Roadmap

- Optimal mutation rate
- Dominance and its implications
  - Why is an allele dominant or recessive?
  - Overdominance (heterozygote advantage)
  - Underdominance (heterozygote inferiority)

One minute responses

- Q: I don't understand degrees of freedom! (About six of these....)
- Q: Show the calculation of μ and ν

Degrees of freedom revisited

Thanks to Patrick Runkel:
http://blog.minitab.com/blog/statistics-and-quality-data-analysis/what-are-degrees-of-freedom-in-statistics

	A	a	Total
A			20
a			10
Total	15	15	

One more look at degrees of freedom

Fictional data for sickle-cell hemoglobin (alleles A and S) in African-American adults

Normal AA	400
Carrier AS	90
Affected SS	10

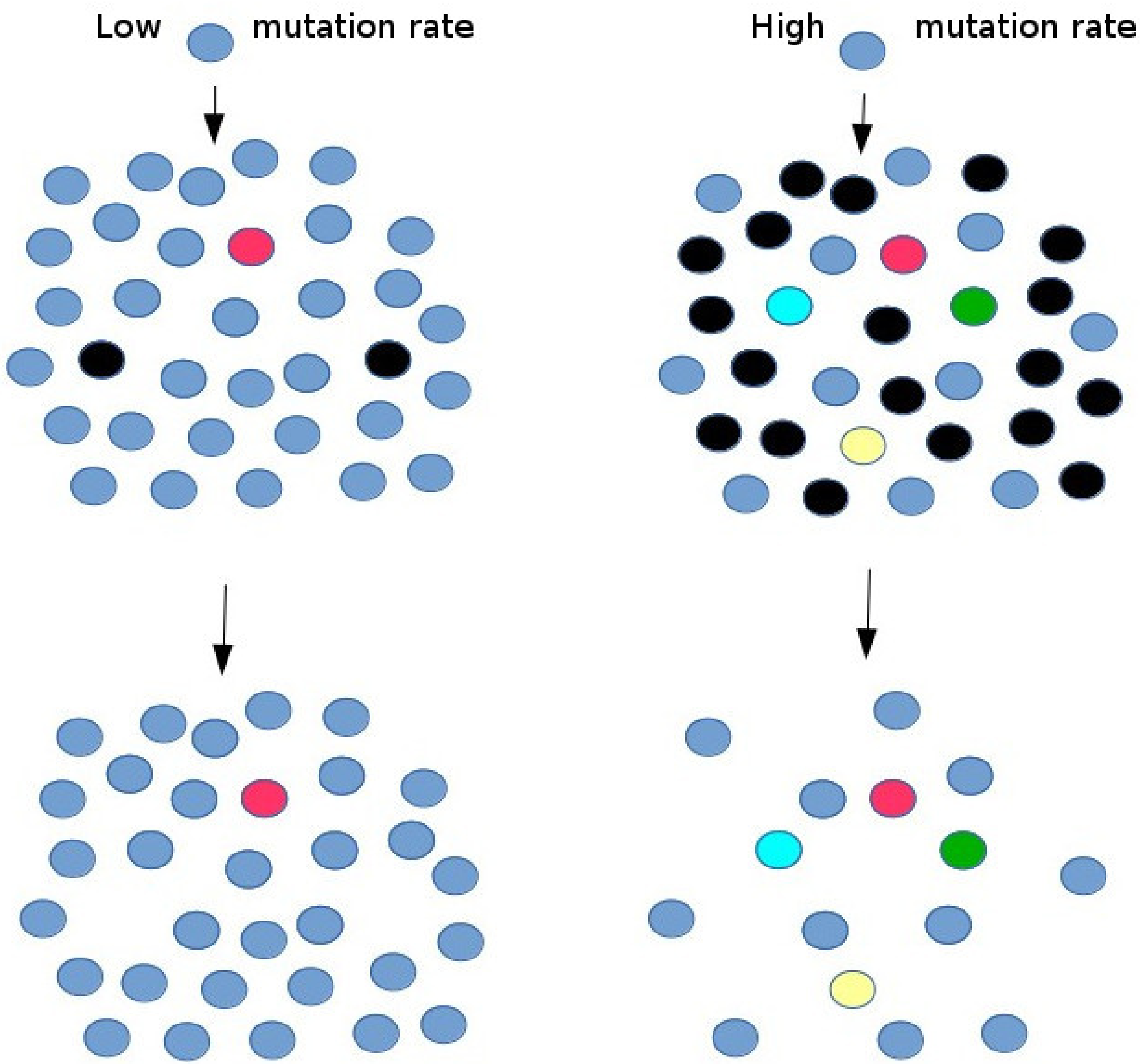
- Suppose I told you:
  - How many people I sampled
  - How many of each allele I found
  - How many AS carriers I found
- Are there any possible surprises left in the data? (AA? SS?)
- This is why there is only 1 df

