18

Analysis of Short-Term Selection Experiments: 1. Least-Squares Approaches

To consult the statistician after an experiment is finished is often merely to ask him to conduct a post mortem examination. He can perhaps say what the experiment died of.
— Fisher (1938)

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This chapter examines the analysis of short-term selection experiments, whose duration is such that changes in allele frequency (from either selection and/or drift) are assumed to be negligible. While selected lines are often used in direct genetic/molecular analysis (e.g., QTL mapping using crosses between selected lines or tests of selection on specific loci/markers), these topics are discussed elsewhere (Chapter 9; LW Chapter 15). Our focus here is strictly on phenotypic effects. We further restrict attention to directional selection as our interest is in the change in mean and the goodness-of-fit of response to the breeder's equation. The bulk of the chapter consists of developing of least-squares (LS) estimates of **realized heritabilities** from the observed response and their standard errors. We also consider the empirical evidence for the goodness-of-fit of the breeder's equation to short-term artificial selection experiments. This followed by a discussion of experimental and optimal design, and the chapter concludes a detailed discussion of **generations means analysis**, the analysis of response when we can cross individuals from different cycles of selection (e.g., through the use of remnant seed).

Under the LS framework (LW Chapter 8), the only data required are sample means, which are usually straightforward to obtain, as single individuals need not be followed. Conversely, when one has access to the phenotypic values of essentially *all* of the individuals in the experiment as well as their complete pedigree, more powerful mixed-model (MM) methods can be used. These are discussed in Chapter 19, while Chapter 20 considers the analysis of response in the much more complex setting of natural populations, where there is little control over either the nature of selection or the environment.

The literature on selection experiments is truly massive, and our goal here is to introduce the important concepts, rather than to exhaustively review all experiments. Reviews of selection experiments include Wilson (1977), Wright (1977), Roberston (1980), Mather (1983), Hill (1984), Sheridan (1988), Hill and Mackay (1989), Eisen (1989), Falconer (1992), Hill and Caballero (1992), Garland and Rose (2009), and Hill (2011). Our focus here is on goodness-of-fit to the breeder's equation, while Chapters 25 and 26 review other empirical trends from long-term selection experiments.

VARIANCE IN SHORT-TERM RESPONSE

As we saw in Chapter 12, the means for a series of initially identical lines diverge over time through the action of genetic drift, generating a between-line variance. The same is true for lines under selection, with the between-line variance being manifested as **variation in response** (Figure 18.1). While the grand mean over a series of replicate lines under pure drift should essentially remain unchanged, the similar mean over a series of replicate selected lines should show a response over time, so that any particular realized response equals this expected response plus noise due to the evolutionary process of drift. Since artificial selection usually involves choosing a small number of parents to form the next generation,

this between-line variance can be considerible. As we saw in Chapter 12, drift also changes the additive variance within any given line. Our short-term assumption implies that $t/N_e \ll 1$, in which case drift can generate a significant between-line variance but with little within-line change in σ_A^2 (Chapters 11, 12). Our focus on short-term response assumes that selection has only a minor role in changing the genetic variance over the course of the experiment. This is the standard infinitesimal model assumption used throughout Chapters 13 – 18 (and relaxed in Chapters 24 – 27). One complication addressed later in the chapter is that selection decreases the additive genetic variance over the first few generations of directional selection by creating gametic-phase disequilibrium (Chapter 16).

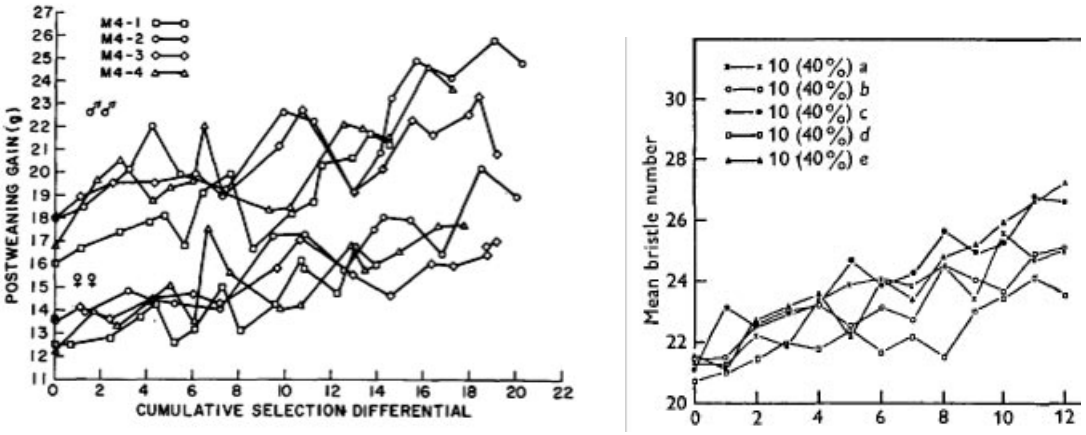


Figure 18.1. Examples of the variance in response to selection among replicate lines. **Left:** Postweaning weight gain in male and female mice (Hanrahan et al. 1973). Each replicate consists of a single family, propagated by selecting the largest pair within each family. **Right:** Abdominal bristle number in *Drosophila melanogaster* (Frankham et al. 1968). Here, 50 pairs of parents were scored and largest 10 of each sex were used to form the next generation. Note that these graphs differ in the way that response is plotted. On the left, response is given as a function of the **cumulative selection differential**, which has expected slope h^2 under the breeder's equation. On the right, response is a function of **number of generations**, which departs from a linear function when the strength of selection varies over time.

Expected Variance in Response Generated by Drift

The expected variation between the means of replicate lines subjected to the same amount of selection was first considered by Prout (1962) and in detail by Hill (1971; 1972c,d; 1974b; 1977; 1980; 1986). The variation between the sample means $\overline{z}_{t,i}$ of a series of replicate lines (in generation t) has two components: an **evolutionary variance** due to differences between the true means $\mu_{t,i}$ generated by drift and selection, and a sampling (or residual) variance from estimating the true mean $\mu_{t,i}$ by a sample mean $\overline{z}_{t,i}$ based on $M_{t,i}$ individuals. Chapter 12 examined these components under pure drift. How are these modified by the joint action of drift and selection? With selection, the M individuals are not chosen at random with respect to their phenotypes, which decreases the drift variance relative to pure drift. This is partly countered by selection generating a lower effective population size that expected from to drift alone (Chapters 3, 26). Further, selection can increase the between-line variance relative to drift by changing allele frequencies more rapidly than expected from drift alone. It is these opposing (and potentially offsetting) changes in variance that lead to suggestions that many of these effects cancel out, leaving the pure drift variance as an adequate approximation

(Robertson 1977; Hill 1977, 1980, 1986; Nicholas 1980). Simulations (Robertson 1977) and experimental results (Falconer 1973, López-Fanjul 1982) suggest this is not an unreasonable approximation.

Using the pure drift results (Chapter 12), the sample mean in generation t for a particular realization (line) can be decomposed as

$$\overline{z}_t = \mu_t + e_t, \tag{18.1a}$$

where μ_t is the true mean of this line and e_t the residual error in estimating this true mean from a population sample. The true mean can be further decomposed as

$$\mu_t = \mu + g_t + d_t \tag{18.1b}$$

where g_t is the mean breeding value and d_t the mean environmental deviation in generation t, giving expected value for the sample mean of a random line in generation t as

$$E(\,\overline{z}_t\,) = \mu + E(\,g_t\,) + d_t \tag{18.2}$$

Under pure drift, $E(g_t) = 0$, while under selection $E(g_t)$ is given by the breeder's equation, $\sum_i^t h_i^2 S_i = th^2 S$ if heritability and selection differential remain constant (given the usual caveats summarized in Table 13.2). The variance about this expected value is

$$\sigma^2_{\overline{z}}(t) = \sigma^2_g(t) + \sigma^2_e(t) + \sigma^2_d. \tag{18.3}$$

As discussed later in the chapter, comparison between contemporaneous populations, such as a selected and control line in the same generation or between an up- versus down-selected line, can remove the shared environmental effect and hence the σ^2_d term.

Given our previous comments, we assume the evolutionary sampling variance $\sigma^2_g(t)$ about the mean breeding value for selected lines is to a good approximation the same as that for lines under drift alone. If M_0 individuals are initially sampled to form each line, then from Equation 12.1,

$$\sigma^2_g(t) = \left(\frac{1}{M_0} + 2f_t\right) h^2\sigma^2_z \tag{18.4}$$

The M_0 term accounts for variation in mean breeding value between lines in the founding generation, while f_t (the amount of inbreeding at generation t) accounts for variation generated by subsequent drift. If population size remains constant,

$$2f_t = 2\left[1 - \left(1 - \frac{1}{2N_e}\right)^t\right] \simeq t/N_e \qquad \text{for } t/N_e \ll 1 \tag{18.5}$$

If different numbers of males (N_m) and females (N_f) are sampled and/or N varies over time,

$$2f_t \simeq \sum_{i=0}^{t-1}\left[\frac{1}{4N_m(i)} + \frac{1}{4N_f(i)}\right] \tag{18.6}$$

The variance $\sigma^2_e(t)$ associated with estimating the true mean from a sample mean depends on the relatedness among the M_t individuals chosen to estimate the mean. If these are unrelated, then $\sigma^2_e(t) = \sigma^2_z(t)/M_t$. If some of are related (such as from the same family), the positive covariance between then reduces the sample variance, with the exact form of

σ_e^2 depending on the distribution of family sizes within the sample. Hill (1971, 1980) shows that it is bounded by

$$\frac{\sigma_z^2 - \sigma_A^2/2}{M_t} \leq \sigma_e^2(t) \leq \frac{\sigma_z^2}{M_t}, \tag{18.7}$$

which corresponds to the range where all individuals are from the same family (lower bound) to all being unrelated (upper bound). Conservatively choosing the upper bound, Equation 18.3 becomes

$$\sigma_{\overline{z}}^2(t) = \left(\frac{1}{M_0} + 2f_t\right) h^2\sigma_z^2 + \sigma_d^2 + \sigma_z^2/M_t \tag{18.8}$$

Since drift variance accumulates each generation (via f_t increasing each generation) while the other variance coefficients do not change, when $h^2\sigma_z^2 > \sigma_d^2$, the drift term is expected to eventually dominate, usually after a few generations. The careful reader will notice that neither h^2 or σ_z^2 are indexed by generation, and hence assumed to be constant in keeping with our assumption that these remain essentially unchanged over the short time course of the experiment.

Equation 18.8 describes the divergence *between* lines due to drift. Drift also introduces a positive correlation between the means at different generations *within* a line (Equation 12.2),

$$\sigma(g_t, g_{t'}) = \left(\frac{1}{M_0} + 2f_t\right) h^2\sigma_z^2 \quad \text{for } t < t' \tag{18.9}$$

Assuming that cross-generational environmental and residual effects are uncorrelated, so that $\sigma(d_t, d_{t'}) = \sigma(e_t, e_{t'}) = 0$, then $\sigma(\overline{z}_t, \overline{z}_{t'}) = \sigma(g_t, g_{t'})$.

The assumption that σ_A^2 and σ_z^2 remain constant is a major one and can be violated in several ways. First, changes in the underlying allele frequencies can change these variances (Chapters 5, 24-27). If major alleles are segregating, large changes in the variance can occur within a few generations. A further complication is that sampling to create lines from a base population where major alleles are segregating at low frequencies can result in a substantial increase in the between-line variance over that predicted by Equation 18.4, as these alleles are lost in some lines and increase in frequency in others. This results in lines sampled from the same base having a larger range of starting additive variances, increasing the variance in response (James 1970).

Second, directional selection generates negative gametic-phase disequilibrium, reducing the additive genetic variance within a line over the first few generations before reaching an equilibrium value (Chapter 16). We will deal with this shortly. Third, inbreeding due to finite population size reduces additive genetic variance within a line. For a completely additive locus, the expected additive genetic variance (in the absence of mutational input) within a line in generation t is given by Equation 11.2,

$$\sigma_A^2(t) = \left(1 - \frac{1}{2N_e}\right)^t \sigma_A^2(0) \simeq \left(1 - \frac{t}{2N_e}\right) \sigma_A^2(0), \quad \text{for} \quad t \ll N_e$$

where $\sigma_A^2(0)$ is the variance in the base population. If dominance and/or epistasis is present, the within-line variance can actually increase under drift (Chapter 11), further inflating the between-line variance. Provided $t/2N_e \ll 1$, the error introduced in Equations 18.8 and 18.9 by ignoring the reduction in the within-line variance due to inbreeding is small. A related complication is that drift generates between-line variance in σ_A^2 itself (Chapter 12), further inflating the between-line variance in means. Finally, when there is heritable variation in the environmental variance, σ_E^2 is expected to increase under moderate to strong directional selection (Chapter 17), increasing σ_z^2 and thus decreasing h^2.

Despite all these potential complications, those few experimental tests of the pure-drift approximation have found it to be fairly reasonably (Falconer 1973, López-Fanjul 1982). Mixed-model (REML/BLUP) methods developed in LW Chapters 26 and 27 (reviewed here in Chapter 19) account for some of these concerns, but as mentioned require significantly more information (the values of all individuals, and their complete pedigree), which may be difficult to obtain.

Variance in Predicted Response vs. Variance in Response

It is important not to confuse the above expressions for variance in response (the variation about the mean response when the genetic parameters and selection differential are *known without error*) with variance in the *predicted* response, which has (at least) two additional sources of variation. The first is the uncertainty produced by using estimates in place of the true values for the genetic and phenotypic variances. The second is uncertainly in the realized selection intensity. While selecting a set fraction p of the population to save specifies the *expected* selection intensity, there is variation about this mean value for any particular realization (Chapter 14). For example, *before* the selection is performed, we expect that truncation selection saving the uppermost 5% has an *average* selection intensity of 2.06 (Example 14.1). However, when selecting the largest 5% from a small population, its realized value can be significantly large , or smaller, generating variation in the predicted response. Several papers (Tai 1979, Knapp et al. 1989, Bridges et al. 1991) have presented confidence intervals for the expected selection response, but these simply focus on the variance given uncertainty in the initial estimates of additive and phenotypic variances. They do not consider the additional variance in response (even if we knew the true genetic parameters) nor do they consider the variance in the particular realization of a pre-specified selection intensity.

ESTIMATION OF REALIZED HERITABILITIES

The breeder's equation $R = h^2 S$ immediately suggests that heritability can be estimated as the ratio of observed response to observed selection differential,

$$\widehat{h}_r^2 = \frac{R}{S}. \tag{18.10}$$

Falconer (1954) referred to Equation 18.10 as the **realized heritability**, a term now more broadly defined to include any estimate of heritability based on the observed response to selection.

While one can use this approach to estimate h^2, any complication in predicting response using the breeder's equation (Table 13.2) will usually make $\widehat{h}_r^2$ a biased estimator. Turning this point around suggests that one test for the success of the breeder's equation is to compare how close realized heritabilities are to estimates based on resemblance between relatives in the unselected base population. If the breeder's equation generally provides an accurate model of selection response, we expect these two different estimates to be similar (i.e., within sampling error).

Example 18.1. An interesting example of applying artifical selection in a natural setting is Flux and Flux (1982), who examined response on clutch size in starlings (*Sturnus vulgaris*) in New Zealand. Eggs were laid almost exclusively in nest boxes, allowing for identification of the mothers and careful monitoring of their offspring. Increased clutch size was selected by removing all eggs from clutches below a specified brood size (artifical truncation selection on clutch size). Lumping results from the entire study, the 516 clutches from the offspring of

selected females had an average size of 5.60 $\pm$ 0.04, while the average size of 2050 clutches from offspring of unselected females was 5.48 $\pm$ 0.02, giving an estimated response of R = 0.12 $\pm$ 0.04. The mean clutch size of selected female parents was 6.20 versus 5.48 for unselected (control) females, giving S_f = 0.72. Since there is no selection on fathers under this design, $S = S_f/2$ (Chapter 13), giving the expected response in daughters as $R = h^2\, S_f/2$, and a realized heritability of

$$\widehat{h}_r^2 = 2R/S_f = 2 \cdot 0.12/0.72 = 0.33,$$

in good agreement with the estimated heritability based on mother-daughter regressions of $\widehat{h}^{\,2}$ = 0.34 $\pm$ 0.08.

