Coalescent Modeling for Distributions of Alleles

Biostatistics 666

Previously:
Introduction to the Coalescent

- Coalescent approach
  - Proceed backwards through time.
  - Model the genealogy of sample of sequences.

- Infinite sites model
  - All mutations distinguishable.
  - No reverse mutation.

Some key ideas …

- Probability of coalescence events
- Length of genealogy and its branches
- Expected number of mutations
- Parameter θ which combines population size and mutation rate

Building Blocks…

- Probability of sampling distinct ancestors for *n* sequences

$$P(n) = \prod_{i=1}^{n-1}\left(1 - \frac{i}{N}\right) \approx 1 - \frac{\binom{n}{2}}{N}$$

- Coalescence time t is approximately exponentially distributed

Some Key Results…

- Coalescence Time (population size units)

$$E(T_j) = 1/\binom{j}{2}$$

- Total Tree Length (population size units)

$$E(T_{tot}) = \sum_{i=1}^{n-1} \frac{2}{i}$$

Some More Key Results …

- Expected Number of Polymorphisms

For a diploid sample

$$E(S) = 4N\mu\sum_{i=1}^{n-1} 1/i = \theta\sum_{i=1}^{n-1} 1/i$$

For an haploid sample

$$E(S) = 2N\mu\sum_{i=1}^{n-1} 1/i = \theta\sum_{i=1}^{n-1} 1/i$$

Estimating θ

- Number of variants S can be used to estimate θ
  - Expected S is simply θ E(T_{tot})
  - To estimate θ, divide by S expected length of genealogy

$$\hat{\theta} = \frac{S}{\sum_{i=1}^{n-1} 1/i}$$

- Could then be used to:
  - Estimate N, if mutation rate μ is known
  - Estimate μ, if population size N is known

Alternative Estimator for θ …

- Count pairwise differences between sequences
- Compute average number of differences

$$\tilde{\theta} = \binom{n}{2}^{-1} \sum_{i=1}^{n} \sum_{j=i+1}^{n} S_{ij}$$

Tajima’s D

- $\tilde{\theta}$ and $\hat{\theta}$ are not equally sensitive to historical changes in population size

- Imagine the following situation:
  - Historically, population of effective size N_e=10,000
  - Population size grew to N_e=1,000,000 in the last 100 generations …
  - What happens to size of coalescent tree for *n*=2? And to $\tilde{\theta}$?
  - What happens to size of coalescent tree for large *n*? And to $\hat{\theta}$?

- Comparing the two estimators is the basis of the Tajima’s D statistic
  - <0 when $\tilde{\theta}$ is less than $\hat{\theta}$
  - 0 when $\tilde{\theta}$ and $\hat{\theta}$ are equal
  - >0 when $\tilde{\theta}$ is greater than $\hat{\theta}$

Tajima’s D

$S = \text{no. of variant sites}$ $\quad \pi = \frac{\sum_{i=1}^{n}\sum_{j=i+1}^{n} S_{ij}}{\binom{n}{2}}$

$$a_1 = \sum_{i=1}^{n-1}\frac{1}{i} \qquad a_2 = \sum_{i=1}^{n-1}\frac{1}{i^2}$$

$$b_1 = \frac{n+1}{3(n-1)} \qquad b_2 = \frac{2(n^2+n+3)}{9n\,(n-1)}$$

$$c_1 = b_1 - \frac{1}{a_1} \qquad c_2 = b_2 - \frac{n+2}{a_1 n} + \frac{a_2}{a_1^2}$$

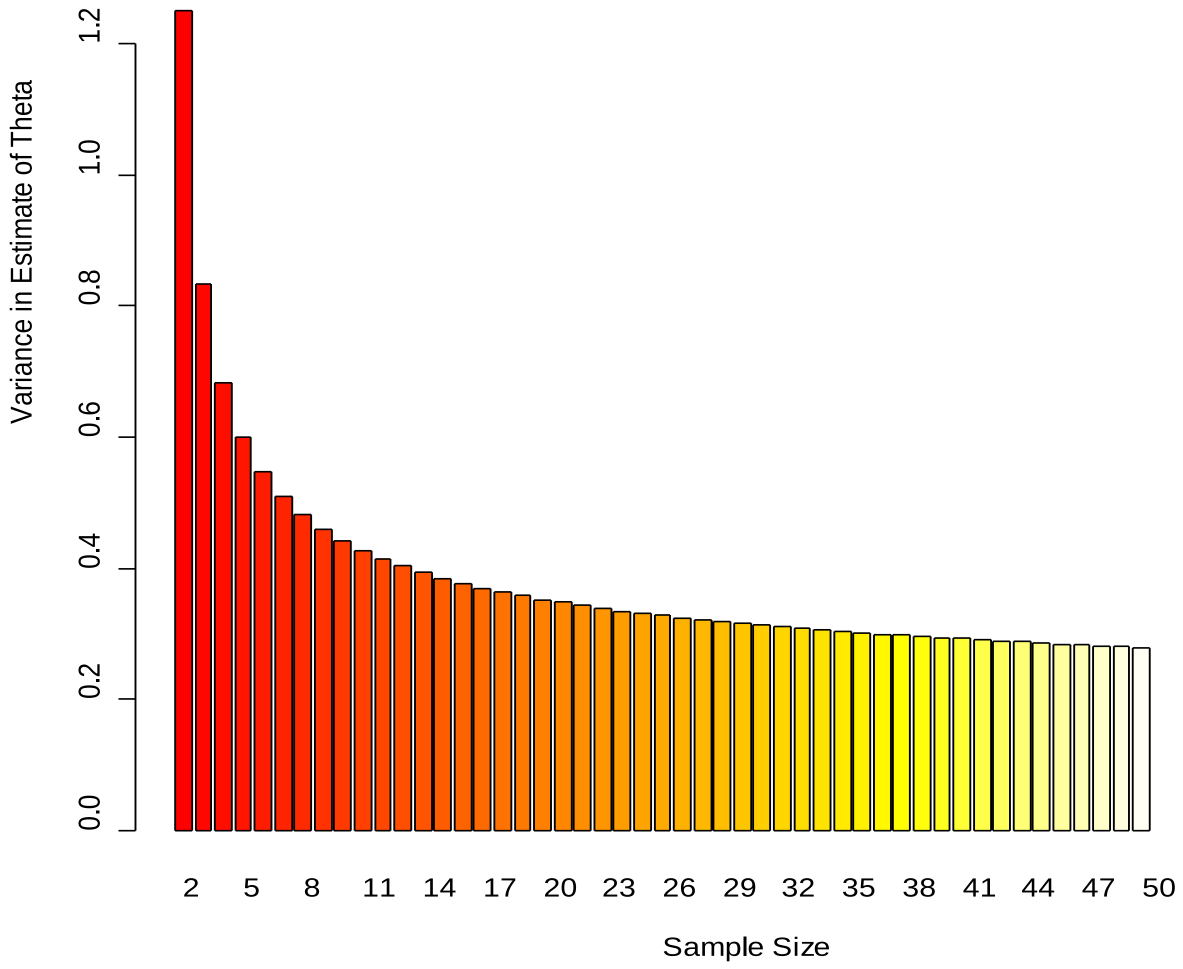
$$e_1 = \frac{c_1}{a_1} \qquad e_2 = \frac{c_2}{a_1^2 + a_2}$$

