25

Long-term Response: Deterministic Aspects

The depletion of the variance by fixation of favored alleles is compensated by bringing previously rare alleles into the range where they contribute substantially to the response. — Crow (2010)

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Previous chapters assumed that genetic variances for traits under selection either remain constant or can be predicted solely from their base population values. Under the infinitesimal model, selection does not alter allele frequencies (Chapters 10, 13, 24) and hence the genic variance σ_a^2 remains unchanged, while the additive variance $\sigma_A^2 = \sigma_a^2 + d$ changes (from selection-induced disequilibrium d) in a predictable way (Chapter 16). With finite population size, allele frequencies are changed by drift, but again in predictable ways under an additive model (Chapters 16, 24). If allele frequency change is entirely due to drift, the expectation is that the amount of change is *independent* of allelic effect size. With selection-induced changes, we expect alleles with larger effects to experience greater allele frequency change. In such cases, while short-term response can be reasonably predicted from the base population variance components alone, long term response depends on the underlying, and generally unknown, genetic architecture (number of genes, allelic effects, allele frequencies). Our discussion of long-term response, which spans the next three chapters, is divided into three major topics: (i) deterministic changes in very large populations (the focus of this chapter), (ii) the special features that emerge due to drift when finite population size is considered (Chapter 26), and (iii) the long-term consequences of mutational input (Chapters 26 and 27). Our focus over the next two chapters is directional selection. The long-term consequences of stabilizing selection are considered in Chapter 27.

We start by examining an idealized model where an initially linear response declines smoothly to an asymptotic **selection limit** as the genetic variation from the initial population becomes exhausted. We will more formally show that while populations with the same variance components show essentially the same short-term response, their long-term responses can be very different, depending on their underlying genetic architectures. We then develop deterministic theory for allele frequency changes under long-term response in order to quantify the expected time until a certain amount of response is seen and what the ultimate selection limit (using only the initial variation) should be. While these models cannot be applied to most real populations (as they required detailed information on the joint distribution of allele frequencies and effects at each locus in the population), they still provide an important framework for examining empirical results. Next, we examine response with a major gene and background polygenes. We conclude by reviewing a few generalizations that emerge from long-term artificial selection experiments and examine the nature of the (apparent) selection limit in these experiments.

IDEALIZED LONG-TERM RESPONSE IN A LARGE POPULATION

The general pattern expected in the long-term response to directional selection is roughly as

follows: in the absence of segregating major genes, additive variance (and hence response) is roughly constant over the first few generations giving a nearly linear response (Figure 25.1). As discussed in Chapter 16, there is a reduction in the additive variance due to the generation of gametic-phase disequilibrium, but this is generally small unless directional selection on the trait is strong, heritability is high, and the number of underlying loci large. As generations proceed, sufficient allele frequency change accrues to significantly alter genetic variances, and in particular the genic variance σ_a^2. At this point, additive variance can either increase or decrease, depending on the starting distribution of allelic frequencies and effects. Assuming no input of new variation (from mutation or migration), the additive variance generated from the initial variation in the base population eventually declines. Ultimately, a **selection limit** or **plateau** is reached, reflecting (in an infinite population) fixation of all favorable alleles and loss of additive genetic variance at those loci still segregating (e.g., loci overdominant for the character under selection). If both major and minor alleles influence the character, an initial rapid response due to large changes in allele frequencies at major loci whose alleles are initially at modest frequency is followed by a much longer period of slower response due to allele frequency changes at loci having smaller effects and from major alleles that were initially very rare. Such differences in rates of response can make it difficult to determine whether a selection limit has actually been reached. As the genetic variation in the base population becomes exhausted, the effects of new mutations become extremely important for continued response, but we defer discussion of their impact until the next chapter.

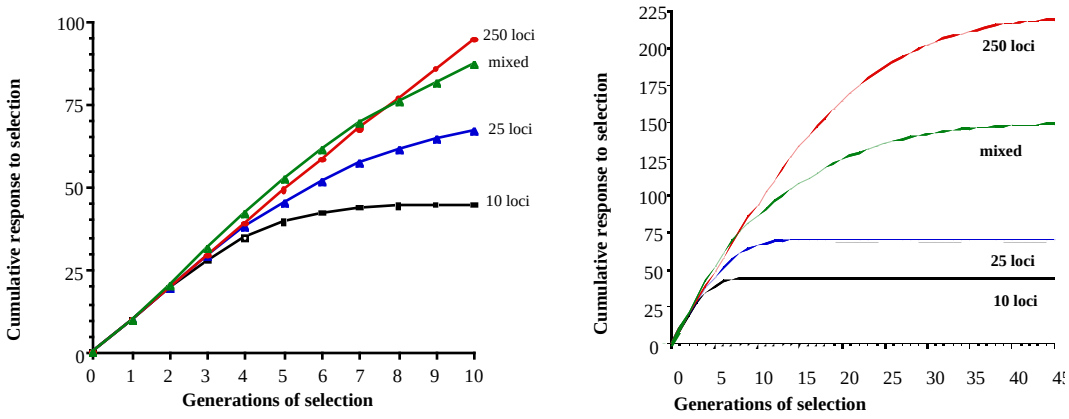


Figure 25.1. Examples of the expected response to selection, here assuming truncation selection (with the upper 20% saved), n identical diallelic loci (each with genotypic values 0 : a : 2a, and favorable frequency p). We further assume no epistasis and ignore any effects of gametic-phase disequilibrium. All populations start with $\sigma_A^2(0) = 100$ and $\sigma_E^2 = 100$, so that $h^2(0) = 0.5$. Curves marked 10, 25, and 250 loci correspond to populations with initial allele frequency $p = 0.5$ and a values of 4.47, 2.82, and 0.89, respectively. The mixed population consists of 5 identical major loci with $p = 0.25$, $a = 5.16$ and 125 identical minor loci with $p = 0.5$, $a = 0.89$ (the resulting total additive variance is equally split over major and minor loci). **Left:** Short-term response over the first 10 generations. **Right:** Response over the first 40 generations. Note that the total response increases with the number of loci. In the infinitesimal model limit, response remains linear over all generations (after correcting for the slight decrease over the first few generations from linkage disequilibrium, see Example 16.2).

Figure 25.1 illustrates differences in the long-term response for four hypothetical populations with the same initial heritability but different genetic architectures. All show essentially the same response over the first few generations. By generation five, selection has changed

allele frequencies in the 10- and 25-locus populations enough to reduce response, while the 250-locus population shows a roughly constant response through 20–25 generations. The mixed population (5 major loci, each with initial frequency of the favored allele p = 0.25, 125 minor loci with p = 0.5) shows an enhanced response relative to the others in generations 3 – 7. This results from an increase in heritability as the frequencies of alleles with large effects increase from $1/4$ to $1/2$, increasing the additive variance contributed by these loci. If rare recessives are present, there can be a considerable time lag until the enhanced response appears (e.g., Figure 25.9A). For all models, the rate of allele-frequency change scales as $1/s$, the selection coefficient, which itself scales with the effect size. Hence, as a rough approximation, if the effect size is halfed, the same amount of allele frequency change takes twice as long.

If alleles favored by selection are dominant, response slows down considerably as these become common, reflecting the rarity of homozygous recessives. In such cases, response can be so slow that the population appears to be at a limit. However, as Figure 25.2 demonstrates, reverse selection on these populations can result in a fairly rapid response. As was mentioned in Chapter 18, divergent selection in this case generates a significant asymmetric response. This apparent limit due to the very slow removal of recessives can be partly overcome by inbreeding. By increasing the frequency of homozygotes relative to a random mating population, inbreeding greatly improves the efficiency of selection, allowing favorable dominant alleles to be more rapidly fixed.

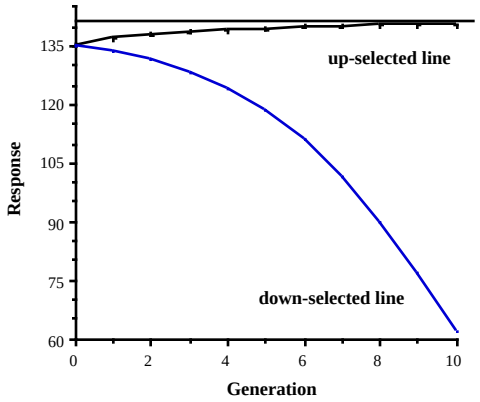


Figure 25.2. With strong directional dominance, an apparent selection limit can result when alleles favored by selection are dominant, as selection is only against increasingly rare recessive homozygotes. Here the genotypes **AA** : **Aa** : **aa** have values $2a : 2a : 0$, and we ignore epistasis and gametic-phase disequilibrium. The population consists of 25 identical loci, with $a = 2.82$ and initial frequency $p = 0.8$. Truncation selection with the upper (or lower) 20% of the population saved is assumed. If all loci are fixed for the favored allele, the selection limit is 141 (indicated by the horizontal line). There is little response to upward selection and the population appears at a selection limit, even though there is still considerable genetic variation. Conversely, the down-selected line responds very rapidly.

Example 25.1. Falconer (1971) examined an apparent limit in a mouse line selected for increased litter size. Four sublines were created from this plateaued line and subjected to inbreeding and selection. Selection on a new line formed by crossing these inbred-selected lines gave an improvement of 1.5 mice/litter over the original limit. Falconer's interpretation was that many recessive alleles decreasing litter size were segregating in the apparently plateaued

line, some of which were lost in during inbreeding within sublines. Crossing the inbred-selected lines generated a population segregating fewer recessives (i.e., fixed for more of the favorable dominant alleles), facilitating response. Several other selection experiments in mouse also found segregating recessives in populations near apparent selection limits. For litter size, Eklund and Bradford (1977) found that inbreeding and selection also increased response. However, Al-Murrani and Roberts (1974) found that while a population plateaued for increased body weight was also segregating a number of recessives, their loss was expected to give only a trivial increase in body weight (less than half a gram) and no increase was detected using Falconer's inbred-selection method.

DETERMINISTIC SINGLE-LOCUS THEORY

The contribution to the selection limit from a single locus, and the half-life associated with this contribution, depend on a variety of genetic parameters — initial allele frequencies, dominance relationship among alleles, and allelic effect sizes. This section quantifies how these factors influence long-term response for a diallelic locus in the absence of drift, mutation, and epistasis. This basic model provides useful insight into the dynamics of response and serves as the foundation for theories incorporating drift and mutation (Chapters 26 and 27).

Expected Contribution From a Single Locus

We start with the expected total contribution from a given diallelic locus. Let **A** be the allele favored by directional selection, where the genotypes $\mathbf{aa} : \mathbf{Aa} : \mathbf{AA}$ have genotypic values of $0 : a(1+k) : 2a$. Assuming genotypes are in Hardy-Weinberg expectations, the contribution to the mean character value from this locus is a function of p (the frequency of **A**),

$$m(p) = 2ap\,[\,1 + (\,1-p\,)k\,] \tag{25.1a}$$

The presence or absence of gametic-phase disequilibrium has no influence on this contribution to the mean, provided there is no epistasis. The total contribution from this locus if **A** is fixed, given it starts at initial frequency p_0, is

$$m(1) - m(p_0) = 2a - 2ap_0\,[\,1 + (\,1-p_0\,)k\,] = 2a\,(\,1-p_0\,)(\,1-p_0k\,) \tag{25.1b}$$

Figure 25.3 plots the total contribution when allele **A** is additive ($k = 0$), dominant ($k = 1$), and recessive ($k = -1$). Total response is largest when **A** is recessive and rare, smallest when **A** is dominant and common. With overdominance ($k > 1$), the highest value for $m(p)$ is not at $p = 1$, but rather at $p = \widehat{p}$, where

$$\widehat{p} = \frac{1+k}{2k} \tag{25.1c}$$

This is obtained by taking the derivation of $m(p)$ and solving for zero. If $p_0 > \widehat{p}$, directional selection on the trait results in p decreasing to $\widehat{p}$, while if $p_0 < \widehat{p}$, p increases to $\widehat{p}$. In either case, the final contribution from this locus is given by

$$m(\,\widehat{p}\,) - m(p_0) \tag{25.1d}$$

The allele frequency p_β at which a preset fraction β of the total contribution occurs is also of interest. This is determined by solving the quadratic equation

$$m(p_\beta) - m(p_0) = \beta\,[\,m(1) - m(p_0)\,] \tag{25.1e}$$

for p_β ($m(1)$ is replaced by $m(\widehat{p})$ when $k > 1$). A case of particular interest is $p_{1/2}$, the frequency at which half the response occurs ($\beta = 1/2$). Expressions for $p_{1/2}$ as a function of initial allele frequency are given in Table 25.1 and plotted in Figure 25.3. Observe that rare recessives have to increase substantially in frequency to give half their ultimate response (e.g., if $p_0 = 0.1$ then $p_{1/2} \simeq 0.71$).

Table 25.1. Total contribution to the selection limit and the allele frequency $p_{1/2}$ at which half this response occurs for a diallelic locus when allele **A** has initial frequency p_0.

	Total Contribution	$p_{1/2}$
A additive ($k = 0$)	$2a(1-p_0)$	$(1+p_0)/2$
A dominant ($k = 1$)	$2a(1-p_0)^2$	$1-\sqrt{[1-p_0(2-p_0)\,]/2}$
A recessive ($k = -1$)	$2a(1-p_0^2\,)$	$\sqrt{(1+p_0^2\,)/2}$

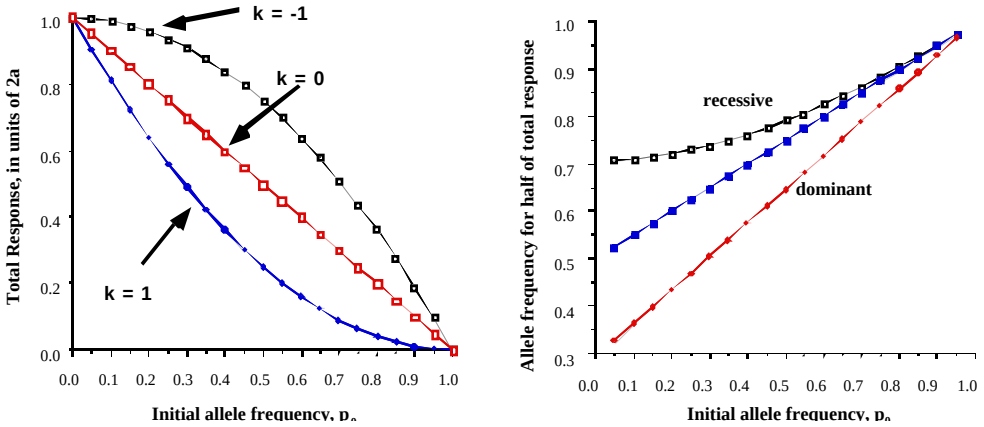


Figure 25.3. **Left**: The contribution to total response from a diallelic locus assuming allele **A**, starting at frequency p_0, is eventually fixed. The genotypes **AA** : **Aa** : **aa** have values $2a : a(1+k) : 0$. The three curves correspond to **A** being additive ($k = 0$), dominant ($k = 1$), and recessive ($k = -1$). The smallest contribution is made by dominant alleles at high frequencies, the largest from recessive alleles at low frequencies. **Right**: The allele frequency $p_{1/2}$ at which half the total response contributed by a locus occurs, as a function of its initial frequency p_0.