Estimators for Several Generations of Selection

While the estimator given by Equation 18.10 is unambiguous for a single generation of selection, two different estimates have been proposed when several generations are considered. Both are based on the **cumulative selection response** $R_C(t)$ and **cumulative selection differential** $S_C(t)$,

$$S_C(t) = \sum_{i=1}^{t} S_i \qquad \text{and} \qquad R_C(t) = \sum_{i=1}^{t} R_i \tag{18.11}$$

where $S_i = \overline{z}_i^{\,*} - \overline{z}_i$ and $R_i = \overline{z}_{i+1} - \overline{z}_i$ are the selection differential and single-generation response (respectively) for generation i.

For an experiment of lenght T generations, the simple **ratio estimator** of the realized heritability is the total response divided by the total differential,

$$\widehat{b}_T = \frac{R_C(T)}{S_C(T)} \tag{18.12}$$

We use the notation throughout the chapter of $\widehat{b}_x$ for a particular estimator, as the realized heritability is some multiple of this, $\widehat{h}_r^2 = c \cdot \widehat{b}_x$, where c depends on the experimental design. With individual selection with only one sex selected, $c = 2$ (Example 18.1), while $c = 1$ when both sexes are selected.

The ratio estimator makes no assumption about a constant heritability, returning an average value over the experiment. In contrast, the linear response in S predicted by breeder's equation leads to an alternative (and much more widely used) approach of estimating the slope of the regression of cumulative response on cumulative selection differential,

$$R_C(t) = b_C S_C(t) + e_t \quad \text{ for } t = 1, \cdots, T \tag{18.13}$$

with $\widehat{h}_r^2 = b_C$ for individual selection on both sexes (Falconer 1954). Modifications of the approach can be used for family selection (Chapter 21) and other designs, such as divergent selection (discussed at the end of this chapter). Since the expected response is zero if there is no selection, the regression line is constrained to pass through the origin and hence lacks an intercept term. Standard (LW Chapter 8) linear model approaches can be used to test for goodness-of-fit, such as testing whether a quadratic regression gives an improved fit (suggesting a changing heritability).

Recall from LW Chapter 8 that regression estimator depends on the assumed covariance structure of the residuals. Most uses of the regression estimator (Equation 18.13) in the literature have assumed ordinary least squares (OLS), which requires that the residuals e_t are homoscedastic and uncorrelated (LW Chapter 8). However, the careful reader will note

from Equations 18.4 and 18.9 the drift generates heteroscedastic and correlated residuals, requiring a generalized least squares (GLS) solution (LW Chapter 8). We return to this shortly.

Recalling LW Equation 8.33a, the OLS estimator for the slope is $\left(\mathbf{X}^T\mathbf{X}\right)^{-1}\mathbf{X}^T\mathbf{y}$. Since the design matrix $\mathbf{X}$ for the regression given by Equation 18.13 is just the vector of cumulative selection differentials $\mathbf{S}$ and $\mathbf{y}$ is the vector of cumulative responses $\mathbf{R}$, it follows that the OLS estimate of the slope is given by

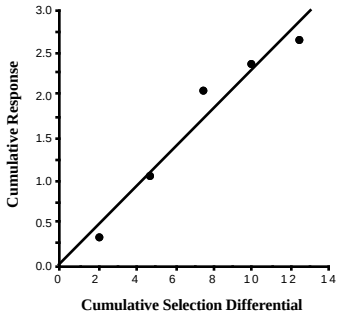
$$\widehat{b}_C(\text{OLS}) = \left(\mathbf{S}^T\mathbf{S}\right)^{-1}\mathbf{S}^T\,\mathbf{R} = \frac{\sum_{i=1}^{T} S_C(i)\cdot R_C(i)}{\sum_{i=1}^{T} S_C^2(i)} \tag{18.14}$$

We will refer to this as the **OLS regression estimator** of the realized heritability. While this is the most common approach used in the literature, by assuming the wrong residual error structure it significantly *underestimates* the standard error for the slope. Richardson et al. (1968) and Irgang et al. (1985) noted that when the number of individuals M_t used to obtain the sample mean varies over generations, that those points based on more individuals contant more information and smaller residual errors. In this setting, the residual variances (roughly σ_z^2/M_t) are no longer homoscedastic, with these authors suggestion that a simple weighted least-squares method (e.g., LW Example 8.11) be used to correct for this. While an improvement over OLS, this approach still ignores the very significant impact from correlations and heteroscedasticity in the residual errors generated by drift.

Example 18.2. Consider the following data from Mackay (1985), who performed a divergent selection experiment on abdominal bristle number in replicate lines of *Drosophila melanogaster*. Fifty males and fifty females were measured in each line, with ten of each sex selected to form the next generation. Her data for the High (up-selected) line from replicate pair 2 for the first five generations of selection are

t	$\overline{z}$	$\overline{z}^*$	$S(t)$	$R(t)$	$S_C(t)$	$R_C(t)$
1	18.02	20.10	20.10−18.02 = 2.08	18.34−18.02 = 0.32	2.08	0.32
2	18.34	21.00	21.00−18.34 = 2.66	19.05−18.34 = 0.71	4.74	1.03
3	19.05	21.75	21.75−19.05 = 2.70	20.07−19.05 = 1.02	8.44	2.05
4	20.07	22.55	22.55−20.07 = 2.48	20.36−20.07 = 0.29	9.92	2.34
5	20.36	22.95	22.95−20.36 = 2.59	20.65−20.36 = 0.29	12.51	2.63
6	20.65					

The ratio estimate of the realized heritability (Equation 18.12) is $\widehat{h}_r^2 = 2.63/12.51 = 0.2102$.



The regression, forced through the origin, of cumulative response (R_C) on cumulative selection differential (S_C) is plotted above. Equation 18.14 gives the OLS regression estimator of

the realized heritability as

$$\widehat{h}_r^2 = \widehat{b}_C(OLS) = \frac{\sum_{i=1}^{5} S_C(i) \cdot R_C(i)}{\sum_{i=1}^{5} S_C^2(i)} = \frac{78.96}{350.45} = 0.2245$$

The theory for estimating realized heritabilities (via a LS analysis) in populations with overlapping generations is less well developed. As will be discussed in volume 3, approaches assuming an asymptotic selection response are flawed in that many generations are required to reach a stable genetic structure starting from an unselected base population. For non-asymptotic response, see Hill (1974a) and Johnson (1977) for the relevant theory and Atkins and Thompson (1986) for an example with Scottish Blackface sheep. Mixed-model approaches (Chapter 19) easily accommodate overlapping generations.

Weighted Least-Squares Estimates of Realized Heritability

Ordinary least-squares regression assumes that the residuals are homoscedastic and uncorrelated, giving the covariance matrix for the vector of residuals $\mathbf{e}$ as Var($\mathbf{e}$) = $\sigma_e^2 \cdot \mathbf{I}$ (LW Chapter 8). Genetic drift causes the covariance structure of the regression given by Equation 18.13 to depart significantly from this simple form. In particular, the residual variance increases with time (Equation 18.8) and residuals from different generations are correlated (Equation 18.9). Thus, Var($\mathbf{e}$) = $\mathbf{V}$ (rather than $\sigma_e^2 \cdot \mathbf{I}$) and generalized least-squares (GLS) must be used to account for this covariance structure. From LW Equation 8.34, the GLS estimator of the regression slope is given by

$$\widehat{b}_C(\text{GLS}) = (\mathbf{S}^T\mathbf{V}^{-1}\mathbf{S})^{-1}\mathbf{S}^T\mathbf{V}^{-1}\mathbf{R} \tag{18.15a}$$

where $\mathbf{V}$ is the variance-covariance matrix associated with selection response,

$$V_{ij} = \sigma_e(i,j) = \sigma\,[\,R_C(i), R_C(j)\,] \tag{18.15b}$$

The elements of $\mathbf{V}$ can be obtained from the pure-drift approximation, with the variances V_{ii} given by Equation 18.8 and covariances V_{ij} given by Equation 18.9,

$$V_{ij} = \begin{cases} \left(\frac{1}{M_0} + 2f_i\right) h^2\sigma_z^2 + \sigma_z^2/M_i & \text{for } i = j \\ \left(\frac{1}{M_0} + 2f_i\right) h^2\sigma_z^2 & \text{for } i < j \end{cases} \tag{18.15c}$$

where $2f_i \simeq i/N_e$ (Equation 18.5). If differences in environmental values across generations are not accommodated by the design, then V_{ii} has an additional term σ_d^2 . Even though OLS assumes an incorrect residual structure, it still provides an unbiased estimate of b_C. However, *OLS significantly underestimates the standard error*, and it is this reason that GLS estimators are greatly preferred and should be used when possible (Hill 1971; 1972c,d; 1974b; 1977; 1980; 1986).

Example 18.3. Computing the GLS regression using the data from Example 18.2 requires the variance-covariance matrix $\mathbf{V}$ of the residuals, which is obtained using the pure-drift approximation. From Example 18.2, $M = 100$, $N = 20$, while the estimated phenotypic

variance is Var(z) = 3.293 (Mackay, personal communication). Assuming that both initial sampling and between-generation environmental effects can be ignored (i.e., $M_0 >> 1$ and $\sigma_d^2 \simeq 0$), Equations 18.8 and 18.5, give the variance associated with the response in generation i as:

$$V_{ii} = 2f_i h^2 \sigma_z^2 + \sigma_z^2/M_i = \left(\frac{i}{N}\right) h^2 \sigma_z^2 + \frac{\sigma_z^2}{M} = 0.1647 \cdot (i \cdot h^2 + 0.2)$$

Similarly, Equations 18.9 and 18.5 give the covariance between generations as

$$V_{ij} = \left(\frac{i}{N}\right) h^2 \sigma_z^2 = i \cdot h^2 \cdot 0.1647 \qquad \text{for } i < j$$

The resuling covariance matrix becomes

$$\mathbf{V} = 0.1647 \cdot \begin{pmatrix} h^2+0.2 & h^2 & h^2 & h^2 & h^2 \\ h^2 & 2h^2+0.2 & 2h^2 & 2h^2 & 2h^2 \\ h^2 & 2h^2 & 3h^2+0.2 & 3h^2 & 3h^2 \\ h^2 & 2h^2 & 3h^2 & 4h^2+0.2 & 4h^2 \\ h^2 & 2h^2 & 3h^2 & 4h^2 & 5h^2+0.2 \end{pmatrix}$$

Since the matrix $\mathbf{V}$ is a function of the unknown heritability, estimation is an iterative process. Starting with some initial estimate of h^2, each new h_r^2 estimate is used to update $\mathbf{V}$ in subsequent iterations until convergence. Using the ratio estimator $h^2 = 0.21$ as the starting value, Equation 18.15 gives a first estimate as

$$\widehat{b}_C(GLS)^{(1)} = (\mathbf{S}^T \mathbf{V}^{-1} \mathbf{S})^{-1} \mathbf{S}^T \mathbf{V}^{-1} \mathbf{R} = 0.222197$$

Substituting this new estimate of h^2 into $\mathbf{V}$ gives upon a second iteration $\widehat{b}_C(GLS)^{(2)} = 0.222135$, which remains unchanged in subsequent iterations.

Standard Errors for Realized Heritability Estimates

The final piece of statistical machinery necessary for assessing the success of the breeder's equation are the standard errors associated with the different realized heritability estimates. Consider first the realized heritability estimated from the unweighted regression (Equation 18.14). Recalling LW Equation 8.33b for the variance for an OLS estimator,

$$\text{Var}\left[\widehat{b}_C(\text{OLS})\right] = \sigma_e^2 \left(\mathbf{X}^T \mathbf{X}\right)^{-1} = \sigma_e^2 \left(\mathbf{S}^T \mathbf{S}\right)^{-1} = \sigma_e^2 \Big/ \sum_{i=1}^{T} S_C^2(i) \tag{18.16a}$$

The residual variance σ_e^2 can be estimated from the residual sums of squares divided by the degrees of freedom (see LW Chapter 8). For an experiment lasting T generations,

$$\widehat{\sigma}_e^2 = \frac{1}{T-1} \sum_{i=1}^{T} \widehat{e}_i^2 = \frac{1}{T-1} \sum_{i=1}^{T} \Big(R_C(i) - \widehat{h}_r^2 \, S_C(i) \Big)^2 \tag{18.16b}$$

As mentioned, because the OLS estimator assumes residuals are uncorrelated and have equal variances (both of which are incorrect), it significantly *underestimates* the correct variance (Example 18.4). The GLS regression estimator (Equation 18.15) avoids these problems

by properly accounting for the residual variance structure generated by drift. From standard GLS theory (LW Equation 8.35),

$$\text{Var}\left[\widehat{b}_C(\text{GLS})\right] = (\mathbf{S}^T\mathbf{V}^{-1}\mathbf{S})^{-1} \tag{18.17}$$

As above, the pure drift approximation is used to obtain the elements of $\mathbf{V}$, with $\widehat{h}_r^2$ used in place of h^2.

Finally, consider the variance for the estimator b_T, the ratio of total response to total selection (Equation 18.12). Since Var(y/c) = Var(y)/c^2 for a constant c, it immediately follows that

$$\text{Var}(\,\widehat{b}_T) = \frac{\text{Var}\,[R_C(T)]}{S_C^2(T)} \simeq \frac{(T/N)\,\widehat{h}_r^2\,\sigma_z^2 + \sigma_z^2/M}{S_C^2(T)} \tag{18.18}$$

The numerator (the variance in response in Generation T) follows from the pure-drift approximation (Equation 18.8), assuming that initial sampling can be ignored (e.g., $M_0 \gg 1$) and no significant between-generation enviromental variance ($\sigma_d^2 = 0$).

Hill (1972c,d) noted that $\widehat{b}_C$(GLS) is generally a slightly better estimator (i.e., returning a smaller standard error) than $\widehat{b}_T$ when h^2 is small, while $\widehat{b}_T$ is slightly better estimator when h^2 and/or the number of generations is large.

Example 18.4. Using the data from Examples 18.2 and 18.3, compare the standard errors associated with the three different realized heritability estimates. Consider the unweighted regression estimator $\widehat{b}_C$(OLS) first. The residual sums of squares is

$$\sum_{i=1}^{T}\Big(\,R_C(i) - \widehat{h}_r^2 S_C(i)\,\Big)^2 = 0.091$$

giving an estimated residual variance of $\widehat{\sigma}_e^2 = 0.091/4 = 0.0228$. Equation 18.16a gives

$$\text{Var}\left[\,\widehat{b}_C(\text{OLS})\,\right] = \sigma_e^2 \Big/ \sum_{i=1}^{T} S_C^2(i) = \frac{0.0228}{350.45} = 0.0000649$$

Taking the square root gives the standard error as 0.0081. Turning to the estimate $\widehat{b}_T$ based on the total response to total selection, Equation 18.18 gives

$$\text{Var}(\,\widehat{b}_T\,) = \frac{(5/20)\cdot 0.21\cdot 3.292 + 0.03292}{12.51^2} = 0.00132$$

for a standard error of 0.0363. Finally, substituting the GLS estimate of $\widehat{h}_r^2 = 0.222135$ in $\mathbf{V}$ (Example 18.3), Equation 18.17 gives variance of this estimate as $(\mathbf{S}^T\mathbf{V}^{-1}\mathbf{S})^{-1} = 1/790.4$, for a standard error of 0.0356.

