Outline

• Selection on:
  – Overdominant traits
  – Underdominant traits
  – Sex-linked traits
One minute responses

• Don’t let the one-minute option stop you from asking questions during lecture!

• Q: If $h = 0.5$ is that incomplete dominance or co-dominance?
  – Yes, must be one or the other
  – Any $h$ between 0 and 1 is incomplete dominance or co-dominance, not just 0.5
  – $h$ has to be measured; it’s hard to predict
Overdominance (heterozygote advantage)

Overdominance = heterozygote most fit

- Sickle-cell trait (in presence of malaria)
- Large size of many cultivated crop plants
## Overdominance

Surprising things happen when the heterozygote is most fit.

This example uses $p_A = p_a = 0.5$.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>AA</th>
<th>Aa</th>
<th>aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitness</td>
<td>0.8</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Before selection</td>
<td>0.25</td>
<td>0.5</td>
<td>0.25</td>
</tr>
<tr>
<td>Death due to selection</td>
<td>0.05</td>
<td>0.0</td>
<td>0.05</td>
</tr>
<tr>
<td>After selection</td>
<td>0.2/0.9</td>
<td>0.5/0.9</td>
<td>0.2/0.9</td>
</tr>
<tr>
<td>After selection</td>
<td>0.22</td>
<td>0.56</td>
<td>0.22</td>
</tr>
</tbody>
</table>

New allele frequencies:

$p_A = 0.5$

$p_a = 0.5$
Overdominance

- Strong selection is acting, but the allele frequencies did not change. The population is at an equilibrium state.

- If the initial frequencies were not 50/50, the population would move towards 50/50 and then stick there.

- The ratio 50/50 is because the homozygotes are equally bad. If they were unequally bad, a different ratio would be obtained.
The classic sickle cell case may have selection approximately like this (in the presence of malaria):

<table>
<thead>
<tr>
<th>Genotype</th>
<th>AA</th>
<th>AS</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitness</td>
<td>0.8</td>
<td>1.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

If we start with \( p_A = 0.6 \), what are the genotype frequencies in adults (after selection) next generation? What are the new allele frequencies?
## Overdominance

The classic Starting with pA=0.6:

<table>
<thead>
<tr>
<th>Genotype</th>
<th>AA</th>
<th>AS</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitness</td>
<td>0.8</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Before selection</td>
<td>0.36</td>
<td>0.48</td>
<td>0.16</td>
</tr>
<tr>
<td>Death due to selection</td>
<td>0.07</td>
<td>0.0</td>
<td>0.16</td>
</tr>
<tr>
<td>After selection</td>
<td>0.29/0.77</td>
<td>0.48/0.77</td>
<td>0.0/0.77</td>
</tr>
<tr>
<td>After selection</td>
<td>0.38</td>
<td>0.62</td>
<td>0.00</td>
</tr>
</tbody>
</table>

pA=0.69, so it’s increasing.

How can we predict the stable equilibrium?
Overdominance

If we write the fitnesses like this:

<table>
<thead>
<tr>
<th>Genotype</th>
<th>AA</th>
<th>AS</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitness</td>
<td>1-s</td>
<td>1.0</td>
<td>1-t</td>
</tr>
</tbody>
</table>

then the equilibrium frequency of A is this:

t/(s+t)

So in our example where s=0.2 and t=1.0, pA at equilibrium is:

1.0 / (0.2 + 1.0) = 0.8333
Overdominance

- Overdominant systems have a stable equilibrium:
  - If undisturbed, they will stay there
  - If moved away, they will return

- Population maximizes its overall fitness **given the laws of Mendelian segregation.**

- An all-heterozygote population would be more fit, but is prevented by random mating and segregation

- A population with HbA and HbS pays two costs:
  - A/A people die of malaria
  - S/S people die of sickle cell anemia
Overdominance
Genetic load

- Every overdominant locus has a cost (bad homozygotes)
- How many can a species stand?
- Depends on:
  - How bad the homozygotes are
  - How much excess reproductive capacity the species has
- Relatively few overdominant loci have been detected in wild populations
Overdominance versus drift effects—discussion question

