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The Population Genetics of Selection

Theoretical population genetics is surely a most unusual subject. At times it appears to have little connection with the parent subject on which it must depend, namely observation and experimental genetics, living an almost inbred life of its own. — Warren Ewens (1994)

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Selection is the focus of much of this book, and here we lay the foundations for the response to selection on quantitative traits by first considering selection situations involving one or two loci. There are two fundamental reasons for this. First, in some settings, the trait of interest may be largely controlled by a single major gene, in which case the models introduced here are directly applicable. Second, these population-genetic models also form the foundation for models of the selection response when trait variation is controlled by multiple loci. As we will detail in later chapters, prediction of the response to selection on a quantitative trait over a few generations can often be reliably done without any knowledge of the underlying genetic architecture beyond a few estimated variance components. Indeed, this is one of the great strengths of quantitative genetics. However, while this approach has been widely successful in predicting the short-term response, as one turns to longer time scales, population-genetic models are central to evaluating how genetic variances (and hence selection response) change.

The key assumption in this chapter is that precise fitness values can be assigned to individual genotypes. Thus, one knows W_g, the fitnesses for all genotypes g at the locus (or loci) of interest, in constrast to the situation in which fitness is indexed by trait value z, with the fitness function $W(z)$ defining the average fitness of an individual with trait value z. We examine how selection on a trait $W(z)$ maps into selection on the underlying genotypes W_g at the end of this chapter, although the bulk of the chapter focuses on the dynamics of allele-frequency change and the behavior of mean fitness $\overline{W}$. This distinction parallels the differences in considerations about selection between breeders and evolutionary geneticists. The former are generally more interested in the change in characters under artificial selection, while the later are generally more interested in how populations adapt to particular environments. This distinction, however, is by no means sharp, as breeders are certainly interested in keeping the fitness of their selected populations as high as possible, and evolutionary biologists are especially interested in the character changes that allow for adaptation.

We start with a review of the theory of single-locus selection, highlighting how the dynamical equations for allele-frequency change can be expressed in terms of quantitative-genetic parameters (such as average excesses and additive variances). Unfortunately, while a rather general theory of single-locus selection has been developed, this is not true for multilocus selection. For such purposes, we will consider two approaches. The first involves exact results for particular two-locus models. The second relies on general approximations, such as **Fisher's fundamental theorem of natural selection** and **Robertson's secondary theorem of natural selection**, which hold reasonably well under weak selection. We conclude by drawing an explict connection to quantitative genetics, showing how selection on a trait maps into selection on the underlying loci, e.g., mapping from $W(z)$ to W_g

The key points of this chapter are as follows: First, when selection acts on a single locus the theory for prediction is standard and essentially complete. Second, when two or more loci are involved, gametic-phase disequilibrium is usually generated. In this case, single-locus equations for allele frequency change no longer hold, and no completely general statement about the behavior under selection can be made. When selection on each locus is weak (relative to the effects of recombination), the results of Fisher and Robertson provide reasonable guidelines for the single-generation behavior of multilocus characters under selection change. However, with strong selection, very complicated dynamics are possible. Thankfully, even with strong selection on any particular trait, the translation from trait selection into selection on individual underlying loci typically results in weak selection on any particular gene, unless a major allele accounts for most of the trait variation.

SINGLE-LOCUS SELECTION: TWO ALLELES

Consider the simplest selection model: one locus with two alleles (A, a) and constant genotypic fitnesses W_{AA}, W_{Aa}, and W_{aa}. The analysis of selection on such systems dates back to a series of papers by Haldane from 1924 to 1932 (summarized in Haldane 1932; see Crow 1992 for an overview of Haldane's fascinating life and legacy). We deal first with **viability selection**, in which case W is the average probability of survival from birth to reproductive age. Once adults reach reproductive age, there is no difference in mating ability and/or fertility between genotypes. Differential survival changes p, the initial frequency of allele A, to a new frequency p' in pre-reproductive (but post-selection) adults. Under the assumption of an effectively infinite population size, random mating among the survivors ensures that genotypic frequencies in the offspring of these surviving parents are in Hardy-Weinberg proportions. As we will show below, analysis of selection based on fertility differences is complicated by the fact that offspring genotypes are generally not in Hardy-Weinberg proportions.

Table 5.1 Genotype frequencies after viability selection. Here p = freq(A) and genotypes are in Hardy-Weinberg frequencies before selection.

Genotype	AA	Aa	aa
Frequency before selection	p^2	$2p(1-p)$	$(1-p)^2$
Fitness	W_{AA}	W_{Aa}	W_{aa}
Frequency after selection	$p^2 \dfrac{W_{AA}}{\overline{W}}$	$2p(1-p) \dfrac{W_{Aa}}{\overline{W}}$	$(1-p)^2 \dfrac{W_{aa}}{\overline{W}}$
where	$\overline{W} = p^2 W_{AA} + 2p(1-p)W_{Aa} + (1-p)^2 W_{Aa}$		

Viability Selection

Consider the change in the frequency p of allele A over one generation, $\Delta p = p' - p$. The number of AA genotypes following selection is proportional to $p^2 W_{AA}$, the frequency of AA genotypes before selection multiplied by their genotypic fitness. To recover frequencies, we divide this proportion by the **mean population fitness** (the average fitness of a randomly drawn individual),

$$\overline{W} = p^2 W_{AA} + 2\,p\,(1-p)\,W_{Aa} + (1-p)^2 W_{aa}, \tag{5.1a}$$

which serves as a normalization constant to ensure that the post-selection genotypic frequen-

cies sum to one. Proceeding similarly for the other genotypes fills out the entries in Table 5.1. From these new genotypic frequencies, the frequency of A after selection is

$$p' = \text{freq}(AA \text{ after selection}) + \frac{1}{2}\,\text{freq}(Aa \text{ after selection})$$

Thus, the expected change in the frequency of A is

$$\Delta p = p' - p = p\left(p\,\frac{W_{AA}}{\overline{W}} + (1-p)\,\frac{W_{Aa}}{\overline{W}} - 1\right) \tag{5.1b}$$

Fitnesses are often rescaled using $w_{ij} = W_{ij}/\overline{W}$ in place of W_{ij}. The usefulness of these **relative fitnesses** is that $\overline{w} = 1$. We will adhere to notation in which upper-case W corresponds to some absolute measure of fitness, while lower-case w corresponds to relative fitness.

Assigning the genotypes $aa : Aa : AA$ fitnesses of $1 : 1+s(1+h) : 1+2s$, Equation 5.1b becomes

$$\Delta p = \frac{sp(1-p)[\,1+h(1-2p)\,]}{\overline{W}} \tag{5.1c}$$

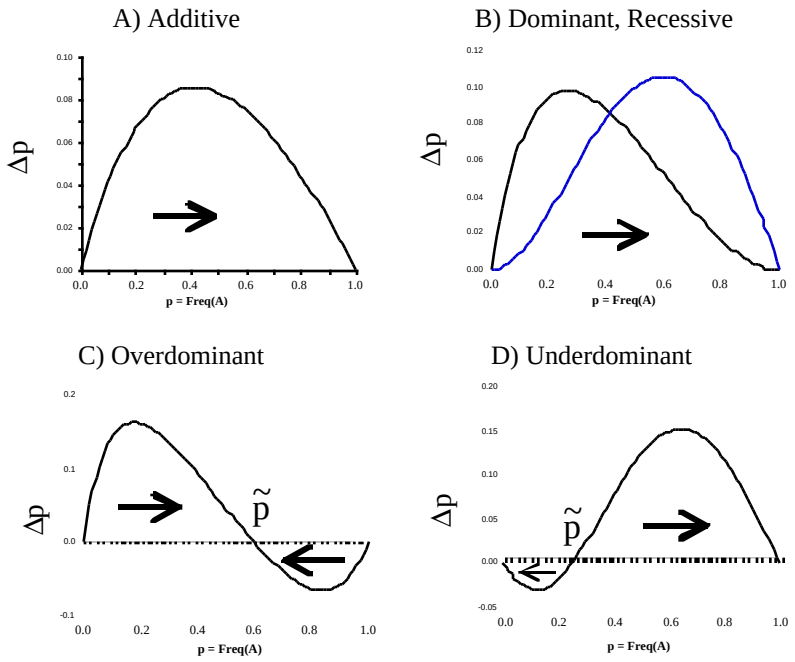


Figure 5.1 A plot of allele-frequency change Δp as a function of p is a useful device for examining how frequencies change under selection. If $\Delta p > 0$, the frequency of A increases (moves to the right), as indicated by rightward pointing arrow. If $\Delta p < 0$, the frequency of A decreases (left-pointing arrow). If $\Delta p = 0$, the allele frequencies are at equilibrium. **A) Directional selection** with additive fitnesses favoring allele A. For $p \neq 0, 1$; $\Delta p > 0$, and p increases to one. Note response is symmetric around $p = 1/2$. **B)** Directional selection with dominance, with allele A favored. Left curve for allele A dominant, right curve for A recessive. $\Delta p > 0$ (provided $p \neq 0, 1$), and the frequency of A increases to one. Here, response is *asymmetric* about $p = 1/2$. **C) Overdominant selection**, where the heterozygote is more fit than either homozygote (Example 5.4), has an internal equilibrium frequency $\widetilde{p}$. For frequencies above the equilibrium ($p > \widetilde{p}$), $\Delta p < 0$, and frequency decreases to $\widetilde{p}$, otherwise if

p is less than $\widetilde{p}$, $\Delta p > 0$, and the allele frequency increases to $\widetilde{p}$. Thus, $\widetilde{p}$ is a **stable equilibrium**. **D)** With **underdominant selection**, the heterozygote is less fit than either homozygote. Again, there is an internal equilibrium allele frequency, but it is **unstable**. If $p < \widetilde{p}$, p decreases toward zero, while if $p > \widetilde{p}$, p increases towards one. The result is fixation of either A or a, depending on the starting allele frequencies.

As shown in Figure 5.1, a graph of Δp as a function of p provides a useful description of the dynamics of selection. In particular, allele frequencies that satisfy $\Delta p = 0$ (i.e., allele frequencies that do not change after selection) are called **equilibrium frequencies**, which we denote by $\widetilde{p}$. Besides trivial equilibria at zero or one, Equation 5.1c shows that $0 < \widetilde{p} < 1$ (so that both alleles are segregating at the equilibrium) requires $1 - h(2\,\widetilde{p} - 1) = 0$, which is satisfied for $h > 1$ (overdominance) or $h < -1$ (underdominance). However, the behavior around the equilibrium is very different in these two cases. Following a small perturbation from a **stable** equilibrium, selection returns the allele frequency to $\widetilde{p}$ (Figures 5.1A, B, and C). At an **unstable** equilibrium (such as for $h < -1$), selection sends the allele frequency *away* from $\widetilde{p}$ following a small perturbation (Figure 5.1D).

Example 5.1. Let p = freq(A). What is Δp when $W_{AA} = 1 + 2s$, $W_{Aa} = 1 + s$, and $W_{aa} = 1$? These are **additive fitnesses**, with each copy of allele *a* adding s to the fitness. Applying Equation 5.1a, mean fitness simplifies to $\overline{W} = 1 + 2sp$ (there are an average of $2p$ A alleles per individual, each of which increments fitness by s). From Equation 5.1b,

$$\Delta p = p\left(\frac{[\,p(1+2s) + (1-p)(1+s)]}{1+2sp} - 1\right) = \frac{sp(1-p)}{1+2sp} \tag{5.2}$$

Which also follows directly from Equation 5.1c with $h = 0$. The equilibrium allele frequencies are $\widetilde{p} = 0$ and $\widetilde{p} = 1$. If A is favored by selection ($s > 0$) $\Delta p > 0$ for $0 < p < 1$, and the frequency of A increases to one (Figure 5.1A), so that $\widetilde{p} = 1$ is a stable equilibrium point. On the other hand, if $s > 0$ $\widetilde{p} = 0$ is unstable, as if even a few copies of A are introduced, selection drives them to fixation. In contrast, if allele *a* is favored ($s < 0$), the frequency of allele A declines to zero (Figure 5.1B) and $\widetilde{p} = 0$ is stable, while $\widetilde{p} = 1$ is unstable.

Expected Time for Allele Frequency Change

A key issue in selection theory is the expected time for a given amount of allele frequency change to occur. Assuming that s and sh are small (weak selection), we can ignore $\overline{W}$ (as $\overline{W} \simeq 1$). Denoting the allele frequency (of A) by x, Equation 5.1c shows the change in allele frequency under weak selection can be approximated by the differential equation

$$\frac{dx}{dt} = sx(1-x)[\,1 + h(1-2x)\,] \tag{5.3a}$$

For additive selection ($h = 0$), this has a simple solution (Stephan et al. 1992) of

$$x(t, p_0) = \frac{p_0}{p_0 + (1-p_0)\exp(-st)} \tag{5.3b}$$

where $x(t, p_0)$ is the frequency of allele A at time t given its initial frequencies are zero. Often of greater interest is $t_{p_0,p}$, the expected time required to move from initial frequency p_0 to

target value of p. This is given by the integral

$$t_{p_0,p} = \int_0^{t_{p_0,p}} dt = \int_{p_0}^{p} \frac{dx}{sx(1-x)[1+h(1-2x)]} \tag{5.3c}$$

Crow and Kimura (1970) present explict results for several important cases. If fitnesses are additive ($h = 0$),

$$t_{p_0,p} \simeq s^{-1} \ln\left(\frac{p\,(1-p_0)}{p_0\,(1-p)}\right), \tag{5.3d}$$

whereas if A is recessive ($h = -1$),

$$t_{p_0,p} \simeq s^{-1}\,\frac{1}{2}\left[\ln\left(\frac{p\,(1-p_0)}{p_0\,(1-p)}\right) - \frac{1}{p} + \frac{1}{p_0}\right] \tag{5.3e}$$

and if A is dominant ($h = 1$),

$$t_{p_0,p} \simeq s^{-1}\,\frac{1}{2}\left[\ln\left(\frac{p\,(1-p_0)}{p_0\,(1-p)}\right) + \frac{1}{1-p} - \frac{1}{1-p_0}\right] \tag{5.3f}$$

Example 5.2. Consider the time for a favored allele to move from a frequency of 0.1 to 0.5. For an additive allele,

$$t \simeq s^{-1} \ln\left(\frac{0.5\,(1-0.1)}{0.1\,(1-0.5)}\right) = \frac{2.2}{s} \text{ generations}$$

When A is dominant,

$$t \simeq s^{-1}\,\frac{1}{2}\left[\ln\left(\frac{0.5\,(1-0.1)}{0.1\,(1-0.5)}\right) + \frac{1}{1-0.5} - \frac{1}{1-0.1}\right] = \frac{1.5}{s} \text{ generations}$$

Finally, if A is recessive,

$$t \simeq s^{-1}\,\frac{1}{2}\left[\ln\left(\frac{0.5\,(1-0.1)}{0.1\,(1-0.5)}\right) - \frac{1}{0.5} + \frac{1}{0.1}\right] = \frac{5.1}{s} \text{ generations}$$

Complications: 1. Differential Viability Selection on the Sexes

Up to now we have assumed equal selection on both sexes, but this need not be the case. To accommodate this complication, again assume random mating and viability selection, with x the current frequency of allele A in males, and y the current value in females. Following random mating, the genotype frequencies and their fitnesses are

Genotype	AA	Aa	aa
Frequency	yx	$x(1-y)+y(1-x)$	$(1-x)(1-y)$
Male Fitness	W_{AA}	W_{Aa}	W_{aa}
Female Fitness	V_{AA}	V_{Aa}	V_{aa}

As in Table 5.1, the relative frequencies of surviving genotypes in males and females are proportionate to the product of their starting frequency times fitness. For example, $yxW_{AA}/\overline{W}$ and $yxV_{AA}/\overline{V}$ are the surviving frequencies of AA in males and females, respectively. The frequency of A in males is the after-selection frequency of AA plus half the frequency of Aa, giving the recursion equations for the allele frequency in males as

$$x' = \frac{xy\,W_{AA} + (1/2)[x(1-y) + y(1-x)]\,W_{Aa}}{\overline{W}} \tag{5.4a}$$

where

$$\overline{W} = xy\,W_{AA} + [x(1-y) + y(1-x)]\,W_{Aa} + (1-x)(1-y)\,W_{aa} \tag{5.4b}$$

with an analogous expression for females being obtained by replacing W by V. Kidwell et al. (1977) explored the conditions under which differential selection in the sexes can maintain variation. For additive selection, they found that **antagonistic selection** (the sign of the selection coefficients changes over sex, such that A favored in one sex and a in the other, can stably maintain variation *only* if the selective differences are fairly close to each other. Strong disproportional selection in one sex will remove variation. See Kidwell et al. (1977) for analysis of more complex cases.

