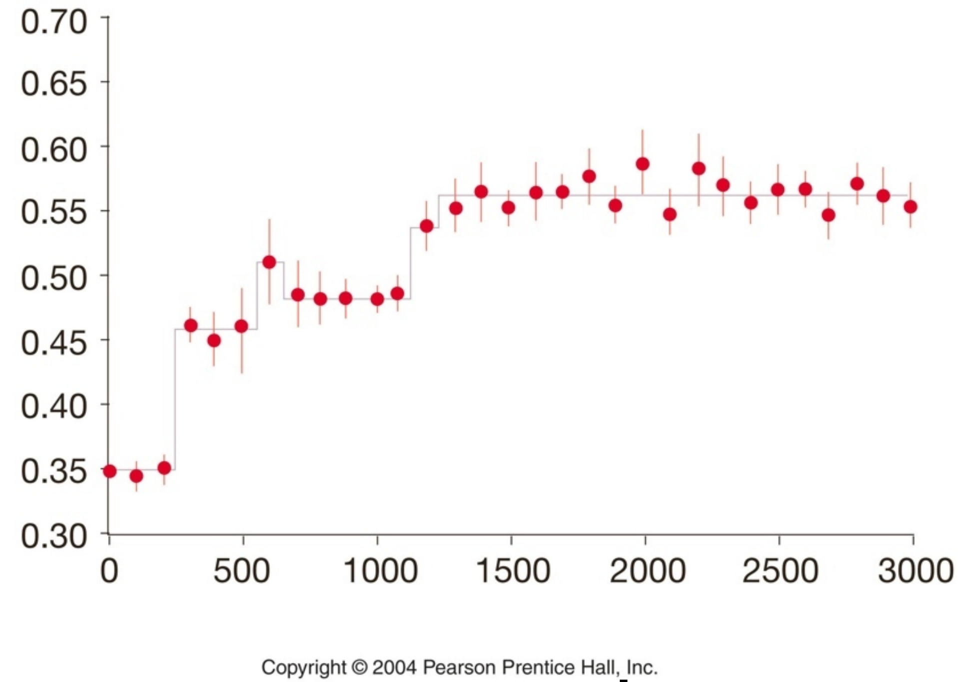
Mutation

cell size



generations

- Experimental evolution in asexual bacteria relies on mutation as the sole source of evolutionary change.
  - Lenski began the 12 population, 30,000 generation (and counting) *E. coli* experiment from a single clone.

Recurrent Mutation

- selection will eliminate unfavourable alleles, ultimately.
- but mutation continuously regenerates them.
- what is the equilibrium frequency of a recurring mutation?
    - i.e., the balance point between mutation and selection

Calculating the μ:*s* balance

- suppose *A* is a dominant harmful mutation arising at a rate μ and found at frequency *p.*
- selection acts against *A* at a value *s*.

genotype	*AA*	*Aa*	*aa*
fitness	ω_{11}	ω_{12}	ω_{22}
	$1-s$	$1-s$	1.0

- a proportion of the genes in the population are *a*, which is $= 1 - p$
- the rate of creation of new mutants is $\mu(1-p)$
- the rate of loss of mutants is ps.

at equilibrium (p^*), gain = loss

$$\mu(1-p^*) = p^*s$$

or approximately…

$$\boldsymbol{p^* = \mu / s}$$

$$p^* \approx \mu / s$$

- if the allele is dominant and lethal, then $s=1$ and $p^* = \mu$.
- for a recessive mutation, the equations simplify to $p^* = \sqrt{(\mu / s)}$

note: the equation for a recessive is a very crude approximation and the degree of dominance (penetrance) is often not known with certainty

- the frequency of the mutant is a rough guide to the mutation rate and selection against it.
- rough calculations:

dominant	recessive
$p^* = 10^{-6} / 10^{-2}$	$p^* = \sqrt{10^{-6} / 10^{-2}}$
$= 10^{-4}$	$= 10^{-2}$

