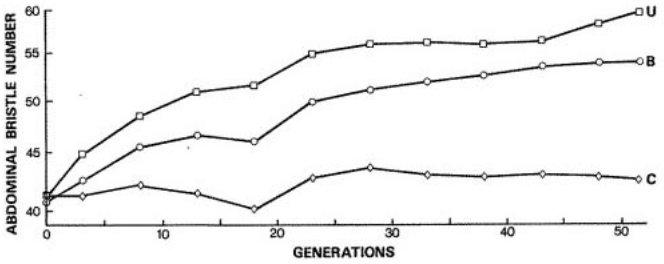

Figure 26.7. The effect of an initial bottleneck on selection for increased abdominal bristle number in *Drosophila*. **B** corresponds to the response in bottlenecked populations formed from a single pair of parents, **U** to a non-bottlenecked population, and **C** the unselected control. All lines were maintained by using 20 pairs of parents each generation. After Frankham (1980).

Frankham (1980) examined founder effects in *Drosophila* populations selected for increased abdominal bristle number. As shown in Figure 26.7, the limit to bottlenecked populations formed from two founders was between 0.69 and 0.72 of that for non-bottlenecked populations, quite close to the value of $[\,1 - 1/(2N_0)\,] = 0.75$ predicted for additive loci under weak selection (Equation 26.24b). Frankham reports similar unpublished thesis results of Da Silva (1961) and Hammond (1973). However, while D. Robertson (1969, reported in James 1970) observed a decrease in response with decreasing number of founders when the number of selected parents (N_e) was 10, there was no obvious effect when $N_e = 40$ (which is not unexpected since $1 - 1/80$ is negligible). We have been unable to find any reports of response increasing significantly when the population is passed through a bottleneck, as can occur if significant nonadditive variance is present (Chapter 11). Clearly, there is a need for further experiments.

An especially interesting experiment on founder effects is the work of Skibinski and Shereif (1989) who examined sternopleural bristle number in *Drosophila melanogaster*. Three initial lines were created from a large base population by taking parents from different parts of the distribution of bristle number to generate a high line, a low line, and a line from the central part of the distribution. The central line had the largest total response to divergent selection. Skibinski and Shereif suggest that these results are consistent with a few major alleles underlying the trait with the central line having higher heterozygosity at these loci (hence more useable genetic variance) than the extreme lines. One complication with this interpretation is that the central line had a larger initial population size than either extreme

line.

Population Subdivision

Thus far, we have been considering the long-term response under mass selection in a single panmictic population. How robust are our results if we subdivide the total population? When only additive variance is present, Robertson (1960) showed that population structure has little effect on the selection limit. In particular, the expected limit for a population formed by crossing N (replicate) plateaued lines of size m is the same as a single line with size Nm. Maruyama (1970) generalized this result by showing (for additive loci and ignoring linkage effects) that any subdivision of the population gives the same limit, independent of when and how lines are crossed, provided there is no selection *between* lines. Madalena and Hill (1972) further showed that linkage has only a minor effect on this conclusion. They also found (again assuming only additive variance) that while between-line selection (i.e., culling some of the lines) may increase short-term response, removing lines decreases the total genetic variance of the entire population, decreasing the limit. This reduction is most severe with free recombination, and is negligible with tight linkage. One caveat with these results is that breeders typically try to maximal gain for a set level of inbreeding, and Smith and Quinton (1993) show that selecting and crossing sublines gives less response for a fixed level of inbreeding as does selection in a single line.

When significant nonadditive variance is present, population subdivision may increase the selection limit. For example, when favorable rare recessives are present, subdividing the population and subsequently crossing these lines when they plateau and then reselecting gives a higher expected limit than using a single panmictic line of the same total size (Madalena and Hill 1972; Slatkin 1981). The increased inbreeding in the sublines increases the frequency of homozygotes, facilitating selection for favorable recessives.

Similarly, **Wright's shifting balance theory** (Wright 1931, 1951, 1978, 1982), assumes that local inbreeding due to population subdivision facilitates the accumulation of rare favorable epistatic combinations of loci. Crossing such fixed (or nearly fixed) lines increases the selection limit relative to a single panmictic population, much akin to what happens with rare recessives. Indeed, Enfield and Anklesaria (1986) found in simulation studies that when additive-by-additive epistatic variance is present, certain population subdivisions give greater short-term and long-term response than a single panmictic population.

Selection experiments with population subdivision (reviewed in Rathie and Nicholas 1980; López-Fanjul 1989) generally give results similar to those expected under the strictly additive model: subdivision usually has no effect on the selection limit. Two experiments reported exceptions to this. Madalena and Robertson (1975) selected for decreased sternopleural bristle number in *Drosophila melanogaster* under two different population structures: a single-cycle structure where sublines were crossed once, and a repeat-cycle structure where sublines were crossed multiple times. The limit under the single-cycle structure was essentially the same as a panmictic population, regardless of whether or not between-line selection was practiced. The limit under the repeat-cycle structure was slightly more extreme than the panmictic population. These results are complicated by the presence of major alleles lethal as homozygotes, but nevertheless suggest the presence of some favorable recessives initially at low frequency. The second exception was the experiment of Katz and Young (1975), who selected for increased body weight in *Drosophila*. Populations that were subdivided with a small amount of migration between them gave a slightly larger response than the panmictic population.

There have been a number of contrasting views on the optimal population structure for evolution. Wright (1931, 1951, 1977, 1978, 1982) suggests that evolution is most rapid when the population is subdivided, while Fisher (1958) viewed a single large panmictic population as the optimal structure. When mostly additive gene action is present, both the Wright and

Fisher structures are expected to give comparable rates of evolution, although the Fisher structure may have a slight advantage when the effects of linkage are considered (in larger populations, the probability that a deleterious allele linked to a favorable allele will hitch-hike to fixation is decreased, increasing the potential response). With non-additive gene action, the optimal structure depends on the exact nature of gene action. With recessives, population subdivision increases the response. With epistasis, the Wright structure offers an advantage if epistatic combinations are such that their formation requires intermediate genotypes that are deleterious. Conversely, in other situations the Fisher structure may offer an advantage in that it allows more gene combinations to be tested. There remains very significant debate over which structure is more relevant (Coyne et al. 1997, 2000; Peck et al. 1998, 2000; Wade and Goodnight 1998; Goodnight and Wade 2000).

One must keep in mind that the optimal population structure for maximizing response under one type of gene action may not be optimal for other types. In particular, many types of population structure that increase the probability of fixation of recessive and/or epistatic genes may retard the fixation of advantageous additive genes. Likewise, even structures that do not decrease the fixation probability may increase the fixation time, reducing the rate of response.

Caballero et al. (1991a) examined the types of mating schemes (following selection) that increase the fixation probability of recessive alleles while not significantly reducing the fixation probabilities nor increasing the fixation times for additive genes. They found that mating full sibs wherever possible following selection increases the fixation probabilities for recessives (relative to random mating following selection) without any significant effect on additive alleles. The tradeoff here is a slight reduction in N_e (due to the increased inbreeding by full-sib mating following selection) versus the increased selection on recessives by inbreeding (compare Equations 7.19b and 7.20c). Recall from Equation 7.20c that the measure f of departures from Hardy-Weinberg frequencies enters into the selection coefficients. Caballero et al. show

$$f = \frac{N_{FS} - 1}{4N_{TM} - 3N_{FS} + 3} + f_r \tag{26.26a}$$

where N_{FS} is the number of full-sib matings, N_{TM} the total number of matings, and f_r the departure from Hardy-Weinberg genotype frequencies under random mating in a finite population, which is given by

$$f_r = -\left(\frac{1}{8N_f} + \frac{1}{8N_m}\right) \tag{26.26b}$$

where N_m and N_f are the number of reproducing males and females. Note that the negative sign implies that under random mating, there is a slight expected excessive of heterozygotes relative to the frequency expected from the allele frequencies alone.

Within-Family Selection

As we have seen, the variance in number of offspring contributed by each selected parent is an important determinant in effective population size — the larger this variance, the smaller N_e (Equation 3.4). Exploiting this, Toro and Nieto (1984) note that deliberately assigning selected parents different probabilities of contributing offspring (according to a specific formula) gives populations with the same selection intensity but different effective population sizes. Suppose 20 individuals are measured ($M = 20$), and we wish the expected selection intensity to be 1.2. This occurs if the best 5 individuals are chosen (using Equation 14.4b to correct $\bar{\imath}$ for finite population size) and each parent has equal probability of contributing offspring. The same selection intensity can be obtained by choosing the best 10 individuals and assigning these individuals unequal probabilities for contributing offspring (see Toro

and Nieto for details). This latter scheme (while holding both selection intensity and the number of measured individuals constant) increases effective population size from 5 to 5.9, which in turn increases the long-term response.

The most extreme example of this occurs when selection is entirely within families: the best male and female are chosen from each full-sib family and mated at random between families. This doubles the effective population size relative to selecting the same number of individuals independent of family structure (recall from Equation 3.4 that if all parents contribute the same number of offspring, there is no variance in offspring number and $N_e = 2N$). We remind the reader at this point of the important, but subtle, distinction between parents having an equal *probability* of contributing offspring versus parents contributing exactly the same *number* of offspring. In the former case, some parents will contribute no offspring and others more than one, generating a non-zero variance. In the latter case, all parents make an identical contribution and there is no variance in offspring number.

Thus, using within-family selection results in a population with twice the effective size as one undergoing mass selection with the same number of individuals selected. However, as Robertson (1960) noted, the usable additive genetic variance within full-sib families is only half that available under mass selection (Equation 21.18a). This exactly cancels the advantage of a larger N_e, suggesting that both methods give the same limit. Dempflé (1975) pointed out that this conclusion relies critically on h^2 being low. Applying Equations 21.20 and 21.23, the response to a generation of within-family selection is (for full-sibs)

$$R_{w\,FS}(1) = \overline{\imath}\, h^2_{w\,FS}\, \sigma_{w\,FS}$$

where

$$h^2_{w\,FS} = \frac{\sigma^2_A/2}{\sigma^2_{w\,FS}} \quad \text{and} \quad \sigma^2_{w\,FS} = \frac{\sigma^2_A}{2} + \sigma^2_{Es}$$

If the additive variance is much larger than the within-family environmental variance (σ^2_{Es}), then $h^2_{w\,FS} \simeq 1$ and $\sigma^2_{w\,FS} \simeq \sigma^2_A/2$, giving $R_{w\,FS}(1) \simeq \overline{\imath}\,\sigma_A/\sqrt{2}$. If the total environmental variance is much smaller than the additive variance, the expected response to individual selection becomes $R(1) \simeq \overline{\imath}\,\sigma_A$. Thus, when additive variance dominates, the ratio of expected limits is

$$\frac{4NR_{w\,FS}(1)}{2NR(1)} \simeq \sqrt{2}$$

and within-family selection increases the limit.

Three other factors can favor within-family selection.

1. *Significant between-family environmental variance*. If most of the environmental variance is due to between-family, rather than within-family, effects (i.e., if $\sigma^2_{Ec} > \sigma^2_{Es}$), within-family selection gives a larger single-generation response than individual selection (see Chapter 21). Coupling this with the decreased loss of variation due to a larger effective population size, within-family selection is superior when the between-family component of environmental variance is sufficiently large.

2. *Retardation of the cumulative reduction in N_e from selection.* Recall that individual selection reduces N_e below the actual number of parents by inflating the between-family variance in offspring number when h^2 and/or $\overline{\imath}$ are large. This variance is zero under within-family selection, giving within-family selection an effective population size greater than twice that for individual selection, so that N_e(within-family) $> 2N_e$(individual).

3. *Gametic-phase disequilibrium*. The presence of gametic-phase (linkage) disequilibrium also increases the effectiveness of within-family selection relative to individual selection. Under the assumptions of the infinitesimal model, the negative gametic-phase

disequilibrium generated by directional selection reduces the between-family component of additive variance, while the within-family component remains unchanged (Chapters 16 and 24). Hence, the usable additive variance in the mass-selection lines is decreased, while the usable additive variance in the within-family lines is unchanged. This effect is largely negligible unless selection is strong and heritability is high.

