

Importance sampling: 4 taxa case

Data. 4 sequences for cats: cat, tiger, leopard, clouded leopard in phylip file `4taxa-cats.phy`:

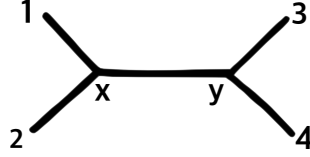
```
Cat  ATGTTTCATAAACCGGTGACTATTTTCAACTAATCACAACTGAGCTGGCATGGTGGGGACTGC...
CloudedLeopard ATGTTTCATAAACCGGTGACTATTTTCAACTAACCATCGCTTGGGCCGGTATAGTA...
Leopard  ATGTTTCATAAACCGGTGACTATTTTCAACCAATCACAAAGATAGCTGGCATGGTGGGGACTGC...
Tiger   ATGTTTCATAAACCGGTGACTATTTTCAACCAATCACAAAGATATTTGGTATAGTGGGGACTGC...
```

Conditional clade distribution. From the phylip input file, we obtain the conditional clade distribution from a sample bootstrapped NJ trees with the perl script `seq2ccdprobs.pl`.

Sample topology. From the conditional clade distribution, we sample one topology. Denote by $p_{ccd}(T)$ the probability of sampling the particular topology T from the conditional clade distribution.

Sample branch lengths given a topology. Let T be the 4-taxon topology sampled from the conditional clade distribution.

1. Choose one tip at random to exclude. Denote the other three sequences by seq_1, seq_2, seq_3 , where seq_1, seq_2 are sisters.



2. Compute the matrices of counts between all pairs of the three sequences: x_{12}, x_{13}, x_{23} , and simulate the branch length between each pair with Tamura-Nei (TN) model, and $\eta = 0.5$ (see JCvsTN.pdf for details on choosing TN and η): d_{12}, d_{13}, d_{23}
3. Compute the distances between seq_1, seq_2 and its parent x :

$$d_{1x} = \frac{(d_{12} + d_{13} - d_{23})}{2}$$

$$d_{2x} = \frac{(d_{12} + d_{23} - d_{13})}{2}$$

4. Convert $seq_1, seq_2, seq_3, seq_4$ to matrices like

$$S_{cat} = \begin{array}{c} \text{Cat ATGTTTCAT...} \\ \begin{array}{cccccccc} \text{A} & 1 & 0 & 0 & 0 & 0 & 0 & 1 & \dots \\ \text{C} & 0 & 0 & 0 & 0 & 0 & 1 & 0 & \dots \\ \text{G} & 0 & 0 & 1 & 0 & 0 & 0 & 0 & \dots \\ \text{T} & 0 & 1 & 0 & 1 & 1 & 0 & 0 & \dots \end{array} \end{array}$$

5. Estimate the sequence distribution at x from the sequences seq_1, seq_2 . The formula for the likelihood at site j for node x , parent of 1, 2 is:

$$L_j^x(s) = \left[\sum_{i \in \{A, C, G, T\}} P_{si}(d_{1x}) L_j^1(i) \right] * \left[\sum_{i \in \{A, C, G, T\}} P_{si}(d_{2x}) L_j^2(i) \right]$$

$s \in \{A, C, G, T\}$

where

$$L_j^k(i) = S_k[i, j], k = 1, 2$$

$$P(t) = \exp(\hat{Q}t)$$

So that the sequence matrix for x is given by S_x :

$$S_x[i, j] = \frac{\pi_i L_j^x(i)}{\sum_{i=1}^4 \pi_i L_j^x(i)}$$

6. Compute the count matrix between seq_3, seq_4 : x_{34} and simulate the branch length d_{34} with TN model and $\eta = 0.5$
7. Compute the equivalent to the count matrix between x and seq_3, seq_4 :

$$x_{x3} = \sum_{j=1}^{nsites} S_3[, j] * S_x[, j]^T$$

8. Simulate branch lengths d_{3x}, d_{4x} with TN model and $\eta = 0.5$
9. Compute the distances between seq_3, seq_4 and its parent y , and between x, y :

$$d_{3y} = \frac{(d_{34} + d_{3x} - d_{4x})}{2}$$

$$d_{4y} = \frac{(d_{34} + d_{4x} - d_{3x})}{2}$$

$$d_{xy} = \frac{(d_{3x} + d_{4x} - d_{34})}{2}$$

10. Compute the density of the branch lengths given the topology, denoted as $f_{TN}(d|T)$ for $d = (d_{1x}, d_{2x}, d_{xy}, d_{3y}, d_{4y})$. We simulate the branch lengths: $d_{12}, d_{13}, d_{23}, d_{3x}, d_{4x}, d_{34}$ with the TN model as gamma random variables. These 6 branch lengths were simulated independently, so the joint density is given by

$$f(d_{12}, d_{13}, d_{23}, d_{3x}, d_{4x}, d_{34}) = \prod_i \frac{\beta_i^{\alpha_i}}{\Gamma(\alpha_i)} d_i^{\alpha_i-1} \exp(-\beta_i d_i)$$

