Chapter 5 – Mutation

Ultimate Source of Genetic Variation

Fate of New Mutations

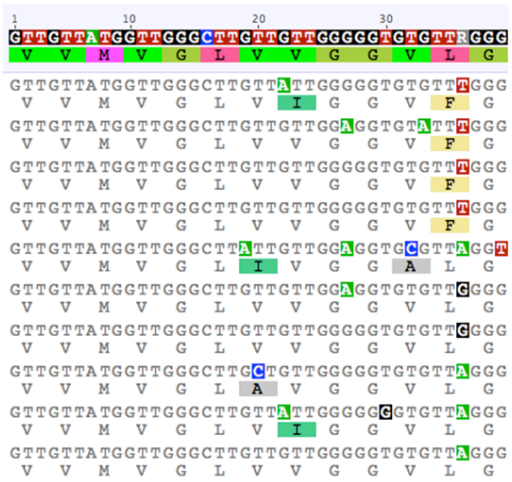
Mutation Models

Effect of Mutation on Genetic Diversity

The Coalescent with Mutation

Mutations

- point mutations
  - synonymous (=silent)
  - non-synonymous (=replacement, missense)
  - nonsense (=premature stop codon)
- SNP (single nucleotide polymorphism)
- insertions, deletions
  - frameshift mutations



Mutations

- point mutations
  - synonymous (=silent)
  - non-synonymous (=replacement, missense)
  - nonsense (=premature stop codon)
- SNP (single nucleotide polymorphism)
- insertions, deletions
  - frameshift mutations
- chromosomal inversions, translocations
- repetitive elements
- transposable elements

Mutation Rates

- allozyme, per gene rates
  - 10^{-4} to 10^{-6} per generation
- nucleotide rates
  - nuclear ~10^{-9} per nucleotide per generation
    - 40 billion new mutations in 6.5 billion humans!
  - mtDNA ~10^{-8} per nucleotide per generation
- microsatellite rates
  - 10^{-2} to 10^{-5} per allele per generation

Hypothetical Distribution of Effects

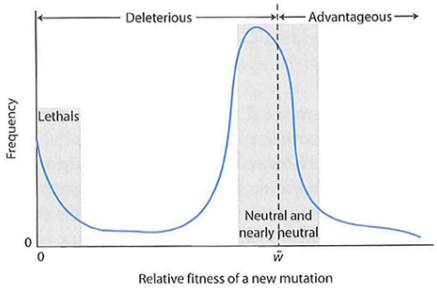


Figure 5.1 A hypothetical distribution of the effects of mutations on phenotypes that ultimately impact the Darwinian fitness of genotypes. Mutations that have a mean fitness less than the mean fitness of the population ($\bar{w}$) are decreased in frequency by natural selection. The shaded area around $\bar{w}$ indicates the zone where mutations have small effects on fitness relative to the effects of genetic drift (the width of the neutral zone depends on the effective population size). The shaded area near zero mean fitness indicates mutations that cause failure to reproduce or are lethal. Lethals are more common since it is a category that includes many degrees of severity resulting from diverse causes. The fitness effects of mutations are inherently difficult to measure because of the rarity of mutation events, the small effect of many mutations, and the dependence of fitness on environmental context.

Mutation Accumulation in *Drosophila*

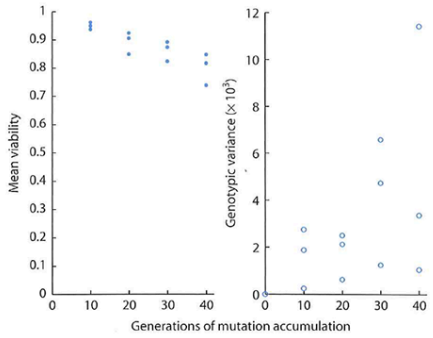


Figure 5.2 The results of the classic *Drosophila melanogaster* mutation accumulation experiment carried out by Mukai et al. (1972). The experiment maintained three distinct sets of mutation-accumulation populations with 25 lines each. The left-hand panel shows the change in mean viability over time and the right-hand panel shows the change in the variance among replicate independent lines. Each point is the value obtained from one set of mutation-accumulation populations. Mutation of any type makes the lines diverge genetically and increases the variance. Mean viability declines over time as deleterious mutations are more common than advantageous mutations. Redrawn from Figure 2 in Mukai et al. (1972).

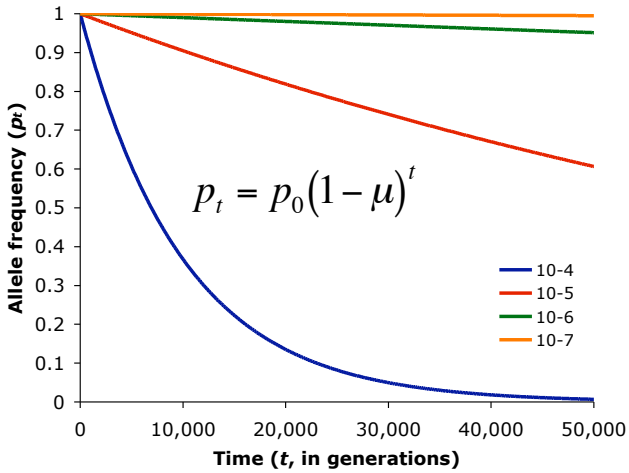
Mutation in an Infinite Population

- start with old school approach
  - mutations of allele **A** to allele **a**
  - recall that pop gen theory was developed before the structure of DNA was known
- recurrent mutation changes allele frequency slowly!

