Evolutionary Mechanisms

Genetic Drift (and Inbreeding)

Sources of Genetic Variation

Natural Selection
Natural Selection acts on genetic or epigenetic variation in a population
Without genetic or epigenetic variation, Natural Selection cannot occur

Mutation generates genetic variation
Epigenetic modification changes expression of genes
Genetic Drift causes fluctuations in allele frequencies and can reduce genetic variation

Migration (fairly obvious)

- Can act as a Homogenizing force
  (If two populations are different, migration between them can reduce the differences)
- A population could go out of HW equilibrium with a lot of migration

Impact of Migration

- Immigration: could introduce genetic variation into a population
- Emigration: could reduce genetic variation in a population

Today's OUTLINE:

1. Migration
2. Genetic Drift
3. Effective Population Size
4. Model of Genetic Drift
5. Heterozygosity
6. A Consequence of Genetic Drift: Inbreeding
Random Genetic Drift

**Sewall Wright (1889-1988)**
- Sewall Wright worked on agricultural stocks (e.g. cows), and was consequently interested in small, inbred populations
- Thus, he regarded Inbreeding and Genetic Drift as particularly important genetic mechanisms
- Genetic Drift and Inbreeding could generate new gene interactions
- These new gene interactions (epistasis caused by new recombinations) are the main substrate for selection

Even after the synthesis the relative importance of Natural Selection and Genetic Drift were debated

- During the Evolutionary Synthesis, Sewall Wright focused more on importance of Genetic Drift, whereas Fisher focused on Natural Selection
- Shortly after the Evolutionary Synthesis many focused on selection to the point of assuming that most phenotypes were the result of Natural Selection
- Emphasis on Genetic Drift resurfaced in the 1970s, 80s with Kimura’s “Neutral Theory”
- Then in the 2000s and 2010s interest in Selection increased with the ability to detect signatures of Natural Selection in genome sequence data

**Motoo Kimura (1924-1994)**

The Neutral Theory of Molecular Evolution


**Molecular Clock**

Observations of amino acid changes that occurred during the divergence between species, show that molecular evolution (mutations) takes place at a roughly constant rate.

This suggests that molecular evolution is constant enough to provide a “molecular clock” of evolution, and that the amount of molecular change between two species measures how long ago they shared a common ancestor.

From this, Kimura concluded that most molecular evolution is “neutral” and dominated by random mutations and genetic drift.

Figure: the rate of evolution of hemoglobin. Each point on the graph is for a pair of species, or groups of species. From Kimura (1983).

**The Neutral Theory of Molecular Evolution** (Lecture #6)

- The Neutral theory posits that the vast majority of evolutionary change at the molecular level is caused by random genetic drift rather than natural selection.
- Neutral theory is not incompatible with Darwin’s theory of evolution by natural selection: adaptive changes are acknowledged as present and important, but hypothesized to be a small minority evolutionary change.
- Purifying selection (negative selection) could still be acting to remove deleterious mutations from the genome. But, the idea here is that most of the genetic variation within and between populations is due to neutral variation (mutations and genetic drift).
- **Ongoing debate on the extent to which variation across the genome is caused by genetic drift vs. natural selection.**
I. Random Genetic Drift

- **Definition:** Changes in allele frequency from one generation to the next simply due to chance (sampling error).
- This is a NON ADAPTATIVE evolutionary force.
- Darwin did not consider genetic drift as an evolutionary mechanism, only natural selection.

Genetic Drift

- Genetic Drift happens when populations are limited in size, violating HW assumption of infinite population size.
- When population is large, chance events cancel each other out.
- When population is small, random differences in reproductive success begin to matter much more.

Effective Population Size

- In Evolution, when we talk about population size, we mean effective population size.

Effective Population Size

- The effective population size is always either equal to or less than the census population size ($N$).
- The effective population size is usually smaller than the real census population size because not everyone breeds and leaves offspring.
- Unequal sex ratio, variation in number of offspring, overlapping generations, fluctuations in population size, nonrandom mating could lead to an effective population size that is smaller than the census size.

$$N_e = \frac{4N_mN_f}{N_m + N_f}$$

where $N_m =$ number of males, $N_f =$ number of females.

