

Lecture 11

Long-Term Response and Selection Limits

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IDEALIZED LONG-TERM RESPONSE IN A LARGE POPULATION

The general pattern expected in 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 11.1). As discussed in Lecture 9, there is a slight reduction in the variance due to the generation of gametic-phase disequilibrium, but this is generally small unless directional selection is very strong, heritability is high, and the number of loci is very large. As generations proceed, sufficient allele frequency change accrues to significantly alter genetic variances. 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 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 is followed by a much longer period of slower response due to allele frequency changes at loci having smaller effects. 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, a point covered in the last half of this lecture.

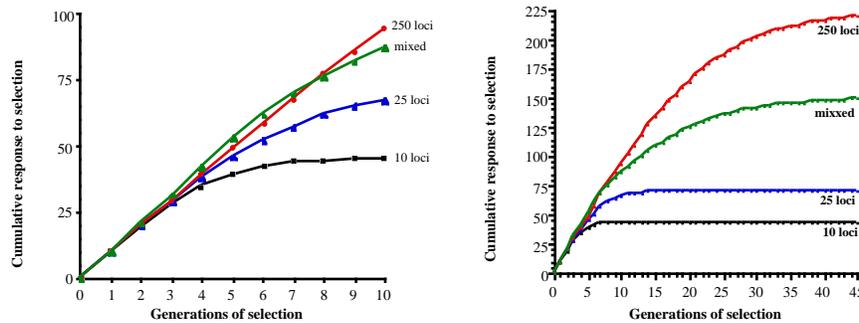


Figure 11.1. Examples of the expected response to selection, here assuming truncation selection (with the upper 20% saved), n identical diallelic loci (at each, the genotypes $AA : Aa : aa$ have genotypic values $2a : a : 0$, and all loci have the same frequency (p) of A). We further assume no epistasis and ignore any effects of gametic-phase disequilibrium. All populations start with $\sigma_A^2(0) = 100$ and $h^2(0) = 0.5$. 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 $p = 0.5$, $a = 0.89$. **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, the response remains linear over all generations (after correcting for the slight decrease over the first few generations in the additive variance from linkage disequilibrium).

Figure 11.1 illustrates differences in the long-term response for four hypothetical populations with the same initial heritability but different numbers of loci. All show essentially the same

response over the first few generations. By generation five, allele frequencies have changed enough in the 10- and 25-locus populations 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.

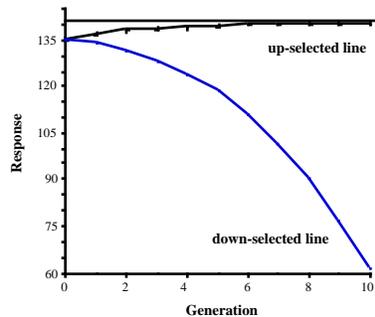


Figure 11.2. With strong directional dominance, an apparent selection limit can result when alleles favored by selection are dominant. Here the genotypes $AA : Aa : aa$ have values $2a : 2a : 0$, and we ignore epistasis and gametic-phase disequilibrium. The population consists of 25 identical loci, with $a = 2.82$ and initial frequency $p_A = 0.8$. 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.

If alleles are favored by selection are dominant, response slows down considerably as these alleles 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 11.2 demonstrates, reverse selection on these populations can result in a fairly rapid response. Note that divergent selection in this case generates a significant asymmetric response (Lecture 10). 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 against heterozygotes, allowing favorable dominant alleles to be more rapidly fixed.

Example 11.1. 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 dominant alleles), facilitating response.

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 effects to name a few. This section quantifies how these effects

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.

We start with the expected total contribution from a given diallelic locus. Let A be the allele favored by directional selection, where the genotypes $aa : Aa : AA$ 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) and is given by

$$m(p) = 2ap [1 + (1 - p)k] \quad (11.1a)$$

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 thus

$$m(1) - m(p_0) = 2a - 2ap_0 [1 + (1 - p_0)k] = 2a(1 - p_0)(1 - p_0k) \quad (11.1b)$$

Figure 11.3 plots the total contribution from this locus when allele A is additive ($k = 0$), dominant ($k = 1$), and recessive ($k = -1$). Total response is largest when A is recessive and rare, and smallest when A is dominant and common.

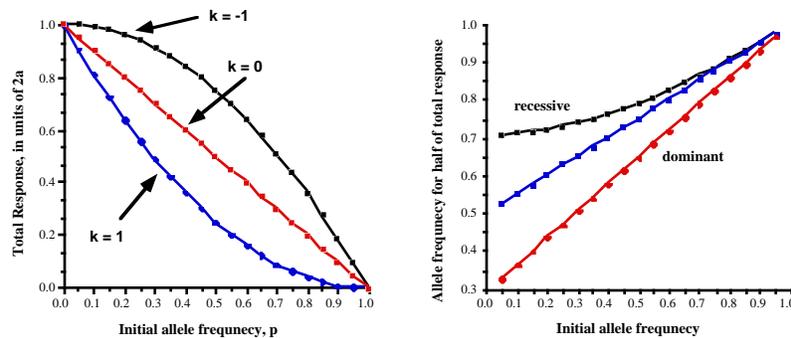


Figure 11.3. **Left:** The contribution to total response from a diallelic locus assuming allele A , starting at frequency p_0 , is eventually fixed. The genotypes $AA : Aa : aa$ have values $2a : a(1 + k) : 0$. The three curves correspond to A being additive ($k = 0$), dominant ($k = 1$), and recessive ($k = -1$). The smallest contribution is made by dominant alleles at high frequencies, the largest is 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 p_0 .

Table 11.1. Total contribution to the selection limit and the allele frequency ($p_{1/2}$) at which half this contribution 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 ($k = -1$)	$2a(1 - p_0^2)$	$\sqrt{(1 + p_0^2)/2}$

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

$$m(p_\beta) - m(p_0) = \beta [m(1) - m(p_0)] \quad (11.2)$$

where $m(p)$ is given by Equation 11.1a. A case of particular interest is $p_{1/2}$, the frequency at which half the response occurs ($\beta = 0.5$). Expressions for $p_{1/2}$ as a function of initial allele frequency are given in Table 11.1 and plotted in Figure 11.3. Observe that rare recessives have to increase substantially in frequency to give half the response (e.g., if $p_0 = 0.1$ then $p_{1/2} \simeq 0.71$).

To obtain approximate expressions for the actual dynamics of response we need to follow allele frequency changes over time. If the character is normally distributed, then $\Delta p \simeq i(\alpha^*/\sigma_z)p$, where p and α^* are the frequency and average excess of A . This is a weak-selection approximation, as it assumes that $|i\alpha^*/\sigma_z| \ll 1$. 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

$$\Delta p \simeq \frac{ai}{\sigma_z} p(1-p)[1+k(1-2p)] \quad (11.3)$$

Example 11.2. The idealized response curves in Figure 11.1 were generated using Equation 11.3 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

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

Strictly speaking, the last expression is a (close) approximation, as $2na^2 p_t(1-p_t)$ 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 Lecture 9. Iteration generates the response curves given in the figure.

