

Maintenance of Quantitative-Genetic Variation

Empirical studies of quantitative genetic variation have revealed robust patterns that are observed both across traits and across species. However, these patterns have no compelling explanation, and some of the observations even appear to be mutually incompatible. (Johnson and Barton 2005)

How wonderful that we have met with a paradox. Now we have some hope of making progress.
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Genetic variation is a ubiquitous feature of natural populations. The nature of the forces responsible for maintenance of this variation, be it the distribution of allele frequencies, the level of heterozygosity, the amount of additive variation in a trait, or the joint distribution of allele frequencies and their effects, have long been of concern to both population and quantitative geneticists. The basic explanation is some balance of forces: mutation/migration introducing new variation which is removed by drift and/or selection against deleterious alleles. Alternatively, selection by itself can maintain variation, such as heterozygote advantage. These various explanations are not mutually exclusive, and theorists have spent a great deal of effort building models to examine the plausibility of each scenario. If the required parameter space to maintain variation is very narrow, a particular mechanism may account for the maintenance of variation in specific cases, but not likely as a general feature.

Despite a wealth of different possible explanations for the maintenance of variation, this is an area of some frustration among quantitative geneticists. At present, there are difficulties in reconciling most (some would say all) explanations with estimates of observable parameters (such as strength of apparent stabilizing selection on a trait, its heritability, and the mutational variance). As this is a subject with a substantial body of complex theory, we present much of the derivational details in examples, allowing us to focus on the key results while still presenting the logic and assumptions behind the models. Reviews of the struggle to explain quantitative genetic variation can be found in Turelli (1984, 1986, 1988), Nagylaki (1984), Bulmer (1989), Barton and Turelli (1989), Bürger (1998, 2000), Barton and Keightley (2002), Johnson and Barton (2005), Zhang and Hill (2005b, 2010), and Mitchell-Olds et al. (2007). Bürger (2000) is the standard reference for much of the theory developed here, and should be consulted by the more mathematically-inclined reader.

OVERVIEW: THE MAINTENANCE OF VARIATION

Earlier chapters explored the roles of the major evolutionary forces (drift, mutation, selection) and important modifiers (recombination and migration) in the maintenance of polymorphisms at individual loci. The effects of drift (removing variation) and mutation (generating variation) are straightforward (Chapter 2), while the effects of selection are more complicated, either retaining or removing variation, depending on its nature (Chapter 5). With constant selection coefficients, overdominance (heterozygote advantage) retains varia-

tion, while all other constant-fitness schemes remove it. Selection can retain variation under a variety of circumstances when fitnesses varies, which we loosely lump together under the umbrella of **balancing selection**. These include frequency-dependent selection when rare alleles are favored, tradeoffs among different fitness components, sex-specific differences, or fitness changes over time and/or space ($G \times E$). The conditions to maintain variation can be rather delicate for many of these strictly-selective explanations. The result of interactions between evolutionary forces can be straightforward, such as the mutation-drift equilibrium (Equation 2.24) or mutation-selection balance for deleterious alleles (Equation 7.6). Their outcome can also be subtle and counterintuitive, e.g., the joint impact of selection, mutation, drift and recombination on the levels of variation under selective sweeps (Chapter 8). Our goal in this chapter is build on these results in an attempt to explain the nature of the evolutionary forces maintaining quantitative traits variation in nature.

Maintaining Variation at Quantitative Traits

Most of our previous results were for population-genetic models, where the focus was solely on allele *frequencies*, and usually quantified by summary statistics such as the heterozygosity or the number of segregating alleles (Chapter 2). In this setting, the most complete equilibrium solution is given by the distribution of allele frequencies, such as Wright's result for a diallelic locus under mutation-selection-drift (Equation 7.31) or the Watterson distribution for the site-frequency spectrum for mutation-drift balance under an infinite sites model (Equation 2.34). For quantitative traits, the allele frequency distribution, by itself, is not sufficient to describe the equilibrium variation. Instead, one needs the full *joint* distribution of allele frequencies and their *effect sizes*, although we typically work with additive-genetic variance as an appropriate summary statistic. Given the number of scenarios outlined above, it should not be surprising that a plethora of models have been proposed for the maintenance of genetic variation in quantitative traits. Figure 27.1 attempts to bring a little structure to this vast zoo.

The simplest models are fully neutral: the trait, and its underlying loci, have no effects on fitness, leading to **mutation-drift models** (Chapters 11, 12). Their problem is that they generate too much variation if the population size is modest to large. The most obvious correction is that there is some selection on the trait and/or on the underlying loci independent of the trait. Models incorporating selection can be broken into two categories: those with at least some **direct selection** on the focal trait and **pleiotropy models** assuming a neutral focal trait whose underlying loci have pleiotropic effects on fitness.

A central issue with direct selection models is that stabilizing selection usually generates underdominance in fitness, removing variation (Example 5.6). Hence, **strict stabilizing selection**, by itself, cannot account for quantitative-trait variance. This removal of variation could be countered by either mutation (**mutation-stabilizing selection**) or by selectively-favored pleiotropic fitness effects. Under the latter scenario, loci underlying the trait under stabilizing selection are under balancing selection for some other independent component of fitness (**balancing-stabilizing selection**). The issue with mutation-selection balance is that the estimated strengths of stabilizing selection and polygenic variation appear to be inconsistent with observed levels of heritability.

Pleiotropic models have also been proposed for a neutral, as opposed to selected, trait. These models generate **apparent** (or **spurious**) **stabilizing selection** on the neutral trait, returning a signature of stabilizing selection in a quadratic regression of fitness on phenotype (Chapters 28, 29). This offers the possibility that some (or perhaps much) of observed stabilizing selection in nature is not real, but rather actually due to pleiotropic fitness effects. Variation at the underlying loci is assumed to be maintained by either overdominant effects

on fitness (**pleiotropic overdominance**) or because the underlying loci are deleterious, but in mutation-selection equilibrium (**pleiotropic deleterious mutation-selection balance**). The problem with pleiotropy models is that the strength of selection on the underlying loci required to recover the observed strength of apparent stabilizing selection seen in nature is usually inconsistent with some other observable feature of the model (such as expected selection response). Various combinations of elements of these basic models have also been proposed, as have refinements adding additional forces (such as drift), but most give inconsistent results when trying to simultaneously account for observed amounts of selection and variation. One potential exception are **joint effects** models that allow for stabilizing selection on a trait whose underlying loci also experience deleterious pleiotropic fitness effects for other components of fitness.

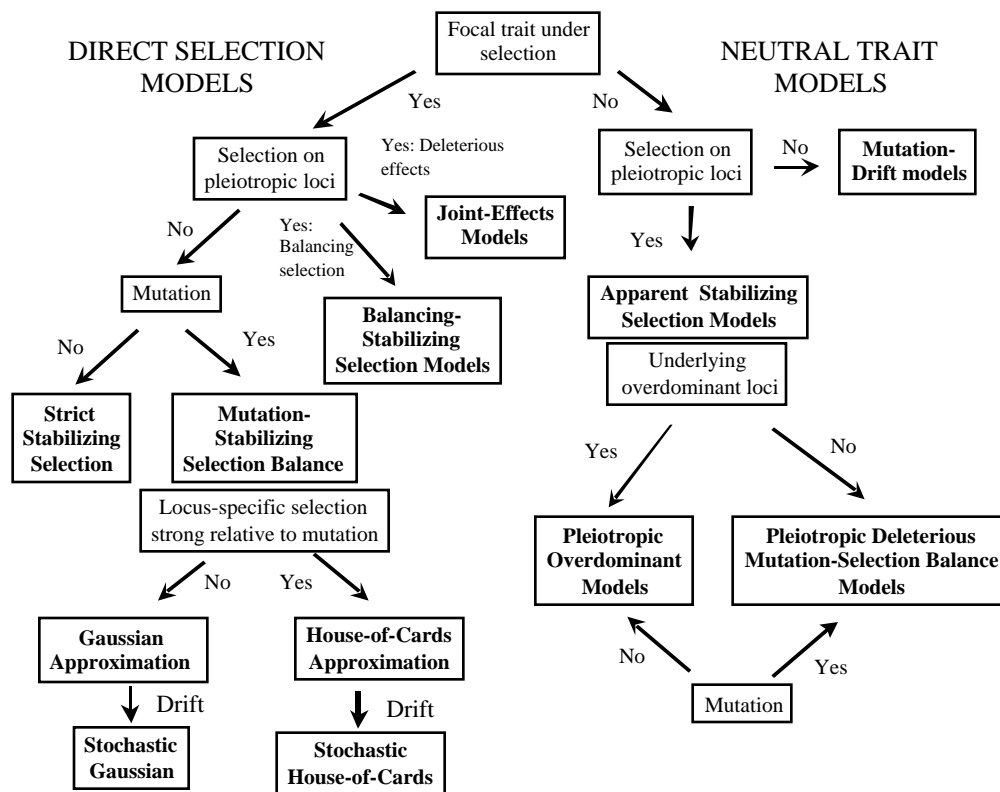


Figure 27.1. Flow chart of the various classes of theoretical models for the maintenance of quantitative-genetic variance. Roughly speaking, there are **direct-effect models** that assume selection is acting on the phenotype of the focal trait (whose variation is trying to be explained) and models that assume this trait is neutral. **Pleiotropic models** assume that loci underlying a trait have fitness effects independent of the focal trait, either because of stabilizing selection on other traits or through unspecified effects on fitness. Models also vary in the importance of mutation in countering the removal of genetic variation by selection and/or drift.

Finally, differences in the assumed *granularity* of the underlying genetic architecture

can significantly impact results. If a few loci, each with a few alleles, underlie a trait, the resulting genotypic values have a fairly granular distribution. The dynamics under stabilizing selection are different when one of these genotypic values matches the optimal stabilizing selection value versus when none do. Likewise, with just a few alleles at a few loci, the opportunity for independent selection on many traits, or other pleiotropic fitness components, is constrained. Conversely, under continuum-of-alleles models, with their large number of alleles at each locus, there is a distribution of allelic effects and the potential for significantly more fine-tuning. A key point of this chapter is that the relative strengths of the underlying evolutionary forces dictates which architecture is more appropriate. If drift is strong relative to the other forces, at most only a few alleles at a locus are likely (besides a constellation of very rare new mutations). The same is true when selection is strong relative to mutation. As we will see, differences in the relative strengths of mutation to selection at a locus leads to qualitatively different results.

The (often fairly technical) analysis of the the large number of models given in Figure 27.1 comprises this bulk of the chapter. There are several possible schemes by which to organize and discuss these. Our presentation is centered around increasing the complexity of evolutionary forces and their interactions. We start with drift interacting with neutral mutation, which serves as a useful baseline. We then consider models invoking only selection, either stabilizing selection on the focal trait and/or loci under balancing selection with pleiotropic effects of the focal trait. These provide the background for the major classes of models, those involving *both* selection and mutation. Much of this discussion is on stabilizing selection countered by mutation, including the incorporation of drift. We conclude with models in which a large fraction of the trait variance is assumed to be from pleiotropic effects of deleterious alleles, maintained by mutation-selection balance. Models where the focal trait is neutral are examined first, followed by joint-effects models allowing for both stabilizing selection on a focal trait and pleiotropic contributions from deleterious alleles. To aid the more casual reader, Table 27.3 summarizes the major inconsistencies for each model, followed by an examination of the current data. This allows the more technical discussions below to be bypassed and yet still obtain a general overview of the problem. The conclusion from this extensive analysis is that all of the models have significant inconsistencies with current estimates of strength of selection, mutational inputs, and amounts of standing genetic variation. The typical pattern seen is that for a model to accommodate one aspect (e.g., the observed strength of stabilizing selection), the required parameter values result in another aspect (say amount of standing variation) being inconsistent with observed values.

MUTATION-DRIFT EQUILIBRIUM

The most basic model for the maintenance of variation considers two universal (and counterbalancing) forces, drift and mutation. Chapter 2 examined the distribution of neutral allele frequencies and various resulting summary statistics under mutation-drift balance. At equilibrium, neutral allele frequencies are given by the Watterson distribution (Equation 2.34), and the expected heterozygosity (for an infinite-alleles model) is $\tilde{H} = \theta/(1 + \theta)$, where $\theta = 4N_e\mu$ is the product of population size times mutation rate. The problem with this expression, as noted by Lewontin (1974), is that heterozygosity should quickly approach one in large populations ($\theta \gg 1$), and this is not seen. One possible explanation is that mutation rate inversely scales with population size (Chapter 4). Another is that selection at linked sites can significantly depresses variation (Chapters 3, 8, 10). The impact of recurrent sweeps is greatest in very large asexual populations, which otherwise would be predicted to have

very high values of \tilde{H} .

Mutational Models and Quantitative Variation

Chapters 11 and 12 developed the quantitative-genetic analog to \tilde{H} by considering the expected additive variance $\tilde{\sigma}_A^2$ maintained by neutral alleles in mutation-drift equilibrium. Two extensions are required when moving from allelic frequencies to quantitative-trait variation. The first is that the **mutational variance** σ_m^2 replaces the mutation rate μ (Chapter 11). The mutational variance contributed by locus i is given by $2\mu_i\sigma_{m_i}^2$, the product of its mutation rate and **variance of mutational effects**. For the latter, we use $\sigma_{m_i}^2$ to denote a specific locus and $\sigma_{m_*}^2$ for an unspecified one. For example, with n equivalent loci, $\sigma_m^2 = 2n\mu\sigma_{m_*}^2$, while $\sigma_m^2 = 2\sum_i \mu_i\sigma_{m_i}^2$ when mutational effects vary over loci.

As reviewed in LW Chapter 12, the mutational variance can be estimated from the accumulation of additive variance in an inbred line. Estimates are usually scaled by the environmental variance to give the mutational heritability, $h_m^2 = \sigma_m^2/\sigma_E^2$, and a typical value is $h_m^2 = 10^{-3}$ (LW Table 12.1). Estimates of the component features of the mutational variance — the number of loci n , the per-locus mutation rate μ , and the variance of mutational effects $\sigma_{m_*}^2$ — are far more difficult to obtain. This is unfortunate, as the values of these components, rather than their composite measure σ_m^2 , are required for many of the following models. Some crude estimates follow from the widespread observation that h_m^2 is typically on the order of 10^{-3} . If $\sigma_{m_*}^2/\sigma_E^2 = 1$, then the total trait mutation rate $2n\mu$ is on the order of 10^{-3} . For $n = 100$ loci, this implies a per-locus mutation rate (to new trait alleles) of $\mu = 5 \times 10^{-6}$. If the scaled mutational variance is lower, then either the number of loci and/or the per-locus mutation rate must be correspondingly higher. Lyman et al. (1996) estimated $\sigma_{m_*}^2/\sigma_E^2 \simeq 0.1$ for P -factor induced mutations in *Drosophila* bristle number. For $h_m^2 = 10^{-3}$, this implies $2n\mu = 0.01$, requiring a ten-fold higher number of loci, or rate of mutation.

The second extension required is some assumption relating the current effect of an allele x with its effect x' after mutation (Table 27.1). The most widely-used is the **incremental model** (also referred to as the **Brownian-motion** or **random-walk** model). Initially introduced by Clayton and Robertson (1955), and more formally by Crow and Kimura (1964) and Kimura (1965), this model assumes that $x' = x + m$, the pre-mutation value plus a random increment where $m \sim (0, \sigma_{m_*}^2)$. Equation 11.19 gives the mutation-drift equilibrium additive variance under this model as $\tilde{\sigma}_A^2 = 2N_e\sigma_m^2$ when all mutations are additive, while Equations 11.21a,b give expressions for the genetic variances when dominance occurs. Equations 11.21a,b. From Equation 11.20a, expected equilibrium heritability is

$$\tilde{h}^2 = \frac{2N_e h_m^2}{1 + 2N_e h_m^2} = 1 - \frac{1}{1 + 2N_e h_m^2} \quad (27.1)$$

Note the connection with \tilde{H} , as both are of the form $2N_e x/(1 + 2N_e x)$, with $x = h_m^2$ for heritability and $x = 2\mu$ for heterozygosity. As with \tilde{H} , even modest values of N_e (~ 1000) give values over 0.5, while larger values give heritabilities close to one. For example, when $h_m^2 = 0.001$, N_e is constrained to be in the range of 50 – 1200 in order to recover typical heritability values (0.1 to 0.6).

The incremental mutational model represents one extreme where the value of the new mutation is closely tied to the evolution history (x) of its parental allele. The other extreme is the **house-of-cards (HOC)** model formally developed by Kingman (1977, 1978; although it was also assumed by Wright 1948, 1969). Under HOC, $x' = m$, independent of its starting value x , where again $m \sim (0, \sigma_{m_*}^2)$, so that past evolutionary history is completely irrelevant.

The incremental and HOC models present two extremes, one strongly influenced by

Table 27.1. Models for the effect of a new mutation on a quantitative trait. All make the infinite-alleles assumption that each new mutation creates a new allele. The effect x' of this new allele is a function of its current value x and a random variable $m \sim (0, \sigma_{m*}^2)$. The incremental and HOC models are special cases of the Zeng-Cockerham regression model, corresponding to $\tau = 1$ and $\tau = 0$, respectively. Derivations can be found in Chapter 11 or in Zeng and Cockerham (1993).

Model	New Effect	$\tilde{\sigma}_A^2$	$\tilde{\sigma}_A^2$ as $N_e \rightarrow \infty$
Incremental, Random-walk, Brownian Motion	$x' = x + m$	$4N_e\mu n\sigma_{m*}^2 = 2N_e\sigma_m^2$	Unbounded
House-of-Cards	$x' = m$	$\frac{8N_e\mu n\sigma_{m*}^2}{1 + 4N_e\mu n} = \frac{4N_e\sigma_m^2}{1 + 4N_e\mu n}$	$2\sigma_{m*}^2 = \frac{\sigma_m^2}{\mu n}$
Regression	$x' = \tau x + m$	$\frac{8N_e\mu n\sigma_{m*}^2}{(1 + \tau)[1 + 4N_e\mu n(1 - \tau)]}$ $= \frac{4N_e\sigma_m^2/(1 + \tau)}{1 + 4N_e\mu n(1 - \tau)}$	$\frac{2\sigma_{m*}^2}{1 - \tau^2} = \frac{\sigma_m^2}{\mu n(1 - \tau^2)}$

evolutionary history, the other completely indifferent to it. Zeng and Cockerham (1993) proposed the more general **regression model**, $x' = \tau x + m$, where $0 \leq \tau \leq 1$ and $m \sim (0, \sigma_{m*}^2)$ (Table 27.1). The regression coefficient τ gives the importance of past evolutionary history, recovering the incremental ($\tau = 1$) and HOC ($\tau = 0$) as special cases. This model is an Ornstein-Uhlenbeck process (Equation A1.33), as $E[\Delta x] = E[x' - x] = -(1 - \tau)x$. This counters the effects of Brownian motion (the incremental random m) by a restoring force towards the origin, producing a bounded equilibrium distribution (for $\tau < 1$). Under the regression model (provided $\tau \neq 1$), the equilibrium additive variance in a large population is bounded by $\sigma_m^2/[\mu n(1 - \tau^2)]$, with a resulting heritability of

$$\tilde{h}^2 = \frac{\sigma_m^2/[\mu n(1 - \tau^2)]}{\sigma_m^2/[\mu n(1 - \tau^2)] + \sigma_E^2} = 1 - \frac{1}{K + 1} \quad (27.2a)$$

where

$$K = \frac{h_m^2}{\mu n(1 - \tau^2)} = \frac{2\mu n\sigma_{m*}^2/\sigma_E^2}{\mu n(1 - \tau^2)} = \frac{2\sigma_{m*}^2/\sigma_E^2}{1 - \tau^2} \quad (27.2b)$$

Figure 27.2 plots this as a function of τ and $h_m^2/(2n\mu) = \sigma_{m*}^2/\sigma_E^2$ (the scaled variance of mutational effects). Expected heritability increases as the role of past evolutionary history of an allele becomes increasingly more important in predicting its mutated value (i.e., \tilde{h}^2 increases with τ). Likewise, \tilde{h}^2 increases with the variance of mutational effects σ_{m*}^2 . Assuming a typical value of $h_m^2 = 0.001$, an underlying total mutation rate of $2n\mu = 10^{-3}$ ($\sigma_{m*}^2 = \sigma_E^2$) and a value of $\tau = 0.5$ gives $K = 1$ and $\tilde{h}^2 = 0.67$. This decreases to 0.5 as we approach the HOC model ($\tau = 0$) and increases to one as we approach the incremental model ($\tau = 1$). Assuming that $h_m^2 = 0.001$ is a standard value for many traits, for this model requires a fairly high total mutation rate ($2n\mu \gg h_m^2 \sim 0.001$), otherwise the predicted heritabilities are too large. As with the incremental model, Equation 27.2 ignores the impact of deleterious mutations, and thus gives an upper limit on the equilibrium heritability.

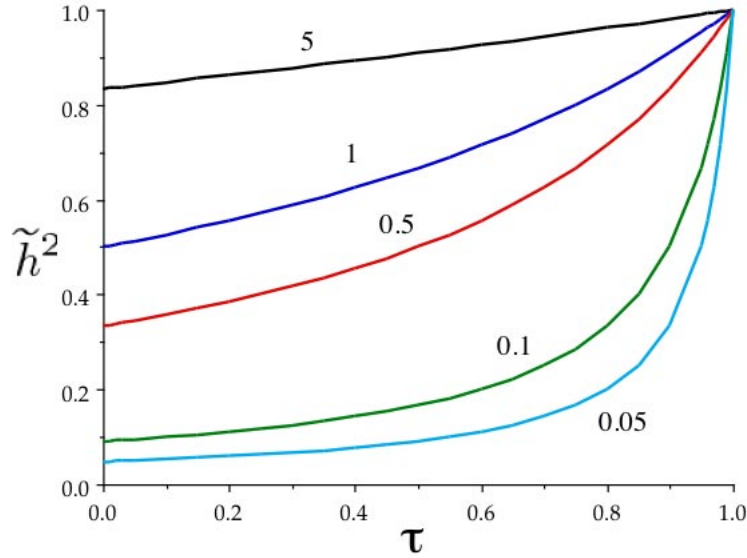


Figure 27.2. Expected heritability at mutation-drift equilibrium under the mutational regression model for mutation of Zeng and Cockerham (Equation 27.2), which includes the incremental ($\tau = 1$) and HOC ($\tau = 0$) models as special cases. Curves correspond to values of $h_m^2 / (2n\mu) = \sigma_{m*}^2 / \sigma_E^2$, the ratio of the mutational heritability to the total mutation rate, which equals the variance of mutational effects scaled in σ_E^2 units.

MAINTENANCE OF VARIATION BY DIRECT SELECTION

As shown in Figure 27.1, a number of models for the maintenance of variation assume stabilizing selection on the focal trait. We start by examining stabilizing selection *per se* on both one and n traits. The conclusion is that only very limited variation can be maintained in such settings, especially if a large number of genes, each of modest to small effect, underlie the trait. One potential selective countering force would be if trait loci have overdominant pleiotropic effects on fitness, and this is discussed next. Such overdominance can arise is when there is strict stabilizing selection on a trait, but homozygotes have a higher environmental variance than heterozygotes. It can also be generated when underlying loci show $G \times E$ in the trait under selection, and we examine both of these. Finally, the impact of a changing optimal value, and when the trait itself is under frequency-dependent selection, are also examined to see if these can help retain variation. As we detail, all of these models fall short in their attempt to account for observed levels of variation.

Fitness Models of Stabilizing Selection

Two standard fitness models of phenotypic (trait value z) stabilizing selection are used in the literature, Wright's (1935a,b) quadratic optimal model

$$w(z) = 1 - s(z - \theta)^2 \quad (27.3a)$$

and the Gaussian (or non-optimal) model of Haldane (1954; also Weldon 1895),

$$w(z) = \exp\left(\frac{-(z - \theta)^2}{2\omega^2}\right) \quad (27.3b)$$

Recalling that $e^{-x} \simeq 1 - x$ for $|x| \ll 1$, the Gaussian reduces to the quadratic model under weak selection ($\omega^2 \gg 1$), as

$$w(z) \simeq 1 - \frac{(z - \theta)^2}{2\omega^2} \quad (27.3c)$$

As a result, these two models are used somewhat interchangeably, with $s \simeq 1/(2\omega^2)$. This is quite reasonable under the assumption of weak selection, but inappropriate under strong selection. While the Gaussian fitness function imposes no restrictions on the strength of stabilizing selection, the quadratic model does (to ensure that fitnesses are not negative), which results in the two models showing very different behavior for loci under strong selection (Gimelfrab 1996b), see Chapter 5.

