# 31

# 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 wiht a few general comments on what the theory suggests about the stability of $\mathbf{G}$.

## CHANGES IN 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 D**

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

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

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

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

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

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

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

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

To place this equation is 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

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

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

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

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

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

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

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

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

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

$$\widetilde{\mathbf{D}} = \left(\mathbf{G}_0 + \widetilde{\mathbf{D}}\right)\left(\mathbf{P}_0 + \widetilde{\mathbf{D}}\right)^{-1}(\widetilde{\Delta\mathbf{P}})\left(\mathbf{P}_0 + \widetilde{\mathbf{D}}\right)^{-1}\left(\mathbf{G}_0 + \widetilde{\mathbf{D}}\right) \tag{31.5}$$

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

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

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,

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

Using Equation 31.7 we can write Equation 31.6 as

$$\Delta\mathbf{P}_t = \mathbf{K}\odot\mathbf{P}_t \tag{31.8}$$

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

$$\widetilde{\Delta\mathbf{P}} = \mathbf{K}\odot\left(\mathbf{P}_0 + \widetilde{\mathbf{D}}\right) \tag{31.9a}$$

and Equation 31.5 becomes

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

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

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

and

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

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

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**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

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

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

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

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It is important to reminder 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 G due to Selection on Variances and Covariances**

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

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

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 $\boldsymbol{\gamma}$ and/or $\boldsymbol{\beta}$ differ in the parents, the appropriate average is used, e.g., $(\boldsymbol{\gamma}_f + \boldsymbol{\gamma}_m)/2$ and $(\boldsymbol{\beta}_f\boldsymbol{\beta}_f^T + \boldsymbol{\beta}_m\boldsymbol{\beta}_m^T)/2$.

When the breeder's equation holds, $\boldsymbol{\gamma}$ and $\boldsymbol{\beta}$ 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

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

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

$$\begin{aligned}\mathbf{G}^* - \mathbf{G} &= -\mathbf{G}\boldsymbol{\beta}\boldsymbol{\beta}^T\mathbf{G} + \mathbf{G}\boldsymbol{\gamma}\mathbf{G} \\ &= -\mathbf{R}\,\mathbf{R}^T + \mathbf{G}\boldsymbol{\gamma}\mathbf{G} \end{aligned} \tag{31.11b}$$

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

$$G^*_{ij} - G_{ij} = -\left(\sum_{k=1}^{n} \beta_k\, G_{ik}\right)\left(\sum_{k=1}^{n} \beta_k\, G_{jk}\right) + \sum_{k=1}^{n}\sum_{\ell=1}^{n} \gamma_{k\ell}\, G_{ik}\, G_{\ell j}$$
$$= -R_i \cdot R_j + \sum_{k=1}^{n}\sum_{\ell=1}^{n} \gamma_{k\ell}\, G_{ik}\, G_{\ell j} \tag{31.11c}$$

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

$$G^*_{ii} - G_{ii} = -\left(R_i\right)^2 + \sum_{k=1}^{n}\sum_{\ell=1}^{n} \gamma_{k\ell}\, G_{ik}\, G_{i\ell} \tag{31.11d}$$

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

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

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 $\beta_i$ and $\beta_j$ 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 $\gamma_{ij}$. If one imagines a population away from some optimal value, then initally 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 frequenctly 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

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

Thus, when $\boldsymbol{\beta}$ 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.

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**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 $\boldsymbol{\beta}(i)$ denote the gradient when selection is directly on trait $i$ and assume the same strenght of selection ($\beta = 0.1$) as the trait under selection changes. Thus,

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

Since

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

we have

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

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

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

while direct selection on trait 2 gives

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

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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 $\kappa = \overline{z}\,\left(\overline{z} - z_{[1-p]}\right)$. 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,

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

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

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

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

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

where $\widetilde{h}_1^2$ 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

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

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 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**,

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

where $\mathbf{W}$ is a symmetric matrix (note that some representations of this function use $\mathbf{W}^{-1}$ in the quadartic 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

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

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 $\theta_i$, while $W_{ii} < 0$ implies disruptive selection about $\theta_i$. 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

$$\mathbf{W} = \mathbf{U}\boldsymbol{\Lambda}\mathbf{U}^T$$

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

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

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

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

where $y_i = \mathbf{e}_i^T\mathbf{z}$. The sign of the eigenvalue $\lambda_i$ 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 MVN($\mathbf{0}, \mathbf{P}$). Following selection, the distribution is proportional to the product of the MVN density and $W(\mathbf{z})$,

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

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

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

Thus, the distribution of $\mathbf{z}$ after selection remains MVN. Note that $\mathbf{P}^*$ is independent of the current mean $\mu$ 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

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

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

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

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

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

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

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

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

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

Equilibrium values satisfies

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

---

**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

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

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

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

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,

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

Further iteration gives

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

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 seem (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 | $\alpha$ | $\beta_1$ | $\gamma_1$ | 0 |
| Trait 2 | 0 | $\beta_2$ | $-\gamma_2$ | $\delta$ |

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

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

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 occuring 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 matter 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 we selected in the same direction. They confirmed the general suggestion by Hazel, Lush, and Lerner than 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 | $1-f$ | $1-h_2f$ | 1 |
| Total Fitness | $1-f$ | $(1-h_1\nu)(1-h_2f)$ | $1-\nu$ |

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.

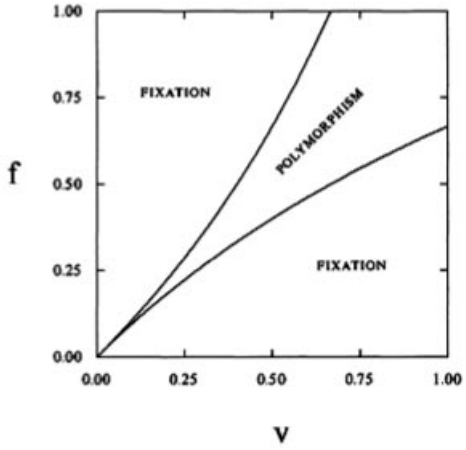


**Figure 31.1.** Conditions for selection to stably maintain two antagonistic pleiotropic alleles in a population under the Curtsinger et al. (1994) model. Complete additivity is assumed (so that $h_1 = h_2 = 0$). Note the extremely restrictive conditions when selection is weak (both $f$ and $\nu$ are 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

$$(1-h_1\nu)(1-h_2f) > \max(1-\nu, 1-f) \tag{31.22a}$$

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

$$\frac{2\nu}{2+\nu} < f < \frac{2\nu}{2-\nu} \tag{31.22b}$$

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, $A_1A_1$ for trait one and $A_2A_2$ for trait 2). Conversely, if there is a deleterious reversal of dominance ($h_1 = h_2 = 1$, with the heterozyogte matching $A_2A_2$ for trait one, and $A_1A_1$ 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 that 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 should 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 disequilibiurm, 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

the analysis of mutation-selection models.

While the generic prediction is for a genetic variance to decline over the course of selection as usable genetic variance removed, as we have seen, this need not be the case. If favorable, but rare, alleles are present at the start of selection, the genetic variance increases (for at time) as selection increases the frequency of these alleles (Chapters 14, 24-26). This uncertainly in whether a genetic parameter with increase or decrease over time is only amplified with genetic covariances, which have the further feature that their actual *sign* can potentially change over the course of the evolution, even in very simple models where pleiotropic alleles only have additive effects (no dominance nor epistasis).

A further cautionary trait regarding evolutionary potential is offered by Carey (1988), who considered genetic *correlations*. Consider a very simple model where two traits are determined entirely by $n$ completely additive (no dominance nor epistasis) pleiotropic loci. Let $a_i$ be the effect on trait 1 from locus $i$ and let $a_i b_i$ be its effect on trait two. Further, rescale the traits to give trait one a genetic variance of one. The resulting genetic correlation can be written as the covariance divided by square roots of both genetic variances (one which we have set to one), giving

$$\rho_A(1,2) = \frac{\sum f_i \cdot a_i \cdot a_i b_i}{\sqrt{1 \cdot \sum f_i \cdot (a_i b_i)^2}} \tag{31.23}$$

where the $f_i$ denote the weight for loci $i$ (which is a function of allele frequencies, see Carey 1988 for details). Note that although *all* loci are pleiotropic, the genetic correlation does not equal one. This would, of course, not be surprising of the $b_i$ term changes sign over loci, giving a small net effect to the covariance. However, even if all pleiotropic loci have *the same sign* (i.e., there is no canceling of positive and negative effects), the genetic correlation, while being positive, will still generally be less than one. Hence, a modest genetic correlation *does not* automatically imply either (1) a mixture of complementary and antagonistic effects, or (2) there are some loci which effect only one trait.

## EXPERIMENTAL STUDIES OF THE RESPONSE TO SELECTION TO CHANGE COVARIANCES

The above theory suggests some general *trends* that we might expect to observe in the evolution of genetic covariances under pleiotropy: (i) asymmetric responses in correlated traits are expected to be common, (ii) when selecting two traits in the same direction, the genetic covariance should eventually become more negative, (iii) likewise, when selecting two traits in the opposite directions, the covariance should eventually become more positive, and (iv) the between-replicate variability in correlated response is expected to be greater than for direct response. Overriding these suggested trends is the major theme that the evolution of covariances under pleiotropy is more unpredictable than changes in variance. Hence, it is very much of an empirical issue as to how "typical" covariances change over time.

Unfortunately, we cannot make any sweeping, or even slightly general, statements from a review of the experimental literature. First, almost all studies suffer from *low power*, making even modest changes in covariances difficult to detect. Second, sample sizes in selection experiments are typically small (both in terms of individuals per replicate and especially number of replicates), resulting in a large variation between replicates (Chapters 14, 15). Thus, large observed differences could simply be normal sampling variation about the expected value. Indeed, Sen and Robertson (1964) note that most selection experiments lack a sufficient number of replications, and it is better to invest resources into the number of replicates as opposed to number of individuals per experiment. For example, a very well designed selection experiment might have five replicates, but $n = 5$ is a very small

sample size from which to obtain a good estimate of the replication variance. Third, in much of the historical literature, no rigorous standard errors are presented on estimates of genetic covariances, making comparisons almost pointless. Finally, and perhaps most surprisingly, we can find very few studies specifically focusing on following the changes in genetic covariances directly in a selection experiment. Many of the studies simply infer these changes from differences in the rates of correlated responses, but this is a rather indirect measure. Chapter 32 examines the changes in $\mathbf{G}$ in natural populations, which is typically done by comparing two populations without much knowledge of their past histories of selection.