A variety of results will be developed using the model where the genotypes $aa : Aa : AA$ have fitnesses $1 : 1 + s(1+h) : 1 + 2s$. For weak selection (e.g., $|s|, |sh| \ll 1$), this model gives $\Delta p \simeq sp(1-p)[1+h(1-2p)]$, which follows from (Lecture 3) Equation 3.19 upon noting that $1/\bar{W} = 1 + O(s, sh)$. Matching terms with Equation 11.3, we find that a QTL under directional selection has approximate selection coefficients of

$$s = \frac{a}{\sigma_z} i \quad \text{and} \quad h = k \quad (11.4)$$

Thus, as an initial approximation, the dynamics at a QTL with a small effect on the character follow those of a locus under these constant fitnesses. With gametic-phase disequilibrium and/or epistasis, these fitnesses change as the background genotype changes. Even without these complications, fitnesses still change as the phenotypic variance σ_z^2 of the character under selection changes. This is especially a problem with major alleles. Even if the locus has a small effect, 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.

The approximate fitnesses given by Equation 11.4, provide insight into the behavior of an allele at a QTL under selection. For example, an additive QTL (of small effect) underlying a character under directional selection behaves approximately like a locus with an additive fitness of $s = ia/\sigma_z$. Alternatively, if the locus displays overdominance in the character ($k > 1$), then under directional selection this locus displays overdominance in fitness and $\hat{p} = (1+k)/(2k)$ is an internally stable equilibrium. Thus, for this locus there is still genetic variation at the selective equilibrium, although none of it is expected to be additive under this simple model. The dynamics at a QTL under stabilizing selection are much more complicated, as the linear approximation given by Equation 11.4 fails near the equilibrium point and the quadratic terms must be considered.

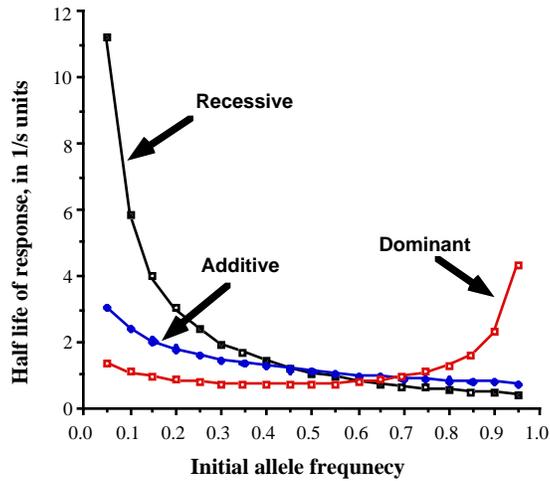


Figure 11.4. The expected times for a diallelic locus to contribute half its total response, assuming A is eventually fixed. These curves are obtained by substituting $p_{0.5}$ from Table 11.1 into the appropriate version of Equation 11.5. Note that the time units for half-life scale as $s^{-1} = (i a / \sigma_z)^{-1}$.

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 ($|s|, |hs| \ll 1$), the expected time for an allele to reach frequency p given it starts at frequency p_0 can be approximated for the fitness model $1 : 1 + s(1 + h) : 1 + 2s$. If A is additive ($h = 0$),

$$t_{p_0,p} \simeq s^{-1} \ln \left(\frac{p(1-p_0)}{p_0(1-p)} \right) \quad (11.5a)$$

Likewise, if A is recessive ($h = -1$),

$$t_{p_0,p} \simeq s^{-1} \frac{1}{2} \left[\ln \left(\frac{p(1-p_0)}{p_0(1-p)} \right) - \frac{1}{p} + \frac{1}{p_0} \right] \quad (11.5b)$$

while if A is dominant ($h = 1$),

$$t_{p_0,p} \simeq s^{-1} \frac{1}{2} \left[\ln \left(\frac{p(1-p_0)}{p_0(1-p)} \right) + \frac{1}{1-p} - \frac{1}{1-p_0} \right] \quad (11.5c)$$

See Crow and Kimura (1970, p. 193) for derivations. These expressions, together with Equations 11.2 and 11.4, allow us to obtain approximate expressions the expected time until β of the total contribution from a single locus occurs (the time for p to reach p_β). Note that the dynamics of evolutionary change scale as $s^{-1} = (i a / \sigma_z)^{-1}$ — the smaller the allelic effect, the slower the expected response time. Substituting $p_{0.5}$ for p gives the expected half-life of response associated with the locus under consideration (Figure 11.4). 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).

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 at linked loci, and vice versa, reducing allelic effects relative to a population in gametic-phase equilibrium). This results in weaker selection and a slower changes in allele frequency. Hence, the half-lives plotted in Figure 11.4 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 are poor approximations. More accurate expressions can be found in Latter (1965) and Frankham and Nurthen (1981).

Example 11.3. As an example of the consequences (in the absence of mutational input) for the limit $R(\infty)$ and half-life $t_{0.5}$ as the number of loci increase, consider the interchangeable locus model with n completely identical additive loci. 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 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 11.1, the selection limit here is $2na(1 - 1/2) = na = 10\sqrt{2n}$. Likewise, with $p_0 = 1/2$, $p_{0.5} = 3/4$ implying (from Equation 11.5a) that $t_{0.5} \simeq (\sigma_z/a) \ln(3)/i = \sqrt{n/2} \ln(3)/i$. The following table gives results for 5 to 500 loci.

n	a	$R(\infty)$	$R(\infty)/\sigma_z(0)$	$t_{0.5} \times i$
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

Thus, at the selection limit the mean phenotype is usually more extreme than any phenotype observed in the initial base population. For example, when $n = 25$, the total response is 5 phenotypic standard deviations, implying that 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 $(1/4)^{25} \simeq 10^{-15}$.

AN OVERVIEW OF LONG-TERM SELECTION EXPERIMENTS

The above theory suggests that populations under selection should show a reasonably smooth response, eventually (in the absence of new mutations) asymptoting 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. 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 (Lecture 10), these parameters are generally estimated by curve fitting. James (1965) suggested fitting the cumulative response R as a function of generation number t by an exponential curve,

$$R = a + b\theta^t + e \quad (11.6)$$

where e the residual error (a slightly different model, transformable into Equation 11.6, was suggested by Frahm and Kojima 1966). The three free parameters (a, b, θ) are estimated from the data, typically by least-squares (see James 1965 for details). Alternatively, a standard quadratic regression can be used, taking the maximum of the regression as the limit (James 1965, Eisen 1972). These

different families of curves all attempt to capture the asymptotic approach to a limit expected for an idealized long-term response. A general problem with any of these models is that the selection limit is *extrapolated* from the data. As Table 11.2 shows, different models can give essentially the same fit of the data, but very different estimates of the limit and half-life.

