Introduction to Coalescent Models

Biostatistics 666

Previously …

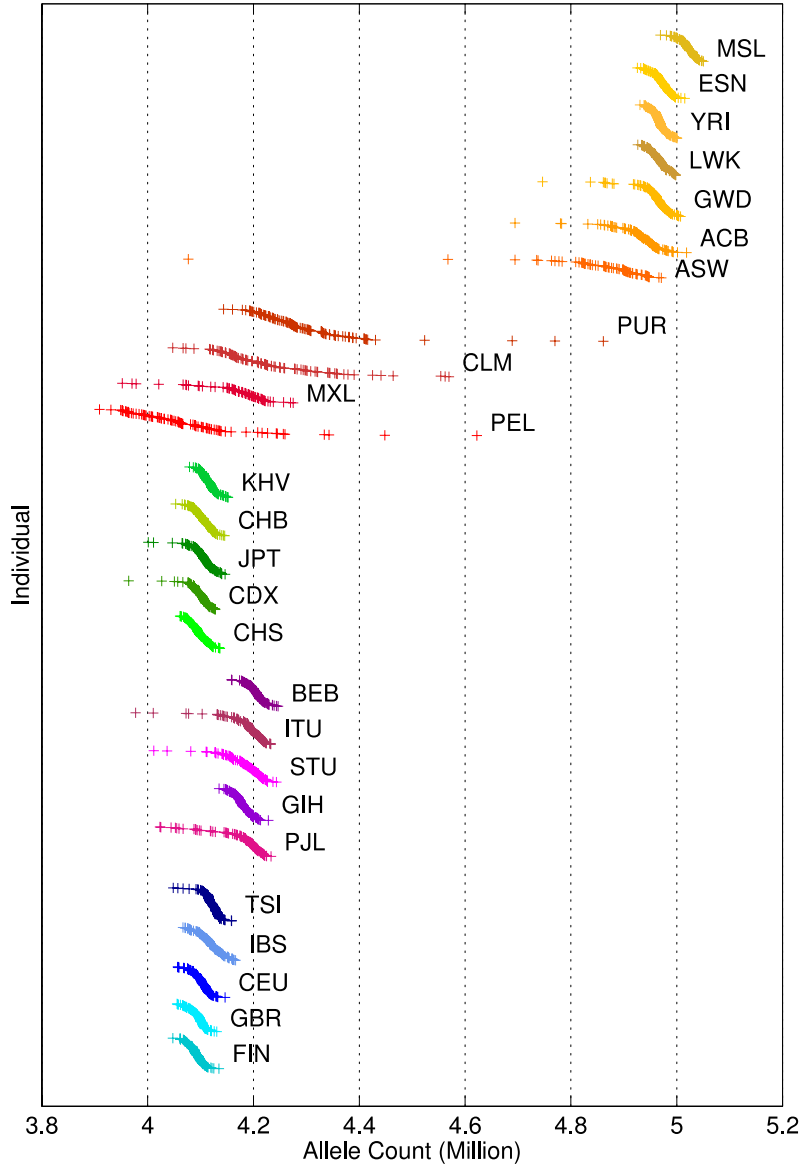
- Allele frequencies
- Hardy Weinberg Equilibrium
- Linkage Equilibrium
  - Expected state for distant markers
- Linkage Disequilibrium
  - Association between neighboring alleles
  - Expected to decrease with distance
- Measures of linkage disequilibrium
  - D, D’ and Δ^2 or r^2

Making predictions…

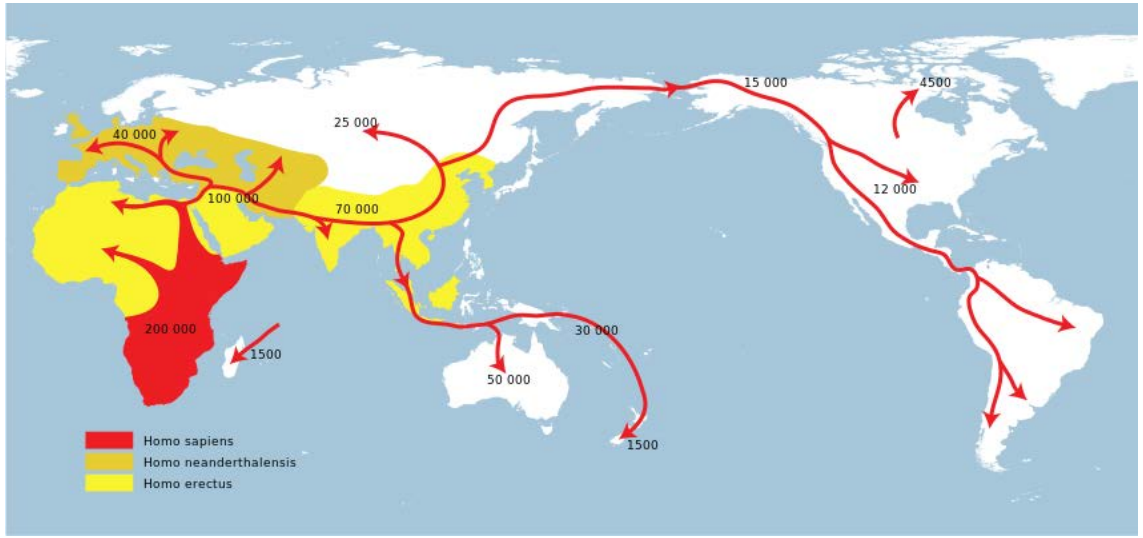
- What allele frequencies do we expect?
- How much variation in a gene?
- How are neighboring variants related?
- Are these predictions “universal”?
  - Do they depend on natural selection or the history of a population?
- How can we use genetic variation to build models of the past?