Summarizing, the three approaches give extremely similar estimates,

Unweighted least-squares regression, $\widehat{b}_C$(OLS)	$\widehat{h}_r^2 = 0.2245 \pm 0.0081$
Total response/total differential, $\widehat{b}_T$	$\widehat{h}_r^2 = 0.2102 \pm 0.0363$
Weighted least-squares regression, $\widehat{b}_C$(GLS)	$\widehat{h}_r^2 = 0.2221 \pm 0.0356$

Note that the difference in the standard error between $\widehat{b}_C$(GLS) and $\widehat{b}_T$ is very small, with $\widehat{b}_T$ considerably more straightforward to compute. Also note that the unweighted regression badly underestimates the standard error, being four-fold smaller that the other two standard errors.

Power: Estimation of h^2 from Relatives or Selection Response?

Estimates of heritability from relatives are based on variance components (e.g., LW Chapters 17 and 18) , while estimates from selection response are based on ratios of means. Thus, one might expect that realized heritability estimates may have greater power than those based on relatives. Is this indeed the case? Consider the sampling variance for the simple ratio estimator, the total response over the total differential (Equation 18.12). Equation 18.18 gives its sample variance as

$$\text{Var}(\widehat{h}_r^{\,2}) = \frac{\text{Var}\,[R_C(T)]}{S_C^2(T)} \simeq \frac{(T/N)\,\widehat{h}_r^2\,\sigma_z^2 + \sigma_z^2/M}{S_C^2(T)} = \frac{(T/N)\,\widehat{h}_r^2 + 1/M}{S_C^2(T)/\sigma_z^2}$$

where T is the number of generations, and M individuals are measured with the most extreme N of these allowed to reproduce. Suppose that the strength of selection is the same each generation, so that the selection differential is essentially constant at S, giving

$$S_C^2(T)/\sigma_z^2 = \sum_{i=1}^{T} S_i^2/\sigma_z^2 = T\,S^2/\sigma_z^2 = T \cdot \overline{\imath}^{\,2}$$

and hence

$$\text{Var}(\widehat{h}_r^{\,2}) \simeq \frac{(T/N)\,\widehat{h}_r^2 + 1/M}{T \cdot \overline{\imath}^{\,2}} = \frac{(1/N)\,\widehat{h}_r^2 + 1/(TM)}{\overline{\imath}^{\,2}} \simeq \frac{\widehat{h}_r^2}{N\,\overline{\imath}^{\,2}} \tag{18.19}$$

The optimal midparent-offspring design (N sets of parents each with a single offspring) has (LW Equation 17.11b) standard error

$$\text{SE}(h^2_{mp}) = \left(\frac{2-h^4}{N}\right)^{1/2}$$

This gives the ratio of sampling variances for the two estimators as

$$\frac{\text{Var}(h^2_{mp})}{\text{Var}(\widehat{h}_r^{\,2})} \simeq \frac{(2-h^4)/N}{h^2/(\,N\,\overline{\imath}^{\,2}\,)} = \overline{\imath}^{\,2}\left(\frac{2-h^4}{h^2}\right) \tag{18.20}$$

This ratio is largest when the heritability is small (Figure 18.2), and increases with the strength of selection $\overline{\imath}$. Equation 14.3a shows that if more than 38% of the population is saved, then $\overline{\imath} < 1$. Thus, if selection is too weak, the inherent advantage of using a realized heritability is diminished.

While Equation 18.20 seems fairly conclusive, a key point is in order. We measure M adults each generation, and let N of these reproduce. Hence, if the limit in our system is raising offspring, then the comparison of N midparents with N adults allowed to reproduce is a fair one. However, if the limit in our system is the actual *measurement* of individuals, then the fair comparison should be designs based on M measured adults vs. M midparents. The tradeoff here is trying to maximize the product $N\,\overline{\imath}^2$ for a fixed M, as increasing selection decreases N but increases $\overline{\imath}$ (Example 18.5).

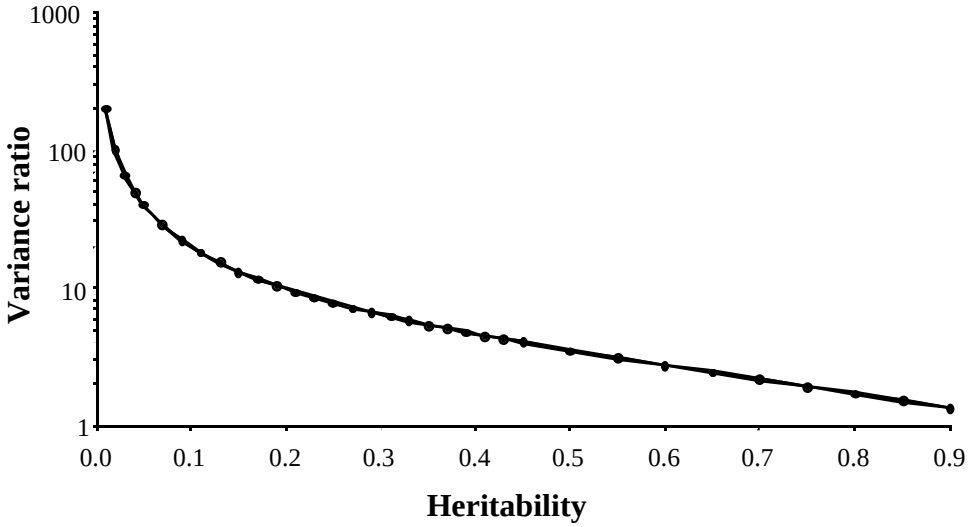


Figure 18.2. Ratio of sample variances Var(h^2_{mp})/Var($\widehat{h}^2_r$) (measured in units of $\overline{i}^{\,2}$, the squared selection intensity) as a function of the true heritability (Equation 18.20). For small values of h^2, realized heritability estimates have a much smaller variance, with the ratio of the midparent regression vs. realized heritability sample variances being approximately $2\,\overline{i}^{\,2}/h^2$.

Example 18.5. Suppose we have a trait with a true heritability of $h^2 = 0.30$ that is expensive to measure, while offspring are inexpensive to rear. Suppose we have funds to measure 3000 individuals, so that two possible designs are to measure 1000 midparent-offspring trios versus measuring a total of 3000 individuals over the course of a selection experiment. The expected standard error for the midparent-offspring regression (LW Equation 17.11b) is

$$\text{SE}(h^2_{mp}) = \sqrt{\frac{2-h^4}{N}} = \sqrt{\frac{2-0.30^2}{1000}} = 0.044$$

For a T-generation selection experiment, we have $T \cdot M = 3000$ as the design constraint. Thus, if we measure M initial parents to select the most extreme N, and do this for six generations (parents = generation 0, generations 1, 2, 3, 4, 5), we measure 3000/6 = 500 each generation. Consider three different designs, with N = 250 (50% selected), 100 (20%), and 25 (5%). Applying Equation 14.3a, these correspond to selection intensities (not correcting for finite population size) of $\overline{i}$ = 0.80, 1.40, and 2.06. From Equation 18.19, the standard errors are given by

$$\sqrt{\frac{h^2}{N\,\overline{i}^{\,2}}}$$

or 0.043 , 0.039, and 0.053 (for 250, 100, and 50, respectively). Thus, for N = 250, both designs (midparent regression and selection) have essentially the same sample variance, while selection is better for N = 100 and worse for the strongest selection (N = 50).

There are a few final caveats in using a realized heritability estimator in place of a more traditional relative-based estimator. Clearly, if any of the assumptions of the basic breeder's equation (Table 13.2) are violated, we obtain a biased estimator. A more subtle issue is what

is the target population for the heritability estimate — the entire population or some subset? Skibinski and Shereif (1989) initiated lines for selection on sternopleural bristle number in *Drosophila melanogaster* by (i) taking parents from the central part of the distribution vs. (ii) taking parents with extreme high or low bristle number. The populations founded from the central part of the distribution had higher heritabilities, and larger response, than lines founded from the extremes of the distribution. This is not expected under the infinitesimal model (Chapter 24), but *is* expected if there are alleles of finite effect segregating in the population. Thus, the subtle point is that realized heritability estimates may actually be sampling a different part of the population than relative-based estimators (this was also stressed in Chapter 6, see Equations 6.38, 6.39). For example, if we sample rare alleles of large effect, then these will rapidly increase in selected populations, inflating the heritability.

Empirical vs. Predicted Standard Errors

While the standard error in response can be directly estimated from the between-line variance in a series of replicate lines subjected to identical selection, this approach is generally not cost-effective given the large standard error on such estimates (Chapter 12). As a result, the standard errors reported for most experiments use the pure-drift approximation discussed previously. How closely do the empiricial (observed) standard errors match those predicted from the drift approximation? Unfortunately, very few experiments have addressed this issue, and those few that do often use OLS-generated standard errors, which are too small.

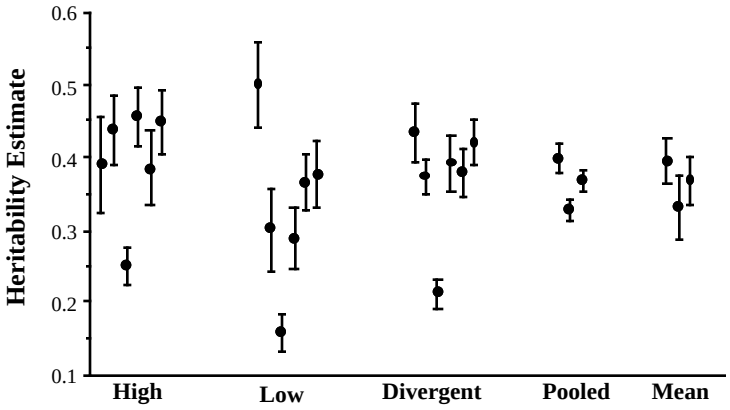


Figure 18.3. Realized heritability estimates (and their associated standard errors) for Falconer's (1973) selection experiment in mice. Six replicates were used and realized heritabilties estimated by comparing up and down selection lines against a control (High and Low, respectively) as well as to each other (Divergent). For each comparison, the estimated heritiabilty plus/minus one standard error (using the OLS regression) is plotted. Pooled data were generated for each of the three designs (High, Low, Divergent) by using an OLS regression taking the average value over the six replicates at the data point for any given generation. The three values for Mean correspond to the mean value of the estimates over the six replicates, with the error bars corresponding to the empirical standard error among the heritability estimates for these six different realizations. While these observed variances were larger than predicted from an OLS regression on the pooled data, this is not unexpected as the OLS method underestimates the true standard errors.

Perhaps the most extensive study is that of Falconer (1973), who performed two-way selection for 6-week weight in mice (Figure 18.3). A total of six replicate sets of lines were used. Each set consisted of a line selected for larger size, a line selected for smaller size, and

an unselected control, for a total of 18 lines in the entire experiment. Realized heritabilities were estimated (by OLS regression) using the three different contrasts available within each replicate set: large versus control (High lines), small versus control (Low lines), and large versus small (Divergent lines). In addition to the six separate estimates of $\widehat{h}_r^2$ for each replication, Falconer also considered a Pooled estimate obtained by using the average of the six means for a given contrast (High, Low, or Divergence) as the data points in the regression. He also considered a Mean estimate given by the average of the realized heritability estimates over all six replications. Its associated standard error is the variation about this mean seen in the replicates, and this is the empirical estimate of the standard error to compare against the theoretical predictions. The average realized heritability estimates under each of the three different contrasts are very similar — 0.395, 0.331, and 0.369 for High, Low, and Divergent lines (respectively). The three Pooled estimates give very similiar estimates. As expected (since OLS estimated standard errors are expected to be downwardly baised), the standard errors for the Mean estimates (based on variation between the replicate lines) were 1.6, 3.3, and 2.3 times larger than the estimated standard error using OLS regression of the pooled data.

A second experiment (López-Fanjul and Domínguez 1982, summarized by López-Fanjul 1982) followed twenty replicate *Drosophila* lines selected for sternopleural bristle number. They found that the empirical standard errors were less than OLS-estimated SEs, which it turn were less than GLS-estimated SEs. This is contrary to the expectation that the OLS-estimated SEs are smaller than the true variances, while the empirical and GLS-estimated SEs are expected to be roughly equal. The authors suggest that this may be at least partly due to a scale effect (LW Chapter 11), as the phenotypic variance greatly decreased during selection.

A final experiment (Bohn et al. 1983) examined the variance in response to selection on pupa weight in *Trioblium castaneum*, examining three replicates from each of six different base populations. The authors found a poor fit when using Hill's (1971) variance formulae that attempt to correct for the effects of selection. Interestingly, a strong correlation was observed between departures in the predicted variance and departures from normality in the base population. The variance among replicate lines draw from base populations with increasing (absolute) amounts of kurtosis showed larger departures from the predicted value.

Realized Heritability With Rank Data

Realized heritability estimates are not limited to normally-distributed traits. Indeed, the heritability of the liability underlying a threshold trait (Chapter 15) is computed using a realized heritability estimator, comparing performance of the offspring from different parental classes (LW Chapter 25). In a similar fashion, Schwartz and Wearden (1959) considered a realized heritability estimator when the data are ranks. Rank-order traits can arise in behavioral genetics, for example an individual's rank in the pecking order. They considered the case where individuals were divided into high versus low dominance groups, by first ranking the dominance of individuals (in their case, chickens) within a flock, and then assigning those in the upper half to the high group, those in the lower half to the low group. The selection differential was computed as the difference in the mean rank of high and low parents, $a_h - a_l$. Conversely, response was measured as the difference in the mean rank of progeny from high parents versus low parents, $b_h - b_l$, with

$$\widehat{h}_r^2 = \frac{b_h - b_l}{a_h - a_l}$$

The authors cleverly noted how this estimator could be related to the Mann-Whitney U statistic (for comparing two sample means based on ranks) and use this to develop large-sample confidence intervals for the resulting heritability estimate.

Infinitesimal-model Corrections for Disequilibrium

Our final comment on estimation is that selection is expected to decrease the additive variance (and hence the hertiability) due to the generation of gametic-phase disequilibrium (Chapters 16, 24). Hence, realized heritability is depressed relative to the (unselected) base population value (Figure 18.4). Under the infinitesimal model, the majority of this decrease occurs over the first few generations, after which the heritability is essentially at its equilibrium value, $\widetilde{h}^2$, where (Equations 16.13a and 16.13c),

$$\widetilde{h}^2 = \frac{\theta}{1+\theta-h^2}, \quad \text{with} \quad \theta = \frac{2h^2 - 1 + \sqrt{1+4h^2(1-h^2)\kappa}}{2(1+\kappa)} \tag{18.21}$$

Here h^2 is the (unselected) base-population heritability and κ is a measure of the reduction in phenotypic variance due to selection. In particular, $\kappa = \overline{t}\,(\overline{t} - z_{[1-p]})$ for truncation selection saving a fraction p of the population for a normally-distributed trait (Table 16.1). One can thus approximately treat the realized heritability as an estimate of the equilibrium heritability ($\widehat{h}_r^2 \simeq \widetilde{h}^2$) and use Equation 18.21 to numerically solve for the base-population heritability (h^2). This correction was first applied by Atkins and Thompson (1986). Figure 18.4 shows the relative percentage by which the base population heritability is underestimated by the uncorrected realized heritability.

