Balancing selection occurs when selection acts to maintain different alleles in a population. This can occur through several different mechanisms.

- **Heterozygote advantage/Overdominance** - heterozygotes have higher fitness than homozygotes.
- **Coevolutionary dynamics** - alleles that are common in one species may become less fit because they are exploited by opposing species (pathogens, predators).
- **Negative assortative mating** - individuals preferentially mate with individuals that carry different alleles.
- **Spatially and temporally fluctuating selection** - different alleles may be favored at different times or in different locations.

What these all have in common is that they lead to **negative frequency-dependent selection**: as an allele becomes more common, its fitness decreases below the mean fitness of the population.
Example: Sickle cell anemia

- The **sickle cell mutation** in the $\beta$-globin gene results in a single amino acid substitution that causes hemoglobin to form long rod-like structures in $\beta^S \beta^S$ homozygotes.

- Heterozygotes $\beta^A \beta^S$ are less susceptible to *P. falciparum* malaria and have higher fitness than either homozygote in areas of high malaria incidence.
Example: Self-incompatibility Loci

Many plants avoid inbreeding through self-incompatibility loci.

- SI is mediated through pollen-pistil interactions.
- Fertilization can occur only if the pollen and pistil carry different SI alleles.
- Common SI alleles are at selective disadvantage because they are more likely to experience incompatibility.
- This leads to strong balancing selection on SI loci, which can harbor tens to hundreds of distinct haplotypes.
Example: Social polymorphism in White-throated Sparrows

- WTSP's come in two morphs (white-striped and tan-striped) that differ in plumage, behavior and mate preference.
- Controlled by a 104 Mb supergene with two divergent haplotypes $2$ and $2^m$.
- Maintained by strong ($> 96\%$) negative assortative mating.
- Recombination is suppressed by inversions.

- $2/2 = \text{tan-striped}$
- $2/2^m = \text{white-striped}$
- $2^m/2^m = \text{lethal}$
Overdominance and Balancing Selection

If the fitness of the heterozygote is greater than the fitness of either homozygote, i.e., if $\sigma_{12} > \sigma_{11}, \sigma_{22}$, then the heterozygote is said to be **overdominant**. In this case, there is an intermediate frequency

$$\bar{p} = \frac{\sigma_{12} - \sigma_{22}}{2\sigma_{12} - \sigma_{11} - \sigma_{22}}$$

such that

- $A_1$ is more fit when $p < \bar{p}$;
- $A_2$ is more fit when $p > \bar{p}$;
- Both alleles are equally fit when $p = \bar{p}$.
Overdominance in Finite Populations

In a finite population, balancing selection will interact with genetic drift and the allele frequencies will fluctuate around their equilibrium values.

- **Neutrality**: $N = 1000, \mu = 0.0002$
- **Directional Selection**: $s = 0.01$
- **Balancing Selection**: $s = 0.01 \cdot (0.5 - p)$

This produces a very different pattern than directional selection, but it may be difficult to distinguish weak or moderate balancing selection from neutral evolution.
The tendency of balancing selection to maintain variation can also be seen in the density of the stationary distribution for this diffusion:

$$\pi(p) = \frac{1}{C} p^{2\mu_1-1} q^{2\mu_2-1} e^{(2\sigma_{12} - \sigma_{11})p(2\bar{p} - p)}.$$

**Symmetric Balancing Selection:** In the following histograms, $\sigma_{11} = \sigma_{22} = 0$, $2\sigma_{12} = 4Ns$, and $4N\mu = 0.1$. 

![Histograms for Ns = 2.5 and Ns = 10]
Genealogical Consequences of Balancing Selection

Balancing selection tends to increase the average coalescent time between haplotypes carrying distinct selected alleles.

- This occurs because the alleles themselves can be maintained at high frequencies for long times.
- Elevated coalescent times can also be seen at linked neutral loci.
- This leads to elevated nucleotide diversity in the vicinity of the selected locus.
Changes to the ancestral process can occur through the following events:

- Two $A_1$ lineages can coalesce.
- Two $A_2$ lineages can coalesce.
- Each lineage can migrate between backgrounds, through:
  - mutation at the selected locus;
  - recombination between the selected and marker loci.
- The allele frequencies at the selected locus change as we go backwards in time.
The impact of balancing selection on linked marker loci is reduced both by high mutation rates at the selected locus and by recombination between the selected and marker loci.