Discussions on the maintenance of variation often involve the mean fitness generated by a particular strength of selection. Under the quadratic model, this is a function of the mean and variance of z . If $z \sim (\bar{z}, \sigma^2)$, then

$$\bar{w}(z) = E[w(z)] = 1 - s(E[z^2] - 2\theta E[z] + \theta^2) = 1 - s(\bar{z} - \theta)^2 - s\sigma^2 \quad (27.3d)$$

For Gaussian selection, we assume that z is normal with $z \sim N(\bar{z}, \sigma^2)$. Following Kimura and Crow (1978),

$$\begin{aligned} \bar{w} &= \frac{1}{\sqrt{2\pi\sigma^2}} \int \exp\left(\frac{-(z - \bar{z})^2}{2\sigma^2}\right) \exp\left(\frac{-(z - \theta)^2}{2\omega^2}\right) dz \\ &= \sqrt{\frac{\omega^2}{\omega^2 + \sigma^2}} \exp\left(\frac{-(\bar{z} - \theta)^2}{2(\omega^2 + \sigma^2)}\right) \end{aligned} \quad (27.3e)$$

Equations 27.3d,e are special cases of our previous Equations 17.7b and 17.8. An important application of Equation 27.3e is the expected fitness associated with genotypic value G . Assuming environmental effects are normally distributed about G , $z|G \sim N(G, \sigma_E^2)$, the resulting strength of stabilizing selection on G is

$$V_s = \omega^2 + \sigma_E^2 \quad (27.3f)$$

Larger V_s corresponds to weaker selection, so that (as expected), variation in phenotype about a genotypic value weakens the strength of selection. V_s is a central parameter in the maintenance of variation literature, and is usually scaled in units of σ_E^2 , with $V_s = \omega^2/\sigma_E^2 + 1 \simeq \omega^2/\sigma_E^2$ under weak selection ($\omega^2 \gg \sigma_E^2$).

Assuming the fitness function is given by Equation 27.3b, Equation 16.18a gives the phenotypic variance $\sigma_{z_s}^2$ following selection as

$$\sigma_z^2 - \sigma_{z_s}^2 = \frac{\sigma_z^4}{\sigma_z^2 + \omega^2} \quad (27.3g)$$

When $\omega^2 \gg \sigma_z^2$ (weak selection), then $\sigma_z^2 + \omega^2 \simeq \sigma_E^2 + \omega^2 = V_s$, and this rearranges to give an estimate of the strength of stabilizing selection as

$$\hat{V}_s \simeq \frac{\sigma_z^4}{\sigma_z^2 - \sigma_{z_s}^2} \quad (27.3h)$$

This is a biased estimate in the presence of directional selection, which also reduces the phenotypic variance following selection (Chapter 28). Less biased estimates can be obtained from the quadratic term in the Pearson-Lande-Arnold fitness regression (Equation 28.26),

$$w = 1 + \beta(z - \mu_z) + \frac{\gamma}{2} \left((z - \mu_z)^2 - \sigma_z^2 \right) + e$$

which adjusts for the reduction in variance from directional selection. Matching terms with Equation 27.3c, $\gamma = -1/\omega^2$ (Keightley and Hill 1990). Under weak selection, $V_s = \omega^2 + \sigma_E^2 \simeq \omega^2$, giving an estimate of V_s as $\simeq -1/\gamma$.

Turelli (1984) suggests a typical value of $V_s/\sigma_E^2 \simeq 20$, which corresponds to $V_s/\sigma_A^2 \simeq 20$ when $h^2 = 0.5$. Under this strength of stabilizing selection ($V_s \simeq 10\sigma_z^2$), a phenotype two standard deviations from the mean has around 80% of the fitness at the optimum. While Turelli's values are widely used in the maintenance of variation literature, more recent estimates (Kingsolver et al. 2001; summarized in Figure 29.5) are less clear. On one hand, the average value among traits experiencing stabilizing selection (those with estimated negative γ values) is stronger than Turelli's figure, with $V_s \simeq 5\sigma_z^2$ ($\simeq 10\sigma_E^2$ when $h^2 \simeq 0.5$). Under this strength of selection, a phenotype two standard deviations from the mean has around 70% of the optimal fitness. On the other hand, Figure 29.5 shows that the distribution of estimated γ values from natural populations is largely symmetric about zero, implying that disruptive selection is as common as stabilizing selection. Although these results are colored by lack of information on the statistical significance of many of these values, they still raise the possibility that a typical trait maybe under much weaker, or even nonexistent, stabilizing selection. Conversely, the long-term stasis of many traits over evolutionary time suggests that stabilizing selection is indeed a major force shaping evolution (Charlesworth et al. 1982; Maynard Smith 1983; Estes and Arnold 2007). Haller and Hendry (2013) also discuss a variety of reasons that might make real stabilizing selection more difficult to detect.

An even larger issue, framing much of the discussion on maintenance of variance, is whether an observed amount of stabilizing selection on a trait is **real** or **apparent**. As we saw in Chapter 20 (and discuss extensively in Chapter 29), selection acting on a hidden feature connected to the trait of interest will impart a signature of selection. Direct selection models assume real selection on the focal trait. Their problem is that reasonable assumptions about the components of σ_m^2 predict heritabilities that are too small given observed values of V_s . Conversely, pleiotropic models that can account for observed levels of heritabilities predict much larger apparent values of V_s (weaker selection) than are typically seen.

Stabilizing Selection on a Single Trait

Chapter 5 examined population-genetic models for alleles under strict selection (no mutation or drift), finding that while heterozygote advantage can stability maintain both alleles at a diallelic locus, most forms of selection tend to remove variation. A critical result, widely used throughout this chapter, is Example 5.6 on the nature of selection on a diallelic locus underlying an trait experiencing stabilizing selection. While at first glance, one might imagine this locus would experience something akin to selective overdominance (the maintenance of variation), in fact it actually experiences selective *underdominance*.

While Fisher (1930) was the first to suggest that stabilizing selection will remove, rather than retain, variation, the initial formal demonstration is due to Wright (1935a,b) and Robertson (1956), and a vast literature has since followed. Assuming Gaussian stabilizing selection, if the genotypes $q_i q_i$, $Q_i q_i$, and $Q_i Q_i$ at locus i have effects $-a_i$, 0, and a_i , then the dynamics for frequency p_i of allele Q_i are given by

$$\Delta p_i \simeq \frac{a_i}{V_s} \left(\frac{p_i(1-p_i)}{2} \right) [a_i(2p_i - 1) + 2(\theta - \bar{z})] \quad (27.4a)$$

See Example 5.6 for a derivation. A useful way to understand the dynamics is to express them in the form of a weakly-selected additive allele (Equation 5.2) $\Delta p = s_i p_i(1-p_i)$, where the selection coefficient becomes

$$s_i = \frac{a_i}{2V_s} [a_i(2p_i - 1) + 2(\theta - \bar{z})] \quad (27.4b)$$

The first term in the square brackets represents stabilizing selection to reduce the variance generated by this locus, while the second is the impact from direction selection. When $|\theta - \bar{z}| > a_i/2$, directional selection determines the dynamics. When this second term is negligible, selective underdominance occurs, as $\Delta p_i < 0$ for $p_i < 1/2$ and $\Delta p_i > 0$ for $p_i > 1/2$ (with $p = 1/2$ an unstable equilibrium point). The initial selection coefficient on a new allele ($p_i \simeq 0$) is

$$s_i \simeq -\frac{a_i^2}{2V_s} \quad (27.4c)$$

as found by Latter (1970), Kimura (1981), Bürger et al. (1989) and Houle (1989).

This is the crux of the problem with stabilizing selection *per se*, it drives allele frequencies towards fixation, removing, rather than retaining, variation at underlying loci (Robertson 1956). Additional analysis of single-locus models (ignoring linkage disequilibrium) found that partial dominance (Kojima 1959; Lewontin 1964; Jain and Allard 1965; Singh and Lewontin 1966; Bulmer 1971) and/or unequal additive effects (Gale and Kearsley 1968; Kearsley and Gale 1968) can result in several polymorphic loci at equilibrium, although the parameter space for this to happen is extremely narrow for unlinked loci.

Two- and multiple-locus models (LD considered) again reach the conclusion that selection removes variation for additive loci of equal effect. However, when selection is strong relative to recombination, multiple-locus polymorphisms can be maintained by stabilizing selection on a single trait when loci have unequal effects, or when dominance or epistasis is present in the trait under selection (Nagylaki 1989; Zhivotovsky and Gavrilets 1992; Gavrilets and Hastings 1993, 1994a, 1994b; Gimelfarb 1989, 1996b). Example 5.11 details Bürger and Gimelfarb's (1999) analysis of the general two-locus model under quadratic selection, while Willensdorfer and Bürger (2003) present a similar analysis under Gaussian selection. Conditions under which stabilizing selection on a single trait can maintain polymorphism at multiple loci are fairly stringent and generally result in high negative levels of disequilibrium, and hence small additive variances (Gimelfarb 1989; Zhivotovsky and Gavrilets 1992). Further, the genetic variance that can be maintained under such models generally decreases very rapidly with the number of loci, reflecting diminished selection coefficients on individual loci (Bürger and Gimelfarb 1999). One subtle issue is the granularity of these models, in that if no genotype exists whose value equals the optimal value under stabilizing selection, then small amounts of directional selection can be present ($|\theta - \bar{z}| > 0$) and multilocus polymorphism (often with alleles at extreme values, and hence contributing little variation) can be maintained (Barton 1986).

Given that most traits seem to be controlled by a moderate to large number of loci of moderate to small effect (Chapter 24), strong selection on *individual loci* (distinct from strong selection on the *trait*) is generally unlikely. Thus, the weak selection results suggest that, at best, only very modest amounts of additive variation are maintained by single-trait stabilizing selection in the absence of other forces.

Stabilizing Selection on Multiple Traits

The assumption that a gene only influences a single trait is biologically rather unrealistic, implying that *the amount of standing variation at a given locus likely reflects the action of multiple targets of selection*. One model of such pleiotropic fitness effects is to assume that a locus influences n independent traits under stabilizing selection. When selection on individual loci is weak relative to recombination, Hasting and Hom (1989) show that at most k loci are polymorphic when k independent traits are under selection. Hence, under weak selection, the addition of pleiotropic stabilizing selection does little to increase the amount of standing additive variation. The effect of strong selection was examined by Gimelfarb

(1986, 1992, 1996a) and Hasting and Hom (1990). Gimelfarb (1986) constructed a model with independent selection on two phenotypically uncorrelated traits (z_1, z_2), determined by two additive loci with effects A $z_1 = z_2 = 0$, a $z_1 = z_2 = 1$, and B $z_1 = 0, z_2 = 1$, b $z_1 = 1, z_2 = 0$. Under this model there is pleiotropy but no genetic correlation between traits at equilibrium. Both loci are polymorphic at equilibrium, yet the traits are phenotypically and genetically uncorrelated, and selection occurs independently on each. The result, in the words of Gimelfarb, is that “even if the investigator will be lucky enough to come across character z_2 , he is almost certain to discard it as having no biological connection with the character z_1 .” This is certainly a worrisome feature of this model, and foreshadows additional complications from pleiotropy discussed below. While multi-trait stabilizing selection can maintain variation at a number of loci, with selection strong relative to recombination there is significant negative disequilibrium and often little additive variance (Gimelfarb 1992).

Barton (1990) raises several key points on the limitations of multiple-trait stabilizing selection. First, simple genetic load arguments (the decrease in population fitness relative to the fittest possible genotype) place upper limits on the number of independently-selected traits. Assume k traits, each under Gaussian selection with a common value of V_s . Equation 27.3e implies that genetic variation reduces fitness by $\sqrt{V_s/(V_s + \sigma_G^2)}$ for each trait. For $V_s \gg \sigma_G^2$ (weak selection), a Taylor series argument shows this is $\simeq \exp(-\sigma_G^2/[2V_s])$. Assuming multiplicative fitnesses across the k independently-selected traits gives the load as $\simeq \exp(-k \sigma_G^2/[2V_s])$. For $V_s = 20\sigma_G^2$, the mean fitness is around 8% of the highest fitness with $k = 100$ traits. For weaker selection, $V_s = 100\sigma_G^2$, this load occurs for $k = 500$, while $k = 25$ for stronger selection ($V_s = 5\sigma_G^2$). Hence, one quickly approaches an upper limit on the number of traits before the fitness load becomes unbearable. As discussed in Chapter 7, such load agreements can be delicate, because departures from the assumed multiplicative fitness model can either lessen (synergistic epistasis) or enhance (diminishing-returns epistasis) the impact on the load. However, the point is still made that selection itself places a limit on the number of independent traits. Further, there are also limits on the number of alleles at a given locus, again constraining the ability of evolve in an unlimited number of directions in phenotypic space.

Barton suggests there may be a modest number of phenotypic dimensions that experience significant real stabilizing selection, which results in apparent stabilizing selection on any trait phenotypically correlated to one, or more, of these dimensions (Example 27.1). Further, we have shown that stabilizing selection *per se*, be it on a single or multiple traits, is unlikely to account for significant additive variance. Coupling these points suggest that stabilizing selection, by itself, is unlikely to explain more than a trivial amount of the genetic variance for a trait that appears to be under stabilizing selection, and that additional factors (such as mutation and pleiotropy) are critical. As succinctly stated by Barton “heritable variation in any one trait is maintained as a side effect of polymorphism which having nothing to do with selection on that trait”, an idea we explore more fully in the rest of this chapter.

Example 27.1. As illustrated in Chapter 20, traits may show signs of directional selection (a covariance between trait value and fitness) without being the actual target of selection. The same is true for stabilizing selection, which appears as a negative covariance between the squared trait value and fitness (Chapters 28, 29). Wagner (1996) emphasizes this point by considering two genetically uncorrelated traits, z_1 and z_2 , that are phenotypically correlated through some shared environmental effect. Trait z_1 is neutral (its trait value has no effect

on fitness), while trait z_2 is under Gaussian stabilizing selection with strength ω_2^2 . If ρ_z is the phenotypic correlation between the two traits, Wagner shows that the fitness of z_1 is given by

$$w(z_1) = \exp \left(-\frac{z_1^2 \rho_z \sigma_{z_2}^2}{2\sigma_{z_1}^2 [\omega_2^2 + \sigma_{z_2}^2 (1 - \rho_z^2)]} \right) \quad (27.5a)$$

Matching terms with Equation 27.3b shows that z_1 experiences apparent stabilizing (Gaussian) selection with strength

$$\omega_1^2 = \frac{\sigma_{z_1}^2 [\omega_2^2 + \sigma_{z_2}^2 (1 - \rho_z^2)]}{\rho_z \sigma_{z_2}^2} \quad (27.5b)$$

Note that $\omega_1^2 \rightarrow \infty$ (no selection) as $|\rho| \rightarrow 0$. Scaling both traits to give each an environmental variance of one, Wagner finds a lower bound of

$$\omega_1^2 \geq 2\omega_2^2 (\sigma_{G_1}^2 + 1)^2 \quad (27.5c)$$

where $\sigma_{G_1}^2$ is the (scaled) genetic variance of trait one. This sets an upper limit on the strength of apparent stabilizing selection (smaller ω_1^2 equals stronger selection), which weakens as the fraction of genetic variance in trait one increases. This is not surprising, as the apparent selection arises through the environmental component, which is decreased by increasing the genetic contribution. What is surprising is that the joint fitness for the genotypic values g_1, g_2 for both traits is

$$w(g_1, g_2) = \exp \left(-\frac{g_2^2}{2[\omega_2^2 + \sigma_{E_2}^2]} \right) \quad (27.6)$$

showing that there is no selection on the genotypic values of trait z_1 , and therefore it evolves neutrally. Hence, heritability in trait one is entirely independent of the strength of the apparent selection on z_1 . Framed in terms of Robertson's secondary theorem (Chapter 6), there is no response because the covariance between relative fitness and the square of the breeding value for trait one is zero. The relative importance of phenotypic versus genetic correlations in selection response was briefly discussed in Chapter 13 and fully explored in Volume Three.

Stabilizing Selection Countered by Pleiotropic Overdominance

Pleiotropic extensions of direct selection models assume loci underlying a trait under stabilizing selection also have effects on other fitness components. The motivation for this traces back to Lerner (1954), who suggested that “inheritance of metric traits may be considered, at least operationally, to be based on additively acting polygenic systems while the totality of traits determining reproductive capacity and expressed as a single value (fitness) exhibits overdominance.” While the support for overdominance has diminished over time (Lewontin 1974), a number of the initial pleiotropy models made this assumption (Robertson 1956; Lewontin 1964; Bulmer 1973; Gillespie 1984). As we will see, such models can still be meaningful even in the absence of classical overdominance.

The basic structure of the **pleiotropic overdominance - stabilizing selection model** is that for locus i , the genotypes $q_i q_i : Q_i q_i : Q_i Q_i$ have effects $-a_i : 0 : a_i$ on a trait under stabilizing selection, and fitness effects $1 : 1 + t_i : 1$ on an independent (and multiplicative) fitness component, with total fitness being the product of $w(z)$ from stabilizing selection and the pleiotropic fitness of the genotype. Under this model, the change in allele frequency from weak overdominance is

$$\Delta p_i \simeq -t_i p_i (1 - p_i) (2p_i - 1) \quad (27.7)$$

Assuming weak selection on the focal trait, we can add the change from stabilizing selection to give the total change. Assuming Gaussian stabilizing selection, Equation 27.4a gives

$$\begin{aligned}\Delta p_i &\simeq -t_i p_i (1 - p_i) (2p_i - 1) + \frac{a_i}{V_s} \left(\frac{p_i (1 - p_i)}{2} \right) [a_i (2p_i - 1) + 2(\theta - \bar{z})] \\ &= p_i (1 - p_i) \left([2p_i - 1] [-t_i + a_i^2 / (2V_s)] + a_i (\theta - \bar{z}) / V_s \right)\end{aligned}\quad (27.8)$$

which has a stable polymorphic equilibrium if $t_i > a_i^2 / (2V_s)$ provided that the population mean is close to the optimal trait value θ (stability analyses are given by Gillespie 1984 and Turelli and Barton 2004). Recalling Equation 27.4c, this can be restated as a stronger selection coefficient from overdominant selection t_i than from stabilizing selection $s_i = a_i^2 / (2V_s)$. If the mean is sufficiently far away, directional selection will dominate (fixing Q_i if \bar{z} is sufficiently below θ , and q_i if \bar{z} is sufficiently above θ). When $\bar{z} \simeq \theta$, this is an example of balancing selection, where the net sum of the two selective forces maintains variation, and can result in significant intermediate allele frequencies at equilibrium.

While mathematically correct, the question is the biological relevance of this model, especially given the difficulty in finding example of loci displaying classic fitness overdominance (Lewontin 1974). However, there are several realistic settings involving *per se* stabilizing selection that result in fitnesses mimicking heterozygote advantage. Zhivotovsky and Feldman (1992) note that pleiotropic overdominance naturally arises when the environment variance associated with a genotype decreases with the number of heterozygotes (Whitlock and Fowler 1999; Chapter 17). To see this, consider quadratic selection. The fitness associated with genotypic value G , where $z|G \sim (G, \sigma_{E(G)}^2)$ is given from Equation 27.3d as

$$w(G) = 1 - s(G - \theta)^2 - s\sigma_{E(G)}^2$$

As the environment variance $\sigma_{E(G)}^2$ decreases, the fitness increases. This creates pleiotropic overdominance as heterozygous individuals have higher fitness than more homozygous individuals with the same genotypic value (also see Curnow 1964).

Gillespie and Turelli (1989, 1990) found that certain patterns of $G \times E$ (allelic effects change over environments while the optimum remains unchanged) can also result in heterozygotes having higher fitnesses than homozygotes, again recovering pleiotropic overdominance. Gimelfarb (1990) noted that the association between fitness and heterozygosity critically depends on strong $G \times E$ symmetry assumptions. A more general analysis of both spatial and temporal $G \times E$ models was provided by Turelli and Barton (2004), who found that a necessary condition for balancing selection to maintain polymorphisms in the face of stabilizing selection is that the coefficient of variation of allelic effects over environments exceeds one. If the standard deviation of allelic effects over environments is less than the mean, loci are fixed. An interesting consequence of this condition is that sex-specific differences in allelic effects are not sufficient to maintain significant variation (i.e., more than one polymorphic locus) in polygenic models of stabilizing selection. While we found in Chapter 5 that antagonistic selection between the sexes can maintain variation in a single-locus model, moving to a polygenic model maintains no additional variation (i.e., no additional polymorphic loci).

Fluctuating and Frequency-dependent Stabilizing Selection

Balancing selection can potentially be generated by **fluctuating selection**. The $G \times E$ models just considered assume constant selection with allelic effects changing over environments.

In contrast, fluctuating stabilizing selection assumes allelic effects are constant, but that the optimum θ varies over time. Variation in θ could be random or include some periodicity, or both. Starting with Dempster (1955) and Haldane and Jayakar (1963), a large body of theoretical literature (reviewed by Felsenstein 1976; Hedrick 1986; Frank and Slatkin 1990a; Gillespie 1991; Lenormand 2002;) shows that the conditions for temporal variation to retain a polymorphism at a single locus are delicate. Are the conditions any less restrictive with a polygenic trait under fluctuating stabilizing selection? Not substantially.

The simplest model is random (uncorrelated) fluctuations in θ , which was considered by Ellner and Hairston (1994) and Ellner (1996). They showed that polymorphisms are maintained provided $\gamma\sigma^2(\theta)/V_s > 1$, where $\sigma^2(\theta)$ is the temporal variance in θ and γ is a measure of the amount of population overlap when overlapping generations are present. Hence, rather large fluctuations are required. Are the conditions less restrictive when the change in θ is periodic? Bürger and Gimelfarb (2002) examined the impact of a fluctuating optimum under a model with build-in periodicity (the expected value of θ varying according to a sine function) plus additional stochasticity (the realization of θ at a particular time is its expected value plus a random increment). An autocorrelated moving optimum had little impact (relative to constant stabilizing selection) on maintaining genetic variation or increasing polymorphism. Further, the longer the period, the less the impact on polymorphism and level of genetic variation. As we will see later, when mutation is also allowed, fluctuating selection can significantly increase the amount of standing variation over models assuming a constant value of θ .

Spatial variation in θ can also maintain at least some variation. A simple example was given by Felsenstein (1977), who assumed a continuum-of-alleles model, with a Gaussian distribution of allelic effects at each locus (we consider such models in detail below). Under Felsenstein's model, the optimal value at position x along some linear cline (such as a river bank) is $\theta(x) = \beta x$. Individuals disperse along this cline with a mean distance of zero and a variance of σ_d^2 . When selection is strong relative to migration ($V_s \ll \sigma_d^2$), the equilibrium variance is approximately $\beta^2 \sigma_d^2$. When selection is weak relative to migration, the equilibrium variance is roughly $\beta \sqrt{\sigma_d^2 V_s}$.

Frequency-dependent selection is another possible mechanism for generating balancing selection. As discussed in Chapter 5, it can maintain variation under selection, and aspects of this have been modeled by a number of workers (Roughgarden 1972; Bulmer 1974, 1980; Felsenstein 1977; Slatkin 1979; Clarke et al. 1988; Mani et al. 1990; Kopp and Hermisson 2006). The most comprehensive analysis (in terms of maintenance of variation when stabilizing selection is occurring) is that of Bürger and Gimelfarb (2004). These authors assume constant stabilizing selection on a trait that is also involved in intraspecific competition (as did Bulmer 1980). Individuals with more distinct trait values have reduced competition, and hence higher fitness, generating disruptive selection on the trait. Stabilizing selection is modeled by a quadratic fitness function with selection effect s , whereas the amount of competition between phenotypes g and h also follows a quadratic, $1 - s_c(g - h)^2$. Assuming these two components of fitness are multiplicative, Bürger and Gimelfarb find that the key parameter is $f = s_c/s$, the ratio of selection from competition to stabilizing selection. If f is below a critical value, the model essentially behaves like a standard model of stabilizing selection. If f exceeds this critical value, there are no stable monomorphic equilibria, and genetic variance and amount of polymorphism rapidly increases with f (as disruptive selection dominates).

Summary of Direct Selection Models

When the focal trait is under direct stabilizing selection, very little variation is maintained

in the absence of other forces such as mutation or countering selection. Likewise, stabilizing selection on multiple traits has little impact on increasing the variance of a focal trait, especially under weak selection (selection on any given underlying locus is small relative to recombination). When underlying loci are overdominant for an independent fitness component, sufficiently strong balancing selection can maintain significant variation. However, given the apparent scarcity of widespread fitness overdominance, this is an unlikely candidate for a general explanation for the maintenance of variation. Certain strictly stabilizing selection scenarios can mimic pleiotropic overdominance, such as environmental variances that decreases as a function of the total heterozygosity or $G \times E$ when the genotypic values (but not the fitness optimal) change over time or space. A fluctuating optimum is unlikely to retain significant variation when only selection is considered, but there are conditions under which density-dependent selection can maintain significant variation. Spatial and/or temporal heterogeneity of environments/selection as a general explanation is unlikely as laboratory populations (of sufficient size) can stably maintain variation for hundreds of generations. As with any explanation presented here, demonstrating a potential, even over a very wide parameter space, is not sufficient, as one also needs to have some idea about how common a particular mechanism actually is in nature.

