5

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 scenarios involving one or two loci. There are two fundamental reasons for this. First, in some settings, the trait of interest is indeed largely controlled by a single major gene, in which case the models introduced here are directly applicable. Second, these relatively simple 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 considers longer time scales, population-genetic models are central to evaluating how genetic variances (and hence selection response) change.

One key assumption of this chapter is that the population size is effectively infinite, so that there is no effect of drift. A second assumption is that precise fitness values can be assigned to individual genotypes — one knows W_g, the fitnesses for all genotypes g at the locus (or loci) of interest. Conversely, in the typical quantitative-genetic setting, fitness is defined for phenotypes, not genotypes, with $W(z)$ denoting the average fitness of individuals with phenotypic value z with little regard for their underlying genotypes. We connect these different views of fitness at the end of the chapter, showing how selection on phenotype maps into selection on an underlying locus, forging a fundamental connection between the population-genetic and quantitative-genetic views of selection.

We start with a review of the theory of single-locus selection, highlighting how the dynamical equations for allele-frequency change can also be expressed in terms of quantitative-genetic parameters for the trait fitness. While a rather general theory of single-locus selection has been developed, unfortunately this is not true for multilocus selection. For such purposes, we will consider two approaches. The first, covered in this chapter, involves exact results for particular two-locus models. The second is to use approximations for the expected response of *traits*, as opposed to allele or gametic frequencies. We start consideration of this trait-based approach at the end of this chapter by showing how single-locus approximations lead to the classic breeder's equation. In Chapter 6, we examine two general approximations for the behavior of traits under selection — **Fisher's fundamental theorem of natural selection** when the trait is fitness itself and **Robertson's secondary theorem** for a general trait.

The key points of these next two chapters 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. If this occurs, single-locus equations for allele-frequency change no longer hold, and no

completely general statement about the behavior under selection can be made.

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 Clark 1984 and Crow 1992 for overviews of Haldane's fascinating life and legacy). We deal first with **viability selection**, in which case W is the probability of survival from birth to reproductive age. Under this model, 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 then ensures that the offspring genotypic frequencies are in Hardy-Weinberg proportions. As we will show below, if fertility differences exist among genotypes, offspring genotypes are generally not in Hardy-Weinberg proportions.

Table 5.1. Genotype frequencies after viability selection. Here, p is the frequency of allele 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	$p^2\,\frac{W_{AA}}{\overline{W}}$	$2p(1-p)\,\frac{W_{Aa}}{\overline{W}}$	$(1-p)^2\,\frac{W_{aa}}{\overline{W}}$
	where $\overline{W} = p^2W_{AA} + 2p(1-p)W_{Aa} + (1-p)^2W_{Aa}$		

Viability Selection

Consider the change in the frequency p of allele A over one generation, $\Delta p = p' - p$. As shown in Table 5.1, the number of AA genotypes following selection is proportional to p^2W_{AA}, the frequency of AA genotypes before selection multiplied by their genotypic fitness. To ensure that post-selection frequencies sum to one, we divide this proportion by a normalization constant, the **mean population fitness** (the average fitness of a randomly-choosen individual),

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

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

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

Applying the results in Table 5.1 gives the expected change in the frequency of A as

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

This equation can also be expressed using **relative fitnesses** $W_{ij}/\overline{W}$, abbreviated as w_{ij}, with mean fitness then scaling to $\overline{w} = 1$. We will adhere to the notation where 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

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

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., no allele frequency change after selection) are called **equilibrium frequencies**, which we denote by $\widehat{p}$. Regardless of the values of s or h, trivial **boundary** equilibria exists when only one allele is present ($\widehat{p} = 0$ or 1). Equation 5.1c shows an **internal** equilibrium, where both alleles are segregating, requires $1+h(1-2\,\widehat{p}) = 0$, or $\widehat{p} = (1+h)/(2h)$. Thus $h > 1$ (**overdominance**) or $h < -1$ (**underdominance**) is required to ensure $0 < \widehat{p} < 1$, However, equilibrium behavior is very different in these two cases. The situation $h > 1$ represents a **stable** equilibrium, where following a small perturbation from $\widehat{p}$ selection returns the allele frequency to $\widehat{p}$ (Figures 5.1a, b, and c). In contrast, with $h < -1$, there is an **unstable** equilibrium, where selection sends the allele frequency *away* from $\widehat{p}$ following a small perturbation (Figure 5.1d).

Example 5.1. Letting 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 an amount s to the fitness. In this case, 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), and applying 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 only equilibrium allele frequencies are $\widehat{p} = 0$ and $\widehat{p} = 1$. 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 $\widehat{p} = 1$ is a stable equilibrium point, while $\widehat{p} = 0$ 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 $\widehat{p} = 0$ is stable, while $\widehat{p} = 1$ is unstable.