We then transform those branch lengths into the desired parameters (keeping the variable d_{13} for the transformation to be bijective):

$$\begin{aligned} d_{1x} &= \frac{(d_{12} + d_{13} - d_{23})}{2} \\ d_{2x} &= \frac{(d_{12} + d_{23} - d_{13})}{2} \\ d_{13} &= d_{13} \\ d_{3y} &= \frac{(d_{34} + d_{3x} - d_{4x})}{2} \\ d_{4y} &= \frac{(d_{34} + d_{4x} - d_{3x})}{2} \\ d_{xy} &= \frac{(d_{3x} + d_{4x} - d_{34})}{2} \end{aligned}$$

The determinant of the Jacobian in absolute value is 4. Thus, the joint density for the transformed variables is

$$\begin{aligned} f(d_{1x}, d_{2x}, d_{3y}, d_{4y}, d_{xy}, d_{13}) &= \left[\prod_i \frac{\beta_i^{\alpha_i}}{\Gamma(\alpha_i)} \right] (d_{1x} + d_{2x})^{\alpha_{12}-1} \exp(-\beta_{12}(d_{1x} + d_{2x})) \\ &\quad * d_{13}^{\alpha_{13}-1} \exp(-\beta_{13}d_{13}) \\ &\quad * (d_{13} - d_{1x} + d_{2x})^{\alpha_{23}-1} \exp(-\beta_{23}(d_{13} - d_{1x} + d_{2x})) \\ &\quad * (d_{3y} + d_{xy})^{\alpha_{3x}-1} \exp(-\beta_{3x}(d_{3y} + d_{xy})) \\ &\quad * (d_{4y} + d_{xy})^{\alpha_{4x}-1} \exp(-\beta_{4x}(d_{4y} + d_{xy})) \\ &\quad * (d_{3y} + d_{4y})^{\alpha_{34}-1} \exp(-\beta_{34}(d_{3y} + d_{4y})) * 4 \end{aligned}$$

We want to integrate out d_{13} ,

$$\begin{aligned} f_{TN}(d_{1x}, d_{2x}, d_{3y}, d_{4y}, d_{xy}) &= \int_0^\infty f(d_{1x}, d_{2x}, d_{3y}, d_{4y}, d_{xy}, d_{13}) dd_{13} \\ &= \left[\prod_i \frac{\beta_i^{\alpha_i}}{\Gamma(\alpha_i)} \right] (d_{1x} + d_{2x})^{\alpha_{12}-1} \exp(-\beta_{12}(d_{1x} + d_{2x})) \\ &\quad * 4 \exp(-\beta_{23}(-d_{1x} + d_{2x})) \\ &\quad * (d_{3y} + d_{xy})^{\alpha_{3x}-1} \exp(-\beta_{3x}(d_{3y} + d_{xy})) \\ &\quad * (d_{4y} + d_{xy})^{\alpha_{4x}-1} \exp(-\beta_{4x}(d_{4y} + d_{xy})) \\ &\quad * (d_{3y} + d_{4y})^{\alpha_{34}-1} \exp(-\beta_{34}(d_{3y} + d_{4y})) \\ &\quad * \int_0^\infty d_{13}^{\alpha_{13}-1} (d_{13} - d_{1x} + d_{2x})^{\alpha_{23}-1} \exp(-(\beta_{13} + \beta_{23})d_{13}) dd_{13} \end{aligned}$$

The integral is finite, but it does not have an analytic expression. The integral is a function of d_{1x}, d_{2x} . We will ignore this integral for the moment, and assume it is a constant.

Importance weight. Let $p(T)$ denote the prior distribution of tree T , and let $L(T, d)$ denote the likelihood of T under the GTR model.

$$L(T, d) = \prod_k L_k(T, d)$$

$$L_k(T, d) = \sum_{i=1}^4 \sum_{j=1}^4 \pi_i P_{ij}(d_{xy}) P_{i1}(d_{1x}) P_{i2}(d_{2x}) P_{j3}(d_{3y}) P_{j4}(d_{4y})$$

Then, the importance weight is

$$w(T) = \frac{p(T)L(T, d)}{g(T)}$$

$$g(T) = p_{ccd}(T)f_{TN}(d|T)$$

Algorithm 1: Importance sampling

- Input:** PHYLIP or NEXUS file with DNA sequences for 4 taxa; likelihood model (e.g. GTR) and prior
- Compute the conditional clade probabilities by bootstrapping and NJ: p_{ccd}
 - **for** $i = 1$ **to** N **do**
 - Sample a topology $T \sim p_{ccd}$
 - Sample branch lengths from TN model $d|T \sim f_{TN}(d|T)$
 - Compute importance weight $w(T)$ with likelihood and prior
 - Normalize importance weights
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