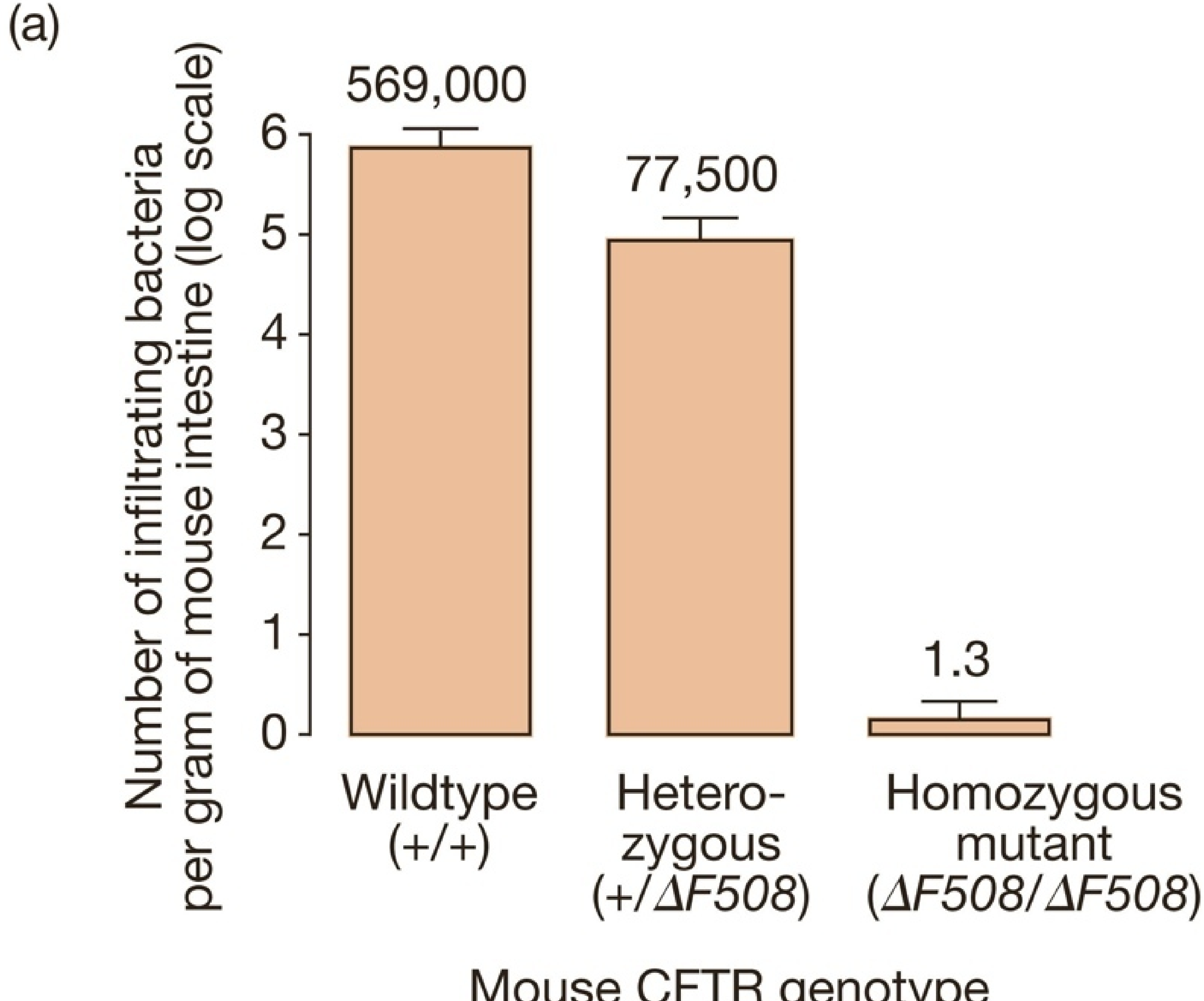
for haploid, asexual organisms, like *E. coli*, all variation is effectively dominant

Mutants

- Spinal muscular atrophy
  - a cV mutation at *telSMN* at frequency about 0.01 in Caucasian populations.
  - devastating neuromuscular disease; *s* est'd at 0.9
  - if the equilibrium frequency = SQRT(μ/*s*), then
  - 0.0001 = μ / 0.9, ... or **μ = 9x10^{-5}**
- Wirth et al. estimated the spontaneous mutation rate from 340 individuals, based on 7 *de novo* cases at 1.1 x 10^{-4}.

