
When you eat your Smarties,
Do you eat the red ones last?
Do you suck them very slowly,
Or crunch them very fast?
Eat that candy-coated chocolate,
But tell me when I ask,
When you eat your Smarties,
Do you eat the red ones last?

Calculating N_e

a crude* approximation of effective size is given by:

$$N_e = (4N_m * N_f) / (N_m + N_f)$$

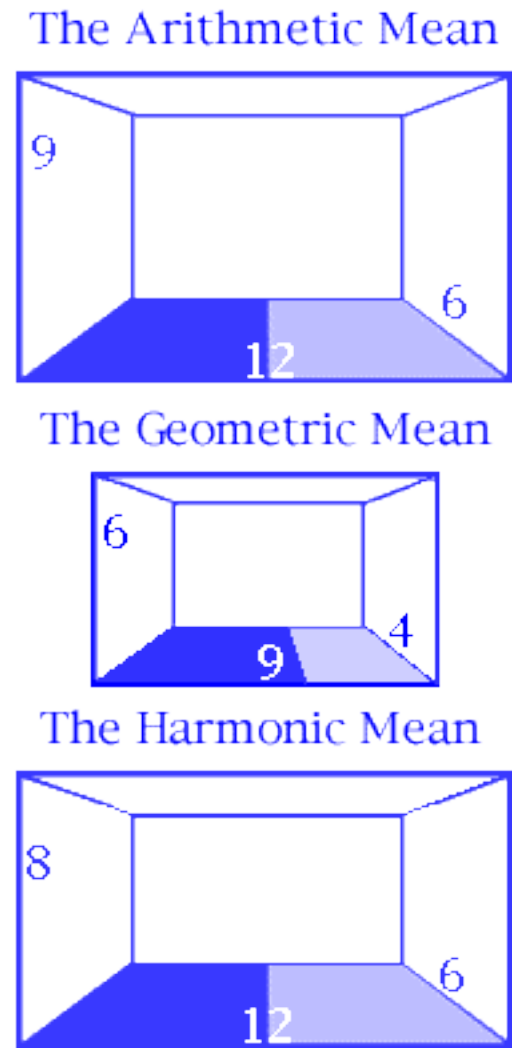
*this is approximate because relative fitness is not estimated.

Sexual Selection & N_e

- a population with 100 breeding males and 900 females has an effective size of 360.
- in lekking species or those with extreme dominance heirarchies, whole social groups of females may mate with the same male.
- $N_e = (4N_m * N_f) / (N_m + N_f) \approx 4$
- note: this calculation assumes only one round of breeding and no migration between groups.

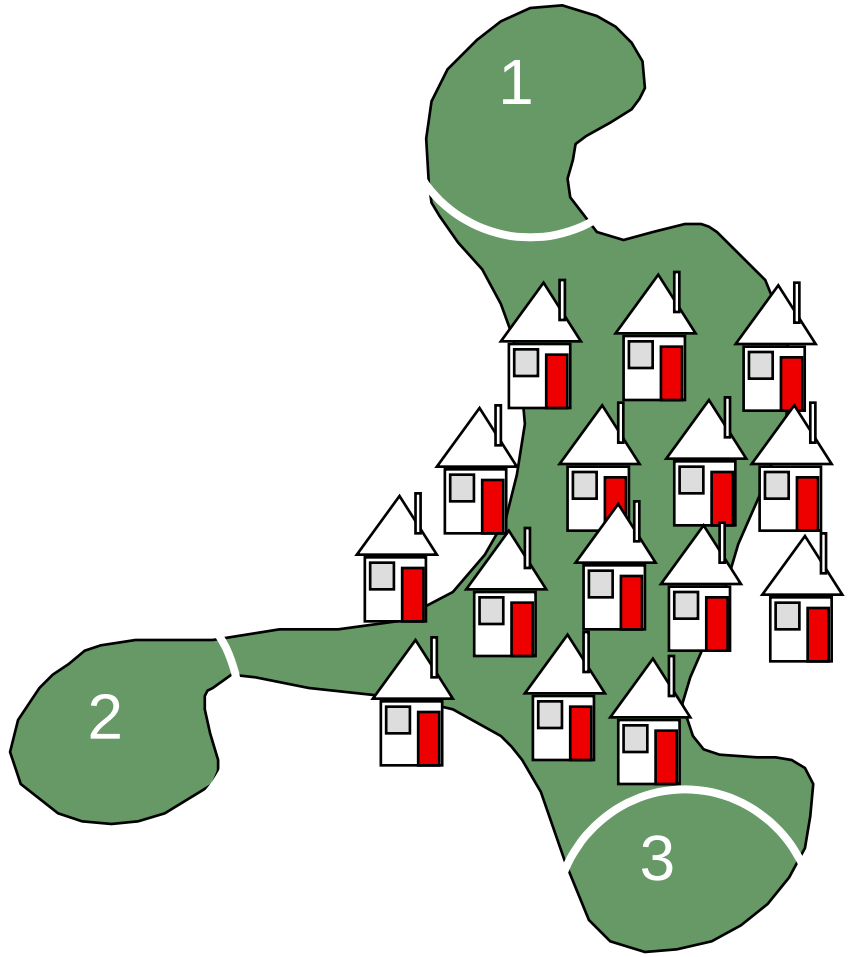
N_e and population fluctuation

- effective population size is extremely sensitive to population bottlenecks
- calculated based on *geometric mean*
- (do not worry about how to calculate this!)



Drift is often the product of reduced gene-flow

- when populations become fragmented, interrupted gene flow will often lead to:
  - increased homozygosity via drift and the Wahlund Effect.
  - inbreeding depression
  - reduced adaptability
    - less variation to resist environmental challenges, disease, parasitism.



Measures of Diversity

Components of Heterozygosity

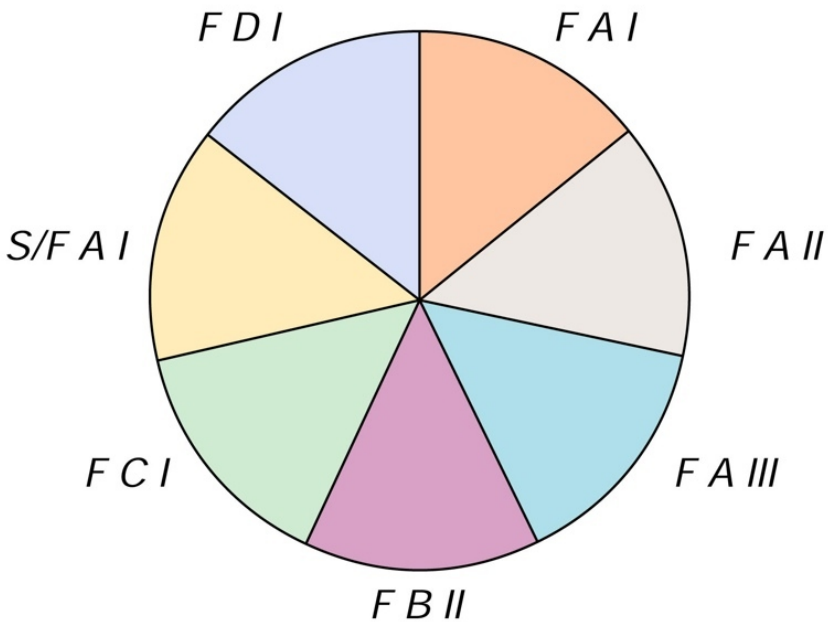
1. Allele Richness: the average number of alleles per locus in the genome.
2. Genetic Polymorphism: the fraction of loci in the genome with 2+ alleles at frequency of >0.01.

Both strongly related to population size (e.g., see study by Young et al. 1996 in F&H)

Collared Lizards

- Relict populations in the Ozark Mountains
  - occupy small glades (remnants of SW deserts) that were once isolated by savannah lands.
  - savannahs burned periodically.
- human intervention:
  - clear cutting & fire extinguishing
    - allowed oak-hickory forest to take over.
    - allowed red cedar to grow into glades.

