Phylogenetic Inference

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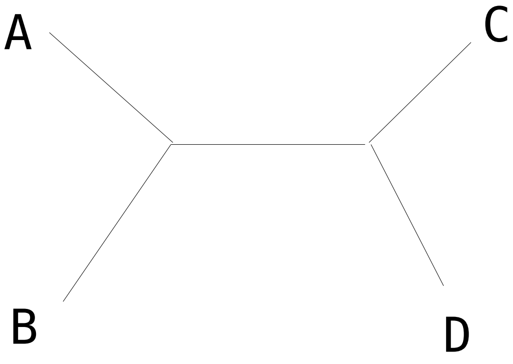
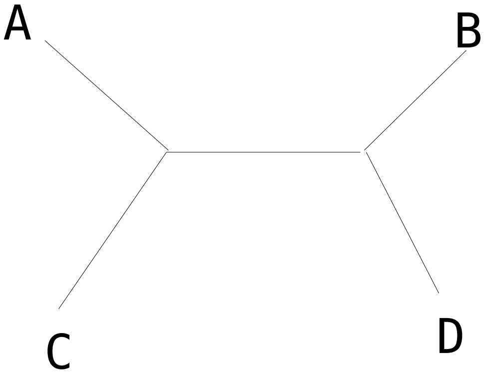
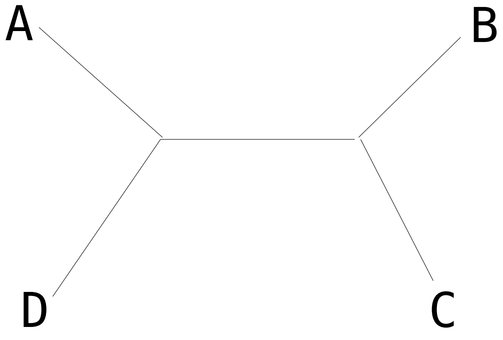
Plan for Today

- Phylogenetic Inference
- Phylogenetic scoring criteria
- Phylogenetic search algorithms

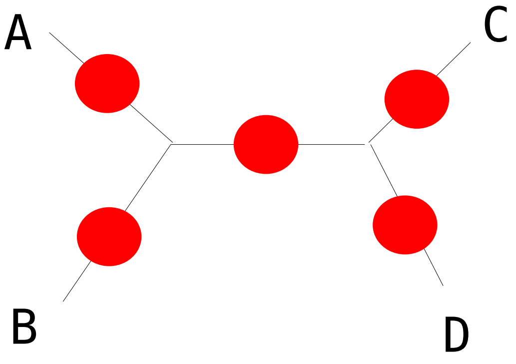
How many unrooted 4-taxon trees exist?

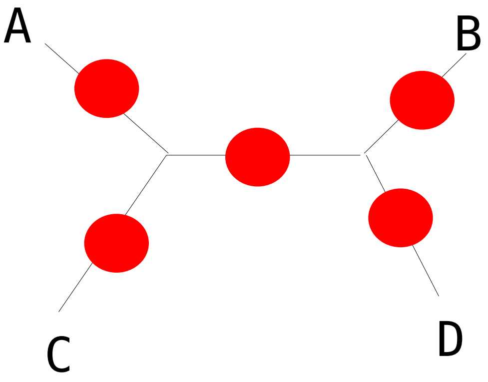


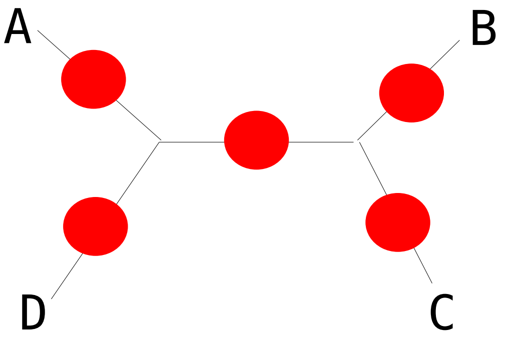




How many rooted 4-taxon trees exist?



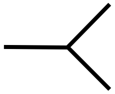




Tree Counts

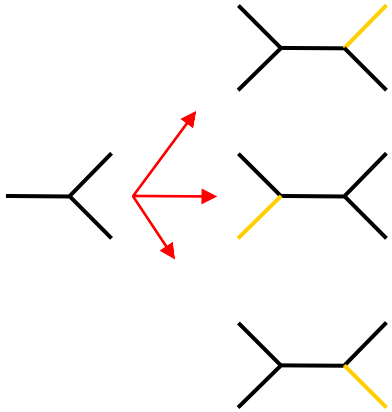
- Unrooted binary trees
  - *4* taxa → *3* distinct trees
  - A tree with *n* taxa has *n-2* inner nodes
  - And *2n-3* branches
- Rooted binary trees
  - *4* taxa → *3* unrooted trees * *5* branches each (rooting points) = *15* trees
  - *n-1* inner nodes
  - *2n-2* branches

The number of trees



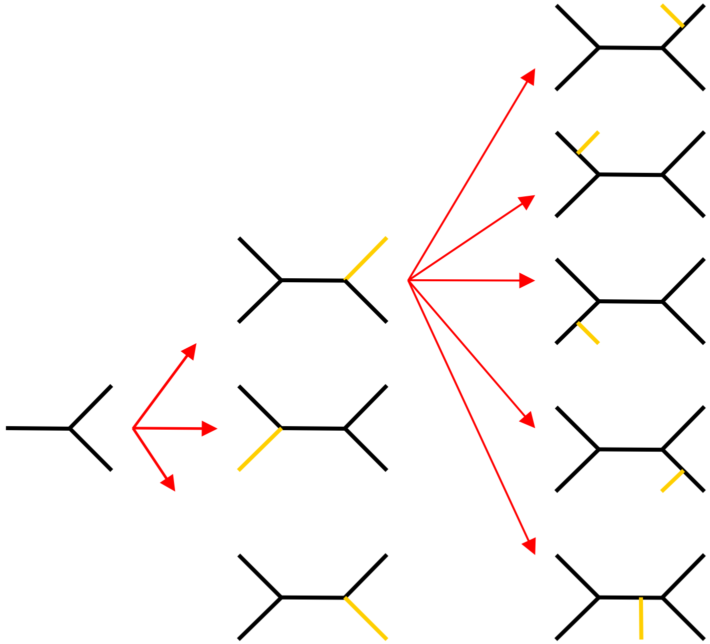
3 taxa = 1 tree

The number of trees



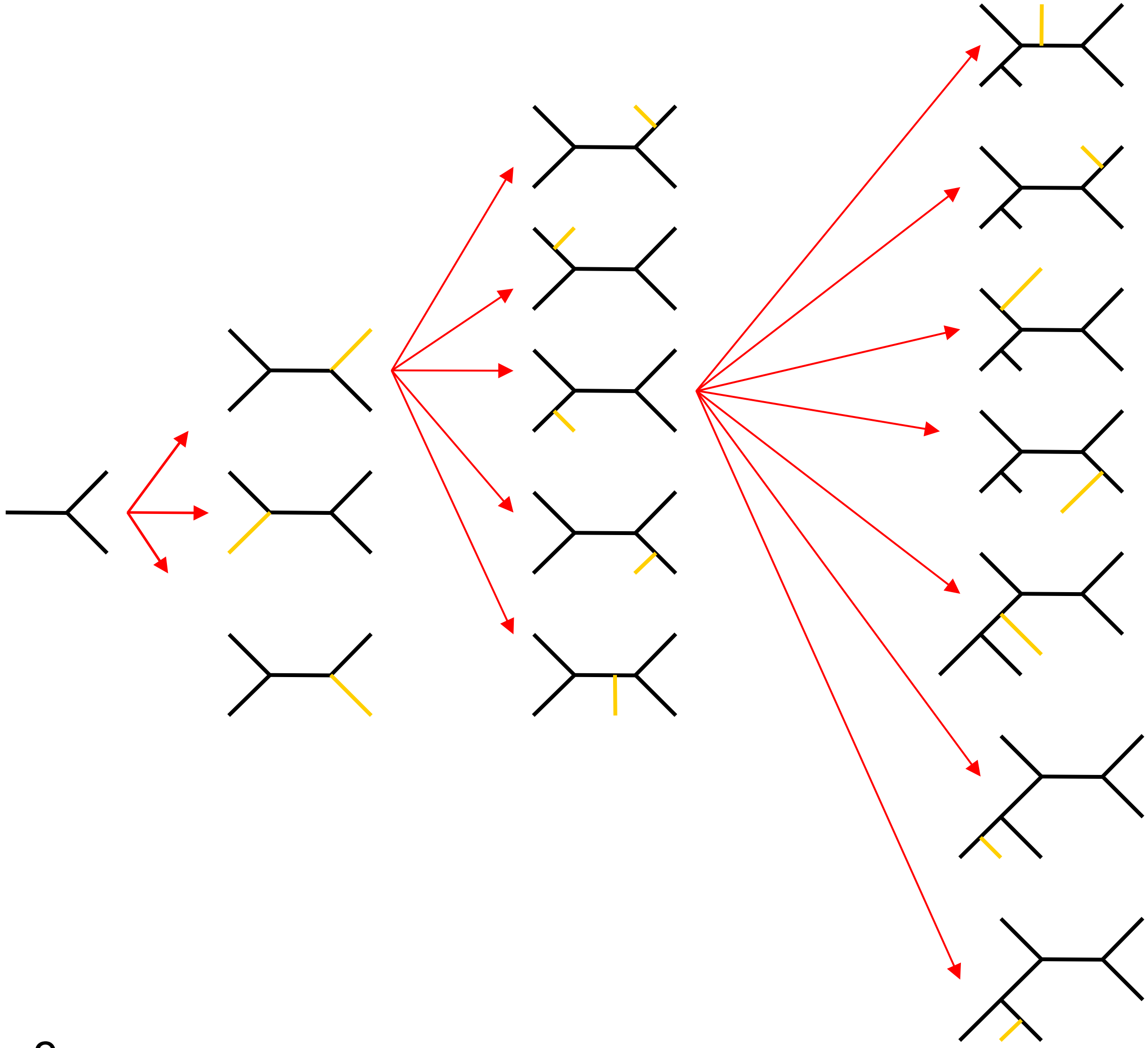
4 taxa: 3 trees
u: # trees of size 4-1 := 1
v: # branches in a tree of size 4-1 := 3
Number of unrooted binary trees with 4 taxa: u * v = 3

The number of trees



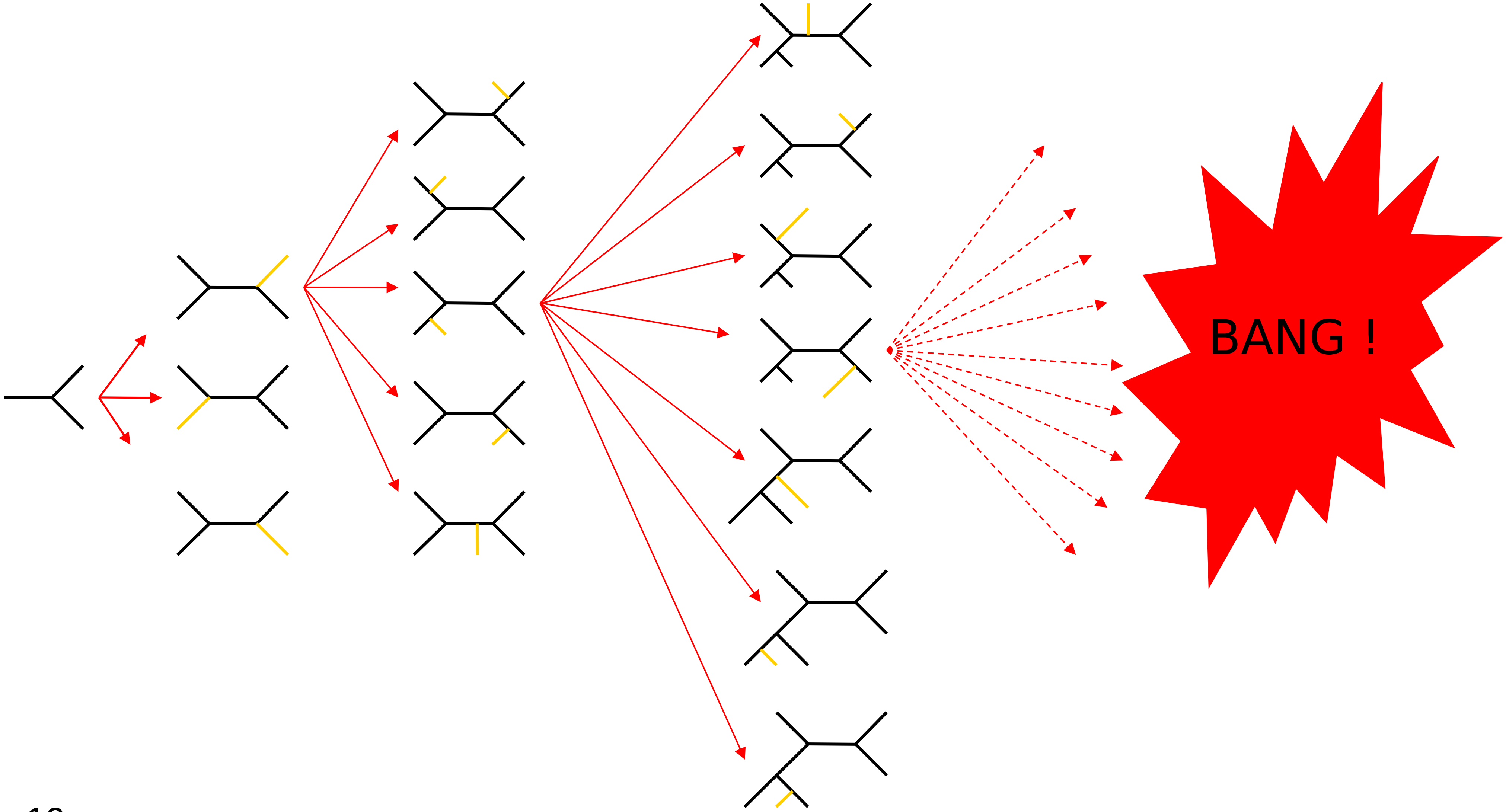
5 taxa: 15 trees
u = 3
v = 5
Number of unrooted trees with 5 taxa: 3 * 5 = 15

The number of trees



6 taxa: 105 trees
u = 15
v = 7
u * v = 105

The number of trees explodes!