Dudley's Estimators of a, n, and p

In a similar fashion to the Wright-Castle estimator for the number of alleles (LW Chapter 9), if we are willing to make the assumption of the exchangeable model (all additive loci with the same effects and initial frequencies, Chapter 24), we can estimate a, n, and p from data on selection limits. Under this model, Equation 25.1b gives the expected response as $R = 2na(1-p)$, while the starting additive variance is $2na^2p(1-p)$. Taking the ratio of these two quantities gives Robertson's (1970a) result,

$$R/\sigma_A = \frac{2na(1-p)}{\sqrt{2na^2p(1-p)}} = \sqrt{2n(1-p)/p} \qquad (25.2a)$$

Dudley (1977) noted that with a divergence selection experiment, Equation 25.2a gives the limit R_H for response in the high direction, while

$$R_L/\sigma_A = \frac{2nap}{\sqrt{2na^2p(1-p)}} = \sqrt{2np/(1-p)} \tag{25.2b}$$

gives the limit to response in the low direction. Taking the ratio of these two limits

$$R_H/R_L = \frac{\sqrt{2n(1-p)/p}}{\sqrt{2np/(1-p)}} = \frac{1-p}{p} \tag{25.2c}$$

suggests an estimate of p as

$$p = \frac{1}{R_H/R_L + 1} \tag{25.2d}$$

Since $R_H R_L = 4n^2a^2p(1-p)$, it follows that $R_H R_L/\sigma_A^2 = 2n$, which suggests an estimator for the number of loci,

$$n = \frac{1}{2}\,\frac{R_H R_L}{\sigma_A^2} \tag{25.2e}$$

Finally, a little algebra shows that

$$a = \sigma_A^2\left(\frac{1}{R_H} + \frac{1}{R_L}\right) \tag{25.2f}$$

These estimates of the genetic architecture of a trait should be regarded as extremely crude (at best), but nonetheless provide potential insight. One of the many caveats in applying these results is that the population must be at the limit, which can be hard to access. Operationally, the limit could be estimated from curve-fitting of the data (Equation 25.10, below).

Dynamics of Allele-Frequency Change

To obtain approximate expressions for the actual dynamics of response we need to follow allele frequency changes over time. Recall from Equation 5.21 that if the character is normally distributed, then $\Delta p \simeq \overline{i}\,(\alpha^*/\sigma_z)\,p$, where p and α^* are the frequency and average excess of **A**. This is a weak-selection approximation, as it assumes that $|\,\overline{i}\,\alpha^*/\sigma_z| \ll 1$. It also assumes that the effects of epistasis, gametic-phase disequilibrium, and genotype $\times$ environment interactions are negligible. Assuming random mating, the average effect of an allele equals its average excess and LW Equation 4.15a gives $\alpha^* = (1-p)a[1+k(1-2p)]$. Substituting yields

$$\Delta p \simeq \frac{a\,\overline{i}}{\sigma_z} p(1-p)[\,1 + k(1-2p)\,] \tag{25.3}$$

Recall that this is correct only to linear order (terms of a^2 and higher order are ignored, see Equation 5.27a). Thus, there are potential pitfalls in applying Equation 25.3 when $\overline{i} \simeq 0$. One important example is strict stabilizing selection, where $\overline{i} = 0$ but allele frequencies can still change due to selection on the phenotypic variance of the character, which enter as quadratic terms, a^2 (e.g., Example 5.6).

Example 25.2. The idealized response curves in Figure 25.1 were generated using Equation 25.3 to compute the expected allele frequency change at each locus, assuming no gametic-phase disequilibrium. We assumed complete additivity ($k = 0$ and no epistasis), $\sigma_E^2 = 100$, and that n identical loci underlie the character. Thus

$$\Delta p_t = \frac{a\,\overline{i}\,p_t(1-p_t)}{\sigma_z(t)} = \frac{a\,\overline{i}\,p_t(1-p_t)}{\sqrt{\sigma_A^2(t) + \sigma_E^2}} \simeq \frac{a\,\overline{i}\,p_t(1-p_t)}{\sqrt{2na^2p_t(1-p_t) + 100}}$$

Strictly speaking, the last expression is a (close) approximation, as $2na^2p_t(1-p_t)$ is the *genic* variance $\sigma_a^2(t)$ at generation t, while the *additive genetic* variance equals the genic variance plus the disequilibrium contribution, $\sigma_A^2(t) = \sigma_a^2(t) + d(t)$, as discussed in Chapters 16 and 24. Iteration generates the response curves given in the figure.

Recall that the results for single-locus selection response in Chapter 5 used the standard parametrization where the genotypes $\mathbf{aa}:\mathbf{Aa}:\mathbf{AA}$ have fitnesses $1:1+s(1+h):1+2s$. For weak selection (e.g., $|s|$, $|sh| \ll 1$), this model gives $\Delta p \simeq s\,p\,(1-p)\,[\,1+h\,(1-2p)\,]$, which follows from Equation 5.1b upon noting that $1/\overline{W} = 1 + O(s, sh)$. Matching terms with Equation 25.3, we find that a QTL under directional selection has approximate selection coefficients of

$$s = \frac{a}{\sigma_z}\,\overline{\imath} \qquad \text{and} \qquad h = k \tag{25.4}$$

Thus, as an initial approximation, the dynamics at a QTL with a small effect on a character under directional selection follow those of a locus under these constant fitnesses. With gametic-phase disequilibrium and/or epistasis, single-locus fitnesses change as the background genotype changes (Example 5.7). In the absence of these complications, fitnesses still change as the phenotypic variance σ_z^2 changes. As other loci become fixed due to selection and drift, σ_z^2 (generally) decreases as the genetic variance decreases, which increases s. Unless heritability is large, this effect is usually small. Assuming all genetic variance is additive, then if $h^2 = 0.1$, the phenotypic standard deviation when all loci are fixed is 95% of its initial value (inflating s by 5%), while for $h^2 = 0.25$ and 0.5, s can be inflated by 15% and 43%, respectively. This decrease in phenotypic variance can be countered if σ_E^2 increases as genotypes become more homozygous (LW Chapter 6) or if there has been selection to increase σ_E^2 (Chapter 17). It is worth stressing that these results are for a trait under directional selection. The dynamics for a locus for a trait under stabilizing selection are quite different (Example 5.6; Chapter 27).

The approximate fitnesses given by Equation 25.4, along with the results from Chapter 5, provide insight into the behavior of an allele at a QTL under selection. An additive QTL (of small effect) underlying a character under directional selection behaves approximately like a locus with an additive fitness of $s = \overline{\imath}\,a/\sigma_z$. Alternatively, if the locus displays overdominance in the character ($k > 1$), then under directional selection this locus displays overdominance in fitness and $\widehat{p} = (1+k)/(2k)$ is an internally stable equilibrium. For this locus there is still genetic variation in the trait at the selective equilibrium, although none of it is expected to be additive. The dynamics at a QTL under stabilizing selection are much more complicated, as the linear approximation given by Equation 25.4 fails near the equilibrium value and the quadratic terms must be considered (e.g., Equation 9.44a). Chapter 27 examines long-term stabilizing selection in more detail.

We can use the above results to compute the expected time to achieve a fraction of the response contributed by a locus in an infinite population. When selection is weak ($|s|$, $|hs| \ll 1$), Equation 5.3c gives the expected time for an allele to reach frequency p given it starts at frequency p_0 for the fitness model $1:1+s(1+h):1+2s$. Equation 5.3d gives the times when $\mathbf{A}$ is additive ($h = 0$), Equation 5.3e when $\mathbf{A}$ is recessive ($h = -1$), and Equation 5.3f when $\mathbf{A}$ is dominant ($h = 1$). These expressions, together with Equations 25.1e and 25.4, allow us to obtain approximate expressions the expected time until β of the total contribution from a single locus occurs (the time to reach p_β). Note that the dynamics of evolutionary change scale as $s^{-1} = (\overline{\imath}\,a/\sigma_z)^{-1}$ — the smaller the allelic effect, the slower the expected response time. Substituting $p_{1/2}$ for p gives the expected half-life of response associated with the locus under consideration (Figure 25.4). The half-life for rare recessives can be quite long.

Note also that the half-life of response for dominant loci *increases* with allele frequency when **A** is common (although in such cases, the additional gain made by fixing **A** is typically very small, see Figure 25.3).

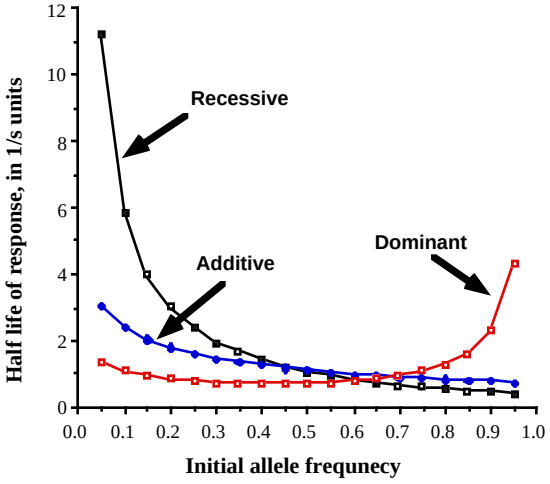


Figure 25.4. The expected times for a diallelic locus to contribute half its total response, assuming **A** is eventually fixed. These curves are obtained by substituting $p_{1/2}$ from Table 25.1 into the appropriate version of Equation 5.3. Note that time for half-life scale as $s^{-1} = (\bar{\imath}\, a/\sigma_z)^{-1}$ generations.

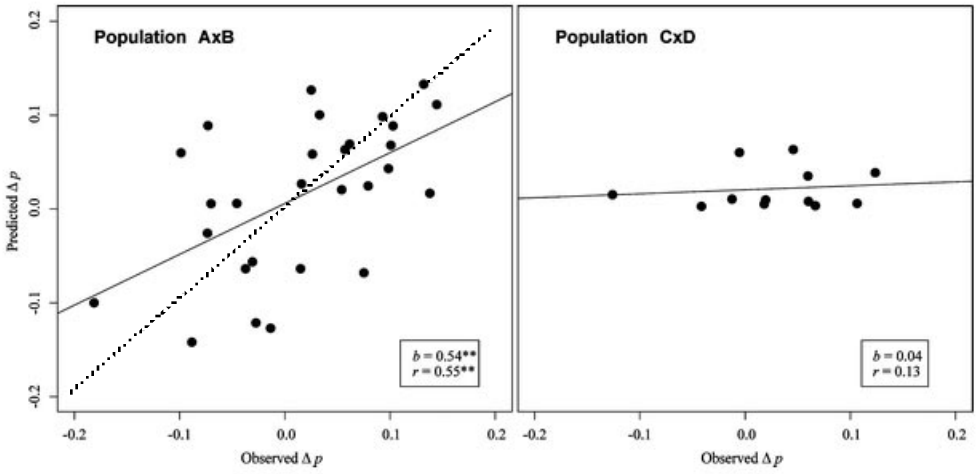
These results ignore the effects of gametic-phase disequilibrium. Negative disequilibrium generated by directional selection reduces the average effect of an allele ($+$ alleles are associated with an excess of $-$ alleles, and vice versa, reducing allelic effects relative to a population in gametic-phase equilibrium). This results in weaker selection and a slower change in allele frequency. Hence, the half-lives plotted in Figure 25.4 are (slight) underestimates. For major alleles, our assumption that $|a|/\sigma_z$ and $|ak|/\sigma_z$ are small no longer holds, and the above expressions for change in allele frequency and expected time to reach a given frequency can be a poor approximations. More accurate versions are given by Latter (1965a) and Frankham and Nurthen (1981).

Example 25.3. An ingenuous experiment examining the fit between estimated QTL effects and their projected allele frequency changes under selection was performed by Falke et al. (2007). By making crosses between inbred lines, the frequency of all segregating alleles in the F_1 is 1/2. Assuming only additive effects, Equation 25.3 reduces to $\Delta p = a\,\bar{\imath}\,/(4\sigma_p)$. Further, the expected frequency change at a marker linked to n QTLs is

$$\Delta p_m = \frac{\bar{\imath}}{4\sigma_p} \sum_{i=1}^{n} a_i(1 - 2r_i) \tag{25.5}$$

where r_i is the marker-ith QTL recombination frequency (this expression is only appropriate, as it ignotes LD among the linked QTLs). Falke et al. examined two sets of crosses involving European flint maizes. The A $\times$ B cross used roughly 270 $F_{2:3}$ lines for QTL mapping and was subjected to four cycles of selection, while the C $\times$ D cross used roughly 130 $F_{3:4}$ for

QTL mapping and was subjected to seven cycles of selection. As the figure below shows, QTL effect was a modest predictor of change in marker allele frequency in the A × B cross ($r^2 = 0.55$), while nonsignificant in the C × D cross ($r^2 = 0.13$). In the A × B cross, the slope of predicted to observed was roughly 0.5, with the observed allele frequency change exceeding that predicted by roughly two-fold. While the lack of fit should not be surprising, the direction was, as one would expect an *overprediction* of allele frequency change due, in part, to Beavis effects — overestimation of the effects of detected QTLs when power is low (LW Chapter 15; Göring et al. 2001; Xu 2003; Goddard et al. 2009). Likewise, the generation of negative linkage disequilibrium among selected sites (Chapter 16) would be expected to further (albeit slightly) reduce response. The dashed curve gives the observed = predicted line. Values below this line are overpredicted, showing that about half of the marker changes are overpredictions.



Example 25.4. As an example of the consequences for the limit $R(\infty)$ and half-life $t_{1/2}$ as the number of loci increase, consider the interchangeable locus model with n completely identical additive loci (in the absence of mutational input). Suppose populations with different numbers of loci underlying the character start with the same initial variances ($\sigma_A^2(0) = 100$, $\sigma_z^2(0) = 200$) and with an initial frequency $p_0 = 0.5$ at all loci. To hold initial additive genetic variance constant as n increases, the allelic effect a must decrease as the number of loci increases. Ignoring gametic-phase disequilibrium, $\sigma_A^2(0) = 2na^2p_0(1-p_0) = na^2/2 = 100$, implying $a = 10\sqrt{2/n}$. From Table 25.1, the selection limit becomes $2na(1 - 1/2) = na = 10\sqrt{2n}$. Likewise, with $p_0 = 1/2$, $p_{1/2} = 3/4$ implying (from Equation 5.3d) that $t_{1/2} \simeq (\sigma_z/a)\ln(3)/\overline{\imath} = \sqrt{n/2}\,\ln(3)/\overline{\imath}$. The following table gives results for 5 to 500 loci.

n	a	$R(\infty)$	$R(\infty)/\sigma_z(0)$	$t_{1/2} \times \overline{\imath}$
5	6.32	31.6	2.2	1.7
10	4.47	44.7	3.2	2.5
25	2.82	70.7	5.0	3.9
50	2.00	100.0	7.1	5.5
100	1.41	141.4	10.0	7.8
250	0.89	223.6	15.8	12.3
500	0.63	316.2	22.4	17.4

At the selection limit the mean phenotype is usually more extreme than any phenotype ob-

served in the initial base population ($R > 3\sigma_z$). For example, when $n = 25$, the total response is 5 phenotypic standard deviations. Since $\Pr(U > 5) = 2.87 \times 10^{-7}$, for a population of size 10^6, the probability that none exceed this value is $\simeq \exp(2.87 \times 10^{-7} \cdot 10^6) = 0.75$. Hence, the limiting mean exceeds any phenotype likely to be found in the initial population. This is not surprising, as probability of observing the most extreme genotype (**AA** at all loci) in the base population is $(1/4)^{25} \simeq 10^{-15}$.

