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CHANGES IN GENETIC VARIANCE INDUCED BY RANDOM GENETIC DRIFT

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We noted in Chapter 2 that when operating as the sole evolutionary force, random genetic drift leads inevitably to the loss of alleles within populations as well as to the fixation of alternative alleles in different populations. These conclusions extend logically to quantitative characters. Following a reduction in population size, for example, we expect the genetic variance within populations to decline and the mean phenotypes of isolated populations to diverge. There are some interesting surprises, however, particularly when the mode of gene action has a nonadditive component. In the latter case, the genetic variance for a trait is not a simple function of the underlying heterozygosity (LW Chapter 4), so we cannot expect the temporal dynamics of genetic variance to strictly reflect patterns of heterozygosity. Indeed, as will be shown below, under certain conditions, the genetic variance for a quantitative trait is expected to transiently *increase* during the early phase of a population bottleneck.

The goal of the following two chapters is to develop a null (neutral) hypothesis for quantitative-trait evolution, under the assumption that selection is a negligible evolutionary force. For the most part, we will continue to adhere to an ideal Wright-Fisher form of population structure, with random mating and discrete generations. In this vein, our conceptual approach will be to consider a series of replicate populations, all isolated at the same time from a large base population, generally assumed to be in Hardy-Weinberg and gametic-phase equilibrium, and all subsequently kept indefinitely at an identical population size. The current chapter focuses on the the expected dynamics of the genetic variance within populations, whereas Chapter 6 focuses on interpopulational divergence.

In both chapters, we will initially assume that the dynamics of evolutionary change are due entirely to genetic properties of the base population, which is essentially the case with short-term population bottlenecks. Then, the role of mutation

will be taken up. In this chapter, for example, we will end by considering the levels of genetic variance expected in the absence of selection, when a stochastic equilibrium has been reached between the input of variation by mutation and the loss by genetic drift. Here we will also consider the statistical underpinnings of the covariance between relatives in inbred populations, as this has special relevance in attempts to derive inferences about the mode of gene action from phenotypic observations.

The subject material of this chapter is particularly technical, as it involves the expected temporal dynamics of higher-order gene-frequency moments, including at the minimum fourth-order moments, as well as a number of quadratic components of gene action not previously encountered with outbred populations. With quantitative traits, we must also worry about the joint distribution of allele frequencies at different loci, so issues of linkage disequilibrium come in as well. The complexities quickly get out of control in considering the sampling variances of genetic variances and covariances, and we will keep our treatment of these issues to a minimum, which is not to deny their substantial practical significance. Finally, we note that most of our coverage will be concerned with genetic *variance,* although all moments of the phenotype distribution are subject to change in the presence of drift and mutation.

RESPONSE OF WITHIN-POPULATION GENETIC VARIANCE TO DRIFT

Consider a diallelic locus indexed by i with a strictly additive genetic basis such that the three genotypic values contributing to a quantitative trait are scaled to be 0, a_i, and $2a_i$. Assuming Hardy-Weinberg equilibrium, at any particular generation t, the total (and additive) genetic variance associated with this locus can be denoted by $2a_i^2 p_i(t)[1 - p_i(t)]$, where $p_i(t)$ is the allele frequency at time t (LW Chapter 4). Assuming gametic-phase equilibrium, this expression is readily extended to a multilocus trait with a purely additive genetic basis. Summing over all n loci contributing to the trait, the expected within-population genetic variance is

$$\sigma_A^2(t) = 2\sum_{i=1}^{n} E\{a_i^2 p_i(t)[1 - p_i(t)]\} \tag{5.1}$$

From Chapter 2, we know that the expected heterozygosity after t generations at effective population size N_e is simply $[1-1/(2N_e)]^t$ times the initial value. Moreover, under the assumption of neutrality, there should be no correlation between allele frequency and effect, so substituting from Equation 2.5,

$$\begin{aligned}\sigma_A^2(t) &= 2\sum_{i=1}^{n} a_i^2 p_i(0)[1 - p_i(0)]\left(1 - \frac{1}{2N_e}\right)^t \\ &= \sigma_A^2(0)\left(1 - \frac{1}{2N_e}\right)^t \end{aligned} \tag{5.2}$$

(Wright 1951).

Equation 5.2 illustrates the simplest possible behavior that can be expected for the genetic variance within a finite population, starting with a baseline level of

$\sigma_A^2(0)$. For a character with a purely additive genetic basis, in the absence of any significant replenishing forces for variation (mutation or migration), the additive genetic variance within populations is expected to decline exponentially at the rate $1/(2N_e)$ per generation. However, a key point to realize about Equation 5.2 is that it describes the *expected* behavior of the genetic variance, averaged over a very large number of replicate populations. As will be discussed below, as a consequence of the stochastic sampling of gene frequencies, any single replicate population can deviate substantially from the expected trajectory.

The Effects of Dominance

Robertson (1952) extended the preceding theory to loci with dominance, obtaining the surprising result that rare recessive alleles can sometimes cause an initial increase in both the additive and dominance components of variance in an inbreeding population. A rare neutral allele will usually be lost from a small population in which case the variance will decline, but if the frequency of a rare recessive allele stochastically increases, the frequency of the extreme genotype must also increase. For completely recessive alleles, a temporary inflation of the expected within-population variance will occur provided the initial frequency of the recessive genotype is less than 0.17 (Robertson 1952). Although an inflation of the expected variance can also occur with partial dominance, the critical initial frequency for the recessive allele becomes progressively smaller as additivity is approached. Regardless of the degree of dominance, however, the within-population variance must eventually decline to zero as loci move toward fixation, as in the case of pure additivity.

Robertson (1952), and thereafter Willis and Orr (1993), considered only a single diallelic locus, and things get much messier with multiple loci and more than two alleles per locus. Fairly general results have been obtained for the case in which all of the genetic variance can be partitioned into additive, dominance, and additive $\times$ additive epistatic components (Cockerham 1984a,b; Cockerham and Tachida 1988; Tachida and Cockerham 1989). But even for this case, and assuming initial conditions of Hardy-Weinberg and gametic-phase equilibrium, the temporal dynamics of genetic variance depend on seven quadratic properties of the base population, as well as on several expectations for the higher-order moments of allele/gamete frequencies. We first present the general model, and then consider some illuminating results that arise under special conditions.

The base-population properties contributing to the dynamics of genetic variance in the absence of epistasis involving three or more factors are outlined in Table 5.1. These include the familiar parameters σ_A^2, σ_D^2, and σ_{AA}^2 (i.e., the additive, dominance, and additive $\times$ additive components of genetic variance; LW Chapter 5); the inbreeding depression ι, here defined to be the difference between the mean phenotypes of outbred and completely inbred individuals; the sum of squared locus-specific inbreeding depressions ι^*; the variance of dominance effects among inbred individuals σ_{DI}^2; and the covariance of additive and dominance effects in inbred individuals σ_{ADI}. Simplification is possible under certain circumstances. Most notably, with only two alleles per locus, $\iota^* = \sigma_D^2$, and if all alleles have frequency 0.5, as in a cross between two pure lines, $\sigma_{DI}^2 = \sigma_{ADI} = 0$.

Table 5.1. Factors contributing to the additive, dominance, and additive × additive components of genetic variance in finite populations, with Cockerham's notation on the right. n is the number of loci, n_k the number of alleles at the kth locus, p_{ki} the frequency of the ith allele at locus k, α_{ki} the additive effect of the ith allele at locus k, δ_{kij} the dominance effect at locus k associated with genotype ij, and $(\alpha\alpha)_{ki,mj}$ the additive × additive effect of alleles i and j from different loci (k and m) (LW Chapters 4,5). The inbreeding depression is defined for individual loci (ι_k for locus k) as well as for the sum over all loci (ι). All properties are defined from the standpoint of the base population.

Additive variance	$\sigma_A^2 = 2\sum_{k=1}^{n}\sum_{i=1}^{n_k} p_{ki}\alpha_{ki}^2 = 2\sum_{k=1}^{n} E(\alpha_{k\cdot}^2)$	σ_A^2
Dominance variance	$\sigma_D^2 = \sum_{k=1}^{n}\sum_{i=1}^{n_k}\sum_{j=1}^{n_k} p_{ki}p_{kj}\delta_{kij}^2 = \sum_{k=1}^{n} E(\delta_{k\cdot\cdot}^2)$	σ_D^2
Epistatic variance	$\sigma_{AA}^2 = 4\sum_{k,m=1}^{n}\sum_{i=1}^{n_k}\sum_{j=1}^{n_m} p_{ki}p_{mj}(\alpha\alpha)_{ki,mj}^2 = 4\sum_{k,m=1}^{n} E[(\alpha\alpha)_{k\cdot,m\cdot}^2]$	σ_{AA}^2
Inbreeding depression	$\iota_k = \sum_{i=1}^{n_k} p_{ki}\delta_{kii} = E(\delta_{kii})$ $\quad \iota = \sum_{k=1}^{n}\iota_k$	H
Sum of squared locus-specific inbreeding depressions	$\iota^* = \sum_{k=1}^{n}\iota_k^2$	H^*
Variance of dominance effects in inbred individuals	$\sigma_{DI}^2 = \sum_{k=1}^{n}\sum_{i=1}^{n_k}(p_{ki}\delta_{kii}^2 - \iota_k^2) = \sum_{k=1}^{n}[E(\delta_{kii}^2) - \iota_k^2]$	D_2^*
Covariance of additive and dominance effects in inbred individuals	$\sigma_{ADI} = 2\sum_{k=1}^{n}\sum_{i=1}^{n_k} p_{ki}\alpha_{ki}\delta_{kii} = 2\sum_{k=1}^{n} E(\alpha_{ki}\delta_{kii})$	$2D_1$

The contributions of the factors in Table 5.1 to the traditional components of genetic variance (e.g., σ_A^2, σ_D^2, and σ_{AA}^2) in a finite population depend upon several one- and two-locus identity coefficients (Figure 5.1). Of the one-locus coefficients, f is the familiar inbreeding coefficient, i.e., the probability that two gametes are identical by descent at a particular locus (Chapter 2). The probabilities that the members of random groups of three and four gametes are identical by descent are denoted by γ and δ (not to be confused with the dominance effects, which are subscripted in Table 5.1). Δ also involves four gametes, but it is the probability of identity by descent within two pairs of gametes (including the possibility that all four genes are identical by descent). For randomly mating monoecious populations under the classical Wright-Fisher model, the transition equations for these coefficients are

functions of N_e and t,

$$f_t = 1 - \lambda_1^t \tag{5.3a}$$

$$\gamma_t = 1 - \frac{3\lambda_1^t}{2} + \frac{\lambda_2^t}{2} \tag{5.3b}$$

$$\Delta_t = 1 - \frac{24\lambda_1^t - 10\lambda_2^t + \lambda_3^t}{15} + \frac{\lambda_1^t - \lambda_3^t}{5(5N_e - 3)} \tag{5.3c}$$

$$\delta_t = 1 - \frac{9\lambda_1^t - 5\lambda_2^t + \lambda_3^t}{5} - \frac{3\lambda_1^t}{20(5N_e - 3)} + \frac{\lambda_2^t}{12(N_e - 1)} - \frac{(8N_e - 3)\lambda_3^t}{30(5N_e - 3)(N_e - 1)} \tag{5.3d}$$

where $\lambda_1 = 1 - (1/2N_e)$, $\lambda_2 = [1 - (2/2N_e)]\lambda_1$, and $\lambda_3 = [1 - (3/2N_e)]\lambda_2$ (Cockerham and Weir 1983).

The three two-locus coefficients (denoted by tildes in Figure 5.1) refer to joint identities by descent at two loci. First, $\tilde{f}$ refers to pairs of genes on two gametes, which under neutrality, random mating, and linkage equilibrium cannot be less than the product of the separate identity probabilities for each locus, f^2. Second, $\tilde{\gamma}$ refers to the situation in which each member of a pair of genes in one gamete is identical by descent with a gene in a separate gamete. Finally, $\tilde{\Delta}$ is the joint identity by descent of genes (two at each locus) in two pairs of different gametes. The transition equations for these double identity-by-descent measures, which have been derived by Weir and Cockerham (1969) for ideal monoecious populations, depend upon the linkage parameter $\rho = 1 - 2c$ (where c is the recombination frequency between loci, which has a maximum value of 0.5), N_e, and t. Letting $\tilde{f}_t = \tilde{f}_t^* + 2f_t - 1$, $\tilde{\gamma}_t = \tilde{\gamma}_t^* + 2f_t - 1$, and $\tilde{\Delta}_t = \tilde{\Delta}_t^* + 2f_t - 1$, the coefficients are obtained by use of Equation 5.3a and the following matrix expression,

$$\begin{pmatrix} \tilde{f}^* \\ \tilde{\gamma}^* \\ \tilde{\Delta}^* \end{pmatrix}_{t+1} = \begin{pmatrix} \frac{(1+\rho)^2}{4} - \frac{\rho}{2N_e} & \frac{(N_e-1)(1-\rho^2)}{2N_e} & \frac{(N_e-1)(1-\rho)^2}{4N_e} \\ \frac{1+\rho}{4N_e} - \frac{\rho}{4N_e^2} & \frac{(N_e-1)[N_e+1+\rho(N_e-2)]}{2N_e^2} & \frac{(N_e-1)(2N_e-3)(1-\rho)}{4N_e^2} \\ \frac{2N_e-1}{4N_e^3} & \frac{(N_e-1)(2N_e-1)}{N_e^3} & \frac{(N_e-1)(2N_e-1)(2N_e-3)}{4N_e^3} \end{pmatrix} \begin{pmatrix} \tilde{f}^* \\ \tilde{\gamma}^* \\ \tilde{\Delta}^* \end{pmatrix}_t \tag{5.4}$$

starting with $\tilde{f}_0^* = \tilde{\gamma}_0^* = \tilde{\Delta}_0^* = 1$.

