Roadmap

Genetic drift is change in allele frequencies due to chance fluctuations; its strength depends on population size.

- Rate of fixation (recap)
- Proportion of homozygotes in population (genetic diversity)
- Drift versus selection: who will win?

One-minute responses

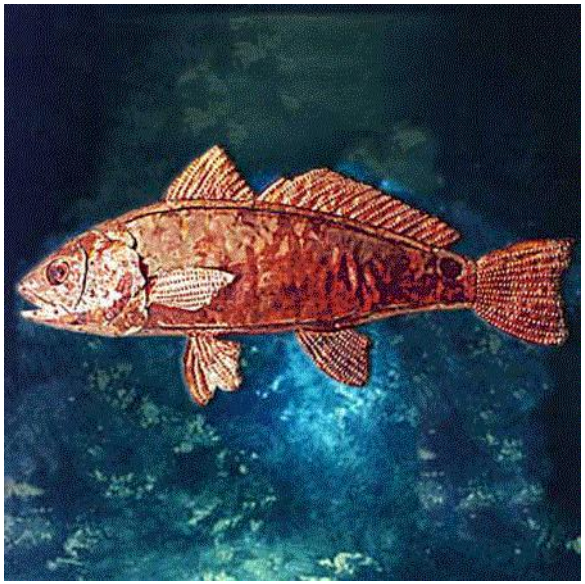
- Q: How is the effective population size equation for a cycling population derived?

- A: It's in Felsenstein's book pp. 258-259
  - Find a term for how much diversity is lost per generation due to drift
  - 1 minus that term is how much is retained
  - Multiply over generations, using each generation's population size
  - This reduces to (approximately) the formula I gave

- Q: Why?

Why N_e matters

- Red drum are large fish of the Gulf of Mexico
- Effective size 1000 times lower than census size
- This species has the numbers of a big population but the genetic drift of a small one
- Likely explanation is very unequal reproductive success



Why N_e matters

- Red drum spawn in very specific estuary environments
- A few lucky clutches have thousands of survivors; most have none
- Allele frequencies change substantially from one generation to the next, reflecting the few lucky individuals

Who cares about N_e?

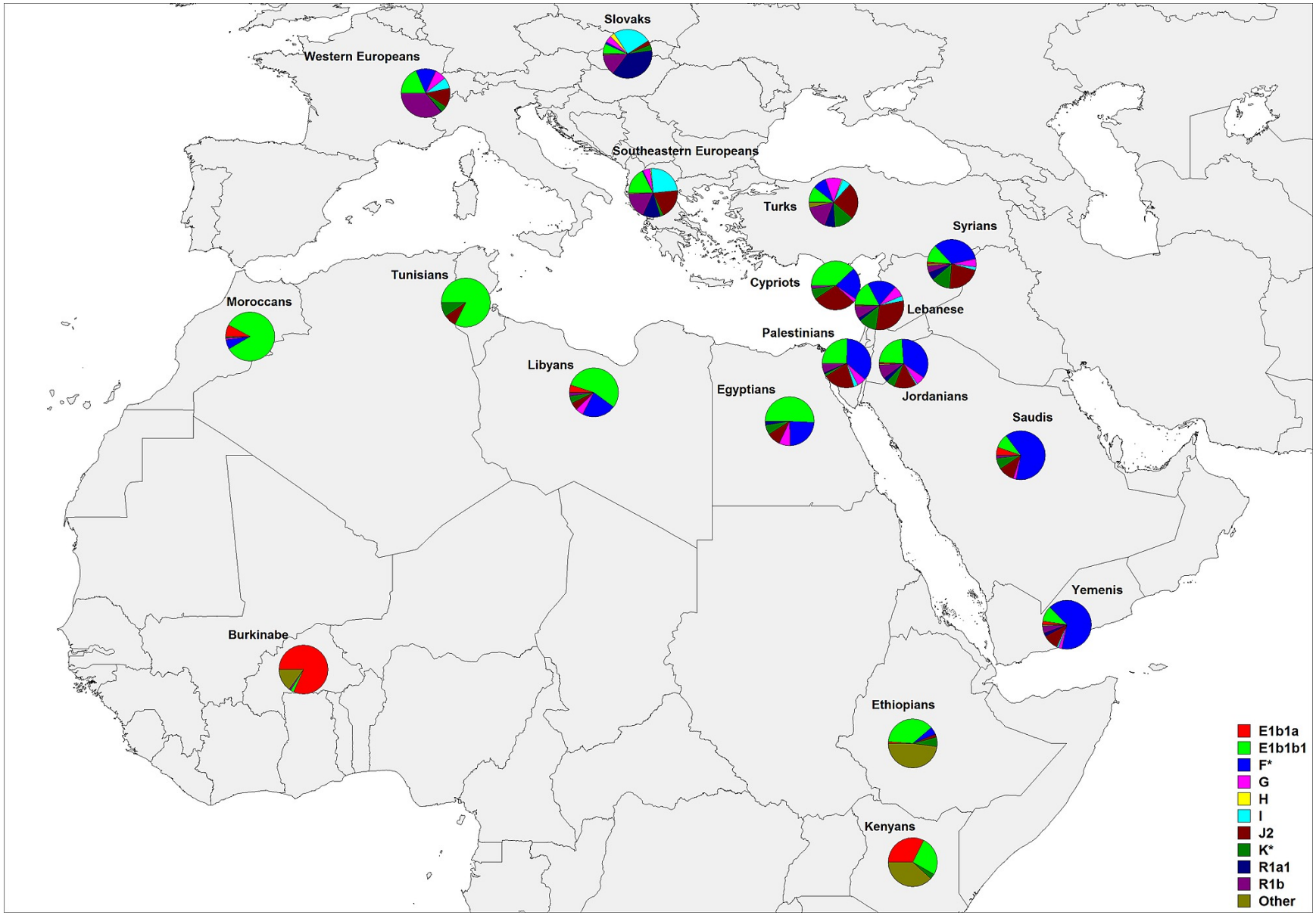
- Conservation biologists
  - How much diversity will a given population size/structure lose?
  - How can we minimize losses?
- Epidemiologists
  - What are a population's likely resources for dealing with a new treatment?
  - How can we reduce them?
- Animal breeders
  - How much trouble will we get in if we mainly breed from the few best males?