$$\text{Tajima}'\text{s } D = \frac{\pi - S/a_1}{\sqrt{\left(e_1 S + e_2 S(S-1)\right)}}$$

Standardized difference between two estimators of θ

Formula is complicated due to variance estimator.

Var($\hat{\theta}$) as a function of *n*

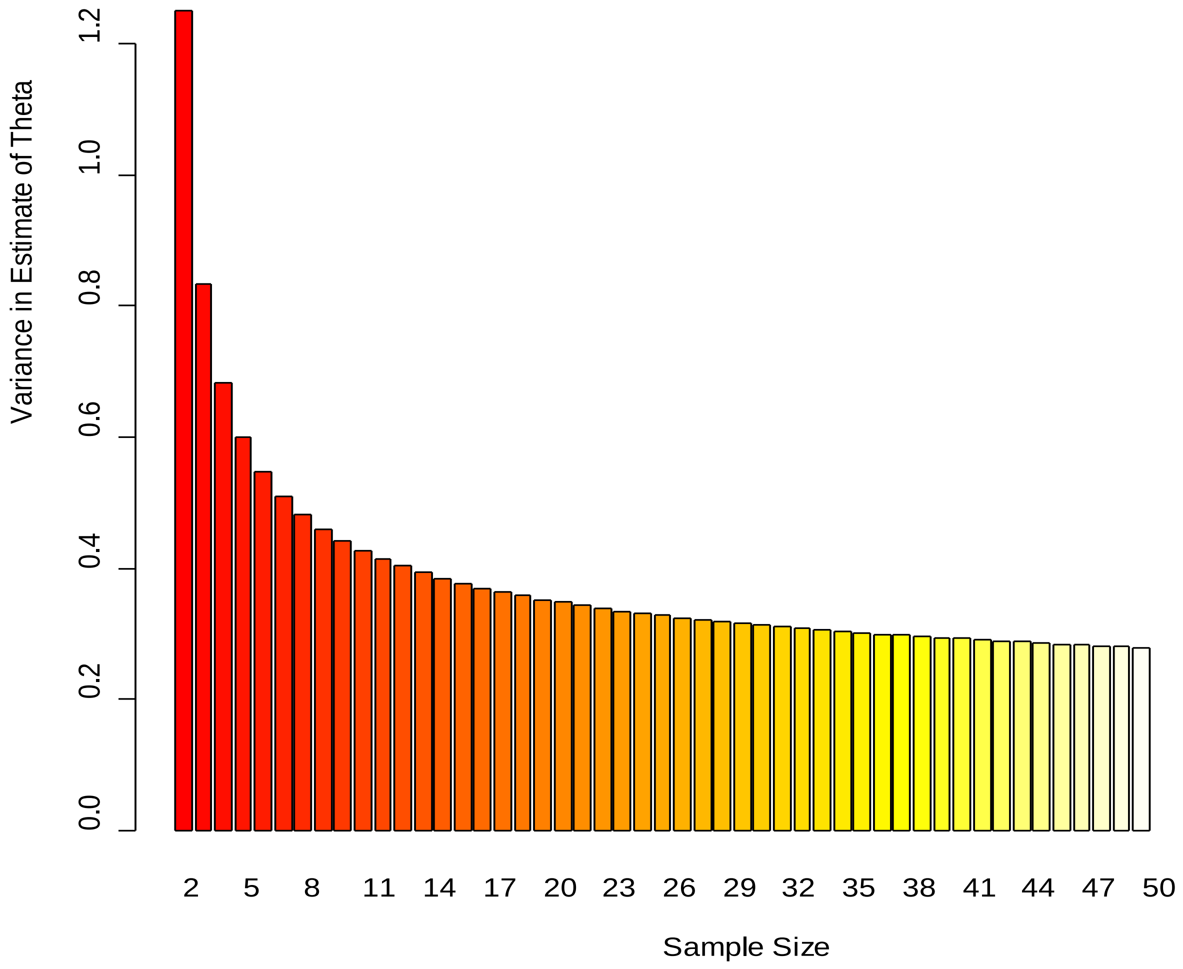


Parameters

N = 10,000 individuals
$\mu = 10^{-4}$

$\theta = 4$

Var($\hat{\theta}$) as a function of *n*



Parameters

N = 10,000 individuals
$\mu = 10^{-4}$

$\theta = 4$

If larger samples don’t help, how else could we improve inferences about θ?

Today …

- More applications of the coalescent

- Predicting allele frequency distributions
  - Using simulations

- Modeling the distribution of S
  - Using analytical calculations

A Coalescent Simulation …

- Let’s consider tracing the ancestry of 4 sequences

When n = 4

Probability of Coalescent Event

$$P(4) \approx \binom{4}{2} \Big/ 2N$$

Time to Next Coalescent Event

$$T(4) \approx 2N \Big/ \binom{4}{2}$$

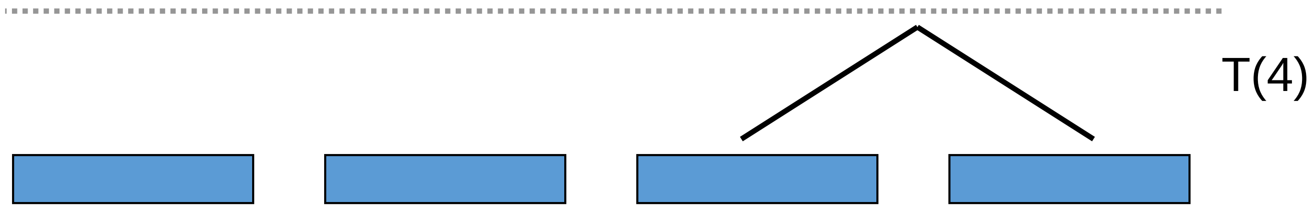
Sample time from exponential distribution