Expected Time for Allele Frequency Change

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

$$\frac{dp}{dt} = sp(1-p)[\,1+h(1-2p)\,] \tag{5.3a}$$

For additive selection ($h = 0$), this has a simple solution of

$$p(t, p_0) = \frac{p_0}{p_0 + (1-p_0)e^{-st}} \tag{5.3b}$$

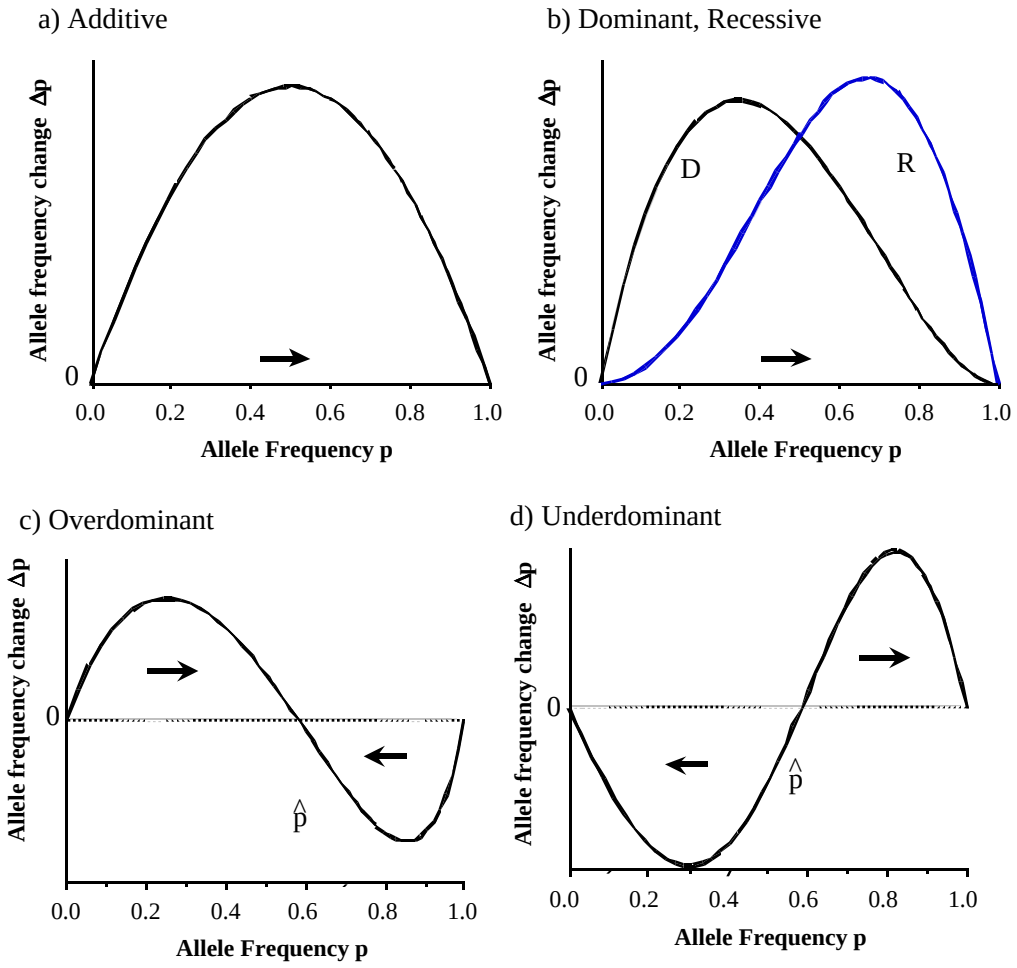


Figure 5.1. A plot of allele-frequency change Δp as a function of p is a useful device for examining how frequencies change under selection. If $\Delta p > 0$, the frequency of A increases (moves to the right), as indicated by rightward pointing arrow. If $\Delta p < 0$, the frequency of A decreases (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, with the rate of change being symmetric around $p = 1/2$. **b)** Directional selection with dominance, with allele A favored. Here the response is *asymmetric* about $p = 1/2$, with curve D corresponding to allele A dominant, and curve R for A recessive. In both cases, $\Delta p > 0$ (provided $p \neq 0, 1$), and the frequency of A increases to one. **c) Overdominant selection**, where the heterozygote is more fit than either homozygote (Example 5.4), has an internal equilibrium frequency $\widehat{p}$. For frequencies above the equilibrium, $\Delta p < 0$ and the frequency decreases to $\widehat{p}$; whereas if p is less than $\widehat{p}$, $\Delta p > 0$ and the allele frequency increases to $\widehat{p}$. Thus, $\widehat{p}$ 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 in this case it is **unstable**. If $p < \widehat{p}$, p decreases toward zero, while if $p > \widehat{p}$, p increases towards one. The result is fixation of either A or a, depending on the starting allele frequency.

where $p(t, p_0)$ is the frequency of allele A at time t given initial frequency p_0, which for simplicity we often denote as p_t. 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

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

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

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

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

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

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

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

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, Equation 5.3d gives

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

On the other hand, from Equations 5.3e and 5.3f, $t \simeq 1.5/s$ generations when A is dominant, and $t \simeq 5.1/s$ generations if A is recessive. The faster rate of response for a dominant occurs because A is fully exposed in a heterozygote, while it is completely covered when recessive. Conversely, this same feature slows down the rate of response in a dominant when A is common, as only rare aa heterozgyotes are selected against.

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, but let x be the current frequency of allele A in males, and y be the current value in females. The genotype frequencies following random mating and their fitnesses can be represented as

Genotype	AA	Aa	aa	Mean
Frequency	yx	$x(1-y)+y(1-x)$	$(1-x)(1-y)$	
Male fitness	W_{AA}	W_{Aa}	W_{aa}	$\overline{W}$
Female fitness	V_{AA}	V_{Aa}	V_{aa}	$\overline{V}$

As in Table 5.1, the frequencies of surviving genotypes in males and females are equal to the product of their starting values and relative fitness. For example, $yx\,W_{AA}/\overline{W} = yx\,w_{AA}$ and $yx\,V_{AA}/\overline{V} = yx\,v_{AA}$ are the frequencies of AA in surviving males and females, respectively.

The frequency of A in males after selection is the sum of the post-selection frequency of AA plus half that of Aa, giving the recursion equation for the allele frequency in males as

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

$$= xy\,w_{AA} + (1/2)[x(1-y) + y(1-x)]\,w_{Aa} \tag{5.4b}$$

where

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

with an analogous expression for y' in females obtained by replacing W by V. At an autosomal locus, in the next generation both sexes start with the frequency of A equal to $(x' + y')/2$, the average of the post-selection frequencies in the two sexes.

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** (where the sign of the selection coefficients differs between sexes, with A favored in one sex and a in the other), can stably maintain variation *only* if the absolute values of 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.

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. The fitness of a genotype may be a function of the other genotypes with which it interacts, giving rise to **frequency-dependent selection**. For example, when a rare genotype has a selective advantage due to preferential mating or avoidance of a search image by a predator, as its genotype frequency increases, its fitness declines. Alleles at self-incompatibility loci in plants also have such a fitness advantage when rare.

If genotype fitness varies with allele frequencies, Equation 5.1 still holds, provided we replace the constant values of W_{ij} by the functions $W_{ij}(p)$. One interesting feature of frequency-dependent selection is that mean population fitness need not increase over time. Indeed, Wright (1948) gives a simple two-allele example where mean fitness is strictly decreasing over time.

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) noted just how subtle this distinction can be, showing that both fitness models can generate identical allele-frequency dynamics. Thus, the two models cannot be distinguished from allele-frequency data alone. Indeed, Denniston and Crow (1990) and Lachmann-Tarkhanov and Sarkar (1994) showed that for *any* set of constant fitnesses, there is always an alternative frequency-dependent fitness set that generates the same allele - frequency dynamics.

Making a case for balancing selection via rare-genotype advantage therefore requires direct estimates of genotype fitnesses at different allele frequencies. Genotype fitnesses are expected to be 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.

Fertility/Fecundity Selection

We have been assuming no differential fertility/**fecundity** (we treat these two terms as synonymous) so that all combinations of genotypic pairs produce on average the same

number of offspring. Obviously, this is often not true. To treat this problem formally, the average number of offspring produced by the (ordered) cross of an A_iA_j male with a A_kA_l female is denoted by the **fertility fitness** f_{ijkl}. In this fully general case, 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. For example, mean viability 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,

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

so that the average fertility of the cross is just the product the fertility fitnesses 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 $w_{ij}f_{ij}$.

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 sexually-preferred trait values conflict with natural selection (viability and/or fertility selection).

Example 5.3. An interesting example of the consequences of sexual selection was presented by 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 a wild population, will it increase in frequency, be neutral, or quickly be lost by negative selection? Muir and Howard (1999, 2001) and Howard et al. (2004) developed population-genetic models to assess such risk, and used them to understand the fate of a transgenic strain of 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 a normal medaka.