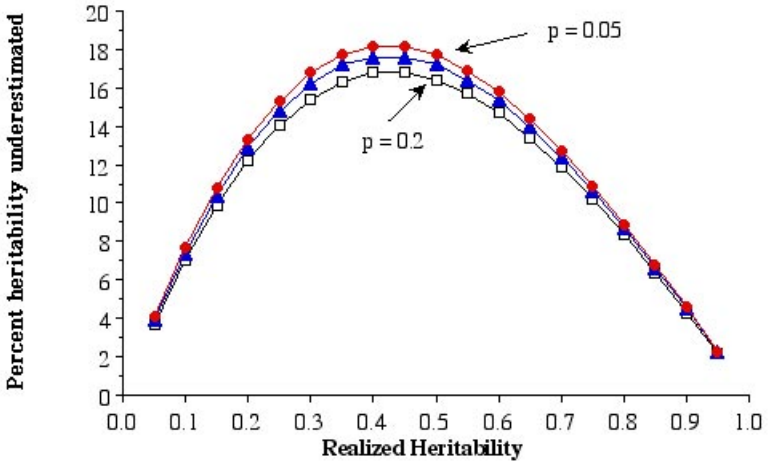


Figure 18.4. The relative percentage by which the base population heritability is underestimated by the realized heritability due to reduction in the additive variance by gametic-phase disequilibrium. The three curves correspond to different levels of truncation selection, with 5 (upper curve), 10 (middle curve), and 20 (lower curve) percent of the population saved. Value were obtained by numerically solving Equation 18.21 and assuming the infinitesimal model (no significant selection-induced changes in allele frequencies).

Example 18.6. What are the disequilibrium-corrected estimates for the realized heritability values obtained in Examples 18.2 and 18.3? Recall that for this experiment, p = 20/100 = 0.2. From Example 16.2, this value of p gives κ = 0.787. Substituting this value into Equation 18.21 and using each of the three previous estimates gives infinitesimal-model corrected realized heritabilities of:

Estimator	Estimate of h_r^2 Uncorrected	Corrected
Unweighted least-squares regression, $\widehat{b}_C$(OLS)	0.2245	0.2541
Total response/total differential, $\widehat{b}_T$	0.2102	0.2368
Weighted least-squares regression, $\widehat{b}_C$(GLS)	0.2221	0.2512

Assuming that the infinitesimal model is a reasonable approximation over the course of this experiment, all three methods underestimated the base population heritability by about 13 percent (see Figure 18.4).

EXPERIMENTAL EVALUATION OF THE BREEDER'S EQUATION

Our concern here is the adequacy of the breeder's equation for artificial selection experiments, with other empirical trends from selection experiments (both short- and long-term) reviewed in Chapters 25 and 26, while response in natural populations is examined in Chapter 20. Although the breeder's equation requires a number of assumptions (Table 13.2) and strictly speaking holds only for a single generation of selection from an unselected base population, the general claim (e.g., Falconer 1981) is that it is usually satisfactory over a few (5-10) generations. A slightly more refined statement is that the time must not exceed $N_e/2$ generations (Hill 1977), as drift significantly changes the genetic variance within a line after this time. After a sufficient number of generations, drift and selection change the genetic variances significantly from their base-population values and the breeder's equation (using the initial heritability value) fails (Chapters 24-26).

Starting with the first formal comparisons by Reeve and Robertson (1953) and Clayton and Robertson (1957), a number of authors have compared their observed short-term responses with those predicted from the breeder's equation. As summarized below, the results are mixed. One complication is that most analyses simply used ordinary (unweighted) least squares, resulting in significantly underestimated standard errors. Likewise, almost all realized heritability estimates have not corrected for the expected decline due to gametic-phase disequilibrium.

Most Traits Respond to Selection

Before delving into the goodness-of-fit of the breeder's equation, it is important to emphasize a fundamental observation in quantitative genetics: ***Most traits in outbred populations respond to selection***. This is such a fundamental observation that the exceptions are classic and well-known. The first is sex-ratio in chickens. Despite enormous economic incentive to create female-biased lines, to our knowledge this has not happened. The second is selection for directional asymmetries (i.e., "handedness") in traits in *Drosophila* (Lewontin 1974). While selection to change the *variance* in asymmetry is usually successful (Chapter 17), attempts to select for a consistently higher trait value on one specific side of an organism (such as more bristles on the right side) have been unsuccessful (Maynard Smith and Sondhi 1960, Purnell and Thompson 1973, Coyne 1987). There are numerous examples (e.g., handedness of the larger claw in fiddler crabs) of such directional asymmetries in nature, so this lack of response is interesting.

When we move from univariate to multivariate traits, the picture is not as clear. Indeed, there often appear to be serious constraints (i.e., little genetic variation) for specific *combinations* of traits, despite significant heritabities in each *component*. We examine this in detail in

Volume 3.

Sheridan's Analysis

One of the most extensive reviews of the fit of the breeder's equation is Sheridan (1988), who examined 198 experiments involving laboratory and domesticated animals, comparing realized heritabilities with estimates of heritability based on resemblances between relatives. Sheridan first considered those experiments whose base populations already had an extensive past history of selection. In these populations the response is very poorly predicted by the breeder's equation, with all 11 experiments (6 in *Drosophila*, 2 in *Tribolium*, 3 in mice) showing greater than 50 percent disagreement between the realized and estimated (i.e., base-population) heritabilities.

Table 18.1 shows the fit for the remaining 187 experiments. As the data show, the fit was rather poor in many experiments — roughly half have a disagreement of at least 30 percent, and one in three exceeds 50 percent. Besides the biological reasons listed in Table 13.2, there are also design issues that could account for the apparently poor fit. First, none of the experiments reviewed by Sheridan corrected for the expected decline in the realized heritability due to gametic-phase disequilibrium. Second, small absolute disagreements can translate into large relative percentages of disagreement for those traits with low heritabilties (Hill and Caballero 1992). For example, $|\,\widehat{h}_r^2 - \widehat{h}^2\,| = 0.04$ is a 20 percent relative disagreement if $\widehat{h}_r^2 = 0.2$, but an 80 percent disagreement if $\widehat{h}_r^2 = 0.05$. Finally, since variance in response will also generate some level of disagreement, which of these differences are significant?

Table 18.1. Comparison of realized heritabilities ($\widehat{h}_r^2$) and heritability estimates based on resemblances between relatives ($\widehat{h}^2$). Within each group, the table gives the distribution of the percent absolute disagreement ($|\,\widehat{h}^2 - \widehat{h}_r^2\,|/\widehat{h}_r^2$) between the two estimates, where n is the number of experiments considered for each species group. For example, 8% of the 60 *Drosophila* experiments had a precent absolute disagreement between estimates of 30 to 50 percent. After Sheridan (1988).

	Percent absolute disagreement (relative to $\widehat{h}_r^2$)					
Species	0–10%	10–20%	20–30%	30–50%	>50%	n
Drosophila	48%	12%	5%	8%	27%	60
Tribolium	31%	8%	12%	38%	12%	26
Mice and Rats	23%	0	13%	23%	41%	39
Poultry and Quail	20%	5%	17%	5%	54%	41
Swine and Sheep	20%	0%	10%	20%	50%	10
Summary over all groups						
Laboratory Species	37%	7%	9%	19%	28%	125
Commerical Species	19%	5%	18%	11%	47%	62
All Species	31%	6%	12%	17%	34%	187

As a rough approximation, Sheridan considered the disagreement to be significant if it exceeded two standard errors (which amounts to $p < 0.05$ if the data are normally distributed). Assuming the two estimates are uncorrelated, the variance for their difference is the sum of the variance for each estimate, giving a standard error of

$$\mathrm{SE}\left(\widehat{h}^2 - \widehat{h}_r^2\right) = \sqrt{\left(\mathrm{SE}[\,\widehat{h}^2\,]\right)^2 + \left(\mathrm{SE}[\,\widehat{h}_r^2\,]\right)^2} \tag{18.22}$$

Taking those 131 experiments that have standard errors for both $\widehat{h}_r^2$ and $\widehat{h}^2$, Table 18.2 shows that 25 percent had realized heritabilities significantly different from $\widehat{h}^2$. One problem with this approach is that most of the reported standard errors for $\widehat{h}_r^2$ used by Sheridan were based on unweighted least-squares (OLS), which underestimates the true standard error, giving confidence intervals that are too narrow, inflating the level of significance. The overall 25% of experiments reported by Sheridan as showing a significant departure from the predicted response is thus an upper bound, suggesting that the breeder's equation may not be doing such a poor job after all.

Finally, Sheridan looked at the goodness-of-fit as a function of the duration of the experiment (Table 18.3). Surprisingly, longer experiments tended to have a better fit. While this is contrary to expectations, it could simply be design artifact. First, longer experiments tend to have smaller standard errors, as the SE scales as the inverse of the total selection differential (equation 18.18). Second, in many cases longer experiments employ larger population sizes than experiments of shorter duration, reducing the effects of drift.

Table 18.2. Tests of significance between estimated and realized heritabilities. Differences of more than two standard errors (computed from Equation 18.22) are regarded as significant. Only those experiments with estimated standard errors for both heritability estimates are included, and n denotes the number of such experiments. After Sheridan (1988).

Species	Significant Differences	NS Differences	Total
Drosophila	14 (23%)	47 (77%)	61
Tribolium	7 (27%)	19 (73%)	26
Mice and Rats	6 (18%)	28 (82%)	34
Poultry and Quail	5 (45%)	6 (55%)	11
Swine and Sheep	8 (53%)	7 (47%)	15
Summary over all groups			
Laboratory Species	27 (21%)	104 (79%)	131
Commerical Species	11 (37%)	19 (63%)	30
All Species	38 (25%)	113 (75%)	151

Table 18.3. Agreement between realized and estimated base-population heritability as a function of the duration of the experiment. After Sheridan (1988).

	Percent absolute disagreement (relative to $\widehat{h}_r^2$)			
Generations	0–10%	10–30%	>30 %	n
1 - 5	18%	27%	55%	44
6 - 10	24%	17%	59%	98
10 - 15	52%	10%	38%	90

Realized Heritabilities and Selection Intensity

In addition to quantitative differences in the predictions of the breeder's equation discussed above, there are also reported cases of major *qualitative* departures as well. For example, the breeder's equation predicts that while response should increase with selection intensity, the ratio of response to selection differential, R/S, should be constant. Some studies have

reported a dependence of realized heritability on the selection intensity, although a survey of selection experiments finds no consistent pattern (Table 18.4).

There are several reasons why some dependence may arise between realized heritability and selection intensity. First, increasing selection intensity increases gametic-phase disequilibrium, reducing σ_A^2 and hence $\widehat{h}_r^2$ (Chapter 16). As Figure 18.4 shows, the prediction is that (uncorrected) realized heritabilities should decrease with increasing selection intensity. Again, essentially none of the reported selection experiments correct for this expected reduction. Second, with increasing selection, allele frequencies are expected to change more rapidly. Whether this results in an increased or decreased response depends on the initial distribution of allele frequencies and effects (see the discussion on genetic asymmetries below). Finally, N_e decreases as selection intensity increases (Chapter 3, 26), increasing the amount of inbreeding and (generally) reducing the additive variance (Chapter 11) . Thus, lines experiencing different amounts of selection have different amounts of inbreeding, even if their census sizes are identical.

Table 18.4. Summary of experiments examining the effects of selection intensity on estimated realized heritability, $\widehat{h}_r^2$.

Clayton and Robertson 1957 abdominal bristles in *D. melanogaster*	$\widehat{h}_r^2$ decreases with increasing selection intensity.
Frankham et al. 1986 abdominal bristles in *D. melanogaster*	Agreement between base population estimate of h^2 and $\widehat{h}_r^2$ best at highest selection intensity, becoming worse as selection intensity decreases.
Hanrahan et al. 1973 postweaning weight gain in mice	No consistent effect of selection intensity on $\widehat{h}_r^2$.
Meyer and Enfield 1975 pupa weight in *Tribolium castaneum*	$\widehat{h}_r^2$ decreases with selection intensity in down-selected lines; no effect in up-selected lines.
Silvela et al. 1989 kernal oil content in maize	No effect of selection intensity on $\widehat{h}_r^2$.

Inbreeding and Short-term Response

When inbreeding occurs, the short-term response is generally found to be less than that predicted from the breeder's equation using variance components estimated from the base population (Table 18.5). This is expected, as inbreeding (generally) decreases the additive genetic variance within a line, reducing response. A rough rule of thumb (Hill 1977) is that the effects of drift on reducing the within-line varation can be ignored provided that the selection experiment lasts less than $N_e/2$ generations. Exceptions can occur if nonadditive variance is present, in which case inbreeding may actually result in an *increase* in the within-line additive variance (Chapter 11), increasing response. The consequences for drift on long-term experiments are examined in detail in Chapter 26. Inbreeding depression is another complication, and we address this shortly.

Asymmetric Selection Response

A common design is to perform a **divergent selection experiment**, wherein replicate lines are selected in opposite directions. Many such experiments (e.g., Figure 18.5) show different amounts of response in the up versus down direction, a phenomenon referred to as an **asymmetric selection response** (Falconer 1954). This is in sharp contrast with the expectation

Table 18.5. Results of experiments examining the effects of finite population size and inbreeding on short-term response.

Tantawy and Reeve 1956 Wing length in *D. melanogaster*	Short-term response for outbreds > double first cousins > sib mating.
Chung and Chapman 1958 Gonadotrophic hormone level in rats	Outbred and crossbred lines had larger short-term responses than inbred lines.
Lewis and Warwick 1953 Body size in mice	Outbred line had a larger short-term response than an inbred line.
Frankham et al. 1968 Abdominal bristles in *D. melanogaster*	Weak trend for larger population sizes to have a greater short-term response
Hanrahan et al. 1973 Postweaning weight gain in mice	Short-term response increased with increasing population size
Silvela et al. 1989 Kernal oil content in maize	Short-term response increased with increasing population size

from the breeder's equation, which predicts that the absolute magnitude of response should depend only the absolute value of S, not its sign.

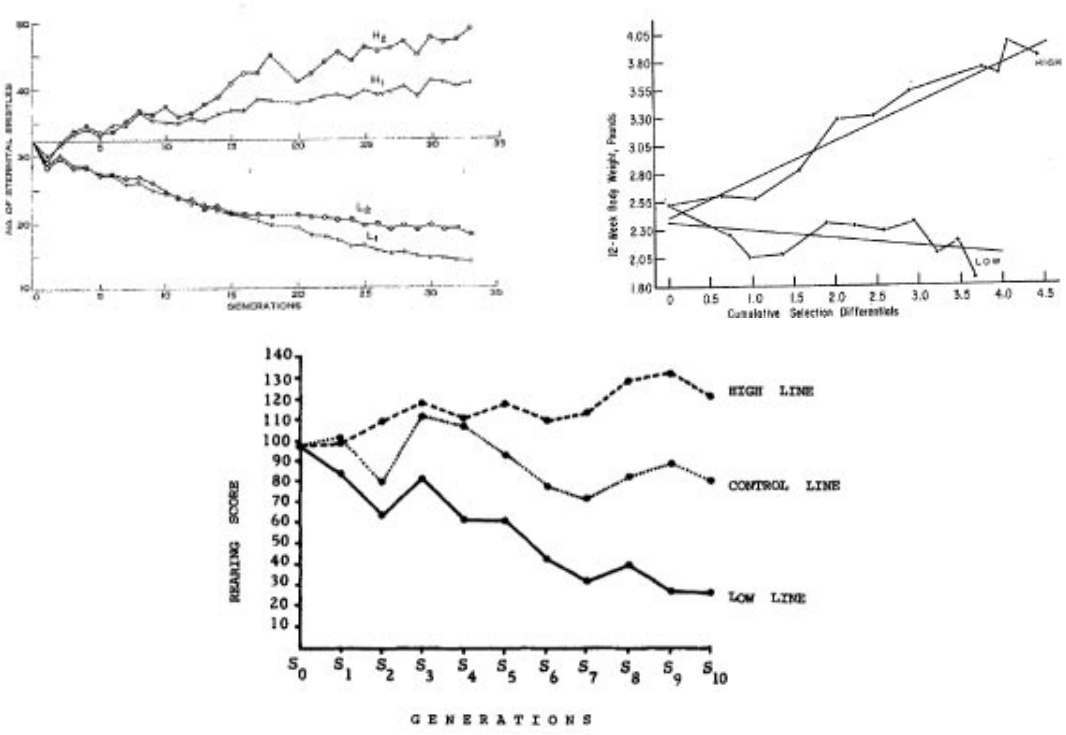


Figure 18.5. Examples of asymmetric response to selection. **A:** (Top left) Abdominal bristles in male *Drosophila melanogaster* (Sheldon 1963). **B:** (Top right) Twelve-week body weight in chickens (Maloney et al. 1963). **C:** (Bottom) Rearing activity in rats (Sanders 1981). The horizontal axis is in generations in **A** and **C** and is the cumulative selection differential in **B**.