Other non-ideal populations

- Unequal males and females (domestic cattle)
- Overlapping generations (redwoods)
- Nonrandom reproductive success (racehorses)

Non-random reproductive success

- Human females have low variance in reproductive success (Wikipedia record: 69)
- Human males have much more variance (Wikipedia record: 860)
- Genetic drift is stronger in male-only than female-only DNA
- Could explain why Y chromosome shows more population-specific traits than mtDNA
- Alternative: sex-specific migration/dispersal



Y-chromosome variation in Europe and North Africa

Describing the drift process

Here are several related, but distinct, questions:

- What is the probability that a specific new mutant will eventually fix?
- What is the overall rate of fixation of new mutants?
  - How many new mutants destined to fix arise each generation?
  - How fast do two species diverge by drift?
- How long does it take a mutant to fix on average?
- How much variation will be present in a population on average?

Describing the drift process

Taking them one at a time:

- What is the probability that a specific new mutant will eventually fix? $\frac{1}{2N_e}$
- What is the overall rate of fixation of new mutants? $\frac{2N_e\mu}{2N_e} = \mu$
- How long does it take a mutant to fix, on average? $2N_e$ generations
- How much variation will be present in a population on average?

Fraction of homozygotes

- Counting alleles is not a good way to quantify variation
  - Too sensitive to very rare alleles
- Measure variation as proportion of homozygotes–the fewer homozygotes, the more variation
  - Call the proportion of homozygotes F
  - With two equally frequent alleles, $F = 0.5$

Fraction of homozygotes

- In cases with mutation and drift, an approximate formula is: $F \approx \frac{1}{1+4N_e\mu}$
- This approximation assumes that every mutation is to a new allele. It is quite accurate in practice even when that's not true, as long as there are a decent number of different alleles possible.

Fraction of homozygotes

$F \approx \frac{1}{1+4N_e\mu}$

Intuitive results of this equation:

- If the population is large, there will be fewer homozygotes (more diversity)
- If the mutation rate is large, there will be fewer homozygotes (more diversity)

(Always ask yourself–does this equation predict results that are in the right general direction?)

Fraction of homozygotes–Practice problem

(Fictional problem inspired by real data of Potts et al.)

$F \approx \frac{1}{1+4N_e\mu}$

- We measure heterozygosity at one gene in the mouse MHC as 92%
- Mutation rate (based on rat/mouse comparison) is around average for rodents: 10^{-6} per gene per generation
- How many mice does this imply, if the MHC were non-selected?
- (You'll actually calculate N_e–that's okay)

Fraction of homozygotes–Practice problem

(Fictional problem inspired by real data of Potts et al.)

- $F \approx \frac{1}{1+4N\mu}$
- $0.08 \approx \frac{1}{1+4Nx10^{-6}}$
- $N = 2,875,000$ mice
- This seems to be too many mice for a local population. The mouse MHC is not neutral....

Selection versus drift

What happens if a new advantageous allele appears?

- Selection will try to fix it
- Drift will push it around randomly and may eliminate it
- Which will win?