MAJOR GENES VERSUS POLYGENIC RESPONSE: THEORY

As highlighted by Example 24.4 and Figure 25.1, the presence of a major gene can change the dynamics of response. A hotly-debated issue in quantitative genetics and evolutionary biology is whether response from major genes or from a polygenic background is more important for a typical trait. At present, the data are still murky. Before reviewing these, we first consider Lande's theoretical work on conditions for major gene versus polygenic response (Lande 1983). A related topic, selection when a known major gene is included in an index of selection (Pong-Wong and Woolliams 1998), is a special case of marker-assisted selection and is covered in Volume 3.

Table 25.2. Lande's (1983) model for simultaneous selection on a major locus and background polygenes. The distribution of phenotypic values at each major locus genotypes is assumed to follow a normal distribution with variance σ^2. Likewise the distribution of genotypic values for each genotype is normal with variance $h^2\sigma^2$. Here $\varphi(z, \mu, \sigma^2)$ denotes the density function for a normal random variable with mean μ and variance σ^2, and $w(z)$ is the expected fitness associated with phenotype z.

	Major locus genotype		
	aa	**Aa**	**AA**
Frequency	$(1-p)^2$	$2p(1-p)$	p^2
Mean Phenotype	μ	$\mu + \alpha_1$	$\mu + \alpha_2$
Natural Selection	1	$1 - s_1$	$1 - s_2$
Mean Fitness	$\overline{W}_0$	$(1-s_1)\overline{W}_1$	$(1-s_2)\overline{W}_2$

$$\overline{W}_i = \int w(z)\,\varphi(z, \mu + \alpha_i, \sigma^2)\,dz, \quad \text{for } i = 0, 1, 2$$

Mean fitness:

$$\begin{aligned}\overline{W} &= (1-p)^2 W_{aa} + 2p(1-p)W_{Aa} + p^2 W_{AA} \\ &= (1-p)^2\overline{W}_0 + 2p(1-p)(1-s_1)\overline{W}_1 + p^2(1-s_2)\overline{W}_2\end{aligned}$$

Population Mean:

$$\overline{z} = \mu\left(1 + 2\alpha_1 p(1-p) + \alpha_2\, p^2\right)$$

Lande's Model: Response with a Major Gene and an Infinitesimal Background

Lande (1983) assumed a single major gene and an infinitesimal background of polygenes, and his concern was how often response (in particular, an adaptation by natural selection) primarily due to a single (or a very few) major genes versus being polygenic. Since genes with major effects on a trait often have deleterious effects on overall fitness (Wright 1977; Lande 1983; Kemper et al. 2012), Lande allowed for natural selection acting on the locus in addition to phenotypic selection on the trait. The basic parameters of the model are given in Table 25.2. For each of the three major locus genotypes, the distribution of phenotypic

values is assumed to follow a normal distribution with mean $\mu + \alpha_i$ and variance σ^2, while the variance in genotypic values about a major locus genotype is $h^2\sigma^2$. As the expresson for the change in mean in Table 25.2 shows, the dynamics of the mean jointly depends on the change in both the major gene (p) and and the background polygenes (μ). While both change over time, to avoid excessive notation we suppress the subscript for generation on each.

Consider the change in major allele frequency p first. Using the mean and marginal fitnesses from Table 25.2, Wright's formula (Equation 5.5) gives the expected change as

$$\begin{aligned}\Delta p &= \frac{p(1-p)}{2\overline{W}}\,\frac{\partial \overline{W}}{\partial p} \\ &= \frac{p(1-p)}{\overline{W}}\,\left[\,(p-1)\overline{W}_0 + (1-2p)(1-s_1)\overline{W}_1 + p(1-s_2)\overline{W}_2\,\right] \qquad (25.6)\end{aligned}$$

with the last step following upon differentiation of the mean fitness. Note that the $\overline{W}_i$ are not constants, but rather change with the polygenic mean.

The expected change in the polygenic mean μ follows from the Lande Equation (13.27a),

$$\Delta\mu = h^2\sigma^2\,\frac{\partial \ln(\overline{W})}{\partial \mu} = \frac{h^2\sigma^2}{\overline{W}}\,\frac{\partial \overline{W}}{\partial \mu} \qquad (25.7a)$$

Taking the derivative of $\overline{W}$ with respect to μ gives $\Delta\mu$ as

$$\frac{h^2\sigma^2}{\overline{W}}\left((1-p)^2\frac{\partial \overline{W}_0}{\partial \mu} + 2p(1-p)(1-s_1)\frac{\partial \overline{W}_1}{\partial \mu} + p^2(1-s_2)\frac{\partial \overline{W}_2}{\partial \mu}\right) \qquad (25.7b)$$

To evaluate the derivatives of the marginal fitnesses of the major locus, first note for the normal density function that since

$$\varphi(z,\mu,\sigma^2) = \frac{1}{\sqrt{2\pi\sigma^2}}\cdot\exp\left(-\frac{(z-\mu)^2}{2\sigma^2}\right)$$

and recalling from the chain rule of differentiation that $\partial \exp[f(x)]/\partial x = (\partial[f(x)]/\partial x)\cdot \exp[f(x)]$, it follows that

$$\frac{\partial \varphi(z,\mu+\alpha_i,\sigma^2)}{\partial \mu} = \frac{z-(\mu+\alpha_i)}{\sigma^2}\,\varphi(z,\mu+\alpha_i,\sigma^2) \qquad (25.8a)$$

Hence,

$$\begin{aligned}\frac{\partial \overline{W}_i}{\partial \mu} &= \int w(z)\,\frac{\partial \varphi(z,\mu+\alpha_i,\sigma^2)}{\partial \mu}\,dz \\ &= \frac{1}{\sigma^2}\left(\int z\,w(z)\,\varphi(z,\mu+\alpha_i,\sigma^2)dz - (\mu+\alpha_i)\int w(z)\,\varphi(z,\mu+\alpha_i,\sigma^2)dz\right) \\ &= \frac{1}{\sigma^2}\left[\int z\,w(z)\,p_i(z)\,dz - (\mu+\alpha_i)\,\overline{W}_i\right] = \frac{\overline{W}_i}{\sigma^2}\,S_i \qquad (25.8b)\end{aligned}$$

where

$$S_i = \int z\,w(z)\,\frac{p_i(z)}{\overline{W}_i}\,dz - (\mu+\alpha_i) \qquad (25.8c)$$

is the selection differential acting on major locus genotype i, as the integral represents the mean value following selection (μ_{s_i}) and the second term the mean before selection (μ_i), with $S_i = \mu_{s_i} - \mu_i$. The expected change in the polygenic mean becomes

$$\frac{\Delta\mu}{h^2} = (1-p)^2 \frac{\overline{W}_0}{\overline{W}} S_0 + 2p(1-p)(1-s_1) \frac{\overline{W}_1}{\overline{W}} S_1 + p^2(1-s_2) \frac{\overline{W}_2}{\overline{W}} S_2 \tag{25.8d}$$

From Table 25.2, the new mean becomes

$$\overline{z} = (\mu + \Delta\mu)\left(1 + 2\alpha_1(p+\Delta p)(1-p-\Delta p) + \alpha_2\left[p+\Delta p\right]^2\right) \tag{25.8e}$$

Note that while changes in p influence changes in μ and vice-versa, Lande assumed the infinitesimal variance σ^2 and heritability h^2 remain unchanged over time. By using the machinery from Chapter 16, we could modify the above expressions to allow for the changes caused by selection generating gametic-phase disequilibrium.

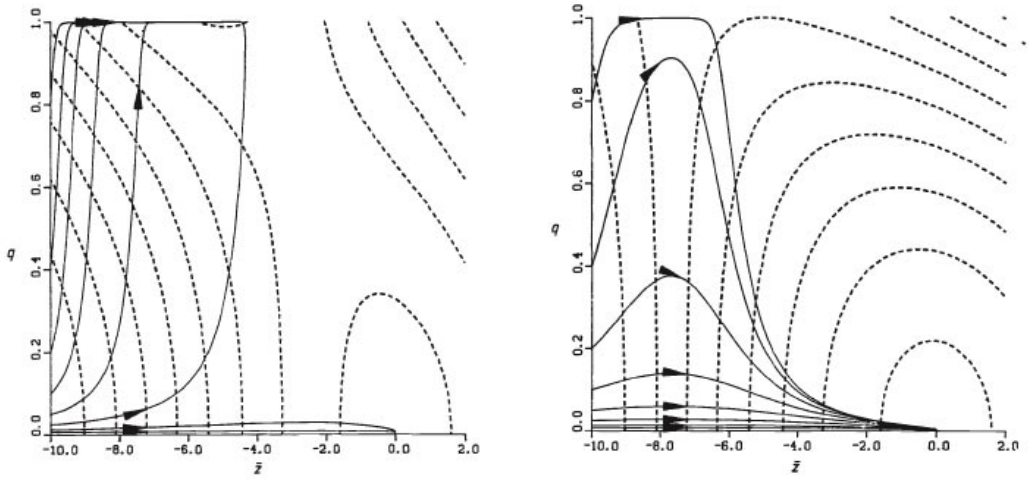


Figure 25.5. Lande's analysis of selection towards a new optimum when a major gene and polygenes are present. In both examples the population initially starts ten units below the new optimum value (zero), and the favored major gene homozygote adds a value of 5. Dashed lines represent contours in the (p, μ) fitness space, while the arrowed solid lines represent the allele frequency trajectories of the major gene. **A (Left):** The favored homozygote has a pleiotropic disadvantage of $s = 0.02$. Here there are two peaks on the (p, μ) fitness surface, on the lower right (p = 0, μ = 0) and in the upper middle (p = 1, μ =$-$5). If its initial frequency is above 0.025, the major allele is fixed, while it is lost if below this frequency. **B (Right):** The favored homozygote has a pleiotropic disadvantage of $s = 0.40$. Here there is a single peak on the fitness surface (p = 0, μ = 0), and although p may initially increase in frequency, it is always lost, with the ultimate response being entirely polygenic. Note, however, that a significant fraction of the initial response can be through the major gene, but eventually this is replaced by the polygenic component, and the pleiotropic disadvantage of the major gene then results in it being lost.

Lande provides extensive analysis of his model in several settings, two of which we consider. The first is the evolution towards a new optimum. Suppose the optimal phenotype suddenly shifts (for example, due to a major environmental change). In such cases, if the frequency of the major allele is sufficiently rare relative to the strength of selection on the

trait (and the strength of pleiotropic selection against the allele), it is lost and the response is entirely polygenic. As Figure 25.5 illustrates, the dynamics can be complex in this case. The key to understanding this frequency-dependent behavior is to recall the dynamics of an underdominant locus (Figure 5.1). Here is an unstable internal equilibrium, with the allele being fixed provided it starts above this value, otherwise it is lost. Lande showed that such an unstable internal equilibrium exists for the major gene in this setting, creating a frequency-dependent behavior.

Two additional remarks concerning Lande's examples in Figure 25.5 are in order. First, since **A** is strictly deleterious before the shift in optimum, its initial frequency is expected to be low, for example for an additive allele with mutation rate ν, $p \simeq 2\nu/s$ (Equation 7.6). While most of the trajectories in Figure 25.5A show fixations, almost all populations would be expected to start with the frequency of **A** below the 0.025 threshold (when $2\nu/0.02 < 0.025$ or $\nu < 0.00025$). Second, this is a deterministic analysis, which has implications for Figure 25.5B. Notice that the trajectory for at allele starting at frequency 0.8 approaches one before eventually declining to zero. As polygenic response moves the trait mean towards the optimum, the deleterious pleiotropic effects of this allele become greater than its favorable effect on the trait, resulting in the major allele becoming selected against, and hence removed. In a finite population, selection may drive its frequency sufficiently close to one for drift to fix **A** before polygenic response negates its favorable effect on the trait. In such cases, a major gene response would be seen.

Lande's analysis of directional selection used an exponential model of trait fitness, $w(z) \propto \exp(\beta z)$, which reduces to a simple linear fitness function, $w(z) \simeq 1 + \beta z$, for weak selection ($|\beta z| \ll 1$). Under exponential fitnesses, the model is nicely behaved, with the polygenic mean evolving at a constant rate

$$\Delta\mu = \sigma_A^2 \, \beta, \tag{25.9a}$$

while the relationships between the major-locus genotypic fitnesses remain constant,

$$\frac{\overline{W}_i}{\overline{W}_0} = e^{\beta \, \alpha_i}, \quad \text{for } i = 1, 2 \tag{25.9b}$$

The resulting relative fitnesses of the three major locus genotypes become

$$W_{aa} = 1, \quad W_{Aa} = (1 - s_1) \, e^{\beta \, \alpha_1}, \quad W_{AA} = (1 - s_2) \, e^{\beta \, \alpha_2} \tag{25.9c}$$

Since these are constants, the machinery of Chapter 5 quickly informs us as to the fate of the major gene. Selection maintains both alleles as a stable polymorphism when $W_{Aa} > W_{AA}, W_{aa}$. There is an unstable internal equilibrium when $W_{Aa} < W_{AA}, W_{aa}$, with **A** being lost if sufficiently rare (below the equilibrium value), and otherwise fixed. Finally, if $W_{aa} < W_{Aa} \leq W_{AA}$ or $W_{aa} \leq W_{Aa} < W_{AA}$, then the major allele is fixed. For weak selection ($e^{\beta \, \alpha_1} \simeq 1 + \beta \, \alpha_1$), this condition reduces to $(1 - s_1)(1 + \beta \, \alpha_1) \simeq 1 + \beta \, \alpha_1 - s_1 > 1$, or $\beta \, \alpha_1 - s_1 > 0$ (or $\beta \, \alpha_2 - s_2 > 0$ for a recessive).