NEUTRAL TRAITS WITH PLEIOTROPIC OVERDOMINANCE

In the proceeding model, pleiotropic effects enter to counter the removal of variation for a trait under stabilizing selection. The other extreme is to imagine *no* selection on a focal trait, with trait variation arising as a result of pleiotropic effects from underlying loci that are under selection for other independent features (e.g., Robertson 1956, 1967, 1972). These underlying polymorphisms could be maintained by strict selection, such as overdominant loci influencing fitness or loci under balancing selection, where in both cases the nature of selection is independent of the value of the focal trait. Alternately, alleles with deleterious fitness effects (maintained by mutation-selection balance) could also have pleiotropic effects on the focal trait. We defer discussion of these models until later in the chapter.

Pleiotropic selection models can generate an association between a neutral focal trait and fitness. In the case of underlying overdominant loci, more homozygous individuals have both lower fitness and more extreme trait values (Example 5.8). Likewise, under the deleterious pleiotropic effects model, individuals carrying more deleterious mutations also have more extreme trait values. In both settings, the neutral trait will show **apparent stabilizing selection** (Robertson 1956, 1967; Barton 1990; Kondrashov and Turelli 1992). Gavrilets and de Jong (1993) find that the conditions required for underlying pleiotropic loci to generate apparent stabilizing selection on a neutral trait are rather minimal. This has led to the suggestion that a significant fraction of apparent stabilizing selection on traits in natural populations is the result of selection on other features (e.g., Example 27.1; Gimelfarb 1996a).

Robertson's Model

As shown in Example 5.8, Robertson (1956, 1967) introduced the strict **pleiotropic overdominance** model wherein loci under overdominant selection also have pleiotropic effects on a neutral focal trait. This is in contrast to the previous pleiotropic overdominance model where the trait was under stabilizing selection, as opposed to being neutral. Consider the i -th such locus, and assume two alleles (the conditions for maintaining more than two alleles by overdominance at a loci are very delicate, so this is not an unreasonable assumption, Lewontin et al. 1978). Let the genotypes $Q_i Q_i : Q_i q_i : q_i q_i$ have fitnesses $1 - s_i : 1 : 1 - t_i$ giving (Example 5.4) an equilibrium frequency for Q_i of $\tilde{p}_i = t_i / (s_i + t_i)$. Under an additive

model where the pleiotropic effects on the focal trait are $a_i : 0 : -a_i$, the equilibrium variance from this locus is $2a_i^2 \tilde{p}_i (1 - \tilde{p}_i)$. Summed over n overdominant loci, the expected equilibrium additive variance is

$$\tilde{\sigma}_A^2 = 2nE[a_i^2 \tilde{p}_i (1 - \tilde{p}_i)] \quad (27.9)$$

with the expectation taken over all segregating overdominant loci that influence the trait. If homozygotes have rather similar fitnesses ($s_i \simeq t_i$), the equilibrium allele frequencies are intermediate ($\simeq 1/2$), giving $\tilde{\sigma}_A^2 \simeq (n/2)E[a_i^2]$. If they have very different fitnesses, the equilibrium frequencies will be close to zero or one, but this results in drift quickly fixing one of the alleles (Figure 7.4). Consequently, balancing selection models are expected to maintain alleles at intermediate frequencies.

Example 27.2. There are significant limitations with the overdominance model as a general explanation for quantitative trait variation. The first is the scarcity of examples of actual overdominant selection in the wild (Lewontin 1974). However, one could argue that it is widespread, but overlooked, as very small selection against both homozygotes still results in overdominance. Such small differences are difficult, at best, to detect in natural populations. Barton (1990) presents an independent argument on the tradeoff between the expected genetic load and the observed response to directional selection on the focal trait. Barton (and Robertson 1956) show that the overdominance model generates a strength of apparent stabilizing selection on the neutral focal trait of

$$V_s \simeq \sigma_A^2 / \bar{S} \quad (27.10a)$$

where

$$S_i = \frac{s_i t_i}{s_i + t_i} \simeq \frac{s_i}{2} \quad \text{when } s_i \simeq t_i \quad (27.10b)$$

is the average segregation load (reduction in fitness from the optimal value), with $1 - S_i$ the equilibrium fitness at locus i . To have a trait show a typically-assumed value of $V_s = 20\sigma_A^2$ requires $\bar{S} = 0.05$. Assuming n independent overdominant loci and multiplicative fitnesses, the expected load on the population is

$$\prod_{i=1}^n (1 - S_i) \simeq \exp(-\bar{S}n)$$

For $\bar{S} = 0.05$, around 20 such loci will result in the mean population fitness being around a third of its maximal possible value, so the number of such loci has to be modest. If loci have weaker effects ($\bar{S} < 0.05$), more loci can be maintained but the strength of apparent stabilizing selection on the neutral trait is correspondingly weaker.

Now consider the response when the focal trait is subjected to artificial directional selection, strong enough to overpower natural selection from overdominance. Assuming $\tilde{p}_i \simeq 1/2$, Equation 25.2a predicts that fixation of all favorable alleles will result in an increase (measured in terms of standard deviations of the initial additive variance) of $\sqrt{2n}$ (this corrects the value given by Barton). An observed response of R standard deviations requires $R^2/2$ such overdominant loci. Coupling this with the above load calculations suggests for a population to show five standard deviations ($5\sigma_A$) of response in a short-term selection experiment (a fairly typically result, Chapter 18), a lower bound of 13 overdominant loci are

required. Given a typical value of observed strength of (in this case, apparent) stabilizing selection of $\simeq 20\sigma_A^2$, this implies the mean population fitness is $(1 - 0.05)^{13}$, or roughly 50%, of the optimal fitness to support such a response. For 10 standard deviations of response, the required reduction in fitness to support the required 50 overdominant loci is over 90% of the fitness of the optimal genotype. Two factors can mitigate these results. First, as mentioned in Chapter 7, load can be diminished (and more loci maintained) under synergistic epistasis (as opposed to multiplicative fitnesses). Conversely, Equation 25.2a gives a lower bound on the required number of loci. The actual number is much larger when their frequencies depart from 1/2 (homozygotes have unequal fitnesses) and/or some directionally-favored loci are lost to drift in the small population sizes that characterize selection experiments (Chapter 26).

MUTATION-STABILIZING SELECTION BALANCE: BASIC MODELS

Recurrent mutation can maintain at least some genetic variation even the face of strong selection (Chapter 7). If μ is the mutation rate to a deleterious allele whose fitnesses are given by $1 : 1 - hs : 1 - s$, then its infinite-population equilibrium frequency is $\tilde{p} \simeq \mu/(hs)$ for $h \gg \sqrt{\mu/s}$ (Equation 7.6d) and $\tilde{p} = \sqrt{\mu/s}$ for a recessive ($h = 0$, Equation 7.6c). While it is obvious that at least some variation can be maintained by the balance between stabilizing selection and mutation, the critical question is just how much. This apparently simple query has generated a large amount of rather technical theory, with some surprising results.

We start our treatment by first considering the very different conclusions reached by Latter (1960) and Bulmer (1972) for diallelic models versus those by Kimura (1965), Lande (1975, 1977, 1980, 1984), and Fleming (1979) for continuum-of-alleles models. We show how these apparently disparate results are connected, with the different outcomes not due to the number of assumed alleles per locus (two versus many) but rather to the relative strengths of mutation and selection (Turelli 1984). Given the rather dense nature of some of the theory, we have placed most of derivations and many of the more technical details in Examples 27.3 - 27.6 at the end of this section.

Latter-Bulmer Diallelic Models

While diallelic models of mutation and stabilizing selection trace back to Wright (1935a,b), it was Latter (1960) and Bulmer (1972, 1980) who first considered their equilibrium additive variance. To obtain their results, we start by slightly rewriting Equation 27.4a for the change in allele frequencies due to Gaussian stabilizing selection as

$$\Delta p_i(\text{sel}) \simeq p_i(1 - p_i) \frac{a_i^2(p_i - 1/2) - a_i(\bar{z} - \theta)}{V_s} \quad (27.11a)$$

Assuming a simple diallelic model with equal mutation rates between alleles, the change from mutation becomes

$$\Delta p_i(\text{mut}) = -2\mu_i(p_i - 1/2) \quad (27.11b)$$

Assuming that $\bar{z} = \theta$ at equilibrium, and setting $\Delta p_i(\text{sel}) + \Delta p_i(\text{mut}) = 0$ gives one solution as

$$\tilde{p}_i(1 - \tilde{p}_i) a_i^2 = 2\mu_i V_s \quad (27.11c)$$

The solutions to this quadratic equation are

$$\tilde{p}_i = \frac{1}{2} \left(1 \pm \sqrt{1 - \frac{8\mu_i V_s}{a_i^2}} \right) \quad (27.11d)$$

An admissible solution ($0 < \tilde{p} < 1$) requires that the strength of selection (a_i^2/V_s) on a locus is strong relative to mutation μ_i (Bulmer 1980, Slaktin 1987),

$$a_i^2 > 8\mu_i V_s \quad (27.11e)$$

Notice that the left-hand term in Equation 27.11c just one half the additive variance contributed by the i th locus. Ignoring linkage disequilibrium (which will be slightly negative, Chapter 17), summing over loci gives the additive variance as

$$\tilde{\sigma}_A^2 \simeq 4n\bar{\mu}V_s \quad (27.12a)$$

where $\bar{\mu} = n^{-1} \sum \mu_i$ is the average mutation rate. Equation 27.12a (obtained by a different approach) is due to Latter (1960). The surprising result is that the size of allelic effects a_i does not appear. This follows from Equation 27.11d as increasing a_i results in a more extreme value of \tilde{p} and hence a smaller value for $\tilde{p}(1-\tilde{p})$, with the two effects (larger effect size versus more extreme equilibrium frequencies) canceling as seen in Equation 27.11c. Considering the contribution from a single locus and recalling Equation 27.4c for the strength of selection against a new mutation ($2V_s = a_i^2/s_i$), we have the contribution from locus i to the additive variance as

$$\tilde{\sigma}_{A(i)}^2 = (2\mu_i)(2V_s) = \frac{2\mu_i a_i^2}{s_i} = \frac{\sigma_{m(i)}^2}{s_i} \quad (27.12b)$$

showing that its contribution is the ratio of its mutational variance divided by the strength of selection against new mutation, namely the ratio of the input to new variation to the rate of its removal (the analog of Equation 7.6d). One interesting consequence of Equation 27.12a is that mean fitness at equilibrium is independent of the strength of selection V_s . From Equation 27.3e,

$$\begin{aligned} \bar{W} &= \sqrt{\frac{V_s}{V_s + \tilde{\sigma}_A^2}} = \sqrt{\frac{V_s}{V_s + 4n\bar{\mu}V_s}} \\ &= 1/\sqrt{1 + 4n\bar{\mu}} \simeq 1 - 2n\bar{\mu} \quad \text{for } 4n\bar{\mu} \ll 1 \end{aligned} \quad (27.12c)$$

This is another example of Haldane's principal (Chapter 7), that the selective load is simply a function of the mutation rate.

Equation 27.12a ignores linkage, simply being the sum of the single locus results. A more careful analysis by Bulmer (1980) accounting for linkage disequilibrium (among unlinked loci) found that

$$\tilde{\sigma}_A^2 \simeq \frac{4n\bar{\mu}V_s}{1 - 8n\bar{\mu}} \quad (27.12d)$$

which reduces to Equation 27.12a unless the total mutation rate is large. The impact of linkage is typically small (unless it is very tight), as the impact of assuming linkage equilibrium is to replace the 8 in the denominator of Equation 27.12c by a 4 (Turelli 1984). Taking V_s measured in units of the environmental variance, the equilibrium heritability becomes

$$\tilde{h}^2 = \frac{4n\bar{\mu}V_s}{4n\bar{\mu}V_s + 1} \quad (27.12e)$$

Using Turelli's (1984) value of $V_s/\sigma_E^2 \simeq 20$ (moderate selection), $n = 100$ and $\bar{\mu} = 10^{-5}$ gives an equilibrium heritability of 7.4%. Increasing the per-locus mutation rate to 10^{-4} gives a value of 44.4%. A total haploid mutation rate of $n\bar{\mu} = 0.0125$ is required to account for a

heritability of 50% under $V_s/\sigma_E^2 = 20$. Hence, unless stabilizing selection is weaker than it appears ($V_s/\sigma_E^2 \gg 20$), or per-locus mutation rates higher than expected ($\mu \gg 10^{-5}$), or the number n of loci is very large, the Latter-Bulmer model alone cannot account for the observed levels of variation, a point made by Latter (1960).

A cautionary note on the Latter-Bulmer model was offered by Barton (1986). Due to the symmetry of the model (all loci with the same effect, heterozygote value equals optimum value) and its diallelic nature, the above analysis assumes that the mean equals the optimum at equilibrium, such that there are an equal number of loci with equilibrium values of \tilde{p} and $1 - \tilde{p}$. When the number of loci is large, Barton showed that equilibria at the underlying loci exist where the population mean *does not* equal the optimum, and in such settings the amount of additive variance exceeds Equation 27.12a, in some cases by a considerable amount. However, Barton (1989) and Hastings (1988, 1990) found that while such equilibria can indeed exist, they tend not to be reached, especially in the face of drift.

Turelli (1984) generalized the Latter-Bulmer result to a triallelic model. As with the Latter-Bulmer model, Gaussian stabilizing selection occurs on n loci assumed to be in linkage equilibrium. At locus i , the alleles $A_{-1}^{(i)}, A_0^{(i)}, A_1^{(i)}$ have values $-a_i, 0, a_i$, with the following mutational structure

$$A_{-1}^{(i)} \xrightleftharpoons[\mu_i/2]{\mu_i} A_0^{(i)} \xrightleftharpoons[\mu_i/2]{\mu_i} A_1^{(i)} \quad (27.13a)$$

This model also has a symmetry assumption, namely that heterozygotes correspond to the optimal value ($\theta = 0$). Provided that $\mu_i \ll a_i^2/V_s \ll 1$, the equilibrium allele frequencies are

$$\tilde{p}_1^{(i)} = \tilde{p}_{-1}^{(i)} \simeq \mu_i V_s / a_i^2 \quad (27.13b)$$

with $\tilde{p}_0^{(i)} = 1 - 2\tilde{p}_1^{(i)}$ (see Turelli for details). The resulting additive variance for locus i is

$$\tilde{\sigma}_{A(i)}^2 = 2 \left[(-a_i)^2 \tilde{p}_{-1}^{(i)} + 0^2 \tilde{p}_0^{(i)} + a_i^2 \tilde{p}_1^{(i)} \right] = 4a_i^2 (\mu_i V_s / a_i^2) = 4\mu_i V_s \quad (27.13c)$$

Under the assumption of linkage equilibrium, summing over loci recovers Equation 27.12a, extending this result beyond diallelic loci.

Kimura-Lande-Fleming Continuum-of-alleles Models

In contrast to the Latter-Bulmer two-allele model, starting with Kimura (1965), a number of continuum-of-alleles models have been proposed that allow for a large number of alleles at a locus (Lande 1975, 1977, 1980, 1984; Fleming 1979). Kimura's original analysis followed the distribution $p_i(x)$ of allelic effects (x) at a given locus i assuming the incremental mutational model (Table 27.1). As detailed in Example 27.4, by assuming mutational effects are small, Kimura was able to use a Taylor series approximation (Equation 27.22a) to show that the distribution of effects at an individual loci are normally-distributed, with mean zero and variance $\sqrt{\mu_i \sigma_{m_i}^2 V_s}$. Kimura's result is for a haploid model, where $\sigma^2(\alpha_i) = \sqrt{\mu_i \sigma_{m_i}^2 V_s}$ denotes the variance in allelic effects in a haploid gamete. Assuming additivity, the additive variance from locus i becomes $\sigma_{A(i)}^2 = 2\sigma^2(\alpha_i)$. Assuming no LD, Example 27.4 shows that summing over loci gives Kimura's expression for the additive variance with n equivalent underlying loci as

$$\tilde{\sigma}_A^2 = \sqrt{2nV_s\sigma_m^2} \quad (27.14a)$$

When effects vary over loci, the above expression holds with the effective number of loci

$$n_e = 2 \left(\sum_{i=1}^n \sqrt{\mu_i \sigma_{m_i}^2} \right)^2 / \sigma_m^2 \quad (27.14b)$$

replacing n .

Lande (1975) extended Kimura's model to a full multi-locus analysis allowing for linkage (Example 27.7). He did so by assuming that the vector of allelic effects for the n loci in a gamete is multivariate normal, and obtained a slightly different expression for n equivalent underlying loci,

$$\tilde{\sigma}_A^2 = \sqrt{2n\sigma_m^2(V_s + n\sigma_m^2/2)} + n\sigma_m^2 \quad (27.14c)$$

which essentially reduces to Kimura's result (Equation 27.14a) when $n\sigma_m^2 \ll 1$. As with Equation 27.14a, when loci differ, n_e (Equation 27.14b) replaces n . Unlike Latter (1960), Lande concluded that mutation-selection balance could indeed account for high levels of additive variation (Figure 27.3). Nagylaki (1984) and Turelli (1984) note for weak selection that Equation 27.14c slightly overestimates the genetic variance and is slightly less accurate than Equation 27.14a.

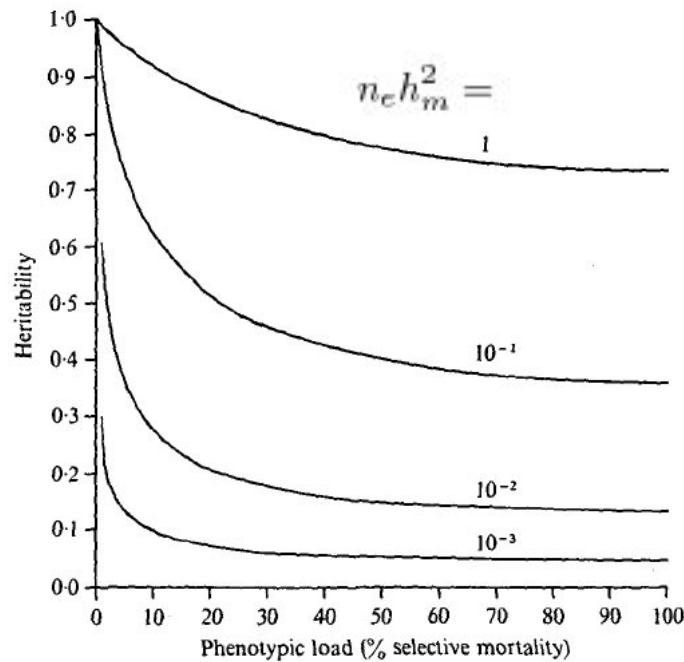


Figure 27.3. Equilibrium heritabilities expected under the Lande model (Equation 27.14c). Per cent selective mortality is $100 \cdot (1 - \bar{W})$, where $\bar{W} = \sqrt{\omega^2 / (\omega^2 + \sigma_E^2 + \tilde{\sigma}_A^2)}$, assuming $\bar{z} = \theta$ (Equation 27.3e). Taking a typical value of $h_m^2 = 10^{-3}$, the plotted curves correspond (from top to bottom) to effective number of loci n_e values of 1000, 100, 10, and 1. Note that modest selection (low selective mortality) with a reasonable number of loci (n_e 10 to 100) can account for the observed heritabilities in natural populations ($0.2 \leq h^2 \leq 0.7$). After Lande (1975).

One can also recover Equation 27.14a from using results from Chapter 24 on Gaussian continuum-of-alleles models (which, like Lande, assumes the distribution of allelic effects at a locus is normal). Ignoring the effects of linkage disequilibrium (i.e., assuming $d = 0$ and that the genic σ_a^2 variance equals the additive-genetic variance σ_A^2), adding a term σ_m^2 for new mutation to Equation 24.2a, and setting $N_e = \infty$ gives

$$0 = -\frac{\kappa \tilde{h}^2 \tilde{\sigma}_A^2}{2n} + \sigma_m^2, \quad \text{or} \quad 2n\sigma_m^2 = \kappa \tilde{h}^2 \tilde{\sigma}_A^2 \quad (27.14d)$$

Recall that κ is a measure of the strength of stabilizing selection, namely the fraction that the phenotypic variance is reduced following selection. Since $\tilde{h}^2 = \tilde{\sigma}_A^2 / \tilde{\sigma}_z^2$, Equation 27.14d can be expressed as

$$\tilde{\sigma}_A^4 = 2n\sigma_m^2(\tilde{\sigma}_z^2/\kappa), \quad \text{giving} \quad \tilde{\sigma}_A^2 = \sqrt{2n\sigma_m^2(\tilde{\sigma}_z^2/\kappa)} \quad (27.14e)$$

Recalling Equation 16.18a, $\kappa = \tilde{\sigma}_z^2/V_s$ so that $\tilde{\sigma}_z^2/\kappa = V_s$, recovering Equation 27.14a.

Fleming (1979) presented an improved (but still approximate) analysis of Kimura's model. He did so by scaling both the strengths of selection and mutation by a small parameter ϵ , with $(2V_s)^{-1} = \alpha\epsilon$ and $\sigma_{m_i}^2 = \beta_i\epsilon$. This scaling (which implies $\mu_i \gg \sigma_{m_i}^2/V_s$) assumes both weak selection and mutation. By letting $\epsilon \rightarrow 0$, Fleming was able to express the equilibrium distribution of allelic effects in terms of zero and first-order expressions of ϵ . His zero-order term is a normal with variance given by Equation 27.14a (and independent of the linkage map). The first-order expression has significant kurtosis, showing that the distribution of allelic effects departs from a Gaussian. When the mutational increment m is drawn from a normal distribution, Fleming's approximation gives

$$\tilde{\sigma}_A^2 \simeq \sqrt{2nV_s\sigma_m^2} \left[1 + \sqrt{\frac{n\sigma_m^2}{2V_s}} \left(1 - \frac{3}{16n\mu} \right) \right] \quad (27.15)$$

Fleming (1979) and Bürger (1998a) give more general expressions allowing for non-Gaussian kurtosis in the distribution of mutational effects. Simulation studies by Turelli (1984) found that Equation 27.15 is accurate over a much wider range of parameter values (such as $1 < \sigma_{m_i}^2/(V_s\mu_i) < 10$) than might be expected given the nature of the approximation. Applied mathematicians aficionados are referred to Fleming's paper, although less technical discussions are provided by Nagylaki (1984) and Turelli (1984). By using methods from applied physics, Bürger (1986, 1988a, 1988c) was able to obtain a number of conclusions regarding the solution to the general Kimura model, but as we now detail, most results are based on one of two different approximations of the equilibrium solution.

Gaussian vs. House-of-Cards Approximations for Continuum-of-alleles Models

Equations 27.12 and 27.14 give very different predictions for the expected genetic variance under mutation-selection balance. Under Kimura's result (and Lande's extension), the effect of the number of loci scales as \sqrt{n} and strength of selection scales as $\sqrt{V_s}$, while under Latter, these scale as n and V_s . The Latter-Bulmer result just requires the total mutation rate (independent of the variance σ_{m*}^2 of mutational effects), while the Kimura-Lande-Fleming results are more pleasingly stated in terms of the mutational variance σ_m^2 . Further, the Latter-Bulmer model does not appear to maintain sufficient variation to account for observed values while the Kimura-Lande-Fleming model does. Why this vast disparity? Which approach (if either) is correct?

Turelli (1984) showed that these rather different outcomes arise from different approximations of the complex integro-differential equation for the distribution of allelic effects for the general Kimura model (Equation 27.21 in Example 27.4). Kimura and Fleming obtained their approximate solutions by assuming the impact from new mutation is small relative to existing variation at a locus. More formally, the variance of mutational effects at a locus (the allelic effects *given* that a mutation has occurred) is much less than the current variance of allelic effects at that locus, $\sigma_{m_i}^2 \ll \sigma^2(\alpha_i)$, a point first stressed by Lande (1975). From Equation 27.14a,

$$\sigma_{m_i}^2 \ll \sqrt{\mu_i \sigma_{m_i}^2 V_s} \quad (27.16a)$$

which can be rearranged as

$$\mu_i \gg \frac{\sigma_{m_i}^2}{V_s} \quad (27.16b)$$

Recalling Equation 27.4c, this condition is equivalent to $\mu_i \gg E[s_i]$, namely mutation is much stronger than selection at a given locus. Turelli (1984) referred to this as the **Gaussian approximation**, as the resulting equilibrium solution approaches a normal distribution of allelic effects at a locus. Note that Lande (1975) *assumed* a Gaussian distribution in his multiple-locus treatment that accounted for linkage, whereas Kimura and Fleming *obtained* it following their assumption that $\sigma_{m_i}^2 \ll V_s \mu_i$ (Kimura exact normality, Fleming as the zero-order term in a more careful analysis).