**Table 31.1**. Examples of experiments showing asymmetric correlated responses. In these experiments, within each replicate direct selection occurs on a focal trait (which may change over replicates) and both the direct response in the focal trait, as well as a correlated response in other trait(s) were followed.

| | |
|---|---|
| ***Drosophila melanogaster*** | |
| Clayton et al. 1957<br>sternopleural & sternital bristles | No correlated responses in sternopleural bristle number when lines were selected for decreased sternital bristles, but a strong correlated response when the lines were up-selected. |
| Sen and Robertson 1964<br>abdominal and steropleural bristles | Asymmetric response, with up-selected lines showing larger increases in correlation. |
| Gromko et al. 1991<br>Copulation duration, courtship vigor & fertility | Correlated responses in two traits were followed in eight lines selected for copulation duration (four up, four down). All eight replicate lines showed consistent behavior in the response to direct selection, only 3/8 had the predicted correlated responses. |
| Phelan et al. 2003,<br>Archer et al. 2003<br>longevity & stress resistance | Initial selection on stress resistance increased longevity, but over time although stress resistance continued to respond, longevity began to decrease. |
| Wilkinson et al. 1990<br>Thorax size & 4 morphological traits | Observed significant changes in $\mathbf{G}$ across selected lines measured for five morphological traits. The $\mathbf{G}$ matrix for line down-selected on thorax size shifted more from the base population than did $\mathbf{G}$ for the up-selected line. Some elements of $\mathbf{G}$ remained constant, while others significantly changed. (Reanalysis by Shaw et al 1995). |
| ***Tribolium castaneum*** | |
| Yamada and Bell 1963<br>larval weight in two environments | Asymmetric correlated response to larval weight in good vs. poor nutrition. |
| Bell and McNary 1963<br>Pupal weight in two environments | Asymmetric correlated response to pupal weight in wet vs. dry environments. |
| **Chickens** | |
| Siegel 1962<br>body weight & breast angle | Different realized genetic correlations depending on target of selection. |
| Nordskog and Festing 1962<br>body & egg weight | Different realized genetic correlations depending on target of selection. |
| **Rat** | |
| Atchley and Rutledge 1982<br>Weight & skeletal traits | Asymmetry of correlated responses in a suite of skeletal traits in up- versus down-selected lines for weight gain. |

| | |
|---|---|
| **Mouse** | |
| Falconer 1960<br>Weight gain<br>in two environments | Asymmetric correlated responses |
| von Butler et al. 1986<br>Early weight gain<br>& late body weight | Asymmetric correlated responses |

We partition experimental results into two classes: single vs. and multiple trait selection experiments. Table 31.1 examines results for single trait selection experiments where (within each replicate) one trait is selected, and correlated responses are followed. The basic message from this table is that very uneven responses in a correlated trait are quite common. Table 31.2 examines multiple-trait selection experiments, where selection is practiced on several (typically two) traits within a replicate. Chapter 33 further examines such experiments in the context of index selection, where a single item (the index score) is selected, but this is comprised of several traits.

**Table 31.2**. Behavior of covariances in multi-trait selection (selection occurs on two or more traits within each replicate).

| | |
|---|---|
| ***Drosophila melanogaster*** | |
| Sen and Robertson 1964<br>abdominal &<br>steropleutral bristles | Slight increase in the genetic correlation under positive selection on both traits. |
| Sheridan and Barker 1974<br>coxal & sternopleural bristles | Realized genetic correlations consistent across 22 generations (sampled at gens. 0-5, 0-10, 0-22, and 10-22). |
| ***Tribolium castaneum*** | |
| Bell and Burris 1973<br>larval and pupal weight | No change in the genetic correlation. |
| **Chickens** | |
| Friars et al. 1962<br>Various Production traits | Genetic correlations measured from 1949 to 1957 in a series of lines under selection. 16 of the 18 correlations showed a negative trend, six of which were significant. |
| **Pitcher-plant mosquito** (*Wyeomyia smithii*) | |
| Scheiner and Istock 1991<br>development time &<br>diapause | Response in the direction of the correlation was more consistent than response in a directional orthogonal to the correlation, which was very erratic. |

Table 31.2 shows that some experiments are consistent with the idea that genetic correlations become more negative over time when traits are selected in the same direction (Friars et al. 1962), while others showed both the opposite trend (Sen and Robertson 1964), and no differences (Bell and Burris 1973, Sheridan and Barker 1974). Note that none of these results necessarily prove, or invalidate, this theoretical expectation of an *eventual* decline in the genetic covariance. This argument is that *after* sufficient allele frequency change, this is the pattern expected, but recall that Bohren et al. (1966) showed that there may actually

be an initial *increase* in the covariance in these settings. Further, findings of no significant differences are not very informative due to low power and high replication variance in these experiments.

## GENETIC MODELS OF COVARIANCES

As the above discussion highlights, the *nature* of pleiotropic interactions is critical in any attempt to understand how the pleiotropic contribution to genetic covariance changes as allele frequencies change. There is no well developed formal theory, but some of the foundations are starting to be laid with consideration of the properties of different structural (i.e., causal) models for how molecular and developmental processes might interact to produce pleiotropic gene effects, and hence correlations.

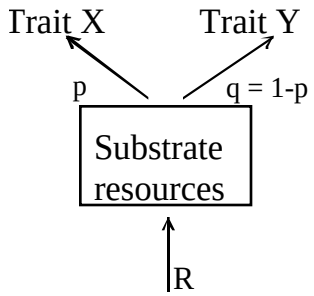


**Figure 31.2.** The partition of resources model. The values of two traits, $X$ and $Y$, are influenced by two different processes. The first are alleles ($R$) that influence the total amount of resources both traits draw upon (given here as a biochemical substrate, but more generally this is simply a shared resources). The second are alleles that partition this total resource between $X$ and $Y$, in the simplest case with a fraction $p$ going to $X$ and the remainder $q = 1 - p$ going to $Y$.

### Resource Partitioning Models: Background

An early structural model for the role of pleiotropy in generating genetic correlations is the **partition of resources model**, apparently first suggested by Rendel (1963, 1967). Figure 31.2 shows the basic idea, as well as illustrating why this has also been called the **Y-model**. For two traits ($X$ and $Y$), one can envisage two different types of pleiotropic loci. First, there are **acquisition alleles** that increase (or decrease) the total amount of a resource $R$ that both $X$ and $Y$ share in their developmental or biochemical pathway. Such alleles show complementary pleiotropy, resulting in positive genetic correlations between $X$ and $Y$. Second, there are **allocation alleles** that partition the common resource between the two traits. In the simplest case, a fraction $p$ is allocated to trait $X$ and the remainder $q = 1-p$ to trait $Y$. Such alleles show antagonistic pleiotropy and are expected to generate negative genetic variances, so that the total genetic covariance associated with a trait depends on the distribution (of frequencies and effects) for these two classes of alleles. Starting with James (1974, in Sheridan and Barker 1974), this simple model has received a fair bit of attention in the ecological and evolutionary genetics literature (van Noordwijk and de Jong 1986, Riska 1986, Slatkin 1987, Houle 1991, de Jong and van Noordwijk 1992, Roff and Fairbairn 2007).

### James' Analysis of Changes in Covariances Under Resource Partitioning Models

The first detailed analyses of the consequences of selection on the genetic covariance under such a model is an important, but infrequently cited, paper by James (1974), which appeared as a brief appendix to the paper by Sheridan and Barker (1974). James assumed that a number of genes contribute to $R$ (acquisition) and $p$ (allocation). Thus, we can write the trait values of $X$ and $Y$ as

$$X = pR + E_X, \qquad Y = (1-p)R + E_Y \tag{31.24}$$

where $E_k$ denotes uncorrelated environmental effects, while we assume (for simplicity) that $p$ and $R$ are the genotypic values. Under this simple model, the correlation between $X$ and $Y$ is entirely genetic, with

$$\sigma(X,Y) = \sigma(pR, [1-p]R) \tag{31.25}$$

While this can be simplified by using the definition of a covariance, we make use of two useful results due to Goodman (1980, 1982). Suppose the random variables $x$ and $y$ are independent, then

$$\sigma^2(xy) = \mu_x^2\sigma_y^2 + \mu_y^2\sigma_x^2 + \sigma_x^2\,\sigma_y^2 \tag{31.26a}$$

and

$$\sigma(xy, x(1-y)) = \mu_y\sigma_x^2 - \sigma^2(xy) = \mu_y(1-\mu_y)\sigma_x^2 - \mu_x^2\sigma_y^2 - \sigma_x^2\,\sigma_y^2 \tag{31.26b}$$

Using these results, Equation 31.25 reduces to

$$\sigma(X,Y) = \sigma^2(R)\left[\,\mu_p(1-\mu_p) - \sigma^2(p)\,\right] - \mu_R^2\sigma^2(p) \tag{31.27a}$$

James' original analysis presented an incorrect version of Equation 31.27a (missing the $-\sigma^2(p)$ term in the square brackets), resulting in some of his quantitative results to be incorrect, but his general qualitative conclusions still hold. Note immediately that if there is no variance in resource acquisition ($\sigma^2(R) = 0$), the covariance between $X$ and $Y$ is negative. Noting that $\sigma^2(p) = \mu_{p^2} - \mu_p^2$, where $\mu_{p^2} = E(p^2)$, Equation 31.27a can also be written as

$$\sigma(X,Y) = \sigma^2(R)\left[\,\mu_p - \mu_{p^2}\,\right] - \mu_R^2\sigma^2(p) \tag{31.27b}$$

Since $p$ lies within (0,1), the term in square brackets is never negative, and has an intermediate optimum (i.e., it decreases when $\mu_p$ is sufficiently close to zero or one). The covariances of $X$ and $Y$ with both components of the model are as follows:

$$\sigma(X,p) = \mu_R\sigma^2(p), \quad \sigma(Y,p) = -\mu_R\sigma^2(p) \tag{31.28a}$$

$$\sigma(X,R) = \mu_p\sigma^2(R), \quad \sigma(Y,R) = (1-\mu_p)\sigma^2(R) \tag{31.28b}$$

Assuming both $R$ and $p$ are controlled by a large number of genes of small effect, we (following James) ignore changes in the variances and focus entirely on changes in the means $\mu_R$ and $\mu_p$.