Mu and nu

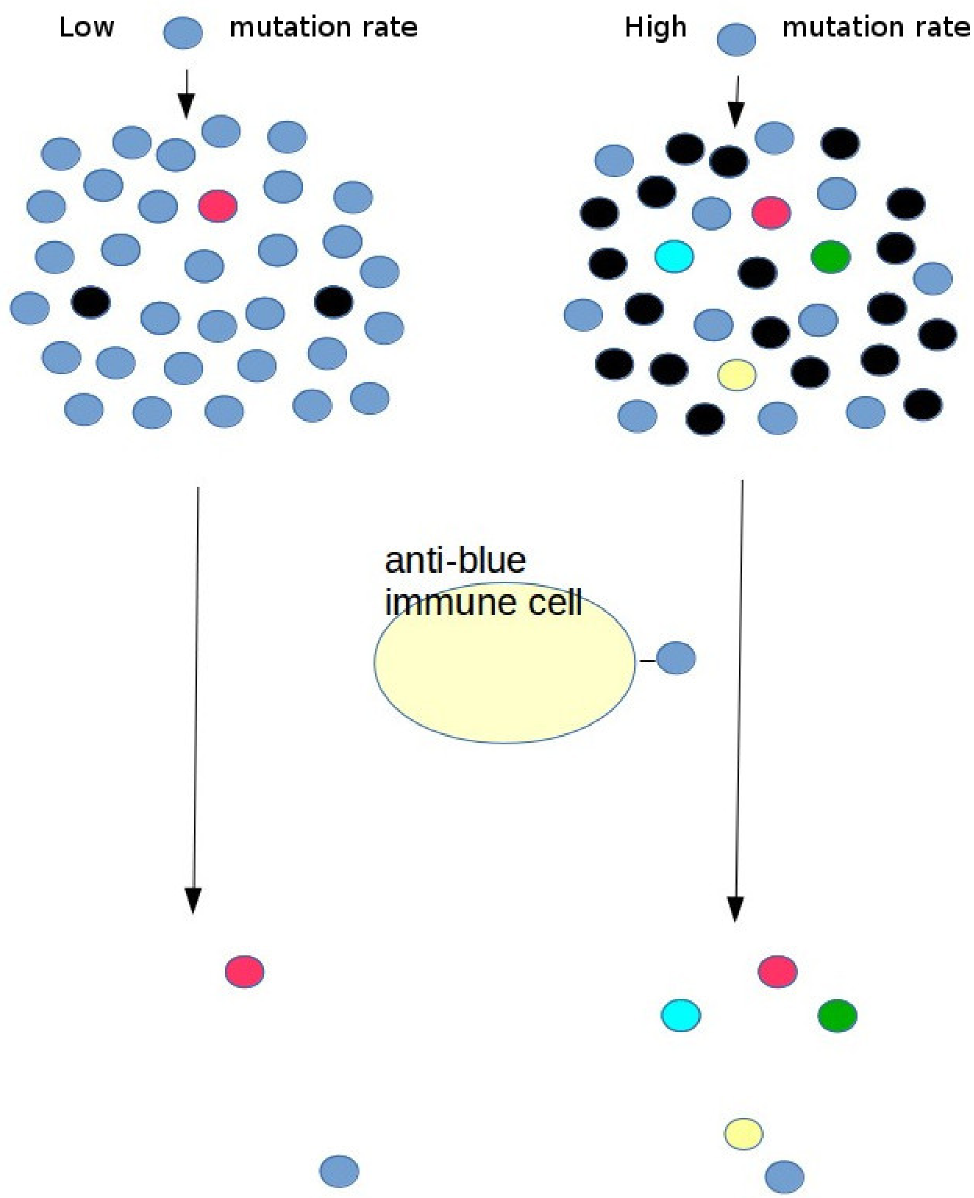
- μ (mu, forward mutation rate)
  - mutation rate per site is observed
  - rate per significant site in gene is:
  - rate per site x number of significant sites
- ν (nu, back mutation rate)
  - mutation rate per site is observed
  - need the right nucleotide (1/3 chance)
  - rate per site x 1/3

