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Multivariate Response: Changes in Covariances

The proportional change in the genetic covariances is likely to be greater than in the genetic variances themselves. It must therefore be expected that the static description of a population in terms of additive genetic variances and covariances will be valid in prediction over a much shorter period for correlated response than it will be for direct response. —Bohren, Hill and Robertson 1966

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The previous chapter assumed that genetic variances and covariances do not appreciably change over our time scale of interest for selection response. We now relax this assumption and consider changes in \mathbf{G} during selection. Much of our development of the dynamics of \mathbf{G} follows along similar lines to our development of changes in the genetic variance under univariate selection. In previous chapters we showed that short-term changes in the genetic variance occur from selection creating linkage disequilibrium (Chapter 13). Under the infinitesimal model, these changes are straightforward to predict using Bulmer's Equation (13.7). Over longer time scales, allele frequencies change, and predicting of the change in variance is no longer simple, requiring extensive knowledge of the distribution of allelic effects (Chapters 14, 24-26). Finally, over even longer time scales, any initially usable genetic variation is eventually removed by selection and drift, and further progress depends upon the creation of new variation (typically by mutation). All of these themes also hold when considering changes in \mathbf{G} . One new theme is that genetic covariances are even more sensitive to allele frequency changes than are genetic variances. We start with development of the multivariate Bulmer's equation for the change in \mathbf{G} solely through the generation of linkage disequilibrium under the infinitesimal model. We then examine the selection pressures on genetic variances and covariances from both directional and quadratic selection, concluding with an analysis under a general multivariate Gaussian fitness function. This class of fitness functions is very flexible and widely used in modeling phenotypic evolution (Chapters 41-43). Next, we consider the changes in genetic covariances under allele frequency change, and review results from multi-trait selection experiments. We then turn to a discussion of genetic models that generate pleiotropic correlations. We conclude by considering long-term selection, first developing the multivariate version of Robertson's results (Chapter 26) for long-term response under selection and drift (but no mutation) in the infinitesimal framework. We then consider various other models of combinations of selection, mutation, and drift that produce equilibrium values of \mathbf{G} for populations under constant selection, and conclude with a few general comments on what the theory suggests about the stability of \mathbf{G} .

CHANGES IN \mathbf{G} UNDER THE INFINITESIMAL MODEL

Under the assumptions of the infinitesimal model (a very large number of loci, each of very small effect, Chapter 24), there is no significant allele frequency change and thus any change in the variances and covariances is due to linkage disequilibrium (LD). As developed in

Chapter 13, Bulmer's Equation (13.7) allows us to predict the change in LD (and hence the change in the genetic and phenotypic variance) under the infinitesimal model. Here we develop the multivariate extension of the Bulmer Equation.

As way of background, recall Bulmer's treatment for the univariate case (Chapter 13). All changes in the genetic and phenotypic variance are due to gametic-phase disequilibrium d changing the additive variance. Thus $\sigma_A^2(t) = \sigma_A^2(0) + d_t$, and $\sigma_z^2(t) = \sigma_z^2(0) + d_t$. The assumption of no allele frequency change allows us to use base genetic variance $\sigma_A^2(0)$ as the linkage equilibrium value of \mathbf{G} in any generation. Assuming unlinked loci, the current value of d is halved each generation by segregation. Likewise, if d_t^* is the amount of new disequilibrium generated by selection in generation t , then the total disequilibrium just before reproduction is $d_t^* + d_t$. Segregation between unlinked loci results in only half of the disequilibrium being passed on to the offspring generation, so that

$$\Delta d_t = d_{t+1} - d_t = -\frac{d_t^* + d_t}{2}$$

The Dynamics of the Disequilibrium Matrix \mathbf{D}

Moving to multiple characters, the additive genetic covariance between traits i and j in generation t can be written as

$$\sigma_t(A_i, A_j) = \sigma_0(A_i, A_j) + d_t(i, j) \quad (31.1a)$$

where $d_t(i, j)$ is the disequilibrium contribution at time t and $\sigma_0(A_i, A_j)$ the linkage equilibrium value from the base population. If allele frequency change has occurred (for example, by drift), then this is replaced by $\sigma_{LE}(A_i, A_j)$, the linkage equilibrium value given the current allele frequencies. As above, selection generates d while recombination removes it, so that

$$\Delta d_t(i, j) = -\frac{d_t^*(i, j) + d_t(i, j)}{2} \quad (31.1b)$$

where (as in the univariate case) d^* corresponds to the new LD generated by selection and d to the current LD before selection.

Thus, in the multivariate case, disequilibrium is measured by the matrix $\mathbf{D}_t = \mathbf{G}_t - \mathbf{G}_0$, and the phenotypic covariance matrix is given by $\mathbf{P}_t = \mathbf{P}_0 + \mathbf{D}_t$. These definitions assume that allele frequencies (and hence \mathbf{G}_0) have not changed. If they have (for example, by drift), then \mathbf{G}_0 is replaced by \mathbf{G}_{LE} , the \mathbf{G} matrix for the current allele frequencies in the absence of LD (Turelli 1988a, Turelli and Barton 1994, Shaw et al. 1995). The change in \mathbf{D} over time is given by

$$\Delta \mathbf{D}_t = -\frac{\mathbf{D}_t^* + \mathbf{D}_t}{2} \quad (31.2a)$$

Further, the amount of new disequilibrium generation by selection is just $\mathbf{D}^* = \mathbf{G}^* - \mathbf{G}$, the difference between the covariance matrix before and after selection. Thus, the multivariate version of Bulmer's equation is given by

$$\Delta \mathbf{D}_t = -\frac{\mathbf{G}_t^* - \mathbf{G}_t + \mathbf{D}_t}{2} \quad (31.2b)$$

To place this equation in a more usable form, we need to replace \mathbf{G}^* with a measure based on the phenotypic covariance matrix before and after selection, both of which we can observe directly. Recall that we did this in Example 30.2, which showed (Equation 30.12) under the assumptions of the multivariate breeder's equation that

$$\mathbf{G}^* - \mathbf{G} = \mathbf{G}\mathbf{P}^{-1}(\mathbf{P}^* - \mathbf{P})\mathbf{P}^{-1}\mathbf{G} \quad (31.3)$$

where \mathbf{P}^* is the covariance matrix after selection, so that the change in the covariance matrix is given by $\Delta\mathbf{P} = \mathbf{P}^* - \mathbf{P}$. Substituting these results into Equation 31.2b gives

$$\Delta\mathbf{D}_t = \frac{1}{2} (\mathbf{G}_t \mathbf{P}_t^{-1} (\mathbf{P}_t^* - \mathbf{P}_t) \mathbf{P}_t^{-1} \mathbf{G}_t - \mathbf{D}_t) \quad (31.4a)$$

$$= \frac{1}{2} (\mathbf{G}_t \mathbf{P}_t^{-1} \Delta\mathbf{P}_t \mathbf{P}_t^{-1} \mathbf{G}_t - \mathbf{D}_t) \quad (31.4b)$$