Young and Skavaril (1976) used computer simulations to examine the consequences of major alleles and linkage on within-family selection. They found that individual selection was superior to within-family selection in small populations, especially when major alleles are rare and/or when h^2 is small.

On the experimental side, von Butler et al. (1984) compared individual and within-family selection on 8-week body weight in mice. In one set of replicates, within-family selection initially showed a reduced response, but after 18 generations had essentially the same response as mass-selected lines. In alternative set of replicates (using a different base population), mass selection did better than within-family selection, but both populations were still responding after the experiment was stopped (after 18 generations). Since within-family selection is expected to show a longer period of response due to a large effective population size, the results for the second set of replicates are inconclusive.

ASYMPTOTIC RESPONSE DUE TO MUTATIONAL INPUT

As reviewed in Chapter 25 (and by Frankham 1980, 1983a; Weber and Diggins 1990; Weber 2004), there is strong evidence that new mutants contribute to selection response even during the short time scales of many "long-term" laboratory experiments. The selection limit resulting from drift and selection removing all initial genetic variation is thus an artifact of time scale as it ignores this mutational contribution. Even if an observed limit is due to a balance between natural and artificial selection, new mutations with less deleterious pleiotropic effects on fitness can arise, resulting in further response.

If a rare recessive is initially present at low frequency, the appearance of homozygotes involving this allele may been taken as new mutations. If a recessive is present as a single copy, the expected time until the first appearance of a homozygote is approximately $2N^{1/3}$ generations, with the appearance time following a nearly geometric distribution (Robertson 1978; Karlin and Tavare' 1980, 1981a, 1981b; Santago 1989). Since $N_e \leq 500$ for most selection experiments, any recessives initially present (and not lost by drift) will be expressed as homozygotes by around generation 15.

Our discussions of the nature of long-term response with mutational input largely follow Hill's pioneering treatment (1982b,c). We start by assuming complete additivity. Recall from Chapter 11 (and LW Chapter 12) that one measure of mutational input is σ^2_m, the amount of new additive variance produced by mutation each generation. Consider the ith locus, where each allele mutates to a new one with a per-generation rate of μ_i. The **incremental mutation model** is assumed: when an allele $\mathbf{A}$ mutates to a new allele $\mathbf{A}'$, the genotypic values of $\mathbf{AA}'$ and $\mathbf{A}'\mathbf{A}'$ are $g_{AA} + a$ and $g_{AA} + 2a$, where g_{AA} is the genotypic value of $\mathbf{AA}$. This model assumes that the genotypic value of the new mutant depends on the state of its parental allele. However, the distribution of increments (a) added to the parental allele are assumed to be independent of the value of the parental allele. For n loci we have

$$\sigma^2_m = 2\sum_{i=1}^{n} \mu_i \, \sigma^2_i(a)$$

We first consider the infinitesimal model before examining a more general model and the

consequences of dominance.

Results for the Infinitesimal Model

We assume complete additivity and ignore any effects of gametic-phase disequilibrium. From Equation 10.19b, the expected additive genetic variance at generation t is given by

$$\sigma_A^2(t) \simeq 2N_e\sigma_m^2 + \left[\sigma_A^2(0) - 2N_e\sigma_m^2\right] \exp(-t/2N_e) \tag{26.27}$$

Setting $\sigma_A^2(0) = 0$ gives the additive variance contributed entirely from mutation as

$$\sigma_{A,m}^2(t) \simeq 2N_e\sigma_m^2\,[\,1 - \exp(-t/2N_e)\,] \tag{26.28a}$$

Hence, the rate of response at generation t from mutational input is

$$r_m(t) = \overline{\imath}\,\frac{\sigma_{A,m}^2(t)}{\sigma_z} \simeq 2N_e\,\overline{\imath}\,\frac{\sigma_m^2}{\sigma_z}\,[\,1 - \exp(-t/2N_e)\,] \tag{26.28b}$$

where we have made the usual assumption that the phenotypic variance σ_z^2 does not significantly change over time (more generally, σ_z^2 can be replaced by $\sigma_z^2(t) = \sigma_A^2(t) + \sigma_E^2$), and disequilibrium is ignored. For $t \gg 2N_e$, the per-generation response approaches an asymptotic limit of

$$r_m(\infty) = 2N_e\,\overline{\imath}\,\frac{\sigma_m^2}{\sigma_z} \tag{26.29}$$

Assuming $\sigma_A^2(0) = 0$, half this rate occurs when $t \simeq 1.4N_e$ (Hill 1982b,c). There are several ways to intuit the value of the asymptotic limit. From Robertson's theory, we expect the final response to be $2N_e$ times the initial response $R(1)$, which for new mutants arising in any particular generation is $R(1) = \overline{\imath}\,\sigma_m^2/\sigma_z$. Alternatively, note that the equilibrium additive variance is $2N_e\sigma_m^2$, which (upon recalling Equation 13.6b) gives an Equation 26.29.

Summing over generations (and using the approximation given by Equation 7.28b) gives the cumulative response due to new mutation as

$$R_m(t) = \sum_{\tau=1}^{t} r_m(\tau) \simeq 2N_e\,\overline{\imath}\,\frac{\sigma_m^2}{\sigma_z}\left(t - 2N_e[\,1 - \exp(-t/2N_e)\,]\right) \tag{26.30a}$$

as found by Hill (1982c, 1990) and Weber and Diggins (1990). For genes of sufficiently large effect ($|\,a\,| \gg \sigma_z/N\,\overline{\imath}$) which can be considered to be fixed essentially instantaneously, the response becomes

$$R_m(t) = 2tN_e\,\overline{\imath}\,\frac{\sigma_m^2}{\sigma_z} \tag{26.30b}$$

as suggested by Hill (1982c). Note from Equation 26.29 that this implies the asymptotic rate of response applies from generation one.

Combining the mutational response with the response due to genetic variation originally in the base population (Equation 26.15a) gives an expected cumulative response of

$$R(t) = 2N_e\frac{\overline{\imath}}{\sigma_z}\left(t\,\sigma_m^2 + [\,1 - \exp(-t/2N_e)\,]\left[\sigma_A^2(0) - 2N_e\sigma_m^2\right]\right) \tag{26.30c}$$

The $t\sigma_m^2$ term, which represents the asymptotic response, will eventually dominate. The other term in the parentheses represents the transient effect of the initial additive variance, and is zero if the population starts at the mutation-drift equilibrium (i.e., $\sigma_A^2(0) = 2N_e\sigma_m^2$).

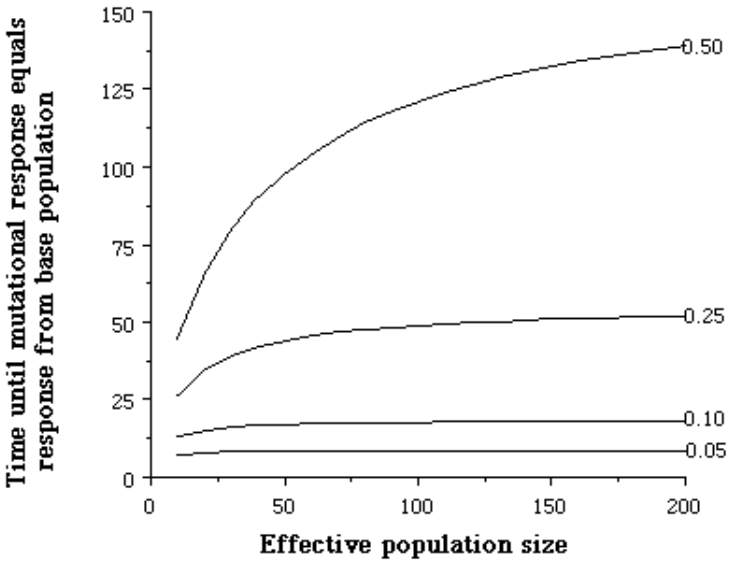

Figure 26.8. The expected generation at which response due to mutational input equals the response due to initial variation in the base population (Equation 26.31a). We used $\sigma_m^2/\sigma_E^2 = 0.005$, which is the average value of the experiments in LW Table 26.1, from which Equation 26.31b gives $\Psi = 100h^2/[(1-h^2)\,N_e]$. The four curves correspond to initial heritabilities of 0.05, 0.10, 0.25 and 0.50.

Of considerable interest is the expected number of generations until response from mutational input exceeds that contributed by the initial variation. Let t^* be the generation when the per-generation response from both sources is equal. Here the initial additive variance remaining at generation t^* equals the new additive variance generated by generation t^*,

$$\sigma_A^2(0)\exp(-t^*/2N_e) = 2N_e\,\sigma_m^2\,[\,1-\exp(-t^*/2N_e)\,]$$

This equation has the solution

$$t^* = 2N_e\,\ln(1+\Psi) \tag{26.31a}$$

where $\Psi = \sigma_A^2(0)/(2N_e\sigma_m^2)$. Denoting the initial heritability by h^2, and recalling that $\sigma_E^2 = (1-h^2)\sigma_z^2$,

$$\frac{\sigma_A^2(0)}{\sigma_m^2} = \frac{h^2\sigma_z^2}{\sigma_m^2} = \frac{h^2}{\sigma_m^2/\sigma_z^2} = \frac{h^2}{(1-h^2)\sigma_m^2/\sigma_E^2}$$

giving

$$\Psi = \frac{h^2}{(1-h^2)\,2N_e\,(\sigma_m^2/\sigma_E^2)} \tag{26.31b}$$

The average value of σ_m^2/σ_E^2 is approximately 0.005, see LW Table 17.1. With this value, t^* is only rather weakly dependent on N_e (see Figure 26.8). If $\Psi \ll 1$, so that the expected additive variance at the mutation-drift equilibrium exceeds the initial additive variance ($\sigma_A^2(0) \ll 2N_e\sigma_m^2$), then using the approximation $\ln(1+x) \simeq x$ for small $|x|$, we have

$$t^* \simeq 2N_e\Psi = \frac{h^2}{(1-h^2)(\sigma_m^2/\sigma_E^2)} \tag{26.31c}$$

Again using $\sigma_m^2/\sigma_E^2 = 0.005$ gives $t^* \simeq 200h^2/(1-h^2)$. This translates into 11, 22, and 67 generations until the rate of response from mutational input exceeds the rate of response due to initial variation for h^2 values of 0.05, 0.10, and 0.25 (respectively). As Figure 26.8 shows, Equation 26.31c tends to slightly overestimate the true value (Equation 26.31a). For $\sigma_m^2/\sigma_E^2 = 0.001$, these values increase five-fold to 52, 111, and 250 generations.

It is important to stress that our expressions for half-life of response assume that drift dominates and tend to overestimate the half-life when selection is moderate to strong. Likewise, we expect that the infinitesimal model underestimates the changes in allele frequencies of new mutants under moderate to strong selection. Thus, our expression for t^* is very likely an overestimate and we should regard Equation 26.31 as an upper bound.