Table 11.2. 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 references to generations. The quadratic and exponential models both explain the same amount of variation ($r^2 = 0.81$ for both models) and cannot be discriminated on this basis. From Eisen (1972).

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

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 meristic character as a result of transforming an underlying continuous variable, we should work on this underlying scale of liability (see Lecture 9, 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 11.2).

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 40 generations. As we will discuss shortly, over longer time scales mutational input becomes very important and observed limits can simply be artifacts of the relatively short time scales used.

General Features of Long-Term Selection Experiments

Long-term 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 are often seen. Additive genetic and phenotypic variances can increase throughout most of the response.
3. *Reproductive fitness usually declines as selection proceeds.*
4. *Most populations approach a selection limit.* An apparent selection limit may be a simple artifact of the short time scales and/or small population sizes of most experiments.
5. *Considerable additive variance in the character under artificial selection often exists at an apparent selection limit.*

It is important to recognize that long-term selection experiments are a biased sample of organisms and characters. Controlled selection experiments exceeding 20 generations are largely

restricted to *Drosophila*, *Tribolium*, mice, and maize, although recently extremely long-term experiments (involving thousands of generations) have been done using bacteria and viruses. Whether the genetic architectures of quantitative characters in populations 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. Likewise, while long-term selection has certainly been practiced on a wide variety of domesticated plants and animals, the selection aims are likely to change over time, with the breeder selecting on a suite of (often changing) characters as opposed to solely focusing on a single character.

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 character. Selection pressures on any particular character are also likely to fluctuate in nature as the environment 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 often *increase* during the course of response, often resulting in bursts of response (e.g., Figures 11.5B, 5C). One obvious source is the presence in the base population of rare alleles whose effects are favorable under artificial selection.

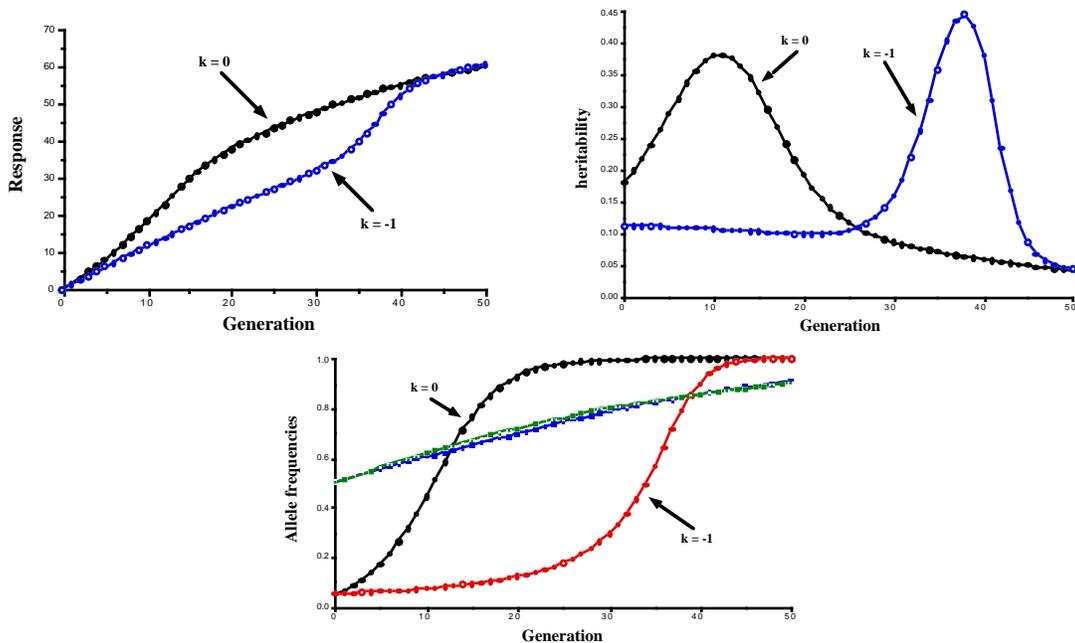


Figure 11.5. Examples of a delayed accelerated response due to the increase of an initially rare allele of major effect. The character is determined by a polygenic background (100 completely additive biallelic loci, with $a = 0.5$ and $p = 0.5$, so that the initially additive variance contributed by the polygenic background is $\sigma_A^2 = 9.5$) plus a major allele initially at low frequency ($a = 10$ and $p = 0.05$). We assume that this locus is either additive ($k = 0$) or recessive ($k = -1$). **A: (upper left)** the 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: (Upper right)** The population heritabilities clearly show the acceleration. **C: (bottom)** The changes in the major allele frequency shows the much longer time for the recessive major allele to increase in frequency. Note that while the change in the polygenic frequency is almost the same under the two different major locus dominance values (middle two lines).

Major alleles can be generated by mutation during the selection experiment, creating bursts of response throughout the course of the experiment. An example of this is the work of Yoo (1980a), who selected for increased abdominal bristles in *Drosophila* for over 80 generations. 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.

Accelerated response can 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). 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 that increases 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 gametes become sufficiently common to increase additive variance.

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. 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. Simply put, selection can generate significant inbreeding depression.
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. 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.* They can do so in two different ways: 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 artificial 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 1950,1954; 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 practical 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 11.4. 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. The logic is 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) 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.

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. Erosion of response, however, does not automatically imply fitness effects are important. For example, some erosion is expected when epistasis and/or maternal effects are present (Lecture 9). 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 11.5. 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 11.6. 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 into Hispaniola 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.

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** (stopped) indicates the possibility of additive variance, although epistasis and/or maternal effects also result in slippage of the mean (Lecture 9). 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 11.3. Nature of the selection limit observed in various laboratory selection experiments.

Reduced thorax length in <i>D. melanogaster</i> 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 <i>D. melanogaster</i> 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 <i>D. melanogaster</i> 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 <i>D. melanogaster</i> Clayton and Robertson 1957 Yoo 1980b	Segregating lethals: major gene increases bristle number as a heterozygote, lethal as a homozygote.
Pupal weight in <i>Tribolium castaneum</i> 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 the frequency of dominant alleles.

Table 11.3 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 1984, Hunton 1984, Kennedy 1984). This is perhaps not surprising given that breeders are constantly shifting the suite of characters under artificial selection.

The general conclusion from long-term experiments seems to be that, more often than not, significant additive variance (in the character) is present at an apparent selection limit. This is rather surprising given that most experiments have such small effective population sizes that drift is expected to remove most variation. The possible bias towards major alleles in laboratory experiments (discussed above) might account for this, given that major alleles with deleterious fitness effects appear to be the rule, rather than the exception.

In some long-term experiments limits have not been reached. One classic is the **Illinois long-term corn selection experiments**, started in 1896 and currently ongoing (Hopkins 1899, Smith 1908). The results after 76 and 90 generations of selection are summarized by Dudley (1977) and Dudley and Lambert (1992). 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, 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.