–Insert Figure 5.1 Here–

With definitions in hand for the quadratic expressions in the base population (Table 5.1) and the temporal dynamics of the identity coefficients (Equations 5.3 and 5.4), we are now in a position to explore the impact of finite population size on the components of variance for a quantitative trait with a nonadditive genetic basis. The expected dynamics are determined by summing the products of the seven quadratic terms listed across the top of Table 5.2 and the tabulated coefficients in the table. For example, the expected within-population dominance variance is $[1 - 3f + 2(\Delta + \gamma - \delta)]\sigma_D^2 + (f + \delta - 2\gamma)\sigma_{DI}^2 + (f + \Delta - 2\gamma)\iota^* + (\tilde{f} - 2\tilde{\gamma} + \tilde{\Delta})(\iota^2 - \iota^*)$.

Table 5.2. Coefficients for the quadratic properties defined in Table 5.1, necessary for the definition of the variance components noted in the first column, for lines derived from a base population. The total within-population genetic variance (first row) is equal to the sum of the additive (A), dominance (D), and additive × additive (AA) components in the next three rows. The among-population expressions are summed over all sources, and the total genetic variance is the sum of the within- and among-population components. The numerical values of the coefficients must be computed with Equations 5.3 and 5.4, and in practice, the two-locus identity coefficients need to be averaged over all pairs of loci, with each two-locus estimate depending on the recombination fraction.

Source	σ_A^2	σ_D^2	σ_{ADI}	σ_{DI}^2	ι^*	$\iota^2 - \iota^*$	σ_{AA}^2
Within	$1-f$	$1-f-2(\Delta-\delta)$	$2(f-\gamma)$	$f-\delta$	$f-\Delta$	$\tilde{f}-\tilde{\Delta}$	$1+2f-2\tilde{\gamma}-\tilde{\Delta}$
A	$1-f$	$2[f-\gamma-2(\Delta-\delta)]$	$2(f-\gamma)$	$2(\gamma-\delta)$	$2(\gamma-\Delta)$	$2(\tilde{\gamma}-\tilde{\Delta})$	$4f-\tilde{f}-2\tilde{\gamma}-\tilde{\Delta}$
D	0	$1-3f+2(\Delta+\gamma-\delta)$	0	$f+\delta-2\gamma$	$f+\Delta-2\gamma$	$\tilde{f}-2\tilde{\gamma}+\tilde{\Delta}$	0
AA	0	0	0	0	0	0	$1-2f+\tilde{f}$
Betw.	$2f$	$2(\Delta-\delta)$	2γ	δ	$\Delta-f^2$	$\tilde{\Delta}-f^2$	$\tilde{f}+2\tilde{\gamma}+\tilde{\Delta}$
Total	$1+f$	$1-f$	$2f$	f	$f(1-f)$	$\tilde{f}-f^2$	$1+2f+\tilde{f}$

To gain a more intuitive feel for the source of the expressions in Table 5.2, we first consider the total genetic variance in a collection of lines each inbred to level f, ignoring epistasis until the following section. Subscripting loci with k and the two alleles at a locus as i and j, the genotypic value of an individual can be written as

$$G = \sum_{k=1}^{n} [(1-\phi_{kij})(\alpha_{ki}+\alpha_{kj}+\delta_{kij}) + \phi_{kij}(2\alpha_{ki}+\delta_{kii})] \tag{5.5}$$

where ϕ_{kij} is equal to one if the two alleles at a locus are identical by descent and zero otherwise. This follows from the fact that the expected value of δ_{ij} is equal to zero for noninbred individuals. Noting that the expected value of ϕ_{kij} is f, the mean genotypic value is $\mu_G = -f \cdot \iota$. In addition,

$$E(G^2) = \sum_{k=1}^{n} \left\{(1-f)E[(\alpha_{ki}+\alpha_{kj}+\delta_{kij})^2] + fE[(2\alpha_{ki}+\delta_{kii})^2]\right\} + \tilde{f}(\iota^2-\iota^*) \tag{5.6a}$$

The final term in Equation 5.6a summarizes the consequences of joint inbreeding at pairs of loci, with $\tilde{f}$ being the probability that two loci in the same individual are inbred (Figure 5.1) and $\iota^2 - \iota^* = 2\sum_{k<m}^{n} \iota_k \iota_m$ being the sum of cross-products of the locus-specific inbreeding depressions. (In obtaining Equation 5.6a, all other products across loci have expectations equal to zero because $E(\alpha_{ki})$ is always equal to zero and $E(\delta_{kij}) = 0$ at noninbred loci (LW Chapter 4)).

Recalling that the genetic variance is defined to be $\sigma_G^2 = E(G^2) - \mu_G^2$, we obtain

$$\begin{aligned}\sigma_G^2 = \sum_{k=1}^{n} &\left[(1-f)[2E(\alpha_{ki}^2)+E(\delta_{kij}^2)] + f[4E(\alpha_{ki}^2)+4E(\alpha_{ki}\delta_{kii})+E(\delta_{kii}^2)\right] \\ &+ \tilde{f}(\iota^2-\iota^*) - f^2\iota^2\end{aligned} \tag{5.6b}$$

Further simplification is achieved by adding and subtracting $f(1-f)\iota^*$ on the right side of this expression, which after using the expressions in Table 5.1 leads to

$$\sigma_G^2 = (1+f)\sigma_A^2 + (1-f)\sigma_D^2 + 2f\sigma_{ADI} + f\sigma_{DI}^2 + f(1-f)\iota^* + (\tilde{f}-f^2)(\iota^2-\iota^*) \tag{5.6c}$$

in agreement with the final row in Table 5.2.

Although the preceding results apply to the genetic variance summed within and among a set of hypothetical isolated subpopulations, an expression for the average within-population variance can be obtained by removing the among-population component. The simplest route to this result is to recall the general rule that the variance among groups is equivalent to the covariance between individuals within groups. Using this principle, the contribution of each quadratic component in Table 5.1 to the among-population variance can be obtained in the following way.

First, in the context of the entire collection of populations, f is equivalent to the probability that single alleles in the same population are identical by descent (the average coefficient of coancestry), so the additive genetic covariance for members of the same population is equal to $2f\sigma_A^2$ (LW Chapter 7). Second, two individuals within a population may also share both genes at a locus, in which case they will exhibit dominance genetic covariance, the magnitude of which will depend on whether the locus is inbred or not. From Figure 5.1, we see that the probability that both individuals are inbred and share the same genotype by descent is equal to δ, so the genetic covariance by this route is $\delta\sigma_{DI}^2$. The probability that the two individuals are not inbred but share identical genotypes by descent is $2(\Delta - \delta)$ (the two accounts for paternal-paternal / maternal-maternal versus cross paternal-maternal sources of identity by descent), so the covariance by this route becomes $2(\Delta - \delta)\sigma_D^2$. Third, the probability that three alleles in two members of a population are identical by descent is equal to γ, and there are two ways in which this can arise, so the covariance between additive and dominance effects is $2\gamma\sigma_{ADI}$. Finally, the covariance resulting from shared inbreeding depression is $(\Delta - f^2)\iota^*$ because Δ is the probability that two members of the same population are jointly inbred at the same locus, while the average fraction of individuals that are inbred over all populations is f per locus, and ι^* is the sum of squared per-locus inbreeding depresions. Similarly, the covariance due to joint inbreeding depression at different loci is equal to $(\tilde{\Delta} - f^2)(\iota^2 - \iota^*)$, with the latter term being the sum of cross products of per-locus inbreeding depressions.

Summing all six of these contributions, we obtain the genetic variance among populations given in the second row from the bottom of Table 5.2. The within-population genetic variance is then obtained by subtracting the among-population component from the total genetic variance. Results such as these provide a mechanistic explanation for the changes in components of genetic variance that can be induced by small population size. For example, it can be seen from the second line of Table 5.2 that inbreeding always converts some initial dominance genetic variance into additive genetic variance. This does not necessarily imply a net increase in additive genetic variance in a bottlenecked population, as the total dynamics depend critically on the relative magnitudes and temporal dynamics of all five of the quadratic components involving dominance in the base population (Figure 5.2). However, it does imply that Equation 5.2 cannot be strictly correct in the presence of dominance. While the contribution to the additive genetic variance from the base population σ_A^2 declines each generation, all other contributions first increase before eventually decreasing to zero. Thus, whether a population bottleneck will induce an increase in additive genetic variance depends critically on the magnitude of σ_A^2

relative to the other quadratic components in the base population.

–Insert Figure 5.2 Here–

Note that the two-locus identity coefficients appear only in association with quadratic terms involving pairs of loci, in this case $(\iota^2 - \iota^*)$. Two-locus identity by descent is of relevance in finite populations because the gametic-phase disequilibrium that inevitably develops by chance causes **identity disequilibrium** between loci (Weir and Cockerham 1968) — individuals that are inbred at one locus are likely to be so at other loci, causing a transient inflation of the genetic variance through the production of extreme phenotypes.

Although it may not be immediately apparent, the coefficients in the final two columns in Table 5.2 are equivalent to measures of identity disequilibrium (Cockerham 1984a). For example, $\tilde{f} - f^2$ is the deviation of the double identity-by-descent within gametes in the same population from that based on the assumption of independence between loci. Although $\tilde{f}$ depends upon the average linkage relationships between all relevant pairs of loci (Weir and Cockerham 1968, 1969), in most cases if most pairs of loci are on different chromosomes, and/or if the population is randomly mated and expanded following the bottleneck, $\tilde{f}$ will be approximately equal to f^2 . Under such conditions, $(\tilde{f} - f^2)$, as well as the other coefficients of $(\iota^2 - \iota^*)$ in Table 5.2 will be very close to zero, removing at least this one term from the variance expressions (Figure 5.2).

The Effects of Epistasis

The fundamental point in the preceding section is that because dominance is a function of a two-gene interaction, the variance in dominance effects can be altered in unexpected ways when inbreeding alters the average background on which an allele appears. This same issue applies to epistatic effects, although on a potentially larger scale because the additive × additive epistatic variance (σ^2_{AA}) is a function of n^2 terms, while all of the other quadratic components in Table 5.1 (except $\iota^2 - \iota^*$, which seems to be of little significance) are functions of just n terms. Assuming unlinked loci, the coefficient of the σ^2_{AA} contribution to the additive genetic variance rises to nearly 1.0 in a little over N_e generations, i.e., the equivalent of all of the base-population σ^2_{AA} is added to the otherwise declining additive genetic variance at this point (Figure 5.2). Thus, the potential exists for a substantial additive × additive epistatic variance in the base population to spawn a prolonged increase in the additive genetic variance following a reduction in population size, or at least slow the erosion relative to the expectation given by Equation 5.2. The matter is of considerable interest because whereas inflations in the additive genetic variance induced by dominance effects is accompanied by the maladaptive effects of inbreeding depression (i.e., a deleterious change in the mean phenotype), those caused by a conversion of epistatic additive effects have no side effects on the mean, and simply increase the range of variation upon which natural selection can act.

To see how this might happen, consider the following. From the standpoint of any locus, variation in epistatic interactions with genes at other loci amounts to a

reduction in the efficiency with which allelic effects are transmitted from generation to generation — segregation and recombination ensure that interlocus interactions in parents are not transmitted loyally through gametes. However, as genetic drift moves genes toward fixation at one or both loci and/or as identity disequilibria increase, this variation in the genetic environment is reduced. In Table 5.3, for example, the $\mathbf{A}_1$ allele is present in genetic backgrounds that lead to five distinct genotypic values in a randomly mating population. If, however, the $\mathbf{B}_2$ allele becomes fixed, then an $\mathbf{A}_1$ allele can only be in two backgrounds ($\mathbf{A}_1\mathbf{A}_1\mathbf{B}_2\mathbf{B}_2$ and $\mathbf{A}_1\mathbf{A}_2\mathbf{B}_2\mathbf{B}_2$). In this case, the epistatic interactions are still present, but they are transmitted reliably as additive effects (the difference between adjacent pairs of **A**-locus genotypes being a constant $(a - i)$.