There are a variety of possible explanations for asymmetric responses (Table 18.6). It may simply be an artifact of the experimental design and/or analysis. In particular, the prediction of equal positive and negative slopes holds only for plots of cumulative response versus cumulative selection differentials ($R_C(t)$ vs. $S_C(t)$). Asymmetry in response based on differences in slope of cumulative response versus *generations* of selection ($R_C(t)$ vs. t) can thus be very misleading as the different lines may have experienced different amounts of selection.

Table 18.6. Possible explanations for asymmetric response (including reversed response).

Design Defects	Drift (Chapter 12)
	Scale effects (LW Chapter 11)
	Different effective selection differentials (Chapter 13)
	Undetected environmental trends (Chapter 20)
	Transient effects from previous selection in the base population, e.g. decay of response from $A \times A$ or genetic maternal effects (Chapter 15)
	Undetected selection on correlated characters (Volume 3)
Nonlinear parent-offspring regressions	Major genes with dominance (LW Chapter 17)
	Genotype-environment interactions (Volume 3)
	Departures from normality (Chapter 24)
Other sources	Genetic asymmetries (this chapter)
	Inbreeding depression (Chapter 23)
	Maternal effects (Chapters 15, 22)
	Associative effects (Chapter 22)

Even if the amount of *artificial* selection is the same in both directions, there may be major differences in *natural* selection — e.g., up-selected lines may experience lower fertility. Using effective selection differentials (Equation 13.9) corrects for this source of bias, but the investigator often lacks the data (e.g., fertilities for each parent) necessarily to compute them. Likewise, we have seen that if a population has been under previous selection, the mean can change even after selection has stopped (Chapter 15). If we start a divergent selection using such a non-equilibrium population as our base, we can bias response in at least one direction, generating an asymmetric response even when the true genetic trend from the experiment is symmetric.

Even though lines may have quite different values of $\widehat{h}_r^2$, there is still the issue of whether these differences are significant. Genetic drift can generate considerable variation between replicate lines and it is important to distinguish between a real difference in response versus the expected variation in two realizations of a process with the same (absolute) expected value. Directional trends in environmental change can also produce asymmetries, accentuating the response in the direction of the trend and retarding it in the opposite direction. Differences in response could simply be scale effects (Figure 18.6, see LW Chapter 11). For example, if the genetic variance increases with the mean, heritability can increase with the mean, giving a faster response in the upwardly-selected lines.

Although spurious asymmetric responses can result from these defects in design and analysis, true asymmetric responses can be generated by a variety of genetic situations. For example, if the parent-offspring regression is nonlinear, S is not sufficient to predict response (Gimelfarb and WiIllis 1994; Chapters 6, 13, and 24) and it is not surprising that asymmetric

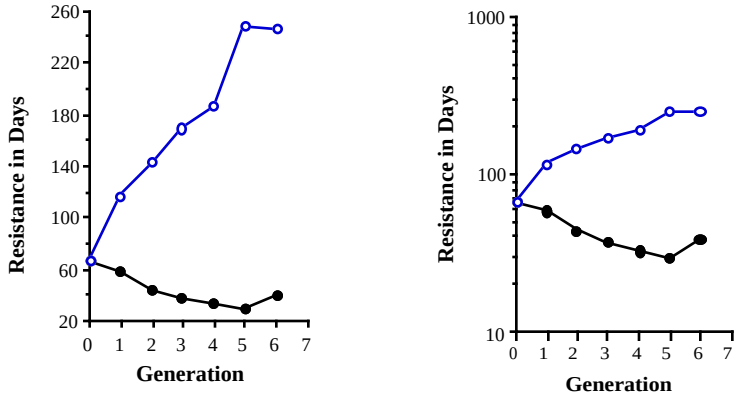


Figure 18.6. An example of a scale effect generating a asymmetric selection response. **Left:** Selection for resistance to dental caries in albino rats (*Rattus norvegicus*), response measured as the expected number of days to develop caries on a standard diet. **Right:** Same data on a log scale shows a symmetric response. Based on Falconer's (1954) analysis of data from Hunt et al. (1944).

responses can be generated in such cases. Failure to detect departures from linearity in the base population does not rule out nonlinearity as an explanation for an observed asymmetric response. The range of variation in the base population may not be sufficient to detect departures at the extreme ends of the initial range of phenotypes. As the selected lines diverge, differences in the tails of the initial phenotypic distribution can become quite important. Likewise, as previously mentioned (Skibinski and Shereif 1989), heritability can be a function of which part of the phenotypic distribution individuals are drawn from.

Characters displaying inbreeding depression (LW Chapter 10) show asymmetric selection response, accentuating the response in one direction and retarding it in the other. A simple test for inbreeding as an explanation of asymmetric response is to see whether the mean of an unselected control population changes in the direction of greater response when inbred. The effects of inbreeding depression can be corrected by inbreeding a control population to the same level as the divergent selection lines, and using the contrast between selected and control lines to estimate response. However, this is not necessarily as straightforward as it appears, as selection generally increases the amount of inbreeding within a line by decreasing its effective population size (Chapter 3, 26). Simply keeping the control line at the same size as the selected lines underestimates the amount of inbreeding (and hence any correction for inbreeding depression), especially when selection is intense.

The assumption of negligible allele frequency change over a few generations of selection can be violated when alleles of major effect are segregating. In this setting, asymmetries can arise as a consequence of allele frequencies changing in different directions in the selected populations. An increase in an allele from its initial frequency usually results in a different additive variance from that produced by an equal decrease in frequency. Falconer (1954) refers to this feature as **genetic asymmetry**. This is most easily seen by considering LW Figure 4.6, which shows additive genetic variation as a function of allele frequency for a single diallelic locus. If alleles are completely additive, σ_A^2 as a function of allele frequency is symmetric about $p = 1/2$. Suppose that the frequency of an allele that increases the character value is initially below $1/2$. In upwardly-selected lines, σ_A^2 (and h^2) increases as this alleles increases to frequency 0.5, and decreases when it exceeds this value. Conversely, in downwardly-selected lines, the contribution to σ_A^2 from this locus always decreases. If dominance is present, σ_A^2 is no longer a symmetric function of allelic frequencies (LW Figure 4.8) and asymmetric changes in the contribution to σ_A^2 from a single locus are almost always

expected.

Frankham and Nurthen (1981) give an interesting example wherein a base population was constructed with the major recessive allele sm^{lab} (which greatly reduces abdominal bristle number in *Drosophila melanogaster*) initially at low frequency. As shown in Figure 18.7, in two of three down-selected lines, this allele increased in frequency, resulting in a large increase in h^2 as the sm^{lab} allele reaches intermediate frequencies. Heritability subsequently returns to the base population value as this allele approaches fixation, suggesting much smaller allele frequency change in the residual genetic variation.

While we have focused on the effects of a single major gene, the effects of unequal allele frequencies and dominance apply to any QTL. Alleles of small effect are expected to have much slower changes in allele frequencies (and thus expected to have smaller effects on asymmetry) over the time scales of most short-term experiments. Hence, if many loci of small effect underlie a character, the effects of genetic asymmetry on selection response are expected to be slight unless the number of generations is large. Further, at least some cancellation is expected between the asymmetries in σ^2_A generated by allele frequency changes at different loci. Analogous to directional dominance (most loci with positive d) being required for inbreeding depression (LW Chapter 10), for genetic asymmetries to occur (in the absence of major genes) there must also be some systematic trend in the allele frequencies at loci underlying the trait. For example, if most alleles that decrease the trait value tend to be rare, then up-versus down-selected lines are expected to show asymmetric response as the allele frequency changes become significant. When might such an asymmetric distribution of allele frequencies be present? One situation is a recent history of selection on the trait before the start of the artificial selection experiment.

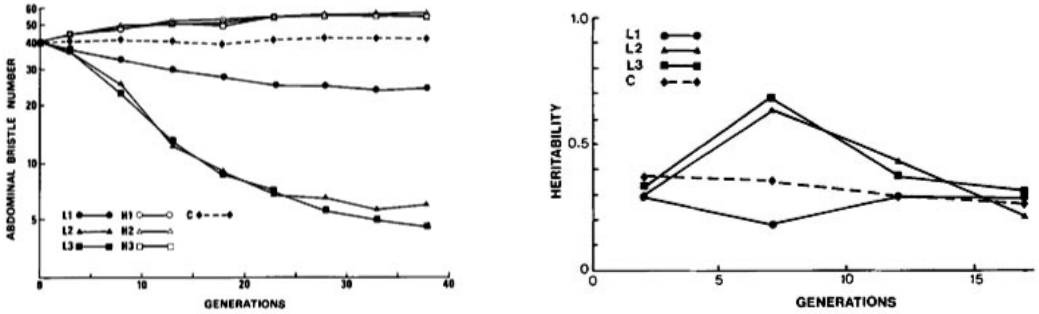


Figure 18.7. **Left**: Asymmetric selection response for abdominal bristle number in *Drosophila melanogaster* from a base population containing a major allele (sm^{lab}) initially at low frequency. L1-L3 are three replicate low lines, H1-H3 three replicate high lines, and C the control line. Data were log-transformed to remove scale effects. Note that low line L1 has a symmetric response with high lines H1-H3, while lines L2 and L3 do not. Further, there is also a greater variance in response among the low lines. **Right**: Changes in heritabilities in the control and lines L1-L3. Heritability was estimated from phenotypic correlations between bristle numbers of adjacent segments of the same fly (see Frankham and Nurthen 1981 for details). Note the large increases in heritability for lines L2 and L3, the lines that show an asymmetric selection response (relative to H1- H3), while the heritability is roughly constant in L1, which does not show an asymmetric response. The increase in h^2 reflects an increase in the major allele sm^{lab} due to selection. This allele increased rapidly in frequency after generation 5 and was essentially fixed by generation 10. This is reflected by a rapid increase in h^2 after generation 5, with h^2 returning to normal (the level in the unselected controls) as the allele becomes fixed. After Frankham and Nurthen (1981).

Components of reproductive fitness, such as fecundity and development time, are expected to have asymmetric allele frequencies as natural selection increases the frequency of alleles increasing fitness. Such characters are also expected to have substantial nonadditive genetic variance (Chapter 6). These conditions suggest that asymmetric responses in reproduction are expected, and further predict that response should be larger in lines selected for a decrease in reproductive fitness. This was seen by Frankham (1990), who found a larger response in the direction of reduced reproductive fitness in 24 of 30 experiments reviewed. Frankham suggested that the presence of rare recessives decreasing reproductive fitness was the most likely cause for this trend. As Figure 25.2 will show, very marked asymmetric responses are expected in such situations.

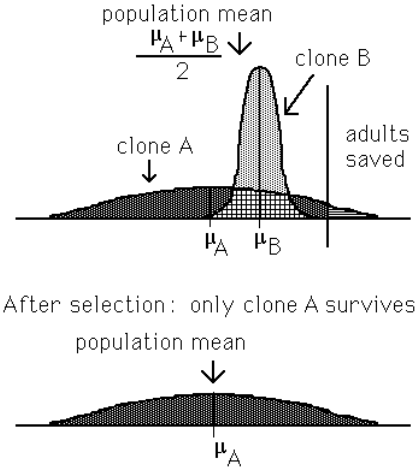


Figure 18.8. Haldane's (1931) example of a reversed response generated by genotype $\times$ environment interaction. The population consists of equal numbers of two asexual clones *A* and *B*. The mean phenotypic value of *A* (μ_A) is less than the mean phenotypic value of *B* (μ_B). However, clone *A* has a larger environmental variance than *B*. Strong truncation selection culls out all *B* clones in the population, leaving only *A*. The new mean in the generation following selection μ_A is less than the mean before selection $(\mu_A + \mu_B)/2$. In this case, selection for *increased* character value *z* resulted in a *lowering* of the population mean.

Reversed Response

The most extreme departure from the breeder's equation is a **reversed response**, a response in the *opposite* direction of selection. Negative maternal effects can result in such a response (Figures 15.3 and 15.4). Likewise, they can arise from sufficiently large genotype-environment interactions (Haldane 1931). Haldane's intuition was based on selection with two asexual clones, the first with a higher mean, but smaller environmental variance, than the second. As shown in Figure 18.8, if the most extreme individuals are selected, there is an excess of the clone with the smaller mean but higher variance, resulting in a decrease in mean value in the next generation. Wright (1969) expanded Haldane's model to a single diallelic locus. Gimelfarb (1986) gives a particularly interesting analysis when there is a multiplicative genotype $\times$ environment interaction, showing for this model that while *phenotypes* are subjected to directional selection, the nature of the interaction between genotype and environment is such that *genotypic* values are actually under either stabilizing or disruptive selection. The interesting feature of both Haldane's and Gimelfarb's models is that reversed response is most

probable when selection is very intense, as this is the setting most favorable to genotypes with high variances (Chapter 17).

An extremely important, and not yet widely appreciated, source of reversed response are **associative effects** (also called **social effects** or **indirect genetic effects**), of which maternal effects is a special case. As introduced by our discussions on maternal effects in Chapter 17, and more fully developed in Chapter 22, the environment that a focal individual experiences can be strongly influenced by its neighbors. In such cases, an individual's phenotype is the result of both **direct effects** due to its own intrinsic genes and **social effects** from its neighbors. If the latter have a heritable component, these can also evolve. If direct and social effects are negatively correlated, a positive response in the direct trait can be overcome by a negative social response, resulting in a net *decrease* in trait value. Consider selecting for egg production in caged chicken. Aggressive individuals gather more food in the cage, producing more eggs. With selection based solely on individual egg production, more aggressive chickens are chosen, creating a deleterious cage environment that can more than overcome for any direct genetic advance in terms of number of eggs, resulting in a reduction on number of eggs per cage in the next generation.

CONTROL POPULATIONS AND EXPERIMENTAL DESIGNS

We conclude this chapter by considering several specialized issues in the analysis of selection experiments, topics that may be skipped by the casual reader. We first examine the strengths and weaknesses of different types of designs (such as the use of a control population), then consider optimal designs, and finish with a discussion of a modified line-cross analysis (LW Chapter 9) to examine the genetic components of a selection response.

One complication with estimating realized heritabilities is distinguishing between genetic versus environmental trends. For example, Newman et al. (1973) found that 60 percent of the increase in yearling weight in a selected line of Shorthorn cattle was due to environmental, rather than genetic, improvement. Using a large unselected **control population** reared under the same environmental conditions as the selected line(s) allows for correction of any such between-generation environmental change. Hill reviews this approach (1972a) and some of the features seen in control populations from a number of different species (1972b). The use of control populations is not a fool-proof approach for removing environmental trends, as the control and selected lines can evolve different genotype-environment interactions. Likewise, extensive genetic drift in the control population can also result in biases. When full pedigree data are available, the powerful methods of mixed-model analysis (Chapter 19) can be used to remove genetic and environmental trends, even in the absence of control populations (although incorporating such controls is preferred). Undetected environmental trends are especially problematic in the analysis of response in natural populations (Chapter 20).