Example 26.5. Yoo (1980a) observed a steady and reasonably constant increase in *Drosophila* abdominal bristle number over 80 generations of selection (Figure 25.7). In particular, he observed an increase of about 0.3 bristles per generation during generations 50 to 80. Assuming the infinitesimal model, how much of this response is due to mutational input? Yoo's base population had $\sigma_E^2 \simeq 4$, $\sigma_z^2 \simeq 5$, $h^2 \simeq 0.2$, $\overline{\imath} \simeq 1.4$, and 50 pairs of parents were chosen each generation. Taking $\sigma_m^2/\sigma_E^2 \simeq 0.001$ (the average for abdominal bristles in LW Table 26.1) gives $\sigma_m^2 = 0.004$. Assuming $N_e \simeq 60$,

$$\Psi = \frac{0.2}{(1-0.2)\,2\cdot 60\,(0.001)} = 2.083$$

Applying Equation 26.31a,

$$t^* = 2\cdot 60\,\ln(1+2.083) = 135$$

The approximation given by Equation 26.31c (which assumes $\Psi \ll 1$) gives $t^* = 167$. The expected asymptotic additive variance is

$$2N_e\sigma_m^2 = 2\cdot 60\cdot 0.004 = 0.48$$

giving an expected asymptotic rate of response of

$$r = \overline{\imath}\,\frac{\widehat{\sigma}_A^2}{\widehat{\sigma}_z} = \overline{\imath}\,\frac{\widehat{\sigma}_A^2}{\sqrt{\widehat{\sigma}_A^2+\sigma_E^2}} = 1.4\cdot\frac{0.48}{\sqrt{0.48+4}} \simeq 0.32$$

This is very close to the observed rate of 0.3 bristles per generation (between generations 50 and 80). However, from Equation 26.28b the expected single-generation response from new mutational input at generation 60 is only

$$1 - e^{-t/(2N_e)} = 1 - e^{-60/120} \simeq 0.40$$

of this, giving 0.13 as the expected response due to new mutants. Assuming the phenotypic variance remains relatively constant with $\sigma_z^2 \simeq 5$, the expected contribution at generation 60 from initial variation is

$$\overline{\imath}\,\frac{\sigma_{A,0}^2(t)}{\sigma_z} = \overline{\imath}\,\frac{h^2(0)\cdot\sigma_z^2\cdot e^{-t/(2N_e)}}{\sigma_z} = 1.4\cdot\frac{0.2\cdot 5\cdot e^{-60/120}}{\sqrt{5}} \simeq 0.38$$

Adding the two sources of response together gives an expected total rate of response of 0.38 + 0.13 = 0.51 bristles/generation. While this is larger than the observed rate, opposing natural selection slowed down response in Yoo's lines, as evidenced by the rather sharp decay in response upon relaxation of selection as well as the presence of segregating lethals within responding lines (Yoo 1980b). Of the expected response, 0.38/0.51 = 75% is due to the initial variation, while 25% is due to new mutation.

A complication with applying the above results is that the presence of major alleles both decreases the time to lose initial variation and increases the expected response from new mutants, resulting in a larger role for mutational input than predicted from the infinitesimal model. Applying the approximation for mutations of large effect (Equation 26.30b), the per-generation response from mutation is 0.32. Assuming the initial variation decays according to the infinitesimal model gives a total response of 0.38 + 0.32 = 0.70, so that mutation now accounts for 0.32/0.70 = 0.46% of the total response. Further, when major genes are present, the initial variation declines even faster than predicted by Equation 26.15a, suggesting an even higher percentage of response from new mutations.

Expected Asymptotic Response Under More General Conditions

The infinitesimal model assumes allele frequency changes are due entirely to drift. Clearly, selection can also change allele frequencies and in this case other methods of analysis are required. One approach (Hill 1982b,c) is to consider the expected contribution resulting from the eventual fixation by drift and selection of some of the new mutants that arise each generation. Provided mutation and selection remain constant over time, at equilibrium the rate of response equals this expected per generation contribution. Assuming M adults are measured, the frequency of a new mutant allele $\mathbf{A}^*$ is $1/(2M)$. To allow for dominance, assume the genotypic values of $\mathbf{AA}^*$ and $\mathbf{A}^*\mathbf{A}^*$ are incremented by $a(1+k)$ and $2a$ relative to the genotypic value of $\mathbf{AA}$. As before we assume that the joint distribution of a and k is independent of the genotypic value of the parental allele. Let $f(a,k)$ denote this joint probability density function and let $\gamma = \sum \mu_i$ be the total gametic mutation rate. The expected contribution from a new mutant appearing as a single copy becomes $2a \cdot u(1/[2M], a, k)$, the change in genotypic value if the new allele is fixed times its probability of fixation (the latter can be obtained by Equation 7.18, using the fitnesses given by Equation 25.4). Since $2M\gamma$ new mutants appear each generation, the asymptotic rate of response is

$$\begin{aligned} r_m(\infty) &= 2M\gamma\, E\left[\, 2a \cdot u\left(\frac{1}{2M}, a, k\right)\right] \\ &= 2M\gamma \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} 2a \cdot u\left(\frac{1}{2M}, a, k\right)\, f(a,k)\, da\, dk \end{aligned} \tag{26.32}$$

Note that the expected asymptotic rate depends critically on the exact shape of the distribution of mutational effects. Fortunately, some fairly general results emerge by using simple approximations for the probability of fixation (similar to Equations 7.19a and 7.19b; see Hill 1982b,c for details).

Consider first the case where all new mutants are additive ($k = 0$). Hill (1982b) found that, provided major alleles are not common among new mutants,

$$r_m(\infty) \simeq 2N_e\, \bar{\imath}\, \gamma\, \frac{E^+(a^2)}{\sigma_z} = \frac{4N_e\, \bar{\imath}\, \sigma_m^2}{\sigma_z}\, \frac{E^+(a^2)}{E(a^2)} \tag{26.33}$$

where

$$E^+(a^2) = \int_o^{\infty} a^2\, f(a)\, da$$

If $f(a)$ is symmetric about zero, then $E^+(a^2) = E(a^2)/2$, and the asymptotic response reduces to Equation 26.29. When major alleles are common among new mutants, correction terms involving $E^+(a^3)$ appear, see Hill (1982b) for details. With divergent selection, effects due to

asymmetry in $f(a)$ cancel and the asymptotic rate of divergence between high and low lines is just twice the rate (for single-direction selection) predicted from the infinitesimal model,

$$4N_e\bar{\imath}\,\frac{\sigma_m^2}{\sigma_z}$$

independent of the shape of $f(a)$. The effect of linkage on asymptotic response was examined by Keightley and Hill (1983, 1987), who found it to generally be small, with the relative effects of linkage increasing as σ_m^2 and/or N_e increase.

Hill and Keightley (1988) incorporate natural selection, assuming new mutants also influence fitness under natural selection. If both character and fitness effects are small, the distribution of a is symmetric, and natural selection changes are also symmetric in a (e.g., the change in fitness is a function only of $|a|$), there is no change in the asymptotic rate of response. When these assumptions are violated, the asymptotic rate can be reduced.

To allow for dominance, we continue to assume the incremental mutation model. From LW Equation 4.12a, the additive variance contributed by a rare allele is $2p(1-p)a^2[\,1+k(1-2p)\,]^2 \simeq 2pa^2(1+k)^2$, giving the contribution from a single new mutation, with $p=(2M)^{-1}$, as approximately

$$a^2(1+k)^2/M$$

Since the expected number of new mutants per locus in any given generation is $2M\mu$, the expected additive variance contributed each generation by new mutants at a given locus is

$$2M\mu\,E[\,a^2(1+k)^2/M\,] = 2\mu\,E[\,a^2(1+k)^2\,]$$

where the expectation is taken over the joint distribution of a and k values in new mutants. Summing over all loci, the expected new additive variance contributed each generation (in the absence of linkage disequilibrium) is

$$\sigma_m^2 = 2\sum_{i=1}^{n}\mu_i\,E[\,a^2(1+k)^2\,] = 2\gamma\,E[\,a^2(1+k)^2\,] \tag{26.34a}$$

Hill (1982b). The last equality assumes that the distribution of mutational values is the same at each locus. When all mutants are additive ($k=0$) and $E(a)=0$, this reduces to our previous definition of σ_m^2. More generally, with complete additivity but removing the assumption that $E(a)=0$,

$$\sigma_m^2 = 2\gamma\,E(\,a^2\,) \tag{26.34b}$$

while with complete dominance

$$\sigma_m^2 = 2\gamma\,E(\,[2a]^2\,) = 8\gamma\,E(\,a^2\,) \tag{26.34c}$$

Thus, all else being equal, the mutational variance with complete dominance is four times larger than that for complete additivity. Finally, it is important to note that with dominance Equation 26.28a (predicting the additive genetic variance from new mutation) no longer holds, even if the other assumptions of the infinitesimal model still do, as the additive variance can actually increase over some interval of time (see Chapters 24, 25).

For the case of complete dominance ($k=1$), Hill (1982b) found that the asymptotic rate of response is approximately

$$r_m(\infty) \simeq 16N_e\,\bar{\imath}\,\gamma\,E^{+}\left(a^2\right)/\sigma_z \tag{26.35a}$$

With a symmetric distribution of mutant effects this reduces to

$$r_m(\infty) \simeq N_e \, \overline{\imath} \, \frac{\sigma_m^2}{\sigma_z} \tag{26.35b}$$

where σ_m^2 is given by Equation 26.34c. Thus, for the same σ_m^2, the response when all mutants are completely dominant is only half the expected response when alleles are additive (compare Equations 26.29 and 26.35b). However, for fixed γ and $E\left(a^2\right)$, σ_m^2 is larger with complete dominance (compare Equations 26.34b and 26.34c) and the response under dominance is twice as large as that expected for complete additivity.

If alleles are completely recessive, allelic effects are small and the distribution of mutational effects is symmetric, the asymptotic response is approximately

$$r_m(\infty) \simeq 2N_e \, \overline{\imath} \, \gamma \, E\left(a^2\right) / \sigma_z \tag{26.36a}$$

Hill (1982b). For recessives with large effects (cf. Equation 7.19b),

$$r_m(\infty) \simeq 2 \, \gamma \, E^+\left(a^{3/2}\right) \sqrt{\frac{2N_e \, \overline{\imath}}{\pi \sigma_z}} \tag{26.36b}$$

Thus, the limiting response when all new mutants are recessive is not predictable from σ_m^2, even if mutational effects are symmetrically distributed. With recessive major alleles, response scales as $\sqrt{N_e \, \overline{\imath}}$, and hence increases much more slowly than with complete dominance and/or additivity.

When loci are linked, the asymptotic response is reduced, but the effect is small unless linkage is tight, as might occur with a few small chromosomes (Keightley and Hill 1983). As mentioned previously, reduction in response also occurs if loci influencing the trait are also linked to loci under natural selection.

Models of Mutational Effects

A critical assumption in any analysis of mutational response is the nature of mutational effects. Given a current allelic effect of a, what can we say about the value a^* from a mutation in this allele? All of the above results make the incremental mutational model assumption: $a^* = a + e$, with the increment $e \sim (0, \sigma^2)$. This is a Brownian motion model (Appendix 1), and implies that the additive variance (for neutral alleles) is unbounded as population size increases. As introduced in Chapter 11, the house-of-cards is another potential mutation model. Here each new mutational value is drawn from a constant distribution independent of its current value, $a^* = e$ with $e \sim (0, \sigma^2)$. Li and Enfield (1992) examined the long-term response under such a model. Starting with a population with no initial variation, they found mutation increases genetic variation up to some maximal value, after which it started to decline, where the time until the maximum increased with the number of loci. Li and Enfield only considered response over the first 120 generations, which was less than the smallest N_e value (150) in any of their simulatons. Hence, the nature of any limit, or any asymptotic response, was not determined. The expectation under such a model is that an apparent selection limit is approached, although the population can still response, but at an ever-diminishing rate as further gain require random draws of every-greater outliers from this distribution. This has connections with extreme-value theory models of adaptive walks, examined at the end of the chapter. A finite-value version of this model, assuming only k possible alleles at a locus, has been examined by Zeng et al. (1989). As expected, such a model results in an ultimate selection limit as mutation cannot continue indefinitely to generate better alleles. Chapter 11 also introduced the Zeng-Cockerhan model (Equation

11.22), $a^* = \tau a + e$, which recovers Brownian motion when $\tau = 1$, and house-of-cards when $\tau = 0$. To our knowledge, selection limits under this model have not be examined.