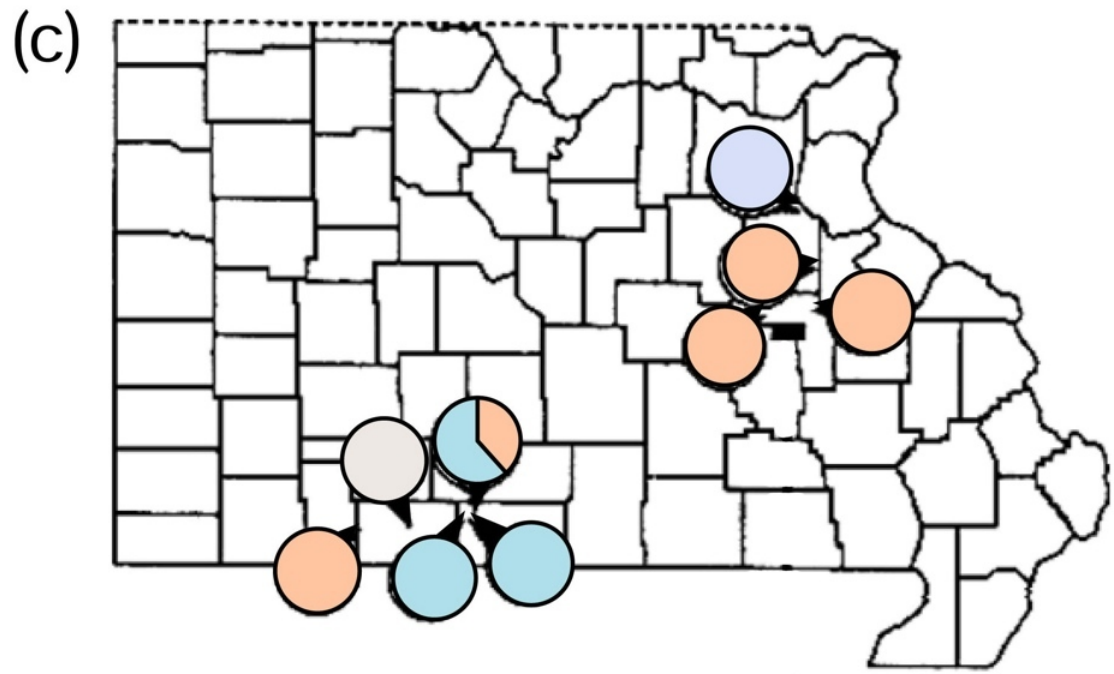
Ozark Collared Lizards



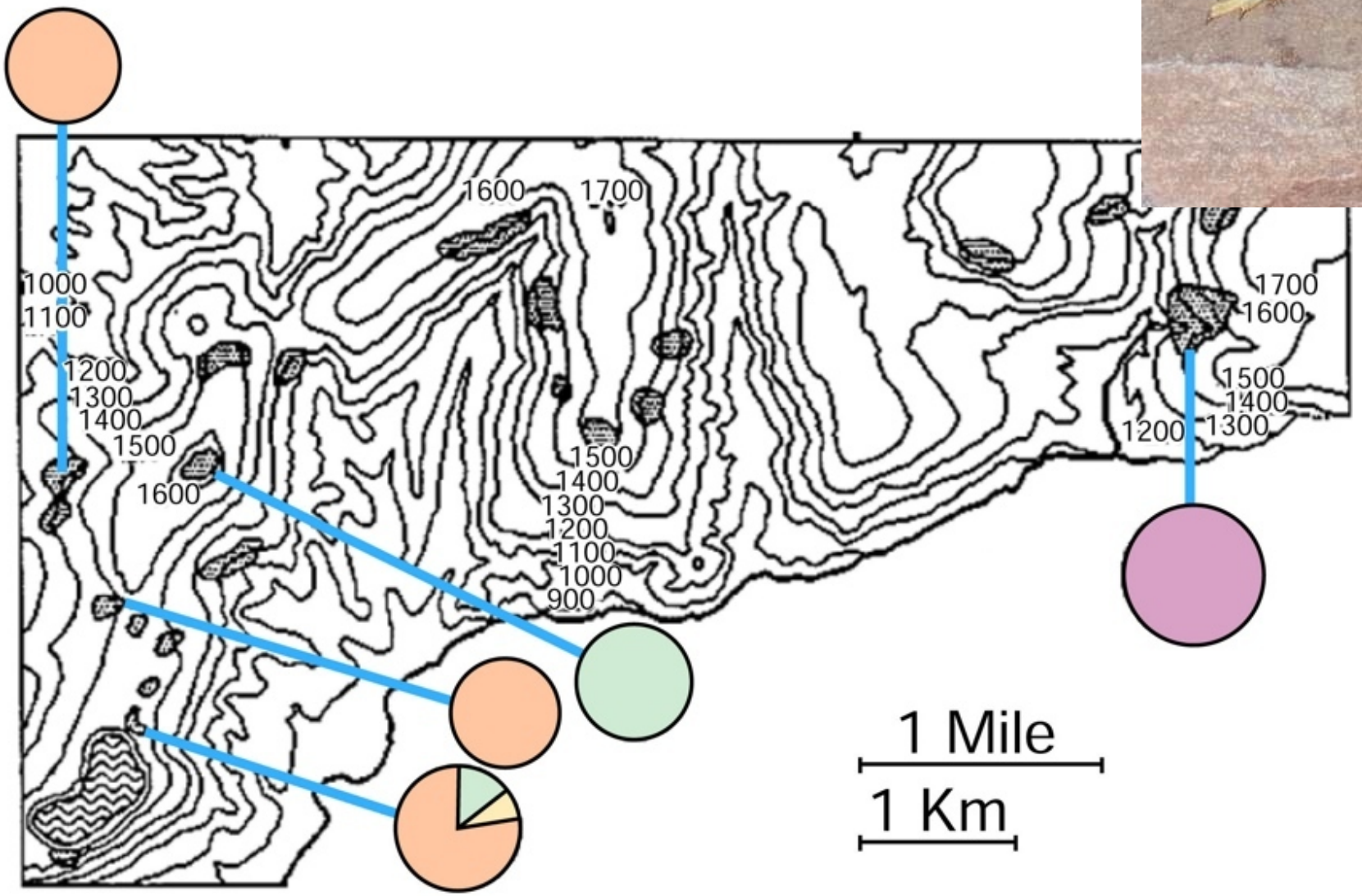
MDH allele *(s/f)*

mt DNA *(a-d)*

r DNA *(i-iii)*



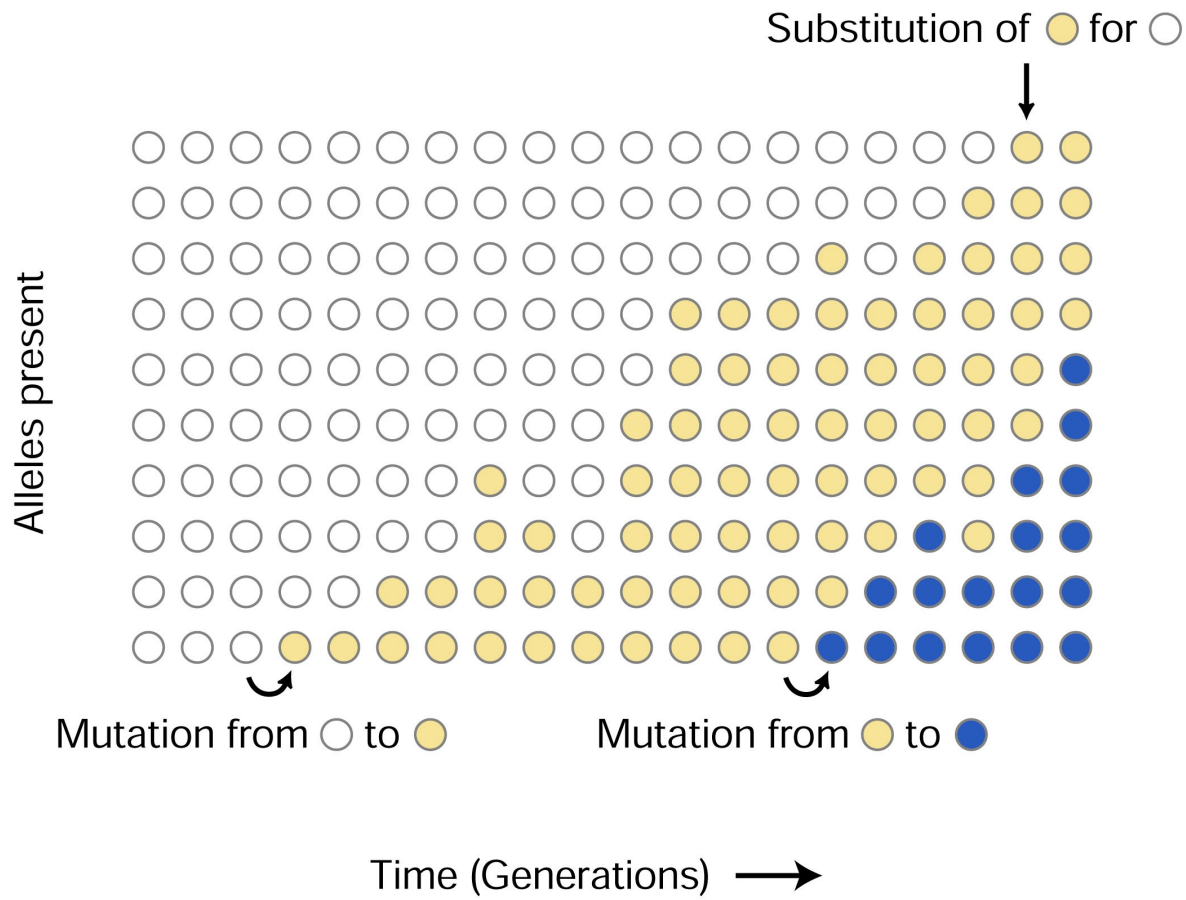
Habitat Fragmentation in Glade Populations



Perils of Fragmentation

- Occupants of any given glade genetically homogeneous
  - unable to adapt to further changes in the environment
  - sitting ducks for diseases
  - ever more sickly due to inbreeding depression.
- Remediate via restoration of empty glade populations, creation of migration corridors with controlled burns.

