Selection, as we have defined it, changes allele frequencies, resulting in corresponding changes in frequencies of genotypes. Equilibrium cannot exist if allele frequencies are changing, because allele frequency changes change the frequencies of genotypes.

$\Delta q_t$ represents the change in allele frequency per generation. For equilibrium to exist, allele frequencies must be constant; only if

$$\Delta q_e = (p_e q_e / 2W_e) (dW_e / dq_e) = 0,$$

(14.1)
can equilibrium occur.

$W_e$ is a function of genotypic frequencies and relative fitness values. Its maximum value, from Eq. (13.4), is 1. Therefore, Eq. (14.1) cannot be driven to 0 because its denominator, $2W_e$, becomes infinitely large.

If either $p$ or $q$ is zero, Eq. (14.1) will be zero. With only one allele in the population, selection cannot change allele frequencies. In fact, selection as we have defined it cannot even take place, since with only one allele, there can be only one genotype, and we cannot have differential fitnesses of different genotypes. “Equilibrium” points with $p$ or $q$ equal to zero are therefore trivial.

Equation (14.1) can also be zero if the derivative of $W_e$ is zero. In its most general terms, we can write $W_e$ as

$$W_e = w_{11}(1-q_t)^2 + 2w_{12}(1-q_t)q_t + w_{22}q_t^2$$

$$= w_{11} - 2w_{11}q_t + w_{11}q_t^2 + 2w_{12}q_t - 2w_{12}q_t^2 + w_{22}q_t^2.$$

The derivative is then

$$dW_e / dq_t = -2w_{11} + 2w_{11}q_t + 2w_{12} - 4w_{12}q_t + 2w_{22}q_t$$

$$= -2(1-q_t)w_{11} + 2(1-q_t)w_{12} - 2w_{12}q_t + 2w_{22}q_t$$

$$= 2p_t(w_{12} - w_{11}) - 2q_t(w_{12} - w_{22}).$$

It follows that if we set the derivative equal to zero at equilibrium,

$$p_e(w_{12} - w_{11}) = q_e(w_{12} - w_{22}).$$

(14.2)

If the difference $w_{12} - w_{11}$ and the difference $w_{12} - w_{22}$ have the same sign, $\Delta q_e$ can be 0 even if neither $p$ nor $q$ is 0. But for these two differences to have the same sign, the heterozygote must be more fit or less fit than either homozygote.

This situation is referred to as overdominance; positive overdominance if the heterozygote is more fit than either homozygote, negative overdominance if it is less. Some authors reserve the term overdominance for positive overdominance, referring to negative overdominance as “underdominance”. The positive-negative dichotomy appears preferable, and this is the terminology we shall use.
The classic example of positive overdominance was elucidated by Allison (1954). The sickle cell anemia gene produces abnormal hemoglobin; homozygotes for this allele suffer from severe anemia, with the further complication that the erythrocytes deform into a sickle shape which can clog minor blood vessels. These homozygotes usually die by their early teens. About 40% of the hemoglobin of heterozygotes is abnormal sickling hemoglobin, but they are clinically normal. The presence in these heterozygotes of the sickling gene and the abnormal hemoglobin which it produces can be detected by appropriate blood tests; for example, subjecting heterozygotes’ blood to abnormally low oxygen tensions will cause sickling of some of the erythrocytes.

The severe effects of the sickling homozygous condition would lead us to expect it to be in very low frequency in human populations. But Allison found this allele in very high frequencies, approaching 0.5, in some African populations living in malarial regions. Further study showed that the heterozygote was less susceptible to malaria than homozygous normals. Thus, in malarial regions, sickle cell homozygotes are selected against because of their abnormal hemoglobin; but there is countervailing selection against normal homozygotes due to the endemic malaria. Only heterozygotes can breed normally. The heterozygote thus has superior fitness due to the selective disadvantages of each of the two homozygotes.

With positive overdominance, the ratio of the fitness values is

\[ W_{11} : W_{12} : W_{22} = 1 - s_1 : 1 - s_2, \]

so that at equilibrium

\[
\begin{align*}
    p_e(1 - 1 + s_1) &= q_e(1 - 1 + s_2), \\
    s_1(1 - q_e) &= s_2q_e, \\
    q_e(s_1 + s_2) &= s_1, \\
    q_e &= s_1 / (s_1 + s_2); \\
    p_e &= s_2 / (s_1 + s_2).
\end{align*}
\]

Equation (14.3) says that the equilibrium frequency of either allele is positively correlated with the selection coefficient against the opposite homozygote. This is intuitively sensible. If selection against \( MM \) increases, the frequency of \( M \) should decrease, and that of \( m \) increase. If there is equal selection against both homozygotes, \( p_e \) and \( q_e \) should be equal.

With positive overdominance,

\[
W_t = 1 - s_1 p_t^2 - s_2 q_t^2
\]

\[
= 1 - s_1 + 2s_1 q_t - s_1 q_t^2 - s_2 q_t^2,
\]

and therefore

\[
\frac{dW_t}{dq_t} = 2s_1 - 2s_1 q_t - 2s_2 q_t
\]

\[
= 2[s_1 - (s_1 + s_2)q_t].
\]

(14.4)

Obviously, if \( q_t = q_e = s_1 / (s_1 + s_2) \) in Eq. (14.4),

\[
\frac{dW_t}{dq_t} = 0.
\]