Coalescent Theory: A brief Introduction

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MPI for Evolutionary Anthropology

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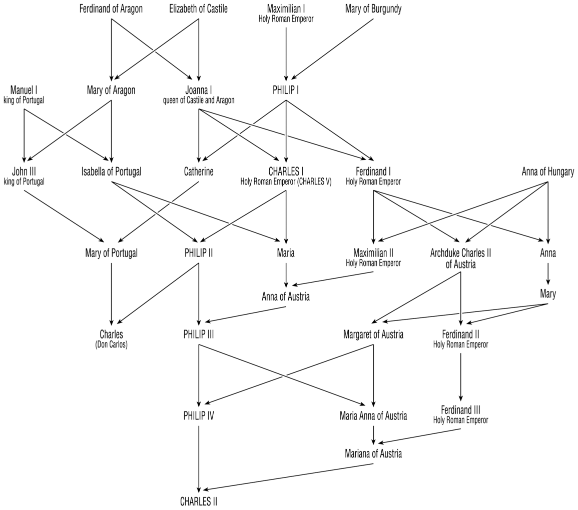
Recommended reading

- John Wakeley (2009): Coalescent Theory: An Introduction
- Joe Felsenstein (2016?): Theoretical Evolutionary Genetics `http://evolution.genetics.washington.edu`
- Rick Durett (2008): Probability Models for DNA Sequence Evolution `https://services.math.duke.edu/~rtd/Gbook/PM4DNA_0317.pdf`

Pedigrees



- backwards-in-time perspective
- identity-by-descent
- not available for most people

Wright (1922): The American Naturalist

Alvarez et al. (2009) PLoS One

The population pedigree

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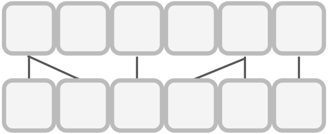

- Neutral WF-model with ancestry relationship

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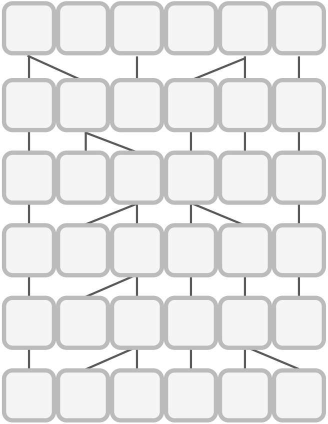

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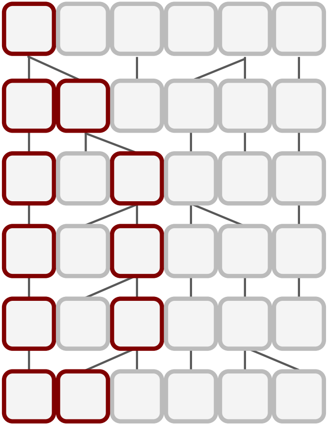

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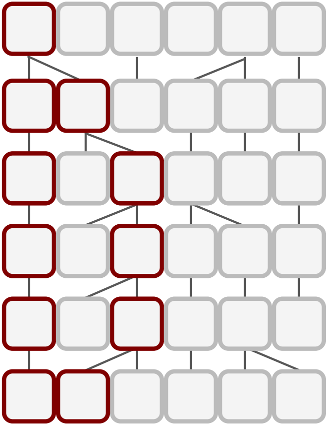

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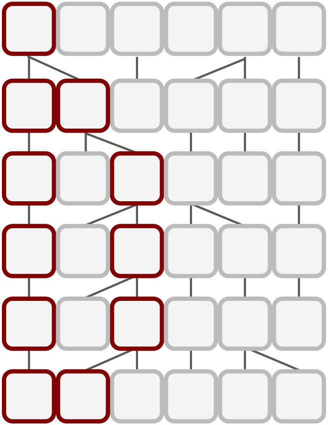

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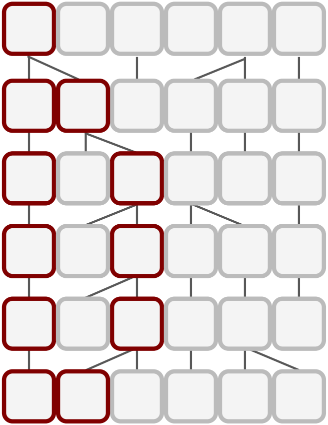

