Lecture Handout 16: Mutations (ch. 7)

Mutations: changes to the nucleotide sequence of the genetic material

Mutagen: chemical/radiation that induces mutation

Spontaneous mutations: immediate cause is unknown. Many are detrimental if they change the normal function of a gene.

Frameshift mutant: indel that changes the reading frame of subsequent codons in a transcript

Transposable elements: regions of DNA that can move or replicate themselves in the genome; eg, 45% of human genome; “junk” or “selfish” DNA.

“Hybrid dysgenesis:” crosses between certain strains of *Drosophila* are sterile--caused by a transposable elements present in only one of the strains.

Example, P and I transposable elements in *Drosophila*. Due to the recent horizontal transfer of elements between species. Spread quickly (in experimental lineages rose from 5% to 100% in 10 generations)

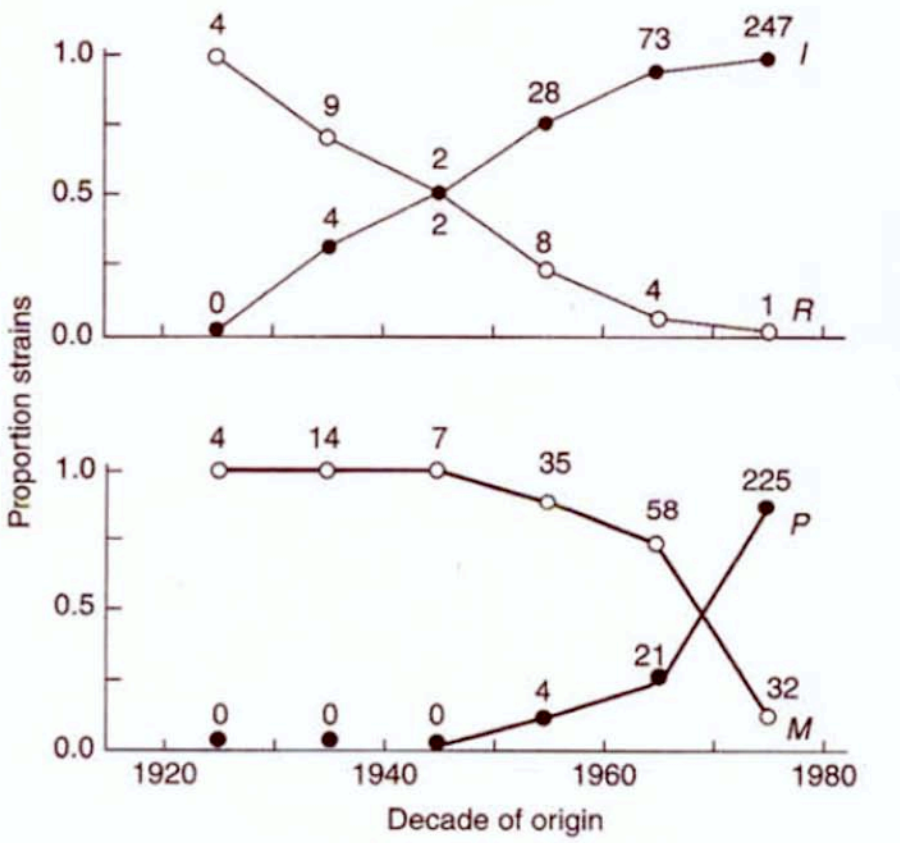
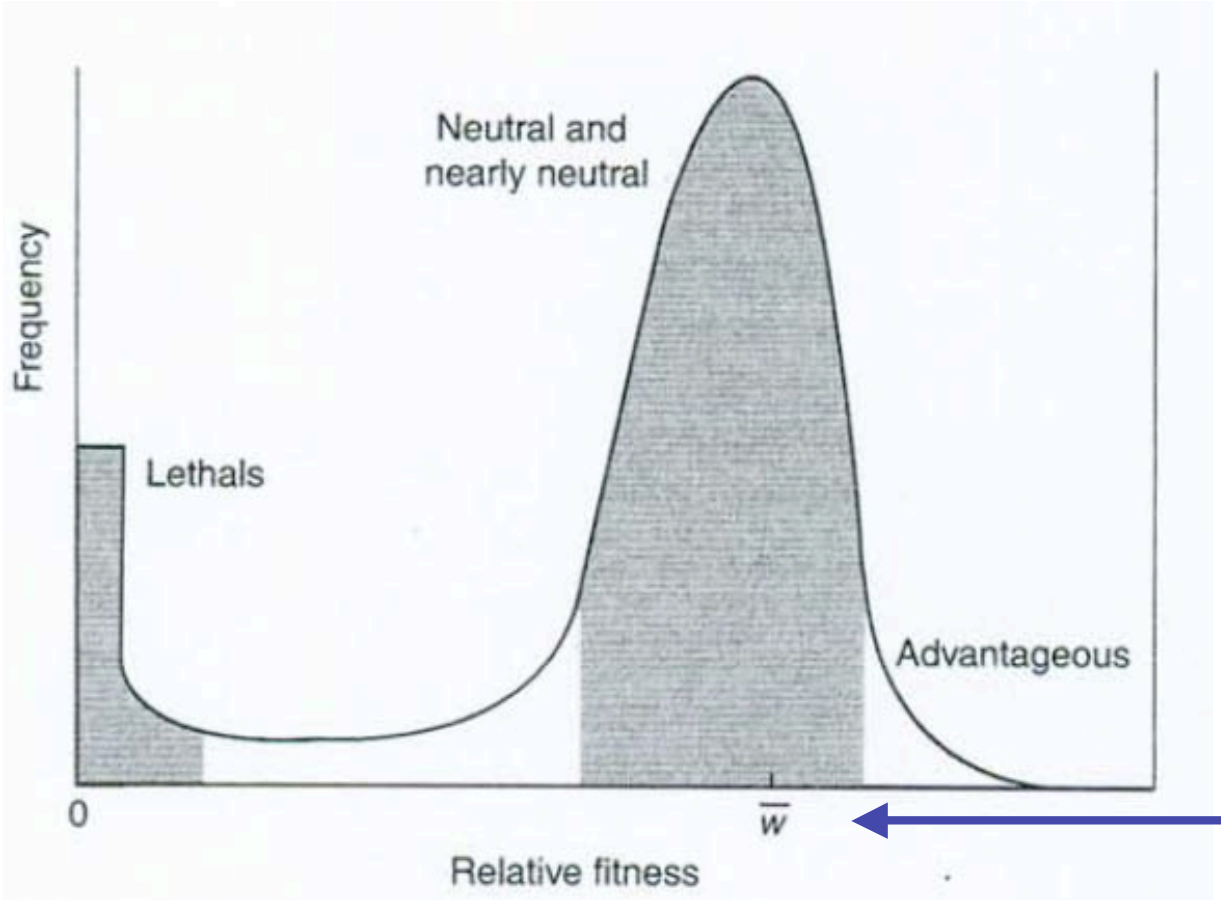


