Coalescent Models With Recombination

Biostatistics 666

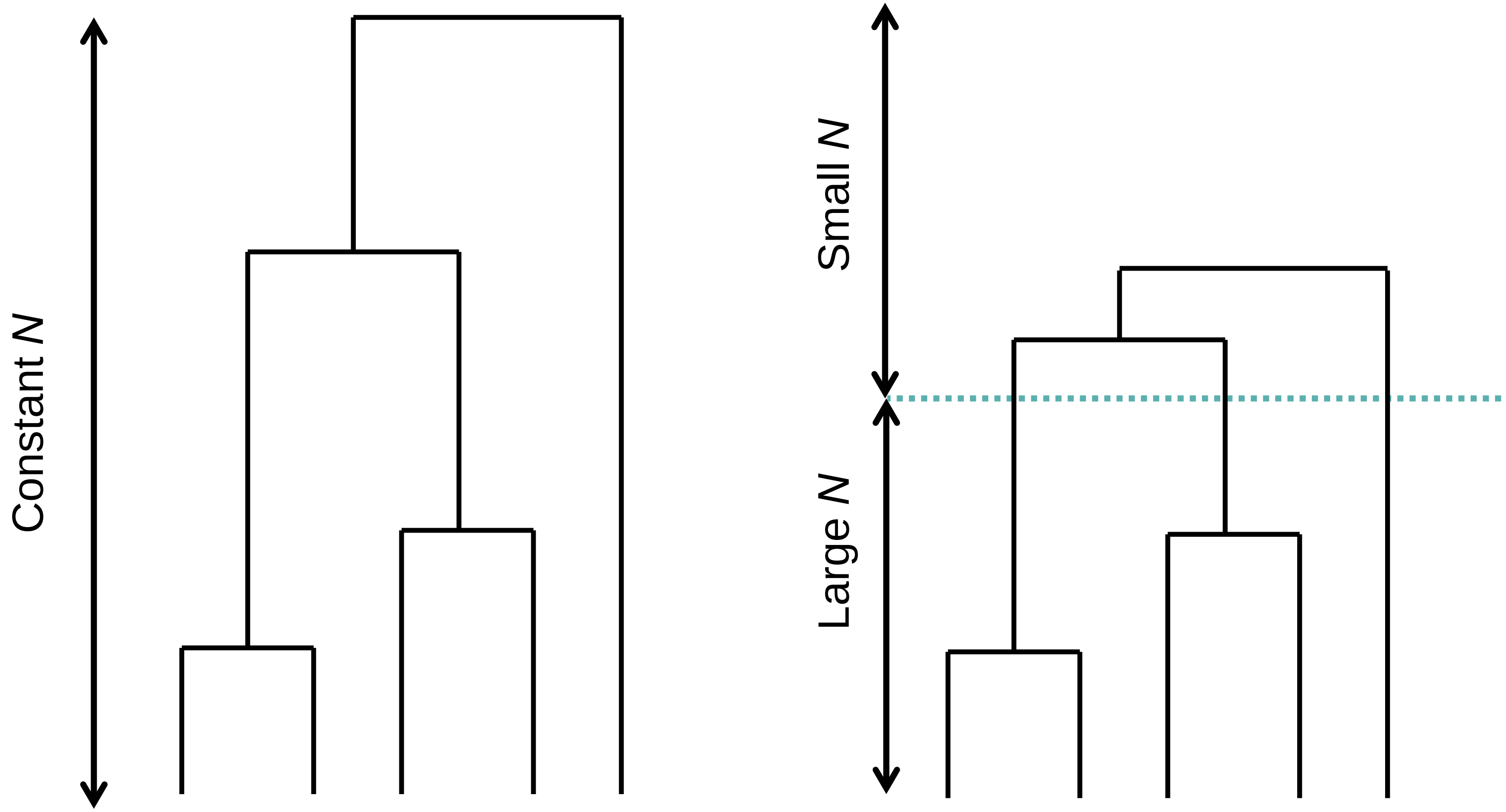
So far …

- Basic Properties of the Coalescent
    - MRCA
    - Coalescence times
    - Number of mutations
- Frequency spectrum of polymorphisms
- Predicting number of variants in a sample

The Parameter $\Theta = 4N\mu$

- Occurs frequently in population genetic models
- Two estimators for θ:
  - One, based on number of segregating sites S
  - Another, using average of pairwise sequence differences
- The two estimators have the same expectation
  - For constant size, equilibrium populations
- Can give consistently different answers when…
  - There are deviations from neutral model, such as …
  - … population growth, bottlenecks, natural selection
- Comparison of the two estimates defines Tajima’s D

How do changes in *N* change the coalescent tree?



Tajima's D

- $S =$ variant sites $\quad \pi = \frac{\sum_{i=1}^{n}\sum_{j=i+1}^{n} S_{ij}}{\binom{n}{2}}$

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

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

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

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

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

- Standardized difference between two estimators of θ
  - Formula is complicated due to variance estimator

Tajima's D

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

Standardized difference between two estimators of θ

Formula is complicated due to variance estimator.

Today …

- Using the coalescent to learn about a population
- Further refining the coalescent
  - Recombination
  - Migration
- Discussion of potential applications

Making Inferences About Population Parameters …

- The coalescent is a very useful tool for simulating data

- Given a set of parameters (population size, mutation rates, etc.) it can generate a plausible sample of sequences

- But how do we learn about parameters, given a sample?

Making Inferences About Population Parameters …

- Select a set of summary statistics
  - For example, the number of observed variants S
- For each of several parameters settings, carry out coalescent simulations
- Record how often each parameter setting results in a simulated dataset that matches the original.

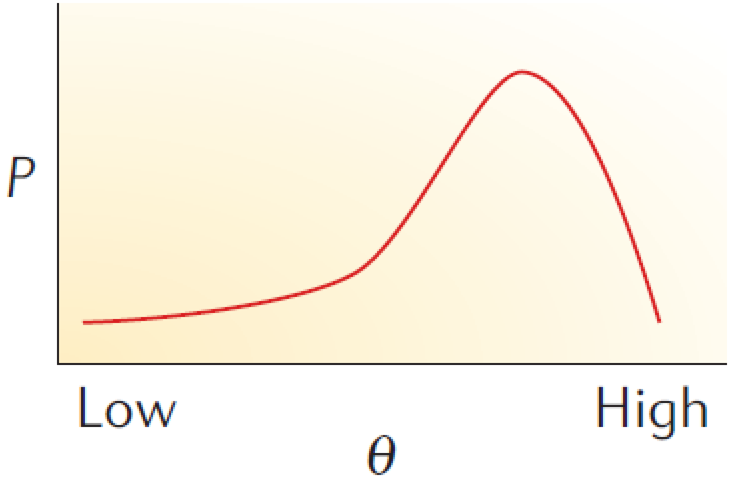
Making Inferences About Population Parameters ...