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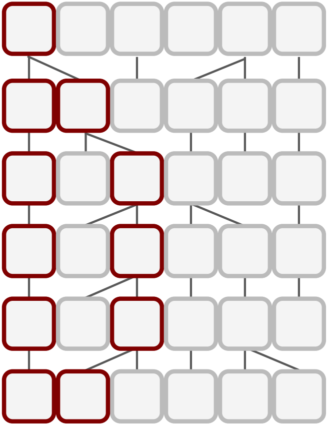
- $T_2 \sim \text{Geometric}\left(\frac{1}{2N}\right)$

Implications



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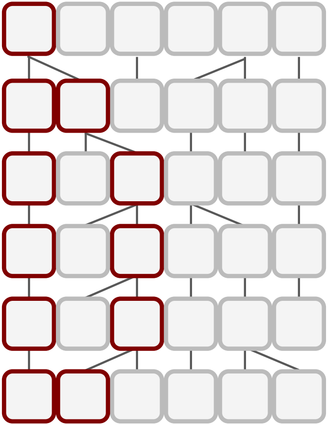

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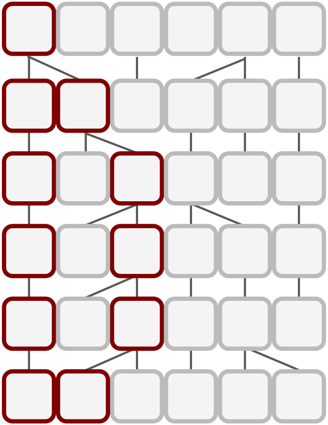

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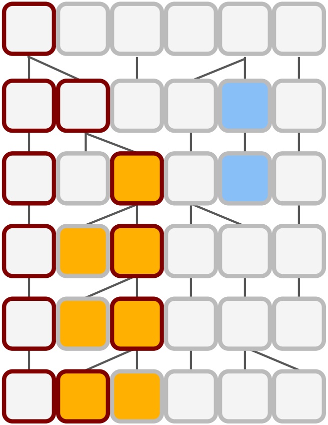
- Rescaling time:
  - $r_{\text{coalescence}} = 1$
  - $T_2 \sim \text{Exp}(1)$

Poisson process formulation



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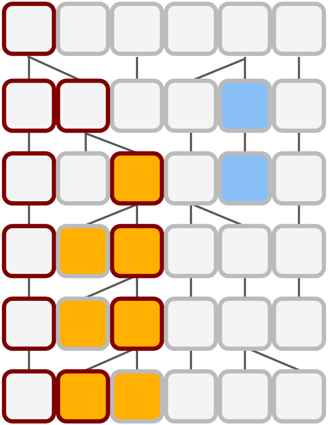

Two types of events:

- Coalescence
- Mutation

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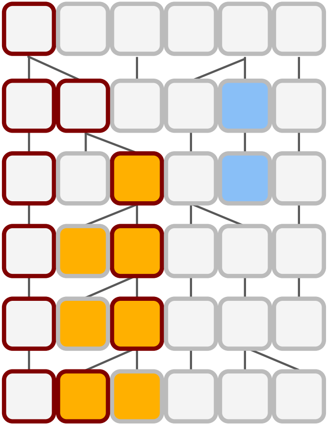

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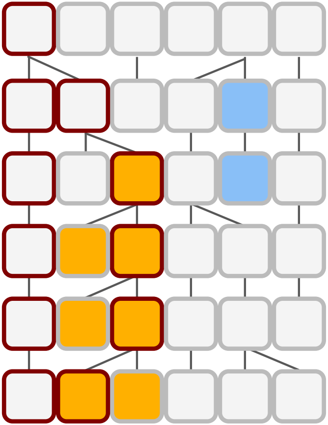

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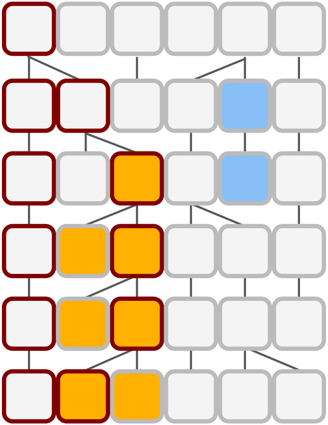
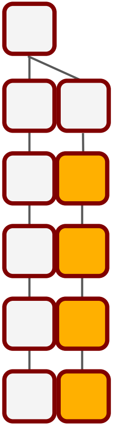
Define $\pi = \#\text{differences}$

