CHAPTER 5

DARWINIAN SELECTION

Thus far in this book, the term *natural selection* has been used in the informal, intuitive sense used by Darwin in *The Origin of Species* (1859):

> Owing to this struggle for life, variations, however slight and from whatever cause proceeding, if they be in any degree profitable to the individuals of a species, in their infinitely complex relations to other organic beings and to their physical conditions of life, will tend to the preservation of such individuals, and will generally be inherited by the offspring. The offspring, also, will thus have a better chance of surviving, for, of the many individuals of any species which are periodically born, but a small number can survive. I have called this principle, by which each slight variation, if useful, is preserved, by the term Natural Selection.

Modern formulations of natural selection are less literary and usually compacted into a form resembling a logical syllogism:

- In all species, more offspring are produced than can possibly survive and reproduce.
- Organisms differ in their ability to survive and reproduce—in part because of differences in genotype.
- In every generation, genotypes that promote survival in the current environment are present in excess at the reproductive age and thus contribute disproportionately to the offspring of the next generation.

Through natural selection, therefore, alleles that enhance survival and reproduction increase gradually in frequency from generation to generation,

and the population becomes progressively better able to survive and reproduce in the environment. The progressive genetic improvement in populations resulting from natural selection constitutes the process of **evolutionary adaptation**.

In the brief description of natural selection quoted above, Darwin uses the term *individual* three times. The unit of selection is the individual organism—not the species, not the subpopulation, not the sibship. It is the performance of the individual organism that matters. Each individual organism competes in the struggle for existence and survives or perishes on its own. Darwin also used the terms "struggle for existence" and "survival of the fittest" as synonyms for natural selection, but he emphasized that he employed the terms in their widest metaphorical sense to include not only the life of the organism but also the success of the organism in leaving progeny: fecundity is as important as survival. In this chapter, we shall see how Darwin's concept of "survival of the fittest" of individual organisms has been made more formal and quantitative and incorporated into models describing the change in allele frequency under natural selection. These models show that natural selection acts simultaneously on different components of fitness and can operate at different levels of population structure. The modern view of natural selection departs a bit from Darwin's view in acknowledging that natural selection may act at haploid stages, at diploid stages, on pairs of mating genotypes, and probably much more weakly, on groups of individuals.

5.1 SELECTION IN HAPLOID ORGANISMS

Selection acts on the phenotype, not on the genotype, and the total phenotype is determined by many genes that interact with each other as well as with numerous environmental factors. However, in exploring the consequences of selection, it is convenient to focus on changes in the frequency of the alleles of a single gene. We shall begin by examining selection in its simplest form operating in a haploid, asexual organism, such as a species of bacteria. In haploids, selection is realized as differential population growth. The overall process of selection is identical whether population growth is in discrete or continuous generations, but the models have a somewhat different parameterization and it is necessary to relate the models to avoid confusion later.

Discrete Generations

Consider two bacterial genotypes, A and B, that reproduce asexually. For simplicity, we will assume a discrete model of geometric population growth such that $A_t = (1 + a)^t A_0$ and $B_t = (1 + b)^t B_0$, where A_t and B_t are the number of cells of genotype A and genotype B, respectively, at time t. Selection takes place when $a \neq b$. Figure 5.1A is an example in which the growth rates of A and B are $a = 0.41$ and $b = 0.26$, respectively. Both populations increase in size exponentially, but that of A increases faster than that of B. In most cases,

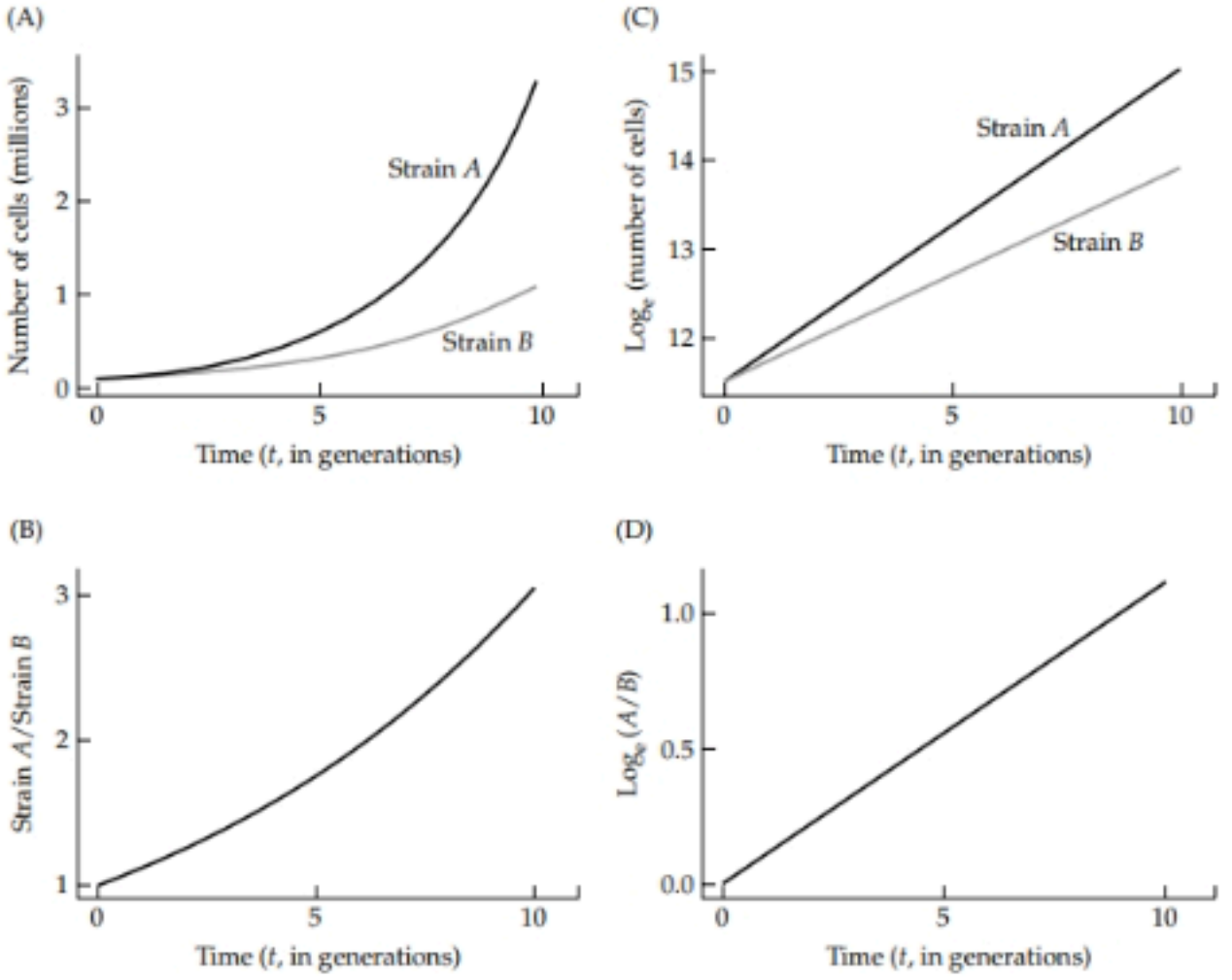


FIGURE 5.1 (A) Population growth of two hypothetical bacterial strains, A and B, in which the growth rates are 41% per generation for A and 26% per generation for B. The initial cell numbers are 10^5 for A and 10^5 for B. (B) Ratio of cell numbers of $A : B$. Because the A population grows faster than the B population, the proportion of A in the total population increases. (C) and (D) are the growth trajectories and their ratio on a log scale.

we are not interested in the actual number of A cells or B cells but in the proportion of all cells that are of type A. Equivalently, we can examine the ratio of the number of A cells to that of B cells at time t, which is given by

$$\frac{A_t}{B_t} = \left(\frac{1+a}{1+b}\right)^t \frac{A_0}{B_0} = w^t \left(\frac{A_0}{B_0}\right) \tag{5.1}$$

The outcome of selection is determined by the ratio of a to b because, if $a < b$, then the ratio of A cells to B cells decreases until, ultimately, A is lost; conversely, if $a > b$, then the ratio of A cells to B cells increases without limit. Figure 5.1B shows the change in A/B for the example in part A. From a value of 1 at the beginning, the ratio increases to a value of 3 in 10 generations;

these ratios correspond to frequencies of A of 0.50 and 0.75, respectively. Whenever there is geometric growth, plotting on a log scale (Figure 5.1C and D) produces straight lines, and this is often useful for statistical analysis (e.g., estimation of a and b from data).

In Figure 5.1 it is not necessary to specify whether a and b differ because of survivorship or fecundity. All that matters is that they do differ. It is also important that the outcome depends only on the ratio $(1 + a)/(1 + b)$, which means that, in practice, we do not need to know the absolute growth rates of A and B but only their relative values (their ratio). In Equation 5.1, w represents the ratio $(1 + a)/(1 + b)$. The symbol w is conventionally used in discrete models of selection and, in this example, it is the *relative fitness* of genotype A to that of genotype B. In other words, in a haploid organism, the relative fitness equals the ratio of the growth rates.

Although it is sometimes instructive to do so, it is not necessary to keep track of population size in models of selection. The variable of interest is usually the allele frequency and not the population size. Therefore, let p_t and q_t represent the frequencies of genotypes A and B, respectively, in generation t, with $p_t + q_t = 1$. A method to relate the frequencies of A and B in any two successive generations is illustrated in Table 5.1. For ease of discussion, we divide each generation into three phases: birth, selection, and reproduction. In generation $t - 1$, the frequencies of A and B at birth are p_{t-1} and q_{t-1}, respectively. The genotypes A and B are assumed to survive in the ratio $w : 1$, which means that w is the probability of survival of an A genotype relative to that of an B genotype. As before, the absolute probabilities of survival of the genotypes are not relevant. All that matters is the ratio. After selection, the ratio of frequencies of $A : B$ equals $p_{t-1} \times w : q_{t-1} \times 1$. If the surviving genotypes repro-

TABLE 5.1 A Model of Selection in a Haploid Organism, in which *w* is the Probability of Survival of an *A* Cell Relative to that of a *B* Cell

	Genotype	
Generation $t - 1$	A	B
Frequency before selection	p_{t-1}	q_{t-1}
Relative fitness	w	1
After selection	$p_{t-1}w$	q_{t-1}
Generation t	$\frac{p_{t-1}w}{p_{t-1}w + q_{t-1}}$	$\frac{q_{t-1}}{p_{t-1}w + q_{t-1}}$

Note: The fractions in the bottom line are expressions for the allele frequencies in generation t in terms of those in generation $t - 1$. Although this model assumes differential survival, $w : 1$ could also be the relative probability of reproduction of A and B. More generally, the relative fitness $w : 1$ represents the net output of $A : B$ for the combined effects of differential survival and reproduction.

duce with equal efficiency, then the frequencies at birth in the following generation are given by the expressions across the bottom in Table 5.1; the denominators in these expressions are necessary to make the allele frequencies in generation t sum to 1.

For comparison with Equation 5.1, consider that p_t is the number of A cells in generation t divided by the total; likewise, q_t is the number of B cells divided by the total. Therefore, the ratio p_t/q_t equals the ratio of A cells to B cells in generation t because the denominators cancel. The expressions in Table 5.1 imply that the ratio of p/q in any generation equals w multiplied by the ratio of p/q in the previous generation, and so

$$\frac{p_t}{q_t} = w\frac{p_{t-1}}{q_{t-1}} = w^2\frac{p_{t-2}}{q_{t-2}} = \cdots = w^t\frac{p_0}{q_0} \tag{5.2}$$

The right-hand side of Equation 5.2 is identical to that in Equation 5.1 except that the relative frequencies p and q replace the absolute number of cells of type A and type B. Hence, to deduce the outcome of selection, we do not need to keep track of population size. All we need to know is the relative fitness w and the initial frequencies p_0 and q_0.

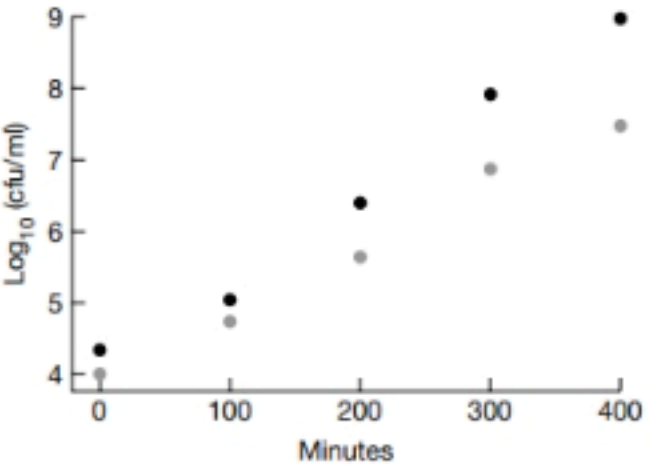
For application to experimental data, Equation 5.2 is often transformed by taking the natural (base e) logarithm:

$$\log\left(\frac{p_t}{q_t}\right) = \log\left(\frac{p_0}{q_0}\right) + t\log(w) \tag{5.3}$$

Equation 5.3 means, for example, that if the values of p_t/q_t are monitored in an experimental population of bacteria over the course of time, then a plot of $\log(p_t/q_t)$ against time (in generations) should yield a straight line with slope equal to $\log w$ (see Figure 5.1D). This kind of experiment is examined in the following problem.

PROBLEM 5.1 Methicillin-resistant *Staphyloccocus aureus* (MRSA) is a serious pathogen that has seen a particularly rapid spread, and with the spread has come an increase in the diversity of MRSA strains. One particular subclass of MRSA strains that spread especially fast is gentamicin sensitive (GS-MRSA). Laurent et al. (2001) reported experiments designed to test the relative growth rates of GS-MRSA and the older gentamicin-resisitant strains (GR-MRSA). Rather than use a chemostat, they simply grew up the strains in 200-ml flasks of medium, taking samples at intervals to measure density in colony forming units per ml (cfu/ml). From the table of $\log_{10}$(cfu/ml) at different times, calculate the relative growth rates of the two strains in the intervals 0–100 minutes and 300–400 minutes (assume a generation time of 100 minutes):

Min	GR-MRSA	GS-MRSA
0	4.000	4.322
100	4.708	5.041
200	5.633	6.398
300	6.669	7.908
400	7.462	8.968



ANSWER First calculate the proportion of the mixed culture that consists of each strain at each time interval, and get 0.6774, 0.6832, 0.8532, 0.9427, 0.9698 as the proportions that are GS-MRSA at the respective times. Then notice that the natural $\log(p_{100}/q_{100}) = 0.76865$ and $\log(p_0/q_0) = 0.74194$, giving a difference of $0.0267 = \log(w)$. In the first 100 minutes, the fitness of GS-MRSA relative to GR-MRSA is $e^{0.0267} = 1.027$, or a 2.7 percent advantage. In the last 100 minutes, we get $\log(p_{300}/q_{300}) = 2.80106$ and $\log(p_{400}/q_{400}) = 3.46789$. The difference is now 0.6668, so the relative fitness is now $e^{0.6668} = 1.95$. Early in the experiment the GS-MRSA strain appears not to have been growing in its maximal or log phase, but later there is nearly a twofold growth advantage to the GS-MRSA strain. If we use all the data we get $\log(w) = 0.748$ per generation. This gives $w = e^{0.748} = 2.11$. You can see from the data that the ratio of GS-MRSA/GR-MRSA increased 16 fold in four generations, consistent with roughly a twofold growth advantage of GS-MRSA.

Continuous Time

Bacterial populations such as those in Problem 5.1 do not reproduce in discrete generations but instead they reproduce continuously. In a continuous model, the exponential population growth of A and B are governed by the equations $dA_t/dt = a'A_t$ and $dB_t/dt = b'B_t$, where a' and b' are the growth rates. Therefore, $A_t = A_0 \exp^{a't}$ and $B_t = B_0 \exp^{b't}$, and so

$$\frac{A_t}{B_t} = \frac{A_0}{B_0} e^{(a'-b')t} = \frac{A_0}{B_0} e^{mt} \qquad [5.4]$$

Equation 5.4 means that, in a continuous population, the outcome of selection depends on the difference between the exponential growth rates $a'-b'$, which is represented by the symbol m on the right-hand side. The value of

m also measures the relative fitness of strain A to strain B, but in a continuously reproducing population. Comparing Equation 5.4 with Equation 5.1 yields the relation between m and w:

$$m = \ln w \tag{5.5}$$

In other words, the relative fitness with continuous growth m equals the natural logarithm of the relative fitness with discrete reproduction w. Selective neutrality means that $w = 1$ or that $m = 0$. For the values of w estimated in Problem 5.1, the corresponding values of m are 0.0267 and 0.6668, respectively. If w is not too different from 1, then $m = w - 1$ is a reasonable approximation.

Change in Allele Frequency in Haploids

Although the discrete and continuous models are completely equivalent under the transformation in Equation 5.5, the equations for change in allele frequency look rather different. In the discrete model, the change in the frequency of strain A in generation t is given by the difference $p_t - p_{t-1}$, which can be calculated in terms of p_{t-1} from the formulas in Table 5.1. The difference $p_t - p_{t-1}$ is usually symbolized Δp and, for simplicity, the subscripts are usually suppressed. Using the expressions in Table 5.1 and the fact that $q = 1 - p$, we obtain

$$\Delta p = \frac{pw}{pw + q} - p = \frac{pq(w-1)}{pw + q} \tag{5.6}$$

Not surprisingly, p increases if the relative fitness of A is greater than 1 and decreases if the relative fitness of A is smaller than 1. If the relative fitnesses of A and B are equal, then p does not change—provided that the population size is very large (theoretically, it has to be infinite).

The analog of Equation 5.6 in a continuous model contains the derivative dp/dt in place of Δp. This we can obtain from Equation 5.4 with a little trickery. Because A_t/B_t equals p_t/q_t, the derivative of Equation 5.4 with respect to t must equal the derivative of p_t/q_t with respect to t. For simplicity, we will write p and q instead of p_t and q_t. The derivative of Equation 5.4 with respect to t equals mp/q and the derivative of p/q with respect to t equals $(1/q^2)(dp/dt)$. Setting these expressions equal to each other and solving for dp/dt, we obtain

$$\frac{dp}{dt} = pqm \tag{5.7}$$

Where did the denominator go? In a technical sense, it disappeared into the difference between the discrete model and the continuous model. In a practical sense, the absence of a denominator in Equation 5.7 greatly simpli-

fies some of the formulas used to describe the effects of selection. Although they look very different, Equations 5.6 and 5.7 are merely different ways of saying the same thing. In this chapter, we will deal mainly with expressions analogous to Equation 5.6 because they are more easily derived for various types of selection. However, when it is necessary to dispose of a troublesome denominator, we will invoke the continuous model in Equation 5.7 and be rid of it.

Darwinian Fitness and Malthusian Fitness

The distinction between the fitness parameters in the discrete and continuous models has been incorporated into the terminology of population genetics in the terms **darwinian fitness**, which refers to the discrete model, and **malthusian fitness**, which refers to the continuous model. The latter is named after Thomas Malthus (1766–1834), whose views on the implications of continued population growth strongly influenced Darwin's thinking on the subject. A darwinian fitness is conventionally represented by the symbol w, often embellished with a subscript, and malthusian fitness is conventionally represented by the symbol m. In this book, the term *fitness*, when used without qualification, will mean darwinian fitness unless it is clear from the context that some other meaning is intended.

5.2 SELECTION IN DIPLOID ORGANISMS

In haploid organisms, some cells are better at avoiding death, or are able to acquire nutrients more efficiently, or divide faster. All these attributes can be collapsed into a single fitness parameter that expresses the differential growth rate of that haploid genotype. In diploid organisms, the consequences of selection can be manifested in more complicated ways. Starting with the fusion of gametes, the zygote has to divide and grow and develop. From one genotype to another there might be different rates of development and different probabilities of survival to the adult stage. We call this component of selection **viability**. The adults must then be successful at attracting mates, and the differences among genotypes in this ability is manifested as **sexual selection**. When heterozygous individuals produce gametes, there can be departures from Mendelian segregation, and this results in a form of selection called **meiotic drive** or **segregation distortion**. Many marine organisms release gametes in the sea, and there might be differential survival of these haploid cells, in a form of selection called **gametic selection**. Once matings occur, genotypes may produce different numbers of offspring, and we call this **fecundity selection**. To make matters more complicated, the number of progeny that are produced by a pair of genotypes might not be expressed as a simple sum of fecundity effects of each genotype, but might instead have to be expressed as a property of the mating pair of genotypes.