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. 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.

LONG-TERM RESPONSE IN FINITE POPULATIONS

Fixation Probabilities of Favorable QTL Alleles

The above results for single loci assume infinite population size, so that all favorable alleles are fixed. Since the population sizes for selection experiments are typically very small, drift can have a significant effect on allele frequencies. The infinitesimal model allows for drift but not selection

as it assumes alleles behave as if they are strictly neutral. A more exact treatment follows from standard population-genetics theory on the interaction of selection and drift at a single locus (e.g., Crow and Kimura 1970). When the genotypes $aa : Aa : AA$ have additive fitnesses $(1 : 1 + s : 1 + 2s)$ the probability $u(q_0)$ that allele A is fixed given its starts at frequency q_0 , was obtained by Kimura (1957) and is

$$u(q_0) \simeq \frac{1 - e^{-4N_e s q_0}}{1 - e^{-4N_e s}} \quad (11.7a)$$

$$\simeq q_0 + 2N_e s q_0 (1 - q_0) \quad \text{when } 2N_e |s| \leq 1 \quad (11.7b)$$

More complex expressions exist for $u(q_0)$ under more general fitnesses $(1 : 1 + s(1 + h) : 1 + 2s)$, see Example 7.8. For weak selection,

$$u(q_0) \simeq q_0 + 2N_e s q_0 (1 - q_0) \left(1 + \frac{h(1 - 2q_0)}{3} \right) \quad \text{when } 2N_e |s| \leq 1 \quad (11.7c)$$

Since the fixation probability for a neutral allele is q_0 (its starting frequency), selection dominates drift when $u(q_0)$ is significantly different from q_0 , while drift dominates when $u(q_0) \simeq q_0$. Noting that $1 - \exp(-x) \simeq x$ when $|x| \ll 1$ shows that drift dominates selection when $4N_e |s| \ll 1$, while selection dominates when $4N_e |s| \gg 1$. Recalling Equation 11.4, selection dominates the fixation dynamics at a QTL when

$$4N_e |s| = 4N_e \frac{|i a|}{\sigma_z} \gg 1 \quad (11.8)$$

or when

$$4N_e |i| \gg \frac{\sigma_z}{|a|}$$

Even if selection dominates, the fixation probabilities can still be very small (for example, one might have $1 \gg u(q_0) \gg q_0$). From Equation 11.7, the probability of fixation exceeds 0.7 when

$$N_e s q_0 = N_e |i| q_0 \frac{|a|}{\sigma_z} \geq 1/2 \quad (11.9a)$$

and exceeds 0.93 when this quantity exceeds 1. We can rearrange Equation 11.9a to show that the fixation probability exceed 0.7 when the initial allele frequency is sufficiently large,

$$q_0 > \frac{\sigma_z}{|a| 2N_e |i|} \quad (11.9b)$$

Hence, if the product of initial allele frequency and the standardized allelic effect $q_0 |a| / \sigma_z$ is sufficiently small, the allele can easily be lost by drift, even when selection on the character is strong. With low values of $N_e i$, only alleles of large effect and/or at moderate to high initial frequencies are likely to be fixed. As $N_e i$ increases, favorable alleles with smaller effects and/or lower frequencies are increasingly likely to be fixed.

Limits Under Drift and Selection

The above fixation probabilities allow one to compute the expected contribution of a particular locus towards the selection limit in a finite population. Let Δ denote the contribution (at the selection

limit) for a particular locus under consideration. If q_0 is the initial starting frequency of the favored allele at this locus, then

$$\Delta = m(q_\infty) - m(q_0) \quad (11.10)$$

where m is given by Equation 11.1a and q_∞ is the final allele frequency. The expected contribution becomes

$$\begin{aligned} E[\Delta] &= E[m(q_\infty)] - m(q_0) \\ &= E[2aq_\infty(1+k) - 2aq_\infty^2k] - m(q_0) \\ &= 2a(1+k)E[q_\infty] - 2akE[q_\infty^2] - m(q_0) \end{aligned} \quad (11.11)$$

The expected allele frequency at the limit is easily obtained, as an allele is either fixed ($q_\infty = 1$) which occurs with probability $u(q_0)$, or it is lost. Hence, $E[q_\infty^k] = 1^k \cdot u(q_0) = u(q_0)$, giving the limiting expected contribution from a particular locus as

$$E[\Delta] = 2a \left[u(q_0) - q_0 - k \left(q_0(1 - q_0) \right) \right] \quad (11.12a)$$

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

$$E[\Delta] = 2a [u(q) - q_0] \quad (11.12b)$$

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

$$E[\Delta] = 2a [u(q) - q_0^2] \quad (11.12c)$$

When A is additive, and there is weak selection on the locus (i.e., $2N_e |s| \leq 1$), substituting Equations 11.7b into Equation 11.12b gives the expected response from that locus as

$$\begin{aligned} E[\Delta] &= 2a [u(q) - q_0] = 2a2N_e s q_0(1 - q_0) \\ &= 2N_e \frac{i2a^2}{\sigma_z} q_0(1 - q_0) = 2N_e i \frac{\sigma_A^2(0)}{\sigma_z} \\ &= 2N_e R(1) \end{aligned} \quad (11.13)$$

Equation 11.13 is a classic result, due to Robertson (1960) selection, namely that the total response is just $2N_e$ times the initial (first generation) response.

Finally, the effects of drift can be quantified by considering the ratio of the expected response under drift with the deterministic response ($u(q) = 1$). For a single locus,

$$\frac{\text{expected response under drift}}{\text{deterministic response}} = \frac{u(q_0) - q_0 - k \left(q_0(1 - q_0) \right)}{1 - q_0 - k \left(q_0(1 - q_0) \right)}$$

Robertson's Theory of Selection Limits

As given by Equation 11.13, when the infinitesimal model holds, Robertson found a very simple relationship between the expected selection limit and the initial response $R(1)$ and the effective population size. More generally, he found that the expected response in generation t is given by

$$R(t) \simeq 2N_e \left(1 - e^{-t/2N_e} \right) R(1) \quad (11.14a)$$

giving an expected limiting total response of

$$R(\infty) \simeq 2N_e R(1) \quad (11.14b)$$

The careful reader will note that we assumed the phenotypic variance remains relatively constant over time, as would occur if h^2 is small. Provided this assumption holds, the total expected response is simply $2N_e$ times the initial response, as first suggested by Dempster (1955) and formally derived by Robertson (1960).

Equation 11.14a can be derived as follows. Assuming the main force for allele frequency change is drift, $\sigma_A^2(t) \simeq \sigma_A^2(0)[1 - 1/(2N_e)]^t$. Writing the response in generation t as $h^2(t)S = \sigma_A^2(t)S/\sigma_z^2$, summing over generations recovers Equation 11.14a.