- $\pi \sim \text{Geometric}\left(\frac{1}{1+\theta}\right)$
- $\mathbb{E}[\pi] = \theta$

From pairs to trees





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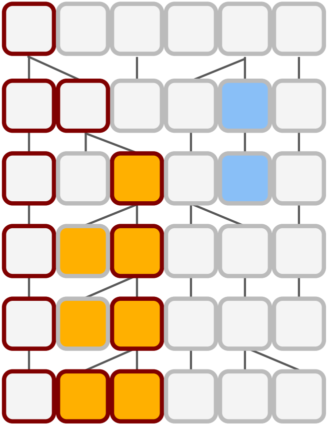

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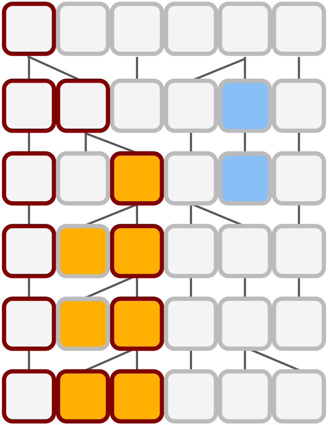

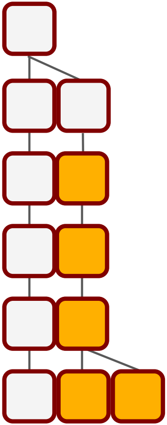

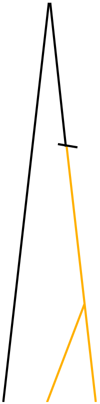

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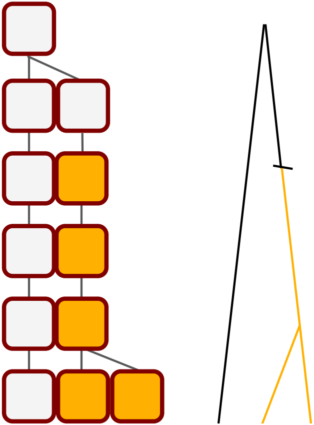

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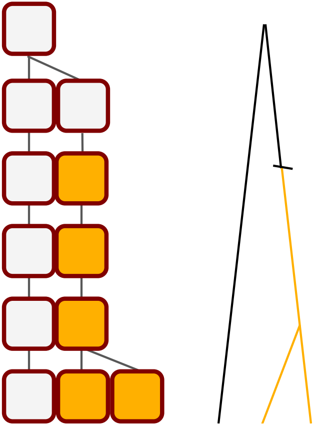

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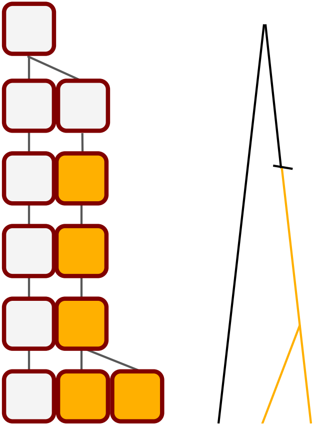

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Rates:

- $r_{\text{coalescence}} = 1 + 1 + 1$
- $r_{\text{mutation}} = 3 \times 2N \times \mu = \frac{3}{2}\theta$

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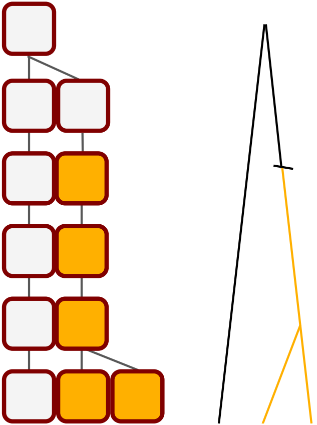

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After coalescence:

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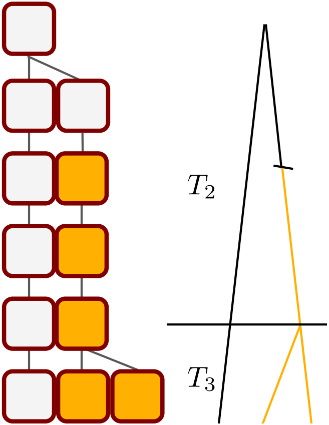