This multivariate version was obtained by Tallis (1987, Tallis and Leppard 1988), who also allowed for assortative mating (see his papers for details). As expected, Equation 31.4b collapses to the univariate Bulmer Equation (13.7b) when only a single trait is considered. Recalling that $\mathbf{D}_{t+1} = \mathbf{D}_t + \Delta\mathbf{D}_t$, we can rewrite Equation 31.4b as

$$\mathbf{D}_t = \frac{1}{2} (\mathbf{D}_{t-1} + \mathbf{G}_{t-1} \mathbf{P}_{t-1}^{-1} \Delta\mathbf{P}_{t-1} \mathbf{P}_{t-1}^{-1} \mathbf{G}_{t-1}) \quad (31.4c)$$

At equilibrium, $\Delta\mathbf{D}_t = 0$, and Equation 31.4b implies

$$\tilde{\mathbf{D}} = \tilde{\mathbf{G}} \tilde{\mathbf{P}}^{-1} \widetilde{\Delta\mathbf{P}} \tilde{\mathbf{P}}^{-1} \tilde{\mathbf{G}}$$

where the tilde denotes an equilibrium value. Expressed as a function of $\tilde{\mathbf{D}}$ this becomes

$$\tilde{\mathbf{D}} = (\mathbf{G}_0 + \tilde{\mathbf{D}}) (\mathbf{P}_0 + \tilde{\mathbf{D}})^{-1} (\widetilde{\Delta\mathbf{P}}) (\mathbf{P}_0 + \tilde{\mathbf{D}})^{-1} (\mathbf{G}_0 + \tilde{\mathbf{D}}) \quad (31.5)$$

If $\Delta\mathbf{P}$, the within-generation change in \mathbf{P} , has a regular pattern, then Equation 31.5 can be solved by iteration.

The Proportional Change Model for $\Delta\mathbf{P}$

One class of models for $\Delta\mathbf{P}$ is the multivariate extension of Equation 13.10a, in which the same proportional change in the variance occurs each generation, $\sigma^2(z_t^*) = (1 + \kappa)\sigma^2(z_t)$, implying

$$\Delta\sigma^2(z_t) = \sigma^2(z_t^*) - \sigma^2(z_t) = \kappa\sigma^2(z_t)$$

The multivariate extension of this would be

$$\Delta\sigma[z_i(t), z_j(t)] = \kappa_{ij} \sigma[z_i(t), z_j(t)] \quad (31.6)$$

We can write this in matrix form by using the **Hadamard product** \odot of two matrices (also know as the **Schur product** and, more descriptively, the **entrywise product**). Suppose \mathbf{A} and \mathbf{B} are matrices of the same dimension. Their Hadamard product is simply the matrix whose ij th element is the product of the ij th elements of the two matrices,

$$(\mathbf{A} \odot \mathbf{B})_{ij} = A_{ij} B_{ij} \quad (31.7)$$

Using Equation 31.7 we can write Equation 31.6 as

$$\Delta\mathbf{P}_t = \mathbf{K} \odot \mathbf{P}_t \quad (31.8)$$

Here \mathbf{K} is a symmetric matrix of constants, with ij th element κ_{ij} as given by Equation 31.6. At equilibrium,

$$\widetilde{\Delta\mathbf{P}} = \mathbf{K} \odot (\mathbf{P}_0 + \tilde{\mathbf{D}}) \quad (31.9a)$$

and Equation 31.5 becomes

$$\tilde{\mathbf{D}} = \left(\mathbf{G}_0 + \tilde{\mathbf{D}} \right) \left(\mathbf{P}_0 + \tilde{\mathbf{D}} \right)^{-1} \left(\mathbf{K} \odot \left(\mathbf{P}_0 + \tilde{\mathbf{D}} \right) \right) \left(\mathbf{P}_0 + \tilde{\mathbf{D}} \right)^{-1} \left(\mathbf{G}_0 + \tilde{\mathbf{D}} \right) \quad (31.9b)$$

Under this proportional change model, Equations 31.4b and 31.4b become

$$\Delta \mathbf{D}_t = \frac{1}{2} \left(\mathbf{G}_t \mathbf{P}_t^{-1} \left(\mathbf{K} \odot \mathbf{P}_t \right) \mathbf{P}_t^{-1} \mathbf{G}_t - \mathbf{D}_t \right) \quad (31.9c)$$

and

$$\mathbf{D}_t = \frac{1}{2} \left(\mathbf{D}_{t-1} + \mathbf{G}_t \mathbf{P}_t^{-1} \left(\mathbf{K} \odot \mathbf{P}_t \right) \mathbf{P}_t^{-1} \mathbf{G}_t \right) \quad (31.9d)$$

As expected, this reduces to Equation 13.12 when only a single trait is considered.

Example 31.1. Suppose that selection is entirely on variances and covariances (the population has evolved to an optimal value, so $\mathbf{R} = \mathbf{0}$), with the pattern of selection on \mathbf{P} given by Equation 31.6, where

$$\mathbf{K} = \begin{pmatrix} -0.75 & 0.05 \\ 0.05 & 0.25 \end{pmatrix}$$

so that

$$\Delta \mathbf{P}_t^* = \mathbf{K} \odot \mathbf{P}_t = \begin{pmatrix} -0.75 \cdot P_{11}(t) & 0.05 \cdot P_{12}(t) \\ 0.05 \cdot P_{21}(t) & 0.25 \cdot P_{22}(t) \end{pmatrix}$$

The variance of trait 1 is reduced by 75% (as would happen with stabilizing selection on this trait), while the variance of trait 2 is increased by 25% (as would happen with disruptive selection). The covariance between these two traits is also increased by 5%. Assume the linkage-equilibrium values of \mathbf{P} and \mathbf{G} are

$$\mathbf{P}_0 = \begin{pmatrix} 400 & -50 \\ -50 & 100 \end{pmatrix}, \quad \mathbf{G}_0 = \begin{pmatrix} 100 & 0 \\ 0 & 40 \end{pmatrix}, \quad \mathbf{K} \odot \mathbf{P}_0 = \begin{pmatrix} -300 & -2.5 \\ -2.5 & 25 \end{pmatrix}$$

