Mutation, Selection & Drift

❖ mutation (infinite N, no selection)

$$p' = p(1-\mu) + (1-p)v$$

❖ single-locus selection (infinite N, no mutation)

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

❖ genetic drift (no selection, no mutation)

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

Mutation-Selection Balance

❖ recurrent mutation generally produces deleterious, recessive alleles - why?

❖ Δp with mutation

$$p' = \frac{p^2 w_{11} + pq w_{12}}{\overline{w}}(1-\mu)$$

❖ effectiveness of selection at eliminating detrimental mutations depends on relative dominance of alleles

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

Mutation-Selection Balance

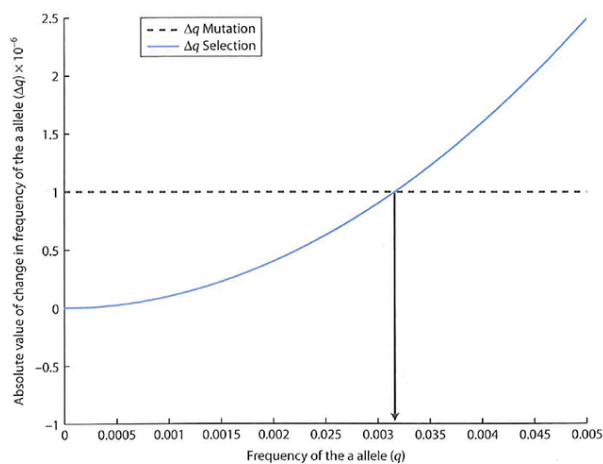❖ equilibrium allele frequency of mutant alleles is:

$$\hat{q} \approx \sqrt{\frac{\mu}{s}}, \text{ for } h = 0$$

$$\hat{q} \approx \frac{\mu}{hs}, \text{ for } h > 0$$

❖ e.g., Huntington's disease:

◇ typical onset at 35+ years

◇ $w_{11} = 1, w_{12} = 0.81$

◇ $q \sim 5 \times 10^{-5}$ (allele frequency in a Michigan population)

◇ thus, $\mu \sim 9.5 \times 10^{-6}$

Mutation-Selection Balance

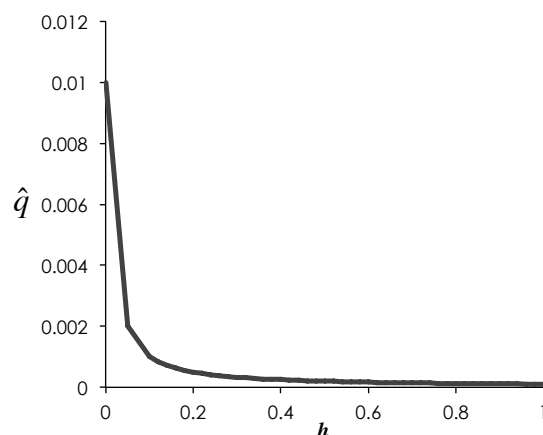$s = 0.1, h = 0,$
$\mu = 0.000001$

Figure 7.9 The absolute value of the change in allele frequency due to mutation ($\Delta q_{\text{mutation}}$) and due to natural selection ($\Delta q_{\text{selection}}$) when there is selection against a recessive homozygote. Mutation continually makes new copies of the recessive allele while selection continually works toward loss of the recessive allele. The equilibrium allele frequency occurs when the processes of mutation and selection exactly counteract each other. Here $s = 0.1$ and $\mu = 1 \times 10^{-6}$ so the expected equilibrium is $q_{\text{equilibrium}} = 0.0032$ as shown by the vertical arrow.

Mutation-Selection Balance

❖ even partial dominance for a deleterious mutation greatly reduces its equilibrium allele frequency

❖ $\mu = 0.00001$,

❖ $s = 0.01$

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

Haldane-Muller Principle

❖ the "mutational load", reduction in mean fitness due to recurrent mutation depends only on the mutation rate and not on the relative selective disadvantage of the mutations

❖ Why?

$$\text{for } h = 0, \ \overline{w} = 1 - \hat{q}^2 s = 1 - \frac{\mu}{s} s = 1 - \mu$$

$$\text{for } h > 0, \ \overline{w} = 1 - 2\hat{p}\hat{q}hs - q^2 s \approx 1 - 2\hat{p}\frac{\mu}{hs}hs \approx 1 - 2\mu$$

