Phylogeny reconstruction

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Why studying phylogenetics?

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The study of the evolution of (taxonomic) groups of organisms (*e.g.* species, populations).

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Phylogenetics

The study of the evolution of (taxonomic) groups of organisms (*e.g.* species, populations).

- Infer the history of taxa
  - Taxonomy
  - Phylogeography
- Necessary to comparative analysis, as species are not “independent”

Phylogenetics applications

Phylogenetic tree

A graph depicting the ancestor-descendant relationships between organisms or gene sequences. The sequences are the tips of the tree. Branches of the tree connect the tips to their (unobservable) ancestral sequences (Holder 2003)

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Some applications:

- Resolving orthology and paralogy
- Datation: estimate divergence times
- Reconstruct ancestral sequences
- Exhibit sites under positive selection
- Predict the structure of a molecule...

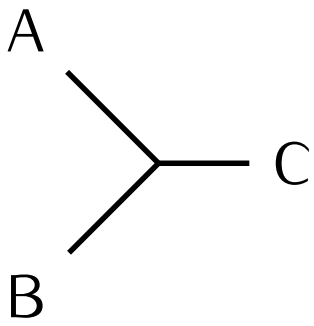
What is a tree?

2 leaves

What is a tree?

2 leaves

3 leaves



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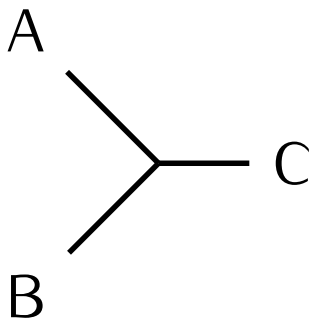
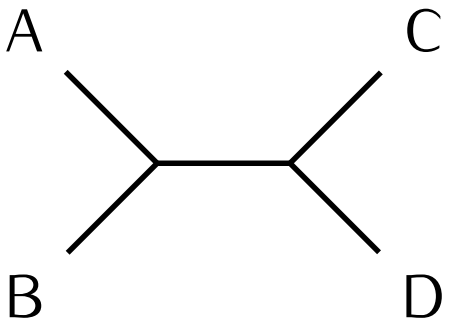
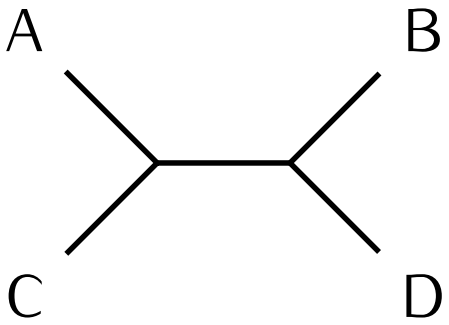


4 leaves





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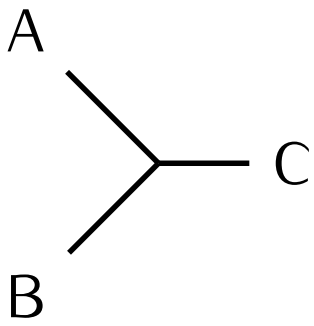

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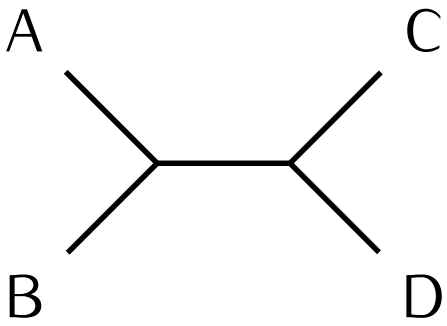

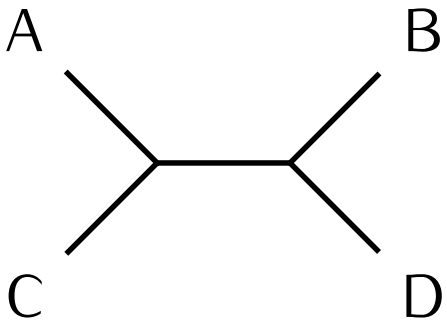

$$\frac{(2n-5)!}{2^{n-3}(n-2)!}$$
distinct unrooted trees

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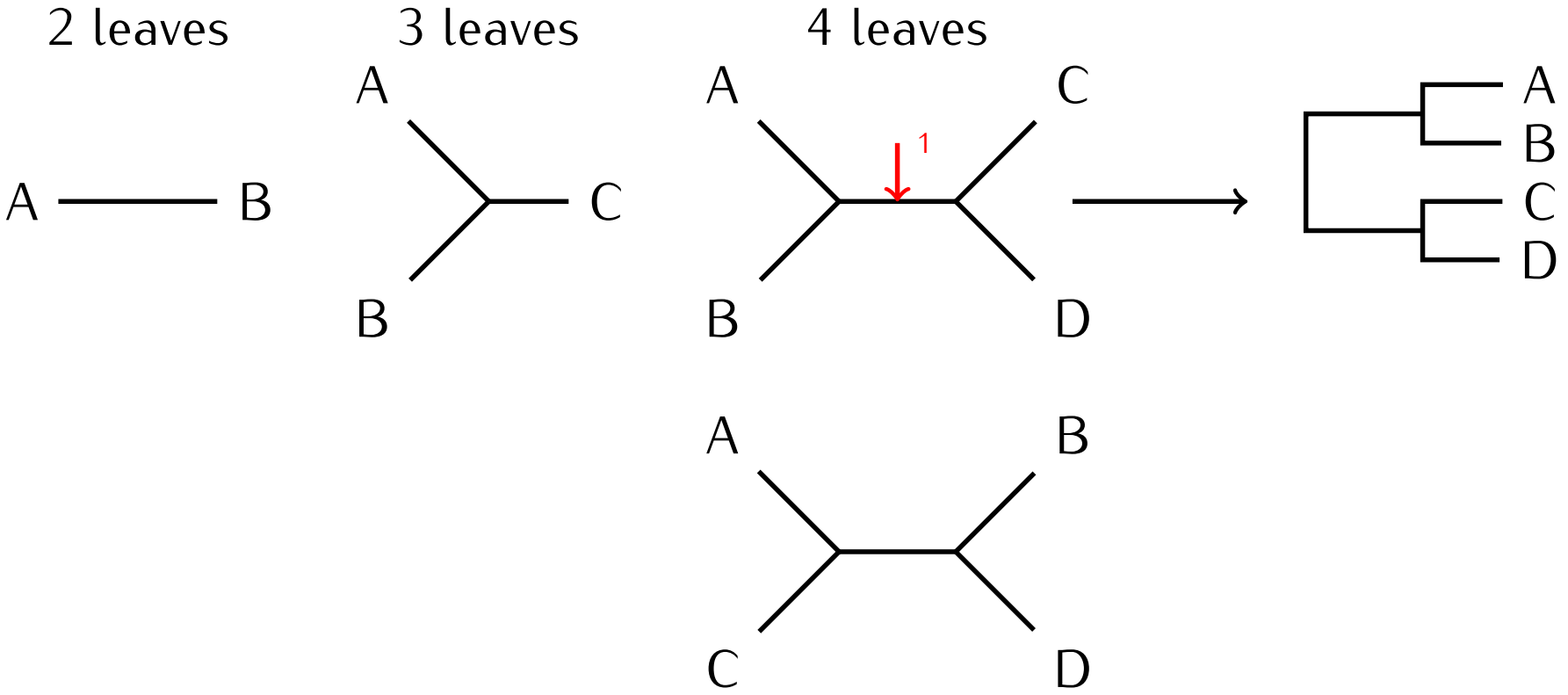

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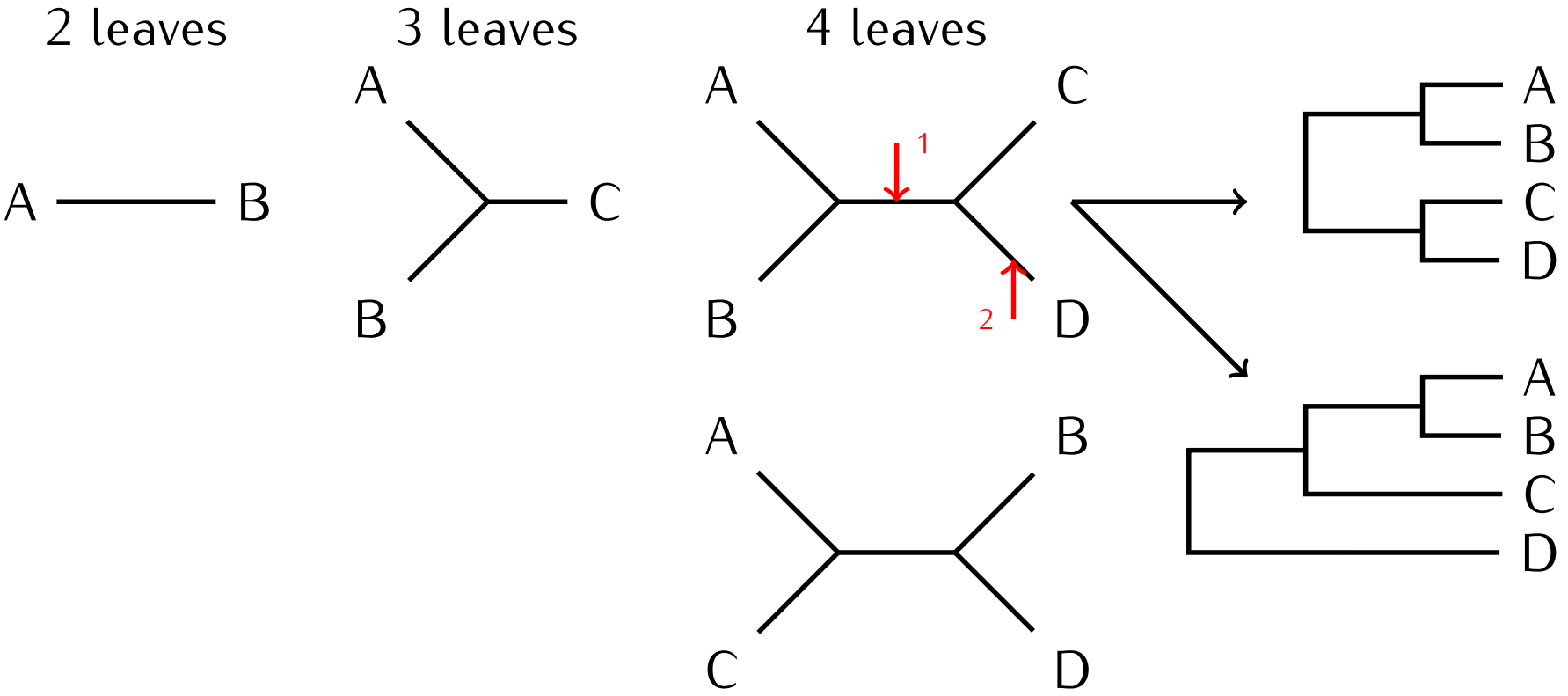

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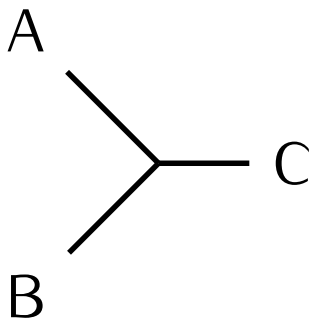

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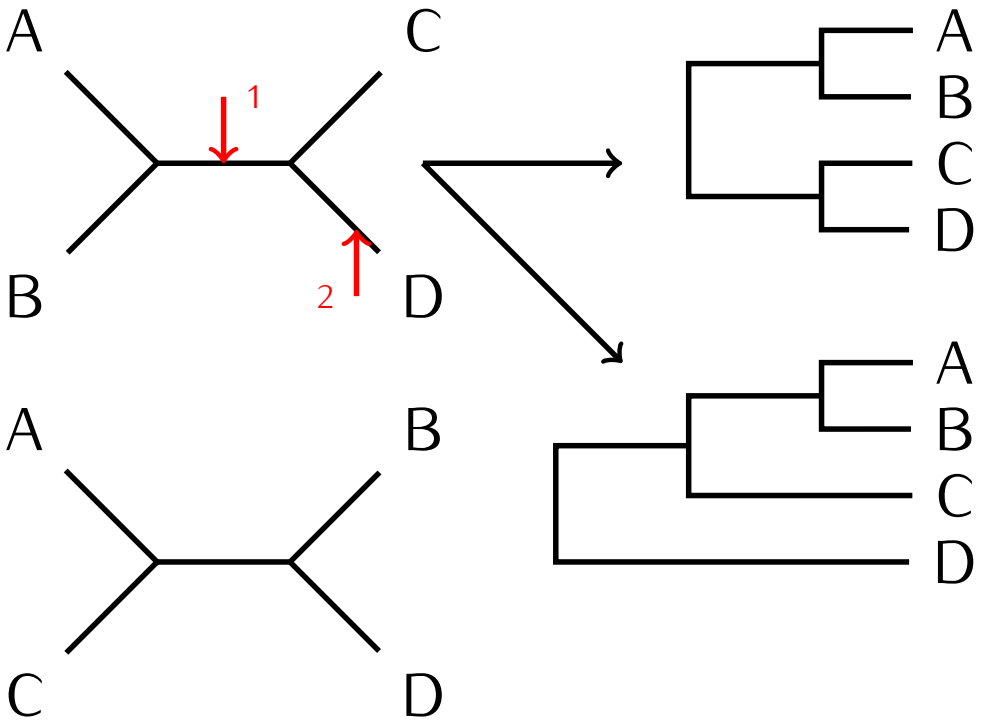
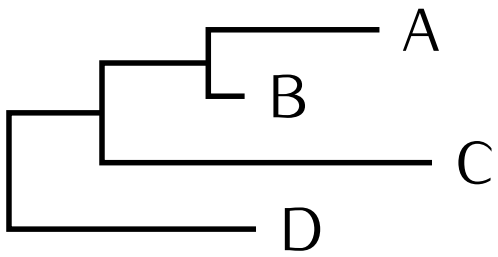