Suppose we select just on $X$. Since both $\sigma(X,p)$ and $\sigma(X,R)$ are positive, both $\mu_p$ and $\mu_R$ are expected to increase. As $\mu_p$ increases (more allocation to $X$ than $Y$), the product $(\mu_p - \mu_{p^2})$ eventually decreases. Since $\mu_R$ is increasing, Equation 31.27 directly shows that the genetic covariance decreases. A similar argument shows that selection for $X + Y$, and hence selection to increase $\mu_R$, always (under this model) results in a decrease in the genetic covariance. For selection on $X - Y$, the genetic covariance may initially increase (if $\mu_p$ starts sufficiently small) , but will decrease when $\mu_p$ becomes sufficiently large. While the general trend under this simple model is for the initial genetic covariances to decrease over time, they can (depending upon starting values) actually increase for a while before eventually declining. Roff and Fairbairn (2007) further examine the consequences of Equation 31.27a,

while the joint evolution of $X$ and $Y$ under this model, is examined by de Jong and van Noordwijk (1992)

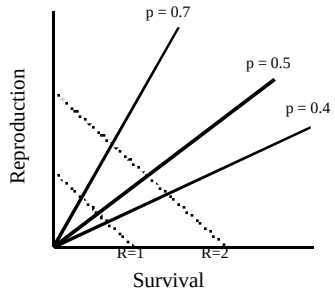


**Figure 31.3.** Final energy allocated to survival and reproduction under a resource partitioning model. Dotted lines correspond to lines of constant total energy (resource $R$), while the specific allocation of energy into these two components for any given individual is given by where their total energy and fraction $p$ partitioned lines intersect. After van Noordwijk and de jong (1986).

### Tradeoffs Can Lead to Positive, as Well as Negative, Covariances

van Noordwijk and de jong (1986) and de jong and van Noordwijk (1992) note that resource partitioning models are not limited to molecular and developmental processes, but also can apply to physiological and behavioral processes as well. Suppose individuals have a total amount of energy $R$ to invest and have to decide what fraction should go into (say) reproduction versus other components of fitness. This is also a resource partitioning model, where the fraction $p$ now refers to what fraction of the energy budget of an individual is devoted to a particular component (say reproduction) rather than other components (Figure 31.3). The historical thinking for such life history components is, because the total amount of energy is fixed within an individual, that there must be *tradeoffs* (Chapter 30) between (say) reproduction and longevity, representing the allocation of a shared resource between two traits. As a consequence, one might expect negative genetic covariances between these components. Such not need be the case, as shown in Figure 31.4.

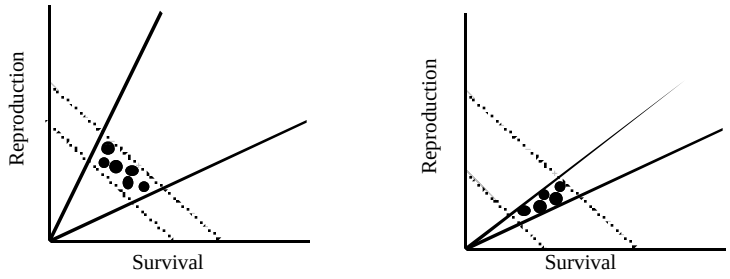


**Figure 31.4.** Although the energy budget $R$ of any single individual is fixed, there is *population level* variation in $R$, as well as in the fraction $p$ partitioned into (say) survival versus reproduction. **Left:** The range of $R$ and $p$ constraints their distribution of their values within a population. In this example, it results in a negative covariance between breeding values for reproduction and survival,. **Right:** However, if the range of $p$ values in the population is narrow relative to the range of $R$, then $R$ and $p$ will show a positive genetic covariance

within the population. This arises because the differences in energy levels among individuals is sufficiently large to swamp signatures of within-individual tradeoffs. After van Noordwijk and de jong (1986).

Thus, even though there are clearly tradeoffs *within* individuals in terms of how they spend their energy budgets, this *does not* automatically imply that the genetic covariance is negative. Individuals with large energy budgets will devote more *total* energy to both components than will individuals with smaller energy budgets. If the amount of energy is more variable than the amount of partitioning, then positive covariances can easily arise. van Noordwijk and de jong (1986) offer a very nice economic analogy: Consider the amount of money that families spend on their house versus their car(s). Clearly, within each family there are tradeoffs. However, very wealthy families spend much more on each than do poorer families, and this can result in the amount spent on a house being positively correlated with the amount spent on a car despite the obvious tradeoffs in total spending between these two. This example also points out while genetic, as opposed to phenotypic, correlations are used for fitness traits, as shared beneficial environmental effects can easily hide negative genetic correlations.

Houle (1991) examined a simple mutation-selection balance model under the partition of resources framework and concluded that positive genetic covariances at equilibrium were not at all unexpected. Essentially, the condition is that the number of loci involved an acquiring resources (those involved in $R$) is sufficiently large relative to the number of loci involved in the partitioning of the resources ($p$). This is consistent with Figure 31.4, which shows a positive covariance when the variance in $R$ is much greater than the variance in $p$. Houle argues on both biological and biochemical grounds that the number of acquisition loci is usually expected to be much greater than the number of allocation loci (for the traits under consideration), and thus positive covariances at equilibrium should not be uncommon. Several authors have further extended the two-trait resource partition model into models where an initial resource is sequentially partitioned over several traits. For example, Laguerie et al. (1991) showed that a three trait model ($R$ is partitioned into $X$ vs. $Y/Z$, and that later is subsequently partitioned into $Y$ and $Z$) can generate positive genetic covariances even when there is no variation in $R$ (all individuals have the same ability for resource allocation). Models with a cascade of $n$ traits sequentially (or **hierarchically**) partitioned were examined by de Jong (1993), Worley et al. (2003), and Björklund (2004).

**Björklund's Analysis**

Björklund's (2004) analysis is especially interesting, and shows the potential predictive power of some of these models. He applied the resource partitioning model to morphological traits by assuming a development model where stem cells are subsequently (and hierarchically) partitioned into different sets of cells that are further partitioned to generate the morphological traits of interest. Figure 31.5 shows a simplified version involving four traits, while Björklund assumed a binary bifurcating tree to generate 32 traits in his simulation model, which included variation in the partitioning at each node of the tree. He was interested in how the ratio of variance in acquisition versus allocation influences the correlations seem among the morphological traits.

When the variation in acquisition is much greater than the variation in allocation, Björklund's simulations showed high (positive) genetic correlations among all traits, with the leading eigenvector being close to isometric (equal loading on all traits). Given that for morphological traits, the leading eigenvector is often taken as a general size measure, equal loading imply that all traits scale equally, as opposed allometrically (LW Chapter 11), with size. By contrast, when the variation in acquisition is much less that in allocation, the pattern

of genetic covariances reflect the bifurcation of the tree. For example, traits 1 and 2 and traits 3 and 4 (in Figure 31.5) would be positive correlated, while all other correlations are negative (reflecting the allocation at the first node). In this case, the loading on the first eigenvector are **bipolar**, showing both positive and negative values. Hence, simply by "tuning" this variance ratio, we can move from a covariance structure where all traits have positive correlations to one when the genetic correlations are both positive and negative.

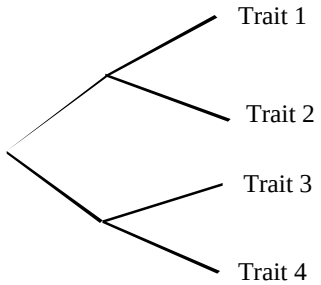


**Figure 31.5.** Björklund's hierarchical resource-partitioning model applied to a set of morphological traits connected via development. This simplified model attempts to capture an initial set of stem sets that become hierarchically partitioned through developmental pathways, eventually leading to the four traits scored.

Björklund's simulations show that this transition can happen quickly, and suggests that model can account for the observation that some estimates of **G** seem to be quite different between environments (e.g., Bégin and Roff 2001, Donoghue and Schmitt 1999, Donoghue et al. 2000). If the shift in environment results in a reduction in the variance in acquisition, this could result in a significant change in the correlation structure if the variance ratio was near this threshold of change. Björklund also notes that this can have a significant impact act on long-term evolution. Strong genetic correlations among morphological traits and a nearly isometric first eigenvalue are common in birds (Björklund 1994), and result in morphological differences between closely-related species being mainly in size when evolution occurs along lines of genetic least resistance. Conversely, differences in shape require that the **G** matrix is influenced by high variation in allocation rather than acquisition. As the variance in acquisition drop below a certain critical value, the correlations quickly shift from being all positive to a state where they change in an unpredictable matter. At the same time, the trait relations shift from being isometric to being either allometric or nonexistent as the loading on the leading eigenvector (size) depart from being isometric. Again, this transition (as measured by the angle between the first eigenvector and an isometric vector) also can occur rather quickly as the variance in acquisition decreases.

### Optimization Models, Functional Constraints, and G

If we fix the value of $R$ in a resource allocation model, then $Y$ can be expressed as a function of $X$ due to the constraint $pX + (1-p)Y = R$, implying $Y = (R - pX)/(1-p)$. This is an example of a **functional constraint**, wherein some aspect of biology (or chemistry or physics) constrains the possible set of values among a set of variables. Allocation of a fixed amount of time over various potential behaviors (such as foraging versus searching for mates) is a classic example. A common problem in ecology and behavior is optimization of fitness under such a constraint. The simplest setting is the two-trait case, where $z_1$ and $z_2$ are components that both contribute to increasing fitness. In the absence of any functional constraints, fitness

is maximized by obtaining the largest value of each. When a functional constraint is present, the problem is to optimize fitness $w = g(z_1, z_2)$ given the constraint $z_2 = f(z_1)$, i.e., optimize $g(z_1, f[z_1])$. **Evolutionary optimality theory** (Parker and Maynard Smith 1990) seeks to find optimal "strategies" (for example, allocation of resources among life history traits or types of behaviors that an organism should display) to maximize individual fitness given functional constraints. Note that this approach is different from *genetic* constraints imposed by the geometry of $\mathbf{G}$, and an obvious (and important) question is how such *biological* constraints become manifested in terms of *genetic* constraints, i.e., how functional constraints ultimately influence the genetic covariance matrix.