Later on in the chapter we will consider some of the consequences of considering these various components of selection. For many organisms, it appears that differential fecundity may actually be the most important fitness component, but for now, the easiest model to consider first is that of viability selection.

To develop a model of natural selection in diploids, we will start with the model of random mating in Chapter 2, but we incorporate selection by permitting the fitnesses of the genotypes to differ. Recall that in this model we made many assumptions – that the population was infinite so that no genetic drift occurs, that there are no new mutations or migration, and that genotypes mate at random. To these assumptions we now add that fitnesses are constant and selection is assumed to take place only through differential zygote-to-adult survival of the diploid genotypes. We shall use the conventional symbols w_{11}, w_{12}, and w_{22} to represent the darwinian fitnesses of the genotypes *AA*, *Aa*, and *aa*, respectively. If the fitness of each genotype is set equal to its probability of survival, then each fitness is an **absolute fitness** because its value is independent of the fitnesses of the other genotypes. In practice, we usually know only the value of the viability of each genotype relative to that of another genotype chosen as the standard of comparison. When a fitness value is expressed relative to that of another genotype, the fitness is a **relative fitness**. The relative fitness of the genotype chosen as the standard of comparison is arbitrarily assigned the value 1.

To consider a specific example, suppose that the genotypes *AA*, *Aa*, and *aa* have probabilities of survival from conception to reproductive age of 0.75, 0.75, and 0.50, respectively. These are the absolute viabilities of the genotypes. They can be judged realistic or not only if we specify the organism. They may be plausible values if the organism is a mammal or a bird because each offspring has a reasonable chance of survival, but implausible if the organism is an insect or an oyster because, in these organisms, most newborns are destined not to survive. Because selection depends on the relative magnitudes of the viabilities, it is usually most convenient to express the viabilities in relative terms. Taking genotype *AA* as the standard, the relative viabilities of *AA*, *Aa*, and *aa* are 0.75/0.75, 0.75/0.75, and 0.50/0.75, or 1.0, 1.0, and 0.67, respectively. Equivalently, we could choose genotype *aa* as the standard, in which case the relative viabilities are 0.75/0.50, 0.75/0.50, and 0.50/0.50, or 1.5, 1.5, and 1.0, respectively. Usually, the relative viabilities are calculated so that the largest relative viability equals 1.0. The relative viabilities are equal to the relative fitnesses of the genotypes provided that the genotypes are equally capable of reproduction. Viabilities expressed in relative terms are as valid for osprey as for oysters because the relative fitnesses are the same whether the absolute fitnesses are 0.75, 0.75, and 0.50 or 0.00075, 0.00075, and 0.00050. We shall see that the dynamics of how the allele frequencies change depend only on the relative fitnesses.

PROBLEM 5.2 A number of mutations in laboratory organisms have been discovered that lengthen the lifespan of the organisms. One particularly dramatic example is *daf-2*, a gene in the insulin signaling pathway of *Caenorhabditis elegans* which, when mutated, can double the lifespan of the worms. Jenkins et al. (2004) hypothesized that there must be negative effects to the *daf-2* mutation; otherwise such a mutation would have gone to fixation in the population. They sought to measure the total fitness differences between wildtype and *daf-2* mutant worms. They started six replicate populations with equal frequencies of the two homozygous genotypes ($p_0 = 0.5$) and observed frequencies of the *daf-2* allele of 0.28, 0.09, 0.02, and 0 in generations 1, 2, 3, and 4. What was the net fitness of *daf-2* relative to wildtype? (Hint: *C. elegans* is diploid but is a selfing hermaphrodite almost all the time, so these two genotypes can be treated as haploid clones.)

ANSWER For the first generation, the frequency of *daf-2* fell from 0.5 to 0.28, and we obtain natural log(0.28/0.72) = log(0.5/0.5) + log(w). Solving for w, we get 0.389. Likewise, for the transitions from generations 1 to 2, and 2 to 3, we get estimates of $w = 0.254$ and $w = 0.206$. If we do a linear regression of log(p/q) against generation, the slope is –1.3 for an average fitness estimate throughout the experiment of $e^{-1.3} = 0.27$. The *daf-2* allele really does much worse than the wildtype allele, and would be very rapidly eliminated, as it was in the lab population. This example confirms the old adage that if something sounds too good to be true, it probably is too good to be true.

Change in Allele Frequency in Diploids

If we write the allele frequencies of A and a as p_t and q_t, respectively, in generation t, then it is straightforward to derive expressions for the allele frequencies in generation t in terms of the allele frequencies p_{t-1} and q_{t-1} in the previous generation. The subscripts t and $t-1$ are rather cumbersome to carry along in equations, so we will use the symbols p and q for p_{t-1} and q_{t-1}, and the symbols p' and q' for p_t and q_t.

The relation between the allele frequencies in two consecutive generations is deduced in Table 5.2, where the fitnesses w_{11}, w_{12}, and w_{22} are the relative viabilities. In generation $t-1$, the genotype frequencies of AA, Aa, and aa among newly fertilized eggs are given by p^2, $2pq$, and q^2, respectively, assuming random mating. By definition, newly fertilized eggs survive in the ratio $w_{11} : w_{12} : w_{22}$, and so the ratio of $AA : Aa : aa$ among surviving adults is

$$p^2 w_{11} : 2pqw_{12} : q^2 w_{22}$$

To proceed, we need to convert the terms in the above expression into relative frequencies by dividing each term by the sum. The value of the sum is indicated in Table 5.2 as

$$\bar{w} = p^2 w_{11} + 2pqw_{12} + q^2 w_{22} \qquad (5.8)$$

TABLE 5.2 Diploid Selection for Survivorship (Viability)

	Genotype			Total
Generation $t-1$	AA	Aa	aa	
Frequency before selection	p^2	$2pq$	q^2	$1 = p^2 + 2pq + q^2$
Relative fitness (viability)	w_{11}	w_{12}	w_{22}	
After selection	p^2w_{11}	$2pqw_{12}$	q^2w_{22}	$\bar{w} = p^2w_{11} + 2pqw_{12} + q^2w_{22}$
Normalized	$\frac{p^2w_{11}}{\bar{w}}$	$\frac{2pqw_{12}}{\bar{w}}$	$\frac{q^2w_{22}}{\bar{w}}$	
Generation t	$p' = \frac{p^2w_{11} + pqw_{12}}{\bar{w}}$			
	$q' = \frac{pqw_{12} + q^2w_{22}}{\bar{w}}$			

Note: The allele frequencies p and q are those in gametes immediately prior to fertilization. The AA, Aa, and aa zygotes survive to reproductive maturity in the ratio $w_{11} : w_{12} : w_{22}$. All genotypes, as adults, are assumed to have the same reproductive capacity.

The symbol $\bar{w}$ is the mean fitness in the population in generation $t-1$, and it is simply the average fitness of all individuals in the population. Division of each term in the ratio of survivors by $\bar{w}$ yields the genotype frequencies among adults:

$$AA : \frac{p^2w_{11}}{\bar{w}} \quad Aa : \frac{2pqw_{12}}{\bar{w}} \quad aa : \frac{q^2w_{22}}{\bar{w}} \tag{5.9}$$

Among the surviving adults, the AA genotypes produce all A gametes, the Aa genotypes produce $\frac{1}{2}A$ and $\frac{1}{2}a$ gametes, and the aa genotypes produce all a gametes. Hence, the frequencies of the gametes that unite at random to form the zygotes of the next generation are:

$$p' = \frac{p^2w_{11} + pqw_{12}}{\bar{w}} \quad q' = \frac{pqw_{12} + q^2w_{22}}{\bar{w}} \tag{5.10}$$

These are the relations we were after because they express the allele frequencies in any generation in terms of the allele frequencies in the previous generation. From these equations, the outcome of selection can be deduced. Because $q' = 1 - p'$, the recursion that describes how the allele frequencies change is fully specified by giving only the equation for p'.

As in the haploid model, it is often useful to know Δp, which is the difference in allele frequency $p' - p$ resulting from one generation of selection. Subtraction of p from the expression for p' in Equation 5.10 and a little manipulation leads to:

$$\Delta p = \frac{pq[p(w_{11} - w_{12}) + q(w_{12} - w_{22})]}{\bar{w}} \qquad (5.11)$$

Equation 5.11 is the diploid analog of that in the haploid model in Equation 5.6.

At this point, an example of the use of these equations is in order. We will use data on the change in the frequency of the *Gl* (*Glued* eyes) allele in a laboratory population of *Drosophila melanogaster*, which are plotted in Figure 5.2. The *Gl* allele is lethal when homozygous, so $w_{11} = 0$. The points in Figure 5.2 pertain to the frequency of *Gl* heterozygotes but, because *Gl*/*Gl* genotypes do not survive, the allele frequency p of *Gl* equals one-half the frequency of *Gl*/+ adults. The points in the figure are each separated by one generation,

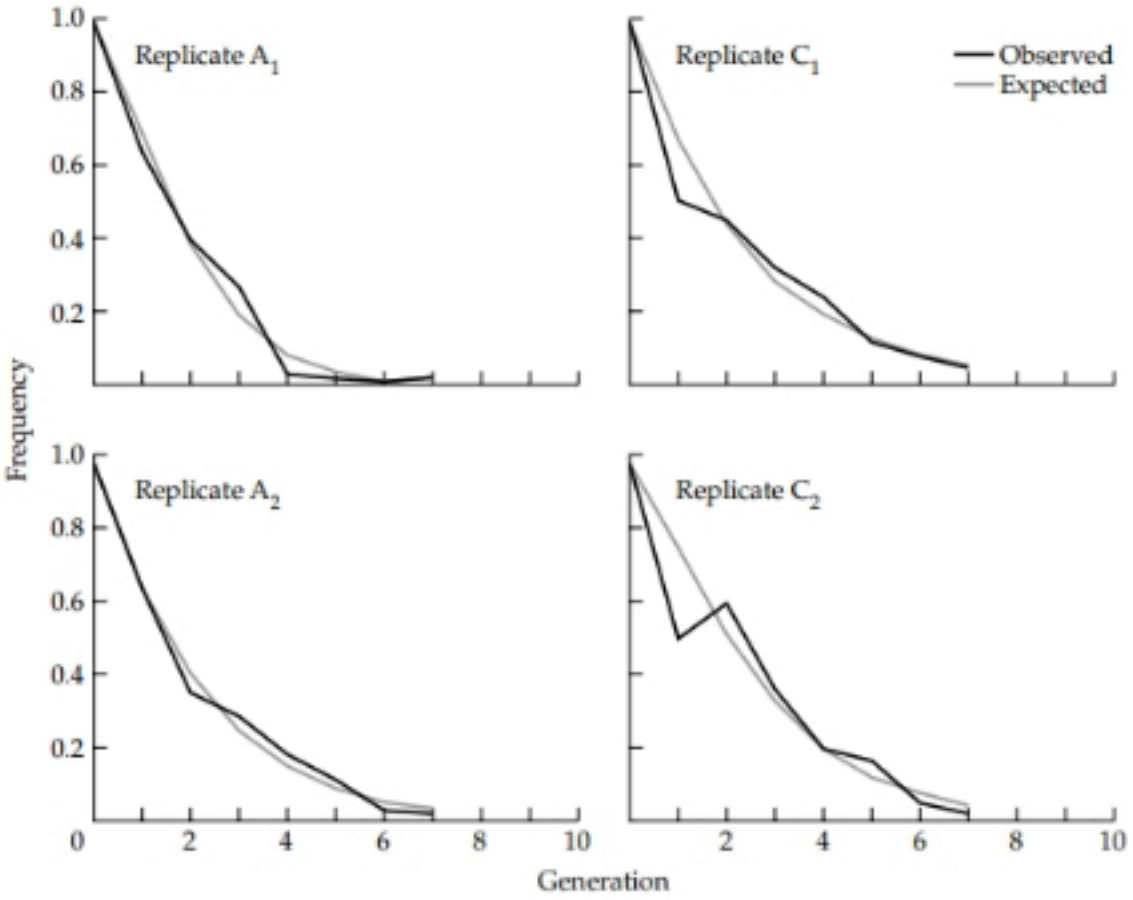


FIGURE 5.2 Change in frequency of adult *Drosophila melanogaster* heterozygous for the dominant mutation *Gl* (*Glued* eyes) in an experimental population. The genotype *Gl*/*Gl* is lethal. The curves represents the theoretical change in frequency when the ratio of viabilities of *Gl*/+ to +/+ is estimated from the data. The four plots are four independent population replicates. (From Clegg et al. 1976.)

and the initial generation has a frequency of *Gl*/+ adults of 0.67; hence $p_0 = 0.335$ and thus $q_0 = 0.665$. The data from Figure 5.2 were used to estimate the fitnesses of the *Gl*/+ vs. +/+ genotypes, and this estimation was done separately for each replicate, giving relative fitness values of 0.383, 0.573, 0.693 and 0.559, for an average of 0.538, relative to a value of $w_{22} = 1.0$ for +/+ genotypes. Substituting these values for p, q, w_{11}, w_{12}, and w_{22} into the expression for p' in Equation 5.10 yields

$$p' = \frac{0.335^2 \times 0 + 0.335 \times 0.665 \times 0.538}{0.335^2 \times 0 + 2 \times 0.335 \times 0.665 \times 0.538 + 0.665^2 \times 1} = 0.292$$

Therefore, the predicted frequency of *Gl*/+ adults in generation 1 is $2p' = 0.584$, which is reasonably close to the observed values that range from 0.504 to 0.646 among replicates.

Note that the four panels of Figure 5.2 are rather different, even though they are supposed to be replicates of each other. Statistical tests showed that they are in fact *not* consistent with the same model of selection. Clegg et al. (1976) set up this experiment to follow not only the dynamics of the *Glued* allele itself, but also to follow the way that linked genes change through a process known as *genetic hitchhiking*. Interestingly, the linked genes did not follow a simple trajectory of allele frequencies that one would predict from the *Glued* lethal allele and recombination. Instead, the linked genes changed frequency in a way that could only be explained by additional selected alleles in the genetic background. An important consideration for any experiment dealing with natural selection in the laboratory is that not all variable can be measured, and other unobserved loci are probably under selection too!

PROBLEM 5.3 Balancer chromosomes with multiple inversions have been important in *Drosophila* population genetics because they allow the investigator to isolate single chromosomes from natural populations for study. Dobzhansky and Spassky (1963) estimated the relative viability of 1063 wild-derived *D. pseudoobscura* second-chromosome homozygotes compared to heterozygotes with a balancer, and found no correlation between the homozygous viability and heterozygous viability for random pairs of these wild chromosomes. In order to get at total fitness, the full dynamics of allele frequencies can be followed by observing changes in allele frequency cage populations. Sved and Ayala (1970) developed an estimator of total fitness of whole chromosomes in *Drosophila* that made use of the same kind of balancer chromosome system, but followed the frequencies in cage populations. Because the homozygotes for the balancer (*Ba*/*Ba*) were lethal, the only two surviving genotypes were *Ba*/+ and +/+. In one cage, the frequency of the *Ba*/+ heterozygotes was 0.486, and in the next generation this frequency was 0.726. What is the net fitness of *Ba*/+ relative to +/+?

ANSWER The allele frequency for the balancer is one-half the heterozygote frequency, so the allele frequency changed from $p = 0.486/2 = 0.243$ to $0.726/2 = 0.363$. If we let the *Ba*/+ genotype have fitness w relative to the +/+ genotype (*Ba*/*Ba* has fitness zero), then the recursion for the wild-type allele is $q' = (wpq + q^2)/(2pqw + q^2)$. Substituting, we get $0.637 = [w(0.243)(0.757) + (0.757)^2]/[w2(0.243)(0.757) + (0.757)^2]$. Solving for w, we get 4.13. Another way to put this is to say that the relative fitness of the wild-type homozygote relative to the balancer heterozygote is $1/(4.13) = 0.242$. Sved and Ayala took pains to try to decompose fitness into viability and fecundity components, and showed that both played an important role in determining fitness differences between second chromosome.

Figure 5.3 shows another important aspect of directional selection. When a new mutation is advantageous, it increases in frequency initially much faster when it is dominant than when it is recessive. The reason is that a rare allele is almost entirely found in heterozygotes, and if the mutation is completely recessive, then its effects on fitness are not manifested nearly to the degree that they are if the allele were dominant. When the allele becomes common, the tables are turned and the dominant allele's frequency changes very slowly, but the common recessive allele changes rapidly in frequency. The same reasoning applies: When a common dominant allele is present in a population, almost all fitnesses are the same, so selection changes allele frequency slowly.

By substituting in the formulae for p' and for q' into $\overline{w}$ one can derive an equation for $\overline{w}'$ that gives a recursion for how the mean population fitness changes over generations. Further algebra shows that $\overline{w}$ in the one-locus two-allele model of selection with constant fitnesses is nondecreasing. One can also show that $\overline{w}$ sits at a local maximum value whenever the population is at equilibrium allele frequencies. This property of the mean fitness is part of Fisher's (1930) *fundamental theorem of natural selection*, which states that the rate of increase in the mean fitness of a population ascribable to gene frequency changes is exactly equal to the additive genetic variance in fitness. It was not until Ewens (1989) that there was a convincing proof of Fisher's principle, in part because of the subtle interpretation of Fisher's statement of the theorem (see Edwards 2002). Somewhat surprisingly, the mean fitness does not always increase in all models, and the equilibrium is often not a maximum of mean fitness.

Marginal Fitness and Selection with Multiple Alleles

We make a slight digression to point out that it is sometimes convenient to think in terms of the marginal fitnesses of the A and a alleles. The **marginal fitness** equals the average fitness of all genotypes containing A or a, respectively, weighted by their relative frequency and the number of A or a alleles they contain. For example, A alleles are found in AA and Aa genotypes in the

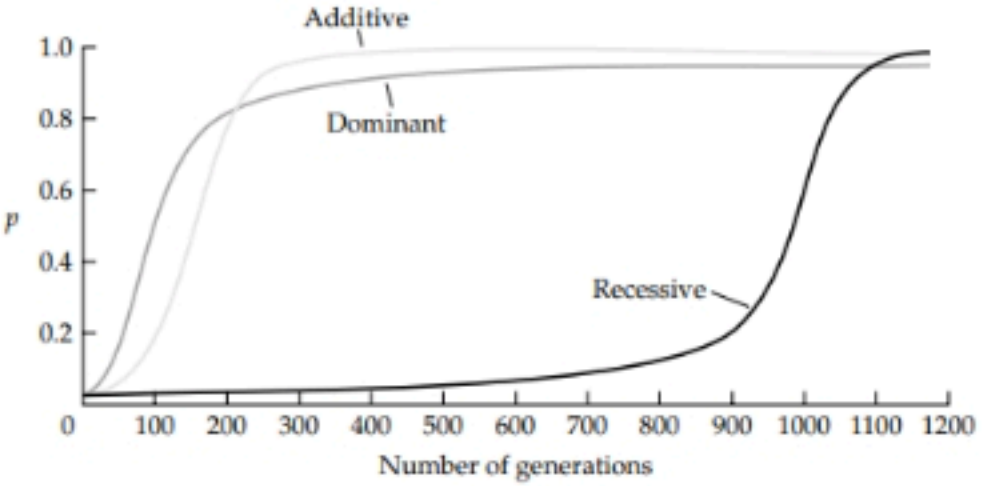


FIGURE 5.3 The change in frequency p of a favorable allele that is either dominant, additive, or recessive in its effect on fitness. The frequency of a favored dominant allele changes most slowly when the allele is common, and the frequency of a favored recessive allele changes most slowly when the allele is rare. In all three examples, the difference in relative fitness between the homozygous *AA* and *aa* genotypes is assumed to be 5%.

proportions p and q and, therefore, the marginal fitness $\overline{w}_1$ of *A*-containing genotypes equals $pw_{11} + qw_{12}$. Similarly, the marginal fitness of *a*-containing genotypes is $\overline{w}_2 = pw_{12} + qw_{22}$. The expression for p' in Equation 5.10 thus becomes $p' = p\,\overline{w}_1/\,\overline{w}$, and Equation 5.11 becomes $\Delta p = p(\,\overline{w}_1 - \overline{w})/\,\overline{w}$. This expression makes it clear that any allele increases in frequency if the marginal fitness of genotypes containing the allele ($\overline{w}_1$) is greater than the average fitness in the population ($\overline{w}$). This approach also generalizes readily to multiple alleles: For an allele with frequency p_i and marginal fitness $\overline{w}_i$, the change in frequency in one generation equals

$$\Delta p_i = \frac{p_i(\overline{w}_i - \overline{w})}{\overline{w}} \tag{5.12}$$

Equation 5.12 has some interesting consequences. Note that one condition for equilibrium is that $\overline{w}_i = \overline{w}$. This implies that the marginal fitness of every allele is the same. In the case of three alleles, the marginal fitnesses can be written:

$$\overline{w}_1 = p_1w_{11} + p_2w_{12} + p_3w_{13}$$
$$\overline{w}_2 = p_1w_{21} + p_2w_{22} + p_3w_{23}$$
$$\overline{w}_3 = p_1w_{31} + p_2w_{32} + p_3w_{33}$$

This system of equations consists of three linear equations in three unknowns, and besides the three fixation equilibria [where the allele frequencies (p_1, p_2, and p_3) are either (1,0,0), (0,1,0) or (0,0,1)], this system has either no polymorphic equilibria, one unique equilibrium, or the full range of

allele frequencies are equilibria. (The latter is an aberrant case that happens, for example, when the fitnesses are all equal.) We will postpone statement of the conditions on the fitnesses necessary to maintain all three alleles in a stable equilibrium under this form of selection until we discuss the stability characteristics of the model.