While such a genetic transformation may be a boon 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 strong viability selection, one might think that any transgenes that escape would quickly be lost. However, Muir and Howard found that larger fish have a roughly 4-fold mating advantage relative to smaller fish. Based on these parameter values, any escaped transgene will spread, as the mating advantage more than offsets the survivability disadvantage. However, simulation studies find a potentially more ominous fate under these parameter values. The transgene not only spreads, but it eventually may drive the population to extinction as a consequence of the reduction in viability. Muir and Howard coin the term **Trojan gene** for such settings. Such genes may also arise naturally. A potential example is Dawson (1969), who found that a newly-arisen eye color mutation in *Tribolium castaneum* rapidly increased in frequency in tandem with the rate at which the line was eliminated in a competition experiment.

WRIGHTS' FORMULA

A more compact way to express allele-frequency change that provides additional insight

was presented by Sewall Wright, one of the founding fathers (with Fisher and Haldane) of modern selection theory. Since

$$\begin{aligned}\frac{d\overline{W}}{dp} &= \frac{d\left(p^2W_{AA} + 2p(1-p)W_{Aa} + (1-p)^2W_{aa}\right)}{dp} \\ &= 2pW_{AA} + 2(1-2p)W_{Aa} - 2(1-p)W_{aa},\end{aligned}$$

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).

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,

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

which upon substituting into Wright's formula gives

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

Setting $\Delta p = 0$ gives three equilibrium solutions: $\widehat{p} = 0$; $\widehat{p} = 1$; and most interestingly,

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

which corresponds to $d\overline{W}/dp = 0$, a necessary condition for a local extremum (maximum or minimum) in $\overline{W}$. Recall from calculus that this extremum is a maximum when $d^2\overline{W}/dp = -2(s+t) < 0$, and a local minimum when this second derivative is positive. With selective overdominance, the heterozygote has the highest fitness ($s, t > 0$), implying $\Delta p > 0$ when $p < \widehat{p}$, and $\Delta p < 0$ when $p > \widehat{p}$ (Figure 5.1c). Thus, *selection retains both alleles in the population*, as first shown by Fisher (1922). Further, $\widehat{p}$ 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, $\widehat{p} = s/(s+t)$ corresponds to a local *minimum* of $\overline{W}$ (as $d^2\,\overline{W}/dp^2 > 0$) and is therefore unstable — if p is the slightest bit below $\widehat{p}$, p decreases to zero, while if p is the slightest bit above $\widehat{p}$, p increases to 1 (Figure 5.1d). In contrast to selective overdominance, *selective underdominance removes, rather than maintains, genetic variation*, with the initial starting frequencies determining which alelle is fixed.

Example 5.5. A classic example of selective overdominance is sickle-cell anemia, 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. *SS* individuals often have near-zero fitness (due to their low survival to reproductive age) and ordinarily this would be expected to result in a very low frequency of the *S* allele. However, in malarial-infested regions, *SN* heterozygotes (*N* denoting the "normal" allele) have increased resistance to malaria relative to *NN* homozygotes. A sample 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 fitnesses of the *SS*, *SN*, and *NN* genotypes as $1-t$, 1, and $1-s$ respectively, the results from Example 5.4 gives an equilibrium frequency of $s/(s+t)$ for allele S. Setting this equal to 0.123 implies that the selection coefficient s against *NN* individuals relative to heterozyotes is

$$t = \frac{(1-0.123)}{0.123}\,s = 7.120\,s, \quad \text{or} \quad s = 0.140\,t$$

If *SS* individuals are either lethal ($t = 1$) or have only 10% fitness ($t = 0.9$), then s = 0.140 and 0.126, respectively. In other words, heteroyzgotes have a 13 to 14% fitness advantage due to increased malaria resistance.

Example 5.6. Consider the dynamics of allele for a trait undergoing stabilizing selection, with some intermediate phenotypic value θ being favored. Naively, one might imagine this would generate selective overdominance at underlying loci. However, an application of Wright's formula shows that this is *not* the case. One standard model for stabilizing selection is to assume a **Gaussian fitness function**, where the expected fitness of an individual with trait value z is given by

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

where s is the strength of selection against the trait (note that $1/s$ is akin to the "variance" of this function, with a larger variance indicating weaker selection). Barton (1986) showed that if phenotypes are normally distributed with mean μ and variance σ^2, then (assuming weak selection, $\sigma^2 \ll 1/s$), the mean fitness is

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

Suppose that n diallelic fully additive (no dominance and no epistasis) loci underlie this character, with the genotypes b_ib_i, B_ib_i, and B_iB_i at locus i having effects 0, a_i, and $2a_i$. Letting p_i be the frequency of allele B_i, the trait mean is some baseline value m plus the genetic contributions, while the trait variance is the additive-genetic plus environmental variances,

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

where the additive-genetic 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,

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

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

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

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 to

$$\Delta p_i = p_i(1-p_i)\,a_i^2\,s\,(p_i - 1/2) \qquad (5.6b)$$

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 tends to drive allele frequencies towards fixation, *removing* rather than retaining, variation at underlying loci (Robertson 1956).

Adapative Topographies and Wright's Formula

The surface $\overline{W}(p)$ of mean population fitness as a function of allele frequency forms an **adapative topography**, showing which p value maximize mean fitness. When Wright's formula holds, 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. For example, 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 5.4). 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 in a large population *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 $\overline{W}(p)$ — 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. 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 (Figure 5.2c), and unstable equilibria to local minima (Figure 5.2d).

