Roadmap

- Midterm total points
- Two corrections from last lecture
- r versus f
- F Statistics and migration
- Quantitative traits:
  - Partitioning variance
  - heritability and its hazards

Midterm total points

- ...only 95
- Will take this into account in interpreting the grades

Corrections

- I wrote: "If allele frequencies are not changing, why does homozygosity continue to go down over time?" which should be "heterozygosity"
- I wrote: "$F_{ST} \approx \frac{t_S}{t_T}$"
- Someone correctly saw this doesn't make any sense; it should be
- "$F_{ST} \approx 1 - \frac{t_S}{t_T}$"

r versus f in a pedigree

- r is the expected proportion of alleles IBD in two relatives
- f is the chance that a hypothetical offspring of two relatives will have its two alleles IBD
- In straightforward cases, $f{=}r/2$
- Not straightforward:
  - Sex linked genes
  - Haplodiploids

Calculate r (in the simple case)

- Start at one individual and trace each possible path to the other
- Each parent-child link in a path is a factor of 1/2, multiply to get probability along that path
- Add the paths together
- (Different paths are ones that go up to different relatives; for example full siblings have a relationship path through mother and a separate one through father)

Logic issues: r for haplodiploids

- What is r between father and daughter?
- From his point of view, 100% of his genes went to his daughter
- From her point of view, 50% of her genes came from her father
- What is r for:
  - Father-daughter?
  - Full sisters?
  - Full brother/sister?
  - Full brothers?

Why all these views of F_{ST}?

- $\hat{F_{ST}} = \frac{\pi_B - \pi_W}{\pi_B}$ is how you would estimate it in practice
- The others are theoretical views of what it means:
  - Relationship of inbreeding coefficient within and between subpopulations
  - Relationship of mean coalescent depth within and between subpopulations
  - Relationship of variance within and between subpopulations

How is $\hat{p}$ related to σ_T^2?

- $F_{ST} = \frac{\sigma_S^2}{\sigma_T^2} = \frac{\sigma_S^2}{\hat{p}(1-\hat{p})}$
- The denominator is a measure of how much variability is in the population as a whole
- The more variability (more even allele frequencies) in the overall population, the more differentiated the subpopulations can become

The dark side of F_{ST}

- $F_{ST} = \frac{\sigma_S^2}{\sigma_T^2} = \frac{\sigma_S^2}{\hat{p}(1-\hat{p})}$
- If $\hat{p}$ is very large or small (one allele is very frequent), F_{ST} can't get big
- None the less, people attempt to give it an absolute interpretation
- Need to average across multiple loci to get meaningful results
- Still vulnerable to unexpected allele frequency spectrum (e.g. in growing/shrinking populations)

The dark side of F_{ST}

- $F_{ST} \approx \frac{\pi_B - \pi_W}{\pi_B}$
- Good luck if your sampling yields $\pi_B < \pi_W$, and it can!
- You can do better with ANOVA and its relatives, or with the coalescent methods to be described later
- ANOVA:
  - Decompose the total variation in the data into explanatory components (e.g. subpopulation structure)
  - Test against null hypothesis of no substructure
  - Program ARLEQUIN is a major tool for this

What is F_{ST} used for?

- In a model of stable population structure
  - Test for presence of structure
  - Estimate migration rate
- In a model of divergence from a common ancestor
  - Test for presence of structure
  - Estimate degree of divergence
- One further flaw: assumes one migration rate and one subpopulation size
- Better methods (ANOVA, AMOVA) are hard to code and explain!