Complications: 2. Frequency-dependent Selection

Although we have been assuming that the genotypic fitnesses W_{ij} are constants, independent of the frequency of genotypes in the population, this need not be the case either. The fitness of a genotype may be a function of the other genotypes with which it interacts, giving rise to **frequency-dependent selection**. Such situations can occur when a rare genotype has a selective advantage due to preferential mating or avoidance of a search image by a predator. As this genotype increases in frequency, its fitness changes (typically decreasing). Self-incompatibility systems in plants also show this feature. We have show that under constant fitnesses, mean population increased over time, but with frequency-dependent selection, this need not be the case. Wright (1948) gives a simple two allele example where mean fitness can strictly decrease over time. If fitness is a function of allele frequencies, Equation 5.1 still holds, provided we replace the constant values of W_{ij} by the functions $W_{ij}(p)$.

Frequency-dependent selection can maintain a polymorphism when rare alleles have the highest fitness. Such a situation is often called **balancing selection**, but some caution is in order with this term, as it is also used for constant-fitness overdominance. Wright and Dobzhansky (1946) note that caution is also in order in attempting to distinguish between rare genotype advantage and overdominance. These authors followed allele frequencies in a caged population of *Drosophila* under selection and found that both these fitness models fit the observed time series of allele frequency changes equally well. They showed that both models can generate identical allele-frequency dynamics, and hence one cannot distinguish between them from allele frequency data alone. Denniston and Crow (1990) and Lachmann-Tarkhanov and Sarkar (1994) expand on this observation by showing that for any set of constant fitnesses there is always an alternative frequency-dependent fitness set that generates the same allele frequency dynamics. Direct demonstration of balancing selection via rare genotype advantage thus needs to directly estimate the fitness of genotypes at different allele frequencies. These are constant under overdominance, but change under frequency-dependence. An example of this approach is Fitzpatrick et al. (2007), who examined the *foraging* gene of *Drosophila melanogaster*, finding that the alternate sitter and rover alleles have their highest fitness when rare.

Complications: 3. Fertility Selection

We have been assuming no differential fertility, so that all combinations of genotypic pairs produce the same number of offspring. Obviously, this is often not true, in which case the (ordered) cross of an A_iA_j male with a A_kA_l female produces (on average) f_{ijkl} offspring. Here f is the **fertility fitness** for the particular ordered genotype. When fertility selection is present, it is no longer sufficient to simply follow allele frequencies. Rather, we must follow $genotypic$ frequencies, and the resulting dynamics can quickly become very complex. Under fertility selection, mean fitness can easily decrease if the genotypes with low viability have sufficiently high fertility. Bodmer (1965) and Kempthorne and Pollak (1970) further explore some of the consequences of fertility selection. A key result is that is that if the fertility fitnesses are multiplicative, .e.g.,

$$f_{ijkl} = f_{ij} \cdot f_{kl}$$

so that the average fertility of the cross is just the product of a genotypic-specific fertility fitness for each genotype (as opposed to a specific value for each cross), then if w_{ij} is the viability fitness, the evolutionary dynamics proceed as with viability selection with fitness $w_{ij}f_{ij}$.

Complications: 4. Sexual Selection

A final complication is **sexual selection**, non-random mating based on traits involved in mate choice. In many species mate choice is at least partly based on trait values, either through male/male competition for access to females and/or female choice of specific males. Sexual selection for particular traits can result in very interesting evolutionary dynamics, especially when its goals conflict with natural selection (such as viability and/or fertility selection).

Example 5.3: An interesting example of the consequences of sexual selection is the **Trojan gene hypothesis** of Muir and Howard (1999). As exotic genes are introduced into domesticated species to create transgenic organisms, an issue of concern is their biosafety, i.e., the potential genetic risk of the introduced transgene. If the gene "escapes" into wild populations, will it increase in frequency, be neutral, or quickly be lost by negative selection? Muir and Howard (1999, 2001) develop population-genetic models to assess such risk and use as a model system the Japanese medaka fish (*Oryzias latipes*). After insertion of a human growth hormone gene under a salmon promoter, the resulting transgenic fish grows faster and to a much larger size than normal medaka. While this may be a boom for aquaculture, what would happen if the growth hormone gene found it way into natural medaka populations?

Muir and Howard found that transgenic fish have only 70% of the survival rate of normal fish. Based on this alone, one might think that any transgenes that escape would quickly be lost given fairly strong viability selection against them. However, Muir and Howard found that larger fish have a roughly 4-fold mating advantage relative to smaller fish. Based on these parameter values, the authors find that any escaped transgene will spread, as the mating advantage more than offsets the survivability disadvantage. However, simulation studies show (for these parameter values) a potentially more ominous fate. The transgene not only spreads, but it eventually drives the population to extinction as a consequence of the reduction in viability. Muir and Howard coin the term **Trojan gene** for such settings. Analysis of the genetic risk based only on viability (and fertility) selection would have suggested no significant risk in that an escaped gene would quickly be lost. Adding in sexual selection (mate choice), not only does the gene spread, but in doing so it can place the entire population at a significant extinction risk.

WRIGHTS' FORMULA

A little algebra shows that Equation 5.1b can be written as

$$\Delta p = \frac{p(1-p)}{2\overline{W}} \frac{d\overline{W}}{dp} = \frac{p(1-p)}{2} \frac{d \ln \overline{W}}{dp} \tag{5.5}$$

The last step follows from the chain rule for differentiation,

$$\frac{d \ln f(x)}{dx} = \frac{1}{f(x)} \frac{df(x)}{dx}$$

Equation 5.5 is **Wright's formula** (1937), which holds provided the genotypic fitnesses are constant and **frequency-independent** (not themselves functions of allele frequencies, which can be formally stated as $\partial W_{ij}/\partial p_k = 0$ for all i, j, and k). We derive the multiple-allele version of Wright's formula shortly, from which Equation 5.5 follows as a special case.

Example 5.4. Consider a locus with two alleles and genotypic fitnesses

$$W_{AA} = 1 - t, \quad W_{Aa} = 1, \quad \text{and} \quad W_{aa} = 1 - s$$

Letting $p = \text{freq}(A)$, Wright's formula can be used to find Δp and the equilibrium allele frequencies. Here mean fitness is given by

$$\begin{aligned} \overline{W} &= p^2(1-t) + 2p(1-p)(1) + (1-p)^2(1-s) \\ &= 1 - tp^2 - s(1-p)^2 \end{aligned}$$

Taking derivatives with respect to p,

$$\frac{d\overline{W}}{dp} = 2[s - p(s+t)]$$

Substituting into Wright's formula gives

$$\Delta p = \frac{p(1-p)[s - p(s+t)]}{1 - tp^2 - s(1-p)^2}$$

Solving $\Delta p = 0$ gives three solutions: (i) $\widetilde{p} = 0$, (ii) $\widetilde{p} = 1$, and most interestingly (iii),

$$\widetilde{p} = s/(s+t)$$

Solution (iii) corresponds to $d\overline{W}/dp = 0$, a necessary condition for a local extrema in $\overline{W}$. Recall from calculus that this extrema is a maximum if $d^2\overline{W}/dp = -2(s+t) < 0$ and a local minimum if the second derivative is positive. With **selective overdominance** the heterozygote has the highest fitness ($s, t > 0$), implying $\Delta p > 0$ when $p < \widetilde{p}$, and $\Delta p < 0$ when $p > \widetilde{p}$ (Figure 5.1C). Thus, *selection retains both alleles in the population*, as first shown by Fisher (1922). Further, $\widetilde{p}$ is the allele frequency that maximizes $\overline{W}$.

With **selective underdominance** (the heterozygote has lower fitness than either homozygote; $s, t < 0$). Although there is still an equilibrium, $\widetilde{p} = s/(s+t)$ corresponds to a local *minimum* of $\overline{W}$ (as $d^2\overline{W}/dp^2 > 0$) and is unstable. If p is the slightest bit below $\widetilde{p}$, p decreases to zero, while if p is the slightest bit above $\widetilde{p}$, p increases to 1 (Figure 5.1D). In contrast to selective

overdominance, *selective underdominance removes, rather than maintains, genetic variation*. In this case, which alelle is fixed depends on the initial starting frequencies.

Example 5.5. The classic example of selective overdominance is **sickle-cell anaemia**, a disease due to a recessive allele at the beta hemoglobin locus. *SS* homozygotes suffer periodic life-threatening health crises due to their red blood cells being sickle-shaped. While *SS* individuals are often listed as having fitness zero (due to their low survival to reproductive age), at least in developed countries such individuals have an average life span of over 40 years. In malarial-infested regions, *SN* heterozygotes (*N* denoting the "normal" allele) have increased resistance to malaria relative to *NN* homozygotes. Asample of 12,387 West Africians yielded 9,365 *NN*, 2,993 *NS*, and 29 *SS* individuals (Nussbaum et al. 2004), giving a frequency of *S* as

$$\frac{(1/2)2993 + 29}{12387} = 0.123$$

Assuming the frequency of *S* is at its selective equilibrium, what is the strength of selection against *NN* individuals due to malaria? Writing the fitness of the *SS*, *SN*, and *NN* genotypes as $1-t$, 1, and $1-s$ respectively, the results from Example 5.4 give the equilibrium frequency of S, 0.123 , is equivalent to $t/(s+t)$. This implies the selection coefficient t against *NN* individuals relative to heterozyotes is

$$t = \frac{0.123\,s}{1-0.123} = 0.140\,s$$

If *SS* individuals are either lethal ($s = 1$) or have only 10% fitness ($s = 0.9$), then t = 0.140 and 0.126 (respectively), giving the fitness of *NN* individuals relative to *SN* as 0.860 and 0.874.

Example 5.6. While the above examples simply recovered previous results, in more complicated situations Wright's formula can be a very powerful tool. It is often assumed that many characters in natural populations are under stabilizing selection, with selection favoring some intermediate phenotypic value. Such a condition is often modeled with the **Gaussian fitness function**, where the expected fitness of an individual with trait value z is given by

$$W(z) = e^{-s(z-\theta)^2}$$

Here θ is the optimal phenotypic value and s the strength of selection. If phenotypes are normally distributed with mean μ and variance σ^2, assuming weak selection ($\sigma^2 \ll 1/s$), then Barton (1986) shows that the mean fitness is approximately

$$\overline{W} \simeq e^{-s[\,\sigma^2+(\mu-\theta)^2\,]/2}, \qquad \text{implying} \qquad \ln \overline{W} \simeq -s[\,\sigma^2+(\mu-\theta)^2\,]/2$$

Suppose segregation at n diallelic, completely additive loci underlie this character, where the genotypes ($aa^{(i)}$, $Aa^{(i)}$, and $AA^{(i)}$ for locus i) have effects 0, $a_{(i)}$, and $2a_{(i)}$. Letting $p_{(i)}$ be the frequency of allele $A^{(i)}$, the trait mean is some starting value m plus the genetic contributions while the variance is the additive plus environmental variances,

$$\mu = m + \sum_{i=1}^{n} a_{(i)}\,2\,p_{(i)} \qquad \text{and} \qquad \sigma^2 = \sum_{i=1}^{n} 2\,a_{(i)}^2\,p_{(i)}\,(1-p_{(i)}) + \sigma_E^2$$

where the variance expression assumes no linkage disequilibrium. Hence,

$$\frac{\partial \mu}{\partial p_{(i)}} = 2\,a_{(i)} \qquad \text{and} \qquad \frac{\partial \sigma^2}{\partial p_{(i)}} = 2\,a_{(i)}^2\,(1-2p_{(i)})$$

Applying the chain rule,

$$\begin{aligned}\frac{\partial \ln \overline{W}}{\partial p_{(i)}} &= -(s/2)\frac{\partial(\sigma^2+(\mu-\theta)^2)}{\partial p_{(i)}} \\ &= -(s/2)\left[\frac{\partial \sigma^2}{\partial p_{(i)}} + 2(\mu-\theta)\,\frac{\partial \mu}{\partial p_{(i)}}\right] \\ &= a_{(i)}\,s\left[\,a_{(i)}\,(2p_{(i)}-1)+2(\theta-\mu)\,\right]\end{aligned}$$

Assuming no linkage disequilibrium (so that the fitnesses of genotypes at this locus are independent of $p_{(i)}$, cf. Example 5.7), Wright's formula gives the expected change in the frequency of allele $A^{(i)}$ as

$$\begin{aligned}\Delta p_{(i)} &= \frac{p_{(i)}(1-p_{(i)})}{2}\left(\frac{\partial\,\ln \overline{W}}{\partial\,p_{(i)}}\right) \\ &= a_{(i)}\,s\left(\frac{p_{(i)}(1-p_{(i)})}{2}\right)\left[\,a_{(i)}\,(2p_{(i)}-1)+2(\theta-\mu)\,\right] \qquad (5.6a)\end{aligned}$$

Thus, even if the population mean μ coincides with its optimal value θ, there is still the potential for selection on the underlying loci, as Equation 5.6a reduces

$$\Delta p_{(i)} = p_{(i)}(1-p_{(i)})\,a_{(i)}^2\,s\,(p_{(i)}-1/2) \qquad (5.6b)$$

This is a form of selective underdominance, as $\Delta p_{(i)} < 0$ for $p_{(i)} < 1/2$, while $\Delta p_{(i)} > 0$ for $p_{(i)} > 1/2$. Hence, selection for an optimum value often tends to drive allele frequencies towards fixation (Robertson 1956).

Adapative Topographies and Wright's Formula

Returning to Equation 5.5, because $p(1-p) \geq 0$, the sign of Δp is the same as the sign of $d\ln \overline{W}/dp$, implying that *allele frequencies change to locally maximize mean fitness*. In a strict mathematical sense, Wright's formula does not imply that mean fitness always increases to a local maximum. If initial allele frequencies are such that mean population fitness is exactly at a local minimum, allele frequencies do not change, as $d\ln \overline{W}/dp = 0$ (Example 7.4). However, this case is biologically trivial, as the resulting equilibrium is unstable. Any amount of genetic drift moves allele frequencies away from this minimum, with mean fitness subsequently increasing to a local maximum. Thus, the implication from Wright's formula is that *mean population fitness either increases or remains constant (never decreases) for viability selection acting on a single locus with constant fitnesses*. Further, it follows that at a stable (one-locus) equilibrium, mean population fitness is at a local maximum (under random mating and frequency-independent viability selection).

When it holds, Wright's formula suggests a powerful geometric interpretation of the mean fitness surface ($\overline{W}$ plotted as a function of p): the local curvature of the fitness surface largely describes the behavior of the allele frequencies. In a random mating population with constant W_{ij}, allele frequency changes move the population toward the nearest local

maximum on the fitness surface. In these settings, the fitness surface is said to describe an **adaptive topography**, as the allele frequencies change each generation so as to move the mean fitness to a higher value. Figure 5.2 plots the mean fitness surface $\overline{W}(p)$ as a function of allele frequency for the same settings as in Figure 5.1. Note that stable equilibria correspond to local maxima and unstable equilibria to local minima.

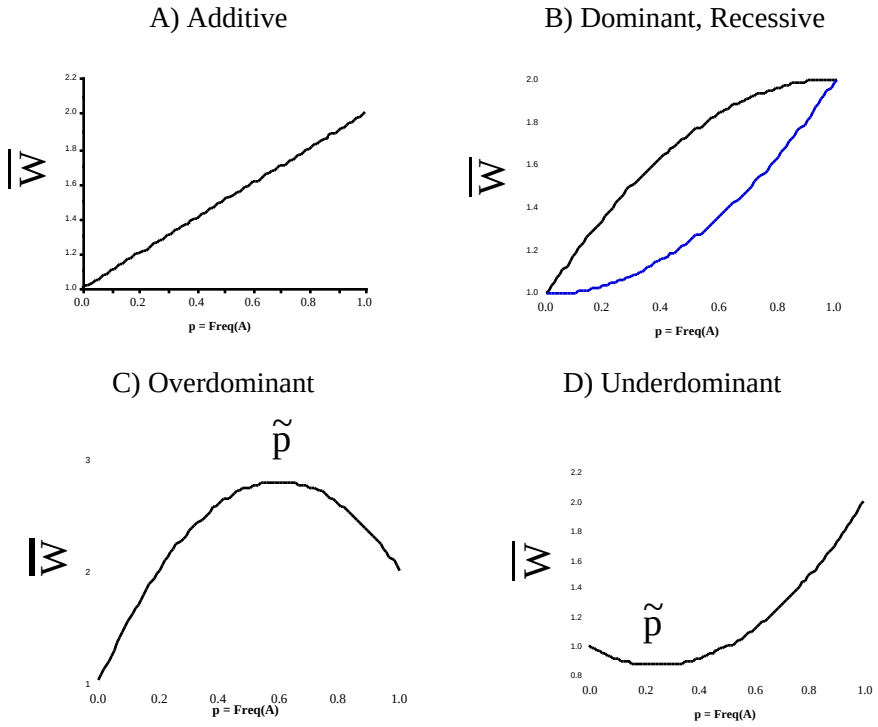


Figure 5.2 A plot of mean population fitness $\overline{W}(p)$ as a function of allele frequency p (compare with Figure 5.1). **A)**: Directional selection with additive fitness, allele A favored. **B)**: Directional selection with dominance, allele A favored. Upper curve for A dominant, lower curve for$A$ recessive. In both A and B, mean fitness is maximized at the stable equilibrium point ($p = 1$). **C)**: With overdominant selection, fitness is again maximized at the stable equilibrium point $\widetilde{p}$. **D)**: With underdominant selection, fitness is *minimized* at the unstable internal equilibrium point $\widetilde{p}$.