Figure 7.1. The estimated proportion of strains with I (top) and P (bottom) elements as detected by hybrid dysgenesis in strains collected in the decades from the 1920s to the 1970s (after Kidwell, 1983). The category R indicates strains without the I element; the category M indicates strains without the P element; and the number of strains in each category are indicated.

What is the fitness of new mutations? Hypothetical distribution is bimodal (has two peaks). One peak is lethal mutations; a higher peak is neutral or nearly neutral; a small but important number are advantageous.



mean population fitness is omega-bar

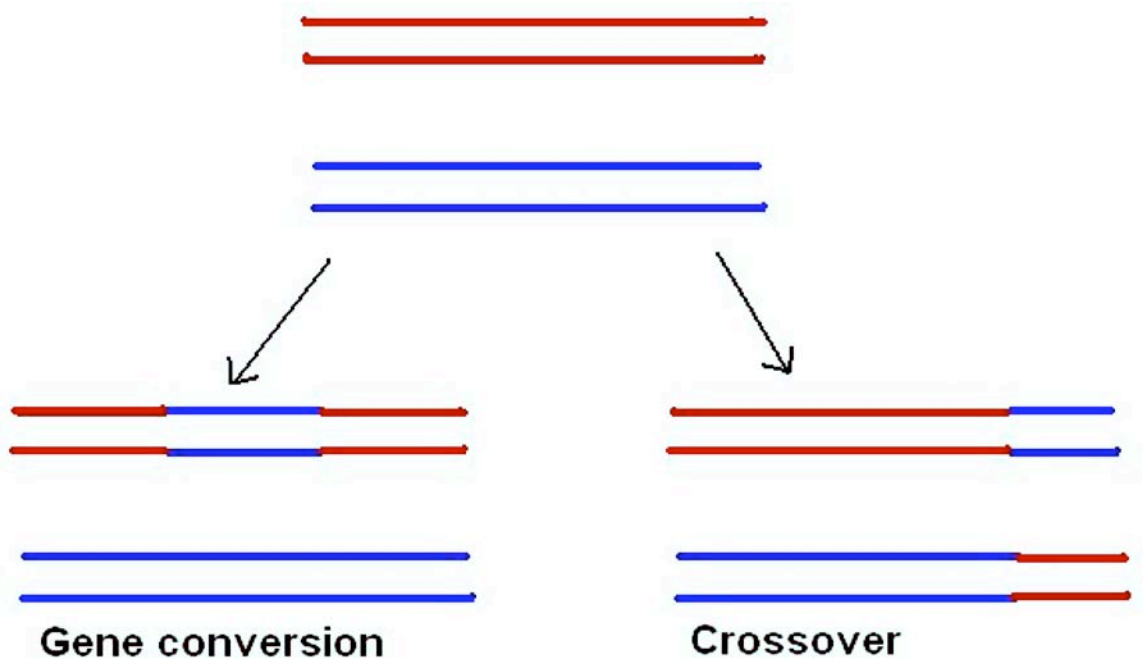
Multigene families: group of homologous (orthologous or paralogous) genes with related functions that are often closely linked on a chromosome. Arise by duplication of an ancestral gene.

Examples: genes for histones, globins, rRNAs, tRNAs, MHC.

Bacteria: 17-44% of genes are duplicate
Eukaryotes: 30-65% are duplicate

Duplicated genes may diverge or converge.

One form of convergence for duplicated genes is **gene conversion**, in which part of the nucleotide sequence from one allele is replaced by the homologous nucleotide sequence of another allele. Note difference versus homologous recombination