Pick two sequences at random to coalesce

Next n = 3 …

Let’s assume that sequences 3 and 4 are selected …

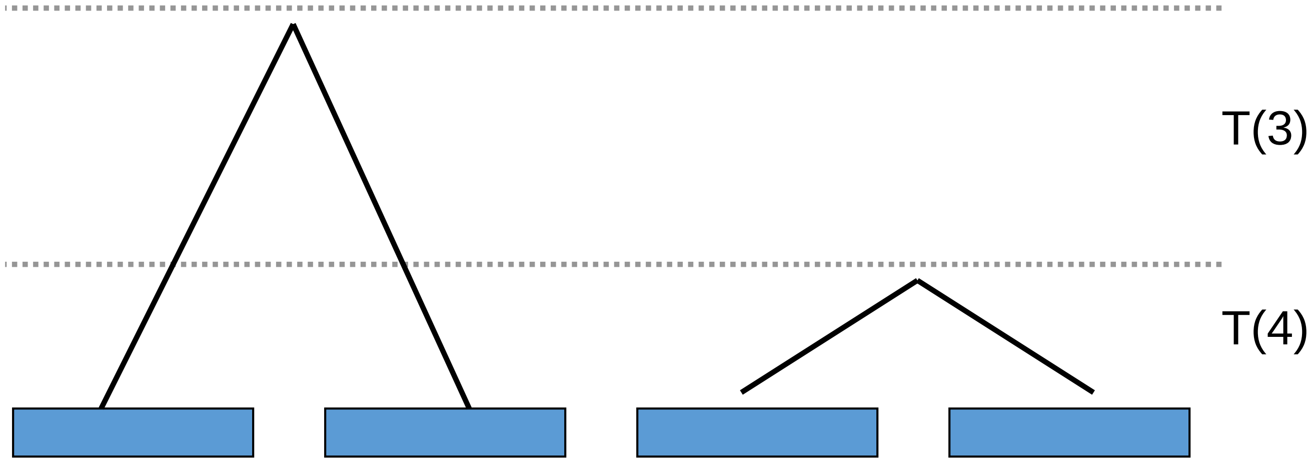
Then, we repeat the process for a sample of 3 sequences



Next n = 2 …

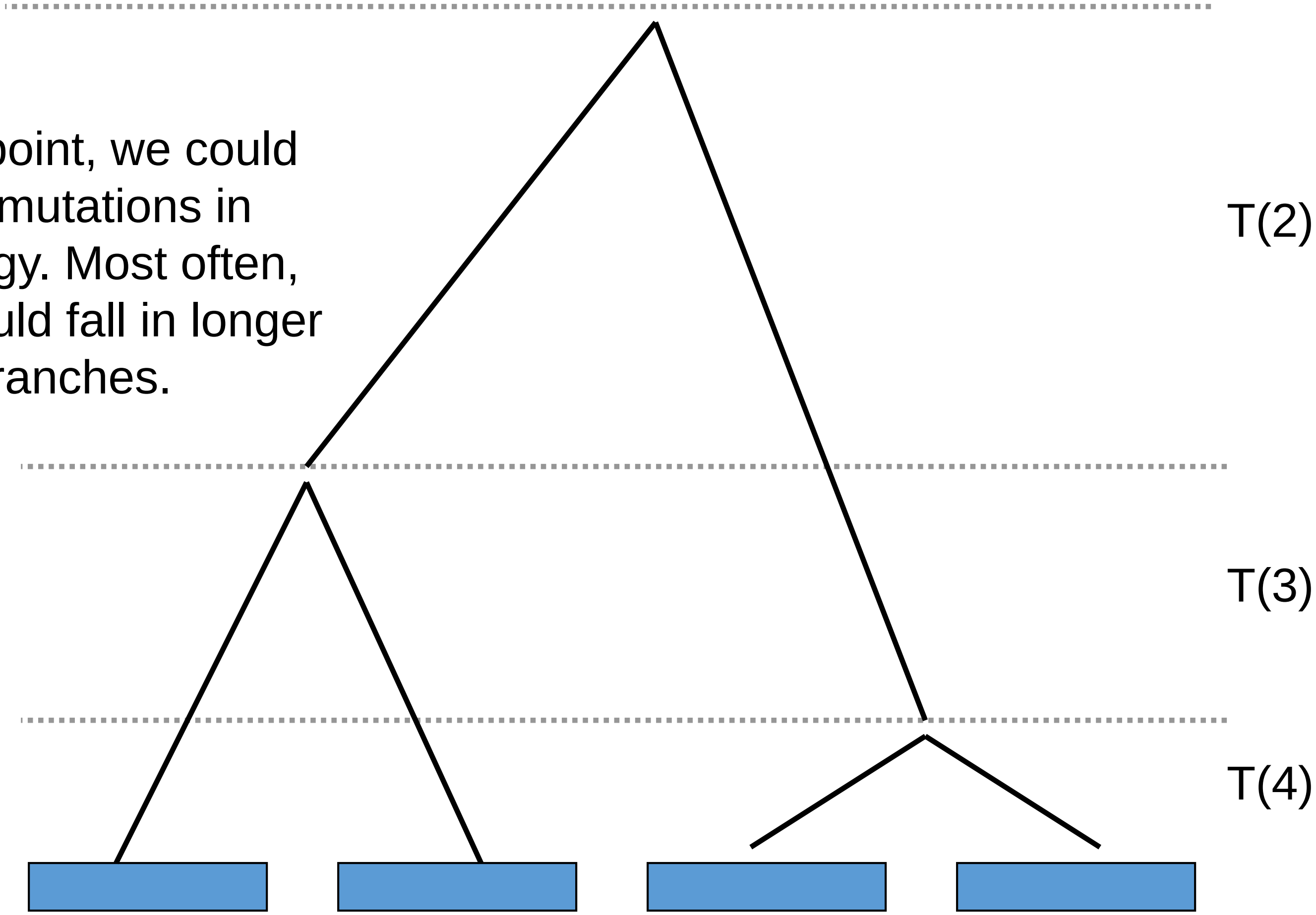
Let’s assume that sequences 1 and 2 are selected to coalesce