Equation for the number of unrooted trees

- Simple proof via induction

$$\prod_{i=3}^{n}(2i-5)$$

- The number of rooted trees for *n* taxa simply is the number of unrooted trees for *n+1* taxa
- The additional ($n+1^{th}$) taxon represents all possible rootings for all unrooted trees with *n* taxa

trees with 2000 tips

```
stamatak@exelixis:~/Desktop/GIT/TreeCounter$ ./treeCounter -n 2000


GNU GPL tree number calculator released June 2011 by Alexandros Stamatakis

Number of unrooted binary trees for 2000 taxa: 30049638174211656151632910065681814981377232074237013089504954043012636525258308210827685996688247000464352735214265634288295
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350341796875

Approximately 3.00 times 10^6328
```
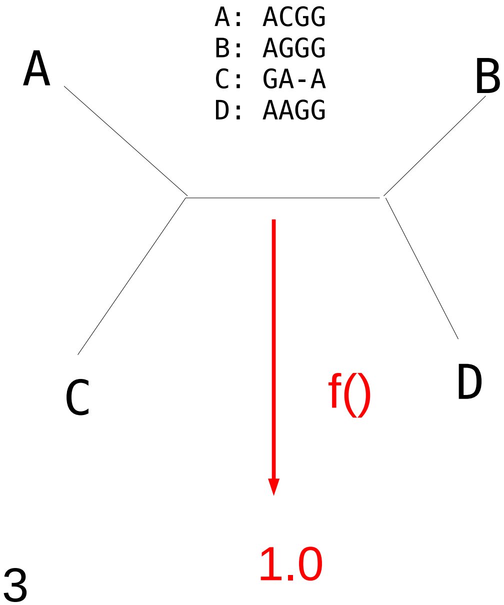
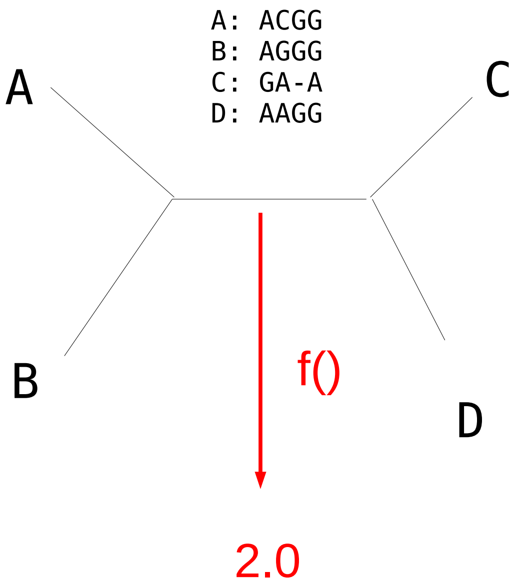
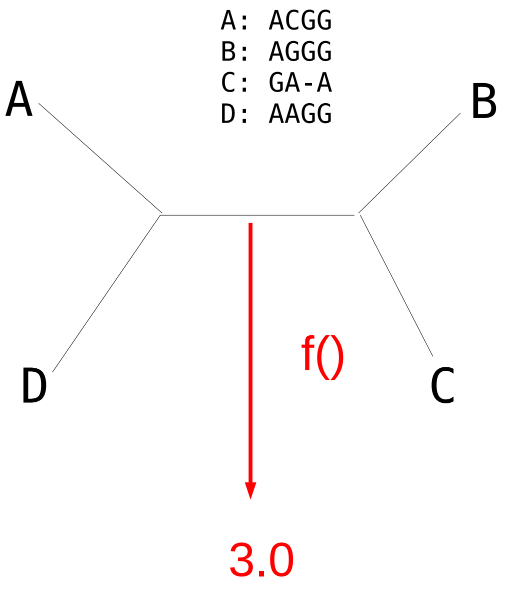

Scoring Trees

- Now we know how many **unrooted** candidate trees there exist for *n* taxa
- How do we chose among them?
  - → we need some scoring criterion f() to evaluate them
  - → finding the optimal tree under most of these criteria is NP-Hard







Scoring Criteria and Tree Inference Algorithms

Building Trees

- We distinguish between
  - *Distance-based methods*
    - → use MSA to compute a matrix of pair-wise distances
    - → build a tree using these distances
    - → Heuristics (essentially hierarchical clustering methods)
      - → *Neighbor Joining:* NJ
      - → *Unweighted Pair Group Method with Arithmetic Mean:* UPGMA
    - → least-squares method: explicit optimality criterion

Less accurate,
but faster

-
  - *Character-based methods*
    - → optimality criteria *f()* operate directly on the MSA & tree
      - → parsimony
      - → maximum likelihood
      - → Bayesian inference
    - → take the current tree topology & MSA to calculate a score
    - → the score tells us how well the MSA data fits the tree

Slow, but more
accurate

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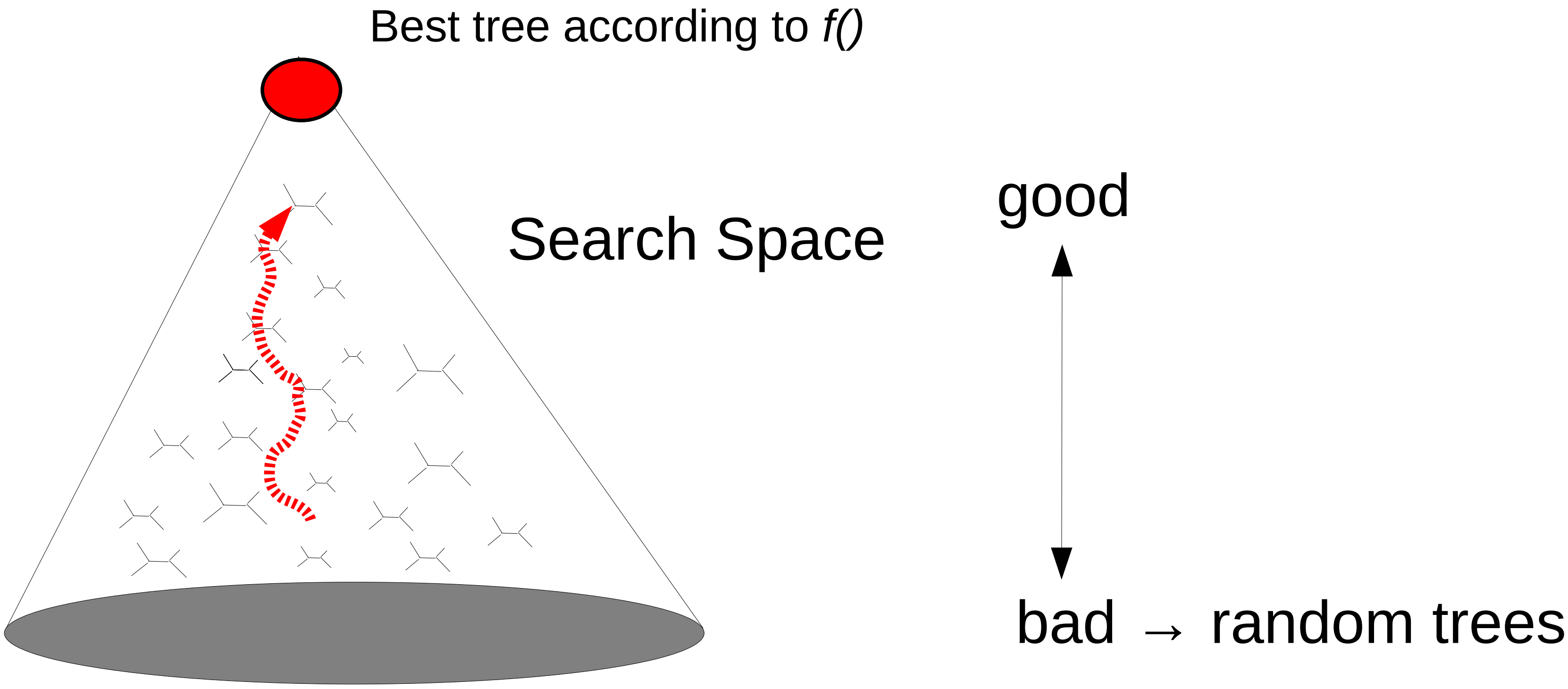
Memory-intensive!

Slow, but more
accurate

NP-Hardness

- Because of the **super-exponential increase** in the number of possible trees for *n* taxa ...
- all interesting optimality criteria on trees are NP-hard:
  - Least squares
  - Parsimony → discrete criterion
  - Likelihood → statistical criterion
  - Bayesian → integrate likelihood over entire tree space

Search Space



Best tree according to *f()*

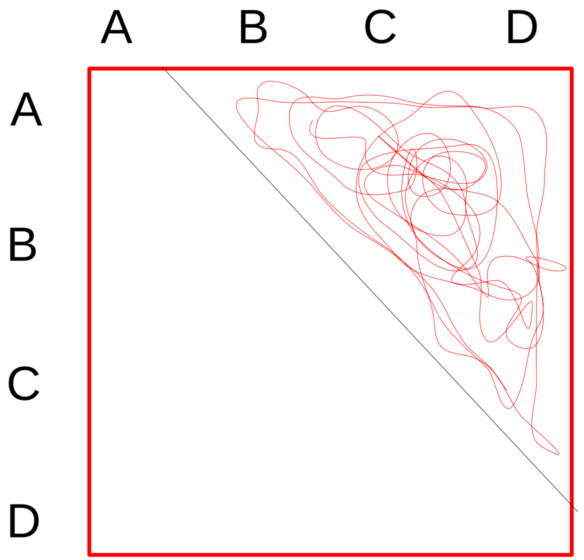
Search Space

good

bad → random trees

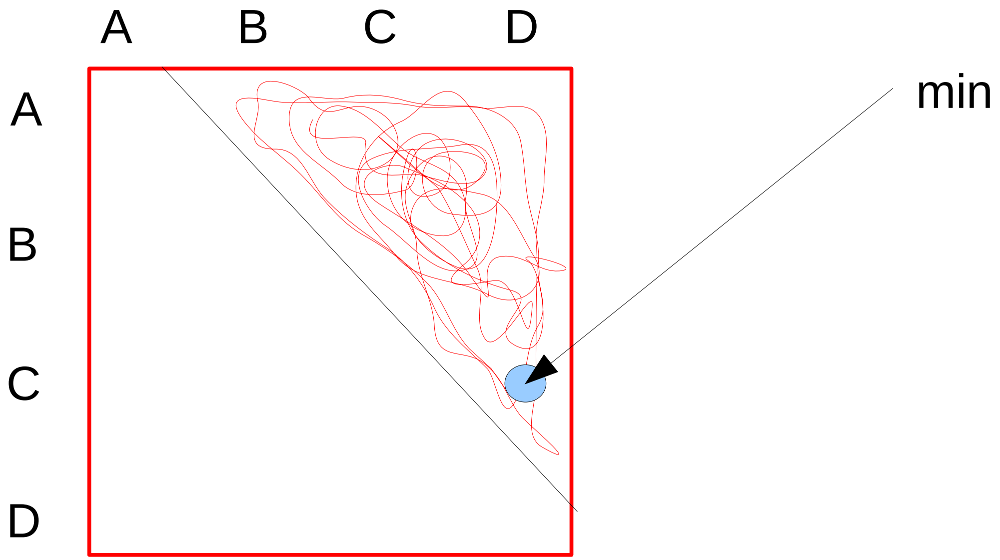
Let’s start with distance based methods/heuristics

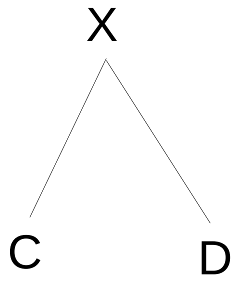
Neighbor Joining → Principle



Given a kind of distance matrix $D_{i,j}$ where $i,j=1...4$

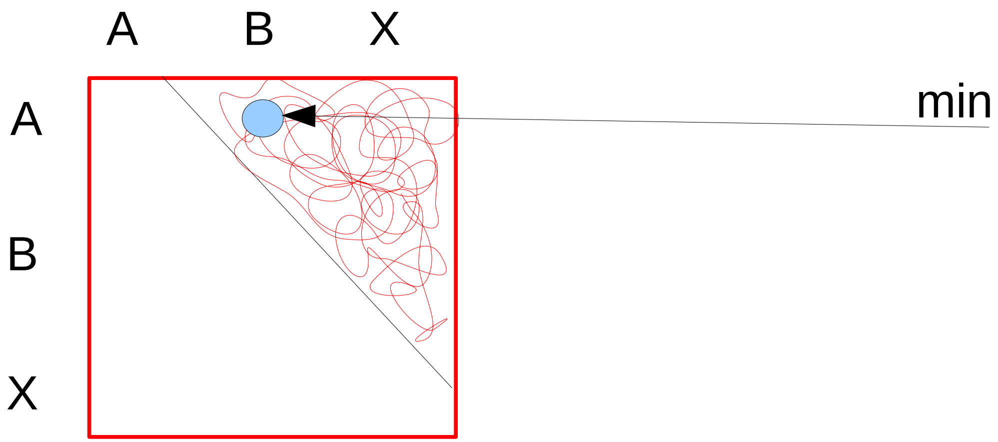
Neighbor Joining → Principle

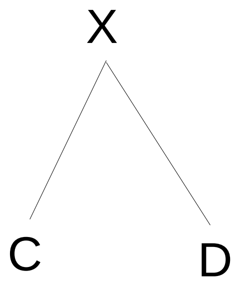




Given a kind of distance matrix $D_{i,j}$ where $i,j=1...4$
Find minimum and merge taxa

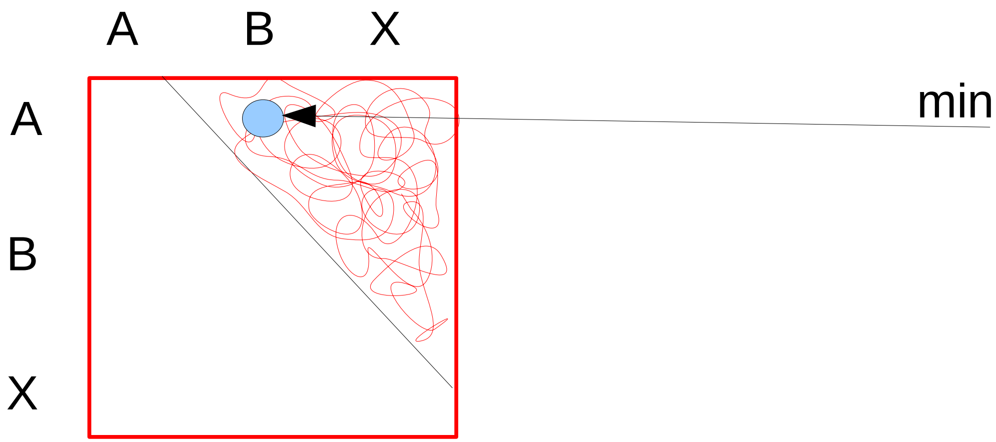
Neighbor Joining → Principle

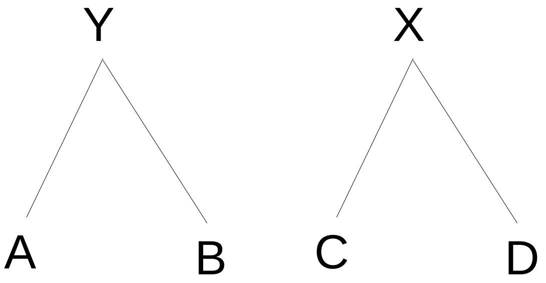




Given a kind of distance matrix $D_{i,j}$ where $i,j=1...4$
Find minimum and merge taxa
Compute a new distance matrix of size $n-1 = 3$
Find minimum