Thus, traits 1 and 2 are genetically uncorrelated at the start of selection, with a heritability of $100/400 = 0.25$ for trait 1 and 0.40 for trait 2. In the first generation of selection, $\mathbf{D}_0 = \mathbf{0}$, and (from Equation 31.9d),

$$\mathbf{D}_1 = \frac{1}{2} \mathbf{G}_0 \mathbf{P}_0^{-1} \left(\mathbf{K} \odot \mathbf{P}_0 \right) \mathbf{P}_0^{-1} \mathbf{G}_0 = \begin{pmatrix} -10.53 & -1.57 \\ -1.57 & 1.79 \end{pmatrix}$$

The resulting covariance matrices after one generation of selection become

$$\mathbf{G}_1 = \mathbf{G}_0 + \mathbf{D}_1 = \begin{pmatrix} 89.47 & -1.57 \\ -1.57 & 41.79 \end{pmatrix}, \quad \mathbf{P}_1 = \mathbf{P}_0 + \mathbf{D}_1 = \begin{pmatrix} 389.47 & -51.57 \\ -51.57 & 101.79 \end{pmatrix}$$

Selection has decreased to genetic variance of trait 1, increased it for trait 2 and created a (small) genetic covariance between the two traits. All of these changes are due to the creation of LD and decay away (\mathbf{G} reverts back to \mathbf{G}_0) once selection stops. Going through a second generation of selection,

$$\mathbf{K} \odot \mathbf{P}_1 = \begin{pmatrix} -292.10 & -2.58 \\ -2.58 & 25.45 \end{pmatrix}$$

giving

$$\mathbf{D}_2 = \frac{1}{2} (\mathbf{D}_1 + \mathbf{G}_1 \mathbf{P}_1^{-1} (\mathbf{K} \odot \mathbf{P}_1) \mathbf{P}_1^{-1} \mathbf{G}_1) = \begin{pmatrix} -13.88 & -2.25 \\ -2.25 & 2.85 \end{pmatrix}$$

with resulting genetic covariance matrix

$$\mathbf{G}_2 = \mathbf{G}_0 + \mathbf{D}_2 = \begin{pmatrix} 86.11 & -2.25 \\ -2.25 & 42.85 \end{pmatrix}$$

Hence, after two generations of selection, the heritability for trait 1 becomes $(100-13.88)/(400-13.88) = 0.22$, while the heritability for trait 2 becomes 0.42, while a genetic correlation of

$$\frac{-2.25}{\sqrt{86.11 \cdot 42.85}} = -0.04$$

It is important to remind the reader that all of the univariate caveats mentioned in Chapter 13 still hold. In particular, the regression argument assumes linearity and homoscedasticity, hence strongly relies on the assumption that the joint distribution of additive genetic and phenotypic values is multivariate normal and remains so after selection. As we showed in Chapter 13, even if these distributions are initially Gaussian, selection usually introduces non-normality, although the departure is often small, especially for weak (as well as very strong) selection. Further, the infinitesimal assumptions must still hold, namely that changes in allele frequencies are sufficiently small that they have no effect on changing the variance.

Within-Generation Changes \mathbf{G} due to Selection on Variances and Covariances

We can also express Equation 31.4 in terms of the quadratic and directional selection gradients, γ and β , which provides additional insight into the nature of selection. Recalling from Chapter 29 the definitions of \mathbf{C} (the quadratic selection differential), β , and γ , we have $\mathbf{P}^* - \mathbf{P} = \mathbf{C} - \mathbf{S}\mathbf{S}^T$. Hence

$$\begin{aligned} \mathbf{P}^{-1}(\mathbf{P}^* - \mathbf{P})\mathbf{P}^{-1} &= \mathbf{P}^{-1}(\mathbf{C} - \mathbf{S}\mathbf{S}^T)\mathbf{P}^{-1} \\ &= \mathbf{P}^{-1}\mathbf{C}\mathbf{P}^{-1} - (\mathbf{P}^{-1}\mathbf{S})(\mathbf{P}^{-1}\mathbf{S})^T \\ &= \gamma - \beta\beta^T \end{aligned} \quad (31.10)$$

If the phenotypic covariance matrices (either before and/or after selection) differ between sexes, then \mathbf{P}^* and \mathbf{P} are replaced by the average of the covariance matrices for males and females. Likewise, if γ and/or β differ in the parents, the appropriate average is used, e.g., $(\gamma_f + \gamma_m)/2$ and $(\beta_f\beta_f^T + \beta_m\beta_m^T)/2$.

When the breeder's equation holds, γ and β are sufficient to describe phenotypic selection on the additive-genetic covariance matrix. From Equations 31.3 and 31.10, the within-generation change in \mathbf{G} becomes

$$\mathbf{G}^* - \mathbf{G} = \mathbf{G}(\gamma - \beta\beta^T)\mathbf{G} \quad (31.11a)$$

Hence, the within-generation change in \mathbf{G} has a component from directional selection and a second from quadratic selection,

$$\begin{aligned} \mathbf{G}^* - \mathbf{G} &= -\mathbf{G}\beta\beta^T\mathbf{G} + \mathbf{G}\gamma\mathbf{G} \\ &= -\mathbf{R}\mathbf{R}^T + \mathbf{G}\gamma\mathbf{G} \end{aligned} \quad (31.11b)$$

In terms of the change in covariance for two particular characters,

$$\begin{aligned} G_{ij}^* - G_{ij} &= - \left(\sum_{k=1}^n \beta_k G_{ik} \right) \left(\sum_{k=1}^n \beta_k G_{jk} \right) + \sum_{k=1}^n \sum_{\ell=1}^n \gamma_{k\ell} G_{ik} G_{\ell j} \\ &= -R_i \cdot R_j + \sum_{k=1}^n \sum_{\ell=1}^n \gamma_{k\ell} G_{ik} G_{\ell j} \end{aligned} \quad (31.11c)$$

Thus the within-generation change in the additive genetic variance of character i is given by

$$G_{ii}^* - G_{ii} = -(R_i)^2 + \sum_{k=1}^n \sum_{\ell=1}^n \gamma_{k\ell} G_{ik} G_{i\ell} \quad (31.11d)$$

Note that directional selection ($R_i \neq 0$) always generates negative disequilibrium (Felsenstein 1965). Additional insight is provided by assuming that \mathbf{G} is initially a diagonal matrix (potentially different additive variances, but no initial genetic covariances). In this case, the within-generation change in the ij th element of \mathbf{G} is

$$\Delta G_{ij} = -R_i R_j + 2\gamma_{ij} G_{ii} G_{jj} \quad (31.12)$$

Thus, even if there is no initial genetic covariance between i and j , both directional and quadratic selection can generate one. If both traits *respond* in the same direction, negative genetic covariance is generated. Note that this does not mean the traits were *selected* in the same direction, as β_i and β_j may have different signs from R_i and R_j . Conversely, if they response in opposite directions, positive disequilibrium is generation. Likewise, in the absence of directional selection, quadratic selection ($\gamma_{ij} \neq 0$) creates genetic covariances with the same sign as γ_{ij} . If one imagines a population away from some optimal value, then initially most of the selection (and hence changes in \mathbf{G}) may be dominated by directional selection (R_i terms). However, as an optimal is approached, directional selection becomes very weak ($R_i \sim 0$) and quadratic terms start to dominate. Thus the same fitness function may result in the sign of G_{ij} changing over time, reflecting these two different patterns of selection.