Sequence Data

```
ACGATCGAT.......ATAT
ACGATCGAA.......ATAA
         ...........
ACGATCGAT.......ATAT
```

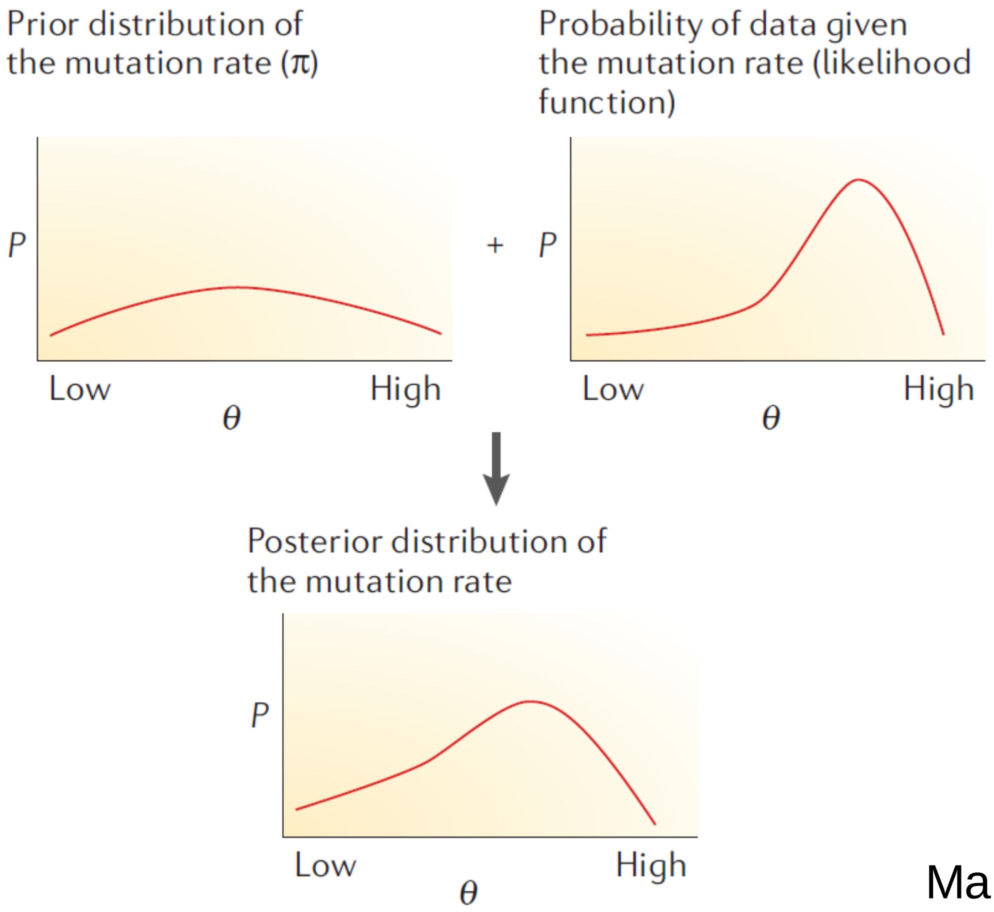
+
Model

Probability of data given the mutation rate (likelihood function)



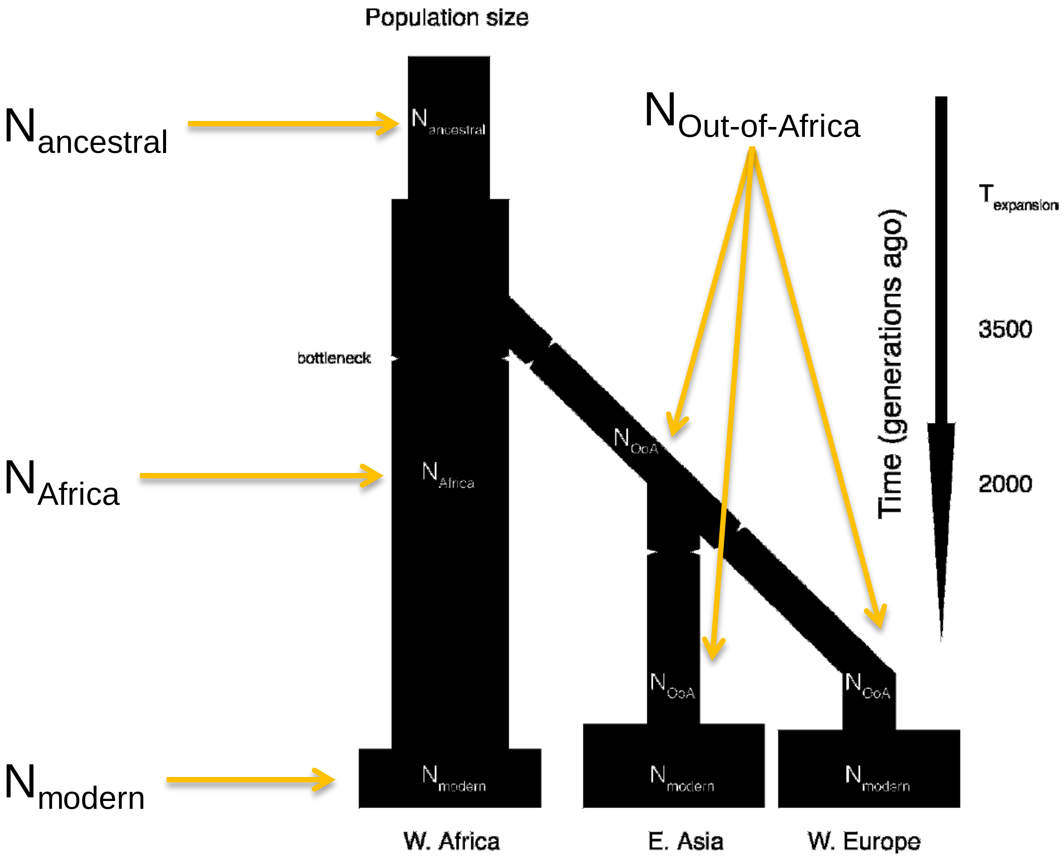
Marjoram and Tavare (2006)

Making Inferences About Population Parameters …



Marjoram and Tavare (2006)

Inferences Not Restricted to θ



$N_{ancestral}$

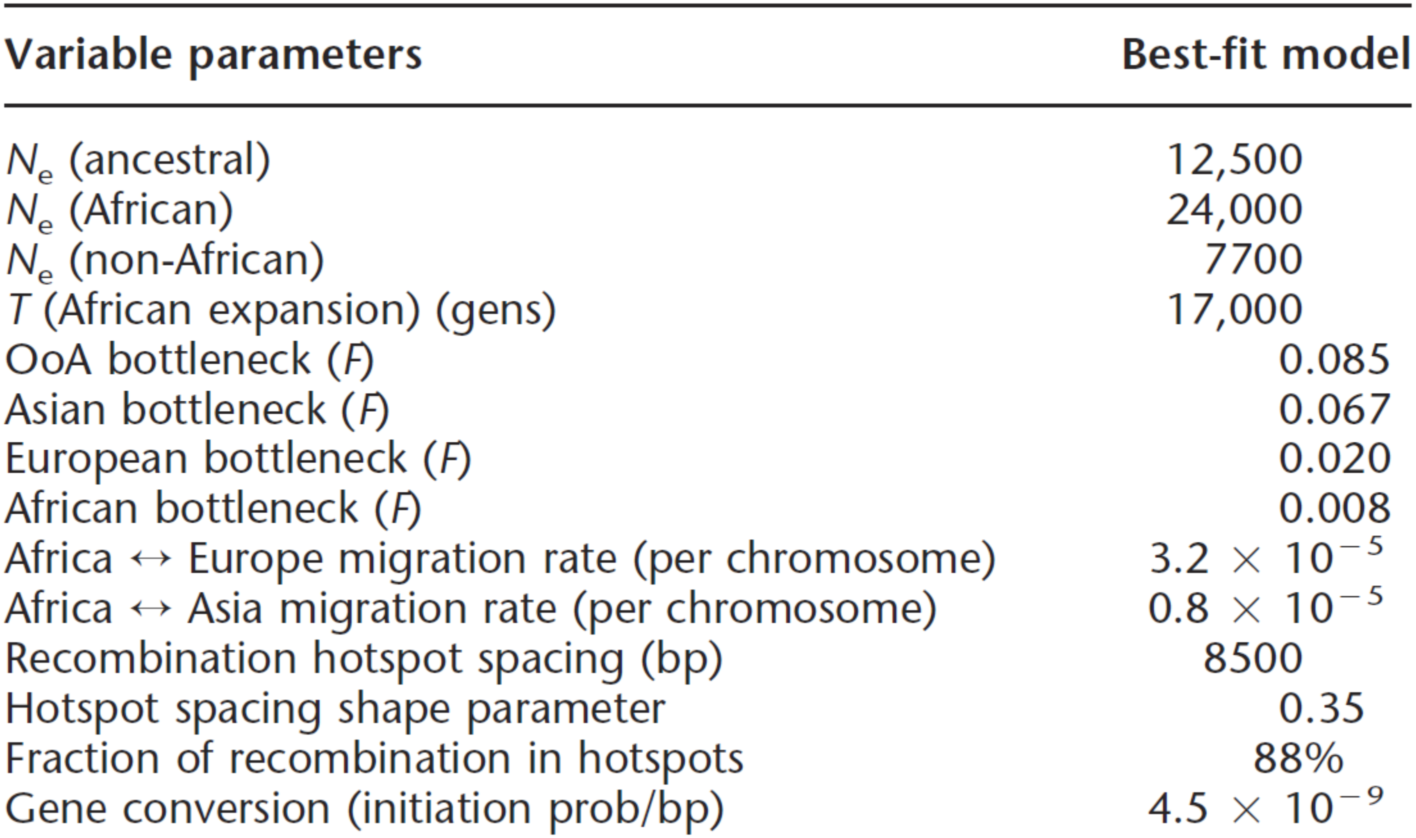
N_{Africa}

N_{modern}

$N_{Out\text{-}of\text{-}Africa}$

Schaffner et al (2005)

