Natural Selection

Evolutionary Mechanisms
- Genetic Drift
- Migration
- Mutations
- Natural Selection

Darwin
- Evolution acts through changes in allele frequency at each generation
- According to Darwin, this happens via Natural Selection

Sources of Genetic Variation
- Natural Selection
  - Mutation generates genetic variation
  - Epigenetic Inheritance changes expression of genes
  - Genetic Drift can reduce genetic variation

OUTLINE
1. General Description of Natural Selection
2. Distinguishing between Phenotypic Plasticity (Acclimation) vs. Natural Selection (Adaptation)
3. Modes of Natural Selection
4. Natural Selection Violating Hardy-Weinberg Equilibrium
Darwin’s contribution:
Population Speciation as a result of Natural Selection

- Too many offspring produced
- Limited resources and competition
- Variation in a population
- Better adapted individuals survive
- Survivors leave more offspring
- Thus, average character of population is altered

Natural Selection
Differential fitness (survival and reproduction) of different heritable (genetically-based inherited) phenotypes (NOT plastic phenotypes) because some are better suited to the environment than others

Natural Selection leads to → ADAPTATION
NOT random, but deterministic

Natural Selection
SO... The important point is that Natural Selection is all about who lives and who dies (and reproduces)

The important factor is: FITNESS

Natural Selection
The important factor is: FITNESS

An organism's ability to survive and reproduce in a particular environment

Higher fitness means that greater numbers of offspring survive in the next generation

Darwin
Natural Selection

Darwin
mutation
Selection on pathogens imposed by Drugs (refer to Lecture 1)

- AZT (Azidothymidine) is a thymidine mimic which stops reverse transcription.
- Mutations in the reverse transcriptase gene of HIV arise such that the enzyme can recognize AZT.
- The drugs impose Selection on the virus. Genetic variation (generated by mutations) allows the virus to respond to selection and evolve drug resistance.

![Image of Selection favors Darwin](Darwin_selection_favors.png)

• In the presence of AZT, Natural Selection favors mutants that are resistant to AZT (blue, have slow & careful enzyme).

Results in % change in the population, toward higher % of AZT resistant mutants.

Evolution of Virulence

- The direction of selection could change as the environment changes.

(Evolutionary Tradeoffs across different environments)

Selection imposed by Transmission Rate on Virulence of HIV

- Need to keep host alive long enough to get passed on to the next host.
  (Evolutionary tradeoff between fast population growth and keeping the host alive)
- High Transmission rate: High Virulence
  (Can grow fast and jump to the next host; ok if host dies; genetic strain that grows faster will win)
- Low Transmission Rate: Low Virulence
  (More virulent strains would die with the host and get selected out; less virulent strain will win)
Selection on Virulence

- High Transmission Rate: will select for High Virulence

  - If the virus is likely to move to a new host, the faster growing (and more virulent) strain is likely to overtake the slower strains and “win”
  - It’s ok to kill the host, since the chances of jumping to a new host is high
  - Natural selection will favor the MORE virulent strain

- Low Transmission Rate: will select for Low Virulence

  - If the virus is not likely to move to a new host the slower growing (and less virulent) strain is likely to “win”
  - It’s not ok to kill the host, since the chances of jumping to a new host is low. If the virus kills the host, it will kill itself
  - Natural selection will favor the LESS virulent strain

Conceptual Confusions

Trait variation is often assumed to be due to Adaptation, when the differences might be due to Phenotypic Plasticity or nonadaptive genetic causes (e.g. genetic drift, linkage)
Phenotypic Change

• What could cause phenotypic change that is NOT due to genetic changes?

• What could cause phenotypic changes that are due genetic changes, but NOT due to selection (adaptation)?

Nature vs. Nurture

• Both environment and genetics affect many traits, but need to experimentally or statistically separate these factors

• How?

• Example: Common-garden experiment or a reciprocal transplant experiment

• Having appropriate controls

• Statistically assessing the effect of environment

Adaptation

Requires Natural Selection

Requires polymorphism in a population

MUST have an effect on Fitness

Is a frequency (%) change in a population

There must be a Selective Force

How can you tell if a trait evolved as a result of Adaptation (and due to Natural Selection)?