Asymmetric Correlated Responses Occurs Under the Infinitesimal Model

In Chapter 30 we noted two different types of asymmetric correlated responses are frequently seen in selection experiments: those that vary with the trait selected and those that vary with the direction of selection on a particular trait. Villaneuva and Kennedy (1992) trait-dependent asymmetric correlated responses can occur under the infinitesimal model (i.e., no allele frequency change is required). To see how this arises, first note from Equation 31.11a that the within-generation change in \mathbf{G} when strictly directional selection is occurring is

$$\mathbf{G}^* - \mathbf{G} = -\mathbf{G}\beta\beta^T\mathbf{G}$$

Thus, when β differs (as would occur when changing which trait is under direct selection), so does the within-generation change, immediately suggesting how trait-dependent asymmetric correlated responses (due to differential changes in \mathbf{G}) can arise. Note that the change in \mathbf{G} requires one generation of selection, so that any asymmetric response is only apparent if we select for a second generation (and hence use the perturbed covariance matrix).

To see this point further, consider the simple case of two traits, one under direct selection, the other changing as a correlated response. The within-generation change with strict directional selection (Equation 31.12) is given by

$$\Delta G_{ij} = -R_i R_j = \begin{cases} -\beta_1^2 \sigma_A^2(1) \cdot \sigma(A_1, A_2) & \text{Direct selection on trait 1} \\ -\beta_2^2 \sigma_A^2(2) \cdot \sigma(A_1, A_2) & \text{Direct selection on trait 2} \end{cases}$$

Thus, even with equal amounts of selection on the two different directly-selected traits (so that $\beta_1 = \beta_2$), the changes in the genetic covariance will be different, except for the case where both traits have the same additive variance. Unless there is a large disparity in the values of the genetic variances, in general this effect will be modest and hence the large asymmetric responses seen in experiments (Table 31.1) are more likely due to allele frequency change than due to generation of LD.

Example 31.2. Consider the differential change in the genetic covariance when we select on trait one versus trait two for the following genetic covariance matrix:

$$\mathbf{G} = \begin{pmatrix} 10 & 2 \\ 2 & 40 \end{pmatrix}$$

Let $\beta(i)$ denote the gradient when selection is directly on trait i and assume the same strength of selection ($\beta = 0.1$) as the trait under selection changes. Thus,

$$\beta(1) = \begin{pmatrix} 0.1 \\ 0 \end{pmatrix}, \quad \beta(2) = \begin{pmatrix} 0 \\ 0.1 \end{pmatrix}$$

Since

$$\beta\beta^T = \begin{pmatrix} \beta_1^2 & \beta_1\beta_2 \\ \beta_1\beta_2 & \beta_2^2 \end{pmatrix}$$

we have

$$\beta(1)\beta(1)^T = \begin{pmatrix} 0.01 & 0 \\ 0 & 0 \end{pmatrix}, \quad \beta(2)\beta(2)^T = \begin{pmatrix} 0 & 0 \\ 0 & 0.01 \end{pmatrix}$$

When we directly select on trait 1, the change in the covariance matrix following selection (half of which persists into the next generation) is given by

$$\mathbf{G}^* - \mathbf{G} = -\mathbf{G}\beta(1)\beta(1)^T\mathbf{G} = -\begin{pmatrix} 1.00 & 0.20 \\ 0.20 & 0.04 \end{pmatrix}$$

while direct selection on trait 2 gives

$$\mathbf{G}^* - \mathbf{G} = -\mathbf{G}\beta(2)\beta(2)^T\mathbf{G} = -\begin{pmatrix} 0.04 & 0.80 \\ 0.80 & 16.00 \end{pmatrix}$$

Further insight into the difference in correlated responses was offered by Villaneuva and Kennedy (1990, 1992), who obtain expressions for the equilibrium covariances when directional truncation selection occurs on a particular trait (trait 1) and other traits i and j show a correlated response. Recall (Table 13.1) that truncation selection with the uppermost p saved reduces phenotypic variance in the directly selected trait by

$$\Delta\sigma^2[z_1(t)] = -\kappa\sigma^2[z_1(t)]$$

where $\kappa = \bar{v} (\bar{v} - z_{[1-p]})$. The corresponding reduction in the additive variance of trait one is

$$\Delta G_{11}(t) = -\kappa h_1^2(t)G_{11}(t)$$

A classic result of Pearson (1903) is that the change in the variance on the selected trait changes the variances of all other phenotypically-correlated traits,

$$\Delta G_{ii}(t) = -\kappa h_1^2(t) \rho_{1i}^2(t) G_{ii}(t) \quad (31.13a)$$

where $\rho_{1i}(t)$ is the additive genetic correlation between traits 1 and i in generation t . Thus, no matter the sign of the correlation, the genetic variance of a trait is reduced by selected on a genetically correlated trait. More generally, the change in the genetic covariance between traits i and j due to selection on trait 1 is given by

$$\Delta G_{ij}(t) = -\kappa h_1^2(t) \rho_{1i}(t) \rho_{1j}(t) \sqrt{G_{ii}(t) G_{jj}(t)} \quad (31.13b)$$