A second, very important, consideration is the role of pleiotropic fitness effects. All of the above mutational models predict that the equilibrium variance should linearly increase with N_e, at least when N_e is less than the reciprocal of the mutation rate (Chapter 11). However, even for modest N_e, the equilibrium variances that are too large (heritabilities approaching one), while the observation is that most heritabilities being are below 0.5. This contradiction between theory and data as N_e increases is analogous to the limited range for molecular heterozygosity, which should also approach one for large N_e (Chapter 2). However, if new mutations have small pleiotropic fitness effects (as is likely), they become more deleterious as N_e increases, limiting the evolutionary importance of most new mutations, and limiting the value of the equilibrium mutational variance. Chapter 27 examines these issues in detail.

Optimizing Asymptotic Selection Response

Since the asymptotic response is a function of $N_e\,\overline{\imath}$, response is maximized by selection strategies that maximize this product. As was the case for maximizing long-term response (the total response using only the initial variation), there is a tradeoff in that the optimal short-term response (maximizing $\overline{\imath}$) is at conflict with the optimal asymptotic response (as increasing $\overline{\imath}$ decreases N_e). Thus if our choice is simply the fraction of individuals to save, our discussions above on the optimal selection intensity for long-term response also applies to considerations of the asymptotic response.

The selection intensity, however, is not the only choice a breeder or experimentalist has in terms of possible selection schemes. We have generally been assuming individual (or mass) selection, which is based solely on an individual's phenotype. There are, however, numerous other selection schemes, such as those incorporating information on the phenotypes of relatives as well (e.g., family and index/BLUP selection). Schemes incorporating such information can improve the accuracy of the estimate of an individual's breeding value, and hence improve the accuracy of short-term response. This can be seen by recalling (Equation 13.11c) that the single-generation response R for any particular selection scheme is given by $R/(\,\overline{\imath}_x\,\sigma_A) = \rho(x, A)$, where selection occurs on the measure x and $\rho(x, A)$ is the accuracy of the method (the correlation between an individual's index x and breeding A values). Holding $\overline{\imath}$ constant, the single-generation response increases with the accuracy $\rho(x, A)$ of the selection method. While different schemes can improve the short-term response over mass selection, what is their effect on asymptotic response? The answer is that, once again, schemes improving the short-term response often do so at the expense of the asymptotic response.

Optimal asymptotic response occurs by maximizing the fixation probabilities of favorable QTLs, which amounts to maximizing $N_e s$, where s is the selection coefficient on the QTL. For an additive trait, Hill (1985) and Caballero et al. (1996) generalize Equation 25.4 to show that

$$s = \left(\overline{\imath}\,\frac{a}{\sigma_z}\right)\,\frac{\rho(x, A)}{h} \tag{26.37}$$

Note that $\rho(x, A) = h$ for individual selection ($x = z$), recovering Equation 25.4. Fixation probabilities under different selection schemes with the same selection intensities are thus functions of the product $N_e\rho(x, A)$. The tradeoff is that increasing $\rho(x, A)$ typically decreases N_e by increasing the between-family variance. Hence, as was the case for the optimal selection intensity, the optimal selection scheme for short-term response may differ from the optimal long-term one.

The accuracy ρ depends on the genetic variance and hence changes over time as these variances change. As shown in Chapters 24-26, predicting these changes in variances can be extremely difficult. Once again, the analysis is greatly simplified by assuming the in-

finitesimal model. Under this model, the additive genetic variance eventually converges to a value of $\sigma^2_{A,\infty} = 2N_e\sigma^2_m$. The effect of different selection schemes on the equilibrium additive variance (and ρ) is entirely determined by the effective population size that the scheme generates. In comparing two different selection schemes (i and j) with the same selection intensity, Wei et al. (1996) show that the ratio of asymptotic responses becomes

$$\frac{\widetilde{R}_i}{\widetilde{R}_j} = \frac{\widetilde{\rho}(i)\,\widetilde{\sigma}_A(i)}{\widetilde{\rho}(j)\,\widetilde{\sigma}_A(j)} = \frac{\widetilde{\rho}(i)}{\widetilde{\rho}(j)}\sqrt{\frac{N_e(i)}{N_e(j)}} \tag{26.38}$$

where tilde denotes the equilibrium value. The careful reader will note that the effect of N_e is two-fold — a direct effect (the square root of their ratio) and an indirect effect through the ratio of the $\widetilde{\rho}$ (which is a function of $\widetilde{\sigma}_A$, and hence of N_e).

Example 26.6. Consider the asymptotic response to mass (m) versus within-family (w) selection. Under within-family selection, $N_{e(w)} \simeq 2N$, as the between-family variance is zero (Equation 3.4). In contrast, $N_{e(m)} < N$, with the difference between $N_{e(m)}$ and N increasing with the selection intensity and heritability (Equation 26.8). Thus,

$$\sqrt{\frac{N_{e(w)}}{N_{e(m)}}} \geq \sqrt{2}$$

Wei et al. (1996) found that the asymptotic accuracies become

$$\widetilde{\rho}_{(m)} = \frac{2N_{e(m)}\sigma^2_m}{\sqrt{2N_{e(m)}\sigma^2_m[\,2N_{e(m)}\sigma^2_m + \sigma^2_e\,]}}$$

$$\widetilde{\rho}_{(w)} = \frac{N_{e(w)}\sigma^2_m}{\sqrt{2N_{e(w)}\sigma^2_m[\,2N_{e(w)}\sigma^2_m + \sigma^2_e\,]}}$$

Using the above inequality and these two identities, it can be shown that

$$\frac{\rho_{(w,\infty)}}{\rho_{(m,\infty)}} \geq \frac{1}{\sqrt{2}}$$

Thus,

$$\frac{\widetilde{R}_w}{\widetilde{R}_m} = \left[\sqrt{\frac{N_{e(w)}}{N_{e(m)}}}\right]\left[\frac{\widetilde{\rho}_{(w)}}{\widetilde{\rho}_{(m)}}\right] \geq \sqrt{2}\,\frac{1}{\sqrt{2}} = 1$$

and hence $\widetilde{R}_w \geq \widetilde{R}_m$. For the same selection intensity, the long-term response is greater under within-family selection than under mass selection, even though mass selection is initially twice as accurate as within-family selection (and hence the inital response is twice as large).

The effects of different selection schemes on the effective population size can be seen by considering the general weighted index of within- and between-family information,

$$I = (z - \overline{z}_f) + \lambda(\overline{z}_f - \overline{z}) = \text{(within-family)} + \lambda\,\text{(between-family)} \tag{26.39}$$

where z is an individual's value, $\overline{z}_f$ is the mean of its family, and $\overline{z}$ is the grand mean. A number of selection schemes can be represented (either exactly or to a good approximation) by this index (Chapter 21). For example, $\lambda = 1$ corresponds to individual selection ($I = z$), while $\lambda = 0$ corresponds to strict within-family selection ($I = z_w$). By choosing the appropriate λ, the accuracy of selection using this index is greater than the accuracy of individual selection ($\rho(I, A) > \rho(z, A)$, Equation 21.53b), and hence selection using the optimal index gives a greater short-term response than mass selection. To a first approximation, BLUP selection corresponds to this optimal index.

Since the reduction in effective population size occurs by inflating the between-family variance, the greater the λ value in the index given by Equation 26.39, the greater the reduction in N_e. Larger values of λ place more weight on family information, resulting in more individuals from the best families being co-selected. The reduction in N_e is greatest when heritability is small, as in these cases the index places the most weight on the between-family component. Yet it is exactly this setting where index/BLUP selection has the greatest short-term advantage over individual selection. While index/BLUP selection gives the largest single-generation response, when care is taken to equalize the amount of inbreeding across methods, individual selection can produce a larger single-generation response than index selection or BLUP (Quinton et al. 1992; Andersson et al. 1998).

Can one balance this tradeoff between increased accuracy for short-term response versus inflation of the between-family variance and the resulting reduction in the long-term response via reduction in N_e? Several authors have proposed schemes for reducing the between–family variance following selection. Toro and colleagues (Toro and Nieto 1984; Toro et al. 1988; Toro and Pérez-Enciso 1990) suggested that selected individuals be mated in ways that minimize the coancestry between them. A slightly different strategy, **compensatory mating**, was suggested by Grundy et al. (1994). Here individuals from families with many representatives following selection are mated to individuals with few family members. This has the effect of reducing the cumulative effect (Q in Equation 26.6) of selection by reducing the variance in family contribution. Grundy et al. also suggested a more subtle approach. They note that by using biased selection parameters in the index (for example, using upwardly biased estimates of h^2 when computing the optimal λ), the slight reduction in the accuracy of the adjusted index from its optimal value is more than offset by a much larger decrease in the reduction in N_e. They suggest that this approach, combined with compensatory mating provides a simple way for ameliorating the reduction in N_e. Verrier et al. (1993) also suggested that schemes placing slightly less emphasis on family information can, in small populations, given greater long-term response than BLUP selection.

This tradeoff between optimal short-term versus optimal asymptotic response certainly has economical consequences for breeders. While breeders are ultimately better off (in terms of total response) using selection schemes that are initially less accurate, competing breeders using the initially more accurate schemes will achieve larger short-term response. Breeders must thus decide between staying in business over the short haul versus a larger payoff (in terms of a greater response) over the long run.

ADAPATIVE WALKS

Our treatment of long-term response first considered the role of existing genetic variation. As this becomes exhausted through drift and selection, new mutations become increasingly important. Here we consider the logical conclusion of this last phase, the fixation of these new mutations and their impact on continued long-term response. In particular, our focus is on the nature of **adaptive walks** — the sequence of fixed mutational steps required to obtain a specific adaptation. There is a rich (and growing) population-genetics literature on

this subject, nicely reviewed by Orr (2005a,b). Much of this work starts with Fisher's (1930) extremely influential **geometric model** (**FGM**) on the probability that a new mutation is adaptive. A number of interesting results follow from this model, which assumes adaptation towards some optimal trait value (stabilizing selection). A second class of models is based on extreme value theory, and instead assumes constant directional selection to always improve a trait (i.e., there is no optimal value). The classic example of such a trait is fitness. Surprisingly, both classes of models give the same general result: the distribution of genetic factors fixed along an adaptive walk is often approximately exponential.

Fisher's Model: The Adaptive Geometry of New Mutations

Fisher (1930) offered a highly simplified, yet elegant and powerful, geometric argument showing that the probability a new mutation increases fitness (i.e., is adaptive) is a simple function of the distance of the original phenotype from the optimal trait value and the mutational size. Although Fisher envisaged that adaptation requires a highly multivariate phenotype to mesh with a multivariate fitness function, Figure 26.9A shows its basic structure in two dimensions. Stabilizing selection is assumed, with the current phenotypic value at distance d from a fitness optimum, where traits are scaled (and rotated) such that they are independent with equal selection intensity on all traits. The phenotypic change by a new mutation is given by a vector of length r extending from the current value (point $\mathbf{z}$) in some random direction. As Figure 26.9A shows, the probability that the new mutation is advantageous is the probability that this vector lies within the contour of equal fitnesses for the current phenotype. For n traits, this is a function of the **Fisher scaling parameter**,

$$x = \frac{r\sqrt{n}}{2d} \tag{26.40a}$$

with the probability of adaptation given by

$$p_{adp} = \frac{1}{\sqrt{2\pi}} \int_x^\infty \exp(-y^2/2)dy = 1 - \Phi(x) \tag{26.40b}$$

where Φ is the cumulative density function of a unit normal. Fisher did not present a derivation, but one is provided by a variety of subsequent authors (Kimura 1983; Leigh 1987; Rice 1990; Hartl and Taubes 1996).