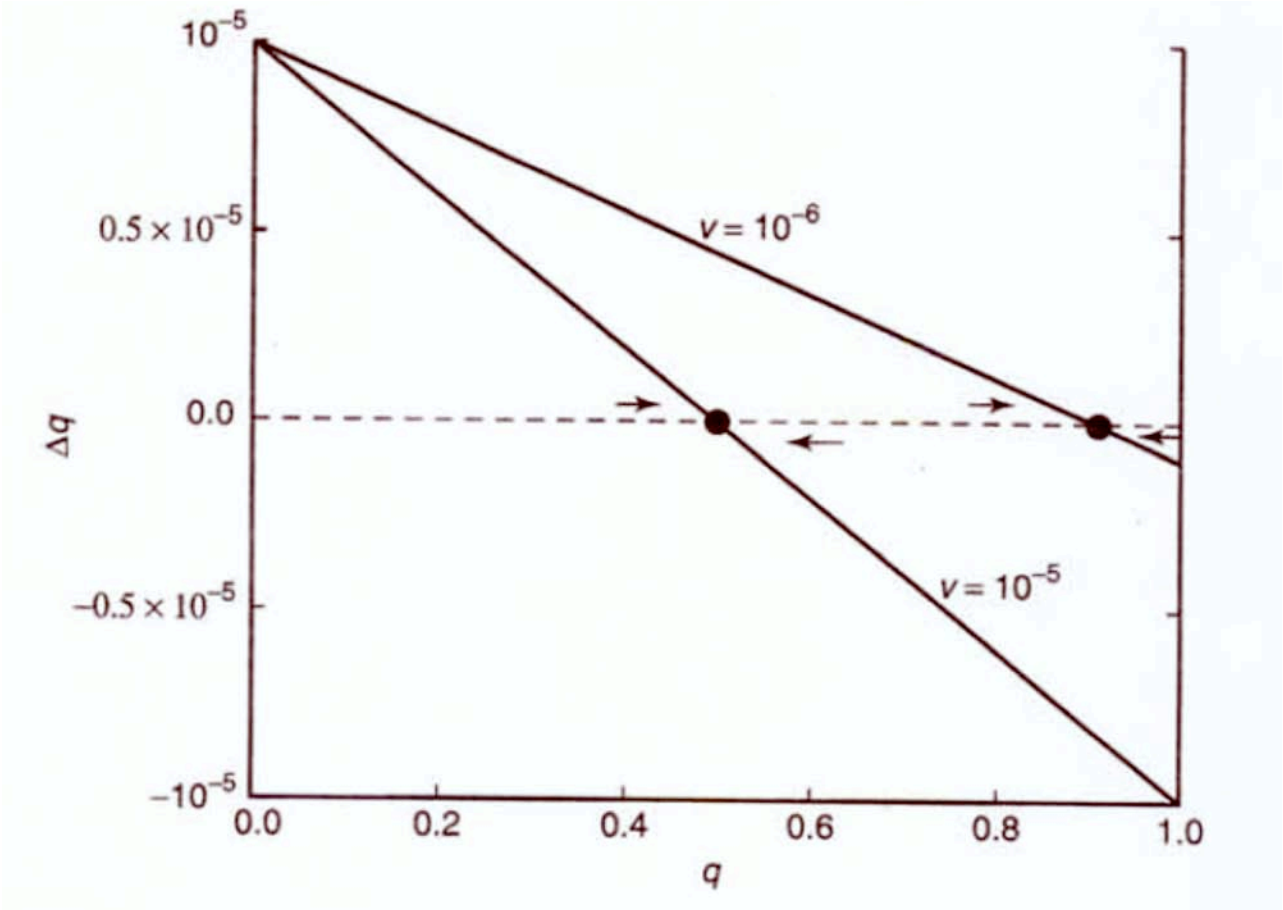
Can also be affected by **non-homologous recombination**, which is unequal crossing over, e.g., endogenous feline leukemia retroviruses

Forward mutations are more common than backward mutations; eg seven million mice examined for spontaneous coat color mutants at the Jackson Laboratory in Bar Harbor, ME

TABLE 7.1 Spontaneous mutation rates at five specific coat-color loci in mice (Schlager and Dickie, 1971).

Locus	*Number of gametes tested*	*Number of mutations*	*Mutation rate* ($\times 10^{-6}$)	95% *confidence limits* ($\times 10^{-6}$)
		Mutations from wild type (forward)		
Nonagouti	67,395	3	44.5	9.2–130.1
Brown	919,699	3	3.3	0.7–9.5
Albino	150,391	5	33.2	10.8–77.6
Dilute	839,447	10	11.9	5.2–21.9
Leaden	243,444	4	16.4	4.5–42.1
Total	2,220,376	25	11.2	7.3–16.6
		Dominant mutations (backward)		
Nonagouti	8,167,854	34	4.2	2.9–5.8
Brown	3,092,806	0	0	0–1.2
Albino	3,423,724	0	0	0–1.1
Dilute	2,307,692	9	3.9	1.8–11.1
Leaden	266,122	0	0	0–13.9
Total	17,236,978	43	2.5	1.8–3.4

For a given value of the forward mutation rate, *u*, changing allele A_1 to allele A_2, and a given value of the backward mutation rate, *v*, changing allele A_2 to allele A_1, there is an equilibrium frequency at which $\Delta q = 0$