Neighbor Joining → Principle





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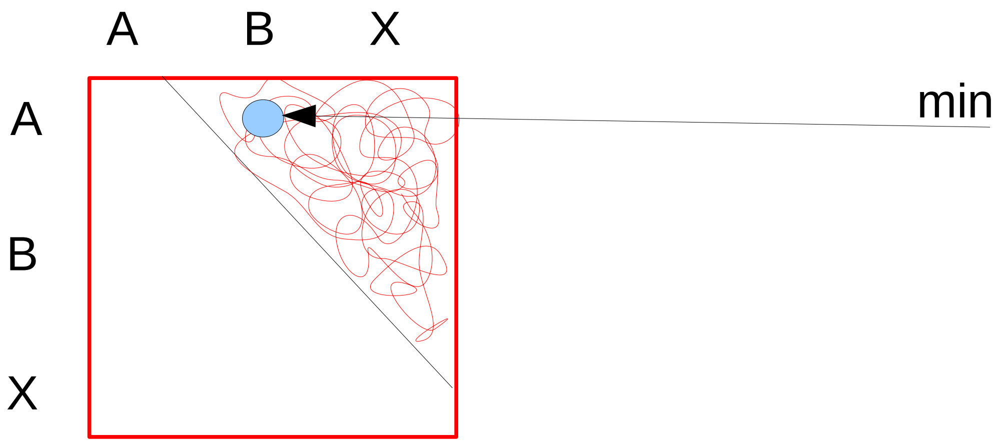

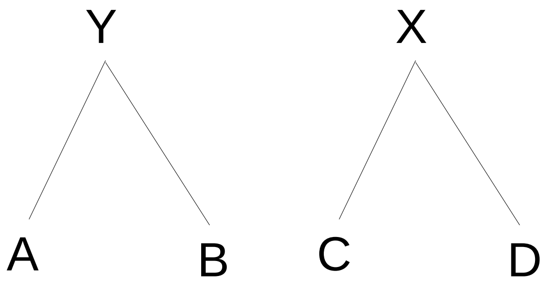

Given a kind of distance matrix $D_{i,j}$ where $i,j=1...4$
Find minimum and merge taxa
Compute a new distance matrix of size $n-1 = 3$
Find minimum and merge taxa
Etc.
Space complexity: $O(n^2)$
Time complexity: $O(n^3)$
Key question: how do we compute distance between X and A or X and B respectively
→ for progressive alignment we may align the profile of X with all remaining sequences

Neighbor Joining Algorithm

- For each tip compute

  $u_i = \Sigma_j D_{ij}/(n-2)$

  → this is in principle the average distance to all other tips

  → the denominator is $n-2$ instead of n, see below why

- Find the pair of tips, (i, j) for which $D_{ij}-u_i-u_j$ is minimal
- Connect the tips (i,j) to build a new ancestral node X
- The branch lengths from the ancestral node X to i and j are:

  $b_i = 0.5\ D_{ij} + 0.5\ (u_i-u_j)$

  $b_j = 0.5\ D_{ij} + 0.5\ (u_j-u_i)$

- Update the distance matrix:
  → Compute distance between the new node X and each remaining tip as follows:

  $D_{ij,k} = (D_{ik}+D_{jk}-D_{ij})/2$

- Replace tips i and j by the new node X which is now treated as a tip
- Repeat until only two nodes remain
  → connect the remaining two nodes with each other

The UPGMA algorithm

- Usually introduced before Neighbor Joining *NJ* → it is simpler and older
- UPGMA is practically not used any more today for phylogeny reconstruction, but it is used for progressive multiple sequence alignment (see MUSCLE algorithm)
- In contrast to NJ it produces *ultrametric* trees!
- It produces rooted trees
- UPGMA stands for: *Unweighted Pair Group Method with Arithmetic Mean*
- Like NJ it uses a distance matrix *D* for clustering/joining nodes
- UPGMA can be used if we know that we have an ultrametric tree!

→ this is usually not the case!

UPGMA example

	A	B	C	D
A		0.4	0.6	0.6
B			0.6	0.6
C				0.2
D				

We will first walk through the algorithm and then look at the formal description!

UPGMA example

	A	B	C	D
A		0.4	0.6	0.6
B			0.6	0.6
C				0.2
D				

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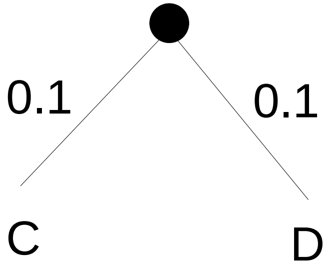

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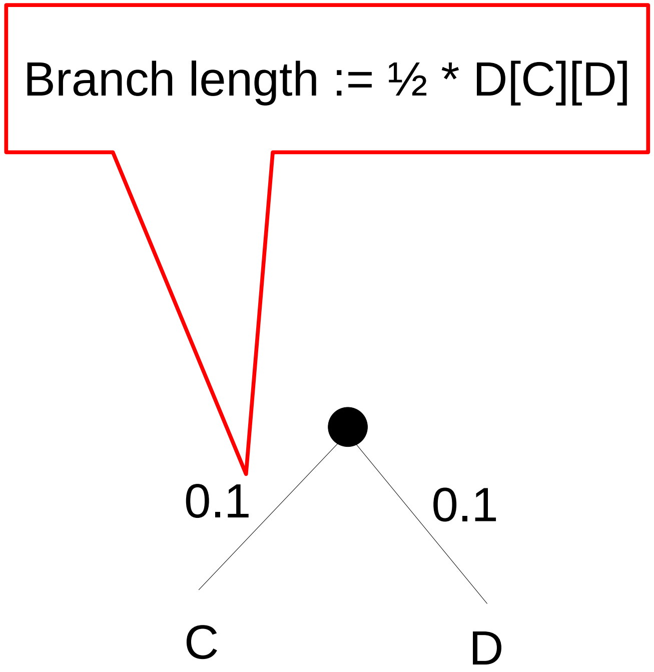
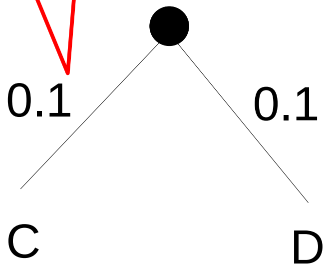


Branch length := ½ * D[C][D]

UPGMA example

	A	B	C	D
A		0.4	0.6	0.6
B			0.6	0.6
C				0.2
D				

Branch length := ½ * D[C][D]
Ensures ultrametricity!



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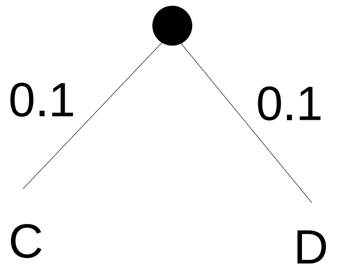
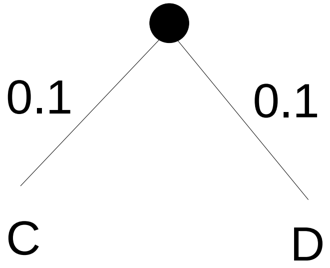


D [A][(C,D)] = ½ * 0.6 + ½ * 0.6
D [B][(C,D)] = ½ * 0.6 + ½ * 0.6

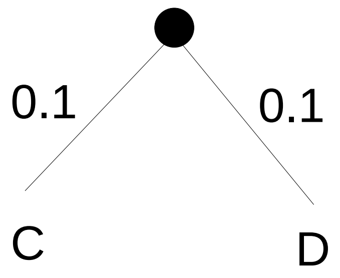
UPGMA example

	A	B	(C,D)
A		0.4	0.6
B			0.6
(C, D)			



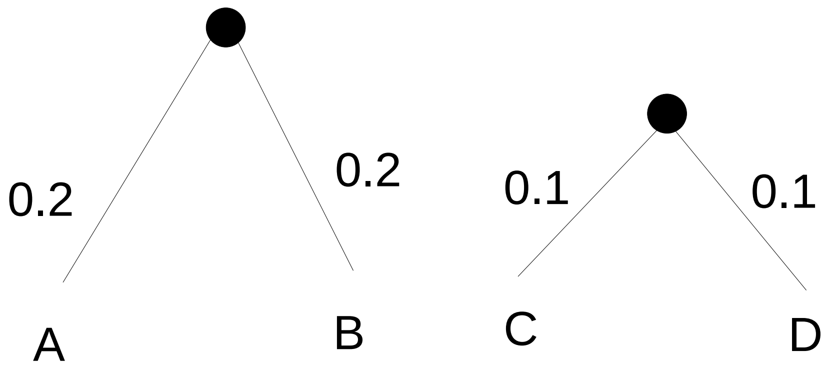
UPGMA example

	A	B	(C,D)
A		0.4	0.6
B			0.6
(C, D)			



UPGMA example

	A	B	(C,D)
A		0.4	0.6
B			0.6
(C, D)			



UPGMA example

	A	B	(C,D)
A		0.4	0.6
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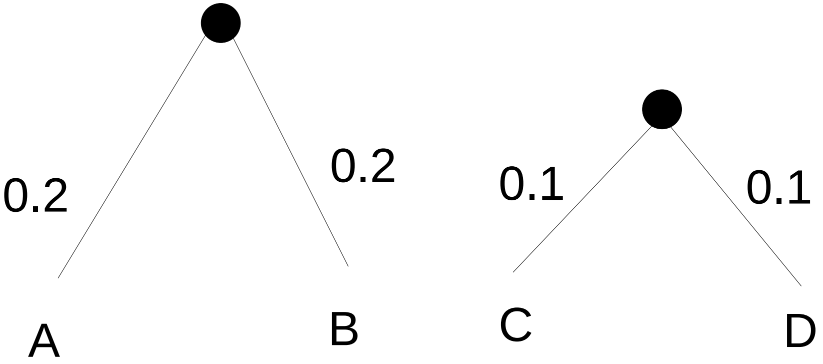
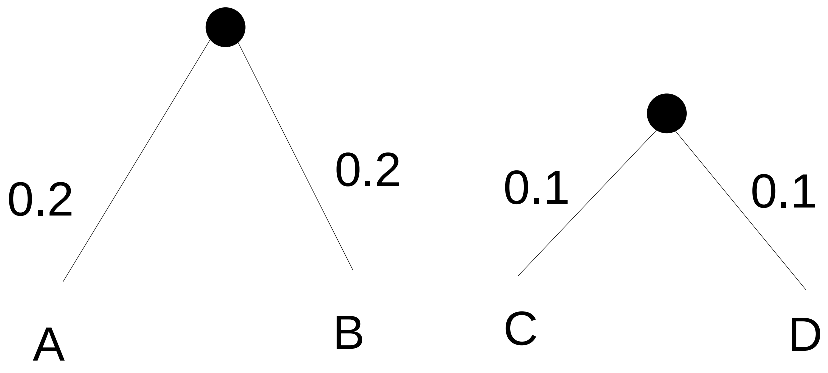
(C, D)			



D[A,B][C,D] = ½ * 0.6 + ½ * 0.6

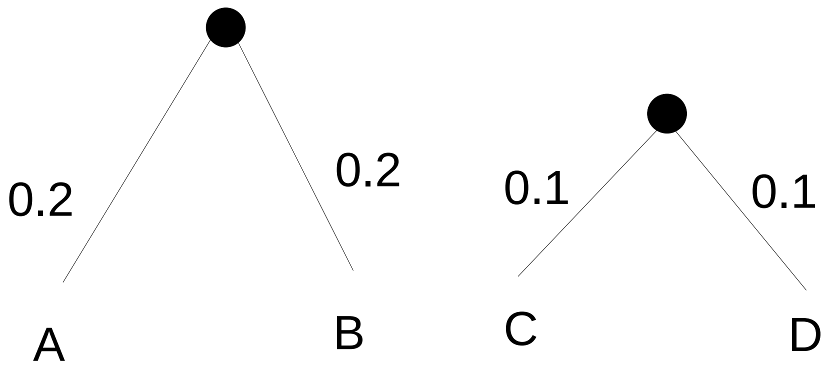
UPGMA example

	(A,B)	(C,D)
(A,B)		0.6
(C,D)		



UPGMA example

	(A,B)	(C,D)
(A,B)		0.6
(C,D)		