With branch lengths:



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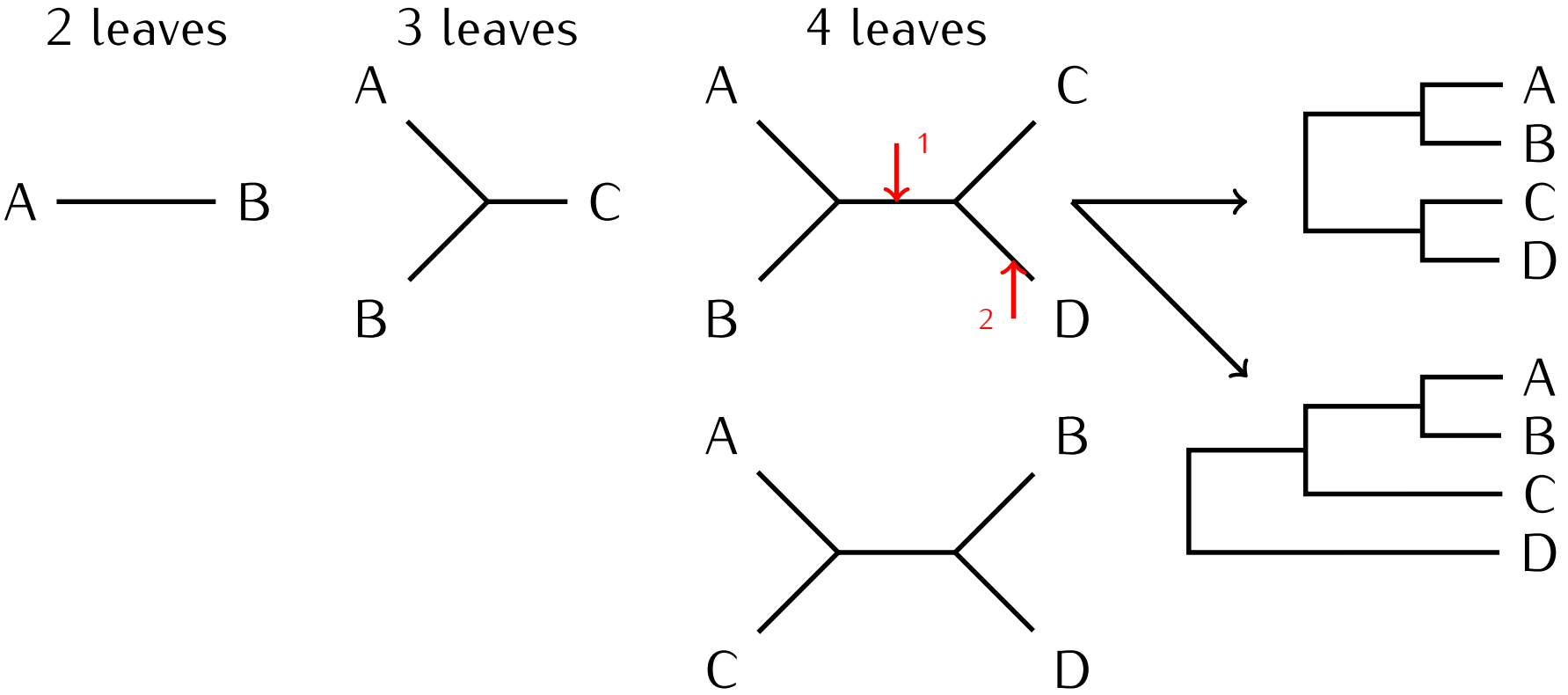

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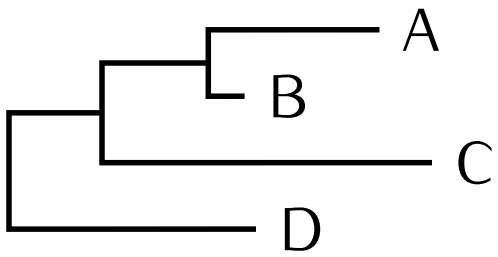
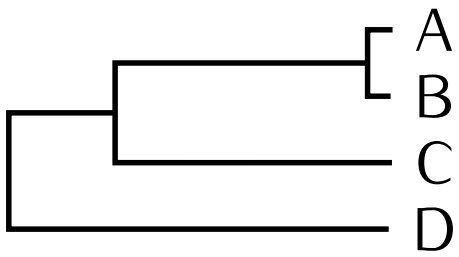


With clock:



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distinct unrooted trees

From sequences to trees

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Taxon 1 AAGACATGTGGCA
Taxon 2 AGGAC-TGTGGCA
Taxon 3 AGTAC-TGTGA-A
Taxon 4 AGCAC-TGTG--T
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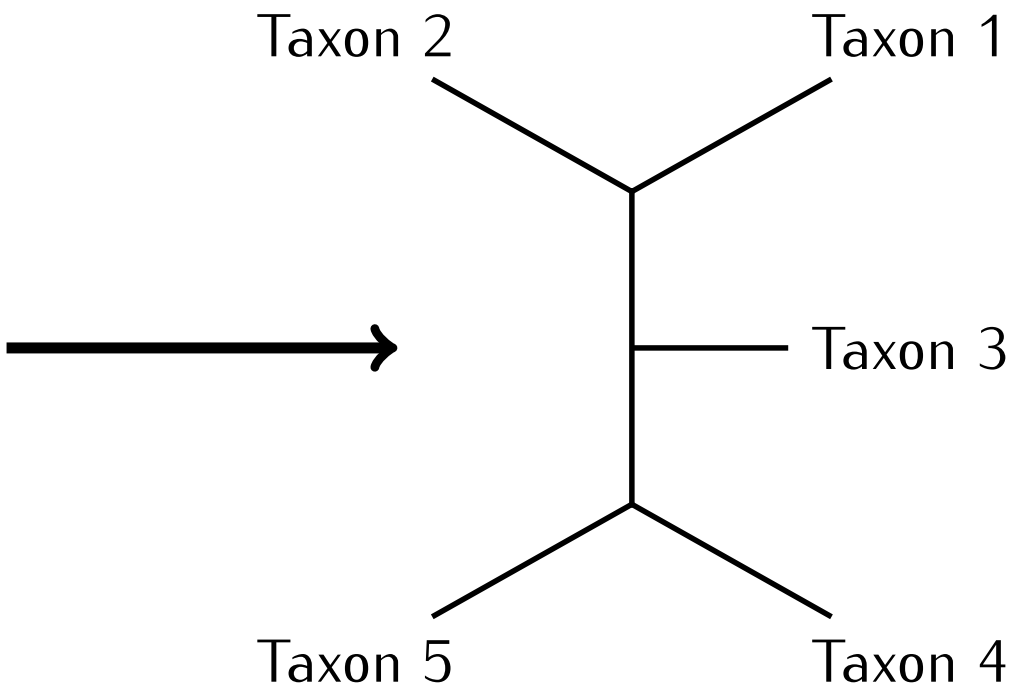

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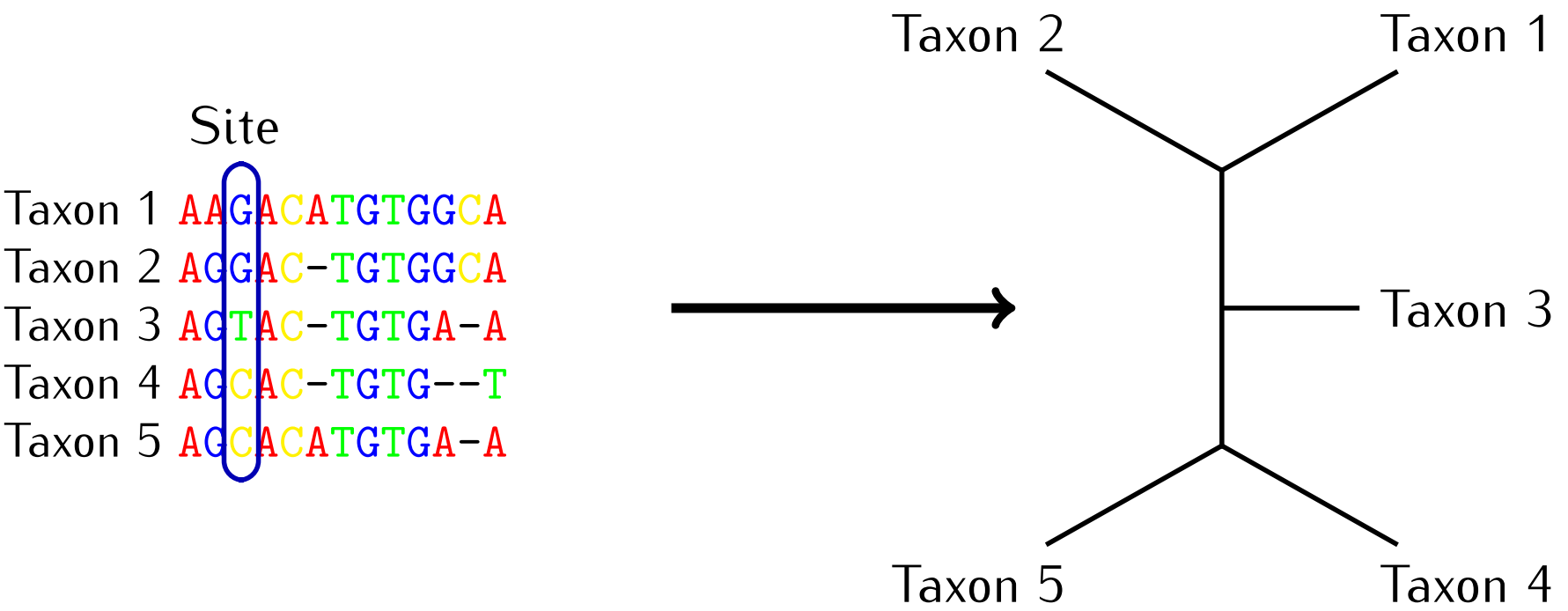

- Aligned homologous positions: sites
- Each site is a realization of a random variable

The phenetic approach

- Uses an overall similarity measure (commonly used in morphology)
- Consider that the similarity is (inversely) correlated to the evolutionary distance
- Build a tree from a pairwise distance matrix:

	T1	T2	T3	T4	T5
T1	0				
T2	2	0			
T3	3.5	4.5	0		
T4	8	10	8	0	
T5	6	8	9	3	0

The WPGMA clustering method

Weighted Pair Group Method using Average

1. Pick the smallest distance

	T1	T2	T3	T4	T5
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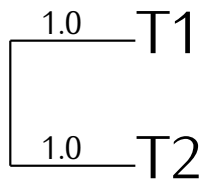


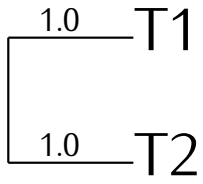
The WPGMA clustering method
Weighted Pair Group Method using Average

	T12	T3	T4	T5
T12	0			
T3	4	0		
T4	9	8	0	
T5	7	9	3	0

3. Recompute distances from the new group:

$$d_{ij,k} = \frac{d_{i,k} + d_{j,k}}{2}$$

(Assumes that the rate of change is constant over time: molecular clock)



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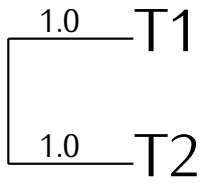

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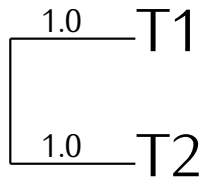

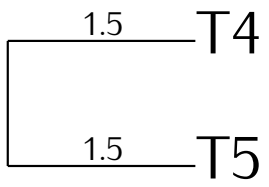

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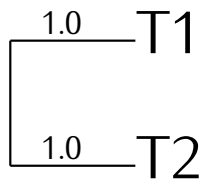

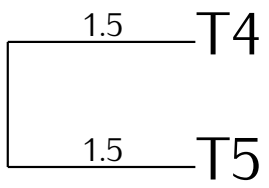

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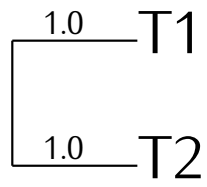

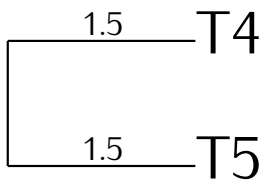

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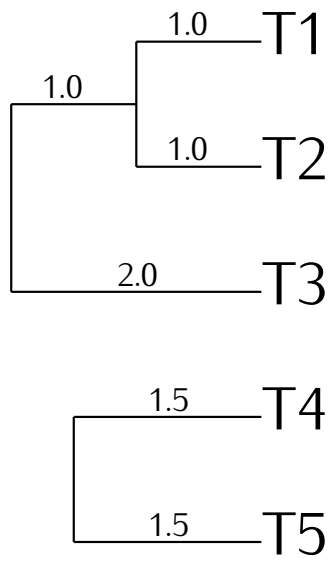

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	T123	T45
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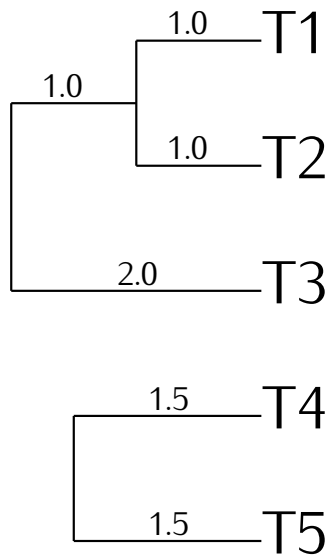