Suppose there is (sufficiently) weak selection on individual traits and sufficiently small variances and covariances among these traits (note that *correlations* can still range over $\pm 1$ in these settings). Under these conditions, $f(z_1)$ can be approximated by a first-order Taylor series,

$$f(z_1) \simeq f(0) + \frac{\partial f}{\partial z_1}\, z_1 \tag{31.29a}$$

and the variance in this function by

$$\sigma^2\left(f(z_1)\right) \simeq \sigma^2\left(f(0) + \frac{\partial f}{\partial z_1}\, z_1\right) = \left(\frac{\partial f}{\partial z_1}\right)^2 \sigma^2(z_1) \tag{31.29b}$$

When Equations 31.29a/b hold, Charnov (1989) and Charlesworth (1990) show a connection between optimal strategies (the solutions from optimality theory) on one hand and the structure of the equilibrium $\mathbf{G}$ matrix on the other. These papers attempt to bridge two approaches, often viewed as competing, for studying evolution — optimality-based solutions (which contain no explicit genetics) and quantitative-genetic approaches. Charnov considered a simple two-trait case, while Charlesworth offered a more general solution (where the assumptions given by Equations 31.29a/b are replaced with linearizations of multivariate functions). Thus, we first present Charnov's simple bivariate example in some detail to provide a feel of this approach, and then present some basic conclusions from Charlesworth's much more general treatment.

Suppose individual fitness is a simple linear function of $z_1$ and $z_2$,

$$w = az_1 + bz_2, \quad \text{where} \quad a, b > 0 \tag{31.30a}$$

where a functional constraint $z_2 = f(z_1)$ relates $z_1$ and $z_2$. The goal is to allocate $a$ and $b$ such that $w$ is optimized. Optimal values of $z_1$ maximize $w$, and hence statisfy

$$\frac{\partial w}{\partial z_1} = \frac{az_1 + bf(z_1)}{\partial z_1} = a + b\frac{\partial f}{\partial z_1} = 0 \tag{31.30b}$$

or

$$\frac{\partial f}{\partial z_1} = -\frac{a}{b} \tag{31.30c}$$

Thus, the optimal value(s) of $z_1$ are those values where the slope of $f$ equals $-a/b$.

This is the solution offered from optimality theory. Now consider the same solution under a quantitative-genetic framework in the extreme case of no environmental variance. First

$$\boldsymbol{\beta} = \begin{pmatrix} a \\ b \end{pmatrix} \tag{31.31a}$$

and at equilibrium $\widetilde{\mathbf{G}}\boldsymbol{\beta} = \mathbf{0}$, hence

$$\begin{pmatrix} \widetilde{G}_{11} & \widetilde{G}_{11} \\ \widetilde{G}_{21} & \widetilde{G}_{22} \end{pmatrix} \begin{pmatrix} a \\ b \end{pmatrix} = \mathbf{0} \tag{31.31b}$$

Since $a$ and $b$ are fixed constants, the equilibrium occurs not by changing the means, but rather by changing the covariance matrix. Assume that the equilibrium values of $z_1$ and $z_2$ show only a small amount of variance, so that we can describe $z_2$ adequately with a linearization about $z_1$,

$$z_2 = c + \delta\, z_1, \quad \text{where} \quad \delta = \left(\frac{\partial f}{\partial z_1}\right) \tag{31.31c}$$

The variation $\widetilde{G}_{11}$ in $z_1$ is unconstrained, while

$$\sigma^2(z_2) \simeq \sigma^2\,(c + \delta z_1) = \delta^2\,\widetilde{G}_{11} \tag{31.31d}$$

Similarly, the covariance between $z_1$ and $z_2$ becomes

$$\sigma(z_1, z_2) \simeq \sigma\,(c + \delta z_1, z_1) = \delta\widetilde{G}_{11} \tag{31.31e}$$

Substituting into Equation 31.31b gives

$$\widetilde{G}_{11}\begin{pmatrix} 1 & \delta \\ \delta & \delta^2 \end{pmatrix}\begin{pmatrix} a \\ b \end{pmatrix} = \mathbf{0} \tag{31.31f}$$

which has solutions of $\delta = \partial f/\partial z_1 = -a/b$, the same as obtained from optimality analysis (Equation 31.30c). Thus optimality analysis and a quantitative-genetic analysis both yield the same equilibrium value. The very careful reader will note that the quantitative-genetic analysis is based on mean fitness $\overline{W}$ while optimality analysis is based on individual fitness $W(\mathbf{z})$. When the variance about the means is small and the fitness function relatively linear, there is not much error moving between these two measures of fitness. Returning to the equilibrium $\widetilde{\mathbf{G}}$, note that there is a negative covariance ($-a/b$) between $z_1$ and $z_2$. Further, note that $\widetilde{\mathbf{G}}$ is *singular*, as its determinant is $1 \cdot \delta^2 - \delta^2 = 0$. The behavior of the distribution of breeding values under this model is shown in Figure 31.6.

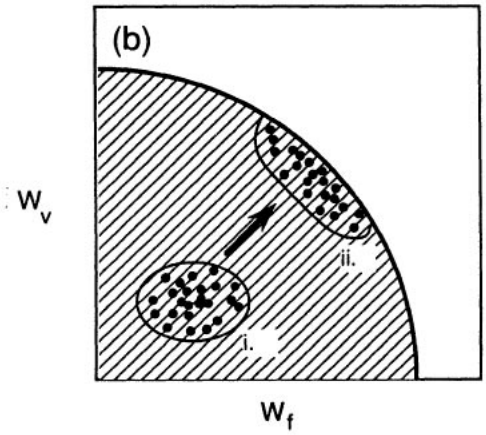


**Figure 31.6.** A graphical representation of the consequences of Charnov's (1989) model for evolution under functional constraints. Here, there are functional, rather than genetic, constraints on the possible trait values. If selection is trying to increase both traits, an initial distribution of values eventually runs up against the constraint (the solid curve) and can move no further (short, of course, of evolving new mechanisms to reduce the constraint). As a result, for the two-trait case negative correlations typically arise as the constraint is approached. After Arnold (1992).

Charlesworth (1990) presented a much more general analysis of the translation of functional constraints into $\mathbf{G}$. He allowed for $p$ of $n$ variables to be fully constrained, with $f_i(\mathbf{z}) = 0$ for $1 \leq i \leq p$, while the remaining $n - p$ variables are assumed to be unconstrained (and uncorrelated). Assumptions based on the multivariate extensions of Equations 31.29a/b were used (each of the $f_i$ can be well-approximated near equilibrium by a simple linearization). Under this more general model, Charlesworth found that the equilibrium conditions for $\mathbf{G}$ are very similar to optimization conditions, except that individual fitness (for optimization) is replaced by mean population fitness under a quantitative-genetic analysis. Charlesworth found that $\widetilde{\mathbf{G}}$ is generally singular and typically contains a negative genetic correlations, although positive correlations can also exist as well (Pease and Bull 1988). With multiple traits, the equilibrium genetic correlations are only indirectly related to the function constraints, through linear combinations of derivatives of the constraint functions. Hence, attempting inference about the constraint function(s) from the pattern of genetic correlations is not a profitable enterprise.

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**Example 31.4.** As an example of how poorly a set of underlying constraints translates into a $\mathbf{G}$ matrix, consider the following model. Assume a vector $\mathbf{f}$ of $k$ factors influence the vector $\mathbf{g}$ of $n$ genotypic values. The simplest model is to assume a linear weighting of the factors plus some residual effects not accounted for by the factors,

$$\mathbf{g} = \mathbf{F}\mathbf{f} + \mathbf{e}$$

Here $\mathbf{F}$ is an $n \times k$ matrix of factor weights and $\mathbf{e}$ the residual effects. The resulting genetic covariance matrix is

$$\mathbf{G} = \mathbf{F}\boldsymbol{\Sigma}_f\mathbf{F}^T + \boldsymbol{\Sigma}_e$$

where $\boldsymbol{\Sigma}_f$ and $\boldsymbol{\Sigma}_e$ are the covariance matrices for the factors and residual errors. Ideally, we would like to estimate the matrix $\mathbf{F}$ of factor loadings, but the eigenvectors of $\mathbf{G}$ provide no information on these. For example, assume the factors are uncorrelated with variances of one ($\boldsymbol{\Sigma}_f = \mathbf{I}$) and the residuals are uncorrelated with variances of 0.5, giving ($\boldsymbol{\Sigma}_e = 0.5 \cdot \mathbf{I}$). Assume two factors influence four traits, with

$$\mathbf{F} = \begin{pmatrix} 1 & -1 \\ -1 & 1 \\ 2 & 0 \\ -1 & 1 \end{pmatrix}, \quad \text{giving} \quad \mathbf{G} = \mathbf{F}\mathbf{F}^T + 0.5 \cdot \mathbf{I} = \begin{pmatrix} 2.5 & -2.0 & 2.0 & -2.0 \\ -2.0 & 2.5 & -2.0 & 2.0 \\ 2.0 & -2.0 & 4.5 & -2.0 \\ -2.0 & 2.0 & -2.0 & 2.5 \end{pmatrix}$$

The resulting eigenvalues of $\mathbf{G}$ are 9.1, 1.9, 0.5, and 0.5 (the first two detect the structure from the factors, the last two the residual error). The resulting eigenvectors are

$$\mathbf{e}_1 = \begin{pmatrix} -0.46 \\ 0.46 \\ -0.60 \\ 0.46 \end{pmatrix}, \quad \mathbf{e}_2 = \begin{pmatrix} 0.35 \\ -0.35 \\ -0.80 \\ -0.35 \end{pmatrix}, \quad \mathbf{e}_3 = \begin{pmatrix} 0.71 \\ 0.71 \\ 0.00 \\ 0.00 \end{pmatrix}, \quad \mathbf{e}_4 = \begin{pmatrix} -0.41 \\ 0.41 \\ 0.00 \\ -0.82 \end{pmatrix}$$

Note that there is no similarity between the eigenvalues of $\mathbf{G}$ and the factor loadings. If we assumed no residual error, then $\mathbf{G}$ is singular (with two zero eigenvalues). However, the eigenvectors for the two positive eigenvalues are still the values of $\mathbf{e}_1$ and $\mathbf{e}_2$ given above.

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## LONG-TERM DIRECTIONAL SELECTION

In parallel with our discussions of the change in the genetic variance under univariate selection, short-term changes in $\mathbf{G}$ due to linkage disequilibrium are fairly predictable (Chapters 13, 24), while longer-term changes involving changes in allele frequencies are essentially unpredictable (Chapters 25, 26), and certainly unpredictable just given an initial value of $\mathbf{G}$.

