

Polymorphism-aware phylogenetic models

MIC-Phy 2021

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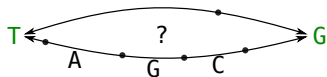
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Comparative genomics and phylogenetics

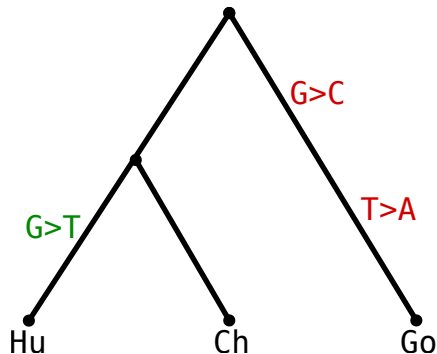
Alignment

Human		ACG	T	ACGT	
Chimp		ACG	G	ACGT	
Goril		ACG	G	AC	CA

Evolutionary model

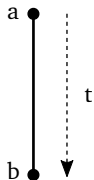


Phylogeny



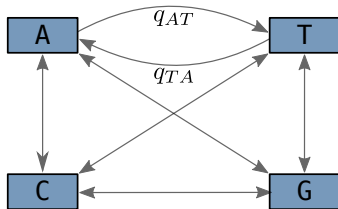
DNA substitution models

Evolution as a series of substitutions



$$a, b \in \{A, C, G, T\}$$

$$\Pr(X_t = b | X_0 = a) = \left(e^{t\mathbf{Q}} \right)_{ab}$$



State space $\{A, C, G, T\}$.

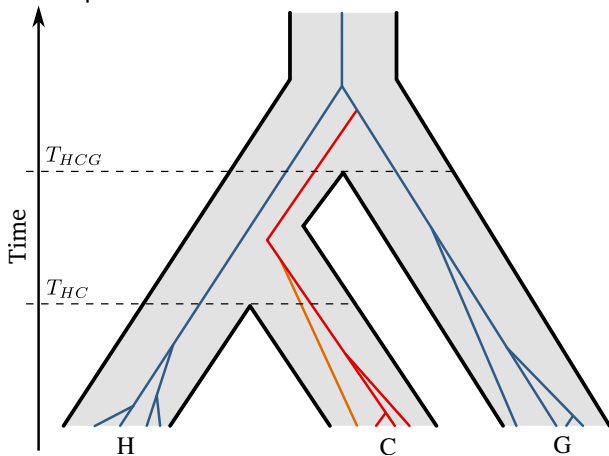
$$\mathbf{Q} = \begin{pmatrix} \cdot & q_{AC} & q_{AG} & q_{AT} \\ q_{CA} & \cdot & q_{CG} & q_{CT} \\ q_{GA} & q_{GC} & \cdot & q_{GT} \\ q_{TA} & q_{TC} & q_{TG} & \cdot \end{pmatrix}$$

Transition rate matrix.

Species are populations and recombination separates histories of genes

Incomplete lineage sorting

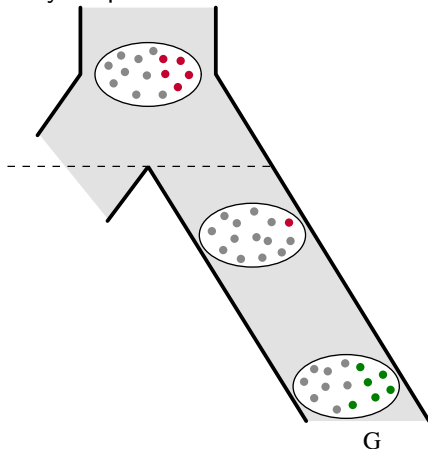
Multispecies coalescent models¹



¹Rannala and Yang (2003).

²De Maio et al. (2015) and Schrempf et al. (2016).

Polymorphism-aware models²



Neutral, K -allelic Wright-Fisher³ model

Discrete-time, discrete-state Markov chain

N constant haploid population size.

K alleles.

\mathbf{z}_τ state of population $(z_\alpha, \dots, z_\kappa)$ in generation τ ; $\|\mathbf{z}_\tau\|_1 = N$;
the total number of states is $\binom{N+K-1}{K-1}$.

\mathbf{U} $K \times K$ mutation probability matrix;
the elements describe the probability to mutate from one state to another.