Then, we repeat the process for a sample of 2 sequences

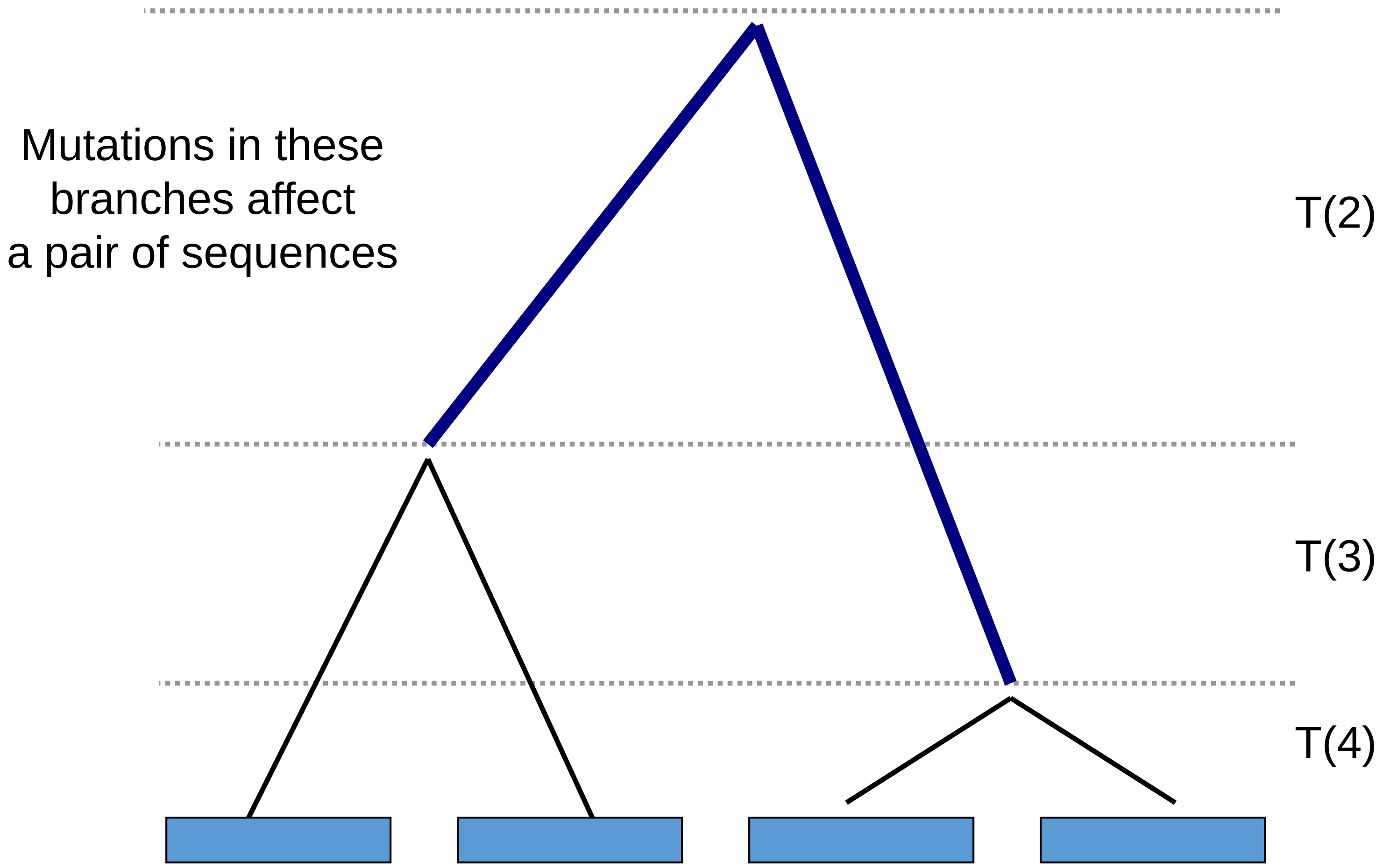


The Simulated Coalescent

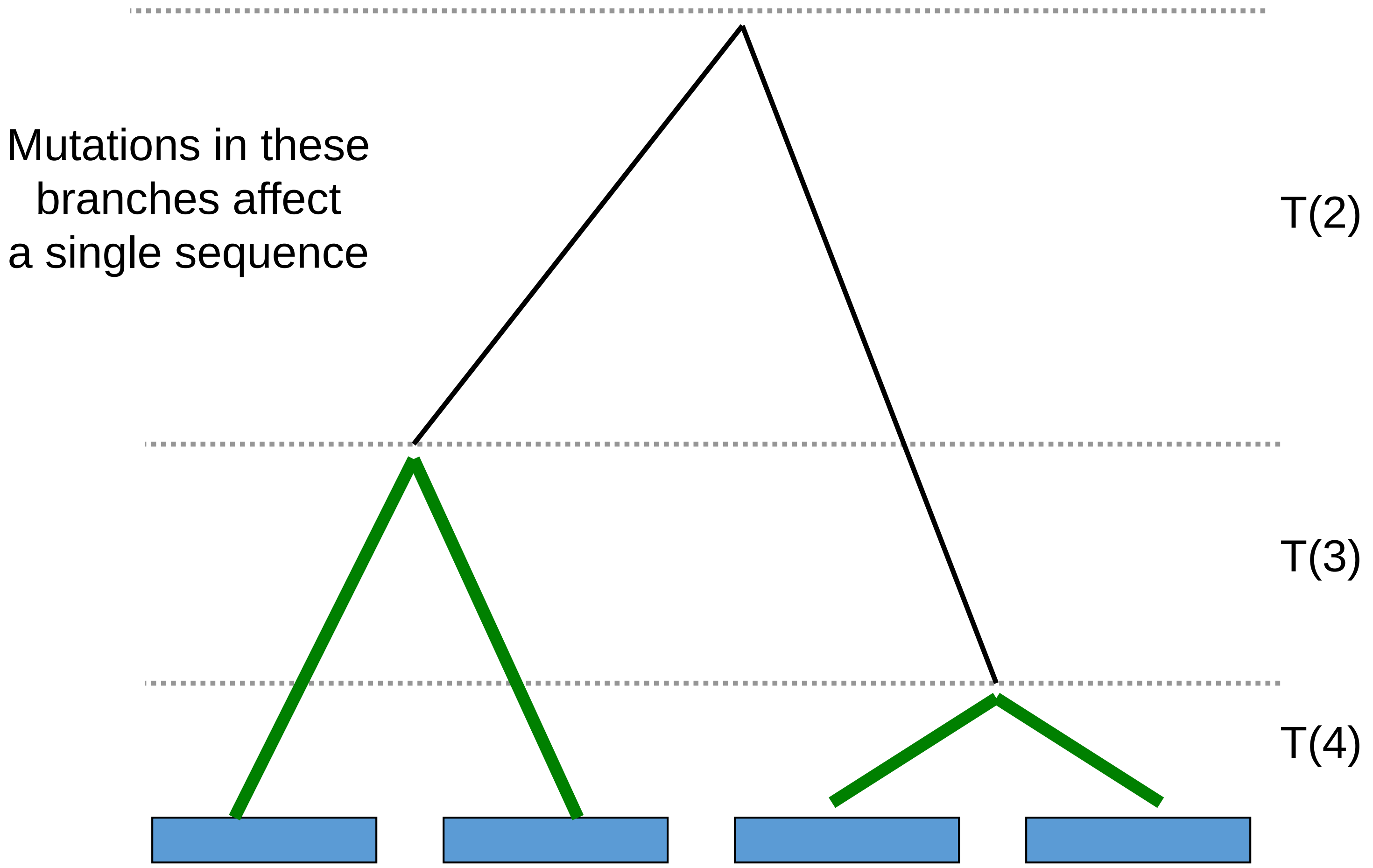
At this point, we could place mutations in genealogy. Most often, these would fall in longer branches.