CFTR

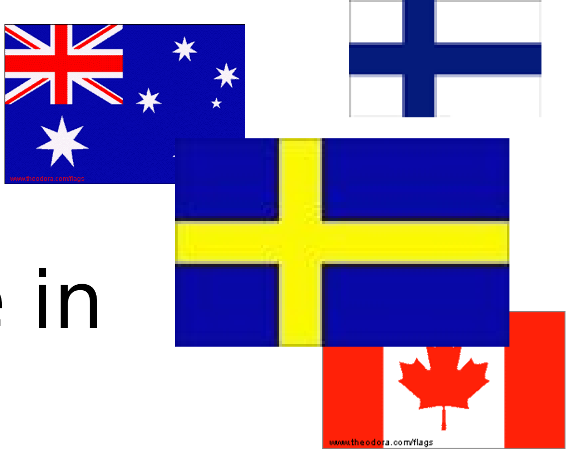
- cystic fibrosis occurs at a frequency of 0.02
  - cVII disease requires a mutation rate of 4×10^{-4}.
  - observed rate is 7×10^{-7}
- Pier et al. (1998) suggested that overdominance might be the root of high CFTR occurrence:
  - heterozygotes for CFTR deficiency may be better at resisting typhoid fever (a Salmonella disease).
  - using the mouse model, wildtype, heterozygote, and homozygous ΔF508 (a CFTR allele), they showed a high degree of resistance in mutant homozygotes and partial resistance of heterozygotes.


(a)
569,000
77,500
1.3
6
5
4
3
2
1
0
Number of infiltrating bacteria per gram of mouse intestine (log scale)
Wildtype (+/+)
Hetero-zygous (+/ΔF508)
Homozygous mutant (ΔF508/ΔF508)
Mouse CFTR genotype

Eugenics

- Eugenics seeks to alter fertility patterns for the betterment of the society, race, or humankind.
  - typically this means sterilizing less desirable individuals through some means.
  - in the extreme, e.g., Nazi Germany, this meant genocide.
  - in milder forms, this has been done through ‘incentives’.
- Many major nations practiced compulsory sterilization of the ‘infirm’ or undesirable until quite recently.

A Liberal Thing?



- The U.S.A: 65,000 sterilized people in 33 states until ‘70s.
  - mentally retarded, gay, blind, deaf, epileptic, alcoholic, homeless, first nation.
- Sweden: compulsory sterilization of 63,000 until 1976.
  - mentally retarded, mixed race (e.g., gypsy), socially undesirable, criminal.
- Japan: 16,500 forced sterilizations up to 1992.
  - schizophrenia, manic depression, epilepsy, “remarkable abnormal sexual desire”, “criminal inclination”.

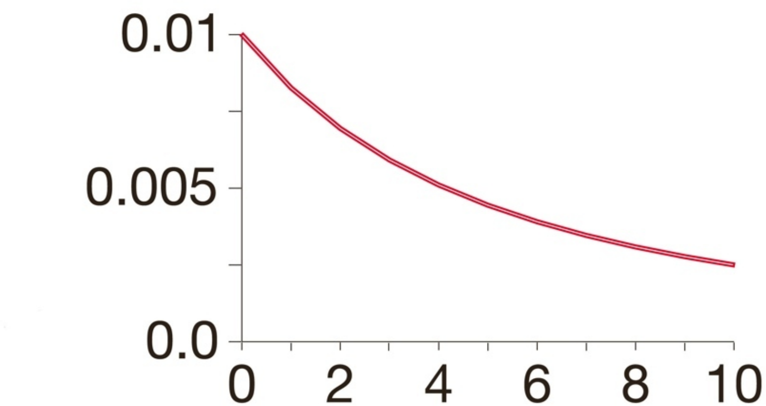
Courtesy of Marty Pernick


Courtesy of Marty Pernick

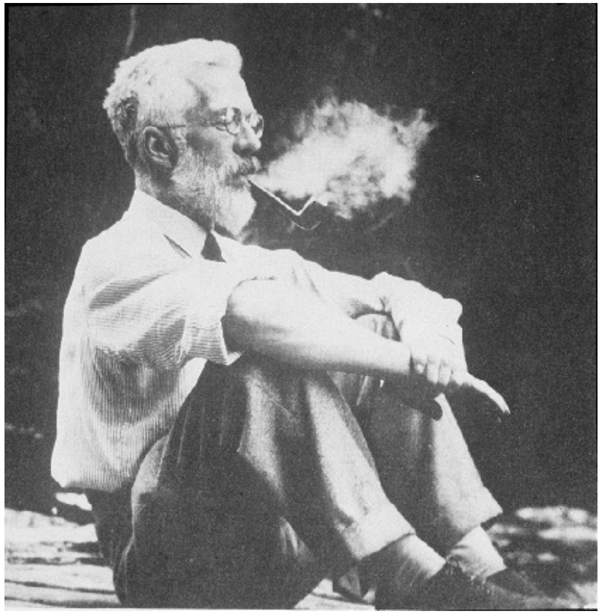

ENGLISH HERITAGE
Sir
RONALD
AYLMER
FISHER
1890-1962
Statistician and
Geneticist
lived here
1896-1904