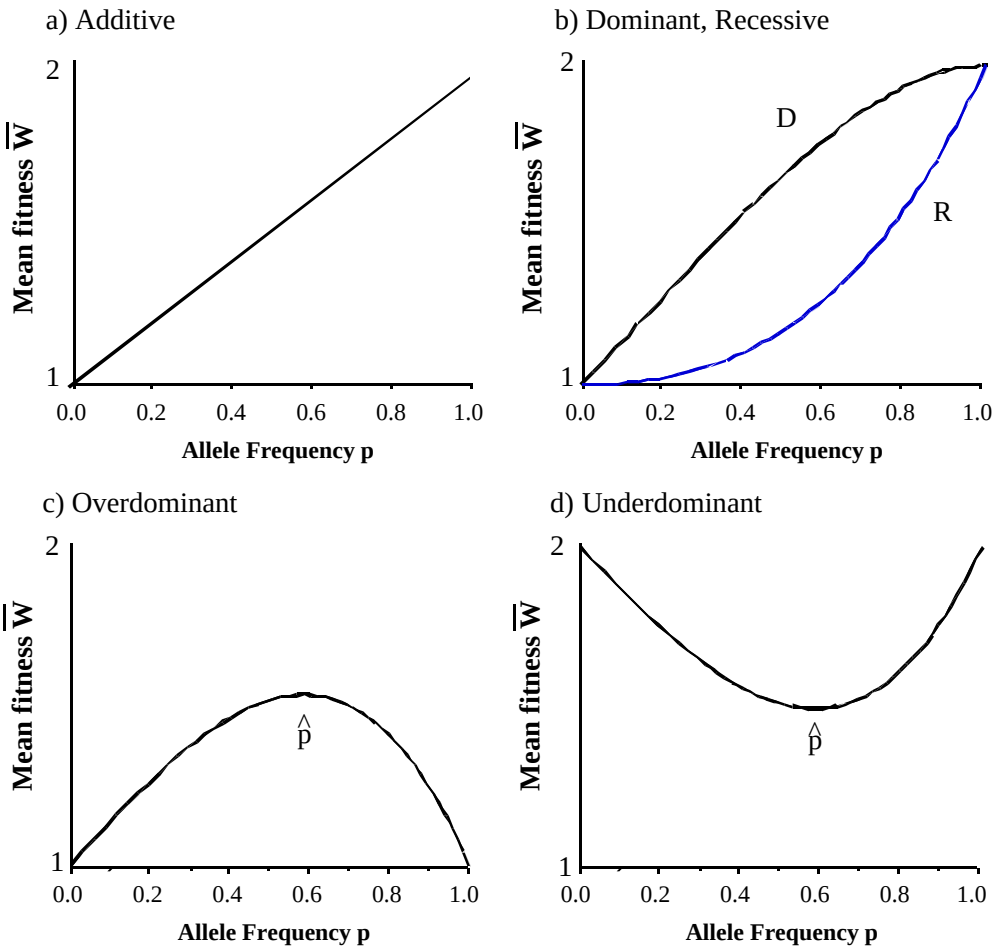


Figure 5.2. A plot of mean population fitness $\overline{W}(p)$ as a function of allele frequency p (compare with Figure 5.1). In all cases, the best genotype has fitness two and the worst fitness one. **a**: Directional selection with additive fitness, allele A favored. **b**: Directional selection with dominance, allele A favored. Upper curve for A dominant, lower 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 maximized at the stable equilibrium point $\widehat{p}$. **d**: With underdominant selection, fitness is *minimized* at the unstable internal equilibrium point $\widehat{p}$.

SINGLE-LOCUS SELECTION: MULTIPLE ALLELES

Extending single-locus models from two to multiple alleles is straightforward and allows us to show connections between quantitative-genetic concepts (such as average excesses and additive variance) and the behavior of population-genetic models.

Marginal Fitnesses and Average Excesses

For a locus with n alleles under viability selection and random mating, the frequencies of the A_iA_j heterozygotes and A_iA_i homozygotes after selection are $2\,p_i\,p_j\,W_{ij}/\overline{W}$ and $p_i^2\,W_{ii}/\overline{W}$, respectively, 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 post-selection frequency of the A_iA_i homozygote plus half the post-selection frequencies 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 **marginal fitness** of allele A_i, i.e., the expected fitness of an individual carrying a copy of A_i. Note that, unlike *genotypic* fitness W_{ij}, W_i is always a function of the allele frequencies, and hence is expected to change over time. The concept of marginal fitness can be understood as follows: under random mating 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., $\widehat{p}_i \neq 0, 1$),

$$W_i = \overline{W} \quad \text{for all } i \text{ with } 0 < \widehat{p}_i < 1 \tag{5.7d}$$

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

Marginal fitnesses provide a direct connection between single-locus and quantitative-genetic theory. Recalling 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), we immediately see that $(W_i - \overline{W}\,)$ is the average excess in absolute fitness of allele A_i, implying

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

is the average excess in *relative* fitness, and that 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*. As there is then no variation in the average excesses and it immediately follows that the *additive genetic variance in fitness is also zero* at the equilibrium allele frequencies.

Equilibrium Frequencies With Multiple Allles

As with a single locus with two alleles, with constant-fitnesses, viability selection, and random mating, mean fitness also increases with n alleles at a single locus. The classical short

proof for this is given by Kingman (1961a). A more interesting question involves the number of polymorphic equilibria that exist with two (or more) segregating alleles. In particular, how many n-allele polymorphic equilibria are possible? The classical result (Kingman 1961b) is that such a system either has no such equilibria, or exactly one, or an infinite number (a line or hyperplane of solutions). We can see this from Equation 5.7d, as the equilibrium marginal fitnesses for all segregating alleles are identical, e.g. $\widehat{W}_i = \widehat{W}_1 \quad \text{for } i = 2, \cdots, n$. Since each marginal fitness is a linear function of the n equilibrium allele frequencies, with

$$\widehat{W}_i = \sum_{j=1}^{n} W_{ji}\widehat{p}_j$$

this leads to n linear equations in terms of the $\widehat{p}_i$, the equilibrium allele frequencies for the n alleles,

$$\widehat{W}_i = \widehat{W}_1, \quad \text{or} \quad \sum_{j=1}^{n} W_{ji}\widehat{p}_j = \sum_{j=1}^{n} W_{j1}\widehat{p}_j, \quad \text{for } i = 2, \cdots, n$$

From LW Appendix 3, as a linear system with n equations and n unknowns, there is 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, as this is just Hardy-Weinberg).

A deeper result obtained by Kingman is that the condition for a single internal (and stable) equilibrium for all n 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 5 reviews eigenvalues). More generally, if $\mathbf{W}$ has m positive eigenvalues, then at most $n-m-1$ alleles can be jointly polymorphic. When there is not a single unique n-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 n possible alleles, the space of potential allele frequencies is given by the **simplex** defined by the constraint $\sum_i^n p_i = 1$. Figure 5.3 shows this for the three-allele case, which is a section of a two dimensional plane. With n alleles, the resulting simplex is a section of a $n-1$ 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 n alleles, there are n corner equilibria. With **edge equilibria**, 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 alleles are segregating (all $p_i > 0$ within the interior of the simplex). Thus, polymorphic equilibria correspond to either edge equilibria (not all alleles are segregating) or internal equilibria (all are segregating). Kingman's result states there is either no internal equilibrium, or a single unique one, or a surface (such as a line or plane) embedded within the simplex.

Far more important that the existence of equilibria is their stability. As noted above, when allele frequencies at an unstable equilibrium are perturbed, they depart the neighborhood of this equilibrium value. Conversely, departures from a close neighborhood of a stable equilibrium value are followed by 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 (the neutral Hardy-Weinberg condition is one such example).