Fisher's critical observation was that the probability a new mutation is adaptive is a decreasing function of x (Figure 26.9B) — increasing x decreases the chance of adaptation, and conversely decreasing x increases the chance of adaptation. Indeed, as x approaches zero, the probability a new mutation is adaptive approaches one half. The analogy Fisher used to explain this result was that of trying to improve the focus on a microscope. A very tiny change has close to a 50% chance of improving focus, while a much larger change is far less likely to do so. This analogy lead to the widespread use of the term **Fisher's microscope** in the literature to describe this feature of the model. One component of x is r/d, the ratio of the jump size r of the mutation relative to the distance d from the optimum. At large distances (large d), large mutations have a reasonable chance of increasing fitness. However, as the phenotype gets close to its optimal value, only small mutational jumps are likely to be adaptive. The second component is the "dimension" n. Since x increases with n, increasing the complexity of the phenotype (n) decreases the chance of mutations being adaptive. The original interpretation of Fisher's model was therefore two-fold: small-effect mutations are the stuff of adaptation and that there is a "**cost of complexity**" (Orr 2000). As we will see, both of these initial statements need significant refinement.

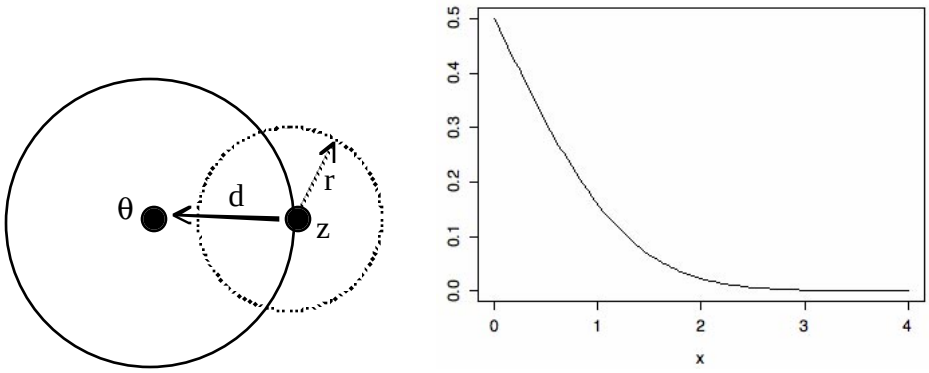

Figure 26.9. **A** (Left): Fisher's (1930) model for the probability that a new mutation increases fitness for the simple case of two independent traits under stabilizing selection. The optimal fitness value occurs at θ, while the phenotype of the genotype about to experience a mutation is $\mathbf{z}$, which is at (Euclidean) distance d from the optimum. The solid circle denotes the fitness contour passing through the current value $\mathbf{z}$, so that all points inside this line have higher fitness. The effect of a new mutation is to move the expected phenotype by some (Euclidean) distance r in a random direction about $\mathbf{z}$, with the space of possible new phenotypes denoted by the dotted circle (the assumption of equal and independent mutational effects on both traits). The probability of increased fitness is the fraction of the circumference of the dotted circle that resides inside (closer to θ) of the solid circle. More generally, with correlated and/or unequal effects (for selection and/or mutation), these circles are replaced by ellipses in two dimensions, and the hyperspheres by hyperellipsoids in $n > 2$ dimensions. **B:** (Right): For an n-dimensional phenotype, the probability that a new mutation is advantageous is $1 - \Phi[r\sqrt{n}/(2d)]$, where $\Phi(x)$ is the cumulative density function of a unit normal (Equation 26.40b).

Orr (2006; also see Hartl and Taubes 1996, 1998) showed that Fisher's model provides a much richer description beyond simply predicting whether a mutation is beneficial — it can generate the full distribution of fitness effects given r. This is done by computing the distribution of displacements towards the optimal value, which is normal with a negative mean. Translating this displacement into fitnesses, the distribution of fitness effects is also normal, with a mean less than the current fitness of the starting genotype. Hence, most new mutations move a trait further away from its optimum, lowering fitness. Only those mutations in the right tail of this displacement distribution (those with positive values) are advantageous. This is an important result and foreshadows a different model of adaptation based on extreme value theory (draws from the extreme tails of a distribution), which will be examined shortly.

One might be concerned by the highly simplistic nature of Fisher's model – n independent traits with equal selection, and mutation, on each trait. These assumptions can be relaxed, for example by replacing Fisher's assumed hyperspheres for fitness contours and mutational effects (the assumption of equal and uncorrelated effects) by hyperellipsoids, allowing for correlation among traits and unequal trait effects both in fitness and mutation (e.g., Waxman and Welch 2005; Waxman 2006, 2007; Martin and Lenormand 2006; 2008). For example, unequal and correlated mutational effects can be introduced by using a mutational covariance matrix $\mathbf{M}$, and unequal and correlated stabilizing selection can be accommodated with a semi-positve definite matrix $\mathbf{S}$, with the eigenvalues of the product of $\mathbf{MS}$ replacing Fisher's scaling parameter. However, the best way to consider Fisher's model is the comment by Fox (2014): "Sometimes, even really abstract mathematical models can make really good

predictions about real-world biology. Further, they do so *because* of their abstractness, not despite it." Fisher's model is so powerful not because it fully captures all of the biology but rather because it *avoids* most of the biological details to make its critical points.

Fisher-Kimura-Orr Adaptive Walks

A subtle feature, first noted by Kimura (1983), makes Fisher's smaller-is-better result very misleading. Examination of Equation 26.40b and Figure 26.9B suggests that the majority of beneficial mutations are those with very small effects ($x \ll 1$). While this is indeed correct (under Fisher's model), Kimura noted that such small mutations also have very small selective advantages, and therefore (while *adaptive*) are less likely to be *fixed* by natural selection. Recall from Chapter 7 that the fixation probability of a favorable allele is $\simeq 2s$, so that the magnitude of s, not just its sign, is important in determining which factors become fixed. Under Fisher's model, conditioning on a mutation being adaptive, $s \propto x$ (Kimura 1983; Orr 1998). Thus, the probability a mutation of effect size x is fixed is a function of both it being adaptive *and* its subsequent selective advantage, or $(2s) \cdot p_{adp} = 2x[1 - \Phi(x)]$. As Figure 26.10 shows, the outcome is a dramatic shift in our interpretation of Fisher's result: selection favors alleles of *intermediate* effect. There is an irony here in that Fisher was a pan-selectionist, yet his model suggested alleles of very small effect (i.e., nearly neutral) are more important. Kimura, the founder of the neutral theory, showed that Fisher's result (when more carefully considered) argues for stronger selection.

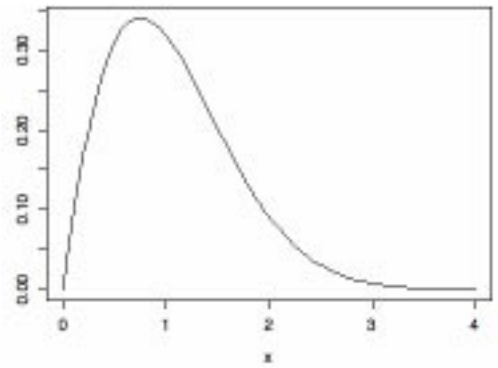

Figure 26.10. The probability of fixation for a new mutation with scaled effect $x = r\sqrt{n}/(2d)$. Figure 26.9b gives the probability that such a mutation is *adaptive*, while this curve (which also incorporates the resulting selection coefficient) is the chance that it is *fixed*.

Assuming a uniform distribution for the r values of new mutations, Kimura found that the expected value for x_1, the first step in the walk, is $E[x_1] \simeq 1.06$, giving

$$\frac{E[r_1]\sqrt{n}}{2d} \simeq 1.06, \quad \text{or} \quad E[r_1] \simeq \frac{2.12\,d}{\sqrt{n}} \tag{26.41a}$$

where $E[r_1]$ is the expected value of r for the first-fixed mutation. Orr (1998, 1999, 2000) noted that Kimura's result is simply the *first step*. To continue the walk, we first need to compute the expected distance moved towards the optimum. Equation 26.41a is *expected length* of the vector associated with the fixed mutation. The amount of adaptation (distance moved towards the optimum) in less than this length, as the vector (being random) almost always points away from the optimum, and thus we need to consider its expected projection

$E[x_p]$ in this direction. Orr (1998) found that this is approximately

$$E[x_p] \simeq \frac{E[x_1]}{\sqrt{n}} \tag{26.41b}$$

Scaling so that $d = 1$, the initial distance from the optimum on the x scale is just $\sqrt{n}/2$, giving the fraction moved towards the optimum as

$$\frac{\sqrt{n}/2 - E[x_1]/\sqrt{n}}{\sqrt{n}/2} = 1 - 2E[x_1]/n \tag{26.41c}$$

Orr's key insight was that the distribution for the size of the second jump is the same as the first jump, provided the distance to the optimum rescaled by Equation 26.41c. Likewise, after the second jump, the distance is this fraction squared, and so forth, generating a self-similar process for each step of the walk towards the optimum. Using this logic, the distribution for x during step k of the walk is given by

$$\psi(x,k) = 4\,c_k^2\,x\,[1 - \Phi(c_k x)]\,, \quad \text{where} \quad c_k = \left(1 - \frac{E[x_1]}{n}\right)^{1-k} \tag{26.42}$$

Assuming a uniform distribution for new x values, Orr showed that Equation 26.42 implies the distribution of the x_i (ignoring very small values) is approximately exponential with parameter $\lambda \simeq 2.9$. Simulation studies by Orr (1998, 1999) show that this result is very robust to different assumptions about the distribution of mutation inputs, especially when small-effect mutations are more common than large-effect ones.

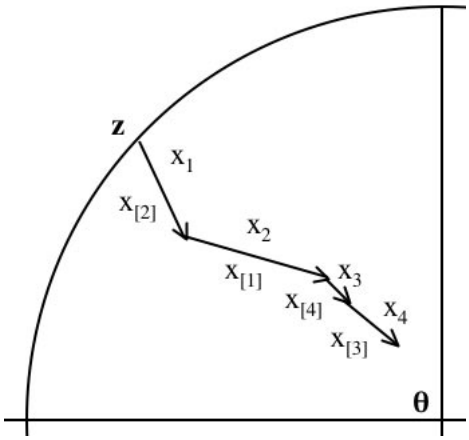

Figure 26.11. An example of an adaptive walk (in two dimensions), starting at **z** and moving towards the optimal value θ. Here x_i denotes the i-th step, while $x_{[i]}$ denotes the i-th *largest* step. For this example, the largest jump $x_{[1]}$ occurs at the second step (x_2), not the first (x_1).

A critical point noted by Orr is that the largest "jump" in the walk $x_{[1]}$ does not necessarily correspond to the first jump x_1 (Figure 26.11). The expected value of the largest jump is approximately

$$E[x_{[1]}] \simeq \frac{1}{\lambda}\left[\ln\left(\frac{\lambda\,n}{2}\right) + 0.5772\right] \tag{26.43a}$$

For $\lambda = 2.9$, this corresponds to $E[x_{[1]}] \simeq 1.68$, while the expected value of the first jump is $E(x_1) \simeq 1.06$. More generally, the expected value of the kth largest jump is

$$E[x_{[k]}] \simeq \frac{1}{\lambda}\left[\ln\left(\frac{\lambda\, n}{2}\right) - \sum_{i=1}^{k-1}\frac{1}{i} + 0.5772\right] \tag{26.43b}$$

Using this result to consider $E[x_{[k]}] - E[x_{[k+1]}]$ provides the expected spacing between the k-th and $k+1$ largest jumps,

$$E[x_{[k]}] \simeq \frac{1}{\lambda\, k} + E[x_{[k+1]}] \simeq \frac{0.349}{k} + E[x_{[k+1]}] \tag{26.43c}$$

since $\lambda \simeq 2.9$. For example, $E[x_{[2]}] = E[x_{[1]}] - 0.349 = 1.33$.

The careful reader might have noted that the exponential distribution refers to the lengths of the vectors for the fixed mutations (the **total effect** of the mutation). This is a bit different from the actual effect size for any particular *character*. Orr (1999) addressed this issue, finding that the projection of a favorable, but random, vector of length r onto any particular trait (say z_i) is roughly normally distributed with an expected absolute value of

$$E[\,|\,z_i\,|\,] = \frac{2\,r}{\pi\sqrt{n}} \tag{26.44}$$

Thus, while the *lengths* of the vectors associated with fixed mutations are roughly exponentially distributed, so to are the resulting changes in any particular *character*.