UPGMA example

	(A,B)	(C,D)
(A,B)		0.6
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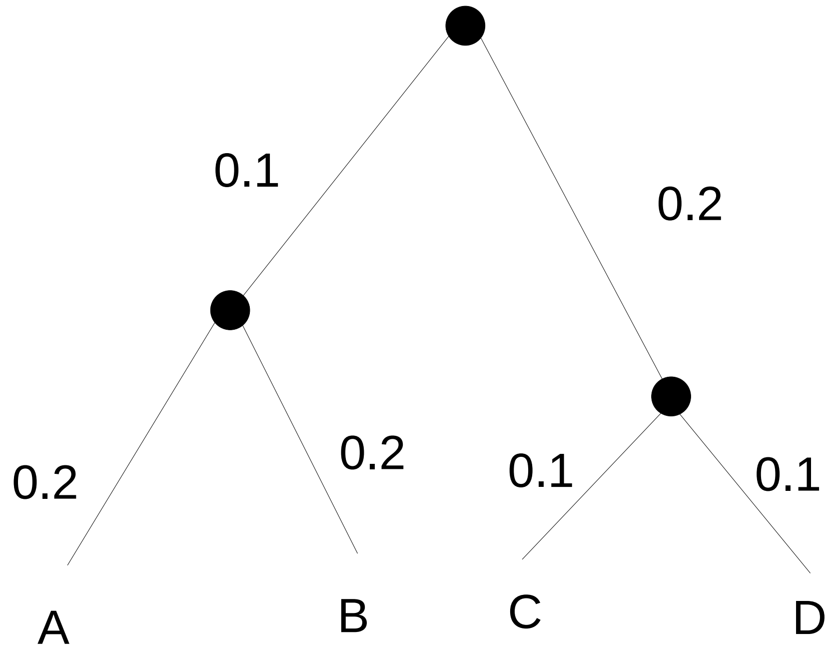
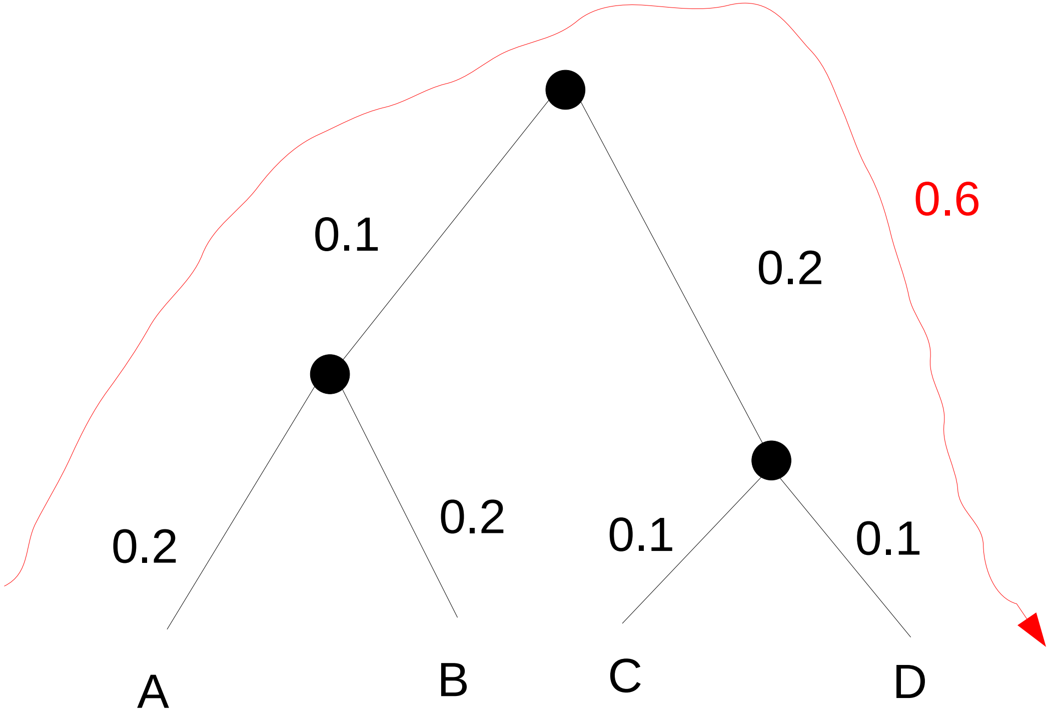


UPGMA example

	(A,B)	(C,D)
(A,B)		0.6
(C,D)		



UPGMA Formal description

- Find the minimum $D[i][j]$
- Merge i and $j \rightarrow (i,j)$
- This new group has $n_{(i,j)}$ members, where $n_{(i,j)} := n_i + n_j$
- Connect i and j to form a new node (i,j)
- Assign the two branches connecting $i \rightarrow (i,j)$ and $j \rightarrow (i,j)$ the length $D[i][j]/2$
- Update the distances between (i,j) and all k, where $k \neq i$ and $k \neq j$ via $D[(i,j)][k] = (n_i/(n_i+n_j)) * D[i][k] + (n_j/(n_i+n_j)) * D[j][k]$
- Naive implementation: $O(n^3)$ → search for minimum in each instance of matrix D
- Maintain a list of per-column (or per-row) minima

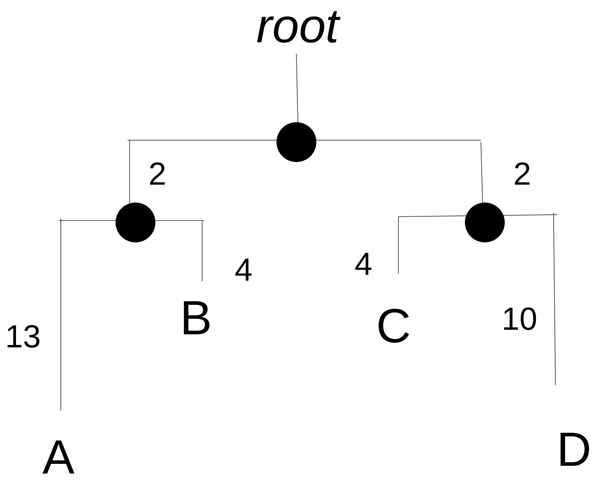
  → update list $O(n)$

  → look for minimum $O(n)$

  → $O(n^2)$
- In contrast to NJ we don't need to update the entire matrix each time, thus only $O(n^2)$

UPGMA on non-ultrametric trees

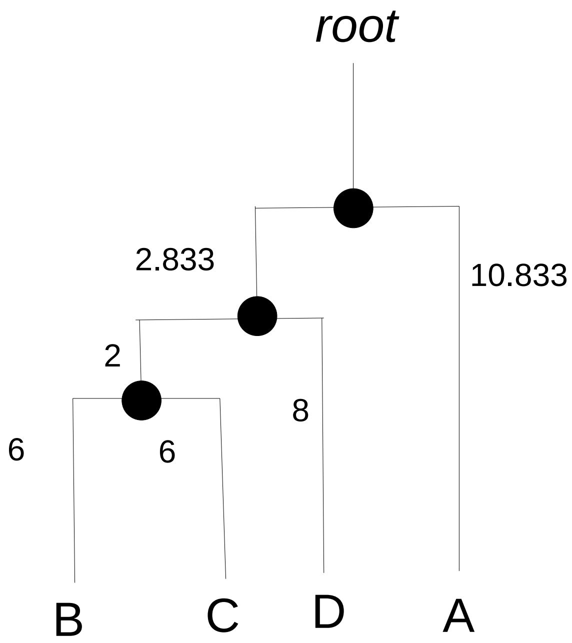
- Can yield misleading results
- Most trees are not ultrametric → do not have equal evolutionary rates among all lineages



True tree

	A	B	C	D
A	0	17	21	27
B		0	12	18
C			0	14
D				0

Patristic distance matrix

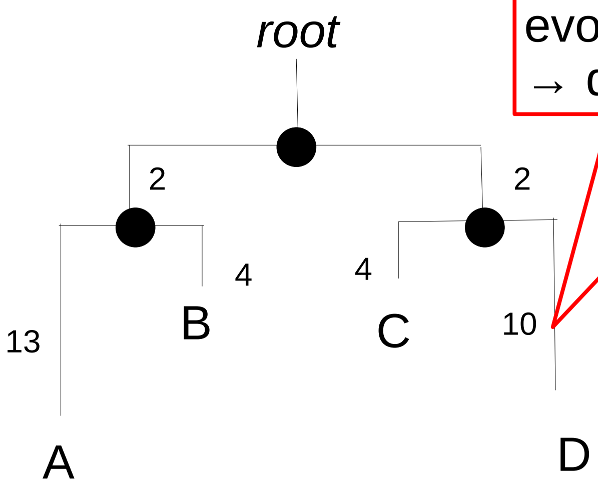


UPGMA tree

UPGMA on non-ultrametric trees

- Can yield misleading results
- Most trees are not ultrametric → do not have equal evolutionary rates among all lineages

Imagine a higher evolutionary pressure!
→ difficult life conditions!



True tree

	A	B	C	D
A	0	17	21	27
B		0	12	18
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D				0

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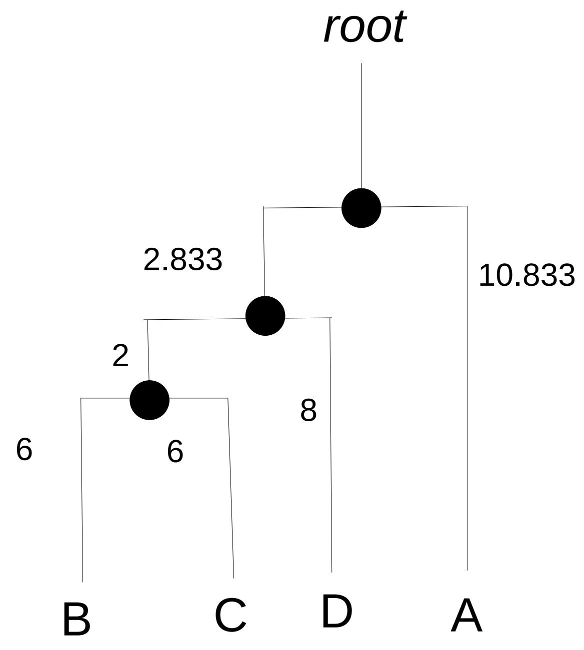


UPGMA tree

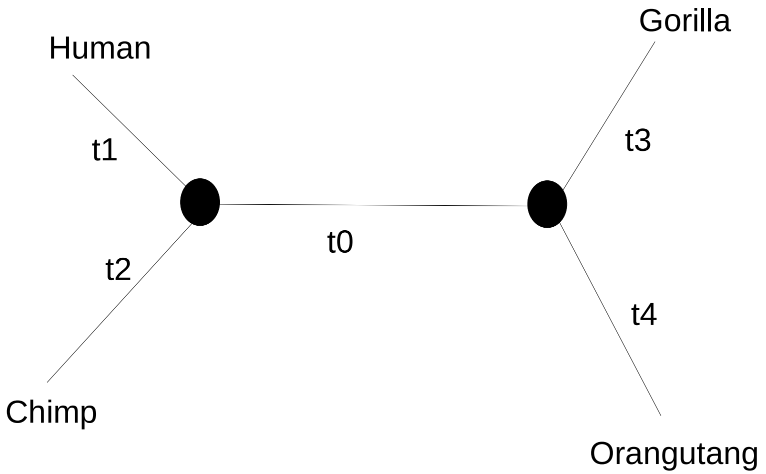
UPGMA and NJ

- Ad hoc heuristics
- Good for clustering any type of data on which you can define a reasonable distance
- Now let us look at explicit criteria

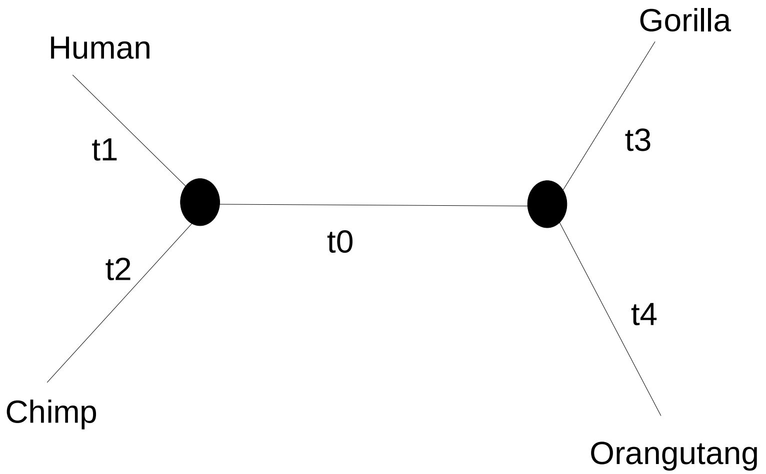
  → given a specific tree tolopology they yield a score

Let’s start with a distance-based criterion

Least Squares



Least Squares



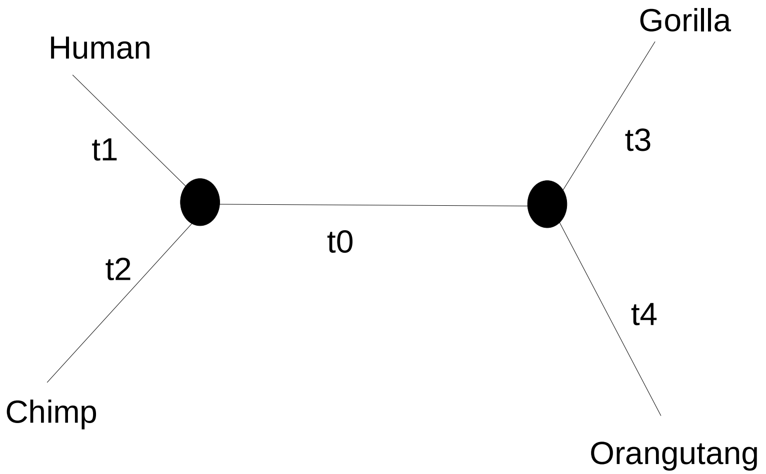
Patristic distances

d[H][C] = t1 + t2
d[H][G] = t1 + t0 + t3
d[H][O] = t1 + t0 + t4
d[C][G] = t2 + t0 + t3
d[C][O] = t2 + t0 + t4
d[G][O] = t3 + t4

Least Squares

Given distance matrix D

	H	C	G	O
H		0.0965	0.1140	0.1849
C			0.1180	0.2009
G				0.1947
O				



d[H][C] = *t1* + *t2*
d[H][G] = *t1* + *t0* + *t3*
d[H][O] = *t1* + *t0* + *t4*
d[C][G] = *t2* + *t0* + *t3*
d[C][O] = *t2* + *t0* + *t4*
d[G][O] = *t3* + *t4*

Least Squares

Given distance matrix D

	H	C	G	O
H		0.0965	0.1140	0.1849
C			0.1180	0.2009
G				0.1947
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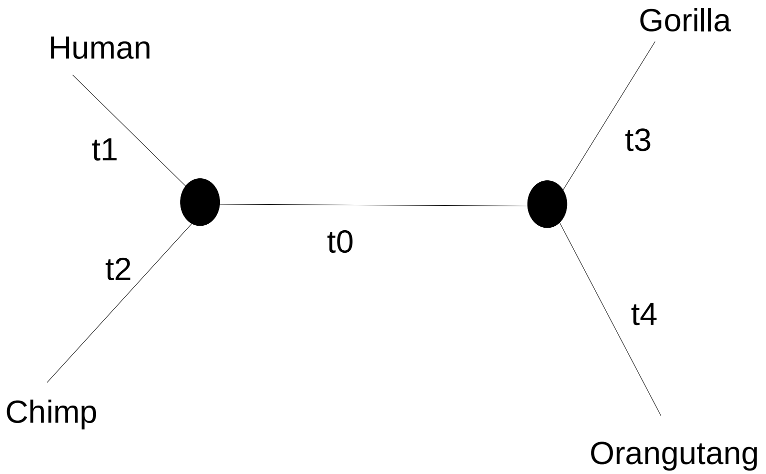


Find $t0, t1, \ldots, t4$ such that deviation of $d[i][j]$ from $D[i][j]$ is minimized!