SINGLE-LOCUS SELECTION: MULTIPLE ALLELES

Marginal Fitnesses and Average Excesses

For multiple alleles with viability selection, under random mating the frequency of the A_iA_j heterozygote after selection is $(2\,p_i\,p_j)W_{ij}/\overline{W}$, and the frequency of the A_iA_i homozygote is $p_i^2\,W_{ii}/\overline{W}$, where mean fitness is given by

$$\overline{W} = \sum_{i=1}^{n}\sum_{j=1}^{n} p_i\,p_j\,W_{ij}$$

The frequency of allele A_i after selection is the (after-selection) frequency of the A_iA_i ho-

mozygote plus half the frequency of all A_iA_j heterozygotes, a sum that simplifies to

$$p_i' = \frac{p_i}{\overline{W}} \sum_{j=1}^{n} p_j W_{ij} = p_i \frac{W_i}{\overline{W}} \tag{5.7a}$$

where

$$W_i = \sum_{j=1}^{n} p_j W_{ij} \tag{5.7b}$$

is the the **marginal fitness** of allele A_i, i.e., the expected fitness of an individual carrying a copy of A_i. Under random mating, Equation 5.7b follows since if one allele is known to be A_i, then with probablity p_j, the other is A_j, and the resulting fitness is W_{ij}. If $W_i > \overline{W}$ (individuals carrying A_i have a higher fitness than a random individual) then A_i increases in frequency. If $W_i < \overline{W}$, A_i decreases in frequency. Finally, if $W_i = \overline{W}$, A_i is unchanged. From Equation 5.7a, the expected allele frequency change is

$$\Delta p_i = p_i \, \frac{W_i - \overline{W}}{\overline{W}} \tag{5.7c}$$

which implies that at a polymorphic equilibrium (e.g., $\widetilde{p}_i \neq 0, 1$),

$$W_i = \overline{W} \quad \text{for all } i \tag{5.7d}$$

Thus, at equilibrium, *all segregating alleles have the same marginal fitness*.

Marginal fitnesses provide a direct connection between single-locus and quantitative-genetic theory. Recall that the **average excess** of allele A_i is the difference between the mean of individuals carrying a copy of A_i and the population mean (LW Equation 4.16). Thus, we immediately see that $(W_i - \overline{W})$ is the average excess in absolute fitness of allele A_i, and that

$$s_i = (W_i - \overline{W}) \, / \, \overline{W} = (w_i - 1) \tag{5.8a}$$

is the average excess in *relative* fitness. Hence, Equation 5.7c can be expressed as:

$$\Delta p_i = p_i \, s_i \tag{5.8b}$$

Thus, at equilibrium, *the average excess in fitness of each allele equals zero*. It immediately follows that the *additive genetic variance in fitness is also zero* at the equilibrium allele frequencies.

Changes in Genotypic Fitnesses, W_{ij}

Two factors can compromise our standard assumption that W_{ij} remains constant over generations: changes in the environment and changes in the genetic background. Besides standard frequency-dependent effects (such as rare genotype advantage), very important (but subtle) genetic-background effects arise on our focal gene if additional loci influence fitness. As selection changes the genotypic frequencies at these other loci, it can change the fitnesses W_{ij} for the locus under consideration (see Example 5.7). In this case, a complete description requires following all loci under selection. In this setting (expected to be the norm, not the exception) it is no longer sufficient to simply follow the allele frequency changes at all loci. The gametic-phase disequilibrium between loci must also be considered.

Example 5.7. Consider two diallelic loci with alleles *A*, *a* and *B*, *b*, and let *p* = freq (*A*) and *q* = freq (*B*). The frequency of the gametes *AB* and *Ab* are *pq* +*D* and *p*(1- *q*) - *D*, respectively, where

D is the linkage disequilibrium between these two loci (LW Equation 5.11). The marginal (or **induced**) fitness W_{AA} of AA individuals is

$$W_{AABB} \cdot \Pr(AABB\,|AA) + W_{AABb} \cdot \Pr(AABb\,|AA) + W_{AAbb} \cdot \Pr(AAbb\,|AA) =$$

$$W_{AABB} \cdot \frac{(pq+D)^2}{p^2} + W_{AABb} \cdot \frac{2(pq+D)\left[\,p\,(1-q)-D\,\right]}{p^2} + W_{AAbb} \cdot \frac{\left[\,p(1-q)-D)^2\,\right]}{p^2}$$

In the absence of linkage disequilibrium (D = 0), the marginal fitness reduces to

$$W_{AABB} \cdot q^2 + W_{AABb} \cdot 2\,q\,(1-q) + W_{AAbb} \cdot (1-q)^2$$

which is independent of the frequency of A. Even though the marginal fitness of W_{AA} changes as the frequency q of allele B changes, Wright's formula still holds, as the fitness of AA does not depend on the frequency of allele A. However, when $D \neq 0$, W_{AA} is a complex function of p, q, and D so that $\partial W_{AA}/\partial p \neq 0$ and Wright's formula does not hold. Note that even when D = 0, W_{AA} changes as the frequency of B changes, so that the marginal fitness of W_{AA} can change each generation.

Changes in Mean Fitness and Equilibrium Values

As with a single locus with two alleles, under constant fitness viability selection and random mating, mean fitness also increases with k alleles at a single locus (the classic short proof for this is given by Kingman 1961a).

A more interesting question involves the of number polymorphic equilibria with two (or more alleles segregating). In particular, how many (if any) k-allele polymorphic equilibria are present? The classic result (Kingman 1961b) is that such a system either has zero, one, or infinitely many equilibria with all k alleles segregating. We can see this from Equation 5.7d, as with a polymorphic equilibrium, the marginal fitnesses for all segregating alleles are identical. With k alleles, this leads to k linear equations in terms of the p_i, the (equilibrium) allele frequencies for the k loci,

$$W_i = W_1 \quad \text{for } i = 2 \cdots, k, \quad \text{and} \quad \sum_{i=1}^{k} p_i = 1$$

Such a system has either zero, one, or infinitely many solutions (an example of the later is that when all the $W_{ij} = 1$, any set of allele frequencies is stable).

A deeper result obtained Kingman is that the condition for a single internal (and stable) equilibrium for all k alleles requires the fitness matrix $\mathbf{W}$ (whose ijth element is W_{ij}) to have exactly one positive and at least one negative eigenvalue (Appendix 4 reviews eigenvalues). More generally, if $\mathbf{W}$ has m positive eigenvalues, then at most $k-m-1$ alleles can be jointly polymorphic. When there is not a single unique k-allele polymorphism, the ultimate state of the population usually depends on the starting frequencies.

Internal, Corner, and Edge Equilibrium; Basins of Attraction

With more than two alleles, a number of different types of equilibria are possible, and some notation is helpful for characterizing these. With k possible alleles, the space of potential allele frequencies is given by the **simplex** defined by the constraint $\sum_i^k p_i = 1$. Figure 5.3 shows the simplex for the three allele case, which is a section of a two dimensional plane. With k alleles, the resulting simplex is a section of a $k-1$ dimensional hyperplane. We

can distinguish between three types of equilibria based on their location on the simplex. **Corner equilibria** are those where the frequency of one allele is one, and hence all others are zero, corresponding to a corner of the simplex (Figure 5.3). With k alleles, there are k corner equilibrium, as if an allele is fixed, allele frequencies remain unchanged (in the absence of mutation or migration) . At a corner equilibrium a locus has no genetic variance. Next, are **edge equilibria**, where the values of one (or more) of the allele frequencies are zero, while the rest are non-zero, i.e., two (or more) alleles are segregating in the population. Finally, we can have an **internal equilibrium**, where all $p_i > 0$, within the interior of the simplex. At an internal equilibrium, all alleles are segregating. Thus, polymorphic equilibria correspond to either edge equilibrium (not all alleles are segregating) or internal equilibrium (all are segregating). Kingman's result states there is either no internal equilibrium, or a single point, or a surface (such as a line or plane) embedded within the simplex.

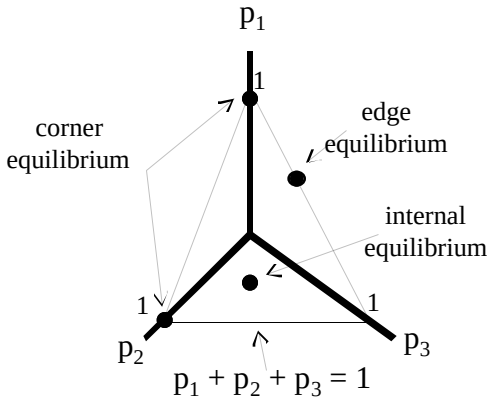


Figure 5.3. The simplex for three alleles, namely the space of all possible allele frequencies, subject to the constraint that they must sum to one. Note that the plane of possible values intersects each allele frequency axis at a value of one for that allele, and zero for all others. Within the simplex, three types of equilibrium are possible. Corner equilibria occur when one allele has frequency one; these are monomorphic equilibria, with no genetic variance. Polymorphic equilibria can either be (i) edge equilibria, when at least two allele frequencies are non-zero; or (ii) internal equilibria, wherein all alleles are segregating.

Biologically, while the existence of equilibria is of some interest, far more important is their stability. When allele frequencies at an unstable equilibrium are perturbed, they depart the neighborhood of this equilibrium value. Conversely, depatures from a close neighborhood of a stable equilibrium value returns to the equilibrium. If we have a surface of equilibria (as might occur if two or more alleles have identical fitnesses), then we can also have a surface of **neutrally stable equilibria**. In such cases, provided we perturb the allele frequencies along the equilibrium surface, the new allele frequencies do not change over time (neutral Hardy-Weinberg is one such example).

When there exist multiple stable equilibria, the history of the process has a great influence on the final value reached. We saw this with underdominance (Example 5.4). If the population starts with frequency in the open interval $(0, \widetilde{p})$ then $p \to 0$. However, if the population starts in the open interval $(\widetilde{p}, 1)$ then $p \to 1$. Thus, with multiple stable equilibria, we are interested in determining the **basin of attraction** for each equilibrium value. Akin to rainfall over a wide area ending up in different rivers depending on which watershed basin it originally fell into, the domain of attraction for a stable equilibrium value is that region in the

simplex for which, if we take allele frequencies within this region as our starting values, the population eventually reaches the stable equilibrium of interest. In very special situations, one can use mathematical tools to determine such basins (Hofbauer and Sigmund 1988). More typically, one systematically samples starting values within the simplex (e.g., using a grid of points) and then numerically iterates the equations of selection response using each starting value to determine where it eventually converges.

WRIGHT'S FORMULA WITH MULTIPLE ALLELES

Equation 5.5 holds for two alleles, in which case the dynamics can be completely described by a single variable (the frequency of either allele). To express Equation 5.7c in a form analogous to Equation 5.5, we again assume that $\partial W_{ij}/\partial p_k = 0$ for all i, j, and k (i.e., frequency-independent fitnesses). Taking the partial derivative of mean fitness with respect to p_i, the frequency of allele A_i,

$$\frac{\partial \overline{W}}{\partial p_i} = \frac{\partial}{\partial p_i}\left(\sum_j^n \sum_k^n p_j\, p_k\, W_{jk}\right) = 2\sum_k^n p_k W_{ki} = 2W_i \tag{5.9a}$$

Hence,

$$W_i = \frac{1}{2}\frac{\partial \overline{W}}{\partial p_i} \tag{5.9a}$$

Further, note that

$$\overline{W} = \sum_{i=1}^n p_i W_i = \sum_{i=1}^n \frac{p_i}{2}\frac{\partial \overline{W}}{\partial p_i} \tag{5.9c}$$

Hence,

$$W_i - \overline{W} = \frac{1}{2}\left(\frac{\partial \overline{W}}{\partial p_i} - \sum_{j=1}^n p_j \frac{\partial \overline{W}}{\partial p_j}\right) \tag{5.9c}$$

Substituting Equation 5.9c into Equation 5.7c gives the allele-frequency change as

$$\Delta p_i = \frac{p_i}{2\overline{W}}\left(\frac{\partial \overline{W}}{\partial p_i} - \sum_{j=1}^n p_j \frac{\partial \overline{W}}{\partial p_j}\right) \tag{5.10}$$

This is the multiple-allele version of Equation 5.5.

It is important to stress that Wright (1937) himself presented a different (and incorrect) version of his formula for multiple alleles, namely

$$\Delta p_i = \frac{p_i(1-p_i)}{2\overline{W}}\frac{\partial \overline{W}}{\partial p_i}$$

which appears widely in the literature. Comparing this with the two-allele version (Equation 5.5), it is easy to see how Wright became seduced with this extension of his (correct) two-allele formula. In various subsequent descriptions of the multiple-allele version Wright attempted to justify his 1937 expression by suggesting that it was not a normal partial derivative, but rather a measure of the gradient in mean fitness along a direction in which the relative proportions of the other alleles do not change (Wright 1942, 1955). However, Edwards (2000)

showed that even this interpretation is not correct, and presents the correct expression for Wright's later interpretation.

Recalling (from the chain rule) that

$$\frac{1}{\overline{W}}\frac{\partial \overline{W}}{\partial p_i} = \frac{\partial \ln(\overline{W})}{\partial p_i},$$

we can also express Equation 5.10 as

$$\Delta p_i = \sum_{j=1}^{n} G_{ij} \cdot \frac{\partial \ln \overline{W}}{\partial p_j}, \tag{5.11a}$$

where

$$G_{ij} = \begin{cases} p_i(1-p_i)/2 & i = j \\ -p_i p_j/2 & i \neq j \end{cases} \tag{5.11b}$$

Thus, we can also conveniently express Equation 5.10 in matrix form as

$$\boldsymbol{\Delta} p = \frac{1}{\overline{W}}\,\mathbf{G}\,\nabla \overline{W} = \mathbf{G}\,\nabla \ln(\overline{W}) \tag{5.12}$$

where $\boldsymbol{\Delta} p$ is the vector of allele-frequency changes, ∇ is the gradient vector (of all first partial derivatives, Appendix 5),

$$\nabla \overline{W} = \begin{pmatrix} \partial \overline{W}/\partial p_1 \\ \vdots \\ \partial \overline{W}/\partial p_n \end{pmatrix}$$

and the elements of the $n \times n$ **genetic variance-covariance matrix G** are given by Equation 5.11b. Recall from calculus that ∇f is the direction of change that produces the greatest local change in the vector-valued function f. Thus, $\nabla \overline{W}$ is the direction that allele frequencies must change to maximize the local change in mean fitness. However, the *actual* vector of change in allele frequencies is rotated away from this direction by the matrix $\mathbf{G}$. The genetic matrix thus constrains the rate of response. This is a prelude to the central theme for multivariate trait selection, namely genetic constraints, where the vector of responses has the form $\mathbf{R} = \mathbf{G}\boldsymbol{\beta}$ (Chapter 28).

It can be shown that Equation 5.12 implies $d\overline{W}/dt \geq 0$ (see ExampleA5.7), and unlike the situation with diallelic case, the sign of Δp_i need not equal the sign of $\partial \ln \overline{W}/\partial p_i$. Alleles with the largest values of $p_i(1-p_i)\,|\,\partial \ln \overline{W}/\partial p_i\,|$ dominate the change in mean population fitness and hence dominate the dynamics. As these alleles approach their equilibrium frequencies under selection (values where $|\,\partial \ln \overline{W}/\partial p_i\,| \simeq 0$), other alleles dominate the dynamics of mean fitness, and their frequencies change so as to continue to increase mean population fitness. We discuss this point further in Chapter 28, in the context of changes in the means of correlated characters under selection.

Summarizing, if the expected fitness W_{ij} of an individual with alleles A_i and A_j is not a function of the frequency of any allele at that locus ($\partial W_{ij}/\partial p_k = 0$ for all i, j, and k that index alleles at this locus), then Wright's formula holds. This condition will be satisfied if the locus is in linkage equilibrium with all other loci under selection and if the fitnesses of the full multilocus genotypes are constant. Since the fitness of $A_i\,A_j$ is the average of fitness over all multilocus genotypes containing these alleles, when linkage disequilibrium is present, correlations between gametes can create a dependency between the average fitness value of $A_i\,A_j$ and the frequency of at least one allele at this locus (Example 5.7). In this case , the assumption that $\partial W_{ij}/\partial p_k = 0$ can be incorrect and Wright's formula no longer holds. If

gamete-frequency changes due to recombination occur on a much quicker time scale than changes due to selection, linkage disequilibrium is expected to be negligible and Wright's formula can be directly applied to certain quantitative-genetic problems (e.g., Barton 1986; Barton and Turelli 1987; Hastings and Hom 1989).