One critical assumption of Orr's analysis is that the change in the optimal value is both sudden and large ($E[r] \ll d$). While this can happen following a sudden shift in the environment, an equally plausible scenario is that the optimal value slowly changes over time. In this setting, Kopp and Hermisson (2007) and Collins et al. (2007) found that *small* effect mutations may be favored if the change in the optimal value is small and/or the rate of environmental change sufficiently slow. A second limitation is the drift barrier, discussed in Chapter 7. As the fitness effects of an allele become sufficiently small, its fixation probability approaches that for neutrality (its initial allele frequency), rather than $2s$. Hence, even in a constant environmental, perfect adaptation does not occur. Rather, as this barrier is approached, there is a constant fixation of mutations of very small effect, random in their direction towards the optimum. Orr's key finding that fixed effects are roughly exponential avoids this concern by ignoring mutations of very small effect. Finally, the view of a random walk as a series of discrete, fixed steps is one extreme. The other is the constant generation of mutations of small effect, mounting a continuous infinitesimal response. Lande's analysis (Chapter 25) shows that polygenic response is favored when major genes have negative pleiotropic effects on other traits unless there is strong selection on a focal trait. Hence, adaptive walks under Fisher's model may be biased towards this latter setting.

Example 26.7. Annual wild rice (*Oryza nivara*) is a photoperiod-insensitive selfer adapted to seasonally dry habits. It is thought to have evolved from a progenitor with properties of its sister species *Oryza rufipogon*, a photoperiod-sensitive, perennial outcrosser found in deep-water swamps. As a potential model system for adaptation to these new conditions, Grillo et al. (2009) crossed these two species and mapped QTLs for flowering time, mating systems, and life history traits. The resulting distribution of effects was roughly exponential, as predicted from Orr's adaptive walk. Further, if directional selection was important, one would expect a huge excess of the detected QTL alleles in *nivara* would be in the direction of the adaptive

phenotypes. Indeed, for flowering time and duration, all six of the *nivara* QTL alleles act in the direction of reduced photoperiod sensitivity and longer flowering. Likewise, all seven of the QTLs for mating system traits in *nivara* acted in the direction of increased selfing.

The Cost of Pleiotropy

The constraint from n on rate of adaptive that follows from Fisher's model is the result of **mutational pleiotropy**, rather than organismal complexity. This distinction is lost in the original Fisher model which assumed **universal pleiotropy**, namely that mutations essentially influence every single trait in an organism. (The term university pleiotropy seems first to have been used by Wright (1968), although, as noted by Wagner and Zhang (2011), his usage appears to be that every gene affects *more than one* trait, as opposed to the Fisherian notion that every gene affects *all* traits.) Under Fisher's assumption, his scaling parameter x increases as $\sqrt{n}$, the number of traits (the complexity of an organism). Thus (for the same r/d values) the probability that a mutation is adaptive is lower in more complex organisms, the so-called cost of complexity. When considering the *rate* of adaptation, Orr (2000; also see Welch and Waxman 2003) noted that the cost of complexity is far greatly than suggested by a superficial analysis of Fisher's model. The rate of adaptation is proportional to the product of three components, the probability a mutation is adaptive, the probability that such a mutation is fixed, and the length of a move (or displacement) towards the optimal value (the increase in fitness) when such a mutation is fixed. These last two factors each scale as $1/\sqrt{n}$, so that together they scale as $1/n$. Given that the probability of adaptation also decreases with n, the net result is that the decrease in the rate of adaptive is greater than $1/n$, suggesting a far higher cost that Fisher's initial analysis.

Given that Fisher's model is clearly biologically unrealistic, how valid is this concern? First, pleiotropy many not be universal, but rather more modular (the notion of **restricted pleiotropy**), with most mutations only influencing the traits within their module (Wagner 1996; Barton and Partridge 2000; Welch and Waxman 2003; Wagner et al 2007; Wagner and Zhang 2011). Under restricted pleiotropy, the focus shifts from the complexity of an organism to the complexity of a module, with a **cost of pleiotropy** (Wagner and Zhang 2011) as the rate of adaptation is decreased in modules of higher complexity (i.e., more independent traits). As reviewed by Wang et. al (2010) and Wagner and Zhang (2011), evidence from extensive QTL mapping and gene knockout studies in yeast, mice, and nematodes suggest that most mutations show restricted pleiotropy. For example, Wang et al. (2010) examined ~ 250 morphological traits in yeast, finding that for the ~ 2500 gene knockouts examined, the medium pleiotropy was only seven traits (two percent of all traits examined). Hill and Zhang (2012), however, suggest some caution before accepting restricted pleiotropy. They performed simulation studies for a model with highly pleiotropic alleles, finding that low power (especially a concern when attempting to correct for multiple comparisons due to the large number of tested traits) can give results similar to those used to support restricted pleiotropy.

A second mitigating factor is that the intensity of selection likely varies over traits. This reduces the actual number of traits n in a module to an effective number of traits which (much like effective population size) decreases as the variance in selection intensity increases (Rice 1990; Orr and Coyne 1992; Orr 2000; Waxman and Welch 2005; Martin and Lenormand 2006, 2008). Hence, if just a few traits in a module face the majority of the selective pressure, this significantly lowers the cost (i.e., increases the rate of adaptation). A similar argument applies if mutational effects are very uneven over traits. Finally, traits within a module may be highly correlated, with a mutation affecting traits in the same, as opposed to random, directions (Wang et al. 2010), which also reduces the effective n. The sum of all of these

factors implies that the effective dimensionality of a module is less, and likely far less, than its actual number of independent traits.

The final mitigating factor is a more subtle one, dealing with the relationship (if any) between the average effect a of a mutation on a trait and the total effect r of that mutation over all the traits that it affects and how this scales with n. Under the **invariant total effect model**, the total effect of any given mutation is independent of the number of traits it influences —- a mutation influencing more and more traits will, on average, see no change in its r value. As it influences more traits, its average effect on a given trait decreases with n (r constant, a decreases with n). The opposite assumption is **Euclidean superposition**, where the effect of a mutation on any given *trait* is independent of n (i.e., independent of how many other traits that mutation impacts). In this case, its total effect scales as $r \simeq \sqrt{n}\sqrt{a^2}$, where a^2 is the average squared effect of a mutation on a random trait (a constant, r increases with n). Both of these models are special cases of the more general scaling $r \simeq a\, n^b$, where $b = 0$ corresponds to the invariant model and $b = 0.5$ to the superposition model (Wang et al. 2010). With a large number of pleiotropic mutations in hand, one can regress their total effect r on their degree of pleiotropy n to estimate b. Surprisingly, studies in mice (Wagner et al. 2008) and yeast (Wang et al. 2010) suggest that the data are best fit by a model with $b > 0.5$, implying that the per-trait effect of a mutation *increases* with the amount of pleiotropy n. Wang et al. show that the consequence of $b > 0.5$ is that that while the probability of a new mutation being advantageous decreases with n, its fixation probability and affect on fitness if fixed both *increase* with n, resulting in the rate of adaptation being maximized at some optimal value of n (akin to Kimura's observation of an intermediate value of x maximizing probability of fixation). However, the observation of $b > 0.5$ needs to the treated with caution. Hermisson and McGregor (2008) note that QTL studies can result in inflated estimated of b due to the presence of linked loci. While the results of Wang et al. avoid this concern (being based on gene knockouts), caution is still in order. These authors themselves noted that genes with a larger standard deviation of effect sizes are more likely to be declared to be pleiotropic, and simulation studies by Hill and Zhang (2012) found that a true value of $b = 0.5$ can easily generate data with values greatly in excess of $1/2$ if the traits and/or measurement error are correlated.

Our conclusion for all of the above results is that any cost-of-complexity is not based on organismal dimensionality, but rather on the amount of pleiotropy that a typical mutation experiences. There are reasons to suggest that this is often modest or small. Further, variances in the strength of selection or in the distribution of mutation effects lowers the effective value of n, further reducing this cost. Finally, unresolved scaling issues (the relationship between total, and individual, effects) can stillfurther reduce this cost if in the appropriate direction.

Walks In Sequence Space: Maynard-Smith-Gillespie-Orr Adaptive Walks

Quantitative geneticists have historically been interested in the phenotypic effects of alleles, while the focus of population geneticists has been on their effect on a particular trait, fitness. The power of Fisher's geometric model is that it addresses both, as effect sizes can be translated into fitnesses (Orr 2006). While the distribution of potential phenotypic values under Fisher's geometry is both unconstrained and continuous, a second class of adaptive walks, based on the much more constrained geometry of **sequence space**, have also been widely examined by population geneticists. The analysis of such models is strictly concerned with the sequence of fitness increases from benefical alleles fixed during a walk, rather than their phenotypic effects (Maynard-Smith 1970; Gillepsie 1983, 1984, 1991; Orr 2002, 2003a). Further, they focus on evolution at a particular locus, while Fisher's model is concerned with the genome-wide response, potentially over a very large number of loci. However, their analysis has several potentially very robust features, making them more general that Fisher's results.

As first noted for protein sequences by Maynard-Smith (1962, 1970), while phenotypic

space is continuous, underlying any evolutionary modification are changes in DNA sequences, which imposes a discrete, and constrained, geometry. For a DNA sequence of length L, there are 4^L possible states, and single mutation can only move to one of $3L$ possible states. Under the weak mutation ($N\mu \ll 1$), selection strong ($Ns \gg 1$) assumption (**WMSS**), each new mutation will either be fixed or lost before the next appears, so that double-mutations are not segregating. This shortened horizon in the sequence space leads to Gillepsie's (1983) **mutational landscape model** (**MLM**), which constrains the possible geometry of evolutionary paths in sequence space to those one mutation step away. Given a starting allele, the set of "local" alleles are those $3L$ sequences one mutational step away, some of which may be more fit than the current allele. When one such adaptive mutation is fixed, there is now a new space of $3L$ sequences, and the walk continues until the most fit local allele is fixed and the walk stops. Gillespie's (1983, 1984) key insight into the analysis of such models was the use of **extreme value theory** (**EVT**), which treats the distribution of extreme draws from some underlying distribution (Gumbel 1958; Leadbetter et al. 1989).

Example 26.8. The body of statistical theory (extreme value theory) which deals with the largest draws from a distribution, provides very powerful machinery for the analysis of new beneficial mutations. Gillesipie's (1983, 1984) insight was that current alleles are likely rather fit (relative to all possible local alleles), and are therefore in the right-most tail of the unknown and likely very complex distribution of potential fitnesses at a locus. *More* fit alleles are even more extreme draws (Figure 26.12), allowing many of their features to be given from extreme value distributions. There is an irony here in that the field of EVT, which provides the basis of an alternative model to Fisher's, was first introduced by Fisher (Fisher and Tippett 1928). Leonard (L. H. C.) Tippett was a statistician working in the textiles industry, and was a leading figure in the early development of quality control methods. He was also the first to publish a table of random numbers (Tippett 1927).