The Punnett / Fisher Calculation

- The offending trait is recessive, a frequency 0.01 homozygous carriers
- Selection is against homozygotes at *s*=1 (because they are sterilized), then the frequency would decline from 100 per 10,000 affected to:
  - 83 per 10,000 in one round of sterilization.
  - 25 per 10,000 after 10 generations.



change over 250y



Migration & Drift

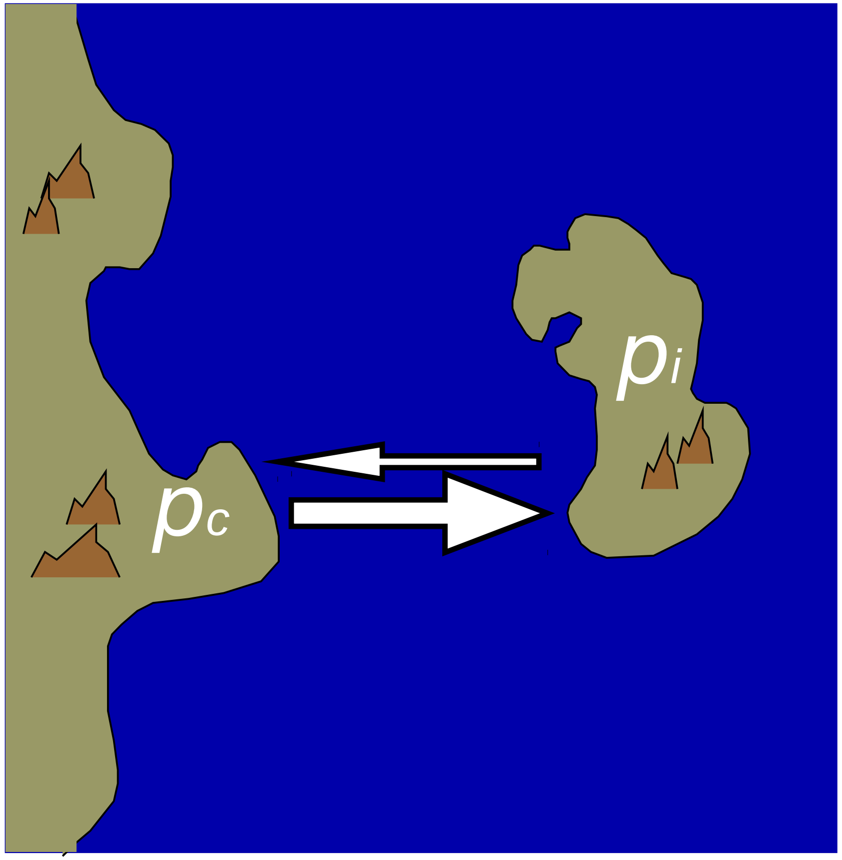
- Migration = **Gene Flow**
  - the movement of alleles between putative populations.
  - gene flow binds biological species together.
- Genetic Drift = **Sampling Error**
  - an inevitable feature of finite populations.
- Both forces are agents of evolutionary change.
- Both impart deviations from H-W equilibrium.

Migration

- a byproduct of population subdivision
- for gene flow to occur:
  - migrants must disperse to a new population at some rate (m)
  - they must reproduce
    - be suitably adapted to the conditions in the new population.
    - not be selected out (e.g., by predators)