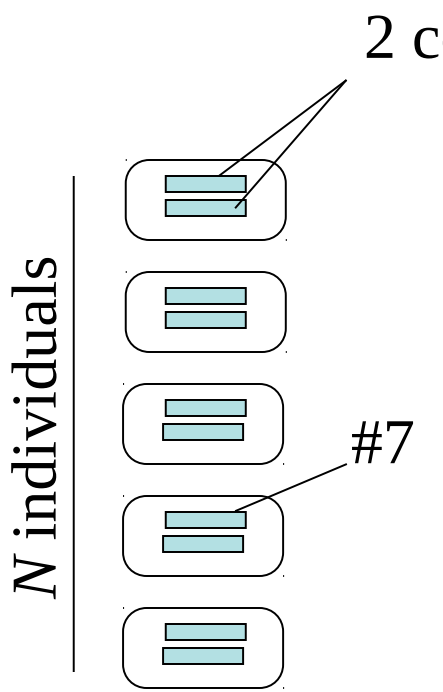
Neutral theory of evolution



Kimura & Neutral Theory

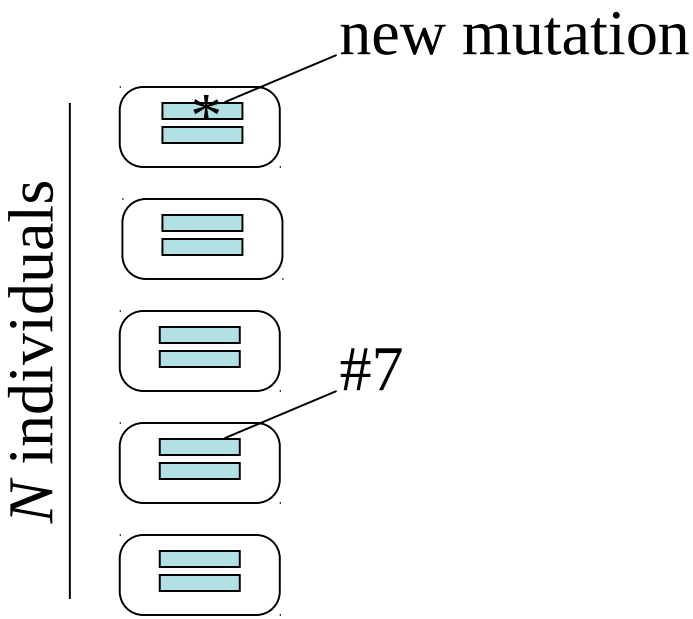
- the vast majority of mutations are selectively neutral.
- rate of evolutionary change = mutation rate for most genes in a population.
- due to drift alone, the chance of an individual copy of a gene fixing is $\boldsymbol{1/2N}$
- if the rate of new mutation at a locus is v, then the number of new mutants in the population is $\boldsymbol{2Nv}$ per generation.

Kimura Model



- 2*N* ‘blue’ genes
- if all equal in fitness (i.e., neutral) then probability of fixing any one copy = 1/2*N*.
- *e.g., probability of blue#7 increasing to 100% is 1/2N = 0.1*

Importance of mutation

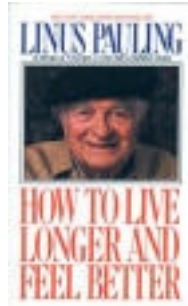


- v is mutation rate per gene per generation.
- $2Nv$ mutations (new copies) happen per generation.
- *if $v=0.1$, then in our population $2Nv = 0.02$.*
- rate of fixation =
- **$(1/2N) \times (2Nv) = v$**

probability by drift (chance)

rate of new mutations.

Molecular Evidence

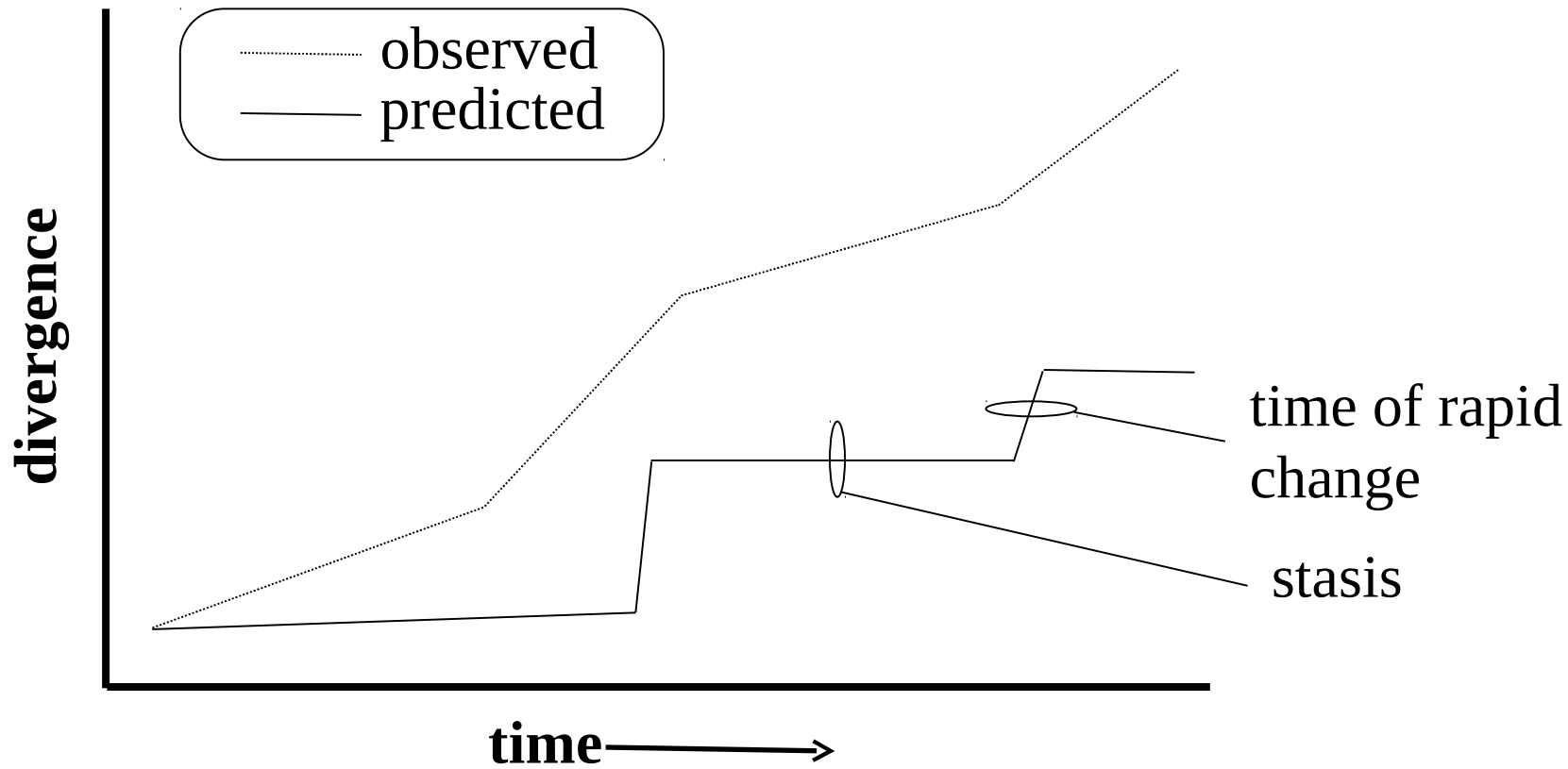


- Early data on amino acid sequences in vertebrate proteins:

  - Kimura: mutations causing amino acid substitution appeared to be occurring at a surprising pace.

  - Zuckerkandl & Pauling: amino acid subs appear t occur at a steady pace
    - could be used as a ‘molecular clock’ to estimate divergence of species.