Table 5.3. A simple two-locus system with epistasis. Elements in the table are the expected genotypic values for the two-locus genotypes.

	$\mathbf{A}_1\mathbf{A}_1$	$\mathbf{A}_1\mathbf{A}_2$	$\mathbf{A}_2\mathbf{A}_2$
$\mathbf{B}_1\mathbf{B}_1$	$4a + i$	$3a$	$2a - i$
$\mathbf{B}_1\mathbf{B}_2$	$3a$	$2a$	a
$\mathbf{B}_2\mathbf{B}_2$	$2a - i$	a	i

Some simple insight into the role of additive × additive epistatic variance in the dynamics of genetic variance of finite populations can be achieved if one is willing to assume that the loci involved are unlinked ($c = 0.5$) and that identity disequilibria are of negligible significance. Returning to Table 5.2, it can be seen that the coefficient for the contribution of base-population additive × additive variance to future additive genetic variance is $(4f - \tilde{f} - 2\tilde{\gamma} - \tilde{\Delta})$, which reduces to $4f(1-f)$ under the assumption that all of the two-locus identities $\simeq f^2$. Ignoring the contributions from dominance, the expression for the dynamics of the additive genetic variance then simplifies to

$$\sigma_A^2(t) \simeq (1 - f_t)\sigma_A^2(0) + 4f_t(1 - f_t)\sigma_{AA}^2(0) \tag{5.7a}$$

and the expression for the additive × additive variance simplifies to

$$\sigma_{AA}^2(t) \simeq (1 - f_t)^2\sigma_{AA}^2(0) \tag{5.7b}$$

(Cockerham and Tachida 1988; Goodnight 1988; López-Fanjul et al. 1999), assuming the absence of any higher-order epistatic variance. Equation 5.7a shows that the conversion of additive × additive to additive genetic variance is maximized at the point at which $f_t \simeq 0.5$, which because $f_t \simeq 1 - \exp(-t/2N_e)$, translates to $t \simeq 1.4N_e$ generations in accordance with Figure 5.2.

Limited attention has been given to the role of two-locus epistasis involving dominance effects in finite populations (Cheverud and Routman 1996; López-Fanjul et al. 1999; Barton and Turelli 2004), and no general formulation exists for the dynamics of genetic variance resulting from higher-order epistatic interactions. We can anticipate that the necessary algebra for such a solution would be extremely tedious, as it would involve descent measures involving three and more loci, and as will be discussed below, the existing data do not support the need for such theory.

For heuristic purposes, however, we will consider the approximate case for higher-order epistasis involving only additive effects, again assuming freely recombining loci and ignoring identity disequilibrium.

As a simple entrée into this matter, recall that in the absence of dominance, the expected covariance between relatives x and y is $\sigma_G(x,y) = 2\theta_{xy}\sigma^2_A + (2\theta_{xy})^2\sigma^2_{AA} + \cdots + (2\theta_{xy})^n\sigma^2_{A^n}$, where θ_{xy} is the coefficient of coancestry (LW Chapter 7), and $\sigma^2_{A^n}$ refers to epistatic variance involving the additive effects of n loci. The total genetic variance (summed over the within- and among-population components) is equivalent to the covariance of individuals with themselves, which is obtained by letting $\theta_{xy} = (1+f)/2$ (LW Chapter 7), whereas the variance among isolated subpopulations is equivalent to the covariance of random members of the same subpopulation, which is obtained by letting $\theta_{xy} = f$. Thus, for any n-locus epistatic interaction, the contribution to the total genetic variance is $(1+f)^n\sigma^2_{A^n}$, to the among-population component of variance is $(2f)^n\sigma^2_{A^n}$, and to the within-population component is the difference $[(1+f)^n - (2f)^n]\sigma^2_{A^n}$. This implies that the base-population additive and additive × additive genetic variances contribute $(1-f)\sigma^2_A$ and $(1+2f-3f^2)\sigma^2_{AA}$, respectively, to the within-population genetic variance, a result that can also be obtained directly from Equations 5.7a,b. The contribution from additive × additive × additive epistatic variance is $(1+3f+3f^2-7f^3)\sigma^2_{AAA}$, etc.

Each of these terms except that involving σ^2_A reaches a maximum at an intermediate level of inbreeding and then declines to zero as $f \to \infty$. For epistatic effects involving $n = 2$, 3, and 4 loci, the peak contributions to the within-population genetic variance occur when f is approximately 0.33, 0.55, and 0.66. For randomly mating populations, these maxima occur at $0.8N_e$, $1.6N_e$, and $2.2N_e$ generations, with the peak contributions to the total within-population genetic variance being equal to $1.33\sigma^2_A$, $2.39\sigma^2_{AA}$, and $4.56\sigma^2_{AAA}$. Thus, even if levels of higher-order epistatic genetic variance are relatively low in a base population, they may have a significant influence on the within-population variance under inbreeding, with the full impact not being revealed for many generations.

Under this model, the components of within-population genetic variance are described by the following general expression,

$$\sigma^2_{A^n} = (1-f)^n \sum_{i=0}^{x-n} \binom{n+i}{n} (2f)^i \sigma^2_{A^{n+i}} \tag{5.8}$$

where x denotes the highest level of epistasis involving additive effects influencing the trait (Barton and Turelli 2004; Hill et al. 2006). When $x = 2$, this expression recovers Equations 5.7a,b, and with x as high as three, we obtain

$$\sigma^2_A(t) = (1-f_t)[\,\sigma^2_A(0) + 2(2f_t)\sigma^2_{AA}(0) + 3(2f_t)^2\sigma^2_{AAA}(0) + \cdots\,] \tag{5.9a}$$

$$\sigma^2_{AA}(t) = (1-f_t)^2[\,\sigma^2_{AA}(0) + 3(2f_t)\sigma^2_{AAA}(0) + \cdots\,] \tag{5.9b}$$

$$\sigma^2_{AAA}(t) = (1-f_t)^3[\,\sigma^2_{AAA}(0) + \cdots\,] \tag{5.9c}$$

with the dots denoting potential contributions from higher-order effects.

These expressions show that under progressive inbreeding the expected values for each variance component depend on all higher-order epistatic variances, and that the erosion of the higher-order components proceeds most rapidly. Most notably,

Equation 5.9a shows that the presence of any epistatic variance will inflate the additive genetic variance above the simple expectation $(1-f)\sigma_A^2(0)$, but whether $\sigma_A^2(t)$ rises beyond the base-population level, $\sigma_A^2(0)$, depends on the magnitude of the base-population epistatic variance components. From Equation 5.8, it can be seen that for any $n > 1$, the peak contribution of $\sim (2^{n-1}/e)\sigma_{A^n}^2$ to the additive genetic variance occurs at $f = 1-(1/n)$ (Turelli and Barton 2006).

A practical way of evaluating the conditions necessary for a net increase in the additive genetic variance is to consider the nature of empirical estimates of the additive genetic variance. As noted in Lynch and Walsh (1998), clean estimates of the causal components of genetic variance are generally unachievable. For example, although twice the parent-offspring covariance is often used as an estimate of the additive genetic variance, the true expectation is actually $\sigma_A^2 + (\sigma_{AA}^2/2) + (\sigma_{AAA}^2/4) + \cdots$. Ignoring all but the additive $\times$ additive genetic variance, Equations 5.7a,b can be used to show that the parent-offspring covariance after inbreeding to level f will exceed that in the base population if $\sigma_{AA}^2 > 2\sigma_A^2/(6-7f)$, which reduces to $\sigma_{AA}^2 > \sigma_A^2/3$ as $f \to 0$.

Although it is exceedingly difficult to obtain perfectly isolated estimates of σ_A^2 and σ_{AA}^2, a survey of the existing data combined with a number of indirect arguments suggests that the condition $\sigma_{AA}^2 > \sigma_A^2/3$ is hardly ever met in natural populations (Hill et al. 2008). As reviewed in Lynch and Walsh (1998) and reemphasized by Hill et al. (2008), this situation is not likely to be a consequence of limited epistatic interactions among genes. Rather the very nature of variance-component partitioning, with higher-order effects being defined as residual deviations from expectations based on lower-order effects, largely ensures that epistatic components of variance will be small relative to σ_A^2, especially when most alleles have frequencies far from 0.5.

Finally, we emphasize that although all of the previous results strictly apply to ideal monoecious populations that become inbred via random genetic drift, the general approach applies to any mating system, provided appropriate modifications are made to the recursion formulae for the identity coefficients. For monoecy with the avoidance of selfing and for separate sexes, the appropriate expressions are given by Weir et al. (1980) and Weir and Hill (1980), and explicit formulae for obligate self-fertilization, full-sib mating, and other special systems of mating are developed in Cockerham and Weir (1968, 1973) and Weir and Cockerham (1968), and a useful review is provided in Cockerham and Weir (1977).

Sampling Error

It cannot be emphasized too strongly that the preceding expressions give only the *expected* change of the within-population variance for a neutral quantitative character. Due to the stochastic nature of random genetic drift, departures from the expectation will arise in any individual population, so a central concern is the degree to which the average behavior of a small number of populations will represent the expected pattern.

In the following discourse, we denote the realized additive genetic variance for any particular population by $\widehat{\sigma}_A^2(t)$. Estimation error on the part of the investigator

aside, three sources of error contribute to the variation in $\widehat{\sigma}_A^2(t)$ among replicate populations: 1) variation in the genetic variance among founder populations caused by sampling; 2) subsequent departures of the within-population heterozygosity from its expectation caused by drift; and 3) deviations from Hardy-Weinberg and gametic-phase equilibrium.

Quantification of these sources of variation is difficult, but some general results have been obtained for characters with a purely additive genetic basis. The additive genetic variance within a particular population can be written as

$$\widehat{\sigma}_A^2(t) = \tilde{\sigma}_A^2(t) + \widehat{\sigma}_{HW}(t) + \widehat{\sigma}_L(t) \tag{5.10}$$

where $\tilde{\sigma}_A^2(t)$ is the variance due to the true gene effects expected if the line were expanded into an infinitely large, randomly mating population with global Hardy-Weinberg and gametic-phase disequilibrium, while $\widehat{\sigma}_{HW}(t)$ and $\widehat{\sigma}_L(t)$ are transient covariances of genic effects within and among loci caused by disequilibria within and between loci. The expected value of $\tilde{\sigma}_A^2(t)$, given by Equation 5.2, is $\sigma_A^2(t)$, and the disequilibria are equally likely to occur in positive and negative directions in the absence of selection. Thus, the expected value of $\widehat{\sigma}_A^2(t)$ is also equal to $\sigma_A^2(t)$.

Each of the terms on the right side of Equation 5.10 has a variance associated with it, so that the expected variance of the within-population additive genetic variance among hypothetical replicate populations can be expressed as

$$\sigma^2[\widehat{\sigma}_A^2(t)] = \sigma^2[\tilde{\sigma}_A^2(t)] + \sigma^2[\widehat{\sigma}_{HW}(t)] + \sigma^2[\widehat{\sigma}_L(t)] \tag{5.11}$$

The variance of the "true" additive genetic variance is

$$\sigma^2[\tilde{\sigma}_A^2(t)] = \sum_{i=1}^{n} a_i^4 \sigma_{H_i}^2(t) \tag{5.12}$$

where $\sigma_{H_i}^2(t)$ is the expected variance of heterozygosity, $H_i(t) = 2p_i(t)[1 - p_i(t)]$, at locus i among replicate populations t generations after divergence. Bulmer (1980) obtained an expression for $\sigma_{H_i}^2(t)$ for a locus with two alleles, and a very close approximation to this is given in Example 2.4. While the exact dynamics of $\sigma^2[\tilde{\sigma}_A^2(t)]$ will depend on the initial allele frequencies at all loci, which are generally unknown, a useful qualitative statement can be made. For fixed initial genetic variance in the base population, the average value of a_i^2 must scale inversely with the number of loci. Thus, since $\sigma^2[\tilde{\sigma}_A^2(t)]$ is the sum of n terms, each a function of $a_i^4 \propto n^{-2}$, $\sigma^2[\tilde{\sigma}_A^2(t)]$ must be inversely proportional to n. Therefore, for characters with large effective numbers of loci, deviations from the true additive genetic variance caused by variance in heterozygosity are potentially of negligible importance.