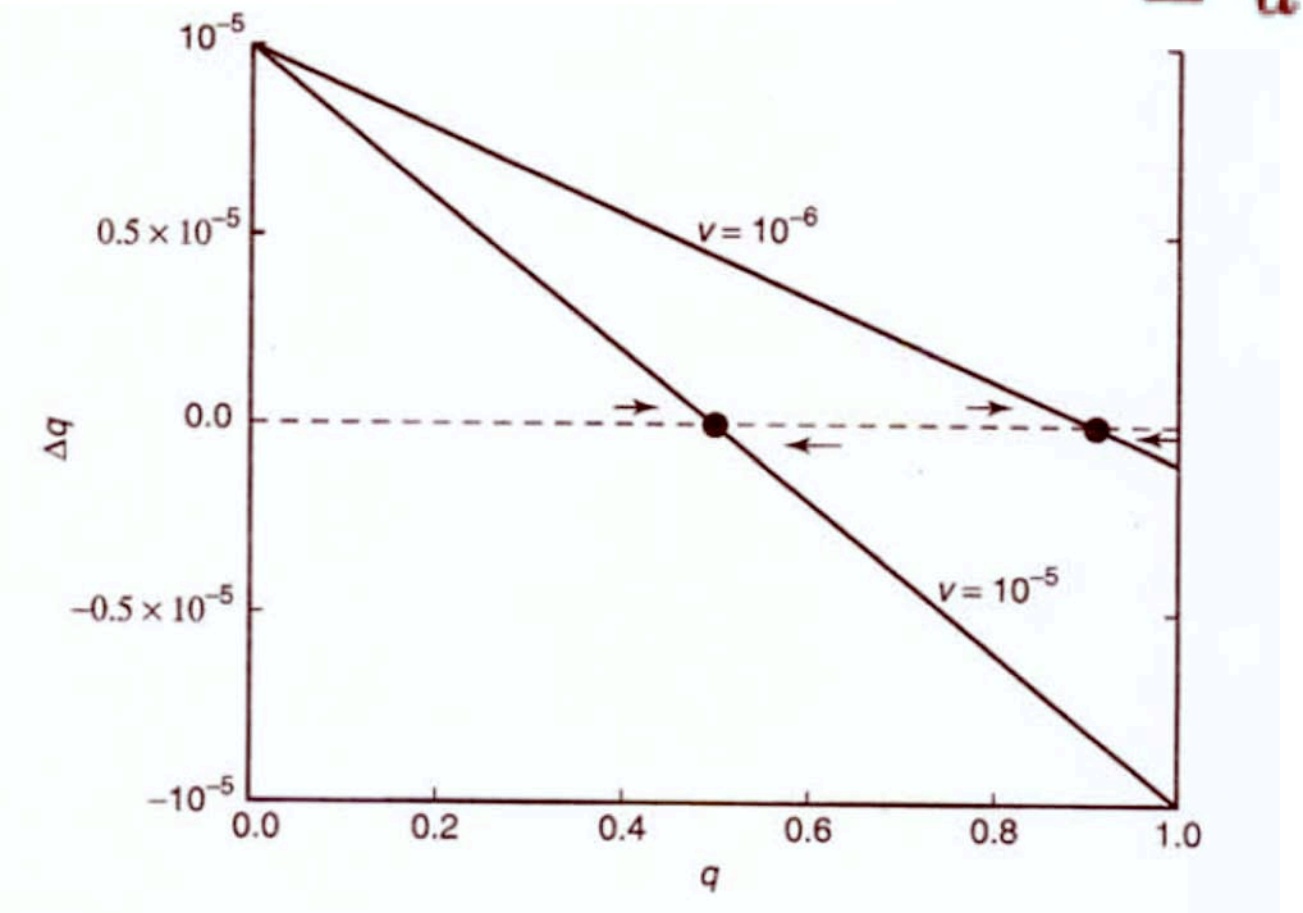
Equilibria for values of v when u = 10^-5

Equilibrium value:

$$q_e = \frac{u}{u+v}$$

If not at equilibrium:

$$\Delta q = up - vq$$
$$= u - q(u+v)$$



Equilibria for values of v when u = 10^-5

BY ITSELF, the mutation rate alone is a slow force for changing allele frequencies. **When v is small** compared to u, then:

$$p_t = (1-u)^t p_0$$

When u = 10^{-5}, then it takes 70,000 generations to half the frequency of the wild type allele in a population

Fate of a single mutation.