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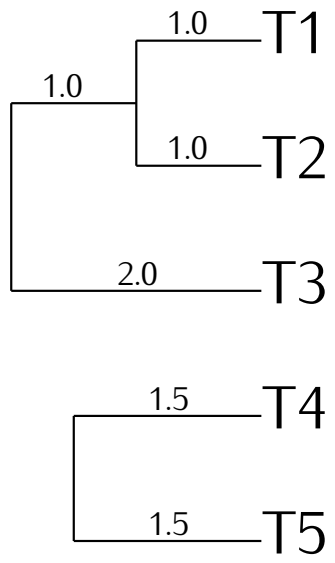

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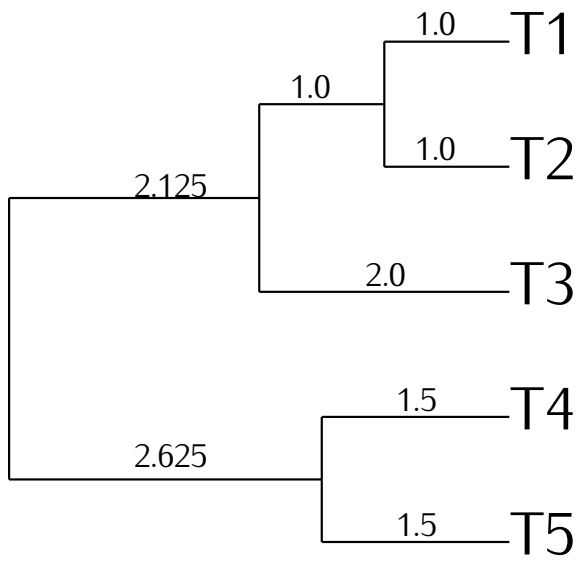

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  2. building a tree from the matrix
- When using molecular sequences, the distance for a pair of species is the divergence estimated from the sequences. It can be
  - an edit distance (alignment score)
  - a proportion of mismatch
  - an estimated divergence from the observed matches (requires a model of evolution)

Additive distance matrix

A distance matrix M is additive if it exists a corresponding phylogenetic tree T so that $d_{a,b} = d_{a,c} + d_{b,c}$, where c depicts the ancestral node for species a and b.

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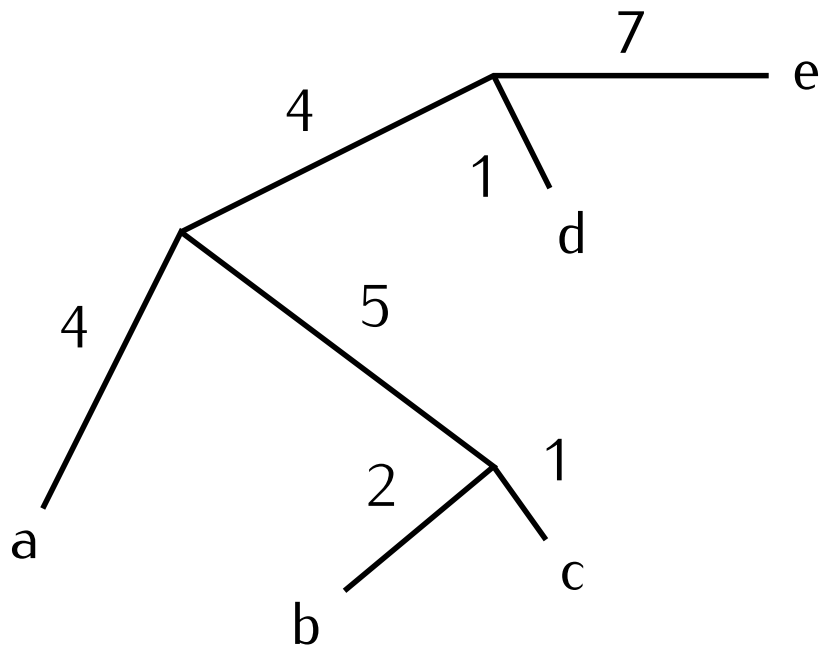
M	a	b	c	d	e
a	0	11	10	9	15
b	11	0	3	12	18
c	10	3	0	11	17
d	9	12	11	0	8
e	15	18	17	8	0

$\Leftrightarrow$



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Biological distance matrices

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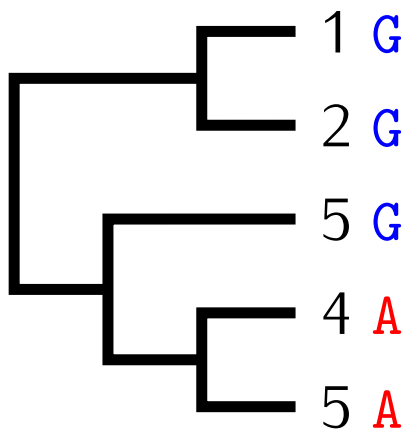
- This is a very difficult problem! Heuristics are needed
- The most famous heuristics: Neighbor Joining • Saitou N and Nei M (1987). Molecular Biology and Evolution, 4:405-425 (one of the most cited biological paper!)
- Other heuristics: BioNJ, FastME

The cladistic approach

- Reconstruct the evolutionary history of the data



"good" site

The cladistic approach

- Reconstruct the evolutionary history of the data
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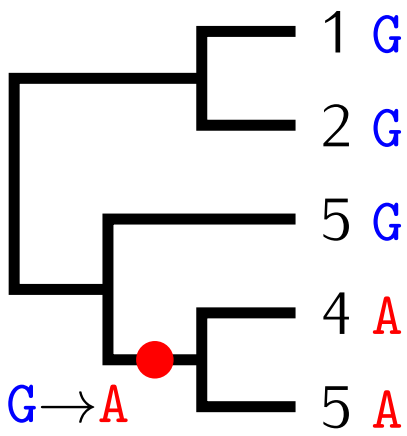
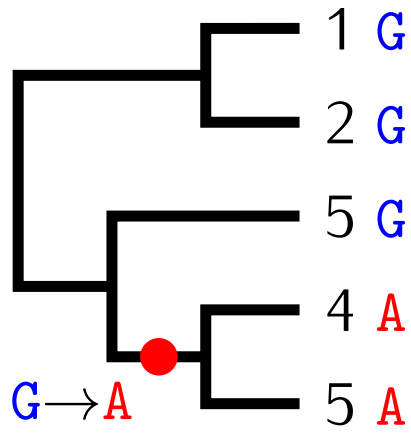


"good" site

The cladistic approach

- Reconstruct the evolutionary history of the data
- A plethora of scenario, not all as likely
- Assess the probability of a given scenario
  - for a site
  - for an alignment



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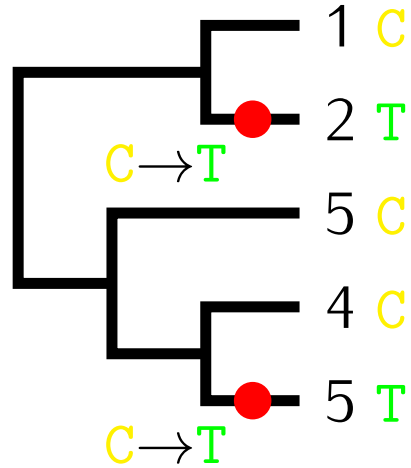


"bad" site

General hypotheses

1. All sites evolve essentially by substitutions (insertions, deletions, inversions are not accounted)
2. All sites evolve independently
3. All sites undergo the same process, notably
   - All sites evolve at the same rate
   - The substitution rate is constant over time

Maximum parsimony

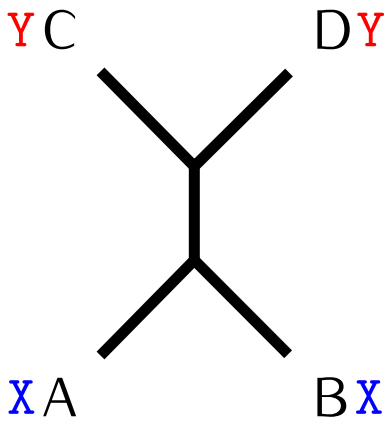
William of Ockham (1288–1346)

English medieval logician and Franciscan friar. Well known for its principle of parsimony, or Ockham's razor: the explanation of any phenomenon should make as few assumptions as possible, eliminating those that make no difference in the observable predictions of the explanatory hypothesis or theory.

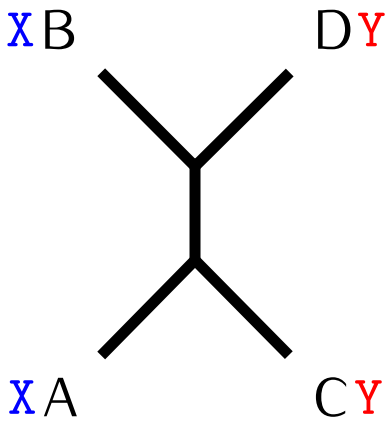
This is often paraphrased as "All other things being equal, the simplest solution is the best."

$\Rightarrow$ General statistic and scientific method.

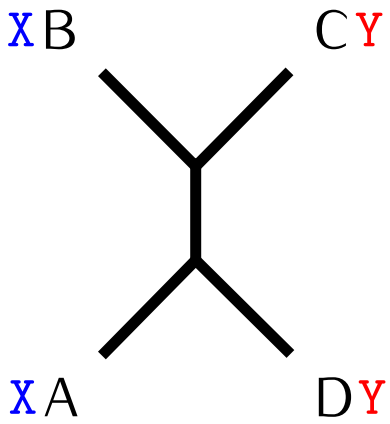
Maximum parsimony



Case 1



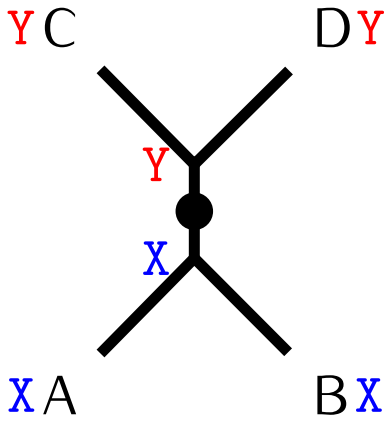
Case 2



Case 3

- Three possible topologies

Maximum parsimony



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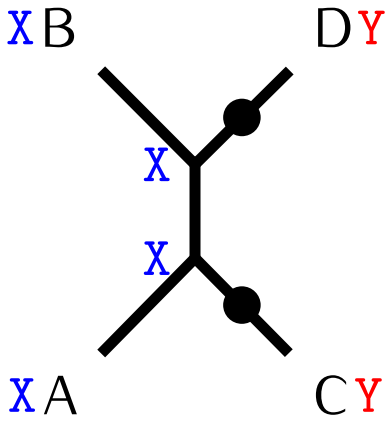
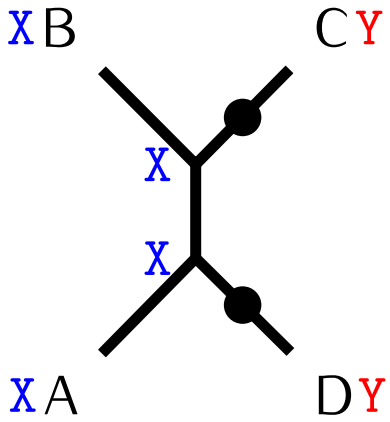


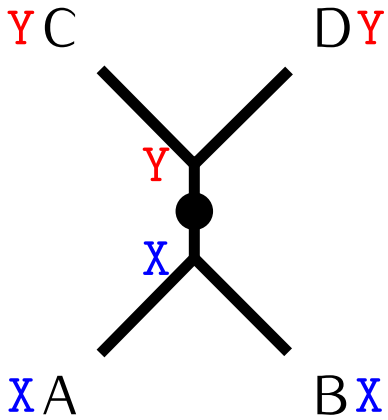
Case 2



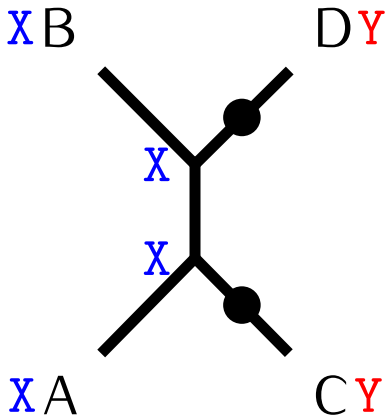
Case 3

- Three possible topologies

Maximum parsimony



Case 1



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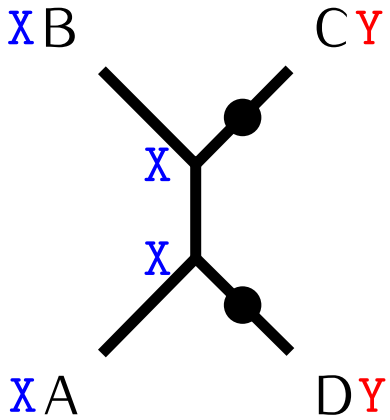
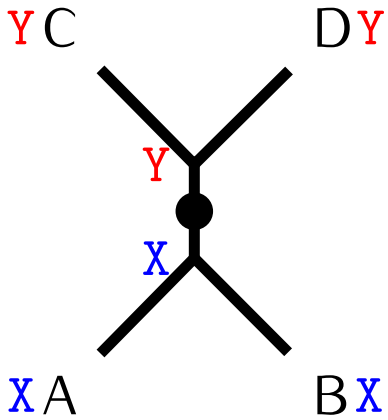