Equation 11.14b is an *upper limit* for total response, which may seem somewhat counterintuitive since it was derived by assuming weak selection. The key is that (everything else being equal) the initial response $R(1)$ when selection dominates is much larger than when drift dominates, so that $2N_e$ times the initial response overestimates the total response when selection dominates.

Another quantity of interest is the expected half-life of response, $t_{0.5}$, the time required to obtain half the final response. Recalling Equation 11.14a and solving $1 - e^{-t_{0.5}/2N_e} = 1/2$ gives the expected half-life as

$$t_{0.5} = N_e \ln 2 \simeq 1.4N_e \quad (11.15)$$

Again, this is an upper limit with the half-life decreasing as the product $N_e i$ increases. An observed half-life considerably below that predicted by Equation 11.15 suggests that a large portion of the response is due to fixation of favorable alleles by selection, as selection (when it dominates) changes allele frequencies much faster than drift.

With dominance, analytic results for the limit and half-life ($R(\infty)$ and $t_{0.5}$) are more complicated than those for no dominance. Strictly recessive alleles have received the most study. In this case, the selection limit can considerably exceed $2N_e$ times the initial response when the character is controlled by a large number of rare recessives (Robertson 1960).

An extremely important result follows from writing the selection limit as $2N_e i \sigma_A^2(0)/\sigma_z$. Notice that the $\sigma_A^2(0)/\sigma_z$ term is fixed, while the choice of i strongly influences N_e . Thus, choosing a small number of individuals (say 5 out of 100) results in a large i (and hence a large initial response), but a small N_e (around 5). Conversely, choosing a larger number of individuals (say 25) resulting in a smaller i (and hence smaller initial response) but a larger effective population size. Thus, the long-term response is maximized by maximizing the product $N_e i$. Robertson showed that this generally occurs by *choosing half* ($p = 0.5$) *of the individuals*. Problem 3 lets you examine this in more detail.

Tests of Robertson's Theory

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

Observed limits and half-lives are usually considerably below the values predicted from Robertson's theory. Table 11.4 gives various results from experiments with mice. These discrepancies between observation and theory are not unexpected. Robertson's theory assumes that the limit is reached as genetic variance is exhausted by fixation at all loci. As we have seen, selection limits can occur in spite of significant additive genetic variance, often because natural and artificial selection are in conflict. Further, as we have stressed, the selection limit of $2N_e R(1)$ and half-life of $1.4N_e$ are

expected *upper* limits and require that drift largely dominates. An additional complication is that the effective population size is generally *overestimated* by simply taking the number of parents as N_e . For example, variation in male mating success in *Drosophila* can decrease the effective population size to less than half of the number of male parents (Crow and Morton 1955).

Table 11.4. Observed and predicted selection limits (scaled in terms of base-population phenotypic standard deviations) and half-lives (scaled in terms of N_e , giving an expected value of 1.4) for a variety of characters in laboratory populations of mice. From Falconer (1977), Eisen (1975), and Hanrahan et al. (1973).

Character Selected	Direction of Selection	Total Response			Half-life	
		Observed	Predicted	Ratio	Obs	Obs/Exp
Weight						
Strain N	Up	3.4	7.2	0.47	0.6	0.43
	Down	5.6	15.9	0.35	0.6	0.43
Strain Q	Up	3.9	15.8	0.27	0.2	0.14
	Down	3.6	9.6	0.38	0.4	0.29
Growth						
	Up	2.0	7.4	0.27	0.3	0.21
	Down	4.5	13.7	0.33	0.5	0.36
Litter Size						
	Up	1.2	2.3	0.52	0.5	0.36
	Down	0.5	7.7	0.06	0.5	0.36
Postweaning weight gain						
Line M4	Up	1.5	5.4	0.27	0.9	0.64
Line M8	Up	2.0	10.0	0.20	0.5	0.36
Line M16	Up	4.3	45.0	0.10	0.3	0.21

A more direct test of Robertson's theory is that the selection limit should increase, and half-life should decrease, as $N_e i$ increases. In general, both these predictions hold. For example, the estimated effective population sizes of lines M4, M8, and M16 in Table 11.4 are 7.7, 18.6, and 40.9, while each line experiences essentially the same value of i . (Eisen 1975). For this data set, half-life decreases as $N_e i$ increases as predicted by theory. In a more extensive experiment, Jones et al. (1968) examined the effects of changing N_e and/or i on otherwise replicate lines of *Drosophila melanogaster*. All their populations were still responding at the end of the experiment (50 generations), so the limit and half-lives could not be estimated. Nevertheless, the data (Table 11.5) are consistent with Robertson's qualitative predictions, as long-term response increases with $N_e i$ (Figure 11.6).

Table 11.5. The cumulative response after 50 generations of selection for increased abdominal bristle number in *Drosophila melanogaster* as a function of effective population size and selection intensity. N_e is estimated as half the number of parents. None of the lines showed an apparent plateau, but the experiment was stopped after 50 generations. After Jones et al. (1968).

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

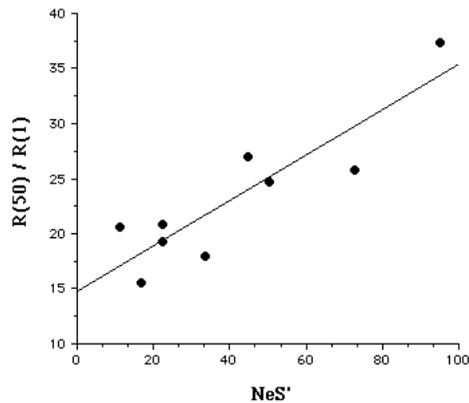


Figure 11.6. Cumulative response at generation 50 as a function of $N_e i$ for selection on increased abdominal bristle number in *Drosophila melanogaster*. After Jones et al. (1968).

Robertson's theory further predicts that when effective population is sufficiently large, further increases in N_e should not change the limit (provided mutational input can be ignored), as all favorable alleles initially present become fixed. This has yet to be observed, which is perhaps not surprising given that most experiments have N_e below 50. By designing ingenious devices to facilitate mass selection in *Drosophila melanogaster*, Weber and colleagues (Weber 1990, 1996; Weber and Diggins 1990) have been able to examine the consequences of larger population sizes. Selection experiments on wing-tip height (Weber 1990) and ethanol tolerance (Weber and Diggins 1990) had effective population sizes on the order of $N_e \simeq 200\text{--}400$. Both characters showed an increased response with increasing N_e . In general, the ratio of total response (after 50 generations) to initial response increases with N_e as predicted. The implication is that there is additional useable genetic variation present in the base population that can be exploited by increasing the strength of selection ($N_e i$). In very small populations, only major alleles are influenced by selection. That response continues to increase with N_e suggests that there is a large pool of loci of smaller effects. As $N_e i$ increases, favorable alleles at these loci are more likely to become fixed, increasing response. Larger populations also provide a greater chance for recombination to remove deleterious linked combinations, which might be fixed in smaller populations, further increasing the potential for response. One complication is that as population size increases, the contribution from mutational input becomes increasingly important over the time scales it takes to remove the initial variation. We will address this point shortly. A second complication is that when the character value is influenced by inbreeding depression (as would occur if directional dominance is present), over the same number of generations, the effects on inbreeding depression will be more dramatic in smaller populations. One test for whether inbreeding depression is reducing response is to cross divergently selected lines and look for significant changes in the mean in the resulting F_1 population (e.g., Eisen 1975, Kownacki 1979).

