**Importance sampling: 4 taxa case**

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

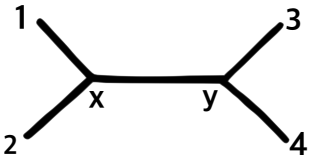
```
Cat ATGTTCATAAACCGGTGACTATTTTCAACTAATCACAAACTGAGCTGGCATGGTGGGGACTGC...
CloudedLeopard ATGTTCATAAACCGCTGACTATTTTCAACTAACCATCGCTTGGGCCGGTATAGTA...
Leopard ATGTTCATAAACCGCTGACTATTTTCAACCAATCACAAAGATAGCTGGCATGGTGGGGACTGC...
Tiger ATGTTCATAAACCGCTGACTATTTTCAACCAATCACAAGGATATTTGGTATAGTGGGGACTGC...
```

**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 $\eta$): $d_{12}, d_{13}, d_{23}$

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

`Cat ATGTTCAT...`

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

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 $d = (d_{1x}, d_{2x}, d_{xy}, d_{3y}, d_{4y})$. how to do this? Bret email: One issue is that we don't really have a bijection.... For the 4-taxon tree, we generate 3 gamma random variables and then 3 more; 6 rvs go to 5 branch lengths. As the tree gets bigger, this difference gets bigger. We discard the distance from the cherry parent to the other node. At one point I considered saving it, but this made the rest of the algorithm messy if we had to keep track of this distance. So, if we add each of these as sort of an auxiliary rv, then we can get the bijection. For the density of the actual branch lengths, we integrate out the auxiliary rvs and hopefully get the same answer.

**Importance weight.** Let $p(T)$ denote the prior distribution of tree $T$ (for topology only, or with bl?), and let $L(T, d)$ denote the likelihood of $T$ under the GTR model.

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

(likelihood correct?)

Then, the importance weight is

$$w(T) = \frac{p(T)L(T, d)}{g(T)}$$
$$g(T) = p_{ccd}(T) f_{TN}(d|T)$$

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**Algorithm 1:** Importance sampling

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**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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