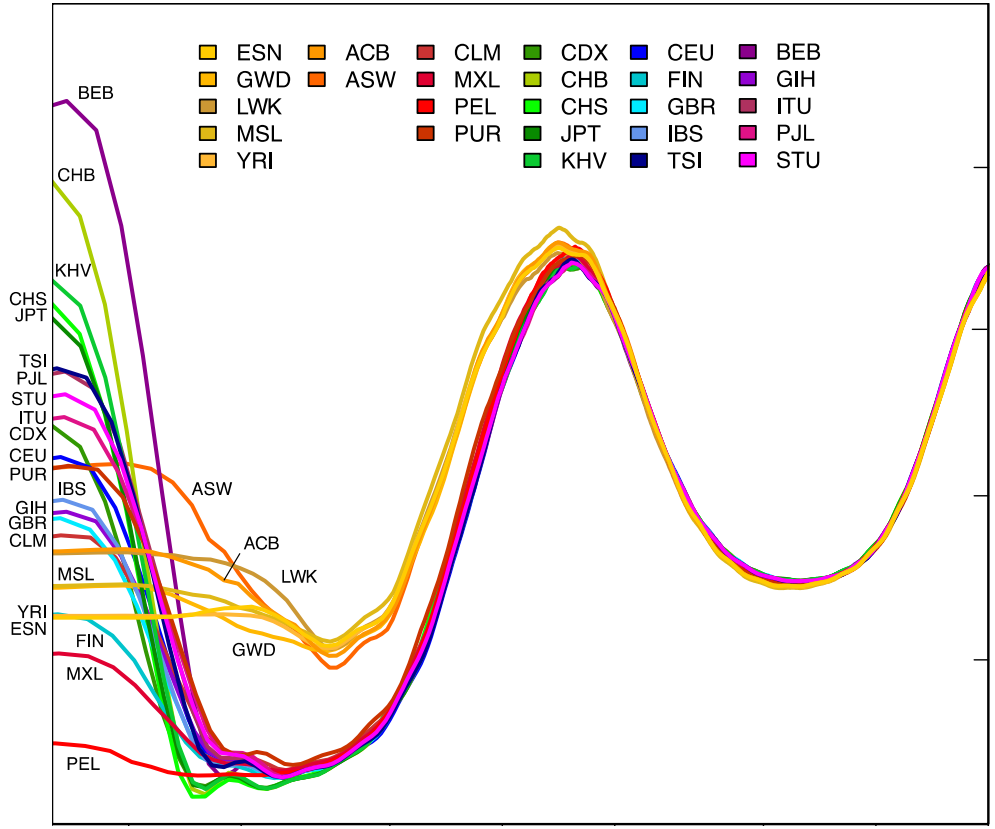
1000 Genomes Data: Variants per Genome

Type	Variant sites / genome
SNPs	~3,800,000
Indels	~570,000
Mobile Element Insertions	~1000
Large Deletions	~1000
CNVs	~150
Inversions	~11