Turelli (1984) argued that this inequality is typically reversed, $\mu_i \ll \sigma_{m_i}^2 / V_s$ (giving $\sigma_{m_i}^2 \gg \sigma_{A(i)}^2$), so that the Gaussian approximation is often inappropriate. His logic follows from the standard value of $\sigma_m^2 = \sigma_E^2 / 10^3$, which implies $\sigma_m^2 \simeq \sigma_A^2 / 10^3$ for a typical heritability ($0.3 \leq h^2 \leq 0.7$). Since both σ_m^2 and σ_A^2 are the sums of single-locus effects, with equivalent loci their single-locus contributions ($\mu_i \sigma_{m_i}^2$ and $\sigma_{A(i)}^2$, respectively) can replace their totals to give $\mu_i \sigma_{m_i}^2 = \sigma_{A(i)}^2 / 10^3$ or that the Gaussian approximation $\sigma_{m_i}^2 \ll \sigma_{A(i)}^2$ requires that $\mu_i \cdot 10^3 \gg 1$ or that $\mu_i \gg 10^{-3}$. This is orders of magnitudes above traditional estimates of per-locus mutation rates.

Based on these concerns, Turelli considered Kimura's model when the inequality in Equation 27.16b is reversed,

$$\mu_i \ll \frac{\sigma_{m_i}^2}{V_s} \quad (27.17)$$

where now mutation is weak relative to selection ($\mu_i \ll E[s_i]$). Turelli's **house-of-cards approximation**, or **HCA**, uses this assumption to obtain an equilibrium solution of the general Kimura equation (Example 27.5). The basis for Turelli's approximation follows from the HOC mutation model (Table 27.1), which assumes new mutational variance is likely to swamp existing variance. Under HOC mutation, the new allelic value x' following mutation is independent of its current value x (i.e., $x' = m$ as opposed to $x' = x + m$). As shown in Example 27.5, the HCA gives

$$\tilde{\sigma}_A^2 \simeq 4V_s n \mu \quad (27.18a)$$

which is simply the Latter-Bulmer result (Equation 27.12a). The connection between the HCA and the Latter-Bulmer model follows since the latter requires $a_i^2 > 8\mu_i V_s$ in order to obtain Equation 27.12a, while the HCA requires $\sigma_{m_i}^2 \gg \mu_i V_s$. The a_i (being mutational effects) essentially equate to the mutational effects variance $\sigma_{m_i}^2$ under a continuum-of-alleles model. Under HCA conditions, selection is strong and the dominant (close to fixation) allele at a locus is expected to be close to the optimum. New mutations are thus deleterious,

and tend to disappear quickly, resulting in most the genetic variation being due to rare alleles with relatively large effects.

As with many of the results in this section, Equation 27.18a is simply the sum of single-locus results. Turelli and Barton (1990) examined the impact of linkage, finding with n identical loci that

$$\tilde{\sigma}_A^2 \simeq 4V_s n \mu \left(1 + \frac{2(n-1)\mu}{r_H} \right) \quad (27.18b)$$

where r_H is the harmonic mean of all pair-wise recombination frequencies between loci, or roughly 1/2 for loose linkage. As with the Gaussian approximation, the impact from linkage is small unless it is very tight.

One measure of departure from normality is the scaled kurtosis κ_4 , which equals one for a normal (LW Equation 2.12a). Under the HCA, the resulting kurtosis for the distribution of allelic effects at locus i is

$$\kappa_{4,i} = \frac{E[x_i^4]}{3E[x_i^2]} \simeq \frac{2V_s \mu_i \sigma_{m_i}^2}{3(2V_s \mu_i)^2} = \frac{\sigma_{m_i}^2}{6V_s \mu_i} \quad (27.18c)$$

which is $\gg 1$ (highly leptokurtic, namely with a long tail) under the HCA ($\sigma_{m_i}^2 \gg \mu_i V_s$). The resulting distribution of allelic effects thus departs significantly from a normal, with its leptokurtosis indicating the presence of rare alleles of large effect.

Kurtosis also influences the accuracy of Equation 27.18a, which is an under bound. When the distribution of mutational effects is normal, the accuracy is quite good. As the distribution of mutation effects becomes increasing leptokurtic, the true variance (even under HCA conditions) can be significantly less than suggested by Equation 27.18a (Bürger and Hofbauer 1994; Bürger and Lande 1994).

Thus, we have Kimura-Lande-Fleming when $\mu_i \gg \sigma_{m_i}^2/V_s$ (the Gaussian assumption, mutation stronger than selection) and Latter-Bulmer when $\mu_i \ll \sigma_{m_i}^2/V_s$ (the HCA assumption, selection stronger than mutation). Extensive simulations by Turelli (1984) refined these domains. The Gaussian approximation overestimates the additive variance by less than 10% when $\sigma_{m_i}^2 \leq \mu_i V_s/5$, while the HCA model gives a good fit when $\sigma_{m_i}^2 \geq 20\mu_i V_s$. Bürger (1988a, b) was able to obtain an upper bound for the equilibrium additive variance under a fairly general Kimura model (assuming only symmetric mutations and quadratic fitnesses near the optimum). He found that the first-order bound is just the HCA value, $\tilde{\sigma}_A^2 \leq 4\mu V_s$. When Kimura's single-locus expression $\sqrt{2V_s \sigma_m^2}$ exceeds this value, the Gaussian approximation has clearly failed, giving the restriction

$$\sqrt{2V_s \sigma_m^2} = \sqrt{2V_s 2\mu_i \sigma_{m_i}^2} \leq 4\mu_i V_s, \quad \text{or} \quad \sigma_{m_i}^2 \leq 4\mu_i V_s \quad (27.18d)$$

with Gaussian approximation always failing when $\sigma_{m_i}^2 > 4\mu_i V_s$.

While the reader may perceive this difference between the Gaussian and HCA approximations as being a function of the assumed mutation *model*, this difference is simply a function of the *relative strengths* of selection to mutation at a locus. When mutation is strong, one might expect a number of alleles at a locus (continuum-of-alleles model), while when mutation is weak relative to selection, one expects very few segregating alleles (the **rare alleles model**). While both the Gaussian and HCA approximations follow from a continuum-of-alleles model, the transition from Gaussian to HCA behavior can be seen in models in models with a modest to small number of assumed alleles per locus. Equation 27.13c shows how the HCA variance follows from a triallelic model when Equation 27.17 holds. An extension of Turelli's triallelic model by Slatkin (1987) provides further insight.

Slatkin assumed an unlimited number of alleles with a stepwise mutation model, with an allele mutating to a new effect with increment a or $-a$ (relative to its current value), with mutation rate $\mu/2$ for each step (a scheme also used by Narain and Chakraborty 1987),

$$\cdots \quad -2a \quad \xleftrightarrow[\mu/2]{\mu/2} \quad -a \quad \xleftrightarrow[\mu/2]{\mu/2} \quad 0 \quad \xleftrightarrow[\mu/2]{\mu/2} \quad a \quad \xleftrightarrow[\mu/2]{\mu/2} \quad 2a \quad \cdots$$

As shown in Example 27.6, if selection is weak relative to mutation (such that many allelic states are present), this model reduces to Kimura's Gaussian result, while if selection is strong relative to mutation (so that a single major and two very minor alleles, each one step away, are present), this reduces to the HCA result (Turelli's triallelic model). Analysis of models assuming five alleles per locus (Turelli 1984; Slatkin 1987) further make this point.

Example 27.3. Cites unpublished work, so embargoed for draft version

Epistasis

Epistasis in models of stabilizing selection can act on several levels. First, the trait itself can show epistasis. In such settings, Hermisson et al. (2003) shows that epistasis reduces the amount of additive variation at equilibrium relative to purely-additive models. While Gavrilets and de Jong (1993) find that certain models of epistasis can both maintain a high amount of additive variation *and* show strong apparent stabilizing selection, these result from balancing selection on the underlying loci, a rather different setting from an epistatic trait itself being under stabilizing selection (see Lawson et al. 2011 for a potential example). However, epistasis *in fitness* naturally arises even for a completely additive trait under stabilizing selection. This is because the mapping from trait value to fitness is nonlinear.

Tachida and Cockerham (1988) examine the expected amount of additive versus additive-by-additive variance in fitness for a trait under stabilizing selection. They found that additive-by-additive variance in fitness is larger than additive variance under conditions for the Gaussian approximation, but that the converse is true (additive being larger than nonadditive) under HCA conditions. However, an important caveat for the latter is that the number of loci per trait is not too large, and the number of traits influenced per locus (their amount of pleiotropy) is also small. A review of the *Drosophila* fitness components literature suggested more additive than additive-by-additive variance in fitness components, which lead Tachida and Cockerham to suggest that the HCA domain might be more applicable in these cases. However, they also note that this distinction between the two classes of approximation breaks down when traits are away from their optimal values.

Effects of Linkage and Mating Systems

The more diligent reader may recall situations in two-locus models where the effects of linkage disequilibrium were quite considerable (Chapter 5). This occurs in cases where selection is much stronger than recombination, while the analysis of polygenic models typically assumes that recombination is much stronger than selection at a given locus, resulting in linkage effects being much smaller, often to the point (depending on the problem) that they can be ignored as a good first approximation.

Most of the above analysis, under either the HCA or Gaussian approximations, extrapolates the additive variance by summing single-locus variances. Recalling Equation 16.2, the additive variance σ_A^2 is the sum of the genic variance σ_a^2 (the additive variance in the absence of linkage disequilibrium) plus the disequilibrium contribution d , with $\sigma_A^2 = \sigma_a^2 + d$. σ_A^2 is often called the **expressed variation**, and σ_a^2 the **hidden variation** (although the “hidden” component is actually $\sigma_a^2 - \sigma_A^2$). Simply summing single-locus results recovers the genic σ_a^2 variance, not the additive variance σ_A^2 , and we expect the genic variance to overestimate the additive variance (as $d < 0$ under stabilizing selection, Chapter 16). While the actual value of d can be considerable, simulations (Turelli 1984; Hastings 1989) and analytic results (Lande 1975; Fleming 1979; Nagylaki 1984; Bürger 1989) show that the relative error by ignoring it is generally small, negative, and increases (slowly) with n . Fleming found that the zero-order approximation of the distribution of allelic effects was independent of the recombination map, which entered as first-order terms. Assuming n equivalent loci ($\mu_i = \mu$, $\sigma_{m_i}^2 = \sigma_{m*}^2$), Turelli (1984) used the Lande and Fleming results to find the relative error in using the linkage equilibrium value (LE) in place of the true additive variance under the Gaussian approximation to be

$$\frac{\tilde{\sigma}_A^2(LE) - \tilde{\sigma}_A^2}{\tilde{\sigma}_A^2} \simeq \left(1 - \frac{1}{n}\right) \sqrt{\frac{n\sigma_m^2}{2V_s}} \quad (27.19)$$

A simulation study by Hastings (1989), essentially using the HCA approximation, found that the impact of LD is again small, scaling with $n\mu$, the total (haploid) mutation rate. If $n\mu < 0.025$, the contribution from LD was small, less than 10% of the total variance. However, for $n\mu > 0.05$, its contribution can be over half the total variance. Turelli and Barton (1990) also found that impact of linkage under HCA scales with $n\mu$, see Equation 27.18b.

In an exact analysis of a two-locus model, Bürger (1989) found that the impact of linkage depends on the relative strengths of mutation and selection, namely the HCA versus Gaussian assumptions. Under the Gaussian assumption, the genic variance remains constant, while the additive variation decreases as linkage becomes tighter. Under the HCA assumption, the genetic variance remains constant under linkage (as long as it is not too tight), while the genic variance increases with decreasing recombination (as seen in Equation 27.18b). If recombination is below a critical value, then the behavior is as for the Gaussian approximation.

A second issue of potential concern is the mating system. Thus far, we have been assuming random mating. However, previous chapters showed that inbreeding (Chapter 11) and assortative mating (Chapter 16) can both impact the additive variance. Given these observations, Lande (1977) obtained the counterintuitive result that these departures from random mating have essentially no impact on the equilibrium additive variance for a Gaussian model with only additive effects. Inbreeding and assortative mating change the rate of approach to the equilibrium, but not its final value. Conversely, Turelli (1986) and Frank and Slatkin (1990b) found that inbreeding *does* change the equilibrium additive variance under HCA assumptions. He suggested that the robustness of the Gaussian model to the mating system may be an artifact of the high mutation rate per locus required for this model to be accurate.

Spatial and Temporal Variation in the Optimum

We saw that spatial and temporal variation in the optimum can maintain some variance under stabilizing selection in the absence of mutation, but that these conditions were fairly

restrictive. Does incorporating of a variable optimum θ increase the additive variance when mutation is present? Yes, and the increase can be substantial.

A number of authors have examined the impact of temporal variation in θ (Kondrashov and Yampolsky 1996a b; Kirzhner et al. 1996a,b; Korol et al. 1996; Bürger 1999), with the most detailed treatment by Bürger and Gimelfard (2002). When there is a periodic change in θ that has a sufficiently long cycle time (> 10 generations) and is of sufficient amplitude ($> \sqrt{V_s}$), the amount of variation significantly exceeds the constant- θ value, often by at least an order of magnitude. When there are consistent directional shifts in the optimum, initially rare and deleterious alleles can become favorable and under directional selection to track the new optimum. If the directional change persists for sufficiently long, and is of sufficient distance, significant allele frequency change occurs, increasing the additive variance. The change, however, must be periodic, in that if it stops at a new value, one returns to a constant- θ model. The open question is not whether the optimum changes, as most ecologists would suspect that it does, but rather if these changes are periodic, and persistent enough, to dramatically impact the additive variance. Entirely random (i.e., no short-term directional trend or positive autocorrelation) changes in θ on the additive variance.

The impact of spatial variation in the optimum under stabilizing selection has been examined by Felsenstein (1977), Slaktin (1978), and Barton (1999). We previously discussed Felsenstein's model, which assumes a linear gradient in the optimum, such that at location x on some linear cline (such as a river bank) $\theta(x) = \beta x$, with individuals randomly dispersing some distance $d \sim N(0, \sigma_d^2)$. Felsenstein showed this model can maintain at least some variation in the face of stabilizing selection without mutation, as migration effectively fills the role of generating variation. Slaktin (1978) and Barton (1999) extend Felsenstein's model to allow for mutation. Felsenstein and Slaktin both assumed a Gaussian distribution of mutational effects at a locus, which Barton showed was a good approximation even under HCA conditions. Slaktin found that the equilibrium additive variance becomes

$$\tilde{\sigma}_A^2 = 2Z\sqrt{V_s + Z^2} + 2Z^2 \quad (27.20a)$$

where

$$Z^2 = \sum_{i=1}^n \sqrt{\mu_i \sigma_{m_i}^2 + \beta^2 \sigma_d^2} \quad (27.20b)$$

This is just Lande's (1975) result (Equation 27.29b) with the $\beta^2 \sigma_d^2$ (a measure of how quickly selection changes relative to migration) augmenting the mutational variance. If this is sufficiently large, $\beta^2 \sigma_d^2 > \mu_i \sigma_{m_i}^2 = \sigma_m^2 / (2n_e)$, then spatial differences in fitness (given by the variation in θ) dominates the role of mutation, and $Z^2 \simeq n\beta\sigma_d$. Here n_e is the effective number of loci, Equation 27.14b.

Summary: Implications of Gaussian vs. HCA Approximations

Table 27.2 summarizes the major features of the Gaussian and House-of-cards approximations and their differences in behavior (some of which are developed in later sections). While the reader might infer that the conditions for the Gaussian approximation to hold are unusual, Bürger (2000) makes the important point that it might be highly relevant in asexual species, or those with a large fraction of the genome in regions of low recombination. In these cases, the mutational size of a "locus" is much larger, resulting in a higher mutation rate.

Table 27.2. Comparison of the Gaussian and House-of-cards (HCA) approximations and their features. V_s is the strength of selection on a genotypic value (Equation 27.3f), $\sigma_{A(i)}^2$ the additive variation

at locus i , n the number of loci, $\sigma_{m_i}^2$ and μ_i are the variance of the effects of new mutations and mutation rate at locus i , and $\sigma_m^2 = \sum 2\mu_i\sigma_{m_i}^2$ is the mutational variance. When mutational effects are constant over loci, we use σ_{m*}^2 (to distinguish it from σ_m^2) and μ rather than retain the subscript i , with $\sigma_m^2 = 2n\mu\sigma_{m*}^2$. See text for further details.

	Gaussian	HCA
Mutational input vs. standing variation	$\sigma_{m_i}^2 \ll \sigma_{A(i)}^2$ Smaller	$\sigma_{m_i}^2 \gg \sigma_{A(i)}^2$ Larger
Strength of mutation to selection	$\mu_i \gg \sigma_{m_i}^2/V_s$ Stronger	$\mu_i \ll \sigma_{m_i}^2/V_s$ Weaker
Domain of applicability (single trait, $N_e = \infty$)	$\sigma_{m_i}^2 \leq \mu_i V_s/5$	$\sigma_{m_i}^2 \geq 20\mu_i V_s$
Impact of drift on domain of applicability	Decreases domain	Little to no effect
Impact of pleiotropy on domain of applicability	Decreases domain	Increases domain
Equilibrium additive variance $\tilde{\sigma}_A^2$	$\sqrt{2nV_s\sigma_m^2}$	$4V_sn\mu$
Finite population $\tilde{\sigma}_A^2$	$\sqrt{\left(\frac{nV_s}{2N_e}\right)^2 + 2n\sigma_m^2 V_s} - \frac{nV_s}{2N_e}$	$\frac{4n\mu V_s}{1 + V_s/(N_e\sigma_{m*}^2)}$
Sensitivity to linkage map	Little unless $r_{ij} \simeq 0$	Little unless $r_{ij} \simeq 0$
Impact of mating system on $\tilde{\sigma}_A^2$	Insensitive	Sensitive
Number of alleles/locuss	Many	One major, few rare
Distribution of allelic effects	Normal – many alleles at intermediate-frequencies	Leptokurtic – rare alleles of large effect
Impact of multiple-trait selection	None for uncorrelated traits	Sensitive to uncorrelated traits

We conclude this section with the derivations for many of the results given above, which can be skipped by the casual reader. A number of these results are also obtained by Zhang and Hill (2010), using the framework of the Price Equation (Chapter 6), offering the reader an independent set of derivations.

Example 27.4. Kimura (1965) considered a haploid continuum-of-alleles model, following the distribution $p_i(x)$ of allelic effects (x) at locus i with no linkage disequilibrium. He assumed a continuous-time model in Hardy-Weinberg and under quadratic stabilizing selection. Our treatment here follows Bulmer (1989), who assumed a discrete time, Gaussian selection model, obtaining the same result but in a more transparent way than Kimura's original derivation. Under Gaussian stabilizing selection (with $\theta = 0$), the expected infinitesimal change from selection is

$$\frac{\partial p_i(x)}{\partial t}(\text{sel}) = \frac{-p_i(x)[x^2 - \sigma^2(\alpha_i)]}{2V_s} \quad (27.21a)$$

where $\sigma^2(\alpha_i)$ is variance in allelic effects for locus i (so that $2\sigma^2(\alpha_i) = \sigma_{A(i)}^2$, the additive variance from locus i). Under the incremental mutational model, $\mu_i f_i(m)$ is the probability that an allele at locus i mutates from value x to value $x + m$, where $E(m) = 0$, and $E(m^2) = \sigma_{m_i}^2$. The resulting rate of change from mutation becomes

$$\frac{\partial p_i(x)}{\partial t}(\text{mut}) = -\mu_i p_i(x) + \mu_i \int p_i(x - m) f_i(m) dm \quad (27.21b)$$

The first term is the loss of alleles with effect x due to mutation, the second the gain of such alleles from new mutation. The latter is expressed as the cumulative probability that alleles at some other state mutate to state x . Formally, if the life cycle is selection followed by mutation, $p_i(x)$ in the above expression is replaced by $p'_i(x)$, the post-selection value. However, for weak selection and mutation, we can simply sum of Equations 27.21a and 27.21b to give the integro-differential equation for the distribution of allelic effects at time t . The equilibrium distribution is reached when

$$\frac{\partial p_i(x)}{\partial t} = \frac{\partial p_i(x)}{\partial t}(\text{sel}) + \frac{\partial p_i(x)}{\partial t}(\text{mut}) = 0$$

or

$$\frac{-p_i(x)[x^2 - \sigma^2(\alpha_i)]}{2V_s} - \mu_i p_i(x) + \mu_i \int p_i(x - m) f_i(m) dm = 0, \quad (27.21c)$$

which Bulmer (1989) calls the **fundamental equation of the continuum-of-alleles model**. Most early workers assumed that such an equilibrium distribution exists, and that it is unique, but this was not formally shown until Bürger (1986, 1988a, 1988b, 1988c, 1991; Bürger and Bomze 1996). The assumption of a Gaussian distribution of allelic effects breaks down in Equation 27.21b. Even assuming a Gaussian distribution following selection *and* a Gaussian distribution of mutational effects, Equation 27.21b is a *weighted* sum of two Gaussians, with different variances, and hence is clearly *not* Gaussian. However, under certain conditions it might be close to normally-distributed.

Different approximations have been used to proceed from Equation 27.21c to an explicit solution. Kimura assumed mutational effects are sufficiently small relative to $p(x)$ to approximate $p_i(x - m)$ by a second-order Taylor series,

$$p_i(x - m) \simeq p_i(x) - m \frac{\partial p_i(x)}{\partial x} + \frac{m^2}{2} \frac{\partial^2 p_i(x)}{\partial^2 x} \quad (27.22a)$$

This approximation requires that $\sigma_{m_i}^2 \ll \sigma^2(\alpha_i)$, namely that the effect of a new mutation is much smaller than the current variance in allelic effects. Substituting this approximation into the integral in Equation 27.21c gives

$$\begin{aligned} & \mu_i \int \left(p_i(x) - m \frac{\partial p_i(x)}{\partial x} + \frac{m^2}{2} \frac{\partial^2 p_i(x)}{\partial^2 x} \right) f_i(m) dm \\ &= \mu_i \left(p_i(x) \int f_i(m) dm - \frac{\partial p_i(x)}{\partial x} \int m f_i(m) dm + \frac{\partial^2 p_i(x)}{\partial^2 x} \int m^2 f_i(m) dm \right) \\ &= \mu_i \left(p_i(x) + 0 + \frac{1}{2} \frac{\partial^2 p_i(x)}{\partial^2 x} \sigma_{m_i}^2 \right) \end{aligned} \quad (27.22b)$$

and Equation 27.21c yields the differential equation

$$\frac{-p_i(x)[x^2 - \sigma^2(\alpha_i)]}{2V_s} + \frac{\mu_i \sigma_{m_i}^2}{2} \frac{\partial^2 p_i(x)}{\partial^2 x} = 0 \quad (27.22c)$$

Kimura (1965) showed that this is satisfied when $p_i(x)$ follows a normal distribution with parameters

$$p_i \sim N\left(0, \sqrt{\mu_i \sigma_{m_i}^2 V_s}\right) \quad (27.22d)$$

This result of allelic effects at individual loci being normally distributed motivated the continuum-of-alleles models introduced in Chapter 24. Equation 27.22a is referred to as the Gaussian approximation, not for any assumption about the nature of stabilizing selection or distribution of mutational effects, but rather because the weak selection assumption leads to a Gaussian distribution of effects. Ignoring LD, the additive variance is just twice (for the two alleles in a diploid) the sum of the locus-specific allelic variances,

$$\tilde{\sigma}_A^2 = 2 \sum_{i=1}^n \sigma^2(\alpha_i) = 2\sqrt{V_s} \sum_i \sqrt{\mu_i \sigma_{m_i}^2} \quad (27.22e)$$

With loci of equal effects, $\sigma_m^2 = 2n\mu\sigma_{m*}^2$, implying $\mu\sigma_{m*}^2 = \sigma_m^2/(2n)$. Substituting into Equation 27.22e recovers Equation 27.14a,

$$\tilde{\sigma}_A^2 = 2\sqrt{V_s n} \sqrt{\sigma_m^2/(2n)} = \sqrt{2nV_s \sigma_m^2} \quad (27.22f)$$

Example 27.5. Under the house-of-cards approximation, the value of a new mutation is independent of its current value (unlike the incremental model), and instead is drawn from a common distribution, so that $x' = m$. Now the mutational input term $\mu_i \int p_i(x - m) f_i(m) dm$ in Equation 27.21c is replaced by $\mu_i f_i(x)$, giving

$$\frac{-p_i(x)[x^2 - \sigma^2(\alpha_i)]}{2V_s} - \mu_i p_i(x) + \mu_i f_i(x) = 0, \quad (27.23a)$$

which has an immediate solution of

$$p_i(x) = \frac{2V_s \mu_i f_i(x)}{x^2 - \sigma^2(\alpha_i) + 2V_s \mu_i}. \quad (27.23b)$$

Since $\sigma^2(\alpha_i) = \int x^2 p_i(x) dx$, Equation 27.23b is not an explicit solution. However, as noted by Bulmer (1989), this term is a constant which can be found by noting that $\int p_i(x) dx = 1$. If $x^2 \gg \sigma^2(\alpha_i) + 2V_s \mu_i$, then

$$p_i(x) \simeq \frac{2V_s \mu_i f_i(x)}{x^2} \quad (27.23c)$$

Hence, the expected value of x^k is

$$E[x_i^k] = \int x_i^k p_i(x) dx = \int x_i^k \frac{2V_s \mu_i f_i(x)}{x^2} dx = 2V_s \mu_i E[m_i^{k-2}], \quad (27.23d)$$

namely a function of the expected $k - 2$ power of the mutational effects. Hence,

$$\sigma^2(\alpha_i) \simeq 2V_s \mu_i E[m_i^0] = 2V_s \mu_i \cdot 1, \quad E[x_i^4] \simeq 2V_s \mu_i E[m_i^2] = 2V_s \mu_i (\sigma_{m_i}^2)$$

Recalling that $\sigma_{A(i)}^2 = 2\sigma^2(\alpha_i)$, this first expression recovers Equations 27.18a, while the second expression yields Equation 27.18c.