**The Infinitesimal Model with Drift**

As was discussed at length in Chapter 24 and 26, there is an intermediate class of models (based on the infinitesimal) that on one hand allow for allele frequency change while on the other are relatively manageable. The critical feature is that selection on each locus is sufficiently weak that no significant allele frequency change occurs via selection. However, if population size is finite, drift can occur at each locus, which causes the expected value of genetic variance (in the absence of dominance or epistasis) to behave in a predictable fashion (Chapters 5, 32). We will build up the model in stages, first ignoring disequilibrium, then adding it, and finally adding mutation.

First, consider the decay of genetic variation from drift. While the infinitesimal framework implies that strength of selection on any particular locus is small enough to ignore, allele frequencies can still change via drift,

$$\mathbf{G}_t = \left(1 - \frac{1}{2N_e}\right)^t \mathbf{G}_0 \simeq e^{-t/2N_e}\mathbf{G}_0 \tag{31.32}$$

Hence, the expected cumulative response $\mathbf{R}^c$ after $t$ generations of selection and drift is

$$\mathbf{R}^c_t = \boldsymbol{\mu}_t - \boldsymbol{\mu}_0 = \sum_{k=1}^{t} \mathbf{G}_k\boldsymbol{\beta}_k = \sum_{k=1}^{t}\left(1 - \frac{1}{2N_e}\right)^k \mathbf{G}_0\boldsymbol{\beta}_k \tag{31.33a}$$

If we assume the same selection gradient, then

$$\begin{aligned}\mathbf{R}^c_t &= \sum_{k=1}^{t}\left(1 - \frac{1}{2N_e}\right)^k \mathbf{G}_0\boldsymbol{\beta} \\ &= \mathbf{G}_0\boldsymbol{\beta}\sum_{k=1}^{t}\left(1 - \frac{1}{2N_e}\right)^k \\ &\simeq 2N_e(1 - e^{t/2N_e})\mathbf{R}_1 \end{aligned} \tag{31.33b}$$

where we have used **Equation 26.4b** to approximate the sum and have noted that $\mathbf{G}_0\boldsymbol{\beta}$ is the response following the first generation of selection, $\mathbf{R}_1$. Equation 31.33b is the multivariate version of Robertson's rule, giving the total response (from the initial variation) as $2N_e$ times the initial response, which follows since

$$\lim_{t\to\infty} \mathbf{R}^c_t = 2N_e\mathbf{R}_1 \tag{31.33c}$$

As with the univariate case, the strength of selection increases the first generation of response, but decreases the effective population size, so that the optimal long-term response occurs at an intermediate level of selection (Chapter 26).

What is the effect of selection generating linkage disequilibrium? It results in Equations 31.33b and 33c slightly overestimating the response, as directional selection generates negative disequilibrium, reducing response. Let's develop a more formal model for the changes

in disequilibrium when the linkage equilibrium version of $\mathbf{G}$ at time $t$ *does not* equal $\mathbf{G}_0$. Under drift, the value of $\mathbf{G}$ in generation $t$ if no disequilibrium is present is given by Equation 31.32,

$$\mathbf{G}_t(LE) = \left(1 - \frac{1}{2N_e}\right)^t \mathbf{G}_0 \tag{31.34a}$$

By analogy with Keightley and Hill's (1987) result (Equation 13.9b), the change in $\mathbf{D}$ under the joint effects of both selection and drift is

$$\Delta\mathbf{D}_t = -\frac{1}{2}\left(1 + \frac{1}{N_e}\right)\mathbf{D}_t + \frac{1}{2}\left(1 - \frac{1}{N_e}\right)\mathbf{G}_t\mathbf{P}_t^{-1}(\Delta\mathbf{P}_t)\mathbf{P}_t^{-1}\mathbf{G}_t \tag{31.34b}$$

Joint iteration of Equations 31.34a and 34b gives $\mathbf{G}_t$, as

$$\mathbf{G}_t = \mathbf{G}_t(LE) + \mathbf{D}_t \tag{31.34c}$$

Likewise, the phenotypic matrix in generation $t$ is given by

$$\mathbf{P}_t = \mathbf{G}_t + \mathbf{E} = (\mathbf{G}_t(LE) + \mathbf{D}_t) + (\mathbf{P}_0 - \mathbf{G}_0) = \mathbf{P}_0 + (\mathbf{G}_t(LE) - \mathbf{G}_0) + \mathbf{D}_t \tag{31.34d}$$

Note from Equation 31.34b that unless effective population size $N_e$ is very small, drift has a very minor effect on the disequilibrium. Its major effect is in changing the linkage equilibrium value of $\mathbf{G}$, reducing variation each generation.

A strong caveat is in order at this point. The above theory is for the *expected* value of $\mathbf{G}$ under drift and the (additive) infinitesimal model. Any particular *realization* may thus be quite a bit different from the expected value, and as well will see in Chapter 32, this difference can be dramatic, especially when the population size is small.

**The Infinitesimal Model with Drift and Mutation**

Under infinitesimal model assumptions (selection does not significantly change allele frequencies), it is straightforward to incorporate the effect of new mutation. As in the univariate case (Chapter 26), drift will eventually remove all initial variation, with continued response requiring the input of new variation.

By analogy with the mutational variance for a single trait (Chapter 26), we can consider the mutational variances and covariances in the form of $\mathbf{M}$, a mutational matrix of per-generation input to the additive genetic variances and covariance. Under the infinitesimal model, selection has no impact (ignoring disequilibrium) on the equilibrium value of $\mathbf{G}$, reached when mutational input balances the loss due to drift, viz.

$$\widetilde{\mathbf{G}} = 2N_e\mathbf{M} \tag{31.35a}$$

The (linkage equilibrium) value of $\mathbf{G}$ in any particular generation is the sum of what remains of the original $\mathbf{G}$ matrix (following the effects of drift) plus the cumulative input of mutation,

$$\mathbf{G}_t = \widetilde{\mathbf{G}} + \left(\mathbf{G}_0 - \widetilde{\mathbf{G}}\right)e^{-t/2N_e} \tag{31.35b}$$

The cumulative response to $t$ generations of constant directional selection $\boldsymbol{\beta}$ thus becomes

$$\mathbf{R}_t^c = \sum_{i=1}^{t}\mathbf{G}_t\boldsymbol{\beta} = \left[\, t\,\widetilde{\mathbf{G}} + 2N_e(1 - e^{-t/2N_e})\left(\mathbf{G}_0 - \widetilde{\mathbf{G}}\right)\right]\boldsymbol{\beta} \tag{31.36a}$$

We can gain further insight by considering two alternative expressions of Equation 31.36a. First, we can represent this as the asymptotic response $\widetilde{\mathbf{G}}\boldsymbol{\beta}$ plus the response contributed during the approach to the equilibrium value of $\mathbf{G}$,

$$\mathbf{R}_t^c = t\,\widetilde{\mathbf{G}}\boldsymbol{\beta} + 2N_e(1 - e^{-t/2N_e})\left(\mathbf{G}_0 - \widetilde{\mathbf{G}}\right)\boldsymbol{\beta} \tag{31.36b}$$

Note that if the population starts out with $\mathbf{G}$ equal to its equilibrium value, the second term disappears and the response (ignoring linkage disequilibrium) remains constant, with

$$\mathbf{R}_t^c = t\,\widetilde{\mathbf{G}}\boldsymbol{\beta} = t\,\mathbf{R}_1$$

Second, we can use Equations 31.33b to decompose the cumulative response into two components, the first due to the initial variation, the second due entirely to new mutation arising since selection started,

$$\mathbf{R}_t^c = 2N_e(1 - e^{t/2N_e})\mathbf{R}_1 + \left(t - 2N_e(1 - e^{-t/2N_e})\right)\widetilde{\mathbf{G}}\boldsymbol{\beta} \tag{31.36c}$$

This decomposition allows us to compute the fraction of response due to initial variation vs. that from new variation. For example, for trait $i$, let $R_i(I)$ denote the $ith$ component in the vector given by the first term (the contribution to response in trait $i$ from the initial variation) and $R_i(m)$ from the second (the mutational contribution). The relative contribution from mutation to the response is $R_i(m)/[\,R_i(I) + R_i(m)\,]$. Note that under constant selection, the effect of $\boldsymbol{\beta}$ cancels, so that this ratio is independent of the nature of selection.

**The Balance Between Directional and Stabilizing Selection: Infinitesimal Model Results**

As with univariate traits, selection limits can appear to be reached when the initial additive variation has been exploited and sufficient new variation has yet to be generated by mutation. Another scenario, which occurs even when ample genetic variation is present, is that directional selection is balanced by some other force, such as stabilizing selection. Zeng (1988) offered an insightful analysis of this problem based on the gaussian fitness function (Equation 31.15). One of Zeng's major findings is that the equilibrium mean is *independent* of $\mathbf{G}$ (provided it is non-singular).

Recall from Equation 31.15a the general form of the Gaussian fitness function,

$$W(\mathbf{z}) = \exp\left(\mathbf{a}^T\mathbf{z} - \frac{1}{2}(\mathbf{z} - \boldsymbol{\theta})^T\mathbf{W}(\mathbf{z} - \boldsymbol{\theta})\right) = \exp\left(-\frac{1}{2}(\mathbf{z} - \boldsymbol{\psi})^T\mathbf{W}(\mathbf{z} - \boldsymbol{\psi})\right) \tag{31.37a}$$

where the equality follows by completing the square to collect the linear term into the quadratic product, with

$$\boldsymbol{\psi} = \boldsymbol{\theta} + \mathbf{W}^{-1}\mathbf{a} \tag{31.37b}$$

Individual fitness is maximized when $\mathbf{z} = \boldsymbol{\psi}$. If the vector of traits (before selection) is multivariate normal with mean $\boldsymbol{\mu}$ and covariance matrix $\mathbf{P}$, then the distribution of $\mathbf{z}$ following selection is MVN with mean $\boldsymbol{\mu}^*$ and covariance matrix $\mathbf{P}^*$. The later is independent of both the current mean and the optimal value $\boldsymbol{\psi}$, and is simply that given by Equation 31.17,

$$\mathbf{P}^* = \left(\mathbf{P}^{-1} + \mathbf{W}\right)^{-1}$$

The new mean (after selection but before reproduction) is given by

$$\boldsymbol{\mu}^* = \mathbf{P}^*\left(\mathbf{P}^{-1}\boldsymbol{\mu} + \mathbf{W}\boldsymbol{\psi}\right) \tag{31.38a}$$

The response (in the vector $\boldsymbol{\mu}$ of means) to selection follows from the breeder's equation,

$$\begin{aligned}\boldsymbol{\mu}_{t+1} - \boldsymbol{\mu}_t &= \mathbf{G}_t \mathbf{P}_t^{-1} \left(\boldsymbol{\mu}_t^* - \boldsymbol{\mu}_t\right) \\ &= \mathbf{G}_t \left(\mathbf{W}^{-1} + \mathbf{P}_t\right)^{-1} \left(\boldsymbol{\psi} - \boldsymbol{\mu}_t\right) \end{aligned} \tag{31.38b}$$

The derivations for Equations 31.38a/b are given in **Chapter 41**. Equation 31.38b coupled with Equation 31.20 describe the joint dynamics (under the infinitesimal model) of changes in the vector of means $\boldsymbol{\mu}_t$ and disequilibrium matrix $\mathbf{D}_t$ (and hence $\mathbf{G}_t$ and $\mathbf{P}_t$).