PROBLEM 5.4 An extension of the use of population cages that allows estimation of heterozygote fitness makes use of a chromosome isolated from a natural population and two balancer chromosomes. Gardner et al. (2005) studied 40 different wild chromosomes using the balancers *TM1* and *TM2*. For the wild chromosomes that were lethal when homozygous, the only genotypes that survive are *+/TM1*, *+/TM2* and *TM1/TM2*, where *TM1* and *TM2* are balancer chromosomes (*TM* stands for "third multiply-inverted"). If the relative fitnesses of *+/TM1*, *+/TM2* and *TM1/TM2* are s, t, and u, respectively, find the equilibrium frequencies of + (p_1), *TM1* (p_2), and *TM3* (p_3). What are these frequencies when $s = 0.8$, $t = 0.3$, and $u = 0.7$?

ANSWER: First note that the fitnesses can be written in the form of a symmetric matrix $w_{ij} = w_{ji}$ as follows:

$$\begin{bmatrix} 0 & s & t \\ s & 0 & u \\ t & u & 0 \end{bmatrix}$$

At equilibrium each of the three marginal fitnesses is equal to the mean fitness, hence:

$$\begin{aligned} \bar{w} &= 0p_1 + sp_2 + tp_3 \\ \bar{w} &= sp_1 + 0p_2 + up_3 \\ \bar{w} &= tp_1 + up_2 + 0p_3 \end{aligned}$$

This is system of three linear equations in three unknowns, and it can be solved by searching the Internet for a method called Cramer's rule. Cramer's rule gives the solutions as:

$$\hat{p}_j = D_j / \sum_{i=1}^{3} D_i$$

where D_1, D_2, and D_3 are the following matrix determinants. (At equilibrium $\bar{w}$ is a constant, and it cancels out in the ratios.)

$$D_1 = \begin{vmatrix} \bar{w} & s & t \\ \bar{w} & 0 & u \\ \bar{w} & u & 0 \end{vmatrix}$$

$$D_2 = \begin{vmatrix} 0 & \bar{w} & t \\ s & \bar{w} & u \\ t & \bar{w} & 0 \end{vmatrix}$$

$$D_3 = \begin{vmatrix} 0 & s & \bar{w} \\ s & 0 & \bar{w} \\ t & u & \bar{w} \end{vmatrix}$$

Solving these determinants, the equations for the $\hat{p}_j$ are

$$\hat{p}_1 = \frac{u(u-s-t)}{u(u-s-t)+t(t-u-s)+s(s-t-u)}$$

$$\hat{p}_2 = \frac{t(t-u-s)}{u(u-s-t)+t(t-u-s)+s(s-t-u)}$$

$$\hat{p}_3 = \frac{s(s-t-u)}{u(u-s-t)+t(t-u-s)+s(s-t-u)}$$

When $s = 0.8$, $t = 0.3$, and $u = 0.7$ these become $\hat{p}_1 = 0.35$, $\hat{p}_2 = 0.45$, and $\hat{p}_3 = 0.20$ These values reproduce almost exactly the equilibrium values observed with one of the wild chromosomes.

Application to the Evolution of Insecticide Resistance

Some of the most dramatic examples of evolution in action result from the natural selection for chemical pesticide resistance in natural populations of insects and other agricultural pests. In the 1940s, when chemical pesticides were first used on a large scale, an estimated 7% of the agricultural crops in the United States were lost to insects. Initial successes in chemical pest management were followed by gradual loss of effectiveness. Today, more than 400 pest species have evolved significant resistance to one or more pesticides, and 13% of the agricultural crops in the United States are lost to insects. Total cost and loss due to insects in 2005 were $1.264 billion (Robinson 2006). In many cases, significant pesticide resistance has evolved in 5 to 50 generations irrespective of the insect species, geographical region, pesticide, frequency and method of use, and other seemingly important variables. Details in actual examples depend on such factors as effective population number and extent of genetic isolation between local populations. The evolution of resistance caused by multiple interacting alleles may be expected to take somewhat longer than single-gene resistance.

PROBLEM 5.5 Resistance to organophosphate and carbamate insecticides in species of the mosquitoes *Culex* and *Anopheles* has been shown to be mediated by four independent mutations in the acetylcholinesterase gene *ace-1* (Weill et al. 2004). The mutations, resulting in G119S (a glycine replaced by a serine at position 119), makes the enzyme insensitive to inhibition by these insecticides. Because the novel form of the protein remains active, this is a gain-of-function mutation, and resistance is therefore dominant. If mosquitoes bearing the resistance allele are 10 times as likely to survive and reproduce as the sensitive allele (relative fitnesses 10:1), how long would it take the allele frequency to rise from 0.01 to 0.50?

ANSWER Substitute $w_{11} = w_{12} = 10$, $w_{22} = 1$, and $p = 0.01$ into Equation 5.10 and calculate the allele frequency the next generation. This calculation is especially easy to do on a spreadsheet, making columns for allele frequencies, genotype frequencies, mean fitness, and allele frequency the next generation. You will find that the allele frequencies are 0.0848, 0.3445, and 0.5617, so in just three generations the frequency exceeds 50%.

5.3 EQUILIBRIA WITH SELECTION

An **equilibrium value** of p in a discrete model is any value for which $\Delta p = 0$. When the allele frequency is at an equilibrium in an infinite population, the allele frequency remains the same generation after generation. Because real populations are finite in size, an allele frequency is subject to chance fluctuations and so cannot usually remain exactly at an equilibrium value. For any

equilibrium, therefore, it is important to consider how the allele frequency behaves when it is close, but not exactly equal, to the equilibrium value. Any equilibrium can be classified as one of several different types according to the behavior of the allele frequency when it is near the equilibrium:

- An equilibrium is said to be **locally stable** if the allele frequency, when it is already close to the equilibrium, moves progressively closer in subsequent generations. A locally stable equilibrium may also be **globally stable**. This term means that the allele frequency always moves toward the equilibrium regardless of where it starts, even if initially far away from the equilibrium. A polymorphism with a stable equilibrium is sometimes called a **balanced polymorphism**.
- An equilibrium is **unstable** if the allele frequency, initially close to the equilibrium, moves progressively farther away in subsequent generations.
- An equilibrium is called **neutrally stable** or *semistable* if the allele frequency has no tendency to change regardless of its initial value. In such a case, every allele frequency represents an equilibrium because $\Delta p = 0$ whatever the value of p. This type of equilibrium is exemplified by the Hardy-Weinberg principle in an infinite population (see Chapter 2).

The concepts of stability can be applied to the case of selection governed by Equation 5.11 in which A is the favored allele. For A to be favored, we need $w_{11} \geq w_{12} \geq w_{22}$, and at least one of the strict inequalities must be true. In such a case, there are only two equilibria, namely $p = 0$ and $p = 1$. Except for $p = 0$ and $p = 1$, when $\Delta p = 0$, it is always true that $\Delta p > 0$. Hence, if p is close to 0, its value increases (moving it farther away from 0), and so the equilibrium at $p = 0$ is unstable. On the other hand, if p is near 1, it moves still closer to 1 (because $\Delta p > 0$), and so the equilibrium at $p = 1$ is locally stable. In this example, p eventually goes to 1 whatever its initial value, and so the equilibrium at $p = 1$ is globally stable also.

Overdominance

In a diploid organism there is the possibility that the heterozygous genotype has a higher fitness than either homozygote. In this case, there is a polymorphic equilibrium in which the equilibrium value of p is between 0 and 1. We call this situation **overdominance** or *heterozygote superiority*. Symbolically, heterozygote superiority means that $w_{12} > w_{11}$ and simultaneously $w_{12} > w_{22}$. With overdominance, $p = 0$ and $p = 1$ are both equilibria because, according to Equation 5.11, $\Delta p = 0$ at these values. There is also a third equilibrium made possible by the fact that $p(w_{11} - w_{12}) + q(w_{12} - w_{22})$ can equal 0. The equilibrium frequency of A is conventionally denoted $\hat{p}$; hence the equilibrium allele frequency of a is $\hat{q} = 1 - \hat{p}$. The equilibrium can be found by solving $\hat{p}\,(w_{11} - w_{12}) + \hat{q}\,(w_{12} - w_{22}) = 0$, from which a little algebra gives

$$\hat{p} = \frac{w_{12} - w_{22}}{2w_{12} - w_{11} - w_{22}} \tag{5.13}$$

Equation 5.13 is often encountered in another form in which the fitnesses are all expressed relative to that of the heterozygote by setting $w_{11} = 1 - s$, $w_{12} = 1$, and $w_{22} = 1 - t$. With these substitutions, Equation 5.13 becomes

$$\hat{p} = \frac{t}{s+t}$$

This relationship makes intuitive sense because it implies that greater selection against *aa* increases the equilibrium frequency $\hat{p}$ of *A*.

The overdominance equilibrium in Equation 5.13 is globally stable, whereas those at $p = 0$ and $p = 1$ are unstable. The time course is indicated in Figure 5.4A, where the arrowheads show the direction of change in allele frequency. Figure 5.4B shows the change in $\bar{w}$ with overdominance. The average fitness in the population is maximized at the stable equilibrium. Maximization of average fitness is a frequent outcome of selection in random-mating populations with constant fitnesses. There are, however, many exceptions when mating is nonrandom, when the fitnesses are not constant, or when

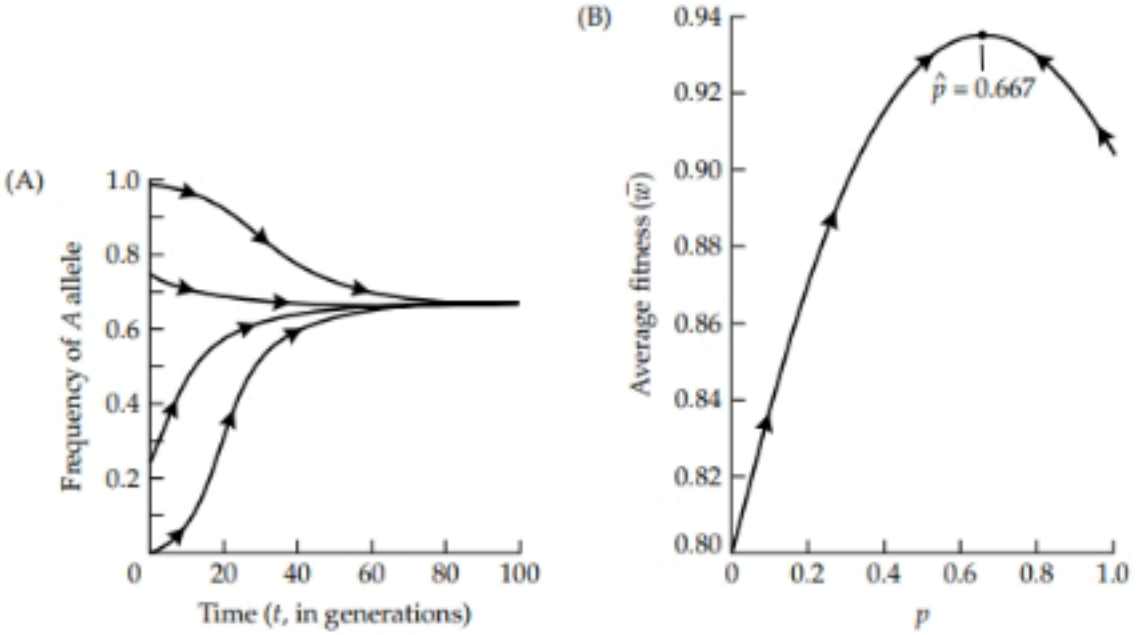


FIGURE 5.4 Selection when there is overdominance. (A) The allele frequencies converge to an equilibrium value irrespective of the initial frequency. In this example, $w_{11} = 0.9$, $w_{12} = 1$, and $w_{22} = 0.8$, and the equilibrium frequency of the *A* allele, $\hat{p}$, is 0.667. (B) Average fitness $\bar{w}$ against p for the same example. Note that $\bar{w}$ is a maximum at equilibrium.

there are interactions between alleles of different genes (Ewens 1979; Curtsinger 1984). Note particularly that $\bar{w}$ is the average fitness *in* the population, not the average fitness *of* the population. The relative survivorships w_{11}, w_{12}, and w_{22} are relevant only to the differential mortality of the genotypes within a population at any given time. The average of the relative survivorships is the average "fitness" $\bar{w}$ *in* the population. However, $\bar{w}$ has no necessary relation to vernacular meanings of "fitness" such as competitive ability, population size, production of biomass, or evolutionary persistence (Haymer and Hartl 1982).

Although overdominance is one mechanism for the maintenance of polymorphisms in natural populations, it has been documented in only a few cases. The classic case is sickle-cell anemia in human beings, which is prevalent in many populations at risk for the type of malaria caused by the mosquito-borne protozoan parasite *Plasmodium falciparum* (Figure 5.5A). The anemia is caused by an allele *S* that codes for a variant form of the β chain of hemoglobin. In persons of genotype *SS*, many red blood cells assume a curved, elongated shape ("sickling") and are removed from circulation. The result is a severe anemia as well as pain and disability because of the accumulation of defective cells in the capillaries, joints, spleen, and other organs. In the absence of intensive medical care, persons of genotype *SS* usually do not survive. The *S* allele is maintained at a relatively high frequency because persons of genotype *AS*, in which *A* is the nonmutant allele, have only a mild form of the anemia but are quite resistant to malaria, perhaps because red blood cells infested with the parasite undergo sickling and are removed from circulation. Homozygous *AA* people are not anemic but, on the other hand, are the most sensitive to severe malaria. The result of the offsetting sickle-cell anemia and malaria resistance is that the heterozygotes have the highest fitness.

In regions of Africa in which malaria is common, the viabilities of *AA*, *AS*, and *SS* genotypes have been estimated as $w_{11} = 0.9$, $w_{12} = 1$, and $w_{22} = 0.2$, respectively (Cavalli-Sforza and Bodmer 1971; Templeton 1982). Substitution into Equation 5.13 leads to a predicted equilibrium allele frequency for *A* of $\hat{p} = 0.89$. Consequently, that of *S* is 0.11. This value is reasonably close to the average allele frequency of 0.09 across West Africa, but there is considerable variation in allele frequency among local populations.

Malaria has been among the most important selective agents acting on the human genome over at least the last 10,000 years. Numerous genes show evidence for selection mediated by malaria. In addition to sickle-cell anemia, another well documented resistance mechanism is associated with deficiency of the red-blood-cell enzyme glucose-6-phosphate dehydrogenase (G6PD), mapped in Figure 5.5B.

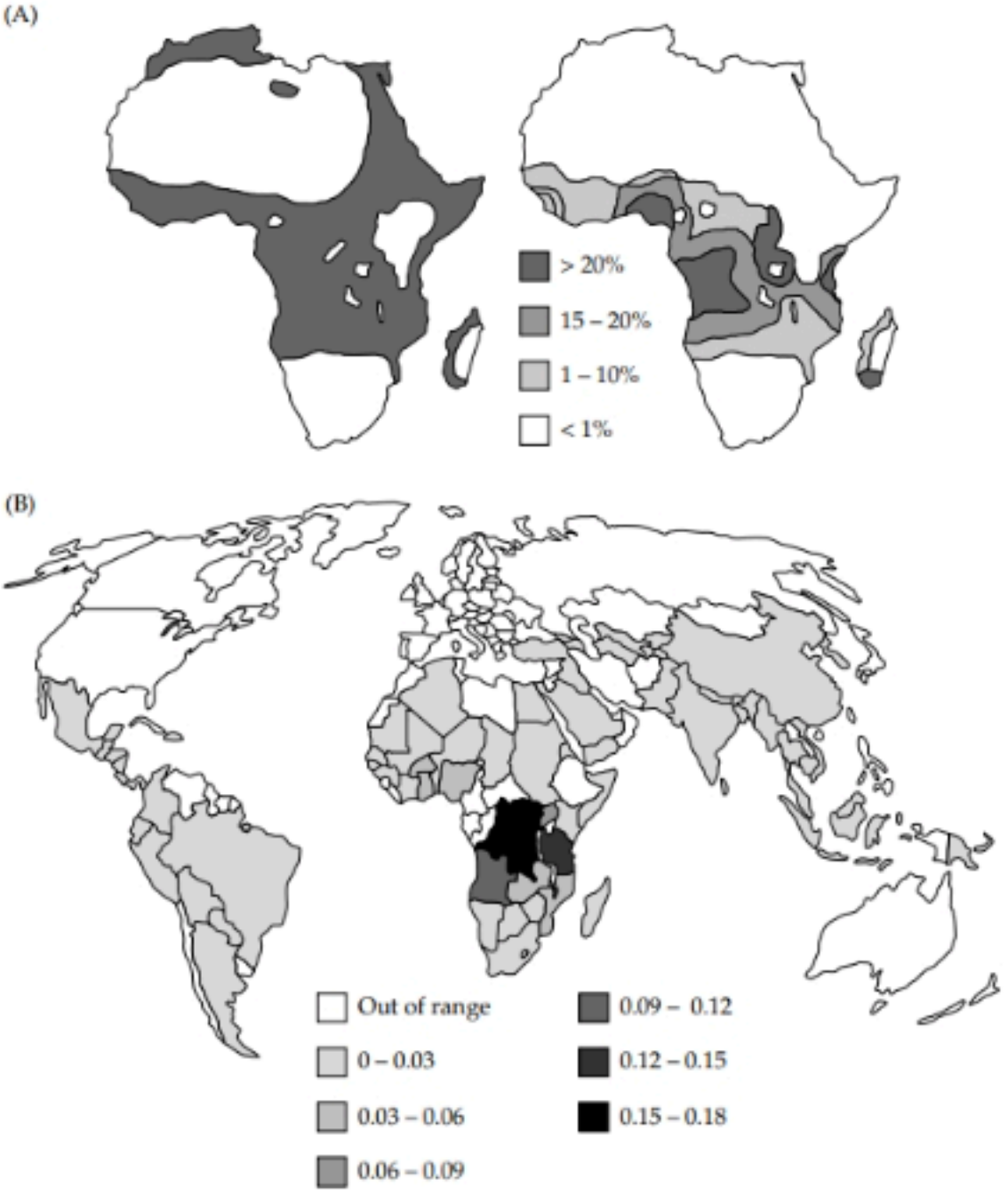


FIGURE 5.5 (A) A map of the distribution of the allele for sickle-cell anemia, and (B) map of the incidence of the *G6PD* deficiency allele. Both mutations are associated with resistance to malaria cause by *Plasmodium falciparum*. (A) The upper left map shows in gray the areas of incidence of falciparum malaria in Africa in the 1920s before mosquito control programs were implemented. The upper right figure shows the distribution of the beta-S globin allele. The global map in (B) shows the frequency of *G6PD* deficiency alleles indicated by the shading. The extensive overlap in the distributions relative to malaria was an early indication that there might be some causal connection.