The simple fate of the major allele is not a complete analysis, as even if the allele is fixed, its contribution could be far outstripped by the polygenic response. Lande examines this by assuming that α is the difference between the two major locus homozygotes and that initially **A** is rare. He then compares the expected amount of time for an **A** allele starting at frequency $p_0 \ll 0.5$ to increase to the point where the response from the locus is $\alpha/2$. This is accomplished by using Equation 25.1e to find the critical frequency, and then apply the appropriate version of Equation 5.3 to obtain the required time for this amount of allele frequency change. If the polygenic response over this amount of time exceeds $\alpha/2$, the response is primarily polygenic, even if **A** is fixed. For weak selection, the resulting

initial starting frequencies above which the major gene exceeds the polygenic response are approximately

$$p_0 > \begin{cases} 2/b & \text{recessive} \\ \exp(-b/4) & \text{additive} \\ \exp(-b/2) & \text{dominant} \end{cases}, \qquad \text{where} \quad b = \left(1 - \frac{s}{\beta\,\alpha}\right)\frac{\alpha^2}{\sigma_A^2} \tag{25.9d}$$

Much of the above discussed is framed by the assumption that genes of large effect on a trait generally have deleterious effects in natural populations. However, as Orr and Coyne (1992) have pointed out, if genes with small effect on the character also have similarly small (and negative) effects on fitness, their advantage over a major locus largely (or completely) disappears. However, if the potential pool of alleles of small effects is large, it will become enriched for those which have nearly neutral pleiotropic fitness effects.

Example 25.5. The above machinery can be used with other fitness functions. Suppose the trait of interest is subjected to truncation selection, with only individuals above the threshold value T being allowed to reproduce. In this case,

$$W(z) = \begin{cases} 1 & \text{for } z \geq T \\ 0 & \text{for } z < T \end{cases}$$

The marginal fitnesses become

$$\overline{W}_i = \int_T^\infty \varphi(z, \mu + \alpha_i, \sigma^2)\, dz = \Pr(U > T^* - \alpha_i/\sigma)$$

where $T^* = (T - \mu)/\sigma$ and U is a unit normal random variable. Usually we express truncation selection in terms of the fraction q of individuals allowed to reproduce, rather than the threshold value T, especially since T changes as the population mean increases. In this case, we have

$$\begin{aligned} \overline{W} = q = (1-p)^2 \Pr(U > T^*) + 2p(1-p)(1-s_1)\Pr(U > T^* - \alpha_1/\sigma) \\ + p^2(1-s_2)\Pr(U > T^* - \alpha_2/\sigma) \end{aligned}$$

For a particular q value and the current μ and p values, one can solve the above equation for T^*. Likewise, from LW Equation 2.13,

$$\mu_{s_i} = \mu_i + \sigma\, \frac{\varphi(T, \mu + \alpha_i, \sigma^2)}{\Pr(U > T^* - \alpha_i/\sigma)}$$

implying

$$S_i = \mu_{s_i} - \mu_i = \sigma\, \frac{\varphi(T, \mu + \alpha_i, \sigma^2)}{\Pr(U > T^* - \alpha_i/\sigma)}$$

To proceed, for a given p, μ value one first finds T^* to obtain the specified strength of truncation selection q, then computes the $\overline{W}_i$ for Equation 25.6 and S_i for Equation 25.8d to update the p and μ values. Example 25.10 uses these results to obtain the equilibrium frequency of a major gene that is lethal as a homozygote, but improves the trait as a heterozygote.

MAJOR GENES VERSUS POLYGENIC RESPONSE: DATA

A long-running debate in evolutionary biology, dating back to the rediscovery of Mendel, is whether the majority of adaptations are due to genes of large effects or due to the accumulation of small changes over a large number of loci. Before the modern evolutionary synthesis, geneticists (the Mendelians) felt that macromutations drove evolution, while supporters of Darwin (the Biometricians) felt that evolution was driven by selection acting on numerous factors of small effect. These differing views (and more importantly their vocal supporters and opponents) greatly retarded the merging of modern genetics with Darwin's theory of evolution. Fisher's (1918) paper, founding quantitative genetics, was a watershed event in helping to fuse these two schools (see Provine 1971 for a historical overview of the Mendelian-Biometrician debate). This same debate, in slightly different forms, resurfaced in the 1940's with Goldschimidt's (1940) idea of **hopeful monsters** (single mutations of large effect driving major evolutionary changes) and also in the late 1970s - early 1980s with the debate surrounding **punctuated equilibrium** (long periods of evolutionary stasis punctuated by rapid change; Eldredge and Gould 1972; Charlesworth et al. 1982). It is also of current interest given our ability to create transgenic individuals. If most response is attributable to a few genes, then genetic engineering is quite a feasible approach for increasing the efficiency of selection. If most of the response is due to numerous polygenes, the impact of transgenics will be less than anticipated.

Major Genes Appear to be Important in Response to Antropogenic-Induced Selection

One of Lande's conclusions was that sufficiently strong selection is required for a major gene response when polygenic variation is available. One situation where this is often assumed to be true is in the response of wild populations to **antropogenically-induced selection**, namely a major (and sudden) environmental change through the action of humans. This could be in the form of toxins (pesticides, herbicides, pollutants) or side effects of pollution such as industrial melanism (Lees 1981).

In the pesticide/herbicide literature, a commonly-expressed theme echoing Lande's theoretical predictions is that weak selection (as might be expected to occur in laboratory settings) leads to a polygenic response, whereas very strong selection (in a newly-sprayed field) leads to major-gene resistance (Greaves et al 1977; Clarke and McKenzie 1987; Macnair 1991; McKenzie et al. 1992; McKenzie 2000). However, a survey by Groeters and Tabashnik (2000) found that the strength of selection on insecticide resistance varies greatly in the field and overlaps the intensities used in laboratory experiments. Further, major gene responses are not uncommon in the laboratory. For example, resistance to Bt toxin (*Bacillus thuringiensis* Cry1Ac toxin), an organic insecticide widely used in both sprayed fields and transgenic crops, is often due to independent recessive mutations in the same genes. Baxter et al. (2011) found that independent recessive mutations in the membrane transporter gene *ABCC2* confers resistance in two very distant moth species. Mutations in a 12-cadherm domain protein confer resistance in laboratory-selected strains from three again very distantly-related moth species, as well as in field populations in China of a fourth species (Zhang et al. 2012). However, Zhang et al. also detected nonrecessive alleles in their China population of cotton bollworms (*Helicoverpa armigera*). This has very important biocontrol implications, because the strategy used to retard the evolution of Bt resistance is to plant refuge rows of non-Bt corps (Gould 1988; Tabashnik et al. 2008). Since most resistance is recessive, crosses of homozygous resistants and susceptibles lead to heterozygous susceptible offspring which are killed when their larvae feed on Bt crops. This strategy fails if response is either polygenic and/or due to nonrecessive major genes.

If strength of selection is not the key factor for explaining the difference between field (usually major genes) and lab (mainly polygenic) responses, what is? One likely explanation

is simply population size. Major mutations, especially those involved in detoxification, likely have deleterious side effects in toxin-free environments, and are expected to occur at very low frequencies. Suppose $p = 0.001$, then the probability that a random sample of 1000 individuals chosen to found a laboratory stock for selection has probability $(1-0.001)^{1000} = 0.37$ of not containing the allele. Using a more realistic founder stock of 100, this increases to 90%. Even if such a mutation is present, it will likely be in just a few copies and can easily be lost by drift, even with strong selection. Conversely, the observation that major genes appear to be commonly involved in Bt resistance in laboratory population can be explained by the observation that many of these appear to be knockout mutations (and hence recessive), offering a much larger mutational target size, and thus a modest rate of mutation in laboratory populations. These arguments illustrate that the interaction of drift and mutation is often critical in determining the nature of response, especially in smaller laboratory populations (Chapter 26).

What is the Genetic Architecture of Response in Long-Term Selection Experiments?

With the advent of dense molecular markers, and subsequent whole-genome sequencing, we now have a new set of tools to examine the genetic makeup of long-term response. One approach is to use QTL mapping with large sample size, to both detect alleles of small effect and to avoid overestimation of effects when power is low (the Beavis effect, LW Chapter 15). While a very large number of such studies crossing divergent lines have been performed (LW Chapter 15), often the actual nature of selection (if any) underlying the observed divergence is either unknown or has been fluctuating over time. Hence, our focus is entirely on crosses from consistently-selected experiments. For these, the general picture emerging is that much, if not most, of the response is often due to QTLs of small effect. Perhaps the most careful studies involve the Illinois long-term selection experiment (Figure 25.8). The F_1s of crosses between 70th-generation high and low oil and protein lines were randomly mated for 7-10 generations before QTL mapping (the advanced intercross, or AIC, design, LW Chapter 15). Such a design allows recombination to randomized even closely-linked QTLs (the effect is a 7-10 fold map expansion relative to the F_2). An excess of 50 detected QTLs, each with small, and additive effects, were detected (Laurie et al. 2004; Clark et al 2006; Dudley et al. 2007). A similar finding is seen in chicken lines divergently selection for 50 generations (resulting in a nine-fold difference in body weight), which also found mainly small-effect QTLs underlie the response (Jacobsson et al. 2005; Wahlberg et al. 2008). Results from mouse lines are more mixed. The majority of the roughly 40 QTLs detected in a cross from a 27 generation line selected for weight gain with a random control had effects of one to three percent, although a few had effects around 5% (Allan et al. 2005). Moody et al. (1999) found QTLs with effects of around 3 - 4% in an analysis of lines divergently selected for energy balance for 16 generations. Hovat et al. (2000) found that just four QTLs could account for most the response in obesity in lines subjected to 53 generations of divergent selection. One caveat with these mouse results is that typically F_2, rather an AIC, designs were used. This can result in significant overestimates of QTL effects due to linkage of multiple QTL. Typically, such large QTL peaks fractionate upon finer mapping (reviewed by Flint and Mackay 2009; Mackay et al. 2009).

A second approach is to look for signatures of selection in the genomes of individuals sampled near the end of a long-term selection experiment, either by alternate fixation of alleles in divergent lines (essentially a localized F_{st} measure, e.g., Johansson et al. 2010) or more classic hard-sweep tests (e.g., Chan et al. 2012). Besides estimating the number of genomic regions under apparent selection, the machinery of Chapters 8 and 9 could also be used to estimate selection coefficients (and hence effect sizes). However, as discussed in Chapter 8, these approaches are strongly biased towards alleles of large effect, detecting hard sweeps as opposed to either soft (existing variation) or polygenic (small changes at a

number of loci) sweeps. Approaches looking for allele-frequency change at markers are also biased in favor of detecting genes of large effect (and hence large frequency changes). While useful for detecting genes of potential interest, these approaches do not provide an unbiased sampling of the underlying architecture.

Countering this bias towards detecting major genes, the founding of experimental populations is usually biased *against* them. The expectation is that alleles of large effect are at low frequencies in natural populations, and unlikely to be routinely captured in a sample used to found a laboratory population. What is clear from these data is that massive responses in long-term experiments can be entirely due to genes of small effect. What is unclear is to what extent these results from long-term laboratory experiments translate to natural or domesticated populations undergoing mild (and/or constantly shifting) artificial selection, as opposed to the constant artificial selection imposed on a single trait.

Finally, the results from examining adaptations (often inferred from species differences) in natural populations are also mixed. Hilu (1983) and Gottlieb (1984, 1985) suggest that major genes have played very important roles in species differences between plants (many of which are, presumably, adaptive), but Coyne and Lande (1985) dispute this view. A literature review by Orr and Coyne (1992) finds that support for the polygenic model (i.e., most adaptations are due to many genes of small effect) is also inconclusive. There may also be a publication bias in that color traits are often controlled by just a few genes and lead to differences that are visually obvious, and thus more easily detected (and therefore studied). Clearly, this is an area of active ongoing research.

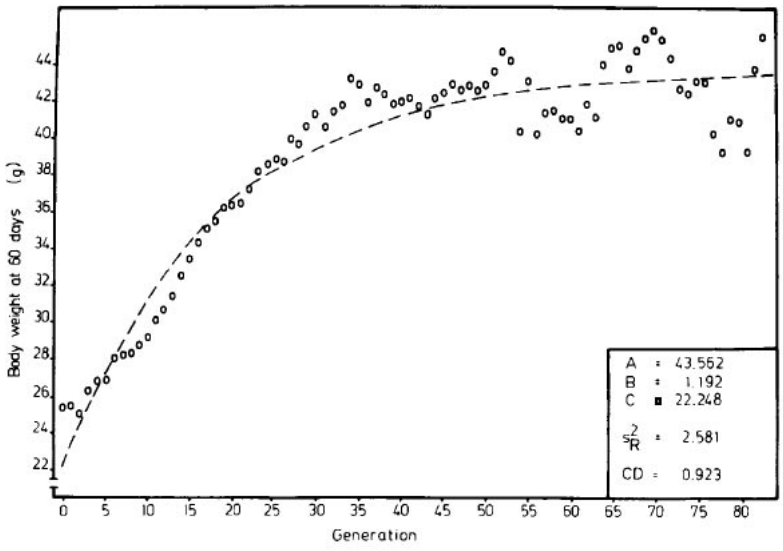


Figure 25.6. Bünger and Herrendörfer's (1994) fit of an exponential regression to the long-term selection experiment of Goodale on mouse weight at 60 days (Goodale 1938; Wilson et al. 1971). The estimated selection limit was 43.5 grams (for a total response of 21.3 grams) with a half-life of 12 generations. The plotted curve regresses cumulative response as a function of generation number. When the regression is plotted as a function of cumulative selection differential (as opposed to generations), the estimated total response was 17.5 grams.

AN OVERVIEW OF LONG-TERM SELECTION EXPERIMENTS

The above theory suggests that populations under selection should show a reasonably

smooth response (albeit often with considerable sampling noise, Chapter 18), which is initially linear, but eventually (in the absence of new mutations) asymptotes to a selection limit as base-population genetic variance is exhausted. Unfortunately, this simple picture is very often wrong. Response can be rather erratic, showing periods of acceleration even after many generations of selection, and limits often occur in spite of significant additive variance in the character under artificial selection. Before reviewing the experimental data, a few remarks on estimating the actual limit and duration of response are in order.

Estimating Selection Limits and Half-Lives

Since the limit is approached asymptotically, the typical measure of duration is the **half-life** of response — the time for half the response to occur. As was the case for short-term response (Chapters 18, 19), these parameters are generally estimated by curve fitting, especially given the inherent sampling noise in selection response data (Chapter 18). Given that the response curve is nonlinear, a number of authors have used quadratic regressions, taking the maximum of the regression as the limit (James 1965; Eisen 1972; Rutledge et al. 1973). A more natural approach is to use **exponential regressions**, with a number of variant expressions appearing in the literature (James 1965; Frahm and Kojima 1966; Harris 1982; Herrendörfer and Bünger 1988; Bünger and Herrendörfer 1994; Árnason 2001). The motivation for this approach is two-fold. First, these curves naturally generate an asymptotically maximal value, as opposed to a quadratic which does not. Second, if the additive variance declines by an approximate constant $(1-\alpha)$ each generation (as would occur under drift with the infinitesimal model; Chapters 24, 26), this leads to a cumulative response of the form

$$R_c(t) = \beta\,(1-[1-\alpha]^t) \simeq \beta\,\left(1-e^{-t\,\alpha}\right)$$

Herrendörfer and Bünger (1988) and Bünger and Herrendörfer (1994) suggested a slightly more general version,

$$\mu(t) = a-(a-c)\exp\left(\frac{-bt}{a-c}\right) \tag{25.10a}$$

$$= a\,(1-\exp[-bt/a])\,, \quad \text{when } c=0 \tag{25.10b}$$

where a is the selection limit, c the initial value (setting the initial mean to zero yields Equation 25.10b, which is the same as considering the cumulative response $R_c(t)$, as $R_c(0)=0$) and b the maximal rate of response (i.e., the response in the first generation). Figure 25.6 shows an application of this method, while optimal experimental design issues are examined by Rudolph and Herrendörfer (1995). An interesting application of such estimated limits is by Árnason (2001). Working with racing speed for standardbred trotters in Sweden, a fitted exponential regression suggested that the limiting trotting speed is around 68 sec/km. In 1950's, the fastest speeds were just under 80, reaching around 73 in the mid-1990's, which is about half of the expected total response (starting from the 1950 benchmark).