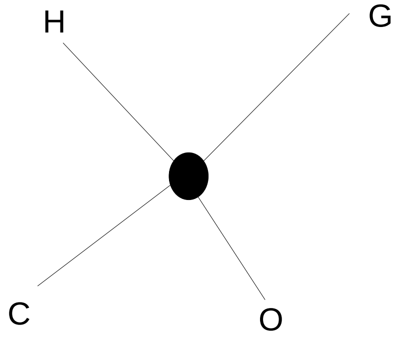
$$Q := (d[H][C] - D[H][C])^2 + (d[H][G] - D[H][G])^2 + (d[H][O] - D[H][O])^2 + (d[C][G] - D[C][G])^2 + (d[C][O] - D[C][O])^2 + (d[G][O] - D[G][O])^2$$

$d[H][C] = t1 + t2$
$d[H][G] = t1 + t0 + t3$
$d[H][O] = t1 + t0 + t4$
$d[C][G] = t2 + t0 + t3$
$d[C][O] = t2 + t0 + t4$
$d[G][O] = t3 + t4$

Least Squares Example

tree	t0	t1	t2	t3	t4	Q
((H,C),G,O)	0.008840	0.043266	0.053280	0.058908	0.135795	0.000035
((H,G),C,O)	0.000000	0.046212	0.056227	0.061854	0.138742	0.000140
((H,O),C,G)	As above	-	-	-	-	-

Least Squares Example



Star tree

tree	t0	t1	t2	t3	t4	Q
((H,C),G,O)	0.008840	0.043266	0.053280	0.058908	0.135795	0.000035
((H,G),C,O)	0.000000	0.046212	0.056227	0.061854	0.138742	0.000140
((H,O),C,G)	As above	-	-	-	-	-

Least Squares Optimization

- Given a fixed, fully binary, unrooted tree *T* with *n* taxa
- Given a pair-wise distance matrix *D*
- Assign branch lengths $t_1 , ..., t_{2n-3}$ to the tree such that:

  the sum of the squared differences between the pair-wise *patristic* (tree-based!) distances d_{ij} and the *plain* pair-wise distances D_{ij} is minimized

- In other words:

  $Q = \Sigma_{i<j} (D_{ij} – d_{ij})^2$ → find an assignment $t_1 ,..., t_{2n-3}$ to the tree such that Q is minimized

  Q can be minimized by taking the derivative and solving a system of linear equations in $O(n^3)$

  Minimization methods for Q that take into account the tree-like structure run in $O(n^2)$ or even $O(n)$

- Then, also find that tree topology *T* that minimizes *Q*
- Finding the minimal least squares tree is NP-hard

W.H.E. Day "Computational Complexity of Inferring Phylogenies from dissimilarity matrices", *Bulletin of Mathematical Biology* 49: 461-467, 1986.

Least Squares

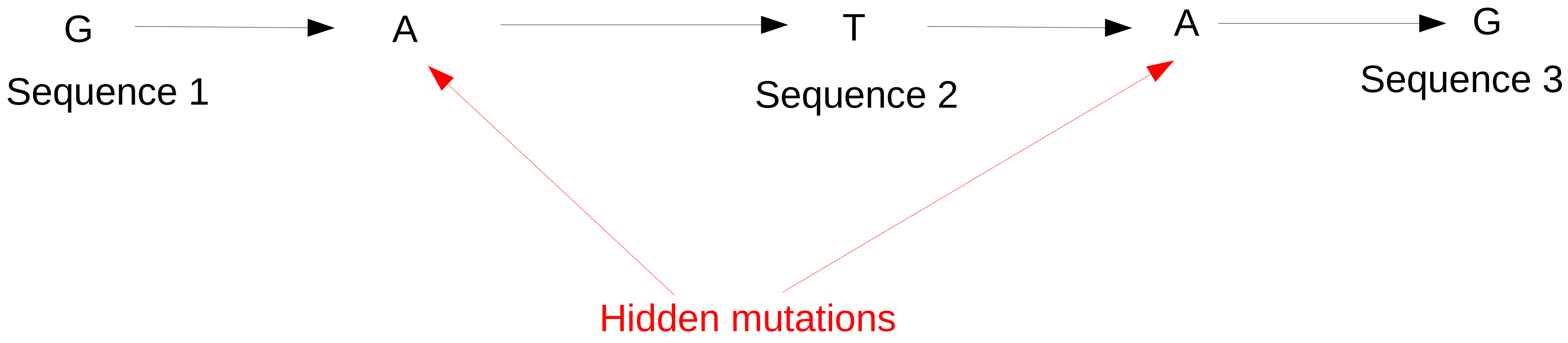
- *NP-hard* because of tree search problem
- Scoring a single tree takes time between $O(n)$ to $O(n^3)$
- There also exist weighted versions:

  $Q = \Sigma_{i<j} w_{ij}(D_{ij} - d_{ij})^2$

  where $w_{ij} := 1/D_{ij}$ *or* $w_{ij} := 1/D_{ij}^2$
- We will see how to search for trees a bit later-on
- Make sure you understand the difference between
  - Scoring a single tree
  - Searching for the tree with the best score

Distances

- A preview of the next lecture
- We need to accommodate multiple substitutions in the evolutionary history of sequences



Distances

- A preview of the next lecture
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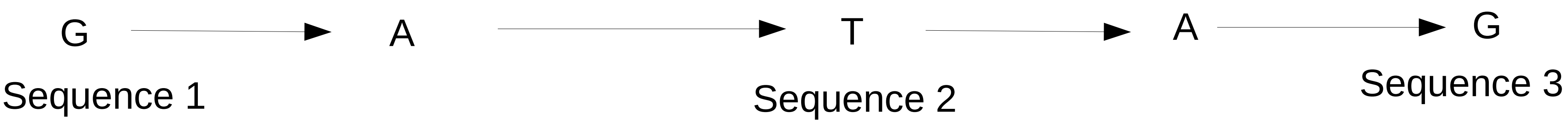


Simple edit distances will not be sufficient → we need statistical modes!

Minimum Evolution Method

- Similar to least squares
- Explicit Criterion → minimize total branch length (tree length) of the reconstructed tree
- Branch lengths are obtained using least-squares method → same time complexity
- Instead of searching for the tree that minimizes the squared difference between $D[i][j]$ and $d[i][j]$ that is denoted by Q we search for the tree where $t0 + t1 + t2 + t3 + t4$ is minimized

tree	t0	t1	t2	t3	t4	Q	Tree length
((H,C),G,O)	*0.008840*	*0.043266*	*0.053280*	*0.058908*	*0.135795*	0.000035	***0.240741***
((H,G),C,O)	*0.000000*	*0.046212*	*0.056227*	*0.061854*	*0.138742*	0.000140	*0.303035*
((H,O),C,G)	As above	-	-	-	-	-	

Distance-based Methods

- Clustering Algorithms/Heuristics
  - Neighbor Joining

    → Heuristic for Minimum Evolution Method
  - UPGMA
- Explicit criteria
  - least squares
  - minimum evolution
- All depend on the accuracy of the pair-wise distance matrix *D*
- The distance matrix needs to be an exact reflection of the tree

Character-based Methods

- Parsimony
- Maximum Likelihood
- Bayesian Inference

The Parsimony Criterion

- Directly operates on the MSA
- Find the tree that explains the data with the least amount of mutations
- Questions:
  - How do we count the least amount of mutations on a given tree?

    → dynamic programming algorithm
  - How do we find the tree topology that requires the least amount of mutations

    → requires a tree search!

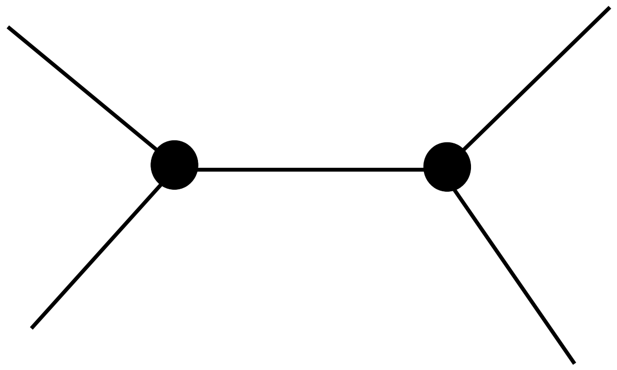
    → remember the number of trees!

    → this is also NP-hard!

Parsimony

MSA

```
S1: AAGG
S2: AAA-
S3: AGAG
S4: TTAT
```



Parsimony

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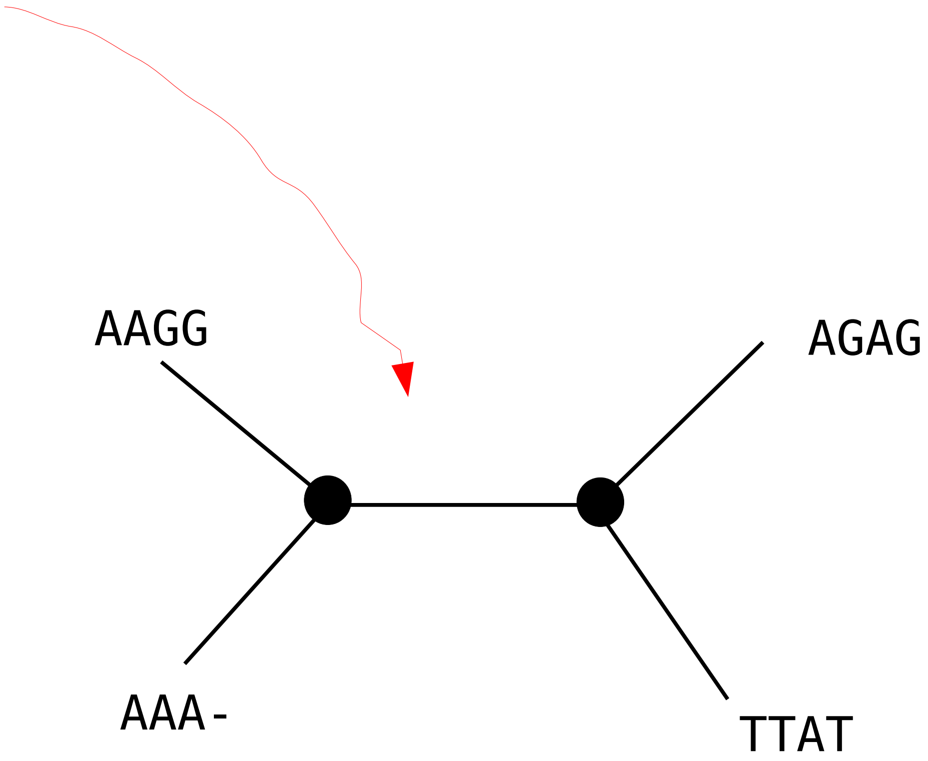
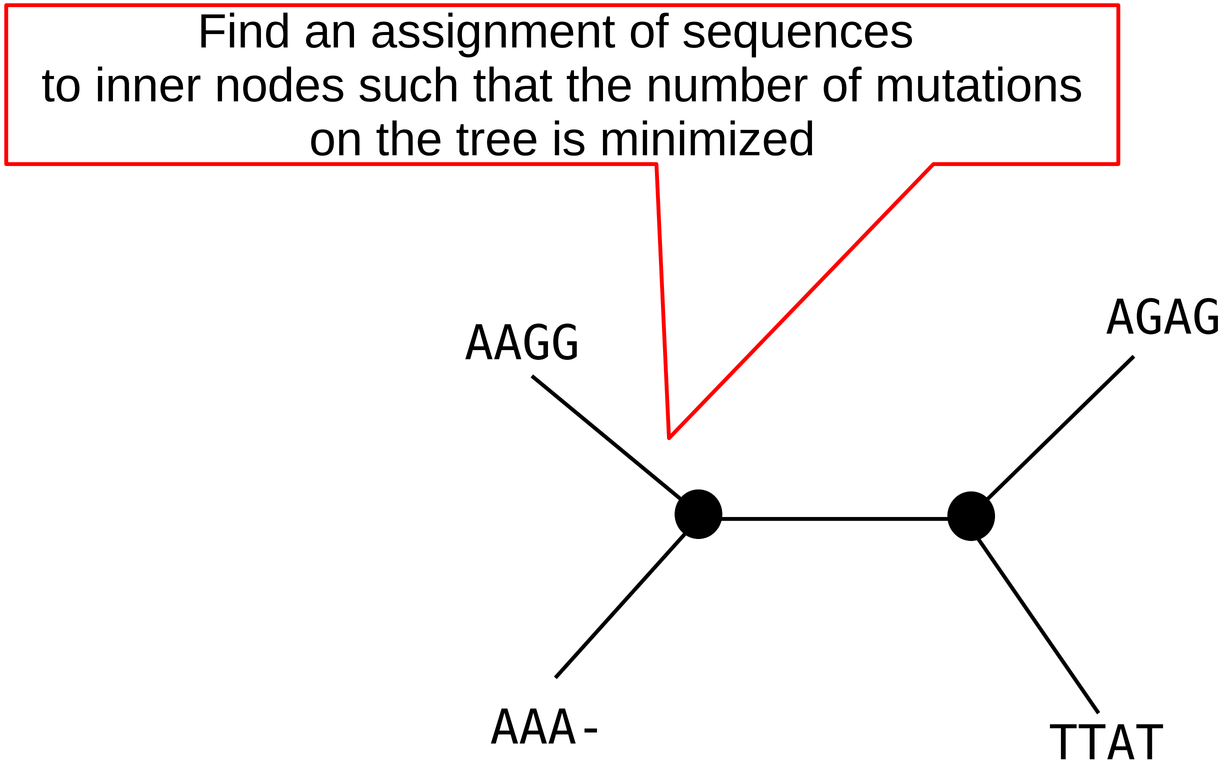