(1) The trait must be heritable

(2) The differences between populations are genetically based (in the genetic code) differences rather than inducible differences (plasticity)

(3) The trait has fitness consequences (promotes survival, performance, and number of offspring)

(If a trait evolved due to genetic drift, linkage or pleiotropy, the change is genetic, but may confer no fitness advantage)

Phenotypic Plasticity

Definition

• Differences in phenotype that a genotype exhibits across a range of environments, because of changes in gene expression

• Changes in gene expression could be cause by environmental cues instigating signal transduction... changes in gene expression could also be caused by epigenetic modifications

• Some traits with a plastic component: intelligence, height, temperature tolerance, salinity tolerance, muscle mass...
Acclimation (≠ Adaptation)

1) Result of Phenotypic Plasticity
2) Not heritable (Not inherited)
3) Short term or developmental response within a single generation
4) Arises through differential gene expression or other regulatory mechanism rather than natural selection

Allele A1 Demo

With Selection, what matters is the RELATIVE fitness of different genotypes

For instance, putting 1.0 and 0.9 is the same as putting 1000 and 900 for fitness values of genotypes

Selection on Dominant vs Recessive Alleles

Herron & Freeman

Selection against recessive allele
Set fitness of genotypes to:
\[ W_{AA} = 1, \ W_{Aa} = 1, \ W_{aa} = 1 - s \]
\( (s = \text{selection coefficient}) \)

Selection against dominant allele
Set fitness of genotypes to:
\[ W_{AA} = 1 - s, \ W_{Aa} = 1 - s, \ W_{aa} = 1 \]
(AA and Aa have same phenotype)

Allele A1 Demo

Likewise, dominant beneficial alleles are more difficult drive to fixation by positive selection, because they are dragging recessive alleles along in the heterozygous state

Although, if recessive beneficial alleles are very rare they will take longer to fix because most will be in the heterozygous (rather than homozygous state)
Selection on Dominant vs Recessive Alleles

- Selection against recessive allele:
  - As recessive allele becomes rare, rate of its disappearance slows down
  - As homozygote recessive allele becomes rare, most are in the heterozygous state and are masked from selection

- Selection against dominant allele:
  - Dominant allele that is disfavored by selection is removed quickly from the population

Modes of Selection

- Positive Selection: Selection favoring an allele or a heritable trait
- Negative Selection (Purifying Selection)
- Balancing Selection

Modes of selection on Loci

- Positive Selection
- Negative Selection (Purifying Selection)
- Balancing Selection

Balancing Selection (on discrete or continuous traits)

- Balancing Selection is a generic term to refer to any type of selection that acts to maintain genetic variation in a population
- There are different mechanisms: Fluctuating selection, selection favoring heterozygote (overdominance), frequency-dependent selection, etc.
- Examples:
  - Selection for heterozygotes (sickle cell anemia, and cystic fibrosis)
  - Selection for different traits in different environments
  - Selection for different traits at different times (fluctuating selection)

Balancing Selection

- An Example of one mechanism:
  - Overdominance: Selection favoring the heterozygote
    - AA 0.25 0.50 0.25
    - Generation 1
    - Generation 2
    - Generation 3
  - Genetic diversity is maintained in a population in this case because the heterozygote maintains both alleles
- Example: Sickle Cell anemia
Balancing Selection

- An Example of one mechanism:
  Overdominance: Selection favoring the heterozygote
  
<table>
<thead>
<tr>
<th>Generation</th>
<th>AA</th>
<th>Aa</th>
<th>aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.25</td>
<td>0.50</td>
<td>0.25</td>
</tr>
<tr>
<td>2</td>
<td>0.20</td>
<td>0.60</td>
<td>0.20</td>
</tr>
<tr>
<td>3</td>
<td>0.10</td>
<td>0.80</td>
<td>0.10</td>
</tr>
</tbody>
</table>

- In this case, allele frequencies (of A and a) do not change. However, the population did go out of HW equilibrium because you can no longer predict genotypic frequencies from allele frequencies.

- For example, for \( p = 0.5 \), the HW expected \( p^2 = 0.25 \), but in Generation 3, the observed \( p^2 = 0.10 \).