Example 27.6. An intermediate model between Kimura's Gaussian and Turelli's HCA approximations was offered by Slaktin (1987), and our derivation here is based on Slaktin as well as Bulmer (1989). As with many of the above analyses, we start with a haploid model, which is extended to a diploid multilocus result by assuming additivity and no significant linkage effects. Again, the trait is scaled so that the optimum $\theta = 0$. Slaktin assumed a step-wise (as opposed to a continuum) series of alleles, where A_j mutates to either A_{j-1} or A_{j+1} , each with rate $\mu/2$ (independent of allelic state j). Further, assume allele A_j has effect $a \cdot j$. Then

$$\frac{\partial p_j}{\partial t}(\text{sel}) = \frac{-p_j[a^2 j^2 - \sigma^2(\alpha)]}{2V_s} \quad (27.24a)$$

where $\sigma^2(\alpha)$ is the variance of allelic effects. The resulting change from mutation becomes

$$\frac{\partial p_j}{\partial t}(\text{mut}) = -\mu p_j + \frac{\mu}{2} (p_{j-1} + p_{j+1}), \quad (27.24b)$$

giving at equilibrium

$$-\frac{p_j[a^2 j^2 - \sigma^2(\alpha)]}{2V_s} + \frac{\mu}{2} (p_{j-1} - 2p_j + p_{j+1}) = 0 \quad (27.24c)$$

The mutation term is a second-degree difference equation, which in the limit approaches a second derivative, as

$$\lim_{\delta \rightarrow 0} \frac{f(x - \delta) - 2f(x) + f(x + \delta)}{\delta^2} \rightarrow \frac{d^2 f(x)}{dx^2}$$

Hence, if many alleles are segregating, these values are small, and we can approximate this term by the second derivation of p_j with respect to t , recovering Kimura's Gaussian approximation (27.22c). Conversely, with selection strong relative to mutation, there are typically only three alleles (one favored and the two single-step mutations), where p_0 is large and $p_{-1} = p_1$ are small. This is just Turelli's triallelic model (Equation 27.13), giving $p_1 = V_s \mu / a^2$, for a variance of $2V_s \mu$, recovering the HCA results.

Example 27.7. A potential deficiency in Kimura's (1965) mutation-selection balance model is that it is a one-locus haploid analysis extrapolated to n diploid loci by assuming no linkage effects. Lande (1975) attempted to remedy this with a model for a single trait with n underlying, potentially linked, loci under Gaussian stabilizing selection. (This paper is often cited as Lande 1976, as while his paper appeared in late 1975, the listed journal publication date was 1976). In order to fully account for linkage effects, Lande followed how the covariances between allelic effects at loci i and j in the maternal gamete and i' and j' from the paternal gamete change over time. Random mating ensures that zygotes start each generation with zero covariances between alleles in different gametes ($C_{ij'} = C_{i'j} = 0$). Because of linkage disequilibrium, the corresponding covariances C_{ij} and $C_{i'j'}$ for loci on the same gamete are nonzero. Further, we expect selection to generate covariances between loci from different gametes, so that

$$b_{ij}(t) = C_{ij'}(t)_s = C_{i'j}(t)_s \neq 0 \quad (27.25a)$$

where C_s denotes a covariance following selection. Assuming the incremental model, the change from mutation is

$$\Delta_m C_{ij} = \delta_{ij} \mu_i \sigma_{m_i}^2, \quad \text{where} \quad \delta_{ij} = \begin{cases} 1 & i = j \\ 0 & i \neq j \end{cases} \quad (27.25b)$$

so that mutation changes the variances, but not the covariances. Finally, let r_{ij} denote the recombination fraction between loci. Combining the joint actions of selection, recombination, and mutation (operating in that order) yields

$$C_{ij}(t+1) = (1 - r_{ij})C_{ij}(t)_s + r_{ij}b_{ij}(t) + \delta_{ij}\mu_i\sigma_{m_i}^2 \quad (27.25c)$$

The last term accounts for mutation, while the first two account for recombination as follows. With probability $1 - r_{ij}$, loci i and j do not recombine, passing their covariance after selection $C_{ij}(t)_s$ to their gametes, while with probability r_{ij} recombination does occur, with the covariance between i and j in a gamete equaling the between-gamete covariance following selection $b_{ij}(t)$. The $C_{ij}(t)$ determine the additive variance at generation t . First, let

$$2R_i(t) = 2 \sum_{j=1}^n C_{ij}(t) \quad (27.25d)$$

denote the genetic variation that is due to locus i (the factor of two arises because C_{ij} is a covariance of single allelic effects, with both alleles contributing to the genetic variance). Recalling Equation 16.1a, the total additive variance at time t is just

$$\sigma_A^2(t) = 2 \sum_{i=1}^n \sum_{j=1}^n C_{ij}(t) = 2 \sum_{i=1}^n R_i(t) \quad (27.25e)$$

In order to proceed, we need to compute the covariance C_s among alleles on the same gamete and the covariance b along alleles on different gametes following selection. Following Lande, we do so by considering the $n \times n$ matrices $\mathbf{C}_s(t)$, $\mathbf{b}(t)$, and $\mathbf{C}(t)$ for the $C_{ij}(t)_s$, $b_{ij}(t)$ and $C_{ij}(t)$ elements. Lande's key assumption is that the joint distribution of allelic affects for the n loci in a gamete is multivariate normal (MVN) before selection. Under Gaussian stabilizing selection, it remains normal after selection. However, Equation 27.25c shows that the distribution of allelic effects following recombination is the weighted sum of two normals (with differing variances), which *is not* normal (Felsenstein 1977; Fleming 1979; Nagylaki 1984; Turelli 1984; Bürger 1986). Hence, the assumption of multivariate normality is an approximation, a point that Lande stressed. The same issue holds with mutation, where even if effects are Gaussian, Equation 27.25c becomes a weighted sum of Gaussians, and hence not normal.

Under a MVN, the joint distribution of the vectors \mathbf{x} and \mathbf{x}' of maternal and paternal allelic effects in a newly-formed zygote are also MVN with covariance matrix

$$\mathbf{V}(t) = \begin{pmatrix} \mathbf{C}(t) & \mathbf{0} \\ \mathbf{0} & \mathbf{C}(t) \end{pmatrix} \quad (27.26a)$$

The matrix $\mathbf{0}$ of zeros on the off-diagonal corresponds to independent union of gametes (random mating) with the nonzero diagonal matrices $\mathbf{C}(t)$ correspond to the variances and LD structure (covariances), associated with each gamete. After Gaussian stabilizing selection this covariance matrix becomes

$$\mathbf{K}(t) = \begin{pmatrix} \mathbf{C}_s(t) & \mathbf{b}(t) \\ \mathbf{b}(t) & \mathbf{C}_s(t) \end{pmatrix} \quad (27.26b)$$

and the task is to compute these elements. Under Gaussian stabilizing selection (with an optimal value $\theta = 0$) the fitness of individuals with genotypic value $g = \sum(x_i + x'_i)$ is

$$W(g) = \exp \left(- \left[\sum_{i=1}^n (x_i + x'_i) \right]^2 / (2V_s) \right) = \exp \left(- \frac{\mathbf{x}\mathbf{1}\mathbf{x}^T + \mathbf{x}'\mathbf{1}\mathbf{x}'^T + \mathbf{x}'\mathbf{1}(\mathbf{x}')^T}{2V_s} \right) \quad (27.26c)$$

where $\mathbf{1}$ is an $n \times n$ matrix of ones (i.e., $\mathbf{1}_{ij} = 1$). The distribution of allelic effects after selection is proportional to $p(\mathbf{x})p(\mathbf{x}')W[\sum(x_i + x'_i)]$. Focusing just on terms in the exponential, this is $\propto \exp(-F/2)$, where F equals

$$[\mathbf{x} - \boldsymbol{\mu}(t)]\mathbf{C}^{-1}(t)[\mathbf{x} - \boldsymbol{\mu}(t)]^T + [\mathbf{x}' - \boldsymbol{\mu}(t)]\mathbf{C}^{-1}(t)[\mathbf{x}' - \boldsymbol{\mu}(t)]^T + \frac{\mathbf{x}\mathbf{1}\mathbf{x}^T + \mathbf{x}'\mathbf{1}\mathbf{x}'^T + \mathbf{x}'\mathbf{1}(\mathbf{x}')^T}{V_s}$$

Since the resulting distribution is also MVN with covariance matrix \mathbf{K} , matching quadratic terms between F and the matrix product

$$\begin{pmatrix} \mathbf{x} - \boldsymbol{\mu}(t) \\ \mathbf{x}' - \boldsymbol{\mu}(t) \end{pmatrix} \mathbf{K}^{-1} \begin{pmatrix} \mathbf{x} - \boldsymbol{\mu}(t) \\ \mathbf{x}' - \boldsymbol{\mu}(t) \end{pmatrix}^T$$

gives

$$\mathbf{K}^{-1}(t) = \begin{pmatrix} \mathbf{C}^{-1}(t) + \mathbf{1}/V_s & \mathbf{1}/V_s \\ \mathbf{1}/V_s & \mathbf{C}^{-1}(t) + \mathbf{1}/V_s \end{pmatrix} \quad (27.26d)$$

Lande noted that since $\mathbf{K}\mathbf{K}^{-1} = \mathbf{I}$, Equations 27.26b and 27.26d imply

$$\begin{pmatrix} \mathbf{C}_s(t) & \mathbf{b}(t) \\ \mathbf{b}(t) & \mathbf{C}_s(t) \end{pmatrix} \begin{pmatrix} \mathbf{C}^{-1}(t) + \mathbf{1}/V_s & \mathbf{1}/V_s \\ \mathbf{1}/V_s & \mathbf{C}^{-1}(t) + \mathbf{1}/V_s \end{pmatrix} = \begin{pmatrix} \mathbf{I} & \mathbf{0} \\ \mathbf{0} & \mathbf{I} \end{pmatrix} \quad (27.26e)$$

Solving this system of equations gives

$$\mathbf{C}_s(t) = \frac{1}{2} \left(\mathbf{C}^{-1}(t) + 2 \cdot \mathbf{1}/V_s \right)^{-1} + \frac{1}{2} \mathbf{C}(t) \quad (27.27a)$$

$$\mathbf{b}(t) = \mathbf{C}_s(t) - \mathbf{C}(t) \quad (27.27b)$$

Taking the inverse in 27.27a yields

$$\mathbf{C}_s(t) = \mathbf{C}(t) - \frac{\mathbf{C}(t) \mathbf{1} \mathbf{C}(t)}{V_s + \sigma_A^2(t)} \quad (27.27c)$$

The ij th term in the matrix $\mathbf{C}(t) \mathbf{1} \mathbf{C}(t)$ is $R_i(t) R_j(t)$, and Equation 27.27c becomes

$$C_{ij}(t)_s = C_{ij}(t) - \frac{R_i(t) R_j(t)}{V_s + \sigma_A^2(t)} \quad (27.27d)$$

Recalling Equation 27.27b, this implies

$$b_{ij}(t) = C_{ij}(t)_s - C_{ij}(t) = - \frac{R_i(t) R_j(t)}{V_s + \sigma_A^2(t)} \quad (27.27e)$$

Substituting Equations 27.27d and 27.27e into Equation 27.25c gives the following set of recurrence equations

$$\Delta C_{ij}(t+1) = -\frac{R_i(t) R_j(t)}{V_s + \sigma_A^2(t)} - r_{ij} C_{ij}(t) + \delta_{ij} \mu_i \sigma_{m_i}^2 \quad (27.28a)$$

At equilibrium, $\Delta C_{ij}(t) = 0$ or

$$\frac{\tilde{R}_i \tilde{R}_j}{V_s + \tilde{\sigma}_A^2} + r_{ij} \tilde{C}_{ij} = \delta_{ij} \mu_i \sigma_{m_i}^2 \quad (27.28b)$$

For $i = j$, $r_{ij} = 0$ and Equation 27.28b reduces to

$$\tilde{R}_i^2 = \mu_i \sigma_{m_i}^2 (V_s + \tilde{\sigma}_A^2), \quad \text{hence} \quad \tilde{R}_i = \sqrt{\mu_i \sigma_{m_i}^2 (V_s + \tilde{\sigma}_A^2)} \quad (27.28c)$$

Likewise, the off-diagonal elements can be shown to have solution

$$\tilde{C}_{ij} = -\frac{\sqrt{\mu_i \sigma_{m_i}^2 \mu_j \sigma_{m_j}^2}}{r_{ij}} \quad \text{for } i \neq j, \quad (27.28d)$$

showing the presence of negative LD at equilibrium, as expected from Chapter 16. Note, however, that the values are independent of the strength V_s of selection. Recalling Equation 27.25d, $\tilde{C}_{ii} = \tilde{R}_i - \sum_{j \neq i} \tilde{C}_{ij}$, giving

$$\tilde{C}_{ii} = \sqrt{\mu_i \sigma_{m_i}^2 (V_s + \tilde{\sigma}_A^2)} + \sqrt{\mu_i \sigma_{m_i}^2} \sum_{j \neq i} \frac{\sqrt{\mu_j \sigma_{m_j}^2}}{r_{ij}} \quad (27.29a)$$

Finally, since the equilibrium additive variance can be expressed in terms of the \tilde{R}_i as $\tilde{\sigma}_A^2 = 2 \sum \tilde{R}_i$, a little algebra yields

$$\tilde{\sigma}_A^2 = 2Z \sqrt{V_s + Z^2} + 2Z^2, \quad \text{where} \quad Z = \sum_{i=1}^n \sqrt{\mu_i \sigma_{m_i}^2} \quad (27.29b)$$

For n equivalent loci, $\sigma_m^2 = 2n\mu\sigma_{m*}^2$, reducing Z to $n\sqrt{\mu\sigma_{m*}^2}$ so that $2Z^2 = n^2 2\mu\sigma_{m*}^2 = n\sigma_m^2$, and we recover Equation 27.14c.

MUTATION-STABILIZING SELECTION BALANCE: DRIFT

Impact on Equilibrium Variances

Since mutation-drift models give too large a genetic variance, and mutation-selection models too small a variance, perhaps a mutation-selection model with drift might be just right. Alas, this is not the case. The incorporation of drift into mutation-selection balance models starts with Latter (1970) and Bulmer (1972). As might be expected, if the strength of selection is sufficiently weak (V_s sufficiently large), the equilibrium variance approaches the pure-drift result (Equation 11.19), while if the effects of drift are small (N_e sufficiently large), it approaches its deterministic value (e.g., Equation 27.18a under HCA).

Ignoring linkage disequilibrium (as above, simply summing the single-locus result), assuming Gaussian selection and the incremental mutational model with $m \sim N(0, \sigma_{m_*}^2)$, Bürger et al. (1989) obtained their **stochastic house-of-cards** approximation

$$\tilde{\sigma}_A^2 \simeq \frac{4n\mu V_s}{1 + V_s/(N_e \sigma_{m_*}^2)} \quad (27.30a)$$

Bürger (1988a), Keightley and Hill (1988), Barton (1989), and Houle (1989) all obtained similar expressions using different approaches. As with the deterministic HCA model, linkage has little effect on this result, which simulation studies find to generally be a good approximation, albeit a slight overestimate (Bürger 1988a; Bürger et al. 1989; Bürger and Lande 1994). Equation 27.30a, which we denote $\tilde{\sigma}_A^2(SHC)$, interpolates between the pure-selection HCA result (Equation 27.18a) denoted $\tilde{\sigma}_A^2(HC)$ and the pure-drift (neutral) result (Equation 11.19) denoted $\tilde{\sigma}_A^2(N)$. Following Bürger et al. (1989), a little algebra shows that

$$\tilde{\sigma}_A^2(SHC) = \frac{\tilde{\sigma}_A^2(HC) \cdot \tilde{\sigma}_A^2(N)}{\tilde{\sigma}_A^2(HC) + \tilde{\sigma}_A^2(N)} \quad (27.30b)$$

which is just half the harmonic mean of the pure selection and pure drift results. Analysis of Equation 27.30a gives the selection- and drift-dominated domains as

$$\tilde{\sigma}_A^2(SHC) \simeq \begin{cases} \tilde{\sigma}_A^2(N) & \text{when } N_e \sigma_{m_*}^2 \ll V_s \\ \tilde{\sigma}_A^2(HC) & \text{when } N_e \sigma_{m_*}^2 \gg V_s \end{cases} \quad (27.30c)$$

An alternative way to recover these domains is to recall that selection overpowers drift at a single locus when $|4N_e s| \gg 1$, while drift dominates when $|4N_e s| \ll 1$ (Chapter 7). Using Equation 27.4c, the expected selection coefficient for a new mutation (effect m_i under HOC) is

$$E(s_i) = \frac{E(m_i^2)}{2V_s} = \frac{\sigma_{m_i}^2}{2V_s} \quad (27.31)$$

Hence, $|4N_e s| \gg 1$ implies $2N_e \sigma_{m_i}^2 \gg V_s$, while $|4N_e s| \ll 1$ implies $2N_e \sigma_{m_i}^2 \ll V_s$, recovering the selection- and drift-dominated domains given in Equation 27.30c.

An important caveat is that finite-population expressions for $\tilde{\sigma}_A^2$ are *expected values*. Simulations show both considerable spread about this expected value and high autocorrelation between successive realizations (Keightley and Hill 1988; Bürger 1989; Bürger et al. 1989; Bürger and Lande 1994). Barton (1989) finds that the variation in the realizations is approximately

$$\sigma^2(\tilde{\sigma}_A^2(SHC)) \simeq \left(\frac{\sigma_{m_*}^2}{1 + \sigma_{m_*}^2 N_e / V_s} \right) \tilde{\sigma}_A^2(SHC) \quad (27.32)$$

This reduces (to leading order) to Equation 11.14 as $V_s \rightarrow \infty$ (the strength of selection approaches zero).

The Gaussian counterpart to the stochastic HCA can be obtained using the same logic leading to Equations 27.14d/e. Again, start with Equation 24.2a, which assumes a Gaussian distribution of allelic effects. Adding a term σ_m^2 for new mutation and ignoring disequilibrium ($d = 0, \sigma_a^2 = \sigma_A^2$), then at equilibrium

$$\sigma_m^2 = \frac{\tilde{\sigma}_A^2}{2N_e} + \left(1 - \frac{1}{N_e}\right) \frac{\tilde{\sigma}_A^4}{2nV_s} \simeq \frac{\tilde{\sigma}_A^2}{2N_e} + \frac{\tilde{\sigma}_A^4}{2nV_s}, \quad (27.33a)$$

where again we used the result that $\kappa h^2 = \sigma_A^2/V_s$ (note that our use of κ here and in Equations 27.14d,e follows from its use in Chapter 16 to measure the reduction in variance following selection, and is distinct from κ_4 which we use denote kurtosis). This yields the quadratic equation

$$\tilde{\sigma}_A^4 + \left(\frac{nV_s}{N_e}\right) \tilde{\sigma}_A^2 - 2n\sigma_m^2 V_s = 0, \quad (27.33b)$$

whose solution is the **stochastic Gaussian** result

$$\tilde{\sigma}_A^2 \simeq \sqrt{[nV_s/(2N_e)]^2 + 2n\sigma_m^2 V_s} - \frac{nV_s}{2N_e} \quad (27.33c)$$

Latter (1970), Keightley and Hill (1988), Houle (1989), Lynch and Lande (1993), and Santiago (1998) all independently obtained slightly different versions of this expression. For sufficiently weak drift (large N_e), Equation 27.33c approaches Kimura's Gaussian result (Equation 27.14a). For sufficiently weak selection (large V_s), the $\tilde{\sigma}_A^4$ term in Equation 27.33b can be ignored, which recovers the pure drift result (Equation 11.19). Bürger (2000) found that the stochastic version of Fleming's Gaussian approximation (Equation 27.15) is also of the form of Equation 27.33c, with the $2n\sigma_m^2 V_s$ term (the square of Kimura's result, Equation 27.14a) replaced by the square of Fleming's result (Equation 27.15).

Finally, drift can impact the domain of applicability of the Gaussian approximation. Houle (1989) notes that even higher mutation rates than those necessary for the deterministic Gaussian approximation are likely required in finite populations to compensate for the loss of alleles from drift. This suggests finite population size further restricts the domain of applicability to an even narrower region than the deterministic Gaussian approximation.

Impact on Underlying Loci

A second issue with drift is its effect on loci underlying a trait under stabilizing selection. Lande (1975) noted that with n loci, selection to move the mean to the optimum uses only a single degree of freedom (the sum of all allelic effects). He argued this leaves ample opportunity for drift at the underlying loci, and an important role for historical events, as well as considerable genetic differentiation between populations while still preserving the same mean and variance. The possibility of extensive neutral evolution at such loci was first examined by Kimura (1981), and later by Foley (1987, 1992), Hastings (1987), Bürger et al. (1989), and Barton (1989). As we will see, this turns out not to be the case.

Kimura (1981) noted that underdominant mutations are far more likely to become fixed than an unconditionally deleterious mutation with the same (initial) selection coefficient. From Equation 27.4c, the initial selection against a new mutation is $s_i = (a_i^2)/(2V_s)$, which decreases to zero (neutrality) as p_i approaches one half. Once the frequency drifts above 0.5, the allele is now favored, and increasingly so, as p_i approaches one. As a result of these frequency-dependent changes in s_i , Kimura found that extensive neutral evolution is possible when $4N_e s_i \ll 8$, a larger region that for a deleterious mutation with constant selection coefficient of the same value. Foley (1987) refined Kimura's result, showing that the expected substitution rate λ at loci underlying a trait under stabilizing selection is

$$\lambda \simeq \frac{\mu}{\sqrt{1 + \sigma_m^2 N_e / V_s}} \quad (27.34a)$$

$$\simeq \begin{cases} \mu & \text{when } \sigma_m^2 N_e \ll V_s \quad (\text{neutrality}) \\ \mu \sqrt{\frac{V_s}{\sigma_m^2 N_e}} & \text{when } \sigma_m^2 N_e \gg V_s \quad (\text{strong constraint}) \end{cases} \quad (27.34b)$$

Kimura also suggested that underdominance results in a more U-shaped frequency distribution (larger probability mass near zero and one) relative to a neutral diallelic locus with the same mutation rates. Foley (1992) gives weak selection approximations for the number of alleles and the frequency spectrum under the infinite-alleles model. These results show that the Lande-Kimura notion of extensive nearly-neutral behavior at the loci of a trait undergoing stabilizing selection does not hold. Rather, their behavior is more akin to loci subjected to weak purifying selection, and Barton (1989) notes that it is not possible to use the allele frequency distribution to distinguish between stabilizing and weak purifying selection.