Basic Theory of Control Populations

Assuming no genotype-environment interaction, the true mean of a line in generation t can be decomposed as $\mu + g_t + d_t$, where μ is the base population mean, g_t the change in mean breeding value due to selection and drift, and d_t the change in mean due to environmental change. Under this model, observed means $\overline{z}$ for a selected (s) and control (c) population reared in a common environment can be decomposed as

$$\overline{z}_{s,t} = \mu + g_{s,t} + d_{s,t} + e_{s,t} \tag{18.23a}$$

$$\overline{z}_{c,t} = \mu + g_{c,t} + d_{c,t} + e_{c,t} \tag{18.23b}$$

where e_t is the error in estimating the mean breeding value ($\mu + g_t$) from the observed mean

corrected for the change in the environment ($\overline{z}_t - d_t$) and has expected value 0.

Assuming that the breeder's equation holds, the expected total response at generation t is $E[\, R_C(t)\,] = E(\, g_{s,t}\,) = h^2 S_C(t)$. Under drift alone, there is no expected directional change in the mean breeding value of the control population, $E(\, g_{c,t}\,) = 0$. Assuming no genotype-environment interactions (i.e., $d_{s,t} = d_{c,t}$), the contrast between the selected and control populations has expected value

$$E(\, \overline{z}_{s,t} - \overline{z}_{c,t}\,) = E(\, g_{s,t}\,) - E(\, g_{c,0}\,) = h^2 S_C(t) \tag{18.24a}$$

If the control population is small, $g_{c,t}$ can drift significantly away from zero, resulting in an over (or under) estimation of the true selection response. If the goal is simply to remove an environmental trend, control populations should be kept as large as possible so that $g_{c,t}$ is close to zero. However, as previously mentioned, control populations are also used to attempt to correct for any effects of inbreeding depression. In such cases, significant drift has likely occurred, and the use of a control population introduces additional uncertainly in the estimate of the response (although this may be more than compensated for by accounting for inbreeding depression and/or environmental trends).

If genotype-environmental interactions are present, then

$$E(\, \overline{z}_{s,t} - \overline{z}_{c,t}\,) = h^2 S_C(t) + (d_{s,t} - d_{c,t}) \tag{18.24b}$$

resulting in $\overline{z}_{s,t} - \overline{z}_{c,t}$ being a potentially biased estimator of $h^2 S_C(t)$. If the environmental trends are positively correlated between populations, then the use of a control will still improve the estimate of the genetic trend. If they are negatively correlated, the use of a control can lead to a more inaccurate estimate than simply using a selected population without a control. As discussed in Chapter 17, mixed-model analysis may be able to provide some insights (as they estimate the $d_{x,t}$), but they require extensive information (full pedigrees) and that the model assumptions hold.

If a control population is used, the responses and differentials are estimated by

$$R_t = (\, \overline{z}_{s,t} - \overline{z}_{c,t}) - (\, \overline{z}_{s,t-1} - \overline{z}_{c,t-1}) \tag{18.25a}$$

$$R_C(t) = \overline{z}_{s,t} - \overline{z}_{c,t} \tag{18.25b}$$

$$S_t = \overline{z}^{\,*}_{s,t-1} - \overline{z}_{s,t-1} \tag{18.25c}$$

where $\overline{z}^{\,*}$ denotes the mean of the selected individuals. No correction is necessary for the selection differential S_t, as we have assumed the environment stays constant within a generation. If selection differs between sexes,

$$S_t = \frac{S_t(m) + S_t(f)}{2}$$

where $S_t(m)$ and $S_t(f)$ are, respectively, the observed differentials on males and females.

Muir (1986a,b) has suggested that an analysis of covariance approach (along the lines of LW Equation 10.12) be used when extensive G $\times$ E is expected. In its simplest form, Muir's idea is to adjust the mean $\overline{z}_i$ in generation i of the selected populations using the mean $\overline{z}_{c,i}$ of the control population in that generation as well as the average mean of the control over the course of the experiment, $\overline{z}_{c,\cdot}$, by

$$\overline{z}_{s,i}{}' = \overline{z}_{s,i} - \beta(\, \overline{z}_{c,i} - \overline{z}_{c,\cdot}\,)$$

If there is no genotype-environment interaction (so that the environmental effect at time i has the same influence on both the selected and control lines), then $\beta = 1$ and we recover

our previous results. However, if there is $G \times E$, such that the environmental deviation influences the control differently from the selected population , then (provided the genotype-environmental interaction has a linear form), the above expression provides a less-biased correction than simply subtracting off the mean of the control. Note that this covariate approach at least partly corrects for the most extreme case, namely the environmental effect results in a different sign in the control and selective populations ($\beta < 0$).

Divergent Selection Designs

A related approach is the **divergent** (or **bidirectional**) selection design, wherein one compares lines selected in opposite directions (typically denoted by the up vs. down or high vs. low lines). Again assuming no significant genotype $\times$ environment interactions between lines, the basic statistical model for this design is

$$\overline{z}_{u,t} = \mu + g_{u,t} + d_t + e_{u,t} \tag{18.26a}$$
$$\overline{z}_{d,t} = \mu + g_{d,t} + d_t + e_{d,t} \tag{18.26b}$$

where u and d refer to the upwardly- and downwardly-selected lines. With this design, the responses and differentials are estimated by

$$R_t = (\,\overline{z}_{u,t} - \overline{z}_{u,t-1}) - (\,\overline{z}_{d,t} - \overline{z}_{d,t-1}) \tag{18.27a}$$
$$R_C(t) = \overline{z}_{u,t} - \overline{z}_{d,t} \tag{18.27b}$$
$$S_t = (\,\overline{z}^*_{u,t-1} - \overline{z}_{u,t-1}) - (\,\overline{z}^*_{d,t-1} - \overline{z}_{d,t-1}) \tag{18.27c}$$

Again, the expected response (using Equations 18.27a and 18.27c for the response and selection differential) is just $R = h^2 S$. More generally, if $S_{x,i}$ denotes the selection differential in line x in generation i, the total (cumulative) expected divergence between lines is just

$$R_C(t) = h^2 \sum_{i=1}^{t} (S_{u,i} - S_{d,i}) = h^2\,(S_{C,u} - S_{C,d}) \tag{18.27d}$$

In addition to previous concerns about genotype-enviroment interactions, asymmetric response to selection also complicates the interpretation of results with divergent selection and can result in a biased estimate of the realized heritability.

Variance in Response

Recall the pure-drift approximation for the variance (Equation 18.8) and the within-line covariance across generations (Equation 18.9) for the design of a single selected line. Here we present corresponding expressions for the selection + control and divergence selection designs (assuming no genotype-environment interactions between lines). For unidirectional selection plus a control population,

$$\begin{aligned} R_C(t) = \overline{z}_{s,t} - \overline{z}_{c,t} &= (\,\mu + g_{s,t} + d_t + e_{s,t}) - (\,\mu + g_{c,t} + d_t + e_{c,t}\,) \\ &= g_{s,t} - g_{c,t} + e_{s,t} - e_{c,t} \end{aligned} \tag{18.28}$$

Similarly, for divergent selection,

$$R_C(t) = \overline{z}_{su,t} - \overline{z}_{sd,t} = g_{su,t} - g_{sd,t} + e_{su,t} - e_{sd,t} \tag{18.29}$$

Since each term in Equations 18.28 and 18.29 is independent, applying Equations 18.4 and 18.5 gives the pure-drift approximations for the variance in response as

$$\begin{aligned} \sigma^2\,[\,R_C(t)\,] &= (2f_t + B_0)\,2f_t\,h^2\sigma_z^2 + B_t\,\sigma_z^2 \\ &\simeq (t\,A + B_0)\,h^2\sigma_z^2 + B_t\,\sigma_z^2 \end{aligned} \tag{18.30a}$$

and the covariance between generations in the same line

$$\begin{aligned}\sigma\,[\,R_C(t), R_C(t')\,] &= (2f_t + B_0)\; h^2\sigma_z^2 \\ &\simeq (t\,A + B_0)\,\sigma_z^2\,h^2 \qquad \text{for } t < t'\end{aligned} \tag{18.30b}$$

where the coefficients A and B_t are given in Table 18.7. If the number of reproducing individuals varies over time, then the tA term is simply replaced by the sum over time of the components in A, for example by $\sum_{i=1}^{t}\,(1/N_i)$ or related expressions. Finally, recall (Equation 18.3) that for unidirectional selection without a control, the variance in response has an additional term, σ_d^2, accounting for the between-generation environmental variation.

Table 18.7. Coefficients for the pure-drift variances and covariances in response (Equations 18.30a and 18.30b). $M_{x,t}$ individuals are sampled in population x at generation t, of which N_x are allowed to reproduce. The subscripts s and c refer to the selected and control populations, u and d to the up- and down-selected lines, respectively. $f_{x,t}$ refers to the amount of inbreeding in population x at time t.

Selection in a single direction without a control line. Equation 18.30a has an extra term, σ_d^2, accounting for the between-generation' variation in environmental effects.

$$f_t = f_{s,t}, \qquad A = \frac{1}{N_s}, \qquad B_t = \frac{1}{M_{s,t}} \quad \text{for } t \geq 0$$

Selection in a single direction with a control line

$$f_t = f_{s,t} + f_{c,t}, \qquad A = \frac{1}{N_s} + \frac{1}{N_c}, \qquad B_t = \frac{1}{M_{s,t}} + \frac{1}{M_{c,t}} \quad \text{for } t \geq 0$$

Divergent Selection Without a Control Line

$$f_t = f_{u,t} + f_{d,t}, \qquad A = \frac{1}{N_u} + \frac{1}{N_d}, \qquad B_t = \frac{1}{M_{u,t}} + \frac{1}{M_{d,t}} \quad \text{for } t \geq 0$$

Control Populations and Variance in Response

When does using a control population reduce the variance in response? Assuming $M = M_s = M_c$ and $N = N_s = N_c$, subtracting the expected variance in response using a undirectionally-selected population adjusted using a control from the response estimated without a control gives

$$\left(\frac{t}{N} + \frac{1}{M_0}\right) h^2\sigma_z^2 + \frac{1}{M}\,\sigma_z^2 - \sigma_d^2 \tag{18.31a}$$

Assuming the between-line drift variance dominates (terms involving M can be ignored), the condition for the variance in response with a control to be larger than the response without one is approximately

$$\frac{t\sigma_z^2 h^2}{N} > \sigma_d^2 \tag{18.31b}$$

Hence, regardless of the value of σ_d^2, if sufficient generations are used, the optimal design (in terms of giving the smallest expected variance in response) is not to use a control. However, this approach runs the risk of an undetected directional environmental trend compromising the estimated heritability. Further, as the number of generations becomes large, the key assumptions of short-term response becomes untenable.

OPTIMAL EXPERIMENTAL DESIGNS

As Equation 18.31b illustrates, it is not entirely clear-cut which design is optimal. What in general can we say? The coefficient of variation in response,

$$\mathrm{CV}\,[\,R_C(t)\,] = \frac{\sigma\,[R_C(t)\,]}{E[R_C(t)]},$$

is especially useful in comparing efficiencies of different designs, as it is independent of σ_z^2. Further, it provides an appropriate measure of comparing efficiencies when the expected response differs between designs. Table 18.8 gives expressions for the CV under some simplifying assumptions. Note that the coefficient of variation is a function of tN, the total number of adults selected during the course of the experiment, provided drift variance dominates error variance. A short experiment with many selected adults per generation thus gives the same expected CV as a long experiment with few adults per generation (provided the total numbers are the same). However, if the error variance is nontrivial relative to the drift variance (as would be expected if h^2 small), increasing the duration of the experiment results in some improvement in precision (Hill 1980).

Table 18.8. Coefficients of variation for various designs, assuming the pure-drift approximation and further that $\sigma^2\,[\,R_C(t)\,] \simeq t\,Ah^2\sigma_z^2$. This assumes that the selection experiment is sufficiently long that the beween-line drift dominates (i.e., $t\,A \gg B_0$ and $t\,Ah^2 \gg B_t$, with these defined in Table 18.7). For all designs, we assume that the absolute selection intensity in all selected lines is $\overline{\imath}$.

Selection in a single direction with a control line

$$E\,[R_C(t)] = t\,h^2\,\overline{\imath}\,\sigma_z, \qquad \mathrm{CV}\,[\,R_C(t)\,] \simeq \frac{1}{h\overline{\imath}}\sqrt{\frac{2}{Nt}}$$

Selection in a Single Direction Without a Control Line

$$E\,[R_C(t)] = t\,h^2\,\overline{\imath}\,\sigma_z, \qquad \mathrm{CV}\,[\,R_C(t)\,] \simeq \frac{1}{h\overline{\imath}}\sqrt{\frac{1}{Nt}} + \frac{1}{t\,h^2\,\overline{\imath}}\left(\frac{\sigma_d}{\sigma_z}\right)$$

Divergent Selection Without a Control Line

$$E\,[R_C(t)] = 2t\,h^2\,\overline{\imath}\,\sigma_z, \qquad \mathrm{CV}\,[R_C(t)] \simeq \frac{1}{h\overline{\imath}}\sqrt{\frac{1}{2Nt}}$$

As an example of using the CV of response, consider unidirectional selection without a control population versus divergent selection. Which is more efficient if the same total number of adults are selected (e.g., N under unidirectional, $N_d = N_u = N/2$ under divergent selection)? If there is no between-generation environmental variance both designs are equally efficient, while divergent selection is more efficient if $\sigma_d^2 > 0$.

Example 18.7. Suppose we plan to select the upper 5% of a population for a normally distributed character with $h^2 = 0.25$. What value of Nt is needed for the expected CV of response to be no greater than 0.01 if no control population is used? From Example 14.1,

$E(\overline{\imath}) = 2.06$ if the population is large, and slightly less in small populations (for simplicity assume the large population value). Further assuming that drift variance dominates error variances (including σ_d^2), applying the expressions from Table 18.8 gives

$$0.01 = \frac{1}{0.5 \times 2.06} \times \sqrt{\frac{1}{Nt}}$$

Solving, gives $Nt \simeq 9426$. Hence, during the entire course of the experiment using a total of at least 9426 selected parents gives an approximate expected CV less than 1%. If the desired CV is 0.05 or 0.10, then $Nt \simeq 377$ and $Nt \simeq 94$, respectively.

Nicholas' Criterion

An alternative criterion for chosing Nt was suggested by Nicholas (1980). Often the investigator is interested in ensuring that at least a certain response will occur with a preset probability. To a reasonable approximation, the expected mean value in any given replicate line after t generations of selection is normally distributed, with mean $E[R_C(t)]$ and variance $\sigma^2\,[R_C(t)]$. Consider the probability that the observed response is at least β of the expected response,

$$\begin{aligned}\Pr\left(R_C(t) > \beta E[R_C(t)]\right) &= \Pr\left(\frac{R_C(t) - E[R_C(t)]}{\sigma\,[R_C(t)]} > \frac{(\beta-1)E[R_C(t)]}{\sigma\,[R_C(t)]}\right) \\ &= \Pr\left(U > \frac{\beta - 1}{\mathrm{CV}\,[\,R_C(t)\,]}\right) \qquad (18.32)\end{aligned}$$

where U is a unit normal random variable. Note that the probability that the observed response *exceeds* the expected response ($\beta = 1$) is one half (as $\Pr[U > 0] = 1/2$).

Example 18.8. Again suppose that $\overline{\imath} = 2.06$, $h^2 = 0.25$, and the design is unidirectional selection without a control population. What value of Nt is required in order for a 95% probability that the observed response is at least 90% of its expected response? Here, $\beta = 0.9$ and $\Pr[U > -1.65] = 0.95$. Hence,

$$\frac{\beta - 1}{\mathrm{CV}\,[\,R_C(t)\,]} = \frac{-0.1}{\mathrm{CV}\,[\,R_C(t)\,]} = -1.65$$

Rearranging gives

$$\mathrm{CV}\,[\,R_C(t)\,] = \frac{1}{0.5 \times 2.06}\sqrt{\frac{1}{Nt}} = \frac{0.1}{1.65}$$

implying that $Nt \simeq 257$.

