Overview

- Hardy-Weinberg
- Relative fitness
- Directional selection:
  - In a haploid
  - In a diploid
- Mean fitness of a population

From the one-minute responses

- Connect concepts to homework more tightly
- TMRCA: generation time versus calendar time? How to convert?

TMRCA

- Coalescent theory predicts TMRCA in generations

- Time in years (calendar time):
  - Need generation time of organism to relate it to the coalescent

- Time in mutations (mutational distance):
  - To convert to years, need μ in mutations/year
  - To convert to generations, need μ in mutations/generation
  - Often used when we don't know μ at all and are just looking at mutations in sequences

Hardy-Weinberg Law

In a random-mating population with allele frequencies p (for A) and q (for a), we expect:

Genotype	Frequency
AA	p^2
Aa	$2pq$
aa	q^2

- Even if this isn't true among parents, it will be true among offspring (at conception)

- Called an equilibrium because frequencies go to H-W with 1 generation of random mating

What pushes a population out of H-W?

- Reasonably often:
  - Population subdivision
  - Natural selection
  - Non-random mating
  - Undetected null alleles

- Hardly ever:
  - Mutation
  - Genetic drift (unless population is tiny)

Undetected null alleles

The experimenter presented us with this, which is not in H-W:

aa	47%
ab	31%
bb	22%

On questioning, she admitted that she really observed this:

aa	450
ab	300
bb	210
test failed	40

Undetected null alleles

aa	450
ab	300
bb	210
test failed	40

What she probably has is this:

aa + ac	450
ab	300
bb + bc	210
cc	40

but she cannot detect allele c. (Could these be in H-W?)

When you can test H-W and when you can't

No problem (use a χ^2 test):

AA	84
Aa	12
aa	4
Total	100

- Calculate the allele frequencies
- Calculate expected numbers
- Compute $\chi^2 = \sum(o - e)^2/e$
- Compare to table (with 1 degree of freedom in this case)

When you can test H-W and when you can't

Not possible:

Brown eyes (BB or Bb)	96
Blue eyes (bb)	4

- Statistician's reason: no degrees of freedom left
- Layman's reason: we'd need to assume H-W to get the allele frequencies, but if we got them with H-W we can't use them to test H-W

Relative fitness

- Assume population size is constant despite selection
- Individual gene copies are competing for a fixed number of slots
- Selection coefficient is observed/expected
- Typically normalized so that the best genotype has fitness 1, or that “wild-type” has fitness 1

Nomenclature

I will use:

- wA for the fitness of the A genotype in a haploid
- wAA for the fitness of the AA genotype in a diploid

Practice problem

p = 0.8, q = 0.2 among gametes

Genotype	Observed	Expected	Fitness	Normalized Fitness
AA	80			
Aa	18			
aa	2			
Total	100			

Practice problem

p = 0.8, q = 0.2 among gametes

Genotype	Observed	Expected	Fitness	Normalized Fitness
AA	80	64	1.25	1.0
Aa	18	32	0.56	0.49
aa	2	4	0.50	0.40
Total	100	100		

Selection in a haploid

In one generation:
p $=$ 0.8, q $=$ 0.2 among gametes (or in previous generation's adults)
$wA = 1.0$, $wa = 0.7$

Genotype	At conception	After selection	Renormalize
A	0.8	0.8	0.85
a	0.2	0.14	0.15
Total	1.0	0.94	1.0

New allele frequencies:

p $=$ 0.85, q $=$ 0.15

Selection over time

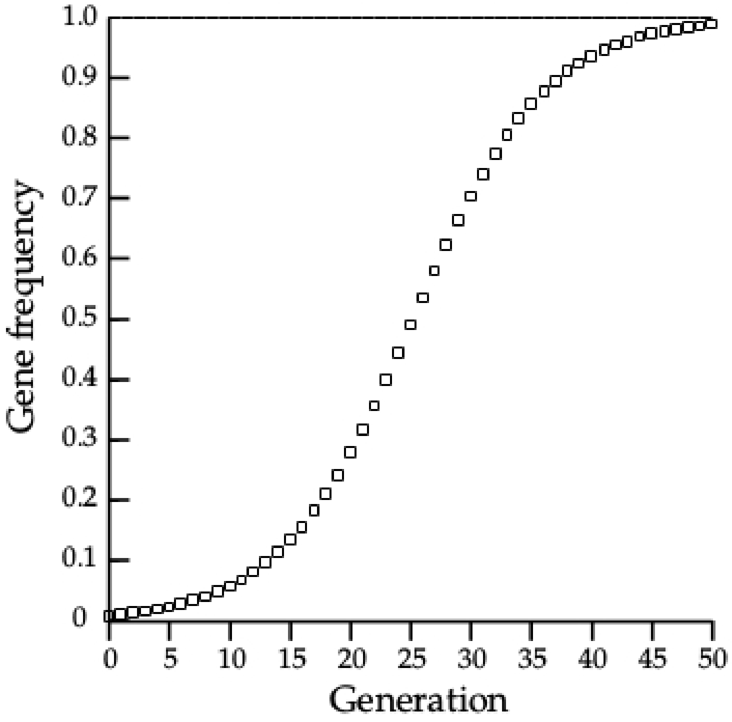


Figure 2.1: Course of gene frequency change in haploid selection with initial gene frequency $p_0 = 0.01$ and relative fitness 1.2 of the A genotype.