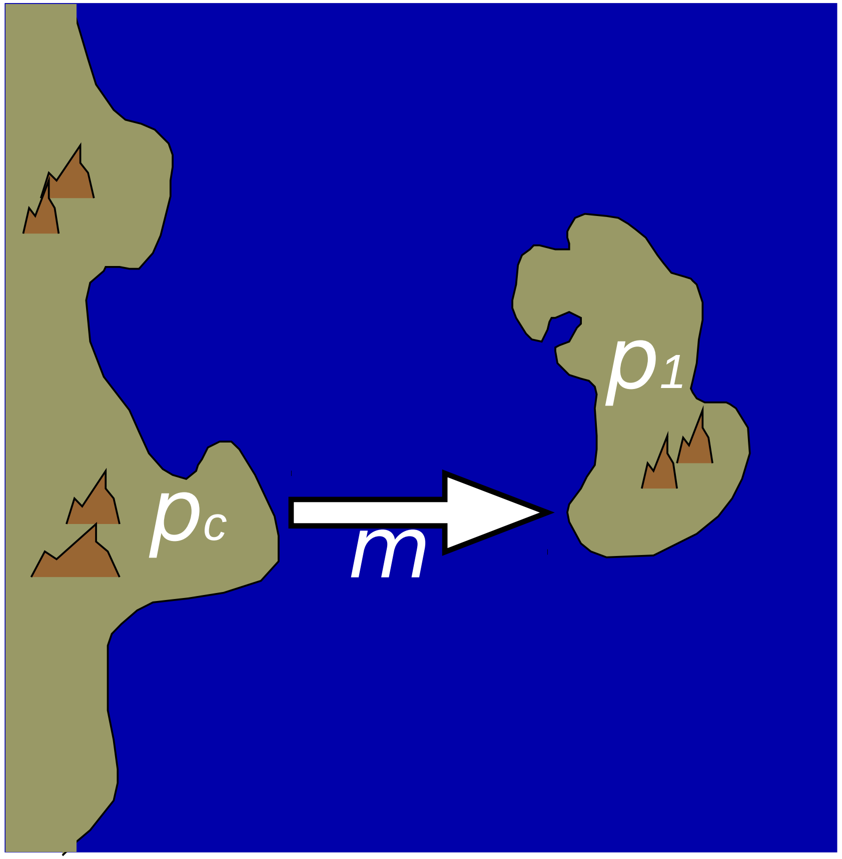
The Island Model

- population is polymorphic at the *A* locus.
- how does frequency of A_1 change due to migration?



- A_1 is at frequency p_i before migration
- m = fraction of migrant individuals.
- $1\text{-}m$ = fraction of resident individuals
- frequ. of A_1 in next generation is:

$$(1\text{-}m)(p_i) + (m)(p_c)$$



$\Delta p_i = m(p_c - p_i)$

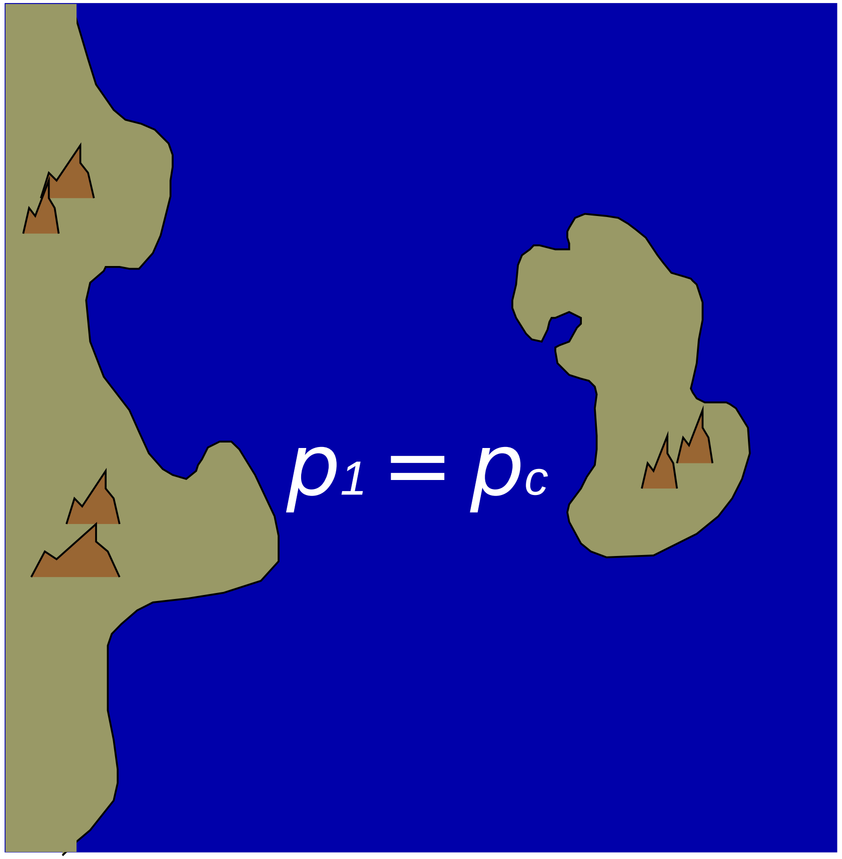
• at equilibrium ($\Delta p_i = 0$) the frequ. of A_1 is always the same in both populations.