Is mutation good or bad?

- Most mutations have no fitness effect
- Of those that do, most are bad
- Most organisms expend significant energy trying to avoid mutations (DNA proofreading, etc)
- Are organisms trying (and failing) to reach a mutation rate of zero?
- Could there be selection in favor of a non-zero rate?



Higher mutation rate is a disadvantage here—fewer surviving offspring

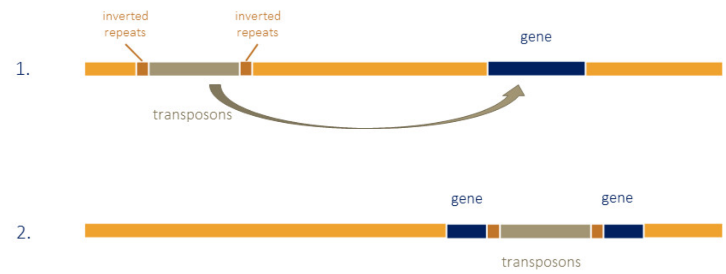


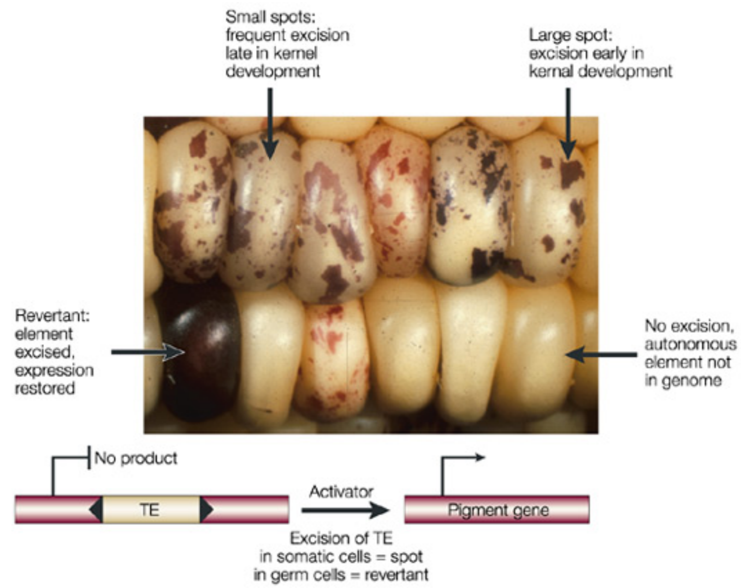
Higher mutation rate is an advantage here

Transposons as mutagens

- Transposons are genetic elements that can move around the genome

- This causes mutations:
  - Break up a coding sequence
  - Separate a gene from its control region
  - Introduce a new control region





Nature Reviews | Genetics

McClintock's genome shock hypothesis

- Transposition in maize increases when the plant is stressed
  - drought
  - salt
  - insects
- Transposition could be adaptive ("genome shock" theory)
  - Gives chance to fix the bad situation
- Transposition could be a symptom of illness
  - Transposons need to be kept under control
  - A sick plant can't do it

How low can mutation rate go?