The expected variance of the within-population variance resulting from Hardy-Weinberg deviations is $\sigma^2[\widehat{\sigma}_{HW}(t)] \simeq \sigma_A^4(t)/N_e$ (Bulmer 1976, 1980), but the variation due to gametic-phase disequilibrium is more substantial, the general details of the rather tedious derivations appearing in Avery and Hill (1977) and Bulmer (1980). Regardless of the degree of linkage, $\sigma^2[\widehat{\sigma}_L(1)] \simeq \sigma_A^4(0)/N_e$ in the first generation of inbreeding, and thereafter for the special case of unlinked loci, $\sigma^2[\widehat{\sigma}_L(t)] \simeq 5\sigma_A^4(t)/(3N_e)$. With linkage $\sigma^2[\widehat{\sigma}_L(t)]$ is necessarily larger, but for most cases it will not be substantially so (Avery and Hill 1977), and regardless of the state of disequilibrium in

the base population, the expected value of $\sigma^2[\widehat{\sigma}_L(t)]$ is almost always attained within five generations.

An advantage of the preceding expressions for the variance of the components of the within-population genetic variance is that they are defined in terms of measurable quantities. However, to achieve this useful property, several assumptions (ideal population structure, no association between map distances and effects of genes, additivity of gene effects) had to be made, violations of which will tend to inflate the variance of $\widehat{\sigma}^2_A(t)$. Thus, summing over the two disequilibrium sources, we find that $\sigma^2[\widehat{\sigma}^2_A(t)]$ must be at least $8\sigma^4_A(t)/3N_e$. A similar conclusion was reached by Zeng and Cockerham (1991), who present a thorough and highly technical analysis.

These theoretical results have significant implications for the interpretation of observed changes of genetic variance in small populations, in particular in the use of such observations to infer any significant conversion of nonadditive to additive genetic variance. Clearly, estimates of $\widehat{\sigma}^2_A(t)$ derived from a small number of replicate populations, even over several generations, provide unreliable assessments of the expected dynamics of $\sigma^2_A(t)$. Averaging over L independent lines, the sampling variance of the mean genetic variance within lines is at least $8\sigma^4_A(t)/(3LN_e)$. Therefore, if it is desirable to keep the standard error of an estimate of the additive genetic variance at a level of 10% of the expectation, $\sigma^2_A(t)$, the design must be such that $N_eL \simeq 270$, i.e., approximately 70 lines of $N_e = 4$, or 17 of $N_e = 16$. For self-fertilizing lines, the sampling variance is closer to $7\sigma^4_A(t)/L$ over the first five generations of inbreeding (Lynch 1988a), so on the order of 700 lines would have to be monitored to achieve a similar level of precision. In practice, one would need to set the target number of lines even higher than these estimates, since the additional variation due to parameter estimation, i.e., the deviation of the observation $\mathrm{Var}(A,t)$ from the realized parameter $\widehat{\sigma}^2_A(t)$, which may be considerable, has been ignored in the preceding arguments.

One final problem that bears mentioning is that the $\widehat{\sigma}^2_A(t)$ observed in successive generations are not independent, the minimum correlation between adjacent generations being equal to one-half for unlinked loci. Thus, if the genetic variation within a particular population exceeds the expectation due to chance in one generation, it is likely to remain in excess for several consecutive generations. When this problem is confounded with the sampling variance described above, there is a substantial possibility that $\widehat{\sigma}^2_A(t)$ for a particular replicate population may on occasion increase for several generations, contrary to the expected trend, even for characters with a purely additive genetic basis (Avery and Hill 1977; Bulmer 1980).

In summary, even in the case of purely additive gene action, a reliable empirical view of the expected dynamics of the additive genetic variance requires a very large number of replicate populations. There are three levels at which sampling error plays a role. First, in each replicate, the variance observed by the investigator, $\mathrm{Var}(A)$, is likely to deviate substantially from the parametric value $\widehat{\sigma}^2_A$ for the replicate, due simply to the finite number of individuals monitored (Lynch and Walsh 1998). Second, the true realized variance $\widehat{\sigma}^2_A$ in each line may deviate considerably from the actual equilibrium value, $\tilde{\sigma}^2_A$, expected in the absence of Hardy-Weinberg and gametic-phase disequilibria. Finally, random genetic drift will cause $\tilde{\sigma}^2_A$ to deviate from the global expectation σ^2_A. One can expect the situation to get even messier in the presence of nonadditive gene action, but the details of the sampling theory

remain a formidable challenge.

Empirical Data

The influence of small population size on components of genetic variance is of substantial relevance to several areas of inquiry. An underlying assumption of much of conservation genetics, for example, is that loss of heterozygosity from small populations translates immediately into a loss of variation for adaptive traits. As noted above, this need not be the case in the presence of nonadditive gene action. However, a key question is whether increases in the additive genetic variance following a population bottleneck, if they do indeed occur, are accompanied by changes in the mean phenotype that are contrary to the maintenance of high fitness. Nothing is gained from a population bottleneck if the extreme phenotypes produced are simply low-fitness individuals resulting from inbreeding depression.

The preceding theory is also of potential relevance to the field of speciation biology. Substantial uncertainty exists over the importance of population bottlenecks for the speciation process (Mayr 1954; Templeton 1980; Carson and Templeton 1984; Barton and Charlesworth 1984), and much of the debate revolves around verbal arguments regarding additive and epistatic gene action. In Carson's (1968, 1975) founder-flush theory, for example, it is assumed that a period of population expansion following a bottleneck will often result in a conversion of various types of epistatic interactions into additive genetic variance, and similar issues were raised by Templeton (1980) in his hypothesis of speciation via genetic transilience. Although such arguments sometimes appear intuitive on the surface, the preceding theoretical examples amply illustrate that intuition can be quite misleading with respect to the dynamics of genetic variance in small populations. The consequences of a population bottleneck are highly sensitive to the nature of gene action and the frequency-distribution of alleles, and establishing whether the appropriate mixes of genetic properties for bottleneck-induced variance increases are common is ultimately an empirical question.

Aside from the results outlined in Example 5.1, few well-designed empirical studies have addressed the influence of inbreeding on the genetic variance within populations. Studies that strictly focus on *phenotypic* variance often reveal essentially linear declines in the phenotypic variance with f, as expected for a character with a purely additive genetic basis, but in other cases the response has been so noisy that no general conclusion could be drawn, and sometimes the within-population variance actually increases over time (Figure 5.3). A substantial limitation of studies of this sort is that the environmental component of variance often increases with inbreeding as a consequence of reduced developmental stability (LW Chapter 6; Whitlock and Fowler 1999; Kelly and Arathi 2003), thereby obscuring the relationship between phenotypic and genetic variance.

–Insert Figure 5.3 Here–

A study by Cheverud et al. (1999) provides a clear example of the creation of additive genetic variance by a population bottleneck. By crossing two long-established

mouse lines, one selected for large and the other for small body size, an F_2 base population with high genetic variance for adult weight was constructed. Thirty-nine replicate inbred lines were then initiated from the F_3 generation, each maintained as two pairs of males and females through four generations of inbreeding to yield an average $f = 0.39$. Two contemporary control strains were maintained by randomly mating 60 pairs of individuals derived from the base (hybrid) population. Using a full-sib analysis, the authors found that the average additive genetic variance for adult weight after inbreeding was about 1.75× greater (and significantly so) than expected under the additive model (a fraction $1 - f = 0.61$ of the additive variation in the base population) and slightly greater than that in the controls. Two lines of evidence suggest that this inflation in σ_A^2 was largely, if not entirely, due to conversion from additive × additive epistatic variance. First, the absence of any significant change in mean adult weight throughout the period of inbreeding implies that dominance genetic variance is negligible for this trait. Second, previous QTL analysis of this experimental population had revealed pervasive epistatic interactions between loci influencing body size (Routman and Cheverud 1997; Kramer et al. 1998). As a caveat, however, it must be emphasized that this study is quite artificial in that by constructing a base population with intermediate gene frequencies, the epistatic genetic variance was maximized at the outset. We now consider the few results that have emerged for more naturally derived populations.

Bryant et al. (1986) put populations of houseflies through single-generation bottlenecks of 1, 4, and 16 pairs, and then rapidly expanded them for several generations prior to the measurement of the additive genetic variance (to reduce the variation in the within-line variance caused by gametic-phase disequilibrium). Analyses of several morphological characters suggested an increase in σ_A^2 in the bottlenecked lines relative to a control (Figure 5.4), which the authors surmised to be a consequence of the conversion of epistatic to additive genetic variance. Although this study has become something of a flagship example of bottleneck-induced increases in genetic variance, it also serves to highlight the extreme difficulties that exist in interpreting the dynamics of genetic variance in inbred populations.

–Insert Figure 5.4 Here–

First, only four replicate populations were maintained at each population density in this study, so there is a substantial chance that the average within-line variance may have increased entirely by chance, even in the absence of nonadditive genetic variance. Second, some characters exhibited a five-fold inflation in the additive genetic variance over the control, and based on the considerations outlined above, this is hard to accept as a real consequence of inbreeding in the essentially non-inbred ($f \simeq 0.03$) 16-pair lines. In contrast, although the evidence that inbreeding created a real increase in additive genetic variance in these lines is not very compelling, it is equally true that there is no evidence of a substantial erosion in additive genetic variance following inbreeding. In subsequent studies involving single-generation bottlenecks of four individuals, Meffert (1995) did not detect any overall change in the additive genetic variance for various aspects of courtship behavior (six replicate populations), and Bryant and Meffert (1996) observed increases in σ_A^2

for two morphological characters but decreases for two others (two replicate populations) thought to have had relatively high levels of additive × additive epistatic variance in the base population.

Replication is less of problem in a few other recent studies. Starting from a large base population of *D. melanogaster,* Whitlock and Fowler (1999) subjected 52 lines to a single generation of full-sib mating ($f = 0.25$) and then expanded them to large size. Within each line, the additive genetic variance for various aspects of wing structure was estimated by parent-offspring regressions involving 90 families, and a similar procedure was applied to a large control population. Similar to the results obtained for abdominal bristle number (Example 5.1), no evidence for an increase in the additive genetic variance emerged from this well-designed study, and a similar conclusion was reached in a study on sternopleural bristles in bottlenecked populations of *D. bunnanda* (van Heerwaarden et al. 2008). Although a few individual lines exhibited moderate increases in σ_A^2, these increases were always compatible with the expectations of additive genetic theory, as was the average reduction in σ_A^2 across all lines.

In a smaller study with the flour beetle *(Tribolium castaneum),* involving three inbreeding levels ($f = 0.000$, 0.375, and 0.672, five replicates each), Wade et al. (1996) also observed average changes in the additive genetic variance for pupal weight that were entirely compatible with expectations of the additive model. Likewise, changes in the additive genetic variance of wing pigmentation patterns in bottlenecked populations of the butterfly *Bicyclus anynana* are consistent with the additive model (Saccheri et al. 2001). Thus, taken together, these diverse studies with insects provide little justification for the view that the *expected* additive genetic variance for *morphological* traits commonly increases during early phases of inbreeding, although transient increases associated with sampling are certainly expected in some replicates.

These results are in striking contrast to those from studies on fitness-related traits. For example, in a parallel study of offspring production in *Tribolium,* Wade et al. (1996) observed no significant decline in additive genetic variance up to inbreeding levels of $f = 0.672$. Likewise, López-Fanjul and Villaverde (1989) took 16 replicate populations of *D. melanogaster* through single generations of full-sib mating and assayed them for egg-to-pupa viability. The average additive genetic variance in the control lines was not significantly different from zero, whereas that in lines inbred to $f = 0.25$ was five-fold (and significantly) higher. In a study involving 32 lines of *D. melanogaster,* again inbred to $f = 0.25$, Fernández et al. (1995) observed a ten-fold increase in the additive genetic variance for viability, whereas that for fecundity remained approximately equal to that of the control; and a similar increase in additive genetic variance for viability following inbreeding was seen in still another study by García et al. (1994). In each of these studies, the characters of interest exhibited significant inbreeding depression.

If any general message can be taken from these limited results, it is that increases in additive genetic variance following a population bottleneck are largely restricted to fitness characters harboring substantial dominance genetic variance, with morphological and behavioral traits exhibiting genetic-variance dynamics that are not greatly different from expectations based on the additive model (Wang et al. 1998; Van Buskirk and Willi 2006). There is, as yet, no firm empirical evidence

that population bottlenecks create significant levels of *adaptive* variation. With the exception of the contrived study of Cheverud et al. (1999), all observed increases in additive variation following inbreeding have been accompanied by substantial inbreeding depression — while the variance increased, the mean changed in a direction contrary to high fitness.