- Problem: steady, clock-like change did not fit predictions of evolutionary theory



Neutral Theory & The Clock

- Episodes of selection should be followed by periods of less change, once a protein is optimized for a particular function.
- Kimura proposed that most molecular evolution is driven by selectively neutral variation:
  - alleles have no selection coefficient
  - genetic drift & mutation the dominant forces in evolution

Neutral Theory-O-Rama

1) Population size does not matter
   - drift stronger in small populations
   - *but* mutation equally less common!

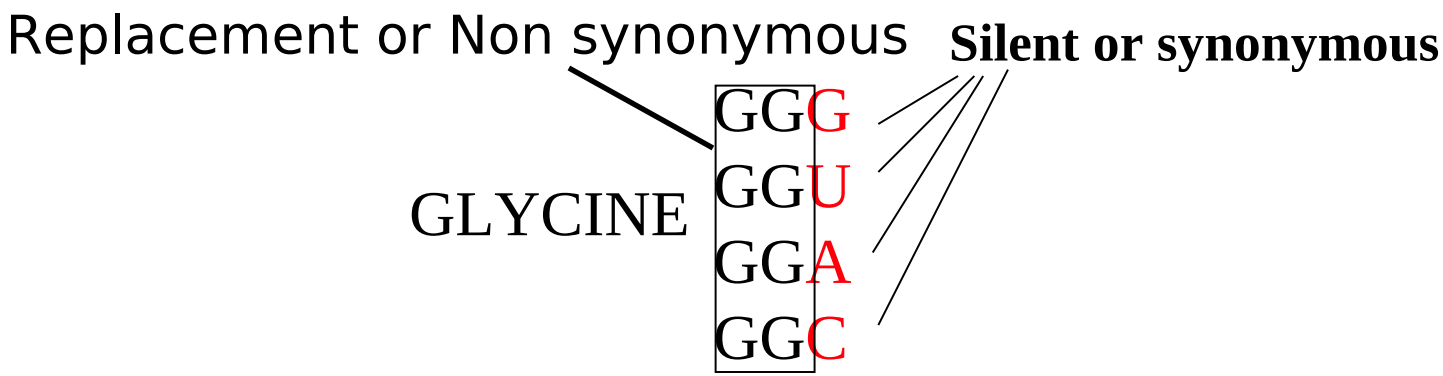
1) Selection for new beneficial genes does not matter
   - most new mutations harmful, eliminated by natural selection.
   - *v* therefore approximates the maximum rate of evolutionary change.

Neutralists vs. Selectionists

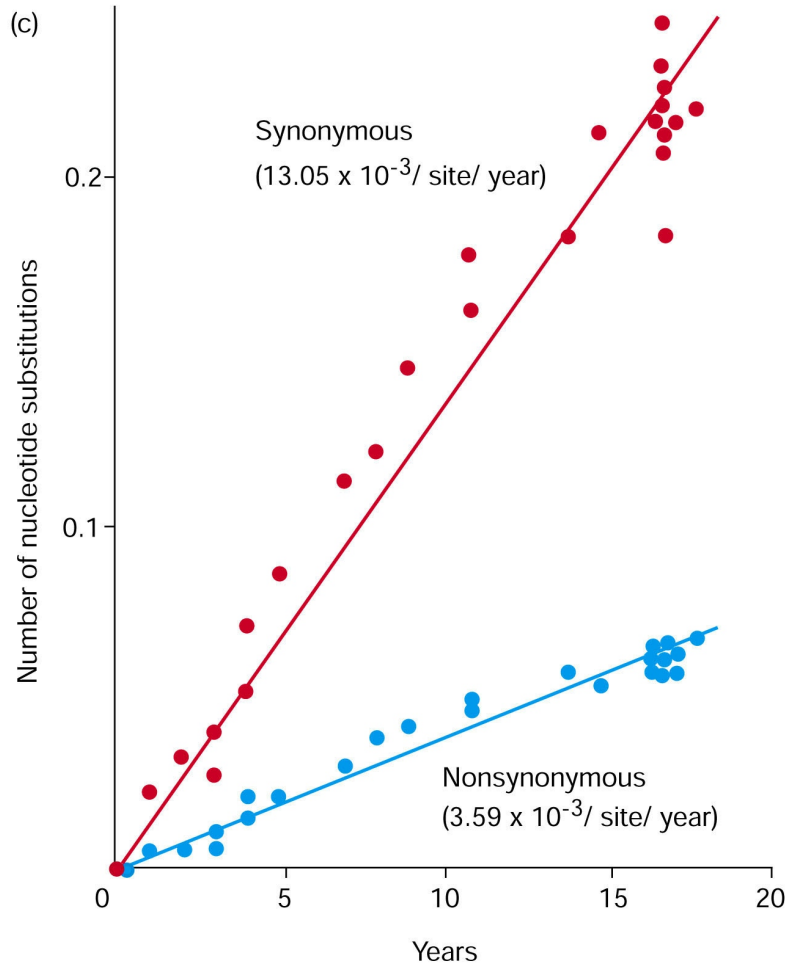
- the neutral view for molecular evolution spread in the ‘80s with the finding of clock-like sequence divergence.
- view was rebutted by John Gillespie and others.
  - selectionists view the incidence of positive mutation as non-trivial,the general effect of mutation to be deleterious and both to be exposed to selection.
  - selection is progressive, even if ‘progress’ is blind.

Testing the Neutral Theory

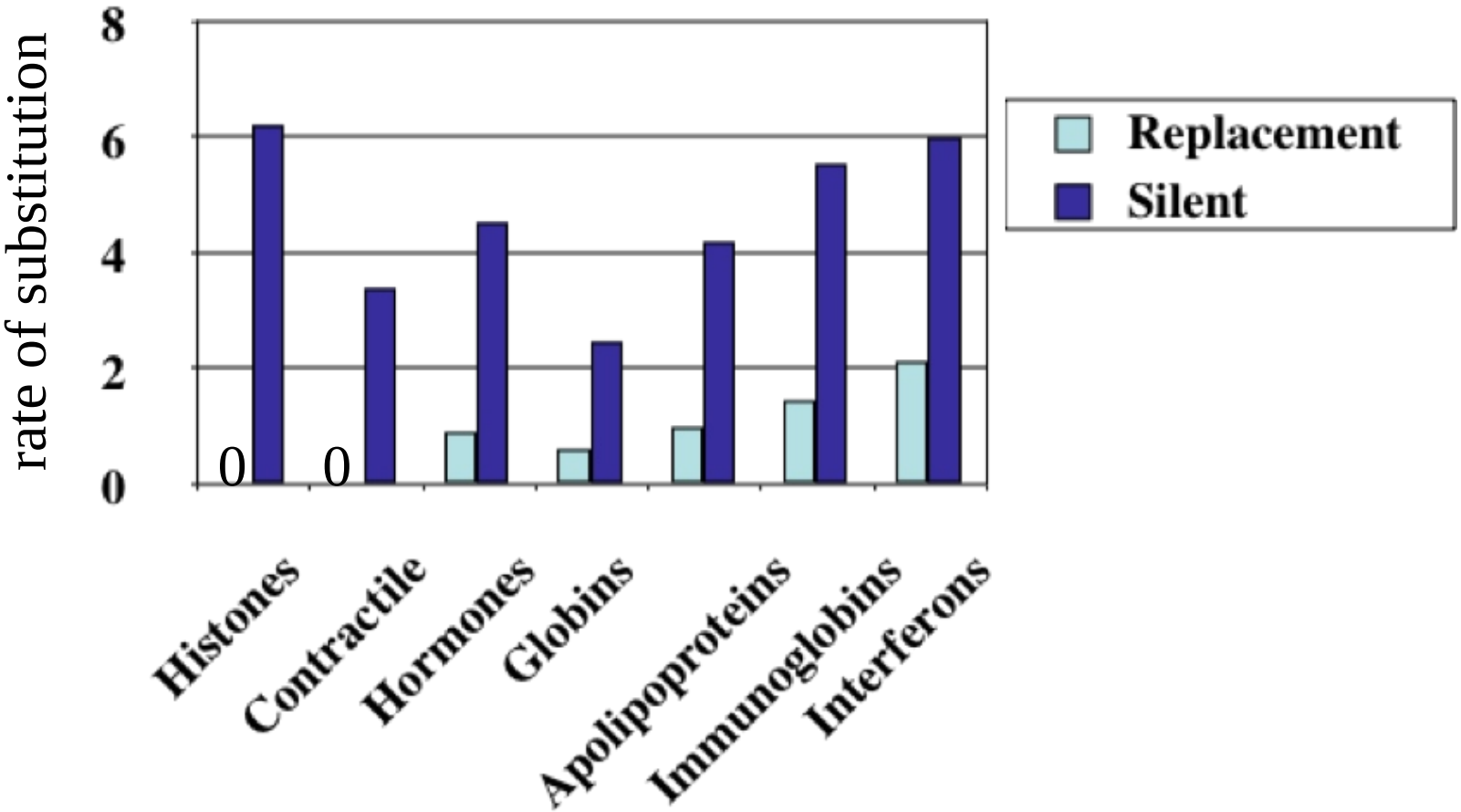
- pseudogenes should undergo neutral evolution:
  - non-coding sequences & junk DNA have the highest rates of sequence divergence.
- codons
  - silent-sites in codons undergo neutral evolution.
  - replacements at silent sites called SYNONYMOUS replacements because AA product unchanged.