- Discovered growing on irradiated meat
- Can withstand 1000x as much radiation as a human cell:
  - Chromosomes broken into about 100 pieces
  - Growth stops while chromosomes are repaired
  - Very few mutations result

Deinococcus radiodurans

Very good replication fidelity is possible

- *D. radiodurans* has 4 copies of its genome (redundant backups)
- Natural environment sunny, salty, and hot
- All three can damage DNA
- Engineered *D. radiodurans* may be useful in biodegrading radioactive chemical waste

Very good replication fidelity is possible

Presumably other cells could repair as well as *D. radiodurans*, but they don't.

- Redundant backups are expensive
- Repair machinery is expensive
- Mutations are expensive too (many are bad)
- Too-low mutation rate might inhibit adaptation
  - Hard to test this: it's a long-term effect

Outline–Dominance and its implications

1. **What makes one allele dominant over another?**
2. **Codominance and incomplete dominance**
3. **Dominance is not superiority!**
4. **Overdominance**
5. **Underdominance**

Some useful terms

- Genotype – the alleles present in an organism
- Phenotype – the traits shown by an organism
- Homozygote – two copies of the same allele
- Heterozygote – copies of two different alleles

Definitions

- Dominant–phenotype is seen in the heterozygote
- Recessive–phenotype is NOT seen in the heterozygote
- Incompletely dominant–heterozygote is intermediate (pink vs. red/white)
- Co-dominant–heterozygote expresses both alleles fully (AB blood type)

What makes one allele dominant over another?

- Usually recessive:
  - Deletion or null allele
  - Allele that makes non-functional or poorly functional product
  - Allele that underproduces product
  - Control mutation that disables an ON switch

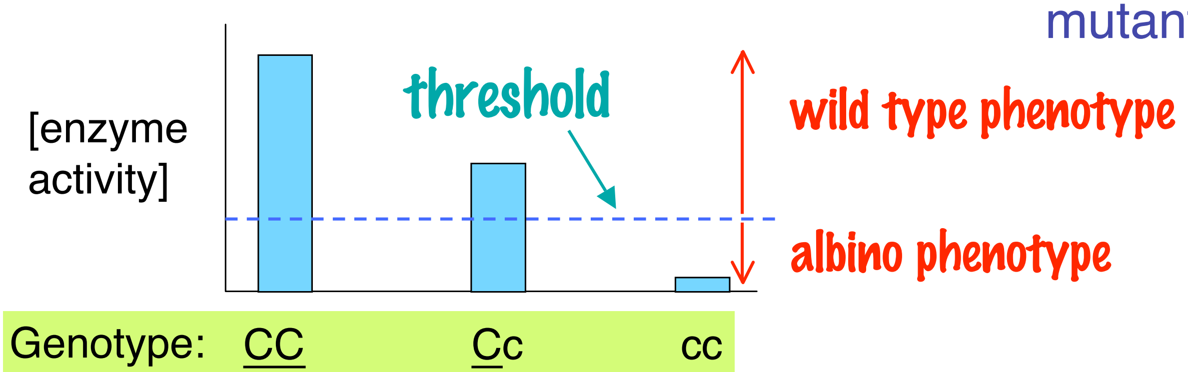
- Examples:
  - dysfunctional CF alleles
  - temperature-sensitive color of Siamese cats
  - O allele of ABO system

General rule for LOF mutations…

Half the amount of wild type gene product is sufficient to give a wild type phenotype