Inferences Not Restricted to θ



Variable parameters	Best-fit model
N_e (ancestral)	12,500
N_e (African)	24,000
N_e (non-African)	7700
T (African expansion) (gens)	17,000
OoA bottleneck (F)	0.085
Asian bottleneck (F)	0.067
European bottleneck (F)	0.020
African bottleneck (F)	0.008
Africa ↔ Europe migration rate (per chromosome)	3.2×10^{-5}
Africa ↔ Asia migration rate (per chromosome)	0.8×10^{-5}
Recombination hotspot spacing (bp)	8500
Hotspot spacing shape parameter	0.35
Fraction of recombination in hotspots	88%
Gene conversion (initiation prob/bp)	4.5×10^{-9}

Schaffner et al (2005)

Recombination …

- No recombination
  - Single genealogy
- Free recombination
  - Two independent genealogies
  - Same population history
- Intermediate case
  - Correlated genealogies

The History of Two Sequences

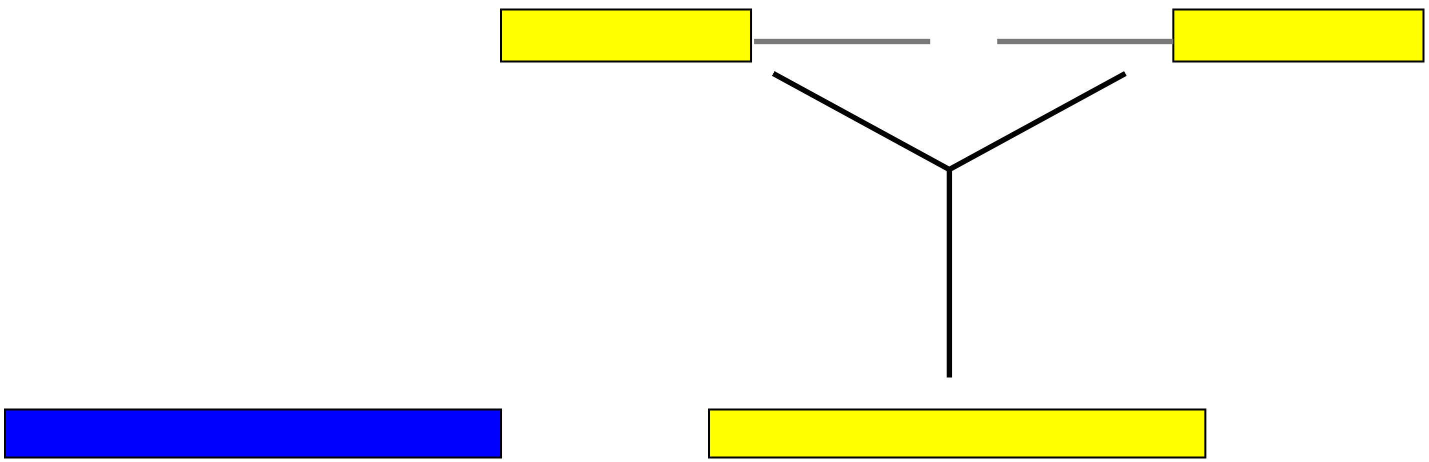
Let’s consider the potential history of two sequences, but this time… with a twist!

Sequence A

Sequence B

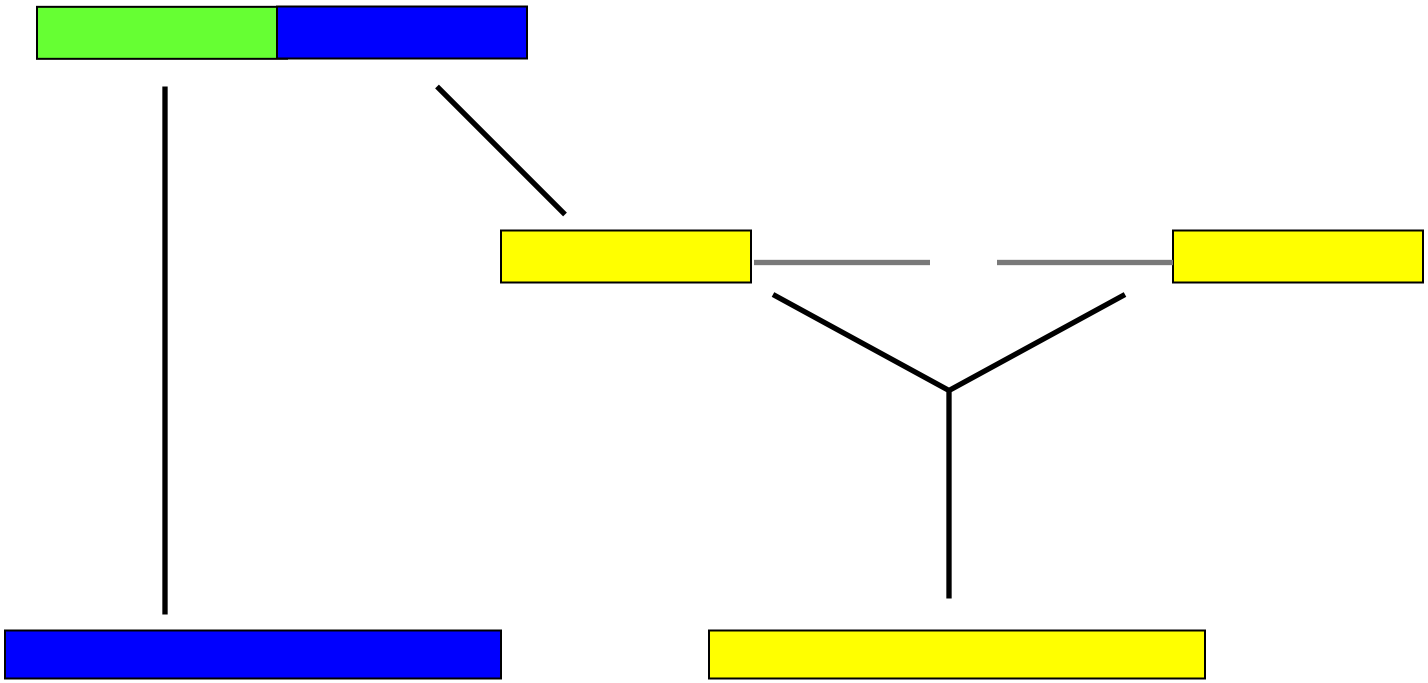
The History of Two Sequences

Before we reach a common ancestor … we find that sequence B is actually the result of recombination between two ancestral sequences