1000 Genomes Data: Demographic Models

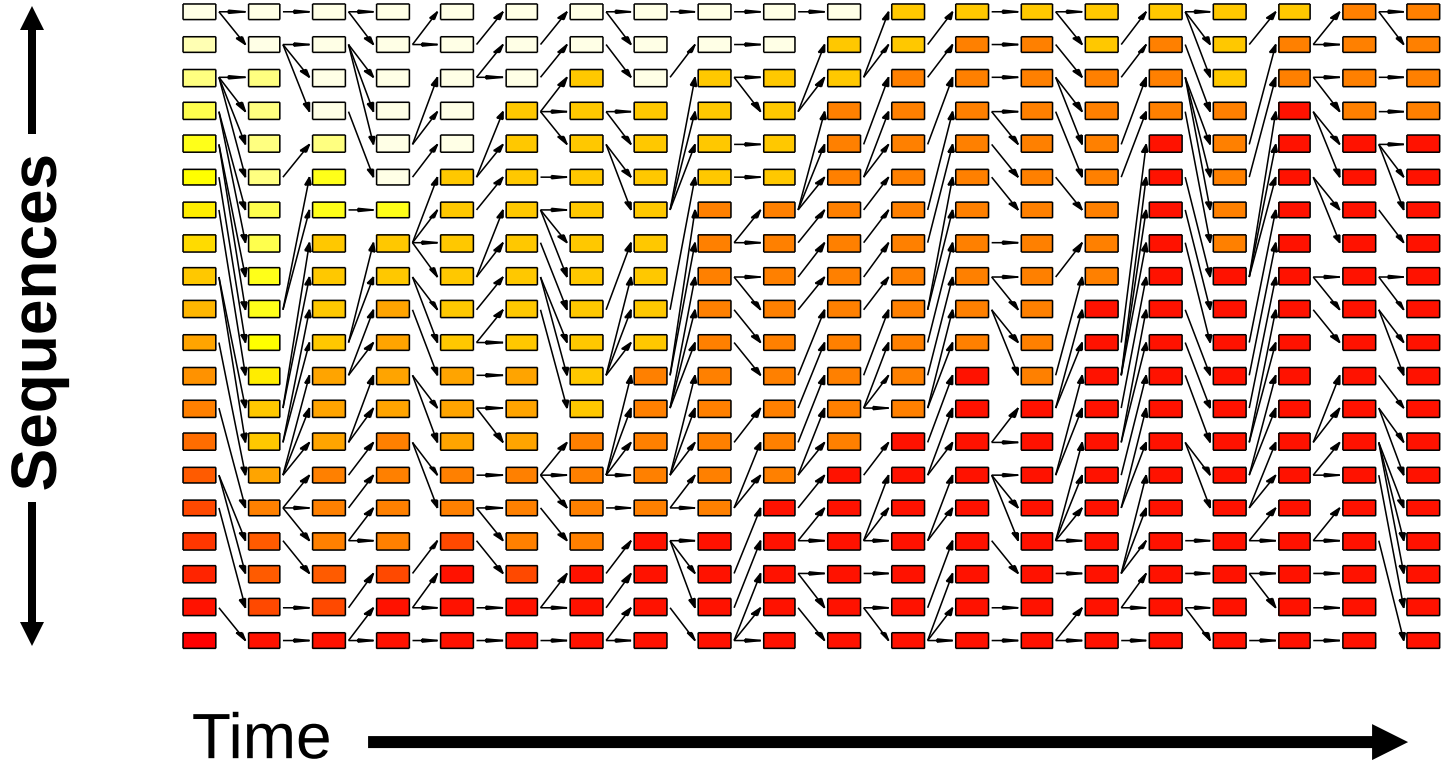




Simple Approach: Simulation

1. N starting sequences
2. Sample N offspring sequences
   - Apply mutations according to μ
3. Increment time
4. If enough time has passed…
   - Generate final sample
   - Stop.
5. Otherwise, return to step 1.

Simulating a Population …



Today

- Introduce coalescent approach
  - Framework for studying genetic variation
  - Provides intuition on patterns of variation
  - Provides analytical solutions

Aim …

- Gene genealogies:
  - Descriptions of relatedness between sequences
  - Analogous to phylogenetic trees for species

- The shape of the genealogy depends on population history, selection, etc.

- Together with mutation rate, genealogy predicts DNA variation

Genealogy

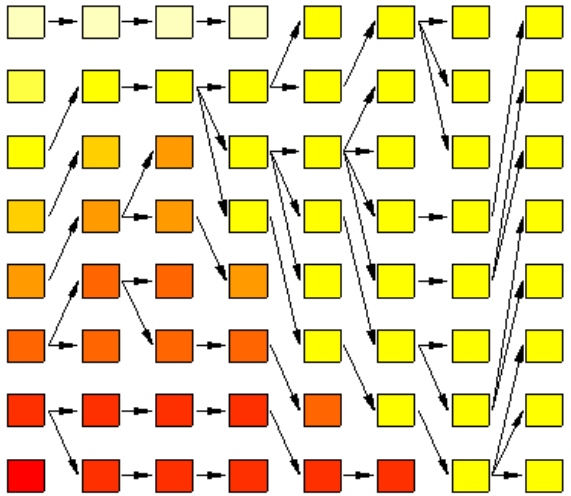
- History of a particular set of sequences
  - Describes their relatedness
  - Specifies divergence times
- Includes only a subset of the population
- Most Recent Common Ancestor (MRCA)

Coalescent approach

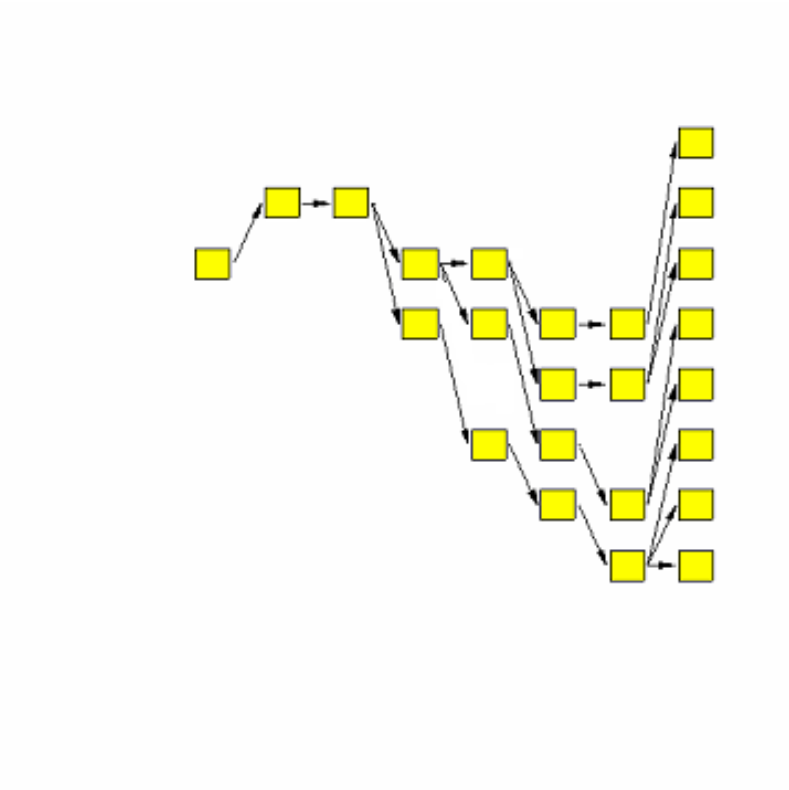
- Generate genealogy for a sample of sequences.
  - Introduces computational and analytical convenience.