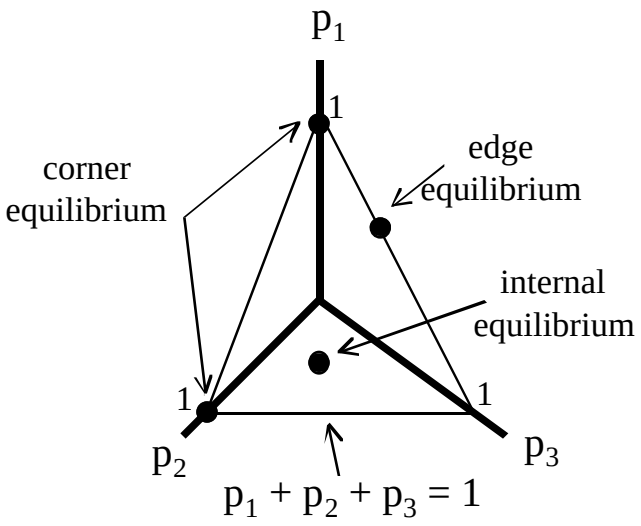


Figure 5.3. The simplex for three alleles, namely the space of all possible allele frequencies, subject to the constraint that they must sum to one. Note that the plane of possible values intersects each allele frequency axis at a value of one for that allele, and zero for all others. Within the simplex, 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 edge equilibria, when at least two allele frequencies are non-zero; or internal equilibria, wherein all alleles are segregating.

When multiple stable equilibria exist, the history of the process has a great influence on the final value reached. We saw this with underdominance (Example 5.4), where if the population starts with frequency in the open interval $(0, \widehat{p}\,)$, $p \to 0$, while if the population starts in the open interval $(\widehat{p}, 1)$, $p \to 1$. Thus, with multiple stable equilibria, we are interested in 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 (e.g., 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 from each starting value to determine where the frequencies eventually converge.

Wright's Formula With Multiple Alleles

With only two alleles, Equation 5.5 completely describes the evolutionary dynamics on terms of 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,

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

Hence,

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

Further, note that

$$\overline{W} = \sum_{j=1}^{n} p_j W_j = \sum_{j=1}^{n} \frac{p_j}{2}\frac{\partial \overline{W}}{\partial p_j} \tag{5.9c}$$

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 (which still differs from Equation 5.10).

A more compact way to write Equation 5.10 follows by again recalling $(\partial \overline{W}/\partial p_i)(1/\overline{W}) = \partial \ln(\overline{W})/\partial p_i$, giving 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

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

We can also conveniently express Equation 5.10 in matrix form as

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

where $\boldsymbol{\Delta}\mathbf{p}$ is the vector of allele-frequency changes, ∇ is the gradient vector (of all first partial derivatives, Appendix 6),

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

and the elements of the $n \times n$ **genetic variance-covariance matrix G** are given by Equation 5.11b. Recall from calculus that the greatest local change in the value of $f(\mathbf{x})$ occurs by moving in the direction given by ∇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 **G**. The genetic matrix thus constrains the rate of response, a prelude to the theme of genetic constraints that arises in multivariate trait selection (Chapter 13).

It can be shown that Equation 5.12 implies $d\overline{W}/dt \geq 0$ (see Example A5.7), and unlike the 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 $p_i(1-p_i) \mid \partial \ln \overline{W}/\partial p_i \mid$ dominate the change in mean population fitness and hence dominate the dynamics. As these alleles approach their equilibrium frequencies under selection (values where $\mid \partial \ln \overline{W}/\partial p_i \mid \simeq 0$), other alleles begin to dominate the dynamics of mean fitness, with their frequencies changing so as to continue to increase mean population fitness.

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).

Changes in Genotypic Fitnesses W_{ij} When Additional Loci are Under Selection

All of the above results for allele-frequency change at locus under selection assume that its genotypic fitnesses W_{ij} remain constant over generations. Changes in the environment can obviously compromise this assumption, as can frequency-dependent effects (such as rare-genotype advantage). A more subtle issue arises when additional loci influence fitness. As shown below in Example 5.7, when selection changes the genotypic frequencies at these other loci, it can change the fitnesses W_{ij} for the locus under consideration. In such cases, a complete description of the dynamics requires following *all* loci under selection. As the next section shows, this is non-trivial, as it requires modeling more than just the allele-frequency changes at each locus. Selection generates non-random associations (linkage, or gametic-phase, disequilibrium) among loci, requiring us to model the dynamics of multi-locus *gamete* frequencies, which account for both the frequencies of alleles over all loci and the disequilibrium between them.

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 (the fitness of *AA* averaged over all genetic backgrounds) is

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

These conditional weights follow from the standard formula for conditional probability,

$\Pr(x \mid y) = \Pr(x, y)/\Pr(y)$. Under random mating $\Pr(AA) = p^2$, while $\Pr(AABB)$ is the probability of getting AB gametes from both parents, or $\text{Freq}(AB)^2 = (pq + D)^2$. Similar results for the remaining two *B* locus genotypes gives

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

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 p, the frequency of *A*. Even though the marginal fitness W_{AA} of *AA* changes as the frequency q of allele *B* changes, Wright's formula (Equation 5.5) for the change in the frequency p of allele *A* still holds, as the fitness of *AA* does not depend on p. 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.

SELECTION ON TWO LOCI

When fitness is influenced by n biallelic loci, we cannot generally 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) thwarts the prediction of gamete frequencies from simple allele frequencies alone (LW Chapter 5). In addition, 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 following *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, disequilibrium is often very small. However, as we will see in Chapter 16, even small disequilibrium values can be considerably significant when summed over a large number of loci underlying quantitative trait variation.

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 rather embryonic stage (but see Kirkpatrick et al. 2002). 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. In addition, 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

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

where r 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, with

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

Observe that selection can change gamete frequencies by changing allele frequencies and/or changing 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 r 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 and a few other special cases, these deceptively simple two-locus equations turn out to be extremely complex. Indeed, there is no general analytic solution for even the simple basic model of arbitrary (but constant) fitness and viability selection.

Example 5.8. If loci have effects on both fitness and 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. Let loci *A* and *B* directly affect fitness (perhaps through some unmeasured character) in addition to influencing character z, not itself under selection, with 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 and expect the trait mean μ_z to increase over time. However, applying two-locus theory (numerical iteration of Equation 5.13) 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* from our initial starting value above of 1.78. This is because, as shown in Chapter 6, the selection response depends on $\sigma(A_z, w)$, the covariance between trait breeding value and fitness, which is negative here.