- We cross purebred domestic plants or animals
- The crosses are larger, healthier, or more productive than their parents
- Two hypotheses:
  - Overdominance
  - Each purebred has bad recessives which are masked in the hybrid
- How could we decide between these hypotheses?
Overdominance versus drift effects

- Repeatedly backcross to one of the parent strains, selecting for the best offspring

- Overdominance
  - Good phenotype never “breeds true” (it’s a heterozygote)

- Bad recessives
  - With enough patience, good phenotype will breed true
Underdominance (heterozygote disadvantage)

Underdominance = heterozygote least fit

- Diabetes risk is worst in HLA-DR 3/4 heterozygote
- Mimic butterflies (see next slide)
Underdominance

In the African butterfly *Pseudacraea eurytus* the orange and blue homozygotes each resemble a local toxic species, but the heterozygote resembles nothing in particular and is attractive to predators.
**Underdominance**

\[ p_A = p_a = 0.5 \]

<table>
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<th>Genotype</th>
<th>AA</th>
<th>Aa</th>
<th>aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitness</td>
<td>1.0</td>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Before selection</td>
<td>0.25</td>
<td>0.5</td>
<td>0.25</td>
</tr>
<tr>
<td>Selection deaths</td>
<td>0</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>After selection</td>
<td>0.25/0.9</td>
<td>0.4/0.9</td>
<td>0.25/0.9</td>
</tr>
<tr>
<td>After selection</td>
<td>0.28</td>
<td>0.44</td>
<td>0.28</td>
</tr>
</tbody>
</table>

New allele frequencies:

\[ p_A = 0.5 \]
\[ p_a = 0.5 \]
Underdominance

- An equilibrium exists where there is no pressure to go up or down
- This equilibrium is UNSTABLE
- If the gene frequencies are not at the equilibrium, they will move away until either A or a is fixed
Underdominance

Again, we can predict the equilibrium by writing the fitnesses as follows:

<table>
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<tr>
<th>Genotype</th>
<th>AA</th>
<th>Aa</th>
<th>aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitness</td>
<td>1-s</td>
<td>1</td>
<td>1-t</td>
</tr>
</tbody>
</table>

but now both $s$ and $t$ are negative. The unstable equilibrium is:

$p_A = \frac{t}{(s+t)}$

- $p_A$ above the equilibrium – $A$ will fix
- $p_A$ below the equilibrium – $a$ will fix
- What happens if we’re right at the equilibrium?
Underdominance
Underdominance practice problem

What about this situation?

<table>
<thead>
<tr>
<th>Genotype</th>
<th>AA</th>
<th>Aa</th>
<th>aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitness</td>
<td>1-s</td>
<td>1</td>
<td>1-t</td>
</tr>
<tr>
<td>Fitness</td>
<td>1.5</td>
<td>1.0</td>
<td>1.2</td>
</tr>
</tbody>
</table>

What is the equilibrium?

If we start at pA=0.2, what will happen?
Underdominance

What about this situation?

<table>
<thead>
<tr>
<th>Genotype</th>
<th>AA</th>
<th>Aa</th>
<th>aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitness</td>
<td>1-s</td>
<td>1</td>
<td>1-t</td>
</tr>
<tr>
<td>Fitness</td>
<td>1.5</td>
<td>1.0</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Start at $p_A=0.2$

- Equilibrium $p_A = 0.28$
- If we start below that, $a$ will fix **even though this does not maximize population fitness**
- The population rolls to a small fitness peak, even though a larger one is possible.
Underdominance

- Population which is fixed for \( a \) resists introduction of \( A \)
- Innovations which are bad in heterozygotes are hard to establish
- How can they ever get established?
  - Genetic drift in a small population
  - Founder effect
  - Bottleneck
  - Inbreeding or self-fertilization (makes homozygotes)
Big changes in genome structure are underdominant

*Homo sapiens* chromosomes

*Pan troglodytes* chromosomes

An underdominance mystery

- Insulin-dependent (juvenile) diabetes is a life-threatening disease

- Prior to insulin treatment most affected individuals died before they could reproduce