Sickle cell anemia

- Example of balancing selection

  - Reduced ability of red blood cells to carry oxygen (mutation in HbS gene, makes defective hemoglobin protein)
  - \( H^A H^A \): homozygous, no effects of disease (sickle cell anemia)
  - \( H^A H^s \): heterozygotes, suffer mild effects
  - \( H^s H^s \): homozygous, usually die before reproduction

Sickle cell anemia

- **BUT...** When Malaria is present, \( H^A H^s \) advantage: red blood cells with abnormal hemoglobin tend to sickle when infected by parasite and are culled out

  - In the presence of malaria, which genotype would be favored? Which mode of selection would be acting?

  - In the absence of malaria, which genotype would be favored? Which mode of selection would be acting?

Sickle cell anemia

- **When Malaria is present** \( H^A H^s \) advantage: red blood cells with abnormal hemoglobin tend to sickle when infected by parasite and are culled out

  - Example from Africa: 73.7% \( H^A H^A \); 24.3% \( H^A H^s \); 2% \( H^s H^s \)

- **When Malaria is not present**, AA advantage:

  - US African Americans: 91.26% \( H^A H^A \); 8.54% \( H^A H^s \); 0.2% \( H^s H^s \)

- With malaria, balancing selection favors the heterozygote

  - Without malaria, directional selection favors \( H^A H^A \)
Hardy Weinberg problem using actual data

- 1 in 5000 individuals have sickle cell disease and are homozygous for the sickle cell hemoglobin ($H^S H^S$)
- What are the expected genotype frequencies of the $H^A H^A$, $H^A H^S$, and $H^S H^S$ genotypes in the population?
- What are the frequencies of $H^A$ and $H^S$ alleles?

Sexual Selection for Heterozygosity at MHC loci

- Major Histocompatibility Complex (MHC) influences mating preferences and, in some cases, this may be mediated by preferences based on body odor
- Studies on rodents, and fish, and several studies on humans have reported a tendency to prefer MHC-dissimilar mates
- This is a sexual selection that would favor the production of MHC-heterozygous offspring, who would be more resistant to pathogens → A type of Balancing Selection favoring heterozygotes

Different Modes of Selection on Traits

**Directional Selection**
- Selection for traits that are either higher or lower on a continuum

**Stabilizing Selection**
- Selection for traits that are at a certain intermediate value

**Disruptive Selection**
- Selection against extreme values of a trait

Selection on Discrete vs Continuous characters

- When phenotypes fall into discrete classes, we can think of selection acting directly on genotypes
  - Such discrete traits are usually coded by one or a few genes (loci)
  - Mendel’s yellow vs. green peas
- However, when phenotypes fall into a continuum, because they are encoded by many loci, you will see changes in the distributions of traits (next slide)
  - Continuous traits such as those Darwin examined, beak shape, body size, hair color, etc.
  - such traits are called "quantitative traits"
**Directional Selection:**
Selection favors an extreme phenotype and causes a shift in allele frequencies toward that direction
- Genetic diversity is reduced at the relevant loci (knock out maladapted genotypes)
- **Examples:**
  - Drug-resistance in tuberculosis and HIV
  - Agriculture: artificial selection for specific traits
  - Sexual selection for a trait (e.g. for bright plumage, peacock tail)

**Directional Selection on a continuous trait**
- Selection favors extreme values
- Genetic diversity is reduced at the relevant loci
- **Examples:**
  - Drug-resistance in tuberculosis and HIV
  - Agriculture: artificial selection for specific traits
  - Sexual selection for a trait (e.g. for bright plumage, peacock tail)

**Stabilizing Selection**
- Selection favoring intermediate trait values
- The average trait value stays the same
- Genetic diversity is reduced at the relevant loci
- **Examples:**
  - Selection for an optimal number of fingers
  - Selection for optimal body size
  - Selection for optimal number of offspring

**Disruptive Selection**
- Selection favors the extremes
- Genetic diversity is increased (favors novel beneficial alleles; knock out alleles that code for intermediate traits)
- Can lead to formation of new species
- **Examples:**
  - Niche Partitioning (Specialization on different resources, food)
  - Differences in habitat use
  - Will discuss more in lecture on Speciation
  - Sexual selection for different traits (blue birds mate with blue, red birds mate with red)—intermediate colors selected against
Disruptive Selection

Some Examples of Directional Selection

- Directional selection in HIV in response to humans

Directional Selection on pathogens imposed by Drugs (refer to Lecture 1)