Replicate Lines

There is no loss of efficiency when replicate lines are used (Hill 1980). To see this, let $\overline{z}_{i,t}$ for $1 \le i \le r$ be the sample mean for replicate population i at time t. The overall mean is

$$\overline{z}_t = \frac{1}{r}\sum_{i=1}^{r} \overline{z}_{i,t} \qquad (18.33a)$$

Taking variances and assuming each line is independent,

$$\sigma^2_{\bar{z}}(t) = \frac{1}{r^2}\sum_{i=1}^{r}\sigma^2_{\bar{z}_i}(t) = \frac{1}{r}\sigma^2_{\bar{z}_1}(t) \tag{18.33b}$$

If the number sampled and number used as parents within a replicate are M^* and N^*, with $N^* = N/r$ and $N^* = M/r$, then it is easily seen from Table 18.8 that the variance of a replicate line is just r times the variance of a population with N and M. Hence, variance in the sample mean from r replicate lines with N^* and M^* is the same as the variance with a single line with N and M, provided that the number of individuals within each replicate line is sufficiently large to avoid significant inbreeding. Richardson et al. (1968), Irgang et al. (1985), and Muir (1986a,b) develope regression approaches correcting for between-generation environmental changes when replicate lines are used.

LINE-CROSS ANALYSIS OF SELECTION EXPERIMENTS

Plant breeding schemes often involve two (or more) generations for each **cycle** of selection (Chapters 21, 32). By saving seeds from each cycle, a breeder can grow the adults in a common environment, offering a direct assessment of the genetic response, for example by regressing line means on cycle number (e.g., Burton et al. 1971). An even more powerful design involves also growing *crosses* between different cycles at the same time. Such a line-cross analysis yields summary statistics about the genetic nature of the divergence between lines, such as the role of additive versus non-additive effects (LW Chapters 9 and 20). As we saw in LW Chapter 20, a large number of parameters are required when one has a collection of *unrelated* lines (i.e., the general and specific combining abilities of each line and each pair, respectively). However, in the analysis of a selection experiment, lines are not unrelated but rather genetically connected, requiring far fewer parameters to model. The key to connecting lines from different cycles is to assume a constant rate of allele frequency change over the course of the experiment (Hammond and Gardner 1974; Smith 1979a, 1979b, 1983; Melchinger and Flachenecker 2006), which is referred to as a **generation means analysis**, or **GMA**. With a large number of loci, each of small effect, this assumption may be reasonable. If there are major alleles present and/or selection runs long enough that substantial allele frequency change occurs, then the model becomes more problematic. While commonly used in plant breeding, GMA is applicable to any organism for which an equivalent of "remnant seed" is available, such as frozen breeding stock or lines extracted from different generations of selection.

The Simple Additive Model

To see the logic of behind a GMA, consider the simplest case: two alleles at each locus, with only additive effects, so there is no dominance nor epistasis. Focusing on a particular locus, the genotypes contribute values of $0 : a : 2a$ to the overall mean, where we sum contributions across all loci (since we assumed no epistasis). If p denotes the frequency of the favorable allele, then the contribution from this locus is $2ap$. If we further assume a roughly constant rate of change in allele frequency (at least over a few generations), then the frequency $p(k)$ of the favorable allele in cycle k is

$$p(k) \simeq p + k\Delta p,$$

where p is the initial frequency and Δp is the per-generation rate of change for this locus. Summing over all loci, the mean following k cycles of selection is

$$C_k = \mu + \sum_i 2a_i\, p_i(k) \simeq \mu + \sum_i 2a_i(p_i + k\Delta p_i) = \mu + \sum_i 2a_i p_i + k\sum_i 2a_i\Delta p_i$$

Next, define

$$m = \mu + 2\sum p_i\, a_i \tag{18.34a}$$

$$A = 2\sum \Delta p_i\, a_i \tag{18.34b}$$

where m is the line mean before selection and A is a weighted measure of change in the mean given a constant allele frequency change. The expected line mean from selection cycle k becomes

$$C_k = m + A \cdot k \tag{18.35a}$$

Now suppose individuals from cycles k and j are crossed, so that the frequencies of the favorable allele are now $p(k)$ and $p(j)$. The chance of getting the 0-valued homozygote is $[\,1 - p(k)\,]\,[\,1 - p(j)\,]$, while $p(k)\,[\,1 - p(j)\,] + p(j)\,[\,1 - p(k)\,]$ is the chance of an a-value heterozygote, and $p(k)\,p(j)$ the chance of a $2a$ homozygote. The resulting contribution from a particular locus to this cross becomes

$$\begin{aligned} 0 \cdot [\,1 - p(k)\,]\,[\,1 - p(j)\,] + a \cdot (p(k)\,[\,1 - p(j)\,] + p(j)\,[\,1 - p(k)\,]) + 2a \cdot p(k)\,p(j) \\ = a \cdot [\,p(k) + p(j)\,] = a \cdot [\,2p + (k + j)\Delta p\,] \end{aligned}$$

Summing over all loci and recalling Equations 18.34a and 18.34b gives the excepted mean for this cross as

$$C_{k\times j} = m + A \cdot \frac{k + j}{2} \tag{18.35b}$$

Under this simple additive model, the mean of any particular population (a line C_k or the progeny from a line cross $C_{k\times j}$) is given by the constants m and A and the selection cycle number. We can test the goodness-of-fit by comparing the predicted and actual mean values (LW Chapter 9).

Equations 18.35a/b have a simple form because of the strict additivity (no dominance or epistasis) assumption. When loci show dominance, the expressions for line and line-cross means are more complex. Line means may change under selfing, but any such change allows us to estimate certain dominance components, and care is required when considering the *progeny* of line crosses. We can regard the progeny from a particular cross (say $C_{k\times j}$) as an F_1, and can generate an F_2 by either selfing individuals (when possible) or by letting the F_1 randomly-mate. Under strict additivity, the means of both types of F_2 offspring are still given by Equation 18.35b, the mean value of the F_1. When loci show dominance, the F_1 mean and the two different types of F_2 all differ from each other. Again, these differences offer opportunities to estimate various dominance components.

The Hammond-Gardner Model

Motivated by the general diallel analysis of Gardner and Eberhart (1966), Hammond and Gardner (1974) extended the simple additive model to allow for dominance, which requires three additional parameters (D_0, D, and D_q). Assuming all lines start from the same base population, as derived below in Example 18.9, the Hammond-Gardner model gives the means for various lines and line crosses as:

$$C_k = m + A \cdot k + D_0 + D \cdot k + D_q \cdot k^2 \tag{18.36a}$$

$$C_k(s) = m + A \cdot k + \frac{1}{2}\left(D_0 + D \cdot k + D_q \cdot k^2\right) \tag{18.36b}$$

$$C_{k\times j} = m + \frac{A}{2}(k + j) + D_0 + \frac{1}{2}\,[\,D \cdot (k + j) + 2D_q \cdot kj\,] \tag{18.36c}$$

$$C_{k\times j}(s) = m + \frac{A}{2}(k + j) + \frac{D_0}{2} + \frac{1}{4}\,[\,D \cdot (k + j) + 2D_q \cdot kj\,] \tag{18.36d}$$

$$C_{k\times j}(rm) = C_{k\times j} + \frac{D_q}{4}(k - j)^2 \tag{18.36e}$$

where (s) and (rm) respectively denote the selfed and randomly-mated next generations given the cross/line. For example, $C_4(s)$ is the mean among the selfed progeny of individuals from cycle four. Likewise, for $C_{2\times6}(rm)$ we cross cycle two and cycle six individuals, let their offspring randomly mate and then measure the resulting progeny. As expected, when all of the dominance terms are zero, Equation 18.36 reduces to Equation 18.35. With no dominance, there is no change in the line mean following inbreeding, so that $C_k = C_k(s)$, and the F_1 progeny mean from a cross has the same mean as the progeny from either a selfed or randomly-mated F_2, $C_{k\times j} = C_{k\times j}(s) = C_{k\times j}(rm)$.

Closer inspection of the coefficients on the model parameters in Equations 18.36a-e informs us what types of crosses are required to estimate parameters of interest. If the investigator only has (unselfed) line means C_k and their F_1 crosses $C_{k\times j}$, A and D are not separately estimable, as they appear as $k(A + D)$ in expressions for these means. Obtaining separate estimates requires different coefficients on A and D terms, as occurs with either selfed lines or F_2 crosses. These particular crosses provide additional information on the genetic nature of the between-generation divergence that is not given by the simple line means, or their F_1s, alone. Likewise, one cannot obtain separate estimates of m and D_0 unless there is at least one selfed line in the study. These terms enter as $m + D_0$ in all randomly-mating populations, but as $m + D_0/2$ in selfed populations.

As with the strictly additive model, we can express the parameters of the Hammond-Gardner model in terms of locus-specific parameters, with m and A as defined by Equations 18.34a,b. Letting d_i be the dominance for locus i, so that the genotypic values are now $0 : a_i + d_i : 2a_i$, the dominance-related parameters D_0, D, and D_q in Equation 18.36 are as follows. D_0 is the contribution (to the mean) from dominance in the initial (cycle 0) population,

$$D_0 = 2\sum p_i(1 - p_i)d_i \tag{18.37a}$$

The role of dominance in response in the line means enters through D and D_q, which are the linear and quadratic regression coefficients on cycle number. D is given by

$$D = 2\sum \Delta p_i(1 - 2p_i)d_i \tag{18.37b}$$

and appears in Equation 18.36 as terms of the form $D \cdot k$, namely D times the appropriate selection cycle number k. Recalling that the average effect α of an allele substitution (replacing an unfavorable allele by a favorable one) is $a + d(1 - 2p)$ (LW Equation 4.10), we have

$$\begin{aligned} A + D &= 2\left(\sum \Delta p_i a_i + \sum \Delta p_i(1 - 2p_i)d_i\right) \\ &= 2\left(\sum \Delta p_i \left[a_i + (1 - 2p_i)d_i\right]\right) = 2\sum \Delta p_i \alpha_i \end{aligned} \tag{18.37c}$$

with $A+D$ representing the per-generation change in the trait mean as a linear regression on cycle number (e.g., $k(A+D)$ for line k), which is also twice the average effect of substituting an unfavorable allele with the favorable one weighted by the allele-frequency change.

The final dominance term,

$$D_q = -2\sum \left(\Delta p_i\right)^2 d_i, \tag{18.37d}$$

appears as a quadratic function of cycle number, with terms of the form $k^2 D_q$ for cycle k and kjD_q for crosses from cycles j and k. This is perhaps the most interesting dominance term, as it measures both inbreeding depression and the expected heterosis when two lines are crossed. As discussed below, it has also been interpreted as the component of change

in the mean due to the effects of drift, with $A + D$ representing the response from selection (deterministic change). Recall (LW Chapter 10) that the heterosis H between two lines,

$$H = \mu_{1\times 2} - \frac{\mu_1 + \mu_2}{2}$$

is the difference between the mean of the F_1 and the average of its parental lines. In the absence of epistasis,

$$H = \sum (\delta p_i)^2 d_i \tag{18.37e}$$

where δp_i is the between-line difference in allele frequency for the favorable allele at the ith locus and d_i the associated dominance term. Since the expected difference δp_i in allele frequency between lines separated by a single cycle of selection is Δp_i, comparing Equations 18.37d and e shows that D_q is minus twice the heterosis generated by a single generation of selection, $D_q = -2H$.

Example 18.9. Here we derive the line and cross means when dominance is present. While the focus is on the contribution from specific locus, we suppress the subscript (on a, d, and p) denoting the locus being followed for ease of presentation. Since we assume no epistasis, the mean follows by summing the contributions over all loci. To allow for dominance, the genotypic values at our target locus become $0 \ : \ a + d \ : \ 2a$ with p the frequency of the favorable allele. The mean contribution from this locus is

$$0 \cdot (1 - p^2) + (a + d) \cdot 2p(1 - p) + (2a) \cdot p^2 = 2ap + 2dp(1 - p)$$

Notice that contribution from a is a linear functions of the allele frequency (and hence a linear functions of allele frequency change). On the other hand, contributions from d have both a linear (p) and a quadratic (p^2) component. The contribution from this locus to the line mean in cycle k follows by replacing p by $p(k) \simeq p + k\Delta p$,

$$\begin{aligned} C_k &= \mu + 2ap(k) + 2dp(k)[\,1 - p(k)\,] \\ &= \mu + 2a[\,p + k\Delta p\,] + 2d[\,p + k\Delta p\,][\,1 - (p - k\Delta p)\,] \\ &= \big(\mu + 2ap\big) + k \cdot 2a\Delta p + 2dp(1 - p) + k \cdot 2d\Delta p \cdot (1 - 2p) - k^2 \cdot 2d\,(\Delta p)^2 \\ &= m + k \cdot A + D_0 + k \cdot D + k^2 \cdot D_q \end{aligned}$$

Now suppose this line is selfed. Homozygotes replicate themselves, while segregation of genotypes occurs when heterozygotes are selfed, with half of the offspring being $a + d$ heterozygotes, $1/4$ being $2a$ homozygotes, and $1/4$ being 0-valued homozygotes. The resulting mean value following a generation of selfing is the sum of these contributions,

$$p^2\,[2a] + 2p(1-p)\,[(1/4)(2a) + (1/2)(a + d) + (1/4) \cdot 0] + (1-p^2) \cdot 0 = 2ap + dp(1-p)$$

Note that all terms involving d are exactly half of their random-mating values, giving

$$C_k(s) = m + k \cdot A + \frac{1}{2}\,\big(D_0 + k \cdot D + k^2 \cdot D_q\big)$$

Now consider the mean of the cross of lines from cycles k and j. As above, the chance of getting a 0-valued homozygote is $[\,1 - p(k)\,]\,[1 - p(j)\,]$, the $a + d$ heterozygote $p(k)\,[\,1 -$

$p(j)\,] + p(j)\,[\,1 - p(k)\,]$, and the $2a$ homozygote $p(k)\,p(j)$, giving the resulting mean as

$$\begin{aligned} C_{k\times j} &= \mu + (a+d)\cdot\Big(p(k)\,[\,1-p(j)\,] + p(j)\,[\,1-p(k)\,]\Big) + 2a\cdot p(k)p(j) \\ &= \mu + a\Big(p(k)+p(j)\Big) + d\cdot\Big(p(k)+p(j)-2p(k)p(j)\Big) \\ &= \big(\mu + 2ap\big) + (k+j)a\Delta p + d\Big(2p(1-p) + (k+j)\cdot\Delta p(1-2p) - k\,j\cdot 2\,(\Delta p)^2\Big) \\ &= m + \frac{k+j}{2}\cdot A + D_0 + \frac{k+j}{2}\cdot D + k\,j\cdot D_q \end{aligned}$$

If we self these individuals to form an F_2, by the same argument used above for selfing a line, each of the dominance terms is reduced by 1/2, recovering Equation 18.36d.