- Instead of proceeding forward through time, go backwards!

History of the Population



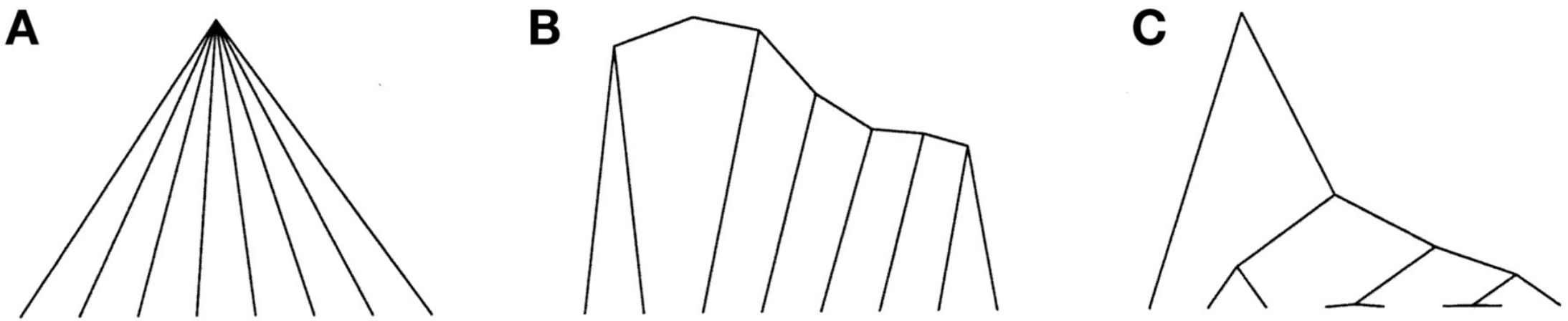
Genealogy of Final Population



Levels of Complexity

- History of the population
  - Includes sequences that are “extinct”
- History of all modern sequences
  - Includes sequences that we haven’t sampled
- History of a subset of modern sequences
  - Minimalist approach!

Examples of Typical Coalescent Trees



Parameters we will focus on…

- Mutation rate (μ)
- Population Size
  - Haploid population (N chromosomes)
  - Diploid population (2N chromosomes)
- Time (t)
- Sample size (n)
- Recombination rate (r)

Other Parameters

- Selection
  - For gene of interest
  - For neighboring gene

- Demographic parameters
  - Migration
  - Population Structure
  - Population Growth

Mutation Model

- The mutation process is complex
  - Rate depends on surrounding sequence
  - Reverse mutations are possible

- Two simple models are popular
  - Infinite alleles
    - Every mutation generates a different allele
  - Infinite sites
    - Every mutation occurs at a different site

Mutation Model

- Focus on infinite sites model
  - Mutation rate in genomic DNA is ~10^{-8} / bp
  - Recurrent mutations should be very rare

- Scaled mutation rate parameter, e.g.:
  - 1000 bp sequence
  - 10^{-8} mutations per base pair per generation
  - $\mu = 10^{-5}$ per sequence per generation

Neutral Variants

- Variants that do not affect fitness
- Accumulate inexorably through time
  - Lost through genetic drift
- Do not affect genealogy

Example:
Modeling Accumulation of Mutations

- Population of identical sequences
- Sample one descendant after t generations
- How many mutations have accumulated?
  - Hint: depends on mutation rate μ and time t
- Tougher questions
  - How many mutations have been fixed?
  - How much variation in the total population?