PROBLEM 5.6 A potentially useful way to estimate the effect on fitness of an environmental insult is to use the cage population approach and estimate fitnesses before and after the insult. In one such study, experimental populations of *Drosophila pseudoobscura* were periodically treated with weak doses of the insecticide DDT. One population was initially polymorphic for five different inversions of the third chromosome. After 13 generations, three of the inversions had essentially disappeared from the population. The two that remained were Standard (*ST*) and Arrowhead (*AR*). Changes in frequency of each inversion were monitored and, from the values for the first nine generations, the relative fitnesses of *ST/ST*, *ST/AR*, and *AR/AR* genotypes were estimated as 0.47, 1.0, and 0.62, respectively (DuMouchel and Anderson 1968). Because the inversions undergo almost no recombination, each type can be considered as an "allele." What equilibrium frequency of *ST* is predicted? What equilibrium value of $\bar{w}$ is predicted?

ANSWER From Equation 5.13, $\hat{p} = (1.0 - 0.62)/(2.0 - 0.47 - 0.62) = 0.42$. (The observed value after 13 generations was 0.43.) The predicted equilibrium value of $\bar{w}$, from Equation 5.8, equals $0.422^2 \times 0.47 + 2 \times 0.42 \times 0.58 \times 1.0 + 0.58^2 \times 0.62 = 0.78$.

PROBLEM 5.7 One of the most widely prescribed drugs for heart patients is the blood anticoagulant warfarin. Its initial use was as a rat poison, and it was initially highly successful, but the effectiveness of the rodenticide gradually diminished because of the evolution of resistance among some target populations. Recently the gene for vitamin K epoxide reductase complex 1 (*VKORC1*) which is the target of warfarin was identified (Rost et al. 2004; Pelz et al. 2005), and there are clear polymorphisms in humans that affect the optimal dose of the drug (Rieder et al. 2005). Among Norway rats in Great Britain, resistance arises due to a mutation in *VKORC1*. If we designate the resistant and sensitive alleles as *R* and *S*, then in the absence of warfarin, the relative fitnesses of *SS*, *SR*, and *RR* genotypes have been estimated as 1.00, 0.77, and 0.46, respectively. In the presence of warfarin, the relative fitnesses have been estimated as 0.68, 1.00, and 0.37, respectively (May 1985). The reduced fitness of the *RR* genotype appears to result from an excessive requirement for vitamin K. Calculate the equilibrium frequency $\hat{q}$ of *R* in the presence of warfarin.

ANSWER From Equation 5.13, the equilibrium frequency $\hat{p}$ of *S* equals $(1.00 - 0.37)/(2 - 0.68 - 0.37) = 0.66$, and so $\hat{q}$ of $R = 0.34$.

Local Stability

Although the curves in Figure 5.4A indicate that the interior equilibrium is locally stable when there is overdominance, an alternative approach can also be applied to the analysis of local stability in models of much greater

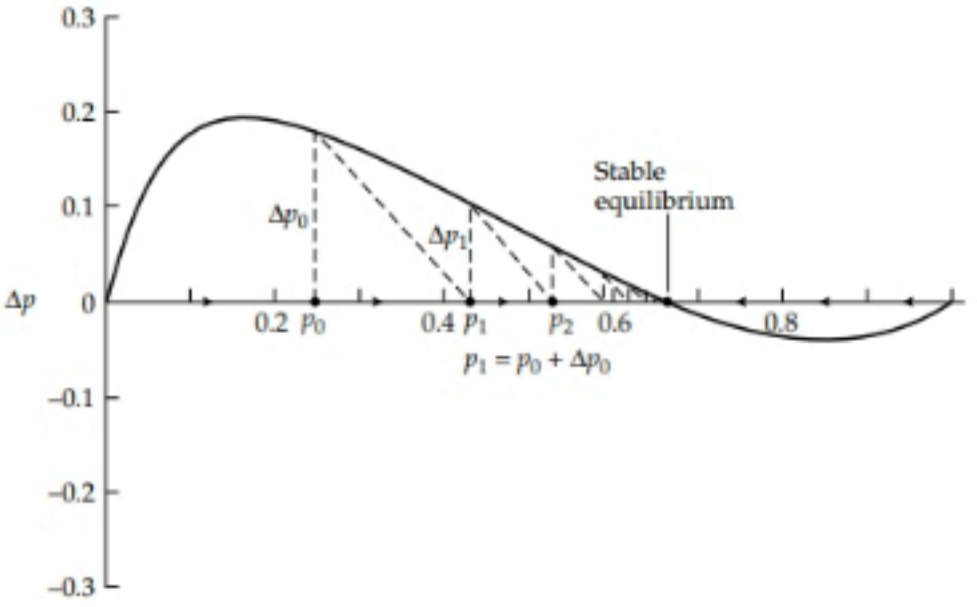


FIGURE 5.6 The change in allele frequency Δp plotted as a function of allele frequency p for a case of overdominance in which $w_{11} = 0.6$, $w_{12} = 1$, and $w_{22} = 0.2$. Starting with an allele frequency p_0 smaller than the equilibrium value, the positive value of Δp_0 indicates that the allele frequency in the next generation, p_1, will be greater than p_0 because $p_1 = p_0 + \Delta p_0$. At an allele frequency of p_1, the value of Δp_1 is also positive, and so p_2 is greater than p_1 because $p_2 = p_1 + \Delta p_1$. The steady increase continues until the population arrives at the equilibrium point $\hat{p}$. The same logic shows that, starting with an initial allele frequency greater than $\hat{p}$, the allele frequency decreases in each succeeding generation and ultimately converges to the equilibrium from the other side.

complexity. It is based on the expression for Δp in Equation 5.11. The local stability of an equilibrium depends on the behavior of Δp for a value of p close to, but not equal to, the equilibrium, as illustrated in Figure 5.6. It is convenient to write $\Delta(p + \varepsilon)$ as the change in allele frequency when the starting point is a small deviation, ε, from any allele frequency p. The function $\Delta(p + \varepsilon)$ can be expanded term by term into an infinite sum:

$$\Delta(p+\varepsilon) = \Delta(p) + \frac{d\Delta(p)}{dp}\varepsilon + \frac{d^2\Delta(p)}{dp^2}\frac{\varepsilon^2}{2!} + \frac{d^3\Delta(p)}{dp^3}\frac{\varepsilon^3}{3!} + \cdots$$

This is known as a *Taylor series expansion*, and it is described in most textbooks on calculus. In evaluating the Taylor series expansion, if ε is sufficiently small, then all terms in ε^2 and higher can be ignored. Therefore, for any value of p, we can approximate $\Delta(p + \varepsilon)$ in terms of Δp itself and its first derivative. Furthermore, if p is one of the equilibrium points, then $\Delta p = 0$ by definition, and so the sign of $\Delta(p + \varepsilon)$ depends on the sign of first derivative of Δp evaluated at the equilibrium in question. By definition, an equilibrium is locally stable if the allele frequency, starting at a point near the equilibrium,

moves ever-closer to the equilibrium. In symbols, this means that $\Delta(p+\varepsilon) < 0$ if $\varepsilon > 0$ and $\Delta(p+\varepsilon) > 0$ if $\varepsilon < 0$. Therefore, any equilibrium point, denoted generically as $\hat{p}$, is locally stable if, and only if,

$$\left.\frac{d\Delta(p)}{dp}\right|_{\hat{p}} < 0$$

where the vertical line and $\hat{p}$ means that the derivative should be evaluated at the equilibrium in question. In practice, calculating the derivative of Δp can be quite tedious without the use of computer software like Maple or Mathematica to do the algebraic manipulations. The result of differentiating Equation 5.11 is that

$$\frac{d\Delta(p)}{dp} = \frac{pqw}{\bar{w}} + \frac{(q-p)(p-\hat{p})w}{\bar{w}} - \frac{2pq(p-\hat{p})^2 w^2}{\bar{w}^2}$$

where $w = w_{11} - 2w_{12} + w_{22}$. With overdominance, $w < 0$. Note that, when $d\Delta p/dp$ is evaluated at $p = 0$ or $p = 1$, both the first and last terms equal 0; when it is evaluated at $p = \hat{p}$, the second and last terms equal 0. The stability analysis proceeds as follows:

$$\text{At } p = 0,\ d\Delta p/dp > 0$$
$$\text{At } p = \hat{p},\ d\Delta p/dp < 0$$
$$\text{At } p = 1,\ d\Delta p/dp > 0$$

Therefore, as is already clear from Figure 5.4A, the equilibrium points at 0, $\hat{p}$, and 1 are unstable, locally stable, and unstable, respectively. This stability analysis is predicated on the assumption of heterozygote superiority, which implies that $w < 0$. Exactly the same equilibrium points are present when there is heterozygote inferiority, but then $w > 0$, which means that the stability property of each equilibrium point is reversed. This situation is discussed next.

Heterozygote Inferiority

Heterozygote inferiority means that the fitness of the heterozygous genotype is smaller than that of both homozygotes: $w_{12} < w_{11}$ and $w_{12} < w_{22}$. An interior equilibrium, given by Equation 5.13, exists in this case also. The analysis in the previous section indicates that this equilibrium is unstable, whereas the equilibria at $p = 0$ and $p = 1$ are both locally (but not globally) stable. An example of heterozygote inferiority is depicted in Figure 5.7A, where the arrows again denote the direction of change in allele frequency. If the initial allele frequency is exactly equal to the equilibrium value (in this example, $\hat{p} = \frac{1}{3}$), then the allele frequency remains at that value. In all other cases, p goes to 1 or 0 depending on whether the initial allele frequency was above or below the equilibrium value.

Figure 5.7B shows the change in average fitness. The unstable equilibrium at $\hat{p} = \frac{1}{3}$ is the minimum average fitness. The shape of the $\bar{w}$ curve has an

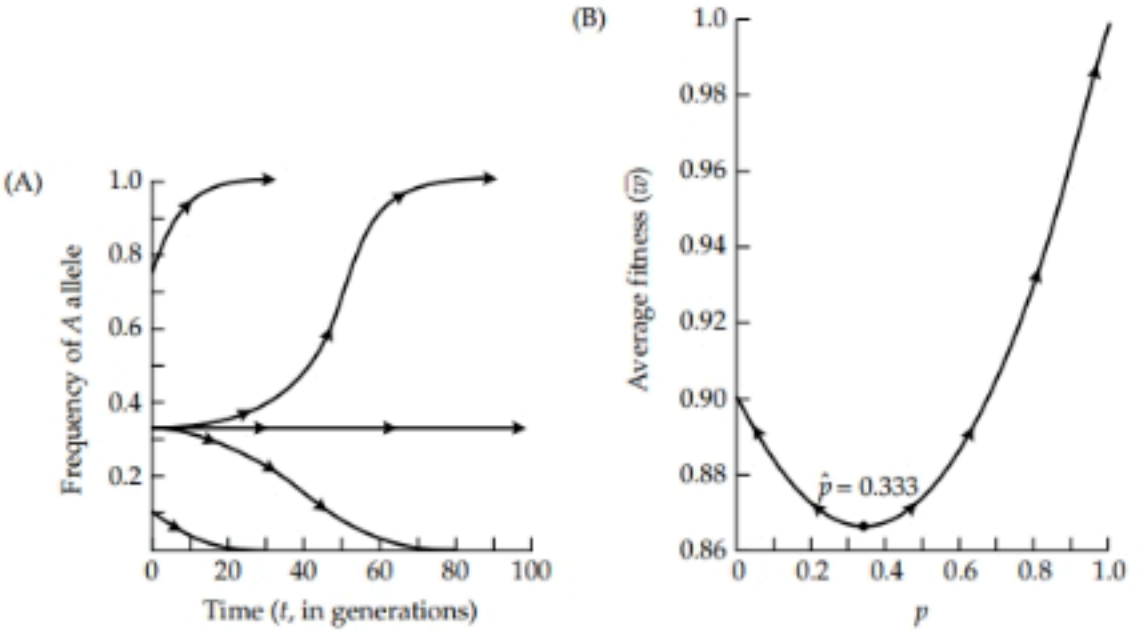


FIGURE 5.7 Selection when there is heterozygote inferiority. (A) The allele frequency goes to 0 or 1 depending on the initial frequency. In this example, $w_{11} = 1$, $w_{12} = 0.8$, and $w_{22} = 0.9$, and there is an unstable equilibrium when the frequency of the A allele is $\hat{p} = \frac{1}{3}$. An infinite population with $p = \frac{1}{3}$ maintains this frequency, but any slight upward change in the frequency of A results in eventual fixation, and any slight downward change in the frequency of A results in ultimate loss. (B) Average fitness $\bar{w}$ against p for the same example. The unstable equilibrium represents the minimum of $\bar{w}$.

important implication that carries over to more complex examples. Imagine a population with an allele frequency near 0, at which $\bar{w} = 0.9$. In terms of average fitness in the population, the population would be better off if the allele frequency were near 1, because then $\bar{w} = 1.0$. However, as shown by the direction of the arrows, the population cannot evolve toward $p = 1$. It cannot get through the "valley" because $p = 0$ is a locally stable equilibrium. The population has no way to escape from the equilibrium even though, in doing so, it would eventually end up with a greater average fitness. This consideration would seem to limit the ability of natural selection to increase average fitness in such cases, but one way out of the impass is suggested in the next section.

Stable Equilibria with Multiple Alleles

The presence of multiple alleles complicates the analysis of selection because the number of fitness parameters increases. With n alleles, there are $n(n + 1)/2$ possible genotypes, each with its own fitness. Furthermore, simple generalizations from two-allele theory do not necessarily carry over to multiple alleles. Consider the example of heterozygote superiority. Intuitively, one

might expect that fitnesses yielding stable, multiple-allele polymorphisms would be easy to generate by requiring that each heterozygous genotype has a greater fitness than the homozygous genotypes formed from the constituent alleles. This is not the case, however. If, for n alleles, the fitnesses of the genotypes are assigned at random between 0 and 1, subject to the condition that, for each i and j, $w_{ij} > \max(w_{ii}, w_{jj})$, then only a relatively small proportion of systems with four or more alleles yields a stable polymorphism with all alleles present. For four, five, and six alleles, the percentage of fitness sets yielding a stable equilibrium is 12.6, 1.2, and 0.03, respectively (Lewontin et al. 1978). The reason for the low percentages is that, even if a heterozygote is more fit than its constituent homozygotes, there might be a different homozygote more fit than all three.

How about requiring that each heterozygote be better than *every* homozygote? Surprisingly, this requirement does not help matters much. In this case, for four, five, and six alleles, the percentage of fitness sets yielding a stable equilibrium is 34.3, 10.4, and 1.3, respectively (Lewontin et al. 1978). The point is that polymorphisms with greater than three or four alleles are extremely unlikely to be maintained by selection for simple heterozygous advantage with constant survivorship. If selection is implicated in such a case, models of selection such as diversifying selection or heterogeneous environments are much more plausible. On the other hand, the fitnesses of genotypes in nature are not chosen simultaneously by a random number generator. Each new allele that arises is tested against the resident alleles, and the new allele is able to invade the population if its marginal fitness exceeds the mean fitness of the population. By this process, multiple allele polymorphisms can be accumulated, and the order in which the mutations appear makes a difference (Spencer and Marks 1988).

The possibility of multiple alleles also creates surprising situations in which the outcome of natural selection depends on the order in which the alleles are introduced into the population. Earlier in this chapter we mentioned the sickle-cell hemoglobin polymorphism in Africa and its relation to malaria resistance. People who are homozygous *AA* for the normal allele are susceptible to falciparum malaria, those who are heterozygous *AS* for the sickle-cell allele are resistant to malaria and have a mild anemia, and those who are homozygous *SS* for the sickle-cell allele have a life-threatening anemia. This is a classic case of heterozygote superiority. There is another allele, *C*, found at low frequency in populations in which the *S* allele is prevalent. The *C* allele is also protective against malaria, but the allele is recessive, and so only the *CC* genotypes are resistant. Unlike the *S* allele, the *C* allele does not cause anemia.

The relative survivorship of each of the various hemoglobin genotypes has been estimated based on studies of more than 32,000 people in 72 populations in West Africa (Cavalli-Sforza and Bodmer 1971). The survivorships are given in the following table, which indicates the genotypes that are resist-

ant and those that have severe hemolytic anemia. The survivorships were estimated in a geographical region where malaria was common. Note that the *S* allele causes a severe anemia in the heterozygous *SC* genotype, but not so serious as that in the homozygous *SS* genotype.

Genotype	***AA***	***AS***	***SS***	***AC***	***SC***	***CC***
Survivorship	0.9	1.0	0.2	0.9	0.7	1.3
Health status		Resistant	Anemic		Anemic	Resistant

Inspection of these survivorships reveals a paradox. The *CC* genotype has the highest fitness, yet the *C* allele is not fixed. The reason is found in the historical order in which the *S* and *C* mutations took place. The *A* allele is the ancestral type and undoubtedly predated the human settlement of regions subject to malaria. In such a region, the appearance of an *S* allele creates a heterozygous advantage, and natural selection quickly attains a stable equilibrium at which the ratio of $A : S$ alleles is approximately $8 : 1$. At this equilibrium, the average fitness in the population is $\overline{w} = 0.911$. Now suppose that mutation or migration were to introduce a small number of *C* alleles. Because *C* alleles are rare, each is present in either the *AC* genotype, with probability $\frac{8}{9}$, or in the *SC* genotype, with probability $\frac{1}{9}$. The average fitness of genotypes heterozygous for *C* is therefore 0.878, which is smaller than the average fitness in the population. Hence, the frequency of *C* decreases, and *C* goes extinct. The *C* allele has no chance of invading an *A*/*S* polymorphism unless the initial frequency of *C* is sufficiently large. But once *C* can get established in the population, it eventually becomes fixed.

Adaptive Topography and the Role of Random Genetic Drift

Any graph of $\overline{w}$ against allele frequency is called an **adaptive topography**. The simplest example is Figure 5.7B. In order to generalize the example, try to imagine an adaptive topography in many dimensions with $\overline{w}$ a function of the allele frequencies at many loci. In many dimensions, the adaptive topography is a complex surface upon which there may be "peaks" and "pits" and even "saddle-shaped" regions. The peaks represent locally stable equilibria. Even if natural selection changes the allele frequencies so as to move $\overline{w}$ to the top of some peak, the peak it perches on may not be the highest peak that exists on the whole surface. However, as illustrated in Figure 5.7B, the population may become stuck there because the peak is a locally stable equilibrium.

By what process can a population stranded on a submaximal fitness peak get off the peak? To do so, it has to travel through a nearby valley to a place where natural selection can carry it to the top of an even higher fitness peak. This is something that natural selection acting alone cannot accomplish because it entails a temporary reduction in fitness. There is, however, a

process that can accomplish the task—random genetic drift. In a sufficiently small population, the allele frequencies can change by chance, even producing a reduction in average fitness. Theoretically, random genetic drift can shift a population from a locally stable equilibrium, through a nearby valley, and into a region where it is attracted by another locally stable equilibrium toward a higher fitness peak. Random genetic drift can therefore play a crucial role in evolution by allowing a population to explore the full range of its adaptive topography. This role of random genetic drift has been particularly emphasized by Wright (1977 and earlier) in his proposed shifting balance theory of evolution. Additional discussion of the theory is found in this chapter's section on interdemic selection.

5.4 MUTATION-SELECTION BALANCE

You may recall from Chapter 4 that outcrossing species typically contain a large amount of hidden genetic variability in the form of recessive, or nearly recessive, harmful alleles, each present at a low frequency. Now we can explain why harmful alleles are not completely eliminated. Selection cannot eliminate them because they are continually created anew through recurrent mutation. To be specific, suppose that a is a harmful allele of the wildtype A and that mutation of A to a takes place at the rate μ per generation. Because the allele frequency of a, which we call q, remains small, reverse mutation of a to A can safely be ignored. The calculation of p' carried out to obtain Equation 5.10 is still valid, except that a proportion μ of A alleles mutate to a in each generation. Therefore,

$$p' = \frac{(p^2 w_{11} + pq w_{12})}{\bar{w}}(1 - \mu) \qquad [5.14]$$

To proceed further, it is convenient to write the relative fitnesses as

$$w_{11} = 1 \qquad w_{12} = 1 - hs \qquad w_{22} = 1 - s$$

The value of s is the selection coefficient against the homozygous aa genotypes and h is the **degree of dominance** of the a allele. If $h = 0$, then a is a complete recessive because AA and Aa have an identical fitness. If $h = 1$, then a is dominant because Aa and aa have an identical fitness. Semidominance means that $h = \frac{1}{2}$, and in this case the allele affects are additive. In mutation-selection balance, we are concerned with harmful alleles that are near the recessive end of the spectrum, and so h will usually be substantially smaller than 0.5.