• the rate of homogenization depends upon:

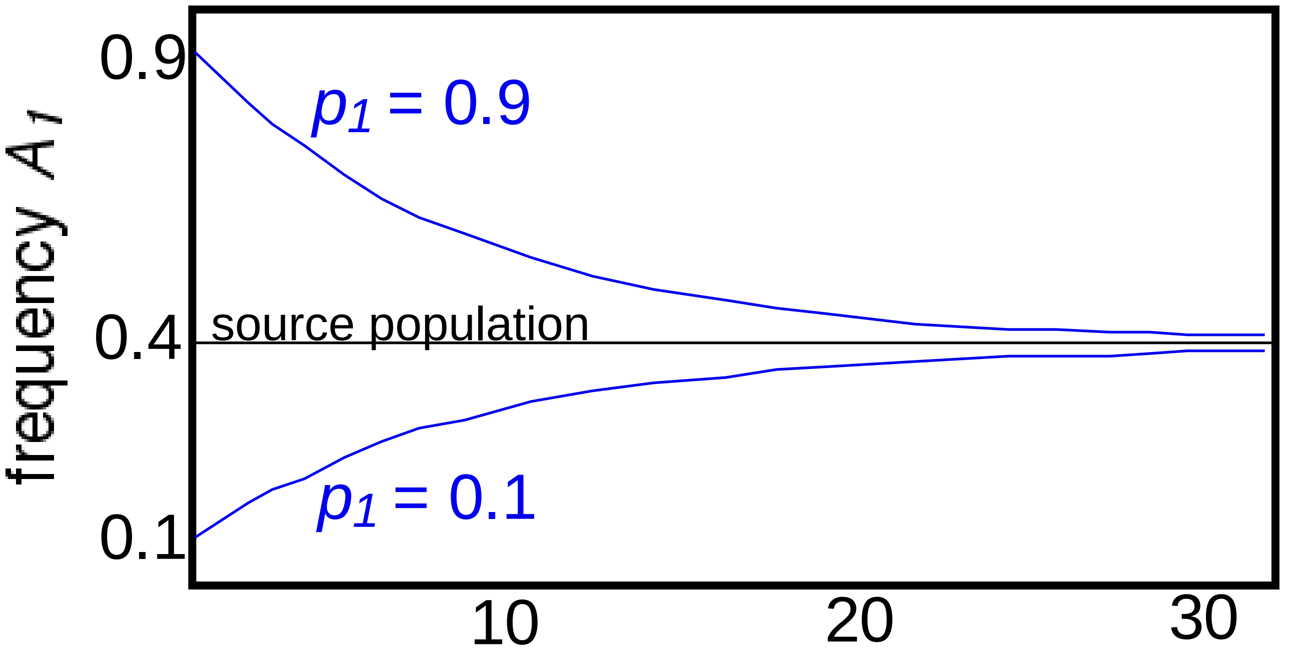
1) the level of migration.

2) the difference in frequency of A_1 between the populations.

