BIS101 F2013 Lecture 6: Population Genetics

Reading

Ch. 20, skip 20.3,20.4,20.5

Ch. 14, skip 14.1

What is a population?

a group of individuals of the same species, usually within some geographically delimited area, usually with the possibility of intermating

Evolution:

change in frequency of an allele over time (not the same as natural selection)

frequency

- A1A1 20 A1A2 13 A2A2 17
- what's the genotype frequency of A1A1 ? 40% (20/50)
- what is the allele frequency of A2 ? (p=47% or 0.47 because 34+13/100)
- what is the frequency of A1 ? (1-p)=0.53 b/c has to add to 1

I come back in 10 years, pop is now A1A1 80 A1A2 52 and A2A2 68

Has evolution occurred ? (not at this locus)

Population genetics is the study of allele frequency change in populations

Could argue it is synonymous with evolution

Hardy-Weinberg Equilibrium

- We talked about Mendel. HWE NOT 1:2:1
- Hardy & Weinberg 1908 (Hardy palyed crickey w/ Punnet)
    - How to solve provlem of blending & loss of diversity
- Model (what's a model ?) (what's an equilibrium?)

- model is a simplified description (mathematical) of a system
- most of the time oversimplified -- "all models are wrong, some models are useful"
- focus on the important parts of a system (noise in biology)
- allow predictions of expected outcome & comparison to real data
- qual. & quant. predictions
- if obs. data do not fit model -- biological interesting
- assumptions wrong, try new model
- what if data fit model? (my model is that aliens came down from outerspace and put chalk in the room)
- data consistent w/ model doesn't PROVE model (that's how science works)
- find out sensitive parts of system

HW Model (write on board assumptions)

- autosomal (which is?)
- locus, 2 alleles, diploid
- mendelian segregation
- random mating
- no other evol. forces (which?)
- no selection
- no migration
- no mutation
- no drift (large. pop size -> inf.)
- equal freq. in both sexes (or all hermaphrodites)
- generations discrete and nonoverlapping (annual plant) (explain)

Define variables (observed outcome of a system), parameters (things that define the model or system)

variables - X, Y, Z obs. freqs of 3 genotypes (AA, Aa, aa) in our population

parameter p = freq. A1 allele, q=freq. A2 allele = 1-p (why?)

if we have sample (not whole pop) of 18 A1A1 and 24 A1A2 and 8 A2A2

X=0.36, Y=0.48, Z=0.16

p=X+(1/2)Y=0.6 (60 copies of A/100 total copies)

Equations

In next generation:

Gamete Table	prob. A1 from parent1	prob A2 from parent1
prob A1 from parent2	p*p	p*(1-p)
prob A2 from parent2	(1-p)*p	(1-p)*(1-p)

use prime to denote next generation

X'=p^2 Y'=p(1-p) Z'=(1-p)^2

and p'=X'+Y'/2

and substituting: p'=p^2+2*p(1-p)/2 = p <- equilibrium

In HWE, genetic composition (genotype and allele freqs) predictable w/ one parameter -> p

Once in HWE, allele freqs. do not change (equilibrium) w/o disturbance

After a single generation of random mating -> HWE

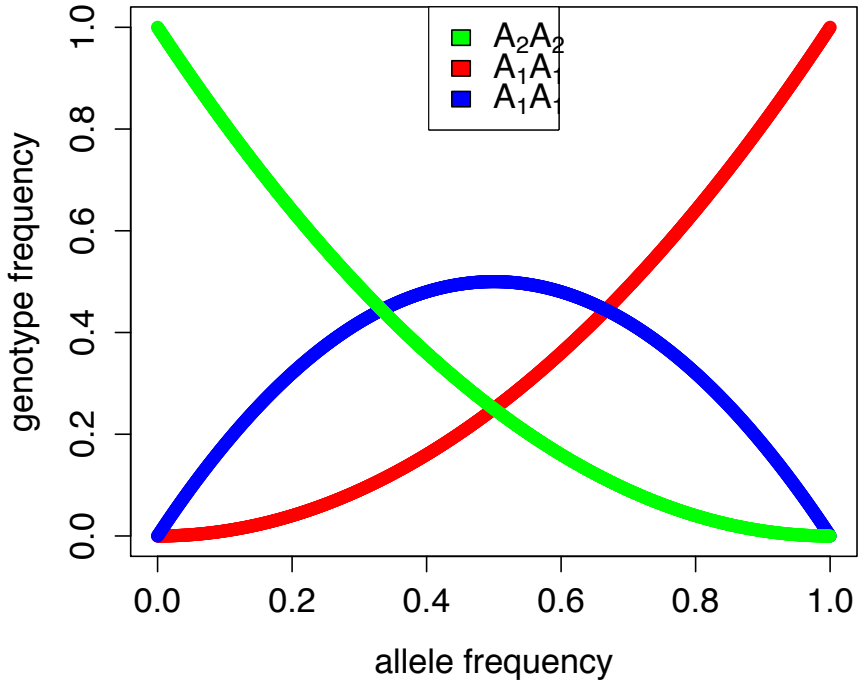
- start with 0.2 A1A1 and 0.8 A2A2 -> figure out what's p, and what's p' -> HWE after one generation

