Introduction to Phylogenetics

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Melbourne Integrative Genomics workshop

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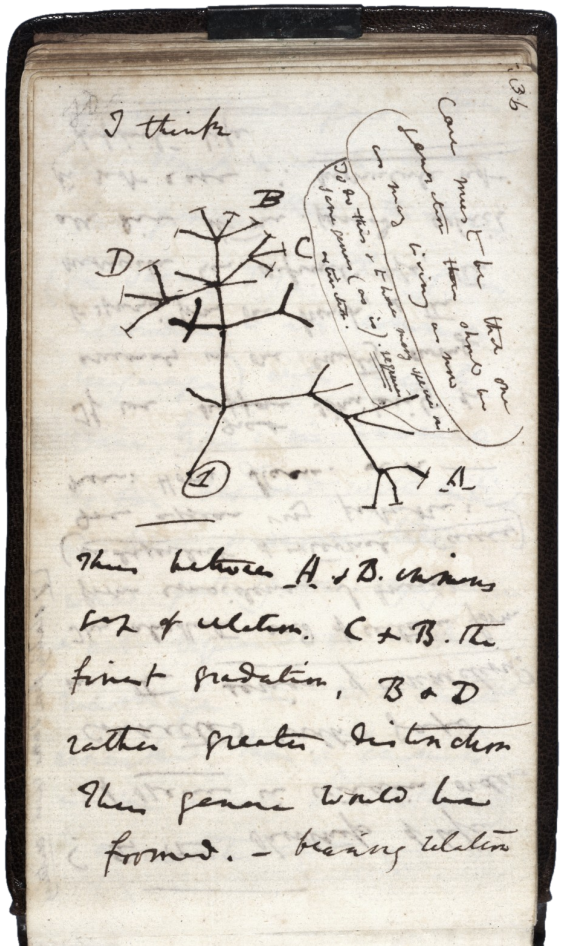
The combination of these two processes produces what we call the Tree of Life.

Ancient phylogenetics



(Darwin's notes, 1837)

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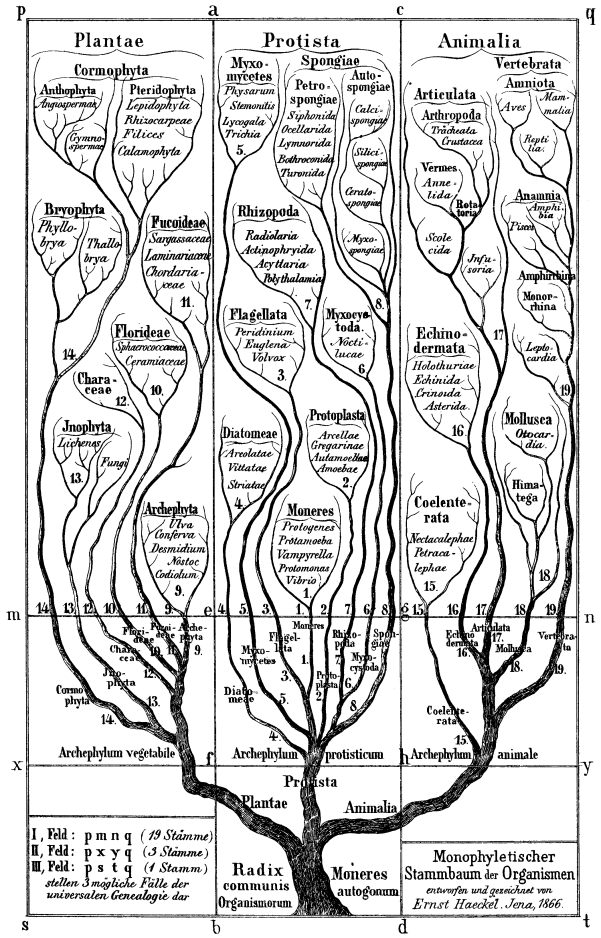
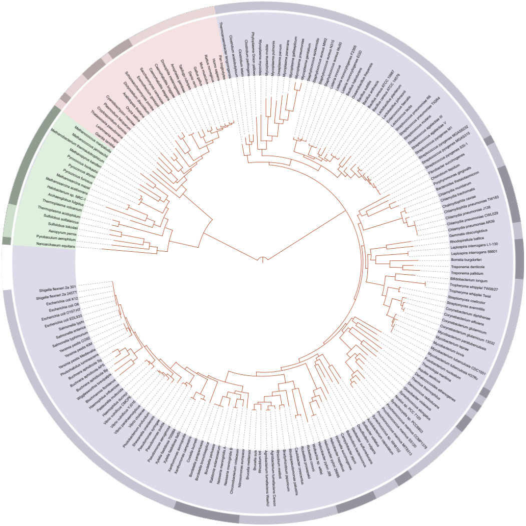


(Haeckel, 1866)

A more modern tree



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In many cases, the samples also come from different times (Covid-19 trees or ancient DNA).

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We will consider only binary trees, where each internal (non-root) node has degree 3.

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Additionally, each branch may have a number corresponding to it, representing evolutionary distance.

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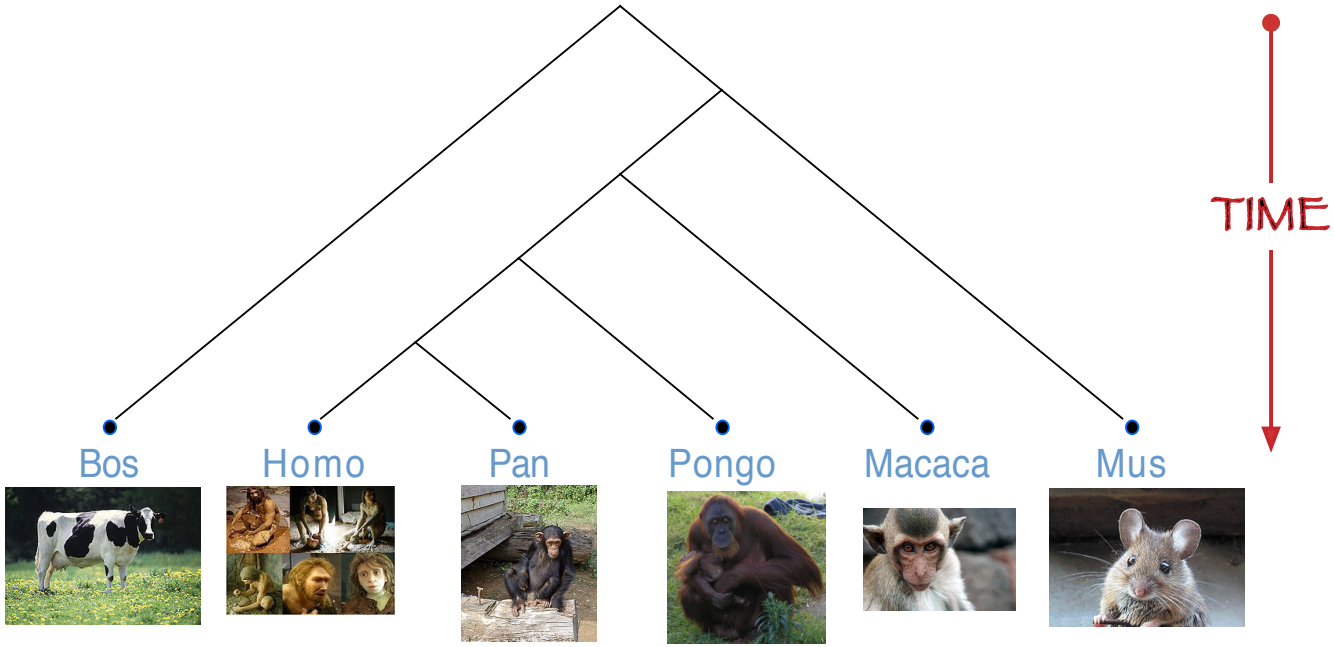

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- Each branch represents the evolution of one sample from ancestor to descendant.