Bürger et al. (1989) examined the heterozygosity at the underlying loci in simulation studies. Generally, there was a reasonable fit between the fully-neutral expectation of $\tilde{H}_n = \theta/(1+\theta)$ where $\theta = 4N_e\mu$ and the observed value \tilde{H}_o , except under strong selection and/or a high variance of mutational effects. Foley (1992) found that a slightly better fit was obtained by replacing θ by

$$\theta_s = 4N_e \frac{\mu}{\sqrt{1 + \sigma_m^2 N_e / (2V_s)}} \quad (27.34c)$$

Both Foley and Bürger et al. noticed that heterozygosity is not necessarily highly correlated with the additive variance. In particular, Bürger et al. noted that the relationship often used (e.g., Bulmer 1972) for a diallelic locus to relate the equilibrium additive variance to the observed heterozygosity, $\tilde{\sigma}_A^2 = n\sigma_{m*}^2 \tilde{H}_o$, generally *does not* hold under the infinite-alleles assumption.

MUTATION-STABILIZING SELECTION BALANCE: PLEIOTROPY

Finally, we conclude our discussion of theoretical models by considering both mutation and pleiotropy. Pleiotropic effects can be added to direct selection models (the trait itself is under selection), the subject of this section. Models can also be purely pleiotropic (the trait is neutral) and these are examined in the final selection. The presence of pleiotropy, where one locus influences multiple traits, introduces considerable complications. Many of the above models depend on difficult to estimate quantities (n , μ , and σ_{m*}^2). Pleiotropy adds additional, usually hidden, players that are very difficult to infer, much less estimate. This is especially problematic as seemingly very small differences in pleiotropy models can lead to qualitatively different outcomes. Johnson and Barton (2005) stress that the lack of understanding of both the nature of pleiotropy and how to robustly model it are the main impediments to a deeper understanding of the maintenance of variation.

Gaussian Results

To model multiple-trait selection with pleiotropic mutations, we follow the standard approach of working with single-locus haploid model, which is then extended to a diploid multilocus model by assuming additivity and that any effects from linkage disequilibrium are small. Several conceptual extensions are required when moving from a single- to a k -trait model. First, the single allelic effect at a given locus i is replaced by the vector $\mathbf{g}^{(i)}$ whose j -th element is the allelic effect for trait $1 \leq j \leq k$. As a result, the variance of allelic effects for a given locus is replaced by a variance-covariance matrix $\mathbf{V}_g^{(i)}$, where

$$\left(\mathbf{V}_g^{(i)}\right)_{\ell,j} = \sigma^2 \left(g_\ell^{(i)}, g_j^{(i)}\right), \quad 1 \leq \ell, j \leq k \quad (27.35a)$$

Similarly, when pleiotropic mutation occurs (a new mutation simultaneously influences several traits), the single-trait mutational effects variance σ_{m*}^2 is replaced by a **pleiotropic mutation matrix** $\mathbf{V}_m^{(i)}$,

$$\left(\mathbf{V}_m^{(i)}\right)_{\ell,j} = \sigma(m_{\ell,i}, m_{j,i}), \quad 1 \leq \ell, j \leq k \quad (27.35b)$$

where $m_{j,i}$ is the mutational increment to trait j from locus i . *Extensive pleiotropy can occur without any mutational covariance between traits*, a condition referred to as **hidden pleiotropy**. Short of actually measuring the joint effects of individual mutations (e.g., Chapter 26), the presence of hidden pleiotropy is difficult, if not impossible, to detect, yet has dramatic consequences for mutation-selection balance and for multivariate evolution in general (the latter discussed in detail in Volume Three).

Finally, modeling selection requires a multivariate extension of Equation 27.3b. If \mathbf{z} is the vector of k trait values, and $\boldsymbol{\theta}$ a vector of optimal values, then

$$w(\mathbf{z}) = \exp\left(-\frac{(\mathbf{z} - \boldsymbol{\theta})\mathbf{V}_\omega^{-1}(\mathbf{z} - \boldsymbol{\theta})^T}{2}\right) \quad (27.36a)$$

where \mathbf{V}_ω is a symmetric, positive-definite matrix (a matrix with all positive eigenvalues, see Appendix 5). For weak selection, expanding the quadratic product in the exponential gives

$$w(\mathbf{z}) \simeq 1 - \frac{1}{2} \sum_{i=1}^k \sum_{j=1}^k (z_i - \theta_i)(z_j - \theta_j) V_{ij} \quad (27.36b)$$

where V_{ij} is the ij -th element of \mathbf{V}_ω^{-1} . From the assumed positive-definiteness of \mathbf{V}_ω , this sum is always positive (unless $\mathbf{z} = \boldsymbol{\theta}$, in which case it is zero), resulting in fitness being maximized at $\mathbf{z} = \boldsymbol{\theta}$ and declining quadratically in any direction around $\boldsymbol{\theta}$ (Chapter 29). Assuming environmental effects are multivariate normal, $\mathbf{z}|\mathbf{g} \sim \text{MVN}(\mathbf{g}, \mathbf{V}_E)$, the multivariate version of Equation 27.3e gives the fitness associated with \mathbf{g} as $w(\mathbf{g}) = K \exp[-(\mathbf{g} - \boldsymbol{\theta})\mathbf{V}_s^{-1}(\mathbf{g} - \boldsymbol{\theta})^T/2]$, where

$$\mathbf{V}_s = \mathbf{V}_\omega + \mathbf{V}_E \quad (27.36c)$$

is the multivariate extension of Equation 27.3f.

Assuming that the vector of phenotypes is multivariate normal, $\mathbf{z} \sim \text{MVN}(\mathbf{0}, \mathbf{V}_z)$, the multivariate analog for the change in phenotypic variance (Equation 27.3g) is the change in the phenotypic covariance matrix \mathbf{V}_z ,

$$\Delta \mathbf{V}_z = -\mathbf{V}_z(\mathbf{V}_\omega + \mathbf{V}_z)^{-1}\mathbf{V}_z \simeq -\mathbf{V}_z\mathbf{V}_s^{-1}\mathbf{V}_z \quad (27.36d)$$

Similarly, when \mathbf{g} is multivariate normality, the change in the covariance for the vector of allelic effects following selection becomes

$$(\Delta \mathbf{V}_g^{(i)})_s = -\mathbf{V}_g^{(i)}(\mathbf{V}_s + \mathbf{V}_g^{(i)})^{-1}\mathbf{V}_g^{(i)} \simeq -\mathbf{V}_g^{(i)}\mathbf{V}_s^{-1}\mathbf{V}_g^{(i)} \quad (27.36e)$$

Following Lande (1980), the change in \mathbf{V}_g from the joint actions of selection and mutation is

$$\Delta \mathbf{V}_g^{(i)} = (\Delta \mathbf{V}_g^{(i)})_s + \mu_i \mathbf{V}_m^{(i)}, \quad (27.37a)$$

which is zero at equilibrium. Recalling Equation 27.36e,

$$\tilde{\mathbf{V}}_g^{(i)} \mathbf{V}_s^{-1} \tilde{\mathbf{V}}_g^{(i)} = \mu_i \mathbf{V}_m^{(i)} \quad (27.37b)$$

which has solution

$$\tilde{\mathbf{V}}_g^{(i)} \simeq \mathbf{V}_s^{1/2} \left(\mu_i \mathbf{V}_s^{-1/2} \mathbf{V}_m^{(i)} \mathbf{V}_s^{-1/2} \right)^{1/2} \mathbf{V}_s^{1/2} \quad (27.37c)$$

If \mathbf{V}_s and $\mathbf{V}_m^{(i)}$ are diagonal (no correlations in the fitness function, no pleiotropic covariance between mutational effects), Equation 27.37c gives the equilibrium variance for trait k at locus i as

$$\tilde{\sigma}_{A(k,i)}^2 \simeq \sqrt{\mu_i \sigma_{m_{k,i}}^2 V_{s,k}} \quad (27.38a)$$

which is simply Kimura's result for a single trait (Equation 27.22d). This is Lande's key finding: *under the Gaussian assumption, the equilibrium additive variance of a trait is unaffected by selection on uncorrelated (selectively and mutationally) traits.*

As noted by Turelli (1985), the condition for the multivariate Gaussian approximation to be reasonable is that

$$\mu_i \gg \frac{\sigma_{m_{k,i}}^2}{V_{s,k}} \quad (27.38b)$$

for *all* i loci and *all* k traits. The presence of *any* single locus that violates this condition invalidates the Gaussian approximation. A second restriction on the plausibility of the Gaussian approximation is the realistic number of functionally distinct alleles that can be maintained at a locus. Turelli (1984) found that a locus with roughly 20 alleles can fairly closely match the continuum-of-alleles model for a single trait. However, with two traits, allowing over 100 alleles still did not provide sufficient granularity to capture the bivariate continuum-of-alleles structure. This problem becomes increasingly more acute as the number of pleiotropic traits grows.

Example 27.8. To be a bit more formal on the conditions required for selection to be uncorrelated, consider the two-trait version of the matrices \mathbf{V}_ω , \mathbf{V}_E , and \mathbf{V}_s . When the off-diagonal element of this last matrix is zero, the two traits are selectively uncorrelated. Since \mathbf{V}_ω is a symmetric, positive definite matrix, it is also a covariance matrix, and hence we can write it as

$$\mathbf{V}_\omega = \begin{pmatrix} \omega_1^2 & \rho_\omega \omega_1 \omega_2 \\ \rho_\omega \omega_1 \omega_2 & \omega_2^2 \end{pmatrix}$$

where a nonzero ρ_ω implies selection favoring a covariance between z_1 and z_2 (Chapter 29). Similarly expressing the covariance matrix of environmental effects as

$$\mathbf{V}_E = \begin{pmatrix} V_{E1} & \rho_e \sqrt{V_{E1} V_{E2}} \\ \rho_e \sqrt{V_{E1} V_{E2}} & V_{E2} \end{pmatrix} \quad \text{gives} \quad \mathbf{V}_s = \mathbf{V}_\omega + \mathbf{V}_E = \begin{pmatrix} V_{s,1} & C_s \\ C_s & V_{s,2} \end{pmatrix}$$

where

$$V_{s,i} = V_i + V_{Ei}, \quad C_s = \rho_e \sqrt{V_{E1} V_{E2}} + \rho_\omega \omega_1 \omega_2 \quad (27.39a)$$

The two traits are selectively uncorrelated when $C_s = 0$, which requires that the phenotypic selection ρ_ω and environmental ρ_e correlations are zero, or the extremely unlikely event that $\rho_e = -\rho_\omega \omega_1 \omega_2 / \sqrt{V_{E1} V_{E2}}$. We can also write \mathbf{V}_s as

$$\mathbf{V}_s = \begin{pmatrix} V_{s,1} & \rho_s \sqrt{V_{s,1} V_{s,2}} \\ \rho_s \sqrt{V_{s,1} V_{s,2}} & V_{s,2} \end{pmatrix}$$

where

$$\rho_s = \frac{C_s}{\sqrt{V_{s,1}V_{s,2}}} = \frac{\rho_e \sqrt{V_{E1}V_{E2}} + \rho_\omega \omega_1 \omega_2}{\sqrt{V_{s,1}V_{s,2}}} \quad (27.39b)$$

HCA Results

An encouraging feature of the single-trait house-of-cards analysis was its relative robustness to the underlying genetical model. Provided that Equation 27.17 (or its diallelic counterpart Equation 27.11e) hold, the equilibrium variance (Equation 27.18a) is independent of details such as the number of alleles per locus. Unfortunately, Turelli (1985, 1986) shows that this robustness vanishes when pleiotropy is introduced. Even more troubling, and unlike the Gaussian result just obtained (Equation 27.38a), selection acting on pleiotropically-connected, but *uncorrelated*, traits influence the additive variance of a focal trait under the HCA (Turelli 1985, 1986, 1988; Wagner 1989; Slaktin and Frank 1990).

Turelli (1985) examined the simplest case of the HCA of a pleiotropic continuum-of-allele model: two traits that are mutationally and selectively uncorrelated, $(\mathbf{V}_m)_{12} = 0$ and $\rho_s = 0$ (defined by Equation 27.39b). He found that the bivariate HCA condition was more lenient than the univariate condition. For two (uncorrelated) traits, it becomes

$$\mu_i \ll \sqrt{\frac{\sigma_{m1,i}^2 \sigma_{m2,i}^2}{V_{s,1} V_{s,2}}} \quad (27.40)$$

which (unlike the Gaussian approximation) can be satisfied even when one of the loci does not itself satisfy the univariate HCA condition (Equation 27.17). Under the bivariate HCA, the equilibrium additive variance in trait one becomes

$$\tilde{\sigma}_A^2 \simeq \frac{4\mu_i V_{s,1}}{1 + \beta_i}, \quad \text{where} \quad \beta_i = \sqrt{\frac{\sigma_{m2,i}^2 V_{s,1}}{\sigma_{m1,i}^2 V_{s,2}}} \quad (27.41a)$$

Even if trait one is mutationally and selectively uncorrelated to trait two, it is still impacted by selection on the latter when $\sigma_{m2,i}^2 > 0$, namely locus i experiences pleiotropic mutations influencing trait 2. Recalling Equation 27.31, we β_i^2 is the ratio of the average selection coefficients (at locus i) for the two traits (Turelli 1985), as

$$\beta_i^2 = \frac{\sigma_{m2,i}^2 / (2V_{s,2})}{\sigma_{m1,i}^2 / (2V_{s,1})} = \frac{E[s_{2,i}]}{E[s_{1,i}]} \quad (27.41b)$$

Under the HCA setting (selection dominates mutation), both traits are near their optimum, so that a change in any direction is likely deleterious. Thus, any new mutations influencing trait one will also change trait two, further lowering fitness. The stronger selection is on trait two, the greater the additional reduction in fitness. When most of the selection on new mutations at locus i is on trait one ($\beta_i \ll 1$), Equation 27.41a is close to the single-trait HCA value. Conversely, when there is much stronger selection on trait two ($\beta_i \gg 1$), the amount of variation maintained for trait one is considerably below its single-trait HCA prediction. If there are a large number of traits under multivariate Gaussian selection, one can easily construct a single synthetic trait (a linear combination of the remaining traits) to reduce this to a two-trait (focal plus synthetic) model (e.g., Zhang and Hill 2003). Hence, for most traits

we expect selection on the “other” trait to be larger, and likely considerably so, resulting in an overprediction of trait one’s variance using the univariate HCA result.

Finally, since the HCA assumes that selection at a locus is much stronger than mutation, a consequence of this additional selection is to make the approximation more plausible. Pleiotropy expands the domain of applicability of the HCA while shrinking that of the Gaussian approximation (Equation 27.38b).

Example 27.9. Under the fitness function given by Equation 27.36a, Turelli (1985) and Zhang and Hill (2003) show that if the population is at (or very close) to its optimal value (here $\theta = 0$), the initial selection coefficient on a new mutation at locus i with effects vector \mathbf{m} is approximately

$$s_i \simeq -\frac{\mathbf{m}^T \mathbf{V}_s^{-1} \mathbf{m}}{2} \quad (27.42a)$$

This is the multivariate equivalent of Equation 27.4c. When \mathbf{V}_s is diagonal, this reduces to

$$s_i \simeq \sum_{j=1}^k \frac{m_{j,i}^2}{2V_{s,j}}, \quad \text{implying} \quad E[s_i] \simeq \sum_{j=1}^k \frac{\sigma_{m_{j,i}}^2}{2V_{s,j}} = \sum_{j=1}^k E[s_{j,i}] \quad (27.42b)$$

namely, the sum of the average selection coefficients of a new mutation associated with each of the k traits. More generally,

$$s_i \simeq \sum_{j=1}^k \sum_{\ell=1}^k m_{j,i} \cdot V_{j,\ell} \cdot m_{\ell,i}$$

where $V_{j,\ell}$ is the $j\ell$ -th element of \mathbf{V}_s^{-1} . Taking expectations,

$$E[s_i] \simeq \sum_{j=1}^k \sum_{\ell=1}^k V_{j,\ell} \cdot \sigma(m_{k,i}, m_{\ell,i}) \quad (27.42c)$$

showing that the selection coefficient now depends on the mutational covariances in addition to \mathbf{V}_s .

If the $1 \leq j \leq n$ traits impact locus i with roughly similar selection coefficients ($E[s_{j,i}] \simeq s$), then Zhang and Hill (2003) note from the central limit theorem that the distribution of s approaches a normal whose coefficient of variation goes to zero as approximately $\sqrt{(3\kappa_4 - 1)/n}$, where κ_4 is the scaled kurtosis of s , the trait-impact on the selection coefficient at a given locus. Thus for a sufficiently large number of independent traits under selection, s_i is approximately a constant with a small amount of normally-distributed error.

Besides generating a dependency on hidden traits, pleiotropy has another, equally insidious, feature. Under single-trait HCA conditions, the equilibrium variance does not depend on the genetic details beyond the total mutation rate (with diallelic, triallelic, and continuum-of-alleles models giving the same result). However, Turelli found that a five-allele model (the bivariate extension of his univariate triallelic model) gave

$$\tilde{\sigma}_A^2 \simeq \frac{4\mu_i V_{s,1}}{1 + \beta_i^2}, \quad (27.43)$$

a different result from the continuum-of-alleles model (Equation 27.41a). Thus, additional genetical details (such as the number of alleles) seem to matter under pleiotropy.

In the univariate case, the qualitative difference in additive variance under continuum-of-alleles (Kimura-Lande-Fleming) versus diallelic (Latter-Bulmer) models was due to the relative strengths of mutation and selection, *not* the number of alleles. Perhaps something similar is behind the difference between Equations 27.41a and 27.43. Wagner (1989) suggests this is indeed the case, and that it is the amount of pleiotropic constraint among the effects of a new mutations, rather than the number of alleles. Turelli's five-allele model is highly constrained due to the limited number of alleles, while this is not the case for the continuum-of-alleles result. Wagner considered a model of constraints where the effect on trait i from a mutation of effect m_j at an underlying generator loci j is $b_{ij}m_j$. This structures implies all of the mutational effects from a given locus are completely correlated, with the two-trait version recovering Turelli's five-allele result. Wagner suggests that differences in the amount of constraint on the pleiotropic nature of new mutations account for the differences between Equations 27.41a (little constraint) and 27.43 (significant constraint). Zhang and Hill (2003) showed this to be the case, recovering Turelli 5-allele result from a continuum-of-alleles model when $\rho_m = 1$.

As in the univariate case, radical differences in behavior between the Gaussian and HCA approximations are the result of differences in the relative strength of selection to mutation, *not* the underlying mutational model. Slatkin and Frank (1990) verified this by considering a nine allele model (giving a 3×3 lattice of trait values), which assumes a bivariate optimum of zero in both traits. The center allele (0,0) is at the bivariate optimum, and this allele is allowed to independently mutation for either trait, e.g., $(-a, 0)$, $(a, 0)$ or $(0, -a)$, $(0, a)$ or jointly mutation for both traits in four possible directions, $(-a, -a)$, $(-a, a)$, $(a, -a)$, (a, a) . This model offers a bit more granularity than Turelli's five allele model. Slatkin and Frank found both the Gaussian behavior of weak/no impact from selection on uncorrelated traits and the HCA behavior of strong impact from uncorrelated selection, depending on the relative strengths of selection and mutation.

MAINTENANCE OF VARIATION BY PLEIOTROPIC DELETERIOUS ALLELES

We conclude our discussion of theory with **pure pleiotropy models**, where fitness consequences of underlying loci are responsible for the maintenance of variation at a neutral trait. We previously considered Robertson's overdominant model, where these fitness effects are favorable, requiring only selection for the maintenance of variation. We now turn to models that maintain variation *in spite of* fitness consequences, which requires mutation to offset their removal by selection. This is the idea behind the **Hill-Keightley** (1988) (or **HK**) model of **pleiotropic side-effects**, where neutral trait variation is determined by pleiotropic effects of deleterious alleles in mutation-selection balance. One observation motivating this model is that mutations of major effects tend to be deleterious (Chapter 26). Coupling this with the belief (and some observations) that mutations often influence multiple traits, and that many are at least slightly deleterious, suggests that at least some variation for any trait is due to such deleterious alleles. As with much of the above analysis, the issues are whether such a model, by itself, can account for sufficient variation and sufficiently strong apparent stabilizing selection.

The Hill-Keightley Pleiotropic Side-effects Model

Organisms, and their underlying genetic systems, are expected to be highly integrated,

with single genes and single traits unlikely to be isolated from others. Hence, pleiotropy and correlated selection are expected to be the norm, not the exception. We have previously considered one special case of this, namely a locus influencing a number of traits all under stabilizing selection. Is there a more general way to model this complex situation? Hill and Keightley (1988) and Keightley and Hill (1990) suggest that one approach is to sweep all pleiotropic selective effects into a single term s , generally expected to be deleterious. We saw a hint of this in Example 27.9. Each new mutation has an effect a on the focal trait and a cumulative deleterious effect s (measured as the fitness reduction in heterozygotes). From Chapter 7, the (infinite-population) equilibrium frequency of such an allele arising under recurrent mutation is $\tilde{p} = \mu/s \ll 1$. Assuming additivity of trait mutations, the contribution to the additive variance of the trait from this locus is

$$2a^2 \tilde{p}(1 - \tilde{p}) \simeq 2a^2 \tilde{p} \simeq \frac{2a^2 \mu}{s}, \quad (27.44a)$$

giving the expected additive variance from this locus as $2\mu E[a^2/s]$. Using a Taylor-series approximation for the expected value of a ratio (LW Equation A1.19a) and $E[a^2] = \sigma_{m*}^2$ gives

$$E[a^2/s] \simeq \frac{\sigma_{m*}^2}{s} \left(1 + \frac{\sigma^2(a^2)}{\sigma^2(s)} - \frac{\sigma(a^2, s)}{\sigma_{m*}^2 \cdot s} \right), \quad (27.44b)$$

showing that the additive variance depends, at a minimum, on the kurtosis of mutational trait effects (which enters through the $\sigma^2(a^2)$ term) and the covariance between selective effects and squared trait values. This Taylor approximation can easily break down, making $E[a^2/s]$ dependent on additional features of the bivariate mutational distribution of (a, s) .

Barton (1990) and Kondrashov and Turelli (1992) examined simplified versions of this model with n identical loci, in which all mutations have the same deleterious effect s (Example 27.9 provides some justification for this assumption). This sidesteps delicate issues on the nature of the bivariate (a, s) distribution such as the covariance $\sigma(a^2, s)$ and its behavior for s near zero. While these **constant-s models** offer important insights, they can also be misleading for some features, as we detail below.

Barton assumed multiplicative fitnesses, with an individual heterozygous at k deleterious loci having fitness $(1 - s)^k \simeq \exp(-sk)$, while Kondrashov and Turelli allowed much more general fitness functions (including synergistic epistasis, and hence less of a selective load), with both reaching essentially the same conclusions. Let $\bar{k} = 2n\mu/s = 2n\tilde{p}$ denote the average number of deleterious alleles per individual. Assuming no linkage disequilibrium, summing over the contributions from the n loci yields

$$\tilde{\sigma}_A^2 \simeq 2n E[a^2] \tilde{p} = \frac{2n\mu\sigma_{m*}^2}{s} = \bar{k} \sigma_{m*}^2, \quad (27.45a)$$

Namely, the product of the average number of deleterious alleles and the average effect σ_{m*}^2 per allele on the trait variance. Alternatively, Equation 27.45a can be expressed as the ratio of the amount of variation introduced by mutation each generation and the rate of its removal by selection,

$$\tilde{\sigma}_A^2 = \frac{\sigma_m^2}{s}, \quad (27.45b)$$

This is also an alternative expression for equilibrium variance under the Latter-Bulmer model (Equation 27.12b), showing that these very different models (pure pleiotropy versus stabilizing selection) have some similar features. This should not be surprising, as under

the HCA, wildtype alleles are near the optimum and all mutations are deleterious. The difference is that the cause of the deleterious allele is specified under the HCA (stabilizing selection), but unspecified under pleiotropy.

Using the standard value of $\sigma_m^2 = 10^{-3}V_E$, Equation 27.45b gives $h^2 \simeq 0.5$ when $s \simeq 0.001$. This looks promising in that very weak deleterious selection can maintain levels of additive variance seen in natural populations. This is largely intuitive in that a strictly neutral model maintains very large amounts of variation in a large population, so a model where the underlying loci are close to neutral should also accommodate significant variation.