Might the creation of new additive genetic variance nevertheless compensate for slippage in the mean via inbreeding depression? In the two *D. melanogaster* studies in which selection for increased fitness was imposed on inbred lines, a substantial increase in the response to selection (relative to the controls) was observed, but this was more than offset by the loss of fitness due to inbreeding depression (López-Fanjul and Villaverde 1989; García et al. 1994) i.e., there was an overall reduction in viability even after selection utilized the released genetic variance. In another study, involving bottlenecked populations of *Drosophila bunnanda,* van Heerwaarden et al. (2008) found that although inbreeding resulted in an inflation of the additive genetic variance for desiccation resistance, there was no increase in the response to selection relative to control populations. The same pattern was seen in selected populations of the plant *Brassica rapa* — bottlenecking led to a significant increase in additive genetic variance for cotyledon size, apparently via a release from the dominance component, but a reduction in the long-term response to selection (Briggs and Goldman 2006).

Example 5.1. The significance of the problem of the variance of the within-population variance is highlighted by a massive experiment performed by López-Fanjul et al. (1989). Starting from a large random-bred base population of *D. melanogaster,* 304 noninbred lines were constructed, and another 300 inbred lines were produced by four generations of full-sib mating followed by population expansion for six generations. The components of variance for abdominal bristle number were evaluated for the initial 304 lines ($f = 0$) and for the fourth and tenth generations after the bottleneck/expansion treatment (both $f = 0.5$) by several techniques including sib analysis. Consistent with the view that this character has a largely additive genetic basis (LW pp. 171–172), the mean ($\bar{z}$) was unaffected by inbreeding (table below). Moreover, averaging over all of the inbred lines, there was an approximately 50% reduction in the additive genetic variance, as predicted by additive theory.

The data from this experiment are in excellent accord with the sampling theory for the additive genetic variance presented above. Summing the expected variances contributed by Hardy-Weinberg and gametic-phase disequilibria, $\sigma_A^4(0)/N_e + \sigma_A^4(0)/N_e$, the expected coefficient of variation for the additive genetic variance in the noninbred lines (random populations with $N_e \simeq 8$ and $t = 0$) is $(2/N_e)^{1/2} = 0.50$, which is reasonably close to the observed value 0.35 (table below). In addition, for both of the inbred generations, the observed values of CV[Var(A)] are close to the theoretical minimum $\sqrt{8/(3N_e)} = 1.04$ (using $N_e = 2.5$ for full-sib mating). In principle, several generations of random mating would be expected to cause a reduction in CV[Var(A)] through the elimination of gametic-phase disequilibrium if significant numbers of linked loci contributed to the genetic variance, but a comparison of results for $t = 4$ and 10 shows that this was not observed.

Generation	f	$\bar{z}$	Var(A)	CV[Var(A)]

1	0.0	41.4	5.2	0.35
4	0.5	41.4	2.5	1.05
10	0.5	41.4	1.8	1.15

COVARIANCE BETWEEN INBRED RELATIVES

In the preceding sections, we assumed a parallel series of small populations, each being propagated across generations as progeny derived from randomly mating populations of size N_e. Even in the simplest case of no epistasis, we found that the dynamics of the genetic variance within populations is a potentially complex function of six quadratic parameters of gene effects in the base population (Table 5.1). What remains to be considered is how these contributions can be estimated in a practical sense. Not surprisingly, the key strategy is the usual one in quantitative genetics — the resemblance between relatives (LW Chapter 7).

When individuals are inbred with respect to the base population, the expressions for the genetic covariance between relatives become functions of all of the parameters outlined in Table 5.1, not just the usual σ_A^2 and σ_D^2. On the other hand, with inbreeding there are many more potential types of relationship than in the conventional case, especially if these are supplemented by conventional non-inbred relatives. One can imagine, for example, a multigenerational series of individuals resulting from continuous selfing or full-sib mating or both. Given phenotypic information on these additional types of relatives, it should be possible to estimate several different factors contributing to phenotypic covariance (as many as the number of observed relationships). The little experience we have gained in this area, however, indicates that the statistical difficulties in achieving accurate estimates are still quite formidable, even in the absence of epistasis, which we will assume in the following.

Three new issues arise in considering the sources of phenotypic resemblance between inbred relatives. First, inbreeding causes a statistical dependence between alleles within individuals, and this creates a covariance between the additive effects in one relative and the dominance effects in the other, as represented in σ_{ADI} (Table 5.1). Second, if two individuals have identical genotypes by descent, their dominance covariance will differ depending on whether they are inbred or outbred (because inbred individuals cannot be heterozygous), and this will generally vary from locus to locus. Third, with dominance, the mean phenotype of inbred individuals will generally differ from that of noninbred individuals, and this can inflate the covariance between certain types of relatives by breaking the population up into classes of inbred vs. noninbred individuals.

Harris (1964) and Gillois (1965) first derived an expression for the covariance between inbred relatives assuming gametic-phase equilibrium and an absence of epistasis, and Cockerham (1984a) extended their analyses to allow for gametic-phase

disequilibrium, showing that the genetic covariance between individuals x and y is

$$\begin{aligned}\sigma_G(x,y) =& 2\Theta_{xy}\sigma_A^2 + \Delta_{7xy}\sigma_D^2 + \Delta_{1xy}\sigma_{DI}^2 + (4\Delta_{1xy} + \Delta_{3xy} + \Delta_{5xy})\sigma_{ADI} \\ &+ (\Delta_{2xy} - f_x f_y)\iota^* + (\tilde{\Delta}_{2xy} - f_x f_y)(\iota^2 - \iota^*)\end{aligned} \tag{5.13}$$

The nine **condensed coefficients of identity** Δ_{ixy}, which are defined in LW Figure 7.2 and sum to 1.0, have a natural connection to the quadratic components in Table 5.1. For example, Θ_{xy}, generally referred to as the coefficient of coancestry is the probability that two genes, one drawn from x and the other from y are identical by descent. In terms of the condensed coefficients of identity,

$$\Theta_{xy} = \Delta_{1xy} + \frac{1}{2}(\Delta_{3xy} + \Delta_{5xy} + \Delta_{7xy}) + \frac{1}{4}\Delta_{8xy} \tag{5.14}$$

(LW Chapter 7), where each condensed coefficient of identity is weighted by the conditional probability that a randomly drawn gene from x is identical by descent with a randomly drawn gene from y.

Accounting for the fact that there are four gene combinations between two individuals, the genetic covariance between individuals resulting from shared additive effects is $2\Theta_{xy}\sigma_A^2$. Similarly, Δ_{7xy} and Δ_{1xy} account for the probabilities that the two individuals share identical genotypes by descent, respectively in the absence or presence of inbreeding, so the dominance genetic covariance is $(\Delta_{7xy}\sigma_D^2 + \Delta_{1xy}\sigma_{DI}^2)$. The term $(4\Delta_{1xy}+\Delta_{3xy}+\Delta_{5xy})$ is a measure of the expected number of ways in which three genes in the two individuals are identical by descent, and when multiplied by σ_{ADI}, yields the expected covariance between individuals resulting from the covariance between additive and homozygous dominance effects. Finally, $(\Delta_{2xy} - f_x f_y)$ is the probability that the two individuals are inbred at the same locus in excess of that expected for random members of the population, whereas $(\tilde{\Delta}_{2xy} - f_x f_y)$ is the excess joint inbreeding at one locus in x and another in y. These latter two coefficients are multiplied, respectively, by the quadratic terms describing inbreeding depression at the same and at different loci.

One conclusion that can be drawn immediately from Equation 5.13 is that with inbreeding, dominance can contribute to the covariance between all types of relatives. All of the terms in this equation are necessarily positive except σ_{ADI}, which can be positive or negative. Thus, while it is likely that inbreeding will inflate the covariance between relatives, this cannot be stated with certainty.

Example 5.2. Consider the situation in which fathers are mated to their daughters. What is the genetic covariance between the offspring (y) of such matings and their fathers (x)? Assuming the father is not inbred, $\Delta_{1xy} = \Delta_{2xy} = \Delta_{3xy} = f_x = \tilde{\Delta}_{2xy} = 0$, so to complete the solution of Equation 5.13, we only require values for the coefficients Θ_{xy}, Δ_{7xy}, and Δ_{5xy}. The inbreeding coefficient of y is the same as the coefficient of coancestry between the parents (which are parent and offspring), $f_y = 1/4$. Moreover, because y inherits only one gene from x directly, if y is inbred, then identity relationship 5 must hold, so $\Delta_{5xy} = f_y \cdot 1 = 1/4$. A gene in x can be identical with one in y by direct

descent from the father or by indirect descent from the father through his first daughter (the mother of y), so $\Theta_{xy} = (1/4) + (1/8) = 3/8$. Finally, given that y has inherited one gene directly from x, the probability that x's other gene has been transmitted through his first daughter is 1/4. Thus, $\Delta_7 = 1/4$. Substituting into Equation 5.13,

$$\sigma_G(x,y) = \frac{3}{4}\sigma_A^2 + \frac{1}{4}\sigma_D^2 + \frac{1}{4}\sigma_{ADI}$$

This may be contrasted with $\sigma_G(x,y) = \sigma_A^2/2$, the expectation under random mating.

Some attention has been given to the contribution of additive × additive genetic variance to the resemblance between inbred relatives (Cockerham 1984b; Cockerham and Tachida 1988; Tachida and Cockerham 1989). In this case, Equation 5.13 requires an additional term, $(\tilde{f}_{xy} + \tilde{\gamma}_{\bar{x}y} + \tilde{\gamma}_{x\bar{y}} + \tilde{\Delta}_{\bar{x}\bar{y}})\sigma_{AA}^2$. Here, the double identity measures are analogous to those described in Figure 5.1, with the overbars denoting that the two gametes contributing to that individual are involved. These coefficients depend upon the previous inbreeding in the population and the amount of recombination that occurs between individuals x and y. The algebraic details may be found in the references given above.

Equation 5.13 provides a practical way to obtain estimates of the quadratic components described in Table 5.1 from estimates of the phenotypic covariances between various types of inbred relatives and solution of the resultant set of equations (the usual method-of-moments approach). An optimal design for such an analysis employs very small population sizes in order to maximize the temporal change in the identity coefficients and to allow a high degree of replication. For systems of selfing and full-sib mating, there is an added advantage of simplicity in formulating the identity coefficients, as we will now show.

Assuming negligible linkage, all of the identity coefficients under obligate self-fertilization can be expressed in terms of the inbreeding coefficient (Cockerham 1983; Wright and Cockerham 1986; Wright 1988). For a set of selfed lines derived from a random-mating base population existing in generation 0, the covariance of relatives in generations i and j whose last common ancestor occurred in generation t is

$$\begin{aligned}\sigma_G(x_i,y_j,t) = (1+f_t)\sigma_A^2 + \left(\frac{(1-f_i)(1-f_j)}{1-f_t}\right)(\sigma_D^2 + f_t\iota^*) + \left(\frac{f_i+f_j+2f_t}{2}\right)\sigma_{ADI} \\ + \left(f_t + \frac{(f_i-f_t)(f_j-f_t)}{2(1-f_t)}\right)\sigma_{DI}^2 + (1+f_t)^2\sigma_{AA}^2 \qquad (5.15)\end{aligned}$$

where $f_k = 1-(1/2)^k$. For example, the covariance of a parent in generation t and a descendant in generation j is

$$\begin{aligned}\sigma_G(x_t,y_j,t) = (1+f_t)\sigma_A^2 + (1-f_j)(\sigma_D^2 + f_t\iota^*) + \frac{f_j+3f_t}{2}\sigma_{ADI} \\ + f_t\sigma_{DI}^2 + (1+f_t)^2\sigma_{AA}^2 \qquad (5.16)\end{aligned}$$

For a parent-offspring analysis, $j = t+1$. Additional terms involving σ_{AA}^2 and $(\iota^2 - \iota^*)$ are required if there are pairs of linked loci with major effects (Cockerham 1983, 1984b).

Although Equation 5.15 applies to an entire collection of selfed lines, within a single selfed line there are two equally frequent alleles per polymorphic locus, which leads to $\sigma_{ADI} = \sigma^2_{DI} = 0$ and $\iota^* = \sigma^2_D$. The expected covariance between relatives *within lines* then becomes

$$\sigma_G(x_i, y_j, t) = (1/2)^t \sigma^2_A + (1/2)^{i+j-t} \sigma^2_D + (1/2)^{2t} \sigma^2_{AA} \tag{5.17}$$

(Wright and Cockerham 1986). Wright (1987) has extended this result to include additive × dominance and dominance × dominance epistasis, but even in the absence of linkage, twelve terms are necessary to define the genetic covariance in this case. Note that for $t > 5$, the within- and among-population components of variance are very close to 0 and $2\sigma^2_A + 2\sigma^{ADI} + \sigma^2_{DI} + 4\sigma^2_{AA}$, respectively.