$$p_1 = p_0(1-\mu)$$

$$p_t = p_0(1-\mu)^t$$

Mutation in an Infinite Population



Mutation in an Infinite Population

- if mutations are reversible, the equilibrium allele frequency reflects the relative rates of forward and backward mutations

$$\hat{p} = \frac{\nu}{\mu + \nu}$$

where μ = the rate of mutation from **A** to **a** and ν = the rate from **a** to **A**

Mutation & Genetic Drift

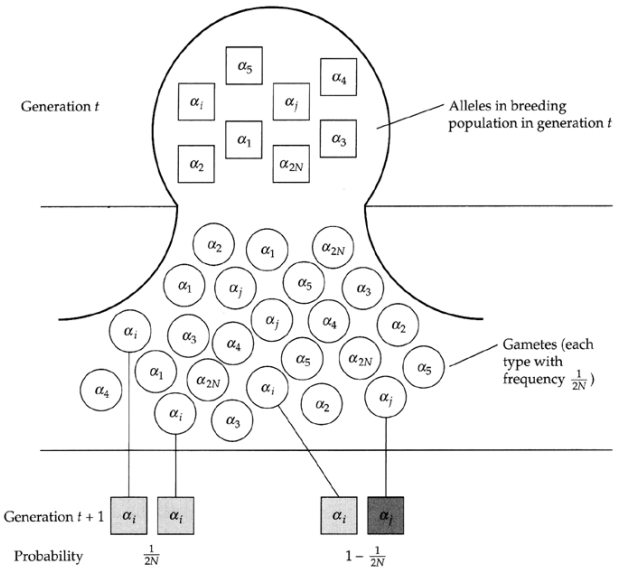


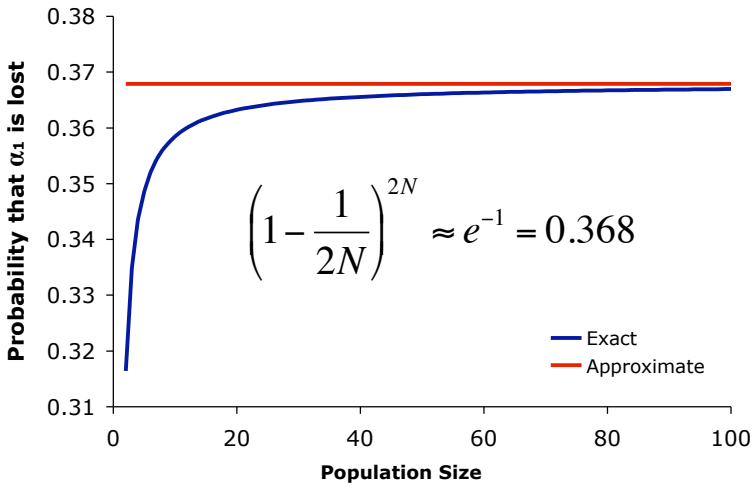
FIGURE 4.5 Random sampling of alleles in a finite population increases the probability of identity by descent. Two randomly chosen alleles, illustrated in the squares at the bottom, may be identical by descent either because they are replicas of the same allele in the immediately preceding generation ($\alpha_i\alpha_i$) or because they are replicas of the same allele in a more remote generation ($\alpha_i\alpha_j$).

Mutation and Genetic Drift

- a substantial fraction of alleles (lineages) will be lost by chance each generation in a random breeding population of finite size
- probability that α_i will be lost in a single generation

$$\left(1-\frac{1}{2N}\right)^{2N} \approx e^{-1} = 0.368$$

- ~37% of individual alleles (assuming $F = 0$) lost each generation regardless of N_e



Mutation and Genetic Drift

- eventually, only one of the original lineages remains
- therefore, probability of fixation for a novel mutation is $1/2N$ (average time to fixation = $4N$ generations) and the probability of loss for a new mutation is $(1\text{-}1/2N)$
- except for very large populations, drift can change allele frequencies much faster than recurrent mutation

The Neutral Theory of Molecular Evolution

- Kimura (1968)
  - initially viewed as a challenge to Darwinian evolution
    - e.g., King & Jukes 1969 *Science* 164:788-798.
- many genetic polymorphisms have no effect on fitness and are therefore selectively neutral
- neutral polymorphisms are maintained by the combined effects of mutation and drift
  - mutations introduce new alleles as others are lost through drift

Origins of the "Selectionist-Neutralist" Debate

- the only "mutations" early biologists saw were ones that had phenotypic effects
- 1953 - structure of DNA (Watson & Crick / *Franklin*)
- 1960-70's - protein electrophoresis
  - revealed allelic diversity for many genes
- 1968 - Motoo Kimura - the neutral theory
  - motivated by allozyme (amino acid) variation
- discovery of "junk DNA"
  - 98.5% of human genome is non-coding
- DNA sequencing has revealed substantial silent and non-coding variation, suggesting that much genetic variation is selectively neutral (or nearly so!)