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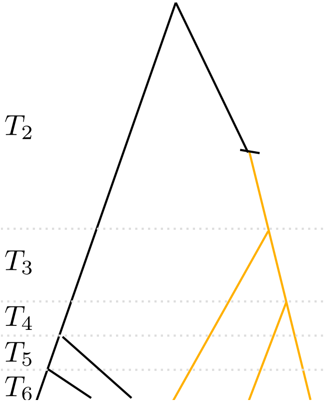

Two types of events:

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- Mutation

Rates:

- $r_{\text{coalescence}} = \binom{n}{2}$
- $r_{\text{mutation}} = n \times 2N \times \mu = \frac{n}{2}\theta$

Distributions:

- $T_n \sim \text{Exp}\left(\binom{n}{2}\right)$
- $S_n \sim \text{Geometric}\left(\frac{n-1}{\theta+n-1}\right)$
- $\mathbb{E}[S_n] = \frac{\theta}{n-1}$

Infinite sites mutation model

- **Assumption:** Each mutation is at a new site

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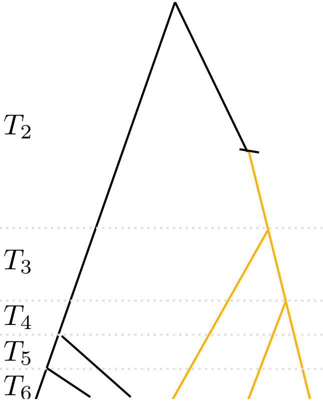
- **Implications:**
  1. $P_i \sim \text{Uniform}(0,1)$
  2. assuming mutations are rare ($\theta^2 \approx 0$)
  3. Good model for humans ($\theta \approx 10^{-3}$)
  4. More problematic for *Drosophila* ($\theta \approx 10^{-2}$)
  5. All mutations on genealogy are observable

Two measures of tree size



Tree height and total size

- $T_{MRCA} = \sum_{i=2}^{n} T_i$
- $T_{Tot} = \sum_{i=2}^{n} iT_i$

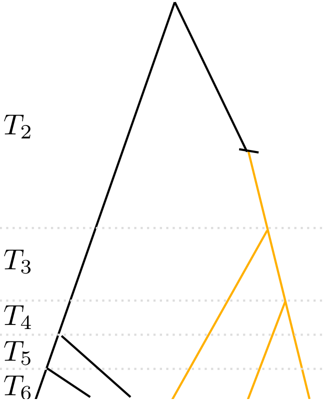
Expectation:

- $\mathbb{E}[T_{MRCA}] = \sum \binom{n}{2}^{-1} = 2\left(1 - \frac{1}{n}\right)$
- $\mathbb{E}[T_{Tot}] = \sum i \frac{2}{i(i-1)} = 2\sum \frac{1}{i}$

Implications:

- $\mathbb{E}[T_{MRCA}] \approx 2$
- $\mathbb{E}[T_{Tot}] \approx K + \log(n)$

Total number of Mutations



Two formulations:

- $S \sim \sum_i S_i$
- $S \sim \text{Poisson}\left(\theta/2T_{Tot}\right)$

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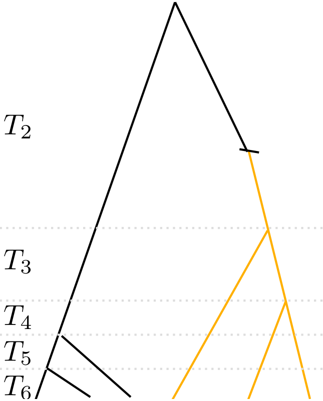

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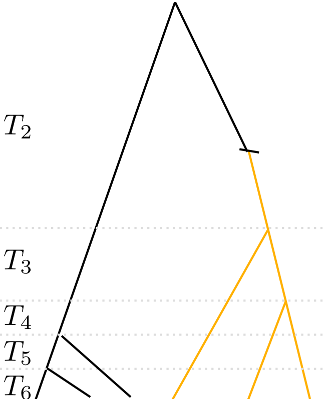