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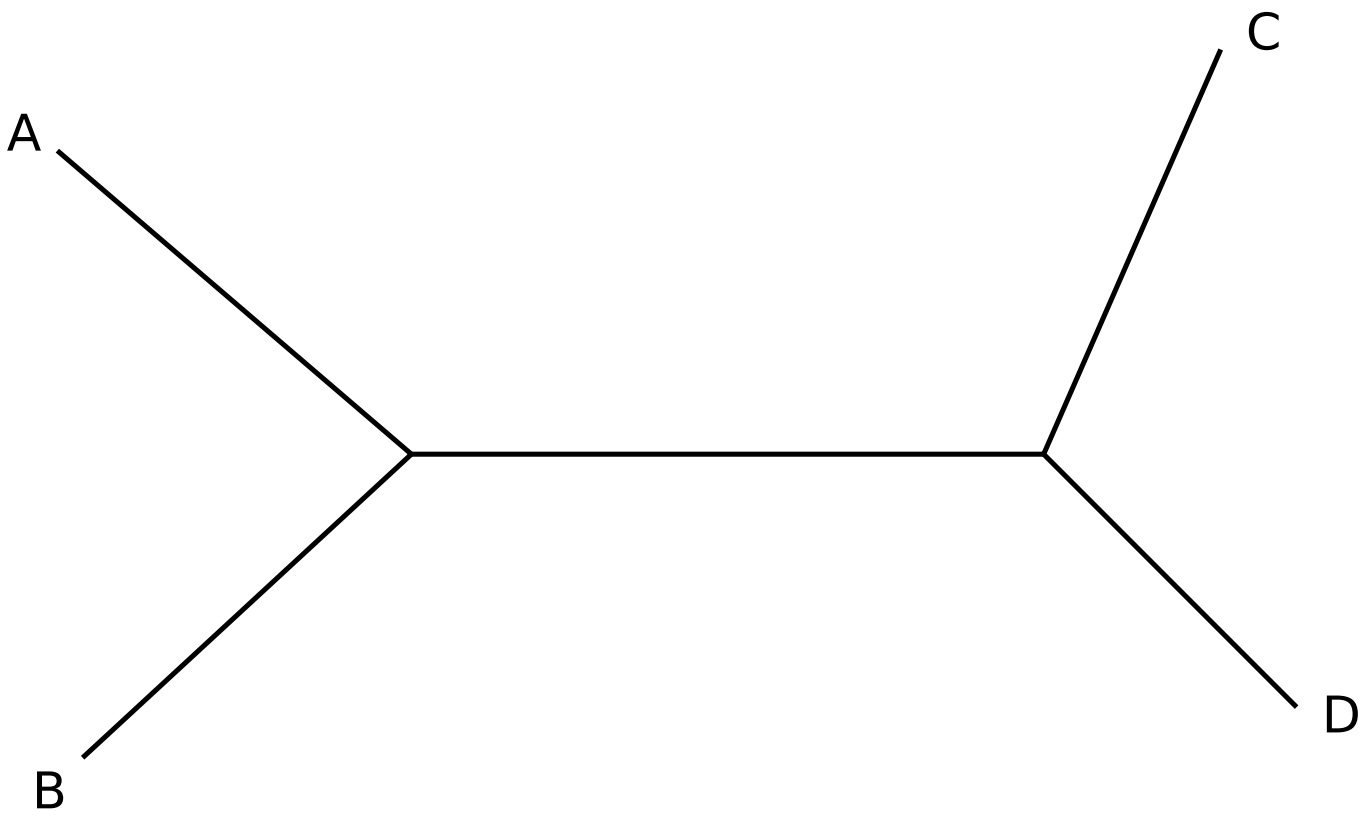
We can root an unrooted tree by means of an outgroup — a sample which we "know" to be more distantly related to any of the original samples than any other.

Rooting an unrooted tree



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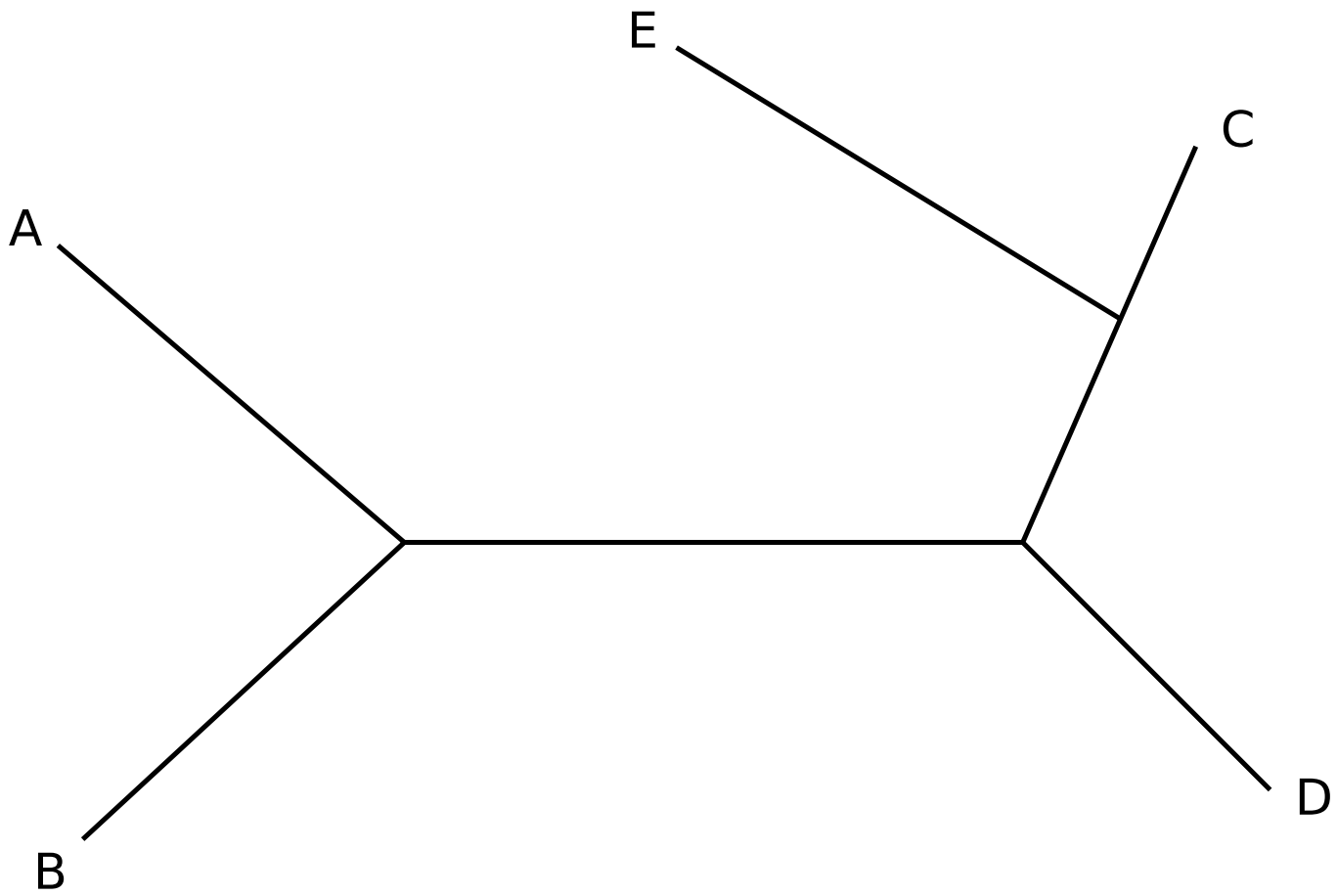