Case 3

	Site 1	Site 2	Site 2		
A	X	X	X	X	X
B	X	Y	Y	X	X
C	Y	X	Y	X	Y
D	Y	Y	X	Y	Z
Case 1	1	2	2	1	2
Case 2	2	1	2	1	2
Case 3	2	2	1	1	2

- Three possible topologies
- Three types of informative sites + non-informative sites

Maximum parsimony



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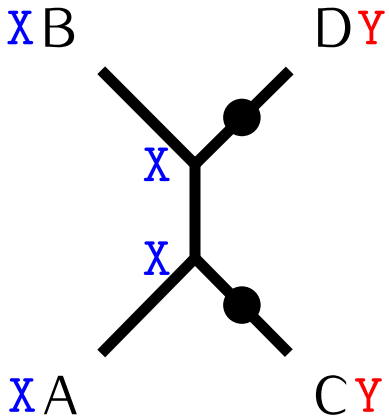

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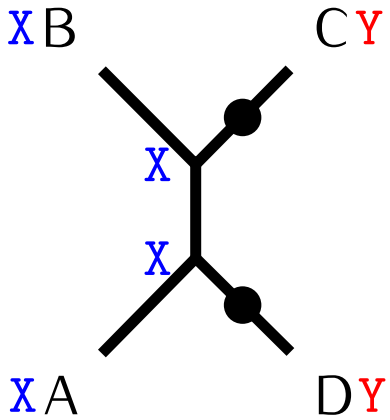

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D	Y	Y	X	Y	Z
Case 1	1	2	2	1	2
Case 2	2	1	2	1	2
Case 3	2	2	1	1	2

- Three possible topologies
- Three types of informative sites + non-informative sites
- For one site, we take the most parsimonious scenario • For an alignment, we take the scenario in agreement with the majority of sites

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   - *etc.*

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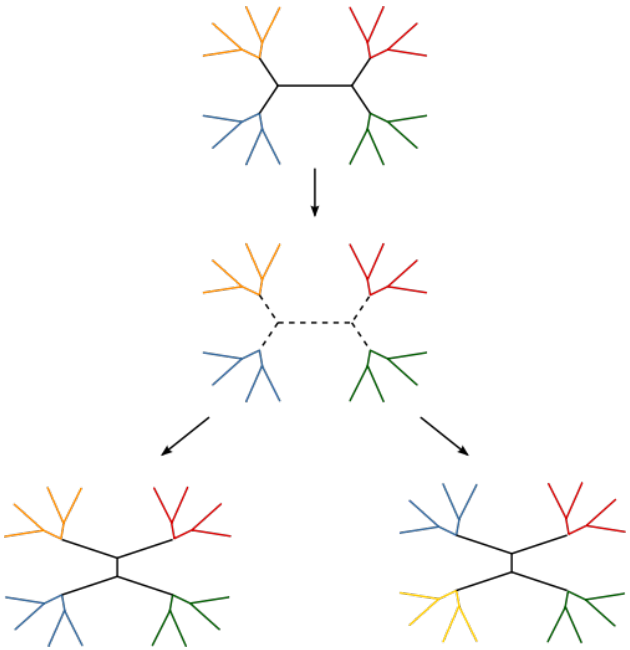
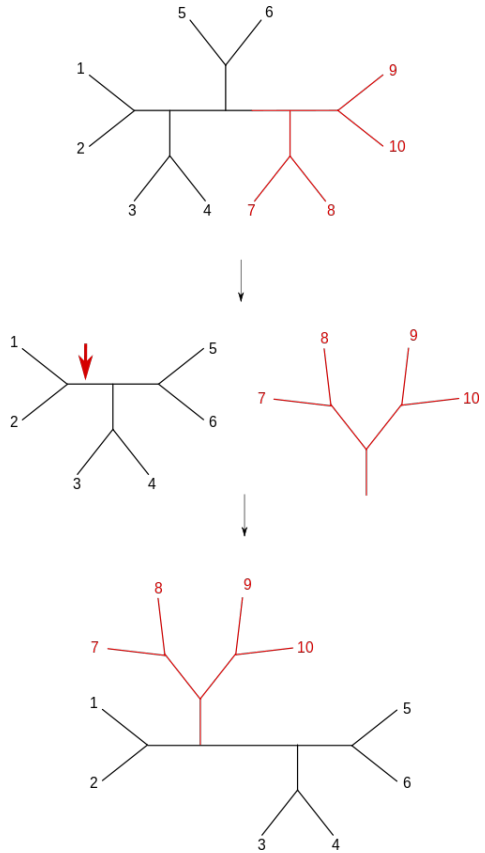
5. A combination of a distance method and '3'

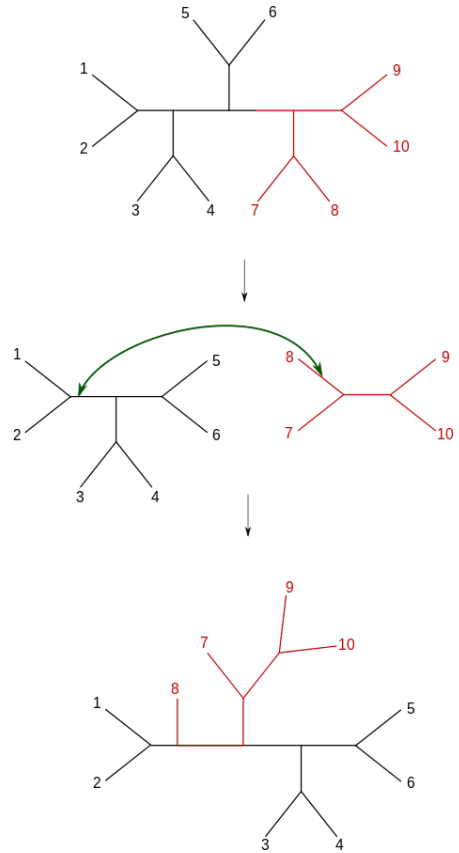
Topology ‘movements’



Nearest Neighbor Interchange (NNI)

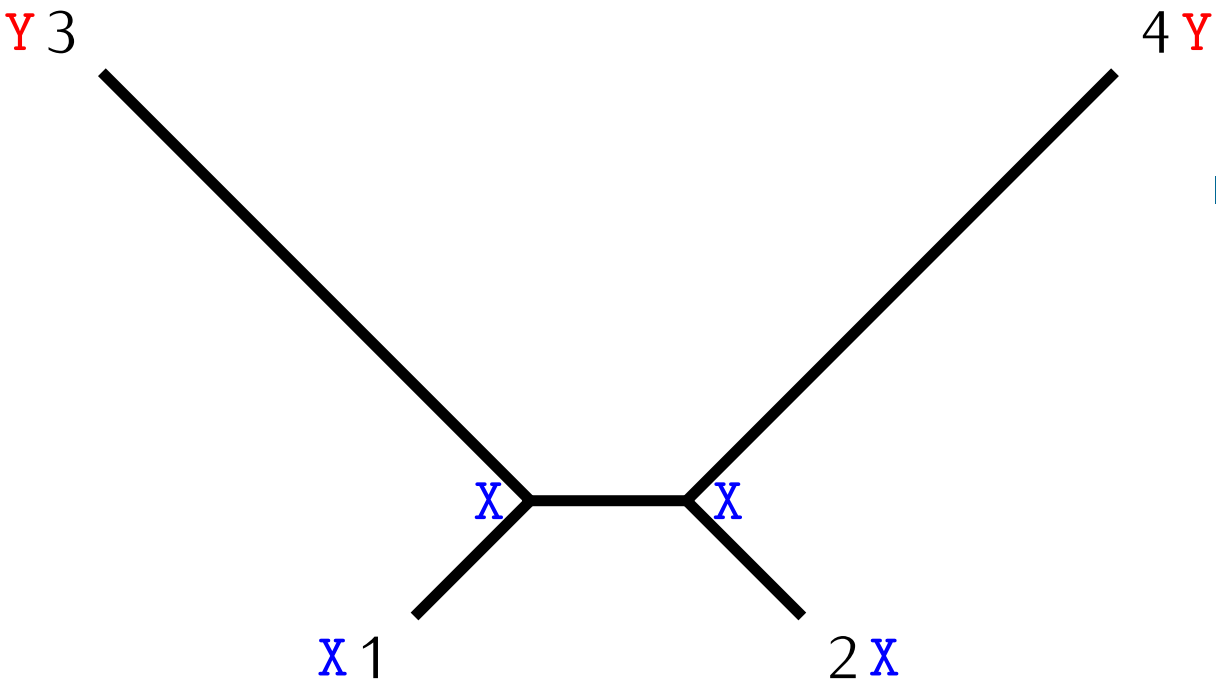


Subtree Pruning Regrafting (SPR)



Tree Bisection Reconnection (TBR)

Problems with the parsimony approach



	a	b	c
1	X	X	X
2	X	Y	Y
3	Y	X	Y
4	Y	Y	X

- The 'right' site is $b : ((1,3),(2,4))$, but sites of type a are more frequent

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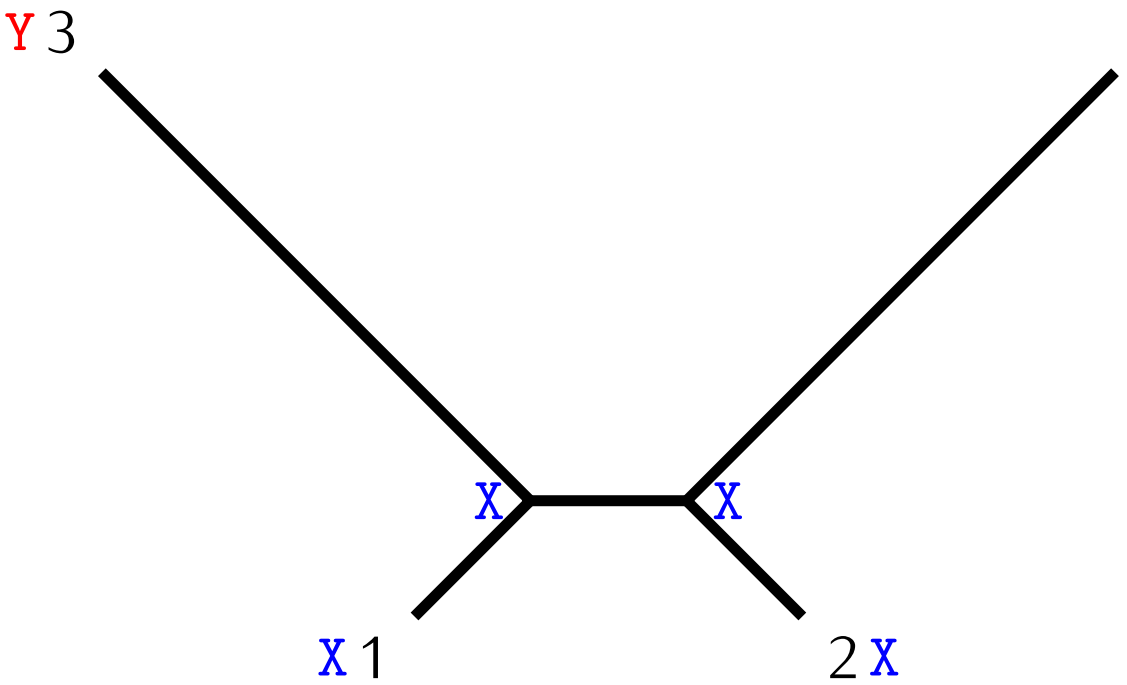

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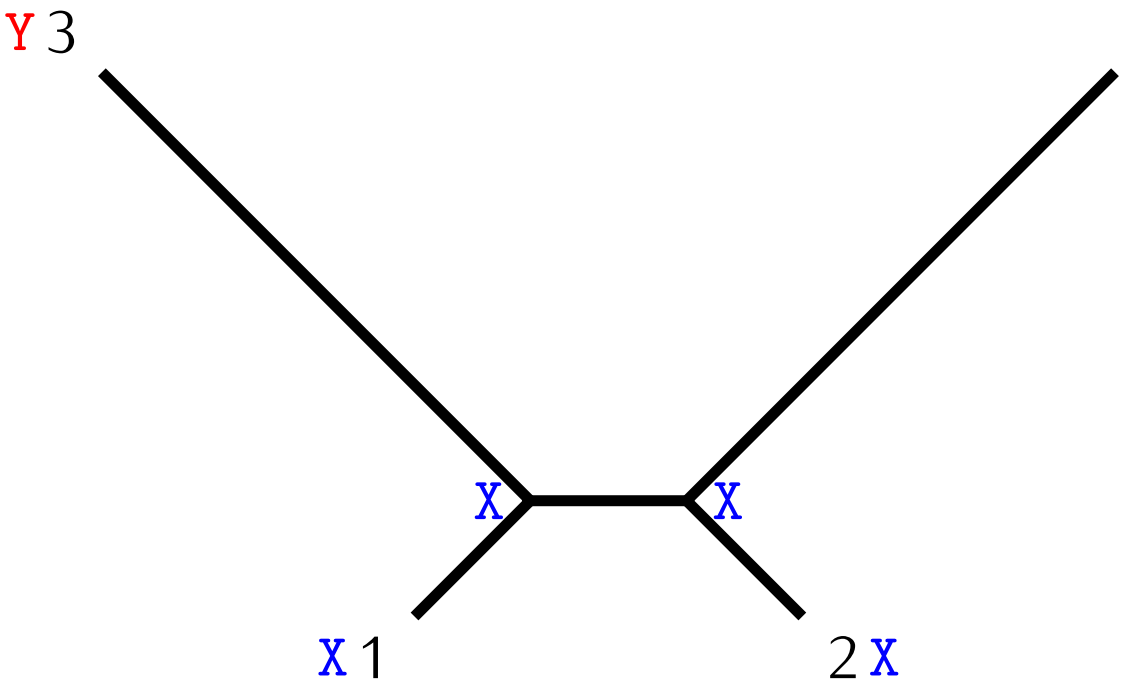

	a	b	c	d	e	f
1	X	X	X	X	X	X
2	X	Y	Y	X	X	X
3	Y	X	Y	Y	X	Y
4	Y	Y	X	Z	Y	X

- The 'right' site is $b : ((1,3),(2,4))$, but sites of type a are more frequent
- According to the maximum parsimony criterion, the a tree is the correct one
- Using non-informative sites can help resolving the issue

Long-branch attraction

Is the guinea-pig a rodent?