Finally, when we form an F_2 by randomly-mating the F_1 progeny from a line cross, the new allele frequency is

$$\frac{p(k)+p(j)}{2} \simeq p + \frac{k+j}{2}\Delta p$$

giving the mean as

$$\begin{aligned} C_{k\times j}(rm) &= \mu + 2a\left(p + \frac{k+j}{2}\Delta p\right) + 2d\left(p+\frac{k+j}{2}\Delta p\right)\left(1-p-\frac{k+j}{2}\Delta p\right) \\ &= (\mu+2ap) + \frac{k+j}{2}2a\Delta p + 2dp(1-p) + \frac{k+j}{2}2d\Delta p(1-2p) - \left(\frac{k+j}{2}\right)^2 2d(\Delta p)^2 \\ &= m + \frac{k+j}{2}\cdot A + D_0 + \frac{k+j}{2}\cdot D + \left(\frac{k+j}{2}\right)^2\cdot D_q \end{aligned}$$

Recalling Equation 18.36c, we can express this as

$$C_{k\times j}(rm) = C_{k\times j} - kj\cdot D_q + \left(\frac{k+j}{2}\right)^2\cdot D_q = C_{k\times j} + \frac{(k-j)^2}{4}\cdot D_q$$

The additional term is just the decay in heterosis following random mating, as the heterosis in the F_1 cross between lines from cycles j and k is

$$\begin{aligned} H &= \sum (p_i(k) - p_i(j))^2 d_i = \sum (p + k\Delta p - p - j\Delta p)^2 d_i \\ &= (k-j)^2 \sum (\Delta p_i)^2 d_i = -(k-j)^2 D_q/2 \end{aligned}$$

Recalling (LW Chapter 9) that heterosis is reduced by half going from the F_1 (H) to a randomly-mated F_2 ($H/2$), gives

$$C_{k\times j}(rm) - C_{k\times j} = -\frac{H}{2} = (k-j)^2\frac{D_q}{4}$$

as found above.

The composite parameters (e.g., m, A, D_0, etc.) are typically estimated by OLS, with the vector of estimates given by $\left(\mathbf{X}^T\mathbf{X}\right)^{-1}\mathbf{X}^T\mathbf{y}$, with $\mathbf{y}$ the vector of population means and the

design matrix $\mathbf{X}$ contains the appropriate coefficients for the parameters of interest (Example 18.10). The machinery introduced in LW Chapter 9 for standard line-cross analysis, such as hypothesis testing, testing goodness-of-fit, and estimation via GLS when the standard errors vary over means, can all be applied to this and other models in a straight-forward fashion. As with a standard line-cross analysis, one starts a GMA with the simple additive model and then tests whether adding additional model terms significantly improves the fit (LW Chapter 9). Typically one ends up with a reduced model, as some of the parameters turn out to be nonsignificant.

Example 18.10: As a simple worked example of the Hammond-Gardner model, we considered eight populations (cycles 0, 4, 7 and their crosses) from a much larger sample generated by a selection experiment for yield in maize analyzed by Smith (1983). Suppose we wish to estimate the parameters in the Hammond-Gardner model, fitting a reduced model where D_q is excluded. The crosses (which includes two selfed populations), their means, and the resulting coefficients (in Equation 18.36) for the parameters to estimate are as follows:

		Coefficients			
Line/cross	mean	m	A	D_0	D
C_0	59.7	1	0	1	0
C_4	63.4	1	4	1	4
C_7	68.9	1	7	1	7
$C_7(s)$	42.3	1	7	$\frac{1}{2}$	7/2
$C_{0\times4}$	61.2	1	$\frac{0+4}{2}$	1	$\frac{0+4}{2}$
$C_{0\times7}$	79.6	1	$\frac{0+7}{2}$	1	$\frac{0+7}{2}$
$C_{4\times7}$	72.3	1	$\frac{4+7}{2}$	1	$\frac{4+7}{2}$
$C_{4\times7}(s)$	40.3	1	$\frac{4+7}{2}$	$\frac{1}{2}$	$\frac{4+7}{4}$

The resulting vector $\mathbf{y}$ of means and the design matrix become

$$\mathbf{y} = \begin{pmatrix} 59.7 \\ 63.4 \\ 68.9 \\ 42.3 \\ 61.2 \\ 79.6 \\ 72.3 \\ 40.3 \end{pmatrix}, \qquad \mathbf{X} = \begin{pmatrix} 1 & 0 & 1 & 0 \\ 1 & 4 & 1 & 4 \\ 1 & 7 & 1 & 7 \\ 1 & 7 & 0.5 & 3.5 \\ 1 & 2 & 1 & 2 \\ 1 & 3.5 & 1 & 3.5 \\ 1 & 5.5 & 1 & 5.5 \\ 1 & 5.5 & 0.5 & 2.75 \end{pmatrix}$$

Solving for the vector of parameter estimates gives

$$\begin{pmatrix} \widehat{m} \\ \widehat{A} \\ \widehat{D}_0 \\ \widehat{D} \end{pmatrix} = \left(\mathbf{X}^T\mathbf{X}\right)^{-1}\mathbf{X}^T\mathbf{y} = \begin{pmatrix} 4.266 \\ 1.072 \\ 57.402 \\ 0.523 \end{pmatrix}$$

Based on this subset of data, we note that there is considerable dominance ($\widehat{D}_0 = 57.402$) influencing the initial value of the trait. Of the per-generation change of 1.595 per generation, roughly 2/3 is from A (1.072), and 1/3 from D (0.5223). Standard errors follow using normal OLS machinery (LW Chapter 9).

GMA can be generalized to situations where some of the crosses are between lines from different base populations (Smith 1979b, 1983; Helms et al. 1989; Butruille et al 2004; Melchinger and Flachenecke 2006). The same logic as above holds, with the frequency of the favorable allele in cycle k from base population j being $p_j(k) \simeq p_j + k\Delta p_j$, with associated parameters $m_j, A_j, D_j, D_{0,j}, D_{q.j}$. Additional terms are required to account for any initial heterosis (cycle zero crosses between base populations j and i), which from Equation 18.37e is a function of their squared difference in allele frequencies, $\delta^2_{i,j} = (p_i - p_j)^2$. Finally, terms for additional heterosis that has accrued during selection are required, again these are functions of the squared allele frequency differences. For a cycle k line from base population i crossed to a cycle ℓ line form base population j, this is

$$[p_j(k) - p_i(\ell)]^2 = [p_j + k\Delta p_j - (p_i + \ell\Delta p_i)]^2$$

The motivation for this type of analysis is examined in our final volume, where the breeding for superior hybrids between lines is discussed. Basically, one tries to improve both the performance of two selected lines in addition to improving the performance of their resulting hybrids. Generations-means analysis can help partition any observed improvement into components of within- and between-line (hybrid) improvement.

Accounting for Inbreeding Depression and Drift

The deterministic assumption of a constant rate of allele frequency change in the Hammond-Gardner model requires large population sizes. Since a typical selection experiment often involves small populations, genetic drift can also be important, with the consequences of drift appearing as inbreeding depression due to some favorable alleles *decreasing* in frequency under drift. Smith (1979a,b; 1983) was the first to incorporate drift and inbreeding depression in to a GMA, while the most general treatment is due to Melchinger and Flachenecker (2006). Their key idea is to separate allele frequency at cycle k into deterministic and drift components,

$$p(k) = p(0) + k\Delta p + \delta_k p \tag{18.38}$$

where the Δp represents the expected large-population change (i.e., the Hammond-Gardner model), while $\delta_k p$ accounts for the additional change due to drift. Recalling from Chapter 2 that under drift $E[\,\delta p_k\,] = 0$, so that $E\left[\,(\delta p_k)^2\,\right] = \sigma^2(\delta p_k)$. Under pure drift, the allele frequency variance after k generations is

$$\sigma^2(\delta p_k) = p(0)[1 - p(0)]f_k \tag{18.39a}$$

where $f_k \simeq k/(2N_e)$ is the amount of inbreeding in cycle k. Melchinger and Flachenecker suggest that with selection, Equation 18.39a can be approximated by using the average frequency over the k cycles,

$$E[\,(\delta_k p)^2\,] \simeq \left(\frac{p(0)[\,1 - p(0)\,] + p(k)[\,1 - p(k)\,]}{2}\right) f_k \tag{18.39b}$$

Using the deterministic approximation $p(k) = p(0) + k\Delta p$, this reduces to

$$E[\,(\delta_k p)^2\,] \simeq p(0)[\,1 - p(0)\,]\, f_k + \frac{k}{2} \cdot (1 - 2p)\Delta p\, f_k - \frac{k^2}{2}\,(\Delta p)^2\, f_k \tag{18.39c}$$

Notice the close similarity of these three terms to D_0, D, and D_q. Using Equation 18.38 as the model for allele frequency and following the logic used in Example 18.9, the adjustment in the mean for inbreeding due to drift becomes

$$I_k = \left(D_0 + \frac{k \cdot D}{2} - \frac{k^2 \cdot D_q}{2}\right) f_k. \tag{18.40a}$$

Assuming $f_k = k\Delta f$ this simplifies to

$$I_k = k\left(D_0 + \frac{k \cdot D}{2} - \frac{k^2 \cdot D_q}{2}\right)\Delta f \tag{18.40b}$$

The resulting line means are

$$C_k = C_k(HG) - I_k \qquad \text{and} \qquad C_k(s) = C_k(s, HG) - I_k/2, \tag{18.41a}$$

while the line cross means become

$$C_{k\times j} = C_{k\times j}(HG) - I_k \quad \text{for } j > k \tag{18.41b}$$

where HG denotes the value under the Hammond-Gardner model (Equations 18.36a-e). The presence of drift ($f_k > 0$) modifies the contributions from the three dominance terms, resulting in a guaranteed reduction in mean when $D_0, D > 0$ (as D_q is always ≤ 0). Smith (1979a, 1983) equated this reduction to inbreeding depression, which arises from drift causing some favorable alleles to decrease in frequency. On average, drift is equally likely to increase, or decrease, the change in frequency of an allele over its deterministic value Δp. Thus, under drift, some alleles have a greater than deterministic increase in frequency, but this is countered by (on average) others having a less than expected increase. For additive genes, the expected value of these changes exactly cancel (as $E(\delta p_k) = 0$). However, with dominance, this variance in allele frequency change around Δp does not cancel, as the mean is a quadratic function of d terms.

While Melchinger and Flachenecker's analysis is exact, the approximate results of Smith (1979a, 1983) had a significant influence on GMA, so a few comments on his approximations are in order. Smith (1979a) added a simple linear term $I_k = k \cdot I$, where $I = (D_0 + D)$, to account for inbreeding. Note by comparison to the exact result (Equation 18.40) that this is only correct when $D_0 \gg D$ and D_q is negligible (as Smith assumed). Further, Smith neglected to include I_k in his expressions for the line cross means (Equation 18.41b). Smith ignored the D_q term, as he felt that Δp was expected to be small, and hence its square likely negligible (or in any case potentially difficult to estimate with precision). Conversely, in Smith (1983), he instead ignored the inbreeding correction, suggesting for experiments with very small effective population size that $E\left[(\delta p_k)^2\right] \gg (\Delta p)^2$, and thus D_q was a surrogate measure for drift, as most of its value was due to the drift variance. Equations 18.40 and 18.41 show that both of these ideas, while correct in spirit, are approximations of the more general solution (Equation 18.40b). However, they may often be fairly good. For example, Flachenecker et al. (2006) found that both the Smith (1983) and Melchinger-Flachenecker models gave rather similar parameter estimates. The critical insight offered by Smith's analysis is that by adjusting for the effects of drift, one could estimate the potential response if a larger population size was used, as the following two examples illustrate.

Example 18.11. Helms et al. (1989) obtained an estimate of $\widehat{D_q} = -0.024$ (which was significant at the 1% level) in an analysis of a maize line, BSS(R), selected for yield. Assuming small effective population size, how much was the population mean at cycle 10 reduced due to drift-generated inbreeding depression? Recalling (Equation 18.36a) that the contribution from D_q in cycle k is $D_q \cdot k^2 = -0.024 \cdot 10^2 = -2.4$. Thus the observed mean (assuming the Smith 1983 model assumptions hold) is expected to be reduced by 2.4 units from the effects of drift generating inbreeding depression.

Example 18.12. Smith (1979b) examined the relative effectiveness of two different section schemes (using half sib (HT) versus S_1 (S) family selection, procedures examined in Chapters 21 and 23) for yield in maize using the cultivar *BSK*. Both the Hammond-Gardner and Smith (1979a) models were fit to the data, obtaining the following values:

		Hammond-Gardner	Smith
BSK(HT)	A	0.7 ± 0.15	1.22 ± 0.15
	I	—	-1.83 ± 0.28
	D, D_q	not significant	—
BSK(S)	A	1.42 ± 0.15	1.97 ± 0.15
	I	—	-1.83 ± 0.28
	D, D_q	not significant	—

Ignoring inbreeding by using the Hammond-Gardner model resulted in a significant underestimation of A. Smith's GMA analysis shows that both selection schemes result in significant amounts of inbreeding depression (-1.83) but also significant gains (1.32 and 1.97). Increasing the effective population size is expected to decrease Δf, and thus the magnitude of I, enhancing response. Both the Smith and Hammond-Gardner analyses show that S_1 selection is about twice as effective as half-sib selection, as measured in terms of average genetic gain ($A + D$) per cycle.

Finally, a very quick back-of–the-envelope calculation suggests when $\sigma^2(\delta p) \gg (\Delta p)^2$. Equation 5.2 shows that $\Delta p \simeq sp(1-p)$ for a very weakly-selected additive locus, while Equation 5.21 gives $s \simeq \overline{\imath}\, a/\sigma_z$, where $\overline{\imath}$ is the selection intensity on the trait and σ_z^2 the phenotypic variance, yielding $\Delta p_i \simeq (\overline{\imath}\, a_i/\sigma_z)p_i(1-p_i)$. Recalling that $\sigma^2(A_i) = 2a_i^2 p_i(1-p_i)$ is the additive variance contribution from locus i,

$$
\begin{aligned}
(\Delta p_i)^2 \simeq (\overline{\imath}\, a_i/\sigma_z)^2 p_i^2(1-p_i)^2 &= \overline{\imath}^2 p_i(1-p_i)\left(\frac{a_i^2 p_i(1-p_i)}{\sigma_z^2}\right) \\
&= \overline{\imath}^2 p_i(1-p_i)\left(\frac{\sigma^2(A_i)/2}{\sigma_z^2}\right) = \frac{\overline{\imath}^2 p_i(1-p_i)}{2} h_i^2
\end{aligned}
$$

where h_i^2 is the heritability due to locus i. Assuming n loci underlying the trait contribute roughly the same to the overall heritability h^2, we arrive at

$$
(\Delta p_i)^2 \simeq \frac{p_i(1-p_i)}{2}\frac{\overline{\imath}^2 h^2}{n} \tag{18.42a}
$$

Drift dominates the expected quadratic change when $\sigma^2(\delta p) \gg (\Delta p)^2$, or

$$
\frac{p(1-p)}{2N_e} \gg \frac{p(1-p)}{2}\frac{\overline{\imath}^2 h^2}{n}
$$

or when

$$
n \gg N_e\left(\overline{\imath}^2 h^2\right) \tag{18.42b}
$$

For example, for a trait with $h^2 = 0.25$ under truncation selection to save the largest 5% (from Example 14.1, $\overline{\imath} = 2.06$), $\overline{\imath}^2 h^2 \simeq 1$, so that drift dominate the quadratic term when the number of loci is much greater than the effective population size (assuming loci have roughly equal effect). Expressed another way, the fractional contribution to the expected square in allele frequency change from drift is

$$
\frac{\sigma^2(\delta p)}{\sigma^2(\delta p) + (\Delta p)^2} \simeq \frac{1/N_e}{1/N_e + \overline{\imath}^2 h^2/n} = \frac{1}{1 + \overline{\imath}^2 h^2 N_e/n} \tag{18.42c}
$$

or

$$\frac{\sigma^2(\delta p)}{\sigma^2(\delta p) + (\Delta p)^2} \simeq 1 - \bar{\imath}^2 h^2 N_e/n, \quad \text{when} \quad n \gg Ne \tag{18.42d}$$

For $h^2 = 0.25, \bar{\imath} = 2.06$, and $n = 100$ and $N_e = 25$, Equation 18.42c gives 0.79, while the approximation given by Equation 18.42d yields 0.74. Hence, in this setting almost 80% of the expected quadratic change is due to drift.

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