momi: a new method for computing the multipopulation sample frequency spectrum

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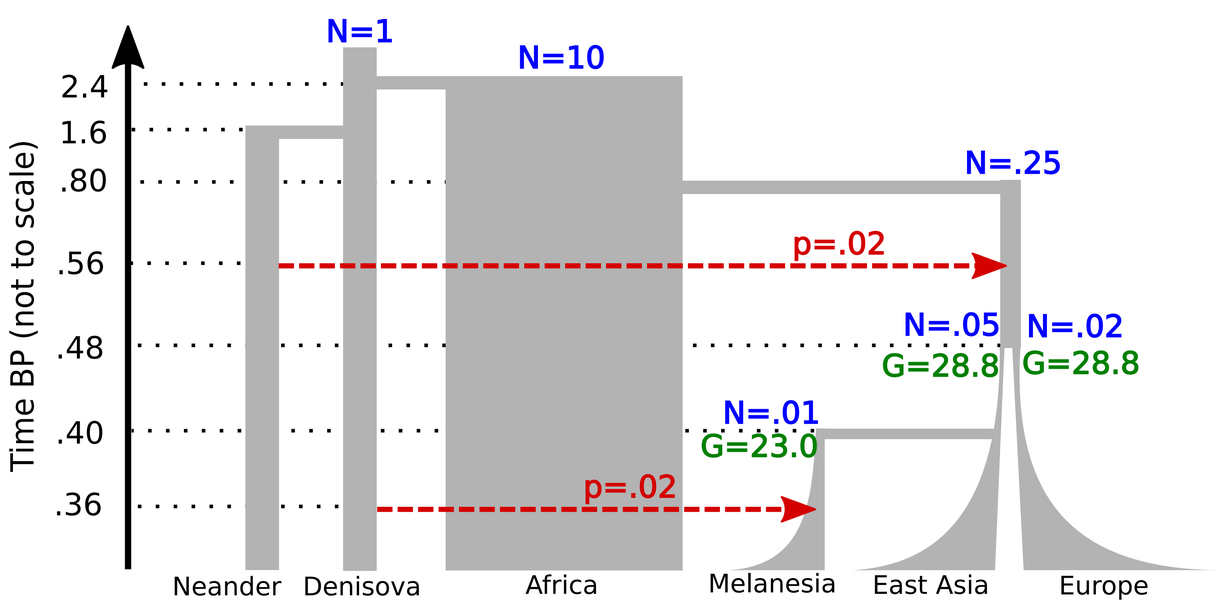
Sample Frequency Spectrum (SFS)

- Distribution of counts of mutant alleles observed at a site
- Used to summarize genetic data and infer biological parameters
- momi (MOran Models for Inference) is a program to compute the SFS for a neutral site under:
  - population size changes (including exponential growth)
  - population splits and mergers
  - pulse migration and admixture events

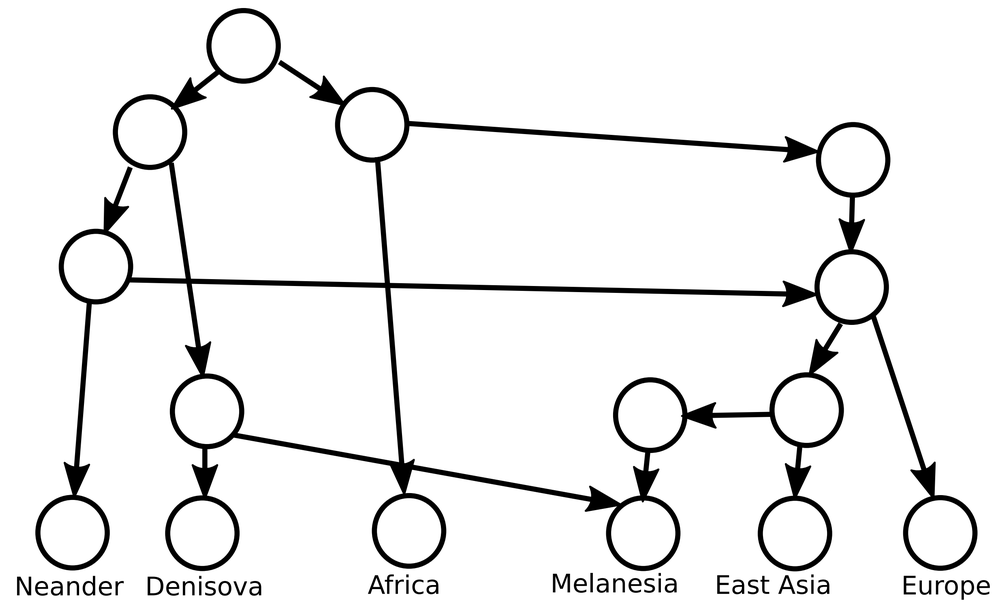
Our approach

- View demography as graphical model, apply variable elimination
  - aka "tree-peeling" when the demography is a tree
- Represent allele frequencies with Moran model
  - Equivalent to using the coalescent
- Polanski-Kimmel equations
  - Quickly and stably compute mutations arising in each subpopulation
- Automatic differentiation to compute gradient and Hessian

Demographic history as graphical model



(a) A demographic history with 18 parameters, very loosely based on human history. All parameters are in coalescent-scaled units.



(b) The same history, represented as a graphical model. The SFS is then computed via variable elimination. Each vertex represents the allele frequency of a particular subpopulation at a particular point in time.