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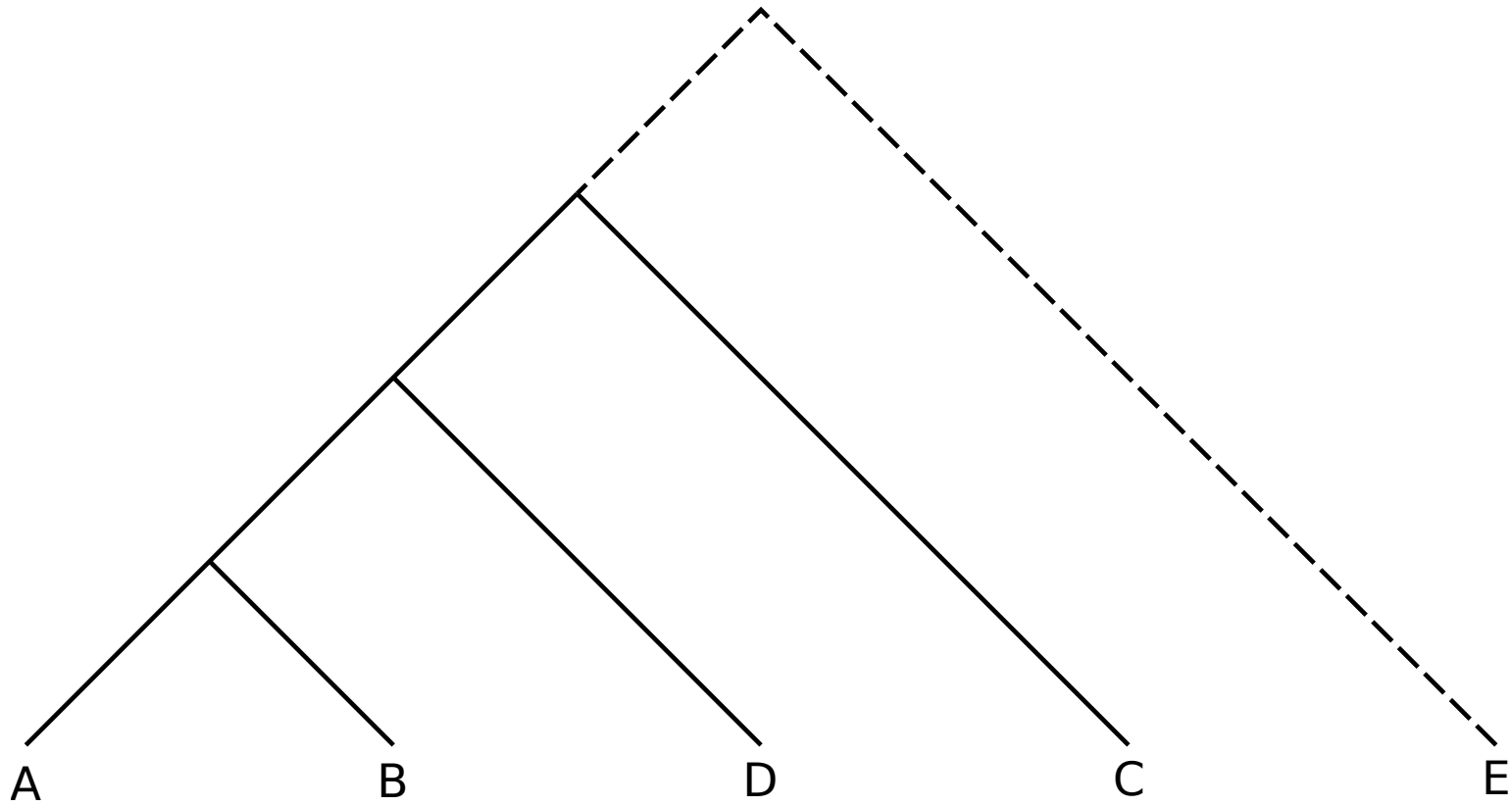

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Rates of evolution can vary among samples, through time, and between sites.

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Internal nodes can also be named: `(((A:1,B:1)E:2,D:3)F:1,C:4)G;`

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Nowadays, we use gene and genome sequences, which provide much more data.

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  - Bayesian methods apply a prior, and sample trees from the posterior distribution.

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This is very important as a first step in phylogenetic inference!

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This works well for a rough calculation, or for sequences which are not too far from each other.

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For longer distances, there is a small problem: for our distance metric, we want to have additive distances, i.e., they should satisfy the relationship

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This can be corrected using a statistical model of evolution, such as the Jukes-Cantor model.

From distances to trees

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The idea of this method is to recursively join taxa (extant or ancestral) which are "close" to each other, until all taxa have been joined into one tree.

Neighbour-joining example

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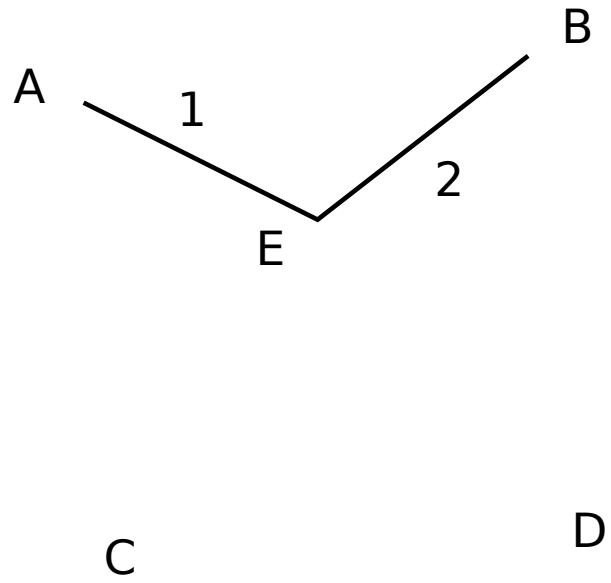

We join A and B, and create a new node E.

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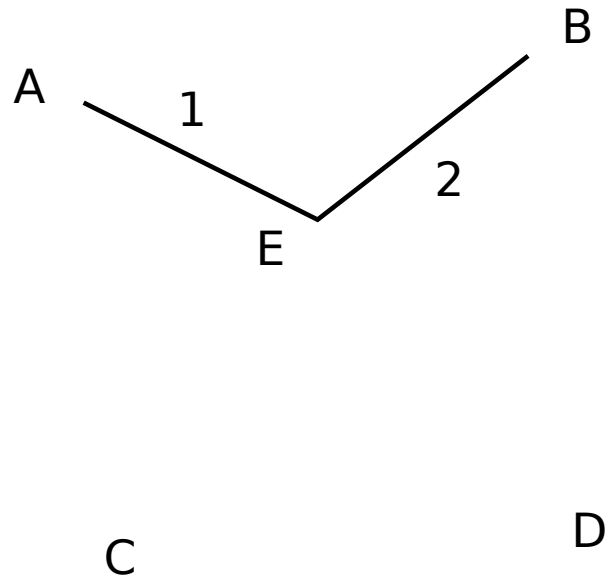

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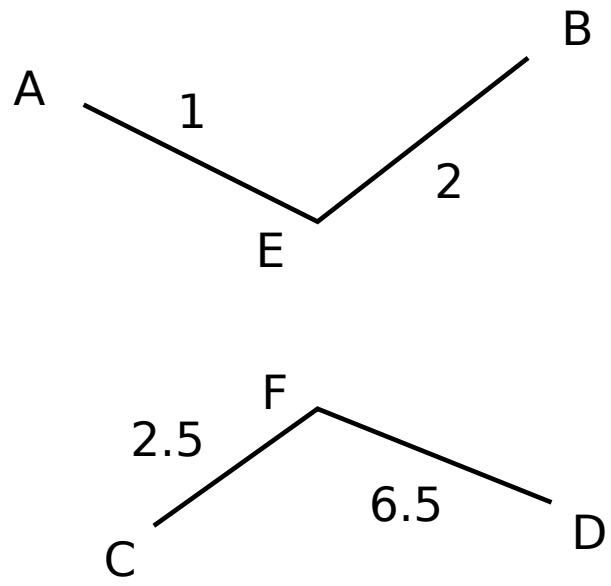