Mutation, Selection & Drift

❖ mutation (infinite N, no selection)

$$p' = p(1-\mu) + (1-p)v$$

❖ single-locus selection (infinite N, no mutation)

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

❖ genetic drift (no selection, no mutation)

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

Mutation, Selection & Drift

❖ combining mutation, selection & drift into a single model

◇ the diffusion approximation can be used to predict the equilibrium **distribution** of allele frequencies (Wright 1931)

$$\phi(x) = C e^{4N_e sx} x^{4N_e v - 1} (1-x)^{4N_e u - 1}$$

◇ where x is the frequency of allele A, s is the selection coefficient, u and v are mutation rates (A to a and a to A), and C is a constant set to make the integral 1

Mutation, Selection & Drift

Hartl & Clark

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

✧ where x is the frequency of allele A, s is the selection coefficient, μ and v are mutation rates (A to a and a to A), and C is a constant set to make the integral 1

Hamilton

$$\phi(p) = Cp^{4N_e u - 1} q^{4N_e v - 1} e^{4N_e sp}$$

✧ where u and v are the forward and backward mutation rates (??)

Nearly Neutral Theory

❖ what happens in small populations when selection is weak?
  ✧ changes in allele frequency due to drift and selection are approximately equal $|2Ns| \approx 1$

❖ probability of fixation for a new, "nearly neutral" allele:

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

$$w_{AA} = 1 + \underline{s}, \quad w_{Aa} = 1 + \underline{s/2}, \quad w_{aa} = 1$$

Probability of Fixation vs Population Size

- s = -0.01
- s = -0.001
- s = -0.0001

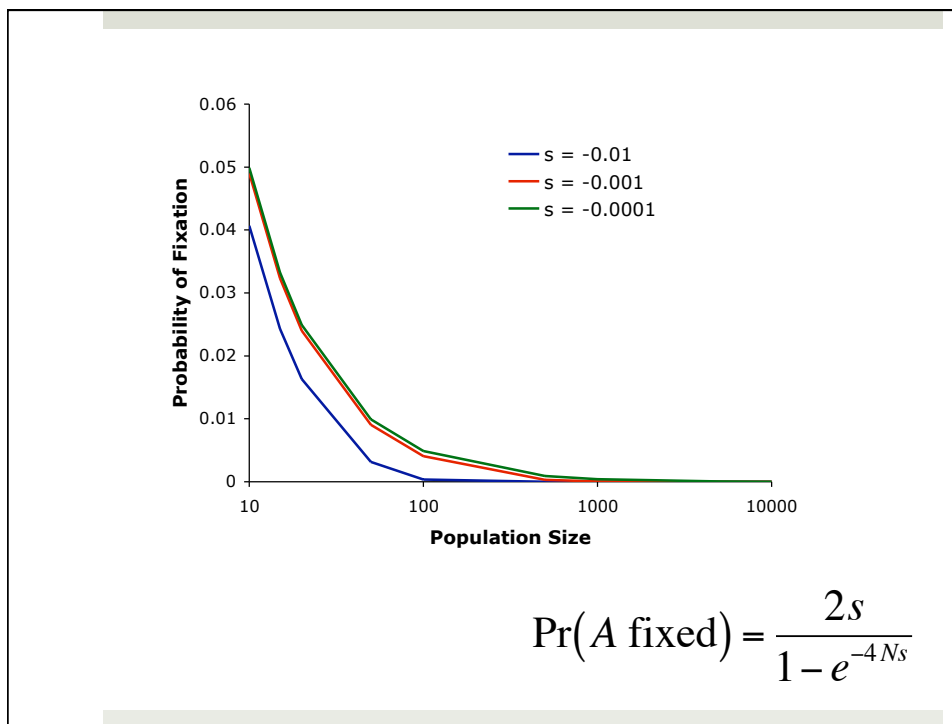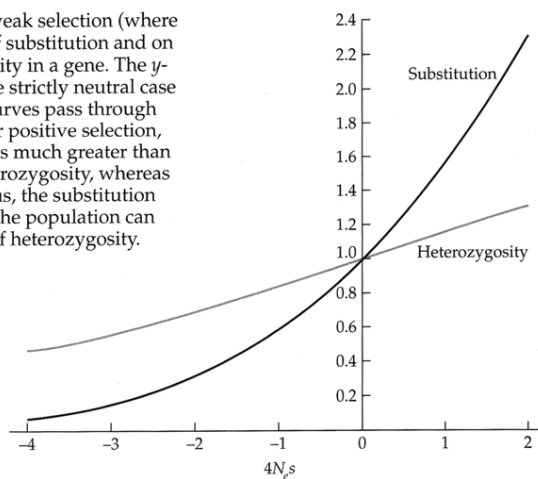$$\Pr\left(A \text{ fixed}\right) = \frac{2s}{1 - e^{-4Ns}}$$

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.