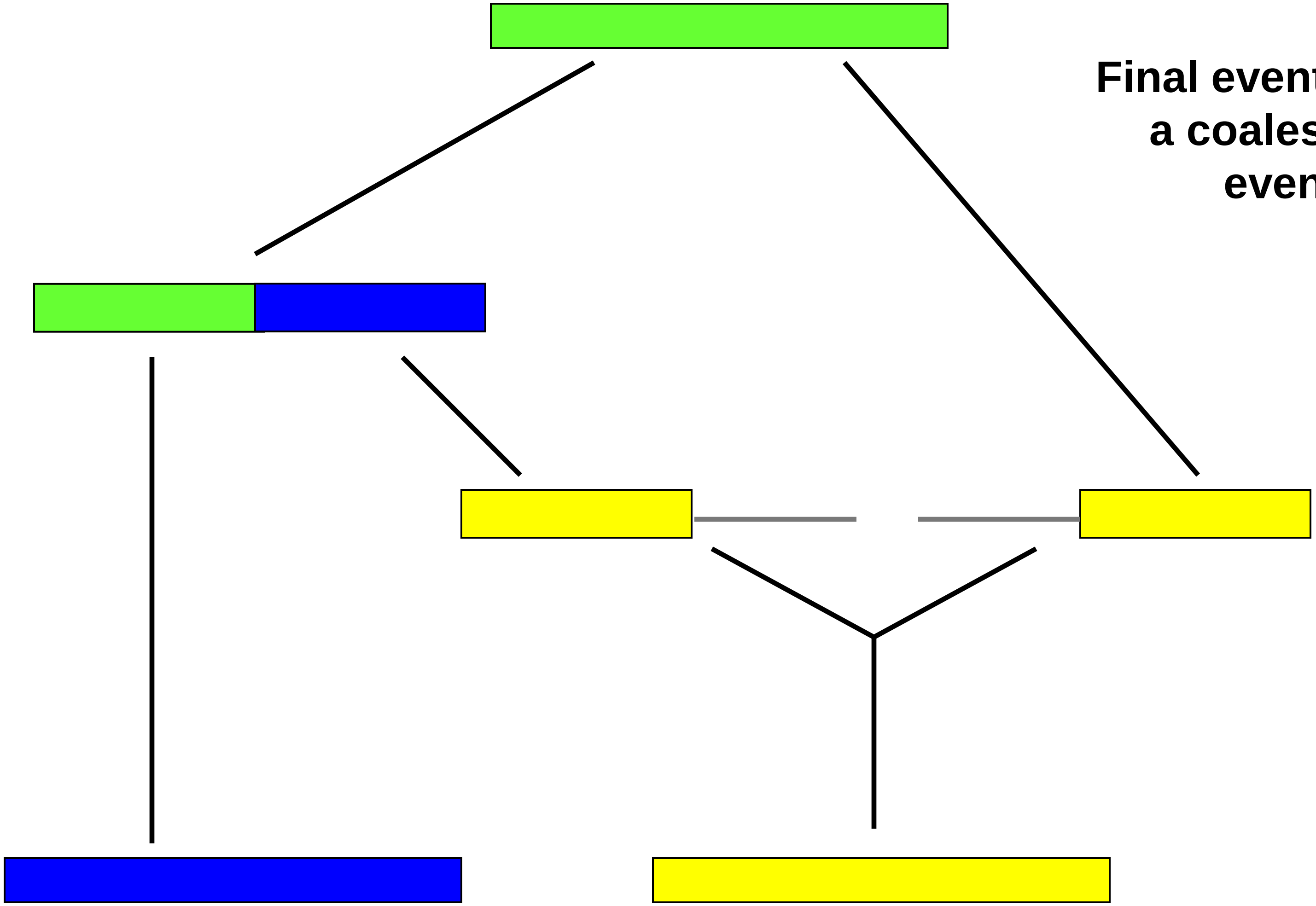


The History of Two Sequences

The next event we encounter is a coalescence event, as expected …



The History of Two Sequences



Final event is again a coalescence event...

Potential Consequences …

- Different portions of the sequence have different coalescence times

- Different portions of the sequence will show more or less variation

Another Consequence …

- Recombination and recurrent mutation can produce similar outcomes …

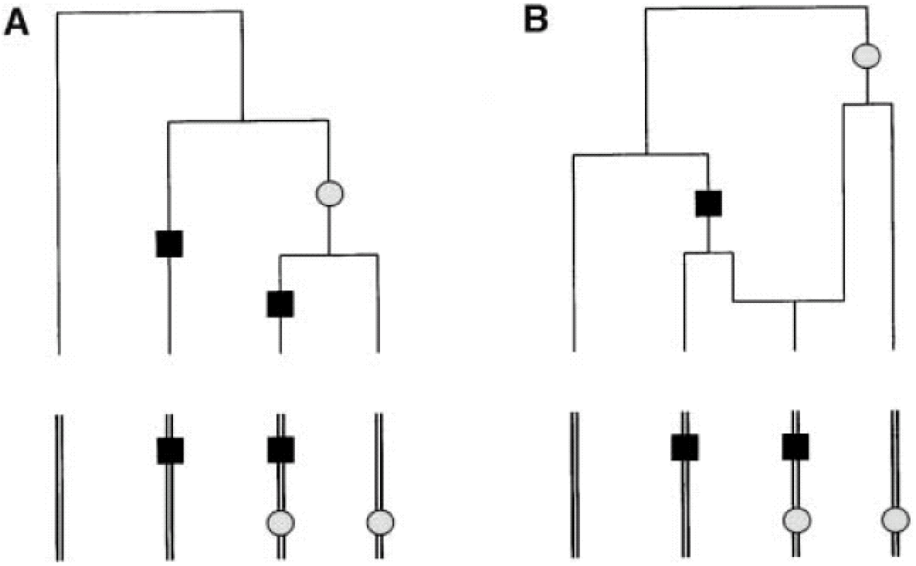


Figure from McVean et al (*Genetics*, 2001)

Simulating the Coalescent with Recombination

- Assume the various alternative events are rare
- Time until the next event is approximately exponentially distributed
- Conditional on something happening, figure out whether it was:
  - Recombination
  - Coalescence

Generating Genealogies

- Proceed backwards in time, until…
  - Coalescent event
    - Reduces number of ancestors by 1

$$P_{CA} \approx \binom{n}{2} / 2N$$

  - Recombination
    - May increase number of ancestors by 1

$$P_{rec} \approx nr$$

P(First Event is CA)

$$P(\text{no rec}) = \frac{P_{CA}}{P_{CA} + P_{rec}} = \frac{\binom{n}{2}/2N}{\binom{n}{2}/2N + nr}$$

$$= \frac{n-1}{4Nr + n - 1}$$

$$= \frac{n-1}{R + n - 1}$$

Coalescent W/ Recombination

- Analytical results are difficult
- Typical approach is to …
- First, simulate ancestral recombination graphs (ARG)
  - Coalescent tree with recombination events
- Study sample properties implied by simulated ARGs
  - For example, similarity in frequencies of neighboring SNPs

Correlated Genealogies

- Produce correlation in
  - Allele frequencies
  - Number of mutations
  - Distribution of alleles among chromosomes
    - Linkage disequilibrium

- Use simulations to evaluate distributions as a function of recombination rate

Example 1

- Consider a sample of *n = 90* chromosomes

- 2 locus coalescent, focus on samples where
  - $n_A = 30$
  - $n_B = 20$

- What is the distribution of n_{AB}?
  - And consequently of D', r^2

Low Recombination

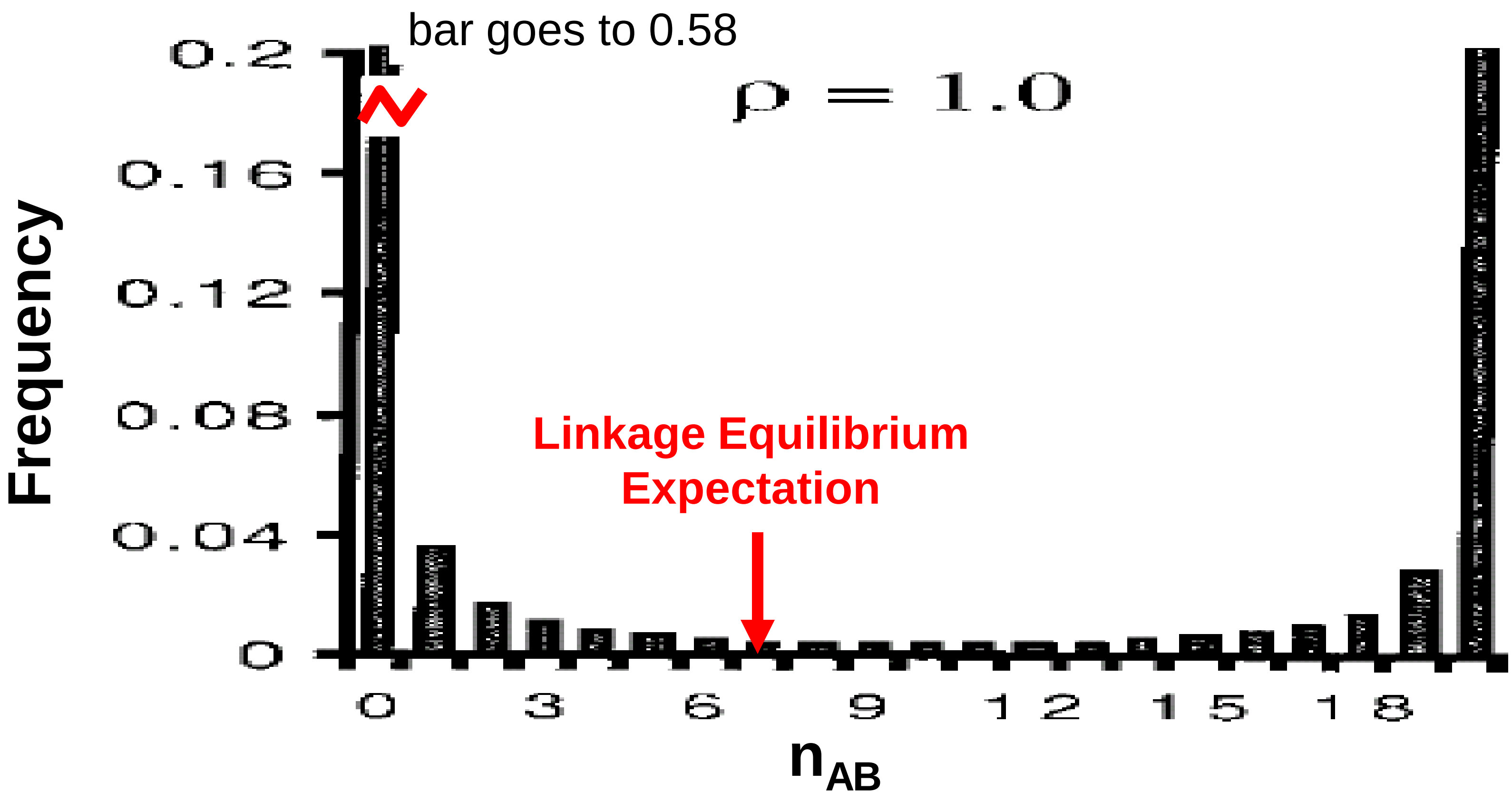


Figure from Hudson et al (Genetics, 2001)