Example : Tyrosinase

wild type allele = C
mutant = c



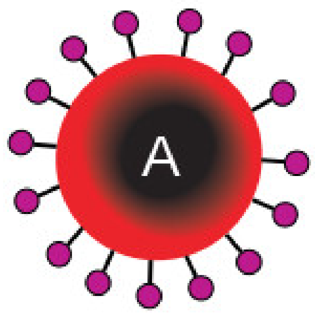
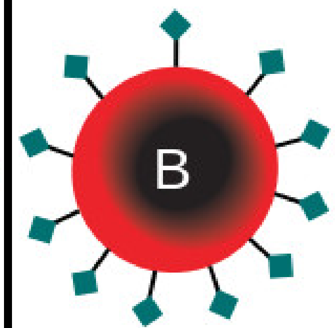
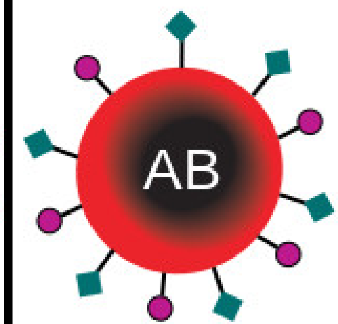
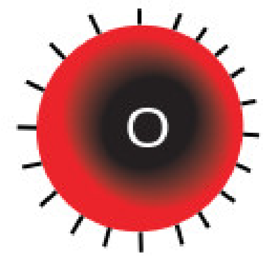
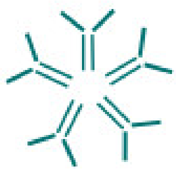
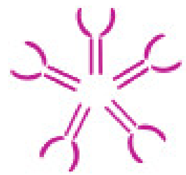
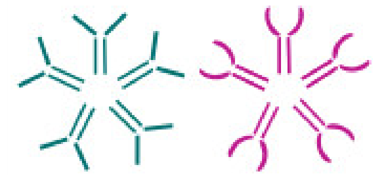
- 1 wild type copy → enzyme activity above threshold needed for normal pigmentation, so **carriers** unaffected (mutant allele → recessive)

What makes one allele dominant over another?

- Usually dominant or incompletely dominant:
  - Allele that overproduces product
  - Control mutation that disables an OFF switch
- Examples:
  - Adult lactase production
  - Achondroplastic dwarfism

What makes one allele dominant over another?

- Often dominant or co-dominant:
  - Allele that produces a novel product
  - Control mutation that introduces a new switch
- Examples:
  - A and B alleles of ABO
  - Adult lactose tolerance in humans

	Group A	Group B	Group AB	Group O
Red blood cell type				
Antibodies in Plasma	 Anti-B	 Anti-A	None	 Anti-A and Anti-B
Antigens in Red Blood Cell	 A antigen	 B antigen	 A and B antigens	None

Allelic series

- Each allele is recessive to the one before it
- Each allele is dominant to the one after it
- Example: tyrosinase locus in cats
- Wild-type tyrosinase used to make melanin (brown-black pigment)

<u>C</u>?

Burmese—c^bc^b or c^bc^s or c^bc

<u>C</u> gene codes for tyrosinase... 1st step in melanin synthesis

Siamese

c^sc^s or c^sc

cc

Different ways to the same phenotype

- Alleles, not phenotypes, have dominance
- White color in cats:
  - Dominant mutation which kills melanin-producing cells
  - Recessive mutation which inactivates melanin gene

Codominance versus incomplete dominance

- *Codominant:* shows the full phenotype of both alleles.
- Both alleles produce functional, but different, products
  - A and B in the ABO blood group system
- *Incompletely dominant:* shows intermediate phenotype.
- Often a dosage effect
  - Pink color in heterozygous flowers
  - White spotting in cats (homozygote has more white than heterozygote)