So far …

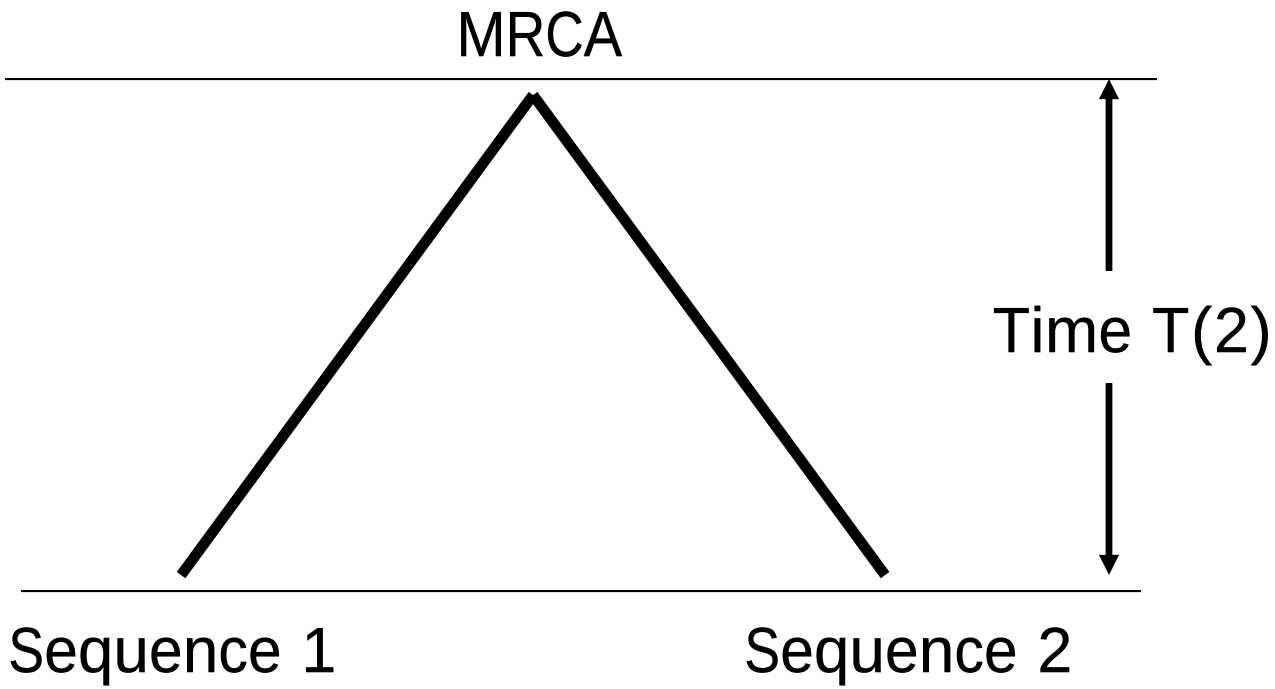
- Divergence of a single sequence
  - Accumulation of mutations
  - Depends on time t
  - Depends on mutation rate μ
  - Does not depend on population size N
  - Does not depend on population growth

- Next: A pair of sequences!

A tougher example …

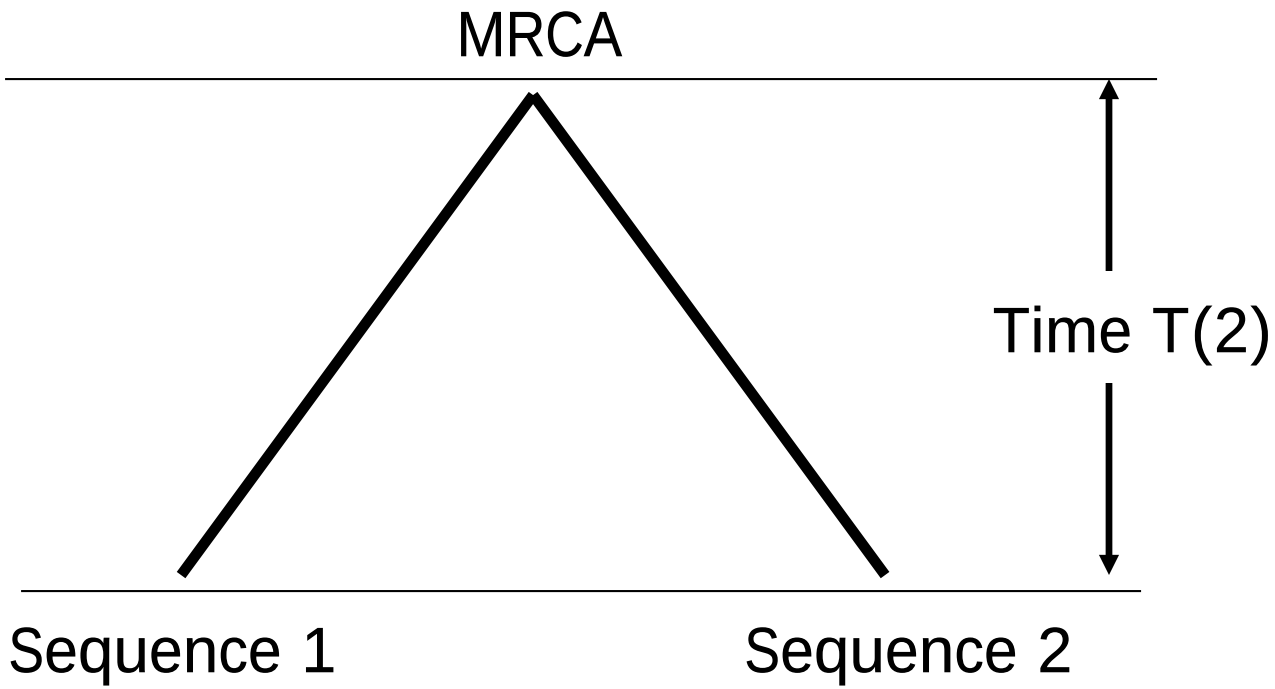
- Sample of two sequences
  - 100 bp each…
- How many differences are expected?
  - Population of size, N = 1000
  - Mutation rate
    - $\mu = 10^{-8}$ / bp / generation
    - $\mu \approx 10^{-6}$ / 100 bp / generation

Genealogy of two sequences



Mutations between MRCA and Sequence 1?