An excellent example of the utility of the selfing theory is provided by a large study with soybeans, a predominantly self-fertilizing species (Horner and Weber 1956). Two inbred varieties were crossed to produce a uniform F_1 population, which was then selfed to produce a segregating F_2. Random F_2 plants were then selfed to produce F_3 plants, and so on down to the F_7. The covariances between many possible types of relatives for the timing of seed maturation were then assessed. Under a simple additive genetic model model, Equation 5.15 reduces to

$$\sigma_G(x_i, y_j, t) = (1 + f_t)\sigma^2_A$$

which indicates that the genetic covariances of all types of direct descendants from generation t plants should be independent of i and j. The observed covariances are in fair accord with these expectations with $\sigma^2_A = 10.9$ (Figure 5.5). Although there is a fair amount of noise in the data, inclusion of other base-population properties does not significantly improve the fit, and it is likely that some of the scatter in the data is caused by year-to-year differences in growth conditions.

-Insert Figure 5.5 Here-

For the special case of full-sib mating, Cornelius and Dudley (1975) provide a general solution (ignoring epistasis and linkage) for the covariance between parents and descendants, full-sibs, and uncle (aunt) – niece (nephew). They present tables of coefficients needed for Equation 5.13 for the first eight generations of consanguineous mating. Cockerham (1971) derived a transition matrix that allows the computation of all of the coefficients for the covariance between full-sibs,

$$\begin{pmatrix} 1-\Delta_1 \\ 1-\Delta_3 \\ 1-\Delta_7 \\ 1-\Delta_2 \\ 1-f \\ 1-\Theta \end{pmatrix}_{t+1} = \begin{pmatrix} 1/4 & 1/2 & 0 & 0 & 0 & 1/4 \\ 0 & 1/2 & 0 & 0 & 0 & 1/2 \\ 0 & 1/4 & 1/8 & 1/8 & 1/4 & 1/8 \\ 0 & 1/2 & 1/4 & 0 & 0 & 1/4 \\ 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 1/4 & 1/2 \end{pmatrix} \begin{pmatrix} 1-\Delta_1 \\ 1-\Delta_3 \\ 1-\Delta_7 \\ 1-\Delta_2 \\ 1-f \\ 1-\Theta \end{pmatrix}_t \tag{5.18}$$

where in this case $\Delta_3 = \Delta_5$.

In closing, it needs to be emphasized that all of the expressions developed above have been written in terms of the quadratic components for the random-mating base

population. Provided that mating remains random in a small population, there is no reason that the simpler and more familiar expressions of LW Chapter 5 cannot be relied upon, provided it is understood that the variance and covariance components apply to the current population. For example, the expected genetic covariance between half-sibs in generation t may be written either as $\sigma_A^2(t)/4$ or in terms of base-population properties with Equation 5.13. The advantage of interpreting the covariance between relatives in terms of the base population properties is that it provides a mechanistic explanation for the temporal changes in the usual components of variance, $\sigma_A^2(t)$ and $\sigma_D^2(t)$.

It is also worth noting that the procedures outlined above can be extended to numerous situations involving natural populations, where individuals vary in inbreeding levels to an unknown degree. For example, a mixed system of selfing and random mating is common in many plant species. If the proportion of selfed progeny is a constant β, then an effectively infinite population will attain the equilibrium level of inbreeding $f = \beta/(2-\beta)$ (Weir and Cockerham 1973; Weir et al. 1980). Under the assumptions that this equilibrium condition has been attained and that epistasis and linkage are of negligible importance, Cockerham and Weir (1984) obtained expressions for the genetic covariances of several types of relatives (Table 5.4). Application of these formulae requires an estimate of the frequency of self-fertilization (β) so that the expectation and variance of f can be computed.

Empirical Observations

Unfortunately, data on the parameters σ_{DI}^2, σ_{ADI}, and ι^* are scant, although some progress has been made with annual plants. Starting from a random-mating base population of maize, Cornelius (1988) produced a series of selfed and full-sib mated lines, all of which were assayed in a common garden experiment. The parameter estimates given in Table 5.5 best describe the overall set of observed covariances. Except for yield, all of the characters exhibit significant additive genetic variance, and four of the six traits exhibit significant squared inbreeding effects, ι^*. However, nearly all of the estimates for σ_D^2, σ_{DI}^2, and σ_{ADI} are nonsignificant.

The few other attempts to estimate quadratic components involving inbreeding have yielded mixed results. For example, starting with 300 inbred lines of the monkeyflower (*Mimulus guttatus*), Kelly and Arathi (2003) crossed triplets of lines to create outbred full-sib and half-sib families, allowing a joint analysis of σ_A^2, σ_D^2, σ_{DI}^2, and σ_{AD} for six floral traits. Although each character exhibited significant inbreeding depression, and σ_D^2 was significant for two and σ_{DI}^2 for six traits, σ_{AD} was significant in only one case. In a study of another flowering plant, *Nemophila menziesii,* > 1000 plants with f up to 0.75 were evaluated in a common garden for two morphological and two floral traits (Shaw et al. 1998). Application of a REML analysis (LW Chapter 27) revealed significant inbreeding depression for all traits, but σ_{DI}^2 was significant only for the floral traits, and σ_{AD} was uniformly nonsignificant. In another application of REML to study of 2000 sheep with variable f up to a high of 0.6, Shaw and Woolliams (1999) found no evidence for significant σ_{DI}^2 or σ_{AD} for body weight or fleece quality, despite the presence of significant inbreeding depression for both.

Although these limited surveys do not rule out important contributions from quadratic inbreeding components in some cases, combined with the observations on the dynamics of genetic variance described above, they do raise questions about the general necessity of incorporating such complexities into expressions for genetic variances and covariances. Again, this is not to deny an important role for dominance and epistasis in the expression of complex traits, for which the evidence is substantial (Lynch and Walsh 1998; Wolf et al. 1980). However, despite arguments to the contrary (Templeton 1980), there is little compelling evidence that we need to abandon the existing theoretical framework for quantitative-trait evolution even in the presence of substantial physiological epistasis. Although substantial progress has been made in the incorporation of the complexities of nonadditive gene action into the theory of quantitative traits in finite populations, the limited empirical evidence to date implies a second-order nature of such effects.

Table 5.4. Coefficients for the components of genetic covariance for an equilibrium population undergoing mixed selfing and random mating (in proportions β and $1-\beta$ respectively). $\sigma_f^2 = f(1-f^2)/(2+f)$, with $f = \beta/(2-\beta)$, is the equilibrium variance in the inbreeding coefficient among individuals. (From Cockerham and Weir 1984).

Relationship	σ_A^2	σ_D^2	σ_{ADI}	σ_{DI}^2	ι^*	$\iota^2 - \iota^*$
Parent and outcrossed offspring	$\frac{1+f}{2}$	0	$\frac{f}{2}$	0	0	0
Parent and selfed offspring	$1+f$	$\frac{1-f}{2}$	$\frac{1+7f}{4}$	f	$\frac{f(1-f)}{2}$	$\frac{\sigma_f^2}{2}$
Parent and mixed offspring (η selfs)	$\frac{1+3f}{2}$	$\frac{2f(1-f)}{2(1+f)}$	$\frac{f(1+3f)}{1+f}$	$\frac{2f^2}{1+f}$	$\frac{f^2(1-f)}{1+f}$	$\frac{f\sigma_f^2}{1+f}$
Selfed sibs	$1+f$	$\frac{1-f}{2}$	$\frac{1+3f}{2}$	$\frac{1+7f}{8}$	$\frac{f(1-f)}{4}$	$\frac{\sigma_f^2}{4}$
Selfed sib and outcrossed sib	$\frac{1+f}{2}$	0	$\frac{1+3f}{8}$	0	0	0
Full sibs	$\frac{1+f}{2}$	$\frac{(1+f)^2}{4}$	0	0	0	0
Half sibs	$\frac{1+f}{2}$	0	0	0	0	0

Table 5.5. Estimates of the quadratic components of Equation 5.13 from phenotypic data on selfed and full-sib mated lines derived from a panmictic base population of maize. The parameter estimates, obtained by a maximum-likelihood procedure, are those that give the overall best fit to a large number of observed relationships. (From Cornelius 1988).

Character	Var(A)	Var(D)	Var(DI)	Cov(ADI)	i^*
Plant height (cm)	370 ± 99	-57 ± 139	225 ± 220	-258 ± 178	1045 ± 341
Ear height (cm)	382 ± 83	-103 ± 98	383 ± 179	-450 ± 152	430 ± 238

Grain yield (g/plant)	-125 ± 231	1403 ± 436	-129 ± 552	330 ± 468	3286 ± 886
% Moisture of seed	5.9 ± 1.7	-1.0 ± 2.5	-5.0 ± 3.6	3.2 ± 2.8	15.3 ± 6.9
% Oil of seed	0.14 ± 0.05	0.05 ± 0.08	-0.02 ± 0.12	0.02 ± 0.10	0.31 ± 0.19
Kernel wt. (g/100)	14.7 ± 4.2	-2.3 ± 6.3	4.5 ± 9.9	-1.6 ± 7.6	15.3 ± 16.0

DRIFT-MUTATION EQUILIBRIUM

The models introduced in the previous sections predict that finite populations eventually lose all of their genetic variation, at which point the genotypic means of isolated populations will have attained a maximum level of divergence. These results arose because we assumed an absence of significant evolutionary forces countering the loss of variance caused by random genetic drift. In reality, there is one such force that cannot be prevented — the continual input of new variation by polygenic mutation. When this is accounted for, we can expect neutral quantitative traits to evolve toward an equilibrium level of within-population variance as a balance is struck between the opposing forces of drift and mutation. The means of such characters should also continue to diverge as isolated populations become fixed for unique mutations, a subject that will be dealt with in detail in Chapter 6.

Consider a character with a purely additive genetic basis in a population with constant effective size. Each generation, a fraction $1/(2N_e)$ of the genetic variation is lost by drift, while new variation in the amount σ_m^2 is introduced by mutation. In mechanistic terms, σ_m^2 is defined as $2\sum_{i=1}^{n} u_i E(a_i^2)$, where u denotes the genic mutation rate, n denotes the number of loci contributing to the trait, and $E(a_i^2)$ is the average squared heterozygous effect of a new mutation on the phenotypic value (LW Chapter 12). This leads to the simple recursion equation,

$$\sigma_A^2(t) = \left(1 - \frac{1}{2N_e}\right)\sigma_A^2(t-1) + \sigma_m^2 \tag{5.19a}$$

(Clayton and Robertson 1955), which has the approximate solution

$$\sigma_A^2(t) = 2N_e\sigma_m^2 + [\sigma_A^2(0) - 2N_e\sigma_m^2]\exp(-t/2N_e) \tag{5.19b}$$

Thus, the equilibrium genetic variance for a neutral quantitative trait (obtained as $t \to \infty$) with an additive genetic basis is simply $2N_e\sigma_m^2$ (Lande 1976; Chakraborty and Nei 1982; Lynch and Hill 1986). Starting from a completely homozygous base population, the times to 50% and 95% of the equilibrium variance are approximately $1.4N_e$ and $6.0N_e$ generations (Lynch and Hill 1986). Thus, because $\sigma_A^2(0)$ will typically be greater than zero, small isolated populations can be expected to reach the equilibrium quite rapidly. On the other hand, if a population is suddenly reduced to an unusually small N_e, such that $\sigma_A^2(0) \ll 2N_e\sigma_m^2$, for the several immediately following generations $\sigma_A^2(t) \simeq \sigma_A^2(0)e^{-t/2N_e}$, justifying the use of Equation 5.2 for the short term.

Letting $h_m^2 = \sigma_m^2/\sigma_E^2$, where σ_E^2 is the environmental variance of the trait, be the mutational heritability and again assuming additivity of genetic effects, the

equilibrium heritability for a neutral character under this model is

$$E(h^2) = \frac{2N_e h_m^2}{1 + 2N_e h_m^2} \tag{5.20a}$$

Almost all estimates of h_m^2 are in the range of 0.01 to 0.0001 with a median value near 0.001 (LW Chapter 12). Thus, populations with $N_e \simeq 100$ are expected to have small to moderate levels of heritability for neutral characters, but nearly all of the phenotypic variation for neutral characters is expected to have a genetic basis if $N_e > 10^4$ (Figure 5.7).

It is informative to note the similarity of Equation 5.20a with the expected heterozygosity for loci in drift-mutation equilibrium

$$E(H) = \frac{4N_e u}{1 + 4N_e u} \tag{5.20b}$$

(derived in Chapter 2). Comparison of these two expressions shows that because u is on the order of 10^{-6} (at the per-locus level, and much smaller at the per nucleotide site level; Chapter 4) while $h_m^2 \simeq 10^{-3}$, substantial heritability can exist for quantitative traits in populations with low or undetectable levels of molecular heterozygosity.