- From this equation, you can see that unequal sex ratio would lead to lower $N_e$.

- Why do we care about effective population size $N_e$?
  - Because $N_e$ is the actual unit of evolution, rather than the census size $N$.
  - Why? Because only the alleles that actually get passed onto the next generation count in terms of evolution… the individuals that do not mate or have offspring are evolutionary dead ends…
  - If a population is completely inbred, its $N_e = 1$, even if the census size is large.

Title goes here
Chance Events (no Selection)

There is always an element of chance, in:
- Who leaves Offspring
- # of Offspring
- Which Offspring survive (which gametes, which alleles)

Example of sampling error

| Green fur:  | G (dominant) |
| Blue fur:   | b (recessive) |

If Gb x Gb mate, the next generation is expected to have: 3:1
Ratio of Green to blue (GG, Gb, bG, bb)

But this might not happen

One family could get this unusual frequency just due to chance:
You might get: bb, bb, bb, bb
And, so you might accidentally lose the G allele not for any reason, but just due to chance

The larger the population, the more these effects average out, and frequencies approach HW equilibrium

Why is this not Selection?

Selection happens when some survive for a reason: better adapted.

Genetic Drift is just a numbers game. Which gamete gets fertilized, which allele gets passed on is RANDOM

Consequences of Genetic Drift

Random fluctuations in allele frequency

If population size is reduced:

1. At the Allelic level: Random fixation of Alleles (loss of alleles)
2. At the Genotypic level: Loss of Heterozygosity (because of fewer alleles)

Random Shift in Allele Frequencies across Generations

(a) Generation 0: 40% A1, 60% A2
(b) Generation 1: 50% A1, 50% A2
(c) Generation 2: 85% A1, 15% A2

Probability of loss of alleles is greater in smaller populations

- For example, if there are 50 different alleles in population
- …and a new population is founded by only 10 individuals
- Then the new population will be unable to capture all 50 alleles, and many of the alleles will be lost
**Bottleneck Effect**

*Random fixation of alleles*

**FIXATION:** When an allele frequency becomes 100%
The other alleles are lost by chance
Fluctuations are much larger in smaller populations

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**Probability of fixation of an allele**

- Probability of fixation of an allele = the allele’s starting frequency (Sewall Wright 1931)
- That is, if the frequency of an allele is 0.10 (10% in the population), then its probability (chances) of fixation (going to 100% in the population) is 0.10, or 10%

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**Probability of fixation of an allele**

- What is the Probability of fixation of an allele if its starting frequency is 0.20, or 20%?
- What is the Probability of fixation of an allele if its starting frequency is 0.60, or 60%?

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**Probability of fixation of an allele**

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**Probability of fixation of an allele**

- If a population has 2N alleles
- The probability of each allele being fixed = \( \frac{1}{2N} \)
- If there are \( X \) # copies of that allele in the population, then the probability of fixation for that allele is \( \frac{X}{2N} \)
- This is the proportion (%) of alleles in the population
After 7 generations, all allelic diversity was lost… the population became fixed for allele #1 just due to chance.

Loss of CYP (detoxification) alleles moving away from African

Greatest diversity in Africa, loss as you leave Africa


Genetic Drift: Random Fixation

As populations get smaller, the probability of fixation or extinction of alleles go up.


Heterozygosity

- Heterozygosity: frequency of heterozygotes in a population (% of heterozygotes)
- Often used as an estimate of genetic variation in a population
- HW expected frequency of heterozygotes in a population (at a locus with two alleles) = 2p(1-p)
- As genetic drift drives alleles toward fixation or loss, the reduction in number of alleles causes the frequency of heterozygotes to go down.

\[ H_{g+1} = H_g \left(1 - \frac{1}{2N_e}\right) \]

Note in this equation that as population size \(2N_e\) gets small, heterozygosity in the next generation \(H_{g+1}\), goes down.