The distribution of alleles in the next generation $\tau + 1$ is derived by sampling with replacement from the alleles of generation τ

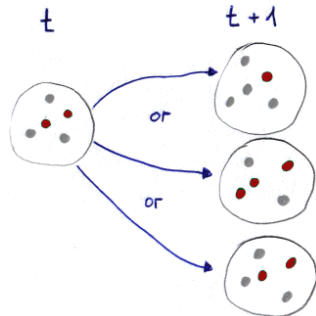
$$\mathbf{z}_{\tau+1} | \mathbf{z}_\tau \sim \text{Mult}(N, \frac{\mathbf{z}_\tau}{N} \mathbf{U}).$$

For $K = 4$, and $N = 10$, we have 286 states.

³Wright (1931) and Fisher (1930).

Neutral, K -allelic Moran⁴ model with mutation

Continuous-time, discrete-state Markov process



Individuals are randomly chosen to reproduce. The offspring is of the same type as the parent and replaces another randomly chosen individual from the population.

For $a, b \in \{\alpha, \dots, \kappa\}$ and with mutation rates q_{ab} , we have

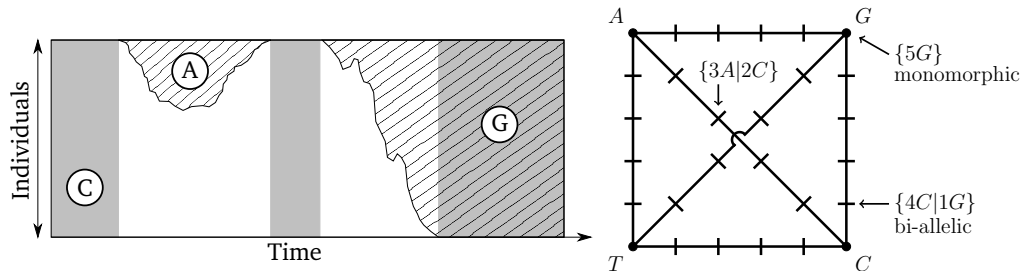
$$(\dots, z_a, \dots, z_b, \dots) \rightarrow (\dots, z_a - 1, \dots, z_b + 1, \dots)$$

$$\text{at rate } N \left(\frac{z_b}{N} \frac{z_a}{N} + \frac{z_a}{N} \frac{q_{ab}}{N} \right).$$

⁴Moran (1958).

Approximation for low mutation rates

Drift removes variation fast; disallow mutations when the population is polymorphic



Examples using nucleotides. Cartoon of evolving population with large size and state space for $N = 5$.

Population can only be

Monomorphic $(\dots, z_a = N, \dots) \equiv \{Na\}$; K states.

Bi-allelic $(\dots, z_a = i, \dots, z_b = N - i, \dots) \equiv \{ia|(N - i)b\}$; $\binom{K}{2}(N - 1)$ states.

For $K = 4$, and $N = 10$, we have 4+54 states.

Discrete multivariate boundary mutation model⁵

From the Moran model with mutation, we have

$$(\dots, z_a, \dots, z_b, \dots) \rightarrow (\dots, z_a - 1, \dots, z_b + 1, \dots)$$

at rate $\frac{z_a z_b}{N} + z_a \frac{q_{ab}}{N}.$

Transition rate matrix M

Boundary mutation leads to

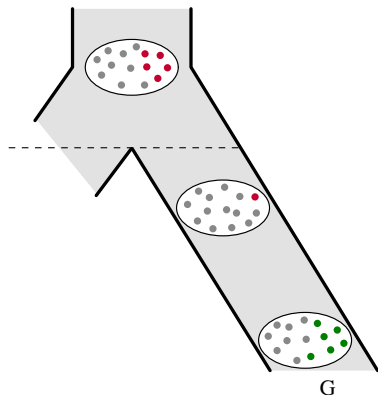
$$m_{\{Na\} \rightarrow \{(N-1)a|1b\}} = q_{ab},$$
$$m_{\{ia|(N-i)b\} \rightarrow \{(i\pm 1)a|(N-i\mp 1)b\}} = \frac{i(N-i)}{N}.$$

⁵Schrempf and Hobolth (2017).

Polymorphism-aware phylogenetic Model (PoMo)

Use discrete multivariate boundary mutation model with

- $K = 4$ nucleotides;
- *virtual* population size N ;
- transition rate matrix \mathbf{M} .