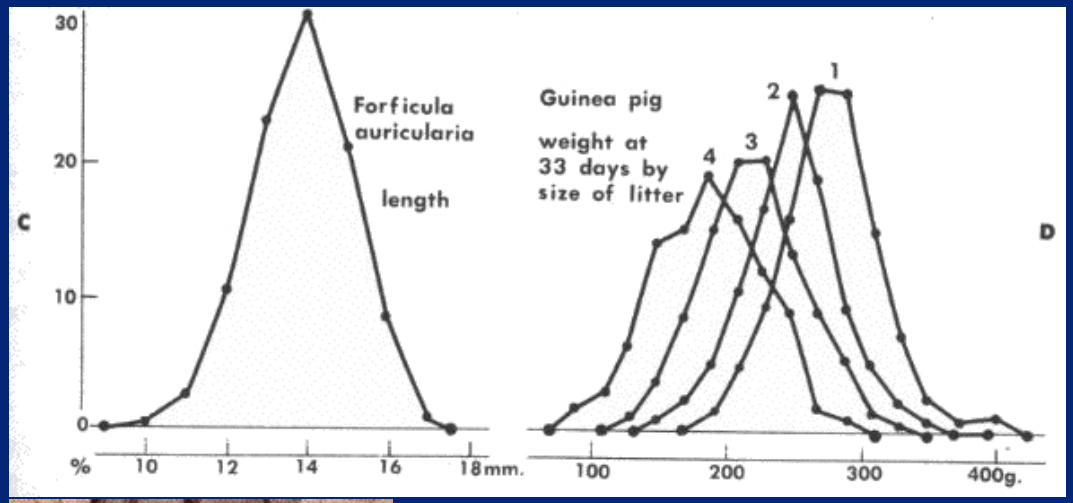
Next topic: Quantitative genetics

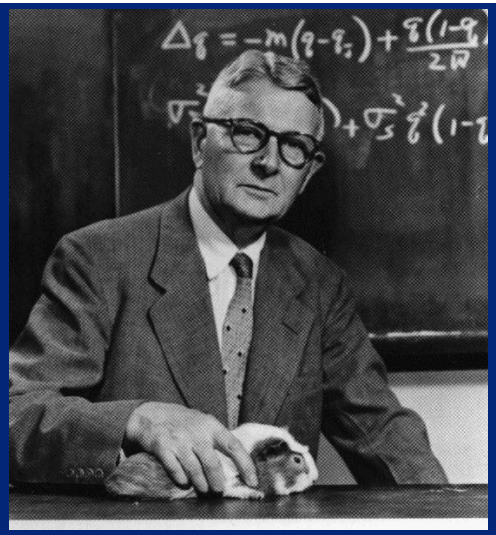
- Conflict between lab genetics and animal/plant breeders:
  - Lab genetics sees individual loci causing traits
  - Breeders see quantitative variation with no identifiable loci for many traits
- How can these views be reconciled?

Quantitative traits

- Traits like height, weight, blood pressure, athletic performance, etc.
  - Likely to be polygenic with most alleles contributing only a small amount
  - Difficult to tackle on a gene by gene basis
  - Environment likely to be a major player
- Quantitative genetics abstracts the individual genes into a simplified model

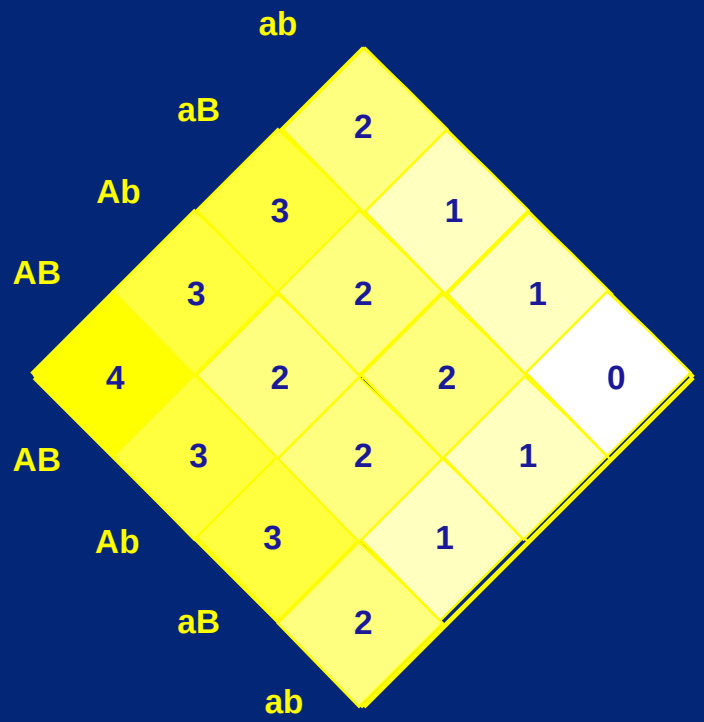
Examples of quantitative traits





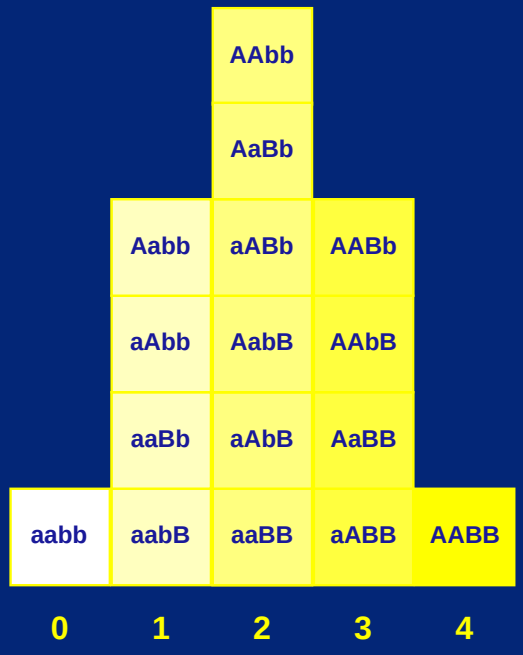
Multiple Mendelian characters $\rightarrow$ a quantitative trait