Loss of Variation

Lots of alleles \(\rightarrow\) Lots of genotypes:

- Allele frequencies
  - 0.36
  - 0.16
  - 0.20
  - 0.24
  - 0.04

Heterozygosity declines faster in smaller populations.
Loss of Allelic Variation

Due to Genetic Drift

Allele frequencies

- 0.53
- 0.067
- 0.20
- 0.20
- 0

Loss of Allelic Variation due to Genetic Drift results in Increased Homozygosity

Fewer possible genotype combinations

Increase in homozygosity

No Genetic Variation = No Natural Selection

Selection has nothing to act on

Genetic Drift and Natural Selection

- Because of the randomness introduced by Genetic Drift, Natural Selection is less efficient when there is genetic drift
- Thus, Natural Selection is more efficient in larger populations, and less effective in smaller populations

Allele A1 Demo

- Impact of Effective Population Size
- Impact of starting allele frequency
- Interaction between Natural Selection and Genetic Drift
How do you detect Genetic Drift?

- Random fluctuations in allele frequencies
- Fluctuations in non-coding and non-functional regions of the genome
- The same pattern of fluctuations across these regions of the genome (same demographic factors would act across the genome) - but mtDNA not same
- Fluctuations in allele frequencies correspond to demography of the population (population size)

Consequences of Genetic Drift

--> Random fluctuations in allele frequency

If population size is reduced and Drift acts more intensely, we get:

1. At the Allelic level: Random fixation of Alleles (loss of alleles)
2. At the Genotypic level: Inbreeding, Reduction in Heterozygosity (because of fewer alleles)

Dilemma for Conservationists

- It is easier to remove genetic diversity than create it... especially variation that is potentially adaptive

Census size: Roughly 2000-3000 cheetahs live in Namibia today

The effective population size is much lower

2. Genetic Drift often leads to Inbreeding

- Inbreeding is a consequence of Genetic drift in small populations, resulting from loss of alleles
- Due to loss of alleles, there is an increase in homozygosity

Inbreeding

- Mating among genetic relatives, often because of small population size
- Alleles at a locus will more likely become homozygous
- A consequence of loss of alleles due to genetic drift (reduction in population size)
Calculations like these are used in genetic counseling and animal breeding to calculate $F$, the coefficient of inbreeding (developed by Sewall Wright)

$F = \sum \{ (1/2)^{n+1} (1 + F_A) \}$

$F$ is the inbreeding coefficient for the common ancestor

$F = \text{fixation index}, \text{a measure of homozygosity; the probability that two alleles at any locus in an individual are identical by descent from the common ancestor(s) of the two parents (homozygous, rather than heterozygous). (F=1 means individuals are genetically identical)}$

$F_A$ is the inbreeding coefficient for the common ancestor

Consequences of Inbreeding

- **Increase in Homozygosity:**
  - Exposure of recessive alleles (that could be subjected to selection)
  - Inbreeding Depression (reduction in survival and fitness)

- Lower genotypic diversity (poor response to natural selection)

Consequences of Inbreeding

- Deleterious recessive alleles are exposed as homozygotes (and less masked in the heterozygous state)

- These deleterious recessive alleles get removed out of an inbred population more rapidly, because they are exposed to natural selection

--- this process is aided by Sex, discussed in Next Lecture (on Variation)
Mechanism:

- Most deleterious alleles are recessive
- On average each of us carries 3-5 lethal recessive alleles
- These deleterious alleles are expressed in inbred individuals
- In Heterozygotes, these deleterious recessives are masked, and not exposed to selection

Examples of Inbreeding

Inbreeding and Conservation
Vexing Problem:

- How do we prevent extinctions?
- How do we maximize genetic variance in a population?
- What should we preserve? (species, populations, habitats, ecosystems???)

Inbreeding and Agriculture:

Because we have focused excessively on a few breeds, effective population sizes of many crops are incredibly small

600 breeds of livestock have disappeared
~78 breeds lost each year

1000-1500 breeds of livestock are considered at risk of extinction (30% of current breeds)
8 million Holstein cows are descendents of 37 individuals!!!

Neurological disorders
Autoimmune diseases
Fertility problems

Actually, only 3.38 million cows (1.28 million dairy cows) in Wisconsin in 2017, as dairy farms have been closing.


