

Mutation

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

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1          10          20          30
GTTGTTATGGTTGGGCTTGTATTGGGGGTGTGTTAGGG
V V M V G L V I G G V F G
GTTGTTATGGTTGGGCTTGTGTGGAGGTGTAATAGGG
V V M V G L V V G G V F G
GTTGTTATGGTTGGGCTTGTGTGGGGGTGTGTTAGGG
V V M V G L V V G G V F G
GTTGTTATGGTTGGGCTTGTGTGGAGGTGCCTTAGGG
V V M V G L I V G G A L G
GTTGTTATGGTTGGGCTTGTGTGGAGGTGTGTTAGGG
V V M V G L V V G G V L G
GTTGTTATGGTTGGGCTTGTGTGGGGGTGTGTTAGGG
V V M V G L A V G G V L G
GTTGTTATGGTTGGGCTTGTATTGGGGCGTGTAGGG
V V M V G L V I G G V L G
GTTGTTATGGTTGGGCTTGTGTGGGGGTGTGTTAGGG
V V M V G L V V G G V L G

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- ❖ point mutations
 - ❖ synonymous (=silent)
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 - ❖ 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 $\sim 10^{-9}$ per nucleotide per generation
 - ❖ 47 billion new mutations in 7.2 billion humans!
 - ❖ mtDNA $\sim 10^{-8}$ per nucleotide per generation
- ❖ microsatellite rates
 - ❖ 10^{-2} to 10^{-5} per allele per generation

Hypothetical Distribution of Effects

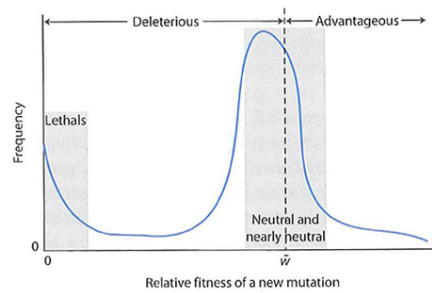


Figure 5.1 A hypothetical distribution of the effects of mutations on phenotypes that ultimately impact the Darwinian fitness of genotypes. Mutations that have a mean fitness less than the mean fitness of the population (\bar{w}) are decreased in frequency by natural selection. The shaded area around \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.

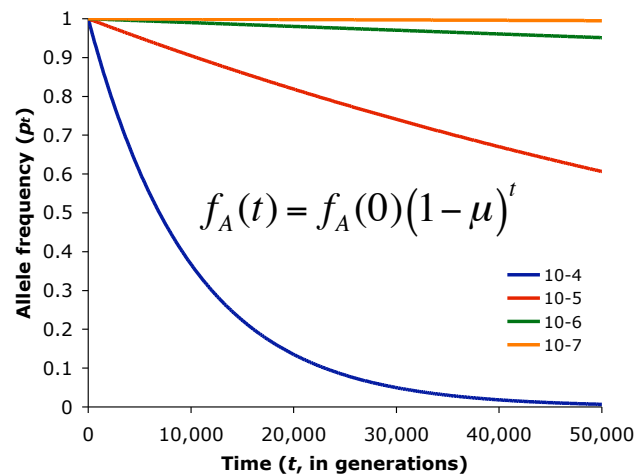
Mutation in an Infinite Population

- ❖ 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!