Using this fitted curve, the resulting half-life of response becomes

$$t_{1/2} = \frac{(c-a)\cdot\ln(0.5)}{b} = -a\cdot\ln(0.5)/b \quad \text{when} \quad c=0 \tag{25.10c}$$

The tangent of this curve at a particular generation provides an estimate of the realized heritability (Frahm and Kojima 1966; Herrendörfer and Bünger 1988). This is given by the derivative of Equation 25.10a evaluated at the generation of interest,

$$b\cdot\exp\left(\frac{-b\,t}{a-c}\right) = b\cdot\exp(-b\,t/a) \quad \text{when} \quad c=0 \tag{25.10d}$$

As was the case for linear regressions of short-term response, one decision is whether to regress cumulative response on number of generations or on cumulative selection differential. Under the breeder's equation, the response is linear in cumulative differential, $R_c(t) = h^2 S_c(t)$, see Chapter 18. For long-term response, if the expectation is a constant decline in additive variation each generation, then regression on number of generations is more logical, *provided* the assumption of a constant differential and a constant decline in variance are appropriate. More generally, this is simply an empirical issue, with the approach yielding the best fit typically used.

A second more subtle issue, which also arose in Chapter 18, is the nature of the residual variance structure. One strandard approach for curve-fitting is least-squares, finding the parameter values for Equation 25.10a that minimizing the sum of squared residuals, $\sum e_i^2 = \mathbf{e}^T\mathbf{e}$, where the ith residual $e_i = R_c(t_i) - \widehat{R}_c(t_i)$ is the difference between the ith observed and predicted values. Ordinary least squares assumes homoscedasticty $\sigma^2(e_i) = \sigma_e^2$ for all i and that residuals are uncorrelated. As with the case for short-term response, the presence of drift compromises both of these assumptions. As was done in Chapter 18 to accommodate this concern, curves should be fitted using generalized least-squares, where parameters are chosen to minimize the quadratic product $\mathbf{e}^T\mathbf{V}^{-1}\mathbf{e}$, where $\mathbf{V}$ is the variance-covariance matrix for the residuals (Equation 18.15c).

Other curves have also been suggested. Wiser et al. (2013) suggested a **hyperbolic function**,

$$\mu(t) = c + \frac{a\,t}{t+b} \tag{25.11a}$$

where the population starts at initial value c (at $t = 0$) and approaches a limiting value of $c + a$, so that a is the total response, while $t_{1/2} = b$. These different families of curves attempt to capture the asymptotic approach to a limit expected for an idealized long-term response. A concern with all of these models is that the selection limit is *extrapolated* from the data. As Table 25.3 shows, different models can give the same fit of the data, but very different estimates of the limit and half-life.

Table 25.3. Estimates of the selection limit and half-life based on 22 generations of selection for increased 12-day litter weight in mice. Selection limit refers to response in grams as a deviation from the control and half life is given in generations. The quadratic and exponential models explain the same amount of variation ($r^2 = 0.81$ for both models) and cannot be discriminated on this basis. From Eisen (1972), data for line W_3.

Estimate	Model	
Selection Limit	Quadratic	5.79 ± 0.84
	Exponential	8.19 ± 0.29
Half-life	Quadratic	8.58
	Exponential	12.48

A much more intriguing function for long-term selection data is the **power curve**,

$$\mu(t) = (b\,t + c)^a \tag{25.11b}$$

which has the feature that while it is decelerating over time (for $a < 1$), it has no upper limit. This curve gave better fit than the hyperbolic for 50,000 generations of selection in *Escherichia coli* for fitness (Wiser et al. 2013), suggesting that slowly diminishing returns, rather than approach to a true selection limit, is a better description of their data.

Some final cautionary notes. First, scale effects (LW Chapter 11) can be important. Many continuous characters have zero as a lower limit, hence on a linear scale these characters always have a lower limit. This is not true on a log-scale. Similarly, if we can view a discrete character as a result of transforming an underlying continuous variable, we should work on this underlying scale of liability (see Chapter 14, LW Chapters 11, 25). A somewhat related problem is the difficulty in detecting whether a limit has actually been reached. For example, the very slow response when recessives are segregating gives the impression of a limit when in fact considerable variation can be present (Figure 25.2).

Finally, the entire issue of selection limits due to exhaustion of additive genetic variation is complicated by mutation. Most "long-term" experiments are long-term only from the viewpoint of the experimenter, rarely spanning more than 50 generations. As is discussed in Chapters 26 and 27, over longer time scales mutational input becomes very important and observed limits can be artifacts of the relatively short time scales used.

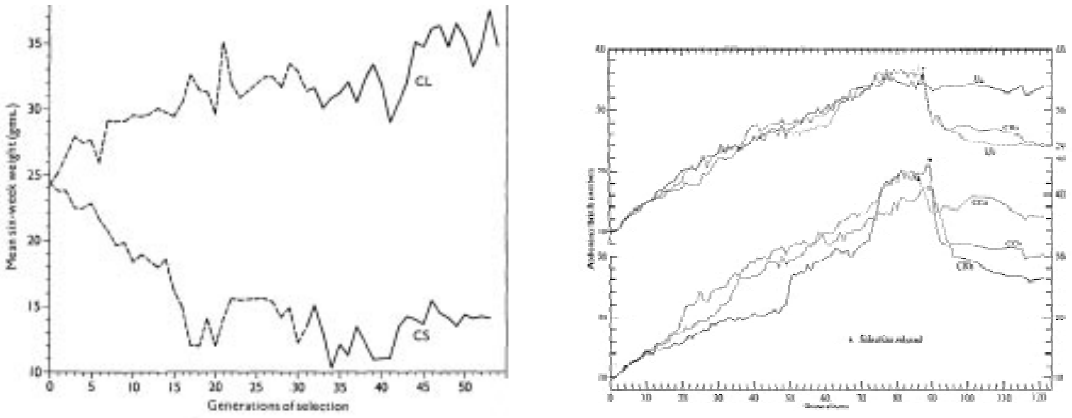


Figure 25.7. A few of the nonstandard behaviors observed in long-term selection experiments. **A:** Delayed accelerated response during selection for increased six-week body weight in mice. An apparent limit of 31 grams had been reached in the up-selected line (CL) by generation 15. During generations 43–44, a second burst of response occurs, with mean weight increasing to around 35 grams (Roberts 1966). **B:** Selection for increased abdominal bristle number in *Drosophila*. At generation 90, selection was relaxed and most lines showed a considerable (but not complete) erosion of response. The presence of segregating lethals accounts for some of this erosion. Note also the bursts of response (for line CRb, lowest curve) around generations 50 and 75 (Yoo 1980a).

General Features of Long-Term Selection Experiments

As Figure 25.7 illustrates, selection experiments display a wide range of behavior. Fortunately, a few generalizations do emerge.

1. *Selection routinely results in mean phenotypes that are far outside the range seen in the base population*. At the selection limit, the mean phenotype is usually many standard deviations from the initial mean.
2. *Response can be very uneven*. Bursts of accelerated response after many generations of selection can be seen seen, and additive genetic and phenotypic variances can increase during part of the response.
3. *Reproductive fitness usually declines as selection proceeds*.

4. *Most laboratory populations approach a selection limit*. As discussed in Chapter 26, an apparent selection limit may be an artifact of the short time scales (and hence insufficient chance for significant mutational input) and/or small population sizes of most experiments. Figure 25.8 gives several examples of long-term experiments that have not yet reached an apparent limit.
5. *Considerable additive variance in the character under artificial selection often exists at an apparent selection limit*.

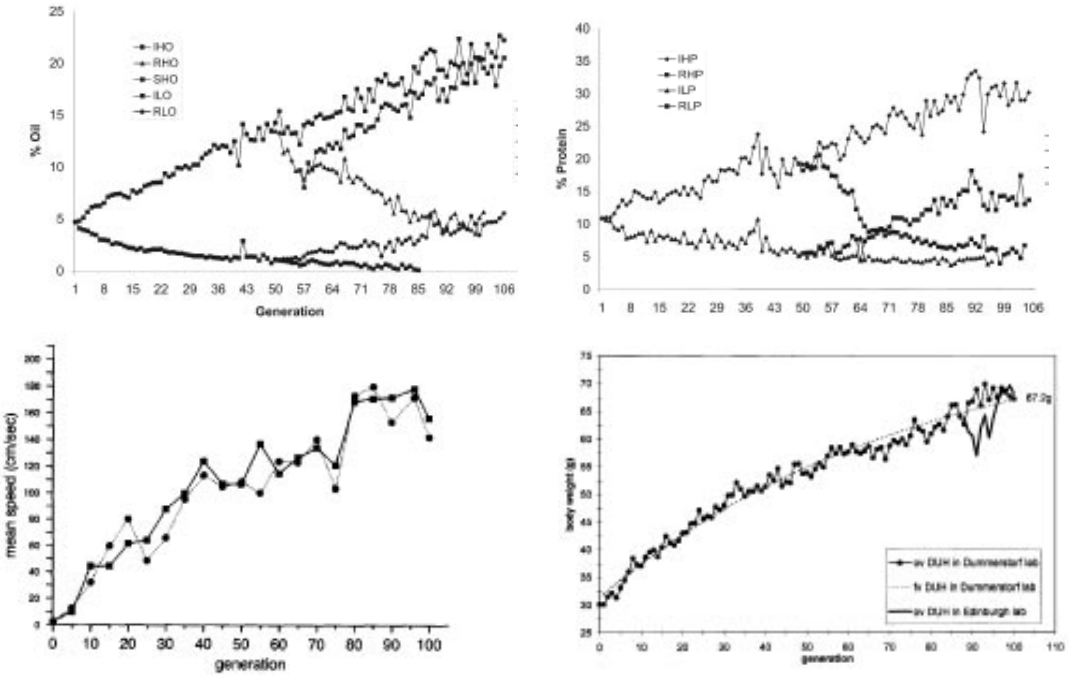


Figure 25.8. Example of long-term selection experiments showing no apparent selection limits. The top two are from the **Illinois long-term selection** experiments on oil and protein content in maize. **A**: 106 generations of selection for increased/decreased oil percentage. Lines IHO and ILO were up- and down-selected, while lines RHO and RIL are lines of IHO and ILO subjected to reversed response around generation 50. Line SHO (switchover high oil) is an up-selected line using RHO. The responses in RHO, RLO, and SHO indicates significant additive variance was present in the population when these new lines were formed (after Dudley 2007). **B:** 106 generations of selection for changes in the percent of protein. Lines IHP and ILP were up- and down-selected, while lines RHP and RLP are the result of reverse selection starting around generation 50. Again, the responses of RHP and RLP indicates significant additive variance (after Dudley 2007). **C:** One hundred generations of response for increased flight speed in *Drosophila melanogaster*. Two replicate lines showed very similar response (after Weber 1996). **D:** Response in the **Dummerstorf long-term** lines (Germany), subjected to continous selection for age 42 day weight in mice. Running over 160 generations (as of 2014), this is the longest continuous selection experiments in mammals (after Bünger et al. 2001).

It is important to recognize that long-term selection experiments are a biased sample of organisms and characters. Controlled selection experiments in multicelluar organisms exceeding 20 generations are largely restricted to *Drosophila*, *Tribolium*, mice, and maize. Whether the genetic architectures of these organisms are representative of typical characters

in natural populations is unclear, although there is no serious reason to suspect that they are not. Another caveat on extrapolating from these model experimental systems to natural and domesticated populations is that the strength of continuous selection on a single character is likely much higher in artificial selection experiments. Under natural selection and most artificial selection on domesticated populations, selection likely operates on a suite of characters, generally reducing the strength of selection on any particular trait. Selection pressures on any particular character are also likely to fluctuate as the environment (or breeding target) varies. Conversely, artificial selection experiments focus on a single character and occur in highly controlled environments.

INCREASES IN VARIANCES AND ACCELERATED RESPONSES

Contrary to the expectations of idealized long-term response, phenotypic and additive genetic variance can *increase* during the course of response, often resulting in bursts of response (Figure 25.7). As we detail here, a variety of different conditions can lead to a burst in response, emphasizing just how unpredictable long-term responses can be.

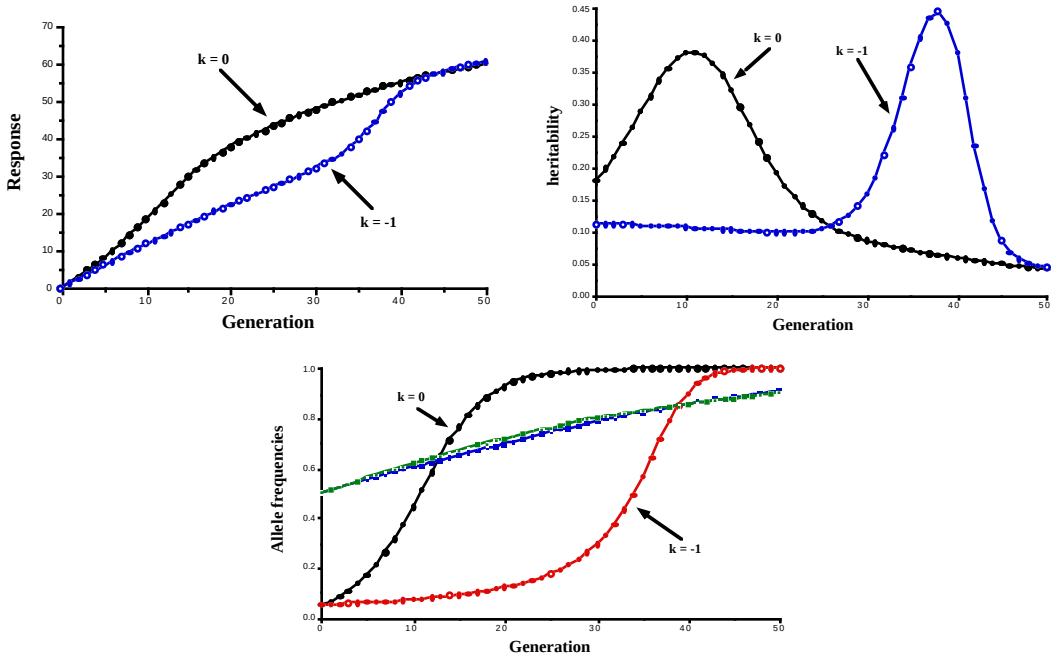


Figure 25.9. Examples of a delayed accelerated response due to the increase of an initially rare allele of major effect. The character is determined by a polygenic background (100 completely additive bialleic loci, with $a = 0.5$ and $p = 0.5$, so that the initial additive variance contributed by the polygenic background is $\sigma_A^2 = 12.5$) plus a major allele initially at low frequency ($a = 10$ and $p = 0.05$). We assume that this locus is either additive ($k = 0$, initial additive variance 9.5) or recessive ($k = -1$, initial additive variance 0.095). **A:** Response under the recessive model shows an accelerated response around generation 30, while the additive major gene results in an acceleration around generation 10. **B:** Heritabilities clearly show the acceleration. **C:** Changes in the major allele frequency shows the much longer time for the recessive major allele to increase in frequency. Note that the change in the polygenic frequencies (the middle two curves) are almost the same under the two different major locus dominance values.

