Phylogenetic inference using maximum likelihood

Comparative Genomic Analyses

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Phylogeny inference

Sequences evolve according to an unknown tree, so within the phylogenetic framework, we want to estimate it.

- tree structure or topology
- branch lengths
- model of sequence evolution (JC, GTR ...) and respective parameters

Maximum likelihood principle

The likelihood function tells us the probability of the data given a set of parameters.

$$L = p(D|\tau, \theta)$$

- D is a set of aligned sequences
- τ represents the tree: branch lengths and topology
- θ represents the model of evolution parameters: substitution rates

Maximum likelihood principle

Some parameters produce the sequences with higher probability than others

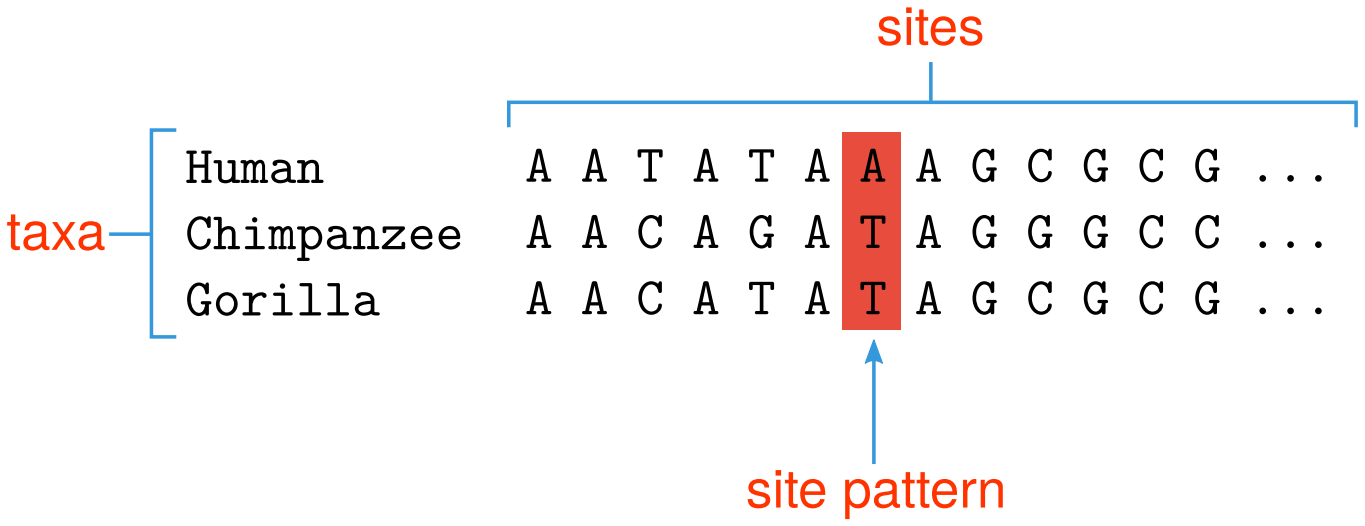
- we want the tree topology, branch lengths, and model parameters that best explain the observed the sequences: i.e., $\hat{\tau}$ and $\hat{\theta}$ that maximize the **likelihood function**

$$L = p(D|\hat{\tau}, \hat{\theta})$$

- $\hat{\tau}$ and $\hat{\theta}$ are the **maximum likelihood estimates**

Alignment and site patterns

A sequence alignment includes information from N taxa and S sites.



- a **site pattern** includes information from a single site an alignment is a collection of site patterns

Alignment and site patterns

The probability of the whole alignment can be obtained from the probability of each site pattern.

$$p(D|\tau,\theta) = \prod_{i=1}^{S} p(d_i|\tau,\theta)$$

- D is the whole alignment and d_i the i-th site pattern
- assume independent evolution at each site