Molecular evolution in influenza virus



However,
Codon position: Human vs. Mouse



from Li & Graur 1991

Rates vary by locus

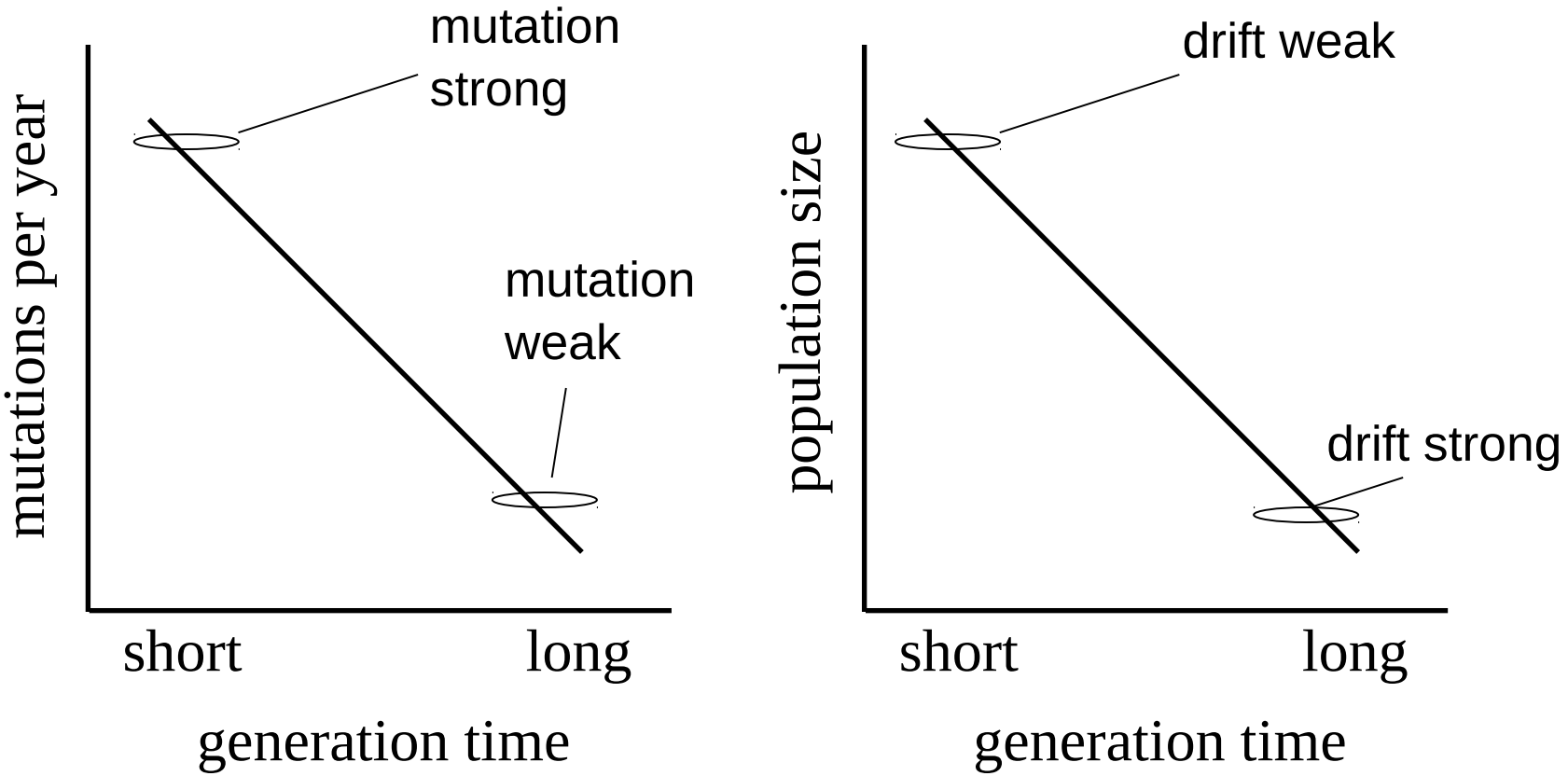
- Frequency of nonsynonymous (replacement) substitutions related to constraints on gene function.
  - EXAMPLE: Histones are vital in cell functioning and show very little replacement substitution; immunoglobins show higher rate of replacement.
- Predictions exactly the same as for coding vs. non-coding sequences, but graduated.

More Trouble for Neutrality

- why do protein sequences change in a steady clocklike fashion among species with very different generation times?
  - i.e., why change with absolute time when organisms have different reproductive rates?
  - fly (11d) vs. albatross (9y): fly should have many more mutations per year than the albatross!

- Ohta & Kimura modified theory to include mutations with slightly deleterious effects
  - makes drift more important in small populations
  - Mutations effectively neutral when $s \leq 1/2Ne$

Reconciling the time paradox



FLY: strong *v* x weak drift
ALB: weak *v* x strong drift

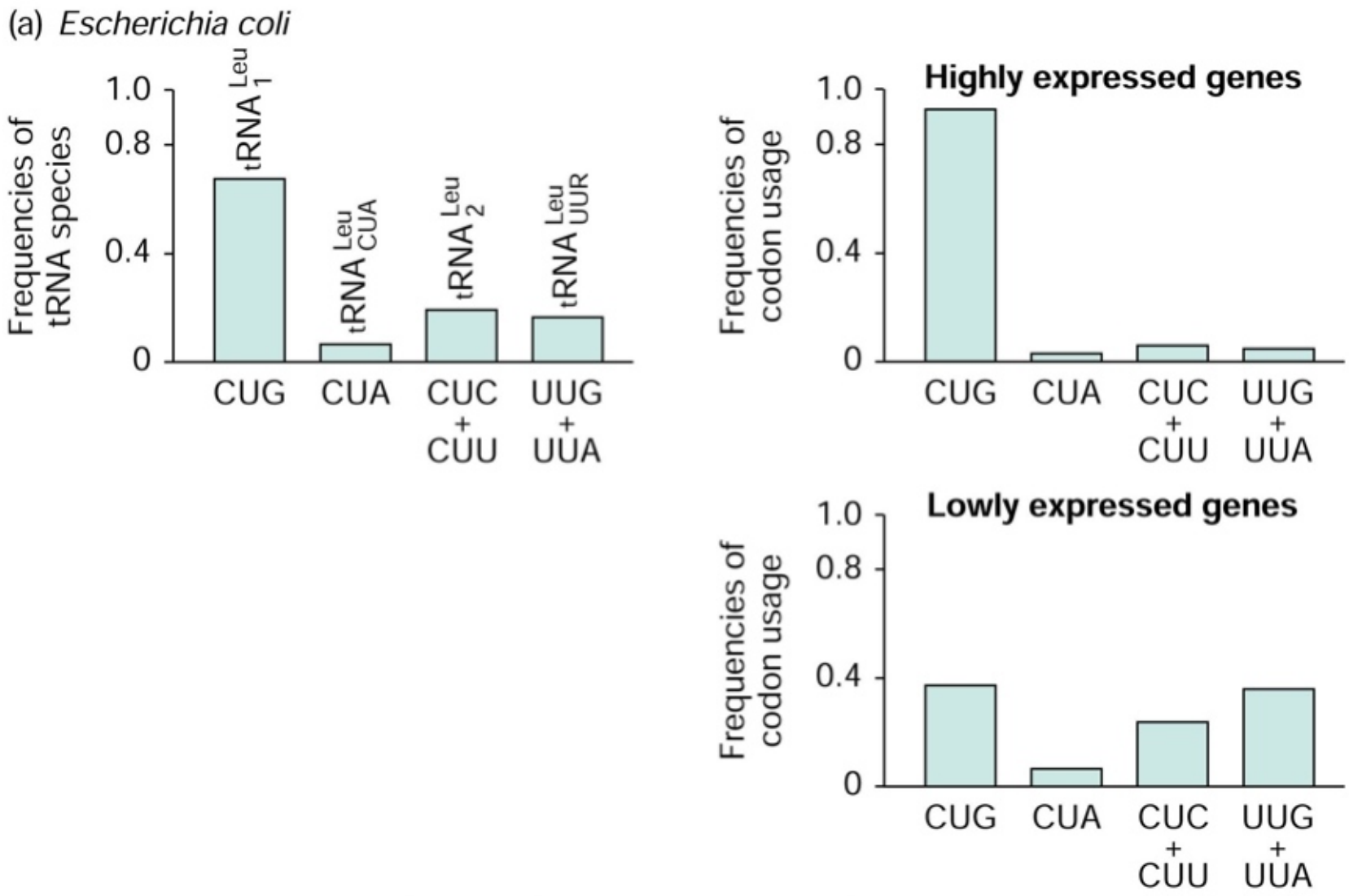
= rate of change

Codon Bias

- most amino acids have multiple codons (20 AAs, 64 combos of bases).
- example: leucine has 6 codons:
- UUA, **UUG,** CUU, CUC, CUA, **CUG**

favoured in *S. cerevisiae*

favoured in *E. coli*, *D. melanogaster*.