Genealogy of two sequences



Total mutations in genealogy?

Number of mutations S

- Distributed as Poisson, conditional on total tree length
  - $E(S) = \mu E(T_{tot})$
  - $Var(S) = \mu E(T_{tot}) + \mu^2 Var(T_{tot})$
- T_{tot} is the total length of all branches

Estimating Coalescence Time…

- Probability that two sequences have distinct ancestors in previous generation

$$P(2) = \frac{N-1}{N} = 1 - \frac{1}{N}$$

- Probability of distinct ancestors for *t* generations is $P(2)^t$

Probability of MRCA at time t+1

$$P(2)^t(1-P(2)) = \frac{1}{N}\left(\frac{N-1}{N}\right)^t$$

$$= \frac{1}{N}\left(1-\frac{1}{N}\right)^t$$

$$\approx \frac{1}{N}e^{-\frac{1}{N}t}$$

For n > 2

- Coalescence when two sequences have common ancestor
  - For simplicity, consider the possibility of multiple simultaneous coalescent events to be negligible

- Requirements for no coalescence:
  - Pick one ancestor for sequence 1
  - Pick distinct ancestor for sequence 2
  - Pick yet another ancestor for sequence 3
  - …

Estimating P(*n*)

- Probability that *n* sequences have *n* distinct ancestors in previous generation

$$P(n) = \prod_{i=1}^{n-1} \frac{N-i}{N}$$

$$\approx 1 - \frac{\binom{n}{2}}{N}$$

- Assume:
  - N is large
  - n is small
  - Terms of order N^{-2} can be ignored

Probability of Coalescence at Time t+1

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

$$\approx \frac{\binom{n}{2}}{N} e^{-\frac{\binom{n}{2}}{N}t}$$

Time to next coalescent event

- Use an exponential distribution to approximate time to next coalescent event…

$$\text{Decay Rate} \quad \lambda = \frac{\binom{n}{2}}{N}$$

$$\text{Mean} \quad \frac{1}{\lambda} = \frac{N}{\binom{n}{2}}$$

T(j)

- For convenience, measure time to next coalescent event in units:
  - N generations for haploids
  - 2N generations for diploids

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

- How would you calculate time to MRCA of *n* sequences?

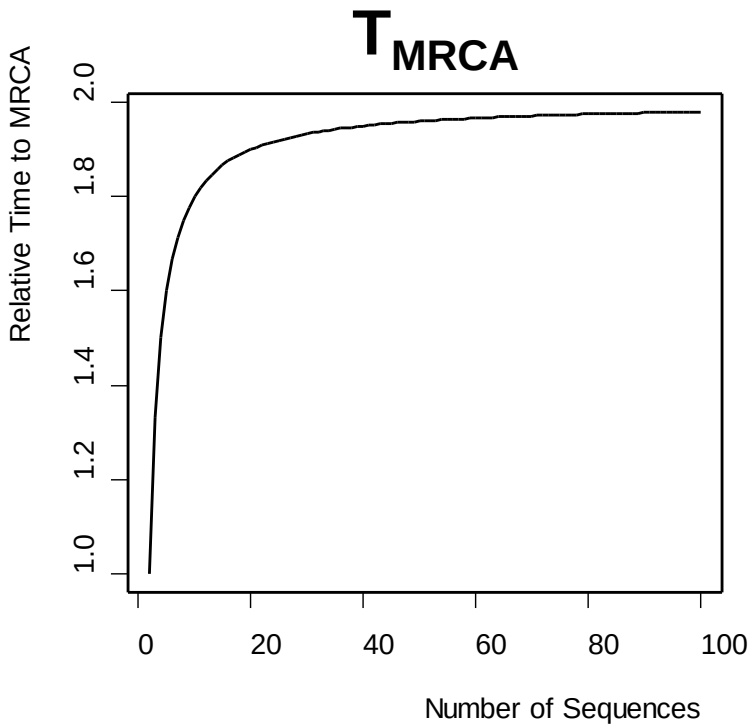
Total “Time in Tree”

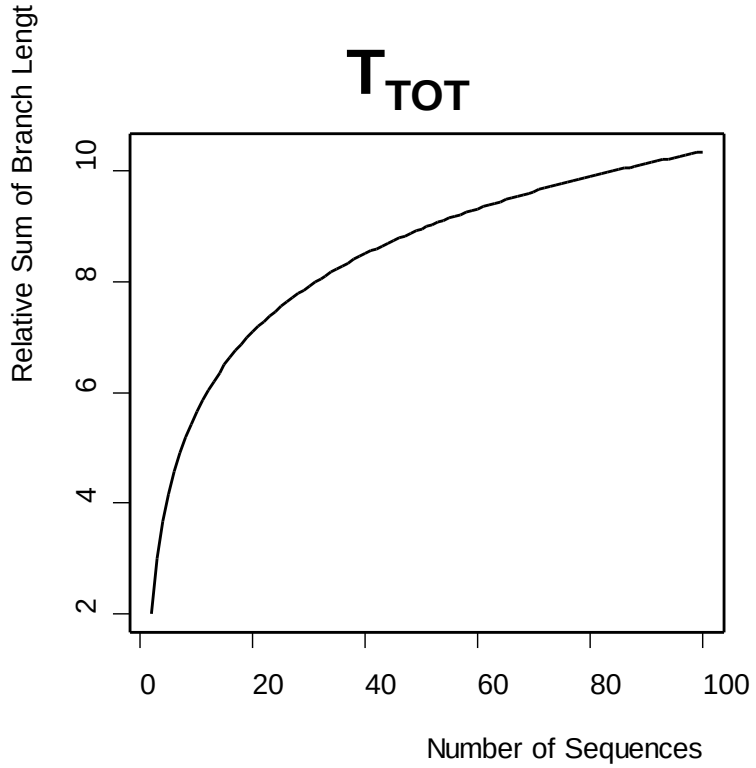
- Sum of all the branch lengths
- Total evolutionary time available
  - e.g. for mutations to occur