Probability of a site pattern

The goal is to compute the probability of each and every observed site patterns in an alignment of N sequences.

```
Human       A A T A T A A A G C G C G ...
Chimpanzee  A A C A G A T A G G G C C ...
Gorilla     A A C A T A T A G C G C G ...
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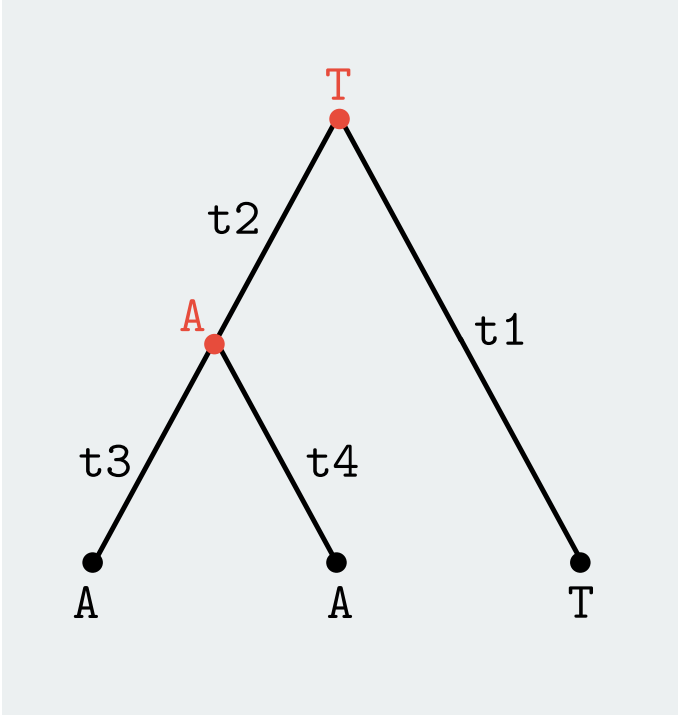
$$p(D|\tau,\theta) = p(\{AAA\}|\tau,\theta) \times p(\{AAA\}|\tau,\theta) \times p(\{TCC\}|\tau,\theta)...$$

- calculating $p(d_i|\tau,\theta)$ is a small likelihood problem

Probability of a site pattern

The probability of a site pattern given the tree, the model of evolution and the ancestral states

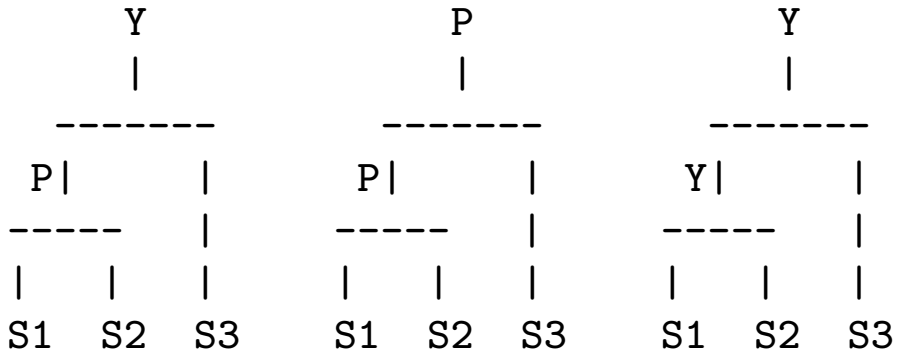


$$p(\{A, T, T\}|\tau, \theta) = p(T \to T|t_1) \times p(T \to A|t_2) \times p(A \to A|t_3) \times p(A \to A|t_4)$$

Probability of a site pattern

Exercise

The pyrimidine $Y = \{C, T\}$ and purine $P = \{A, G\}$ content in a certain site of a protein coding genes, was observed for three species: $\{S_1, S_2, S_3\} = \{P, P, Y\}$. Despite one does not know the species tree and the ancestral states, six scenarios for the evolution of this site were proposed:



Assuming that transitions between pyrimidines and purines occur with probability

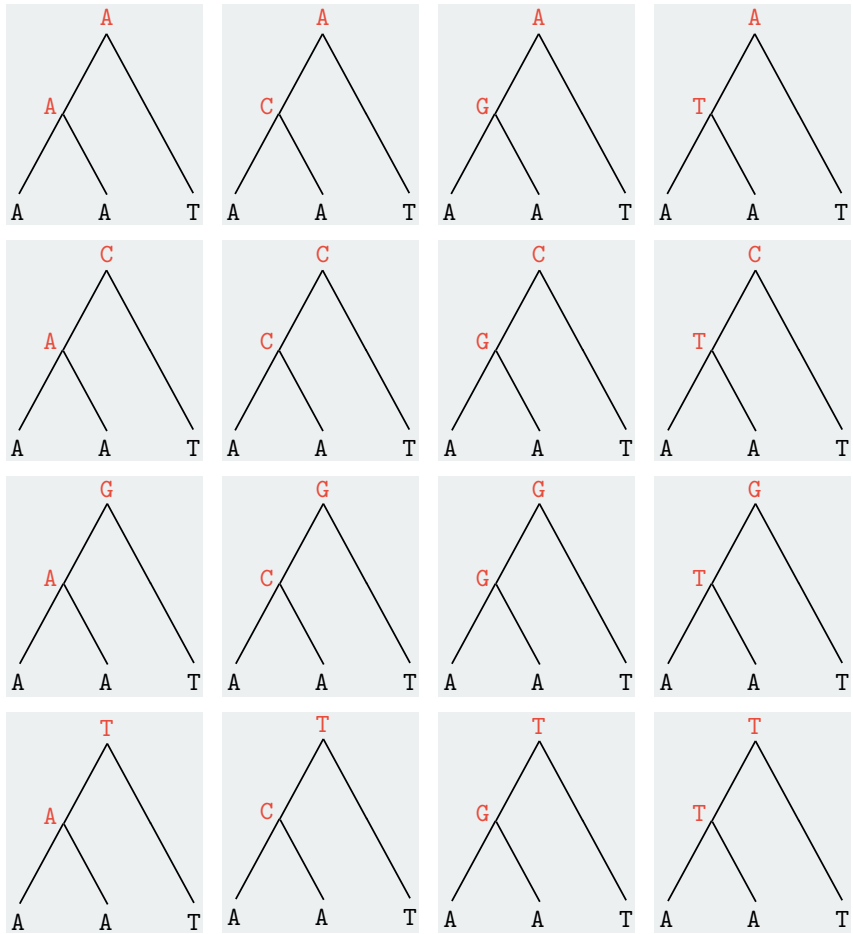
$$\begin{array}{c} \\ P \\ Y \end{array} \begin{array}{c} \begin{array}{cc} P & Y \end{array} \\ \begin{bmatrix} 0.9 & 0.1 \\ 0.2 & 0.8 \end{bmatrix} \end{array},$$

what is the most likely scenario?

Probability of a site pattern

We know how to calculate the likelihood of a site patterns when the ancestral states and the topology are both known.

- the ancestral states are unknown
- there are $n-1$ internal nodes in a tree with n taxa meaning that there are 4^{n-1} possible sets of ancestral states
- efficient algorithms exist: Felsenstein's pruning algorithm
  Felsenstein (1981)



Maximum likelihood tree

A possible approach to finding the maximum likelihood tree.

- maximizing the likelihood of an alignment for a given tree and model parameters is feasible, but we want the tree that best described the data
- try out several trees and find the one that maximizes the likelihood function

Maximum likelihood tree

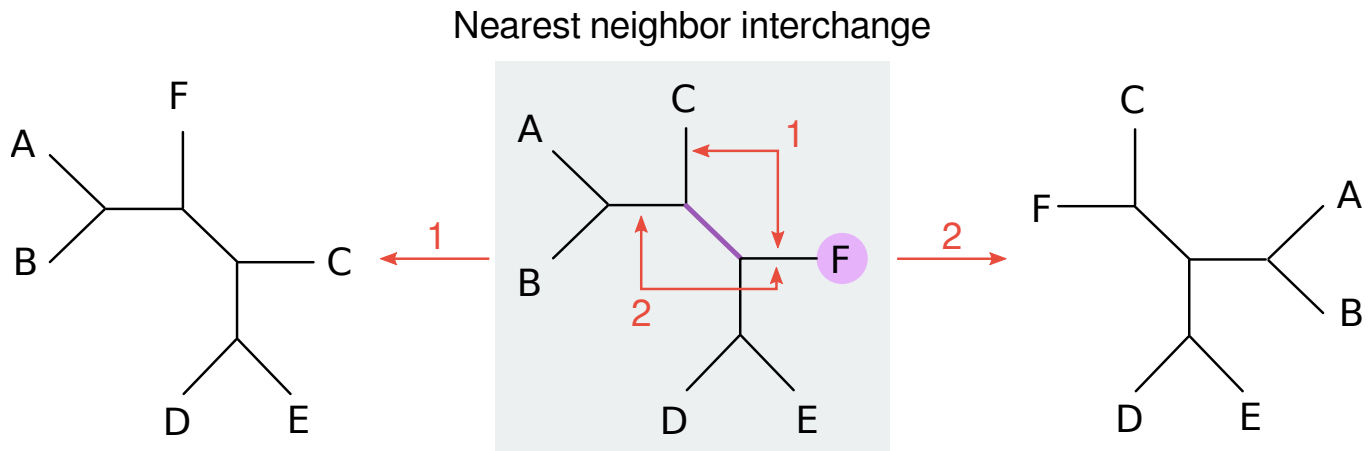
Finding the maximum likelihood tree has some computational limitations.