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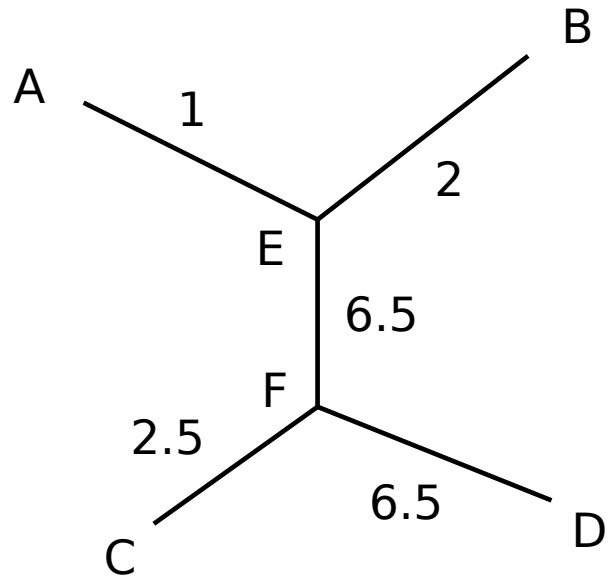

We join C and D, and create a new node F.

We have two nodes left, so we join them and stop.

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It also doesn't necessarily produce ultrametric trees.

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As a stand-alone method, neighbour-joining has largely been superseded by more accurate character-based methods.

However it is still useful for very large datasets, or more generally as a way to get an initial tree which can be further improved by other methods.

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They require two parts: how to evaluate any given tree, and how to propose a new tree to evaluate.

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Of course, it depends on having a realistic (and simple!) model of evolution.

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In this model, every nucleotide is equally likely, and they transition to each other at identical rates.

The mathematics of this is expressed as a continuous-time Markov process.

Jukes-Cantor model

After some math, the transition probabilities for the Jukes-Cantor model are given by:

$$P_{i,i}(t) = \frac{1}{4}\left(1 + 3e^{-4\alpha t}\right),$$
$$P_{i,j}(t) = \frac{1}{4}\left(1 - e^{-4\alpha t}\right) \qquad \text{for } i \neq j.$$

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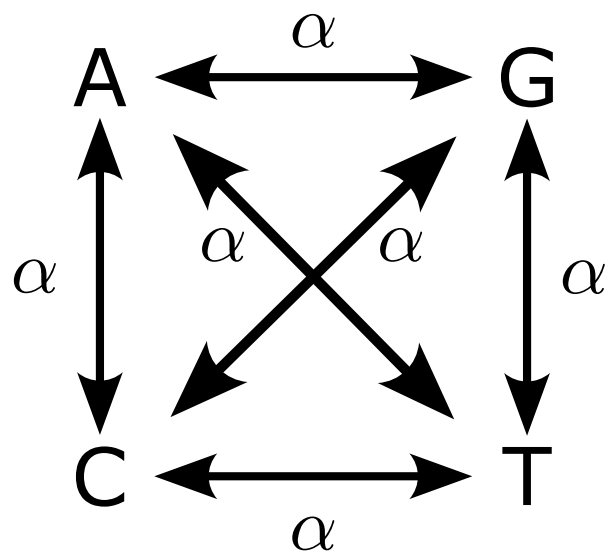
This can then be used in a distance-based method such as neighbour-joining, etc.

Other models of evolution

The Jukes-Cantor is only the simplest model of nucleotide evolution, and not very realistic.



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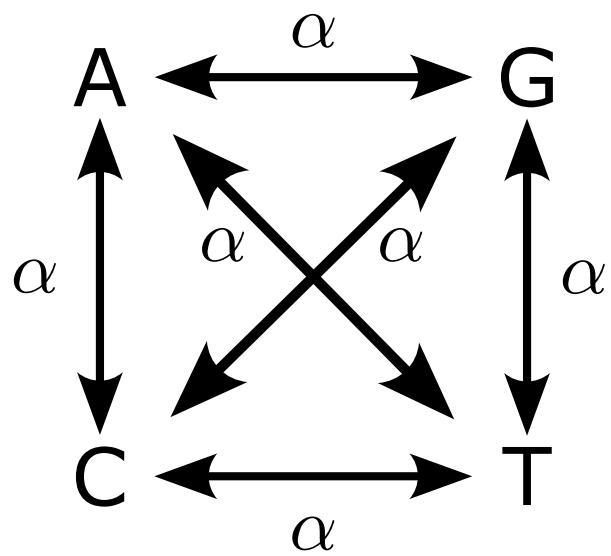

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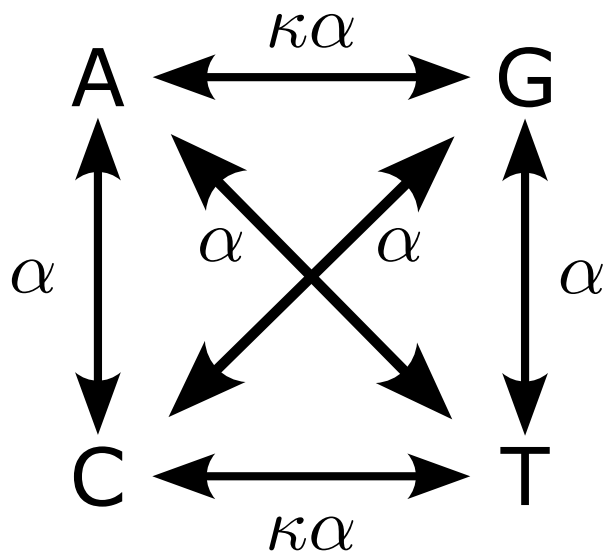
K80 (Kimura, 1980)

Equal base frequency, but transitions ($A \leftrightarrow G$, $C \leftrightarrow T$) and transversions (everything else) happen at different rates.



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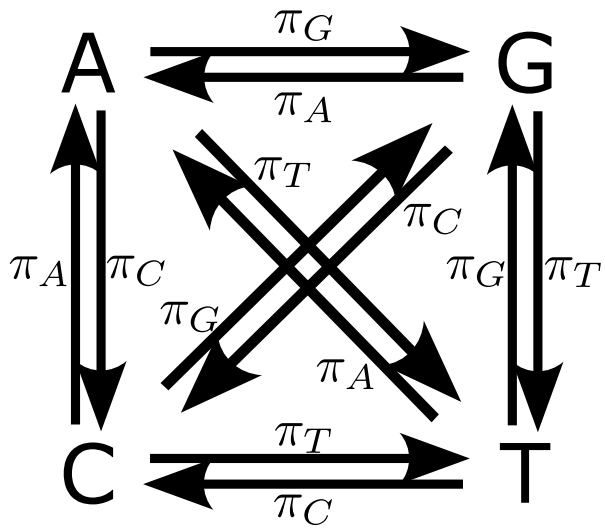
F81 (Felsenstein, 1981)

Unequal base frequency, but transitions to the same state happen at the same rate.