SELECTION ON TWO LOCI

If fitness is influenced by n biallelic loci, then generally we cannot predict how genotype frequencies will evolve by simply considering the n sets of single-locus allele-frequency change equations (Equation 5.7a). The major complication is gametic-phase disequilibrium, which (if present) implies that gamete frequencies cannot be predicted from allele frequencies alone (LW Chapter 5). Further, the marginal fitnesses W_{ij} associated with any one of the loci can themselves be functions of the frequencies of alleles at other locus (see Example 5.7). These complications necessitate us to follow *gamete* rather than *allele* frequencies, requiring many more equations. Further, when disequilibrium occurs and there is epistasis in fitness, complicated multiple equilibria can result. Although most forms of selection generate some disequilibrium, even between unlinked loci, if selection is weak relative to recombination, then disequilibrium can often be ignored.

We focus here on the simplest case of two diallelic loci (alleles A, a and B, b) with random mating and frequency-independent viability selection. Even in this case, the general behavior with constant fitnesses has not been solved outside of a few special cases, and the development of theory beyond two loci is still in a highly embryonic stage. Our purpose is simply to introduce some of the complications that arise due to linkage and gametic-phase disequilibrium, rather than to examine the theory in detail. For comprehensive reviews see Karlin (1975), Nagylaki (1977a, 1992a), Hastings (1990b,c), Christiansen (2000), Bürger (2000), and Ewens (2004.)

Dynamics of Gamete Frequency Change

Denote the frequencies of the four different gametes by x_i, where

$$\begin{aligned} \text{freq}(g_1) = \text{freq}(AB) = x_1, \qquad & \text{freq}(g_2) = \text{freq}(Ab) = x_2, \\ \text{freq}(g_3) = \text{freq}(aB) = x_3, \qquad & \text{freq}(g_4) = \text{freq}(ab) = x_4 \end{aligned}$$

Under random mating (random union of gametes), the frequency of the different (unordered) genotypes is given by

$$\text{freq}(g_i\, g_j) = \begin{cases} 2\, x_i\, x_j & \text{for } i \neq j \\ x_i^2 & \text{for } i = j \end{cases}$$

Let the fitness of an individual formed from gametes g_i and g_j be $W_{g_i g_j} = W_{g_j g_i}$ (we use the $g_i\, g_j$ subscript notation to stress that these fitnesses are for specific *gametic*, as opposed to *allelic*, combinations). $W_{g_1 g_4}$ and $W_{g_2 g_3}$ are of special note, being the fitness of **cis** (AB/ab) and **trans** (Ab/aB) heterozygotes, respectively. One would normally expect these two to be equal, but certain genetic interactions (such as position effects) can complicate matters. For example, if the two loci being considered are themselves in gametic-phase disequilibrium with other loci affecting fitness, cis and trans fitnesses are generally expected to differ (Turelli 1982). Denoting the gamete frequencies after selection by x_i', then (Kimura 1956; Lewontin and Kojima 1960) with constant viability selection ($W_{g_i g_j}$ constant), no cis-trans effect ($W_{g_1 g_4} =$

$W_{g_2 g_3}$), and discrete non-overlapping generations, the gametic recursion equations become

$$x_1' = [\, x_1 W_{g_1} - c\, D\, W_{g_1 g_4}\,]/\overline{W} \tag{5.13a}$$
$$x_2' = [\, x_2 W_{g_2} + c\, D\, W_{g_1 g_4}\,]/\overline{W} \tag{5.13b}$$
$$x_3' = [\, x_3 W_{g_3} + c\, D\, W_{g_1 g_4}\,]/\overline{W} \tag{5.13c}$$
$$x_4' = [\, x_4 W_{g_4} - c\, D\, W_{g_1 g_4}\,]/\overline{W} \tag{5.13d}$$

where c is the recombination fraction between loci, $D = x_1\, x_4 - x_2\, x_3$ is a measure of gametic-phase disequilibrium, and W_{g_i} is the average fitness of a g_i-bearing individual,

$$W_{g_i} = \sum_{j=1}^{4} x_j\, W_{g_i g_j}, \qquad \text{and} \qquad \overline{W} = \sum_{i=1}^{4} x_i\, W_{g_i}$$

Selection can thus change gamete frequencies by changing allele frequencies and/or the amount of gametic-phase disequilibrium.

Equation 5.13 is similar in form to the multiple-allele equation (being identical to Equation 5.7a when c or D equals zero). Unlike allele frequencies (which do not change in the absence of selection under our assumption of infinite population size), gamete frequencies can change from generation to generation even in the absence of selection due to changes in D from recombination (LW Chapter 5). If D is zero and remains zero after selection (as occurs when fitnesses are **multiplicative** across loci, so that $W_{ijkl} = W_{ij} W_{kl}$), then the new gamete frequency is simply given by the product of the new allele frequencies, e.g., $x_1' = p_A'\, p_B'$, and the dynamics can be followed by considering each locus separately (i.e., following Δp_A and Δp_B). However except in this special case, these deceptively simple equations turn out to be extremely complex. Indeed, there is no general analytic solution for even the simplest possible basic model, arbitrary (but constant) fitness and viability selection.

Example 5.8. If loci have effects on both fitness and also on a character not under selection, an incorrect picture as to which characters are under selection can result. The following example, due to Robertson (1967), illustrates some of the problems that can arise. Loci *A* and *B* directly affect fitness (perhaps through some unmeasured character) in addition to influencing character z, not itself under selection, generating the following fitnesses and character values:

	Fitness				Character z		
	AA	*Aa*	*aa*		*AA*	*Aa*	*aa*
BB	100	101	100	*BB*	0	1	1
Bb	101	102	101	*Bb*	1	2	2
bb	100	101	100	*bb*	1	2	2

Alleles *a* and *b* are dominant in the character z, while fitness increases with the number of loci that are heterozygous. Assume gametic-phase equilibrium and that the frequencies of alleles *A* and *B* are both $2/3$, in which case $\overline{W} = 100.89$, $\mu_z = 1.78$, and the expected fitnesses for each phenotype are:

z	0	1	2
$W(z)$	100	100.8	101.6

If we measured the value of z and fitness in a random sample of individuals from this population, we would conclude that z is under directional selection with μ_z expected to increase. However, applying two-locus theory shows that at equilibrium, $p_A = p_B = 1/2$, $\overline{W} = 101$, and $\mu_z = 1.50$. Hence, despite the positive correlation between z and W, selection causes μ_z

to decline. The observed positive correlation between z and W results from the negative additive covariance between fitness and phenotype being outweighed by their (larger) positive dominance covariance. Robertson's secondary theorem of natural selection (discussed below) states the additive genetic component of the covariance between z and W, rather that the total covariance, determines the response to selection, and hence the reduction in the mean in this example.

Gametic Equilibrium Values, Linkage Disequilibrium, and Mean Fitness

At equilibrium, $x_i' = x_i$. Denoting the equilibrium values by $\tilde{x}_i$ then from Equations 5.13a-d we have

$$\overline{W} = W_{g_i} + \eta_i c\, W_{g_1 g_4} \frac{\widetilde{D}}{\tilde{x}_i}, \quad \text{where} \quad \eta_i = \begin{cases} -1 & \text{for } i = 1, 4 \\ 1 & \text{for } i = 2, 3 \end{cases} \tag{5.14}$$

Several results immediately follow from this. First, if linkage is complete ($c = 0$), then all marginal fitnesses are equal at equilibrium, and equilibrium mean fitness is at a local maximum. This result can be understood as a consequence of complete linkage, causing the system to behave like a single locus with four alleles, so that the previous results for multiple alleles hold. However, when $c \neq 0$, then because in general $\widetilde{D} \neq 0$ (there is gametic-phase disequilibrium at the equilibrium gamete frequencies), the equilibrium values are a function of the recombination frequency c. Most interestingly, when $\widetilde{D} \neq 0$ the marginal fitnesses are *not* equal, and equilibrium mean fitness is not at a local maximum. Indeed, it can be shown that if one is sufficiently close to the equilibrium that mean fitness actually decreases as the equilibrium values are approached. Typically, this decrease is quite small, but it no longer holds that mean fitness always increases over time (Kojima and Kelleher 1961).

Example 5.9. Suppose the fitness of *AaBb* is 1+*s* (where $s > 0$), while all other genotypes have fitness 1. If we form a population by crossing *AABB* and *aabb* parents, then in the F_1 all individuals are *AaBb*, and the mean population fitness is 1+*s*. In each subsequent generation, mean population fitness decreases as the frequency of *AaBb* heterozygotes is reduced by recombination until equilibrium is reached (which because of selection, takes several generations, even if $c = 1/2$). In this example, mean fitness decreases each generation until equilibrium is reached. For example, if $s = 0.1$, $\overline{W} = 1.1$ for the F_1, while iteration of Equation 5.13 shows at equilibrium (under loose linkage), $\overline{W} = 1.025$.

Recombination removes gametic-phase disequilibrium while most forms of selection create it (Chapters 15 and 22). If the recombination rate between loci is large relative to selection, D is expected to be small, while if selection is stronger than recombination, D can be considerable. Hastings (1981b, 1986) gives bounds for $\widetilde{D}$, the equilibrium value of gametic-phase disequilibrium. Importantly, for $\widetilde{D} \neq 0$, there must be epistasis in fitness.

A few additional remarks about gametic-phase disequilibrium are in order. Let *A* and *B* alleles increase the character value relative to *a* and *b* alleles. With this ordering, selection generally tends to generate negative *D* (negative gametic-phase disequilibrium) — an excess of repulsion (*Ab*, *aB*) over coupling (*AB*, *ab*) gametes. Following selection, gametes containing mixtures of "high" and "low" alleles are more common (i.e., at higher frequencies than expected from their new allele frequencies) than gametes containing all "high" or all "low"

alleles. An exception is disruptive selection (Chapter 15) and directional selection on characters displaying certain patterns of epistasis (Felsenstein 1965), which generates positive gametic-phase disequilibrium. One consequence of negative D is to slow down the rate of response to directional selection, as favorable alleles at one locus tend to be coupled with unfavorable alleles at other loci. A second consequence of negative D is that it reduces additive genetic variance. Recall that gametic-phase disequilibrium alters the amount of additive genetic variance relative to a base population in gametic-phase equilibrium. For two diallelic loci (LW Equation 5.16a),

$$\sigma_A^2 = \sigma_A^2(0) + 2\,\alpha_A\,\alpha_B\,D$$

where $\sigma_A^2(0)$ is the additive genetic variance under gametic-phase equilibrium, α_A is the effect of substituting *A* for *a* and α_B the effect of substituting *B* for *b* (again, under gametic-phase equilibrium). Both of the α are positive since *A* and *B* have been defined as the "high" alleles. Hence, if $D < 0$ the last term is negative and additive variance is reduced relative to a base population in gametic-phase equilibrium. The important consequence of this is that since additive genetic variance in fitness is zero at equilibrium (see below), when selection is relaxed, D decays to zero and additive variance can be generated without any change in allele frequencies. Thus negative *D* can "store" additive variance that only becomes apparent following recombination (Chapter 15).

Results for Particular Fitness Models

There are a number of ways to parameterize the general two-locus fitness model (Table 5.2). Under the assumption of no cis-trans effects, there are eight free parameters (one of the nine fitnesses can always be normalized to 1). When fitnesses are additive across loci (i.e., no epistasis but the possibility of dominance at each locus), two-locus systems (or multi-locus systems for that matter) are well behaved in that: 1) there is at most one polymorphic equilibrium for any given set of segregating alleles, and 2) at equilibrium $\widetilde{D} = 0$ (no gametic-phase disequilibrium) and $\overline{W}$ is at a local maximum (Karlin and Liberman 1979). In contrast, when epistasis in fitness exists, the behavior of gamete frequencies can be extremely complicated. For example, with sufficiently tight linkage and certain fitness values, there can be as many as seven polymorphic equilibria (up to four of which can be simultaneously stable) for the symmetric viability model given in Table 5.2 (Hastings 1985). Hence, even with constant fitnesses, the final equilibrium state is potentially highly sensitive to initial conditions, and hence highly dependent on historical effects. Further, stable limit cycles can also exist, where equilibria are cycles, rather than point values (Akins 1979, 1982, Hastings 1981a), although point equilibria always exist if epistasis and/or selection are sufficiently weak (Nagylaki et al. 1999).

Table 5.2 Alternative parameterizations and specific models for viability selection on two loci.

General Fitness Matrix

	BB	*Bb*	*bb*
AA	$W_{g_1g_1}$	$W_{g_1g_2}$	$W_{g_2g_2}$
Aa	$W_{g_1g_3}$	$W_{g_1g_4} = W_{g_2g_3}$	$W_{g_2g_4}$
aa	$W_{g_3g_3}$	$W_{g_3g_4}$	$W_{g_4g_4}$

Additive Fitness Model

	BB	*Bb*	*bb*
AA	$1-a-b$	$1-a$	$1-a-c$
Aa	$1-b$	1	$1-c$
aa	$1-d-b$	$1-d$	$1-d-c$

Symmetric Viability Model

	BB	*Bb*	*bb*
AA	$1-a$	$1-b$	$1-d$
Aa	$1-e$	1	$1-e$
aa	$1-d$	$1-b$	$1-a$

Example 5.10. The symmetric viability model arises naturally when considering stabilizing selection on a character determined by additive loci. Suppose that two loci contribute in a completely additive fashion (e.g., no dominance or epistasis) to a character under stabilizing selection, with $W(z) = 1 - s(z-2)^2$, which implies an optimal phenotypic value of two. Quadratic fitness functions of this general form were first introduced by Wright (1935) with his **quadratic optimum model**. Assuming each capital letter allele adds 1 to z (and that there is no environmental variance), the resulting phenotypic and fitness values are

	Character value z			Fitness		
	AA	*Aa*	*aa*	*AA*	*Aa*	*aa*
BB	4	3	2	$1-4s$	$1-s$	1
Bb	3	2	1	$1-s$	1	$1-s$
bb	2	1	0	1	$1-s$	$1-4s$

Observe that while the character has completely additive genetic basis, the fitness function mapping from phenotype to fitness introduces epistasis in fitness. This is an important point: it is *fitness* that determine the evolutionary dynamics of a quantitative trait and simply showing that a trait under selection has an additive genetic basis is *not* sufficient to imply that fitnesses are also additive.

Phenotypic Stabilizing Selection and the Maintenance of Genetic Variation

Example 5.10 shows that stabilizing selection on a trait with an additive genetic can easily lead to a situation where the double heterozygote has the highest fitness. We have seen that when the heterozygote is favored at a single locus, selection maintains both alleles (Example 5.4). However, Example 5.6 shows that when a number of loci underlie an additive trait under stabilizing selection, overdominant selection occurs (encouraging removal, rather than maintenance, of genetic variation). All of this begs the simple question (with a very complex answer): under what conditions does stabilizing selection maintain genetic variation at a number of loci? This of one of several questions that follow from one of the most perplexing observations in quantitative genetics — the apparent maintenance of high levels of genetic variation for most traits under apparent stabilizing selection. We take up this topic in earnest in Chapter 25, confining our remarks here to the prospects for selection alone maintaining variation.

A number of models for this superficially simple problem can be found in the literature, with very different outcomes. Indeed, one major take-home message from the literature is that seemingly quite subtle changes in models (e.g., quadratic vs. Gaussian selection, slightly different effects at the underlying loci, whether the double heterozyote exactly coincides with the fitness optimum) can lead to very different behaviors.

Example 5.11. The generalized version of Wright's quadratic optimum model provides sig-

nificant insight into many of the issues with maintenance of variation strictly by selection. This model has been examined by numerous authors (e.g., Wright 1935; Hastings 1987; Gavrilets and Hastings 1993, 1994b; Bürger and Gimelfarb 1999), and we follow the excellent treatment of Bürger (2000, pages 204–210), which should be consulted for more details and additional references. The generalized model makes three key assumptions. First, fitness is a quadratic function, $W(z) = 1 - sz^2$, with an implict optimum at $z = 0$. Second, the genotypic value of the double-heterozygote exactly corresponds with the phenotypic optimum. Lastly, the trait under stabilizing election is completely additive. Thus $-a_1 : 0 : a_1$ are the genotypic values at the first locus (corresponding to $aa : Aa : AA$), while the values for the second locus are $-a_2 : 0 : a_2$. Wright's original analysis (and that of several other authors) assumed that allelic effects are identical ($a_1 = a_2$), but the generalized version does not assume this. The resulting trait values become:

	aa	Aa	AA
bb	$-(a_1 + a_2)$	$-a_2$	$a_1 - a_2$
Bb	$-a_1$	0	a_1
BB	$a_2 - a_1$	a_2	$a_1 + a_2$

Since $W(z) \geq 0$, the values of the a_i constrain the maximum value of s as

$$1 - s(a_1 + a_2)^2 \geq 0, \qquad \text{or} \qquad s \leq 1/(a_1 + a_2)^2$$

The above fitnesses correspond to the symmetric viability model given in Table 5.2, with

$$a = s(a_1 + a_2)^2, \quad b = sa_2^2, \quad d = s(a_1 - a_2)^2, \quad e = sa_1^2$$

Note that there is a relationship among these selection coefficients, namely $a + d = 2(b + e)$, which follows from the quadratic fitness function used (this relationship does not hold under Gaussian selection).