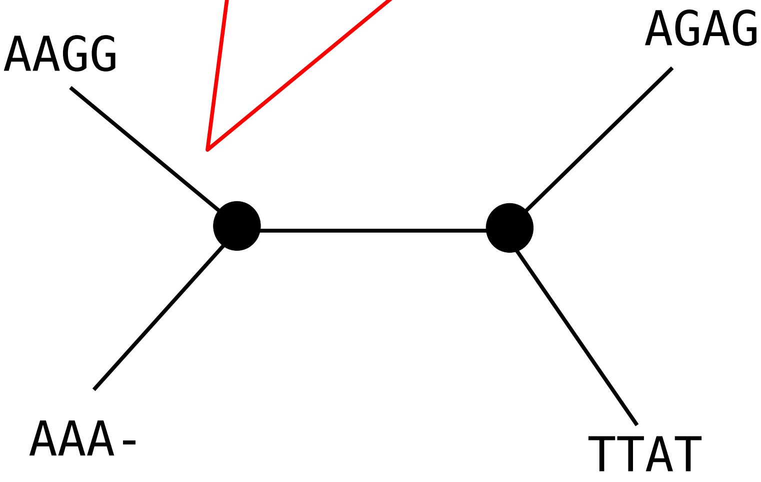
Parsimony



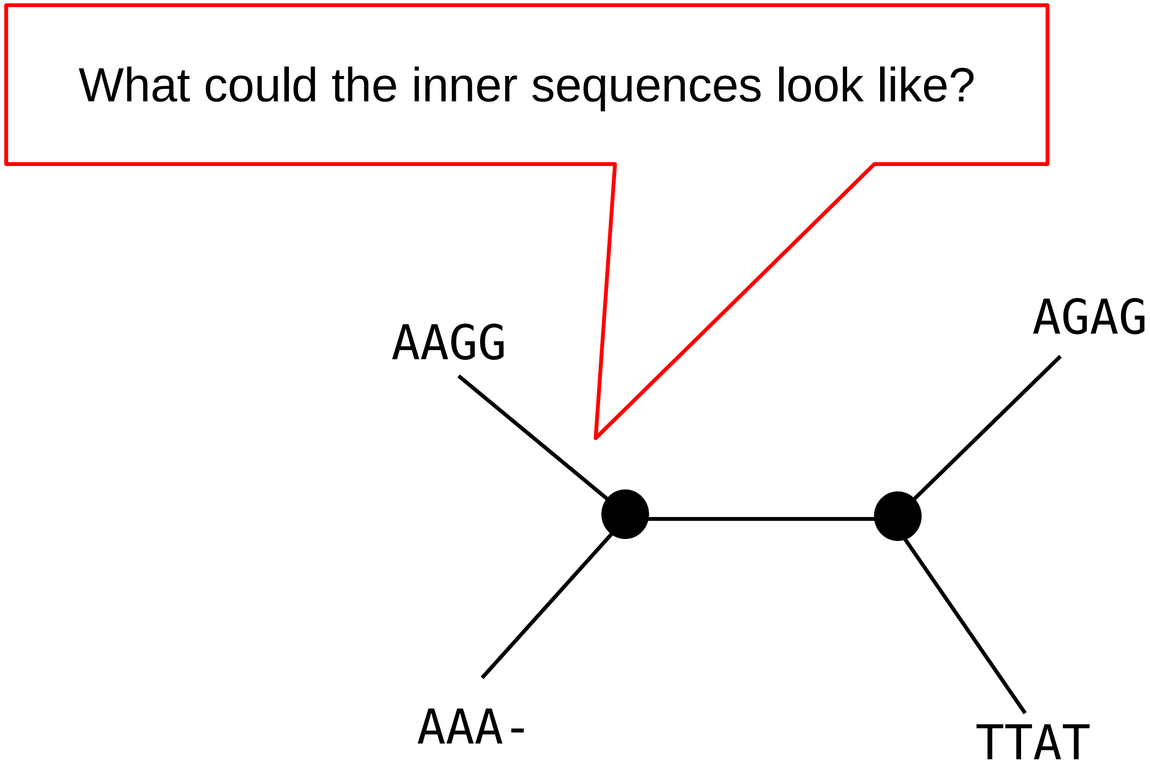
Find an assignment of sequences
to inner nodes such that the number of mutations
on the tree is minimized

Parsimony

This is somewhat similar to the tree alignment problem, but here, we are given an alignment!



Parsimony



What could the inner sequences look like?

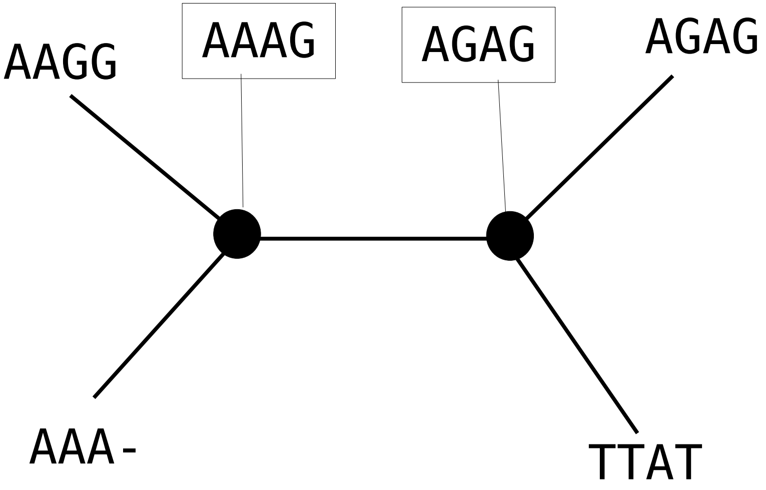
AAGG

AGAG

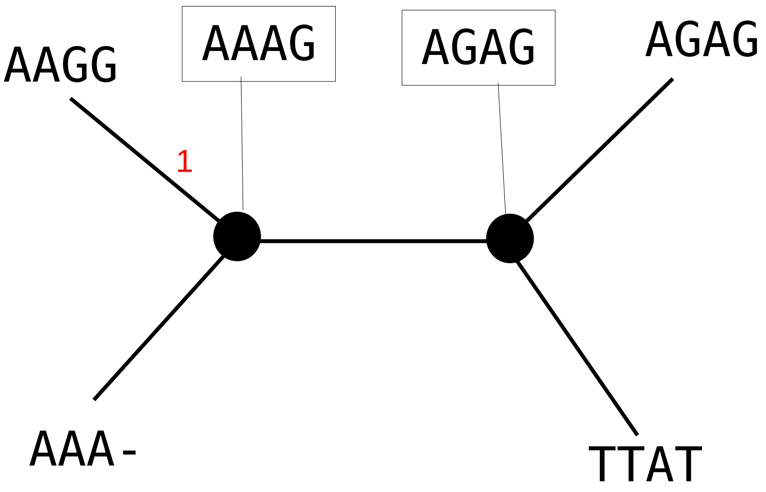
AAA-

TTAT

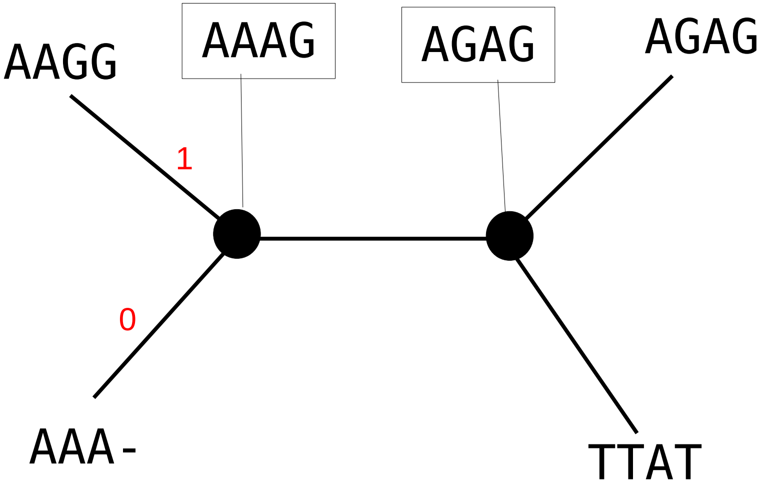
Parsimony



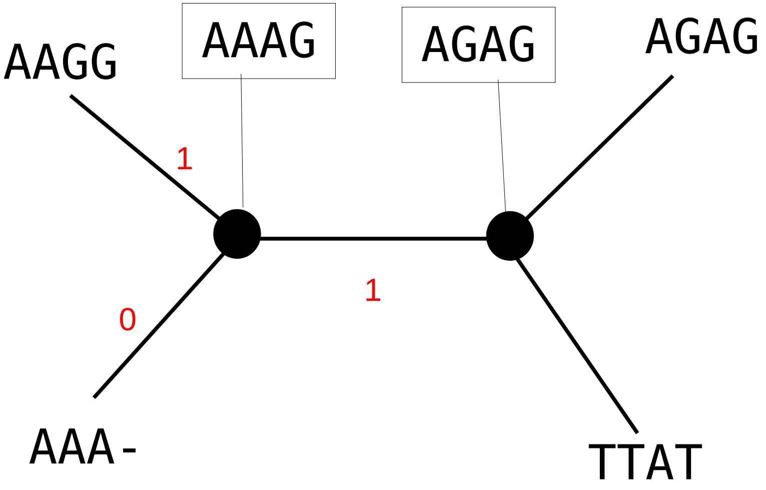
Parsimony



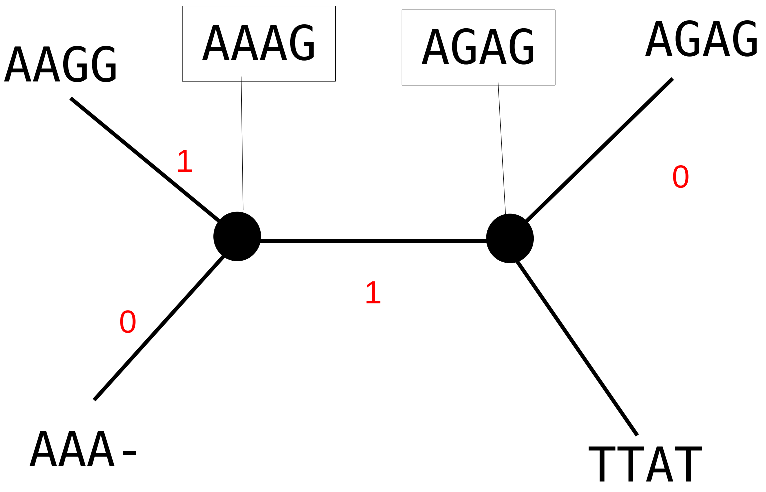
Parsimony



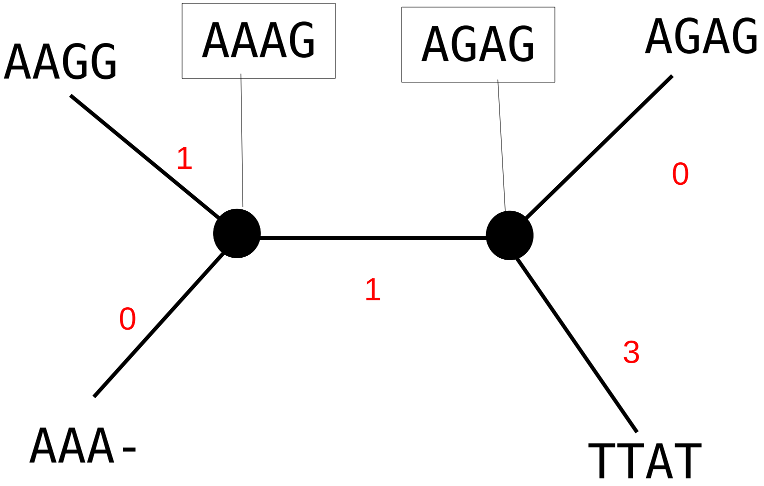
Parsimony



Parsimony

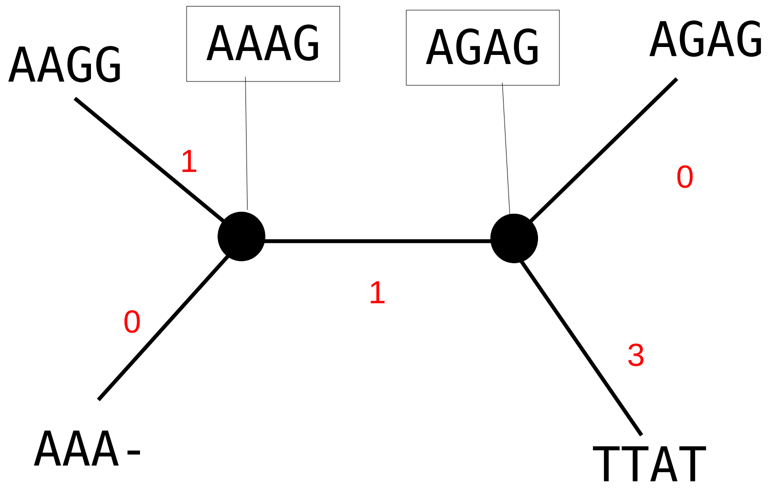


Parsimony



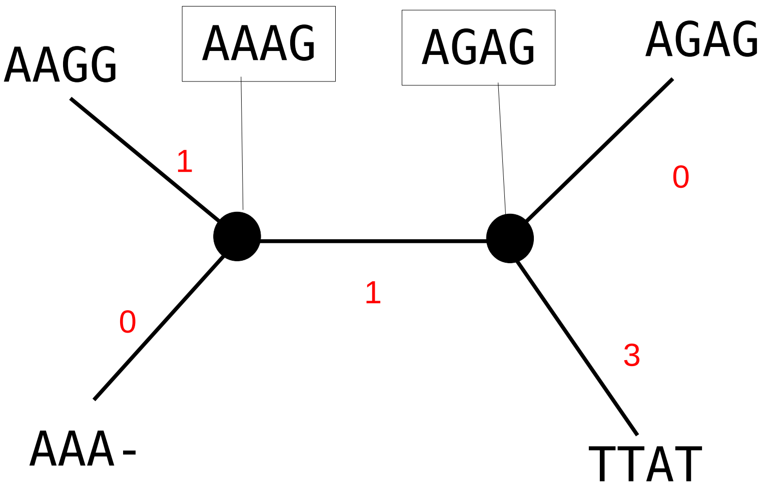
Parsimony

Parsimony Score of this tree = 5



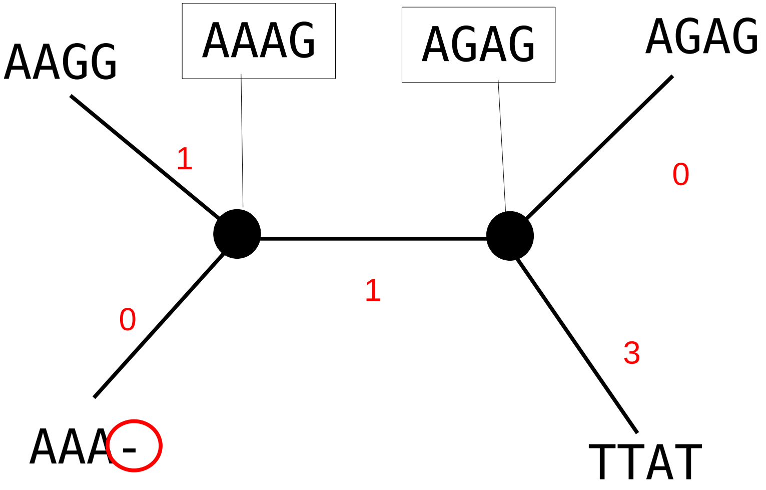
Parsimony

Parsimony Score of this tree = 5
This is also the minimum score for this tree.