Zeng's key result follows from Equation 31.38b, which gives the equilibrium mean as satisfying

$$\mathbf{0} = \widehat{\mathbf{G}} \left(\mathbf{W}^{-1} + \widehat{\mathbf{P}}\right)^{-1} \left(\boldsymbol{\psi} - \widehat{\boldsymbol{\mu}}\right) \tag{31.39a}$$

*Provided* that $\mathbf{G}$ is nonsingular, then

$$\widehat{\boldsymbol{\mu}} = \boldsymbol{\psi} = \boldsymbol{\theta} + \mathbf{W}^{-1}\mathbf{a} \tag{31.39b}$$

is the unique solution. Notice that the values of $\mathbf{G}$ and $\mathbf{P}$ *do not* enter into the equilibrium mean, only the strength and form of directional ($\mathbf{a}$) and quadratic ($\mathbf{W}$) selection. Hence, while the genetic covariance structure has a strong influence in the dynamics (the path and time) to reach the equilibrium point, the value of the equilibrium point is *independent* of the pattern of genetic covariances (again provided $\widehat{\mathbf{G}}$ is not singular). In particular, if $\mathbf{W}$ is diagonal (no selection on combinations of characters) then for the $i$th trait,

$$\widehat{\mu}_i = \theta_i + \frac{a_i}{W_{ii}} \tag{31.39c}$$

so that the *long-term* evolution of each character is independent unless at least one genetic correlation is perfect (so that $\mathbf{G}$ is singular).

Zeng also consider the case where stabilizing selection occurs first followed by truncation selection on some index $I = \mathbf{b}^T\mathbf{z}$ of trait values (Chapter 32). This is one model of artificial selection, wherein existing phenotypes are first culled by natural selection (and hence often unseen by the breeder or experimentalist) with the remaining individuals then subjected to artificial selection. The change in mean in this case is still given by Equation 31.38b, with $\mathbf{a} = c \cdot \mathbf{b}$ where the constant $c$ is a function of the selection intensity on the index as well as its phenotypic variance (see Zeng for details). Thus the above argument still holds, with the equilibrium mean vector given by Equation 31.39b. The value of $\mathbf{P}^*$ is slightly different from Equation 13.15, now depending on $\mathbf{b}$ (again see Zeng), but this only influences the equilibrium dynamics of $\widehat{\mathbf{D}}$ and does not affect the equilibrium mean.

**Long-term Response is a Function of the Distribution of Allelic Effects**

The above models are highly stylized, offering a look at certain features of long-term response. However, as was the case for univariate long-term response, the initial estimator of genetic variance (be it $h^2$ or $\mathbf{G}$) gives essentially no information as to the behavior of long-term response. What is needed, and never available, is the distribution of allelic effects over all loci. We have already seen how fragile genetic covariances are expected to be under allele frequency change, especially when the population consists of mixtures of complementary and antagonistic pleiotropic alleles. An initial estimate of a covariance provides very little information on the frequencies of these sets of alleles, yet this information is critical for long-term response. A zero covariance could arise because no pleiotropic alleles exists, and therefore any future correlations are build up solely by disequilibrium. It could also occur when a large reservoir of pleiotropic alleles are present, but whose net effects cancel. If this

is the case, there is ample opportunity for large positive, or negative, correlations to be build up by selection.

Thus long-term response depends on both the pattern of genetic variation present at the start of selection and how this pattern changes over time. A general view is that most traits eventually fall under some sort of stabilizing selection (in that their range is bounded), and hence models of the variation maintained under a mutation-selection balance may provide some insight. Chapter 27, and the next section, discuss these. Recall from Chapter 27 that two different approximations are used for the analysis of mutation-selection models, one where allelic effects are roughly gaussian at each locus (the **gaussian genetic model**) and one where rare alleles are important (the **house of cards model**, or HOC). Under the house of cards model, the distribution of allelic effects is expected to be highly leptokurtic, with rare alleles having significant effects. Under univariate selection, selection with such a distribution of allelic effects should result in an increase in the heritability as these rare alleles move to higher frequencies.

Reeve (2000) used simulation studies to examine the consequences of gaussian versus house of cards models for long-term directional response. In his simulations, a population initially under a stabilizing selection-mutation balance has its optimal value shifted by a significant amount (many standard deviations) and the response to selection followed, using the initial estimate of $\mathbf{G}$ (the mutation-selection balance value) to predict response. Reeve found that if allelic effects follow the gaussian model, then the initial $\mathbf{G}$ does a good job of predicting response, despite modest allele frequency changes. If, however, the house of cards model is more appropriate, then the initial $\mathbf{G}$ does a very poor job in predicting response, underestimating the rate of direct and correlated response and overestimating the time to reach the new optimum. This occurs because rare alleles increase in frequency, significantly altering $\mathbf{G}$.

Another situation in which the long-term behavior of $\mathbf{G}$ is made even more unpredictable is the presence of major genes, for example genes of large effect for insecticide resistance (Carriére and Roff 1995). Often, genes of large effect have strong pleiotropic effects on a number of traits (Chapter 25). As these genes are driven to fixation, they can substantially alter $\mathbf{G}$. While they clearly change the genetic variance associated with the trait under selection, they can also have significant impact on the genetic covariances between other traits. Even if this change in $\mathbf{G}$ is transient, it can still significantly impact the dynamics, in the extreme case potentially moving the population into a new domain of attraction on a multiple-peaked fitness surface (Price et al. 1993, Agrawal et al 2001). If one views the $\mathbf{G}$ matrix as consisting of the contributions from the major-gene effects $\mathbf{G}_*$ and an infinitesimal-like background of other genes of much smaller effects $\mathbf{G}_I$, then the selection dynamics may be largely governed by $\mathbf{G}_*$, but as this gene becomes fixed, all the investigator observes is $\mathbf{G}_I$, creating a misleading picture of the constraints during selection (Agrawal et al 2001). Of course, this need not be the case. Stinchcombe et al. (2009) find that while different alleles at the *erecta* gene in *Arabidopsis* result in significantly different $\mathbf{G}$ matrices, the predicted response to selection remains roughly similar.

### The Balance Between Directional and Stabilizing Selection: Finite Locus Models

Zeng's analysis was under the infinitesimal model framework, so that allele frequency changes are ignored and changes in the variance can only occur through the generation of linkage disequilibrium. When allele frequency changes are allowed, hidden pleiotropic effects (a reservoir of pleiotropic alleles in the population, but no *net* genetic covariance) can have an important impact on selection response. Baatz and Wagner (1997) examined a simple selection model involving two traits, one under directional, the other stabilizing, selection. Such models where the directional selection of some traits is restricted to a narrow region due to strong stabilizing selection on other traits are often called **corridor models**

(Rechenberg 1973). When allele frequency changes can alter the variance, Baatz and Wagner note that the present of hidden pleiotropic can result in stabilizing selection on the second trait either slowing down, or speeding up, the rate of directional selection in the first. Thus, when hidden pleiotropy is present, allele frequency change can result in the dynamics of one trait being strongly influenced by the dynamics of a genetically *uncorrelated* trait. Given all of our focus on the importance of genetic correlations, just how does this happen? Building on Robertson's secondary theorem of natural selection (Chapter 5), Baatz and Wagner show that the change in the mean for the trait under directional selection is a function of $\sigma(g_1, g_2^2)$, namely the correlation between breeding value at the trait under directional selection and the *square* of breeding value for the trait under stabilizing selection. Note that it is easy to have no correlation among the breeding values for both traits, $\sigma(g_1, g_2) = 0$, and yet still have a very large covariance involving a breeding value at one trait and the square of a breeding value at the second. This is the impact from hidden pleiotropy.

Consider a situation where favorable alleles for trait one are rare. Directional selection on trait one will try to increase their frequency. If such alleles also have pleiotropic effects on trait two, then even if the breeding values between the two traits are uncorrelated, increasing the frequency of favorable alleles for trait one may increase the *variance* in trait two, which is counted by stabilizing selection (as the increased variance results in a decreased mean fitness for trait two). If stabilizing selection is strong, this can retard the speed of directional selection. In the extreme, it may stop directional selection entirely, a phenomena Baatz and Wagner quaintly refer to as the **Pooh effect**, after Winnie the Pooh getting stuck in a rabbit hole after eating too much honey. Thus when favorable alleles are rare, the Pooh effect retards the rate of directional selection even in the absence of correlations among breeding values ($\sigma(g_1, g_2) = 0$), provided $\sigma(g_1, g_2^2) \neq 0$. Conversely, when favorable alleles for trait one are present at high frequency, then the variance in trait two declines as these further increase in frequency. This situation results in higher mean fitness for trait two (as its variance is reduced), and the net result is an *acceleration* of directional selection.

The key message from the above analysis is that while genetic covariances are excellent for providing a quick snap-shot of the local dynamics, when allele frequency change occurs, all bets are off. Thus, one can have a situation where selection on an unobserved trait that is *not* genetically correlation with our focal trait can still influence its fitness if pleiotropy is present and allele frequency change occurs.

## LONG-TERM QUADRATIC SELECTION

Stabilizing selection removes variation, and thus long-term stabilizing selection will eventually remove most (if not all) of any initial genetic variation (Chapters 5, 25, 27). As discussed at length in Chapter 27, the maintenance of additive variation under stabilizing selection is a major area of theoretical research. While the notion that existing levels of variation can be accounted for by a balance between mutation and selection is quite appealing, as both forces are expected to be operating in the background for most traits, current models do not adequately account for the levels of variation given realistic estimates of the model parameters (genome mutation rates, strengths of selection).