When \mathbf{G} reaches its equilibrium value, Villaneuva and Kennedy (1990) show that the additive genetic covariance between traits 1 and i is given by

$$\tilde{G}_{i1} = \frac{G_{i1}(0)}{1 + \kappa \tilde{h}_1^2} \quad (31.14a)$$

where \tilde{h}_1^2 is the equilibrium heritability of the trait under selection (Equation 13.13d). Equation 31.14a makes two key points. First, the effect of selection on a correlated trait is to *shrink the genetic covariance towards zero*, with the amount of shrinkage increasing with the heritability of the trait under selection. Second, if two experiments are done, one with direct selection on trait 1, the other with selection on trait i , then whichever trait has the highest heritability will show the greatest change in the genetic covariance. Further, Villaneuva and Kennedy obtained the equilibrium genetic correlation between traits 1 and i as

$$\tilde{\rho}_{1i} = \frac{\rho_{1i}(0)}{\sqrt{1 + \tilde{h}_1^2 \kappa [1 - \rho_{1i}^2(0)]}} \quad (31.14b)$$

showing that the genetic correlation is also shrunk towards zero, with the amount of change increasing with the heritability of the trait under direct selection. Both Equation 31.14a and b predict that when disequilibrium-driven selection asymmetries occur, *the correlated response will be smaller when selecting on the trait with the higher heritability*, as this produces the largest reduction of the genetic covariance. Note that the infinitesimal model predicts equal amounts of correlated response in trait i independent of whether trait 1 is up- or down-selected. Hence, this second type of asymmetric correlated response (depending on the direction, as opposed to the trait, selected) arises from allele frequency change, not disequilibrium. Finally, Villaneuva and Kennedy (1990) note that the ratio of direct to correlated response remains unchanged, so that the effect of disequilibrium is to reduce the correlated response by the same proportion as it reduces the direct response.

Response in \mathbf{G} Under a Multivariate Gaussian Fitness Model

As we observed in Chapter 24, selection generally introduces non-normality even if the initial distribution is Gaussian. Ideally, we would like to have a class of fitness functions that on one hand models directional, stabilizing, disruptive, and correlational selection and yet still preserves normality. One such class is the general **Gaussian fitness function**,

$$\begin{aligned} W(\mathbf{z}) &= \exp \left(\mathbf{a}^T \mathbf{z} - \frac{1}{2} (\mathbf{z} - \boldsymbol{\theta})^T \mathbf{W} (\mathbf{z} - \boldsymbol{\theta}) \right) \\ &= \exp \left(\sum_i \alpha_i z_i - \frac{1}{2} \sum_i \sum_j (z_i - \theta_i)(z_j - \theta_j) W_{ij} \right) \end{aligned} \quad (31.15a)$$

where \mathbf{W} is a symmetric matrix (note that some representations of this function use \mathbf{W}^{-1} in the quadratic product of Equation 31.15a in place of \mathbf{W} , in order to emphasize the connection with a covariance matrix). While the univariate version dates back to Weldon (1895, 1901) and Haldane (1954), the more general multivariate form is due to Felsenstein (1977). A fuller analysis of this general version starts later in the chapter and is finished in Chapter 41. For now, consider the simpler version

$$W(\mathbf{z}) = \exp\left(-\frac{1}{2}\mathbf{z}^T\mathbf{W}\mathbf{z}\right) \quad (31.15b)$$

The elements of \mathbf{W} measure quadratic selection. If \mathbf{W} is a diagonal matrix, then $W_{ii} > 0$ implies stabilizing selection on z_i about an optimal value of θ_i , while $W_{ii} < 0$ implies disruptive selection about θ_i . The larger the magnitude of W_{ii} , the stronger selection. As we saw in Chapter 29, some care must be taken in interpreting the nature of the fitness surface when \mathbf{W} has non-zero off-diagonal elements. Note from our discussions on the canonical axes of a quadratic form (Equation 29.26) that we can write

$$\mathbf{W} = \mathbf{U}\mathbf{A}\mathbf{U}^T$$

where \mathbf{A} is a diagonal matrix of the eigenvalues of \mathbf{W} and $\mathbf{U} = (\mathbf{e}_1, \dots, \mathbf{e}_n)$ is the matrix of the eigenvalues of \mathbf{W} . Noting that

$$\mathbf{z}^T\mathbf{W}\mathbf{z} = \mathbf{z}^T\mathbf{U}\mathbf{A}\mathbf{U}^T\mathbf{z} = \mathbf{y}^T\mathbf{A}\mathbf{y}, \quad \text{where } \mathbf{y} = \mathbf{U}^T\mathbf{z}$$

we can transform the original vector of characters \mathbf{z} to a new vector \mathbf{y} of trait combinations, such that

$$W(\mathbf{z}) = \exp\left(-\frac{1}{2}\mathbf{y}^T\mathbf{A}\mathbf{y}\right) = \exp\left(-\frac{1}{2}\sum_{i=1}^n \lambda_i y_i^2\right) \quad (31.15c)$$

where $y_i = \mathbf{e}_i^T\mathbf{z}$. The sign of the eigenvalue λ_i indicates whether selection is stabilizing or disruptive along the particular trait combination given by y_i ($\lambda_i > 0$ indicates stabilizing selection, $\lambda_i < 0$ indicates disruptive selection), while the magnitude indicate the strength of selection (the larger the magnitude, the stronger the effect). If \mathbf{W} has k zero eigenvalues, the fitness surface has no curvature (is a plane) in k dimensions.

Suppose that before selection the distribution of \mathbf{z} is $\text{MVN}(\mathbf{0}, \mathbf{P})$. Following selection, the distribution is proportional to the product of the MVN density and $W(\mathbf{z})$,

$$\begin{aligned} p(\mathbf{z}^*) &= \text{const} \cdot \exp\left(-\frac{1}{2}\mathbf{z}^T\mathbf{P}^{-1}\mathbf{z}\right) \exp\left(-\frac{1}{2}\mathbf{z}^T\mathbf{W}\mathbf{z}\right) \\ &= \text{const} \cdot \exp\left(-\frac{1}{2}\mathbf{z}^T(\mathbf{P}^{-1} + \mathbf{W})\mathbf{z}\right) \\ &= \text{const} \cdot \exp\left(-\frac{1}{2}\mathbf{z}^T(\mathbf{P}^*)^{-1}\mathbf{z}\right) \end{aligned} \quad (31.16)$$