Dan Graur*†, Winston A. Hide†‡ & Wen-Hsiung Li†§

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† Center for Demographic and Population Genetics, University of Texas, PO Box 20334, Houston, Texas 77225, USA
‡ Department of Cell Biology, Baylor College of Medicine, Houston, Texas 77030, USA

THE guinea-pig (*Cavia porcellus*), traditionally classified as a New World hystricomorph rodent, often shows anomalous morphological and molecular features in comparison with other eutherian mammals[1–14]. For example, its insulin differs from that of other mammals in anabolic and growth-promoting activities and in its capability to form hexamers[5,6]. Indeed, the literature about the molecular evolution of guinea-pigs abounds in references to 'convergent evolution', 'extremely rapid rates of substitution', and 'unique evolutionary mechanisms'. These claims are based on the assumption that the guinea-pig is a rodent. Our phylogenetic analyses of amino-acid sequence data, however, imply that the guinea-pig diverged before the separation of the primates and the artiodactyls from the myomorph rodents (rats and mice). If true, then the myomorphs and the caviomorphs do not constitute a natural clade, and the Caviomorpha (or the Histricomorpha) should be elevated in taxonomical rank and regarded as a separate mammalian order distinct from the Rodentia. If, as suggested by recent data[15,16], the myomorphs branched off before the divergence among the carnivores, lagomorphs, artiodactyls and primates, then the new order would represent an early divergence in eutherian

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- Similar equations are writable for $\Pr(X(t) = C)$, $\Pr(X(t) = G)$ and $\Pr(X(t) = T)$.

Matrix notation

- We can gather all equations in a more compact form. We note

$$x(t) = \begin{pmatrix} X(t) = A & X(t) = C & X(t) = G & X(t) = T \end{pmatrix}$$

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$$x(t) = x(t_0) \times \underbrace{\begin{pmatrix} p_{AA} & p_{AC} & p_{AG} & p_{AT} \\ p_{CA} & p_{CC} & p_{CG} & p_{CT} \\ p_{GA} & p_{GC} & p_{GG} & p_{GT} \\ p_{TA} & p_{TC} & p_{TG} & p_{TT} \end{pmatrix}}_{P}$$

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  where $p_{ij} = \Pr(i \to j)$.

- 'P' defines the substitution process.

A few more considerations

- We have

$$\forall i, \sum_j p_{i,j} = 1$$

that is

$$\Pr(A \to A) + \Pr(A \to C) + \Pr(A \to G) + \Pr(A \to T) = 1$$

- If we assume that all types of mutations are equi-probable (Jukes and Cantor, 1969), we can simplify:

$$P_{(JC69)} = \begin{pmatrix} 1-3r & r & r & r \\ r & 1-3r & r & r \\ r & r & 1-3r & r \\ r & r & r & 1-3r \end{pmatrix}$$

Continuous time

We assume that the process does not change over time, so we can write the equations for any time t:

$$t = t_0 + dt_0, \quad r = \alpha \cdot dt_0$$

$$x(t_0 + dt_0) = x(t_0) \times \begin{pmatrix} 1 - 3\alpha dt_0 & \alpha dt_0 & \alpha dt_0 & \alpha dt_0 \\ \alpha dt_0 & 1 - 3\alpha dt_0 & \alpha dt_0 & \alpha dt_0 \\ \alpha dt_0 & \alpha dt_0 & 1 - 3\alpha dt_0 & \alpha dt_0 \\ \alpha dt_0 & \alpha dt_0 & \alpha dt & 1 - 3\alpha dt_0 \end{pmatrix}$$

$$x(t_0 + dt_0) = x(t_0) + x(t_0) \cdot Q dt_0$$

$$\frac{x(t_0 + dt_0) - x(t_0)}{dt_0} = x(t_0) \cdot Q$$

Continuous time

- We obtain a differential equation by having $dt_0 \to 0$:

$$\frac{\partial x(t)}{\partial t} = Q \cdot x(t)$$

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$$Q_{(JC69)} = \begin{pmatrix} -3\alpha & \alpha & \alpha & \alpha \\ \alpha & -3\alpha & \alpha & \alpha \\ \alpha & \alpha & -3\alpha & \alpha \\ \alpha & \alpha & \alpha & -3\alpha \end{pmatrix}$$

with

$$\forall i, \sum_j q_{i,j} = 0$$

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with

$$\forall i, \sum_j q_{i,j} = 0$$

- This resolves into

$$x(t) = x(t_0) \cdot \exp(Q \cdot t)$$

Conclusion

We can compute the probability that a certain sequence ($x(t_0)$) transforms into another given sequence ($x(t)$) after a known time (t) and given a certain substitution process specified by its generator (Q).

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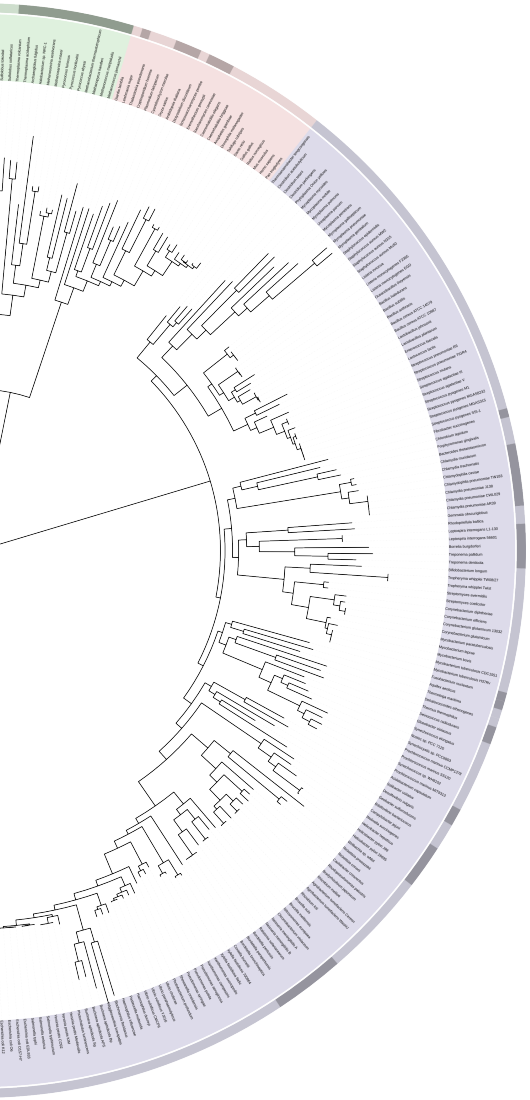
So what???

If we have two sequences and Q, we can compute t which maximizes this probability $\rightarrow$ unbiased estimate of the divergence between the two sequences!

Evolution along a tree



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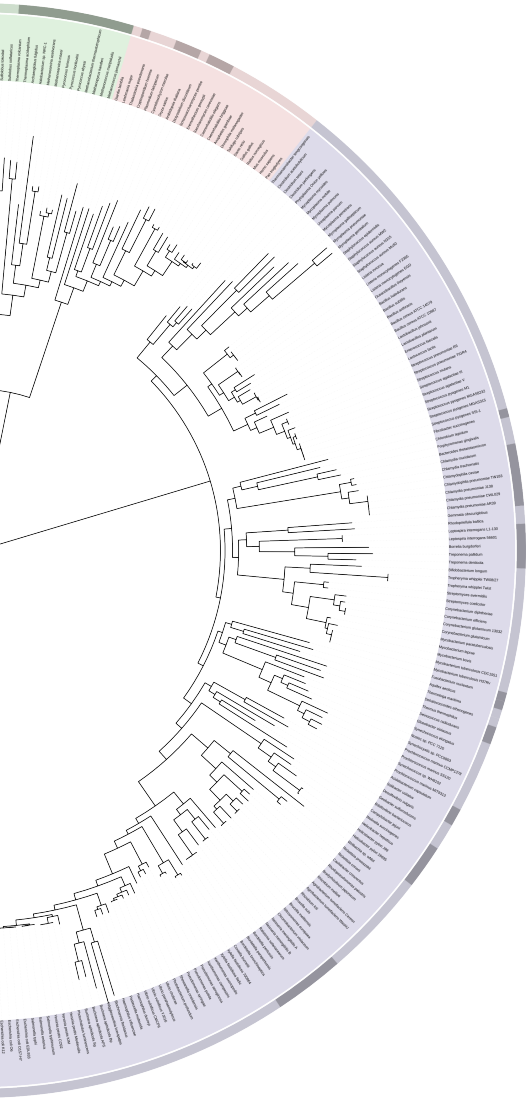

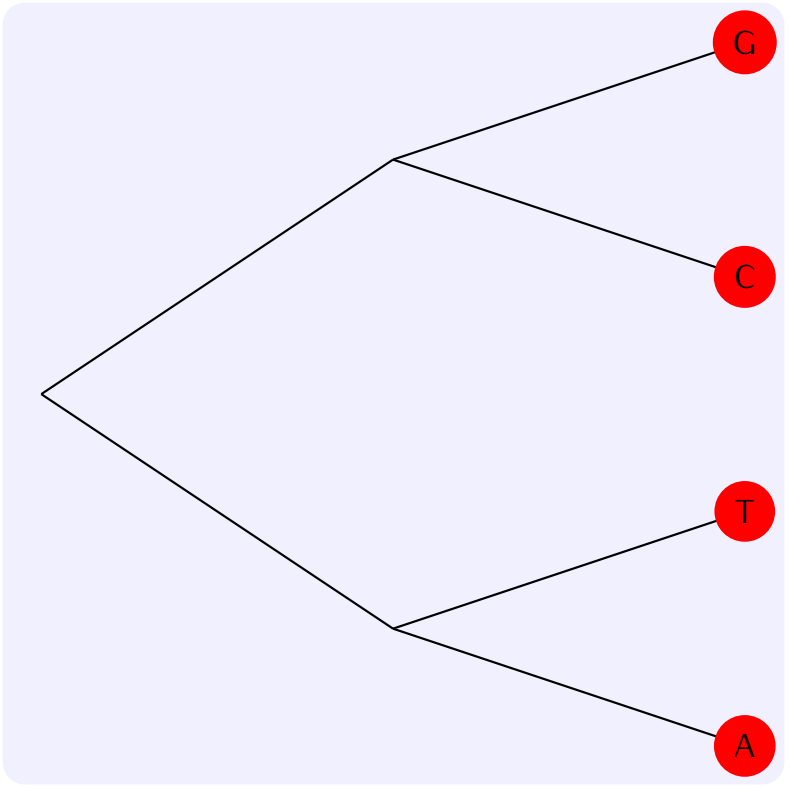

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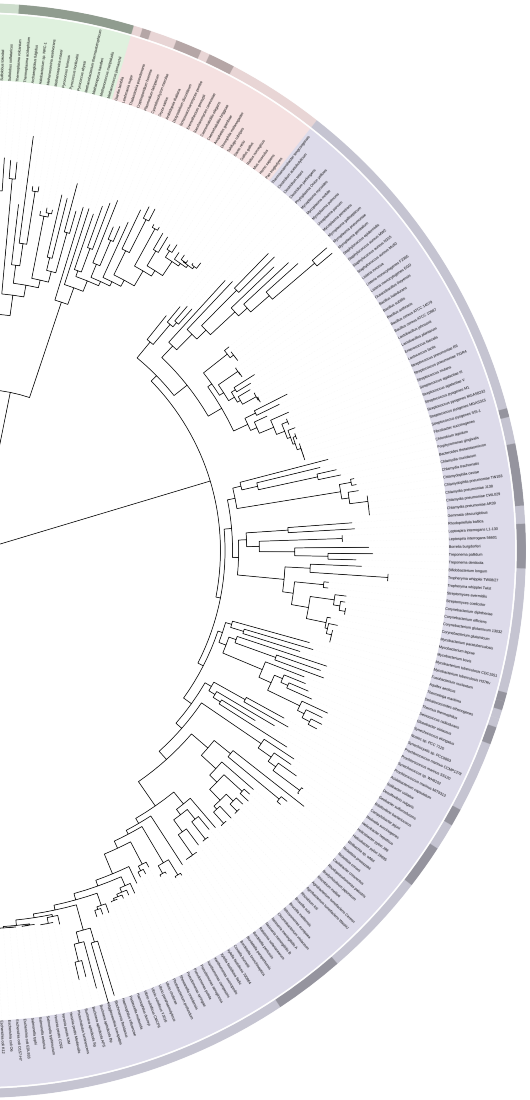