Higher Recombination

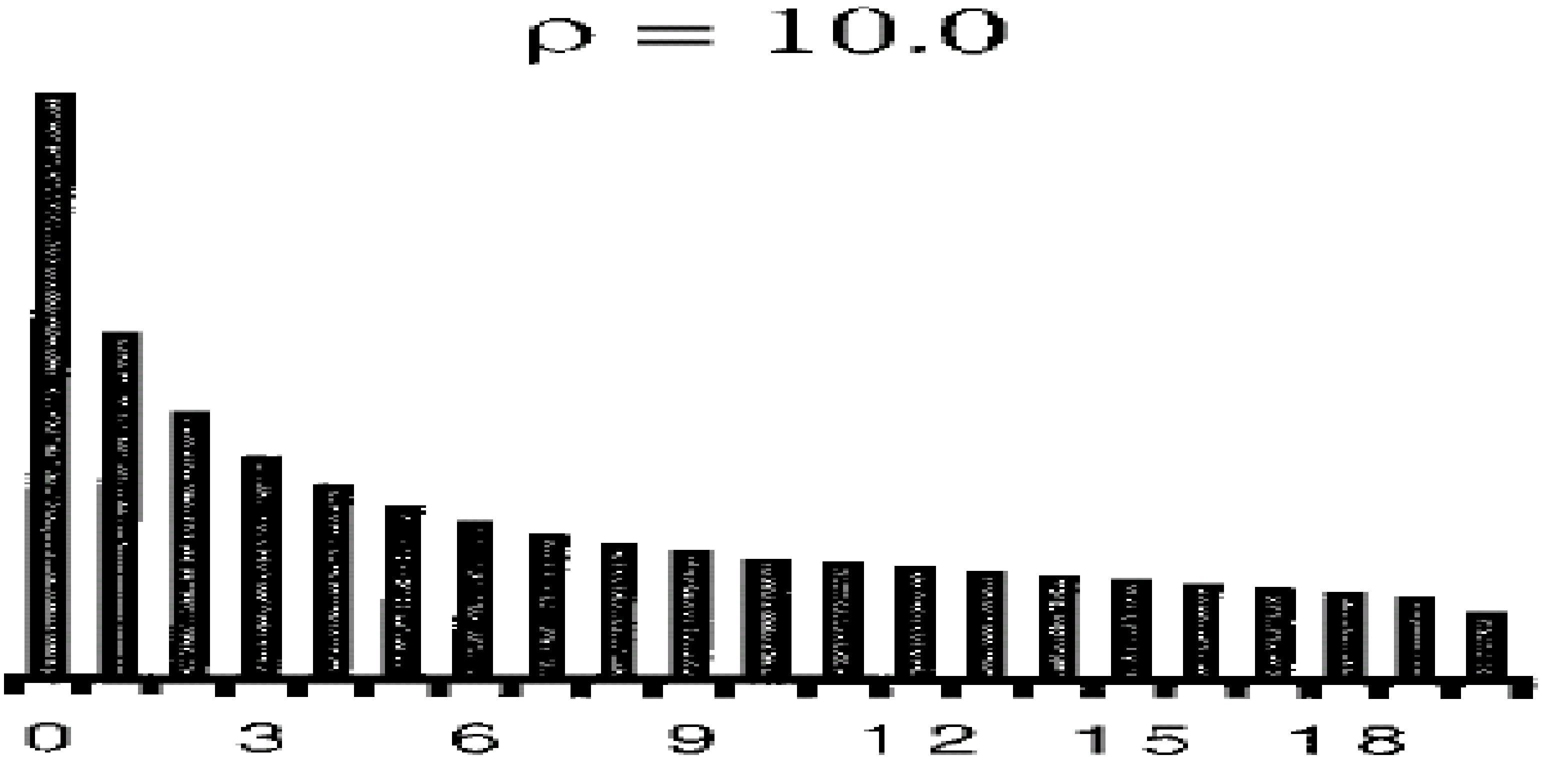


Figure from Hudson et al (Genetics, 2001)