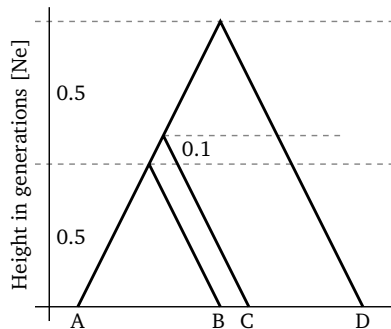


Likelihood calculation similar to DNA substitution models, for example,

$$\Pr(X_t = \{(N-1)a|1b\}) X_0 = \{Na\} = \left(e^{t\mathbf{M}}\right)_{\{Na\}\{(N-1)a|1b\}}.$$

Assessment of tree estimation error

Incomplete lineage sorting



Infer phylogeny from data.

Measure branch score distance between original and estimated species tree.

Simulate

- ① Up to 1000 gene trees with the multispecies coalescent model; 10 samples per species⁶.
- ② Sequences with 1000 base pairs per gene (HKY⁷ model); $\theta = 0.025$ ⁸.

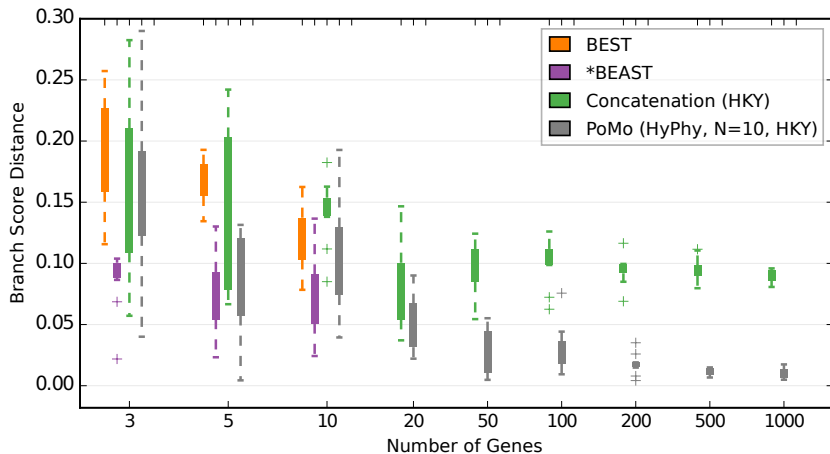
⁶MSMS, Ewing and Hermisson (2010).

⁷Hasegawa et al. (1985).

⁸SeqGen, Rambaut and Grassly (1997).

Tree estimation error

Incomplete lineage sorting, $1N_e$ generations height, 10 samples per species



BEST (Liu 2008), *BEAST (Heled and Drummond 2010), and HyPhy (Pond et al. 2005).

Exchangeabilities, stationary distributions, and reversibility

Some mathematical prerequisites

The mutation rates can be separated into

$$q_{ab} = r_{ab}\pi_b,$$

where

π_a is the stationary distribution of allele frequencies, and
 r_{ab} are the exchangeabilities.

If the mutation model is reversible, the exchangeabilities are symmetric $r_{ab} = r_{ba}$.

Theorem (Retention of reversibility of mutation model)

The discrete multivariate boundary mutation model is reversible if and only if the underlying mutation model is reversible.

Stationary distribution (reversible mutation model)

Theorem

For $K, N > 1$ and reversible mutation models, the discrete multivariate boundary mutation model defined by the transition rate matrix \mathbf{M} has a stationary distribution of

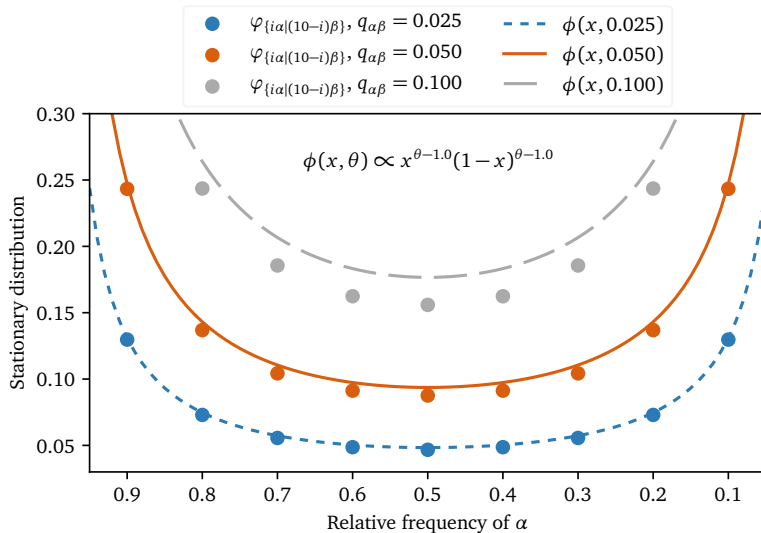
$$\varphi_{\{Na\}} = \frac{1}{Z} \pi_a,$$
$$\varphi_{\{ia|(N-i)b\}} = \frac{1}{Z} \pi_a \pi_b r_{ab} \left(\frac{1}{i} + \frac{1}{N-i} \right)$$