- there is a huge space of possible topologies
- testing all possible trees is just impossible, even for moderately sized data sets

number of taxa	possible unrooted trees
3	1
5	15
10	2 027 025
50	8.5×10^{74}
100	5.1×10^{182}

Maximum likelihood tree

Because testing all the possible trees is not computationally feasible, several algorithms are used to suggest reasonable trees.



- **full-tree arrangement operations**: change the structure of a given tree within its neighborhood

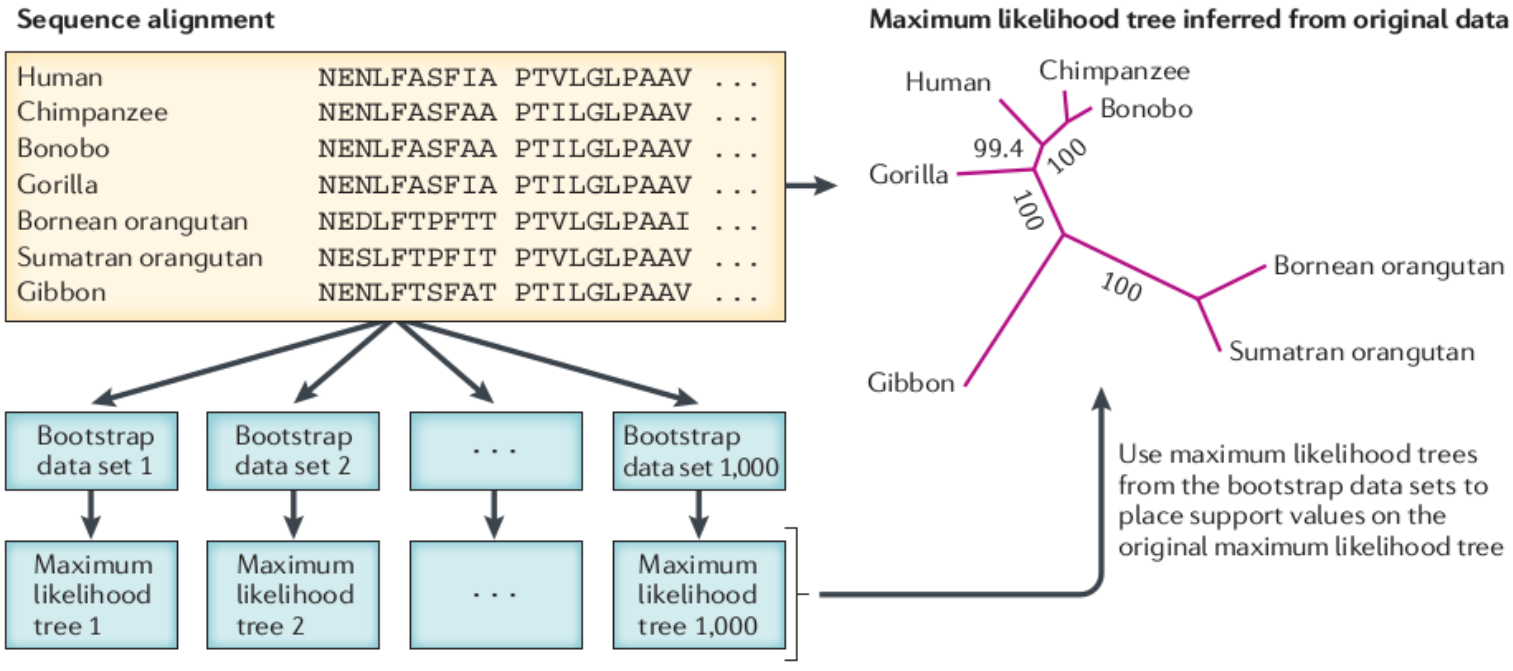
Maximum likelihood tree

Several measures are used to assess the certainty of a tree or its clades: the most widely used approach is the **bootstrapping**.

Efron (1979) and Felsenstein (1985)

- pseudo-alignments are created by subsetting the alignment
- pseudo-trees are inferred for each pseudo-alignment
- bootstraps represent the number of times a certain clade is present in the pseudo-trees

Maximum likelihood tree



Yang & Rannala (2012)

Literature

The Phylogenetic Handbook by Lemey, Salemi and Vandamme (2009) Cambridge University Press

- Chapter 6: sections 6.1, 6.2 and 6.3, 6.4 and 6.5