Since there is no assumed selection on the focal trait, can this model also generate sufficiently strong apparent stabilizing selection? Individuals carrying more deleterious alleles also have more extreme (positive and negative) trait values, generating a quadratic relationship between trait value and fitness, and a spurious signature of stabilizing selection. For example, an individual with k deleterious alleles has an approximate fitness of $1 - sk$ (under Barton's model) and $z^2 = \sum_i^k a_i^2$, where $E[z^2 | k] = k\sigma_{m*}^2$. Barton (1990), Kondrashov and Turelli (1992), and Zhang et al. (2002) show that the resulting apparent strength of stabilizing selection becomes

$$\hat{V}_s = \frac{\sigma_{m*}^2 (3\kappa_4 + 2\bar{k})}{2s} \quad (27.46a)$$

Here κ_4 , the scaled kurtosis of trait mutations, is greater than 1/3 if there is any variation the values of trait mutations. From Equation 27.45b, we can express this as

$$\frac{\tilde{\sigma}_A^2}{2\hat{V}_s} = \left(\frac{2n\mu\sigma_{m*}^2}{s} \right) \left(\frac{s}{\sigma_{m*}^2 (3\kappa_4 + 2\bar{k})} \right) = \frac{2n\mu}{3\kappa_4 + 2\bar{k}}, \quad (27.46b)$$

which we can rearrange to give

$$\tilde{\sigma}_A^2 = \frac{4n\mu\hat{V}_s}{3\kappa_4 + 2\bar{k}} < 4n\mu\hat{V}_s \quad (27.46c)$$

where the last step follows since $3\kappa_4 \geq 1$. Hence, for the same apparent strength of stabilizing selection, less additive variation is maintained under the constant- s pleiotropy model than under the HCA (Equation 27.18a). Likewise, from Equation 27.46b, we have

$$\hat{V}_s / \tilde{\sigma}_A^2 = \begin{cases} 3\kappa_4 / (n\mu) & \text{for } \bar{k} \ll 1 \\ 1/s & \text{for } \bar{k} \gg 1 \end{cases} \quad (27.47a)$$

In contrast to the similarity of $\tilde{\sigma}_A^2$ for the HCA and pleiotropy models (Equations 27.18a and 27.45b), the ratio of equilibrium variance to apparent strength of stabilizing selection is rather different,

$$\tilde{\sigma}_A^2 / \hat{V}_s = \begin{cases} 4n\mu & \text{HCA} \\ s & \text{Deleterious pleiotropy} \end{cases} \quad (27.47b)$$

Under direct selection V_s determines s (Equation 27.12c), while under pleiotropy, s determines \hat{V}_s .

Can the constant- s model account for *both* observed levels of variation *and* strengths of stabilizing selection? No. For $s = 0.001$ (corresponding to $h^2 = 0.5$), the induced apparent strength of stabilizing selection is $1000V_E$, far too weak relative to estimates from natural populations. Conversely, taking observed values of V_s around $20V_E$ implies $s = 0.05$. Using this value of s and $\sigma_m^2 = 10^{-3}V_E$, Equation 27.45a gives $\tilde{\sigma}_A^2 = 10^{-3}V_E / 0.05 = 0.02V_E$,

for a heritability of $h^2 = 0.02/(1 + 0.02)$, or just under two percent. The problem with the constant- s model is that it either does not produce enough additive variance (s is too large) or gives apparent stabilizing selection that is too weak (s is too small). This follows since s influences both $\tilde{\sigma}_A^2$ and \hat{V}_s , imposing a constraint on their relationship (Barton 1990; Kondrashov and Turelli 1992; Gavrilet and de Jong 1993; Zhang et al 2002). From Equation 27.46b,

$$\frac{\hat{V}_s}{\tilde{\sigma}_A^2} = \frac{3\kappa_4 + 2n\mu/s}{2n\mu} = \frac{3\kappa_4}{2n\mu} + \frac{1}{s} \geq \frac{1}{s} = \frac{\tilde{\sigma}_A^2}{\sigma_m^2} \quad (27.47c)$$

Noting that $\sigma_A^2 = [h^2/(1 - h^2)]\sigma_E^2$, Equation 27.47c becomes

$$\frac{\hat{V}_s}{\sigma_E^2} \geq \left[\frac{\tilde{h}^2}{1 - \tilde{h}^2} \right]^2 \frac{\sigma_E^2}{\sigma_m^2} \quad (27.47d)$$

Typical values for selection ($\hat{V}_s/\sigma_E^2 = 20$) and mutational variance ($\sigma_E^2/\sigma_m^2 = 10^3$) imply an equilibrium heritability of less than 0.17. As with previous models, the joint levels of variation and strength of selection under the constant- s pure pleiotropy are inconsistent with observations.

While the constant- s model is mathematically tractable, it is also biologically unrealistic, as we expect s and a^2 to vary and be at least somewhat correlated, as mutations with large absolute effects are expected to be more deleterious. Does incorporating these features resolve the inconsistencies between equilibrium additive variance and strength of apparent stabilizing selection? The short answer is no, while the longer answer is that variation in s introduces additional complications. As illustrated by Equation 27.44b, to proceed one must (at least) specify both the correlation ρ between fitnesses s and trait effects a^2 as well as the kurtosis of the distribution of trait mutational effects. Further, different bivariate distributions with the same values for these parameters can give very different results, making the outcome *extremely* model-dependent (Hill and Keightley 1988; Keightley and Hill 1990; Caballero and Keightley 1990; Johnson and Barton 2005), see Example 27.11.

One immediate problem arises from ρ . If $\rho = 1$, the HK model recovers mutation-stabilizing selection balance, with the additive variance approaching a limiting value as N_e increases (e.g., Equations 27.30a, 27.33c). For $\rho < 1$, the additive variance continues to increase without limit with N_e . This occurs because some small fraction of new mutations are effectively neutral, with the additive variance approaching the neutral result (Equation 11.19), but with a lower mutation rate. Since the effectively neutral mutation rate decreases as N_e increases, the result is a less than linear increase in additive variation with N_e , but the resulting variance is still unbounded under many distributions. As Johnson and Barton (2005) note, the conditional distribution of a for those values of s very near zero (near neutrality) determines whether the additive variance is unbounded in N_e , and very slight differences can result in dramatic differences in behavior.

Despite these issues, a few general features emerge from extensive simulation of this model by Keightley and Hill (1990) and Caballero and Keightley (1990), as well as from analytic results assuming a general bivariate gamma distribution for a and s (Zhang et al. 2002). As mentioned, with $\rho < 1$, the additive variance increases (without limit) with N_e . Such increases in additive variation are not seen in nature beyond the trivial case of an increase in variance when moving from very small (drift-dominated) to moderate-sized populations. Second, allowing s to vary increases both $\tilde{\sigma}_A^2$ and V_s relative to a constant- s model (with the same mean), so that the strength of apparent stabilizing selection is generally very weak, although abundant variation can potentially be maintained. Third, dominance in *trait* mutations has little effect (this is not the case for fitness mutations, as we discuss shortly). Fourth,

increasing the kurtosis (generating a longer tail) of the distribution of effects has opposite effects for trait and fitness mutations. Additive variance increases with the kurtosis of the fitness mutants (and can be much larger than that for a constant- s model), but decreases with the kurtosis of trait mutants. Increased fitness kurtosis implies more nearly-neutral mutations (and hence higher equilibrium frequencies), while increased trait kurtosis gives a larger fraction of small-effect mutations (with a smaller variance contribution per mutation). Recall that Example 27.9 showed if the pleiotropic effects are the result of stabilizing selection on a number of independent traits, the distribution of s values approaches a normal, so that the resulting fitness distribution is *not* leptokurtic and does not generate extra variation. Fifth, increasing the correlation ρ between a^2 and s decreases $\tilde{\sigma}_A^2$, as does increasing the average strength of deleterious selection $E[s]$. Sixth, the volume of mutations in the effectively neutral region ($0 \leq N_e|s| \leq 1$) significantly impacts the resulting genetic architecture. Finally, and related to this last point, the actual shape of the bivariate distribution is critical, with different distributions with similar moments often producing very different results (Johnson and Barton 2005).

Example 27.10. McGuigan and Blows (2012) used a clever mutation accumulation (MA) design in *Drosophila serrata* to examine the genetic covariance between fitness and two standard metric traits (wing size and shape). First, they used extinctions of MA lines as a measure of total fitness. Second, they allowed a female to choose among five brothers, allowing for sexual selection based on mate choice versus a control population where a random brother was chosen for her. Both designs have the same effective population size (the female with a choice was allowed to only mate once), so that consistent differences in trait values are the consequences of selection for mate choice. Previous work demonstrated that wing features are not involved in mate choice, so that changes are due to pleiotropic effects on metric traits from loci under selection for mate choice. Finally, they scored productivity (number of offspring) in the lines. Larger MA flies had higher productivity, but lower male sexual fitness and lower total fitness. Wing shape evolved only in the absence of sexual selection and tended to evolve the greatest in lines that eventually went extinct. Both observations suggest deleterious alleles (for either total fitness or sexual selection) also had pleiotropic effects on the metric traits.

Example 27.11. While parameters of the joint distribution of a and s for spontaneous mutations are extremely difficult to obtain, Mackay et al. (1992) were able to estimate these (for bristle number) using a set of spontaneous P-factor induced mutations in *Drosophila melanogaster*. The mean effect of an insertion on bristle number was around 0.4 standard deviations (σ), the mean s effect was 0.2, and the haploid genome mutation rate was about 0.1. The distributions of s and a were both leptokurtic, with many mutations with little to no effect and a few mutations with major effects. Finally, the correlation between the selection coefficient and absolute mutational effect was around 0.4. Caballero and Keightley (1990) used these values to parameterize an (a -reflected) bivariate gamma distribution ($s \leq 0, -\infty < a < \infty$) for simulations to estimate the resulting genetic architecture. For an assumed effective population size of 10^4 , the estimated heritability was 0.4. On average, just under 2000 new mutations appear in the population each generation, the vast majority (87%) of which are highly deleterious ($N_e s < -30$). The table below gives the expected number of mutations (each generation) in various (s, a) classes and the fraction of total additive variance attributable to each. The presented classes account for 77% of the total variance, with the remaining 23% associated with highly deleterious mutations ($N_e s < -5$). The

bulk of additive variation is due to weakly deleterious alleles of modest effect. Indeed, 56% of the expected additive variance is from roughly one percent of the total mutations arising each generation. These contributing mutations are slightly deleterious with small-modest effects on bristle number (between 0.125 and 0.5 standard deviations).

a/σ	$-1 \leq N_e s \leq 0$		$-5 \leq N_e s < -1$	
	Num.	% σ_A^2	Num.	% σ_A^2
0 - 0.125	33	4	47	2
0.125 - 0.25	7	13	7	6
0.25 - 0.5	3	23	6	14
0.5 - 1	< 1	7	< 1	3
> 1	< 1	7		

Caballero and Keightley also used a second, more crude, set of estimates from mutation-accumulation lines (and hence more reflective of spontaneous mutations). The kurtosis and correlation were unknown, but the haploid mutation rate was much higher (~ 1), while the average effects on fitness ($s \sim 0.01 - 0.02$) and bristle number ($\sim 0.07\sigma$) were much lower. Note that σ_m^2 only differs by roughly a factor of two between these different sets of estimates and both gave roughly similar heritabilities. Thus, when judged by the two easiest-to-measure macroscopic parameters, σ_m^2 and h^2 , these distributions appear rather similar. Their resulting genetic architectures, however, are radically different, with the bulk of additive variation now due to alleles of small a effects (58% with a less than 0.125σ), most of which are highly deleterious $N_e s < -30$. These disparate results arose from assumed differences in the bivariate distribution of effects and thus depend on microscopic parameters that are extremely difficult to measure, much less with any precision.

Example 27.12. An interesting example of apparent stabilizing selection was given by McGuigan and Blows (2009). Recall from Chapter 13 (e.g., Equation 13.26a) that the genetic variance-covariance matrix \mathbf{G} is critical to understanding multivariate evolution (discussed in great deal in volume 3). The first principal component of this matrix is often called \mathbf{g}_{max} and represents the linear combination of the traits under consideration that accounts for the most genetic variation. McGuigan and Blows classified male *Drosophila bunnanda* into those that were successful in a mate-choice experiment (high fitness) and those that were not (low fitness). Mating success, in part, is based on a set of cuticular hydrocarbons (CHC), with females favoring a particular combination (weighted index, e.g., $\sum \alpha_i \text{CHC}_i$) of CHC scores. Since this combination has been under strong directional selection, it is not surprising that there is very little genetic variation in this index. Surprisingly, when the additive variance in the (very different) index whose weights are given by \mathbf{g}_{max} was examined, low-fitness males had almost twice as much variation as high-fitness males. Looked at another way, individuals showing variation from an optimal value in the index given by \mathbf{g}_{max} had reduced fitness, showing stabilizing selection on this index. However, there is no direct selection on this index (indeed, it is almost orthogonal the index under selection by female choice), so the appearance of stabilizing selection likely arises from pleiotropic effects on other fitness components that also influence CHC scores. Sztepanacz and Rundle (2012) also observed this in mate-choice experiments in the sister species *D. serrata*. Building on this observation, McGuigan et al. (2011) suggest that “ \mathbf{g}_{max} is expected to capture a greater portion of the accumulated pleiotropic mutation in a set of traits, including mutations with pleiotropic effects on fitness. Consequently, strong stabilizing selection should be generated on \mathbf{g}_{max} , providing the opportunity to investigate the genetic basis of fitness using this simple summary statistic.”

Deleterious Pleiotropy-Stabilizing Selection (Joint-effects) Models

Our final class of models is the most realistic, allowing for direct stabilizing selection, deleterious pleiotropic effects, and drift, but as such is also the most highly parameterized. These are extensions of the Hill-Keightley model where the trait itself is under stabilizing selection. They have all of the inherent complexity just seen for the HK model plus the additional complication of (real) stabilizing selection. They also appear to provide the best resolution of simultaneously accounting for levels of variation and strengths of apparent stabilizing selection.

While the most detailed analyses are by Zhang and Hill (Zhang and Hill 2002, 2003, 2005b; Zhang et al. 2004a), and indeed the term **joint effects model** was coined by Zhang and Hill (2002), their roots trace back to brief comments by Kondrashov and Turelli (1992). These were expanded on by Tanaka (1996, 1998), who considered a model with a constant pleiotropic selection coefficient and (what amounts to) a constant effect a on the trait. We present these results first, which are substantially altered when either vary (Zhang and Hill 2002).

For relatively weak selection, Kondrashov and Turelli noted that the total selection coefficient s_T on a locus is approximately the sum of a (constant) pleiotropic deleterious s_p effect and (under HCA conditions) a deleterious effect s_d from stabilizing selection (Equation 27.31),

$$s_T \simeq s_p + s_d = s_p + \frac{\sigma_{m*}^2}{2V_s} \quad (27.48a)$$

Kondrashov and Turelli suggest that even when fairly strong stabilizing selection occurs on a trait, most of the selection on its underlying loci is from its pleiotropic effects. Note from Equation 27.48a that the impact s_d from direct stabilizing selection increases with the mutational effects variance σ_{m*}^2 and decreases with V_s . To bias our results in favor of larger values of s_d , assume $\sigma_{m*}^2/\sigma_E^2 = 0.1$ and the standard assumption of $V_s/\sigma_E^2 \simeq 20$, giving $s_d \simeq 0.1/40 = 0.0025$. Using the Crow and Simmons (1983) estimate of $s_p = 0.02$ for deleterious mutations in *Drosophila* gives an eight-fold higher selection coefficient from pleiotropy, even under a setting that should be biased for higher s_d values. Even assuming a much larger mutational-effects variance ($\sigma_{m*}^2/\sigma_E^2 = 1$ and hence $s_d = 0.025$) still leaves almost half of the selection from pleiotropic effects.

With this value of s_T , Equation 27.45b suggests the equilibrium variance as

$$\tilde{\sigma}_A^2 \simeq \frac{\sigma_m^2}{s_T} = \frac{\sigma_m^2}{s_p + \sigma_{m*}^2/(2V_s)} = \frac{2V_s\sigma_m^2}{2V_s s_p + \sigma_{m*}^2} \quad (27.48b)$$

As expected, this recovers Equation 27.45b for sufficiently large V_s (very weak stabilizing selection) and Equation 27.18a for sufficiently small s_p (very weak pleiotropic effects). Adding even a very weak amount of stabilizing selection results in a reduction of the equilibrium variance relative to the pure pleiotropy model, a consequence of such selection increasing the value of s_T (albeit perhaps trivially). This immediately resolves the delicate issue of additive variance increasing without limit under the HK model. As the effective population size increases, eventually $N_e|s_d| \gg 1$, and none of the trait mutations are effectively neutral, limiting the increase in additive variance. Zhang and Hill (2002) note that Equation 27.48b is modified significantly if s_p and/or a vary, as we will see shortly.

Tanaka (1996) and Zhang et al. (2004a) note that the strength \hat{V}_s of *apparent* stabilizing selection under the joint actions of *real* stabilizing selection V_s and deleterious pleiotropic

effects s_p is

$$\hat{V}_s^{-1} = V_p^{-1} + V_s^{-1} \quad (27.49a)$$

where V_p is the induced strength of stabilizing selection from the pleiotropic effects. Equation 27.49a implies $\hat{V}_s \leq V_s$, giving the apparent strength as greater (\hat{V}_s smaller) than the true amount V_s of actual stabilizing selection. Incorporating real stabilizing selection breaks the constraint given by Equation 27.47c between \hat{V}_s and σ_A^2 that prevents a pure pleiotropy model generating *both* significant variance and strong apparent stabilizing selection. When s_p and a are constant, Equation 27.49a becomes

$$\frac{\sigma_A^2}{2\hat{V}_s} \simeq s_p + \frac{\sigma_A^2}{2V_s} = \frac{2V_s s_p + \sigma_A^2}{2V_s} \quad (27.49b)$$

or

$$\frac{\hat{V}_s}{\sigma_A^2} \simeq \frac{V_s/\sigma_A^2}{1 + 2(V_s/\sigma_A^2)s_p} \quad (27.49c)$$

For s_p near zero, Equation 27.49c reduces to V_s , while for very large V_s (weak selection), this recovers Equation 27.46.

Example 27.12 For $V_s/\sigma_A^2 = 100$ and $s_p = 0.001$, Equation 27.49a gives

$$\frac{\hat{V}_s}{\sigma_A^2} \simeq \frac{100}{1 + 200 \cdot 0.001} = 83.3,$$

much weaker than Turelli's benchmark of 20, but stronger than the real stabilizing selection. For this value of s_p and our standard value of $10^3 \sigma_m^2 = \sigma_E^2$, we previously found that $\tilde{h}^2 = 0.5$ under the HK model. For these values, and assuming $\sigma_{m*}^2 = \sigma_E^2$ (the effect of an average new mutation is one standard deviation), Equation 27.48b gives

$$\tilde{\sigma}_A^2 \simeq \frac{2V_s \sigma_m^2}{2V_s s_p + \sigma_{m*}^2} = \frac{2 \cdot 100 \cdot 10^{-3} \sigma_E^2}{2 \cdot 100 \cdot 0.001 \sigma_E^2 + 1 \cdot \sigma_E^2} = 0.167$$

for a heritability of $0.167/(1+0.167)$, or roughly 14%. The addition of rather weak stabilizing selection significantly lowered the heritability. We can see the cause from Equation 27.31, with

$$s_d = \frac{1}{200} = 0.005$$

so that even this weak amount of stabilizing selection results in a selection coefficient five times larger than our assumed pleiotropic effect. Conversely, if we assume $\sigma_{m*}^2 = \sigma_E^2/10$ (corresponding to $s_d = 0.0005$), heritability is 40%, while \hat{V}_s is unchanged.

While joint-effects models with a and s constant give some insight as to how pure pleiotropy and real stabilizing selection interact, they also miss important consequences when either (or both) vary. A simple example makes the point. Suppose that there are two equally-frequency classes of pleiotropic mutants. The first has $s_p = 0.001$, while the second has $s_p = 0.1$. Further suppose in both cases that $s_d = 0.001$, generating half the mutations

with $s_T = 0.002$ and the other half with $s_T = 0.101$. Substituting their average $\bar{s}_T = 0.0515$ into Equation 27.48b gives $\sigma_m^2/0.0515 \simeq 19\sigma_m^2$. However, the correct value is the average of the variation generated by each class,

$$\frac{\sigma_m^2/0.002 + \sigma_m^2/0.101}{2} \simeq 255\sigma_m^2$$

Note that this same argument applies to the pure pleiotropy model, and is the reason that variation in s generates more variance than a constant s with the same mean value.

Zhang and Hill (2002) show that the connection between the observed strength of apparent stabilizing selection \hat{V}_s and any real selection on the trait V_s is

$$\hat{V}_s^* = \frac{\tilde{\sigma}_A^4}{\tilde{\sigma}_A^4/V_s + \sigma_m^2} \leq \hat{V}_s = V_s \left(\frac{\tilde{\sigma}_A^4/V_s + \sigma_m^2 - \sigma_p(w, z^2)}{\tilde{\sigma}_A^4/V_s + \sigma_m^2} \right) \leq V_s \quad (27.50)$$

where $\sigma_p(w, z^2)$ is the covariance (from pleiotropy) between relative fitness and squared trait deviations. When the effects from pleiotropic selection dominance, $\sigma(w, z^2) \rightarrow \sigma^2$, recovering the lower bound \hat{V}_s^* (corresponding the strongest amount of apparent selection), while when the effects of pleiotropy are very small ($\sigma_p(w, z^2) \rightarrow 0$) the apparent strenght of selection approaches its upper limit V_s .

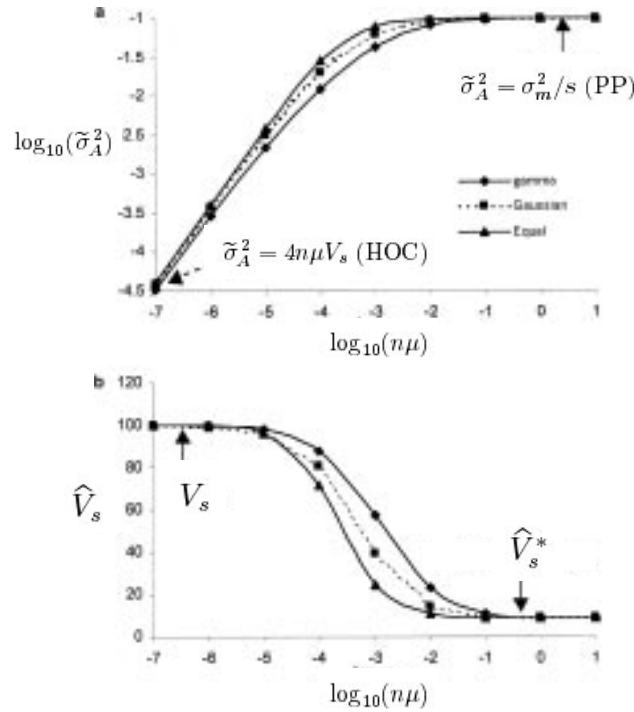


Figure 27.4. The behavior of the equilibrium additive variance $\tilde{\sigma}_A^2$ and the apparent strength \hat{V}_s of stabilizing selection under the joint-effects model. Here $E[s_p] = 0.02$ and $E[a] = \sqrt{\sigma_{m*}^2}$ as a function of mutation rate. Note that σ_M^2 is head constant, so an increase in the genomic mutation rate decreases σ_{m*}^2 , resulting in weaker selection on loci under true stabilizing selection. For low mutation, the additive variance is given by the

house-of-cards approximation (Equation 27.18a) and the apparent strength of selection is just the true strength of selection V_s . For high mutation rates (small σ_{m*}^2 and hence $s_r \ll s_p$) the equilibrium variance is given by the pure pleiotropy result (Equation 27.45b) and the apparent strength of selection approaches its lower limit (strongest value), \hat{V}_s^* given by Equation 27.50.

When s is constant, but a varies, then for $s_p \gg E[s_r]$, s is Equation 27.45b is replaced by

$$s_T \simeq s_p + 3\kappa_4 E[s_r] = s_p + 3\kappa_4 \frac{\sigma_{m*}^2}{2V_s} \quad (27.51a)$$

Here $\kappa_4 = E[a^2]/(3E[a^2])^2$ is the scaled kurtosis, equaling 1/3 when all the effects are the same (uniform a value), 1 if they are from a normal and > 1 for a leptokurtotic distribution. This shows (as mentioned above) that increasing the kurtosis of the trait mutations values lowers the equilibrium additive variance. For $s_p \ll E[s_r]$, the equilibrium variance is given by the HCA (Equation 27.12a).

Finally, when *both* a and s vary independently,

$$s_T = E[s_r] + \sqrt{E[s_r] \cdot E[s_p]} \quad (27.51b)$$

showing that when both vary, these no longer act in an additive fashion. For $E[s_r] \gg E[s_p]$, this reduces to (Equation 27.12a), while for $E[s_r] \ll E[s_p]$,

$$\sigma_A^2 = \sqrt{2n\mu V_{s,r} \sigma_m^2 / E[s_p]} \quad (27.51c)$$

which is the geometric mean of the HCA and pure-pleiotropy (with constant fitness $s = E[s_p]$) models (Zhang and Hill (2002).

HOW WELL DO THE MODELS FIT THE DATA?