High Recombination Rate

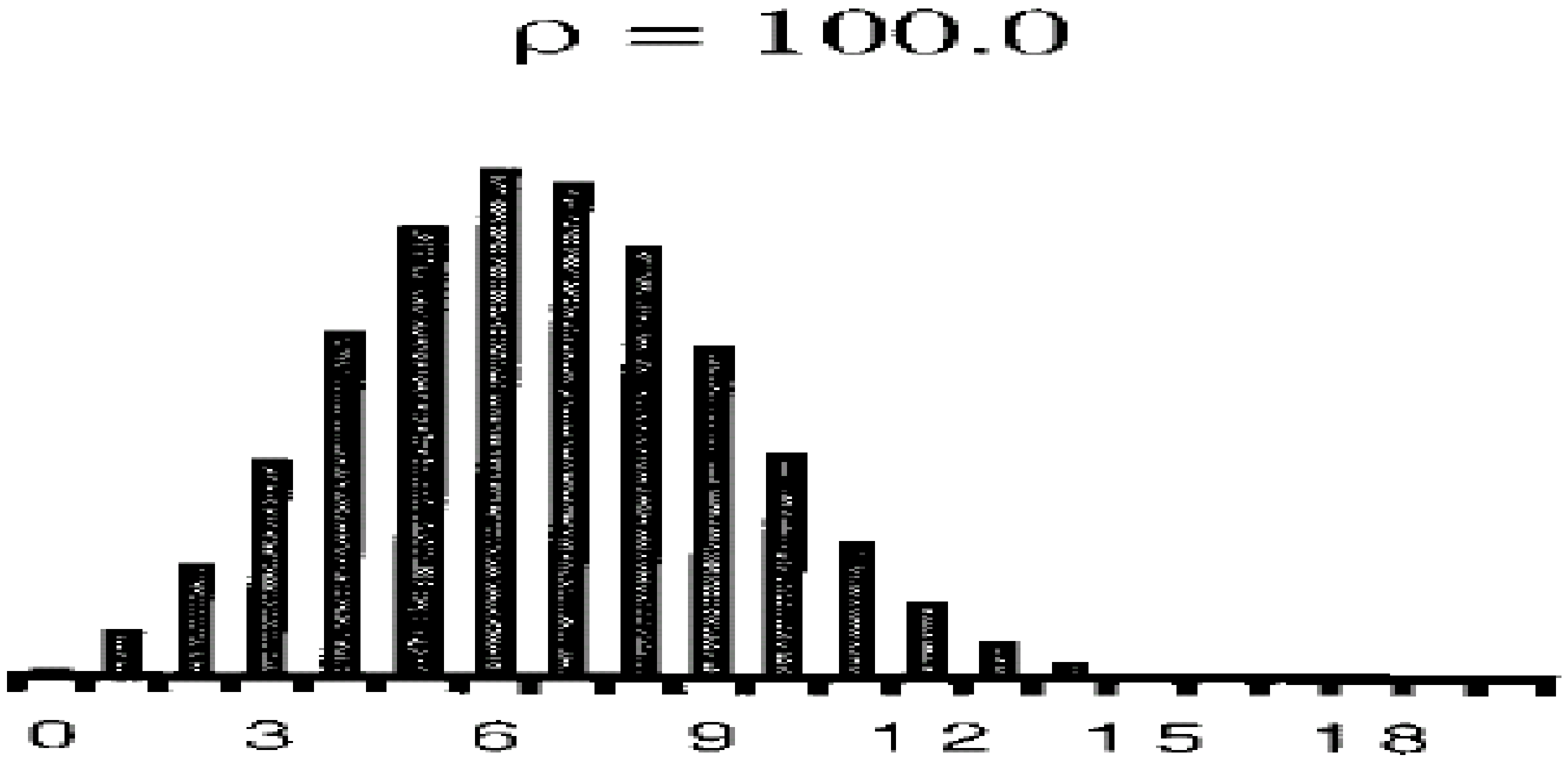
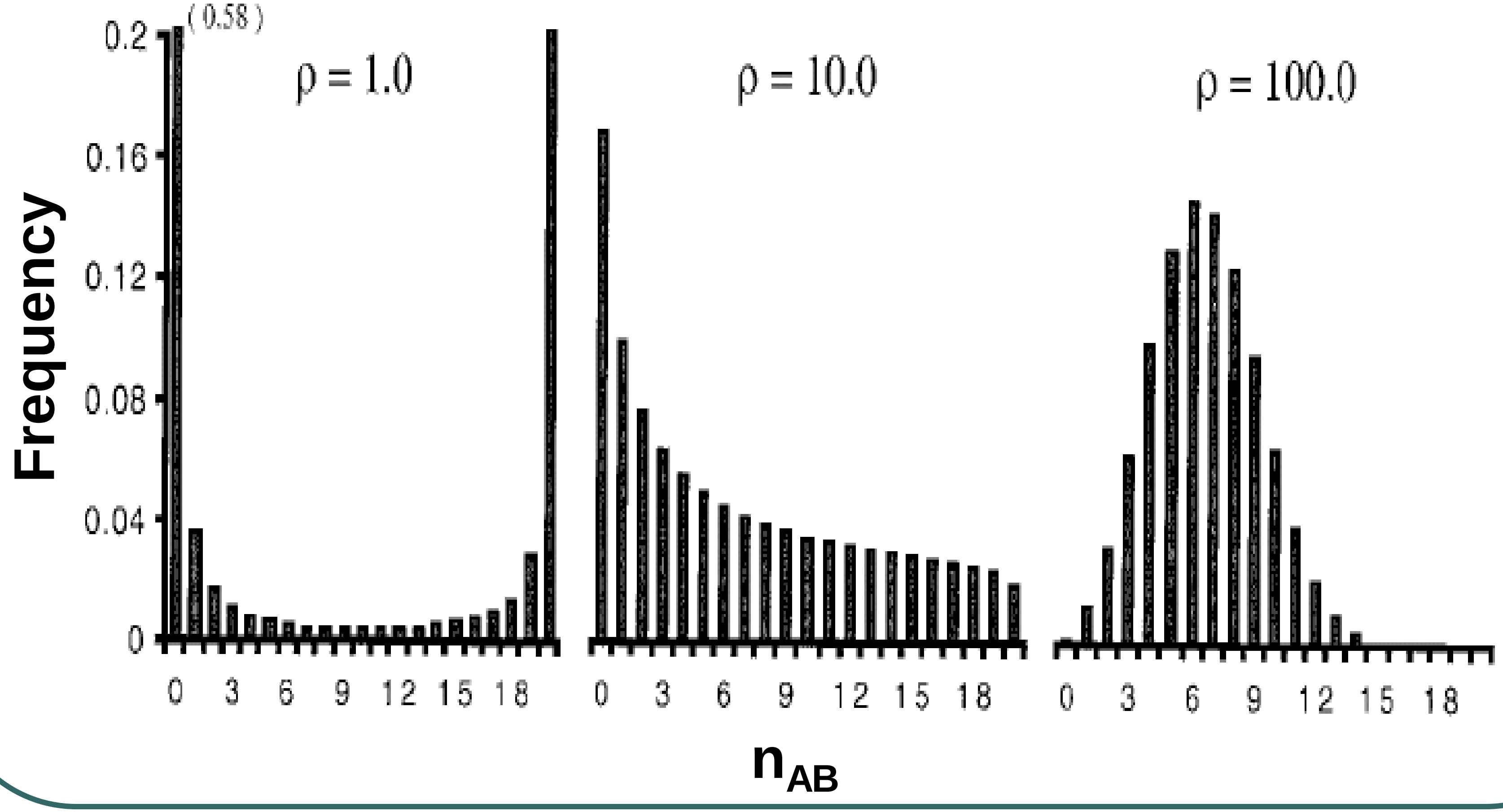


Figure from Hudson et al (Genetics, 2001)

Impact of Recombination on Haplotype Distribution



Some Notes …

- If we are interested in studying the local recombination rate, neither r^2 or D’ retain all the information contained in n_A, n_B, n_{AB}
- We can estimate R or ρ by finding the value that maximizes the probability of the observed sample configuration

Estimating Recombination Rates

- McVean et al. (*Science*, 2004) estimated the following “pseudo-likelihood” for a sample of haplotypes:

$$\ell(4Nr) = \sum_{ij} \ell(n_i, n_j, n_{ij} \mid 4Nr_{ij})$$

(summation is over all pairs of markers)

- Estimated recombination rates allow us to predict what other chromosomes or samples from the population might look like.

Recombination Rate Within HLA

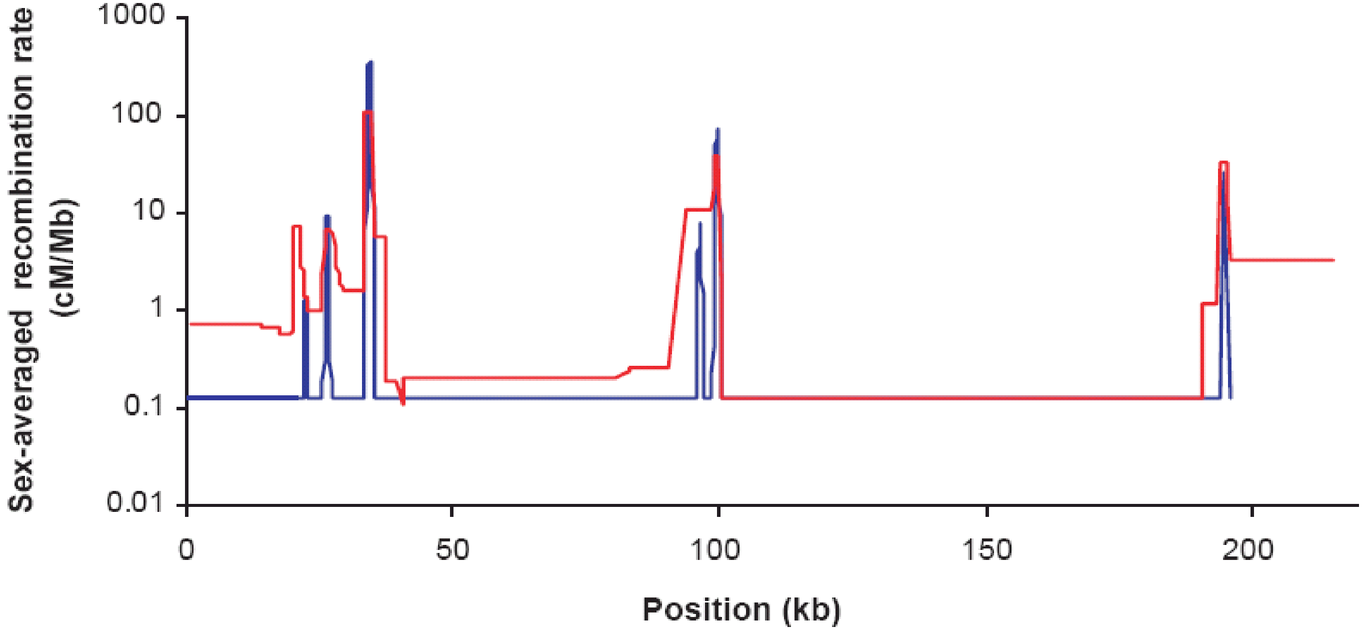
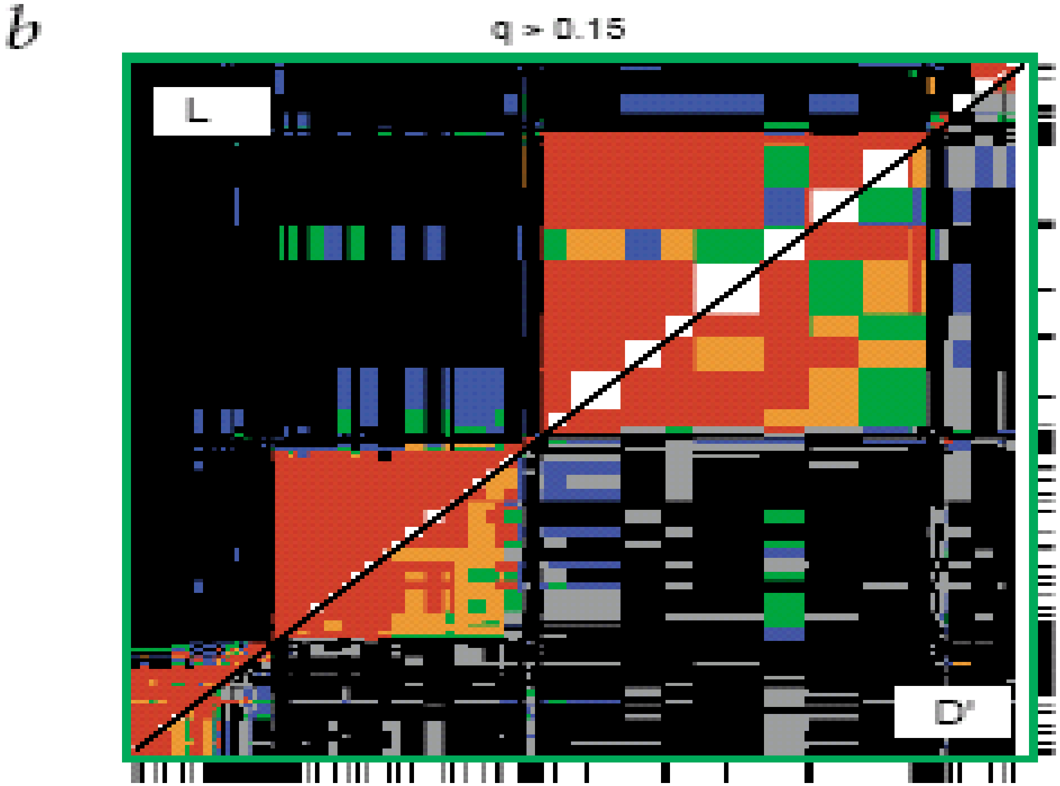