- AZT (Azidothymidine) is a thymidine mimic which stops reverse transcription
- Mutations in the reverse transcriptase gene of HIV arise such that the enzyme can recognize AZT
- The drugs impose Selection on the virus. Genetic variation (generated by mutations) allows the virus to respond to selection and evolve drug resistance

- In the presence of AZT, Natural Selection favors mutants that are resistant to AZT (blue, have slow & careful enzyme)
- Results in % change in the population, toward higher % of AZT resistant mutants

- Directional selection in Human populations in response to HIV
**The CCR5-Δ32 Allele**

- C-C chemokine receptor 5 (CCR5) is expressed on the surface of white blood cells (T cells, macrophages, etc). The HIV-1 virus uses CCR5 as a co-receptor to enter the cell.

- CCR5-Δ32 (or CCR5-D32 or CCR5 delta 32) is a mutant allele of the receptor CCR5, where the deletion of a 32 base pair segment makes the receptor nonfunctional.

- Homozygotes for this allele are resistant to HIV-1, which cannot enter the cell.

Amy D. Sullivan et al. 2001. The co-receptor mutation CCR5Δ32 influences the dynamics of HIV epidemics and is selected for by HIV. Proc Natl Acad Sci USA. 98: 10214–10219.

---

**Frequency shift in CCR5-Δ32 allele in HIV prevalent regions**

Frequency shift in CCR5-Δ32 allele showing a high frequency in Northern Europe.

---

**The first gene-edited humans using CRISPR-CAS**

He Jiankui created the world’s first gene-edited babies to have the delta32 allele.

- We do not know if there are any tradeoffs associated with this allele.

- https://www.nature.com/articles/d41586-019-03032-2

---

**Directional selection in Human populations in response to a novel nutritional source:**

- The ability to consume milk (lactose) as adults.

Mammals lose their ability to consume milk (lactose) as adults, but some human populations are unusual in their ability to retain the ability.

Global Map of Lactase Persistence
(based on indigenous populations of the Old World)

Global Map of Lactase Persistence Genotypes
(based on indigenous populations of the Old World; Itan, Yuval (2010), BMC Evolutionary Biology 10: 36)

Mutations in the LCT promoter that result in alleles that significantly enhance transcription of LCT (Lactase)

(a) Distribution of 123 SNPs included in genotype analysis. (b) Map of the LCT and MCM6 gene region. (c) Map of the MCM6 gene. (d) Location of lactase persistence–associated SNPs within introns 9 and 13 of the MCM6 gene in African and European populations. (Tishkoff et al. 2007)

Directional Selection for Lactase Persistence

Evolution of lactase persistence (LP) in Europe over the last 10,000 years. The curves show theoretical expectations of the trajectory of an allele under selection for various selection coefficients (s) with a final allele frequency of 50% (light purple lines) or 60% (dark purple lines) superposed on −13.910:T allele frequencies observed in ancient DNA data sets (colored squares). The allele frequencies of 50% and 60% correspond to LP frequencies of 75% and 80%, respectively, as observed in modern populations from central Europe. The sizes of the colored squares are proportional to the number of samples (from 1 to 35), and the colors indicate the area of origin of the human remains. We used a generation time of 30 years to obtain dates in years (Ségurel & Bon, 2017)

Sequencing of Ancient DNA from humans

Paleolithic Europeans were lactose intolerant

Directional Selection during Domestication

- Rapid evolution under intense directional selection for large and numerous kernals
- Selection by humans for a few regulatory genes (affecting transcription)
- Reduced genetic diversity in domesticated corn

Morphological differences between teosinte and maize

- Has branching patterns like teosinte
Major morphological differences are due to directional selection on 5 genes

Genes:
• Teosinte branched1 (tb1): single mutation affects branching and inflorescence
• Regulator of tb1
• tga glume (outer coating) reduction on chromosome X
• teosinte – 6-12 kernels
• F1 hybrid 8 rows, corn 20+ rows

Evidence for selection in 2-4% of genes, ~1200 genes

Does sexual selection typically act on more on males or females?