Note that the form of Equation 31.16 is that of a multivariate normal centered at zero, with covariance matrix

$$\mathbf{P}^* = (\mathbf{P}^{-1} + \mathbf{W})^{-1} \quad (31.17)$$

Thus, the distribution of \mathbf{z} after selection remains MVN. Note that \mathbf{P}^* is independent of the current mean μ of the trait. Equation 31.17 imposes a constraint on \mathbf{W} , in that \mathbf{P}^* is a covariance matrix, and hence does not contain any negative eigenvalues. While this does not constrain the strength of stabilizing selection (positive eigenvalues for \mathbf{W} can be arbitrarily

large), it *does* constrain the allowable strength of disruptive selection, which if sufficiently strong, (a sufficiently negative eigenvalue) may result in Equation 31.17 having one (or more) negative eigenvalues and hence not be a proper covariance matrix. To see this, suppose both \mathbf{P} and \mathbf{W} are diagonal, and hence their sum is also diagonal, with the diagonal elements corresponding to the eigenvalues of \mathbf{P}^* . For \mathbf{P}^* to be a proper covariance matrix, the diagonal element corresponding to trait i needs to be positive, or

$$\frac{1}{P_{ii}} + W_{ii} > 0, \quad \text{or} \quad W_{ii} > -\frac{1}{P_{ii}} \quad (31.18)$$

this is always satisfied with $W_{ii} > 0$, but only satisfied under very narrow conditions for a negative W_{ii} . The reason while the analysis of disruptive selection using a Gaussian fitness model is so delicate is that fitness arbitrarily increases at an exponential rate as we move away from the minimum (see Equation 31.15c), so that even a small change equates to strong selection. Thus, the distribution must fall off at an appropriate rate (i.e., have a sufficiently small variance) to keep mean fitness bounded. Further, the net result of distributive selection is to increase the variance, generating more extreme individuals. While Equation 31.18 may initially be satisfied, the amount of disequilibrium added must be sufficiently small to ensure that $W_{ii} > -1/(P_{ii} + D_{ii})$ still holds. Thus, while a very robust model for stabilizing selection, the Gaussian fitness function is quite fragile for disruptive selections.

To apply the multivariate Bulmer Equation to obtain changes in \mathbf{G} under Gaussian fitness, first note that

$$\mathbf{P}^{-1} (\mathbf{P}^* - \mathbf{P}) \mathbf{P}^{-1} = -(\mathbf{W}^{-1} + \mathbf{P})^{-1} \quad (31.19a)$$

which is proved in **Chapter 41**. Thus,

$$\mathbf{G}^* - \mathbf{G} = -\mathbf{G} (\mathbf{W}^{-1} + \mathbf{P})^{-1} \mathbf{G} \quad (31.19b)$$

The dynamics of \mathbf{D} (and hence \mathbf{G}) under this general fitness function are given by

$$\Delta \mathbf{D}_t = -\frac{1}{2} \left(\mathbf{G}_t (\mathbf{W}^{-1} + \mathbf{P}_t)^{-1} \mathbf{G}_t + \mathbf{D}_t \right) \quad (31.20a)$$

Since $\mathbf{D}_{t+1} = \mathbf{D}_t + \Delta \mathbf{D}_t$, we can also write

$$\mathbf{D}_t = \frac{1}{2} \left(\mathbf{D}_{t-1} - \mathbf{G}_{t-1} (\mathbf{W}^{-1} + \mathbf{P}_{t-1})^{-1} \mathbf{G}_{t-1} \right) \quad (31.20b)$$

Equilibrium values satisfies

$$\tilde{\mathbf{D}} = -(\mathbf{G}_0 + \tilde{\mathbf{D}}) \left(\mathbf{W}^{-1} + (\mathbf{P}_0 + \tilde{\mathbf{D}}) \right)^{-1} (\mathbf{G}_0 + \tilde{\mathbf{D}}) \quad (31.20c)$$

Example 31.3. Consider the following quadratic fitness matrix

$$\mathbf{W} = \begin{pmatrix} 5.0 & -3.0 \\ -3.0 & 4.0 \end{pmatrix}$$

which implies an individual fitness of

$$W(\mathbf{z}) = \exp(-2.5 z_1^2 + 3z_1 z_2 - 2.0 z_2^2)$$

The eigenvalues of W are $\lambda_1 = 7.54$ and $\lambda_2 = 1.46$, so there is convex (i.e., stabilizing) selection along both axes (i.e., the eigenvalues of \mathbf{W}). Assume no initial disequilibrium with \mathbf{P} and \mathbf{G} matrices of

$$\mathbf{P} = \begin{pmatrix} 8 & -2 \\ -2 & 10 \end{pmatrix}, \quad \mathbf{G} = \begin{pmatrix} 3 & 0 \\ 0 & 4 \end{pmatrix}$$

Since $\mathbf{D}_0 = \mathbf{0}$, following one generation of selection Equation 31.20b gives

$$\mathbf{D}_1 = -\frac{1}{2} \left(\mathbf{G}_0 (\mathbf{W}^{-1} + \mathbf{P}_0)^{-1} \mathbf{G}_0 \right) = \begin{pmatrix} -0.55 & -0.12 \\ -0.12 & -0.79 \end{pmatrix}$$

implying

$$\mathbf{G}_1 = \begin{pmatrix} 2.44 & -0.12 \\ -0.12 & 3.01 \end{pmatrix}$$

Thus, selection has generated a (small) genetic covariance between the two traits. This is entirely due to disequilibrium and will decay to zero once selection stops. Proceeding to the next generation,

$$\mathbf{D}_2 = \frac{1}{2} \left(\mathbf{D}_1 - (\mathbf{G}_0 + \mathbf{D}_1) (\mathbf{W}^{-1} + (\mathbf{P}_0 + \mathbf{D}_1))^{-1} (\mathbf{G}_0 + \mathbf{D}_1) \right) = \begin{pmatrix} -0.67 & -0.12 \\ -0.12 & -0.94 \end{pmatrix}$$

Further iteration gives

$$\tilde{\mathbf{D}} = \begin{pmatrix} -0.708 & -0.111 \\ -0.111 & -0.989 \end{pmatrix}, \quad \tilde{\mathbf{G}} = \begin{pmatrix} 2.292 & -0.111 \\ -0.111 & 3.011 \end{pmatrix}, \quad \tilde{\mathbf{P}} = \begin{pmatrix} 7.292 & -2.111 \\ -2.111 & 9.011 \end{pmatrix}$$

At equilibrium, the heritabilities for traits 1 and 2 become $h_1^2 = 2.292/7.292 = 0.314$ and similarly $h_2^2 = 0.334$, as compared to their initial values of 0.375 and 0.4, respectively. Likewise, the equilibrium genetic correlation becomes

$$\rho_A = \frac{-0.111}{\sqrt{2.292 \cdot 3.011}} = -0.04$$

ALLELE FREQUENCY CHANGES AND INSTABILITY OF GENETIC COVARIANCES

Two very different genetic phenomena (linkage and pleiotropy) contribute to genetic covariances and both can change over time. We have seen (under the infinitesimal model framework) how selection can generate linkage disequilibrium (LD). When LD is present, alleles at different loci that only effect single traits are nonetheless co-inherited to some extent, creating a correlation between their breeding values. Thus, unlinked loci, initially in linkage equilibrium, can nonetheless contribute to genetic covariances (all the contribution is generally small, e.g., Example 31.1). The second feature is **pleiotropy**, where an allele genetically influences two (or more) traits. Under the infinitesimal mode, covariance changes under LD are straightforward (if you like matrices). However, just as we saw for changes in variances, the genetic details (distribution of allelic effects) are *critical* in predicting medium to long term selection response in covariances. Just like different genetic models may all yield the same initial heritability but very different long-term responses (Chapter 25), *even more* models can yield the same initial genetic covariance. Indeed, as we argue below, a genetic

covariance is much more fragile than a genetic variance, and changes in it are likely to be more unpredictable than changes in genetic variances.