3) the absence of



Gene flow rapidly homogenizes populations



$m = 0.1$

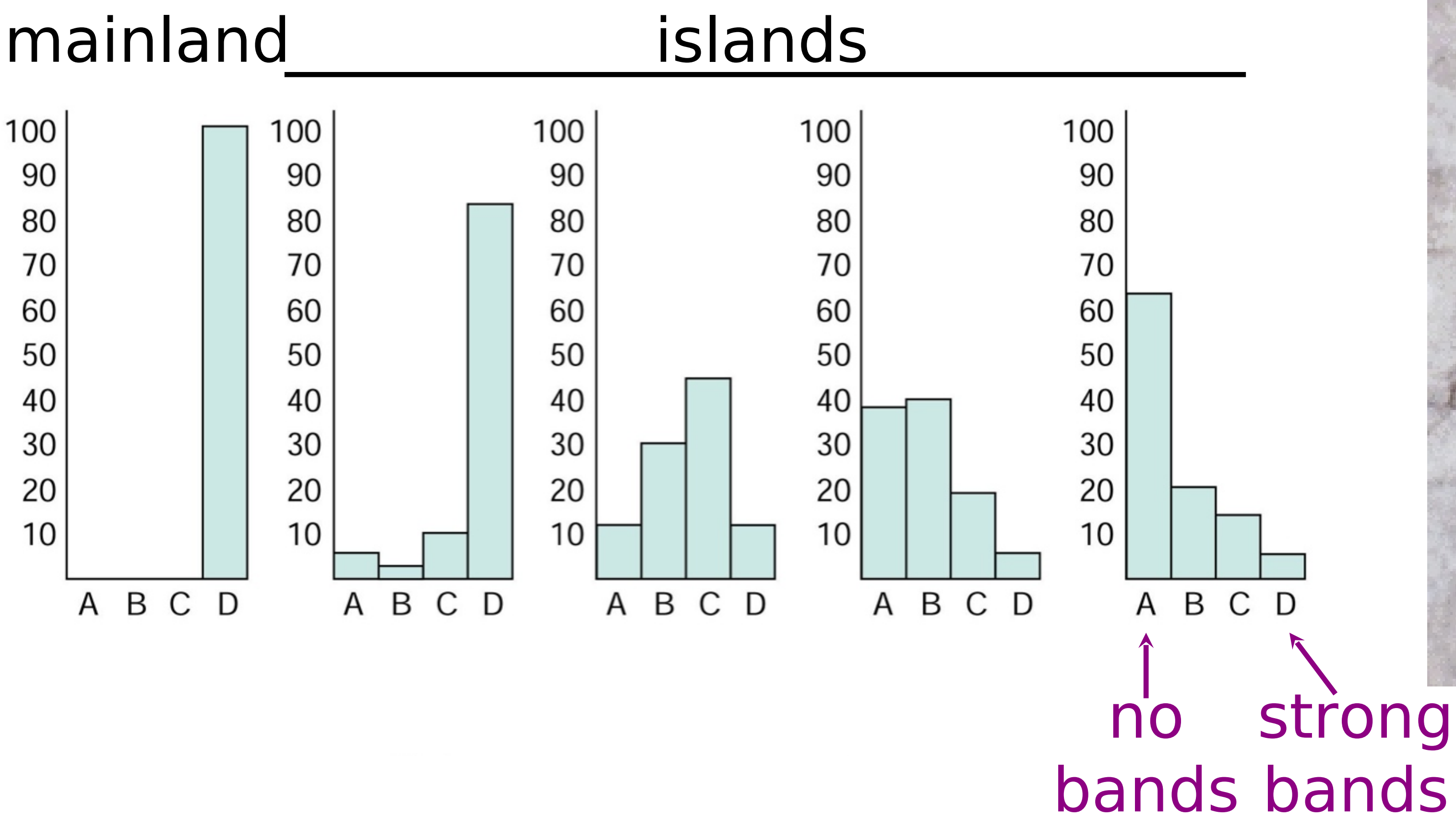
at m=10%, it takes about 30 generations to equalize gene frequencies