❖ slightly deleterious alleles can achieve relatively high levels of heterozygosity even when their substitution (fixation) probability is low

Nearly Neutral Theory - Summary

❖ the rate of neutral evolution is independent of population size

$$2N\mu \times \frac{1}{2N} = \mu$$

◇ substitution rate equals mutation rate

❖ in contrast, the fate of nearly neutral mutations depends on population size

$$|2Ns| \approx 1$$

◇ when N is small, the effect of genetic drift can be greater than that of selection, making slightly deleterious mutations "effectively neutral"

❖ thus, lineages experiencing small population size should accumulate both neutral and nearly neutral mutations, leading to a faster rate of sequence evolution
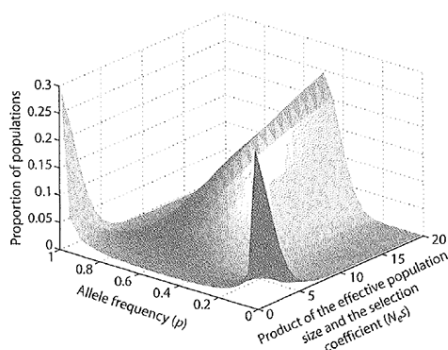
Selection-Drift Balance

Figure 7.7 The expected distribution of allele frequencies for a very large number of replicate finite populations under natural selection where there is overdominance for fitness ($w_{AA} = w_{aa} = 1 - s$ and $w_{Aa} = 1$). In an infinite population the expected allele frequency at equilibrium is 0.5. However, in finite populations the equilibrium allele frequency will depend on the balance of natural selection and genetic drift. This balance is determined by the product of the effective population size and the selection coefficient ($N_e s$). Low values of $N_e s$ mean that selection is very weak compared to drift and each population reaches fixation or loss. High values of $N_e s$ mean that selection is strong compared to drift and most populations reach an equilibrium allele frequency near 0.5. Here forward and backward mutation rates are equal ($\mu = \nu = 0.00001$).
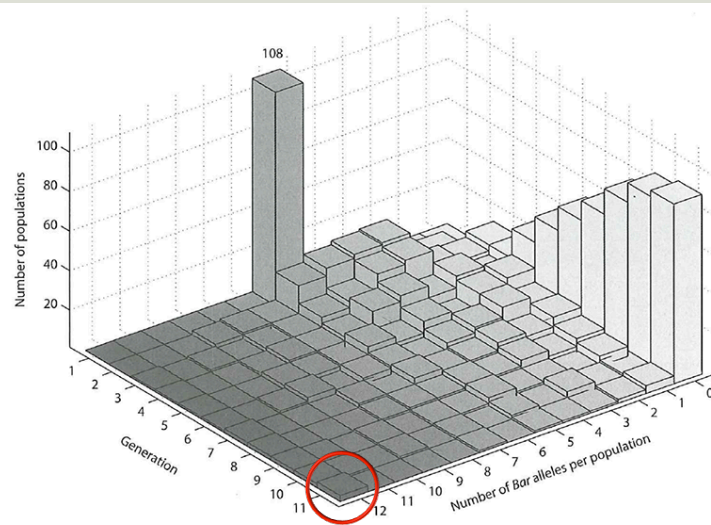
Figure 7.8 Frequency of the *Bar* allele in 108 replicate *D. melanogaster* populations over 10 generations (Wright & Kerr 1954). Each population was founded from four males and four females. The *Bar* locus is found on the X chromosome and so is hemizygous in males, making the effective population size equivalent to about six individuals. The eyes of *D. melanogaster* individuals homozygous for the wild-type allele are oval, but heterozygotes and homozygotes for the partially dominant *Bar* allele have bar-shaped eyes with a reduced number of facets. Females homozygous for the Bar allele produced 37% of the progeny compared to females homozygous or heterozygous for the wild-type allele. Despite this strong natural selection against *Bar*, three populations fixed for *Bar* by the end of the experiment. Compare with the similar example in Figure 3.11 where the locus is selectively neutral.