Gametic Equilibrium Frequencies, Linkage Disequilibrium, and Mean Fitness

Now let us consider the equilibrium behavior of two-locus systems. The equilibrium value $\widehat{D}$ represents the balance between recombination driving disequilibrium to zero and selection generating new disequilibrium. Bounds on $\widehat{D}$ for general two-locus systems were given by Hastings (1981b, 1986). Importantly, a nonzero value of $\widehat{D}$ requires epistatis in fitness, and such a nonzero value has implications for the behavior of mean population fitness. To see this later point, first note that at equilibrium, the gamete frequencies remain unchanged ($\widehat{x}_i' = \widehat{x}_i$), and Equations 5.13a to 5.13d simplify to

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

Several results immediately follow. First, if linkage is complete ($r = 0$), then all marginal fitnesses are equal at equilibrium, and equilibrium mean fitness is at a local maximum. This second result follows because complete linkage causes the system to behave like a single locus with four alleles, so that Kingman's (1961a) result that equilibrium mean fitness is at a local maximum applies. However, when $r \neq 0$, then because in general $\widehat{D} \neq 0$ (there is gametic-phase disequilibrium at the equilibrium gamete frequencies), the equilibrium values are a function of the recombination frequency r. Most interestingly, when $\widehat{D} \neq 0$ the marginal gametic fitnesses W_{g_i} are *not* equal, and equilibrium mean fitness is not at a local maximum. Indeed, it can be shown that mean fitness often decreases as the equilibrium values are approached. Typically, this decrease is quite small, but it no longer holds that mean fitness always increases under constant-fitness viability selection (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 all F_1 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 takes several generations even if $r = 1/2$). For example, if $s = 0.1$, $\overline{W} = 1.1$ for the F_1, while iteration of Equation 5.13 shows $\overline{W} = 1.025$ at equilibrium (under loose linkage).

Selection usually generates gametic-phase disequilibrium between loci under selection, and (as fully developed in Chapter 15) this has important consequences for the selection response of a quantitative trait. In particular, the presence of gametic-phase disequilibrium between underlying loci has consequences for the additive variance of a trait, which in term effects response (Chapters 13, 15). 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). If we code alleles such that *A* and *B* alleles increase the character value relative to *a* and *b* alleles, both α terms are positive, and the sign of D alone determines whether additive variance is increased or decreased. In particular, negative D, an excess of repulsion (*Ab*, *aB*) over coupling (*AB*, *ab*) gametes, results in a lower additive variance than in the base population. Generally speaking, selection on a trait generates such negative D, and hence lowers the additive variance of that trait (Chapter 15). 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. When selection stops, D decays to zero, increasing the additive variance when $\widehat{D} < 0$. Thus, negative D can "store" additive variance that only becomes apparent following recombination (Chapter 15).

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 Between-Loci 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	$1-d$	$1-b$	$1-a$

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 there is at most one polymorphic equilibrium for any given set of segregating alleles, $\widehat{D} = 0$ (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 nine polymorphic equilibria (many of which can be 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. 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).

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	$1-s$	$1-4s$

Hence, while the trait has a completely additive genetic basis, the mapping from phenotype to fitness introduces epistasis in fitness. This is an important point: *fitness* determines the evolutionary dynamics of a quantitative trait. 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 basis can 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, underdominant 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 many 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 consider this in earnest in Chapter 27, confining our remarks here to the prospect that selection alone can maintain variation.

A number of models examing this problem can be found in the literature. One major take-home messages is that seemingly quite subtle changes in models (such as quadratic vs. Gaussian selection, slightly different effects at the underlying loci, or 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

significant insight into many of the issues concering the 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, pp, 204–210), which should be consulted for more details.

The generalized model makes four key assumptions. First, fitness is a quadratic function, $W(z) = 1 - sz^2$, with an implicit optimum at $z = 0$. Second, the genotypic value of the double-heterozygote exactly corresponds with the phenotypic optimum. Third, there are no environmental effects. 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	$a_1 + a_2$

Substituting these trait values into the quadratic fitness function shows that this model corresponds 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 equilibria 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 either

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

which corresponds to the major locus A segregating and the other locus fixed for b or

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

corresponding to A segregating in a fixed BB background. 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 as 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

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

with r being the recombination frequency between the two loci, and α_i being the effects of allelic substitution at the two loci. Because the term in parentheses is negative, $\widehat{D} < 0$ and there is hidden genetic variation, with the additive variance for this trait increasing following the cessation of selection (Chapter 15). At this internal equilibrium, the additive variance for the trait is

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

Although there is additive variance in the *trait* under selection, as we will see in the next chapter (Example 6.4), there is no additive variance *in fitness* at the equilibrium value.

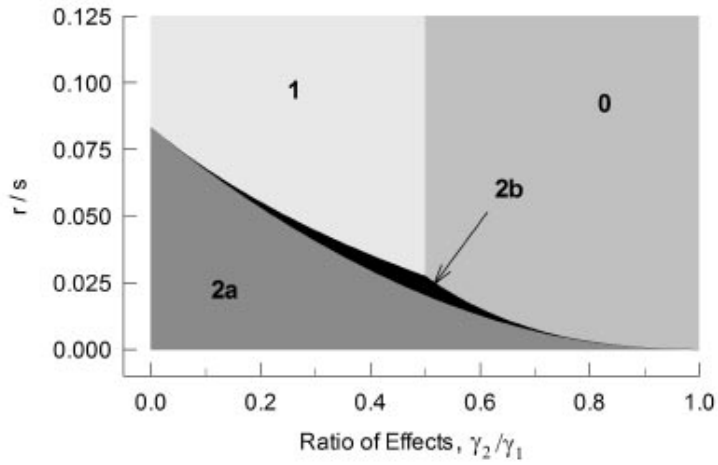
While the symmetric internal equilibrium seems straightforward, there can also be two other interior equilibria, the so-called *unsymmetric equilibria*. The expressions for these are complex (see Bürger p. 205), and the conditions for their existence is that the recombination fraction be in the range $r_1 < r < r_2$, where

$$r_1 = -\frac{1}{3}s(a_1^2 + a_2^2) + \frac{2}{3}s\sqrt{a_1^4 - a_1^2a_2^4 + a_2^4}$$

and

$$r_2 = \min\left[s(a_1 - a_2)^2, \frac{1}{3}s(a_1^2 - a_2^2)\right]$$

Turning to stability of the various potential equilibria, when $r \leq r_1$, 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 is sufficiently large ($r > 1/3$), 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 ($r_1 < r < r_2$). The edge equilibria are stable whenever they exist, which requires sufficiently unequal allelic effects ($a_1 > 2a_2$) and sufficiently loose linkage ($r \geq r_2$). 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 ($r \geq r_2$). 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).



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 ($a_1 \geq 2a_2$) 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 relationship between selection and recombination. Finally, with uneven allelic effects and recombination weak relative to selection (region 2a), the symmetric equilibrium exists. Thus, provided allelic effects are uneven and selection is strong relative to recombination, selection can maintain both alleles at both loci (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 mean trait value at equilibrium 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.

As detailed in the above example, even Wright's simple quadratic optimum model exhibits considerable complexity. Further, in the virtually certain 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 (Gimelfarb 1996). One reason is that 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 collapses 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 equal to 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 are reduced, and the behavior of many models becomes 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, implying that if only one trait is under stabilizing selection under these conditions, at most only one underlying locus is polymorphic. As Example 5.6 shows, it can easily be the case that no loci remain polymorphic (in the absence of new mutation). Chapter 27 examines these issues in more detail.

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 the 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. We explore these in the next chapter.