A new mutation exists as the only copy in the entire population. Very easy for it to be lost due to stochastic effects. Model: chance of loss in the first generation is 0.368

Even if retained at low frequency, it can be lost in subsequent generations.

For neutral mutant allele, chance of fixation is close to zero if population size is very large.

Mutant allele with selective advantage: little effect on probability of loss during first generations; probability of fixation is increased

TABLE 7.3 The probability of loss and of survival of a new mutant when there is neutrality or a 1% selective advantage (after Fisher, 1930).

	Neutral		$s = 0.01$	
Generation	*Loss*	*Survival*	*Loss*	*Survival*
1	0.368	0.632	0.364	0.636
2	0.532	0.468	0.526	0.474
3	0.626	0.374	0.620	0.380
4	0.688	0.312	0.681	0.319
5	0.732	0.268	0.725	0.275
⋮	⋮	⋮	⋮	⋮
15	0.887	0.113	0.878	0.122
⋮	⋮	⋮	⋮	⋮
127	0.985	0.015	0.973	0.027
⋮	⋮	⋮	⋮	⋮
∞	1.0	0.0	0.98	0.02

Mutation-selection balance: although mutation produces new deleterious alleles each generation; purifying selection against the deleterious alleles prevents them from increasing in frequency, eg recessive alleles:

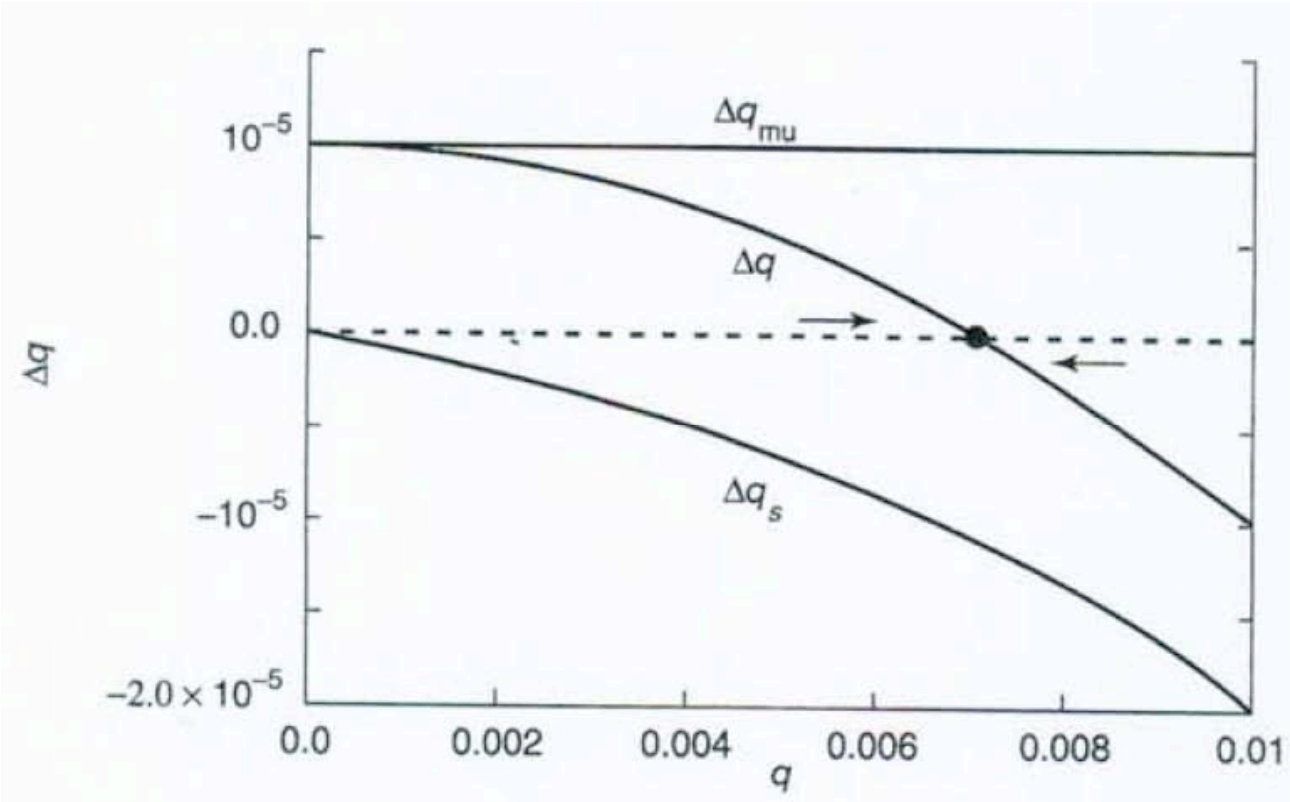
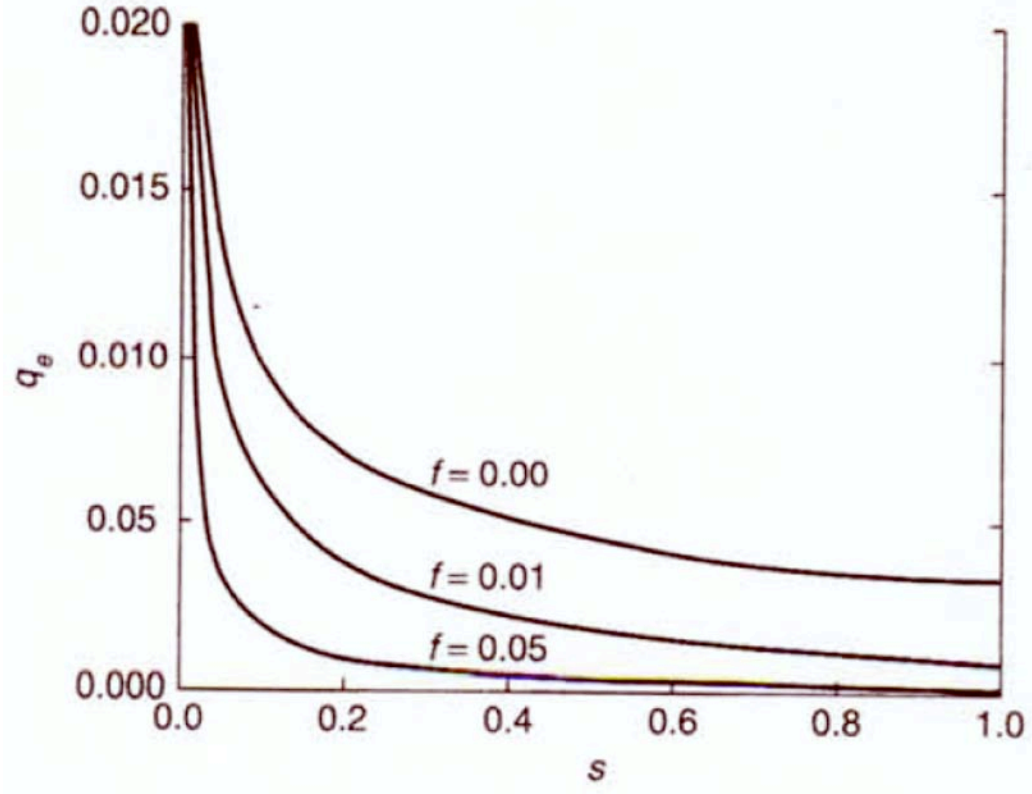