Equilibrium Allele Frequencies

When selection is balanced by recurrent mutation, there is a globally stable equilibrium at an allele frequency of $\hat{p}$, which is the value of p in Equation 5.14 for which $p' = p$. The equilibrium frequency of the harmful a allele is therefore $\hat{q} = 1 - \hat{p}$. There are two important cases:

- When the harmful allele is a complete recessive ($h = 0$), then

$$\hat{q} \approx \sqrt{\frac{\mu}{s}} \tag{5.15}$$

- When the harmful allele shows partial dominance ($h > 0$), then, to an excellent approximation for realistic values of μ, h, and s,

$$\hat{q} \approx \frac{\mu}{hs} \tag{5.16}$$

Use of these equations is exemplified by Huntington disease in human beings. This severe inherited disorder is characterized by a degeneration of the neuromuscular system that typically appears after age 35. Although the disease itself results from a dominant mutation, the effects on fitness show only partial dominance owing to the late age of onset of the disease. Relative to a value of $w_{11} = 1$ for the homozygous nonmutant genotype, the fitness of the heterozygous genotype has been estimated as $w_{12} = 0.81$ (Reed and Neel 1959). Homozygous mutant genotypes also have the disease, but they are so rare that the equilibrium frequency of the mutant allele is determined by the fitness of the heterozygote. Equation 5.16 with $hs = 0.19$ is appropriate in this example. If we knew either μ or $\hat{q}$, we could estimate the other. In a Michigan population, $q = 5 \times 10^{-5}$ for the Huntington allele (Reed and Neel 1959). Assuming that the population is in equilibrium, we can estimate μ from Equation 5.16 as $\mu = 5 \times 10^{-5} \times 0.19 = 9.5 \times 10^{-6}$. This use of Equation 5.16 illustrates one of the common indirect methods for the estimation of mutation rates in human beings.

The degree of dominance of a harmful allele is a primary factor in determining its equilibrium frequency. Harmful alleles held in mutation-selection balance are rare. Thus the great majority of harmful alleles are present in heterozygous genotypes. Because there are so many heterozygous genotypes, relative to homozygous mutant genotypes, even a small reduction in fitness in the heterozygote has a large effect in decreasing the equilibrium allele frequency. The wavy equals signs in the expressions for the equilibrium under mutation-selection balance actually indicate approximations. These approximations fail near the boundary where $h \approx 0$. In this case we can do a little more algebra to obtain the full solution to the internal equilibrium for one-locus mutation-selection balance:

$$\hat{q} = \frac{\sqrt{(h^2\mu^2 + 2h^2\mu + h^2)s^2 + (4 - 8h)\mu s + (\mu + 1)hs}}{(4h - 2)s}$$

The terms in μ^2 will likely be small enough to ignore, but this expression permits one to consider the region where $h \approx 0$. Figure 5.8 shows the relation between the equilibrium allele frequency and the degree of dominance h for mutations that are homozygous lethal ($s = 1$). Notice how even a small degree of dominance can cause a large reduction in equilibrium frequency. In

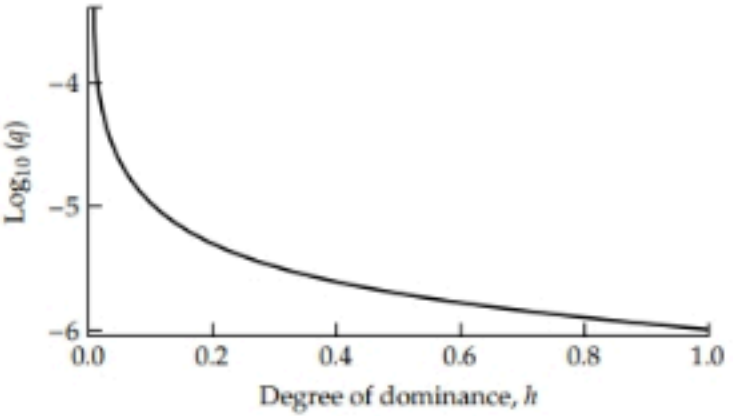


FIGURE 5.8 Allele frequencies maintained at equilibrium by mutation-selection balance as a function of the dominance of the newly arising homozygous-lethal mutations. (From Clark 1998.)

general, for realistic values of μ, s, and h, the value of $\hat{q}$ is typically less than 0.01. Therefore, although mutation-selection balance can account for low-frequency deleterious alleles, it cannot readily account for a harmful allele with a frequency greater than 0.01.

PROBLEM 5.8 To confirm for yourself that a small amount of dominance can have a major effect in reducing the equilibrium frequency of a harmful allele, imagine an allele that is lethal when homozygous ($s = 1$) in a population of *Drosophila*. Suppose that the allele is maintained by mutation-selection balance with $\mu = 5 \times 10^{-6}$. Calculate the equilibrium frequency of the allele for a complete recessive and for partial dominant when $h = 0.025$.

ANSWER For a complete recessive, $\hat{q} = \sqrt{\mu/s} = \sqrt{(5 \times 10^{-6})} = 2.24 \times 10^{-3}$. For partial dominance, $\hat{q} = \mu/hs = (5 \times 10^{-6})/0.025 = 2.00 \times 10^{-4}$. With partial dominance, the equilibrium allele frequency is reduced more than tenfold, and the frequency of homozygous recessive genotypes at equilibrium is reduced more than a hundredfold. It is of interest that $h = 0.025$ is near the average degree of dominance estimated for "recessive" lethals in *Drosophila* (Simmons and Crow 1977).

The Haldane-Muller Principle

The Haldane-Muller principle, named after the geneticists J. B. S. Haldane (1892–1964) and H. J. Muller (1890–1967), deals with the effect of mutation-selection balance on the average fitness of a population. Ignoring recurrent mutation, selection would be able to rid a population completely of a harmful allele, in which case $\hat{q} = 0$ and $\overline{w} = 1$. Because of recurrent mutation, the equilibrium allele frequency is greater than 0. When $h = 0$, the average fitness in the population at equilibrium equals $1 - \hat{q}^2 s = 1 - (\mu/s)s = 1 - \mu$. The reduction in average fitness due to mutation therefore equals $1 - (1 - \mu) = \mu$, which is called the **mutation load**. When a is partially dominant, the muta-

tion load is approximately 2μ because the average fitness at equilibrium is $1 - 2\hat{p}\hat{q}hs - \hat{q}^2 s = 1 - 2\mu$. This result is obtained by ignoring terms in $\hat{q}^2$ because they are so small. With or without partial dominance, therefore, the effect of recurrent mutation in reducing the average fitness in the population is independent of how harmful the mutation is. That the effect of recurrent mutation on average population fitness depends only on the mutation rate is the **Haldane-Muller principle**. The implication is that the harmful effect of an increase in the mutation rate is the same irrespective of whether the mutations produced are mildly detrimental or severely harmful. The effects of severe and mild mutations balance out because a more harmful mutation comes to a lower equilibrium frequency.

5.5 MORE COMPLEX TYPES OF SELECTION

Most mutations affect more than one phenotypic attribute of the organism, and so the two-allele model of viability is a simplification that ignores the complications of multiple, or *pleiotropic*, effects of mutations. Such pleiotropic effects may be easy for an experimentalist to miss. For example, a gene affecting embryonic growth rate may also affect age at first reproduction. When the pleiotropic effects act in opposing directions (for example, increasing viability but reducing fertility), the net effect on fitness may be quite small. As a result, mutations with offsetting effects on different components of fitness may remain segregating in a population for many generations.

Additional complications arise because fitness is determined by many genes that interact with each other. Simple models of selection are valid only when the alleles interact in such a way that their effects on fitness are additive or multiplicative across genes. Other complications result when the fitnesses of the genotypes are not constant but variable in time or space. In this section we briefly examine a sample of more complex models. Many of the models are of interest because they can maintain genetic polymorphisms. Although the list is extensive, it is by no means complete. An active area in population genetics research is the determination of means by which natural selection can maintain variation in populations, and this invariably means embracing the complexity of pleiotropic effects on multiple components of fitness imposed by genetic variation.

Differential Selection in the Sexes

Some genes may have different effects in the two sexes. If the fitnesses of genotypes differ between the sexes, then genotypes that are disfavored in one sex may be favored in the other. The offsetting effects increase the opportunity for a balanced polymorphism. The survivorship model of selection can be extended to include this case by supposing that the relative viabilities of the genotypes AA, Aa, and aa are given by w_{11}, w_{12}, and w_{22} in females and by v_{11}, v_{12}, and v_{22} in males. One of the w's and one of the v's

can be set arbitrarily to 1, which leaves four fitness parameters rather than two. A more serious complication is that the allele frequencies in gametes are no longer the same in males and females. If we let p_f and p_m be the allele frequency of A in female and male gametes, respectively, then the genotype frequencies of AA, Aa, and aa in the zygotes are $p_f p_m$, $p_f q_m + q_f p_m$, and $q_f q_m$, respectively, where $q_f = 1 - p_f$ and $q_m = 1 - p_m$. One of the consequences of differential selection in the sexes is that, with an appropriate choice of fitnesses, it is possible to have more than one stable polymorphic equilibrium. A stable equilibrium is also possible with heterozygote inferiority in one sex or with incomplete dominance when selection works in opposite directions in the two sexes.

X-Linked Genes

Genes located in the X chromosome can have the same sort of complications as differential selection in the sexes, but the possibilities for polymorphism are not quite so numerous because there are only three fitness parameters instead of four. If A and a are alleles of an X-linked gene, then there are three genotypes in females (AA, Aa, and aa) and two genotypes in males (either A or a along with the Y chromosome). One fitness parameter in each sex can be set arbitrarily to 1, leaving three free parameters. As with differential selection in the sexes, the allele frequencies differ in eggs and sperm. However, in any generation, the frequency of A in male zygotes equals the frequency of A in female gametes of the preceding generation. If you do not understand why, think about the parental origin of the X chromosome in a male.

Frequency-Dependent Selection

Frequency-dependent selection takes place when fitness is a function of either allele frequencies or genotype frequencies. There is no restriction on the type of frequency dependence except that each Darwinian fitness must be nonnegative. A simple example that illustrates frequency dependence is one in which the fitness of each genotype decreases in proportion to its frequency with a constant of proportionality equal to c:

$$AA : w_{11} = 1 - cp^2 \qquad Aa : w_{12} = 1 - 2cpq \qquad aa : w_{22} = 1 - cq^2$$

In this example, $\Delta p = cpq(q - p)(p^2 - pq + q^2)/\overline{w}$, and so there are equilibria at $p = 0$, $\frac{1}{2}$, and 1. (The factor $p^2 - pq + q^2$ does not have a root for p in the range [0, 1].) A curious feature of this type of frequency-dependent selection is that, at equilibrium, w_{12} is smaller than either w_{11} or w_{22}, so there is heterozygote inferiority; yet $p = \frac{1}{2}$ is a globally stable equilibrium and $\overline{w}$ is a maximum at this equilibrium. The peculiarities of this example are illustrative of frequency-dependent selection in general. Because the fitnesses can be any functions of allele or genotype frequency, nearly anything can happen.

Density-Dependent Selection

Density-dependent selection means that the fitnesses are functions of the population size. Models of density-dependent selection must explicitly include population size and population growth. The classic model of logistic growth says that the population grows initially at an exponential rate, but as the population size approaches the carrying capacity of the environment, K, then the rate slows down as $(K - N)/K$. This produces the differential equation $dN/dt = rN(K - N)/K$. With two haploid genotypes whose numbers at time t are A_t and B_t, the equation for logistic growth becomes:

$$\frac{dA_t}{dt} = r_1 A_t \left(\frac{K_1 - [A_t + B_t]}{K_1} \right) \qquad \frac{dB_t}{dt} = r_2 B_t \left(\frac{K_2 - [A_t + B_t]}{K_2} \right)$$

Each genotype has its own intrinsic rate of increase (r_1 or r_2) and its own carrying capacity (K_1 or K_2), but they affect each other's growth through the total population size ($A_t + B_t$). At any time, the outcome of selection depends on the total population size. When the population size is much smaller then either K_1 or K_2, then the right-hand factor in each growth equation equals approximately 1, and so the selection is determined by the relative values of r_1 and r_2. When the population size becomes approximately equal to the smaller of K_1 or K_2, then the genotype with the smaller carrying capacity stops growing while the other continues, and so the selection is determined by the relative values of K_1 and K_2. Interesting events happen when the selection for r favors one genotype and the selection for K favors the other, especially in situations in which stochastic factors also affect population size or there is a time lag between population size and its affect on growth rate. For further information on these types of models, see Roughgarden (1979), May (1981), Bulmer (1994), and Cohen (1995).

Fecundity Selection

In **fecundity selection**, differences in fitness between the genotypes result from the differing abilities of mating pairs to produce offspring. Because both genotypes in a mating pair contribute to the total number of offspring, the number of fitness parameters potentially equals the number of distinct kinds of mating pairs. For two alleles of one gene, there are nine possible types of mating because reciprocal matings may differ in the expected number of offspring; for example, the expected number of offspring from the mating *Aa* females × *aa* males may differ from that from the mating *Aa* males × *aa* females. The presence of so many fitness parameters complicates the mathematical analysis. An analysis of selection based on individual genotypes, analogous to viability differences, is not possible unless the overall fecundity of any mating pair can be written as either the product or the sum of two parameters, one for each genotype in the mating pair. When this strong sim-

plification does not hold, models of selection with fertility differences become rather complex (Ewens, 1979; Clark and Feldman 1986). Models in which differences in fecundity are combined with differences in survivorship can retain genetic polymorphisms even if there is directional selection in one or the other component of fitness.

Age-Structured Populations

Age-structured populations with overlapping generations present problems even more formidable than those caused by fecundity and survivorship differences in populations with discrete, nonoverlapping generations. In each short interval of time, a new cohort of newborns comes into existence and, as it ages, the fate of each organism in the cohort is governed by the functions l_x, which is the probability of survival from birth to age x, and b_x, which is the probability that an organism of age x (actually in the infinitesimal age interval x to $x + dx$) reproduces. If the functions l_x and b_x maintain the same form over time, then it can be shown that the population eventually reaches a stable age distribution in which the number of organisms in each age group increases or decreases at a constant rate. At the stable age distribution, the overall growth rate of the population is the value of m that satisfies the equation:

$$1 = \int_0^\infty e^{-mx} l_x b_x dx$$

(See Crow and Kimura, 1970, for a derivation.) For this value of m, $dN/dt = mN$, where N is the total population size. In an age-structured population, m corresponds to the intrinsic rate of increase for an exponentially growing population.

So far so good, but genetics complicates this situation enormously. If the l_x and b_x functions differ for different genotypes, then the allele frequencies change through time. As the allele frequencies change, so does the age structure, and the genotype frequencies in each age class may be different. The result is that the age structure may not become stable until selection reaches some equilibrium (possibly fixation). The sorts of complexities that can arise have been examined by Charlesworth (1980).

Heterogeneous Environments and Clines

Heterogeneous environments refer to models in which the relative fitnesses change according to the environment. The environmental heterogeneity may be spatial or temporal or both. Selection of this type can maintain polymorphisms in the absence of overdominance. If each homozygous genotype is favored in a different subset of environments, then there can be **marginal overdominance**, in which the heterozygous genotype has the highest fitness when averaged across all the environments, even though it is not the most fit genotype in any particular environment.

In some cases, the relative fitnesses of the genotypes vary geographically across a more or less smooth environmental gradient, for example, according to latitude, altitude, aridity, or salinity. If sufficiently stable in time, a gradient of selection across a region can result in a gradient of allele frequency across the region. A geographical trend in an allele frequency is called a **cline**. An unusually extreme example of a cline is found in the *hemoglobin-I^1* allele in the eelpout fish *Zoarces viviparus*, the allele frequency of which drops from a value of nearly 1 in the North Sea to a value of nearly 0 in the Baltic Sea (Christiansen and Frydenberg 1974). In human aboriginal populations, there is a cline of increasing frequency of the allele I^B in the ABO blood groups from Southwest to Northeast Europe.

Although clines can result from selection—for example, when one genotype is favored at one extreme of the environmental gradient but disfavored at the other extreme—clines can also result from other processes. Migration is one possibility: Differences in allele frequency in local populations at the extremes of the range may result from chance processes (for example, different founding populations), and migration of organisms from the extremes into the intermediate zone produces the cline.

The strongest evidence that a cline results from selection is when a cline is reproduced in different locations along a similar environmental gradient. A example of parallel clines played out on a grand scale is found in the electrophoretic polymorphism of alcohol dehydrogenase (the *Adh* gene) in *D. melanogaster*. In Eastern North America, the frequency of the Adh^F allele increases as one goes north, whereas DNA polymorphisms flanking *Adh* show no such geographic trend (Berry and Kreitman 1993). The cline is shown in the upper part of Figure 5.9. The frequency of Adh^F is correlated with cooler temperatures and less rainfall in the more northern latitudes. In Australia, as shown in the lower part of Figure 5.9, the frequency of the Adh^F allele increases as one goes south (Oakeshott et al. 1982). This pattern is in apparent contradiction to that in Eastern North America but, because Australia is in the Southern Hemisphere, the clines are actually parallel. Both show an increase in the frequency of Adh^F as one proceeds from the equator toward the polar cap—the North Pole in the Northern Hemisphere and the South Pole in the Southern Hemisphere. On a much smaller geographical scale, in mountainous regions, the frequency of the Adh^F allele shows a clinal increase with altitude, which is again correlated with cooler temperature and less rainfall.

An interesting angle on the physiological basis for this cline was recently suggested (Montooth et al. 2006). It appears that ethanol toxicity is in part mediated by changes in membrane fluidity, and that the sensitivity to the changes in membrane fluidity are highly temperature- and *Adh*-genotype-dependent. Further suggestion that the cline is temperature driven comes from the amazing observation that the entire cline has shifted toward the poles over the last two decades in a manner consistent with the degree of global warming (Umina et al. 2005).

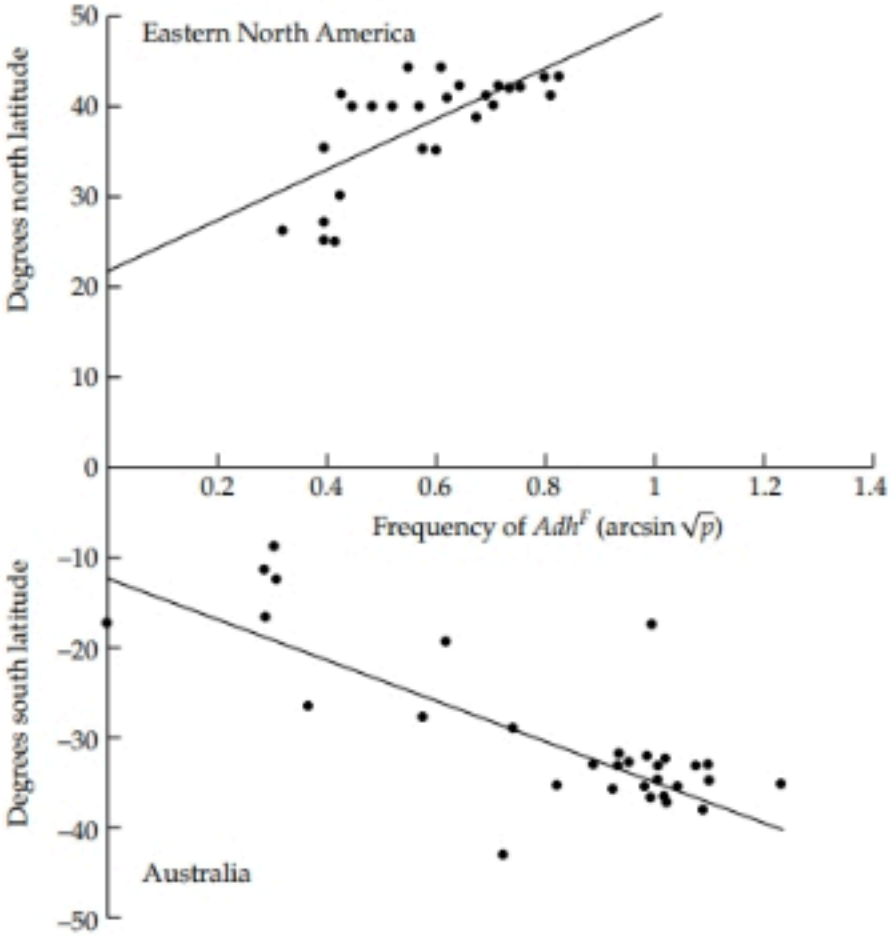


FIGURE 5.9 Parallel clines of the Adh^F (*alcohol dehydrogenase fast*) allele in Eastern North America and in Australia. The allele frequency is given as $\arcsin(\sqrt{p})$, where p is the allele frequency of Adh^F. The angular transformation stretches the scale near the extreme values of p: For values of $p = 0.1$, 0.5, and 0.9, the values of $\arcsin(\sqrt{p})$ are 0.322, 0.785, and 1.249, respectively, where the angles are measured in radians. The angular transformation is often used for proportions because it separates the variance of an estimate from the estimate itself: For a binomial proportion p based on n observations, the variance of p is $p(1-p)/n$, whereas the variance of $\arcsin(\sqrt{p})$, with the angle expressed in radians, is approximately $1/(4n)$. (North American data from Berry and Kreitman 1993; Australian data from Oakeshott et al. 1982.)