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Trees as a random quantity

- Tree is a latent variable that will change across genome
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- $\mathcal{T}_{10} = 2.5 \times 10^9$
- how is this addressed in practice?
  1. Focus on quantities independent of topology, e.g. branch lengths
  2. sample size of two, three or four
  3. Monte Carlo integration

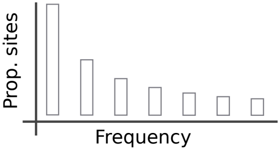
Some extensions

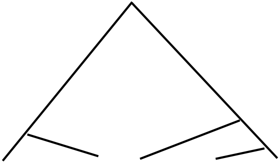
- Population size changes
- Population structure & Migration
- Recombination
- Linkage to selected site
- Analytical work often tricky, but simulations easy & very efficient

Part 2: Applications of the coalescent

1. The Site Frequency Spectrum (SFS)
2. Structured Populations
3. PCA
4. 2D-SFS

Neutral SFS

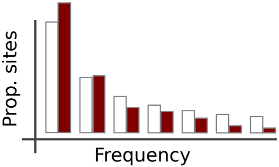


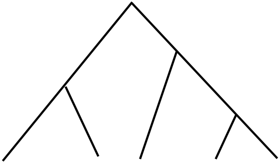


Definitions:
ξ_i : $\#$ mutations with i derived copies
η_i : $\#$ mutations with $i, n - i$ copies
Comments:

- For a particular tree: $\xi_i = 0$ is common
- Over many trees: $\mathbb{E}\xi_i = \frac{\theta}{i}$

Excess rare alleles





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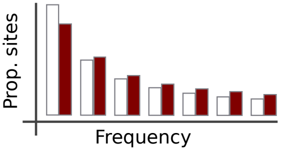
- population growth
- negative selection

Excess common alleles



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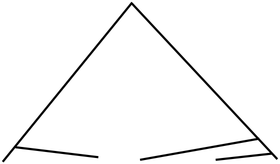
Caused by:

- population decline
- positive selection



Inference Frameworks

There are a few frameworks that calculate expected SFS for (almost) arbitrary models:

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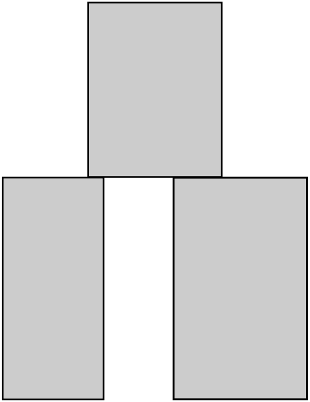
- Excoffier et al. (2012): `simcoal2`, simulation based

Population Structure: Isolation without migration



How do things change when we consider multiple populations?

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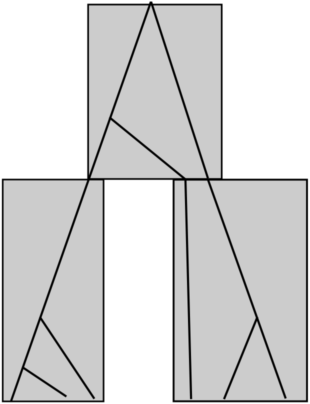

Rules:

1. Disconnected populations coalesce independently
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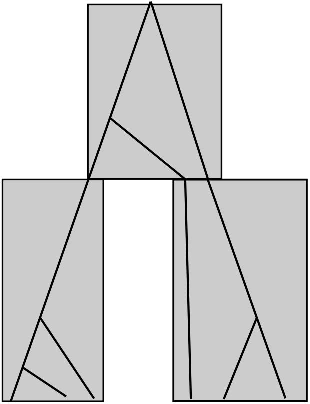
Coalescence times



Simplest case: $N_1 = N_2 = N_{ancestral}$

1. calculation for sample of size 2
2. $\mathbb{E} T_{11} = T_{22} = 1$
3. $\mathbb{E} T_{12} = 1 + t_{split}$

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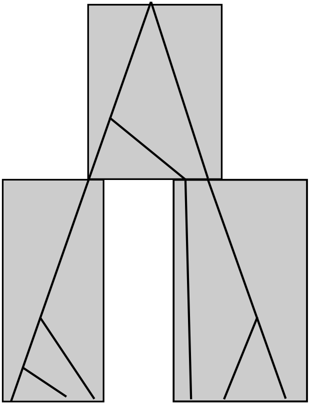