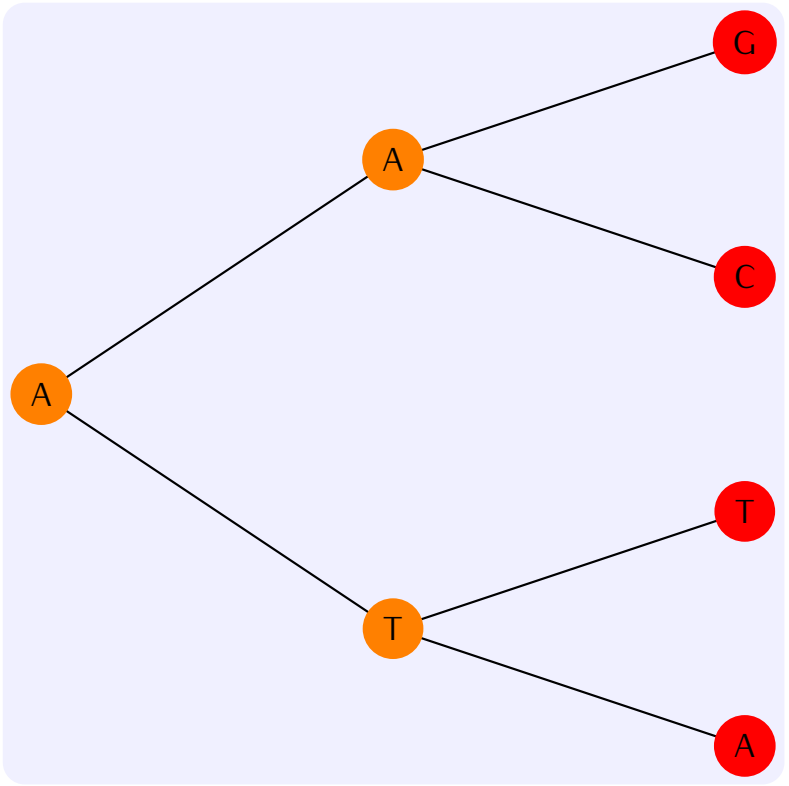

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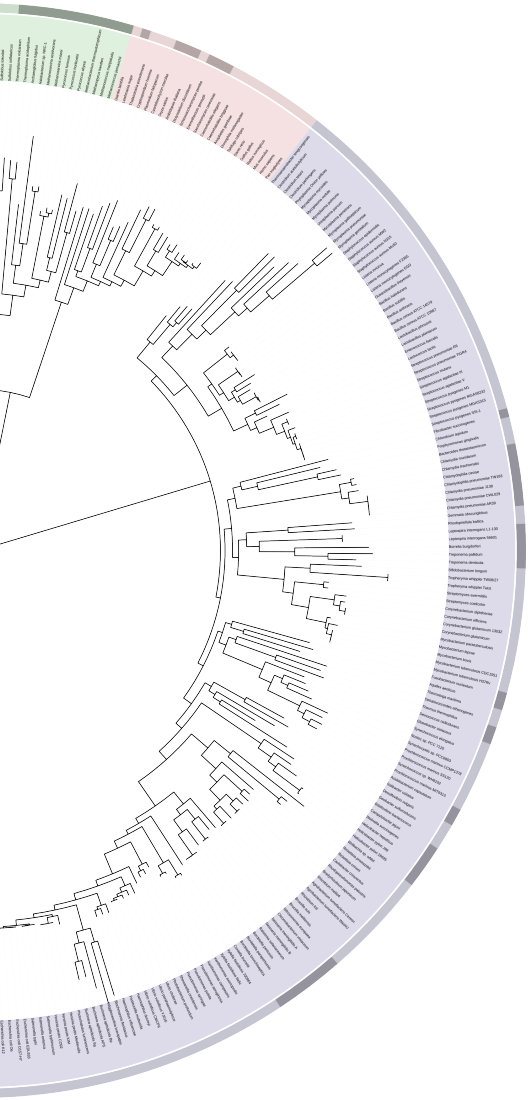

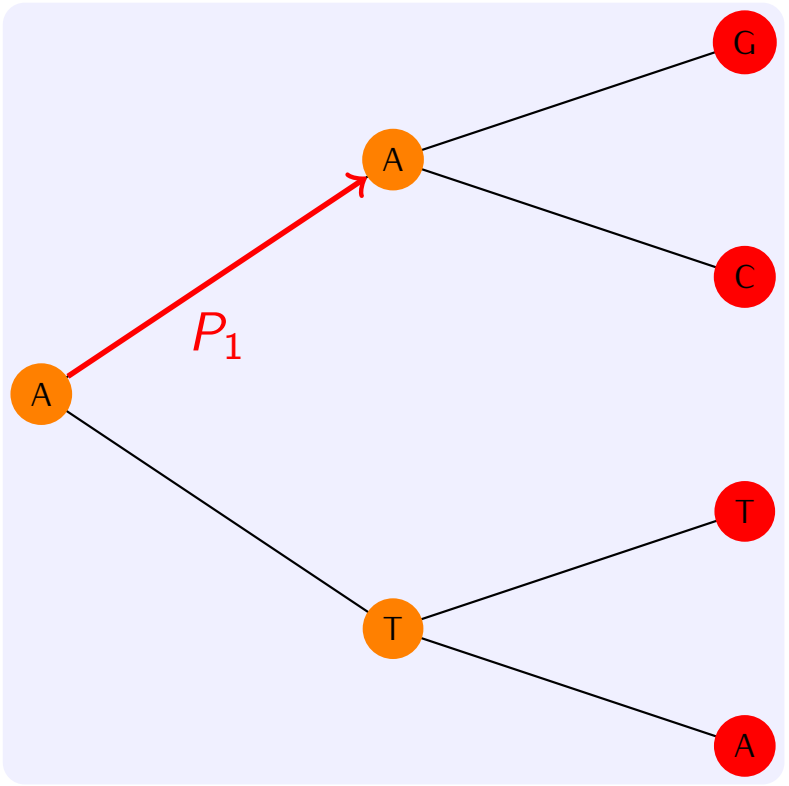

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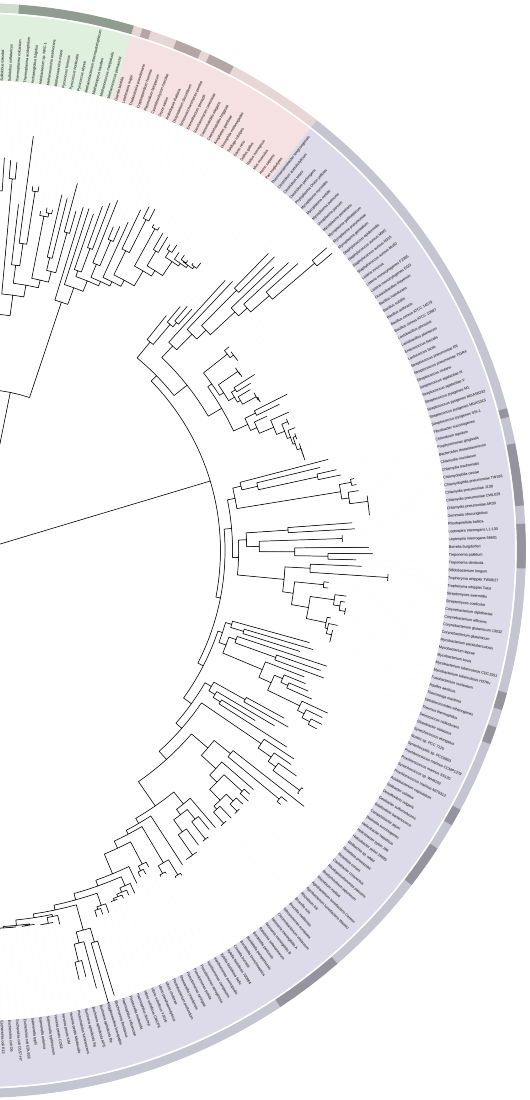

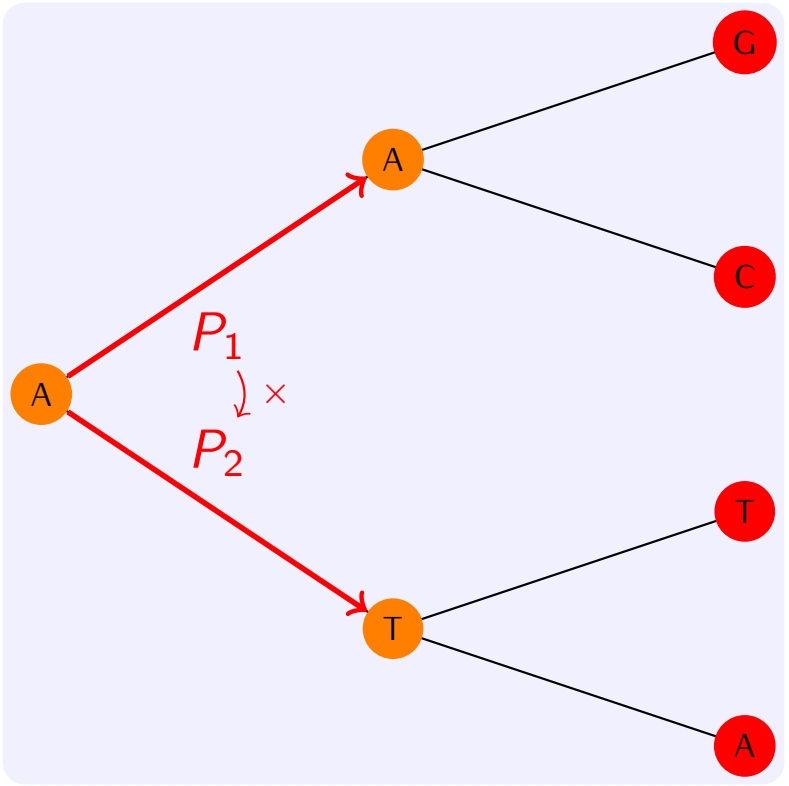

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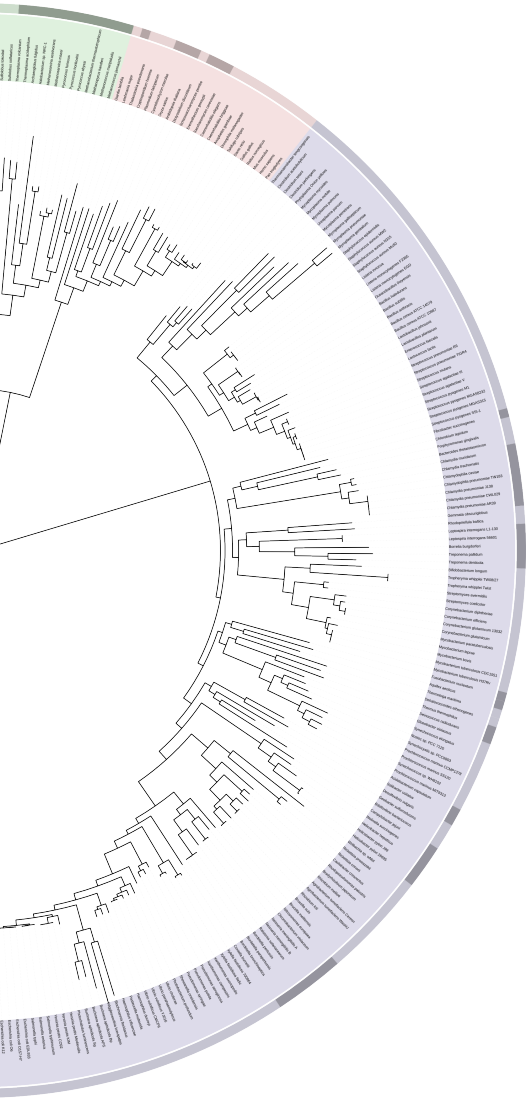

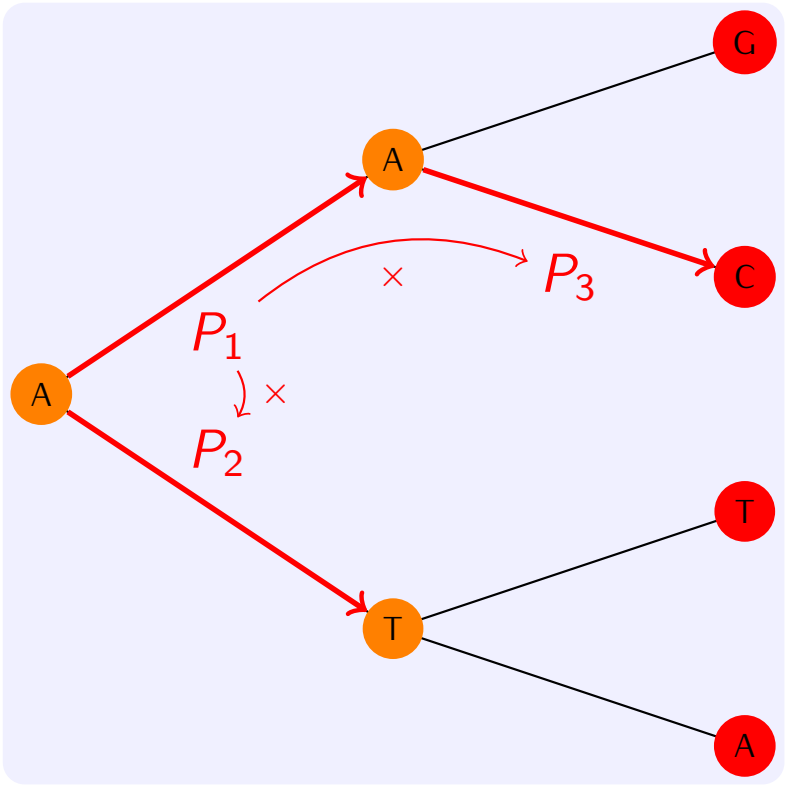

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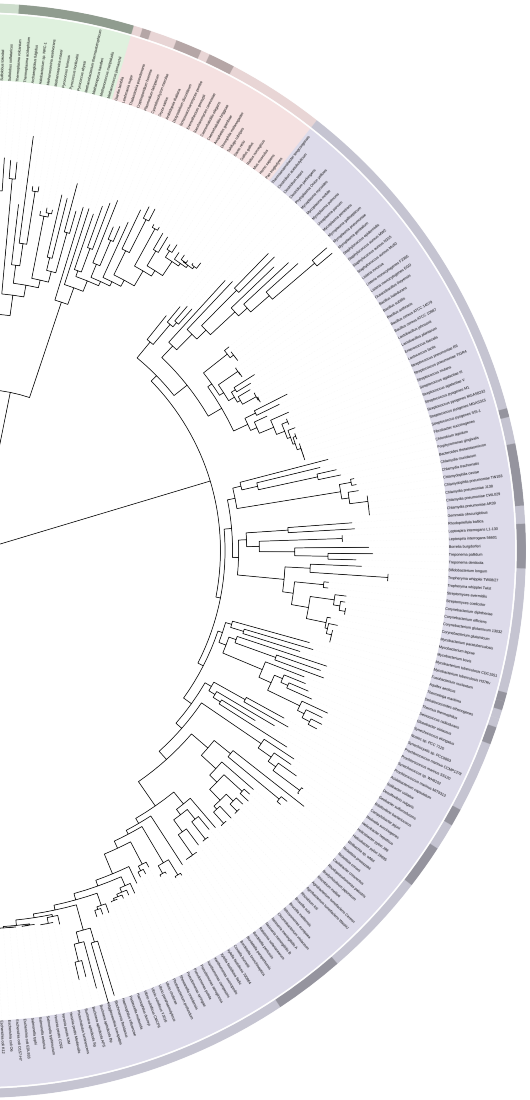