Pleiotropic-based Genetic Correlations May Become More Negative Over Time

One of the first suggestions about the behavior of genetic correlations under selection was offered by Hazel (1943), Lush (1948), and Lerner (1950, 1958). Suppose we are selecting two traits in the same direction. Alleles that effect only one of these two traits do not make any pleiotropic contribution to the genetic variance and are ignored (of course, they can make a linkage disequilibrium contribution). When an allele has an effect on both traits, it can take one of four forms. Two forms show **complementary pleiotropy**, changing both traits in the same direction, namely $++$ and $--$ alleles. Here $++$ denotes an allele that increases both the first and second traits, while $--$ decreases both traits. Thus, these classes have effects in the same direction and are quickly increased and (ultimately) fixed ($++$ alleles when both traits are positively selected) or else are quickly lost by selection. The two remaining classes of alleles show **antagonistic pleiotropy**, with effects on the two traits in *opposite* directions: $+-$ and $-+$ alleles. Such alleles (the argument goes) are under less selection than alleles whose pleiotropic effects are in the same direction. Hence, selection *enriches* the frequencies of alleles with these antagonistic pleiotropic effects, resulting in genetic covariances declining (becoming more negative) as selection (to increase both traits) proceeds.

Under the same argument, if we are selecting for an increase in one trait and a decrease in the other, then $++$ and $--$ alleles become enriched, and the genetic covariances should *increase* (become more positive) over time. Thus, the genetic covariance should evolve (at least to some extent) *away* from the direction favored by selection. While this may seem somewhat counterintuitive, recall that quantitative genetics is concerned with *segregating* variation. Hence, selection may result in two lines showing increases in both traits (as complementary pleiotropic alleles are fixed), the remaining genetic variation upon which future selection must act for response shows a more negative covariance over time.

Genetic Covariances are More Fragile Than Genetic Variances

One of the first more formal analyses of the evolution of genetic covariances under selection is the classic paper by Bohren et al. (1966), who were interested in how likely asymmetric correlated responses were to occur. Recall from Chapter 30 that experiments can show significantly different realized correlations between traits x and y in some cases depending upon whether x was up- or down-selected (e.g., Clayton et al. 1957), in others depending on which trait was directly selection and which trait was the correlated response (e.g., Falconer 1960). Under the standard infinitesimal theory of selection response, the *direction* of selection should have minimal impact on selection response. While asymmetric responses can occur when different traits are selected, the effects are small unless the trait heritabilities are very different. However, large asymmetric responses can occur as a result of differential changes in genetic covariances as allele frequencies are changed in different directions.

Bohren et al. investigated the consequences of such allele frequency change on genetic covariances, and found that they were much for “fragile” than genetic variances, i.e., they were much more likely to show asymmetric changes, and do so quicker, than the corresponding effects would have on genetic variances. They assume four different classes of loci,

	Class A	Class B	Class C	Class D
Trait 1	α	β_1	γ_1	0
Trait 2	0	β_2	$-\gamma_2$	δ

Loci in classes A and D influence only single traits (and hence do not contribute to covariances in the absence of LD), class B loci show complementary pleiotropy, while class C show antagonistic pleiotropy. Assuming all effects are additive within and between loci (no dominance nor epistasis), the genetic covariance is given by

$$\sigma(g_1, g_2) = 2p_B(1 - p_B)\beta_1\beta_2 - 2p_C(1 - p_C)\gamma_1\gamma_2 \quad (31.21)$$

where p_x is the frequency of an allele in class x . They found that the simplest conditions for asymmetry depending on which trait was directly selected is the presence of class C alleles (antagonistic pleiotropy) at frequencies differing from 1/2, with the maximal effect occurring when alleles frequencies are around 0.2 or 0.8 (i.e., one allele is much more common than the other). Note that when populations are formed for artificial selection by first crossing two divergent lines, alleles differentially fixed (or at least at extreme frequencies) in the two lines have their starting frequencies at (or close to) 0.5 in the resulting base population. Thus, experiments starting with base populations formed in this manner can give a biased (underestimate) picture about the frequency of asymmetric responses.

Bohren et al. note that asymmetric correlated responses are expected whenever the relative rates of response for the class B and class C loci are functions of which trait is being selected and which trait is the correlated response. While most of Bohren et al.'s analysis concerned the case where one trait was selected and the other changed as a correlated response, they briefly examine the situation where both traits were selected in the same direction. They confirmed the general suggestion by Hazel, Lush, and Lerner that eventually the genetic covariances generally become more negative. However, they also found, depending on the distribution of allele frequencies and effects, that the genetic covariance may actually increase in the first few generations. Simulation studies by Parker et al. (1969, 1970a/b) showed that genetic covariances decline with time, and decrease most rapidly with higher heritabilities. However, the only pleiotropic alleles included in the simulations were ++, so this likely simply reflects a decline in the overall genetic variance. An additional (small scale) simulation by Bennett and Swiger (1980) also showed that selection to increase two positively-correlated traits resulted in a decrease in their correlation, as well as showing that the genetic correlation increased when the two traits were selected in the opposite directions. As with Parker et al., pleiotropy only appear through ++ alleles, but the results for selection within and against the correlation were consistent with the suggestion by Hazel et al.

It is Difficult for Antagonistic Pleiotropy to Maintain Variation

The argument by Hazel, Lush, and Lerner that alleles showing antagonistic pleiotropy will segregate in the population longer than those showing complementary pleiotropy naturally leads to the question of the conditions for such alleles to be permanently maintained in the face of selection. Rose (1982, 1985) was an early champion that alleles having antagonistic pleiotropic effects on different life-history fitness components (such as reducing fecundity while increasing life span) might be maintained in the population, but later felt that the conditions for this were perhaps too restrictive (Rose et al. 1987).