Selection versus drift

- A new malaria-resistance allele arises in Africa (in a single copy)
- It gives heterozygotes a 10% survival advantage
- Intuitively, what is the chance that this allele will spread throughout Africa?

Selection versus drift

- When an allele is rare, it is in heterozygotes
- Need a variable for the advantage of heterozygote over common homozygote
- Call it g
- (Textbooks call it s but I find this very confusing!)
- Chance of fixation is approximately $2g$

Selection versus drift

Here are some exact results and approximation results for the chance that a favorable allele (with an advantage in the heterozygote) will fix:

g	exact result	approximation
0.01	0.0197	0.02
0.02	0.0390	0.04
0.05	0.0937	0.10
0.10	0.1761	0.20
0.20	0.3137	0.40
0.50	0.5828	1.00
1.00	0.7968	2.00

Clearly the approximation has failed in the last two rows, but for weak selection it's okay.

Selection versus drift

- A new malaria-resistance allele arises in Africa (in a single copy)
- It gives heterozygotes a 10% survival advantage
- What is the probability that it will survive and spread?
- Was your intuition wrong? Why?

Drift in a large population?

- Rare alleles are always vulnerable to drift
- The bigger the population, the rarer a newborn allele is
- Population 1000:
  - New allele starts at 0.0005
  - Lost by drift 99.95%
- Population 100,000:
  - New allele starts at 0.000005
  - Lost by drift 99.9995%
- So in a large population, drift is weaker but new alleles start out rarer and more vulnerable

Drift in a large population?

- Large populations have an additional advantage: the same mutation will occur more often, giving more chances for it to fix
- With 7 billion people and a mutation rate around 1 in a billion, humans try almost every single-base-pair mutation every generation!
- *E. coli* tries every combination of up to 3 mutations every thousand years

Too-weak selection

- In general, selection will be too weak to have a visible effect if $g << 1/(2N_e)$
- Selection will overcome drift **if the allele survives its vulnerable early period** when $g >> 1/(2N_e)$
- Both forces are very significant when $g \approx 1/(2N_e)$

What about a favorable recessive?

- Our formula gives it no chance, but this is wrong
- An advantageous recessive has a hard time initially
- Most such alleles are lost from the population no matter how good they are
- The bigger the population, the more rapidly it can "try again"
- Try this in PopG for yourselves (be sure to make it rare!)

Drift and underdominance

- In a small enough population, drift can overcome underdominance
- In a large population, an underdominant locus will fix one allele or the other depending on which side of the equilibrium it's on
- This can lead to fixation of a worse allele
- In a small population, drift can push the allele frequencies past the equilibrium