Diversifying Selection

The term **diversifying selection** refers narrowly to selection that favors extreme phenotypes. In a normal distribution of phenotypes, for example, diversifying selection means that organisms in the tails of the distribution are favored relative to those in the middle. More generally, diversifying selection refers to any type of selection in which genotypes are favored merely because they are different. Genes under diversifying selection tend to maintain a

relatively large number of alleles. Examples include genes of the major histocompatibility complex in mammals, in which the selective agent is thought to be through resistance to parasitic microorganisms (Satta et al. 1993) and bacterial genes that produce toxins (colicins) that kill other bacteria, in which the selective agent is the destruction of competitors (Riley 1993; Ayala et al., 1994; Wertz and Riley 2004).

Some plants have genes for gametophytic self-incompatibility, in which a pollen grain that carries any self-incompatibility allele is unable to pollinate a plant that carries the same allele. Self-incompatibility of this type implies that no plant can fertilize itself. Because a plant of genotype S_iS_j can produce only S_i and S_j pollen, the pollen cannot fertilize S_iS_j plants. Furthermore, homozygous genotypes are not normally found because their formation would require that S_i pollen fertilize an S_iS_j plant. It is easy to show that there is positive selection for new self-sterility alleles and that, at equilibrium, every allele has the same frequency. For n alleles, if S_i has frequency p_i, then the frequency of S_iS_j genotypes with random mating is $2p_i(1 - p_i)/(1 - \Sigma p_i^2)$. The denominator is necessary because of the absence of homozygous genotypes. The probability that an S_i pollen can be successful in fertilization is therefore the probability of genotypes other than S_iS_j, which equals $1 - 2p_i(1 - p_i)/(1 - \Sigma p_i^2)$. At equilibrium, we must have $p_i(1 - p_i) = p_j(1 - p_j)$. From these expressions follow some important conclusions summarized in Problem 5.9. For more information on gametophytic self-incompatibility systems, see Ioerger et al. (1991) and Uyenoyama (1995). The loss of self-incompatibility is an especially interesting problem, and analysis of the *SI* loci in *Arabidopsis thaliana* (which mostly self-pollinates) and its outcrossing relatives has identified three major haplotypes of *SRK*, suggesting either more than one loss of selfing or ancient recombination (Bechsgaard et al. 2006).

PROBLEM 5.9 Show that $p_i(1 - p_i) = p_j(1 - p_j)$ for all i and j implies that $p_i = p_j = 1/n$, where n is the number of self-incompatible alleles and $n \geq 3$. Use these equilibrium allele frequencies to show that the probability that a pollen grain lands on a compatible style equals $(n - 2)/n$. Finally, show that the probability of successful fertilization by a new mutant S allele, relative to that of any preexisting allele, equals $n/(n - 2)$.

ANSWER $p_i(1 - p_i) = p_j(1 - p_j)$ implies that $p_i - p_j = p_i^2 - p_j^2 = (p_i - p_j)(p_i + p_j)$ so that either $p_i = p_j$ for all i and j or $p_i + p_j = 0$. Because $n \geq 3$, $(p_i + p_j) \neq 1$. Because there are n alleles, we must have $\Sigma p_i = 1$, and so $p_i = 1/n$. The probability of a pollen grain landing on a compatible style is $1 - 2p_i(1 - p_i)/(1 - \Sigma p_i^2) = 1 - 2/n = (n - 2)/n$. A pollen grain containing a newly arising S allele will always land on a compatible style, and so its probability of fertilization, relative to that of a preexisting allele, equals $1/[(n - 2)/n] = n/(n - 2)$. In effect, this is the relative fitness of a new mutation. For $n = 3$, 4, 5, 10, 50, and 100, it equals 3, 2, 1.67, 1.25, 1.04, and 1.02, respectively.

Gametic Selection

Many plants go through a life cycle in which both haploid products of meiosis and the diploid products of fertilization are exposed to selection. In mosses and vascular plants, for example, a diploid organism (the *sporophyte*) produces spores, each of which germinates to form a haploid organism (the *gametophyte*) that reproduces asexually by mitosis. The gametophytes give rise to haploid male and female gametes, which undergo fertilization creating a new diploid generation. In mosses, the prominent stage of the life cycle is the gametophyte, whereas in higher plants, the prominent stage is the sporophyte.

When the haploid phase of the life cycle is exposed to selection, the selection is called **gametic selection**. As a concrete model, suppose that the relative survivorships of A and a gametophytes (the haploid phase) are given by v_1 and v_2, respectively. In the sporophytes (the diploid phase), the survivorships can be written as before as w_{11}, w_{12}, and w_{22}. If p and q are the allele frequencies of A and a at the beginning of the haploid phase, then after the differential haploid mortality has taken place, the frequencies will be $p^* = pv_1/\bar{v}$ and $q^* = qv_2/\bar{v}$, where $\bar{v} = pv_1 + qv_2$. With random fertilization among the gametes, the diploid genotypes AA, Aa, and aa are formed in the proportions p^{*2}, $2p^*q^*$, and q^{*2}, and these survive in the relative proportions w_{11}, w_{12}, and w_{22}. You may verify for yourself that, at the beginning of the haploid phase of the next generation, the allele frequency of A is

$$p' = \frac{p^2 w_{11} v_1^2 + pq w_{12} v_1 v_2}{p^2 w_{11} v_1^2 + 2pq w_{12} v_1 v_2 + q^2 w_{22} v_2^2}$$

This equation has the same form as the equation for p' in Equation 5.10 except that w_{11} is replaced with $w_{11}v_1^2$, w_{12} with $w_{12}v_1v_2$, and w_{22} with $w_{22}v_2^2$. The conditions for fixation or for a stable or unstable equilibrium are therefore determined by the relative magnitude of the composite "fitness" of the heterozygous genotype relative to those of the homozygous genotypes.

Meiotic Drive

A situation analogous to, but distinct from, gametic selection takes place when there is non-Mendelian segregation in the heterozygous genotype. In females, unequal recovery of reciprocal products of meiosis can be caused by nonrandom segregation of homologous chromosomes to the functional egg nucleus, which is why non-Mendelian segregation is known generically as **meiotic drive**. In other cases, the unequal recovery is caused by a gene or genes that act to render gametes carrying the homologous chromosome nonfunctional. Examples include "sperm killers" such as *segregation distortion* in *Drosophila melanogaster* (Charlesworth and Hartl 1978) and the *t* alleles in the house mouse (Lewontin and Dunn 1960; Hammer and Silver 1993) as well as "spore killers" described in filamentous fungi (Raju 1994).

Because meiotic drive acts only in the heterozygous genotype, its effect is to alter the term pqw_{12} in Equation 5.10 for p'. This term comes from the expression $\frac{1}{2} \times 2pqw_{12}$ for the proportion of A-bearing gametes from surviving Aa genotypes, and the $\frac{1}{2}$ is the Mendelian segregation ratio. If the ratio of $A : a$ gametes from Aa heterozygotes is $k : 1 - k$ instead of $\frac{1}{2} : \frac{1}{2}$, then the expression for p' becomes

$$p' = \frac{p^2 w_{11} + 2kpqw_{12}}{\bar{w}} \tag{5.17}$$

where $\bar{w}$ is the average survivorship in the population defined in Equation 5.8. Since A is the driven allele, $k > \frac{1}{2}$. Equation 5.17 is illustrative of meiotic drive even though it requires that the non-Mendelian segregation affect both sexes equally, a case that is not generally found in practice. One implication of the equation is that, unless selection counteracts the meiotic drive, the driven allele goes to fixation (Figure 5.10). In particular, if the relative viabilities are equal, then $p' = p^2 + 2kpq$ and $\Delta p = pq(2k - 1)$, so that $p \to 1$ because $k > \frac{1}{2}$. In some examples of meiotic drive, including *segregation distortion* and the t alleles, the driven allele is lethal when homozygous (Hartl 1970). Assuming that the lethality is completely recessive, the survivorships are $w_{11} = 0$, $w_{12} = 1$, and $w_{22} = 1$. Equation 5.17 implies that $p' = 2kp/(1 + p)$ and so $\Delta p = p[(2k - 1) - p]/(1 + p)$. There is an interior equilibrium at $\hat{p} = 2k - 1$, which intuition suggests (correctly) is locally stable. It is also globally stable (see Figure 5.10). Note that $\hat{p}$ is between 0 and 1 for any value of k between $\frac{1}{2}$ and 1. The calculations for a recessive-lethal driven allele are a special case of the slightly more general model discussed in Problem 5.10.

PROBLEM 5.10 Suppose that the AA genotype has a survivorship given by $1 - s$ relative to a value of 1 for both Aa and aa genotypes. Use Equation 5.17 to show that $\Delta p = pq[(2k - 1) - ps]/(1 - p^2 s)$. Find $\hat{p}$ and define the conditions, in terms of k and s, for which $\hat{p}$ is between 0 and 1. Show also that the equilibrium is locally stable.

ANSWER Equation 5.17 implies that $p' = [p^2(1 - s) + 2kpq]/(1 - p^2 s)$. $\Delta p = p' - p$ simplifies to the formula given. Setting $\Delta p = 0$ yields equilibria at 0, 1, and $\hat{p} = (2k - 1)/s$. For $\hat{p} > 0$, we need $(2k - 1)/s > 0$, or $k > \frac{1}{2}$. For $\hat{p} < 1$, we need $(2k - 1)/s < 1$, or $k < (s + 1)/2$. Note that, as the selection against the A allele becomes smaller (s closer to 0), more values of k result in fixation of the unfavorable A allele and fewer result in an interior equilibrium. The stability of $\hat{p}$ can be deduced by evaluating the derivative of Δp. For this purpose, it is convenient to write Δp as $pqs(\hat{p} - p)/(1 - p^2 s)$. In taking the derivative, remember that any term containing $\hat{p} - p$ becomes 0 when $p = \hat{p}$, so these terms can be neglected. The derivative, evaluated at $\hat{p}$, equals $-\hat{p}\hat{q}\, s/(1 - \hat{p}^2 s)$, where $\hat{q} = 1 - \hat{p}$. The sign of this number must be negative, and so the equilibrium at $\hat{p}$, when it exists, is locally stable.

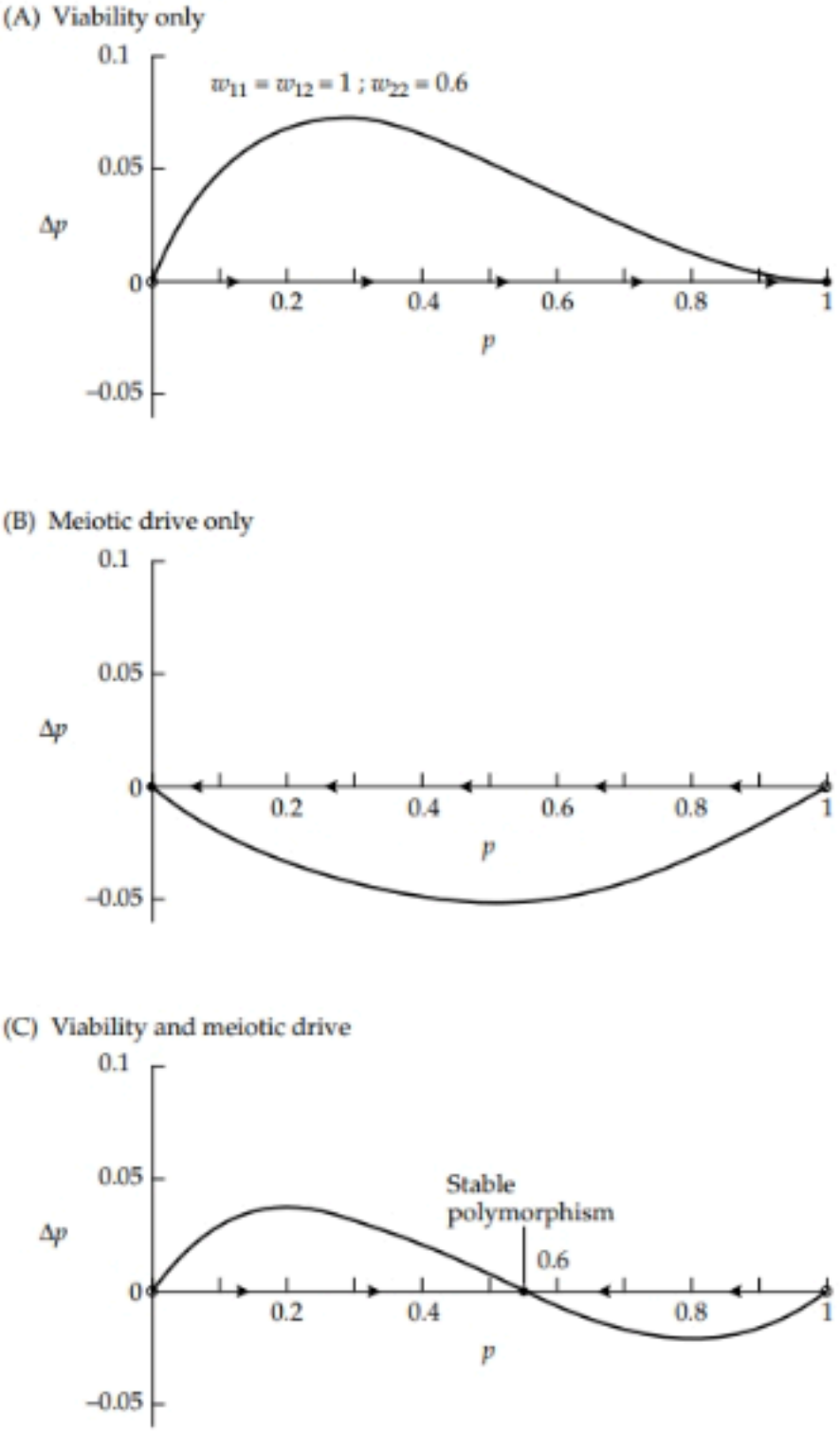


FIGURE 5.10 The balance between meiotic drive and viability selection. (A) Δp versus p for viability alone, when the fitnesses are $w_{11} = w_{12} = 1$ and $w_{22} = 0.6$. With these fitnesses, viability selection would eliminate the a allele. (B) Meiotic drive alone, where the heterozygous genotype Aa produces 40% A-bearing gametes and 60% a-bearing gametes. With meiotic drive alone, the A allele would be lost. (C) Δp versus p when both viability selection and meiotic drive are operating at the same time, using the same fitness and meiotic drive parameters as above. In this example, when both processes operate simultaneously, their offsetting effects create a stable polymorphism.

Multiple Loci and Gene Interaction: Epistasis

With multiple loci, as many types of gametes are possible as there are combinations of alleles. The simplest example is the two-locus, two-allele case, in which the possible gametes are AB, Ab, aB, and ab. In the absence of recombination ($r = 0$), each type of gamete can be regarded as an "allele" of one locus with four alleles. The principles of multiple-allele selection then apply, and some of the "alleles" may be eliminated by selection. The presence of recombination complicates matters because each gametic type is continually recreated by recombination even if it is disfavored by selection. The influence of recombination on the outcome of selection is determined by the recombination fraction and by the degree of interaction between the loci. When selection acts on the phenotype produced by the joint effects of multiple loci, there are two general situations:

- Changes in allele frequency are driven primarily by the selection coefficients and recombination plays a minor role.
- Selection and recombination are about equally important in determining the outcome.

The former is usually the case with weak epistasis and moderate or loose linkage; the latter is more prevalent with strong epistasis and tight linkage. The term **epistasis** is often used in population genetics as a synonym for gene interaction; it applies to any situation in which the genetic effects of different loci that contribute to a phenotypic trait are not additive. How much epistasis is there for fitness in real populations? Opinions vary widely on this point, but it seems that whenever a study is designed to be able to detect epistasis, it is not hard to find abundant examples of gene-gene interactions playing a role in fitness (Figure 5.11).

In the two-locus, two-allele example, the fitnesses (survivorships) of the genotypes can be written as shown in Table 5.3, where it is assumed that the

TABLE 5.3 Two-Locus Fitnesses

Genotype at *A* locus	Genotype at *B* locus: *BB*	*Bb*	*bb*	
AA	w_{11}	w_{12}	w_{13}	w_{AA}
Aa	w_{21}	$w_{22} = 1$	w_{23}	w_{Aa}
aa	w_{31}	w_{32}	w_{33}	w_{aa}
	w_{BB}	w_{Bb}	w_{bb}	

Note: The table assumes that the two types of double heterozygotes, AB/ab and Ab/aB, have the same fitness, w_{22}.

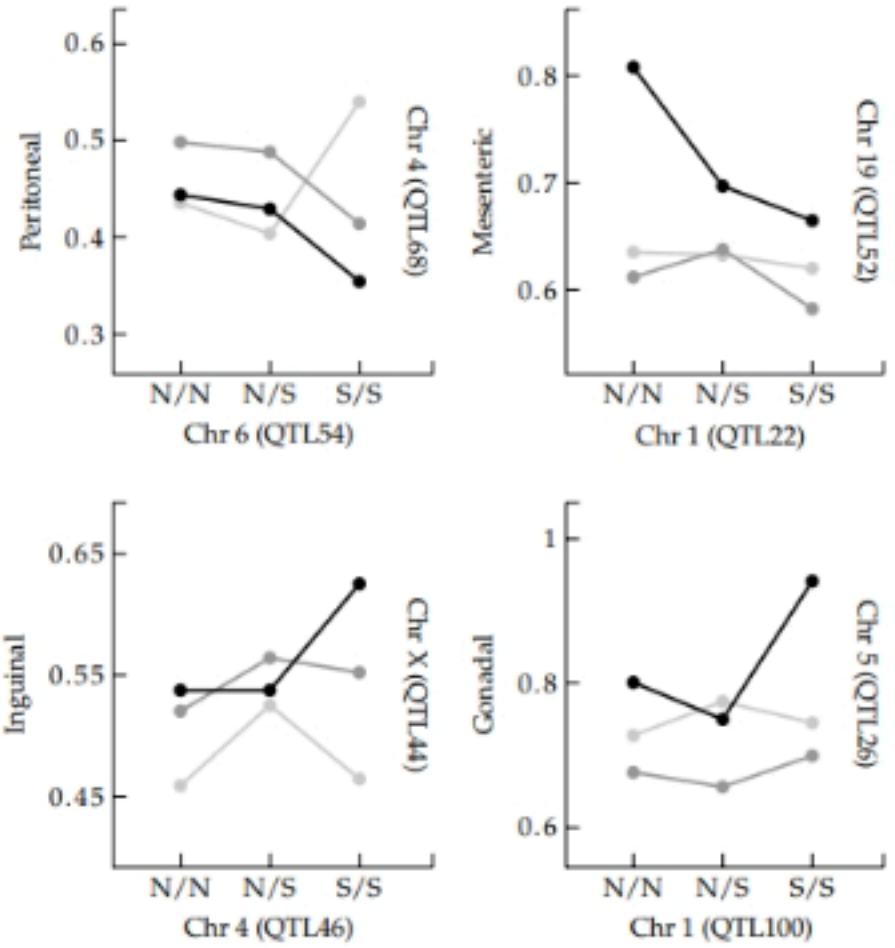


FIGURE 5.11 The mean phenotypes for the 9 genotypes as depicted in Table 5.3 for a series of mouse SNP-pairs. In this study, tests of epistatic interactions were done by measuring fat pad weights in mice from 513 F_2 progeny generated from the SM/J × NZB/BINJ inbred mouse strain cross. The fact that the line segments are not parallel is an indication of the nonadditivity (epistasis) of effects of each given SNP pair. Each QTL is designated according to its relative position along the chromosome. (From Stylianou et al. 2006.)

two types of double heterozygote (AB/ab and Ab/aB) have the same fitness; for convenience, this value is often set at $w_{22} = 1$. For each single-locus genotype, the average survivorship is equal to the weighted average across each genotype at the other locus. In Table 5.3, these averages are denoted w_{AA}, w_{Aa}, and so on. Additivity across loci means that $w_{11} = w_{AA} + w_{BB}$, $w_{12} = w_{AA} + w_{Bb}$, and so forth for all genotypes, including $w_{22} = w_{Aa} + w_{Bb} = 1$. If additivity does not apply across all nine genotypes, then epistasis is said to be present.