A Coalescent Simulation …

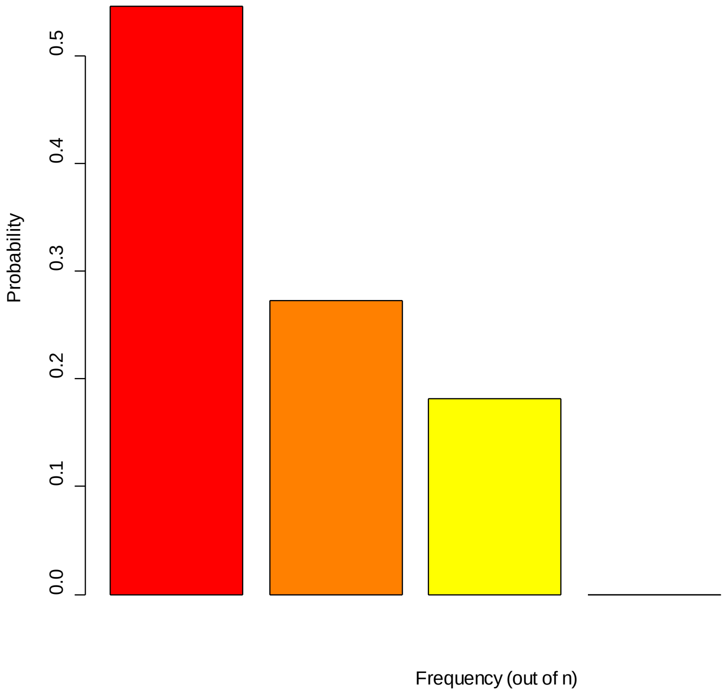


A Coalescent Simulation …

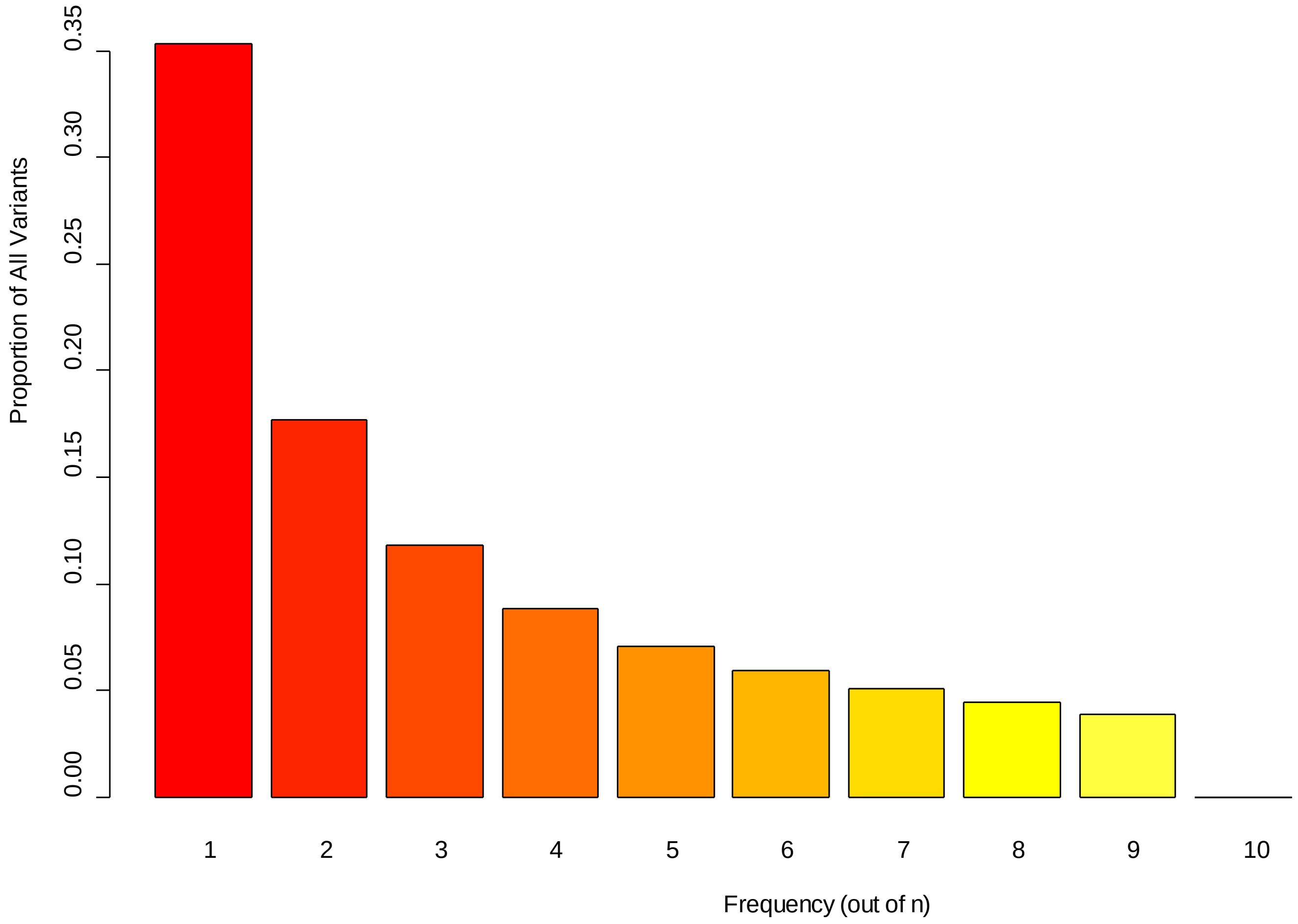


Frequency Spectrum

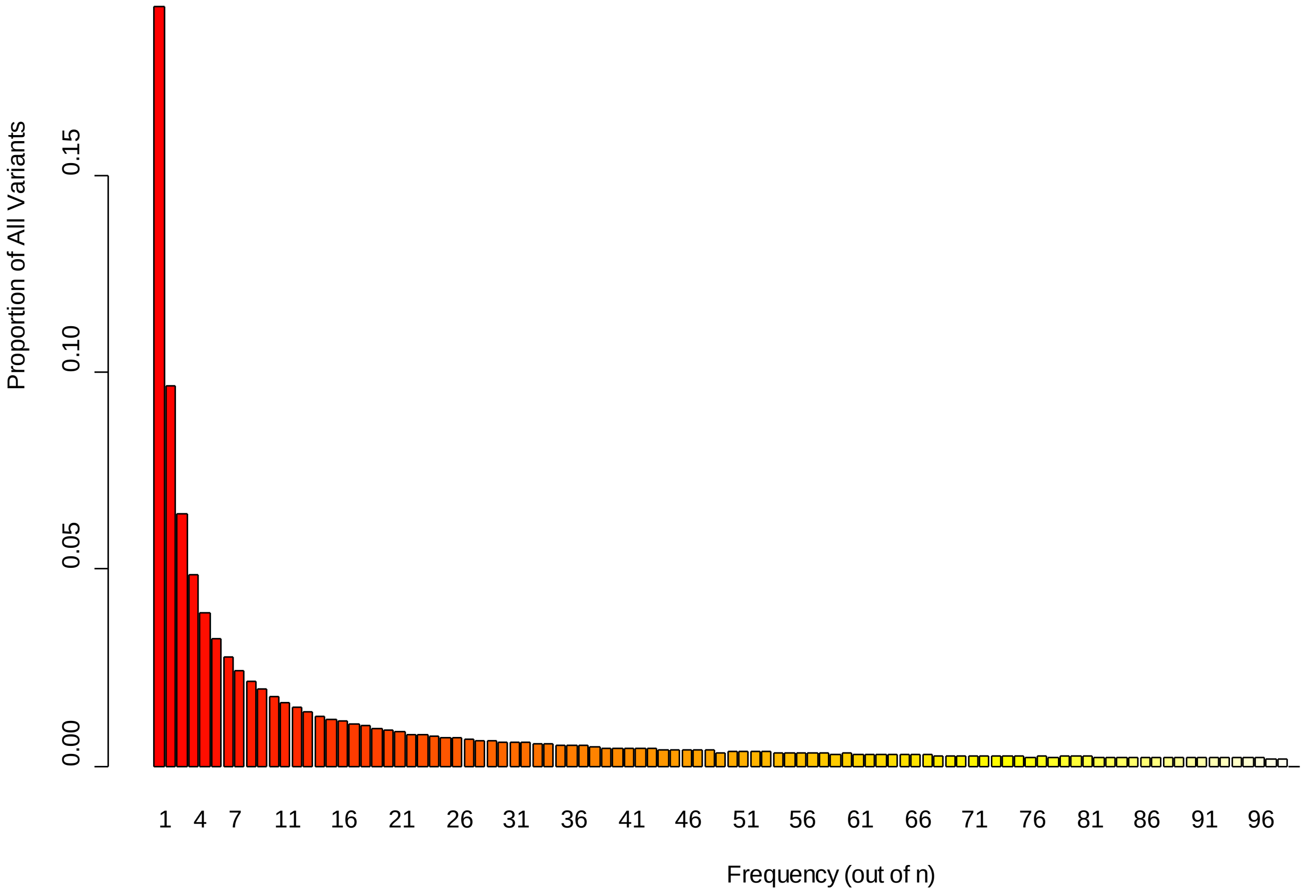
- Repeating the simulation multiple times, would give us a predicted mutation spectrum.



Frequency Spectrum (n = 10)



Frequency Spectrum (n = 100)



Frequency Spectrum

- Constant size population
- Exponentially growing population

- Most variants are rare
  - For n = 100, ~44% of variants occur < 5/100.
  - For n = 10, ~35% of variants observed once.

- In contemporary human populations, the proportion of rare variants is even larger (~½ of variants are singletons when 1,000 < *n* < 100,000)

Mutation Spectrum

- Depends on genealogy
  - Population Size
  - Population Growth
  - Population Subdivision

- Does not depend on
  - Mutation rate!

- Could there be exceptions?