$$f_A(1) = f_A(0)(1 - \mu)$$

$$f_A(t) = f_A(0)(1 - \mu)^t$$

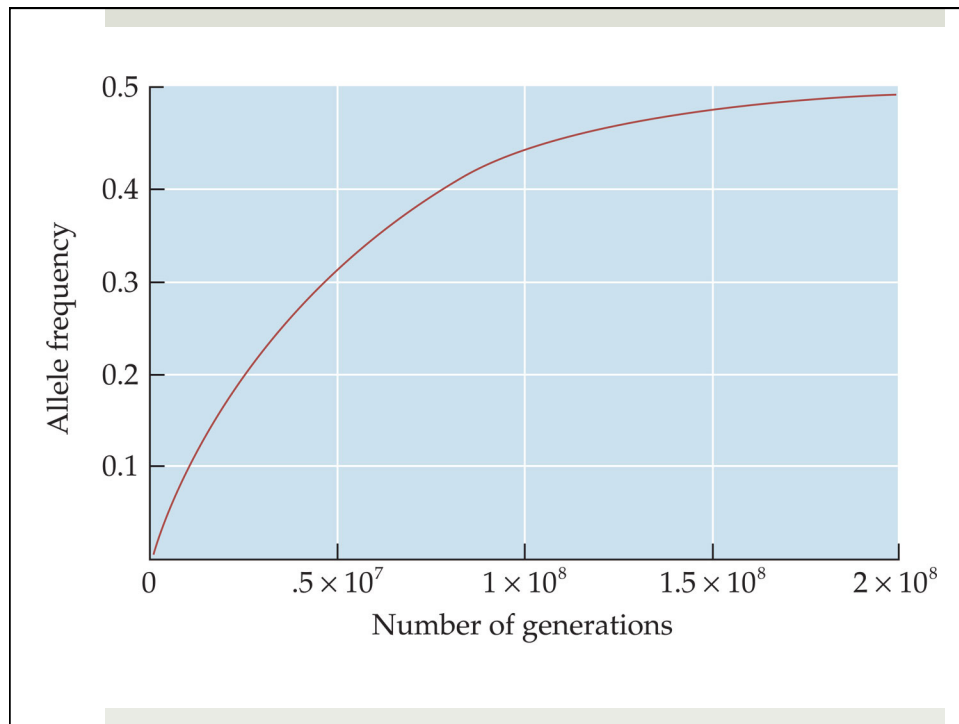
Mutation in an Infinite Population



Mutation in an Infinite Population

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

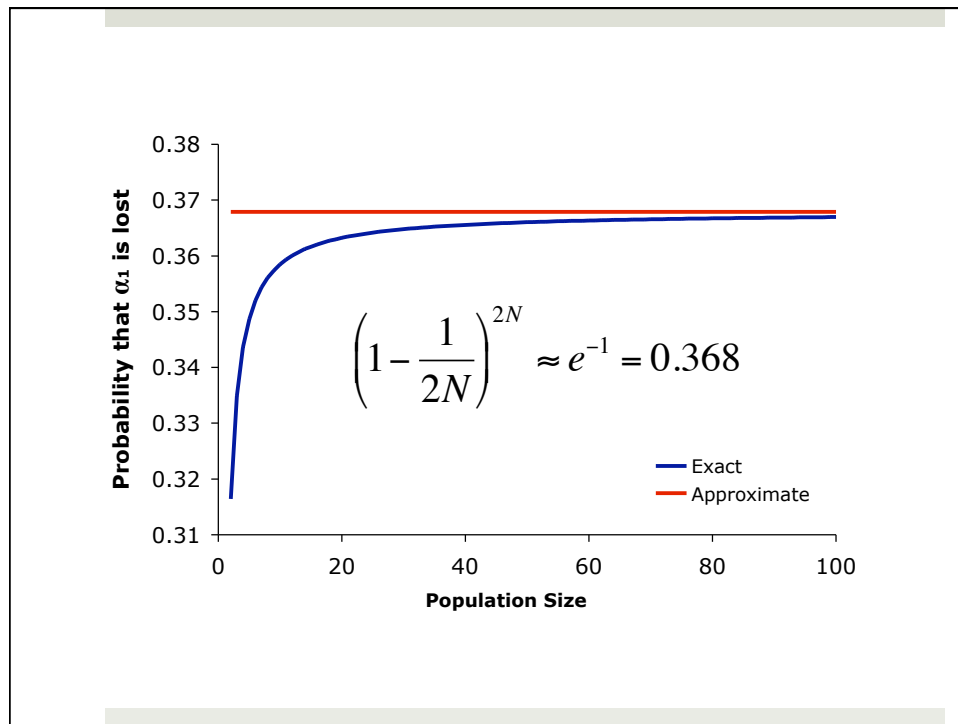
$$f_A = \frac{\mu_{a \rightarrow A}}{\mu_{a \rightarrow A} + \mu_{A \rightarrow a}}$$



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 allele_i will be lost in a single generation

$$\left(1 - \frac{1}{2N}\right)^{2N} \approx e^{-1} = 0.368$$
- ❖ ~37% of individual alleles lost each generation, largely independent 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 $(1-1/2N)$
- ❖ except for very large populations, drift can change allele frequencies much faster than recurrent mutation

Mutation vs. Fixation/Substitution

Average time to fixation/substitution

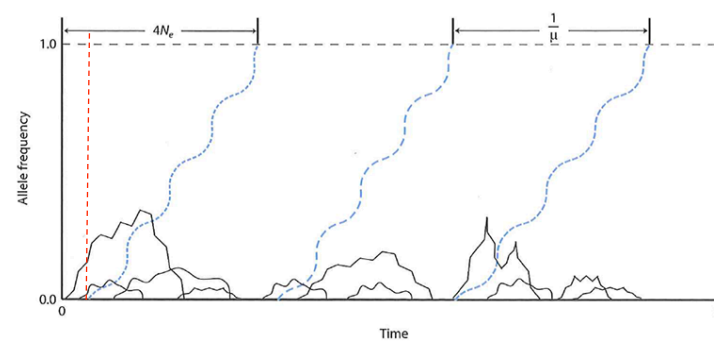


Figure 8.2 The fate of selectively neutral mutations in a population. New mutations enter the population at rate μ and an initial frequency of $\frac{1}{2N}$. Allele frequency is a random walk determined by genetic drift. The time that a new mutation segregates in the population, or the dwell time of a mutation, depends on the effective population size. However, the chance that a new mutation goes to fixation (equal to its initial frequency) is also directly related to the effective population size. These two effects of the effective population size cancel each other out for neutral alleles. The neutral theory then predicts that the rate of fixation is μ and therefore the expected time between fixations is $1/\mu$ generations. For that subset of mutations that eventually fix, the expected time from introduction to fixation is $4N_e$ generations. After Figure 3.1 in Kimura (1983a).

Neutral Expectations...

- ❖ the rate of neutral evolution is independent of population size
- ❖ substitution rate (k) equals mutation rate

$$k = 2N\mu \times \frac{1}{2N} = \mu$$

Probability of Fixation & Rate of Evolution

- ❖ new mutations have a frequency of $1/(2N)$ and therefore have a probability of fixation of $1/(2N)$
- ❖ new mutations become fixed at a rate equal to μ (see previous slide)
 - ❖ mutation rate equals "substitution" rate
 - ❖ neutral rate is independent of population size!
- ❖ average time interval between fixation of new mutations is $1/\mu$