Implications of codon bias

1) Strongest in most highly expressed genes.
2) Selection is *not* silent at the third position after all.
3) Transcriptional efficiency is probably the driving factor in codon bias:
   - tRNAs match most common mRNAs produced in cells.
   - mismatch (i.e., mutation to a new codon) reduces translational efficiency of transcript -> selected against.

Neutrality in the Docket

- silent site changes and pseudogenes support a neutral model.
- The variation in functional positions and coding loci do not support a strictly neutral view.
- Conclusion: parts of the genome will evolve neutrally.
  - these portions will prove very useful in some population genetic analyses.
  - estimates suggest 95% of human genome is non-coding (junk) DNA.

More Uses of Neutral Theory

- Explains several important patterns in molecular evolution.
- Like Hardy-Weinberg Equilibrium, provides a null hypothesis for testing adaptive evolution:
  - *compare change to neutral expectation to determine if natural selection has shaped the sequence.*

Looking for Positive Evolution

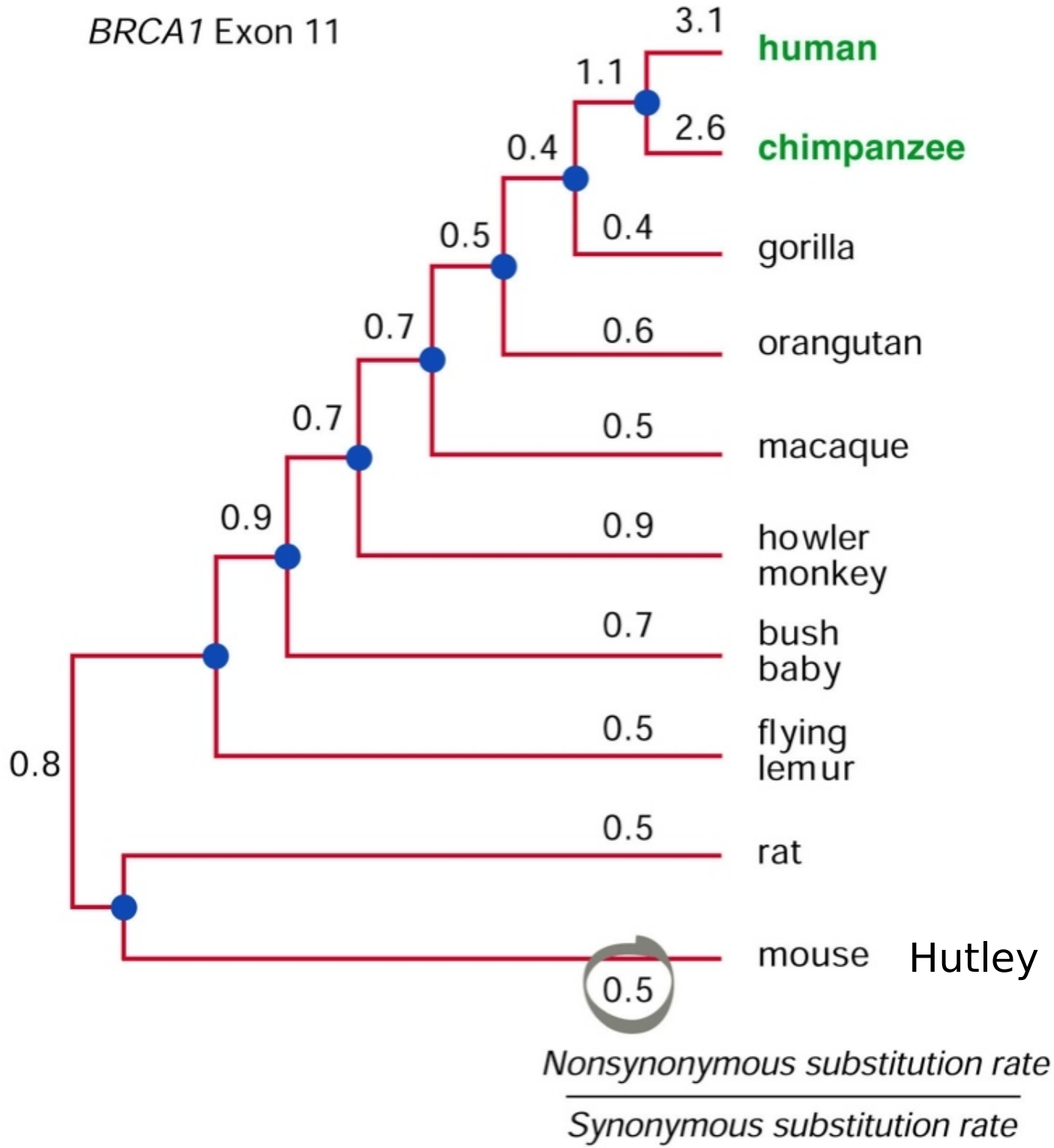
- Hughes & Nei looked at major histocompatibility complex (MHC) gene sequences.
  - membrane proteins important in immune system recognition of infected cells.

- synonymous substitution rate used to estimate the mutation rate, ***v***.
  - provides a benchmark for gaugeing non-synonymous (replacement) rate of change.

- H & N found *higher* Non synonymous rates in the antigen recognition system than predicted by the Synonymous site benchmark.

- Higher replacement rate can only be explained by positive selection.
- i.e.,
- $\boldsymbol{d_{NON} / d_{SYN} > 1}$ only when replacements advantageous.

- $\boldsymbol{d_{NON} / d_{SYN} < 1}$ when replacements disadvantageous.



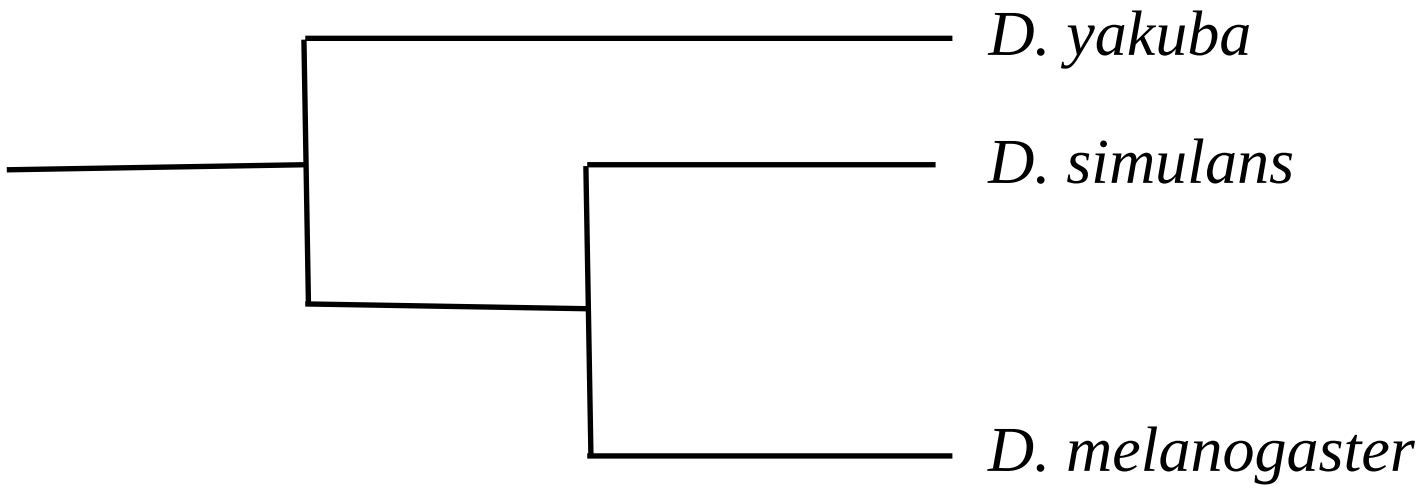
Hutley G et al. 2000

$$d_{NON} / d_{SYN} > 1$$

- Unduly conservative index of positive selection (Sharp 1997).

- McDonald & Kreitman refined the silent vs. replacement hypothesis:
  - ratio silent:substitution is constant through time according to neutral theory.
  - use ratio to compare within-species change to between-species change.