Conclusions

Single generation of random mating will almost always -> HWE

- start with 0.2 AA and 0.8 aa -> figure out p and p' -> HWE in one generation

Rare alleles more common in hets (p^2 < 2pq for whenever p < q)



Does dominance change HWE? - no because we haven't said anything about phenotype -- just genotype - so will recessive alleles go extinct?

Surprising # of loci in diff. organisms cannot reject HWE - does this mean no selection, drift, mutation? why not?

Can use Chi-square to test if loci are in HWE!

- e.g.sample AA= 72 (68.1) Aa = 21 (28.9) aa = 7 (3.1)
    - X^2 >7.28 so not in HWE (tell them to show for selves)
- e.g. AA= 82 Aa = 38 aa = 5
    - is in nigh-perfect HWE (test it)

Violate an assumption

Can show effects of violating an assumption (nonequal # of sexes etc.)

Some assumptions have sm. FX

- nonequal sexes, takes longer than 1 gen of random mating to reach HWE but still reach it
- drift or selection -> never reach

nonrandom mating -- inbreeding

decrease in (2p(1-p)) beyond expectations

can use inbreeding coefficient F to detect

- F = 1-Ho/He = 1 - (obs # heterozygotes)/(expected number) = 1-X/2p(1-p)
- F is probability of IBD (identity by descent)
- Draw IBD vs. IBS (two A1 alleles that are IBS but not IBD)
- probability that allele picked at random from each individual is identical

Decrease in population size -> inbreeding. Imagine only 10 unrelated individuals. Eventually everyone will be mating with a relative!

Skip:

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F=0\*r0+1/4\*r1+1/2\*r2
or think of it as, for offspring with alleles (gi,gk) and ()gl,gj)
1/4P(gi≡gk) + 1/4P(gi≡gl) + 1/4P(gj≡gk) + 1/4P(gj≡gl)

Relationship | r0 | r1 | r2 | F
--- | --- | --- | --- | ---
parent-child | 0 | 1 | 0 | 1/4
full-sib | 1/4 | 1/2 | 1/4 | 1/4
identical twins | 0 | 0 | 1 | 1/2
1st cousins | 3/4 | 1/4 | 0 | 1/16
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Gamete Table	prob A1 from parent1	prob A2 from parent1
prob A1 from parent2	p*p+F*p	p*(1-p)*(1-F)
prob A2 from parent2	(1-p)*p*(1-F)	(1-p)*(1-p)F*(1-p)

LD

We've looked at single loci, and multiple loci with recombination.

Linkage

- what is linkage?
- leads to nonrandom assoc. called LD
- show phase A_B / a_b and ask:
    - will I ever see a_B ❓ yes
    - will A_B be more common in population or A_b ❓ (first)

Why care?

- mapping
- for mutations in complex traits, most important feature of genome
- history: demography, structure, selection

What is LD?

- nonrandom association of alleles at two loci -- if nonrandom assoc., loci are "in LD"
- NOT same as linkage. can have LD even if unlinked or far apart

Unlinked loci

- haplotype (define?): combination of alleles at multiple loci along a stretch of chromosomes

for two biallelic loci unlinked 4 gametes (which?):

- Ab AB ab AB
- locus 1: A and a w/ freqs p_A and (1-p_A)
- locus 2: B and b w/ freqs p_B and (1-p_B)

Table: freqs of gametic haps if unlinked

Hap	Exp. freq.
AB	p_Ap_B
Ab	p_A(1-p_B)
aB	(1-p_A)p_B
ab	(1-p_A)(1-p_B)

When observed = this, gamete phase equilibrium (linkage equil)

- if not, we say LD
- not the same as HWE -- not arrived at in one generation if out of Equil. (but eventually)
- but is an equil. -- under W-F w/ inf. N, once reached what happens? stay same

measuring LD

For two biallelic loci

Define D: D_AB = p_AB-p_A*p_B

- Where p_AB is freq. AB gamete

- and D_aB = p_Ab-p_a*p_B
- D_AB=D_ab=-D_aB=-D_Ab
- D>0 means exces of AB, D<0 means deficit

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b. Example (check table labels)
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Hap	No (freq)
ab	600 (0.3)
aB	500 (0.25)
AB	800 (0.4)
Ab	100 (0.05)