The Lake Erie Water Snake

Northern Water Snake
Nerodium sipedon sipedon

L. Erie Water Snake
Nerodium sipedon insularum

Selection on Banding Pattern

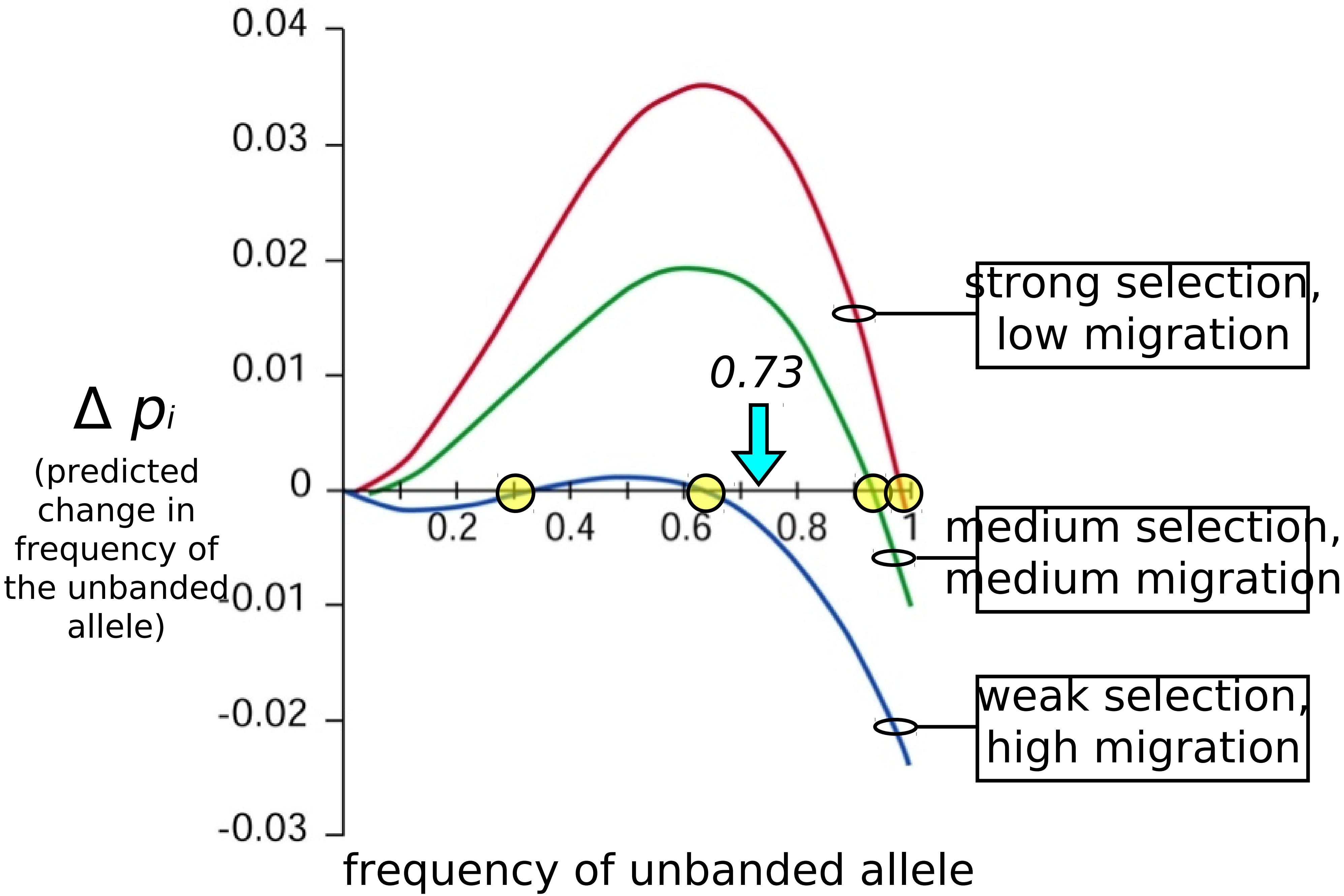


- banding determined by a single locus two allele system.
- King (1993) used mark & recapture experiments to document selection differentials.
- found higher survival rate for unbanded snakes on isles

Assignment: Using real data

- relative fitness of banded snakes on islands due to predation pressure = 0.78 to 0.90
- island population ≈ 10^3
- molecular genetic estimate of 13 migrants / year (about 1% of population)
- calculate equilibrium frequency of the unbanded (recessive) allele.

Modeling Migration, Selection



Possible Reasons for Inaccuracy

1. mark-recapture underestimates selection against banded (other characteristics important in natural or sexual selection).
2. parameter estimates variable, based on limited sampling.
3. nature & human intervention changing the habitat.
4. population sizes fluctuate.

Population Subdivision

	AA	***Aa***	***aa***
subpop. 1	$(0.3)^2 = 0.09$	0.42	$(0.7)^2 = 0.49$
subpop. 2	$(0.7)^2 = 0.49$	0.42	$(0.3)^2 = 0.09$
Mean	**0.29**	**0.42**	**0.29**

frequ. A = 0.5

frequ. a = 0.5

The Wahlund Effect

	AA	***Aa***	***aa***
Mean Observed	0.29	0.42	0.29
H-W Frequencies	**0.25**	**0.50**	**0.25**

- a population with subdivision always displays a deficit of heterozygotes in the equilibrium calculation.
- occurs even though the two populations are themselves at equilibrium.

Wahlund Effect Cont’d

- one needs to know the population structure before believing equilibrium frequencies.
  - *or, a deficit of heterozygotes may signal subdivision.*
- when two distinct populations fuse, the proportion of homozygotes declines.
  - fitness loss due to deleterious homozygous recessive variation (e.g., many genetic diseases) will decline.