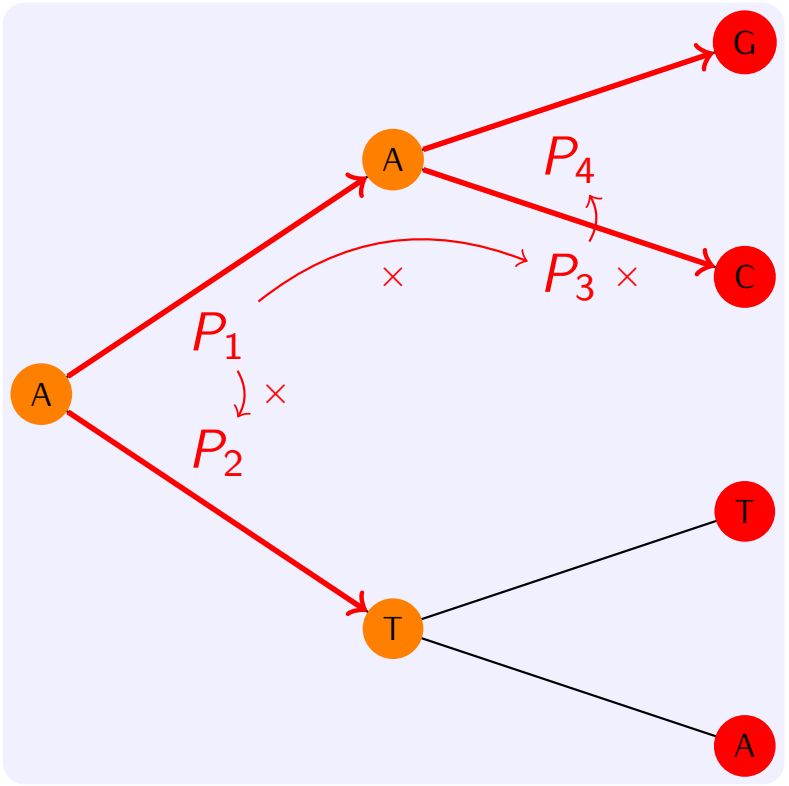

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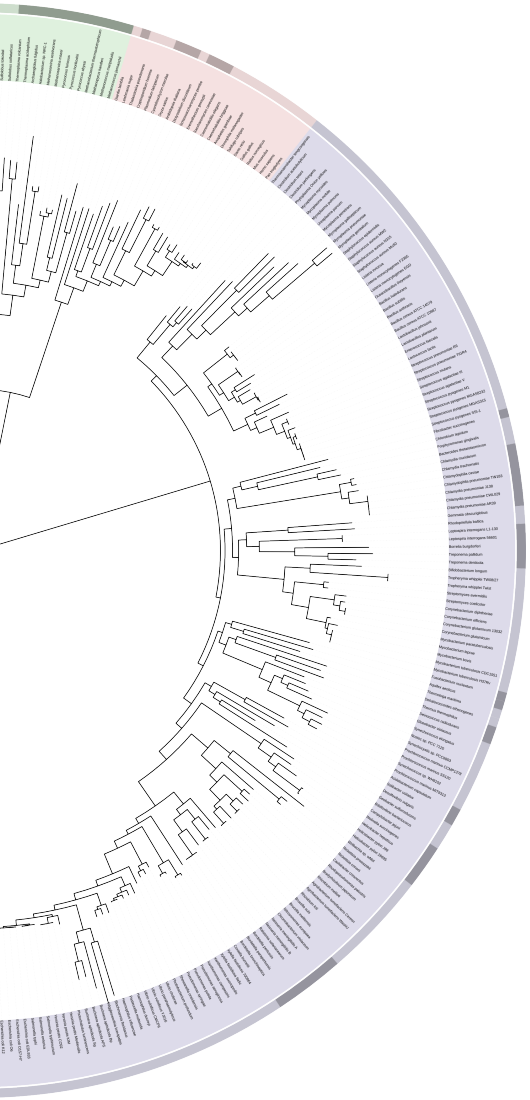

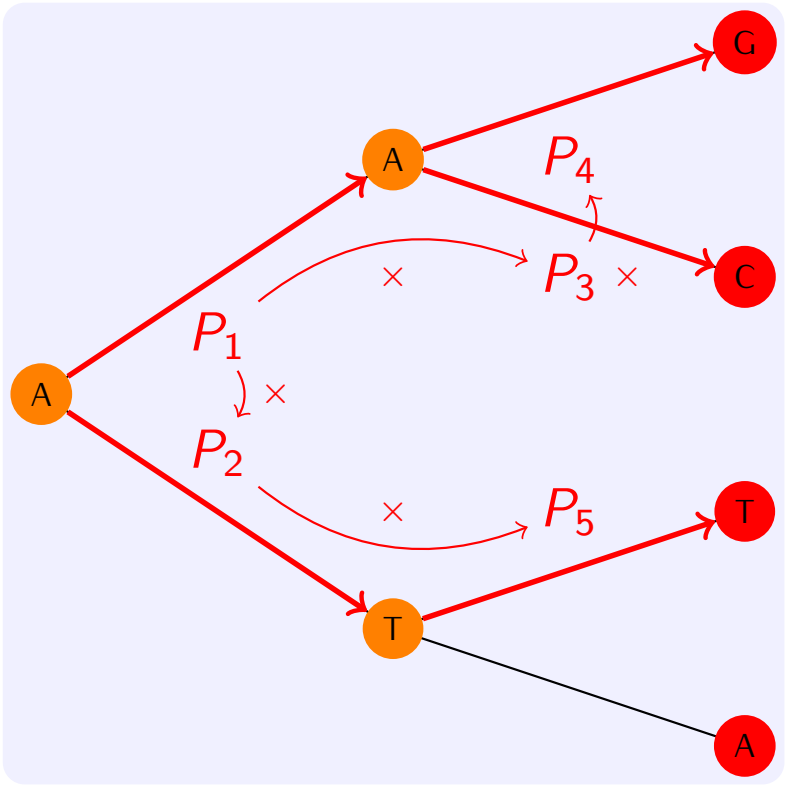

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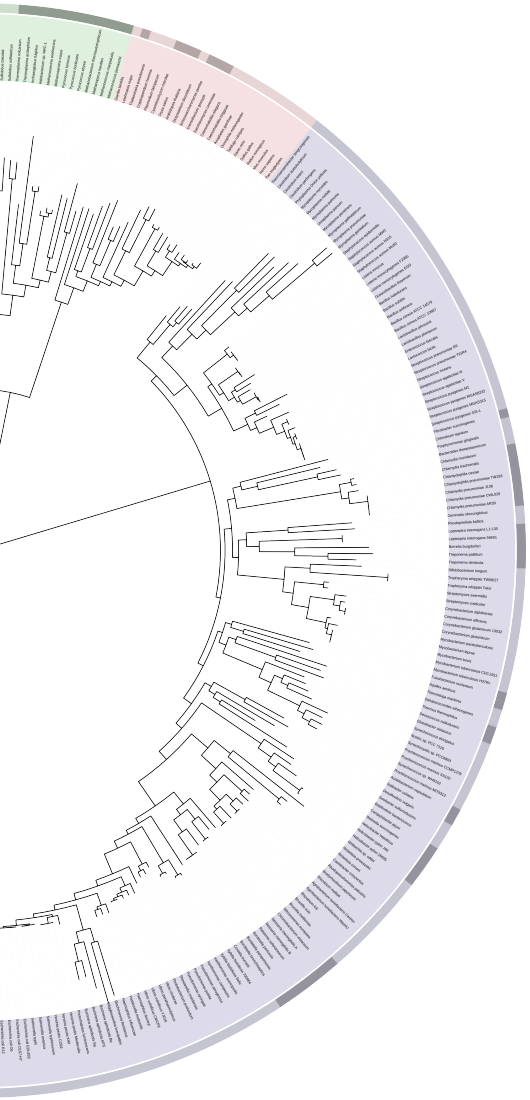
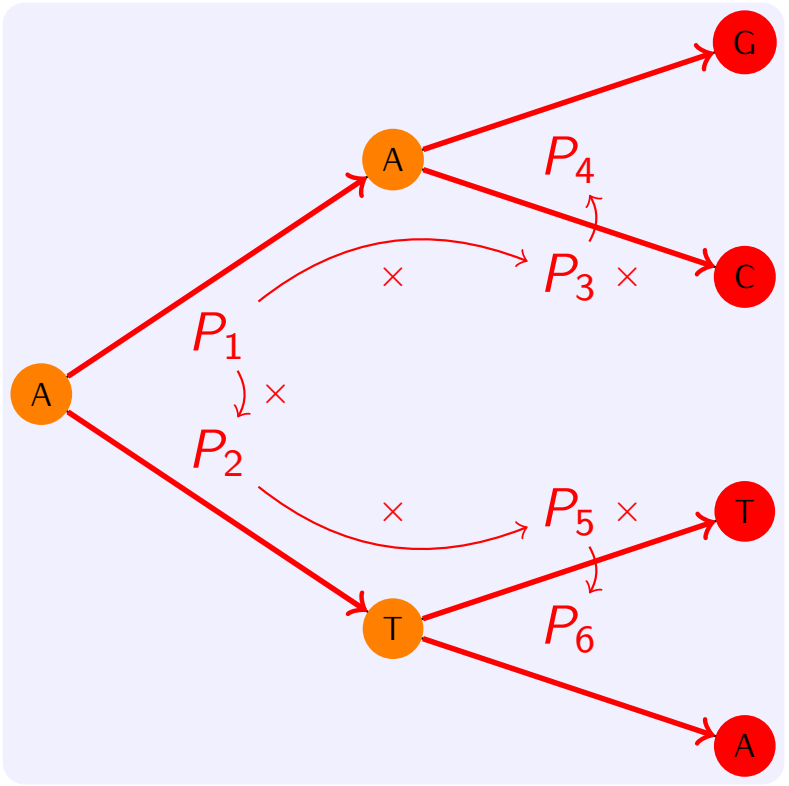
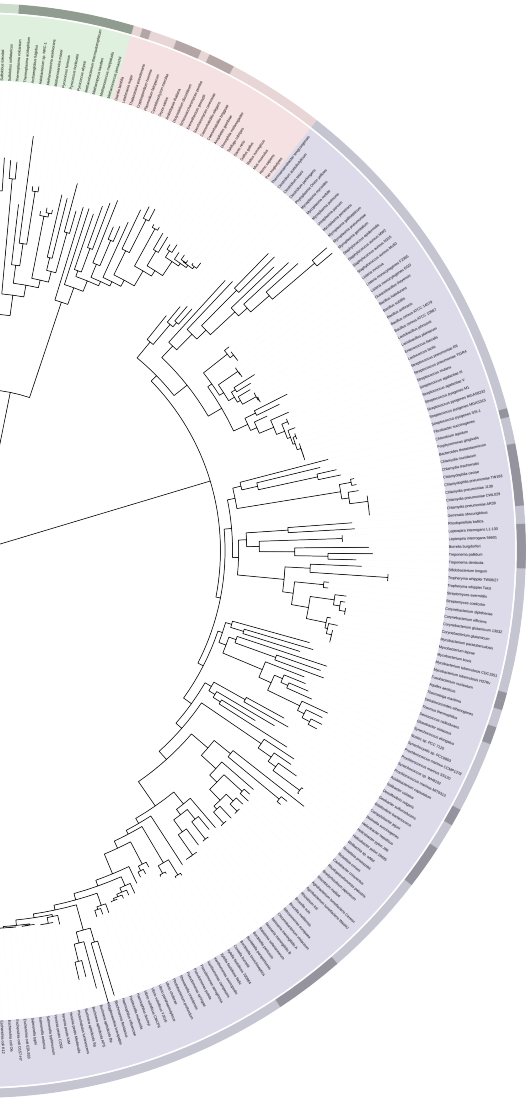
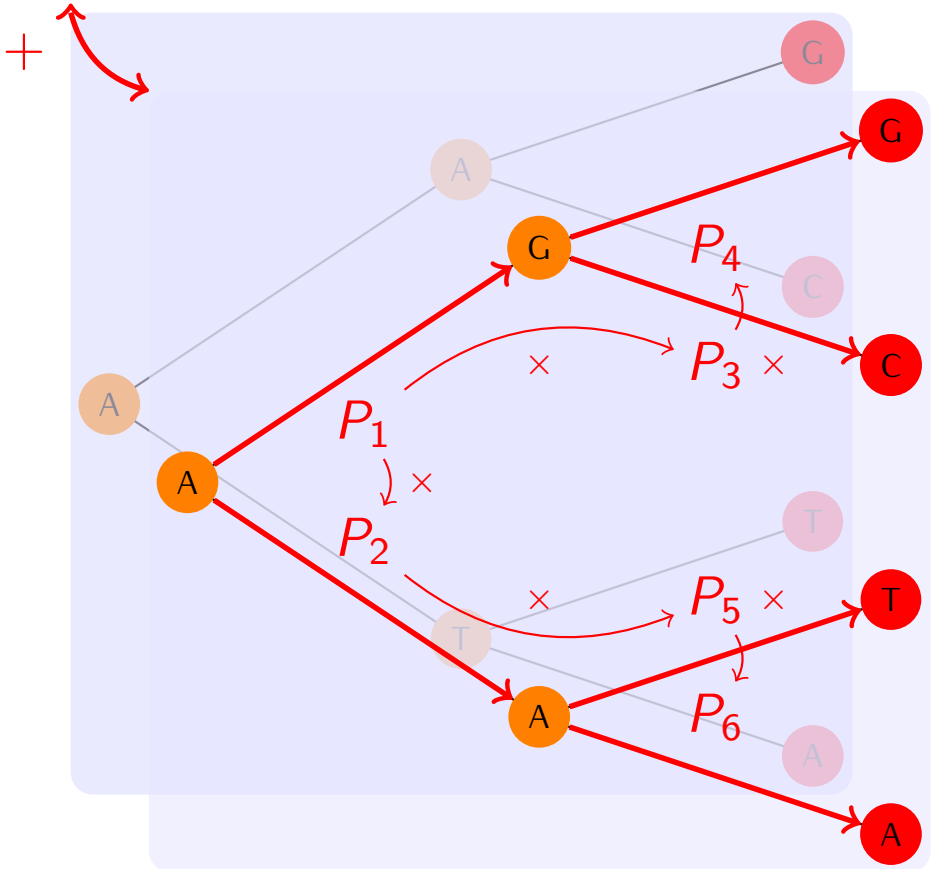