D_ab=p_ab-p_a*p_b=0.3-0.55*0.35=.1075 (what are #s here)

so excess of ab gametes

D depends on allele freqs a. in principle each pair of alleles has own D in multilocus systems b. in biallelic SNPs or other markersD_AB=D_ab=-D_aB=-D_Ab

How to get LD?

mutation

- origin of all LD is mutation (draw: pop of ab & Ab mutates Ab->AB now you have LD until recombine)

demography

- admixture ancestor ab -> Ab and ab->aB now all 1st gen will be Ab/aB and no AB gametes until recombination
- other demography (Slatkin) i.e. bottlenecks

selection

Example

- let's say ab gametes lethal (gametes die)
- p_A=0.75 p_B=06
- ask for after frequency

Hap	freq. before	freq. after
ab	0.1	0
aB	0.15	0.167
AB	.45	0.5
Ab	.3	0.333

D_ab (before) = 0 (D before?) D_ab (after) = -0.056 (too few AB haps) (D after? interpr?)

selection can cause LD, even for loci on diff. csomes

mating system

- if things self, no chance for gametes to recombine

How to lose LD

LD breaks down as things recombine

1-c = prob. no crossover; do some math (use t+1 because ' is confusing here)

D_AB(t+1)= D_AB(t)*(1-c)

D_AB(t)=D_AB(0)*(1-c)^t

LD decays at rate dependent on crossovers.

this is why things closer together are usually in higher LD and how you map stuff

LD in Drosophila decays (to 1/2 value) after ~500bp

- in maize ~1kb (teosinte <500bp)
- humans ~ 10's of kb or more
- why dif? higher recombo and bigger pop sizes (remember slatkin, pop size matters)

DRIFT

in HWE with N-> inf what happens to allele freqs over time (nothing)

in small pops, random chance is imp. (think about freq. heads depends on sample size)

Smaller N -> more drift; Bigger N -> less drift

Draw on board 6 individuals (1 AA 3 Aa 2 aa) (can do X^2 and show sample is in HWE)

- If this is whole pop.: (calculate freqs.) use die roller app to pick mates for next gen.
- Recalculate freqs. (has evolution happened?)
- do a couple more (maybe until fixation?)

Other things associated with drift (define):

- bottleneck
- foudner effect

Effective pop size: size of a theoretical population meeting all assumptions that has same allele freq. behavior as your pop.

- because most pops violate assumptions, Ne almost always << N
- Ne is what matters for drift.
    - Big census size w/ lots of size fluctuation similar drift to smaller pop w/ constant size
- e.g. Ne for Humans is 10K
- for dairy cows 100
- for drosophila 2M

Will skip the math, but:

Drift causes inbreeding: random mating in pop of sample 10, soon you're mating w/ relatives by random!

Chance of fixation = frequency. So most new mutations (at freq. 1/2N) are lost by to drift!

Differences between species: 2N*mu mutations per gen. * 1/2N chance of fixing = mu differences between species per gen. (or between genes, i.e. Ks)

Selection

Natural Selection not same as evolution

- change in frequency of a variant due to its effect on fitness
- multiple components to fitness: viability, mating success, fecundity
- Think in terms of relative fitness: some most fit genotype, and all other genotypes are competing with it
- variant that makes you compete better and make more copies of your genes -> natural selection will increase freq.

Fitness Table

Genotype	**A1A1**	**A1A2**	**A2A2**
Freq.	p^2	2p(1-p)	(1-p)^2
Fitness	w11	w12	w22

relative fitness of AA is w_AA

- not faster than the bear, faster than the other guy

mean fitness of populatons is weighted avg.

wbar = p^2w11+2p(1-p)w12+(1-p)^2w22

genotype freq. change depends on rel. fitness, so

- X'=p^2w11/wbar
- Y'=2p(1-p)w12/wbar
- Z'=(1-p)^2w22/wbar

allele freq:

- p'=X'+Y'/2 = (p^2*w11+p(1-p)w12)/wbar

RESULTS:

- change in allele freq. depends on difference in fitness b/t heterozygote and homozygote for the allele
- allele freq. (greater change with more middling allele freq)
- stronger s -> faster change in p,
- this general formula allows variation.
    - e.g. wAA=1 w12=1-s w22=1-2s -- when het is intermediate additive or codominant
    - w11=1 w12=1 w22=1-s (dominance of A1)
    - w11=1 w12=1-s w22=1-s (recessive A1)
- draw graph for recessive, dominant, codominant

Other forces

Gene flow: movement of genes from one population to another

- can impact allele frequencies and counteract selection and drift
- different pops should drift independently, but even one migrant/generation enough to prevent extensive divergence

Mutation

- fairly straightforward, increases freq of particular allele

Combos

Mutation-selection balance:

- assuming selection against recessive: p=(mu/s)^0.5
- for a completely recessive mutation, even under lethal selection (s=1) the freq. of A will be mu