Recent efforts have focused on outcrossing to increase fitness in agricultural stocks

Genetic Diseases due to Inbreeding have afflicted many Royal Families

Examples:
Porphyria: accumulation of porphyrin precursors, causes insanity; Dominant, but more intense in the homozygous form
Mary, Queen of Scots
George III, loss of American colony

Acromegaly: Overproduction of GH by the pituitary gland, recessive
Charles II, King of Spain (1665-1700)

Hemophilia: “Victoria’s Secret” X-linked, shows up in males
Daughters spread it among the royals, downfall of Russian monarchy

Porphyria in the Royal Families of Europe

Dominant, but more intense in the homozygous form

Royal Pedigree of the “Hapsburg Jaw”

In small populations, individuals tend to mate with relatives
Inbreeding within the Royal Families of Europe was genetically “disastrous.”

Inbreeding within Royal Families has been reduced in recent years.

Diana was a 7th cousin of Charles, rather than a first or second cousin (which was the normal practice previously).

Kate Middleton and Meghan Markle are neither aristocrats nor royals, but the marriages were approved (against tradition) given the modern recognition of the perils of inbreeding… these marriages are examples of genetic immigration (Migration) into an enclosed population.

Articles on British Royalty and Inbreeding:

News Article:

Original Scientific Article:
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0005174

Examples of Diseases that Afflict Amish Populations

- High levels of infant mortality
- High Incidence of brain damage
- Large number of metabolic disorders, such as PKU
- Ellis-van Creveld (dwarfism) syndrome
  1/14 in Amish
- Glutaric aciduria type I
  1/200 in Amish
- High incidence of bipolar disorder
- Polydactyly (6 fingers)

There is nothing special about the Amish, genetically speaking (or Royal Families).

- There are about ~200 of you here, similar to the size of the founding Amish population in Lancaster county, Pennsylvania.
- If all of you were stranded on a desert island, eventually your descendents would be related and mating with one another.
- Each of us carries 3-5 lethal recessive alleles.
- If 200 people each had 3-5 different recessive lethals and started forming a closed population, eventually, hundreds of genetic disorders would emerge.
FIND Your Genetically Most Distant Mate!!!!

Examples of Genetically-based dating services (genotypes MHC loci → attraction is not a coincidence; we will discuss in lecture on Sexual Selection)

GenePartner: "Love is no coincidence!"
http://www.genepartner.com/

Instant Chemistry
https://instantchemistry.com/

DNA Romance
https://www.dnaromance.com/

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Song that appears to discuss MHC Loci (DNA)
https://www.youtube.com/watch?v=MBdVXkSdhwU

Summary

1. Genetic Drift occurs when a population is small, and leads to random loss of alleles due to sampling error

2. Inbreeding, an extreme consequence of Genetic Drift, results in increases in homozygosity at many loci, including recessive lethals

CONCEPTS

Genetic Drift
Effective population size
Fixation
Heterozygosity
Inbreeding
Inbreeding Depression
Heterozygote advantage

1. When is Genetic Drift LEAST likely to operate?
   (A) When there is low migration between populations
   (B) When populations are fragmented and isolated
   (C) When population size is small
   (D) When population size is very very large
   (E) When strong selection is acting on a population

2. Which of the following is FALSE regarding inbreeding?
   (A) Inbreeding could result as a consequence after genetic drift has acted on a population
   (B) Populations with lower allelic diversity tend to have lower genotypic diversity (more homozygous)
   (C) Selection acts more slowly in inbred populations to remove deleterious recessive alleles
   (D) One way to reduce inbreeding in a population is to bring in migrants from another population

3. Which of the following is FALSE regarding Genetic Drift?
   (A) Genetic Drift occurs more intensely in smaller populations
   (B) In populations of finite size, random changes in allele frequency occur at each generation
   (C) Genetic Drift could lead to inbreeding due to loss of alleles
   (D) Genetic Drift occasionally leads to the creation of favorable alleles
Answers to sample exam questions:

- 1D
- 2C (deleterious alleles are exposed to selection in inbred populations)
- 3D