–Insert Figure 5.6 Here–

Lynch and Hill (1986) generalized the preceding results to allow for dominance and linkage. Assuming a population size small enough that no more than two alleles are likely to be segregating simultaneously per locus, and letting $\bar{k}$ and σ_k^2 be the mean and variance of dominance effects, with $k = 0$ implying additivity, the equilibrium levels of additive and dominance genetic variance are

$$\sigma_A^2 \simeq \frac{2N_e\sigma_m^2(3 + 2\bar{k})}{3} \tag{5.21a}$$

$$\sigma_D^2 \simeq \frac{2N_e\sigma_m^2(\bar{k}^2 + \sigma_k^2)}{3} \tag{5.21b}$$

Thus, unless new mutations tend to be highly dominant, highly recessive, or highly variable in their dominance effects, most of the genetic variation will be additive in nature. Assuming no overdominance, the bounds on σ_A^2 are $(2/3)N_e\sigma_m^2$ and $(10/3)N_e\sigma_m^2$. Although these formulae ignore the fact, discussed above, that dominant mutations in gametic-phase disequilibrium can inflate the genetic variance, this effect only magnifies the variance by a factor of approximately $0.02\overline{ak}/\overline{a^2}$, which is unlikely to be very large (Lynch and Hill 1986).

The preceding results were obtained by use of Kimura and Crow's (1964) **infinite-alleles model**, which postulates that although a large number of alleles need not be segregating at a particular locus at any point in time, each new mutation gives rise to a novel allele. From a quantitative-genetics perspective, the additive effect of each new mutant allele is assumed to equal to that of the ancestral allele plus a random deviate with mean zero. Under this Brownian-motion model of mutational

effects, there is no directional change of the mean but also no upper or lower bound on the range of mutational effects. This implies that $\sigma_A^2 \rightarrow \infty$ as $N_e \rightarrow \infty$.

Taking exception to this assumption, Cockerham and Tachida (1987) assumed a finite number of possible additive allelic states, following the so-called **house-of-cards** model of Kingman (1977, 1978). Under this model, each new mutant allele has a new effect drawn randomly from the distribution of possible effects and independent of the prior state. Under these conditions, the equilibrium genetic variance within a finite population becomes $\sigma_A^2 = E(H)\sigma_A^2(\infty)$, where $\sigma_A^2(\infty)$ is the equilibrium level of genetic variance expected in a hypothetical population of infinite size, and $E(H)$ is the equilibrium heterozygosity for the loci underlying the trait. Under the Cockerham-Tachida model, $\sigma_A^2(\infty) = nE(a^2)$, and $E(H)$ is defined by Equation 5.20b. Thus, when $4N_eu \ll 1$, the Cockerham-Tachida expression for the equilibrium variance is very close to $4N_eunE(a^2) = 2N_e\sigma_m^2$, which is identical to the Lynch-Hill expression.

As it is not likely that mutant alleles will have effects that are entirely independent of their ancestral alleles, nor that mutational effects can grow without bounds, reality must lie between these two extremes. Zeng and Cockerham (1993) presented an approach that joins the two limiting cases. They imagine a situation in which the effect of a mutant allele (a_m) is a random deviate around a linear regression on the ancestral state (a_0), i.e.,

$$a_m = \tau a_0 + e_a \tag{5.22}$$

where e_a denotes the deviation around the expectation. When $\tau = 1$, Equation 5.22 is equivalent to the Lynch-Hill model, whereas $\tau = 0$ is equivalent to the Cockerham-Tachida model. The general solution to the equilibrium additive genetic variance under this model is

$$\sigma_A^2 = \frac{2N_e\sigma_m^2}{1 + 4N_eu(1-\tau)} \tag{5.23}$$

Thus, both approaches predict a linear increase in the equilibrium genetic variance with population size so long as N_e is smaller than the reciprocal of the mutation rate to alleles affecting quantitative-trait expression ($4N_eu \ll 1$). As noted in Chapter 4, when defined at the nucleotide level, $4N_eu$ is generally in the range of 0.001 to 0.05 in eukaryotes. Because a typical protein-coding locus contains ~ 1000 amino-acid replacement sites (where a nucleotide substitution will lead to an amino-acid change) and regulatory sequences may comprise another 100 to 2000 sites/gene (Lynch 2007), then assuming a moderate fraction of such sites yield mutations with phenotypic effects, a typical mutational target size per locus will be ~ 1000 sites. Recalling the survey in Chapter 4, the mutation rate per site per generation is a minimum of $\sim 10^{-9}$ in microbes and a high of $\sim 2.5 \times 10^{-8}$ in humans, then u for a quantitative-trait locus is expected to be in the range of 10^{-6} to 2.5×10^{-5}. Thus, the equilibrium h^2 for a neutral trait given by Equation 5.20a appears to be quite robust (Figure 5.6), although the additive genetic variance given by Equation 5.23 may sometimes be a considerable overestimate.

Finally, due to the randomness of both the drift and mutation processes, the within-population genetic variance is expected to vary considerably around the expectation both among populations of the same size and from generation to generation in the same population. Assuming a large number of unlinked loci, the

coefficient of variation of the average within-population genetic variance under the infinite-alleles model is

$$\mathrm{CV}(\tilde{\sigma}_A^2) \simeq \left[\frac{1}{L}\left(\frac{E(a^4)}{12N_eU[E(a^2)]^2} + \frac{2}{3N_e} + \frac{2}{s}\right)\right]^{1/2} \tag{5.24}$$

where $U = nu$ is the gametic mutation rate for the trait, L is the number of lines examined, and s is the sample size per line (Lynch and Hill 1986; Keightley and Hill 1989; Zeng and Cockerham 1991). If the effects of new mutations are approximately normal with an average of zero, then $E(a^4) = 3[E(a^2)]^2$. Further considering only the true evolutionary variance, and assuming $u \ll 1$, the CV for a single line reduces to $\sim (4N_eu)^{-1/2}$, or the square root of twice the number of new mutations entering the population per generation. Büger and Lande (1994) further consider the temporal correlation in σ_A^2 over consecutive generations.

Subdivided Populations

In closing, we emphasize that the results given in the previous section apply to the ideal situation in which individual demes are completely isolated from each other. In nature, however, it is common for a total metapopulation to be fragmented into multiple demes held together in a genealogical sense by restricted gene flow. Borrowing from results presented in Chapter 3, we now explore the quantitative-genetic consequences of population subdivision. Throughout, it will be assumed that there is some possible migratory route, either direct or indirect, between all pairs of demes under consideration. In other words, even if two particular demes are incapable of directly exchanging genes, they are assumed to be connected by a corridor through other subpopulations. In this case, at least for characters with an additive genetic basis following the Lynch-Hill model, the average within-deme genetic variance exhibits some remarkably general behavior, although the results for traits with a nonadditive genetic basis remain to be worked out.

Recall Wright's (1951) ideal island model, discussed in Chapter 3, in which the metapopulation consists of d demes, each consisting of an equivalent number (N) of ideally randomly mating individuals, with each deme contributing an identical fraction m of its genes to a pool of migratory genes. Under this model, with equal exchange rates between all deme pairs, the migration rate from any subpopulation to any other is $m/(d-1)$. In Chapter 3, we noted the "geographic invariance principle" for this model under neutrality, which indicates that the mean coalescence time between random alleles within a deme is simply equal to $2dN$ independent of the migration rate (Li 1976; Slatkin 1987; Strobeck 1987; Nagylaki 2000). Letting u be the genic mutation rate, it then follows that the mean number of mutations separating two random alleles is $4dNu$, or more generally with unequal deme sizes (Slatkin 1987; Strobeck 1987) $4N_Tu$, where $N_T = \sum_{i=1}^{d} N_i$ is the sume of effective sizes of the individual demes. Noting that the expected variance based on the sampling of two alleles is $E(a^2)/4$, and that the population-level of variance is acquired by multiplying by $2/(2-1)$ (to account for finite sampling), the contribution of each haploid mutational change to the genetic variance is $E(a^2)/2$. Thus, with $2n$ genes contributing to the character, the average within-deme additive genetic variance is

$$\sigma_A^2 = 4N_Tu \cdot 2n \cdot E(a^2)/2 = 2N_T\sigma_m^2 \tag{5.25}$$

which is identical in form to the expectation for a single isolated deme, $2N_e\sigma_m^2$, with N_T being substituted for the N_e of a single deme. Depending on the exact population structure, individual demes may have higher or lower equilibrium variances than this quantity, but Equation 5.25 gives the expectation over all demes.

That the preceding result was obtained by a much more detailed route by Lynch (1988b) for two demes and Lande (1992) for an arbitrary number of demes illustrates the substantial utility of results from coalescence theory for problems in quantitative genetics involving traits with an additive-genetic basis. As anticipated from the coalescent, with an ideal island structure, the equilibrium additive-genetic variance is not only completely independent of the migration rate, but most remarkably, it behaves as though the average deme is panmictic with effective size N_T. Although lower migration rates imply a lower rate of replenishment of alleles lost locally by random genetic drift, a greater degree of isolation also increases the level of interpopulation divergence of alleles, so that a rare immigration event will likely introduce a more substantial allelic variant. Under the ideal island model, these two opposing effects perfectly compensate for each other.

Because the expected coalescence time $2Nd$ applies to all types of population structures, so long as they allow for migratory routes between all pairs of subpopulations, the above result generalizes to situations well beyond the ideal island model, including the **stepping-stone model** in which migration events are restricted to adjacent demes. Slatkin and Voelm (1991) evaluated the genealogical properties of a population with a hierarchical metapopulation where there are k neighborhoods, each containing d demes, and even this structure yields a result analogous to that presented above. Again, provided there are potential migratory routes between demes within neighborhoods as well as between neighborhoods, the expected genetic variance within a deme can be shown to be $\sigma_A^2 = 2Nkd\sigma_m^2$, where Nkd is the sum of demic effective population sizes (over all neighborhoods). Thus, we again see that provided the trait has an additive genetic basis, the expected within-population additive variance under neutrality (and assuming the Lynch-Hill model) is $2N_T\sigma_m^2$. This result does assume that gametic-phase disequilibria do not substantially influence the expected standing level of variation, but this is reasonable for a neutral trait, as there will be no tendency for disequilbria to favor coupling over repulsion effects.

The above results apply to the variation within single demes, and it is of additional interest to determine the equilibrium features of the entire metapopulation. This requires a measure of among-deme divergence in addition to the within-deme variance, as the total genetic variation in the metapopulation is the sum of the two. This matter is also readily resolved using results from coalescence theory, again assuming a character with an additive genetic basis. Consider, for example, Wright's island model. If two genes are randomly drawn from an entire metapopulation, they will be derived from the same subpopulation with probability $1/d$, in which case they will have an average coalescence time of $2Nd$ generations, and from different subpopulations with probablity $(d-1)/d$, in which case they will have an elevated average coalescence time of $2Nd + [(d-1)/(2m)]$ as a consequence of divergence during isolation (Li 1976). Weighting these two coalescence times by their respective probabilities yields the average coalescence time given as Equation 3.26. Again noting that the expected number of mutations separating two alleles is $2u$ times the

average coalescence time, and that there are $2n$ genes involved, each with respective contributions to the variance of $E(a^2)/2$, the total additive genetic variance for the metapopulation is

$$\sigma^2_{A,T} = \left(2Nd + \frac{(d-1)^2}{2dm}\right)\sigma^2_m \tag{5.26}$$

Again, essentially the same result was obtained by Lande (1992) by a more circuitous route.

Thus, for the island model, the within- and among-deme components of additive-genetic variance are equal to $2Nd\sigma^2_m$ and $([(d-1)^2/(2dm)]\sigma^2_m$, respectively. Recalling that $m/(d-1)$ is the genic migration rate per deme, this shows that the among-deme component of genetic variance is inversely proportional to the exchange rate among demes, and for moderate to large numbers of demes (such that $(d-1)/d \simeq 1$), is essentially independent of the number of demes. It is also notable that the among-deme component of genetic variance is completely independent of the sizes of the individual demes. Assuming large d, the fraction of the total genetic variance associated with the interdemic component is $1/(1+4Nm)$, showing that under this type of population structure, the relative contribution from interdemic variance is relatively low unless the expected number of migrants per deme per generation (mN) is less than one.

Note that Equation 5.26 can be obtained directly from our general expression for the equilibrium additive-genetic variance, $2N_e\sigma^2_m$, using the coalescent-based definition of N_e for the entire metapopulation under the island model, Equation 3.27. Using this general strategy, the expressions for N_e given in Chapter 3 can be used to obtain results for a variety of other types of population structures. Moreover, as summarized in Lynch (1994), coalescent results can also be used to estimate the genetic variances and covariances for pairs of populations separated by various distances for situations in which migration is spatially restricted. Provided there are possible migratory routes between demes, the expected excess variance between any pair of demes is simply the product of the coalescence time (in excess of the within-deme expectation) and the rate of polygenic mutation, σ^2_m.