SELECTION ON A QUANTITATIVE TRAIT LOCUS

While population genetics is concerned with how the frequencies of specific *genotypes* change under selection, quantitative genetics is concerned with the evolution of a composite feature of these underlying genetic changes, i.e., the change in the distribution of a *trait* under selection. Population-genetic models assume we know the genotype-specific fitnesses and use these to generate expressions for the change in allele (one locus) or gamete (multiple-locus) frequencies. In contrast, quantitative genetics assumes fitness is a function $W(z)$ of the value z of the focal trait. The connection between these two approaches starts by considering how selection on a particular trait maps into the average excess s_i in fitness for an allele at a locus underlying this trait.

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, with $p_{ij}(z)$ denoting the distribution of character values for an individual of genotype A_iA_j. The fitness for this genotype is the average over the distribution of phenotypes for this genotype,

$$W_{ij} = \int W(z)\, p_{ij}(z)\; dz \tag{5.15a}$$

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 5.15a 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

$$W_i = \int W(z)\, p_i(z)\, dz \tag{5.15b}$$

Again, this can be directly substituted into Equation 5.7c to compute Δp_i. Note, however, that while $p_{ij}(z)$ can be independent of allele frequency, this is not the case for $p_i(z)$.

Many Loci of Small Effect Underlying the Character

When two or more loci underlie the character of interest, Equations 5.15a and 5.15b 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^* of the trait (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.

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 5.4, the conditional phenotypic distribution is to a good approximation the unconditional phenotypic distribution shifted by α_i^*, which can be written as

$$p_i(z) \simeq p(z - \alpha_i^*) \tag{5.16a}$$

Nagylaki (1984) has shown that this approximation is correct only to linear order, e.g., to terms of order α_i^* (we will shortly consider 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

$$p_{ij}(z) \simeq p(z - a_{ij}) \tag{5.16b}$$

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

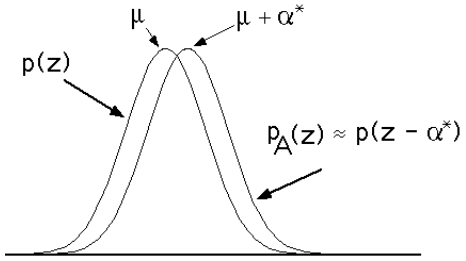


Figure 5.4. The unrestricted distribution of phenotypes $p(z)$ has mean μ, while the conditional phenotypic distribution $p_A(z)$ for an individual carrying a copy of allele A has mean $\mu + \alpha^*$, the mean plus the average excess for allele A. If α^* is small, then (to order α^*) we can approximate $p_A(z)$ 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.

The approximation given by Equation 5.16a motivates two alternative expressions for the relative fitness w_i. First, we have directly (Bulmer 1971; Kimura and Crow 1978)

$$w_i = \int w(z)\, p_i(z)\, dz \simeq \int w(z)\, p(z - \alpha_i^*)\, dz \tag{5.17a}$$

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

$$w_i \simeq \int w(z + \alpha_i^*)\, p(z)\, dz \tag{5.17b}$$

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 5.16 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^* for the trait value is small,

$$p(z - \alpha_i^*) \simeq p(z) - \alpha_i^* \frac{d\,p(z)}{dz} \tag{5.18a}$$

$$w(z + \alpha_i^*) \simeq w(z) + \alpha_i^* \frac{d\,w(z)}{dz} \tag{5.18b}$$

Substituting into Equation 5.17 and recalling that $\int w(z)\, p(z)\, dz = 1$ gives the average excess in relative fitness (Equation 5.8b) as

$$s_i = w_i - 1 \simeq -\alpha_i^* \int w(z) \frac{d\,p(z)}{dz}\, dz \tag{5.19a}$$

and

$$s_i = w_i - 1 \simeq \alpha_i^* \int p(z) \frac{d\,w(z)}{dz}\, dz \tag{5.19b}$$

Equation 5.19a is applicable if phenotypes are distributed continuously. For meristic traits, Equation 5.19b applies, provided $w(z)$ is differentiable. Note that Equations 5.19a,b connect population genetics (the average excess s_i in fitness) with quantitative genetics ($w(z)$ and the average excess α_i^* in the trait value).

The integrals in Equations 5.19a,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

$$p(z) = \left(2\pi\sigma^2\right)^{-1/2} \exp\left(\frac{-(z-\mu)^2}{2\sigma^2}\right) \tag{5.20a}$$

gives

$$\frac{d\,p(z)}{dz} = -\left(\frac{z-\mu}{\sigma_z^2}\right) \cdot p(z) \tag{5.20b}$$

Substituting into Equation 5.19a and applying a little algebra yields

$$s_i \simeq \alpha_i^* \cdot \left(\frac{S}{\sigma_z^2}\right) = \overline{\imath} \cdot \left(\frac{\alpha_i^*}{\sigma_z}\right) \tag{5.21}$$

where $S = \mu^* - \mu$ is the selection differential, i.e., the within-generation change in the mean from selection and $\overline{\imath} = S/\sigma_z$ is the standardized selection differential (or selection intensity, Chapter 13). Hence, to first order, the selection on an individual allele of small effect is approximately equal to its standardized average excess in z multiplied by the selection intensity on the trait. This approximation (Equation 5.21) is a well-known result for certain

fitness functions, e.g., truncation selection (Haldane 1930; Griffing 1960). The result that it is a good approximation for arbitrary fitness functions when z is normally distributed is due to Kimura and Crow (1978) and 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 to this point shortly.

A Population-genetic Derivation of the Breeder's Equation

The classic equation for the expected response R (the change in mean) of a single trait from selection is the **breeder's equation** $R = h^2 S$ (Chapter 13). This expresson is typically derived by assuming a linear midparent-offspring regression with slope h^2, although a few additional, and subtle, assumptions are required (Chapter 6). Here we show how the breeder's equation is obtained as an approximation of a population-genetic model of the response. As developed in Example 5.12 (below), the expected response R_k from a single locus (k) can be expressed in terms the average effects α_i^k on the trait and the average excesses on selection s_i^k for all alleles at that locus and their dominance deviations δ_{ij}^k,

$$R_k = 2\sum_j \alpha_j^k s_j^k\, p_j^k + \sum_{i,j} \delta_{ij}^k\, p_i^k\, s_i^k\, p_j^k\, s_j^k \tag{5.22}$$

where the sums are taken over alleles of locus k. Recalling Equation 5.19, we can write $s_i \simeq \alpha_i^*\, I$, with I being the appropriate integral, giving

$$R_k = I\sum_j 2\,\alpha_j^k\,\alpha_j^{k*}\,p_j^k + I^2\sum_{i,j}\delta_{ij}^k\,\alpha_i^{k*}\,\alpha_j^{k*}\,p_i^k\,p_j^k \tag{5.23a}$$

This expression also holds when linkage disequilibrium is present, although the average excesses, average effects, and dominance deviations are expected to be different from their linkage-equilibrium values.