with normalization constant

$$Z = 1 + \sum_{k=1}^{N-1} \frac{1}{k} \sum_{\substack{a,b \\ a \neq b}} r_{ab} \pi_a \pi_b.$$

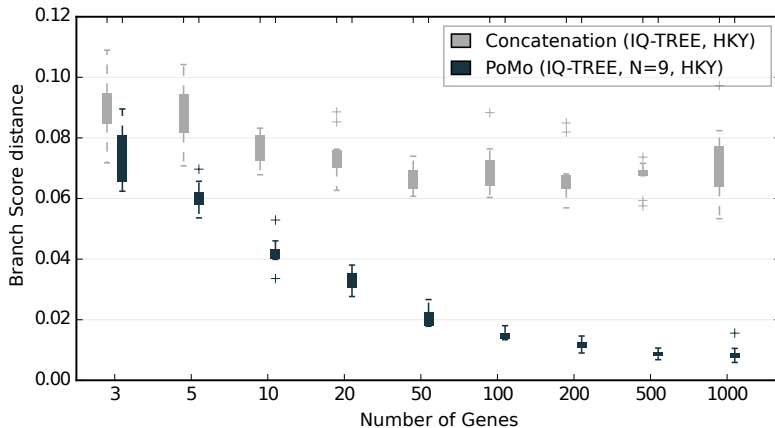
Stationary distribution

Alleles α and β ($K = 2$), $N = 10$, $q_{\alpha\beta} = q_{\beta\alpha} = \theta$; comparison to diffusion theory



Tree estimation error

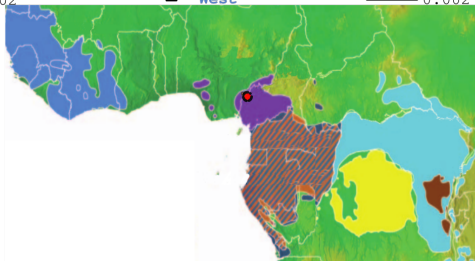
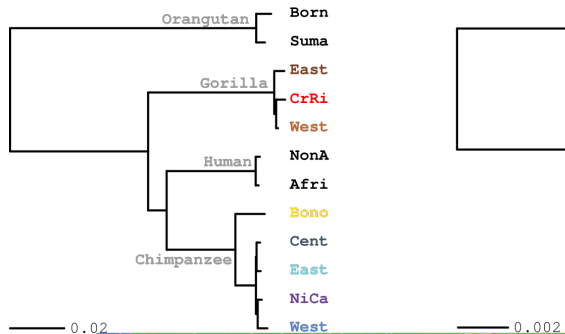
Yule⁹ tree with 60 species, $3N_e$ generations height, 10 samples per species



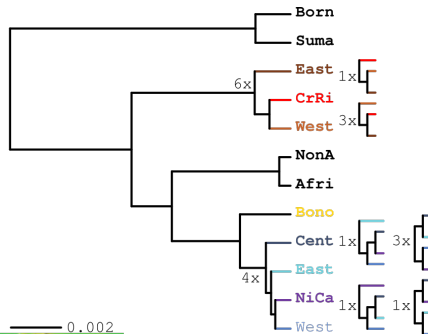
IQ-TREE (Minh et al. [2020](#)).

⁹Yule ([1925](#)).