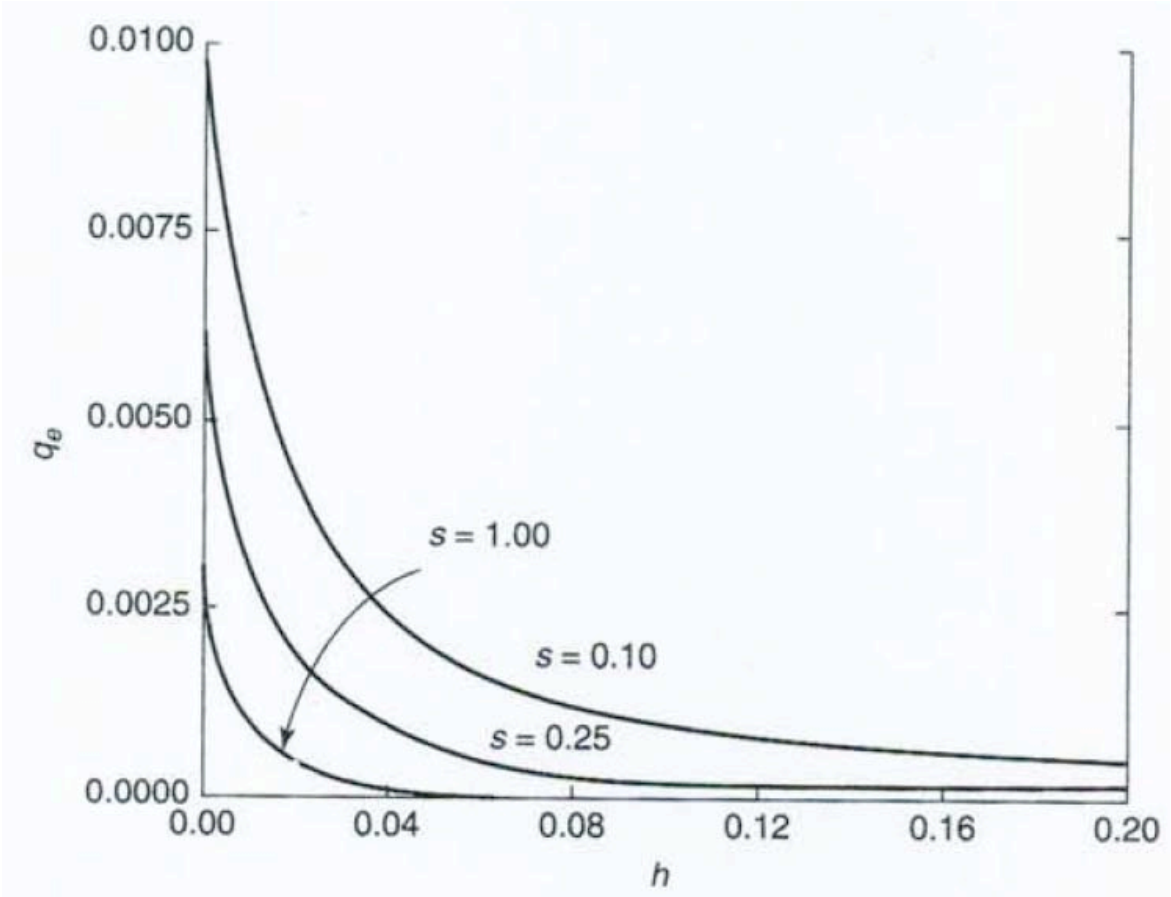
Figure 7.4. The change in allele frequency due to both mutation to and selection against recessive alleles. The line labeled Δq is the summation of Δq_{mu} and Δq_s, and the closed circle indicates the equilibrium.

Mutation-selection balance, effects of inbreeding: inbreeding coefficient, f, means alleles are identical by descent and reduced population heterozygosity, so a larger proportion of A_2 **recessive** deleterious alleles are subject to the effects of selection.



Mutation-selection balance, effects of dominance: alleles with higher levels of dominance have a greater effect of selection on heterozygotes, so a larger proportion of A_2 deleterious alleles are subject to the effects of selection.

eg for u = 10^{-5}



Mutation-selection balance, effect on **genetic load**, which is the reduction in fitness in a population compared with the fitness if the population were composed only of the optimal genotype. In a biallelic system where A_2 is deleterious, the optimum genotype is A_1A_1, and the **mutation load** is

$$\begin{aligned} L &= 1 - \overline{w} \\ &= sq(2ph + q) \end{aligned}$$

Mutation load is between the mutation rate and twice the mutation rate, depending on the level of dominance.