A simple population-genetic model of this process was analyzed by Curtsinger et al. (1994). Their concern was not the *persistence time* of such alleles under directional selection to increase both traits (which is really the crux of the argument by Hazel et al.), but rather the conditions under which they would be maintained in the population. They assumed a single locus with two alleles that have alternative effects on two different fitness components. The basic structure of their model is as follows:

	A_1A_1	A_1A_2	A_2A_2
Fitness component 1	1	$1 - h_1\nu$	$1 - \nu$

Fitness component 2	$1 - f$	$1 - h_2 f$	1
Total Fitness	$1 - f$	$(1 - h_1 \nu)(1 - h_2 f)$	$1 - \nu$

Allele A_1 has a positive effect on fitness component (or trait) one but a negative effect on component/trait two. Allele A_2 has the opposite effects. A critical feature of this model is the amount of dominance on both traits (measured by h_1 and h_2). The fitness components are assumed to be multiplicative, with the total fitness for each genotype the product of the two components.

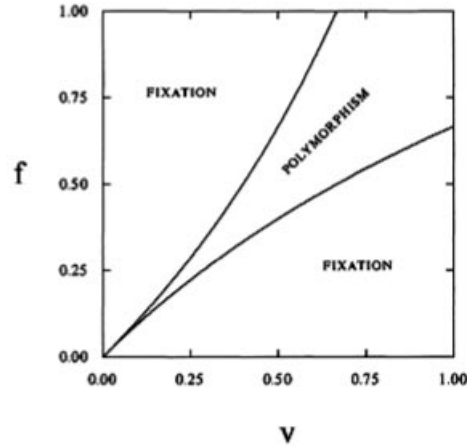


Figure 31.1. Conditions for selection to stably maintain two antagonistic pleiotropic alleles in a population under the Curtsinger et al. (1994) model. Complete additivity is assumed (so that $h_1 = h_2 = 0$). Note the extremely restrictive conditions when selection is weak (both f and ν are small). Also note that roughly equal amounts of selection $f \simeq \nu$ is also required, although this is less of a constraint as the amount of selection on both increases. After Curtsinger et al. (1994).

A stable polymorphic equilibrium exists when the heterozygote has the highest fitness (Chapter 5), or

$$(1 - h_1 \nu)(1 - h_2 f) > \max(1 - \nu, 1 - f) \quad (31.22a)$$

Figure 31.1 plots the space of stable equilibrium (i.e. polymorphism) as a function of f and ν for the completely additive case ($h_1 = h_2 = 0.5$), which is given by

$$\frac{2\nu}{2 + \nu} < f < \frac{2\nu}{2 - \nu} \quad (31.22b)$$

Note that the conditions are very restrictive for weak selection. Further, note that roughly equal amounts of selection on both traits/components is also required.

Curtsinger et al. note when a beneficial **reversal of dominance** occurs ($h_1 = h_2 = 0$), then Equation 31.22a is always satisfied (Rose 1982, 1985 also noted an important role for beneficial reversals). This occurs when the dominance is reversed in a favorable direction for the two traits (the heterozygote matches the higher fitness genotypes for both traits, $A_1 A_1$ for trait one and $A_2 A_2$ for trait 2). Conversely, if there is a deleterious reversal of dominance ($h_1 = h_2 = 1$, with the heterozygote matching $A_2 A_2$ for trait one, and $A_1 A_1$ for trait 2, the lower-fitness genotypes) then Equation 31.22a is never satisfied. Thus, the conditions for antagonistic pleiotropy to maintain a polymorphism at a locus are fairly restrictive, especially

for weak selection. Curtsinger et al. suggest that a beneficial reversal of dominance is unlikely for biochemical reasons. They also observed that expanding these results to two (or more) loci makes the conditions even more restrictive.

Hedrick (1999) further extends the Curtsinger et al. model, using an important result from Roberston (1962) on the maintenance of a polymorphism through heterozygote superiority in a finite population. Roberston noted that unless the deterministic equilibrium allele frequency was within 0.2 to 0.8, that selection actually *enhances* the loss of one allele relative to drift (Chapter 26). Hence, the condition for the maintenance of a polymorphic locus for a reasonable amount of time in a finite population is much more restrictive than Equation 31.22a, being the subset of this space that gives an equilibrium allele frequency within 0.2 to 0.8.

An important prediction of this model was noted by both Rose et al. (1987) and Curtsinger et al. (1994): if a reversal of dominance occurs (which is largely required for a stable polymorphism), then large amounts of dominance variance are expected in at least one component/trait. In particular, Curtsinger et al. notes that

“if antagonisms of fitness components often plays a role in maintaining polymorphism, then the dominance variance for fitness components should, on average, be about half as large as the additive genetic variance for those same fitness components.”

They note that *Drosophila* quantitative traits typically do not show such large amounts of dominance variance. However, Charlesworth and Hughes (1996) find that such high amounts of dominance variance can often be avoided in an age-structured population.

The picture which emerges is that while antagonistic pleiotropy can indeed result in a stable polymorphism in the face of selection, the conditions for this to occur at even a single locus are very restrictive. Further, the generally low levels of dominance variation also suggest that this is not a widespread phenomena. However, it is also important to stress that these models examine conditions for the *permanent persistence* of such alleles, while all that is required for the genetic covariances to become more negative over time is that they persist longer than alleles showing complementary pleiotropy.

Hidden Pleiotropy: A Zero Genetic Covariance Can Still Harbor Many Pleiotropic Alleles

One reason for the greater unpredictability of changes in covariances (versus variances) is that the observed genetic covariance is an extremely weak summary statistic for the underlying amount of pleiotropic alleles present, and hence a very poor prediction of the evolutionary potential for a change in the covariance (Lande 1980, Cheverud 1984, Wagner 1984, Gromko et al. 1991, Gromko 1995). For example, if the number of complementary and antagonistic pleiotropic alleles are roughly equal, then the *net* effect of pleiotropy on the genetic covariance is small. Indeed, it is zero when these effects exactly cancel. Thus, two trait combinations, both with zero covariances, could mask very different evolutionary potentials. Suppose there are no pleiotropic alleles in trait combination one, while trait combination two consists of nothing *but* pleiotropic alleles (i.e., there are no alleles that contribute to only one trait). In the first case, the genetic covariance will only evolve over time through linkage disequilibrium, and this effect will decay quickly when selection stops. In the second case, depending on the nature of selection, either large positive or large negative genetic covariances can evolve, depending on whether selection enhances the frequencies of complementary vs. antagonistic alleles. Further, as favorable pleiotropic alleles become fixed, the remaining segregating pleiotropic alleles determine the genetic covariance seen in the population, which can change the sign in the opposite direction. Turelli (1985) has coined the term **hidden pleiotropy** to describe situations when there is a zero (or nearly so) genetic covariance but a large reservoir of pleiotropic alleles for selection to exploit. As we will see, hidden pleiotropy has important consequences for the response to selection and in