A random−mating population with two genes having 2 alleles each, at equal frequencies, symmetrically affecting a quantitative character



Multiple Mendelian characters $\rightarrow$ a quantitative trait

The distribution of the genotypes and the quantitative character before artificial selection



Handling this type of bell-curve variability

- Estimate total variance in population for a trait:
  $V_T = \frac{\sum_i (x - \bar{x})^2}{i}$
  - x is a measurement of the trait on an individual
  - $\bar{x}$ is the mean of the trait
  - i are the sampled individuals

- Quantitative methods try to partition this variance into genetic, environmental, and interaction terms

- (Should sound a bit familiar from F_{ST})

Why variance?

- If:
  - Multiple factors (f1, f2, ...) affect a trait
  - Each is distributed as a normal (bell curve)
  - An individual's trait is the sum of these factors
- Then:
  - $V_T = V_{f1} + V_{f2}...$
- I wrote a small program to prove this to myself (available on request)

Partition the variance – a first attempt

- $V_T = V_G + V_E$
- V_G = genetic variance, V_E = environmental variance
- Pleasingly simple but not useful–why?
  - We'd like the "genetic" term to relate parents to offspring
  - Not all genetic variation can be used that way

Additive and non-additive genetic variation

- Assume variation in the trait purely due to one locus
- Additive variation:
  - AA = mean 10 kg, Aa = mean 8 kg, aa = mean 6 kg
  - Having an A allele increases your weight by 2 kg
  - It also increases your mean offspring weight by 2 kg
  - Creates a clear correlation between parent and offspring

Additive and non-additive genetic variation

- No additive variation:
- Assume A and a equally frequent
  - AA $=$ mean 8 kg, Aa $=$ mean 10 kg, aa $=$ mean 8 kg
  - Having an A allele has no reliable effect on your weight
  - Passing one to your offspring has no reliable effect on offspring weight
  - No parent/offspring correlation
- Yet the trait is genetic! Not all genetic variation behaves the same....

A second try at decomposing variance

- $V_T = V_A + V_D + V_E + V_{GE}$
  - V_A – additive genetic variance
  - V_D – dominance genetic variance (all other genetic variance besides the additive component)
  - V_E – environmental variance
  - V_{GE} – covariance between genotype and environment

Genotype/environment interaction

- V_{GE} can arise when:
  - Your chance of having a genotype is correlated with your environment (ducks with lowland hemoglobin avoid mountains)
  - The effect of the environment depends on your genotype (highland hemoglobin only improves performance in mountains)
- "Common garden" experiment tries to remove these factors, BUT:
  - Results will not generalize back to wild population
  - Tendency to think a term we are "removing" is unimportant?
- Socioeconomic status is a common V_{GE} issue in humans

Appropriate scaling

- This theory is for genes with additive effects on phenotype
- Consider using log(phenotype):
  - Loci of multiplicative effect create additive effect on log(phenotype)
  - Avoids unreasonable results like negative weight of an organism....
- Finding the "natural scale" of your trait would be even better, but is difficult

How to estimate the variance components?

- Pairs of relatives related through only one ancestor are easiest
- Phenotypic correlation between such relatives:
  - Depends on r
  - Depends on $h^2 = \frac{V_A}{V_T} = \frac{V_A}{V_A+V_D+V_E}$
- With only one shared ancestor, correlation $= rh^2$
  - Parent/child $= \frac{1}{2}h^2$
  - Half-sib $= \frac{1}{4}h^2$
- More complex formulas for multiple shared ancestors
- (Note that we are hoping V_{GE} will quietly go away–a particularly poor assumption for $relatives$)

Heritability

- h^2 is properly "narrow-sense heritability"
- (Broad-sense would be $\frac{V_G}{V_T}$ but is seldom used)
- "Of the phenotypic variation in this population, what proportion is due to additive genetic factors?"

What people actually want from heritability

- We'd like to answer questions like:
  - Is this trait genetic or environmental?
  - Can this trait possibly be affected by the environment?
  - What is the largest change in this trait possible via environmental manipulation? via breeding? via genetic manipulation?
- Heritability does not, and cannot, answer these questions
- Not clear they $have$ answers

An illustrative paradox

- Consider traits essential for survival
- Heritability of such traits is generally low
- Why?

What is this actually good for?

- Predict one-generation phenotype response to selection on the trait
- $R = h^2 S$
- R is the response (the change in offspring relative to parents)
- S is the selection, measured as the difference between mean trait of breeding stock and mean trait of population

Friday

- Response to selection on a quantitative trait
- Long-term breeding experiments

One-minute responses

- Please:
  - Tear off a slip of paper
  - Give me one comment or question on something that worked, didn't work, needs elaboration, etc.