For a random-mating population, the first sum is the contribution from locus k to the additive variance (under linkage equilibrium) of this trait (LW Equation 4.23a). Assuming no epistasis and no linkage disequilibrium, summing over all loci gives the response as

$$R \simeq I\,\sigma_A^2 + I^2\sum_{k=1}^{n}\sum_{i,j}^{n_k}\delta_{ij}^k\,\alpha_i^{k*}\,\alpha_j^{k*}\,p_i^k\,p_j^k \tag{5.23b}$$

As shown in Equation 5.21, if phenotypic values are normally distributed before selection, $I = S/\sigma_z^2$, and the response becomes

$$R = Sh^2 + \frac{S^2}{\sigma_z^4}\sum_{k=1}^{n}\sum_{i,j}^{n_k}\delta_{ij}^k\,\alpha_i^{k*}\,\alpha_j^{k*}\,p_i^k\,p_j^k \tag{5.23c}$$

which recovers the breeder's equation plus a correction term. In the absence of dominance (all $\delta_{ij}^k = 0$), the second term is zero. Even with dominance, the second term is of lower order than the first, and vanishes as the number of underlying loci becomes large (Example 5.12). 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 breeder's equation (among other things, see Chapter 6) assumes this regression is linear.

Example 5.12. Here we obtain Equation 5.22, the expected response to selection associated with a single locus. For ease of presentation, we suppress the super-and subscripting indicating this locus. Assuming random mating, Equation 5.8b gives the single-generation allele-frequency dynamics as $p_i' = p_i(1+s_i)$, 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 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} is the dominance deviation (LW Chapter 4). The contribution of this locus to the change in mean phenotype after a generation of selection is

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

The careful reader will note that we 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

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

for

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

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 this equation further, recall (LW Chapter 4) that

$$\sum_i \alpha_i\, p_i = 0 \quad \text{and} \quad \sum_i \delta_{ij}\, p_i = 0$$

Breaking the first term of our equation for R into two parts based on s_i and s_j, from this last expression, these become

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

with an identical sum for the s_i term and a total contribution of twice the above sum. Likewise, a little more algebra (Nagylaki 1989b, 1991) simplifies the second sum in our expression for R to give the expected contribution to response as

$$R = 2 \sum_j \alpha_j s_j\, p_j + \sum_{i,j} \delta_{ij}\, p_i\, s_i\, p_j\, s_j,$$

recovering Equation 5.22. While (as shown above) the first term of Equation 5.22 recovers the breeder's equation, the second term

$$B_k = \sum_{i,j} \delta_{ij}^k \, p_i^k \, s_i^k \, p_j^k \, s_j^k$$

is a measure of departure from the breeder's equation generated by the response at locus k. Nagylaki (1991) shows that the total departure $B = \sum_k B_k$ is bounded by

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

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

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

where $\sigma_D^2(z)$ is the total dominance variance. Hence, assuming no epistatic genetic variance, even if dominance is present, as the number of loci increases, any depature from the breeder's equation becomes increasingly small.

Thus, with a normal distribution of phenotypes and no dominance in the character, we recover the breeder's 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 24), 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*. At its limit, we have the **infinitesimal model** (Chapter 24): an effectively infinite number of loci, each contributing an infinitesimal amount to the total phenotype. We see from Example 5.12 that as the number of loci approaches infinity, the second sum in Equation 5.23c becomes vanishingly small, and we recover the breeder's equation even when dominance is present.

Another class of models (Kimura 1965b; Lande 1975) allows for $n \geq 1$ loci by assuming a normal distribution of allelic effects at each locus underlying the character (effectively assuming an infinite number of alleles per locus). These two models (infinite number of loci versus infinite number of alleles at n loci) represent extreme approximations to the view that a moderate number of loci, each with a moderate number of alleles, underlie many quantitative characters. Chapter 24 explores these two models in greater detail.

Correct Quadratic Terms for s_i

As mentioned earlier, the approximations given by Equations 5.16a,b are correct only to linear order, whereas quadratic (second) order terms are required to properly account for selection acting directly on the trait 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,

$$\sigma_k^2 = \sum_{i,j}^{n_k} a_{ij}^2 \, p_i \, p_j \tag{5.24}$$

where $a_{ij} = G_{ij} - \mu_G$ is the deviation of the genotypic value from the mean and n_k is the number of alleles at locus k (Nagylaki 1984; Walsh 1990). Using an expansion that accounts for this reduction in variance, Hastings (1990a) showed that s_i is correctly approximated to quadratic order by

$$s_i \simeq -I_1 \alpha_i^* + \frac{I_2}{2}\left[\sum_j a_{ij}^2 \, p_j - \sigma_k^2\right] \tag{5.25a}$$

Here

$$I_1 = \int w(z) \, \frac{d\, p(z)}{dz} \, dz, \quad I_2 = \int w(z) \, \frac{d^2\, p(z)}{dz^2} \, dz \tag{5.25b}$$

Hastings (1992) shows how this approach extends to a locus that influences n characters under selection.

As mentioned previously, I_1 measures the effects of selection on the mean, while I_2 measures its effect on the variance. To see this, if phenotypes are normally distributed, then differentiating Equation 5.20b a second time gives

$$\frac{d^2 p(z)}{dz^2} = -\frac{p(z)}{\sigma_z^2} + \frac{(z-\mu)^2}{\sigma_z^4} \, p(z) \tag{5.26a}$$

and a little algebra yields

$$I_2 = \frac{\delta_{\sigma^2} + S^2}{\sigma_z^4} \tag{5.26b}$$

where δ_{σ^2} is the within-generation change in phenotypic variance due to selection (Chapters 16, 24). Hence, if phenotypes are normally distributed,

$$s_i \simeq \alpha_i^* \, \frac{S}{\sigma_z^2} + \frac{\delta_{\sigma^2} + S^2}{2\sigma_z^4}\left[\sum_j a_{ij}^2 \, p_j - \sigma_k^2\right] \tag{5.27a}$$

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 5.22 and summing over all loci gives the response to selection as

$$R = h^2 S + \frac{\delta_{\sigma^2} + S^2}{2\sigma_z^4} \sum_{k=1}^{n} \sum_{i}^{n_k} \left(\alpha_i^k\right)^3 \, p_i^k \tag{5.27b}$$

where the superscript k on the α_i and p_i terms reminds the reader that these can vary over loci. As shown in Chapter 28, selection acting only on the mean still results in a change in the variance, with $\delta_{\sigma^2} = -S^2$. In this case, the second term is zero and we recover the breeder's equation. More generally, if selection is also acting directly on the trait variance, δ_{σ^2} departs from $-S^2$ (Chapter 28). Since the double sum in Equation 5.27b is the skewness in the genotypic distribution, if skew is present, changes due to selection on the variance also changes the mean. Equation 5.27b raises several issues that will be examined in detail in Chapter 24. 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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