When there is strong epistasis and tight linkage, complications abound. With two loci and two alleles at each, there are as many as 15 equilibria. Most of them are unstable, but examples are known in which four interior equilibria are simultaneously stable. The average fitness in the population is not necessarily a maximum at equilibrium, and there are cases in which none of the four stable equilibria is a point of maximum average fitness. In addition, not only is average fitness not necessarily a maximum at equilibrium, natural selection can cause a decrease in average fitness. Despite all this odd behavior, extensive computer simulation and approximate solutions (Ewens 1979) show that if epistasis is not too strong, and linkage is not too tight, then the average fitness in the population usually increases.

Evolution of Recombination Rate

With constant fitnesses, the population can only maintain particularly favorable combinations of alleles when the rate of recombination is low. So long as it is possible to arrive at these favorable combinations, theory has shown that alleles at a modifier locus that controls the rate of recombination will usually be favored only if they reduce the recombination rate. Why then is recombination so prevalent? Many arguments have been raised, but the essential idea is that recombination can increase the efficacy of natural selection. The **Hill-Robertson effect** arises when favorable combinations of alleles are created more rapidly with increasing rates of recombination (so that recombination accelerates fixation of favorable alleles) and conversely, deleterious mutations arising on an otherwise favorable background have their elimination from the population retarded until recombination breaks them away from those favorable background alleles. This recombination can also accelerate the rate of elimination of deleterious alleles. The situation is more complicated when there is epistasis.

Regardless of the form of epistasis, recombination is advantageous when it allows for a more rapid generation of favorable recombinant gametes, as can happen when different individuals in a population carry different advantageous alleles. Recombination accelerates the process of adaptation by allowing these favorable alleles to recombine onto one gamete. But models for recombination modifiers show that genes that foster sex and recombination invade the population only if the rate of adaptive mutation is high. Recently Keightley and Otto (2006) showed that background selection against deleterious mutant alleles provides an advantage to sex and recombination that increases with population size. With low levels of recombination, selection at other loci severely reduces the effective population size and decreases genetic variance in fitness. Natural selection becomes less effective at ridding the population of deleterious alleles when the population size is small and recombination is rare (due to the Hill–Robertson effect). Recombination results in an increase in genetic variance in finite populations and this directly improves the response to selection. A substantial advantage occurs for sex and recombination that is surprisingly insensitive to the form of epistatic interactions between deleterious alleles.

Sexual Selection

It seems that, wherever one looks in nature, animals have physical adornments or behavioral displays to help them in obtaining mates. In some cases, there is direct competition between animals, usually males, as exemplified by the contests of antler clashing in moose or head butting in bighorn sheep. In other cases, there is indirect competition, as seen in the behavioral displays of male peacocks in full plumage strutting their stuff. These are dangerous activities. A bighorn sheep can get his skull fractured or fall off a cliff. The

male peacock is conspicuous, burdened, and preoccupied—vulnerable to any predator.

Darwin (1871) was the first to draw attention to competition for mates as a source of selection not necessarily related to adaptation of the organism to its environment. This type of selection he called **sexual selection**. In the case of direct competition for mates, it is easy to understand that a successful male leaves more progeny than an unsuccessful male, and so alleles promoting the physical adornments, strength, and aggressiveness needed for successful competition for mates are perpetuated even though they may occasionally be detrimental. The example of indirect competition is considerably more subtle because the male is merely advertising. The female does the choosing. One theory for the evolution of male sexual displays is that, in the early stages of their evolution, the displays take advantage of a female preference. The origin of the initial preference is unclear. Darwin suggested that female choosiness and offspring number are both associated with superior nutrition; hence choosy females may, at the beginning, have had more offspring. Whatever the cause, given an initial choosiness among females, males with more effective displays are chosen preferentially as mates, and their offspring receive alleles that create both the displays in the males and the preferences in the females. If these traits are genetically correlated—as, for example, through common hormonal or neurological pathways or through linkage disequilibrium—then selection becomes a self-accelerating process promoting increasingly elaborate displays and increasingly greater choosiness. According to Fisher (1930):

> The two characteristics affected by such a process, namely plumage development in the male, and sexual preference for such developments in the female, must thus advance together, and so long as the process is unchecked by severe counterselection, will advance with ever-increasing speed. In the total absence of such checks, it is easy to see that the speed of development will be proportional to the development already attained. There is thus, in any situation in which sexual selection is capable of conferring a great reproductive advantage, the potentiality of a runaway process which will, however small the beginnings from which it arose, must, unless checked, produce great effects, and in the later stages with great rapidity.

The ever-accelerating process is called **runaway sexual selection**, and the conditions under which it takes place have been studied theoretically (Lande and Arnold 1985; Kirkpatrick and Barton 1995; Iwasa and Pomiankowski 1995).

Because males can produce an excess of sperm and matings typically do not involve nearly as much investment in energy as for a female producing progeny, there arises a tension between the roles of selection optimizing male reproductive fitness and those optimizing female reproductive fitness. **Sexual conflict** is the name given to this topic; it is an area of active research (Chapman 2006). By rearing flies under conditions where they are forced to

be monogamous, there is relaxation of selection on male-male competitive ability, and the males become poorer at courting and at sperm competition (Rice and Holland 2005). Other experimental designs favor increased response to male-male competition by allowing males to evolve in the laboratory without their genes facing selection in females (Rice et al. 2006). The simplest experimental design for this purpose is to allow for selection to occur in a male lineage, such that recombination with female-passed genes does not occur, and females are drawn from outside the selected line in each generation. When this is done, the males become more aggressive, they outcompete nonselected males for matings, and their matings do more damage to females. In addition, when the alleles from such selected males are present in females, they have a negative effect on female fitness.

Kin Selection

One alternative type of selection, called **kin selection**, makes use of an extended concept of "fitness." In kin selection, a positive selection for certain alleles takes place indirectly through enhanced reproduction of the genetic relatives of carriers of the alleles rather than directly through an increased fitness of the carriers themselves. Kin selection has been postulated in attempts to account for the evolution of altruism. A behavior is regarded as altruism if it increases the fitness of other organisms at the expense of one's own fitness. Altruistic behavior is exhibited most dramatically by social insects such as termites, ants, and bees, in which certain worker castes exert their labors for the care, protection, and reproduction of the queen and her offspring but do not reproduce themselves.

A central consideration in kin selection is that relatives have genes in common. Therefore, a gene that causes altruistic behavior can increase in frequency if the increase in the recipient's fitness as a result of altruism is sufficiently large to offset the decrease in the altruist's own fitness. The essentials of the situation can be made clear by considering the case of identical twins. Because identical twins are genetically identical, the reproduction of one's twin is genetically equivalent to reproduction by oneself. Thus, it makes no difference if an altruistic organism decreases its own fitness for the sake of an equal increase in fitness of an identical twin; from an evolutionary point of view, it is an even trade because the combined number of offspring from both twins remains unchanged. By the same token, if an altruistic act decreases the fitness of an organism by an amount less than the increase gained by an identical twin, then the altruism results in a net increase in the combined number of offspring. One would, therefore, expect altruism between identical twins to be favored by natural selection as long as the risk to the altruist is no greater than the benefit to the recipient.

These considerations of identical twins can be extended to other degrees of relationship as well, but the risk to the altruist must be correspondingly smaller than the benefit to the recipient because other types of relatives share

fewer genes than identical twins. The break-even points for altruism toward various degrees of relationship have been wittily summarized by J. B. S. Haldane, who is said to have quipped that he would lay down his life for two brothers, four nephews, or eight cousins. In any case, fitness considerations that take into account not only an organism's own fitness but also the fitness of relatives (other than direct descendants) constitute what is called the **inclusive fitness** of the organism.

To be concrete, suppose that altruism results in a decrease in fitness c of the altruist that is offset by an increase in fitness b in the recipient. The gene for altruism increases in frequency if the ratio of cost to benefit is small enough, relative to the genetic relationship between the altruist and the recipient; that is, the gene for altruism increases in frequency if

$$\frac{c}{b} < r \tag{5.18}$$

as shown first by Hamilton (1964) and discussed in detail by Cavalli-Sforza and Feldman (1978) and Uyenoyama and Feldman (1980). In this context, r is a measure of genetic relationship between the altruist X and the recipient of the altruism Y, defined as

$$r = \frac{2F_{XY}}{(1+F_X)} \tag{5.19}$$

where F_X is the inbreeding coefficient of the altruist X, and F_{XY} is the inbreeding coefficient of a hypothetical offspring of X and Y. As illustrated in Figure 5.12, r equals the probability that two gametes from X and Y contain alleles that are identical by descent, F_{XY}, relative to the probability that two gametes from X contain alleles that are identical by descent, $(1 + F_X)/2$. The cost-

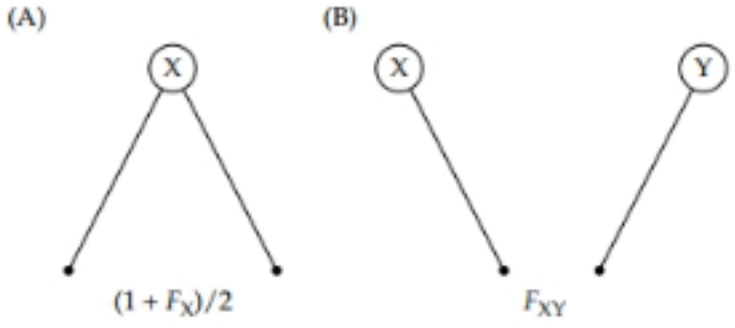


FIGURE 5.12 Definition of the genetic relationship between an altruist X and the recipient of the altruism Y. (A) Two alleles chosen at random from an organism X are identical by descent with probability $(1 + F_X)/2$. (B) Two alleles chosen at random, one from X and the other from Y, are identical by descent with probability F_{XY}, which is the inbreeding coefficient of a hypothetical offspring of X and Y. The ratio of F_{XY} to $(1 + F_X)/2$ is the appropriate measure of genetic relationship in the consideration of kin selection.

benefit tradeoff in Equation 5.19 is generally valid for weak selection when $F_X = 0$ and valid for additive alleles even when $F_X \neq 0$ (Aoki 1981).

5.6 INTERDEME SELECTION IN GEOGRAPHICALLY SUBDIVIDED POPULATIONS

When a population is composed of a set of semi-isolated subpopulations of the same species, then it is possible that the environments may differ across these subpopulations, giving rise to different pressures of natural selection upon allele frequencies. If subpopulations, or demes, composed of certain genotypes are more likely to become extinct and have their vacated habitats recolonized by migrants from other subpopulations composed of other genotypes, then the more successful subpopulations can, in some sense, be considered as having a greater "fitness" than the less successful ones. Since this concept of population fitness is a characteristic of the entire population and not merely the average fitness of the genotypes within it ($\overline{w}$), interdeme selection is outside the realm of most conventional models of selection.

Interdeme selection plays an essential role in the **shifting balance theory** of evolution of Wright (1977 and earlier). In the shifting balance theory, a large population that is subdivided into a set of small, semi-isolated subpopulations (demes) has the best chance for the subpopulations to explore the full range of the adaptive topography and to find the highest fitness peak on a convoluted adaptive surface. If the subpopulations are sufficiently small, and the migration rate between them is sufficiently small, then the subpopulations are susceptible to random genetic drift, which allows them to explore their adaptive topography more or less independently. In any subpopulation, random genetic drift can result in a temporary reduction in fitness that would be prevented by selection in a larger population, and so a subpopulation can pass through a "valley" of reduced fitness and possibly end up "climbing" a peak of fitness higher than the original. Any lucky subpopulation that reaches a higher adaptive peak on the fitness surface increases in size and sends out more migrants to nearby subpopulations, and the favorable gene combinations are gradually spread throughout the entire set of subpopulations by means of interdeme selection.

The shifting balance process includes three distinct phases:

1. An exploratory phase, in which random genetic drift plays an important role in allowing small subpopulations to explore their adaptive topography.
2. A phase of mass selection, in which favorable gene combinations created by chance in the random drift phase become rapidly incorporated into the genome of local subpopulations by the action of natural selection.
3. A phase of interdeme selection, in which the more successful demes increase in size and rate of migration; the excess migration shifts the

> allele frequencies of nearby subpopulations until they also come under the control of the higher fitness peak. The favorable genotypes thereby become spread throughout the entire population in an ever-widening distribution. Where the region of spread from two such centers overlaps, a new and still more favorable genotype may be formed and itself become a center for interdeme selection. In this manner, the whole of the adaptive topography can be explored, and there is a continual shifting of control from one adaptive peak to control by a superior one.

The shifting balance theory has played an important role in evolutionary thinking, in part because of its use of mountain-climbing terms as tropes for stages in the evolutionary progress: "exploration" of the adaptive topography, chance "discovery" of a route to a higher adaptive peak, and ultimately the "conquest" of the highest adaptive peak by the whole species. However, as a comprehensive theory of evolution, many aspects of the theory remain untested. For the theory to work as envisaged, the interactions between alleles must often result in complex adaptive topographies with many peaks and valleys. The population must be split up into smaller subpopulations, which must be small enough for random genetic drift to be important, but large enough for mass selection to fix favorable combinations of alleles. Although migration between demes is essential, neighboring demes must be sufficiently isolated for genetic differentiation to take place, but sufficiently connected for favorable gene combinations to spread. Because of uncertainty about the applicability of these assumptions, the shifting balance process remains a picturesque metaphor that is still largely untested. However, computer simulations have been carried out to investigate the range of magnitudes of the key parameters that are necessary for the shifting balance process to be effective; these parameters include the size of the subpopulations, the rate of migration and range of dispersal of the migrants, the degree of epistasis between genes, and the rate of recombination (Bergman et al. 1995). Some empirical studies have also explored the partitioning of genetic variance within and between groups for traits associated with fitness (Wade and Goodnight 1991).

One important implication of interdeme selection is that alleles that are harmful in themselves may nevertheless be favored because they are beneficial to the group. This principle is illustrated in the model in Table 5.4, where the allele A' is harmful to organisms within demes but favorable to the deme as a whole. Equation 5.11 implies that, within the ith deme, $\Delta q_i = -cq_i(1 - q_i)$ (assuming that $\overline{w} \approx 1$). Averaging across all of the subpopulations, the change in allele frequency resulting from selection within subpopulations, Δq_w, equals $-c\overline{q}(1 - \overline{q})(1 - F)$, where F is the fixation index F_{ST} discussed in Chapter 3. At the same time within-subpopulation selection takes place, interdeme selection favors demes containing A', and the change in allele frequency resulting from between-subpopulation selection, Δq_b, equals $2(b - c)\overline{q}(1 -$

TABLE 5.4 Model of Interdeme Selection

Genotype	AA	AA'	$A'A'$
Frequency in deme i	p_i^2	$2p_iq_i$	q_i^2
Within-population fitness	1	$1-c$	$1-2c$
Between-population fitness of deme i		$1+2(b-c)q_i$	

$\bar{q})F$, as shown by Crow and Aoki (1982). Putting the within-subpopulation and between-subpopulation selection together, the total change in the frequency of A' is

$$\Delta q = \Delta q_w + \Delta q_b = -c\bar{q}(1-\bar{q})(1-F)+2(b-c)\bar{q}(1-\bar{q})F \qquad (5.20)$$

The terms on the right-hand side can be interpreted by considering the extremes of $F = 0$ and $F = 1$. When $F = 0$, there is no population substructure, which means that all subpopulations have the same allele frequency $\bar{q}$; in this case, the change in allele frequency is just $-c\bar{q}(1-\bar{q})$. At the other extreme, when $F = 1$, each subpopulation is fixed for either A or A', and the proportion fixed for A' equals $\bar{q}$. The between-subpopulation selection is therefore analogous to selection between alleles in a haploid organism in which the fitnesses of A and A' demes are in the ratio $1 : 2(b-c)$. In this case, therefore, the change in allele frequency is $2(b-c)\bar{q}(1-\bar{q})$ (from Equation 5.11, assuming that $\bar{w} = 1$).

Equation 5.20 implies that $\Delta q > 0$ if

$$\frac{b-c}{c} > \frac{1-F}{2F} \qquad (5.21)$$

This is the condition necessary for selection between demes to override selection within demes, and the formulation is quite general (Crow and Aoki 1982). A biological interpretation of the inequality in Equation 5.21 can be inferred by comparison with the break-even point for kin selection given in Equations 5.18 and 5.19. Expressing Equation 5.21 in terms of $r = 2F/(1+F)$, which means that $F = r/(2-r)$, yields $c/b < r$; this condition is identical to Equation 5.18. In these models, the equivalence between kin selection and interdeme selection results from the shared remote ancestry of the members of each subpopulation caused by random genetic drift among the subpopulations. The members of each subpopulation are related by kinship, and so interdeme selection is the same phenomenon as kin selection; the break-even point is that at which the benefit b to one's kin through interdeme selection equals the cost to one's self c through direct selection against the A' allele.

5.7 SELECTION IN A FINITE POPULATION

In order to derive the dynamical behavior of alleles under selection, we have ignored lessons learned in previous chapters that populations are finite and that the sampling of alleles over generations can result in substantial allele frequency change. It is important to determine how the dynamics of alleles under selection changes when the population is no longer infinite, so that random drift intervenes as well. The model that we would like to explore couples together the standard model for natural selection with one locus and two alleles:

$$p' = \frac{p^2 w_{11} + pq w_{12}}{\bar{w}}$$

with the usual way that Fisher and Wright used to model random genetic drift, namely as a binomial sampling process:

$$p_{ij} = \binom{2N}{j}\left(\frac{i}{2N}\right)^j\left(\frac{2N-i}{2N}\right)^{2N-j}$$

where p_{ij} is the probability of transitioning from i copies to j copies of allele A the next generation, when the current frequency of allele A is $p = i/(2N)$. This is enough to specify the model for forward simulation on a computer, but Wright wanted solutions that were easy to interpret. Recall from Chapter 3 that the diffusion approximation allowed one to consider effects of random drift and other pressures on allele frequencies. Let the fitnesses be additive, also known as genic selection, such that $w_{11} = 2s$, $w_{12} = s$, and $w_{22} = 1$. Wright (1931) also considered the case of bidirectional mutation, with a rate from A to a of u and a mutation rate from a to A of v. With these assumptions, the stationary distribution of allele frequencies under mutation, genic selection, and random genetic drift is given by

$$\phi(x) = Ce^{4N_e s x} x^{4N_e v - 1}(1-x)^{4N_e u - 1} \tag{5.22}$$

where C is a constant to make the integral from $x = 0$ to $x = 1$ equal 1. Figure 5.13 shows graphically some of the resulting site frequency spectra that arise from this model, showing the conditions when there is much greater (or less) intermediacy of allele frequencies than expected under mutation-drift balance.