Incomplete dominance of white-spotting gene

Homozygous wild type

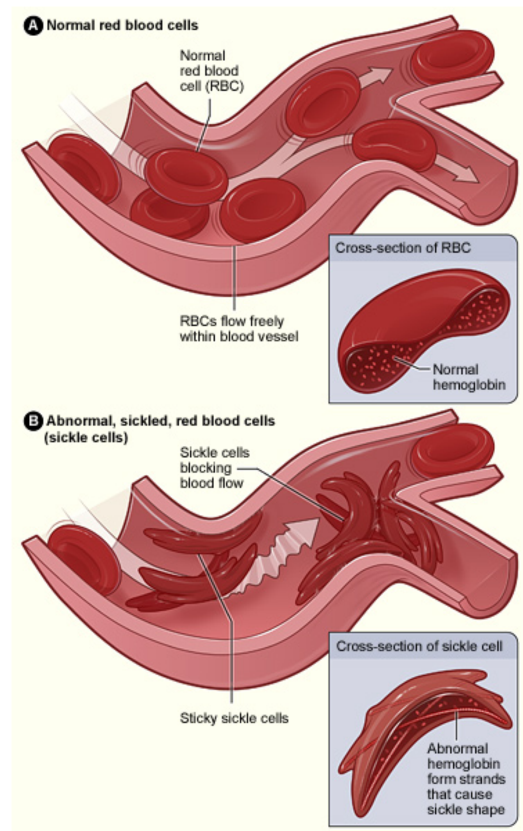
Heterozygous

Homozygous mutant

This mutation reduces spreading of pigment cells during development.

Discussion question

- Sickle cell hemoglobin forms into long, stiff chains; normal hemoglobin doesn't
- Sickle cell homozygotes have severe disease due to chain formation which damages ("sickles") red blood cells
- Heterozygotes show some sickling but not severe disease
- Is this codominance or incomplete dominance?



One gene can have multiple effects

- Dominant-mutation white cats generally deaf
- White-spotting gene also affects eye color

Dominance is not superiority!

Examples:

- Huntington's disease–dominant is worse than recessive
- Cystic fibrosis–dominant is better than recessive
- Tongue rolling–probably neutral

Dominant alleles can be common ("wild type") or rare.

In the absence of selection, dominant alleles have no particular tendency to increase over recessive ones.

Overdominance

Watch out! This term sounds as though it's the same kind of thing as "dominance", but it refers to an advantage or disadvantage, not just to which allele is expressed.

- *Overdominant* alleles are alleles with codominance or incomplete dominance in which the heterozygote is *fitter* than either homozygote.
- Sometimes called "hybrid vigor"
- Examples:
  - Many commercially sold grains and vegetables
  - Sickle-cell anemia (in presence of malaria)

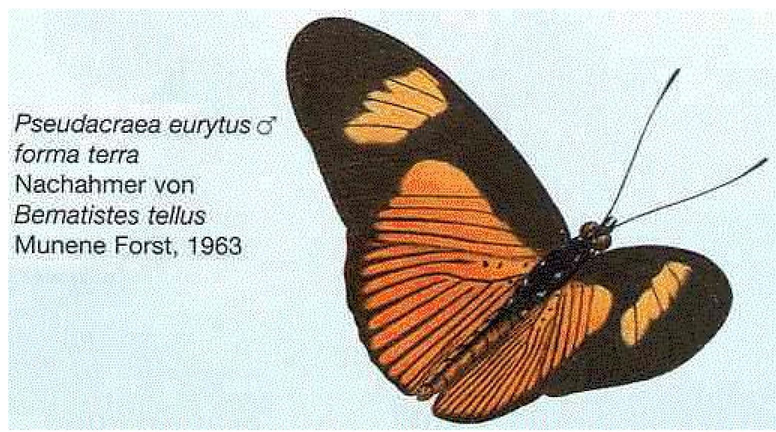
Underdominance

Again, watch out! Underdominance is not the same kind of thing as dominance.

- *Underdominant* alleles are alleles with codominance or incomplete dominance in which the heterozygote is *less fit* than either homozygote.
- Examples:
  - Heterozygote of HLA-DR3 and HLA-DR4 has higher diabetes risk than either homozygote
  - Mimicry in butterflies

Underdominance

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



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