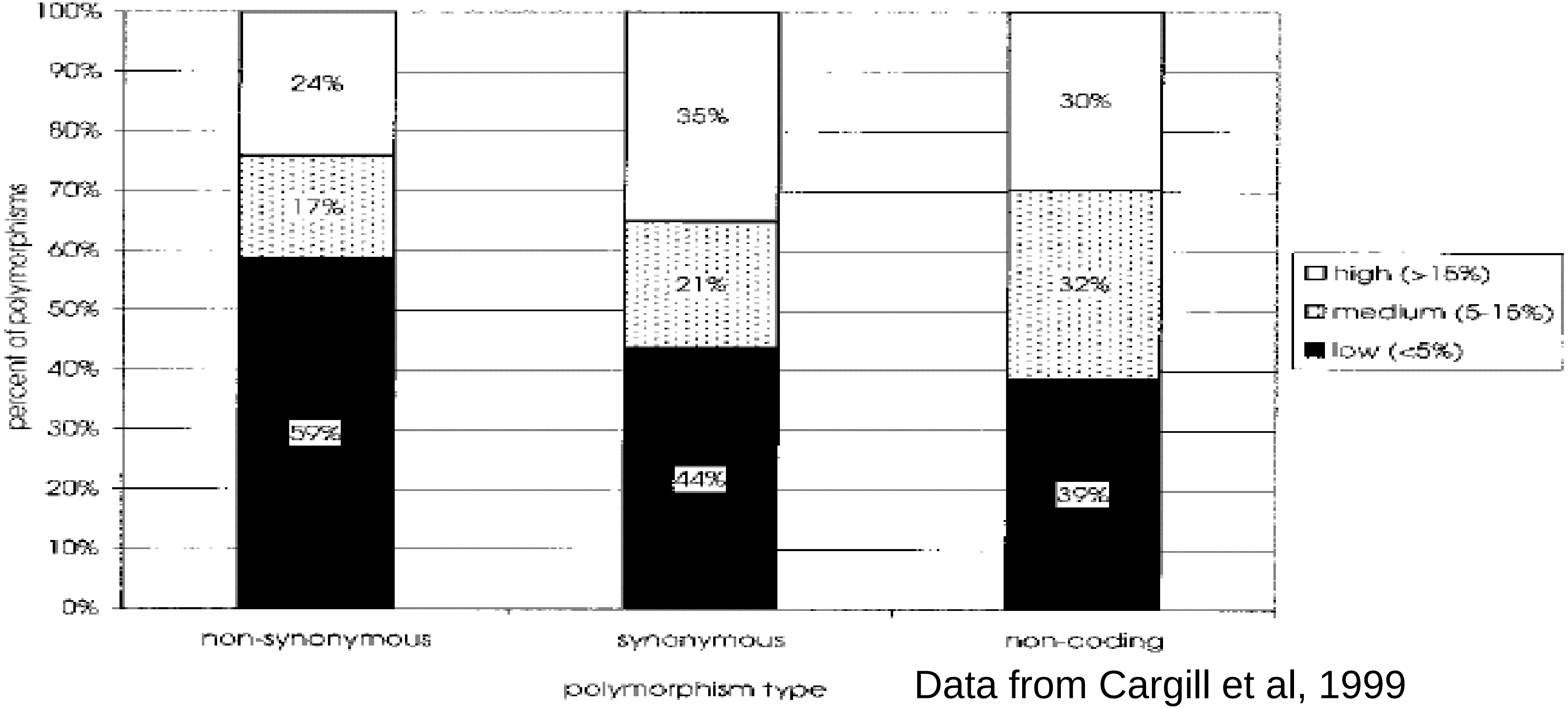
Deviations from Neutral Spectrum

- When would you expect deviations from the spectra we described?

- What would you expect for …
  - A rapidly growing population?
  - A population whose size is decreasing?

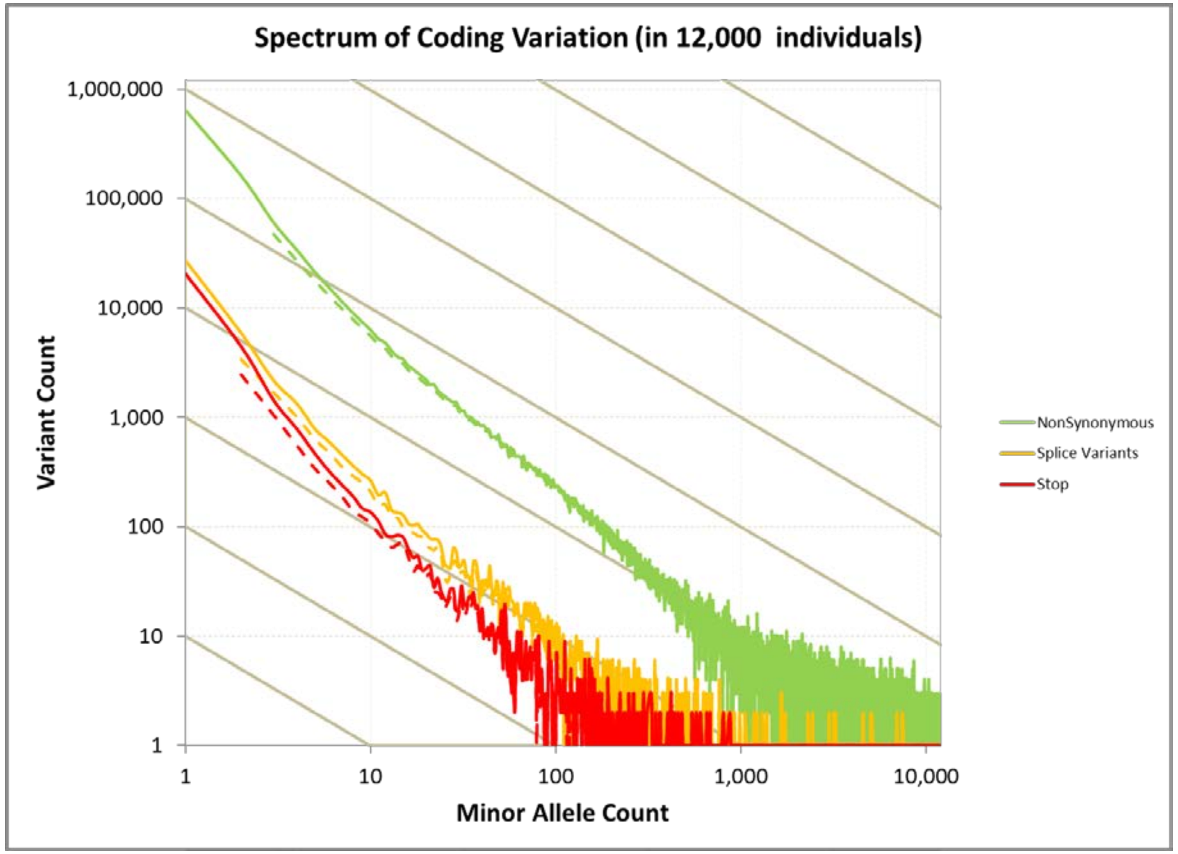
- Why?

Effect of Polymorphism Type



Data from Cargill et al, 1999

Frequency Spectrum of Protein Altering Variants



Exome Chip Consortium (2011)

3.7M Coding Variants

Category	Count	Singletons
All SNPs	438M	46.1%
-- Missense SNPs	3.4M	47.7%
-- Stopgain SNPs	103K	54.4%
-- Essential Splice SNPs	111K	54.2%
All Indels	33M	47.0%
-- Inframe Coding Indels	65K	48.6%
-- Frameshift Indels	97K	59.9%
-- Splice Site	12K	52.7%

Number of Mutations

- Can be derived from coalescent tree
  - What are the key features?
- Analytical results possible
  - Trace back in time until MRCA, tracking mutation events

Sample of Two Sequences

- Track coalescences and mutations
    - Probability of a coalescent event?
        - Depends on population size …
    - Probability of a mutation?
        - Depends on mutation rate …

- Proceed backwards until either occurs…
    - Conditional probability for each outcome?