Our focus in the section is on two issues not fully addressed in Chapter 27. The first is what current theories about mutation-selection balance tell us about the *stability* (or lack thereof) of the $\mathbf{G}$ matrix over time. As we have seen, this is critical for an retrospective selection analysis over evolutionary time scales (Chapter 30). While selection changes $\mathbf{G}$, one line of thought (which we examine here) is the $\mathbf{G}$ may be relative stable over time once it reaches a mutation-selection equilibrium, *provided* the patterns of mutations and selection is relatively constant. Our second issue is to highlight the qualitative differences in the behavior

of models making what (at first sight) appear to be relatively-minor differences in assumptions. We have already noted differences in behavior in directional selection starting from a $\mathbf{G}$ in mutation-selection equilibrium under a gaussian versus house of cards approximation. These models have even more dynamic differences when hidden pleiotropy is present.

**Lande's Multivariate Model of Pleiotropic Mutation-Selection Balance**

Lande (1980, 1984) examined the equilibrium value of $\mathbf{G}$ under the balance between stabilizing selection, mutation, and recombination using a gaussian genetic model: allelic effects at each locus are assumed follow a multivariate distribution (large population size was assumed so that the effects of drift are ignored). Considering a particular locus $i$, let $\mathbf{x}_i$ be the vector of allelic effects influencing $k$ traits, so that $\mathbf{x}_i + \mathbf{x}_i'$ is the vector of contributions of this locus to the vector of trait values, where the unprimed and primed $\mathbf{x}$ denote the contributions from the two alleles at this locus. Assume gaussian stabilizing selection (Equation 31.15) occurs on the vector of traits, and recall from Equation 31.19b that the resulting change in $\mathbf{G}$ from selection is given by

$$\mathbf{G}^* - \mathbf{G} = -\mathbf{G}\left(\mathbf{W}^{-1} + \mathbf{P}\right)^{-1}\mathbf{G}$$

Here $(\mathbf{W}^{-1}+\mathbf{P})^{-1}$ is the resulting strength of selection on breeding values given the strength of selection $\mathbf{W}$ on phenotypes. Under weak selection and with free recombination between loci, Lande (1980, 1984) showed that the contribution from linkage disequilibrium was minimal and that pleiotropic mutations largely determine the equilibrium genetic covariances. Let $\mathbf{C}_i$ denote the covariance matrix associated with locus $i$, so that the $kj$th element is the genetic covariance of traits $k$ and $j$ (contributed by locus $i$). Assuming weak selection, Lande approximates $\mathbf{W}^{-1} + \mathbf{P} \simeq \mathbf{W}^{-1} + \mathbf{E}$, which removes $\mathbf{P}$, which is dependent on the current value of $\mathbf{G}$. Under this approximation, Equation 31.19b reduces to

$$\Delta\mathbf{G} = -\mathbf{G}\,\boldsymbol{\omega}\,\mathbf{G}, \quad \text{where} \quad \boldsymbol{\omega} = \mathbf{W}^{-1} + \mathbf{E} \tag{31.40}$$

Selection thus removes variation, which is countered by the addition of new variation from mutation. We encapsulate this for locus $i$ by $\mathbf{M}_i$, the pleiotropic mutation matrix. If there are off-diagonal elements, then (on average) new mutations at loci $i$ show a genetic covariance for those traits. Note that we can also have $\mathbf{M}_i = c_i\mathbf{I}$, namely a model with a constant mutation variance for each trait and *average* mutational covariance of zero. Such a model *does not* mean that pleiotropic mutations are not produced, rather it simply says that complementary and antagonistic pleiotropic mutants are equally frequent, canceling out their effects and giving no *net* genetic mutational covariance *despite* the potential for abundant pleiotropic among the mutations themselves.

With weak selection, we can use a continuous-time approximation for the change in $\mathbf{C}_i$, giving Lande's (1980) result of

$$\frac{d\mathbf{C}_i}{dt} \simeq -\mathbf{C}_i\,\boldsymbol{\omega}\,\mathbf{C}_i + \mathbf{M}_i \tag{31.41a}$$

where the change is the loss due to selection countered by mutational input. This has an equilibrium solution of

$$\widetilde{\mathbf{C}}_i = \boldsymbol{\omega}^{1/2}\left(\boldsymbol{\omega}^{-1/2}\mathbf{M}_i\boldsymbol{\omega}^{-1/2}\right)^{1/2}\boldsymbol{\omega}^{1/2} \tag{31.41b}$$

showing (as expected) that the equilibrium covariance matrix contributed by locus $i$ is a balance between selection $\boldsymbol{\omega}$ and mutational $\mathbf{M}$ effects. Lande's original (1980) paper had

his formula (21c) misprinted, with Equation 31.41b being the corrected version given by Lande (1984). Summing over both copies in a diploid and over all loci gives the equilibrium covariance matrix as

$$\begin{aligned}\widetilde{\mathbf{G}} &= 2\sum_{i=1}^{n} \boldsymbol{\omega}^{1/2} \left(\boldsymbol{\omega}^{-1/2}\mathbf{M}_i\boldsymbol{\omega}^{-1/2}\right)^{1/2} \boldsymbol{\omega}^{1/2} \\ &= 2\boldsymbol{\omega}^{1/2}\left[\sum_{i=1}^{n} \left(\boldsymbol{\omega}^{-1/2}\mathbf{M}_i\boldsymbol{\omega}^{-1/2}\right)^{1/2}\right] \boldsymbol{\omega}^{1/2} \end{aligned} \tag{31.42}$$

Cheverud (1982, 1984) suggested that, under certain conditions, the equilibrium genetic covariance matrix might be geometrically similar to the fitness surface (i.e., the orientations of the eigenvalues of the $\mathbf{G}$ and $\boldsymbol{\omega}$ or $\boldsymbol{\gamma}$ matrices may be very similar). In particular, Cheverud (1984) noted that if there is no *net* pleiotropy, then substituting $\mathbf{M}_i = c_i\mathbf{I}$ into Equation 31.42 yields

$$\widetilde{\mathbf{G}} = 2\boldsymbol{\omega}^{1/2}\left[\sum_{i=1}^{n} (c_i\mathbf{I})^{1/2}\right] = k\boldsymbol{\omega}^{1/2} \tag{31.43}$$

In this case, $\widetilde{\mathbf{G}}$ aligns with the fitness surface as (recalling the discussing following Equation 29.25) the eigenvectors of $\boldsymbol{\omega}$, $\boldsymbol{\omega}^{-1}$ and $\boldsymbol{\omega}^{1/2}$ are identical. Thus, while there are indeed conditions under which the covariance structure approaches of the fitness surface, how often they apply is uncertain. At a minimum, *net* mutational pleiotropy must be small and the fitness surface must be constant for long periods of time. Equation 31.42 also shows that in the presence of strong pleiotropy, the orientation of $\widetilde{\mathbf{G}}$ can significantly deviate from the orientation of $\boldsymbol{\omega}$ (and also $\boldsymbol{\gamma}$, as we show below).

**$\boldsymbol{\gamma}$ and $\mathbf{G}$**

While the gaussian stabilizing selection is a common model used by theorists, empiricists generally use the Lande-Arnold fitness regression (Equation 29.13) where $\boldsymbol{\gamma}$ is the matrix of quadratic selection gradients. For weak selection, there is an equivalence between the two models. It is important to remind the reader that gaussian *selection* and a gaussian *genetic model* refer to different assumptions, the first on the nature of phenotypic selection, the second on the distribution of allelic effects at individual loci. Assume the population mean is near the optimum so that there is no significant directional selection gradient $\boldsymbol{\beta}$. Further (for ease of notation, with no loss of generality) rescale the traits so that zero is the optimum value. We then have

$$W(\mathbf{z}) = \exp\left(-\frac{1}{2}\mathbf{z}^T\mathbf{W}\mathbf{z}\right) \simeq 1 - \frac{1}{2}\mathbf{z}^T\mathbf{W}\mathbf{z} \tag{31.44a}$$

This approximation follows from the weak selection assumption. Using Equation 31.15c we can diagonal $\mathbf{W}$, in which case Equation 31.44a can be written as

$$W(\mathbf{z}) \simeq 1 - \frac{1}{2}\sum_{i=1}^{n} \lambda_i\, y_i^2 \tag{31.44b}$$

and we see that weak selection implies the eigenvalues of $\mathbf{W}$ are small. Matching quadratic terms in the Lande-Arnold regression gives (Lande 1979, Arnold et al. 2001),

$$-\mathbf{W} = \boldsymbol{\gamma} \tag{31.45}$$

Alternatively, from Equation 31.11a, in the absence of directional selection ($\boldsymbol{\beta} = \mathbf{0}$), the analog to Equation 31.41a (assuming the gaussian *genetic* mode) becomes

$$\Delta\mathbf{G} = \mathbf{G}\boldsymbol{\gamma}\mathbf{G} + \mathbf{M} \tag{31.46}$$

At equilibrium,

$$-\widehat{\mathbf{G}}\,\boldsymbol{\gamma}\,\widehat{\mathbf{G}} = \mathbf{M} \tag{31.47}$$

Jones et al. (2007) remark that if $\boldsymbol{\gamma}$ and $\mathbf{M}$ are positive-define and share common eigenvalues, then $\mathbf{G}$ shares these eigenvalues as well. If we again assume $\mathbf{M} = k{\cdot}\mathbf{I}$, we have $-\widehat{\mathbf{G}}\,\boldsymbol{\gamma}\,\widehat{\mathbf{G}} = k{\cdot}\mathbf{I}$, giving

$$\widehat{\mathbf{G}} = k(-\boldsymbol{\gamma})^{1/2} \tag{31.48}$$

Thus, under certain conditions the geometry of the equilibrium genetic covariance matrix and the quadratic fitness surface $\boldsymbol{\gamma}$, at least in terms of eigenvectors, may be quiet similar. Blows et al. (2004), building upon the results of Krzanowski (1979), suggest an approach for comparing the major subspaces of $\mathbf{G}$ and $\boldsymbol{\gamma}$ (Chapter 32 reviewer Krzanowski's method).