Selection in a diploid

p = 0.8, q = 0.2 among gametes (or in previous generation's adults)

$wAA = 1.0$, $wAa = 0.9$, $waa = 0.8$

Genotype	At conception	After selection	Renormalize
AA	0.64	0.640	0.667
Aa	0.32	0.288	0.300
aa	0.04	0.032	0.033
Total	1.0	0.96	1.0

New allele frequencies:

p = AA + 1/2 Aa = 0.817

q = aa + 1/2 Aa = 0.183

The selection coefficient s

- Convenient to attach a number to these fitness differences
- Unfortunately this is done two different ways in the literature
- Haploid example:
  - Way 1: fitnesses are 1+s and 1
  - Way 2: fitnesses are 1 and 1-s
  - These won't in general yield the same numeric s!
- If a study says "We estimated the selection coefficient" you will have to read the fine print to see what they did....
- I am going to use Way 2 everywhere

Specific fitness patterns

- Dominant/recessive: 1 : 1 : 1-s
- Additive: 1 : 1-s : 1-2s
- Multiplicative: 1 : 1-s : $(1-s)^2$

Intuitively I'd expect additive to be the same as haploid. In fact, multiplicative is the same as haploid. Why?

Selection over time

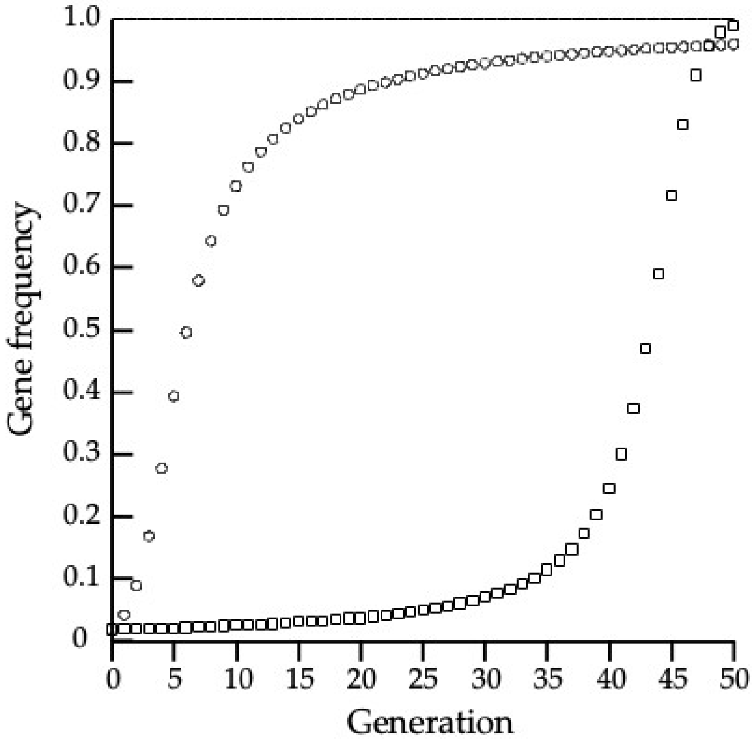


Figure 2.3: The course of gene frequency change over 50 generations when fitnesses of *AA*, *Aa*, and *aa* are 2.3 : 2.3 : 1 (circles) and 2.3 : 1 : 1 (squares). Initial frequency of *A* is 0.02.