Fig. 2. Comparison between estimates of local recombination rates from population genetic data (red) and sperm analysis (blue) in the HLA region; data from (*3*). To convert the male crossing over rates to sex-averaged rates, we used the previous observation that the female crossing-over rate in this region is about four times that of males (*42*).

Pairwise LD in HLA



Pairwise LD data from Jeffrey's et al (2001)

Other Multi-Locus Coalescents

- Predicting correlation in number of mutations for neighboring regions
- If mutation rate were constant, would correspond to correlation of T_{TOT} between the two regions

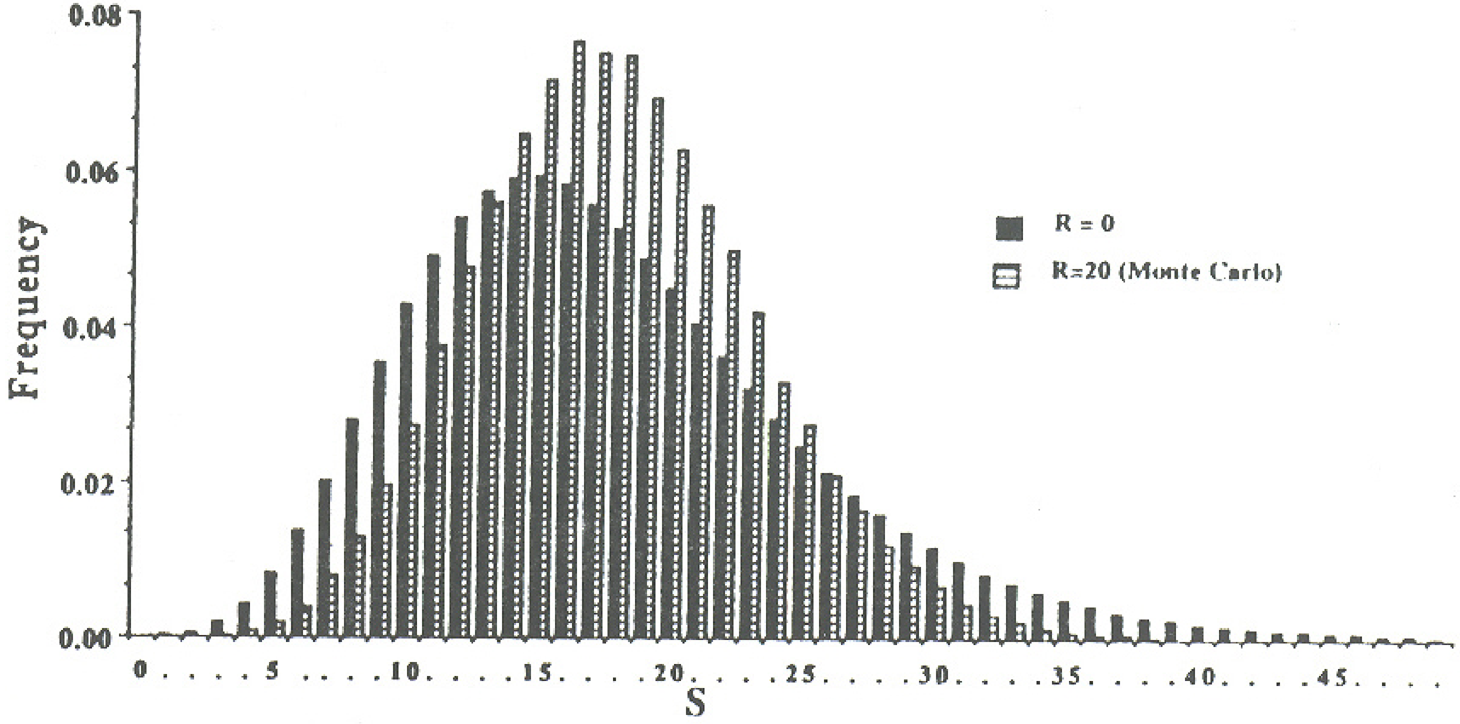
Total number of mutations

- Recombination does not change expectation for S…

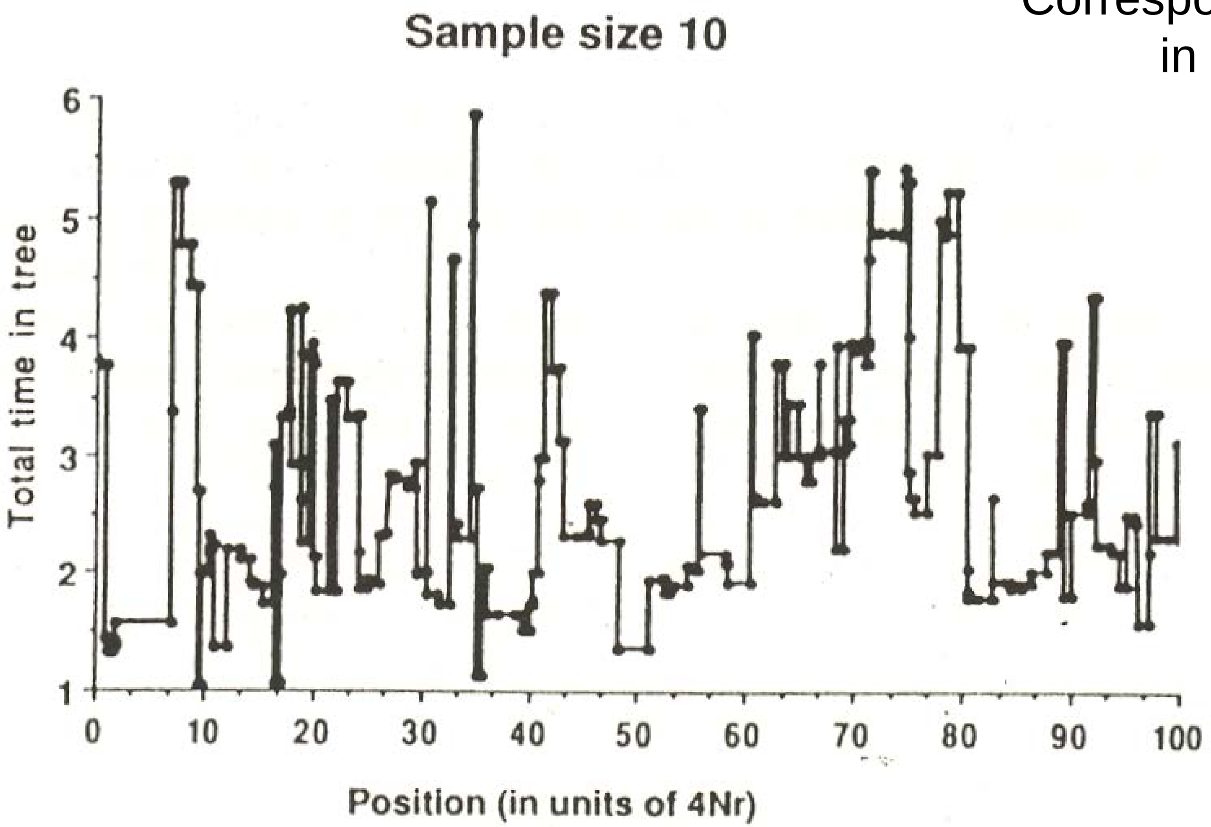
$$E(S) = 4N\mu \sum_{i=1}^{n-1} 1/i = \theta \sum_{i=1}^{n-1} 1/i$$