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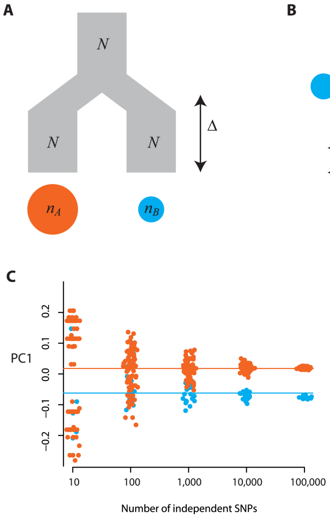
Structure often described using

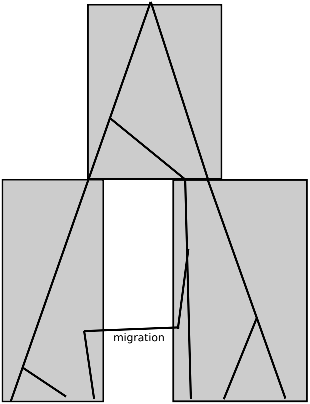
$$
\begin{aligned}
F_{ST} &= 1 - \frac{T_{within}}{T_{overall}} \\
&= 1 - \frac{T_{11} + T_{22}}{T_{12} + T_{11}/2 + T_{22}/2} \\
&= \frac{t_{split}}{2 + t_{split}}
\end{aligned}
$$

Principal componenet analysis



McVean (2009): PLoS Genetics

Isolation with migration



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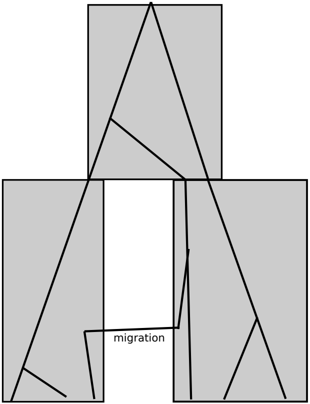

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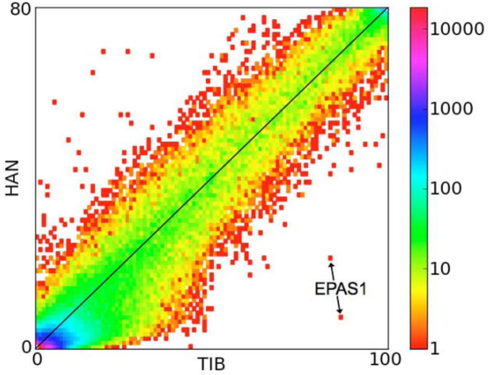
5. Lineages *migrate* at some rate m $(2, 3) \rightarrow (1, 4)$

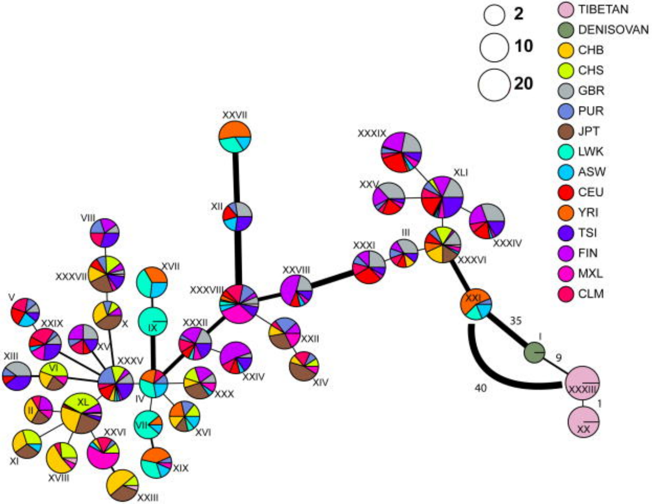
The 2D-SFS



Yi et al (2010): Science

- Matrix where M_{ij} is number of SNP at frequency i, j in pops A, B.
- For closely related populations, most mass is near diagonal.
- Outliers often biologically interesting

EPAS1



Huerta-Sanchez et al. (2014): Nature

Summary

1. Coalescent is a backwards-in-time model of evolution
2. Quantities directly related to sampling
3. Can easily simulate
4. Incorporate recombination, population size changes, migration
5. SFS is a key summary statistic (both for coalescent/diffusion)