Theory fits experiment

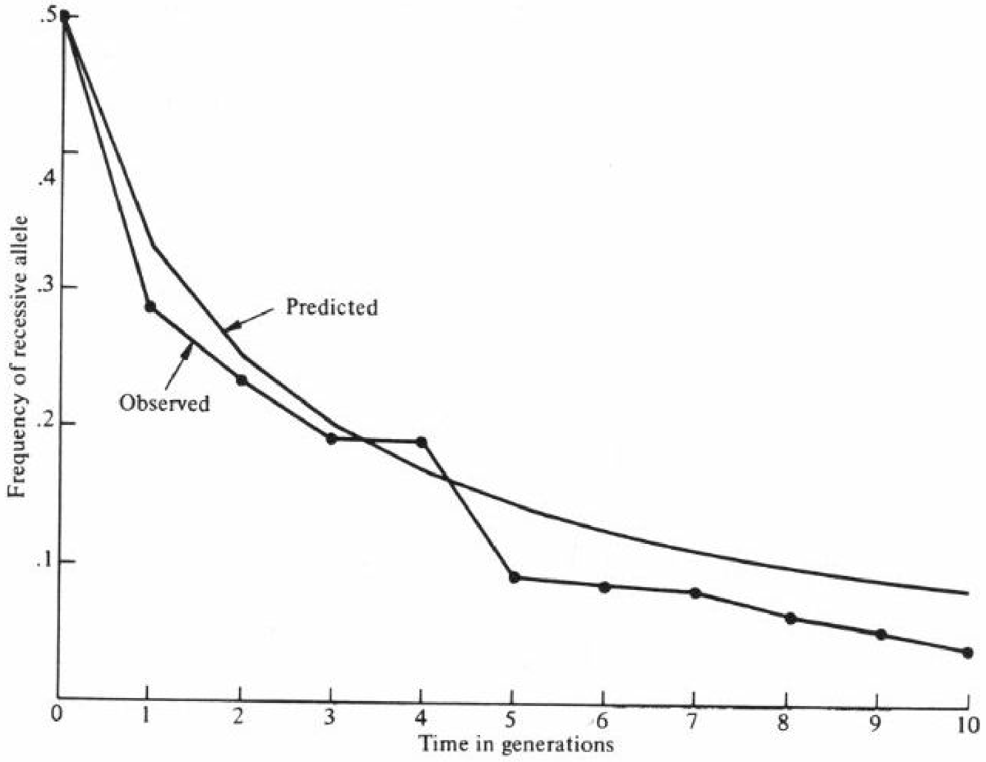
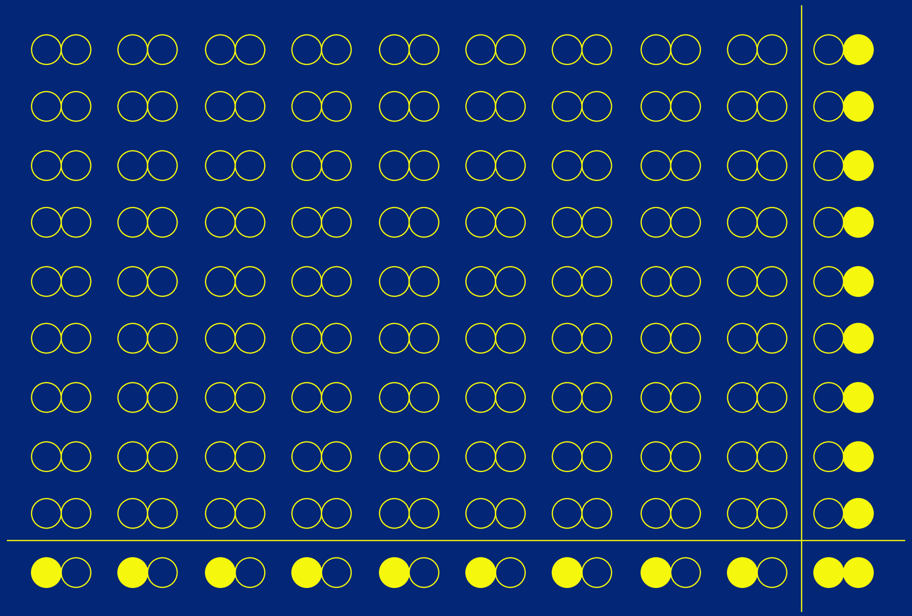


FIGURE 3.4. *Experiment illustrating selection against a recessive lethal gene. The frequency of the recessive allele is on the vertical axis, time in generations is on the horizontal axis.* [Data from B. Wallace (1963), The elimination of an autosomal lethal from an experimental population of *Drosophila melanogaster*, *Amer. Natur.* **97**: 65–66.]

Rare alleles occur mostly in heterozygotes



This shows a population in Hardy−Weinberg equilibrium

at gene frequencies of 0.9 A : 0.1 a

Genotype frequencies:

0.81 AA : 0.18 Aa : 0.01 aa

Note that of the 20 copies of a,

18 of them, or 18 / 20 = 0.9 of them are in Aa genotypes

Mean fitness of a population

- Genotype fitnesses weighted by genotype frequencies (before selection):
- $W = wAA \times p^2 + wAa \times 2pq + waa \times q^2$
- In the cases we have considered, this increases over time under the influence of selection

Summary

- Hardy-Weinberg gives us a prediction for the frequencies of the genotypes in a random-mating population before selection
- Relative fitness is the excess or deficit of a genotype after selection has happened
- Combine the two to predict change in allele frequencies
- In diploids, the shape of the frequency curve depends on dominance

Friday

- Overdominance (heterozygote advantage)
- Underdominance (heterozygote disadvantage)
- Local optimization misses the global optimum

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.