The critical result from EVT is the so-called **trinity theorem** (also know as the **Fisher–Tippett–Gnedenko theorem**), which states that the distribution of draws of extremes (the **extreme value distribution**) from any underlying distribution are given by the generalized Pareto distribution (Pickards 1975), a family of distributions determined by a scale τ and shape parameter κ, which falls into one of three limiting types (or domains) depending on κ (also called the tail index). Since our interest is in the distribution of fitness values for new benefical alleles, if we set the current fitness to zero, the distribution X of fitness increases for beneficial alleles are draws from the tail of the underlying distribution to the right of zero. Following Beisel et al. (2007),

$$\Pr(X \leq x \,|\, \tau, \kappa) = \begin{cases} 1 - (1 + \kappa\, x/\tau)^{1/\kappa}, & x \geq 0, \text{ if } \kappa > 0 \quad \text{(Fréchet)} \\ 1 - (1 + \kappa\, x/\tau)^{1/\kappa}, & 0 \leq x < -\tau/\kappa, \text{ if } \kappa < 0 \quad \text{(Weibull)} \\ 1 - \exp(-x/\tau), & x \geq 0, , \text{ if } \kappa = 0 \quad \text{(Gumbel)} \end{cases} \tag{26.45}$$

Most common distributions (normal, gamma, etc.) have a **Gumbel** EV distribution ($\kappa = 0$), with an exponential tail. This is the most commonly assumed EV distribution for beneficial mutations. When the underlying distribution is truncated to the right, $\kappa < 0$, giving raise to the **Weibull domain**. This distribution can be appropriate for loci near their fitness optimum, as the most fit possible allele simply moves to the optimal value (Martin and Lenormand 2008). The final possible EV distribution (when $\kappa > 0$) is the **Fréchet domain**, which has much heavier tails than an exponential. Biologically, this implies that highly beneficial new mutations are rather likely, and hence is generally not used (Orr 2006). Noting that κ determines the domain family, Beisel et al. (2007) develop a likelihood ratio test for $\kappa = 0$. They found that the

power against the Weibull domain alternative ($\kappa < 0$) is reasonable if ten or more beneficial mutations are scored.

Under Gillespie's model, fitness values for new mutations are drawn from some unknown, and likely very complex, distribution. However, the current allele is likely rather fit (even if moved to a new environment) relative to all of the possible $3L$ alleles one step removed. Hence, its current fitness value is already in the right-hand tail of the fitness distribution, with new favorable alleles being drawn from values even more extreme (farther to the right), see Figure 26.12. In such settings, EVT states that one of three possible limiting distributions (domains) occur (Example 26.8). Gillespie (1983, 1984) assumed that **Gumbel domain**, which arises for a very wide range of underlying distributions. Joyce et al. (2008) examine the properties of adaptive walks under the two other EVT limiting distributions, the Weibull (truncated right tails) and Fréchet (tails heavier than exponential) domains.

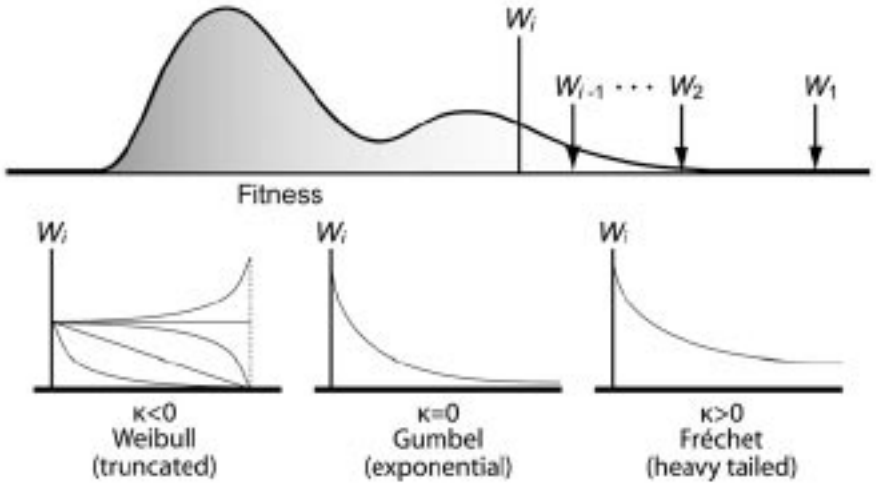

Figure 26.12. (**Top**): The extreme value theorem applied to the distribution of fitness effects of new beneficial alleles. Assume some arbitrary, and unknown, fitness distribution for alleles at a given locus. Provided the current allele is fairly fit, it is a draw from the right-hand tail (extreme upper values) of this distribution. Let W_i denote its current fitness, with i the fitness rank of the current allele relative to the set that it can mutate to. W_1 is the most fit possible allele at this locus, W_2 the next most fit, and so on. (**Bottom**) The trinity theorem (Example 26.8) states that the limiting distribution of draws from the extreme tail of a distribution is one of only three possible types (or domains). Under the **Gumbell domain**, the distribution is exponential. If there is a finite upper limit, the extreme value distribution is from the **Weibull domain**, while if the tail is heavier than an exponential, it is from the **Fréchet domain**. (After Beisel et al. 2007).

Given that the limiting EVT distribution is largely independent of the details of the underlying distribution generating it, several interesting results follow for fairly general fitness functions. First, letting s_i denote the fitness advantage of a new allele relative to the current one, under weak mutation and strong selection (WMSS), Gillespie showed that the

probability of allele j being the next fixed during the walk is

$$\pi_j = \frac{s_j}{\sum_{\ell=1}^{k} s_\ell} \tag{26.46a}$$

where there are k more fit alleles than the current one. Hence, the chance that a mutation is fixed is proportional to its fitness advantage, but the most fit allele is by no means guaranteed of being fixed. Mutation rates do not appear as change to any of the $3L$ adjacent sequences is assumed to be equally likely (Equation 7.37 recovered a similar result for a somewhat different problem wherein i indexes the mutational sequence of alleles). Next, Gillespie showed that the mean number of steps during the walk was small,

$$\left(1 + \sum_{k=1}^{i-1} \frac{1}{j}\right) / 2 \tag{26.46c}$$

where i indicates the fitness rank of the wild-type allele among all local alleles. Since this scales as $\sim \ln(i)$, values typically range between two to five (Gillespie 1991). This results in bursts of substitutions and hence a molecular clock with a higher variance than expected from the Poisson distribution for substitutions generated under drift, which was Gillespie's motivation for considering this model.

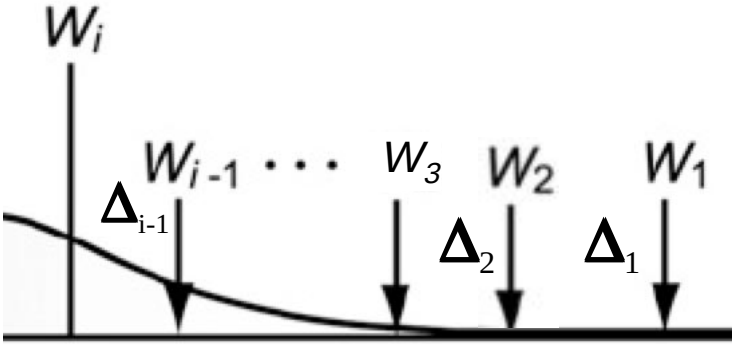

Figure 26.13. Let $\Delta_i = W_i - W_{i+1}$ denote the spacing (difference) in fitnesses between the genotype of fitness rank i and $i-1$. When the current genotype has high fitness (its rank i is not to large) and the undelying fitness distribution is in the Gumbel domain, then Δ_i follows an exponential distribution (Gillespie 1983; Orr 2003b).

Orr (2002) used Gillespie's WMSS process as an adaptive walk model, making use of a key result from EVT on the **spacing** between extreme values. Let $\Delta_i = W_i - W_{i+1}$ denote the spacing between the fitness values for alleles of fitness rank i and $i+1$ (Figure 26.13). When the fitness extreme value distribution is in the Gumbel domain, then $E[\Delta_j] = E[\Delta_1]/j$ (Gumbel 1958; Weissman 1978), so that there is a regular pattern in the spacing that only depends on their rank and the expected value of the most fit allele. (Note that Equation 26.43c shows that a similar spacing, C/j, occurs between steps in a FGM walk.) This result allows us to obtain a simple form the s_j. If the current allele has fitness rank i, the selection coefficient on a higher-ranked ($j < i$) allele is

$$s_j = \frac{\Delta_j}{W_i} = \frac{E[\Delta_1]/j}{W_i} = \frac{C_i}{j} \tag{26.47a}$$

where $C_i = E[\Delta_1]/W_i$. Substitution into Equation 26.46a gives the transition probability from the current allele with rank i to one with rank j as

$$\pi_{j,i} = \frac{1}{i-1} \sum_{k=j}^{i-1} \frac{1}{k} \tag{26.47b}$$

Using this to compute the mean, if the current sequence is the ith-fittest local allele, the mean rank of the next fixed allele is $(i+2)/4$ (Rokyta et al. 2006 suggest a slight refinement of this result, $(i+6)/4$). For example, if the wild-type is the 10th fittest, the expected rank following one substitution is the third fittest. Thus, large jumps in fitness rank occur during the walk. Orr also notes that the adaptive process over this walk is the average of perfect adaptation ($i = 1$ is fixed) and random adaptation (a randomly-chosen more fit allele is fixed, for an average rank of $i/2$), as $(1 + i/2)/2 = (i+2)/4$. Unlike Fisher's model, Orr found that jumps are few, and substantial, with over 30% of the total fitness change from the final walk occurring on the first jump, and over 50% from the largest jump. Finally, Orr showed that the distribution of fixed selective effects over a number of such walks (ignoring the very smallest final steps), is again roughly exponential (we refine this more below). Hence, two very different geometries (phenotypic and sequence space) both generate that same rough pattern of fixed effects, but differ in that a random walk in sequence spaces typically has only a few, mostly substantial, steps.

Example 26.9. Evolution in experimental microbial populations offers the opportunity to test certain features of the mutational landscape model (MLM), in particular the number of steps during a walk and the prediction of rapidly-diminishing returns (provided the initial genotype is itself reasonably fit). Holder and Bull (2001) looked at the fitness increases during adaptive walks for growth at high temperature in the bacteriophages ϕX174 and $G4$. The response seem for ϕX174 fit the pattern expected from the MLM: the first mutation accounted for roughly 3/4 of the total gain in fitness, and the first two mutations for 85%. A more complicated picture was seem for $G4$, which had to pass through an intermediate temperature for any response. While one of the first two mutations had a large fitness effect, there was otherwise no evidence of diminishing returns. In part this could be do to the low fitness of the initial genotype in the target environment (which was essentially zero). Adaptive walks in the fungus *Aspergillus nidulans* were studied by both Schoustra et al. (2009) and Gifford et al. (2011). The number of steps in the walk was short (mean of ~ 2), with diminishing fitness returns for fixed sites. By placing the genotype in different environments with very different starting fitnesses, Gifford et al. were able to show that the length of the walk (still $\sim$ two steps) was insensitive to the starting fitness.

Perhaps the most direct test of Orr's model was Rokyta et al. (2005), who examined 20 single-step adaptations (rapid replication under standard culture conditions) in the single-strand DNA bacteriophage ID11 (a relative of ϕX174). Genome sequencing showed that these 20 single-step events comprised nine different mutations, with selection coefficients (relative to the wildtype) ranging form 0.30 to 0.11. Orr's theory states the most beneficial mutation should be fixed most often, here predicted to be in roughly 6 of the twenty observed events. However, it was only fixed once. The authors noted that this highest-fitness mutation (in their sample) required a transversion mutation, which occurs at lower rates than the transition mutations to reach other beneficial alleles. When correcting the distribution of mutations for relative mutation rates, a good fit was seem between the observed transition probabilities (from the current allele to one of these nine new mutations) and the value predicted by the mutation-corrected version of Equation 26.47b.

We have already discussed how the abstractness of Fisher's model is perhaps its greatest strength, freeing one from the tyranny of the idiosyncratic details for any particular organism. A similar feature occurs in sequence space through the use of EVT to again obtain fairly general statements for unknown distributions of fitness effects of new alleles at a particular loci. What are some of the potential weaknesses of the sequence-space walk model? First and foremost, the fitness distribution may not be in the Gumbel domain, a point discussed further below. Strong selection assumes no slightly deleterious mutations can be fixed, while the weak mutation assumption considers only two segregating alleles (the original and the mutation) at any point in time. Under these conditions, advantageous mutations that must be accessed through a deleterious intermediate cannot be fixed. However, as reviewed in Chapter 7, a deleterious intermediate step can be overcome by stochastic tunneling — the second (advantageous) mutation can arise in the small fraction of segregating initially deleterious mutations. The strong selection assumption implies no neutral alleles, but this is not a serious issue. If a neutral allele is fixed, it can regarded as being a member of the same fitness class as the initial allele. For positively-selected alleles as fitness coefficients become progressively smaller (but still positive), the drift barrier (Chapter 7) is reached, and numerous substitutions of small (and effectively neutral) effect can occur.