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**Figure 12**

The coalescence time is almost independent of the recombination rate, but balancing selection must be very strong to reduce coalescence times by significant amounts. This is because coalescence times are determined by the effective number of individuals, which is typically high in large populations. As a result, the effect of selection is small when the population is large.

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**Figure 13**

The effect of balancing selection on linked marker loci is reduced both by high mutation rates at the selected locus and by recombination between the selected and marker loci. This is because coalescence times are determined by the effective number of individuals, which is typically high in large populations. As a result, the effect of selection is small when the population is large.

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**Figure 14**

The effect of balancing selection on linked marker loci is reduced both by high mutation rates at the selected locus and by recombination between the selected and marker loci. This is because coalescence times are determined by the effective number of individuals, which is typically high in large populations. As a result, the effect of selection is small when the population is large.

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**Figure 15**

The effect of balancing selection on linked marker loci is reduced both by high mutation rates at the selected locus and by recombination between the selected and marker loci. This is because coalescence times are determined by the effective number of individuals, which is typically high in large populations. As a result, the effect of selection is small when the population is large.

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**Figure 16**

The effect of balancing selection on linked marker loci is reduced both by high mutation rates at the selected locus and by recombination between the selected and marker loci. This is because coalescence times are determined by the effective number of individuals, which is typically high in large populations. As a result, the effect of selection is small when the population is large.

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**Figure 17**

The effect of balancing selection on linked marker loci is reduced both by high mutation rates at the selected locus and by recombination between the selected and marker loci. This is because coalescence times are determined by the effective number of individuals, which is typically high in large populations. As a result, the effect of selection is small when the population is large.
Balancing Selection and Transpecific Polymorphism

When balancing selection is both sufficiently strong and consistent, it can maintain ancestral polymorphisms in multiple descendant species.

- This is best documented for several MHC loci, which exhibit TSP in both primates and rodents.
- Other suspected examples involve loci involved in adaptive immunity.
- Proving TSP is difficult because one needs to rule out convergent molecular evolution and horizontal exchange.

Source: Azevedo et al. (2015)
Fluctuating Selection

In some cases, the fitness of an allele may depend on environmental conditions that change over time. How such loci evolve will then depend on how rapidly the environmental fluctuations occur relative to the generation time of the population.

- If the environment fluctuates rapidly within the lifespan of an individual, then the fitness of each allele will be approximately the same from generation and classical theory will apply.
- If environmental fluctuations take place over a small number of generations, then the fitness of each allele will change rapidly in relationship to genetic drift.
- If environmental fluctuations take place over a large number of generations, then the locus may experience successive selective sweeps when a previously deleterious allele becomes beneficial.
A Model of Fluctuating Selection in a Finite Population

We can incorporate fluctuating selection into the bi-allelic Wright-Fisher model by allowing the fitnesses of the alleles $A_1$ and $A_2$ to vary at random from one generation to the next. Here we will consider two scenarios.

**Haploid model:** Suppose that in generation $t$ each allele $A_i$ and $A_2$ has fitness

$$w_i(t) = 1 + \bar{s}_i + s_i(t),$$

where $1 + \bar{s}_i$ is the mean fitness of that allele (averaged over environments) and $(s_1(t), s_2(t))$ are IID random vectors.

**Additive diploid model:** Suppose that in generation $t$ each genotype $A_iA_j$ has fitness

$$w_{ij}(t) = 1 + \bar{s}_{ij} + (s_i(t) + s_j(t)),$$

where $1 + \bar{s}_{ij}$ is the mean fitness of that genotype (averaged over environments) and $(s_1(t), s_2(t))$ are IID random vectors.
The effects of the environmental fluctuations on the allelic fitnesses are captured by the random vectors \((s_1(t), s_2(t))\), which we will assume are independent and identically-distributed (IID) with the following properties:

\[
\begin{align*}
\mathbb{E}[s_i(t)] &= 0 \\
\mathbb{E}[s_i(t)s_j(t)] &= \sigma_{ij}
\end{align*}
\]

The first condition is purely for convenience, since we have already explicitly specified the mean fitness of each allele or genotype as \(\bar{s}_i\) or \(\bar{s}_{ij}\). This then allows us to interpret the quantities \(\sigma_{ij}\) given in the second equation as the variances \((\sigma_{11}, \sigma_{22})\) or covariances \((\sigma_{ij})\) of the environmental components of fitness.