- … but it reduces its variance.
  - With large *r*, S is effectively averaged over multiple genealogies

Number of Mutations



Total Time in Tree

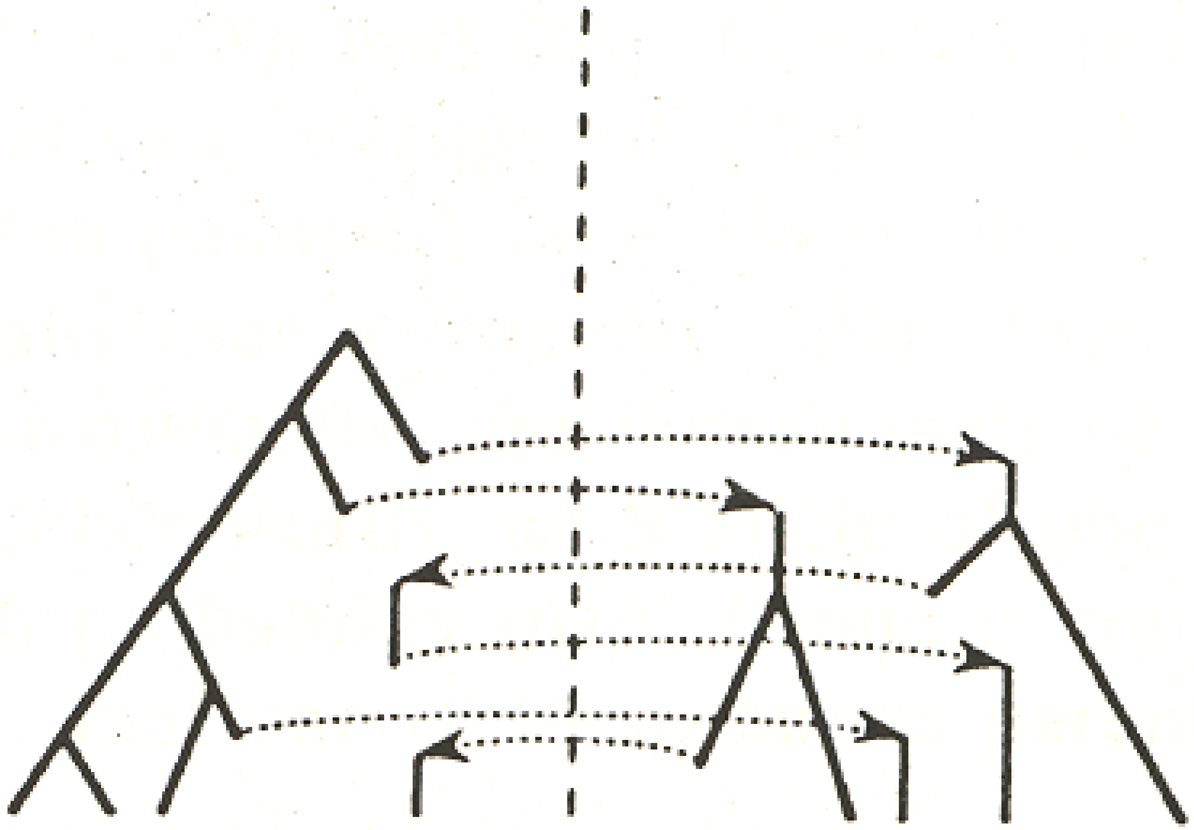


Corresponds to ~250kb
in humans

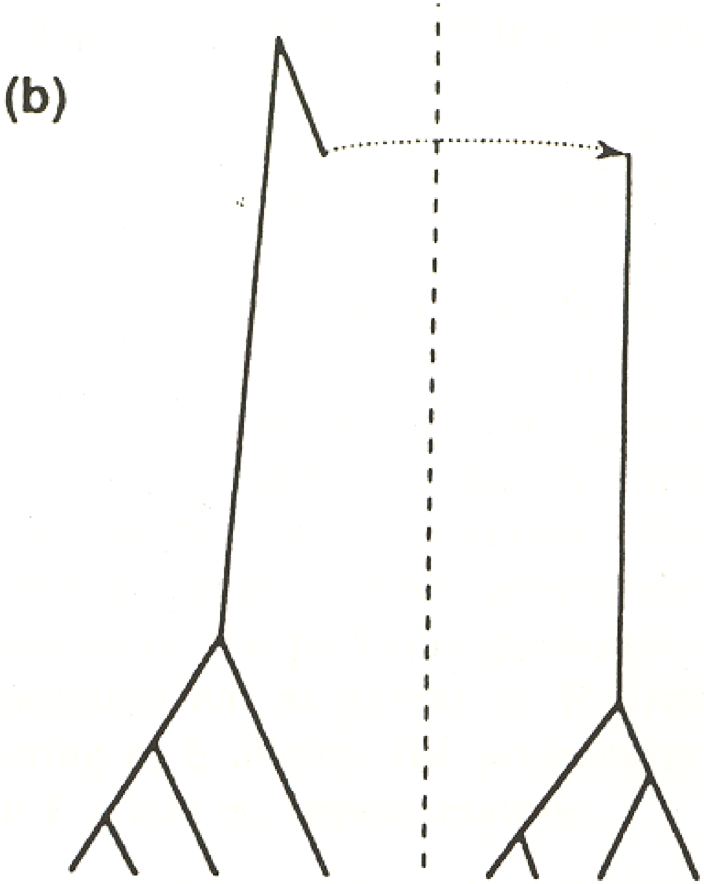
Population Subdivision

- What if the population is not mating at random, but is made up of multiple small groups?
- Track migration among ancestors…

High Migration rate …



Low Migration rate …



Formulae:

If the two subpopulations each have N diploids

Coalescent among n_1 lineages in population 1

$$\binom{n_1}{2}\Big/ 2\mathrm{N}$$

Coalescent among n_2 lineages in population 2

$$\binom{n_2}{2}\Big/ 2\mathrm{N}$$

Migration

$$(n_1 + n_2)m$$

Conditional Probabilities

Conditional Probability of Coalescence

$$\frac{\binom{n_1}{2}}{\binom{n_1}{2}+\binom{n_2}{2}+(n_1+n_2)\frac{M}{2}}$$

is the conditional probability of coalescence in population 1.

Here, $M = 4Nm$, is the scaled migration rate.

Conditional Probabilities

Conditional Probability of Migration

$$\frac{n_1 \frac{M}{2}}{\binom{n_1}{2} + \binom{n_2}{2} + (n_1 + n_2)\frac{M}{2}}$$

is the probability of migration from population 1 to 2.

Models with Migration

- As in the case with recombination, most predictions are based on simulations

- The models for migration are analogous to those with balancing selection
  - Replace migration rate with the mutation rate between the two alleles

Questions that Coalescent Can Tackle…

- Frequency spectrum of observed mutations
  - Impact of population growth
  - How many mutations are unique?
- Disequilibrium coefficient
  - Joint distribution of (p_A, p_B, D_{AB})
  - Impact of population growth

MS Computer Program

- Coalescent Simulator
  - by Richard Hudson at U. of Chicago

- Generates samples of sequences
  - Population and subpopulation sizes
  - Mutation rate ($\theta = 4N\mu$)
  - Recombination rate ($R = 4Nr$)

- http://home.uchicago.edu/~rhudson1/

Recommended Reading

- Richard R. Hudson (1990) “Gene Genealogies and the coalescent process”
  - from Oxford Surveys in Evolutionary Biology, Vol. 7. D. Futuyma and J. Antonovics (Eds). Oxford University Press, New York.

Further Reading

- Marjoram P and Tavare S (2006).
  Modern computational approaches for analysing molecular genetic variation data.
  Nature Reviews Genetics **7**:759-770

- Schaffner SF, Foo C, Gabriel S, Reich D, Daly MJ and Altshuler D (2005).
  Calibrating a coalescent simulation of human genome sequence.
  Genome Research **15**:1576-83