MK test: *Adh* in *Drosophila*



• *Adh* (Alcohol dehydrogenase) important for fruit flies because they live on rotting fruit.

• M&K scored number of fixed vs. polymorphic sites based on sequence data.

Replacements 6x more frequent than predicted by neutrality

• Null (neutral prediction): within species ratio of silent:replacement substitutions ≈ **20:1**

• Measured ratio between species ≈ **3:1** *(p=0.0006)*

The Genes to Watch: Evolving at Warp Speed

- genes recruited to new functions (e.g., duplications)
- sex-determination genes
- fertilization interactions (sperm-egg; pollen-stamen)
- some enzymes, regulatory proteins
- immune-system genes
- sexual conflict genes?

Inbreeding

- Mating between related individuals
- F = inbreeding coefficient (probability that two homologous alleles in an individual are identical by descent)

- Identity by Descent: Two alleles created from the same ancestral copy of the gene

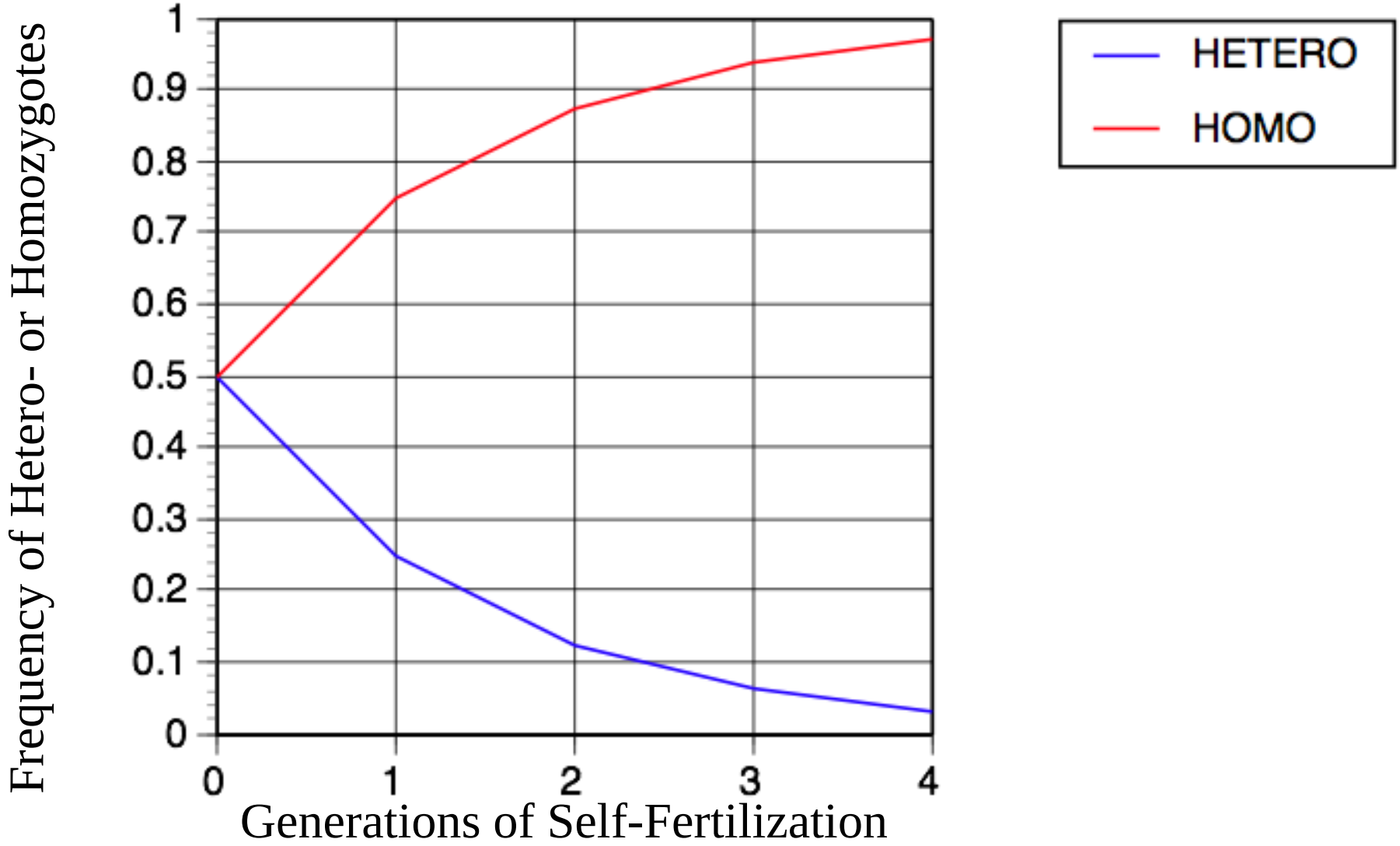
- Identity by Type: Two alleles sharing the same nucleotide sequence but not a common ancestor.

  - Some more terms-
  - Autozygous (Always homozygous)
  - Allozygous (Homozygous or heterozygous).

Genotype frequencies with Inbreeding

- $AA = p^2(1-F) + pF$
- $aa = q^2(1-F) + qF$
- $Aa = 2pq(1-F)$
- $H = H_0(1-F)$
- Pedigrees are used to compute F
- Inbreeding INCREASES genotypic variance
- Inbreeding does not change allelic frequencies

Inbreeding via Selfing

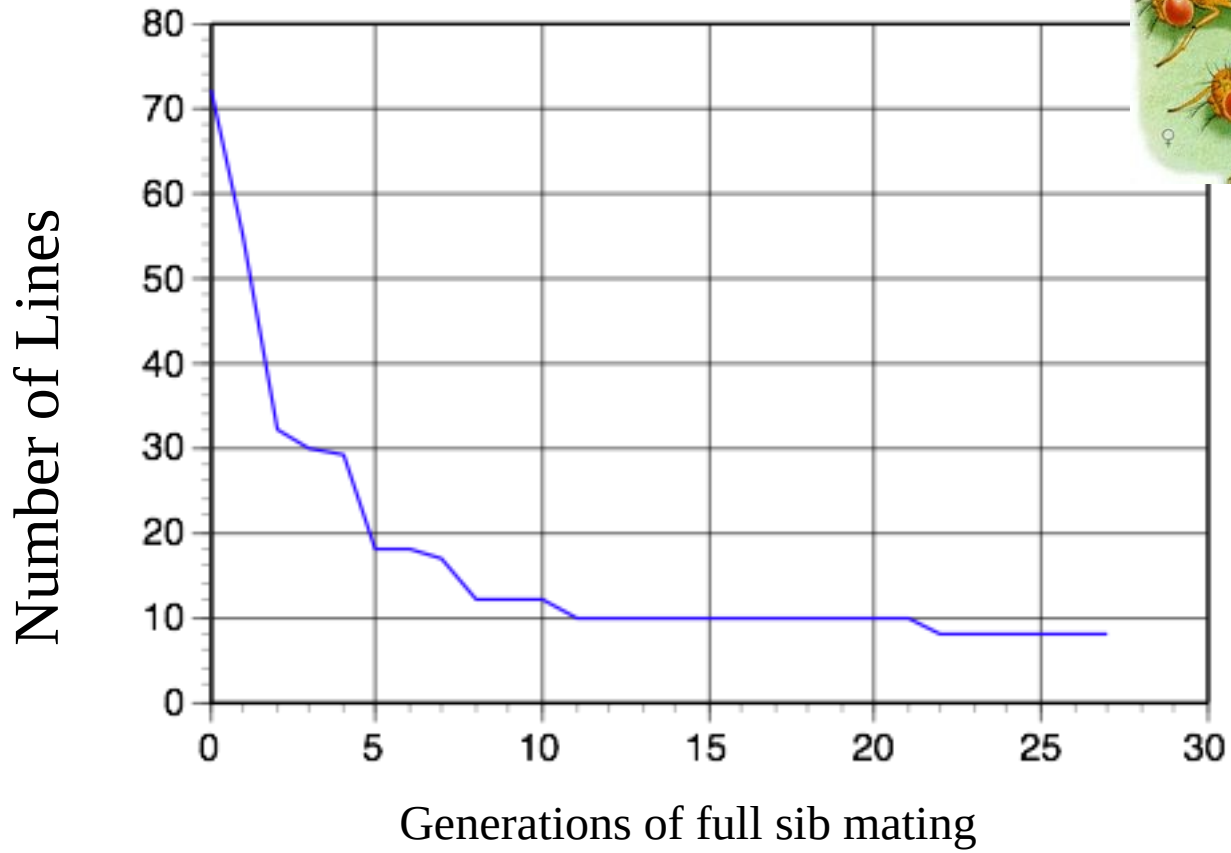


Despite changes in GENOTYPE FREQUENCIES, inbreeding has no effect on ALLELE FREQUENCIES.