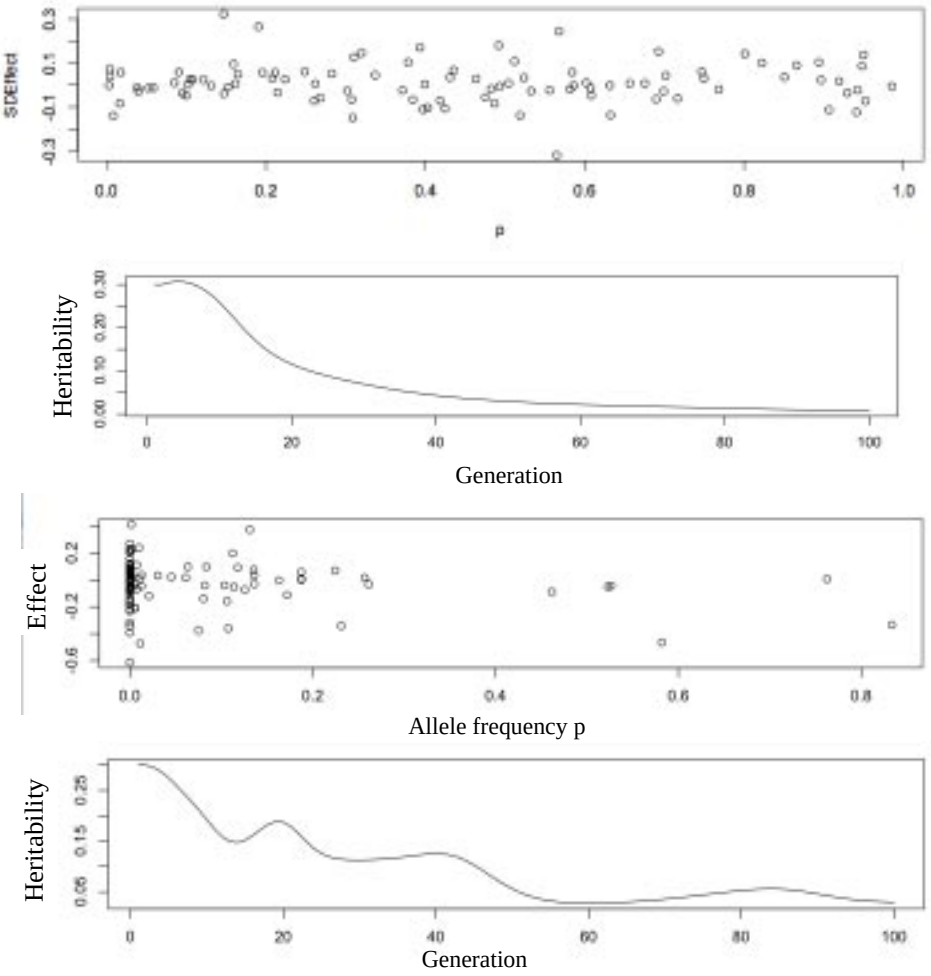


Figure 25.10. The impact of a distribution of initial allele frequencies and effects on the long-term response to selection. The model simulated here assumes 100 completely additive loci (no dominance or epistasis), ignores the effects of linkage disequilibrium, with Equation 25.3 is used for the dynamics. Allelic effects were randomly sampled from an exponential distribution reflected about zero (effects are equally likely to be positive or negative). Initial allele frequencies were either sampled from uniform or Watterson (Equation 2.34) distributions, with randomly-assigned allelic effects. Given the initial distribution of allele frequencies and effects, a base-population additive variance $\sigma_A^2(0)$ was computed, and σ_E^2 was set at (7/3) $\sigma_A^2(0)$ to give the trait a starting heritability of 30% (a typical value for many traits). Typical results from two realizations are presented here. The joint distribution of initial frequencies and their effects (in standard deviations) is given in the top (uniform) and third (Watterson) panels. As panel two shows, the resulting heritabilities under the uniform were generally well-behaved (here, a slight initial increase, followed by a nearly monotonic decrease), while the final panel shows that the heritabilities under the Watterson were highly erratic. While the specific realization shown here for the Watterson was typical for a number of simulations (the initial drawing of allelic effects and their frequencies were random, which then deterministically determines the response), even more erratic patterns (i.e., heritabilities rapidly increasing over 30% after many generations of selection) were seen in some realizations.

Rare Alleles

One obvious source for increases in variance is the increase of favorable rare alleles under selection. For an additive locus, σ_A^2 is maximized at $p = 1/2$ (LW Figure 4.8). Additive loci with favorable alleles below 50% show an increase in additive variance as the frequency approaches 1/2, after which it starts to decline to zero as the allele becomes fixed. If the allele is rare, and of large effect, the result can be an increase in response many generations after the start of selection (Figure 25.9). The magnitude of this effect depends on both the initial frequency of the allele and its allelic effect. Alleles of large effect are subjected to stronger selection and hence show more rapid increases in allele frequencies, and larger effects on response. As Figure 25.10 illustrates, if there is a distribution of allele frequencies (and allelic effect sizes) at the underlying loci, then different alleles are increasing at different speeds, and can result in a very erratic pattern of response. This is especially true when the allele frequencies follow the Watterson distribution (Chapter 2), the distribution of allele frequencies expected under drift-mutation balance, resulting in most minor alleles being rather rare. The effects of nature selection may further exaggerate this distribution. If alleles of large effect also tend to be slightly deleterious, then these frequencies may be even less than expected under the Watterson distribution, with a negative correlation between frequency and effect size.

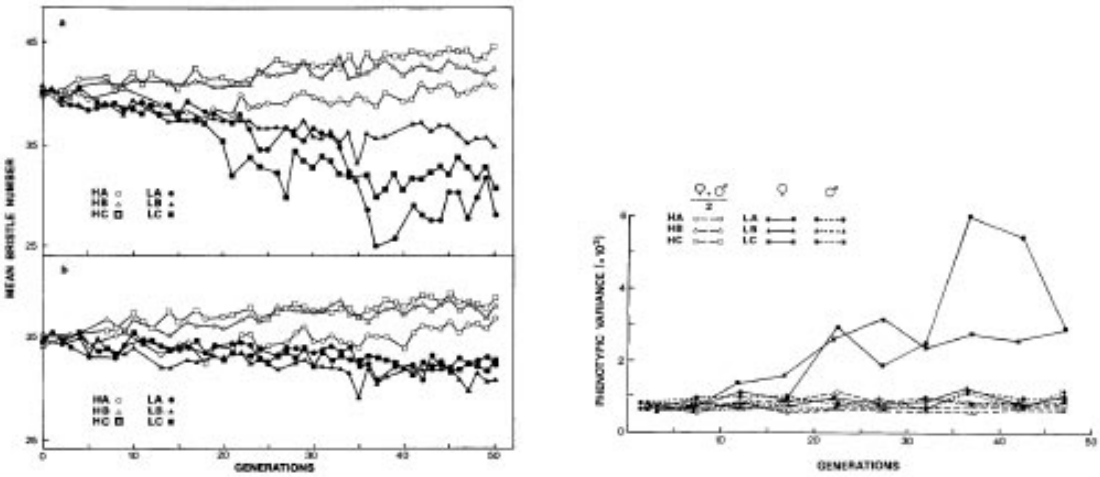


Figure 25.11. **Left:** Response to selection for high and low abdominal bristle numbers in females (top panel) and males (bottom panel). Note that while two of the down-selected lines (LA and LC) show bursts of response in females, no such response is seen in the males from this line. **Right**: The phenotypic variances for these lines. Note that the variance increases only in females from the two lines showing a burst of response. After Frankham et al. (1980).

Major Mutations

Major alleles can be arise by mutation during selection, creating bursts of response throughout the course of the experiment. An example of this is Yoo (1980a), who selected for increased abdominal bristles in *Drosophila* for over 80 generations (Figure 25.7B). Five of the six replicate lines showed various periods of accelerated response after 20 generations of selection. Yoo was able to correlate many of these with the appearance of new alleles of major effects on bristle number that were also lethal as homozygotes.

A second example of a mutation-induced burst of response in bristle number was seen by Frankham's group (Frankham et al. 1978, 1980; Frankham 1988), who examined response in lines initially containing very little variation. In two of the down-selected lines, females (but not males) showed a burst of response (Figure 25.11). This was accompanied by an increase in the phenotypic variance and heritability in females, but not in males. Females also showed reduced fitness, as indicated by a male-biased sex ratio in these lines. These effects were attributable to the appearance of *bobbed* mutants at the ribosomal gene cluster, a deficiency in the number of rRNA genes. The *bobbed* mutants arose on the X-chromosome rRNA cluster, while the Y-chromosome rRNA cluster remained normal, accounting for the sex-limited nature of the response. These mutants were generated by unequal crossingover (within the rRNA cluster) during the course of the selection experiment. These examples involve mutations of major effects, with an almost immediate impact. The implications of ongoing mutations of minor effects is considered in Chapter 26.

Scale Effects

Scale effects can also result in increases in variances and/or response, for example when the variance increases with the mean (LW Chapter 11). A possible example is Enfield's (1972) selection experiments for increased pupal weight in *Tribolium*. Both additive variance and total phenotypic variance increased over time while heritiability remained roughly constant (so that response was fairly constant). Comstock and Enfield (1981) suggest that a multiplicative model of gene action was more appropriate in this case than an additive model, and that this can account for the observed increases in variance. As was discussed in Chapter 14, scale effects can be especially important in threshold characters (also see LW Chapters 11, 25). Variances can also increase due to environmental effects. For example, environmental variance can increase as genotypes become more homozygous, although this is not inevitable (see LW Table 6.1). Likewise, we showed in Chapter 17 that directional selection on a trait can result in an increase in σ_E^2 when the environmental variance has heritable variation. Finally, changes in the environment during the course of selection can also increase the additive variance. A possible example of this is long-term selection in milk yield in North American dairy cows, where additive variance in yield has been increasing rather than decreasing (Kennedy 1984). One explanation is changes in the environmental, as improved management techniques likely allow for greater discrimination between genotypes, although scale effects may also play a role.

Linkage Effects

Recombinational break-down of pre-existing gametic-phase disequilibrium can also generate an accelerated response. Why might such disequilibrium be present? Mather (1941, 1942, 1943) suggested that QTLs are often in negative disequilibrium as a result of previous natural selection (he considered mainly stabilizing selection), referring to this genetic architecture as **polygenic balance**. More generally, selection tends to build up negative associations based on fitness, such that loci influencing fitness tend to be in negative gametic-phase disequilibrium (Chapters 16, 24). Hence, alleles favored by artificial selection on a character tend to become associated with alleles at linked loci having deleterious effects on other components of fitness (Sved 1977). A character with extensive negative disequilibrium (either between QTLs controlling the character and/or between QTLs for the character and other fitness loci) can show accelerated response as this disequilibrium decays (Figure 25.12).

Accelerated response can also occur when recombination generates coupling gametes for alleles that increase character value. A classic example is Thoday's selection experiments for increased sternopleural bristle number in *Drosophila* (Thoday and Boam 1961; Thoday et al. 1964). As shown in Figure 25.13, a burst of response was seen after about 20 generations

of selection. Using polygenic mapping, Thoday et al. (1964) were able to show that the initial population consisted mainly of $--$ gametes with only a few $+-$ and $-+$ gametes at a pair of linked loci (each $+$ indicates a major allele increasing bristle number). Selection reduced the frequency of $--$ gametes, increasing the frequency of $+-/-+$ heterozygotes, which in turn increased the frequency at which $++$ gametes were generated. Response accelerates as these newly-created gametes become sufficiently common to increase additive variance.

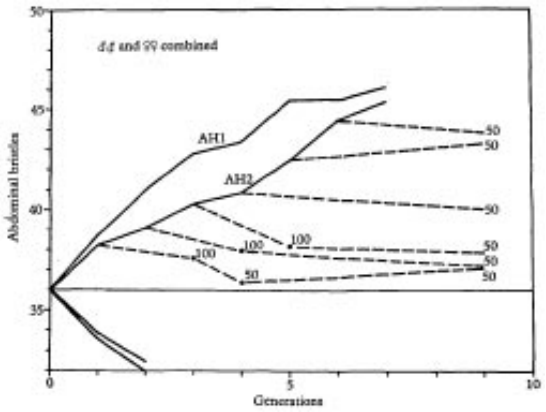


Figure 25.12. An apparent example of linkage between QTLs and deleterious fitness loci. Latter and Robertson (1962) selected for increased abdominal bristle number in *Drosophila melanogaster*, creating sublines (indicated by the dashed lines) from the selected lines at various generations and subjecting these sublines to relaxed selection. Sublines of line AH2 extracted in the first three generations of selection showed significant erosion of response upon relaxation of selection, while sublines extracted in later generations show little erosion. Note that line AH2, which has a depressed response relative to line AH1 over generations 1-4, shows an accelerated response following generation 4. One explanation is that alleles increasing the character were initially in gametic-phase disequilibrium with alleles having deleterious effects on fitness. By generation four, this disequilibrium had largely broken down, allowing the frequencies of alleles increasing character value to remain stable following relaxation of selection and allowing a faster response to selection. After Latter and Robertson (1962).

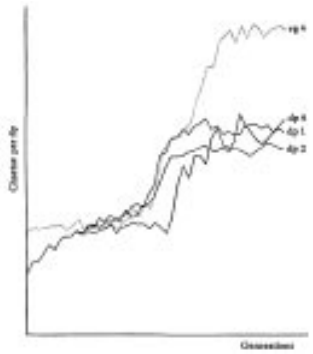


Figure 25.13. Accelerated response in sternopleural bristle number in one line (*vg 4*) of *Drosophila melanogaster* selected by Thoday and Boam (1961). Two other lines (*dp1, dp2*) also showed a slight acceleration in response around generation 20, but not as dramatic as that seen in line *vg 4*.