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HKY85 (Hasegawa, Kishino and Yano, 1985)

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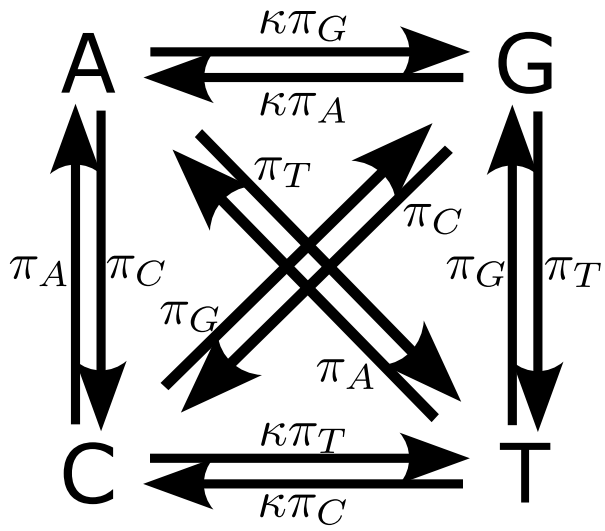

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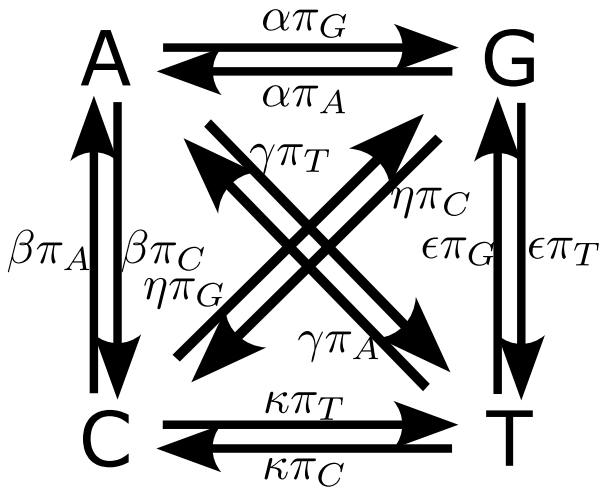
GTR (Tavaré, 1986)

Unequal base frequency and all transition rates, but the model must be time-reversible: transitions from one state to another must happen at the same rate as the reverse transition.



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These can also be combined (e.g., GTR$+\Gamma+$I).

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We must select the most appropriate model according to the fit to the data and the model complexity.

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Parsimony suggests that evolutionary "events" (here, substitutions) are rare, and so we seek to minimise their occurrence.

The parsimony score of a tree is the minimum number of substitutions required for the tree to generate the given data.

It is easy and fast to calculate the parsimony score for any one tree, but (NP-)hard to calculate the most parsimonious tree. In practice it is not as accurate as likelihood-based methods.