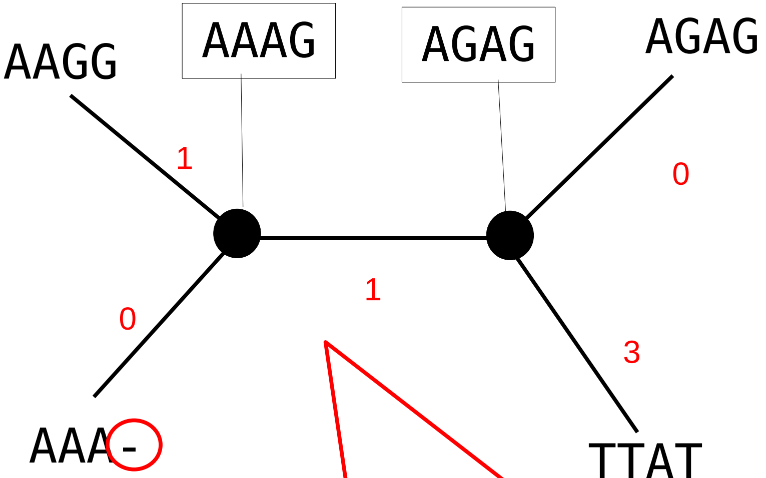
Parsimony

Parsimony Score of this tree = 5



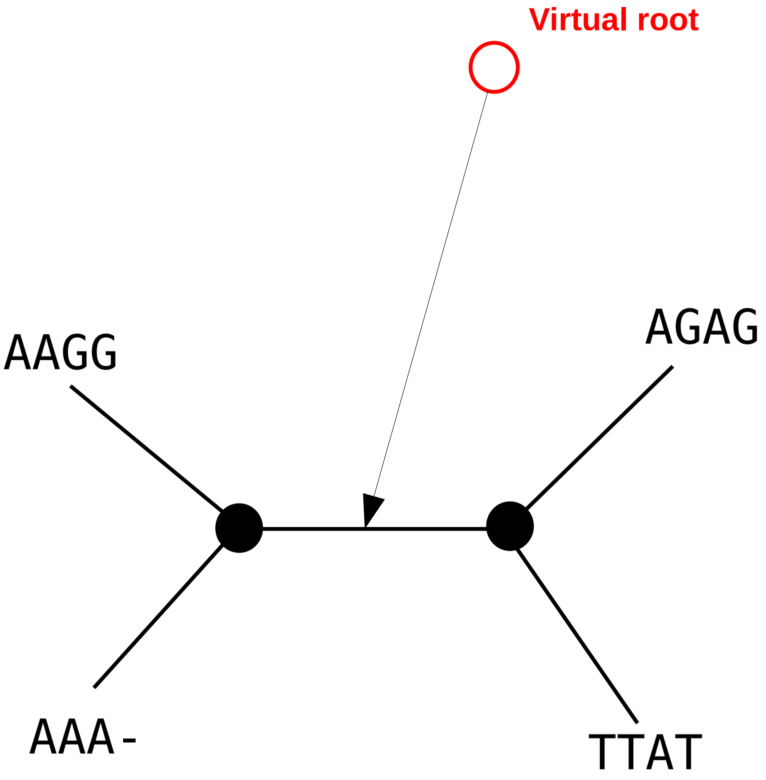
Gaps (also called Indels → Insertions or Deletions) are treated as so-called undetermined characters, also frequently denoted as ***N*****.**
The interpretation is that *N* could be either *A, C, G*, or *T*.

Parsimony

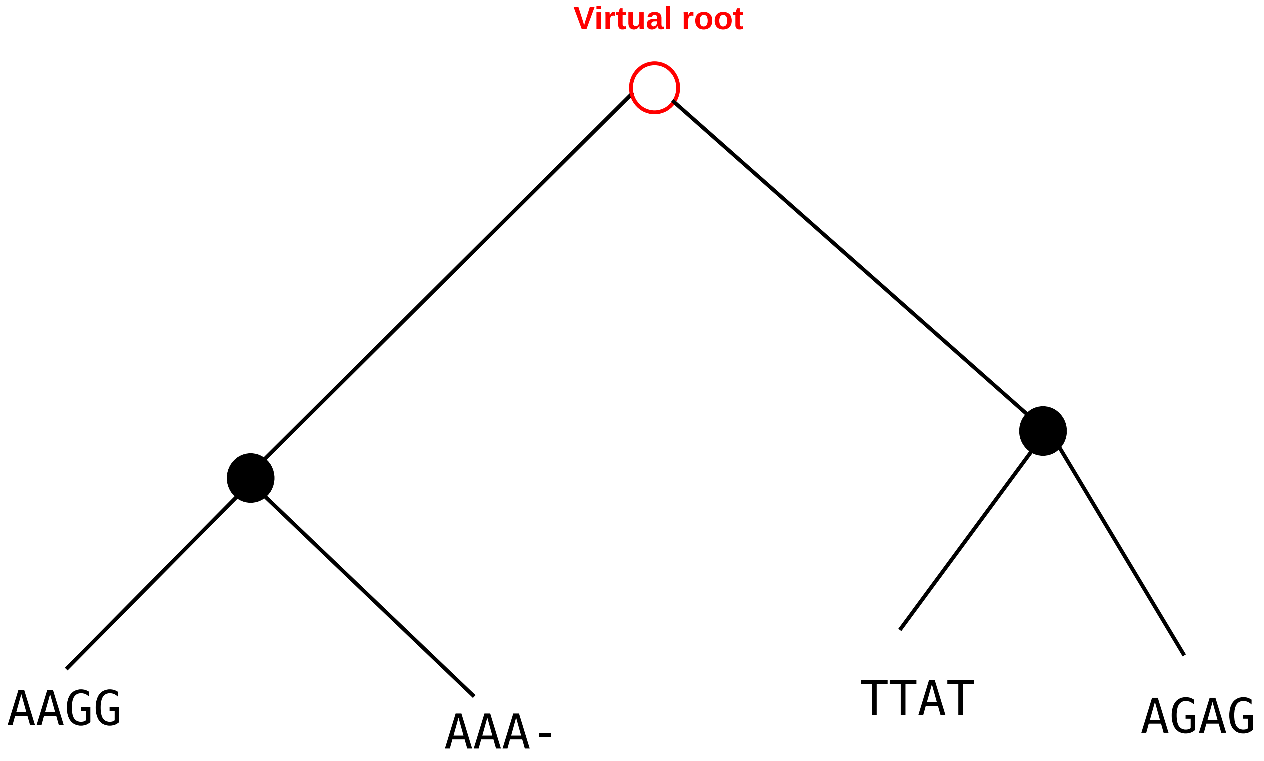


So, how do we compute the score?

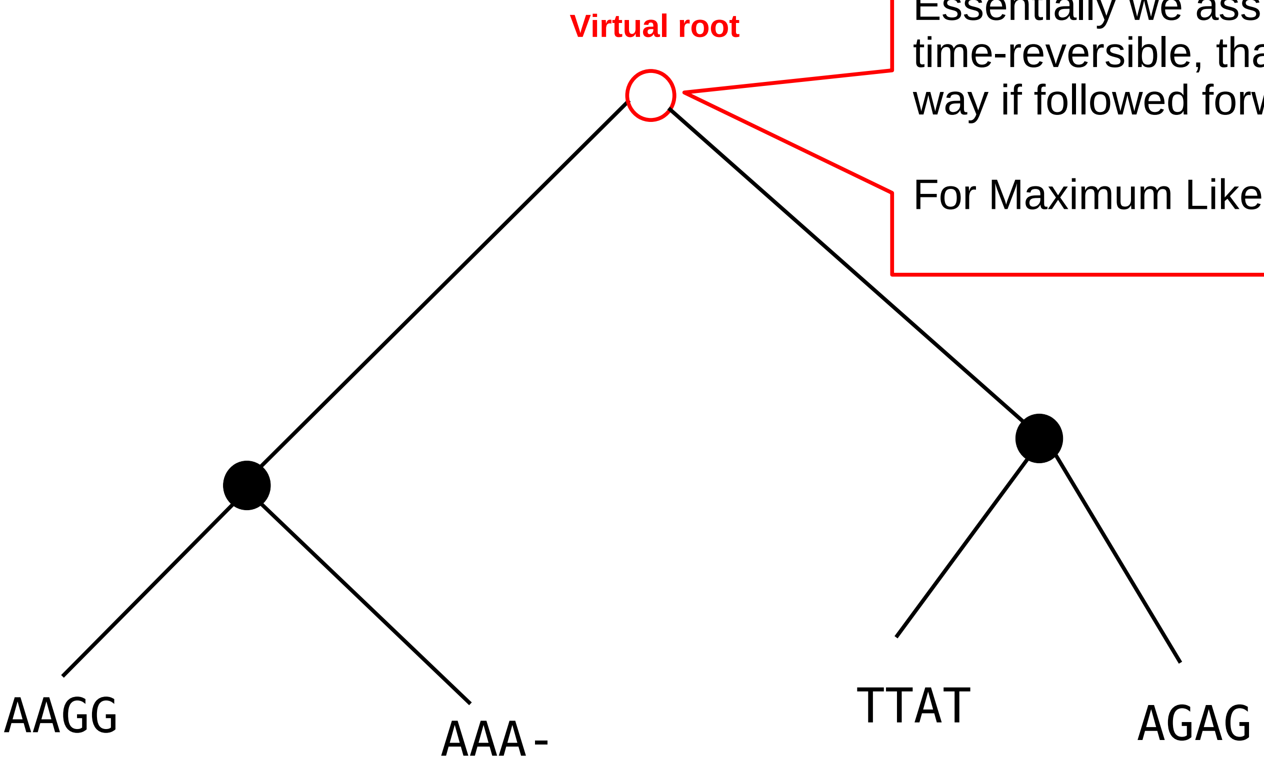
Parsimony



Parsimony



Parsimony



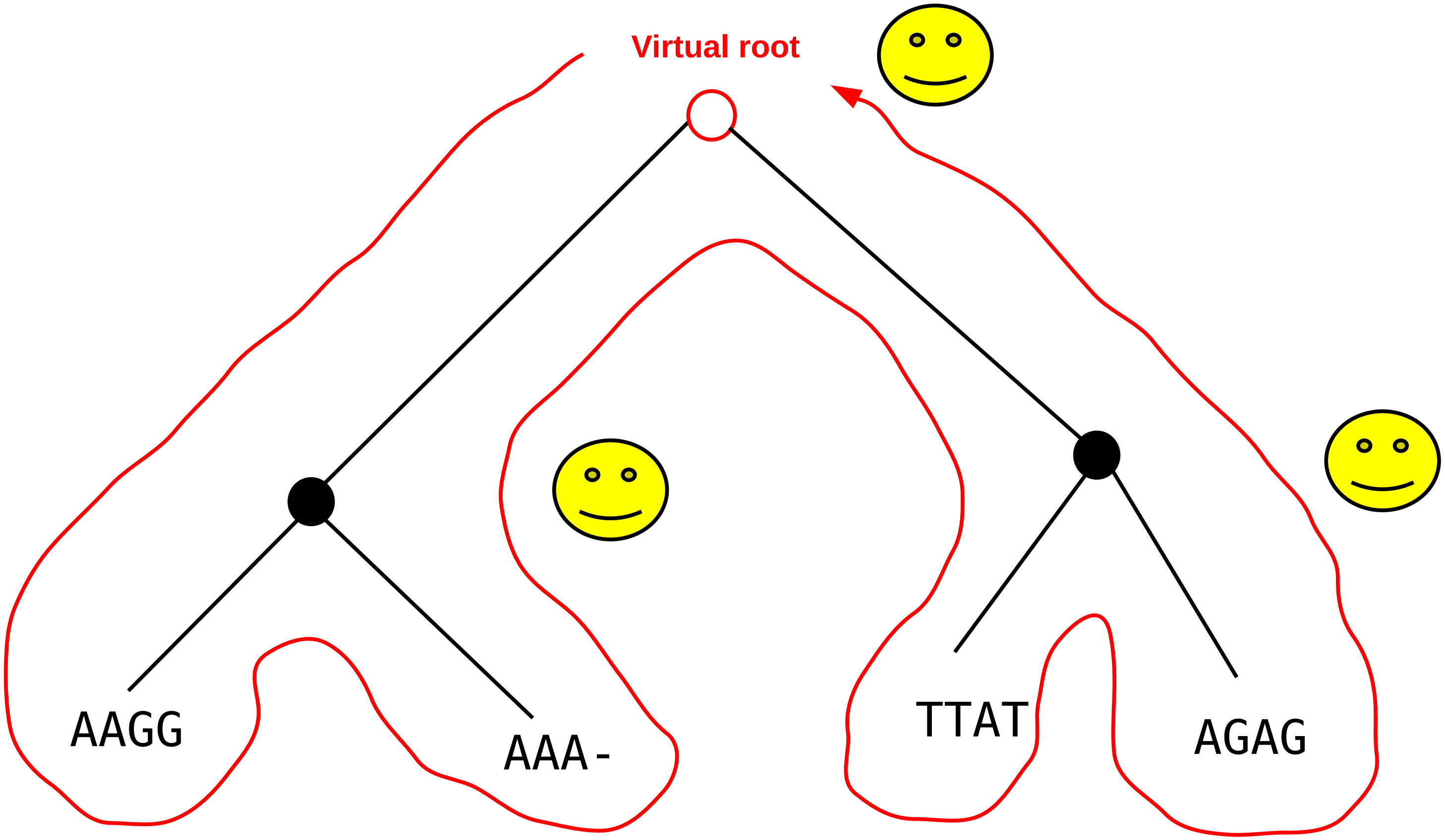
The score will be the same, regardless of where we place the root
→ makes computations much easier

Essentially we assume that evolution is time-reversible, that is, it occurred in the same way if followed forward or backward in time

For Maximum Likelihood we use a similar concept!