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Figure 5.1. Measures of identity by descent for single loci (f, γ, δ, Δ) and pairs of loci ($\tilde{f}$, $\tilde{\gamma}$, $\tilde{\Delta}$). The large circles denote gametes, and the open and closed dots within them represent alleles from two loci. Identity by descent is indicated by a horizontal line.

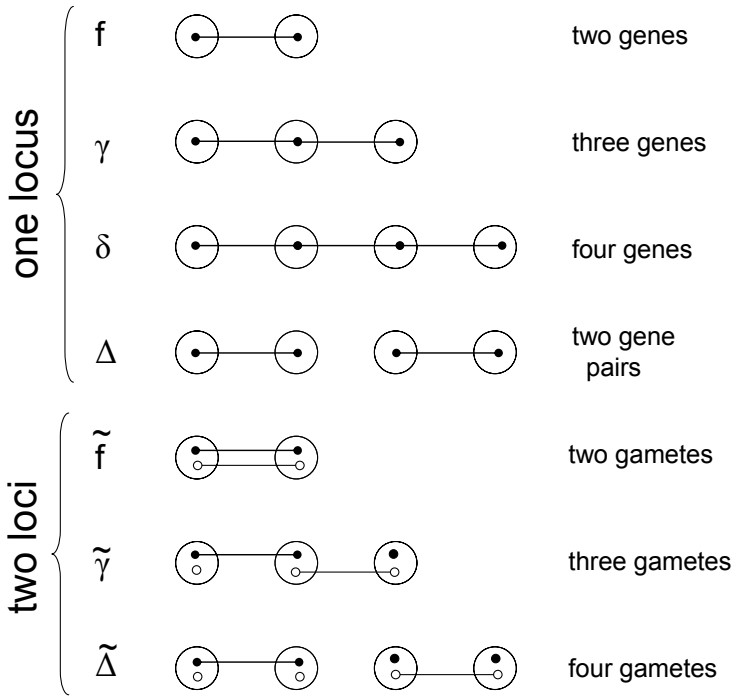

Figure 5.2. Dynamics of the coefficients for the terms contributing to the additive, dominance, and additive × additive genetic variance within populations for an effective population size of 10 and freely recombining loci ($c = 0.5$), obtained by use of the equations described in the text. The coefficient for the contribution of $(\iota^2 - \iota^*)$ to the additive genetic variance is not visible on the scale in the graph. These results apply approximately to any other population size N_e, if the time scale is transformed by multiplying by $N_e/10$. To obtain the actual dynamics of the variance components, the coefficients need to be multiplied by the base-population properties. For example, the additive genetic variance in generation 50 is approximately $0.08(\sigma_A^2 + \sigma_{ADI}) + 0.04\sigma_{DI}^2 + 0.01(\sigma_D^2 + \iota^*) + 0.28\sigma_{AA}^2$, while the additive × additive genetic variance is $\simeq 0$, and the dominance genetic variance is $\simeq 0.04(\iota^* + \sigma_D^2)$.

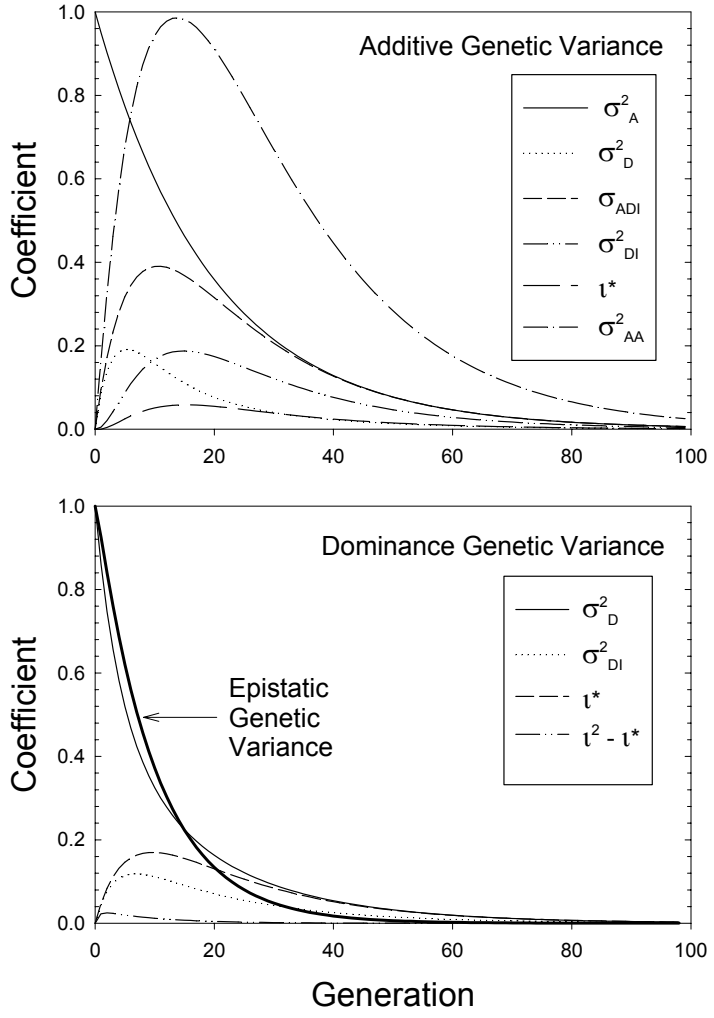

Figure 5.3. Response of the average within-line and among-line phenotypic variance to inbreeding in experimental lines. References and system of mating from top to bottom: Top) Horner and Weber (1956), selfing; Middle) López-Fanjul and Jódar (1977), full-sib mating, control-corrected; Bottom) Bateman and Mather (1951), selfing. Solid and open points denote the within- and among-population components of phenotypic variance.

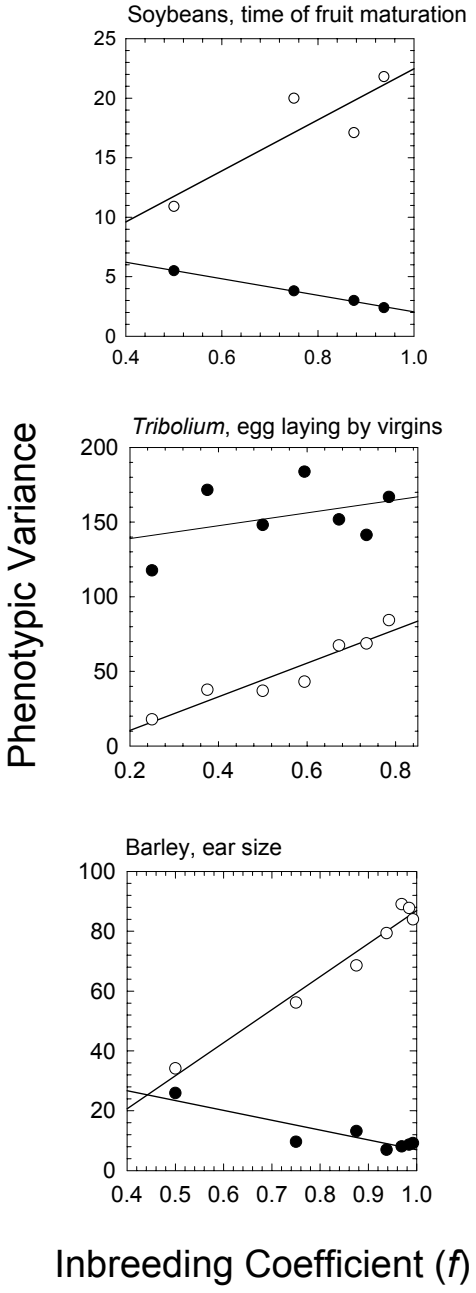

Figure 5.4. Additive genetic variances for eight morphometric traits averaged over four replicate lines of bottlenecked housefly populations. Horizontal lines connect variances that were not significantly different at the 0.05 level. C denotes a large randomly mating control population, whereas the remaining populations were propagated as one, four, and sixteen pairs per generation. WL denotes wing length, WW wing width, HW head width, SL scutellum length, IE inner eye separation, SW scutellum width, ML metafemur length, and TS thoracic suture length. (From Bryant et al. 1986).

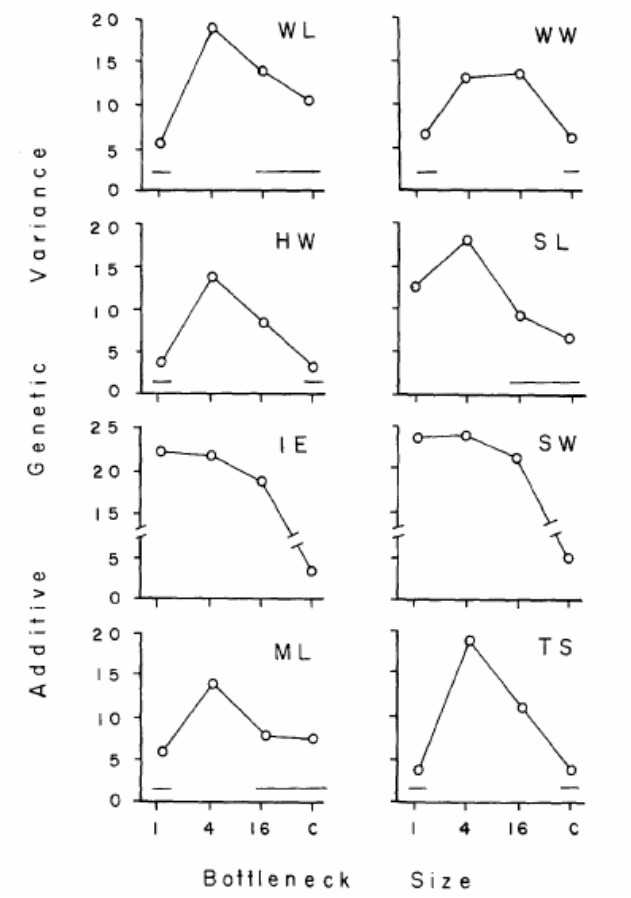

Figure 5.5. Observed covariances between relatives in a selfing series starting from a highly heterozygous F_2 synthetic population of soybeans ($t = 0$). i and j denote the generations of the individuals under consideration, and t is the generation of their last common ancestor. For example, the covariance between individuals in generations 2 and 3 with a last common ancestor at generation 0 is indicated by $i = 2$, $j = 3$, $t = 0$. The lines represent the expectations under the assumption of an additive model, $(1 + f_t)\sigma_A^2$ with $f_t = 1 - (1/2)^t$ and $\sigma_A^2 = 10.9$. Data are from Horner and Weber (1956).

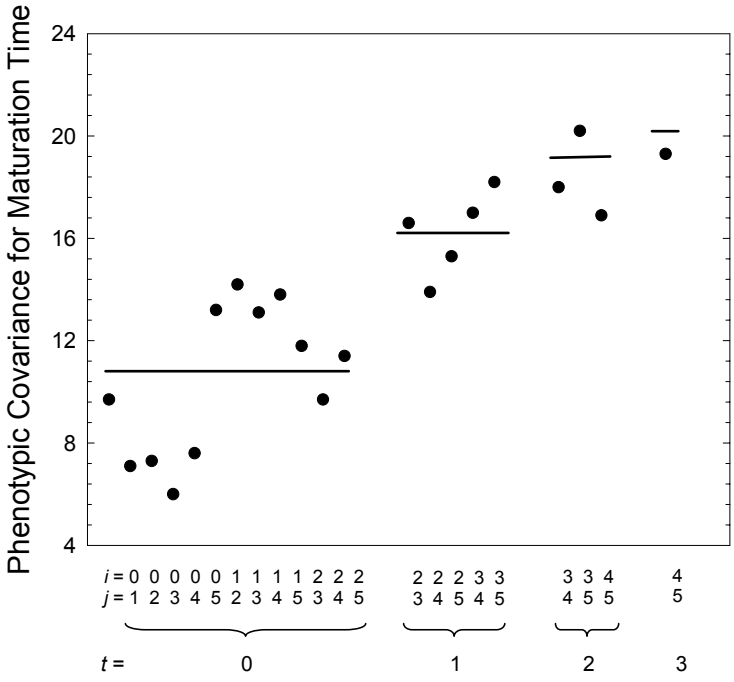

Figure 5.6. Upper Panel: Levels of heritability expected for neutral characters with an additive genetic basis under drift-mutation equilibrium, assuming the Lynch-Hill (1986) model. The three levels of mutational heritability, σ_m^2/σ_E^2, span the range of observed values. Lower Panel: Comparison of the predictions of the Lynch-Hill model with that of the Cockerham-Tachida model for three different gametic mutation rates for the trait (dotted and dashed lines), with $h_m^2 = 0.001$ in both cases.