Weber's Selection Experiment on *Drosophila* Flight Speed

Perhaps the largest long-term artificial selection experiment (in terms of effective population size) is the heroic effort of Weber (1996), who scored a total of over 9,000,000 *Drosophila* for flight speed in two replicate lines subjected to 100 generations of selection. The resulting N_e was in the 500-1000 range, with a percent selected of $p = 0.045$ (for a selection intensity of $i = 2.11$). The average speed before selection was around 2 cm/second, while the mean speed at generation 100 was 170 cm/sec, and 200-220 cm/sec by generation 250. Response continued in both lines for 100 generations, but

was diminishing with time, as indicated by a significant quadratic component in the response curve. Around generations 220-250, the response appeared to plateau.

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

Finally, Weber gained some insight into the genetic nature of the response by examining the selection response in hybrid lines formed by crossing each replicate selection line at generation 75 (lines AA1 and AA2) back to control lines (CN1 and CN2). As Figure 17.7B shows, both the F_1 and F_2 were close to the control line values, indicating very strong dominance for reduced flight speed. Evidence for epistasis was more equivocal. From the theory of line cross analysis (LW Chapter 9), an estimate of composite epistatic effects is provided by the linear contrast of means of the parental and first two filial populations, $4\bar{z}_{F_2} - 2\bar{z}_{F_1} - \bar{z}_{P_1} - \bar{z}_{P_2}$, but the resulting value was not significantly different from zero (-38.5 ± 37.5). Selection on both resulting F_2 lines required only six generations to recover essentially all of the response seen in the 75-generation lines.

Variance In Response

Equation 11.12a gives the expected selection limit under drift, but there is also a variance about this expected expected limit. The variance (and indeed all higher moments) of the total response at the selection limit is easily computed, as the single locus contribution Δ takes on only two values,

$$\Delta = \begin{cases} 2a - m(q_0) & \text{with probability } u(q_0) \\ 0 - m(q_0) & \text{with probability } 1 - u(q_0) \end{cases} \quad (11.16)$$

In particular, the variance in response contributed by a given locus is

$$\sigma^2 [\Delta] = E [\Delta^2] - \left(E [\Delta] \right)^2 = 4a^2 u(q_0) [1 - u(q_0)] \quad (11.17)$$

With weak selection, $u_i(q_0) \simeq q_0$ (i.e., the allelic dynamics are governed by drift), implying

$$\sigma^2 [R^{(\infty)}] \simeq 4 \sum a^2 q_0 (1 - q_0) \quad (11.18)$$

If all loci are additive, this is simply $2\sigma_A^2(0)$, the expected between-line divergence under pure drift.

Under sufficiently strong selection, almost all favorable alleles are fixed and the variance is close to zero as $u(q_0) \simeq 1$. When selection is moderate to weak, then it is often the case that $u(q_0)[1 - u(q_0)] > q_0(1 - q_0)$, as the function $x(1 - x)$ is maximized (for $0 \leq x \leq 1$) when $x = 1/2$. If this condition holds over enough loci, then selection *increases* the between-line variance relative to drift.

The variance in the selection limit across replicate lines has a direct bearing on whether further response can occur by crossing plateaued lines and then reselecting. If drift has played a significant role in response, a line formed by crossing replicate plateaued lines should show further response to selection, as each line should be fixed for a considerable number of unfavorable alleles.

RESPONSE FROM MUTATIONAL INPUT

Given that both initial variation and new mutation can contribute to a selection response, we will use the term **long-term response** to refer to that component of the response expected from the initial variation in the population at the start of selection. Eventually, all the initial variation will be exhausted and the response from this component will have reached a selection limit. The actual response, however, can continue past this limit due to the input from new mutation, eventually reaching (under constant selection) an **asymptotic response**, wherein the response reaches a steady-state value when the contribution to the genetic variance from new mutation is balanced by its removal from drift and selection.

Contributions from New Mutation

There is strong evidence that new mutants contribute to response even over the short time scales of many “long-term” selection experiments. The apparent limit resulting from drift and selection removing all initial genetic variation is thus an artifact of time scale as it ignores this mutational contribution. Even if an observed limit is due to a balance between natural and artificial selection, new mutations with less deleterious pleiotropic effects on fitness can arise, resulting in further response.

If a rare recessive is initially present at low frequency, the appearance of homozygotes involving this allele may be taken as new mutations. If a recessive is present as a single copy, then the expected time until the first appearance of a homozygote is approximately $2N^{1/3}$ generations, with the distribution of appearance time being nearly geometric. Since for most selection experiments $N \leq 500$, any recessives initially present will be expressed as homozygotes by generation 15. For more typical values of population sizes, namely $N = 20, 50, \text{ and } 100$, the expected time is 6, 8, and 10 generations (respectively).

Mutational Response Under the Infinitesimal Model

Let σ_m^2 be the mutational variance (the per-generation contribution by mutation to the additive variance). The equilibrium additive variance under drift and mutation becomes $\tilde{\sigma}_A^2 = 2N_e\sigma_m^2$ (Lecture 7). Assuming the infinitesimal model, completely additive loci, and ignoring any effects of gametic-phase disequilibrium, the expected additive genetic variance at generation t is given by

$$\sigma_A^2(t) \simeq 2N_e\sigma_m^2 + [\sigma_A^2(0) - 2N_e\sigma_m^2] \exp(-t/2N_e) \quad (11.19)$$

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

$$\sigma_{A,m}^2(t) \simeq 2N_e\sigma_m^2 [1 - \exp(-t/2N_e)] \quad (11.20a)$$

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

$$r_m(t) = i \frac{\sigma_{A,m}^2(t)}{\sigma_z} \simeq 2N_e i \frac{\sigma_m^2}{\sigma_z} [1 - \exp(-t/2N_e)] \quad (11.20b)$$

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

$$\tilde{r}_m = 2N_e i \frac{\sigma_m^2}{\sigma_z} = i \frac{\tilde{\sigma}_A^2}{\sigma_z} \quad (11.21)$$

Assuming $\sigma_A^2(0) = 0$, half this rate occurs when $t \simeq 1.4N_e$ (Hill 1982a,b). One way to intuit the value of the asymptotic limit follows from Robertson's theory: we expect the final response to be $2N_e$ times the initial response $R(1)$, which for new mutants arising in any particular generation is $R(1) = i\sigma_m^2/\sigma_z$.