Depending on parameter values, this model can have up to nine equilibria, seven of which may be potentially stable (but not simultaneously) There are always four trivial corner equilibria corresponding to each of the four gametes being fixed. The equilibrium corresponding to either AB or ab being fixed are always unstable, but the other two corner equilibria, corresponding to Ab or aB being fixed, can potentially be stable. There may also be two edge equilibria, corresponding to fixation at one locus and segregation at the other. If these exist, their values are

$$\widehat{x}_1 = \widehat{x}_3 = 0, \quad \widehat{x}_2 = \frac{1}{2} + \frac{a_2}{a_1}, \quad \widehat{x}_4 = \frac{1}{2} - \frac{a_2}{a_1}$$

which corresponds to the major locus A segregating and the other locus fixed for b. Likewise, the other edge equilibrium corresponds to A segregating in a fixed BB background,

$$\widehat{x}_2 = \widehat{x}_4 = 0, \quad \widehat{x}_1 = \frac{1}{2} - \frac{a_2}{a_1}, \quad \widehat{x}_3 = \frac{1}{2} + \frac{a_2}{a_1}$$

For either of these edge equilibria to be admissible (the equilibrium x_i values lying on the simplex), we require that $a_1 > 2a_2$ (and hence the designation of A at the major locus). By definition, disequilibrium is zero at both the corner and edge equilibria.

Finally, there are three potential internal equilibria. The first is the so-called symmetric equilibrium, where both loci are segregating with all alleles at frequency 1/2,

$$\widehat{x}_1 = \widehat{x}_4 = \frac{1}{4} + \widehat{D}, \qquad \widehat{x}_2 = \widehat{x}_3 = \frac{1}{4} - \widehat{D}$$

where

$$\widehat{D} = \frac{1}{4s\alpha_1\alpha_2}\left(c - \sqrt{s^2\alpha_1^2\alpha_2^2 + c^2}\right)$$

and c is the recombination frequency between the two loci. Notice that $\widehat{D} < 0$ and hence there is hidden genetic variation, with the additive variance increasing following the cessation of selection (Chapter 15). At this equilibrium value, the additive variance for the trait is

$$\widehat{\sigma}_A^2(x) = \frac{\alpha_1^2 + \alpha_2^2}{2} + 4\alpha_1\alpha_2\widehat{D}$$

While there is additive variance in the *trait* under selection, as we will see shortly (Example 5.12), there is no additive variance *in fitness* at the equilibrium value.

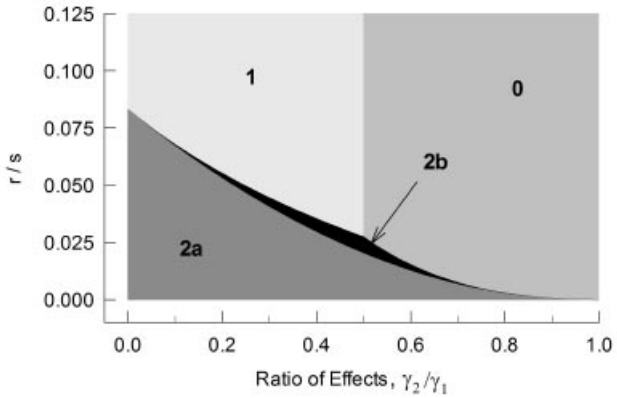
While the symmetric internal equilibrium seems straightforward, there can also be two other interior equilibria, the so-called *unsymmetric equilibria*. The expressions for these is complex (see Bürger page 205), and the conditions for their existence is that the recombination fraction be in the range $c_1 < c < c_2$, where

$$c_1 = -\frac{1}{3}s(\alpha_1^2 + \alpha_2^2) + \frac{2}{3}s\sqrt{\alpha_1^4 - \alpha_1^2\alpha_2^4 + \alpha_2^4}$$

and

$$c_2 = \min\left[s(\alpha_1 - \alpha_2)^2, \frac{1}{3}s(\alpha_1^2 - \alpha_2^2)\right]$$

Turning to stability of the various potential equilibria, if $c \leq c_1$, then the symmetric internal equilibrium is stable and likely globally stable. This requires both tight linkage and unequal allelic effects (see the figure below). If recombination if sufficiently large ($c > 1/3$), then the symmetric internal equilibrium is never stable. Next, the unsymmetric polymorphic equilibria are stable whenever they exist, which only occurs over a narrow region of recombination values ($c_1 < c < c_2$). The edge equilibria are stable whenever they exist, which requires sufficiently unequal allelic effects ($a_1 > 2a_2$) and sufficiently loose linkage ($c \geq c_2$). The corner equilibria are also stable whenever they exist, which requires that allelic effects are not too dissimilar ($a_1 \leq 2a_2$) and linkage is sufficiently loose ($c \geq c_2$). Thus, for this model there are four mutually exclusive sets of stable equilibria, and the regions of the parameter space that corresponds to these different sets are shown in the figure below (from Bürger).



As this figure shows, there are four different regions of the parameter space, corresponding to stability of different classes of equilibria. In region 0, only the two monomorphic equilibria are stable. Note that if the two loci have equal effects (as Wright originally assumed), these are the only stable equilibria, and the result of stabilizing selection is to remove variation at both loci. In region 1, the two edge equilibria with the major locus being polymorphic are the only stable equilibria. Note that this requires both rather uneven effects ($\alpha_1 \geq 2\alpha_2$ and recombination sufficiently large relative to selection. Finally, there are two regions where the internal equilibrium is stable. The very narrow region 2b corresponds to the two unsymmetric internal equilibria being stable, which requires a very specific constraint between selection and recombination. Finally, with uneven allelic effects and recombination weak relative to selection, the symmetric equilibrium is stable. Thus, provided allelic effects are uneven and that selection is strong relative to recombination, selection can maintain both alleles (Nagylaki 1989a; Gavrilets and Hastings 1993, 1994a, b). That stabilizing selection can maintain both alleles was originally shown, using a different fitness function, by Gale and Kearsey (1968) and Kearsey and Gale (1968). Gavrilets and Hastings showed that, with strong selection, the equilibrium mean does not necessarily coincide with the optimum fitness value, so that in general $\widehat{\mu}_z \neq 0$. Hence, at equilibrium there can be the appearance of apparent directional selection.

Thus, even Wright's simple quadratic optimum model exhibits considerable complexity. Further, in the (very likely) event that the double heterozygote does not exactly correspond to the optimal phenotypic value, the fitness matrix immediately becomes asymmetric, leaving the general (and hence unsolved) two-locus model, with all of its potentially complex behavior. The same is true if there is epistasis in the trait under selection. The final subtlety is that very different results can arise by a simple change in the fitness function, for example from a quadratic to a Gaussian. One reason for this is that there is an absolute bound to the strength of selection s with a quadratic fitnesse function for fitnesses to remain nonnegative. However, such is not the case with a Gaussian fitness function, where the strength of selection s can only take on positive values. Further, with a Gaussian fitness function, the identity among coefficients of the general symmetric fitness model that held for a quadratic, namely $a + d = 2(b + e)$, no longer holds. When this identity holds, the normally cubic equation that must be solved to obtain solutions for the equilibrium value of D collapse to a quadratic equation (Gimelfarb 1996). Thus, the equilibrium structure is potentially more complex under a Gaussian relative to a quadratic fitness function. Indeed, Gimelfarb (1996) shows that under sufficiently strong Gaussian selection, very unusual behavior can occur, such as the appearance of two internal symmetric equilibria with D values of opposite sign.

So where does all this modeling leave us? The highly symmetric Wright model (equal allelic effects, quadratic fitness function, double heterozygote value is the optimal phenotypic value) showed that stabilizing selection on an additive trait cannot maintain variation. As we start to break these symmetries (e.g., unequal allelic effects), we find conditions under which stabilizing selection can maintain variation at one or both loci. Indeed, superficially minor issues, such as subtle differences in fitness functions or noncorrespondence of double heterozygote and the optimal trait value, can result in qualitatively different behavior relative to the Wright model.

As we moved from a single locus to two loci, disequilibrium became a significant issue, and the dynamics of response changed from being relatively simple to potentially quite complex. What happens when we move beyond two loci? Ironically, things may start to get simpler again. Bürger and Gimelfarb (1999) simulated stabilizing selection under the generalized Wright model and found for randomly-generated parameter sets (linkage, allelic effects, and strength of selection) that roughly 17% of two-locus systems maintained both

alleles. However, as they considered 3-, 4-, and 5-locus systems, this probability (of two or more loci being polymorphic) fell dramatically, being less that half a percent in the five-locus models.

Further, as one moves to systems with still more loci, the effects of selection on any individual locus is reduced, and the behavior of many models becomes even much simpler. For example, under weak selection, Hastings and Hom (1989, 1990) showed that the number of polymorphic loci that can be maintained by stabilizing selection is bounded above by the number of independent traits under selection. Thus, with sufficiently weak selection, stabilizing selection on k independent traits can maintain variation at no more than k loci.

In closing this section, our analysis of strong selection two-locus models instills caution about general statements of selection in multi-locus systems. These concerns are quite valid when a major gene (or genes) accounts for most of the variation in our trait of interest. However, if selection tends to be weak relative to recombination (as might be expected in systems with a large number of roughly equal loci), the response under such genetic architectures may have simpler and more predicable behavior. This leads to investigations about general statements of the behavior of fitness and trait evolution under weak selection (on the individual underlying loci). While any such general statements are not true in all settings (as the strong-selection two locus results bear out), they may be largely true in many biological settings.

THEOREMS OF NATURAL SELECTION: FUNDAMENTAL AND OTHERWISE

Given the preceeding results, what general statements, if any, can we make about the behavior of multilocus systems under selection? One off-quoted relationship is Fisher's **fundamental theorem of natural selection**, which states that "The rate of increase in fitness of any organism at any time is equal to its genetic variance in fitness at that time." This simple statement from Fisher's 1930 book (which was dictated to his wife as he paced about their living room) has generated a tremendous amount of work, discussion, and sometimes heated arguments. Fisher claimed his result was exact, a true theorem. The common interpretation of Fisher's theorem, that the rate of increase in fitness equals the additive variance in fitness, has been referred to by Karlin as "neither fundamental nor a theorem" as it requires rather special conditions, especially when multiple loci influence fitness.

Since variances are nonnegative, this classical interpretation of Fisher's theorem implies that mean population fitness never decreases in a constant environment. As we discuss below, this interpretation of Fisher's theorem holds *exactly* only under restricted conditions, but is often a good approximate descriptor. However, an important corollary holds under very general conditions (Kimura 1965a; Nagylaki 1976, 1977b; Ewens 1976; Ewens and Thompson 1977; Charlesworth 1987): in the absence of new variation from mutation or other sources such as migration, *selection is expected to eventually remove all additive genetic variation in fitness*. This can be seen immediately for a single locus by considering Equation 5.8b — if the population is at equilibrium, all average excesses are zero, as all segregating alleles have the same marginal fitness and hence $\sigma_A^2 = 0$ (Fisher 1941).

The Classical Interpretation of Fisher's Fundamental Theorem

We first review the "classical" interpretation and then discuss what Fisher actually seems to have meant. To motivate Fisher's theorem for one locus, consider a diallelic locus with constant fitnesses under random mating. The change in mean fitness is a function of the allele frequency change Δp,

$$\Delta \overline{W} = \overline{W}(p + \Delta p) - \overline{W}(p)$$

If the allele frequency change is small, a first-order Taylor series approximation gives

$$\overline{W}(p+\Delta p) \simeq \overline{W}(p) + \frac{\partial \overline{W}}{\partial p}\,\Delta p.$$

implying from Wright's formula (Equation 5.5) that

$$\begin{aligned}\Delta\overline{W} = \overline{W}(p+\Delta p) - \overline{W}(p) &\simeq \frac{\partial \overline{W}}{\partial p}\,\Delta p \\ &= \frac{p(1-p)}{2\overline{W}}\left(\frac{\partial \overline{W}}{\partial p}\right)^2.\end{aligned}$$

From Equation 5.1a,

$$\begin{aligned}\frac{\partial \overline{W}}{\partial p} &= 2pW_{AA} + 2(1-2p)W_{Aa} + 2(p-1)W_{aa} \\ &= 2\,[\,p(W_{AA}-W_{Aa}) + (1-p)(W_{Aa}-W_{aa})\,] = 2(\alpha_A - \alpha_a)\end{aligned}$$

where the last equality follows from the definition of the average effects (under random mating, see LW Chapter 4) of alleles A and a on fitness,

$$\alpha_A = p\,W_{AA} + (1-p)\,W_{Aa} - \overline{W} \qquad \text{and} \qquad \alpha_a = p\,W_{Aa} + (1-p)\,W_{aa} - \overline{W}$$

Recall that the quantity $\alpha = \alpha_A - \alpha_a$ is the **average effect of an allelic substitution** (LW Equation 4.6), as the difference in the average effects of these two alleles gives the mean effect on fitness from replacing a randomly-chosen a allele with a A allele. The additive genetic variance is related to α by $\sigma_A^2 = 2p(1-p)\alpha^2$ (LW Equation 4.12a), giving

$$\Delta\overline{W} \simeq \frac{p(1-p)(2\alpha)^2}{2\overline{W}} = \frac{\sigma_A^2(W)}{\overline{W}} \tag{5.15}$$

Thus, in this setting the change in mean fitness is indeed proportional to the additive genetic variance in fitness. Why does the change in mean fitness (assuming a single locus) depend on the additive genetic variance instead of the total genetic variance? Recall that selection changes allele frequencies, and (under random mating and no fertility selection) allele frequency changes are sufficient to fully predict the genotypes at the start of the next generation. Additive variance reflects changes caused by the effects of individual alleles and hence if these allele frequencies change, it is the additive variance that predicts the amount of change in the next generation, not the total genetic variance. This statement is a function of the mating system. If offspring are asexual clones, then the total genetic variance is in play. Likewise, under inbreeding, non-additive variances can also contribute to selection response (Chapter 19).

Example 5.12. Consider a locus with two alleles (A_1 and A_2) and overdominance in fitness,

$$W_{11} = 1 \quad W_{12} = 1+s \quad W_{22} = 1$$

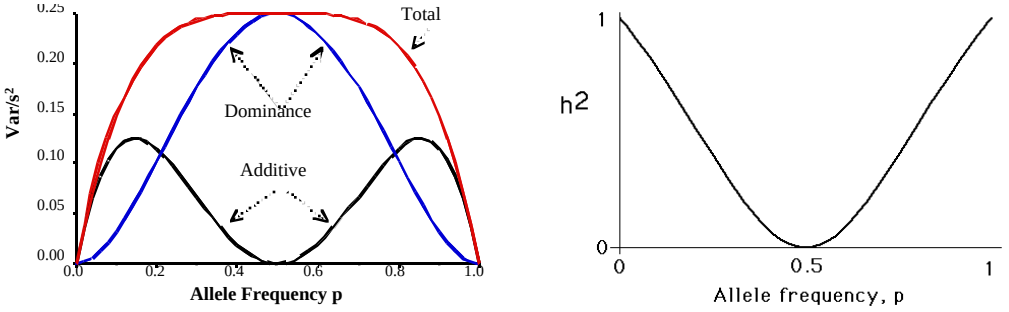
Letting $p = \text{freq}(A_1)$, under random mating we have from our above definition of the average effect of a substitution

$$\alpha = p[\,1-(1+s)\,] + (1-p)[\,(1+s)-1)\,] = s(1-2p)$$

giving the additive variance as

$$\sigma_A^2(W) = 2p(1-p)s^2(1-2p)^2$$

Likewise, the dominance variance is easily computed as $\sigma_D^2(W) = [2p(1-p)s]^2$ (LW Equation 5.12b). As plotted below, these variances change dramatically with p. The maximum genetic variance in fitness occurs at $p = 1/2$, but none of this variance is additive, and heritability in fitness is zero. It is easily shown that $\Delta p = 0$ when $p = 1/2$, and at this frequency $\sigma_A^2(W) = 0$, as the corollary of Fisher's theorem predicts. Thus, even though *total* genetic variation in fitness is maximized at $p = 1/2$, no change in $\overline{W}$ occurs as the *additive* genetic variance in fitness is zero at this frequency. From simplicity, the plot of h^2 for fitness assumes no environmental effects, $h^2 = \sigma_A^2/\sigma_G^2$.