Two Identical Sequences

$$P_2(S \text{ is } 0) \approx \frac{P_{CA}}{P_{CA} + P_{mut}}$$

$$= \frac{1/2N}{1/2N + 2\mu}$$

$$= \frac{1}{1+\theta}$$

Full distribution of S…

- Probability that first *j* events are mutations…

$$P_2(j) = \left(\frac{\theta}{1+\theta}\right)^j \left(\frac{1}{1+\theta}\right)$$

Example…

- 2 sequences
- Population size N = 25,000
- Mutation rate $\mu = 10^{-5}$

- Probability of 0, 1, 2, 3… mutations

And for multiple sequences…

- Describe number of mutations until the next coalescence event

- Proceed back in time, until:
  - One of *n* sequences mutates…
  - A coalescent event occurs…
    - Then track mutations in (n-1) sequences

Formulae …

$$Q_n(j) = \left(\frac{n\mu}{n\mu + \frac{\binom{n}{2}}{2N}} \right)^j \frac{\frac{\binom{n}{2}}{2N}}{n\mu + \frac{\binom{n}{2}}{2N}} = \left(\frac{\theta}{\theta + n - 1} \right)^j \frac{n-1}{\theta + n - 1}$$

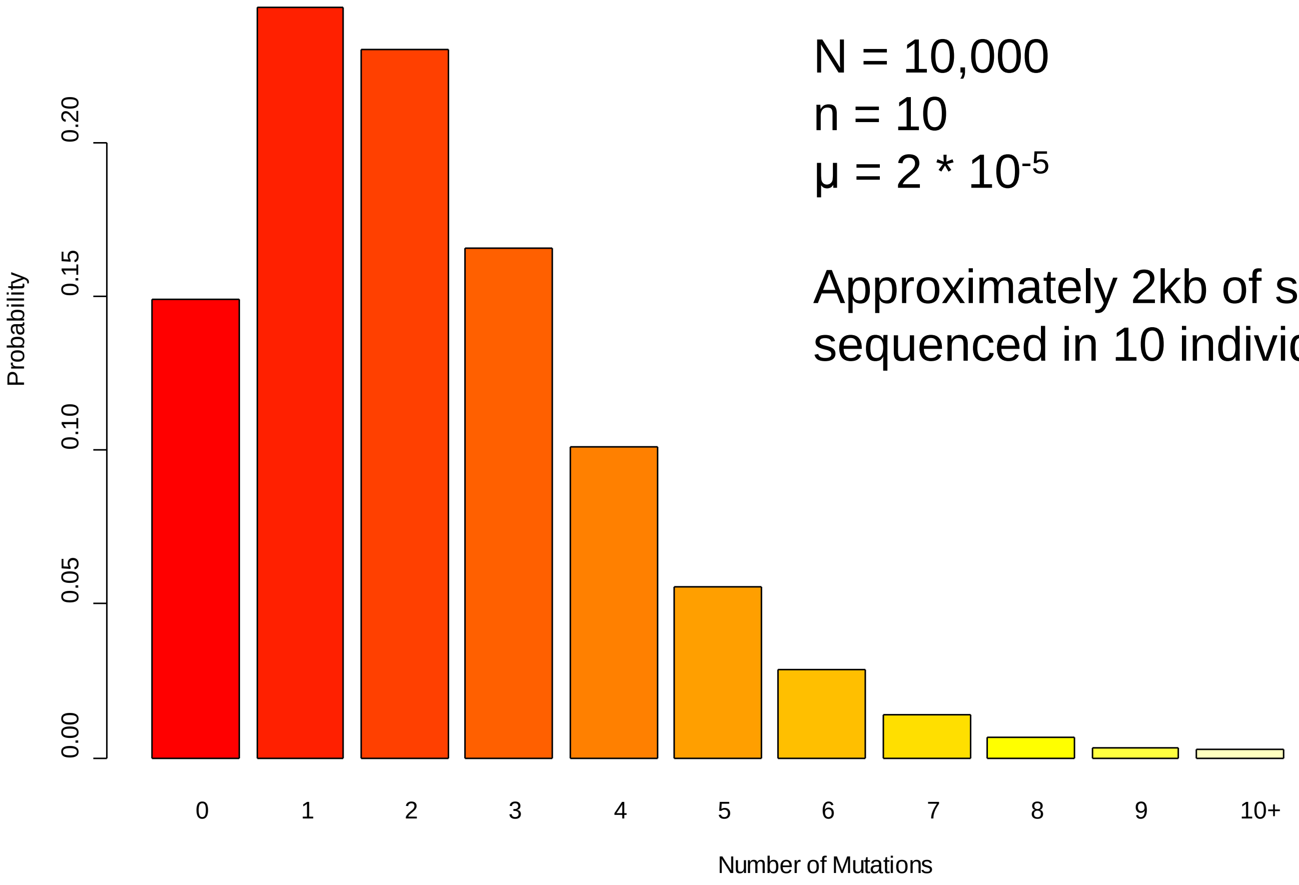
$$P_n(j) = \sum_{i=0}^{j} P_{n-1}(j-i) Q_n(i)$$

Example…

- 3 sequences
- Population size N = 25,000
- Mutation rate $\mu = 10^{-5}$

- Probability of 0, 1, 2, 3… mutations

Number of Mutations



N = 10,000
n = 10
$\mu = 2 * 10^{-5}$

Approximately 2kb of sequence, sequenced in 10 individuals

So far …

- One homogeneous population
    - Coalescence times
    - Number of mutations
        - Expectation
        - Distribution
    - Spectrum of mutations

- Several assumptions, including …
    - Single population
    - No recombination
    - Constant population size

Next: Models w/ Recombination

- No recombination
  - Single genealogy

- Free recombination
  - Two independent genealogies
  - Same population history

- Intermediate case
  - Correlated genealogies

Recommended Reading

Richard R. Hudson (1990)

Gene genealogies and the coalescent process

Oxford Surveys in Evolutionary Biology, Vol. 7.
D. Futuyma and J. Antonovics (Eds).
Oxford University Press, New York.