Sexual Directional Selection:
Selection favors an extreme phenotype and causes a shift in allele frequencies toward that direction

- Most of the males do not mate, so their genotypes (and phenotypes) are removed from the population → genetic diversity reduced at the relevant loci
- The population shifts toward the extreme trait (e.g. plumage, body size, etc)

Detecting Selection

Large variance in male reproductive success, with many producing few to no offspring, and a few males producing lots of offspring
So, how does one detect Natural Selection in a population?

- Many types of tests
- The challenge is distinguishing natural selection from signatures of Genetic Drift

**RNA Codons**

In the case of amino acids

- Mutations in Position 1, 2 lead to Amino Acid change
- Mutations in Position 3 often don’t matter

---

**Simplest Test: \( K_a/K_s \) Test**

\[
\frac{\text{Nonsynonymous substitution rate}}{\text{Synonymous substitution rate}} = \frac{K_a}{K_s} > 1
\]

- Need coding sequence (sequence that codes proteins)
- \( K_s \) is used here as the “control”, proxy for neutral evolution
- A greater rate of nonsynonymous substitutions (\( K_a \)) than synonymous (\( K_s \)) is used as an indication of selection (\( K_a/K_s > 1 \))
- Substitution rate: out of all the possible number of mutations, how many fixed

**\( K_a/K_s \) Test**

\[
\frac{\text{Nonsynonymous substitution rate}}{\text{Synonymous substitution rate}} = \frac{K_a}{K_s} > 1
\]

- In the absence of selection, you’d expect \( K_s = K_a \), and for \( K_a/K_s = 1 \)
- A greater rate of nonsynonymous substitutions (\( K_a \)) than synonymous (\( K_s \)) is used as an indication of positive selection (\( K_a/K_s > 1 \))
- If \( K_s > K_a \), or \( K_a/K_s < 1 \), that would suggest purifying selection, that selection might be preserving amino acid composition

---

**Summary**

1. Of the evolutionary forces that can disrupt HW Equilibrium, Natural Selection is the only one that is adaptive
2. Selection occurs through differential reproduction which is NOT random
3. Natural selection requires genetic variation upon which it can act
4. There are different ways in which selection can act (favoring the extremes, or heterozygotes, or unidirectional)

**Concepts**

- Natural Selection
- Fitness
- Directional, Stabilizing, Disruptive Selection
- Balancing Selection
- Selection on dominant vs recessive alleles
The following are numbers of red, pink, and white flowers in a population.

<table>
<thead>
<tr>
<th>(A1A1)</th>
<th>(A1A2)</th>
<th>(A2A2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red</td>
<td>Pink</td>
<td>White</td>
</tr>
<tr>
<td>400</td>
<td>200</td>
<td>400</td>
</tr>
<tr>
<td>600</td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>500</td>
<td>0</td>
<td>500</td>
</tr>
</tbody>
</table>

Generation 1: 400 200 400
Generation 2: 600 100 300
Generation 3: 500 0 500

1. Is the population above in Hardy-Weinberg Equilibrium?
   (A) Yes
   (B) No
   (C) Yes in the first generation, but No in the third generation
   (D) No in the first generation, but Yes in the third generation

2. What are the frequencies of alleles and genotypes at Generation 3?
   (A) A1: 0.50, A2: 0.50
       A1A1: 0.25, A1A2: 0.50, A2A2: 0.25
   (B) A1: 0.65, A2: 0.35
       A1A1: 0.60, A1A2: 0.10, A2A2: 0.30
   (C) A1: 0.50, A2: 0.50
       A1A1: 0.50, A1A2: 0, A2A2: 0.50
   (D) A1: 0.50, A2: 0.50
       A1A1: 0.25, A1A2: 0, A2A2: 0.25

3. In the previous example (from question #1), what might be going on?
   (A) Genetic Drift
   (B) Balancing Selection
   (C) Recombination
   (D) Directional Selection
   (E) Disruptive Selection (but, rare for single locus trait)

4. What would Darwin say?
   (A) Genetic drift is also an important evolutionary force that occurs through random survival and reproduction
   (B) Individuals pass alleles onto their offspring intact (inheritance is particulate)
   (C) Selection acts on genetic variation such as Mutations
   (D) Selection acts on differential fitness of individuals that vary in heritable traits in a population
   (E) Evolution occurs at the level of the individual

Answers:
1B
2C
3E
4D