Example 5.13. Even if Fisher's theorem holds exactly, it's implication for character evolution can often be misinterpreted as this example illustrates (also see Example 5.11). Reconsider Example 5.12, but now suppose that locus A completely determines a character under stabilizing selection. Let the genotypes AA, Aa, and aa have discrete phenotypic values of $z = -1$, 0, and 1, respectively (so that this locus is strictly additive) and let the fitness function be $W(z) = 1 - sz^2$. If we assume no environmental variance, this generates very nearly the same fitnesses for each genotype as in Example 5.12, as the fitnesses can be normalized as $1 : (1-s)^{-1} : 1$, where $(1-s)^{-1} \simeq 1 + s$ for small s. The additive genetic variance for the *trait* z is maximized at $p = 1/2$, precisely the allele frequency at which the additive genetic variance in *fitness* $\sigma_A^2(W) = 0$. This stresses that Fisher's theorem concerns additive genetic variance in *fitness*, not in the *character*. In this example, the transformation of the phenotypic character value z to fitness takes a character that is completely additive and introduces overdominance in fitness. Similarly, the mapping from character to fitness can introduce epistasis when multilocus systems are considered (Example 5.8).

Our above derivation of Fisher's theorem was only approximate. Under what conditions does this classical interpretation actually hold? While it is correct for multiple additive loci (i.e., no dominance nor epistasis) under both random and nonrandom mating (Kempthorne 1957; Ewens 1969), it is generally compromised by nonrandom mating and departures from additivity (such as dominance or epistasis). Even when the theorem does not hold exactly, how good an approximation is it? Nagylaki (1976, 1977a,b, 1991, 1992b, 1993) has examined ever more general models of fitness when selection is weak (the fitness of any genotype can be expressed as $1 + as$ with s small and $|\,a\,| \ll 1$) and mating is random. Selection is further assumed to be much weaker than the recombination frequency c_{min} for the closest pair of loci ($s \ll c_{min}$). Under these fairly general conditions, Nagylaki shows that the evolution of mean fitness falls into three distinct stages. During the first $t < 2\ln s/\ln(1-c_{min})$ generations,

the effects of any initial disequilibrium are moderate, first by reaching a point where the population evolves approximately as if it were in linkage equilibrium and then reaching a stage where the linkage disequilibrium remains relatively constant. At this point, the change in mean fitness is

$$\Delta\overline{W} = \frac{\sigma_A^2(W)}{\overline{W}} + O(s^3) \tag{5.16}$$

where $O(s^3)$ means that terms on the order of s^3 have been ignored. Because additive genetic variance is expected to be of order s^2, Fisher's theorem is expected to hold to a good approximation during this period. This phase of evolution lasts roughly $1/s$ generations. However, as gametic frequencies approach their equilibrium values, additive variance in fitness can be much less than order s^2, in which case the error terms of order s^3 can be important. During the first and third phases, mean fitness can decrease, but the fundamental theorem holds during the central phase of evolution. Note that these are **weak-selection** results (selection is much weaker than recombination). Biologically, we except the bulk of evolution to occur during this middle phase and hence Fisher's theory approximately holds over the major part of evolutionary change. Further, we often expect weak selection to be the norm for quantitative traits —even strong selection on a trait translates into weak selection on the underlying loci if each has a small effect (Equation 5.33).

What Did Fisher Really Mean?

Fisher warned that his theorem "requires that the terms employed should be used strictly as defined", and part of the problem stems from what Fisher meant by "fitness". Price (1972) and Ewens (1989b, 1992) have argued that Fisher's theorem is always true, because Fisher had a very narrow interpretation of the change in mean fitness (see also Edwards 1990, 1994; Frank 1995; Lessard and Castilloux 1995; Lessard 1997). They argue that Fisher, rather than considering the *total* rate of change in fitness, was instead concerned only with the *partial* rate of change, that due to changes in the contribution of individual alleles (specifically, changes in the average excesses/effects of these alleles). In particular, Ewens (1994) states

> "I believe that the often-made statement that the theorem concerns changes in mean fitness, assumes random-mating populations, is an approximation, and is not correct in the multi-locus setting, embodies four errors. The theorem relates the so-called partial increase in mean fitness, makes no assumption about random mating, is an exact statement containing no approximation, and finally is correct (as a theorem) no matter how many loci are involved."

What exactly is meant by the partial increase in fitness? A nice discussion is given by Frank and Slatkin (1992), who point out that the change in mean fitness over a generation is also influenced by the change in the "environment", E. Specifically,

$$\Delta\overline{W} = \left(\overline{W}' \,\middle|\, E'\right) - \left(\overline{W} \,\middle|\, E\right) \tag{5.17a}$$

where the prime denotes the fitness/environment in the next generation, so that the change in mean fitness compounds both the change in fitness and the change in the environment. We can partition out these components by writing

$$\Delta\overline{W} = \left[\left(\overline{W}' \,\middle|\, E\right) - \left(\overline{W} \,\middle|\, E\right)\right] + \left[\left(\overline{W}' \,\middle|\, E'\right) - \left(\overline{W}' \,\middle|\, E\right)\right] \tag{5.17b}$$

where the first term in brackets represents the change in mean fitness under the initial "environment" while the second represents the change in mean fitness due to changes in the environmental conditions. Fisher's theorem relates solely to changes in the first component, $(\overline{W}' \,|\, E) - (\overline{W} \,|\, E)$, which he called the change in fitness due to natural selection. Price (1972) notes that Fisher had a very broad interpretation of "environment", referring to both physical and genetic backgrounds. In particular, Price claimed that Fisher

> "regarded the natural selection effect on fitness as being limited to the additive or linear effects of changes in gene (allele) frequencies, while everything else — dominance, epistasis, population pressure, climate, and interactions with other species — he regarded as a matter of the environment."

Hence the change in fitness referred to by Fisher are solely those caused by changes in allele frequencies and nothing else. Changes in gamete frequencies caused by recombination and generation of disequilibrium beyond those that influence individual allele frequencies are consigned to the "environmental" category by Fisher. Given this, it is perhaps not too surprising that the strict interpretation of Fisher's theorem holds under very general conditions as nonrandom mating and nonadditive effects generate linkage disequilibrium, changing gametic frequencies in ways not simply predictable from changes in allele frequencies.

Nagylaki (1993) suggests that that the statement $\Delta\overline{W} = \sigma_A^2(W)/\overline{W}$ be referred to as the **asymptotic fundamental theorem of natural selection**, while Fisher's more narrow (and correct) interpretation be referred to as the **Fisher-Price-Ewens theorem of natural selection**. This distinction seems quite reasonable given the considerable past history of confusion. At the risk of stating the obvious, both of these "versions" of the fundamental theorem are totally different. Warren Ewens (personal communication) said it best by noting for these two "versions" that

> "one should think of two totally different results, holding under totally different sets of circumstances, not intersecting with each other much, and which should not be put under the same umbrella."

Mean Fitness, Wright's Adaptive Topography, and Fisher's Fundamental Theorem

Although Wright and Fisher were two of the principal founders of modern population genetics, they held very different views about many aspects of evolution (Provine 1986). In particular, they differed greatly on the importance of mean fitness $\overline{W}$, with Wright viewing it as a key feature for describing and predicting evolution through adaptive topographies while Fisher regarded it as of considerably less importance (Frank and Slatkin 1992; Edwards 1994). It is ironic, therefore, that much of the population-genetics literature asserts that Fisher's theorem implies mean fitness never decreases. This really a restatement of Wright's adaptive topography, rather than a consequence of Fisher's rather strict interpretation of his theorem which says nothing about the change in *overall* mean fitness.

HERITABILITIES AND ADDITIVE VARIANCES OF TRAITS CORRELATED WITH FITNESS

The corollary of Fisher's theorem, that selection in the absence of any other force such as mutation drives the additive variance in fitness to zero, makes a general prediction. Characters strongly genetically correlated with fitness should show reduced h^2 relative to characters less well correlated with fitness (Robertson 1955), reflecting the removal of additive variance by selection (which may be partly countered by new mutational input). As we now review, such a pattern is indeed seen, but a closer look shows that the additive variance is actually *greater* for traits correlated with fitness, but this increase is overwhelmed by an increased residual variance, resulting in a lower heritability.

Traits More Highly Correlated With Fitness Have Lower Heritabilties

Because of the past action of natural selection, ignoring (for now) mutational input, traits correlated with fitness are expected to have reduced levels of additive variance, while charac-

ters under less direct selection are expected to retain relatively greater amounts of additive variance. How well does this prediction hold up? Many authors have noticed that characters expected to be under selection (e.g., life-history traits, such as clutch size) tend, on average, to have lower heritabilities than morphological characters measured in the same population/species (reviewed by Robertson 1955; Roff and Mousseau 1987; Mousseau and Roff 1987; Charlesworth 1987; also see LW Figure 5.10). However, some notable exceptions are also apparent (Charlesworth 1987). The difficulty with these general surveys is knowing whether a character is, indeed, highly *genetically* correlated with lifetime fitness. Clutch size, for example, would seem to be highly correlated with total fitness, but if birds with large clutch sizes have poorer survivorship, the correlation with lifetime fitness may be weak. Negative genetic correlations between components of fitness allow significant additive variance in each component at equilibrium, even when additive variance in $total$ fitness is zero (Robertson 1955; Rose 1982).

Estimates of lifetime fitness in nautral populations and their correlation with components of fitness (such as clutch size) are rare. One example is that of Gustasfsson (1986; also see Merilä and Sheldon 2000), who was able to measure lifetime reproductive success in a closed natural population of collared flycatcher birds (*Ficedula albicollis*) in the Baltic Sea, as well as the heritabilities of fitness and other characters. Lifetime reproductive success had an estimated heritability not significantly different from zero, as expected from the corollary to Fisher's theorem. Clutch size had a rather high heritability, 0.32 ± 0.15, but the estimated phenotypic correlation between clutch size and total fitness was very low, $r^2 = 0.03$. In general, character heritabilities increased as their phenotypic correlation with fitness decreased (Figure 5.4). A second example is the study by Schwaegerle and Levin (1991), who examined a wild population of the plant *Phlox dummondii*. As shown in Figure 5.4, they found no significant association between the heritiability of a character and its phenotypic correlation to fruit production (chosen as one measure of total fitness). McCleery et al. (2004) also found a negative relationship between h^2 and fitness in an English population of Great tits ($Parus\ major$) followed for almost 40 years. Taken together, these studies show evidence of a trend for characters phenotypically correlated with fitness to have reduced heritabilities relative to other characters. One important caveat is that this association is based phenotypic, rather than genetic, correlations with fitness.

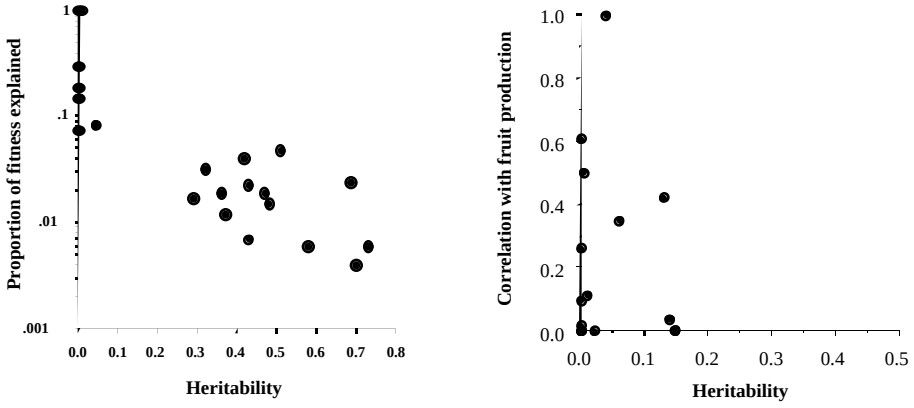


Figure 5.4. Two studies examining the association between a character's heritability and its phenotypic correlation with total fitness. **Left**: Gustafsson's (1986) work on the collared flycatcher *Ficedula albicollis* on the island of Gotland in the Baltic sea. The percent of total fitness explained by that character (measured by r^2, the squared phenotypic correlation between the character and lifetime fitness) are plotted against the heritability of the character. **Right**:

Schwaegerle and Levin's (1991) study of Texas populations of Plox (*Phlox drummondii*). Here the phenotypic correlation of that character with fruit production as a measure of total fitness is plotted against character heritability.

Based on these observations, one might be tempted to assume that the heritability should be low for a trait under selection that is at (or very near) its selective equilibrium, and conversely if h^2 is high, a trait under selection is not near its equilibrium. Both statements are false. As Example 5.13 highlighted, modest to high heritability can occur in a trait under fitness even when additive variance in fitness is near zero if there is a nonlinear transformation of the trait value (z) into fitness (w), such as occurs with stabilizing selection. Likewise Price and Schluter (1991) have cautioned against assuming that a low heritability implies that the population is near a selective equilibrium for that character. The following simple model makes most of their main points. Assume fitness is entirely determined by a metric character, with fitness a linear function of the phenotypic value z, $W(z) = a + \beta\, z + e$, the expected fitness for an individual of that phenotype ($a + \beta\, z$) plus a residual deviation e, giving the total variance in fitness as $\sigma^2[\,W(z)\,] = \beta^2\sigma_z^2 + \sigma_e^2$. Writing $z = A + E$, the additive genetic value A plus all other sources of variance (environmental and genetic), the additive variance in fitness is $\beta^2\sigma_A^2$. The heritiability of fitness can be expressed in terms of the variance components for z as follows:

$$h_z^2 = \frac{\sigma_A^2}{\sigma_A^2 + \sigma_E^2} > h_W^2 = \frac{\beta^2\,\sigma_A^2}{\beta^2\,(\sigma_A^2 + \sigma_E^2) + \sigma_e^2} = \frac{\sigma_A^2}{\sigma_A^2 + \sigma_E^2 + \sigma_e^2/\beta^2} \tag{5.18}$$

Thus, even when fitness is entirely determined by a single character, the heritability of fitness is less than the heritability of the character under selection, due to the residual deviation e in mapping from z to W (see Chapters 26, 27). If the heritability of fitness is measured and found to be close to zero in this case, there still could be a significant heritability in the actual character under selection and hence the population could still be far from a selection equilibrium.

Traits Correlated with Fitness have Higher Levels of Both Additive and Residual Variances

One consequence of the argument made by Price and Schluter is that traits more closely associated with fitness may also have higher residual variances. While a reduced h^2 value is often interpreted as resulting from a decrease in the additive variance, it can also result from an increase in the residual variance. Thus a simple comparison of heritabilities can be misleading (Houle 1992), and a more careful examination is required to determine the cause of reduced h^2 values for fitness-related traits. If one is to compare additive variances directly across traits, a standardized measure is required. A common approach in statistics to assess relative variability is to compare coefficients of variation σ/μ, where μ is the trait mean, leading Houle (1992, also Charlesworth 1984) to suggest that the **coefficient of additive genetic variance**, $CV_A = 100 \cdot \sigma_A/\mu$ is the appropriate scale-free measure for comparing the amount of additive genetic variation across traits. To distinguish this measure from the heritability, Houle coined the term **evolvability** for CV_A. As the represenative sample of *Drosophila* traits in Table 5.3 illustrates, traits with low h^2 values can have very high CV_A values.

Table 5.3 Heritabilities and coefficients of additive genetic (CV_A) and residual (CV_R) variation for representative traits in *Drosophilia melanogaster*. Here n is the number of studies and the median estimates are reported. (After Houle 1992)

Trait	n	h^2	CV_A	CV_R
Sternopleural bristles	21	0.44	7.97	8.39
Wing lenght	31	0.36	2.09	1.56
Fecundity	12	0.06	39.02	11.90
Longevity	7	0.11	27.73	9.89

Surprisingly, Houle found that a survey of over 800 estimates for CV_A from a variety of traits reveals that traits assumed to be closely related to fitness (such as life-history traits) have higher evolvabilities (larger CV_A values) than do traits more loosely associated with fitness. The pattern of heritabilities decreasing with their correlation with fitness is thus not due to proportionately smaller additive variances, but rather proportionately larger residual (nonadditive plus environmental) variances, quantified by CV_R, the coefficient of residual variation.