Weak Selection and the Nearly Neutral Theory

In a finite population with natural selection operating, the intuition is clear that for a very large population, the classical equations for natural selection will hold, but in a very small population, random drift can get quite strong and the picture is less clear. Another way to approach the problem is to let the population size be constant at some intermediate level and to consider what happens when the selection coefficient gets smaller and smaller. When

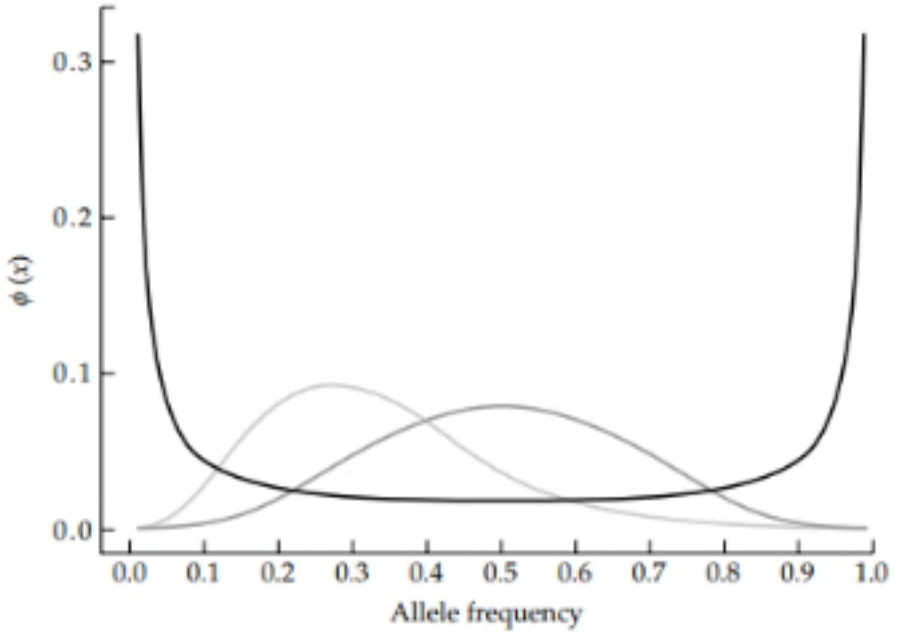


FIGURE 5.13 Site frequency spectra, $\phi(x)$, under a balance of selection, mutation and drift, following Wright's diffusion approximation (see Equation 5.22). The U-shaped solid curve has $4Nv = 4N\mu = 1$ and $4Ns = 0$, so that this represents a simple mutation-drift balance with most alleles being near fixation. The dark gray curve has $4Nv = 4N\mu = 4$ and $4Ns = 0$, so this case also lacks selection, but allele frequencies are intermediate because the population size is large enough that intermediate allele frequency is maintained just by mutation pressure. The light gray curve has $4Nv = 4N\mu = 4$ and $4Ns = -7$, and directional selection pushes the site frequency spectrum toward rarer frequencies.

the fitnesses of all genotypes are nearly equal, there is an interesting tension between selection and drift, and we call this situation **weak selection**. The study of weak selection took off when Tomoko Ohta first developed a theory for the fate of mutations with very small selection coefficients, which she called the *nearly neutral theory* (Ohta 1973). In this first paper, Ohta primarily focused on mutations that are "slightly deleterious" and ignored mutations that were "slightly advantageous." Later, when empirical evidence supported the idea that population also harbored slighted advantageous mutations as well, she modified the nearly neutral theory to include any mutations where $|2Ns| \approx 1$ (Ohta and Tachida 1990; Ohta 1992). Mutations that have this property of being nearly neutral (also called "weak selection") present an interesting challenge because for a large population size, natural selection can dominate their dynamics, but when the population size gets small, the mutations behave as if neutral.

One feature of the weak selection model that is particularly instructive is the probability of ultimate fixation of an allele. Following Kimura (1957), let

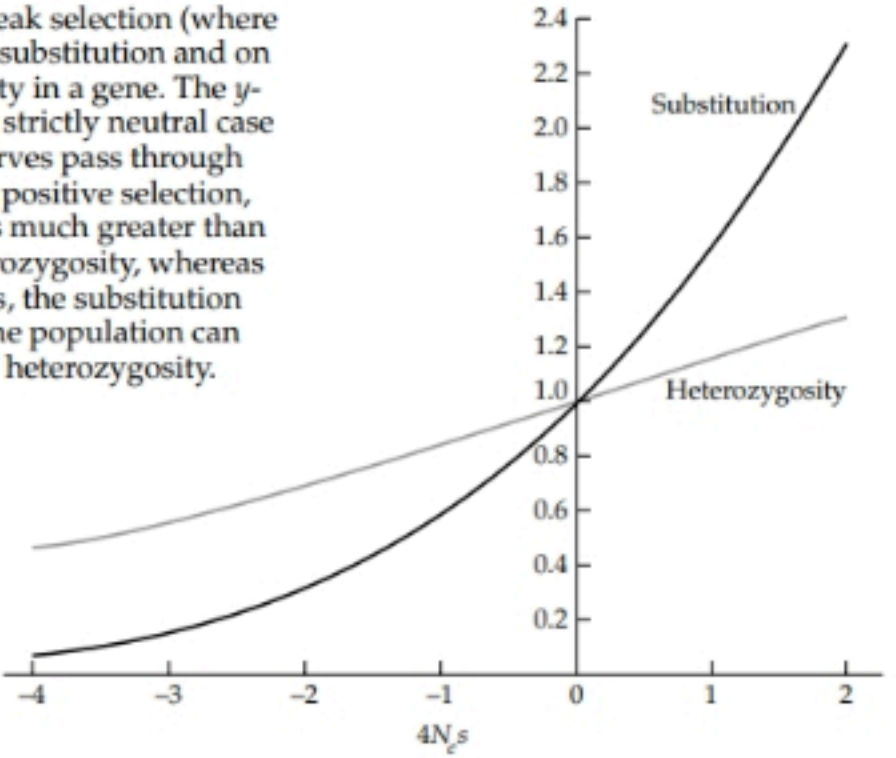


FIGURE 5.14 The effect of weak selection (where $-10 < 2N_e s < 10$) on the rates of substitution and on standing levels of heterozygosity in a gene. The y-axis is expressed relative to the strictly neutral case (so that when $2N_e s = 0$, both curves pass through 1.0 on the y-axis). Note that for positive selection, the effect on substitution rate is much greater than the impact of selection on heterozygosity, whereas when mutations are deleterious, the substitution rate falls nearly to zero while the population can still retain appreciable levels of heterozygosity.

$u(p)$ be the probability that a mutant allele whose frequency is currently p will ultimately be fixed in the population. If the fitnesses w_{11}, w_{12}, and w_{22} are replaced with $1+2s$, $1+s$ and 1, then Kimura (1957) showed that:

$$u(p) = \frac{1 - e^{-4Nsp}}{1 - e^{-4Ns}} \tag{5.23}$$

For a newly arisen mutation when $p = 1/(2N)$, Kimura found that the probability of ultimate fixation of allele A is:

$$\Pr(A \text{ fixed}) = u = \frac{2s}{(1 - e^{-4Ns})} \tag{5.24}$$

In the limit as s is reduced to zero (neutrality), the probability of fixation is $u = 1/(2N)$, as expected. Figure 5.14 plots Equation 5.24, and shows the relationship between the selection coefficient s to the probability of fixation with weak selection (scaled by the probability of fixation in the strictly neutral case).

This figure also shows the scaled heterozygosity in a population with weak selection. Without showing the derivation, this heterozygosity (scaled to the expected heterozygosity for a neutral allele integrated over generations until fixation) is:

$$\frac{H_t}{H_0} = \frac{2(4Ns - 1 + e^{-4Ns})}{4Ns(1 - e^{-4Ns})} \tag{5.25}$$

Figure 5.14 shows that weakly deleterious alleles ($s < 0$) can have substantial heterozygosities, despite the fact that their probability of fixation is quite low. The reason is that when they are rare, they are mostly in heterozygotes and selection against them is even weaker, so random drift predominates in their dynamics. Selection against deleterious alleles becomes more effective if the deleterious allele attains an intermediate frequency, and so the probability of fixation is very low.

Genetic "Draft"

Context can be of key importance in evolution, and this is certainly true for the fate of selected genes. When many mutations are undergoing selective fixation, they tend to drag flanking variation to fixation with them through a process of **genetic hitchhiking** (Maynard Smith and Haigh 1974). Selection of this sort results in a reduction in the genetic variation for a region surrounding each selected target. A fundamental question raised by John Gillespie (2000) was whether the frequency of such selective events served to dominate the dynamics of neutral variants over the effect of random genetic drift. In an earlier paper, Gillespie (1999) was bothered by the failure of the standard neutral theory to explain why levels of standing variation are so poorly predicted by population size. He reasoned that one possible explanation could be that there are sufficiently many selective sweeps that levels of variability may be dominated by selection at linked sites. Many empirical papers have shown that levels of genetic variation are lower in regions of reduced local recombination rate (Aguadé et al. 1989; Begun and Aquadro 1992), and this could be partly due to hitchhiking and selective sweeps, or it could also be due to the effect of selection on deleterious mutations, which reduces the local effective size (Charlesworth et al. 1993). At any rate, it appears that something decouples population size from levels of variation, and Gillespie's work shows the conditions under which natural selection would have this effect. He furthered showed that the rate of substitution of weakly selected advantageous mutations decreases with increasing population size, whereas that for deleterious mutations increases with population size. The conclusion one draws from this model of weak selective sweeps, which Gillespie has whimsically (and confusingly) called "genetic draft," is that population size and binomial sampling may not be as relevant to a species' evolution as was once thought!

It should be clear by now that even the classical problems of natural selection are far from being totally understood. The complex interplay of mutation, random drift, and selection present many unsolved problems to challenge and engage the imaginative student.

SUMMARY

1. Natural selection occurs when any genetic difference results in differential representation of alleles over generations.
2. In haploid organisms with constant fitnesses, we can write equations that specify the full trajectory of allele frequency changes. In these models, the fitness is equivalent to the malthusian growth parameter for each haploid clone.
3. In a diploid organism, even the simplest model of constant fitnesses does not allow a closed-form equation specifying allele frequencies at arbitrary future generations.
4. Instead, most models of natural selection have specified changes in allele and genotypic frequencies across discrete generations, and the models are represented as one-generation difference equations.
5. The equilibrium behavior is especially of interest and is often easily solved analytically. For one locus and two alleles, when the fitnesses of AA, Aa, and aa (w_{11}, w_{12} and w_{22}) are ordered $w_{11} > w_{12} > w_{22}$, then the A allele goes to fixation. With overdominance ($w_{12} > w_{11}$ and $w_{12} > w_{22}$), then there is a stable polymorphic equilibrium. With underdominance ($w_{12} < w_{11}$, $w_{12} < w_{22}$) then there is an unstable polymorphic equilibrium, and the population goes to one fixation state or the other depending on initial genotype frequencies.
6. Mutation-selection balance refers to the maintenance of a harmful allele in a population at a low equilibrium frequency, because in every generation the elimination of preexisting harmful alleles by selection is offset by the introduction of new harmful alleles by mutation.
7. For a completely recessive harmful allele a, where the fitness of aa is $1 - s$, the equilibrium allele frequency is $\hat{q} = \sqrt{\mu/s}$, where μ is the rate of mutation from A to a. For a partially dominant allele, where fitnesses of Aa and aa are $1 - hs$ and $1 - s$, and h is the degree of dominance, the equilibrium allele frequency is approximately $\hat{q} = \mu/hs$.
8. Many other aspects of the life cycle may impact the way that natural selection works in a population, including X-linkage, frequency-dependent selection, differential fecundities, density-dependent selection, and so on.
9. Differential selection across geographically separted demes results in variation in allele frequencies across subpopulations. The interplay of migration and selection in subdivided populations may create conditions in which random genetic drift can produce slightly deleterious combinations of alleles at frequencies high enough for a subpopulation to come under the control of a superior adaptive peak (Wright's shifting balance theory).
10. When selection coefficients are close to satisfying $2Ns = 1$, there is an interplay between selection and drift that produces complex patterns of variation.

PROBLEMS

1. Explain how the average fitness in a population, $\bar{w}$, can be increasing at the same time that the population is going extinct.
2. In many mammals, birds, insects, and other bisexual animal populations, males develop elaborate physical or behavioral features that are used in attracting females. These include large antlers in male moose and elk, and the male peacock's tail. The energy expended in such ornaments is thought to be rewarded by reproductive success in attracting "choosy" females. Explain how male ornamentation and female choosiness can result in the process of *runaway sexual selection*, which leads to extraordinary allocation of resources to the imperatives of sexual attractiveness in males and extraordinary reproductive restraint in females. What can counteract runaway sexual selection?
3. Consider a population of diploid organism with genotypes *AA*, *Aa*, and *aa* for some gene. Suppose that genotype *AA* is an embryonic lethal and that genotype *aa* is fully viable but completely sterile. What genotype frequencies would be found among adults in a population at equilibrium? Do these genotype frequencies require the assumption of random mating?
4. Suppose that in the *i*th generation of a haploid population the fitnesses of *A* and *a* are given by $s_i : 1$. Show that $p_n/q_n = (p_0/q_0)(s_0 s_1 s_2 \ldots s_{n-1})$. If this is written as $p_n/q_n = (p_0/q_0)s^n$, then how can s be interpreted?
5. If the fitnesses of *AA*, *Aa*, *aa* are 1.0, 0.9, 0.6, and $p_0 = 0.7$, calculate p_1, p_2, and p_3, the allele frequencies after 1, 2, and 3 generations of selection.
6. Calculate the equilibrium allele frequency with overdominance when the fitnesses of *AA*, *Aa*, and *aa* are, respectively:
   (a) 0.300, 1, 0.700.
   (b) 0.930, 1, 0.970.
   (c) 0.993, 1, 0.997.
7. Calculate $\bar{w}$ for $w_{11} = 0.9$, $w_{12} = 1$, $w_{22} = 0.6$, and $p = 0.8$, assuming random mating. Does any other p give a larger $\bar{w}$? Why or why not?
8. If a rare allele that is lethal when homozygous ($s = 1$) decreases in frequency by 1% each generation (i.e., $q' = 0.99q$), then what is the selection coefficient ($h = hs$) against heterozygotes? (Hint: Assume that q and qh are small compared to 1.)
9. If selection is not too intense, an additive gene yielding fitnesses $1 + s$, $1 + s/2$, and 1 in *AA*, *Aa*, and *aa* genotypes will increase in frequency approximately according to $\ln(p_t/q_t) = \ln(p_0/q_0) + (s/2)t$. Calculate the approximate number of generations required to evolve significant insecticide resistance in an insect population when $s = \frac{1}{2}$ and $p_0 = 10^{-5}$. Significant resistance in the population may be taken as $p_t = 10^{-1}$. Show that, when q_0 and q_1 are both close enough to 1 that $\ln(p_t/q_t) \approx \ln(p_t)$and $\ln(p_0/q_0) \approx \ln(p_0)$, then $t \approx (2/s)\ln(p_t/p_0)$.

10. Show that a random mating diploid population with fitnesses 1, $1-s$, and $(1-s)^2$ for AA, Aa, and aa gives the same change in the allele frequency p of A as a haploid population with fitnesses 1 and $1-s$ of A and a.

11. If selection is not too strong, the time required for the allele frequency of a favored dominant allele to change from p_0 to p_t is given approximately by

$$\ln(p_t/q_t) + (1/q_t) = [\ln(p_0/q_0) + (1/q_0)] + st$$

Use this equation to derive the analogous equation for a favored recessive.

12. The following equation has equilibria at $\hat{p} = 0$, $\frac{1}{2}$, and 1. Classify the equilibria as to stability. If there is a stable equilibrium, is it locally or globally stable?

$$\Delta p = p(\tfrac{1}{2} - p)(1-p)$$

13. Show that the allele frequency of a recessive lethal in generation n is given by $q_n = q_0/(1 + nq_0)$. (Hint: It is easiest to derive an expression first for $1/q_n$.) How many generations are required to reduce the allele frequency by half?

14. Consider a haploid organism in which genotypes A and a have frequencies p and q ($p + q = 1$) and relative fitnesses 1 and $1 - s$, respectively. Suppose that A mutates to a at a rate of μ per A allele per generation. Deduce the equilibrium frequency of a at the steady-state when there is a balance between mutation and selection.

15. The mutation rate to a dominant gene for neurofibromatosis is approximately 9×10^{-5} and the reproductive fitness of affected individuals is estimated as $\frac{1}{2}$. What is the expected equilibrium frequency of affected individuals at birth?

16. What is the equilibrium frequency of a recessive allele arising with a mutation rate of 4×10^{-6} and a reproductive fitness in homozygotes of 0.8? What would it be if the gene were partially dominant with $h = 0.05$?

17. What is the equilibrium frequency of a complete recessive allele arising with a mutation rate of 10^{-6} when the fitness in homozygous genotypes is 0.4? How much would the equilibrium frequency be reduced if the homozygous genotypes did not reproduce at all?

18. For a lethal allele maintained at an equilibrium frequency of $q = \mu/h$, where h is the selection coefficient against heterozygous genotypes, show that the proportion of heterozygous zygotes resulting from new mutations is approximately equal to h.

19. A polymorphism is said to be *protected* if all of the fixation states are unstable equilibria. Suppose the viabilities of males and females are as follows:

	AA	*Aa*	*aa*
Females	0.9	1	0.8
Males	1.0	v_{12}	0.5

What is the smallest value of v_{12} that ensures a protected polymorphism? (Hint: Some algebra shows that a condition for polymorphism is $w_{12}/w_{11} + v_{12}/v_{11} > 2$ and $w_{12}/w_{22} + v_{12}/v_{22} > 2$.)

20. If an allele a is a recessive lethal in zygotes and the relative fitness of A : a among gametes is $1 - s : 1$, then what is the equilibrium allele frequency of a? Hint: If an equilibrium exists in this situation, it satisfies

$$p' = \frac{p^2 w_{11} v_1^2 + pq w_{12} v_1 v_2}{p^2 w_{11} v_1^2 + 2pq w_{12} v_1 v_2 + q^2 w_{22} v_2^2} = p$$

21. In a *Drosophila* population cage containing a chromosome known as *segregation distorter* (*SD*) that exhibits meiotic drive, the segregation ratio in heterozygous genotypes was about $k = 0.75$. When the chromosomes in the population cage had reached approximate equilibrium, the relative frequencies of the *SD* and non-*SD* chromosomes were approximately 0.11 and 0.89. The SD chromosome is homozygous lethal in both sexes. In this case a balance between viability and meiotic drive is reached when $\hat{p} = (2kw_{12} - 1)/(2w_{12} - 1)$, where $\hat{p}$ is the equilibrium frequency of the *SD* chromosome. Use this equation to estimate the approximate value of w_{12} consistent with these data.

22. Consider a gene with multiple alleles in which each heterozygous genotype is superior to the homozygous genotypes for each of the alleles it contains. Explain why this condition is not sufficient to ensure that all of the alleles will be maintained in a balanced polymorphism.

23. For a random-mating population with genotype frequencies of AA, Aa, and aa equal to p^2, $2pq$, and q^2, respectively, suppose that frequency-dependent selection occurs in such a way that the relative fitnesses of AA, Aa, and aa are given by $w_{11} = c/p^2$, $w_{12} = c/pq$, and $w_{22} = c/q^2$, respectively, where c is a constant. Derive an expression for p' and explain in words what it means. Also explain why this model breaks down when $p = 0$ or $p = 1$.

24. Suppose that the relative viabilities of genotypes $A'A'$, $A'A$, and AA are 0.5, 1, and 0.7, respectively. If the initial frequency of allele A' is 0.05, what will its frequency be when the population reaches an equilibrium? Now suppose that a mutation occurs in the equilibrium population that introduces a novel allele A^*, such that the relative fitnesses of A^*A^*, A^*A', and A^*A are all equal to 0.8. Will the A^* allele increase in frequency in the population? Why or why not?

25. Suppose alleles A_1, A_2, A_3, and A_4 are additive in their effects on fitness and the fitnesses of the homozygous genotypes are 0.8 for A_1A_1, 0.6 for A_2A_2, 0.4 for A_3A_3, and 0.2 for A_4A_4. What are the fitnesses of the heterozygous genotypes? In a random mating population in which all of the alleles are equally frequent, what is the average fitness in the population?