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

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

T_{MRCA} vs. T_{TOT}





Number of Segregating Sites

- Commonly named S

- Total number of mutations in genealogy
  - Assuming no recurrent mutation

  - A function of the total length of the genealogy
    - T_{tot}

Expected number of mutations

- Factor N for haploids, 2N for diploids

$$E(S) = 2N\mu \sum_{i=2}^{n} iE\left(T(i)\right)$$

$$= 4N\mu \sum_{i=1}^{n-1} 1/i$$

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

- Population geneticists define θ=4Nμ (for diploids)
  - For gene mappers, θ is usually the recombination rate
  - For population geneticists, *r* is the recombination rate

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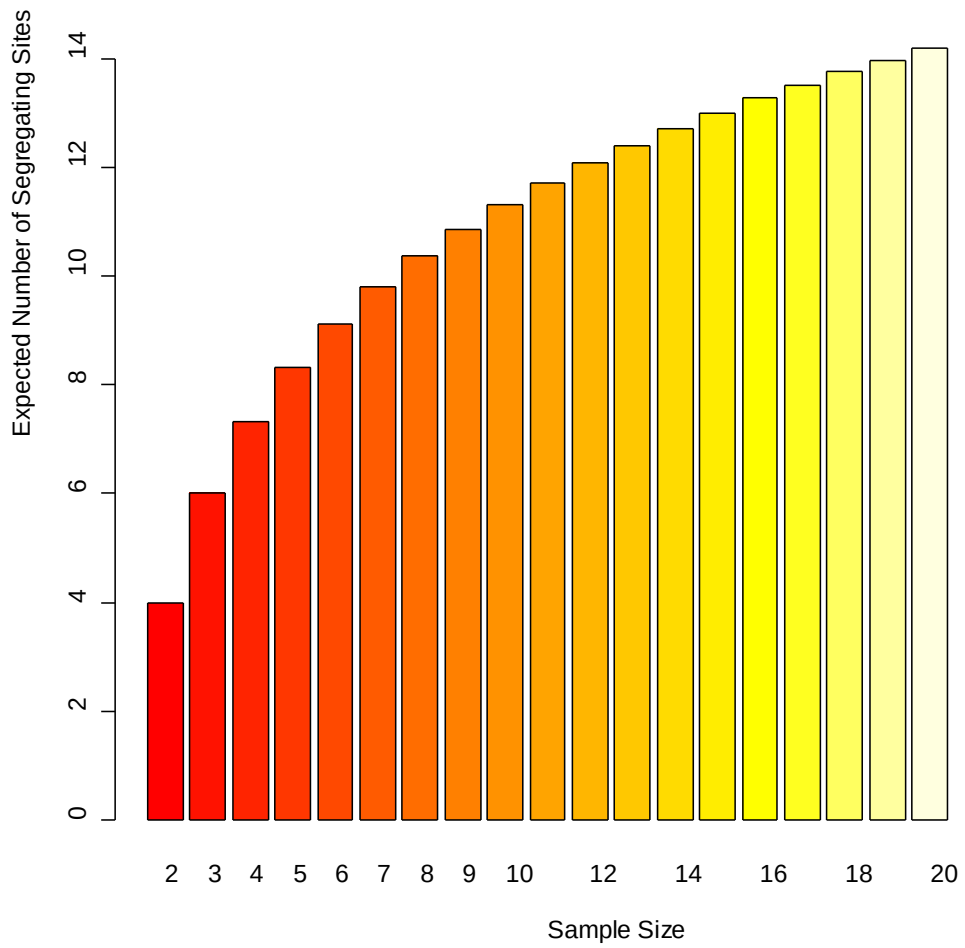
E(S) as a function of *n*