While recombination removes gametic-phase disequilibrium, selection generates it (Chapters 5, 16, 24). It follows that if linkage effects are important, relaxation of selection should facilitate long-term response by allowing negative gametic-phase disequilibrium to decay, which increases the additive variance (Chapter 16). Thoday and Boam (1961) observed a large increase in sternopleural bristle number in *Drosophila* by reselecting a line in which selection was relaxed for several generations following an apparent selective plateau. Similar patterns were seen by Mather and Harrison (1949) in some of their lines selected for increased abdominal bristle number. On the other hand, Rathie and Barker (1968) compared the effects of cycles of selection followed by no selection versus continuous selection on abdominal bristles, finding no differences in response. However, the continuously selected lines showed larger erosions of response upon relaxation of selection and had greater decreases in reproductive fitness, suggesting that disequilibrium between QTLs and fitness loci was greater in these lines.

The above discussion of the effects of linkage has been restricted to infinite populations. Here, in the absence of epistasis, linkage influences the rate, but not the ultimate limit, of response. When population size is finite, linkage can have important effects on the ultimate selection limit even in the absence of epistasis. For example, in a small population selection and drift could have fixed $+-$ gametes in Thoday's experiment before $++$ gametes reached frequencies sufficiently high to overcome the effects of drift. These interactions are complex and we defer further discussion of them until Chapter 26.

Epistasis

While the permanent component of response in any particular generation is a function of the additive variance (Chapter 15), this changes as the frequencies of underlying genotypes changes. While it is generally true that most variance is additive, even when strong epistasis is present (Hill et al. 2008), it is also true that changes in genotype frequencies can result in some of the epistatic variance being converted into additive variance (Goodnight 2004; Chapter 11). Eitan and Soller (2004) proposed the idea of **selection induced genetic variation**, wherein the process of selection generates variance, as opposed to strictly removing it. An example of this is Carlborg et al. (2006), who found a strongly epistatic locus in chicken lines divergently selected for growth. Alleles at three growth-specific loci (*Growth4, 6, 12*) had much higher effects in a (high-growth) homozygous *Growth9* genotypic background. While Eitan and Soller were concerned with new variation being generated via epistasis, recall the very erratic pattern of response seen in Figure 25.10 for a *purely additive* model. If such a pattern were observed in an experiment, many would declare that it could only be due to epistasis. This is based on the expectation that additive variance is continually declining, which requires the assumption that the majority of loci are at, or above, their frequencies for maximal additive variation. If this is not correct, they can (for at least part of the response) generate new additive variance as they increase towards the frequency giving maximal σ_A^2, after which further allele frequency change causes σ_A^2 to decline. As Figure 25.10 shows, bursts of response for rare additive alleles can occur > 50 generations after the start of selection.

There is a healthy debate about the impact of epistasis on directional selection (Carlborg and Haley 2004; Malmberg and Mauricio 2005; Le Rouzic and Carlborg 2007; Crow 2008, 2010; Hansen 2013), with some even claiming that models not incorporating it are fundamentally flawed (Nelson et al. 2013). However, from the standpoint of predicting long-term response, epistasis is, in some sense, the least of our worries. If even a completely additive model gives very erratic response, incorporating an additional source of uncertainly (epistasis) only complicates matters further. Further, one might imagine being able to generate some insight for an additive model (obtaining rough estimates of additive effects), while the nature of strong epistasis makes such insights for strongly-interacting loci far less likely.

As the various above processes illustrate, a large number of different genetic conditions can result in increases in response, and determining the underlying cause for a particular burst in a particular experiment is far from trivial.

CONFLICTS BETWEEN NATURAL AND ARTIFICIAL SELECTION

It is frequently seen that components of fitness (such as viability and fertility) decline rather dramatically during artificial selection experiments. Lines can even die out due to extreme declines in fitness. There are several (not mutually exclusive) reasons for these declines, which have quite different implications for long-term response.

1. *Selection increases the amount of inbreeding* relative to control populations of the same size, a point developed in Chapters 3 and 26. Drift effects associated with inbreeding can increase the frequency of deleterious recessives as well as move overdominant fitness loci away from their equilibrium frequencies. If inbreeding is sufficiently strong, deleterious alleles can be fixed.
2. *Loci favored by artificial selection can be in gametic-phase disequilibrium with loci having deleterious effects on fitness*. Fitness declines as these deleterious alleles increase in frequency due to hitch-hiking with alleles favored under artificial selection. As mentioned above, this disequilibrium need not be present initially — it can be generated during artificial selection (Chapter 16). In infinite populations, the gametic-phase disequilibrium between QTL and fitness loci eventually decays, and deleterious alleles are not fixed. In small populations, however, deleterious alleles can be dragged along to fixation by linked major alleles.
3. *Alleles favored by artificial selection can have deleterious effects on fitness*. There are two different routes by which this can occir: the artificially-selected character may itself be under natural selection, or loci controlling this character can have pleiotropic effects on other characters under natural selection. Two particular models have been examined in some detail, the **optimum model** where the character under artifical selection is also subjected to natural stabilizing selection (Latter 1960; James 1962), and the **homeostatic model** where heterozygotes have the highest fitness under natural selection (Lerner 1954; Robertson 1956). While the genetic basis for these models is very different, Nicholas and Robertson (1980) noted that "despite the profound differences between the two models, the practial implications of each are essentially the same *in the context of artificial selection*. Consequently there seems to be no aspect of observable response which would enable a distinction to be made between the two models."

Example 25.6. Frankham et al. (1988) selected *Drosophila melanogaster* for increased ethanol tolerance. Following the suggestion of Gowe (1983), they attempted to reduce the expected decline in reproductive fitness by culling those artificially selected pairs showing reduced reproductive fitness. Their logic was that if the deleterious fitness effects during selection were largely caused by rare recessives (which increase by inbreeding during selection), then culling a very small fraction of the lowest fitness individuals would cull those rare individuals homozygous for deleterious recessives. Following selection for tolerance, Frankham et al. placed single mated pairs in vials that were subsequently ranked according to the number of pupae produced. Vials with the lowest number of pupae were culled. The HS line, subjected to both selection for tolerance and culling on reproductive fitness, had the same response as the HO line which was selected just for increased tolerance. The unselected control line and

the HS line had the same fitness, as measured by Knight and Robertson's (1957) very general competitive index measure. The HO line had significantly reduced fitness. If alleles increasing tolerance had either pleiotropic and/or linkage effects on fitness, the HS line should have reduced response relative to the HO line. Given that the responses were identical, Frankham et al. suggested that the reduction in fitness in the HO line was mainly due to the effects of inbreeding, rather than linkage or pleiotropy.

A similar study was reported by Gowe et al. (1993), who examined 30 years of selection on laying hens, where the lower 10% of selected hens (those with the highest egg production) were culled on the basis of fertility and hatchability. The control and selected lines maintained the same levels of fertility and hatchability.

A final example of an experiment attempting to control for deleterious fitness effects is that of Imasheva et al. (1991), who combined directional selection for increased *radius incompletus* expression in the wing venation of *Drosophila melanogaster* with stabilizing selection on a suite of wing morphological characters. After 16 generations of selection, the control and directional plus stabilized selected lines had similar population sizes, both of which were higher than the population subjected to strict directional selection. The three lines, however, did not differ when fitness was measured by looking at competitive ability.

What are the implications of these different fitness-decreasing mechanisms for long-term response? The inbreeding effect of selection is a consequence of finite population size being further exaggerated by selection — these effects should largely disappear as population size increases, provided that deleterious alleles have not already been fixed. Inbreeding can also influence the selection limit if the fertility and/or viability of the selected line has been sufficiently lowered to the point that further selection is difficult.

If loci influencing the character also influence fitness (either directly and/or because of gametic-phase disequilibrium with other fitness loci), response is expected to decay upon relaxation of selection, provided alleles decreasing fitness are not fixed (e.g., FIgure 25.7b). Erosion of response, however, does not automatically imply fitness effects are important. For example, some erosion is expected when additive epistasis and/or maternal effects are present (Chapter 15). If erosion is largely due to fitness effects, it should be correlated with increases in fitness. If the decline in fitness is due entirely to inbreeding effects, the population mean should remain stable (assuming we can ignore epistatic and maternal effects).

Example 25.7. Enfield (1980) subjected the flour beetle *Tribolium castaneum* to selection for increased pupal weight. As mean pupal weight increased, components of reproductive fitness (percent sterility, mean number of progeny per fertile matings) decreased. Upon relaxation of selection, pupal weight decreased and fitness increased. When relaxed lines were again subjected to selection, fitness components again decreased as pupal weight increased. Enfield reported evidence that increased pupal weight, by itself, does not necessarily decrease fitness, finding that lines can be created with rather large mean pupal weight, which remain stable upon relaxation of selection. Thus, it appears that reproductive fitness declines as a result of a correlated selection response with pupal weight, rather than natural selection acting directly on pupal weight itself.

Example 25.8. An interesting potential example of a decay in response upon relaxation of selection in a natural population is given by Cruz and Wiley (1989), who examined egg-

rejection behavior in the Village Weaver bird (*Ploceus cucullatus*) in Hispaniola. This bird was introduced onto the island from western Africa about 200 years ago. Studies in western Africa by Victoria (1972) showed that female Weavers can recognize their own eggs and eject foreign eggs with different markings from the nest, with the rate of rejection proportional to the amount of difference between eggs. Victoria postulated that this rejection behavior evolved in response to selective pressure from the Didric Cuckoo (*Chrysococcyx caprius*), which is a brood parasite, laying its eggs in the nests of other species. Victoria found the average rejection rate of eggs with a different appearance from their mothers was around 40-55%, while Cruz and Wiley found a rejection rate on Hispaniola of 12%. Since Hispaniola was free of brood parasites until the mid 1970's, they suggest this difference amounts to a slippage in the selection gain following relaxation of selection. This natural experiment continues today, as in the mid 1970's the Shiny Cowbird (*Molothrus bonariensis minimus*), a brood parasite, was introduced into Hispaniola. It will be interesting to follow the egg rejection rates over future generations to see if the presence of the Cowbird results in selection pressure to increase egg rejection.

Accumulation of Lethals in Selected Lines

Lethal alleles are often detected in lines subjected to long-term selection. If these also influence the character under selection, they can result in increases in additive variance during response, significant additive variance at the selection limit, and some erosion of both the response and variance upon relaxation of selection.

Example 25.9. The following data are estimated variance components from a selection experiment by Reeve and Robertson (1953) for increased wing length in *Drosophila melanogaster*.

Population	σ_z^2	σ_A^2	σ_E^2	h^2
Selected	4.65	2.50	1.72	0.54
Relaxed	4.50	1.80	1.72	0.40
Base	3.20	1.02	1.72	0.32

The selected line shows large increases in additive variance and heritability, while upon relaxation of selection both additive variance and heritability decline to values intermediate between those in the base and selected lines. Reeve and Robertson attributed this behavior to the presence of at least two major alleles that are also lethal as homozygotes. As these alleles increase in frequency, they increase additive variance. Since these alleles are never fixed (as is discussed below, their maximum frequency is 1/3), variance does not subsequently decline as selection proceeds. However, upon relaxation of selection, the component of response due to these alleles decays as their frequency is reduced by natural selection. Additive variance is also expected to decline as these alleles are eventually lost due to natural selection following the relaxation of artificial selection.

In other *Drosophila* experiments, lethals have been observed in lines subjected to directional selection on sternopleural bristles (Madalena and Robertson 1975; García-Dorado and López-Fanjul 1983), abdominal bristles (Clayton and Robertson 1957; Frankham et al. 1968; Hollingdale 1971; Yoo 1980b), dorsocentral bristles (Domínguez et al. 1987), and wing length (Reeve and Robertson 1953). Skibinski (1986) also found that lethals accumulated during stabilizing selection on sternopleural bristle number. Yoo (1980b) and Skibinski (1986) found that most lethals arose during the course of the selection experiment, rather than being ini-

tially present in the base population. A similar example in mice is the homozygous sterile allele *pygmy*, which reduces body size when heterozygous (King 1955; Warwick and Lewis 1954). This mutant arose during MacArthur's (1949) long-term selection experiments for decreased body size.

Newly arising lethals could be due to new mutation (such as the insertion of a mobile element, Mackay 1988) or could be generated by recombination between strongly epistatic genes creating **synthetic lethals** (LW Chapter 10; Phillips and Johnson 1998). Once a lethal with a strong effect on the character appears, it partly shelters closely linked sites from further selection, creating linked clusters of lethals (Madalena and Robertson 1975; García-Dorado and López-Fanjul 1983).

Expected Equilibrium Frequency of Recessive Lethals

What accounts for the presence of lethals in selected lines? In many cases, it appears to be fitness overdominance resulting from a balance between natural and artificial selection — the allele increases character value as a heterozygote, but is lethal (or sterile) as a homozygote. Such alleles can be maintained at rather high frequencies if artificial selection acting on that locus is strong (i.e., the allele has a major effect on the character under strong directional selection). We can show this informally as follows: let the **AA** homozygote be lethal, while the **Aa** heterozygote increases the genotypic values of the character under selection (relative to **aa**). Under directional selection, the fitness of **Aa** relative to **aa** can be written as $1+s$, where s increases as the effect of **A** on the character under selection increases. Putting these together gives total fitnesses of $1:1+s:0$ for the genotypes **aa** : **Aa** : **AA**. Hence $\overline{W} = 1+2sp(1-p)-p^2$, where p is the frequency of **A**. Applying Wright's formula (Equation 9.4) and solving $\Delta\widehat{p} = 0$ gives the equilibrium frequency of **A** in newly formed zygotes (before natural selection) as

$$\widehat{p} = \frac{s}{1+2\,s} \tag{25.12}$$

Following the loss of lethal homozygotes, p decreases to $\widetilde{p} = s/(1+3s)$. For large s, the equilibrium frequency of the allele approaches $1/3$ before artificial selection, increasing to $1/2$ after artificial selection. A more formal treatment of this problem is given in Example 25.10.

While many lethal alleles have a demonstrated major effect on the character under selection, in some cases their frequencies are not consistent with the above theory. Skibiniski (1986) found no evidence that artificial selection accounts for the maintenance of lethals observed in his lines. Instead, one lethal showed evidence of segregation distortion that could account for its observed frequency. Likewise, none of the lethals isolated by Domínguez et al. (1987) had a significant effect on the character under selection. They also found evidence that at least one lethal allele was preferentially transmitted (by males). The increased inbreeding generated by artificial selection can increase the frequency of even strongly deleterious alleles and this, especially when interacting with other factors such as segregation distortion, might account for the increase in lethals not affecting the character under artificial selection.