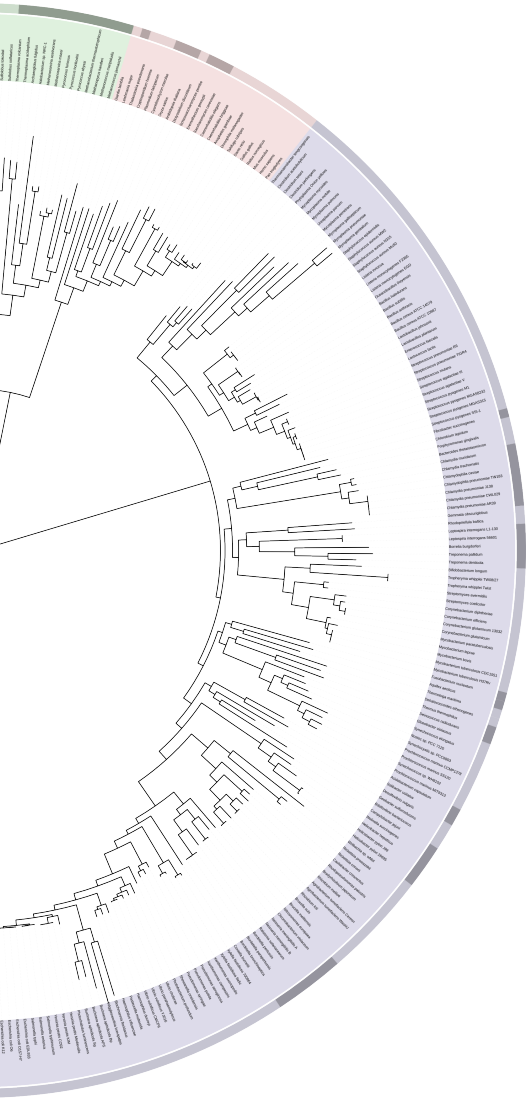


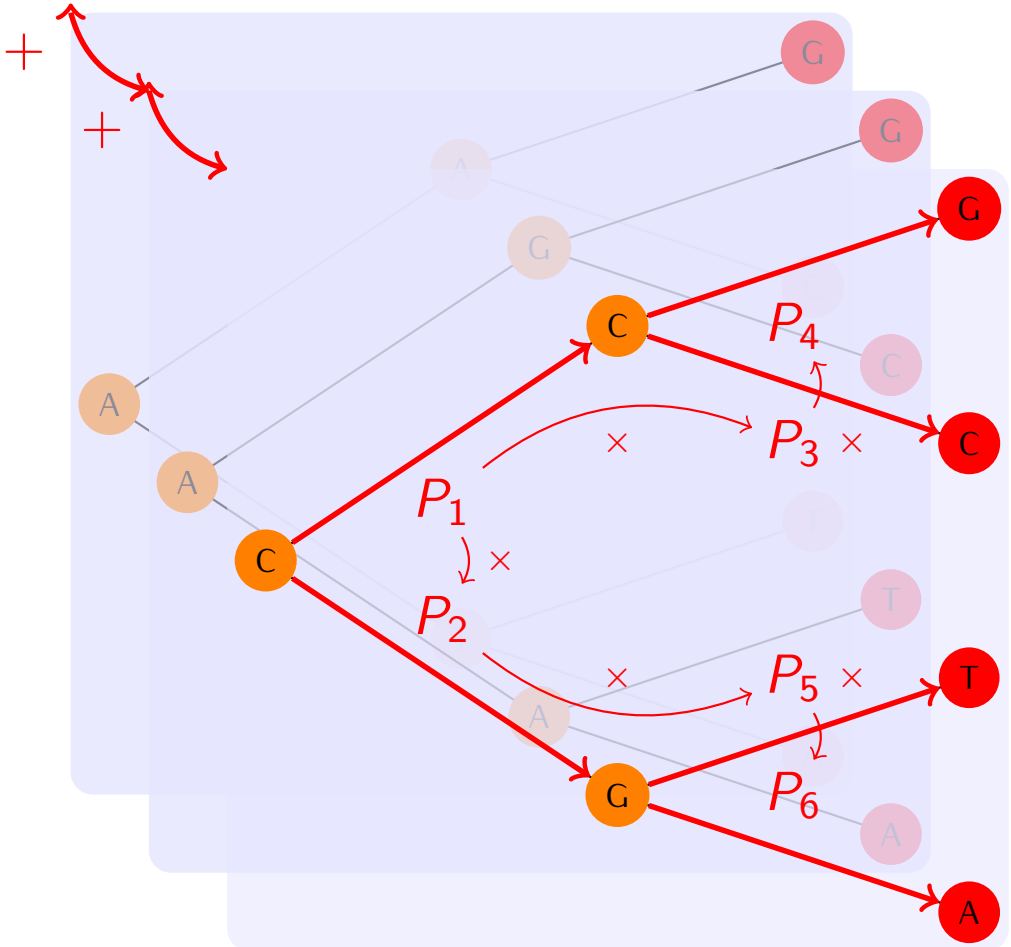
Evolution along a tree





Evolution along a tree





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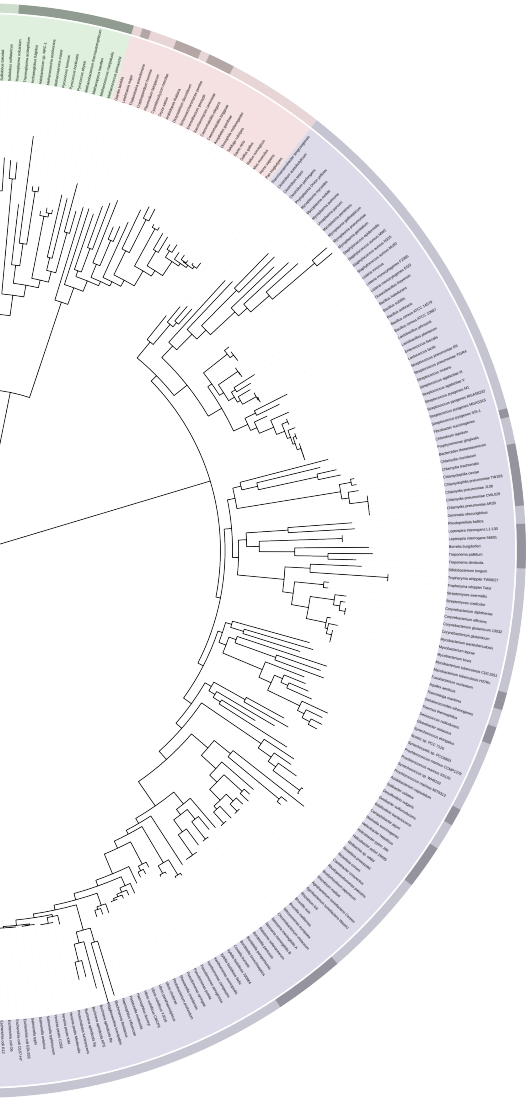

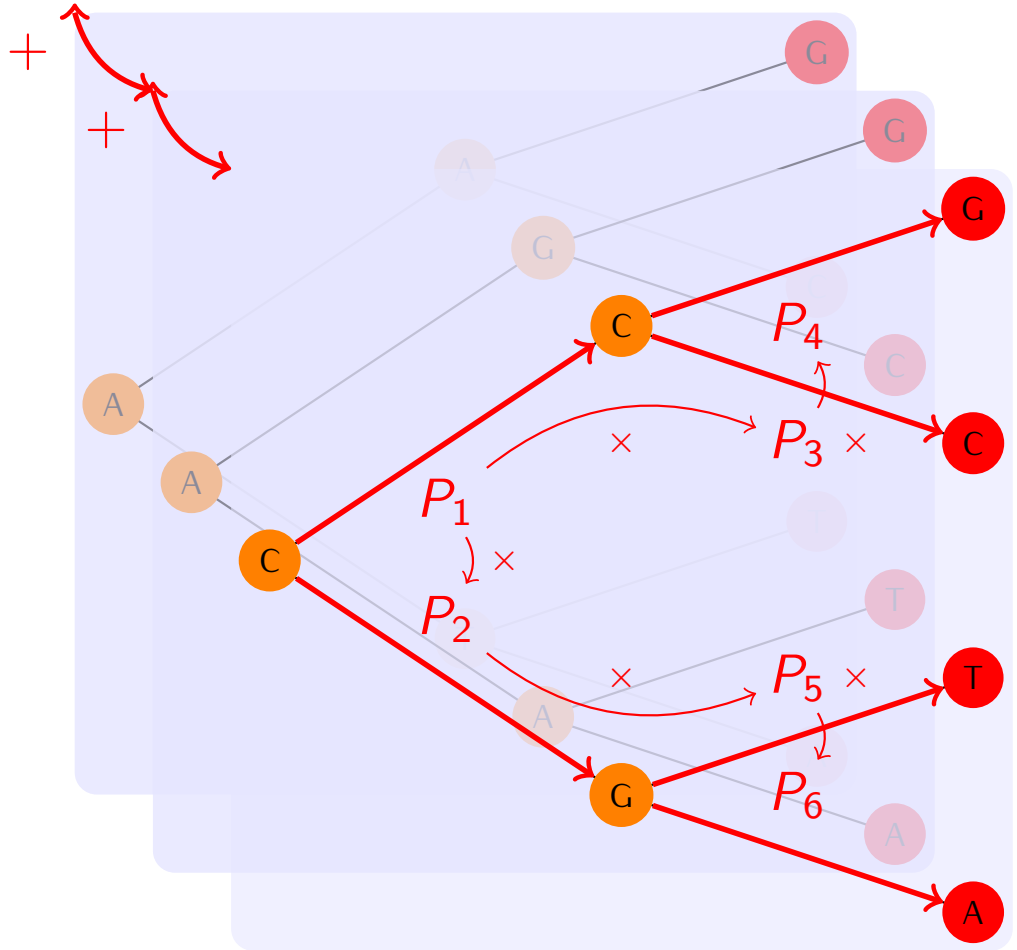

$$L = \sum_{\text{Ancestors}} P_1 \times P_2 \times P_3 \times P_4 \times P_5 \times P_6$$

Maximum likelihood

Maximum-likelihood estimation (MLE)

MLE is a method of estimating the parameters of a statistical model. For a given dataset and underlying statistical model, the maximum likelihood estimator corresponds to the set of values of the model parameters that maximizes the likelihood function. (The method was initially proposed by statistician Ronald Aylmer Fisher in 1922.)

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- General statistical framework
- Allows to perform model comparisons
- Allows to get confidence intervals of estimates

[However...]

...is tree topology (really) a parameter?

The bootstrap procedure

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$\Rightarrow$ Allows to compute to which extent each internal branch is supported by the data

What can bias the reconstruction?

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- Long branch attraction
- Model misspecification
- Inconsistency between the history of sequences and the history of species:
  - Stochasticity, incomplete lineage sorting
  - Introgression, horizontal gene transfer
  - Selection, convergence