**Caveat:** The results that follow also assume that the higher order moments \(\mathbb{E}[\sigma_{ij}^4]\) are small relative to \(1/N\).
Fluctuating selection affects the distribution of allele frequencies \((p + q = 1)\) at the selected locus in three ways. First, it increases the variance of the frequency of \(A_1\), as can be seen in the following identity:

\[
\text{Var}(\Delta p) = \nu_1 p(1-p) + \nu_2 p^2(1-p)^2
\]

where

\[
\nu_1 = \frac{1}{N} \text{ (haploid) or } \frac{1}{2N} \text{ (diploid)}
\]

\[
\nu_2 = \text{Var}(s_1(t) - s_2(t)) = \sigma_{11} - 2\sigma_{12} + \sigma_{22}
\]

Remarks:

- This result shows that fluctuating selection can mimic genetic drift in the sense that it increases the rate at which the allele frequencies will fluctuate from one generation to the next.
- Like genetic drift, this effect will tend to reduce variation at the selected locus.
In addition, fluctuating selection can also give rise to a mix of directional and balancing selection on the alleles. Specifically,

$$\mathbb{E}[\Delta p] = d_1 p(1 - p) + d_2 p(1 - p)(1 - 2p)$$

where

\[ d_1 = \begin{cases} \bar{s}_1 - \bar{s}_2 + \frac{1}{2}(\sigma_{22} - \sigma_{11}) & \text{(haploid)} \\ \frac{1}{2}(\bar{s}_{11} - \bar{s}_{22}) + (\sigma_{22} - \sigma_{11}) & \text{(diploid)} \end{cases} \]

and

\[ d_2 = \begin{cases} \frac{1}{2}v_2 & \text{(haploid)} \\ v_2 + \bar{s}_{12} - \frac{1}{2}(\bar{s}_{11} + \bar{s}_{22}) & \text{(diploid)} \end{cases} \]

Here, \( d_1 \) is the strength of directional selection for or against \( A_1 \), while \( d_2 \) is the strength of balancing selection. Notice that \( d_1 \) is affected by differences in mean fitness and in the variance of fitness.
Qualitative impacts of fluctuating selection:

- Fluctuating selection can both increase and reduce the amount of variation maintained in a population.
- Increased variation can be maintained by the balancing selection that occurs in a fluctuating environment. The strength of this effect depends on the variance of the environmental fluctuations, as measured by $d_2$ (which also accounts for overdominance in the diploid model).
- Variation will tend to be reduced both by the directional component of fluctuating selection (measured by $d_1$) and by the increased variance of the allele frequencies (measured by $v_2$).
- Whether variation will be increased or reduced depends on the relative sizes of $v_2$, $d_1$ and $d_2$.
- Alleles can be favored both because they have higher mean fitness or because they have lower fitness variance. The latter effect can be thought of as selection for bet hedging.
Sample paths under neutrality, fluctuating selection and balancing selection

- All cases: $v_1 = 1$, $\mu_1 = \mu_2 = 0.01$, $d_1 = 0$ (no directional selection)
- (A) haploid fluctuating: $d_2 = 0.5v_2 = 25$
- (B) neutral: $v_2 = 0$
- (C) diploid fluctuating: $d_2 = v_2 = 50$
- (D) balancing $d_2 = 5.53$
- (E) diploid fluctuating: $d_2 = 1.5v_2 = 75$
- (F) balancing: $d_2 = 10.1$

The strength of balancing selection in (D) and (F) was chosen to match the expected heterozygosity maintained by fluctuating selection in (C) and (E).
Figures show the distribution of the $T_{mrca}$ of a sample of 20 chromosomes at a neutral marker locus linked to a locus under fluctuating (or balancing) selection in a diploid population.

- All cases: $v_1 = 1$, $\mu_1 = \mu_2 = 0.01$, $d_1 = 0$ (no directional selection)
- (A): $d_2 = v_2 = 50$
- (B): $d_2 = 1.5v_2 = 75$
- (C): $d_2 = 2v_2 = 100$

In each case, the strength of balancing selection was chosen to match the expected heterozygosity of the fluctuating selection model.