Parameters

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

$\theta = 4$

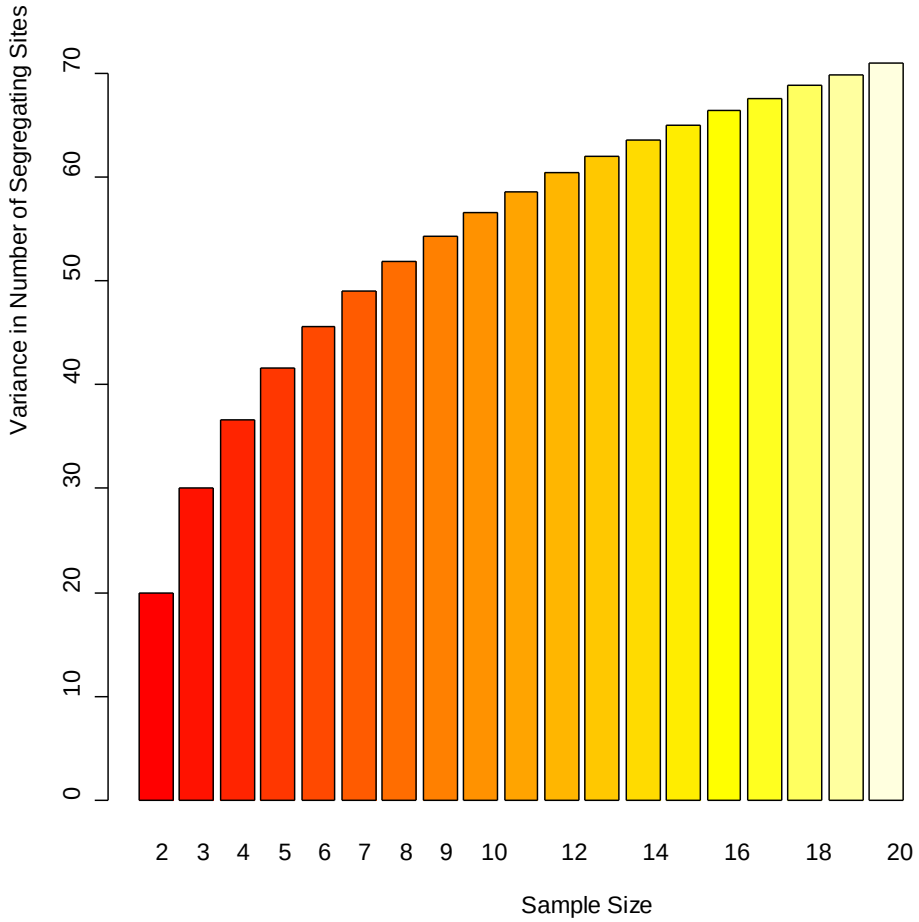
More about S…

- Very large variance

$$Var(S) = \theta \sum_{i=1}^{n-1} 1/i + \theta^2 \sum_{i=1}^{n-1} 1/i^2$$

- Most of the variance contributed by early coalescent events (i.e. with small *n*)

Var(S) as a function of *n*



Parameters

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$\mu = 10^{-4}$

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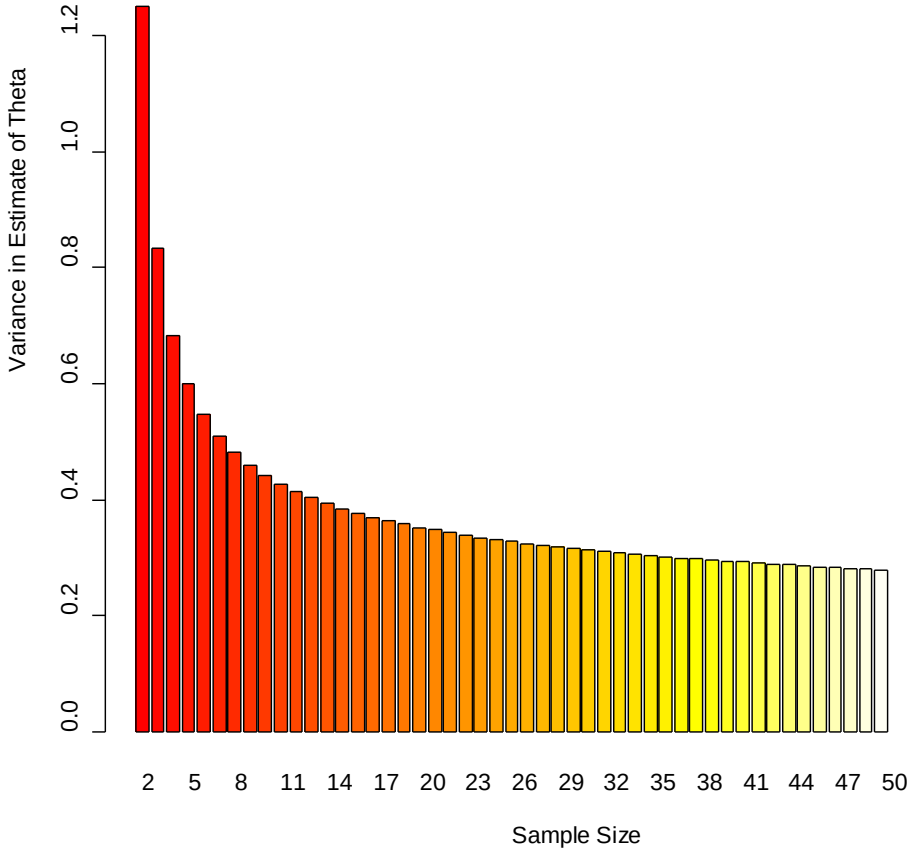
Inferences about θ

- Could be estimated from S
  - Divide by 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

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



Parameters

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

$\theta = 4$

Alternative Estimator for θ …

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

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

Today…

- Probability of coalescence events
- Length of genealogy and its branches
- Expected number of mutations
- Simple estimates of θ

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.