Parsimony

```
A     ...CTGCGATTACACCGGAGTCGACCTAG...
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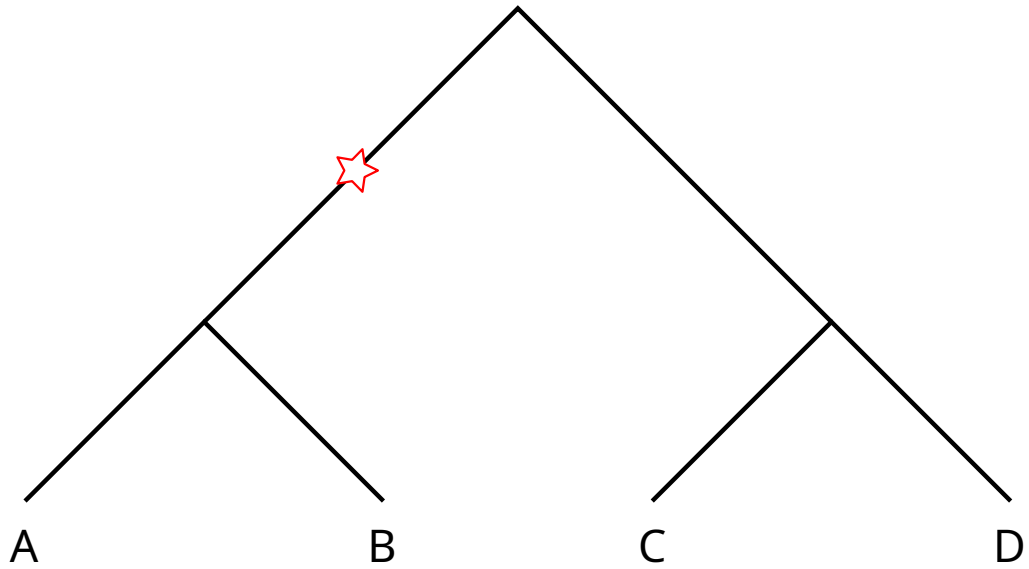

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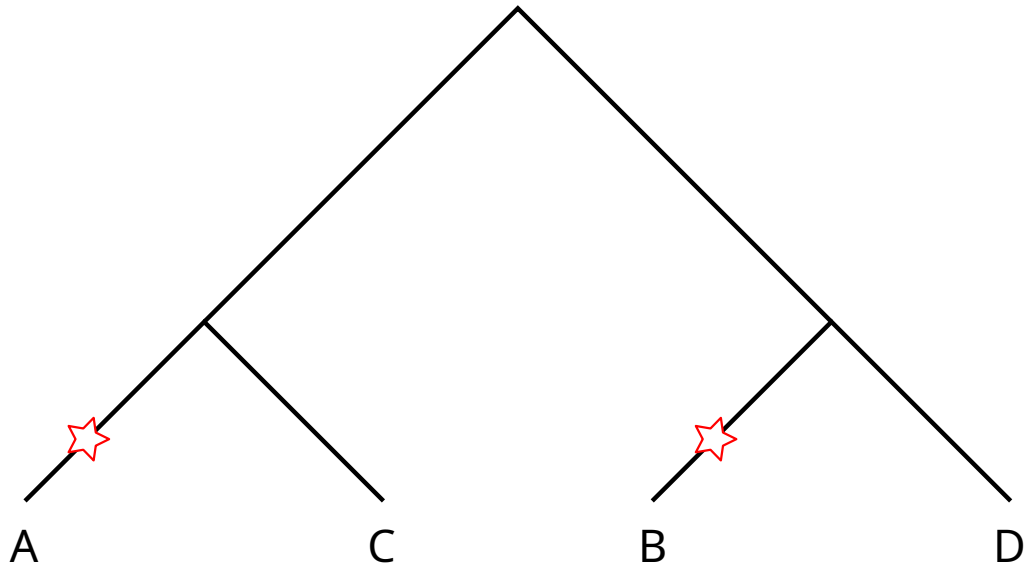

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We first assume that characters evolve independently, so we can compute the likelihood of each character and multiply them.

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Instead, we use dynamic programming, starting from the leaves and working back to the root.

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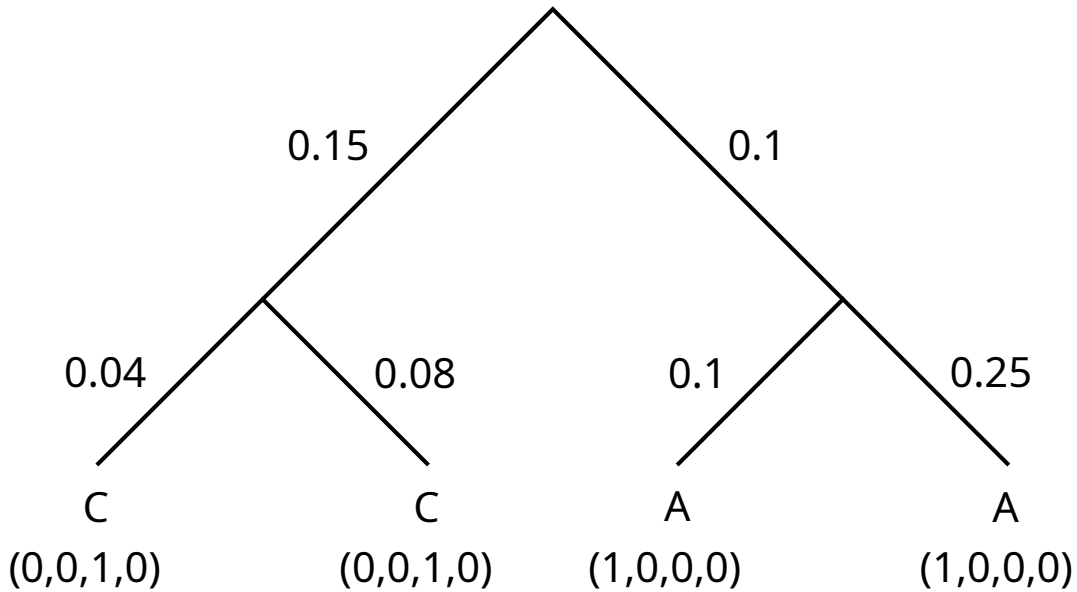

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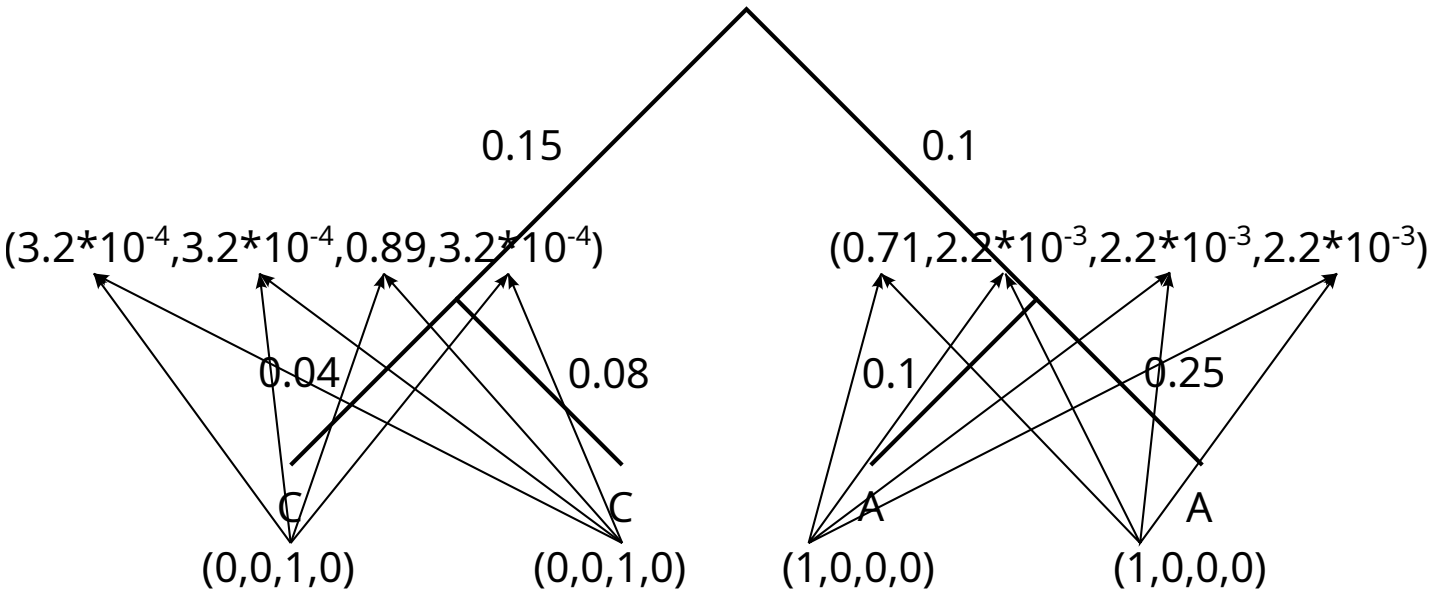

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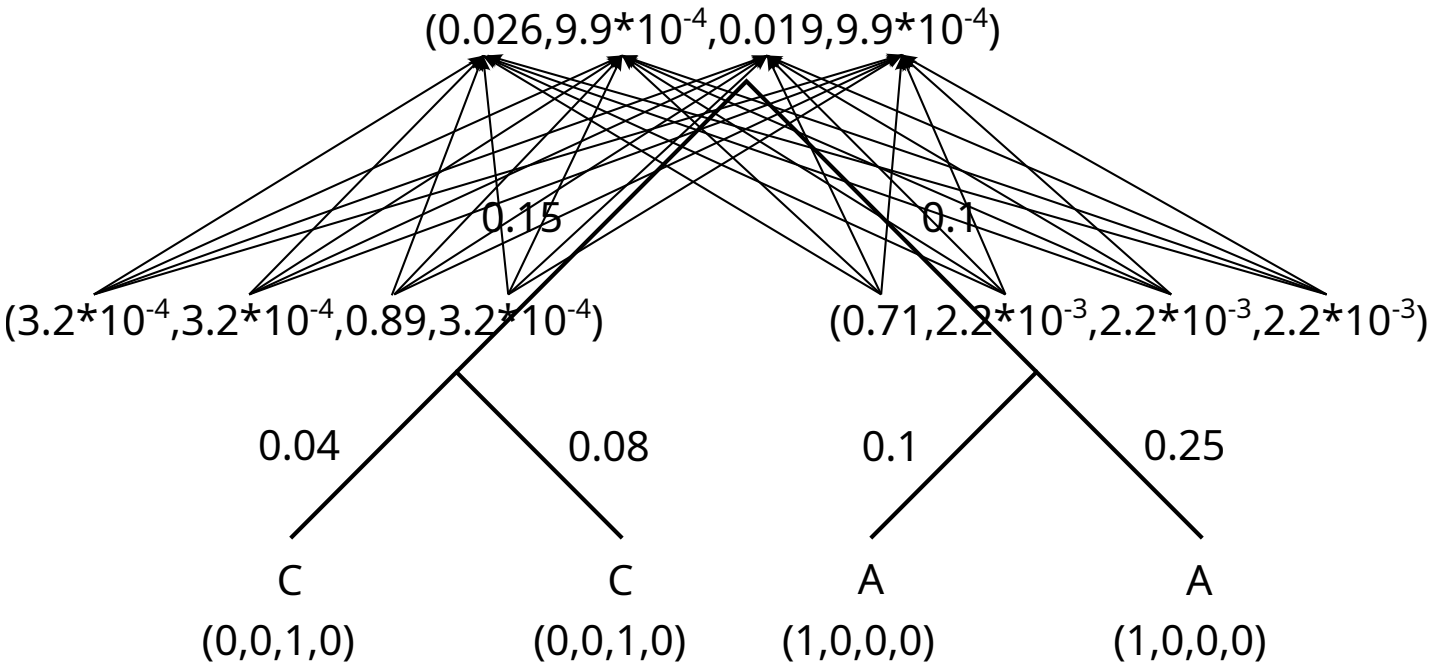

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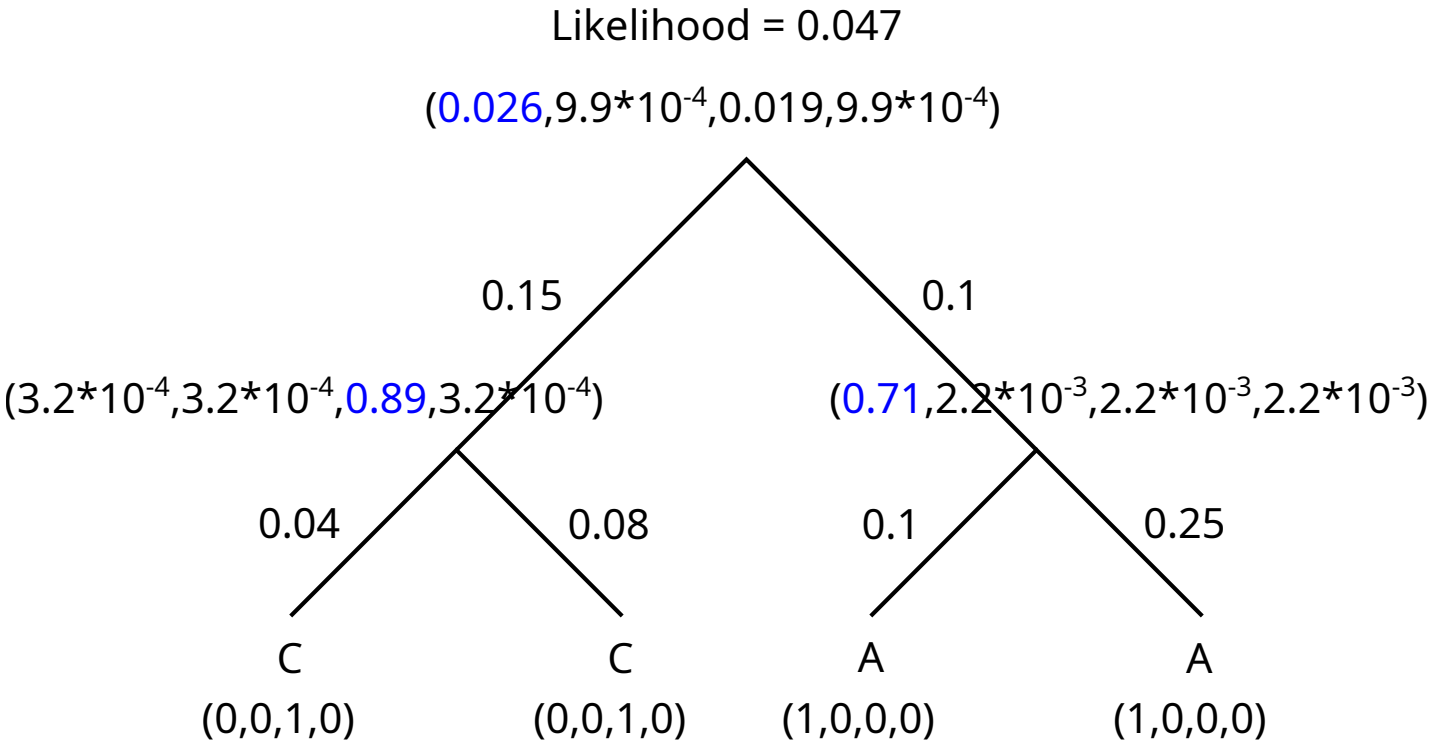

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Branch lengths can be found (for a given topology) by optimising the likelihood numerically.