Summing over generations gives the cumulative response due to new mutation as

$$R_m^{(t)} = \sum_{\tau=1}^t r_m(\tau) \simeq 2N_e i \frac{\sigma_m^2}{\sigma_z} \left(t - 2N_e [1 - \exp(-t/2N_e)] \right) \quad (11.22a)$$

Combining the mutational response with the response due to genetic variation originally in the base population (Equation 11.14) gives an expected cumulative response of

$$R^{(t)} = 2N_e \frac{i}{\sigma_z} \left(t\sigma_m^2 + [1 - \exp(-t/2N_e)] [\sigma_A^2(0) - 2N_e\sigma_m^2] \right) \quad (11.22b)$$

The $t\sigma_m^2$ term, which represents the asymptotic response, will eventually dominate (i.e., for large t). The remaining term in the parentheses of Equation 11.22b represents the transient effect of the initial additive variance, and is zero if the population starts at the mutation-drift equilibrium (i.e., $\sigma_A^2(0) = 2N_e\sigma_m^2$).

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

$$\sigma_A^2(0) \exp(-t^*/2N_e) = 2N_e \sigma_m^2 [1 - \exp(-t^*/2N_e)] \quad (11.23)$$

This equation has the solution

$$t^* = 2N_e \ln(1 + \phi) \quad (11.24a)$$

where $\phi = \sigma_A^2(0)/(2N_e\sigma_m^2)$ is the ratio of the initial to the equilibrium additive variance. Denoting the initial heritability by h^2 , a little rearrangement gives

$$\phi = \frac{h^2}{(1 - h^2) 2N_e (\sigma_m^2/\sigma_E^2)} \quad (11.24b)$$

The average value of σ_m^2/σ_E^2 is approximately 0.005. Using this value, it is seen that t^* is only rather weakly dependent on N_e (see Figure 11.7). If $\phi \ll 1$, so that the expected additive variance at the mutation-drift equilibrium exceeds the initial additive variance ($\sigma_A^2(0) \ll 2N_e\sigma_m^2$), then using the approximation $\ln(1 + x) \simeq x$ for small $|x|$, we have

$$t^* \simeq 2N_e \phi = \frac{h^2}{(1 - h^2)(\sigma_m^2/\sigma_E^2)} \quad (11.24c)$$

Again using $\sigma_m^2/\sigma_E^2 = 0.005$ gives $t^* \simeq 200h^2/(1 - h^2)$. This translates into 11, 22, and 67 generations until the rate of response from mutational input exceeds the rate of response due to initial variation for h^2 values of 0.05, 0.10, and 0.25, respectively.

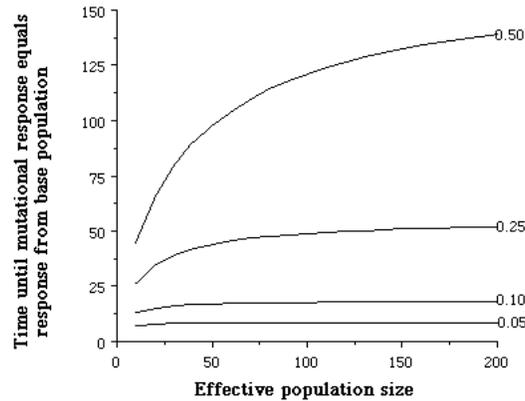


Figure 11.7: The expected generation at which response due to mutational input equals the response due to initial variation in the base population, assuming $\sigma_m^2/\sigma_E^2 = 0.005$. The four curves correspond to initial heritabilities of 0.05, 0.10, 0.25 and 0.50.

It is important to stress that Equation 11.24 for mutational half-life of response assumes that drift dominates and thus tends to overestimate the half-life when selection is moderate to strong. Likewise, we expect that the infinitesimal model underestimates the changes in allele frequencies of new mutants under moderate to strong selection. Thus, our expression for t^* is very likely an overestimate and we should regard Equation 11.24 as an upper bound.

Example 11.7. Yoo (1980a) observed a steady and reasonably constant increase in *Drosophila* abdominal bristle number over 80 generations of selection. In particular, he observed an increase of about 0.3 bristles per generation during generations 50 to 80. Assuming the infinitesimal model, how much of this response is due to mutational input? Yoo's base population had $\sigma_E^2 \simeq 4$, $\sigma_z^2 \simeq 5$, $h^2 \simeq 0.2$, $i \simeq 1.4$, and 50 pairs of parents were chosen each generation. Taking $\sigma_m^2/\sigma_E^2 \simeq 0.001$ (the average for abdominal bristles in LW Table 17.1) gives $\sigma_m^2 = 0.004$. Assuming $N_e \simeq 60$, the limiting mutational variance is

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

giving an expected asymptotic rate of response of

$$r = i \frac{\hat{\sigma}_A^2}{\hat{\sigma}_z} = i \frac{\hat{\sigma}_A^2}{\sqrt{\hat{\sigma}_A^2 + \sigma_E^2}} = 1.4 \cdot \frac{0.48}{\sqrt{4 + 0.48}} \simeq 0.32$$

This is very close to the observed rate of 0.3 bristles per generation (between generations 50 and 80). However, from Equation 11.205b the expected single-generation response from new mutational input at generation 60 is only

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

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

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

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

A complication with applying the above results is that the presence of major alleles both decreases the time to lose initial variation and increases the expected response from new mutants, resulting in a larger role for mutational input than predicted from the infinitesimal model. For example, if we assume that mutational input has reached its asymptotic value by generation 60, then the per-generation response from mutation is 0.32. Assuming the initial variation decays according to the infinitesimal model gives a total response of $0.38 + 0.32 = 0.70$, so that mutation now accounts for $0.32/0.70 = 46\%$ of the total response. However, when major genes are present, the initial variation declines even faster than predicted by Equation 11.14a, giving an even higher percentage of response from new mutations.