To aid the reader who either skipped or skimmed the above rather dense theory sections, Table 27.3 summarizes the major conclusions from all of this analysis. Essentially all of the models have issues, generally being unable to simultaneously generate a high value of $\tilde{\sigma}_A^2$ (and hence a heritability in the 0.2 to 0.6 range) *and* sufficiently strong apparent (or real) stabilizing selection ($\hat{V}_s \leq 20\sigma_E^2$). This is what lead Johnson and Barton (2005) to lament that “it is puzzling that levels of heritability are so pervasive, so high and roughly constant” yet “we are in the somewhat embarrassing position of observing some remarkably robust patterns ... and yet seeing no compelling explanation for them.” Before condemning the models, a more careful look at the data is in order.

Table 27.3. Inconsistencies between model predictions and observed amount of genetic variation and strengths of natural selection. A model has to simultaneously generate large $\tilde{\sigma}_A^2$ and small \hat{V}_s .

Neutral focal trait, no selection

Mutation-drift

Does not account for apparent stabilizing selection.

Additive variance increased without limits as $N_e \rightarrow \infty$.

Neutral focal trait, selection on pleiotropic underlying loci

Fitness overdominance	Required strength at overdominant loci generates a very large genetic load.
Mutation-selection balance	Equation 27.27d prevents a small \widehat{V}_s without a small $\widetilde{\sigma}_A^2$
Direct selection on focal trait	
Strict stabilizing selection	Fitness underdominance generated at underlying loci. Very little additive variance at equilibrium.
Stabilizing selection - mutation balance	Too much additive variance for the observed strengths of stabilizing selection.
Pleiotropic overdominance	Load and selection response arguments
Pleiotropic deleterious alleles (Joint-effects models)	

Strength of Selection: Direct Selection on a Trait

Most of the above models can easily generate sufficient genetic variation. Indeed, a strictly neutral model generates *too much* variation. The more problematic issue is accounting for real (or apparent) strong stabilizing selection, warranting a more careful look at the assumed literature values. If the real/apparent stabilizing selection is weaker than typically assumed, many of the apparent contradictions disappear, and indeed a number of models can potentially account for the observations.

While Turelli's (1984) benchmark of $V_s \simeq 20\sigma_E^2$ is typically used, the data are more problematic than when Turelli extracted this value from the literature. The classic paper by Lande and Arnold (1983) that launched an entire cottage industry on the estimation of these parameters appeared at essentially the same time as Turelli's analysis. We examine fitness estimation in detail in Chapters 28 and 29, but the basic point is that there is considerable uncertainty on the strength of selection on a typical trait. The relative constancy of many morphological phenotypes over evolutionary time is consistent with some form of stabilizing selection, as are the divergence data on gene expression (Chapter 12). The strength of such selection is far less clear. The meta-analysis (Figure 29.5) by Kingsolver et al. (2001) on the quadratic terms of a Lande-Arnold fitness regression show it is equally likely to be positive (disruptive selection) or negative (stabilizing selection). Conditioning on this value being negative, the mean strength is slightly stronger than Turelli's value.

Besides the standard concern of measurement error and power (especially with an inherently noisy trait like fitness), there are three issues that significantly obscure the actual strength of selection (Chapters 28, 29). First, almost all fitness-trait regressions in the literature use a *component* of fitness (such as mating success, fecundity, or viability), *not* total fitness. Such component-based estimates can be very misleading. Second, selection acting on phenotypically correlated characters obscures not just the actual strength of selection on a target trait. More fundamentally, it can also disguise its true nature (directional, stabilizing, or disruptive). As Example 27.1 shows, a neutral trait can show a strong signal of stabilizing selection simply from selection on phenotypically-correlated traits. The standard approach for dealing with this concern is a multivariate regression with a number of traits, in the hope that some of these, if not the actual targets of selection, are highly correlated with the targets. Their inclusion acts as a covariate to reduce spurious associations. However, this approach is far from foolproof (Chapter 29). Finally, as Example 27.1 highlights, what matters is not the strength of selection on the phenotype but rather the strength of selection on the *breeding value*. A highly heritable trait under strong apparent stabilizing selection can

still have little to no selection on genotypic values if the target of selection is not the trait itself (Chapters 20, 28-29).

Finally, there is also the issue of load discussed previously, which suggests an upper bound on the number of independent traits under selection. Barton (1990) and Walsh and Blows (2009) suggest that strong selection is likely confined to a few indices of trait values, so that selection impacts a very large number of traits, but each only weakly. We return shortly to the implications of this idea on the maintenance of variation.

Example 27.13. Hunt et al. (2007) examined selection of mate calls in the cricket *Teleogryllus commodus*. One advantage of this system is that the multivariate trait, call signal, can have any of its individual components artificially changed via computer software and its fitness component (mate attraction) assessed through acoustic playback trails in natural populations (Brooks et al. 2005). Five call components were examined, whose heritabilities ranged from 17% to 72%. These components were also strongly genetically correlated, with values ranging from -0.65 to 0.40 . Factor-analysis modeling (Hine and Blows 2006; see Volume 3) gave strong support for three dimensions of the resulting genetic variance-covariance (\mathbf{G}) matrix for these five traits, with the first three eigenvalues (λ_1 to λ_3) accounting for 90% of the total genetic variation. Their associated eigenvectors are denoted \mathbf{g}_{max} , \mathbf{g}_2 , and \mathbf{g}_3 . There was also close to significant support for the fourth eigenvalue, but no support for the final (fifth) dimension.

Using the methods of Chapter 29, the 5×5 matrix γ of quadratic selection gradients of call components on mate attractiveness was estimated (Brooks et al. 2005). Its diagonal components γ_{ii} corresponds to the amount of quadratic selection on trait (call component) i , with a large negative value indicating strong stabilizing selection. Likewise, the amount of quadratic selection acting on some linear combination of trait values $\sum a_i z_i = \mathbf{a}^T \mathbf{z}$ is given by the quadratic product $\mathbf{a}^T \gamma \mathbf{a}$ (Appendix 5 and Chapter 29). Hunt et al. used this result to examine the strength of stabilizing (negative values) or disruptive (positive values) selection along the dimensions of variation given by each eigenvector, namely $\mathbf{g}_i^T \gamma \mathbf{g}_i$ for eigenvector i . As the table below shows, there was very weak disruptive selection along the first eigenvector \mathbf{g}_{max} (not significantly different from no selection), and increasingly strong selection on eigenvectors 2 through 4. As the strength of stabilizing selection increased (-0.12 , -0.51 , -0.97), the amount of genetic variation in that direction decreased (25.6%, 12.9%, 6.9%).

	\mathbf{g}_{max}	\mathbf{g}_2	\mathbf{g}_3	\mathbf{g}_4	\mathbf{g}_5
λ_i	0.930	0.468	0.235	0.125	0.065
% Var	51.0	25.6	12.9	6.9	3.6
$\mathbf{g}_i^T \gamma \mathbf{g}_i$	0.005	-0.012	-0.051	-0.097	-0.011
$\mathbf{g}_i^T \Delta \mathbf{G} \mathbf{g}_i$	0.00400	-0.00283	-0.00285	-0.00212	-0.00009
	6.6%	-7.8%	-11.0%	-13.0%	-3.8%

Another measure of the impact of selection is the expected within-generation change in the covariance matrix from selection, which is given by $\Delta \mathbf{G} = \mathbf{G} \gamma \mathbf{G}$ when there is no directional selection (Volume 3). As above, the amount of change in the additive variance of a composite trait given by $\mathbf{a}^T \mathbf{z}$ is just $\mathbf{a}^T \Delta \mathbf{G} \mathbf{a}$, so that the amount of change in the genetic variance along the direction given by eigenvector i is just $\mathbf{g}_i^T \Delta \mathbf{G} \mathbf{g}_i$. The fractional change in the genetic variance along this direction is given in the final row of the above table, and shows that the expected change in the genetic variance along the directions given by eigenvectors 2 through 4 are -8% , -11% , and -13% , respectively. The eigenvector associated with λ_5 breaks this pattern of lower genetic variance associated stronger selection, but

this eigenvalue is not significantly different from zero, and hence could simply be residual noise, not any structure (Volume 3 examines the estimation of the true dimensionality of \mathbf{G} matrices in some detail).

When examined one trait at a time (but still correcting for the correlation among traits), the heritability and strengths of selection on the individual traits were

Trait	CPN	CIPD	TN	ICD	DF
h^2	0.719	0.388	0.257	0.167	0.293
γ_{ii}	0.006	-0.006	-0.040	-0.070	-0.047

While the above pattern of lower heritabilities for traits under stronger selection still holds, note that stabilizing selection on the direction given by the eigenvectors of \mathbf{G} is stronger than selection on any given trait. If the strength of stabilizing selection was estimated in a truly univariate fashion (ignoring the other four call components), estimates of the strength of quadratic selection are even more untrustworthy given the strong correlations among these traits. The message here is that a full multivariate analysis gives a much more accurate picture than a series of univariate analyses focusing on single traits, which can be very misleading (Volume 3). Discussions about the forces behind the maintenance of variation should always be set within a multivariate framework.

Strength of Selection: Persistence Times of New Mutants

A potentially cleaner measure of the strength of selection on the breeding values of a trait is offered by the ratio $\tilde{\sigma}_A^2/\sigma_m^2$ of additive to mutational variance. As the equilibrium is reached when the variation introduced by mutation σ_m^2 is balanced by its removal, this ratio is a measure of the strength of selection against new mutations (whatever the cause, be it direct selection on the trait or pleiotropic fitness effects). It corresponds to the average number of individuals affected by a mutation before its removal (Li and Nei 1972), which Crow (1979, 1993) calls the **persistence time**. The weaker selection, the slower the removal and the higher the ratio. More formally, we can use this ratio to assign approximate selection coefficients. Under strict pleiotropy, Equation 27.45b gives this ratio as $\tilde{\sigma}_A^2/\sigma_m^2 = 1/s$ (when mutations have a fixed selected value). Likewise, recalling Equations 27.31 and 27.30a, a little algebra gives the stochastic house of cards as

$$\tilde{\sigma}_A^2/\sigma_m^2 = \frac{2N_e}{1 + 2N_e s} = \begin{cases} 2N_e & \text{for } N_e s \ll 1 \\ s^{-1} & \text{for } N_e s \gg 1 \end{cases} \quad (27.50)$$

Large values of this ratio (> 1000) are more consistent with drift, smaller values with deleterious mutation-selection balance, be it pleiotropy and/or direct selection (Barton 1990). We can also (approximately) relate this ratio to the apparent strength of stabilizing selection by recalling that $s \simeq 1/(2V_s)$ under stabilizing selection. In a survey over several traits and organism, Houle et al. (1996) found an average value of $\tilde{\sigma}_A^2/\sigma_m^2 \simeq 50$ for life history traits and $\simeq 100$ for morphological traits. Note that these values (roughly) correspond to $V_s/\sigma_E^2 \simeq 100$ and 200, respectively, which are higher (weaker selection) than the standard Turelli value of $\simeq 20$. Nonetheless, they clearly indicate an important role for selection. Houle et al. note that these estimates raise a dilemma, in that if most of the genetic variation is associated with deleterious pleiotropic effects, it may have little bearing on adaptive evolution, which may largely due due to rare mutations that have only weak pleiotropic side effects.

Number of Loci and Mutation Rates

A second issue, which is important when real stabilizing selection is assumed to occur, is Turelli's point that a haploid mutation rate $n\mu$ must be sufficiently large to account for observed levels of variation. Recalling Equation 27.12e, for $V_s = A\sigma_e^2$, to obtain a heritability of h^2 requires

$$\frac{4V_s n\mu}{4V_s n\mu + \sigma_e^2} = \frac{4A\sigma_e^2 n\mu}{4A\sigma_e^2 n\mu + \sigma_e^2} = \frac{4An\mu}{4An\mu + 1} = h^2$$

or that $n\mu = h^2/[4A(1 - h^2)]$. For Turelli's value ($A = 20$), $h^2 = 1/3$ requires $n\mu = 0.0065$, while $h^2 = 1/2$ requires $n\mu = 0.0125$. For a standard mutation rate of 10^{-5} , this value of $n\mu$ requires over a thousand loci ($n = 1250$). This argument lead Latter (1960) to conclude that stabilizing selection-mutation balance could not account for standing levels of variation, a point echoed by Turelli, assuming standard assumptions ($n < 100$, $\mu < 10^{-5}$) are correct. Have more recent data shifted this view?

Consider n first. Results from genome-wide association studies (GWAS) in humans typically find a large number of factors, each of very small effect (Chapter 24). The massive power loss in a typical GWAS due to conservative control over multiple comparisons (often over 10^6 SNPs tested), likely means that the number of sites declared as significant is only a small fraction of the number of truly causative sites. This is one factor leading to the "problem" of "missing heritability" (Example 24.1). Thus the notion that a "typical" trait may be influenced by hundreds of loci ($n > 500$) is less surprising that it once was. For example, Kemper et al. (2012) suggest that GWAS studies imply at least 1500 genes are involved in human height, while gene knock-out studies in mice suggest around 6000 loci for body size. Taken as a whole, the GWAS data has certainly shifted the consensus to a much larger number of number loci for a typical trait. Indeed, the method of genomic selection (Volume 3), which has rapidly been adopted by commercial breeders, rests on the assumption of a very large number of underlying loci.

Likewise, as noted by Turelli (1984), the "typical" value of 10^{-5} to 10^{-6} for the mutation rate a locus is based on alleles of large effect, and one can easily imagine a much higher mutation rate to alleles of smaller effect. Why? Under the view that much of quantitative-genetic variation is regulatory as opposed to changes in amino acid sequences, there is a much larger mutational target, with many of the resulting mutations resulting in very slightly regulatory changes. Likewise, other factors such as the transposition of a mobile element (often with its own regulatory sequences) can occur at higher rates than point mutations, as can the potential for copy number variation (CVN), which again has a regulatory impact. Gametic mutation rates for fitness components have been estimated to be in the 0.1 to 0.01 range (LW Chapter 13; Shaw et al. 2002; Halligan and Keightley 2009), while the few estimates for non-fitness traits are also in this range (LW Chapter 13). Assuming both a larger number of loci *and* a higher mutation rate per locus can both account for these values, and also allow stabilizing selection-mutation balance to maintain sufficient variation even in the face of fairly strong selection ($V_s = 20\sigma_E^2$). However, while one can certainly make a case for plausibility, it is also true that we are very uncertain on many of the parameter estimates (V_s , $n\mu$), and one can reasonably and rationally take values on the lower end of both values, demonstrating that this does not account for variation. Further, as have noted above, load arguments imply that only a limited number of independent traits can be under stabilizing selection.

WHAT DOES GENETIC ARCHITECTURE TELL US?

A potential window for deciding which forces are predominantly responsible for quantitative variation is that different models predict somewhat different genetic architectures. As noted by Kelly (2008), ideally such predictions are both **robust** and **exclusive**. Robust predictions imply that slight departures from model assumptions do not dramatically change the prediction, while exclusivity (predictions unique to a given model) is much more elusive.

One fairly robust prediction is that alleles in mutation-selection balance (MSB) should be at low frequencies. While this prediction is exclusive to MSB models, but cannot (by itself) distinguish between direct selection versus pleiotropic deleterious effects. In the case of direct stabilizing selection, alleles with larger trait effects have reduced fitness, generating a strong negative correlation between effect size and frequency. For trait alleles maintained by MSB due to pleiotropic deleterious fitness effects, the prediction is less clear. If there is a strong positive correlation between trait effect size and fitness, the same negative correlation between frequency and effect size is expected. Conversely, if there is a weak, or very little, correlation, then any such pattern is greatly diminished.

These observations lead to a standard prediction of rare alleles of large effect under MSB scenarios (especially direct stabilizing selection), while allele frequencies are expected to be more intermediate if balancing selection is involved. If trait alleles are largely neutral, (i.e., under selection, but only weakly so), then the distribution of allele frequencies is expected to be more U-shaped (Chapter 2), and (at best) only a weak coupling between effect size and frequency is expected. What do the data suggest? As we detail, the results from several independent lines of evidence are mixed.

Accelerated Responses in Artificial Selection Experiments

If rare alleles of large effect are the norm, this would imply an increase in the additive variance when such alleles are favored by artificial selection (Barton and Turelli 1987; Maynard Smith 1989). While such accelerated responses are typically not seen (Chapter 25), their absence may not be very damning to the rare alleles model (Keightley and Hill 1989; Zhang et al. 2004b; Zhang and Hill 2005a). Most experiments start with a small sample from a natural population is that bred at modest size in the laboratory for several generations before selection. This implies significant drift and founder effects, resulting in rare alleles either being lost (the majority of the time) or (rarely) increasing to modest frequencies (Zhang et al. 2004b). For example, if the effective population size is 10, then an initially segregating allele at the beginning of the experiment starts out at a frequency no less than five percent (in a diploid), no matter its actual value in its natural population. Keightley and Hill (1989) and Zhang and Hill (2005a) showed that the effects of such sampling, coupled with the effects of linkage disequilibrium (Chapter 16), make the predicted response under rare-alleles models very close to that under the infinitesimal model. Thus, lack of accelerated response is not a fatal observation against rare-alleles models under many experimental designs.

However, as noted by Curtsinger and Ming (1997), using an appropriate design can significantly improve the chances of rare alleles being detected (also see simulations by Kelly 2008). Curtsinger and Ming constructed a number of replicate lines with favorable alleles at low frequency. They did so by five generations of backcrossing three different inbred lines to a line selected for 50 generations for high ethanol tolerance, for an expected frequency of increased tolerance alleles of around 3%. They also constructed three control lines using the same scheme by backcrossing to an unselected population (from which the tolerant line was selected). Thirty generations of selection for increased ethanol tolerance was performed using these six lines. All three lines with favorable alleles showed an acceleration in response around generation 15, while none of the control lines did. One key feature was large population size, with 1000 flies scored each generation and the top 20%

used for the next generation. Motivated by this “proof-of-concept” experiment, Kelly (2008) selected for both large and small flower size in the monkey flower *Mimulus guttatus*, using population sizes on the scale of the Curtsinger-Ming experiment. After accounting for potential scale effects (i.e., the variance increasing with the mean), Kelly found that the additive variance increased in the up-selected line, but decreased in the down-selected line. Such an asymmetric change in the variance is expected if rare alleles (presumably in MSB) disproportionately increase. However, Kelly noted that such an asymmetric response could also occur with alleles at intermediate frequencies. He concluded that his results were, at best, only partly explained by the presence of rare alleles.

A related test for most of the variation being due to rare alleles is to compare selection response using a bottlenecked versus a larger initial population (Robertson 1960; James 1971; Frankham 1980). As reviewed in Chapter 26, these results are more consistent with intermediate-frequency alleles, but Zhang and Hill (2005a) caution that when linkage is considered, the bottleneck test does not have very strong discriminating power. Conversely, Nuzhdin et al. (1999) examined QTLs in high- and low-selected lines for abdominal and sternopleural bristle number. While almost 30 QTLs were mapped, no QTL had both positive and effective effects on response. This suggests loci in the base population were not segregating intermediate frequencies of both positive and negative alleles, indicating a pre-selection architecture closer to a rare-alleles model. This is somewhat surprising as Long et al. (2000) found intermediate-frequency polymorphisms in the *achaete scute* gene complex in natural populations that generated significant variation for both types of bristle number. However, both polymorphisms resulted in a reduction in both types of bristles, suggested that directional mutation bias at a given locus could have also generated the result observed by Nuzhdin et al.

Kelly's Test for Rare Recessives

A related prediction from MSB is that deleterious alleles will not only be rare, but will also tend to be recessive (as additive alleles are removed much more quickly). Further, there should be directional dominance with heterozygotes being closer in fitness to wildtype homozygotes, leading to inbreeding depression (LW Chapter 10). Kelly (1999) used this to construct a creative test for the presence of rare, recessive alleles. He noted that if genetic variation is due to rare recessives, the ratio of the covariance of additive and dominance effects $\sigma(a, d)$ to the additive variance should be greater than or equal to one. Recall that $\sigma(a, d)$ appeared in Chapter 11 and arises in discussions of the covariance between inbred relatives. Conversely, the ratio $\sigma(a, d)/\sigma_A^2$ should be close to zero, or even negative, if most of the variation is due to alleles at intermediate frequencies. Kelly assumed no epistasis, see Charlesworth et al. (2007) for a discussion of how this can impact this test. Kelly (1999, Kelly and Willis 2001) note that while $\sigma(a, d)$ can be (rather imprecisely) estimated from covariances of inbred relatives (Chapter 11), a much cleaner estimate of this ratio follows from a selection experiment, contrasting the change in the mean ΔM with the change in the coefficient B for inbreeding depression (the second term in LW Equation 10.3). B (as well as M) is measured over several generations of selection (see Kelly 1999 for details), and the ratio of their respective changes is computed. A value of $\Delta B/\Delta M$ (which tracks $\sigma(a, d)/\sigma_A^2$) greater than or equal to one is consistent with rare, recessive alleles. Negative values, consistent with intermediate alleles, were seen in three independent selection experiments on flower size in *Mimulus guttatus* (Kelly and Willis 2001), leading the authors to suggest that some form of balancing selection maintains flower size. Charlesworth et al. (2007) used Kelly's method to find evidence of intermediate-frequency alleles underlying female fecundity in *Drosophila melanogaster*.

GWAS Results

As shown in Figure 27.5, the prediction under MSB of an inverse relationship between effect size and frequency clearly holds for human height. Alleles of large effect tend to be rare, although the poor resolution currently offered by mapping methods for genes of intermediate frequency and effect may temper this view somewhat. These data leave unresolved the issue of whether this MSB pattern is due to direct stabilizing selection on height, pleiotropic fitness effects (especially for mutations of large effects), or both.

A second interesting example is the genetics of human personality. Using four dimensions (trait indices) of personality, Verweij et al. (2012) showed that common SNPs accounted for 14 - 29% of the total genetic variation of these composite traits, with an average value of 22.5%. The finding that only a small fraction was captured by common SNPs suggests the majority of genetic variation is either due to rare alleles or nonadditive variation. Consistent with the later, they noted higher levels of inbreeding (for three of the four traits) in individuals with socially less desirable trait scores. These authors suggest that MSB best accounts for this observed pattern of variation, echoing the earlier suggestion by Keller and Miller (2006, but see the extensive commentaries following their article for different perspectives).

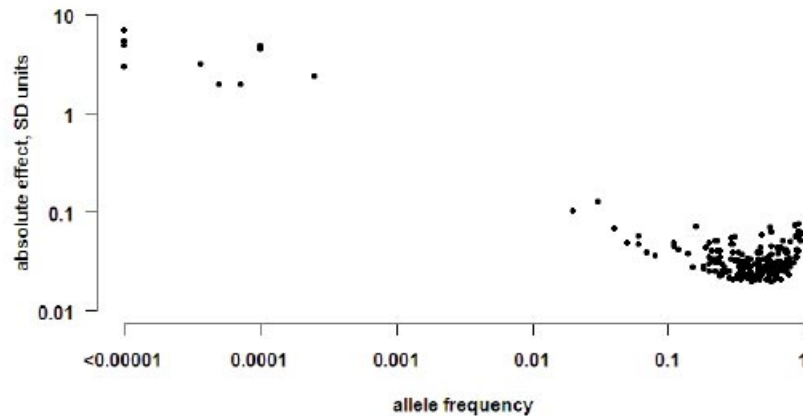


Figure 27.5. Plot of allele frequency versus affect size for known sites influencing human height. The gap in the middle of the figure reflects a lack of power for either GWAS or linkage studies to detect genes in these regions. After Kemper et al. (2012).

SUMMARY: WHAT FORCES MAINTAIN QUANTITATIVE-GENETIC VARIATION?

Bottom line: a lot of fuzzy numbers, especially for the strength of selection, and the mutational parameters (n , μ , $\sigma_{m_*}^2$) can allow advocates of a particular model to proclaim that it largely fits the data, and opponents to insist that it fails.

Two major conflicts: account for high apparent levels of stabilizing selection while still maintaining variation. Most of the models can adequately accomplish both of these, but not at the same time, so that different parameter sets are required to account for each feature.

Genetic architecture suggests an important role for selection (the negative association between trait effect and frequency), but also suggests intermediate frequency alleles are important for selection response. One resolution is two classes of mutations, large effect (and rare) mutations under fairly strong selection, small effect (either on the trait if under

stabilizing selection or fitness if from pleiotropy) mutations are intermediate frequency.

direct selection: Load arguments, not sufficiently high gametic mutation rates (arguable)

pleiotropy: Deleterious alleles have minor impact under adaptation (unless there new advantage for a trait overwhelms their otherwise deleterious effects). Suggests much of the variation is effectively off-limits for adaptation, unless selection is strong. Slippage of response (of alleles not fixed) under selection experiments.

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