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We may also choose to accept (with some probability) a tree with a lower likelihood, to escape local maxima.

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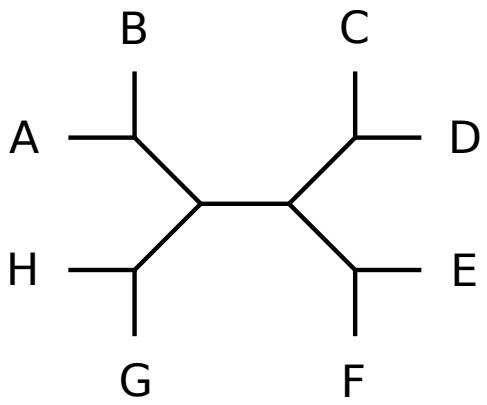

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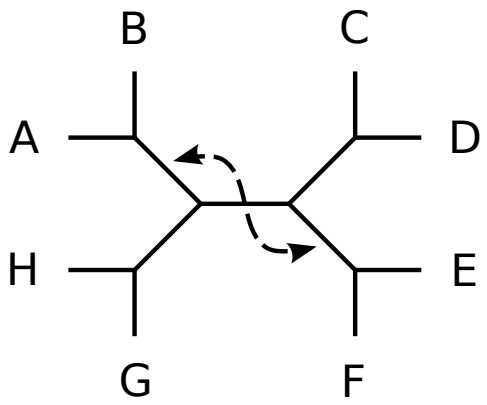

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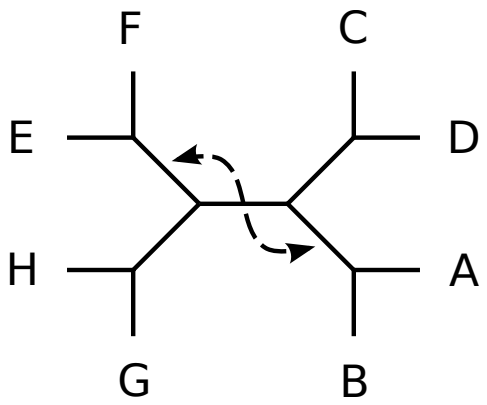

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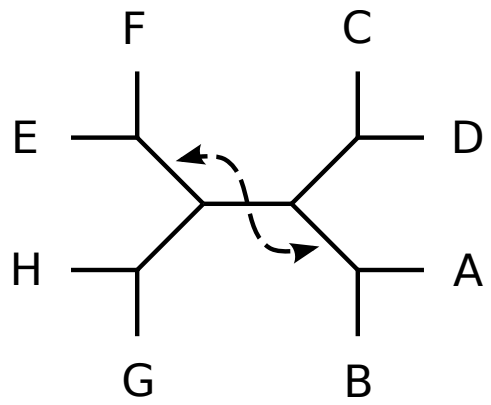

This is quick, but a "small" move, so it is difficult to escape local maxima.

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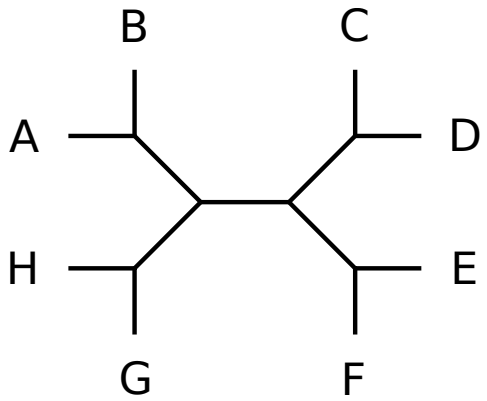

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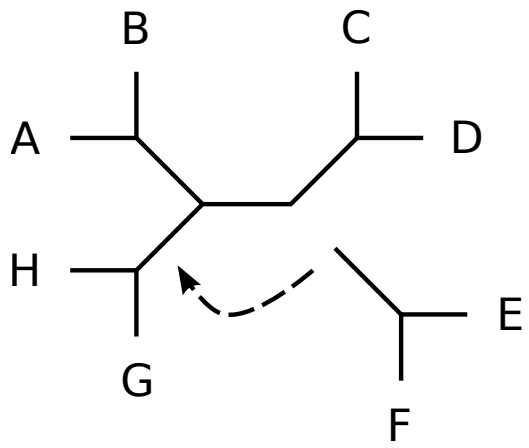

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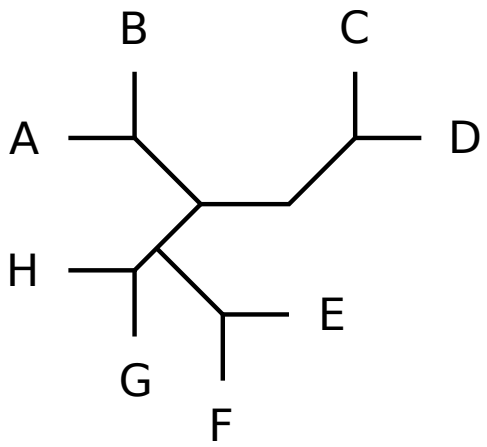

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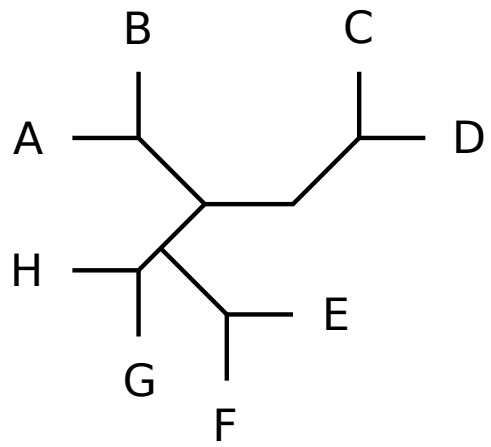

This is a "bigger" move, but more computationally intensive.

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- IQ-TREE (Nguyen *et al.*, 2015) uses a combination of hill-climbing and stochastic perturbation.