Drift and underdominance

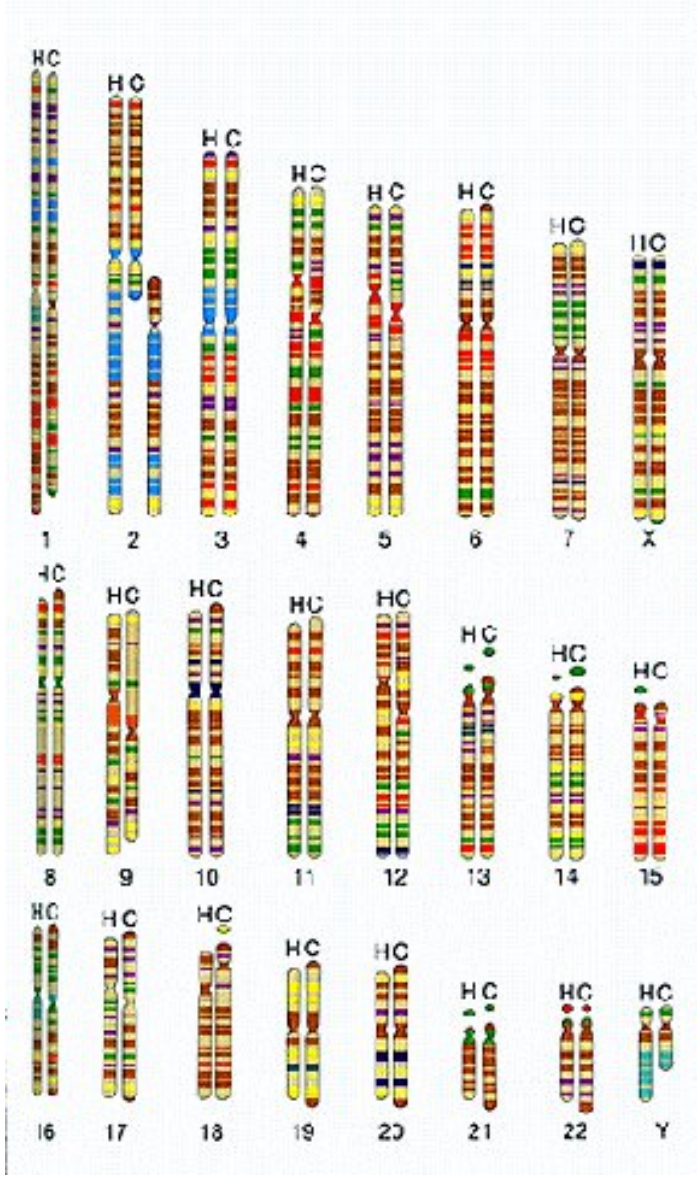
Genotype	BB	BO	OO
Fitness	1.0	0.8	0.9

- Big orange population:
  - A new mutation to blue is doomed
  - It will be in heterozygotes and they are inferior
- Tiny orange population (size 10)
  - A new mutation to blue has frequency 0.05
  - Without selection it would fix 5% of the time
  - Even with selection it has a chance (I used PopG to estimate 4%)

- PopG suggests there is also around a 0.5% chance that an all-blue population can turn orange, even though orange is worse than blue

Drift and underdominance

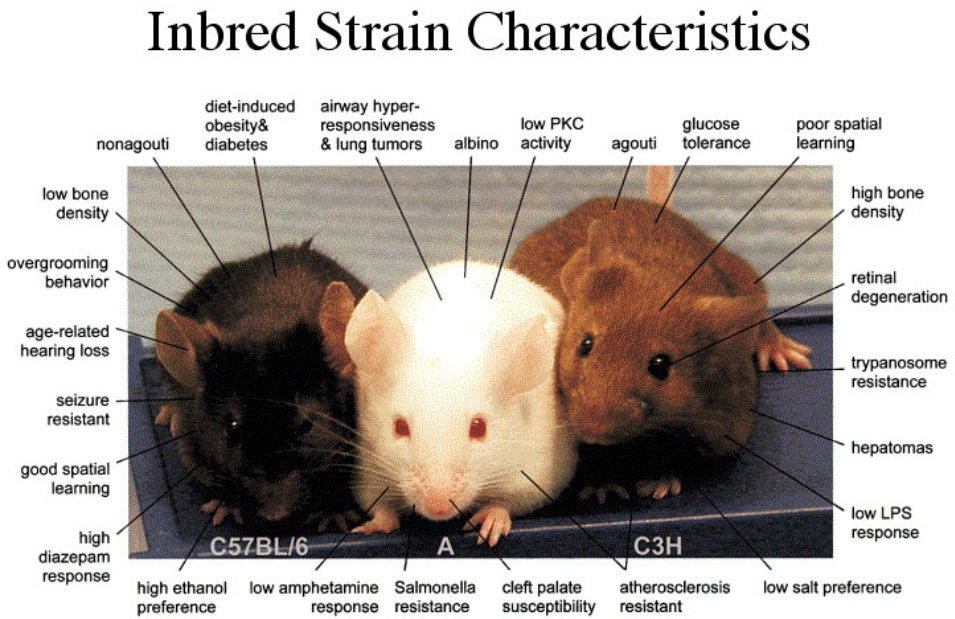
- Usually underdominant:
  - Change in chromosome number
  - Change in chromosome arrangement (big inversions, etc)
  - Major change in developmental program (the "hopeful monster")
- In a large population these changes are eliminated by selection
- In a small population they may be able to succeed
- Small populations are key players in the origin of species



Human versus chimpanzee chromosomes

Risks of small populations

- Inbred mice strains come from repeated brother-sister mating (population size 2)
- About half the time all the mice die between generations 7 and 15
- Drift pushes up the frequency of a harmful or fatal allele



Risks of small populations

- Sample of 82 cheetahs tested for 52 blood enzyme loci
  - In other cat species, 20%-50% of loci would differ
  - Zero variation found in cheetahs

African Cheetah (photo by Mukul2u, from Wikipedia)

Risks of small populations

- Wildlife Safari lost 60% of its cheetahs in 1 year due to viral epidemic
- Multiple fixation of poor alleles leads to:
  - Low sperm counts (10% of normal for cats)
  - High rates of bone malformation
  - High infant mortality
- Bottleneck estimated 12,000 years ago (Ice Ages)
- There is no way for the population to quickly recover its diversity

Risks of small populations

Could cloning dangerously reduce human population size?

- Cloning a few individuals many times reduces N_e (violates "equal reproductive success")
- Current human population is MUCH LARGER than needed to maintain current variation
- Bad idea to colonize a planet by cloning a few people many times

Discussion question

- I keep saying human genetic diversity is *increasing*
- Many sources say it is *decreasing* due to globalization
- What is really happening?

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