The Fitness Distribution of Benefical Alleles

In addition to predicting certain features about an adaptive walk, extreme value theory also provides insight into the distribution of the fitness effects of new beneficial mutations (Orr 2003, 2006, 2010; Martin and Lenormand 2008). When the fitness extreme value distribution is in the Gumbel domain, the Δ_i are independent exponential random variable (Gumbel 1958; Weissman 1978). Thus, when the fitness of an initial allele is high and the fitness distribution is in the Gumbel domain, the distribution of fitness values in new beneficial mutations is exponential (Gillespie 1983; Orr 2003b). A remarkable second finding is **Orr's invariance result**: this distribution has the same mean *independent* of the fitness of the current allele, as long as it is high (Orr 2003b). This invariance applies to the distribution of fitness increment Δ_i, but not necessarily to selection coefficients. If the current allele has fitness rank i, the resulting selection coefficient on a higher-ranked ($j < i$) allele is $s_j = \Delta_j/W_i$, where W_i is also drawn from a distribution.

As summarized in Table 26.5, a number of experiments with microbes have attempted to test the Gillespie-Orr prediction of an exponential distribution of fitness effects for beneficial mutations (also recall Example 26.9). There are two important caveats when considering these results. First, the Gillespie-Orr prediction applies to the distribution of *all* newly beneficial mutation, *not* the distribution of those beneficial mutations that are fixed. While studies looking at the distribution of selective effects for fixed mutations are certainly of interest, strictly speaking, they fall outside of the Gillespie-Orr prediction. Second, the use of EVT assumes that the starting genotype is already of high fitness. A number of studies detect beneficial mutations by rescue from deleterious mutations or by placing the genotype in a radically new, and very deleterious, environment. While the later provides a rapid screen for adaptive mutations (those that grow), the starting genotypes may not be sufficiently extreme in the fitness distribution for EVT to apply. Studies where the exponential did not fit either found that mutations of intermediate fitness effect where most common and/or that they were drawn from the Weibul domain (fitness distribution is truncated to the right).

Table 26.5. Bacterial and bacteriophage experiments on the distribution of fitness effects among beneficial mutations. Studies involve experiments considering either only fixed (Fixed = Yes) beneficial or all detected beneficals (Fixed = No). In order to detect all (as opposed to only fixed) beneficial mutations, some experiments looked for rescue mutants starting with a genotype in a low-fitness environment (Low = Yes). The Gillespie-Orr model predicts an exponential distribution (Gumbel domain of the

EV distribution) when *all* beneficial mutations are considered (Fixed = No) *and* the genotype starts out at high fitness (Low = No). Distributions using the term domain used the formal likelihood-ratio approach of Beisel et al. (2007) was used to test the null (EV distribution shape parameter $\kappa = 0$ for Gumbel domain) versus κ significantly negative (for Weibull domain). The Barrett et al. study found a Weibull *distribution* of effects (which is unimodal), which is *different* from the Weibull *domain* (if the underlying distribution is Weibull, its EV domain is actually Gumbel), and is denoted by as asterisk to remind the reader of this difference.

Species	Fixed?	Low?	Benefical Fitness Effects	Auhors
Escherichia coli	Yes	No	Exponential distribution	Imhof & Schlötterer 2001
	Yes	No	Normal distribution	Rozen et al. 2002
Pseudomonas fluorescens	No	Yes	Weibull distribution*	Barrett et al. 2006
	No	No	Exponential distribution	Kassen & Bataillon 2006
	No	Yes	Weibull domain	Bataillon et al. 2011
	No	Yes	Normal distribution	McDonald et al. 2011
Pseudomonas aeruginosa	No	No	Exponential distribution	MacLean & Buckling 2009
	No	Yes	Weibull domain	MacLean & Buckling 2009
ID11 (ssDNA phage)	No	No	Weibull domain	Rokyta et al. 2008
$\phi 6$ (RNA phage)	No	Yes	Weibull domain	Rokyta et al. 2008

Fisher's Geometry or EVT?

Fisher's geometric model (FGM) and the mutational landscape model (MLM) are, on the surface, very different models of adaptation. The former looks at the evolution of effect size for trait under stabilizing selection, the later examines evolution of fitness during a walk in a single linked region under much more general fitness functions. However, at some fundamental level, we should be able to connect results from the models, as the MLM ideally is modeling the loci that result in phenotypes adapting under FGM. Results of Orr (2006) and especially Martin and Lenormand (2008) start to bridge this gap.

Recall for FGM that Orr showed the distribution of fitness effects for *all* alleles (not just the beneficial ones) roughly normal. As a result, under FGM, the underlying fitness distribution is in the Gumbel domain, and the fitness distribution for beneficial alleles (when they are rare) is exponential. Thus, when beneficial alleles are rare (the probability of an adaptive allele is small), EVT results also apply to FGM. Provided the initial genotype starts a sufficient distance from the optimum that many steps are needed in the walk, both the distribution of the phenotypic values of fixed mutations and the fitnesses of newly beneficial mutations are exponential under FGM.

Likewise, the fitness distribution of *all* beneficial mutations is also exponential under a Gillespie-Orr walk when the Gumbel EV conditions hold (starting genotype has high fitness, fitness distribution is in the Gumbel domain). The distribution of fitness values among mutations *fixed* during the walk, however, departs from exponential (Rozen et al. 2002; Barrett et al. 2006; Martin and Lenormand 2008; Good et al. 2012). One reason is seen in Figure 26.10 — while beneficial mutations with small fitness advantages are expected to be more common (given that they follow an exponential distribution), they also have lower fixation probabilities. The set of mutations surviving stochastic lose has a distribution shifted towards higher values (Figures 26.10, 26.14).

When considering the fixation of mutations in clonal populations, a second evolutionary process is involved (Gerrish and Lenski 1998; Rozen et al. 2002). First, a new beneficial mutation must avoid stochastic loss when rare. While these **competing** mutations are then fixed in a sexual population, in an asexual population, they are fully linked to genomes that may experience additional beneficial mutations, before the initial mutation becomes fixed. When $N\mu \ll 1$, the presence of multiple segregating beneficial mutations is unlikely.

However, when $N\mu \gg 1$, **clonal interference** (Gerrish and Lenski 1998) can occur where the most fit genomes compete with each other (this is just an extreme from of the Hill-Robertson effect occurring when complete linkage is present). The result is that only a subset of the competing mutations that survive stochastic loss are fixed, and this further shifts the distribution towards higher values. As noted by Barrett et al. (2006), the winning genome often does so by accruing *several* beneficial mutations, which can result in an investigator overestimating the fitness effect under the assumption of a single beneficial mutation.

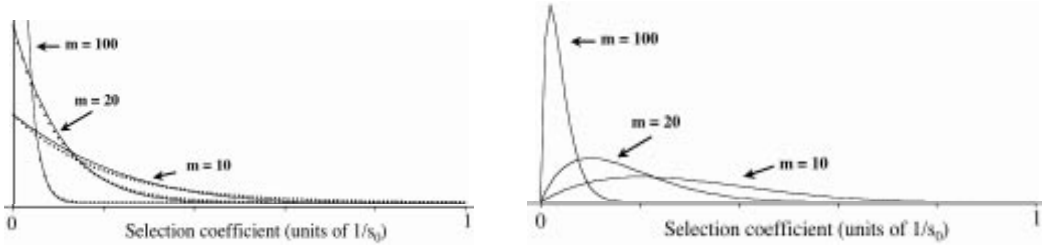

Figure 26.14. The distribution of the fitness effects for beneficial mutations at a locus underlying a phenotype under stabilizing selection, with the current allele close to the optimum. Let $s_0 \ll 1$ denote the maximal fitness advantage for any new mutation (which occurs when a mutation jumps the phenotype to the optimum). **A** (Left): The distribution of fitness effects among *all* beneficial mutations follows a beta distribution, Beta(1, $m/2$), where m is a measure of pleiotropy. The dotted curves show the corresponding exponential distribution, with the two distributions being very similar for m modest to large (> 10). **B** (Right): The distribution of fitness effects among *fixed* beneficial mutations also follows a beta distribution, but now with the first shape parameter changing from one to two, giving a unimodal distribution, Beta(2, $m/2$). Note that the exponential provides a very poor fit to this distribution unless m is very large and small values are ignored.

Can we account for this difference in the distribution of fixed effects (exponential for trait values under FGM, unimodal under EVT)? Likewise, that happens when the fitness distribution is not in the Gumbel domain? As Martin and Lenormand (2008) show, these questions are connected. Recall that the trinity theorem (Example 26.8) states when an underlying distribution has a limiting extreme value distribution, it most resides in one of three domains. Most of our focus has been on results for the Gumbel domain. The Fréchet domain, with its heavier than exponential tails, is unlikely, as this implies an excess of high fitness mutations (Orr 2006). The Weibull domain, however, is biological feasible, and states that there is an upper limit on fitness (the underlying fitness distribution is truncated on the right). Indeed, this is exactly the domain expected for a locus underlying a trait experiencing stabilizing selection, namely the FGM. A mutation at such a locus can have no higher fitness than that of a mutation which exactly jumps the genotype to the optimum, setting a strict upper limit on the fitness distribution. If s_0 denotes the selection coefficient for such a maximally-beneficial mutation, for $s_0 \ll 1$ (the population is near an optimum), Martin and Lenormand (2008) not only show that the distribution the fitness effects of beneficial mutations is in the Weibull domain, but further that it is a beta distribution (Equation A2.38), with

$$\frac{s}{s_o} \sim \text{Beta}(1, m/2), \quad 0 < s < s_0 \tag{26.48a}$$

where m is a measure of pleiotropy (m is the rank of the product of the mutational covariance matrix $\mathbf{M}$ and the stabilizing selection matrix $\mathbf{S}$). Figure 26.14A plots this distribution, showing that is close to an exponential for m modest to large. A more analytic way see

this connection is that the shape parameter of the generalized Pareto distribution (Equation 26.45) in this case is $\kappa = -m/2$, which approaches zero (and the Gumbel domain) when m is large, and FGM has the distribution of beneficial mutations being roughly exponential, in concordance with EVT. This relationship also suggests an approach for estimating m, using the ML approach Beisel et al. (2007) to estimate κ, with $\widehat{m} = -2\,\widehat{\kappa}$.

Applying Equation A2.38b gives the mean fitness value of all newly-arising beneficial mutations as

$$E(s_b) = \frac{2s_0}{2+m} \tag{26.48b}$$

Note the cost of pleiotropy, with the expected fitness decreasing with m. Martin and Lenormand find that the distribution of selection coefficients for fixed beneficial alleles is also beta, but now with a shape parameter that generates a unimodal distribution (Figure 26.14B),

$$\frac{s}{s_o} \sim \text{Beta}(2, m/2), \quad 0 < s < s_0 \tag{26.49a}$$

Again applying Equation A2.38b, the mean fitness value of fixed beneficial mutations is

$$E(s_b) = \frac{4s_0}{4+m} \tag{26.49b}$$

showing both a cost of pleiotropy among fixed mutations and that the mean of fixed mutations is larger than the mean of all beneficial mutations. Although this distribution is unimodal, if m is sufficiently large (a great number of weakly-correlated traits are under selection) and small effects are ignored (the assumptions made by Orr), then it can be reasonably approximated by an exponential. Outside of this range, however, the use of an exponential overestimates the fraction of fixed beneficial mutations with large fitness effects.

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