Algorithms in Computational Biology, 2019
Exercise 3 - Evolution

Due date: 20/01/2019

Please submit a tar file containing the code (Python3), a README file and a pdf containing plots and answers.

1 MLE for Branch Length

Suppose we are given two aligned sequences $a_1, ..., a_n$ and $b_1, ..., b_n$ (assume no gaps). In class we derived the following probabilistic model for two single character sequences:

$$P(a \xrightarrow{t} b) = P(X^{t_0+t} = b | X^{t_0} = a) = [e^{tR}]_{a,b}$$

We want to derive the MLE for branch length for the two sequences, e.g:

$$\hat{t} = \arg\max_t \prod_i \pi_{a_i} [e^{t\mathbf{R}}]_{a_i,b_i}$$

Assume R is the Jukes-Cantor rate matrix introduced in class with $\alpha = \frac{1}{4}$:

$$\mathbf{R}_{\mathrm{JC}}(\alpha) = \begin{pmatrix} -3\alpha & \alpha & \alpha & \alpha \\ \alpha & -3\alpha & \alpha & \alpha \\ \alpha & \alpha & -3\alpha & \alpha \\ \alpha & \alpha & \alpha & -3\alpha \end{pmatrix}$$

with transition probabilities:

$$P_{JC}(a \xrightarrow{t} b) = \begin{cases} \frac{1}{4}(1 + 3e^{-4\alpha t}) & a = b \\ \frac{1}{4}(1 - e^{-4\alpha t}) & a \neq b \end{cases}$$

1. Define the sufficient statistics for this likelihood and derive equation for calculating the maximum-likelihood estimator $\hat{t}$.

2. **Building a sampler for a branch**

   (a) Given distance t and character a build a procedure that samples b from $P_{JC}(a \xrightarrow{t} b)$.

   (b) Use the procedure to generate N samples of b and compare between the actual frequency of b and the predicted frequency (based on the JC model). Repeat the process for $t = 0.15, 0.4, 1.1$ and $N = 10, 100, 1000$.

   (c) Discuss your results. What are your conclusions about the sampling process?

   Submit a table/graph that summarizes the comparison and your code.

3. **Estimating the evolutionary distance**

   (a) Now you will use the sampler that you wrote to sample a pair of nucleotides (a, b). Write a procedure that given t, samples a from an uniform distribution and b using the sampler.

   (b) Use the procedure from the previous item to sample a pair of sequences of length N nucleotides that are distance t from each other (i.e., apply the procedure above N times).

   Repeat this procedure M times, and examine the relation between the "real" t you used in generating the data and the MLE estimate.

   For each value of t, visualize the distribution of the estimated distances. Plot the box-plot of estimates for each value of $t = 0.15, 0.4, 1.1$ with $N = 500$ and $M = 100$.

   (c) What are your conclusions about the branch length estimate? How will it affect distance-based methods for tree reconstruction?

2 Probabilistic Model of Evolution

Suppose we are given a binary tree T with leaves labeled 1...n and n-1 internal nodes. Assume 2n-1 is the root of the tree and let $\tau = \{t_{ij} | (i \xrightarrow{t_{ij}} j) \in T\}$ be the set of branch lengths.

Let $X_1, X_2, ...X_n, ...X_{2n-1}$ be random variables representing the characters in the tree. Then we derived:

$P(X_1, X_2, ...X_{2n-1}) = P(X_{2n-1}) \prod_{(i \to j) \in T} P(X_i \xrightarrow{t_{ij}} X_j)$

(We sample the root and then sample each node given its parent)

1. Show that if $P(a \xrightarrow{t} b) = [e^{tR}]_{a,b}$ and $P(X_{2n-1} = a) = \pi_a$ for the matching stationary distribution, then we can write the probability:

   $P(X_1, X_2, ...X_{2n-1}) = [\prod_i \pi_{X_i}] \prod_{(i \to j) \in T} \frac{[e^{t_{ij}R}]_{X_i X_j}}{\pi_{X_j}}$

2. Now assume the underlying Markov process is reversible. Recall the Detailed Balance property defined in class for such a case:

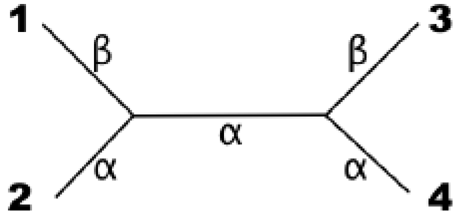
   $\forall a, b, t \; \pi_a P(a \xrightarrow{t} b) = \pi_b P(b \xrightarrow{t} a)$. Then use the formula derived above to show that re-rooting of the tree will not change the joint distribution.

3 Quad-trees

In this exercise we will examine the ability to recover trees with four leaves.

1. **Sampling from a given topology**

   (a) Consider a tree with the following topology:

   Write a procedure that samples from the tree. (Hint: Choose a root, sample its value, and then proceed along the branches using the code from Question 1.)

   (b) Sample a multiple sequence alignment (MSA) with N columns using the procedure from the previous section.

   Now let us consider this MSA as input for tree learning. Calculate the estimated time distance between the sequences using the Jukes-Cantor method from Question 1. What is the preferred tree based on the Neighbor Joining algorithm (you can write code for evaluating the three different topologies over four species). Repeat this process M times and compute the percent of correct reconstructions.

   Repeat the process for the following values of α, β: $(0.1, 0.1), (0.5, 0.1), (0.1, 0.5)$, $(0.5, 0.5)$, with $N = 1000$ and $M = 100$.

   (c) What are your conclusions?

   Submit the graphs and your code.