PoMo IQ-TREE (HKY, N=10)



Concatenation (HKY)

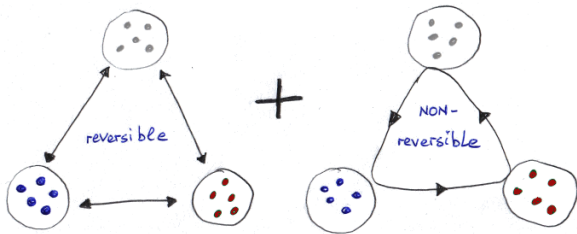


Prado-Martinez et al. (2013)

Separation of mutation rate matrix¹⁰

$$Q = Q^{\text{rev}} + Q^{\text{flux}},$$
$$q_{ab} = r_{ab}\pi_b + \phi_{ab}\pi_b.$$

Parameter	Description
π_a	Stationary distribution of allele frequencies
$r_{ab} = r_{ba}$	Symmetric exchangeabilities ($\sum_c r_{ac}\pi_c = 0$)
$\phi_{ab} = -\phi_{ba}$	Antisymmetric excess of flux ($\sum_c \phi_{ac}\pi_c = 0$)



Example with $K = 3$ and $N = 5$. Only boundary states are shown.

¹⁰Burden and Tang (2016) and Schrepf and Hobolth (2017).

Stationary distribution (general mutation model)

Theorem

For $K, N > 1$, the discrete multivariate boundary mutation model defined by the transition rate matrix \mathbf{M} has a stationary distribution of

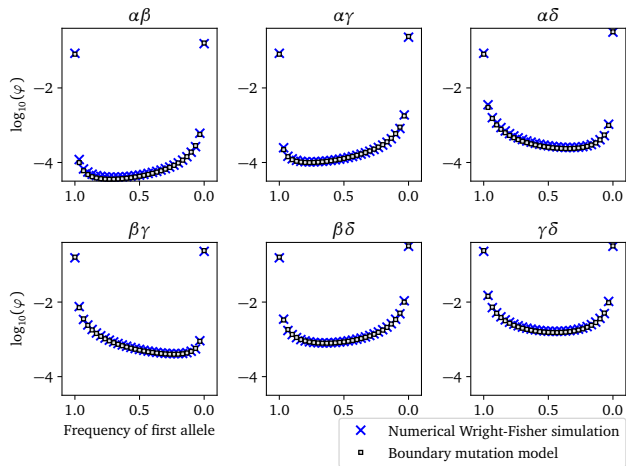
$$\varphi\{Na\} = \frac{1}{c} \pi_a,$$
$$\varphi\{ia|(N-i)b\} = \frac{1}{c} \pi_a \pi_b \left[r_{ab} \left(\frac{1}{i} + \frac{1}{N-i} \right) - \phi_{ab} \left(\frac{1}{i} - \frac{1}{N-i} \right) \right]$$

with normalization constant

$$c = 1 + \sum_{k=1}^{N-1} \frac{1}{k} \sum_{\substack{a,b \\ a \neq b}} r_{ab} \pi_a \pi_b.$$

Stationary distribution with flux

Alleles α , β , γ and δ ($K = 4$) and $N = 30$



The stationary distribution with parameters
 $r_{ab} = 0.01 \cdot (1, 2, 3, 4, 5, 6)$,
 $\pi_a = (0.1, 0.2, 0.3, 0.4)$ and
 $\phi_{ab} = 0.01 \cdot (-0.8, -1.7, 1.6, 3.3, -2.7, 1.3)$.

Summary

Idea of PoMo

Improve phylogenetic inference by modeling the evolution of populations and not of individuals.

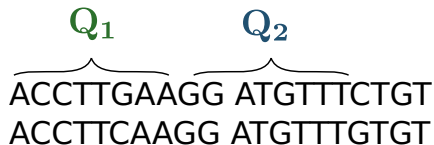
Discrete multivariate boundary mutation model

- ① Moran model.
- ② Approximation for low mutation rates.
- ③ Separation of mutation rate matrix Q .

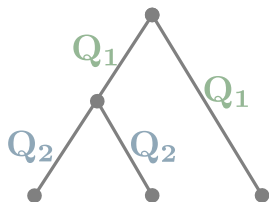
Stationary distribution fits well if $\theta < 0.1$.

Advanced mutation models¹¹

Partition models



Branch models



Mixture models

$$m_1 Q_1 + m_2 Q_2$$

ACCTTGAAGG
ACCTTCAAGG

Allelic selection

$$w_a = 1$$

$$w_b = 1 + s$$

¹¹Schrempf et al. (2019) and Borges et al. (2019).

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University





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