Example 25.10. For a more formal treatment of the expected equilibrium value, consider a major gene that is lethal as a recessive (**AA**), but increases character value as a heterozygote (**Aa**). What are the dynamics of this locus when truncation selection is used to increase character value? Suppose that the distribution of phenotypes for the two viable genotypes is normal, with $z_{\mathbf{Aa}} \sim N(\mu+a, \sigma^2)$ and $z_{\mathbf{aa}} \sim N(\mu, \sigma^2)$, and let p be the frequency of **A**. Following random mating, the expected zygotic frequencies are in Hardy-Weinberg frequencies, with freq(**Aa**) = $2p(1-p)$, freq(**aa**) = $(1-p)^2$, and freq(**AA**) = p^2. After natural selection, only the

genotypes **Aa** and **aa** remain, and these now have frequencies

$$\text{freq}(\mathbf{Aa}') = \frac{2p(1-p)}{1-p^2} = \frac{2p}{1+p}, \qquad \text{freq}(\mathbf{aa}') = \frac{(1-p)^2}{1-p^2} = \frac{1-p}{1+p}$$

Truncation selection occurs on the survivors of natural selection, generating a mixture distribution for the trait value (LW Chapter 13), with

$$\begin{aligned} z &= \text{freq}(\mathbf{Aa}')\, p_{\mathbf{Aa}}(z) + \text{freq}(\mathbf{aa}')\, p_{\mathbf{aa}}(z) \\ &= \left(\frac{2p}{1+p}\right) p_{\mathbf{Aa}}(z) + \left(\frac{1-p}{1+p}\right) p_{\mathbf{aa}}(z) \end{aligned}$$

If the threshold value above which individuals are allowed to reproduce is T, then the fraction q of individuals allowed to reproduce is given by

$$q = \left(\frac{2p}{1+p}\right) \Pr(z_{Aa} > T) + \left(\frac{1-p}{1+p}\right) \Pr(z_{aa} > T)$$

since $(z_{Aa} - \mu - a)/\sigma \sim U$ and $(z_{aa} - \mu)/\sigma \sim U$, where U denotes a unit normal, this rearranges to give

$$q(1+p) = 2p \Pr\left(U > T^* - \frac{a}{\sigma}\right) + (1-p) \Pr(U > T^*) \tag{25.13}$$

where $T^* = \mu/\sigma$. The frequency of **Aa** following artificial selection becomes

$$\text{freq}(\mathbf{Aa}'') = \left(\frac{2p}{1+p}\right) \frac{\Pr(U > T^* - a/\sigma)}{q}$$

giving the frequency after a single round of both natural and artificial selection as

$$p'' = \frac{1}{2}\,\text{freq}(\mathbf{Aa}'') = \left(\frac{p}{1+p}\right) \frac{\Pr(U > T^* - a/\sigma)}{q} \tag{25.14}$$

Letting $\widehat{p}$ denote the equilibrium frequency in the zygotes before natural selection, it follows from Equation 25.14 that

$$q\,(1+\widehat{p}\,) = \Pr(U > T^* - a/\sigma)$$

Combining this result with Equation 25.13 gives

$$2\,\widehat{p}\Pr\left(U > T^* - a/\sigma\right) + (1-\widehat{p}\,)\Pr(U > T^*) = \Pr(U > T^* - a/\sigma)$$

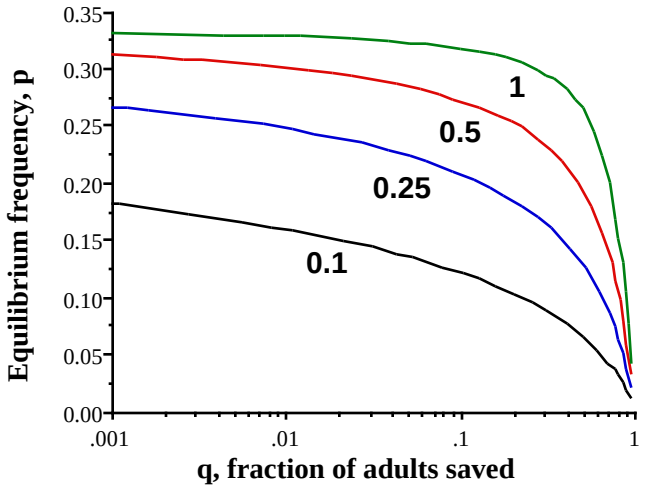
solving for $\widehat{p}$ gives

$$\widehat{p} = \frac{\Pr(U > T^*) - \Pr(U > T^* - a/\sigma)}{\Pr(U > T^*) - 2\Pr(U > T^* - a/\sigma)} \tag{25.15a}$$

Likewise, the equilibrium frequency $\widetilde{p}$ following removal of lethals (**AA** homozgyotes) is

$$\widetilde{p} = \frac{(1/2)\text{Freq(Aa)}}{1 - \text{Freq(AA)}} = \frac{\widehat{p}\,(1-\widehat{p}\,)}{1-\widehat{p}^{\,2}} = \frac{\widehat{p}}{1+\widehat{p}} \tag{25.15b}$$

The following figure plots $\widetilde{p}$ as a function of q and a/σ (the four curves are values of $a/\sigma = 1$, 0.5, 0.25, and 0.1, respectively.) The figure was generated applying Equations 25.15a and 15b for a given value of T^*, and then using Equation 25.13 to obtain the value of q given the T^*, a/σ, and $\widehat{p}$ values.



Lerner's Model of Genetic Homeostasis

A second class of models assuming pleiotropic fitness effects are based on Lerner's (1954) theory of **genetic homeostasis**, which was motivated by the notion that natural selection tends to favor heterozygotes, a view that is still controversial and has weak support at best. Under Lerner's model, alleles segregating at a QTL are favored as heterozygotes by natural selection. The simplest case is when the QTL is additive for the character under selection. Let the genotypes $\mathbf{aa}:\mathbf{Aa}:\mathbf{AA}$ have fitnesses (under natural selection) of $1-s_2:1:1-s_1$. If the character is normally distributed and the locus has a small effect on z, the fitnesses under directional selection are approximately $1-\overline{\imath}\,a/\sigma_z:1:1+\overline{\imath}\,a/\sigma_z$, giving total fitnesses of $(1-s_2)(1-\overline{\imath}\,a/\sigma_z):1:(1-s_1)(1+\overline{\imath}a/\sigma_z)$. If artificial selection is sufficiently strong ($\overline{\imath}\,a/\sigma_z > s_1$), $\mathbf{A}$ is fixed. However, if $s_1 > \overline{\imath}\,(a/\sigma_z)$, total fitness is overdominant and there is an internally stable equilibrium,

$$\widehat{p} = \frac{s_2 + \overline{\imath}\,(a/\sigma_z)\,(1-s_2)}{s_1 + s_2 + \overline{\imath}\,(a/\sigma_z)\,(s_1 - s_2)} \simeq \frac{s_2 + \overline{\imath}\,(a/\sigma_z)}{s_1 + s_2} \tag{25.16}$$

This result is due to Verghese (1974) and Nicholas and Robertson (1980), while Minvielle (1980) gives a more general equilibrium condition for alleles of major effect. The additive genetic variance for the trait contributed by this locus at equilibrium is $2a^2\,\widehat{p}\,(1-\widehat{p}\,)$, which can be considerable.

Changes in reproductive fitness in divergent selection lines are often asymmetric, with lines selected in one direction showing a much larger decrease in fitness than lines selected in the opposite direction. Such asymmetries are not necessarily inconsistent with genetic homeostasis, as they can be accounted for by directional dominance in fitness (e.g., if $s_1 < s_2$ — alleles increasing the character under artificial selection also tend to be more fit as homozygotes — holds for most loci).

Lerner's model is an example where the QTL influencing a character z under artificial selection also influences fitness under natural selection independent of the phenotype of z — extreme phenotypes are less fit because they are more homozygous than intermediate phenotypes. Alternatively, the phenotypic value z itself could be under natural selection — extreme phenotypes are intrinsically less fit, independent of their genotypes. For example, z could be under natural selection for an intermediate optimal, with directional artificial selection being opposed by stabilizing natural selection. This can also lead initially to an

apparent selection limit in the presence of additive variance in z (Latter 1960; James 1962; Zeng and Hill 1986). However, as is discussed in Chapter 13, this situation is similar to strict stabilizing selection, which eventually results in the loss of essentially all genetic variation in the absence of mutation (Robertson 1956).

CHARACTERIZING THE NATURE OF SELECTION LIMITS

What is the nature of selection limits observed in artificial selection experiments? In particular, is there any genetic variation present at an apparent limit, and if so is any of it additive? Changing selection schemes and inbreeding offer two approaches for characterizing the nature of any residual genetic variation. If additive variance is present, the line should response to **reversed selection** (subjecting the line to selection in the opposite direction). Likewise, a decay in the mean of a plateaued line after selection is **relaxed** indicates the possibility of additive variance, although epistasis and/or maternal effects also result in slippage of the mean (see Chapter 15). If nonadditive variance is present, the line can show inbreeding depression, with the mean changing as the line is inbred. The *absence* of inbreeding depression does not imply a lack of genetic variation. If all residual variance is additive or if there is no directional dominance, inbreeding depression is not seen (LW Chapter 10). Correlations between relatives can also be used to characterize the nature of residual variation. One caveat to this approach is that selection can generate strong gametic-phase disequilibrium, complicating standard methods for estimating components of variance (Robertson 1977).

Table 25.4 highlights some of the causes of selection limits seen in long-term artificial selection experiments. This is by no means a comprehensive listing. Selection limits appear to be rare in many important commercial traits in domesticated animals (Fredeen 198; Hunton 1984; Kennedy 1984). This is perhaps not surprising given that breeders are constantly shifting the suite of characters under artificial selection. A more dubious possibility is that while not currently at a limit, breeders are quickly approaching one.

The general conclusion from long-term experiments seems is that significant additive variance in the selected character is often present at an apparent limit. This is rather surprising given that most experiments have such small effective population sizes that drift is expected to remove most variation (Chapters 3, 26).

Table 25.4. Nature of the selection limit observed in various laboratory selection experiments.

Reduced thorax length in *D. melanogaster* F. W. Robertson 1955	Apparent exhaustion of all genetic variation: no further change under inbreeding, no response to reversed selection.
Increased body weight in mice Falconer and King 1953 Roberts 1966	Exhaustion of σ_A^2: no response to reversed selection.
Egg production in *D. melanogaster* Brown and Bell 1961, 1980	Exhaustion of σ_A^2: significant nonadditive genetic variance present at selection limit. Lethals and sterility factors negligible.
Wing length in *D. melanogaster* Reeve and Robertson 1953	Significant σ_A^2 at limit: complicated interaction due to segregating lethals and an overdominant gene influencing wing length.
Reduced body weight in mice Falconer 1955 Roberts 1966	Opposing natural selection: response to reverse selection, relaxation of mean. Likely due to reduction in viability.

Abdominal bristles in *D. melanogaster* Clayton and Robertson 1957 Yoo 1980b	Segregating lethals: major gene increases bristle number as a heterozygote, lethal as a homozygote.
Pupal weight in *Tribolium castaneum* Enfield 1980	Opposing natural selection: significant σ_A^2 at limit, large decay in response with relaxed selection. Sterility reduced and fertility improved in relaxed lines.
Shank length in chickens Lerner and Dempster 1951	Opposing natural selection: shank length negatively correlated with hatchability.
Litter weight in mice Eisen 1972	Negative genetic correlation between direct and maternal effects.
Increased body weight in mice Wilson et al 1971	Negative correlation between weight and litter size.
Increased litter size in mice Falconer 1971	Apparent limit due to slow changes in in the frequency of dominant alleles.

One celebrated apparent selection limit is racing performance in thoroughbred horses, where the winning times in classic English races have not fallen substantially over the past 50 years (Gaffney and Cunningham 1998; Hill 1998). To be fair, this is a nonstandard trait, namely the best single performance within a set of individuals, not their mean performance. However, if mean times have responded to selection, we also expect these outlier times (best of a dozen or so) to fall as well. One possibility is that while means have fallen, so to has the genetic variance, potentially keeping low outliers at a roughly constant value. Gaffney and Cunningham (1998) found ample additive variance in a strong correlate of performance, namely handicap weight, which Hill predicts should result in a mean improvement of roughly 0.1 per cent per year. A more recent analysis by Wilson and Rambaut (2008) on the genetics of lifetime earning of racing horse (again correlated with speed) found that while roughly 90% of the variation is environmental (diet, trainer, etc.), there was a significant heritable component that should respond to selection.

Some long-term experiments have yet to reach their limit (Figure 25.8). One classic is the **Illinois long-term corn selection experiments**, started by the agricultural chemist Cyril Hopkins in 1896 and currently ongoing (Hopkins 1899; Smith 1908). The results after 76, 90, 100, and 106 generations of selection are summarized by Dudley (1977), Dudley and Lambert (1992, 2004), Moose et al. (2004), and Dudley (2007). As shown in Figure 25.8A, a fairly constant response for increased oil content is seen over 90 generations with no apparent selection limit, with an increase of $22\sigma_A^2$. Selection for low oil was stopped after 87 generations due to difficulty of selecting among individuals with nearly zero percent oil. While a limit appears to have been reached for low oil, it is due to a scale effect as oil percentage is bounded below by zero. If one were able to select on a log-scale, presumably response would continue. Selection for protein shows a similar pattern to that for oil (Figure 25.8B), with the up-selection line (IHO) currently showing an increase of $26\sigma_A^2$ after generation 90 with no apparent limit, while the down-selected lines show an apparent plateau, again likely due to scale effects. The interesting, and far-reaching, intellectural legacy of this experiment is nicely summarized by Goldman (2004).

A few other classical experiments continue to show response without an apparent limit. The **Dummerstorf long-term** selection lines (started in Dummerstorf, Germany) are the mammalian counterpart to the Illinois maize lines. Selecting for mouse weight at 42 days, this experiment has run for over 160 generations, making it the longest continuous selection experiments in mammals (Bünger et al. 2001). As shown in Figure 25.8, it has not yet reached

a limit. Holt et al. (2005) selected mice for litter size for over 122 generations, but the selected population had at least two waves of migration of new genetic material to break the selection limit. **Weber's long-term selection for flight speed** in *Drosophila* has over 300 generations of continuous selection (Weber 1996, 2004). Figure 25.8 shows no apparent limit after 100 generations, while by generation 300, the response was slowing down. Unpublished results by Weber (pers comm.) have the line still slowing response, although slowing, after 640 generations of selection. The champion of continuous long-term experiments is the **Long-term evolution experiment** (**LTEE**) of Lensky (Lenski et al. 1991; Lenski and Travisano 1994; Barrick , et al. 2009; Wiser et al. 2013) for the bacteria *Escherichia coli*, which continues to respond for selection for increased fitness after 50,000 generations. The roles of both finite population size (larger populations have larger limits) and new mutation input are critical to the ongoing response in these experiments, and we examine this further in Chapter 26.

When response appears to have reached a selection limit, several strategies may break this limit and allow for some further response. As mentioned earlier, relaxing selection for several generations followed by directional selection can break a limit caused by strong gametic-phase disequilibrium between segregating loci. Likewise, if the limit results from a balance between natural and artificial selection, increasing the amount of artificial selection can result in further response. If the limit is caused by a lack of genetic variation, crossing different lines can introduce additional variation. This is especially true when drift has been important (Chapter 26). Over longer time scales, a limit can be broken simply by waiting for mutational input, either to increase additive variance or perhaps generate alleles with less deleterious effects on fitness (Chapters 26, 27). A final approach is selection in a new environment, which can often exploit genetic variation not usable in the current environment. Abplanalp (1962) was able to improve a chicken line, apparently at a plateau for increased egg number, by selecting in a different environment (females being subjected to one day without food every two weeks).

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