Moran model

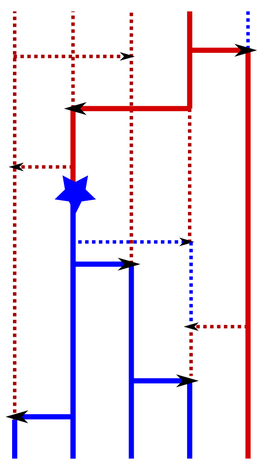
Moran model is a finite population model where lineages copy alleles onto each other at some rate λ.

We model alleles within each vertex v by a Moran model with n_v lineages.

- n_v = number of samples with some ancestry in v
- Copying rate $\lambda = \frac{1}{N(t)}$ inverse population size

Kingman's coalescent embedded within Moran model via sample genealogy.

- $\Rightarrow$ Moran is equivalent to using coalescent



Comparison with other population genetic models

Moran model: $O(n_v)$ states per vertex

- # derived alleles at time t

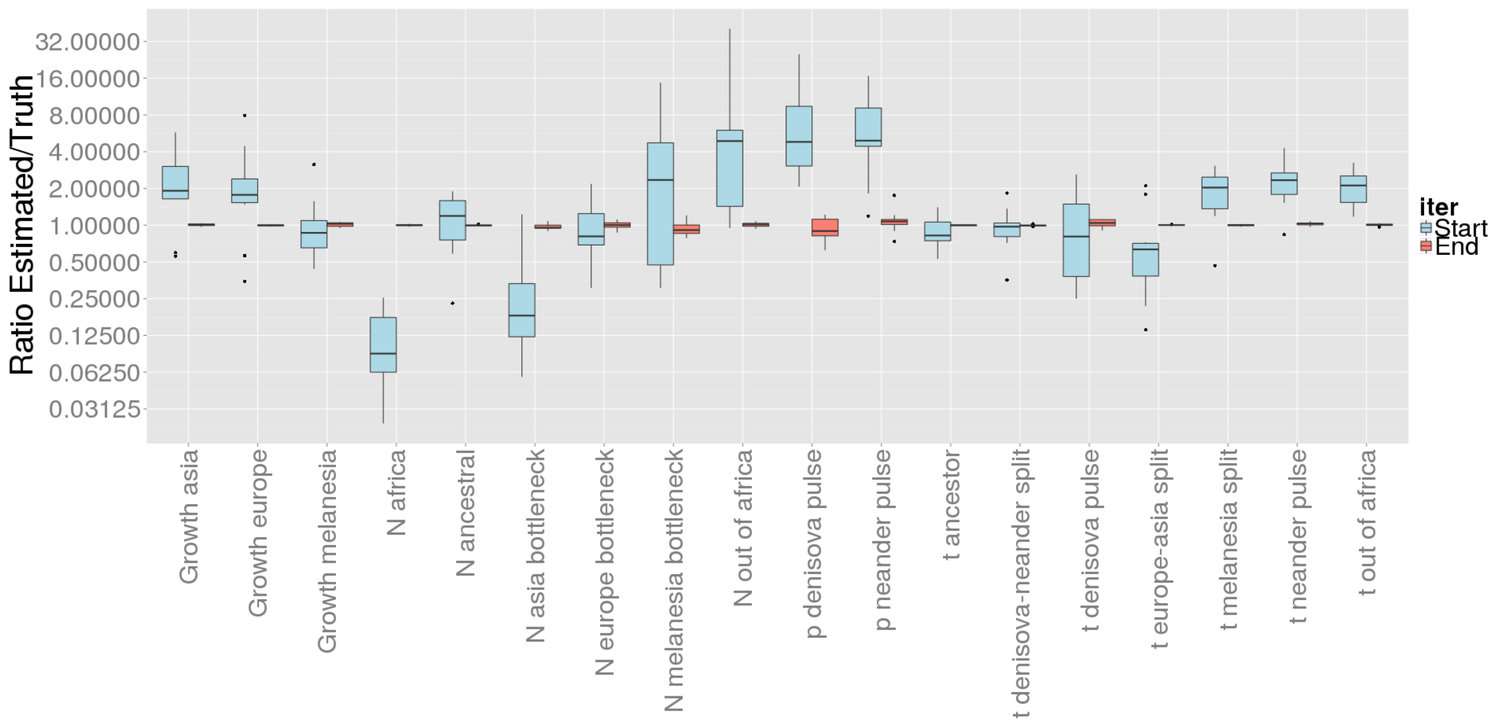
Coalescent: $O(n_v^2)$ states per vertex

- # ancestors and # derived alleles at time t

Diffusion: $O(D)$ states per vertex

- Continuous state space: fraction of population with derived allele
- "Discretize" into D states
- Typically $D \gg n_v$

Inference



Use automatic differentiation to compute gradient

- Infer parameters via hill-climbing algorithm

Example demography with 18 parameters:

- Simulated 10 datasets with ms
  - $n = 10$ samples per deme in Africa, East Asia, Melanesia, Europe.
  - $n = 2$ samples per deme in Neanderthal, Denisova.
- For each dataset:
  - Choose random initial parameters (shown in blue)
  - Find local optimum (shown in red) with single run of a conjugate gradient method
- On average, each dataset had 186505.9 SNPs and 1516.3 observed SFS entries.
- Average running time of parameter search on a single dataset (start to finish) was 13.3 hours.

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