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- If your statistical model is wrong...

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To (partly) answer these questions, we use bootstrapping.

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We then apply our method of choice to construct a new tree. Then we repeat this many times.

Bootstrapping

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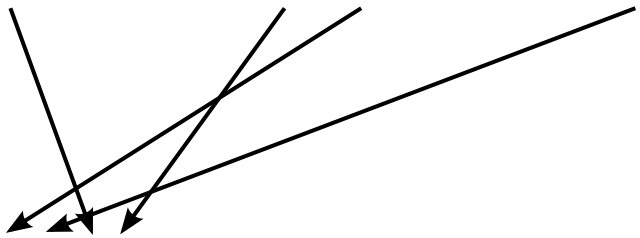

...CGCTTTGACGAGCAAGATGAAGACAC...

...CGCTTAGCCGGGTAATGTGCCGCTCA...

...CAAGTAGACGGTTAGAGTGCCTCTAT...

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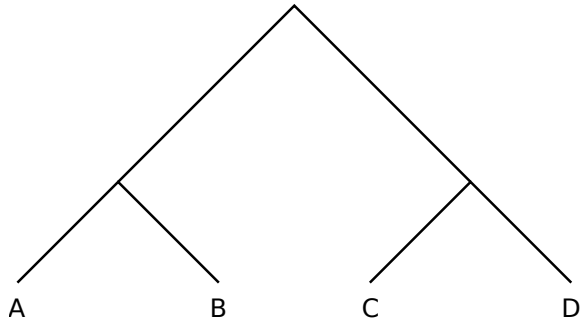
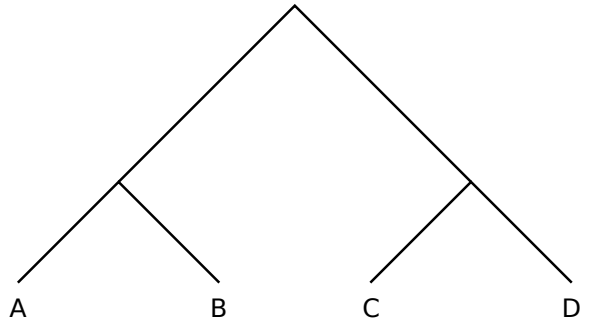
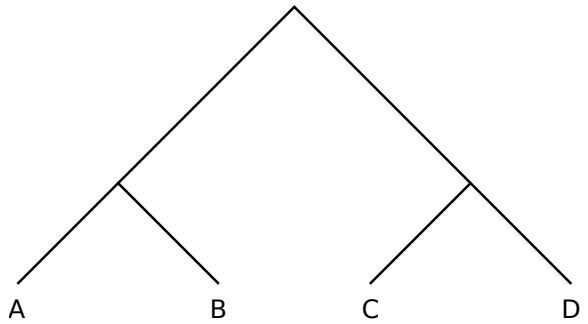
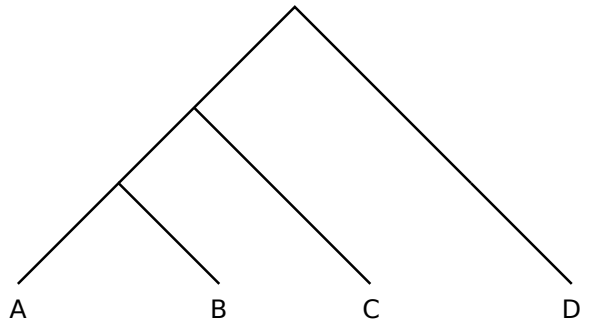
We then attach the bootstrap support value to each branch in our final tree.

Bootstrapping

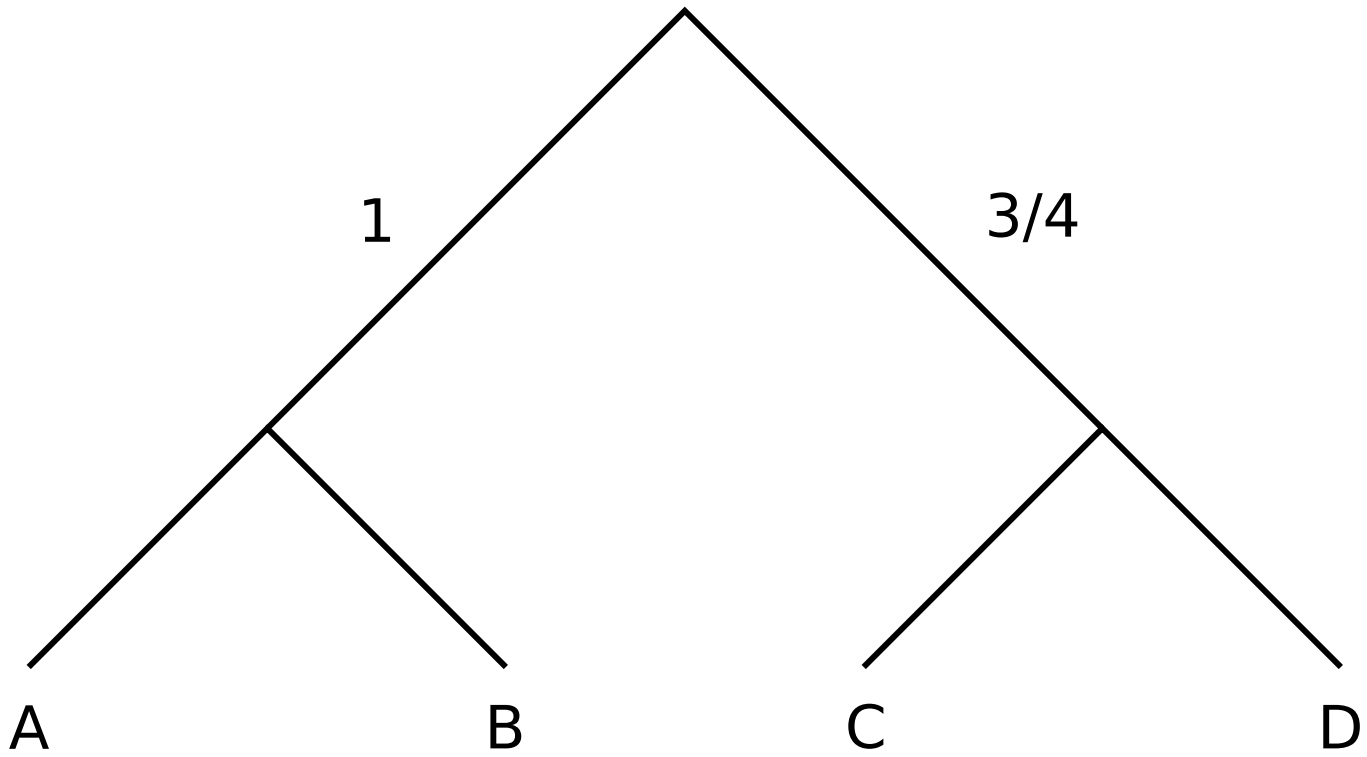








Bootstrapping



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UFBoot (Minh *et al.*, 2013) combines this approach with an efficient way of sampling nearby alternative trees.