Melting down the Vortex

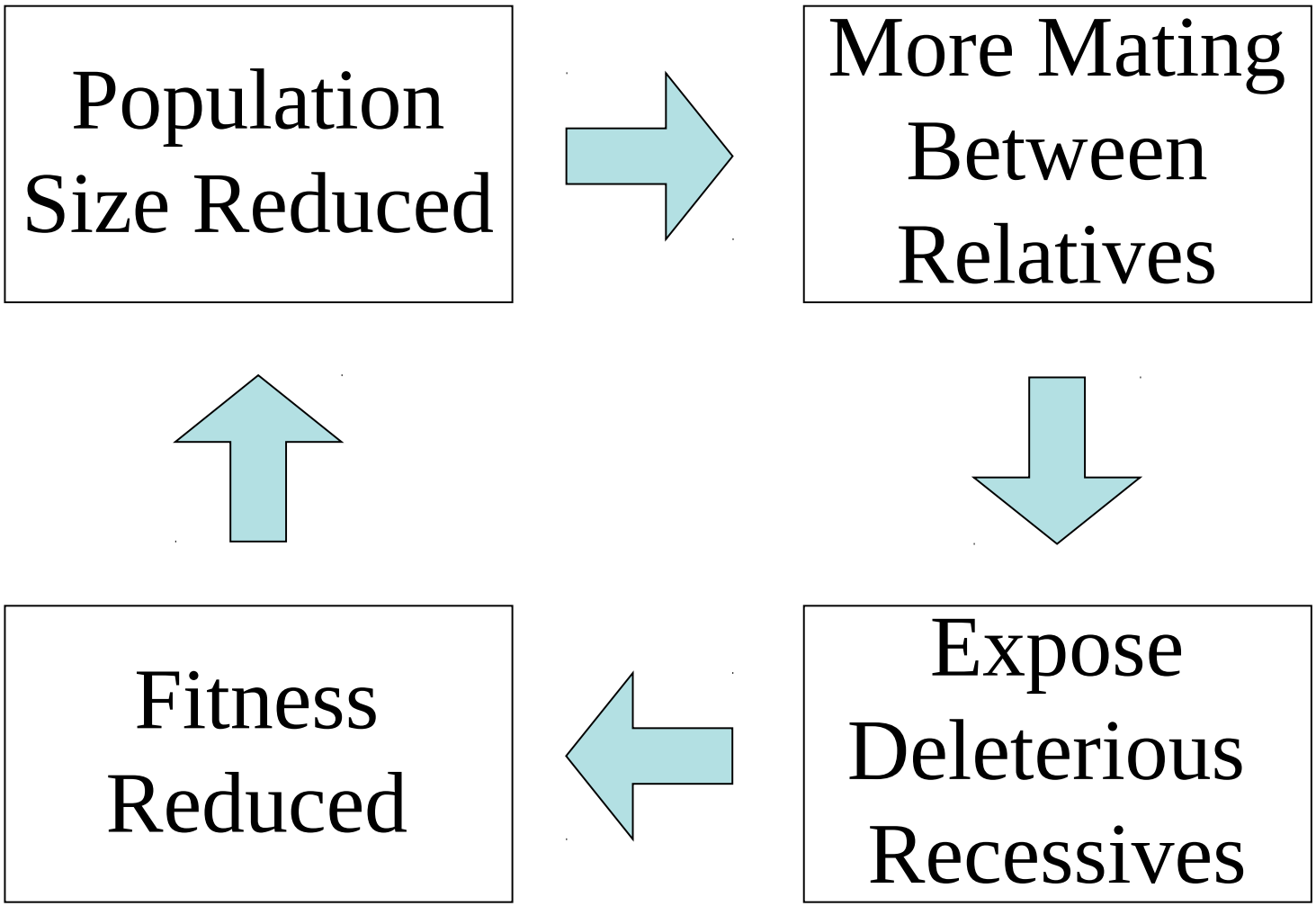
- Inbreeding and drift have similar effects – increased homozygosity.
- Genetic Drift & Mutation have profound implications for the conservation of populations.
- recall the Wahlund Effect:
  - as continuous populations become fragmented, the frequency of homozygotes increases due to drift.
  - homozygosity increases; relatives mate with relatives to an ever greater degree.

Inbreeding depression



- exposure of recessive deleterious variation leads to a syndrome of low performance:
  - low survival & low fertility

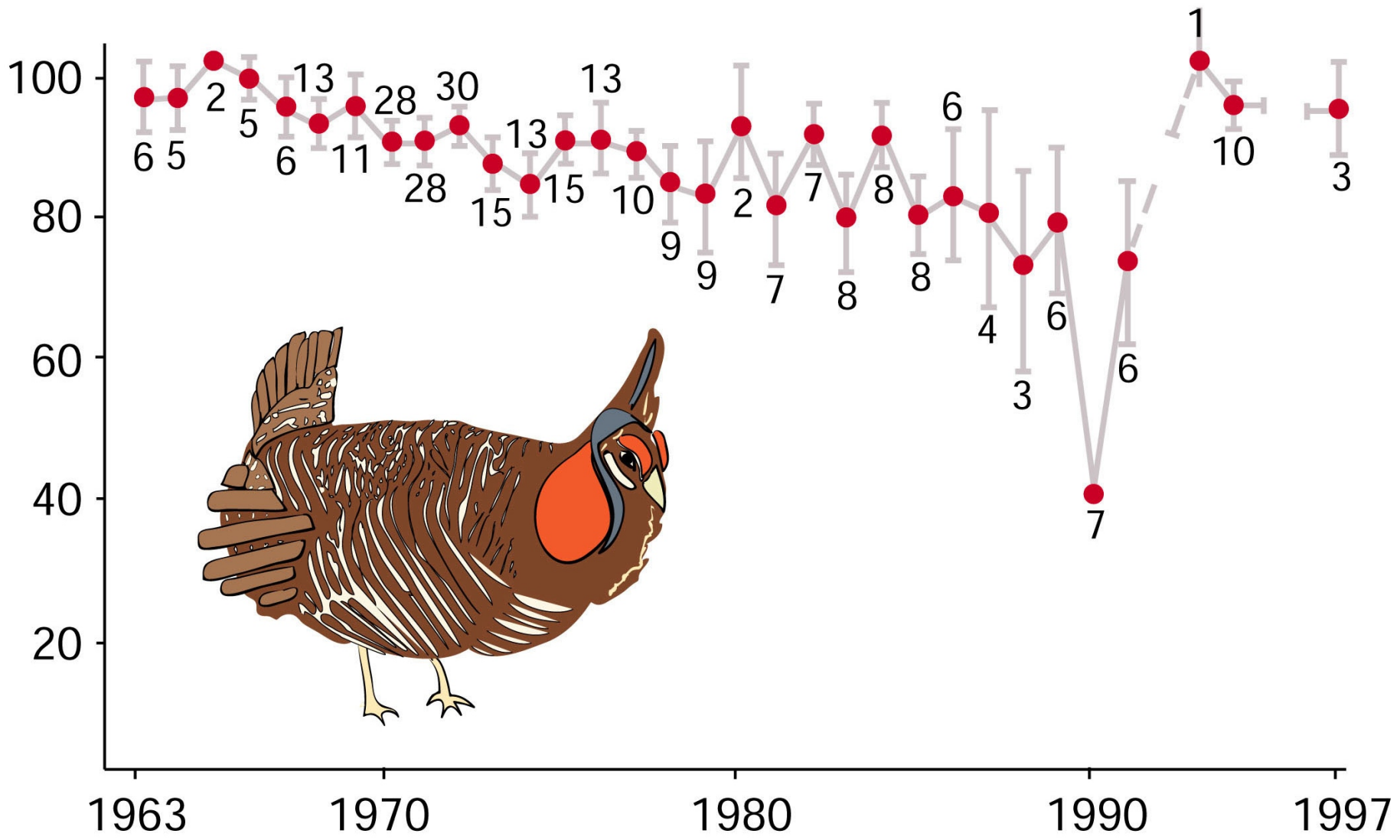
Mutational Meltdown



genetic load increases

Meltdown or Vortex?

- Inbreeding is a strong form of genetic drift
- Causes exposure of deleterious recessive variation hidden in large populations.
- As fitness declines because of increased Genetic Load, population size shrinks further.
- This intensifies drift (i.e., further inbreeding)
- Synergism of effects leads to extinction.



Conservation of the Greater Prairie Chicken

- allelic richness had declined to about 60% of neighbouring populations (or since the 1930s).
- strategies based on habitat recovery were largely unsuccessful.
- importation of neighbouring stock from other states lead to dramatic reversal
  - a little bit of gene flow goes a long way
  - conservation also needs to be cognizant of the breeding system and effective population size