Lecture 11 Problems

1. Consider the following three loci and their genotypic values

	AA	Aa	aa	Freq(A)
Locus 1	2	1	0	0.3
Locus 2	2	2	0	0.3
Locus 3	2	0	0	0.3

For each locus compute the following

- a: The contribution to response (if fixed)
 - b: $p_{1/2}$, the allele frequency needed for half this total contribution
 - c: $t_{1/2}$, the time to reach $p_{1/2}$. (Assume $i = 1.4$ and $\sigma_z^2 = 100$).
2. Consider an additive QTL with $a = 1$, $\sigma_z^2 = 500$, and initial frequency $q_0 = 0.2$.
- a: If the selection intensity is $i = 1.5$, what value of N_e is needed to have a 99% probability that this allele is fixed. (*Hint*: You will likely need to use trait and error to solve the equations.)
 - b: If the effective population size is $N_e = 25$, what value of i is needed to have a 99% probability that this allele is fixed.
3. Suppose the initial variances are $\sigma_A^2 = 50$ and $\sigma_z^2 = 100$. Consider Robertson's selection limit when we start with 100 individuals and select different numbers. For this point of this exercise, take N_e as the number of selected individuals and simply use Equation 11.4 for i (i.e., ignore the finite-population size correction). Compute the initial response $R(1)$, the expected selection limit $R(\infty)$, and the half-life of response when 50, 25, 10, 5, and 2 individuals are selected. Which value gives the largest selection limit?
4. Suppose $N_e = 25$, $\sigma_m^2 = 0.025$, $\sigma_A^2(0) = 5$, $\sigma_z^2 = 100$, and $i = 1.4$.
- a: What is the initial response?
 - b: What is Robertson's selection limit?
 - c: What is the mutation-drift equilibrium variance.
 - d: At which generation does the mutational response equal the response from the genetic variation in the base population?
 - e: What is the expected total response at generation 250?

Solutions to Lecture 11 Problems

1a: From Table 11.1,

$$\begin{aligned} \text{Locus 1} \quad R &= 2a * (1 - p_0) = 2 * (1 - 0.3) = 1.4 \\ \text{Locus 2} \quad R &= 2a * (1 - p_0)^2 = 2 * (1 - 0.3)^2 = 0.98 \\ \text{Locus 3} \quad R &= 2a * (1 - p_0^2) = 2 * (1 - 0.3^2) = 1.82 \end{aligned}$$

1b: Again from Table 11.1,

$$\begin{aligned} \text{Locus 1} \quad p_{1/2} &= (1 + p_0)/2 = (1 + 0.3)/2 = 0.65 \\ \text{Locus 2} \quad p_{1/2} &= 1 - \sqrt{[1 - p_0(2 - p_0)]/2} = 1 - \sqrt{[1 - 0.3(2 - 0.3)]/2} = 0.51 \\ \text{Locus 3} \quad p_{1/2} &= \sqrt{(1 + p_0^2)/2} = \sqrt{(1 + 0.3^2)/2} = 0.74 \end{aligned}$$

1c: From Equation 11.4, $s = (a/\sigma_z)i = 1/\sqrt{100} \cdot 1.4 = 0.14$, so that $s^{-1} = 1/0.14 = 7.14$
For locus 1, Equation 11.5a gives

$$t_{p_0,p} \simeq s^{-1} \ln \left(\frac{p(1-p_0)}{p_0(1-p)} \right) = 7.14 \cdot \ln \left(\frac{0.65(1-0.3)}{0.3(1-0.65)} \right) = 10.5$$

For Locus 2, Equation 11.5c gives

$$\begin{aligned} t_{p_0,p} &\simeq s^{-1} \frac{1}{2} \left[\ln \left(\frac{p(1-p_0)}{p_0(1-p)} \right) + \frac{1}{1-p} - \frac{1}{1-p_0} \right] \\ &= 7.14 \cdot \frac{1}{2} \left[\ln \left(\frac{0.51(1-0.3)}{0.3(1-0.51)} \right) + \frac{1}{1-0.51} - \frac{1}{1-0.3} \right] = 15.5 \end{aligned}$$

For Locus 3, Equation 11.5b gives

$$\begin{aligned} t_{p_0,p} &\simeq s^{-1} \frac{1}{2} \left[\ln \left(\frac{p(1-p_0)}{p_0(1-p)} \right) - \frac{1}{p} + \frac{1}{p_0} \right] \\ &= 7.14 \cdot \frac{1}{2} \left[\ln \left(\frac{0.74(1-0.3)}{0.3(1-0.74)} \right) - \frac{1}{0.74} + \frac{1}{0.3} \right] = 23.4 \end{aligned}$$

2: Here $s = (a/\sigma_z)i = 1/\sqrt{500}i = 0.045i$, so that $4N_e s = 0.18 N_e i$ and $4N_e s q_0 = 0.036 N_e i$. Hence Equation 11.7a gives

$$u(q_0) \simeq \frac{1 - e^{-4N_e s q_0}}{1 - e^{-4N_e s}} = \frac{1 - e^{-0.036 N_e i}}{1 - e^{-0.18 N_e i}}$$

2a: We take $i = 1.4$ and need to solve for N_e in

$$0.99 = \frac{1 - e^{-0.036 N_e 1.4}}{1 - e^{-0.18 N_e 1.4}} = \frac{1 - e^{-0.0501 \cdot N_e}}{1 - e^{-0.252 \cdot N_e}}$$

Trying various values gives $N_e = 90$.

2b: We take $N_e = 25$ and need to solve for i in

$$0.99 = \frac{1 - e^{-0.036 \cdot 25 i}}{1 - e^{-0.18 \cdot 25 i}} = \frac{1 - e^{-0.9 \cdot i}}{1 - e^{-4.5 \cdot i}}$$

Trying various values gives $i = 4.7$.

3: Here $R(1) = h^2 \sigma_z i = 0.5 \cdot 10 \cdot i = 5i$, and a selection limit of $2N_e R(1) = 10N_e i$. We compute the selection intensity using Equation 9.14a, $i = \varphi(z_{[1-p]})/p$. We can quickly compute this in **R** using the command `dnorm(qnorm(1-p))/p`.

Number Saved	p	i	$R(1)$	$N_e R(1)$
50	0.50	0.80	4.0	200
25	0.25	1.27	6.36	159
10	0.10	1.75	8.78	87.8
5	0.05	2.07	10.3	51.5
2	0.02	2.42	12.1	24.2

4a: $R(1) = h^2 \sigma_z i = (5/100) \cdot 10 \cdot 1.4 = 0.7$

4b: $2N_e R(1) = 50 \cdot 0.7 = 35$

4c: $\widehat{\sigma}_A^2 = 2N_e \sigma_m^2 = 2 \cdot 25 \cdot 0.025 = 1.25$

4d: Using Equation 11.24

$$t = 2N_e \ln(1 + \phi), \quad \text{where} \quad \phi = \frac{\sigma_A^2(0)}{2N_e \sigma_m^2} = \frac{5}{1.25} = 4$$

giving

$$t = 50 \cdot \ln(5) = 35$$

4e: Using Equation 11.22b

$$R^{(t)} = 2N_e \frac{i}{\sigma_z} \left(t \sigma_m^2 + [1 - \exp(-t/2N_e)] [\sigma_A^2(0) - 2N_e \sigma_m^2] \right)$$

giving

$$R^{(250)} = 50 \frac{1.4}{10} (250 \cdot 0.025 + [1 - \exp(-250/50)] [5 - 1.25]) = 69.8$$

Note that if each generation had the same response as $R(1)$, the total response would have been 175. Likewise, if the response is entirely due to the equilibrium response under mutation-drift equilibrium ($\widehat{\sigma}_A^2 = 1.25$), the total response would have been 43.75.