- High-risk HLA genotype is DR3/DR4 heterozygote

- In Europeans, $p(DR3)$ around 0.12 and $p(DR4)$ around 0.15

- In a system with only DR3 and DR4, what would you expect in the long term?
An underdominance mystery

- DR3 and DR4 are both old alleles
- The problems in the heterozygote could drive one of them extinct
- (We don’t know which one without knowing fitness of homozygotes)
- This hasn’t happened: why?
An underdominance mystery

• Some possibilities:
  – DR3/DR4 could be a generally good genotype despite diabetes risk
  – Diabetes risk could reflect a linked gene that hasn’t been there long
  – Presence of many other alleles may interfere with selection on 3 and 4
  – Modern environment may be different from the past
  – Genetic drift

• Human fitnesses are hard to measure, so this question is still unsolved
Sex linked traits

- Traits on the Y are easy to analyze
- They are haploid, so dominance and recessiveness don’t matter
- Traits on the X behave more strangely
Suppose that among X chromosomes, \( p(X^H) = 0.8 \) and \( p(X^h) = 0.2 \) in both sexes.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>( X^H X^H )</th>
<th>( X^H X^h )</th>
<th>( X^h X^h )</th>
<th>( X^H Y )</th>
<th>( X^h Y )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitness</td>
<td>1.0</td>
<td>1.0</td>
<td>0.1</td>
<td>1.0</td>
<td>0.1</td>
</tr>
<tr>
<td>HW</td>
<td>0.32</td>
<td>0.16</td>
<td>0.02</td>
<td>0.40</td>
<td>0.10</td>
</tr>
</tbody>
</table>

We can see immediately that a rare recessive sex-linked disease shows up mostly in males.
Sex linked traits

<table>
<thead>
<tr>
<th>Genotype</th>
<th>$X^H X^H$</th>
<th>$X^H X^h$</th>
<th>$X^h X^h$</th>
<th>$X^H Y$</th>
<th>$X^h Y$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitness</td>
<td>1.0</td>
<td>1.0</td>
<td>0.0</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>HW</td>
<td>0.32</td>
<td>0.16</td>
<td>0.02</td>
<td>0.40</td>
<td>0.10</td>
</tr>
<tr>
<td>Post-Selection</td>
<td>0.36</td>
<td>0.19</td>
<td>0.0</td>
<td>0.45</td>
<td>0.0</td>
</tr>
</tbody>
</table>

The new allele frequencies are:

Females: $p(X^H) = 0.91$, $p(X^h) = 0.09$

Males: $p(X^H) = 1.0$, $p(X^h) = 0.0$
Sex linked traits are weird

- Even if selection stops, system won’t go straight to HW:
  - Mating is non-random with respect to sex
  - Males and females have different allele frequencies
Sex linked traits

- X-linked recessive decreases faster than an autosomal recessive
- Exposed to selection when in males
- Sex-linked traits don’t go to Hardy-Weinberg in one generation even if there is no selection
- Without selection, they go to Hardy-Weinberg slowly over many generations
- With selection, they may never get there
Sex linked traits

- A point to bear in mind:
  - Most sex-specific traits are not sex-linked (on X or Y)
  - Most sex-linked traits (on X) are unrelated to sex
  - Examples: hemophilia, color vision
  - The Y chromosome contains a few “switch” genes which control sex in humans
  - Almost all of the genes controlled by these switches are autosomal

- Why?
The only Y-linked non-sex gene I know of
Sex linked traits

• Why aren’t sex-related traits sex-linked?

• Both males and females have X

• Why aren’t male traits on the Y?
  – If sex-related traits evolved from other traits, they would start off on the autosomes
  – The Y is haploid and mostly non-recombining, which can cause its genes to deteriorate
  – Having one master switch rather than many independent sex-related trait genes may be less fragile
One-minute responses

• Tear off a half-sheet of paper

• Write one line about the lecture:
  – Was anything unclear?
  – Did anything work particularly well?
  – What could be better?

• Leave at the back on your way out