A study by Kruuk et al. (2000) on a Scottish red deer (*Cervus elaphus*) offers some additional insight into the suggestions of Price and Schluter and Houle. The authors used REML methodology (LW Chapter 27; Chapters 16, 17) to estimate variance components (for additive genetic, maternal, and residual effects) from pedigree data for this wild population (on the Isle of Rum in Scotland), following five life-history and three morphological traits in addition to lifetime fitness. As shown in Figure 5.5, they also found trait heritabilities negatively correlated with fitness. Following Houle, the coefficient of additive genetic variance CV_A, was *positively* correlated with fitness in males (but negatively correlated in females). Moreover, CV_A values were higher for life-history traits than for morphological traits. The coefficient of residual variation CV_R was also positively correlated with fitness. Similar patterns of both CV_A and CV_R being positively correlated with fitness were seen by Messina (1993) in insects (the seed beetle *Callosobruchus maculatus*), in an Alberta population of bighorn sheep (Coltman et al. 2006), and in natural bird populations (collared flycatchers by Merilä and Sheldon 2000; great tits by McCleery et al 2004). Thus, high residual variance, not low σ_A^2, accounts for the observed lower h^2 values for traits related to fitness. This point is emphasized by a ten-year study of Campbell (1997) on life history traits on a monocarpic perennial herb (*Ipomopsis aggregata*) that lives up to a decade before a single period of flowering. Survival to flowering and total flowers per offspring had very low heritabilities (4% and 2.5%, respectively) but very high CV_A values (53.8 and 55.2).

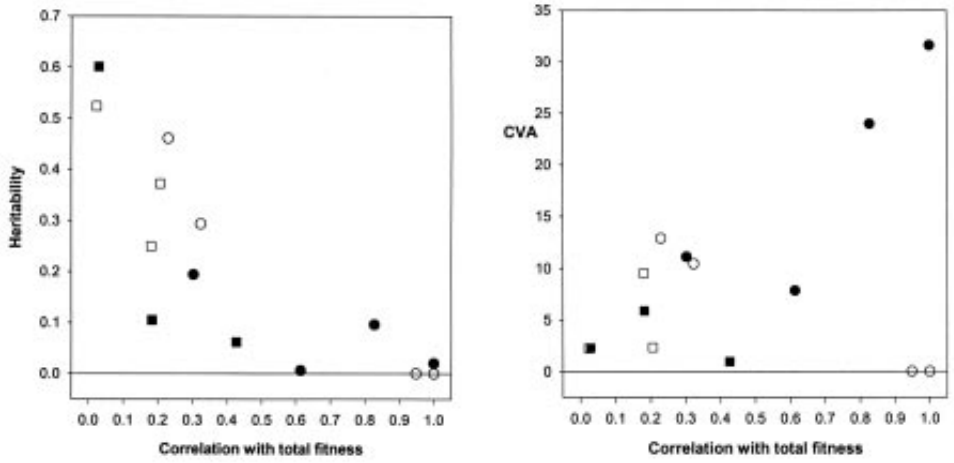


Figure 5.5 Kruuk et al.'s (2000) study of life history and morphological traits in the Scottish red deer (*Cervus elaphus*). Circles denote life-history traits, squares morphological traits. Filled

symbols are for males, open for females. **Left**: Heritabilties of a trait are negatively associated with the correlation of that trait with fitness. **Right**: The coefficient of additive genetic variation (the square root of the additive genetic variance of a trait divided by the trait mean, $CV_A = 100\ \sigma_A/\mu$) is positively associated with fitness in males, and negatively associated with fitness in females.

What accounts for the higher additive variance in traits associated with fitness? The prediction of lower additive variance is based on the removal of σ_A^2 by selection, but this is counted by new mutational input. If all traits have similar mutational variances, the faster removal of σ_A^2 by selection for traits more closely related to fitness would suggest lower equilibrium levels of additive variance. However, it appears that traits more closely associated with fitness actually have *higher* mutational variances (Houle et al. 1996), most likely do to a larger number of underlying loci that influences fitness (Houle 1992; Houle et al. 1996; Merilä and Sheldon 1999). Thus while the corollary of Fisher's theorem suggests that additive genetic variance in fitness is driven to zero, mutational input counters this decline, leaving some nonzero (but often small) amount of additive variation in fitness. How much variation is unclear, as estimates of $\sigma_A^2(w)$ are scare. Fowler et al. (1997) and Gardner et al. (2005) found significant additive variation for fitness in a laboratory population of *Drosophila* selected for domestication for close to 500 generations. Three studies have examined the additive variation associated with lifetime reproductive success in pedigreed natural populations of vertebrates. Kruuk et al. (2000) found no evidence for a significant heritability in red deer (estimates of σ_A^2 under a REML analysis were zero), McCleery et al. (2004) found positive, but not significant, estimates in great tits, while Merilä and Sheldon (2000) found a significant additive variance for females, and a positive (but not significant) variance for males in collared flycatchers. One issue in all studies is the expected low power to detect small amounts of variances, so negative results should be viewed cautiously.

Non-Additive Genetic Variances for Traits Under Selection

As selection drives the additive variance in fitness to near zero, any remaining genetic variance is expected to be increasingly composed of non-additive terms. As Example 5.12 highlights, this non-additive variance can be considerable. Thus, characters more closely associated with fitness are expected have a higher fraction of non-additive variance. Suggestions of this trend can be seen for the results of chromosomal analysis (e.g., Example 5.14), which tend to show epistatic interactions for life-history characters but not for general morphological characters (see also LW Table 5.1).

Example 5.14: Mackay (1985) examined total fitness (measured by competition against a marked balancer stock) of 41 third chromosomes extracted from a natural population of *Drosophila melanogaster*. If there is significant additive variance in fitness, a correlation between homozygote and heterozygote fitness is expected. Such a correlation was found for viability, suggesting some additive genetic variance in this character. However, when total fitness was examined, no correlation was found, suggesting no significant additive variation in total fitness. By constrast, in a very simliar experiment using segregating third chromosomes within a population selected for domestication, Fowler et al. (1997) and Gardner et al. (2005) found high homozygote-heterozygote correlations. Mackay observed strong inbreeding depression, consistent with variation in fitness in her study being caused by segregation of rare deleterious recessive alleles (see LW Chapter 10).

Crnokrak and Roff (1995) examined roughly 340 estimates of dominance variance in both life history and morphological traits over 17 wild and 21 domestic species. In the wild species, traits assumed more closely connected with fitness (life-history traits) showed significantly higher dominance (measured as a ratio of estimated dominance to estimated total variance) that did morphological traits. In domesticated species, however, there were no significant differences in dominance between life-history and morphological traits. The presumption is that many of the morphological traits examined in the domesticated species were themselves the result of strong recent selection during domestication. Consistent with this was the finding that morphological traits in domesticated species showed significantly higher dominance than morphological traits in wild species. While certainly not conclusive, these results are quite consistent with the prediction of higher dominance genetic variance in traits more closely associated with fitness.

Roff and Emerson (2006) present a somewhat complementary analysis, using ninety estimates for life history traits and over 140 estimates for morphological traits from line cross data. Recall (LW Chapter 9) that line-cross analysis examines the components (additive, dominant, ect.) of the among-line variance, rather than the variance segregating in any particular population. It is by no means clear if additive variance being driven to zero by selection translates into significant non-additive components contributing to differences between line means. This caveat aside, Roff and Emerson found that the magnitude of dominance (relative to additive) effects in line differences was much greater for life-history traits. Further, epistatic effects were more often detected for life-history traits, and the ratio of total nonadditive effects (dominance plus epistasis) relative to additive effects for life-history traits was roughly double that for morphological traits. Finally, DeRose and Roff (1999) showed that (n animals) inbreeding depression is greater for life history than morphological traits, indicating higher amounts of directional dominance among segregating alleles for life history traits (also see LW Chapter 10).

As we have seen, there is an increase in residual variation for traits associated with fitness. What accounts for this? One obvious source, as suggested by Price and Schluter (1991), is higher environmental variance associated with fitness. As we have just seen, a second source is an increase in nonadditive variance. While both factor likely play a role, their relative importance is unknown (Merilä and Sheldon 1999). Due to the difficulty of estimating nonadditive genetic variance components without special mating designs, resolution of this question for natural populations is likely to provide quite difficult.

ROBERTSON'S SECONDARY THEOREM OF NATURAL SELECTION

While the fundamental theorem predicts the rate of change of mean population fitness, we are often more interested in predicting the rate of change of a particular *character* under selection. Using a simple regression argument, Robertson (1966, 1968; also see Crow and Nagylaki 1976; Falconer 1985) suggested the **secondary theorem of natural selection**,

$$R = \mu_z' - \mu_z = \sigma_A(z, w) \tag{5.19a}$$

namely, that *the rate of change in a character equals the covariance between the additive genetic value of the character and the additive genetic value of relative fitness*. If this assertion holds, it provides a powerful connection between the fundamental theorem and the response of a character to selection. For example, it predicts that the character mean should not change when additive variance in *fitness* equals zero, regardless of the additive variance in the *character*. Akin to the breeder's equation $R = h^2 S$ following from the assumption of a linear parent-offspring regression (Chapter 12), the argument leading to Equation 5.19a

This follows by considering the regression between the breeding values for the trait (A_z) and relative fitness (A_w). The change in a trait in the next generation is just the change ΔA_z in its breeding value caused by selection (Chapter 12). We can think of this in turn as the change in the breeding value of relative fitness ΔA_w times the regression of the trait breeding value A_z on A_w, or

$$R = \Delta A_z = \Delta A_w \beta_{A_z, A_w} \tag{5.19b}$$

From standard univariate regression theory (LW Chapter 3), the slope of the regression of A_z on A_w is just

$$\beta_{A_z, A_w} = \frac{\sigma(A_z, A_w)}{\sigma^2(A_w)} \tag{5.19c}$$

Likewise, under the fundamental theorem, $\Delta A_w = \sigma^2(A_w)/\overline{w} = \sigma^2(A_w)$, as we use relative fitness ($\overline{w} = 1$). Substituting these two results into Equation 5.19b recovers Robertson's theorem,

$$R = \sigma^2(A_w) \left(\frac{\sigma(A_z, A_w)}{\sigma^2(A_w)} \right) = \sigma(A_z, A_w)$$

To investigate the conditions under which the secondary theorem holds, we first examine a single-locus model in some detail before considering what can be said for increasingly general multi-locus models. Assuming random mating, then (Equation 5.8b) a single generation of selection changes the frequency of allele A_i from p_i to $p_i' = p_i(1 + s_i)$, where s_i is the average excess in relative fitness for allele A_i. To map these changes in allele frequencies into changes in mean genotypic values, decompose the genotypic value of A_iA_j (for the trait of interest) as $G_{ij} = \mu_G + \alpha_i + \alpha_j + \delta_{ij}$, where α_i is the average effect of A_i on character value and δ_{ij} the dominance deviation (LW Chapter 4). The contribution from this locus to the change in mean phenotype after a generation of selection is then

$$\begin{aligned}
R &= \sum_{i,j} G_{ij}\, p_i' p_j' - \sum_{i,j} G_{ij}\, p_i\, p_j \\
&= \sum_{i,j} G_{ij}\, p_i(1 + s_i)\, p_j(1 + s_j) - \sum_{i,j} G_{ij}\, p_i\, p_j \\
&= \sum_{i,j} G_{ij}\, p_i p_j (1 + s_i + s_j + s_s s_j - 1) \\
&= \sum_{i,j} (\alpha_i + \alpha_j + \delta_{ij})\; p_j\, p_i\, (s_i + s_j) + \sum_{i,j} (\alpha_i + \alpha_j + \delta_{ij})\; p_i\, p_j\, s_i\, s_j
\end{aligned} \tag{5.20a}$$

The careful reader will note that we have already made an approximation by using the decomposition of G_{ij} instead of decomposition of G_{ij}' in the very first sum, as we used the approximation

$$G_{ij}' \simeq \mu_G + \alpha_i + \alpha_j + \delta_{ij}$$

Because α_i and δ_{ij} are functions of the allele frequencies, these actually change as p_i changes, but we have assumed that these deviations are much smaller than the change in p_i itself (so that $\alpha_i' \simeq \alpha_i$ and $\delta_{ij}' \simeq \delta_{ij}$). To simplify Equation 5.20a further, recall from the definition of average effect (see LW Chapter 4) that

$$\sum_i \alpha_i\, p_i = 0 \tag{5.20b}$$

and similarly

$$\sum_i \delta_{ij}\, p_i = 0 \tag{5.20c}$$

Using Equations 5.20b-c, the first term in Equation 5.20a becomes

$$\begin{aligned}
&\sum_{i,j} (\alpha_i + \alpha_j + \delta_{ij})\; p_i\, p_j\, s_j \\
&= \sum_j s_j\, p_j \left(\alpha_j \sum_i p_i + \sum_i (\alpha_i + \delta_{ij})\; p_i \right) \\
&= \sum_j s_j\, p_j\, (\alpha_j \cdot 1 + 0 + 0) = \sum_j \alpha_j s_j\, p_j
\end{aligned}$$

Likewise, a little more algebra (Nagylaki 1989b, 1991) simplifies the second sum in Equation 5.20a to give the expected contribution to response as

$$R = \sum_j \alpha_j s_j\, p_j + \sum_{i,j} \delta_{ij}\, p_i\, s_i\, p_j\, s_j \tag{5.21}$$

The first sum is the expected product of the average effect α_j of an allele on character value times the average excess s_i of that allele on relative fitness. Recall (LW Equation 3.8) that $\sigma(x, y) = E[x \cdot y] - E[x] \cdot E[y]$. Since (by definition), $E[\alpha_j] = E[s_i] = 0$, the first sum in Equation 5.21 is the covariance between the average effect of the character with the average excess on fitness, in other words, the additive genetic covariance between *relative* fitness and the focal trait. Hence we can express Equation 5.20a as

$$R = \sigma_A(z, w) + B = \frac{\sigma_A(z, W)}{\overline{W}} + B \tag{5.22}$$

If the character has no dominance (all $\delta_{ij} = 0$), the correction term B vanishes, recovering Robertson's original suggestion. If $\sigma_D^2(z)$ denotes the dominance variance in the trait value,

$$|\, B \,| \leq \frac{\sigma_D(z) \cdot \sigma_A^2(w)}{2} \tag{5.23}$$

where $\sigma_A^2(w)$ is the additive variance in *relative* fitness (Nagylaki 1989b). Assuming no epistasis, Nagylaki (1989b, 1991) shows that Equation 5.22 holds for n loci, with error term

$$B = \sum_{k=1}^{n} \sum_{i,j}^{n_k} \delta_{ij}(k)\, p_i(k)\, s_i(k)\, p_j(k)\, s_j(k) \tag{5.24}$$

where k indexes the loci, the kth of which has n_k alleles. This also holds when linkage disequilibrium is present, although the dominance deviations and average excesses in fitness are then expected to be different than those under linkage equilibrium. Nagylaki (1991) shows that Equation 5.24 is bounded by

$$\left|\, B \,\right| \leq \left(\sum_{k=1}^{n} \sigma_{D(k)}(z) \right) \cdot \frac{\sigma_A^2(w)}{2} \tag{5.25a}$$

where $\sigma_{D(k)}^2(z)$ is the dominance variance in the character contributed by locus k. If all loci underlying the character are identical (the **exchangeable model**), this bound reduces to

$$\left|\, B \,\right| \leq \frac{\sigma_D(z) \cdot \sigma_A^2(w)}{2\sqrt{n}} \tag{5.25b}$$

Even when dominance variance is present, then in the absence of epistatic variance, as the number of loci increases, the error in the secondary theorem becomes increasingly small. Nagylaki (1992b, 1993) further showed that the response with arbitrary epistasis (in both fitness and character value) under the assumption of linkage equilibrium can be expressed in terms of the gametic covariance between the character and fitness plus an error term which can be bounded.

The most general statement on the validity of the secondary theorem is due to Nagylaki (1993) and assumes weak selection and random mating, but allows for arbitrary epistasis and linkage disequilibrium. Similar to his weak selection analysis of Fisher's theorem discussed above, Nagylaki shows that after a sufficient time the change in mean fitness is given by

$$R = \sigma_A(z, w) + O(s^2) \tag{5.26}$$

As with the fundamental theorem, when gametic frequencies approach their equilibrium values, terms of order s^2 can become significant and mean response can differ significantly from Robertson's prediction, but again, the bulk of evolutionary change likely occurs before we approach the equilibrium value too closely. Consequently, the amount of change during the final approach to the equilibrium is generally expected to be quite small, so that (as with the fundamental theorem) under weak selection on the underlying loci, Robertson's theory holds for the bulk of evolutionary change.

Nagylaki (1992b, 1993) further showed that the response with arbitrary epistasis (in both fitness and character value) under the assumption of linkage equilibrium can be expressed in terms of the *gametic* covariance between the character and fitness plus an error term which can be bounded.

SELECTION ON A QUANTITATIVE TRAIT LOCUS

Finally, we consider the response at a particular *locus* underlying a character under selection. Because expressions for the amount and nature of selection acting on particular QTLs will be used in subsequent chapters, this section starts to forge the connections between population-genetic models of selection on single loci with models for selection on multilocus traits.