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**Example 31.5.** Although some theory suggests that the orientations of $\mathbf{G}$ and the fitness surface $\boldsymbol{\gamma}$ may be similar, there is only one study we are aware of which attempted to compare them. A limiting factor is unbiased estimation of $\boldsymbol{\gamma}$, as correlated (but unmeasured) traits under selection result in a biased estimate. Hunt et al. (2007) used a system based on selection on male mating calls of Black field crickets (*Teleogryllus commodus*), which the authors defined by five traits. The power of this system is that acoustic components of the call can be artificially constructed and the attractiveness of these artificial calls can be assessed on wild females, allowing a fitness surface to be constructed free of the concern of unmeasured correlated fitness traits (Brooks et al. 2005, Bentsen et al. 2006). Previous studies by these authors found that these traits are under multivariate stabilizing selection and that populations reside near the peak on the fitness surface (Brooks et al. 2005). The association between nonlinear selection (measured by $\boldsymbol{\gamma}$) and the eigenstructure of $\mathbf{G}$ is shown in the table below, which gives the eigenvectors (or PCs) $\mathbf{g}_i$ of $\mathbf{G}$ and the amounts of selection and genetic variation associated with each. Using factor-analytic modeling (Chapter 32), there was statistical support for the first three eigenvectors of $\mathbf{G}$ (which account for 90% of the total genetic variance) and a good suggestion of support for a fourth PC. For completeness, all five eigenvectors are given:

| | $\mathbf{g}_{max}$ | $\mathbf{g}_2$ | $\mathbf{g}_3$ | $\mathbf{g}_4$ | $\mathbf{g}_5$ |
|---|---|---|---|---|---|
| % Variation | 51.0 | 25.6 | 12.9 | 6.9 | 3.6 |
| $\mathbf{g}_i^T\boldsymbol{\gamma}\mathbf{g}_1$ | 0.005 | -0.012 | -0.051 | -0.097 | -0.011 |
| $\mathbf{g}_i^T\boldsymbol{\Delta}\mathbf{G}\mathbf{g}_1$ | 0.00400 | -0.00283 | -0.00285 | -0.00212 | -0.00009 |
| % change in Genetic SD | 6.6 | -7.8 | -11.0 | -13.0 | -3.8 |

The strength of selection along the $i$th eignevector was estimated using $\mathbf{g}_i\boldsymbol{\gamma}\mathbf{g}_i$, with positive values indicating an positive curvature in the fitness surface that axis (disruptive selection), while a negative value indicates negative curvature (stabilizing selection). The key observation of Hunt et al. is that the amount of genetic variation along a particular direction decreases with the strength of stabilizing selection along that axis (genetic variation decreases, and the strength of stabilizing selection increases, as we move from $\mathbf{g}_2$ to $\mathbf{g}_4$). While the fifth (and final) PC shows a departure from this pattern, given there is no support for this PC, estimates associated with it must be viewed with some caution. Hunt et al. also measured the expected change in genetic variation from selection (using Equation 31.11a, $\boldsymbol{\Delta}\mathbf{G} = \mathbf{G}\boldsymbol{\gamma}\mathbf{G}$), with $\mathbf{g}_i\boldsymbol{\Delta}\mathbf{G}\mathbf{g}_i$ measuring the selected-induced change in genetic variation along the $i$th eigenvector. The observed pattern for these data is that the orientations corresponding to the strongest amounts of stabilizing selection have the lowest level of genetic variation.

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**Model Assumptions, Genetic Correlations, and Hidden Pleiotropy**

As we saw in Chapter 27, the theoretical framework for mutation-selection balance for a single trait is both extremely technical and very fragile. Very subtle differences in mutational models can lead to qualitatively different conclusions. As one might expect, moving to multivariate space only exacerbates these concerns. Again recall the two general approximations used for the locus-specific distribution of allele effects. Gaussian genetic models assume the distribution of allelic effects are each locus is approximately normal (or multivariate normal under pleiotropy), which requires the assumption that mutation is strong relative to selection at each locus. HOC approximations, on the other hand, assume that selection is strong relative to mutation, and thus the phenotypic variation associated with a new mutation exceeds the standing variation from alleles segregating at the time of the mutation. These two approximations result in fundamentally different behavior for equilibrium genetic variances under a multivariate mutation-selection balance.

Two types of correlations, phenotypic and genetic, enter into our discussion of multivariate models. Under Gaussian *fitness* models, selection on one trait reduces the phenotypic variance of any phenotypically-correlated traits (Equation 31.13a), which imparts selection on the second trait. Genetic correlations also influence selection response and can be generated by pleiotropic mutations. Under the gaussian genetic assumption, if there are no correlations among pleiotropic mutations and no phenotypic correlations in the selection function ($\mathbf{M}$ and $\mathbf{W}$ are diagonal), then the equilibrium amount of variation maintained at each trait is independent of selection at the others (Lande 1980, 1984; Turelli 1985). However, under the HC approximation if there is hidden pleiotropy, then selection on a trait can be significantly influenced by selection on uncorrelated (genetically and phenotypically) traits (Turelli 1985, 1988b; Wagner 1989; Slatkin and Frank 1990). With hidden pleiotropy, the equilibrium genetic variance that a trait can maintain is significantly reduced by selection on uncorrelated traits. If the results from the HOC approximation are a good reflection of the true biological reality, then selection from uncorrelated traits can significantly impact the long-term behavior of traits.

The key here is that uncorrelated only implies independence under a gaussian. Hidden pleiotropy can generate significant *associations*, all the while showing no genetic *correlation*. Indeed, the expected genetic correlation at equilibrium under either the Gaussian (Jones et al. 2007) or house of cards (Zhang and Hill 2003) assumption is approximately

$$\rho_A = \frac{1 + \rho_s\rho_m - \sqrt{1-\rho_s^2}\sqrt{1-\rho_m^2}}{\rho_s + \rho_m} \tag{31.49}$$

where $\rho$ is the correlation among pleiotropic mutational effects and $\rho_s$ the correlations among phenotypes in the fitness surface $\mathbf{W}$. Under both models, the equilibrium genetic correlation is zero when mutational and selective effects are uncorrelated ($\rho_m = \rho_s = 0$).

**The Stability of G**

Thus far, theoretical results on the stability of $\mathbf{G}$ have been a very mixed bag. On one hand, the infinitesimal models results are well-behavior, and are determined by parameters that one could imagine being able to measure under realistic scenarios. On the other, the allele-frequency change results suggest that genetic covariances are likely extremely liable. Over the long-term, mutation-selection equilibrium results are required, but these are extremely sensitive to subtle features of the assumed underlying genetics.

So, just what can be said about the expected stability of $\mathbf{G}$ in natural populations over evolutionary time? In part, this depends on the general nature of selection. Some traits, such as life-history components, may potentially experience continuous directional selection to improve, and we expect little genetic variance along the direction of selection. Evidence supporting this view is starting to appear (Blows et al. 2004, Hine et al. 2004, Van Homright

et al. 2007). However, for most traits the basic model envisioned by evolutionary biologists is stabilizing selection, with directional selection occurring when the population is moved off a (potentially local) optimal value (the **adaptive peak**). Such a displacement occurs when the environment (biotic or abiotic) shifts, moving populations away from an adaptive peak. Subsequent directional selection attempts to move the mean towards the new peak. In these settings, constancy of **G** requires several conditions. First, that the environmental change itself does not influence **G** directly (i.e., no genotype-environment interactions). This assumption is quite problematic, as there are numerous examples of genetic correlations differently substantially (even in sign) across environments (reviewed by Sgró and Hoffmann 2004). Second, it requires that the curvature (**W**) of the fitness surface remains unaltered by the environmental shift. Finally, the distribution of mutational effects **M** also remains constant. Even if all of these conditions hold, other factors can change the constancy of **G**, for example the effects of a major gene or gene frequency changes in general. Thus, while theory does not ensure a relatively constant **G**, it also has fairly little to say about instability in **G**, leading Turelli (1988a) to succinctly summary the theory by stating that no robust predictions are possible.

While *robust* predictions are lacking, computer simulations by Jones et al. (2003, 2004, 2007) point to some potential *trends* promoting **G** stability. It is important to stress that stability does not mean *stasis*. **G** does indeed change over time, the only issue is the time scale. Conditions promoting "stability" are those where the change is slow over time. The basic structure of the simulations by Jones et al. (2003, 2004) was to follow two traits controlled by a modest (50) number of unlinked loci, with finite population size, gaussian stabilizing selection, and mutation where the effects of new mutations are given from the continuum of alleles mode. Here a normal random random variable is added to the current value of an allele to obtain the effect of the new mutation and pleiotropy is accounted for by allowing correlations in these values between the two traits. Three measures to used to characterize **G**. Two are measures of eigenvalues: the total size of **G** (the sum of both eigenvalues) and its **eccentricity** (the ratio $\lambda_1/\lambda_2$ of its eigenvalues), namley how cigar-shaped is **G**. An eccentricity of one corresponds to a circular **G**, while its shape becomes more needle-like as the eccentricity increases. The third measure was the orientation $\theta$ of the leading eigenvector over time with respect to a fixed standard.

Strictly stabilizing selection was considered by Jones et al. (2003), while stabilizing selection with a constantly moving optimum was examined by Jones et al. (2004). The basic conclusions were that stability in size and eccentricity was largely determined by population size (drift) with stability increasing with $N_e$, while selection and mutation largely determined the stability of $\theta$ (the orientation). A number of conditions results in strong stability of the orientation over time. Correlations among new mutations (be they positive or negative) had a significant impact on increasing the stability of **G**. Correlation selection (non-zero diagonal elements in **W**) also promoted stability, as did asymmetric stabilizing selection, where the strength of selection differs considerably on the two traits. Finally, increasing the alignment between the selection matrix **W** and the mutational matrix **M** increases stability.

When considering a moving optimum (and hence constant directional selection), **G** stabilization was further increased when the optimum moved in roughly the same orientation as the major axis of **G** (i.e., along genetic lines of least resistance), but selection orthogonal to this direction decreases stability. They also found that directional selection tends to increase the genetic variance (increasing $\lambda_i$) , presumably reflecting new mutations being brought up to higher frequency by selection. Thus, under fairly wide conditions, we might expect some stability in the orientation of **G**, but not in its eigenvalues. Given these various conditions for stability, Jones correctly point out that some sets of traits are more likely to be more stable over time than others.

Jones et al. (2007) expanded upon their earlier simulations by allowing the mutational

matrix **M** itself to evolve. Specifically, they assumed that the correlation between mutational effects was itself a quantitative trait with variation and simply allowed it to change under drift and selection (via stabilizing selection on the traits of interest). They found that the mutational correlation did indeed evolve and exhibits a weak tendency to further align the **M** with the fitness surface **W**. However, the mutational correlation experiences disruptive selection with an intermediate unstable point, and can show very erratic fluctuations, especially when near zero. Overall, Jones et al. found that allowing the **M** matrix to evolve further increases the stability (i.e., the orientation) of the **G** matrix under most of the situations they simulated.

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