Suppose selection acts directly on the phenotypic value of a character, with the **fitness function** $W(z)$ giving the expected fitness of an individual with trait value z. In artificial-selection settings, we generally know the form of the fitness function, as it is imposed by the investigator/breeder. Conversely, in natural populations it is only with considerable effort that $W(z)$ can be estimated, provided we have information on the fitnesses and trait values of individuals (Chapters 18, 26, 27). Our concern here is to show how the fitness function $W(z)$ on a trait translates into changes in allele frequencies at underlying QTLs for that trait.

Assuming selection is entirely described by $W(z)$, we have already seen one approach, namely computing $\overline{W}$ and then applying Wright's formula (Example 5.6). This requires computing $\partial\overline{W}/\partial p_j$, which is usually nontrivial. Here we consider another approach, using the average excess of alleles to approximate the conditional phenotypic distribution, which we then use with $W(z)$ to compute the desired genotypic/allelic fitnesses.

Monogenic Traits

The simplest situation is when a single locus (with alleles $A_1, \cdots, A_n$) entirely determines the genetic variation in the trait of interest, whose value in an individual is denoted by z. Let $p_{ij}(z)$ denote the distribution of character values for an individual of genotype A_iA_j. The fitness for this genotype is then just the average of fitness over the distribution of phenotypes

for this genotype,

$$W_{ij} = \int W(z)\, p_{ij}(z)\; dz \tag{5.27a}$$

In many situations, we expect environmental values to be (roughly) normally distributed about the mean genotypic value, so that $p_{ij}(z) \sim \mathrm{N}(\mu_{ij}, \sigma^2_{ij})$, where μ_{ij} and σ^2_{ij} are the phenotypic mean and variance for genotype A_iA_j. If the mean and variance are known for each genotype and no other loci influence variation in z, then the W_{ij} are constant from one generation to the next (assuming no frequency-dependent selection nor changes in the environment) and the values from Equation 5.27a can be substituted into Equation 5.1b or 5.7c to directly compute the change in allele frequencies.

Likewise, if $p_i(z)$ denotes the phenotypic distribution for individuals carrying an A_i allele, the average fitness of individuals carrying an A_i allele is

$$W_i = \int W(z)\, p_i(z)\, dz \tag{5.27b}$$

Again, this can be directly substituted into Equation 5.7c to compute Δp_i. Either Equation 5.27a or 5.27b can be used to compute $\overline{W}$ because

$$\overline{W} = \sum_{i=1}^{n} W_i\, p_i = \sum_{j=1}^{n} \sum_{i=1}^{n} W_{ij}\, p_i\, p_j$$

Many Loci of Small Effect Underlying the Character

When two or more loci underlie the character of interest, Equations 5.27a and 5.27.b become problematical because the conditional densities $p_{ij}(z)$ and $p_i(z)$ are likely to change each generation as selection changes the genotype frequencies at other loci. Ideally, we would like to have an approximation that uses only the unconditional phenotypic distribution $p(z)$ and some simple property of the locus being considered. Fortunately, in many situations, the average excess α^*_i (LW Chapter 4) provides such a connection for loci of small effect. It will prove slightly easier to work with relative fitnesses, so we use $w(z) = W(z)/\overline{W}$, the expected relative fitness of an individual with phenotypic value z, throughout.

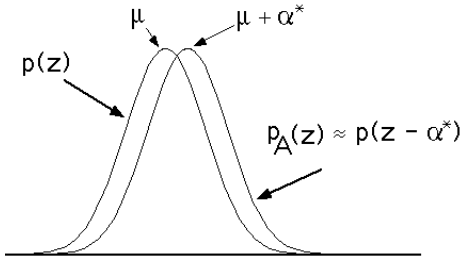


Figure 5.6. The unrestricted distribution of phenotypes $p(z)$ has mean μ, while the conditional phenotypic distribution $p_A(z)$ for an individual carrying a copy of allele A has mean $\mu + \alpha^*$, the mean plus the average excess for allele A. If α^* is small, then (to order α^*) we can approximate $p_A(z)$ by $p(z - \alpha^*)$, which shifts the unrestricted phenotypic distribution to the right (for $\alpha^* > 0$) by α^*. This is only approximate as knowing which allele is present at one locus decreases the genetic variance and results in the conditional phenotypic distribution having a (slightly) smaller variance.

Following Bulmer (1971) and Kimura and Crow (1978), assume that the average excess is small relative to the variance of z, as would occur if many loci of roughly equal effect underlie the character or if there are large environmental effects. Because having a copy of A_i increments the phenotype on average by α_i^*, as is shown in Figure 5.6, the conditional phenotypic distribution is to a good approximation the unconditional phenotypic distribution shifted by α_i^*, which can be written as

$$p_i(z) \simeq p(z - \alpha_i^*) \tag{5.28a}$$

Nagylaki (1984) has shown that this approximation is correct only to linear order, e.g., to terms of order α_i^* (the next section considers an approximation correct to quadratic order). Alternatively, we could also consider the distribution given the *genotype* at this locus (rather than a specific *allele*), in which case we could use

$$p_{ij}(z) \simeq p(z - a_{ij}) \tag{5.28b}$$

where a_{ij} is the deviation from the mean of the character value for an individual of genotype A_iA_j (again, this is correct only to linear order).

The approximation given by Equation 5.28a motivates two alternative expressions for w_i. First, we have directly (Bulmer 1971; Kimura and Crow 1978)

$$w_i = \int w(z)\, p_i(z)\, dz \simeq \int w(z)\, p(z - \alpha_i^*)\, dz \tag{5.29a}$$

Alternatively, following Kimura and Crow (1978), a change of variables gives

$$w_i \simeq \int w(z + \alpha_i^*)\, p(z)\, dz \tag{5.29b}$$

For certain phenotypic distributions and fitness functions, these integrals can be evaluated exactly (Latter 1965; Lynch 1984). However, even in these cases, the resulting w_i values are still only approximations because Equation 5.28 itself is only approximate. When the integral cannot be evaluated, a Taylor series expansion provides a useful approximation, often without having to completely specify the phenotypic distribution and/or fitness function. If the average excess α_i^* is small,

$$p(z - \alpha_i^*) \simeq p(z) - \alpha_i^* \frac{d\,p(z)}{dz} \tag{5.30a}$$

$$w(z + \alpha_i^*) \simeq w(z) + \alpha_i^* \frac{d\,w(z)}{dz} \tag{5.30b}$$

Substituting into Equation 5.29 and recalling that $\int w(z)\, p(z)\, dz = 1$ gives the average excess in relative fitness as

$$s_i = w_i - 1 \simeq -\alpha_i^* \int w(z) \frac{d\,p(z)}{dz}\, dz \tag{5.31a}$$

and

$$s_i = w_i - 1 \simeq \alpha_i^* \int p(z) \frac{d\,w(z)}{dz}\, dz \tag{5.31b}$$

Equation 5.31a is applicable if phenotypes are distributed continuously. For meristic traits, Equation 5.31b applies, provided $w(z)$ is differentiable.

The integrals in Equations 5.31a,b represent the change in fitness associated with linear deviations of a character value from its mean (i.e., directional selection). To see this, consider

the case where phenotypic values are normally distributed with mean μ and variance σ_z^2. Differentiating the normal density function

$$p(z) = \left(2\pi\sigma^2\right)^{-1/2} \exp\left(\frac{-(z-\mu)^2}{2\sigma^2}\right) \tag{5.32a}$$

gives

$$\frac{d\,p(z)}{dz} = -\left(\frac{z-\mu}{\sigma_z^2}\right) \cdot p(z) \tag{5.32b}$$

Substituting into Equation 5.31a and applying a little algebra yields

$$s_i \simeq \alpha_i^* \cdot \left(\frac{S}{\sigma_z^2}\right) = \overline{\imath} \cdot \left(\frac{\alpha_i^*}{\sigma_z}\right) \tag{5.33}$$

where S is the selection differential ($S = \mu^* - \mu$ is the within-generation change in the mean from selection) and $\overline{\imath} = S/\sigma_z$ the standardized selection differential (or selection intensity). Hence, to first order, the selection on an individual allele of small effect is approximately equal to the standardized average excess in z multiplied by the selection intensity (for the trait). This approximation (Equation 5.33) is a well-known result for certain fitness functions, e.g., truncation selection (Haldane 193; Griffing 1960). The result that Equation 5.33 is a good approximation for arbitrary fitness functions when z is normally distributed is due to Kimura and Crow (1978) and (in a restricted form) to Milkman (1978).

One consequence of the first-order terms in s_i corresponding to the effects of directional selection is that for strictly stabilizing selection (i.e., no directional selection component), the first order terms are zero, and we must consider second-order terms in order to have a proper approximation for s_i. We will return this point shortly.

A Population-Genetic Derivation of the Breeders' Equation

If the midparent-offspring regression is linear with slope h^2, the response R to selection (measured as the change in mean) is given by the **breeders' equation**, $R = h^2 S$, which is extensively discussed in Chapter 12. The breeders' equation can be obtained directly from the secondary theorem of natural selection in certain special cases, relating the this purely statistical motivation with an explicit underlying population-genetic model. Recalling Equation 5.31, we can write $s_i \simeq \alpha_i^* I$, with I being the appropriate integral. Assuming gametic-phase equilibrium and that the character does not display epistasis, substituting into Equation 5.21 gives the expected contribution to the response from a single locus as

$$I \sum_j 2\,\alpha_j\,\alpha_j^*\,p_j + I^2 \sum_{i,j} \delta_{ij}\,\alpha_i^*\,\alpha_j^*\,p_i\,p_j \tag{5.34}$$

where the sum is over all alleles at this locus. For a random-mating population, the first sum is the contribution to additive variance from this locus (LW Equation 4.23a). Summing over all loci gives the response as

$$R \simeq I\,\sigma_A^2 + I^2 \sum_{k=1}^{n} \sum_{i,j}^{n_k} \delta_{ij}(k)\,\alpha_i^*(k)\,\alpha_j^*(k)\,p_i(k)\,p_j(k) \tag{5.35a}$$

Expressing s_i as $\alpha_i^* I$ requires that the approximation given by Equations 5.31a,b is reasonable. If the fraction of total phenotypic variation attributed to any particular locus is large enough to be non-negligible (e.g., when a major gene underlies the character), this approximation breaks down. A second potential complication is s_i as given by Equation 5.31

is correct to only linear order. While we will not do so here, we can improve on Equation 5.35a by using an approximation for s_i that is correct to quadratic order (Equation 5.44).

If phenotypic values are normally distributed before selection, then from Equation 5.33 $I = S/\sigma_z^2$ and the response becomes

$$R = Sh^2 + \frac{S^2}{\sigma_z^4} \sum_{k=1}^{n} \sum_{i,j}^{n_k} \delta_{ij}(k)\, \alpha_i^*(k)\, \alpha_j^*(k)\, p_i(k)\, p_j(k) \tag{5.35b}$$

which gives the breeders' equation plus a correction term. If there is no dominance ($\delta_{ij}(k) = 0$ for all i, j, and k), the second term is zero. Even with dominance, the second term is of lower order than the first. One way to view the correction term is to recall that when dominance is present, the parent-offspring regression is slightly nonlinear (LW Chapter 17), while the breeders' equation requires a linear parent-offspring regression.

Thus, with a normal distribution of phenotypes and no dominance in the character, we recover the breeders' equation. *Exact* normality requires that the genotypic values at *each* locus are normally distributed (Nagylaki 1984). Since there are only a finite number of alleles, and hence a discrete number of genotypic values, this never holds exactly (the consequences are examined in Chapter 22), but if the number of loci is large, the central limit theorem implies that the genotypic distribution is approximately normal. This points out one of the central assumptions of many quantitative-genetic selection models: *the number of loci is assumed sufficiently large that the amount of phenotypic variation attributable to any single locus is small, and hence the amount of selection on any locus is also small*. This is formally stated as the **infinitesimal model** (Chapter 22): there are effectively an infinite number of loci, each contributing an infinitesimal amount to the total phenotype. We see from Equation 5.25b that as the number of loci approaches infinity (the infinitesimal model), the second sum in Equation 5.35b becomes vanishingly small and we recover the breeders' equation even when dominance is present.

Another class of models (Kimura 1965b; Lande 1975) assumes a normal distribution of allelic effects at each locus underlying the character (effectively assuming an infinite number of alleles per locus). This also allows for smooth changes in genotypic values, even when a single locus underlies the character. These two models (infinite number of loci versus infinite number of alleles per locus) represent extreme approximations to the view that a moderate number of loci, each with a moderate number of alleles, underlie many quantitative characters. Chapter 22 explores these two models in greater detail. Considerable complications are introduced into the dynamics of underlying alleles when allelic effects are limited to a discrete set of values (e.g., Barton 1986), and this is far from being sorted out.

Correct Quadratic Terms for s_i

As mentioned earlier, the approximation given by Equation 5.28 is correct only to linear order, whereas approximations to quadratic (second) order are required to properly account for selection acting directly on the variance. One source of error is that the conditional distribution of phenotypes for individuals carrying a particular allele has a lower variance than the unconditional phenotypic distribution. Partial knowledge of the genotype reduces the uncertainty in genotypic value, reducing the variance (Bulmer 1971; Lynch 1984; Nagylaki 1984; Walsh 1990). The phenotypic variance of individuals with genotype A_iA_j at the kth locus is $\sigma^2 - \sigma_k^2$, where σ_k^2 is the amount of variance the kth locus contributes to the total phenotypic variance. In the absence of epistasis, gametic-phase disequilibrium, and genotype-environment interaction/correlation, this is

$$\sigma_k^2 = \sum_{i,j}^{n_k} a_{ij}^2\, p_i\, p_j \tag{5.36}$$

where $a_{ij} = G_{ij} - \mu_G$ is the deviation of the genotypic value from the mean (Nagylaki 1984; Walsh 1990). Using an expansion that accounts for this reduction in variance, Hastings (1990a) developed an approximate expression for $p_i(z)$ correct to quadratic order. Using this, s_i can be correctly approximated to quadratic order by

$$s_i \simeq -I_1\alpha_i^* + \frac{I_2}{2}\left[\sum_j a_{ij}^2\, p_j - \sigma_k^2\right] \tag{5.37a}$$

Here

$$I_1 = \int w(z)\,\frac{d\,p(z)}{dz}\,dz, \quad I_2 = \int w(z)\,\frac{d^2\,p(z)}{dz^2}\,dz \tag{5.37b}$$

Hastings (1992) shows how this approach extends to a locus that influences n characters under selection. If $\mathbf{z}$ denotes the vector of characters and $p(\mathbf{z})$ the resulting n-dimensional probability density, then I_1 is an n-dimensional vector of partials of $p(\mathbf{z})$ with respect to each z_i (i.e., the gradient vector of $p(\mathbf{z})$ with respect to $\mathbf{z}$) and I_2 is the Hessian matrix (the $n \times n$ matrix whose ij-th element is the second partial of $p(\mathbf{z})$ with respect to z_i and z_j, see Appendix 6).

As we mentioned previously, I_1 measures selection on the mean. Similarly, I_2 measures selection on the variance. To see this, if phenotypes are normally distributed, then differentiating Equation 5.32b a second time gives

$$\frac{d^2p(z)}{dz^2} = -\frac{p(z)}{\sigma_z^2} + \frac{(z-\mu)^2}{\sigma_z^4}\,p(z) \tag{5.38a}$$

and a little algebra yields

$$I_2 = \frac{\delta_{\sigma^2} + S^2}{\sigma_z^4} \tag{5.38b}$$

where δ_{σ^2} is the within-generation change in phenotypic variance due to selection (Chapters 15, 22). Hence, if phenotypes are normally distributed,

$$s_i \simeq \alpha_i^*\,\frac{S}{\sigma_z^2} + \frac{\delta_{\sigma^2} + S^2}{2\sigma_z^4}\left[\sum_j a_{ij}^2\, p_j - \sigma_k^2\right] \tag{5.39a}$$

When alleles are completely additive, $a_{ij} = \alpha_i + \alpha_j$ and the term in brackets reduces to $\alpha_i^2 - \sum_j \alpha_j^2\, p_j$. Assuming no dominance, substituting this improved value of s_i into Equation 5.21 gives the response to selection as

$$R = h^2 S + \frac{\delta_{\sigma^2} + S^2}{2\sigma_z^4}\,\sum_{k=1}^{n}\sum_{i}^{n_k}\alpha_i^3(k)\,p_i(k) \tag{5.39b}$$

If there is no selection on the variance itself, $\delta_{\sigma^2} = -S^2$ (Chapter 26) and we recover the breeders' equation. Under our assumption of no dominance or gametic-phase equilibrium, double sum in Equation 5.39b is the skewness in the genotypic distribution. Thus if the genotypic distribution is skewed, changes due to selection on the variance also changes the mean. Equation 5.39b raises several issues that will be examined in detail in Chapter 22. In particular, even if the distribution of *phenotypes* is normal, the response still depends on rather fine details (such as the third moment of allelic effects *at each locus*) of the *genotypic* distribution.

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