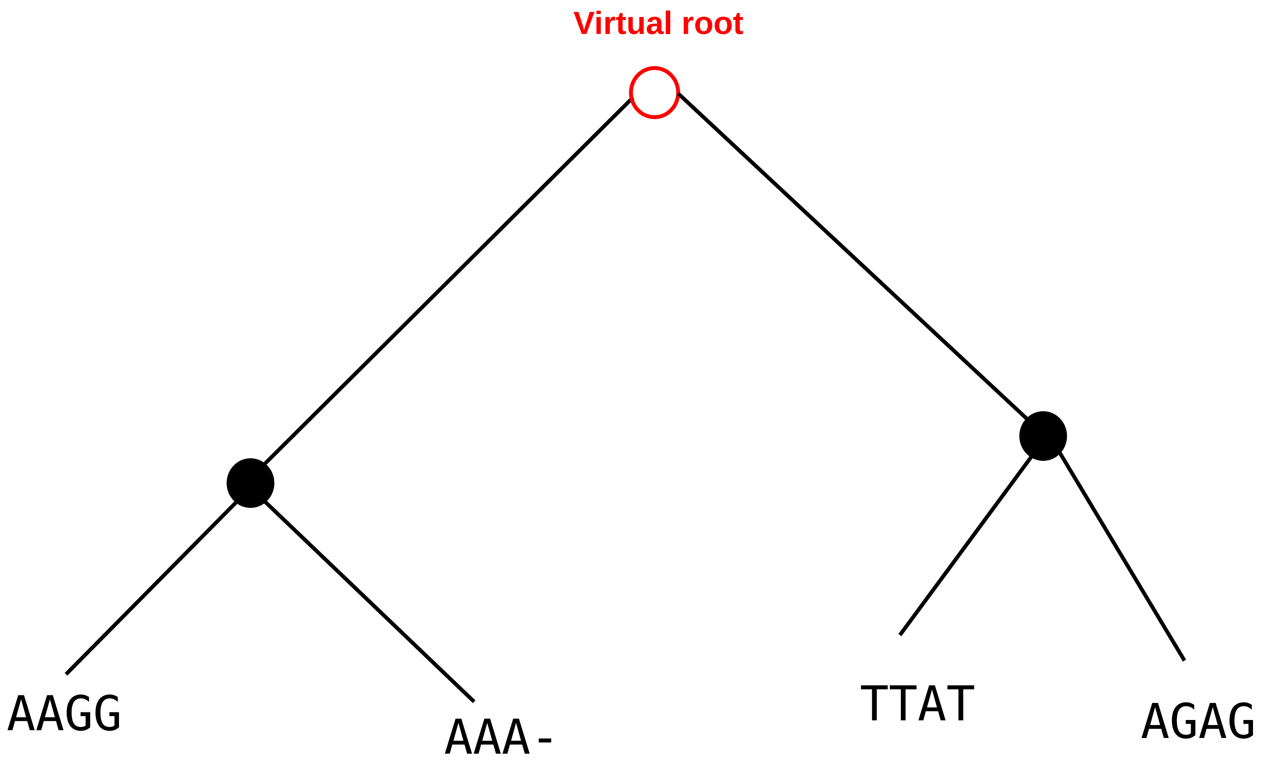
Parsimony

Post-order traversal to compute inner states

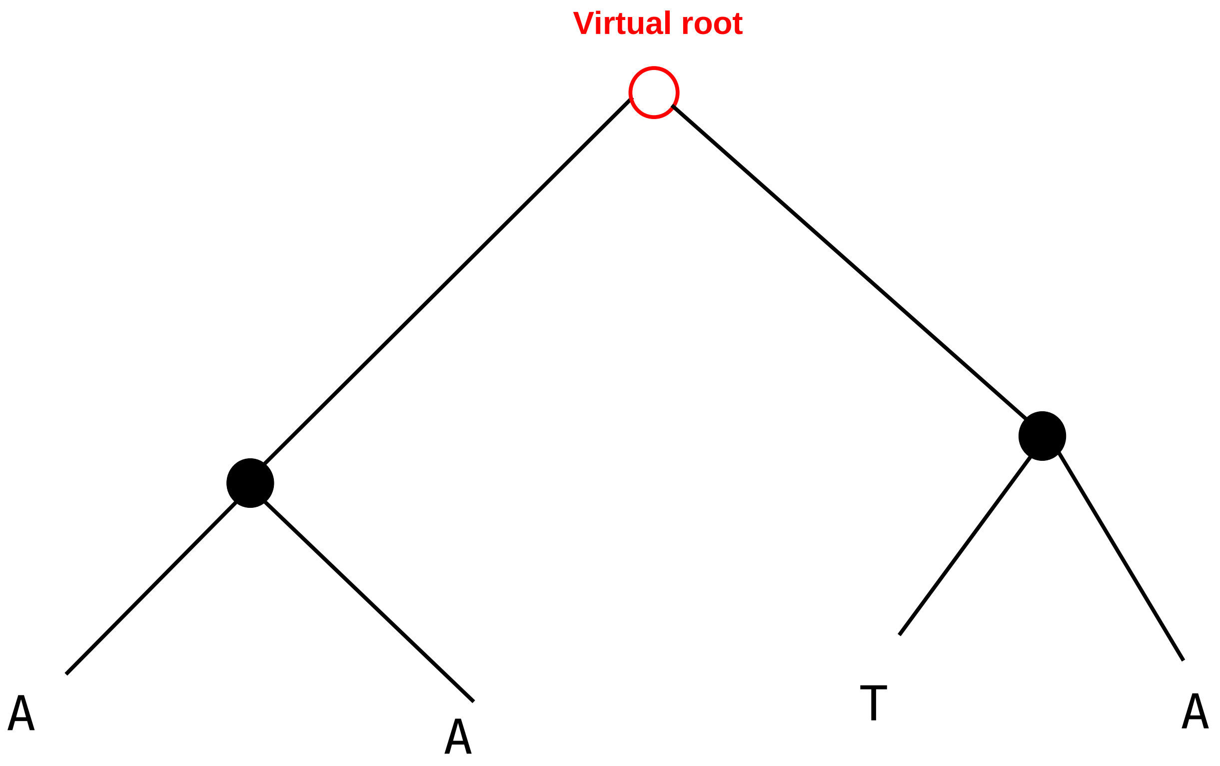


Parsimony

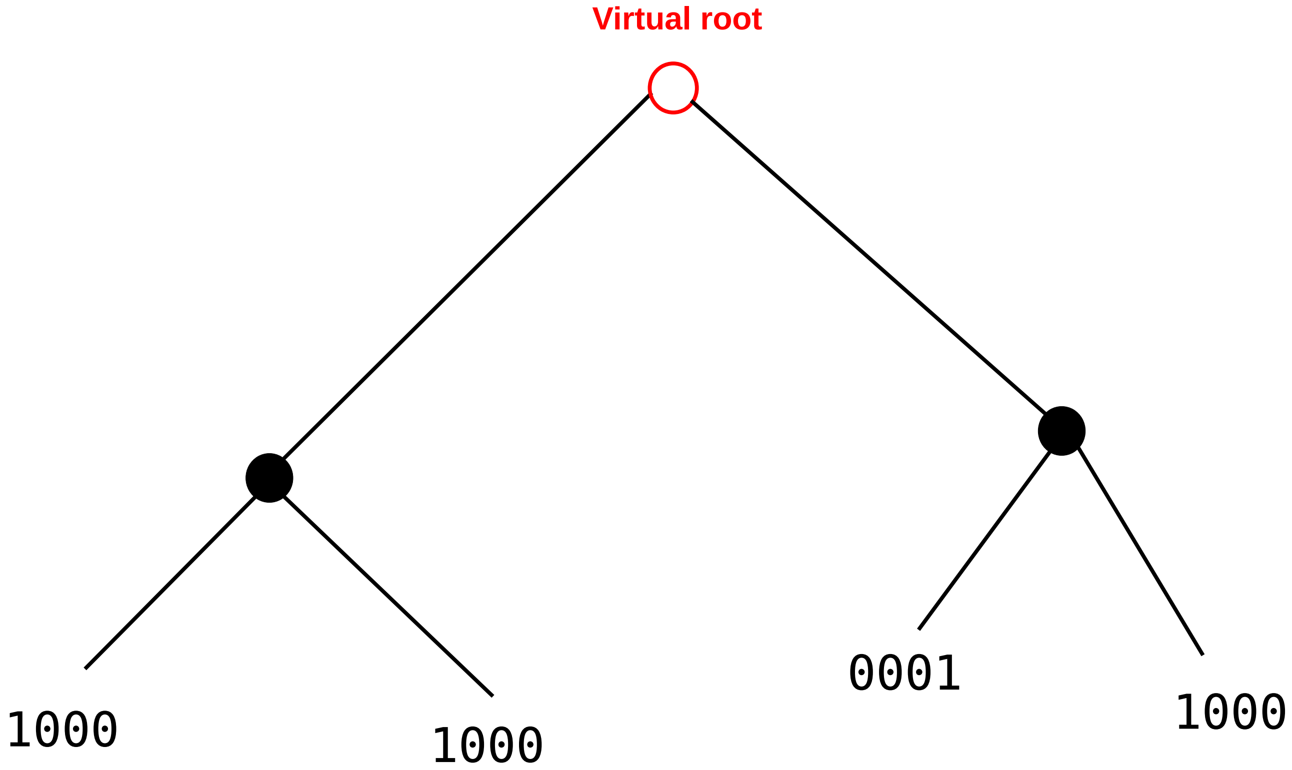
Compute scores on a site-per-site basis
→ we assume that sites evolve independently!



Parsimony



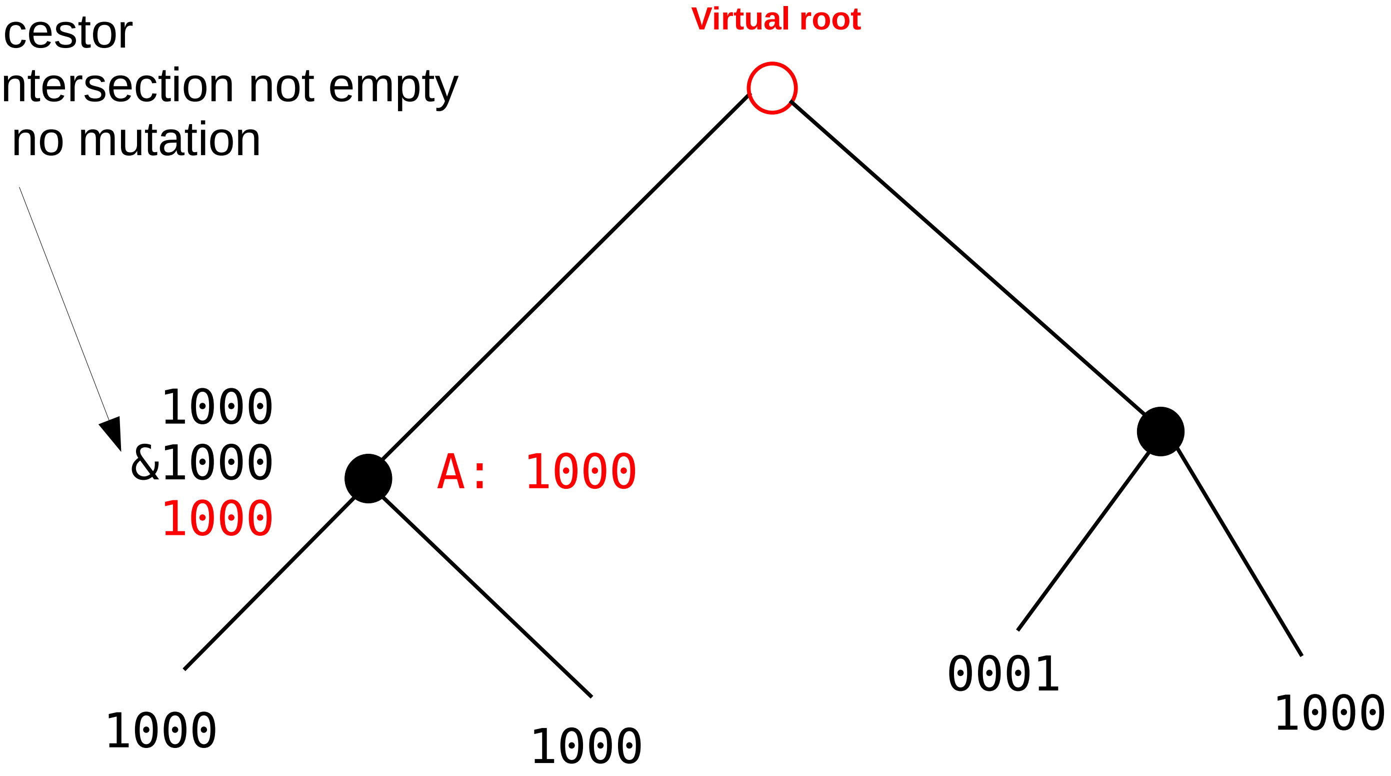
Parsimony



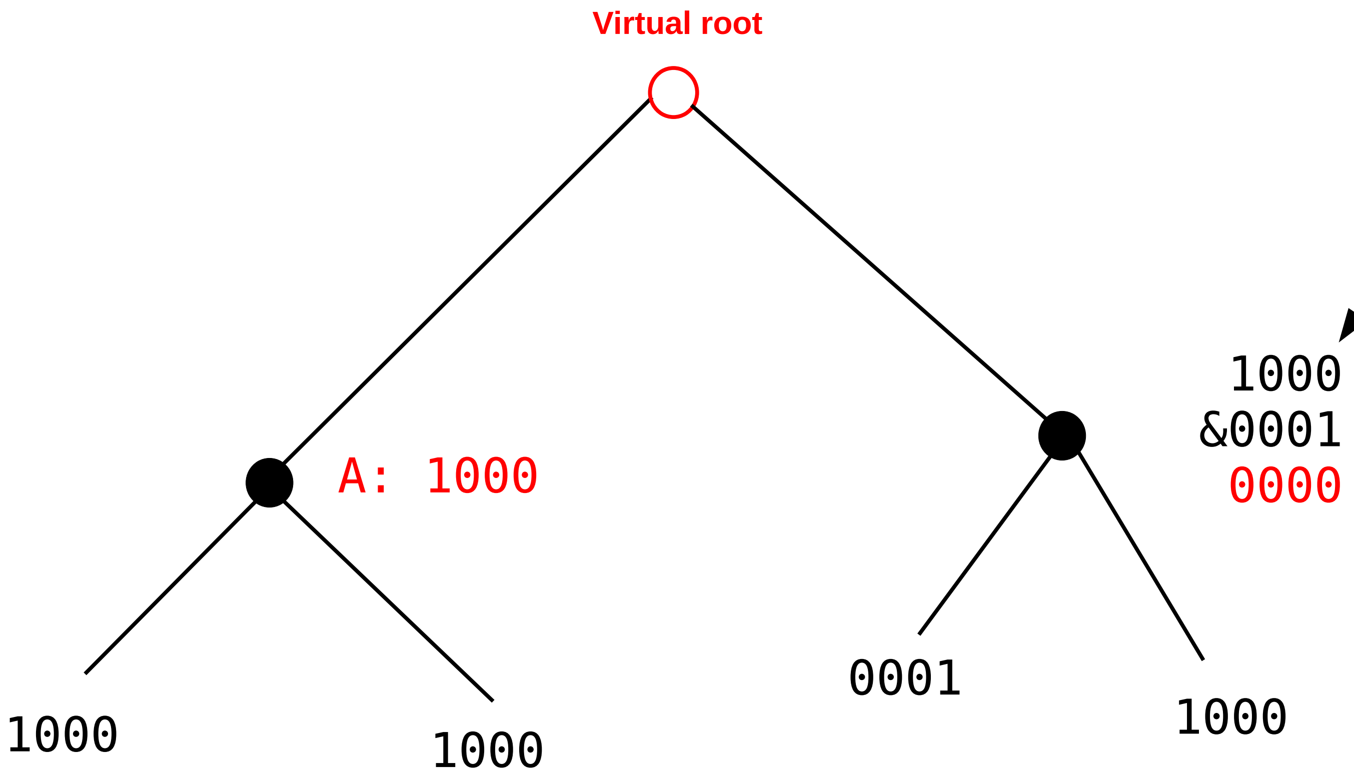
Parsimony

Intersection of sets of possible states at ancestor

If intersection not empty → no mutation



Parsimony

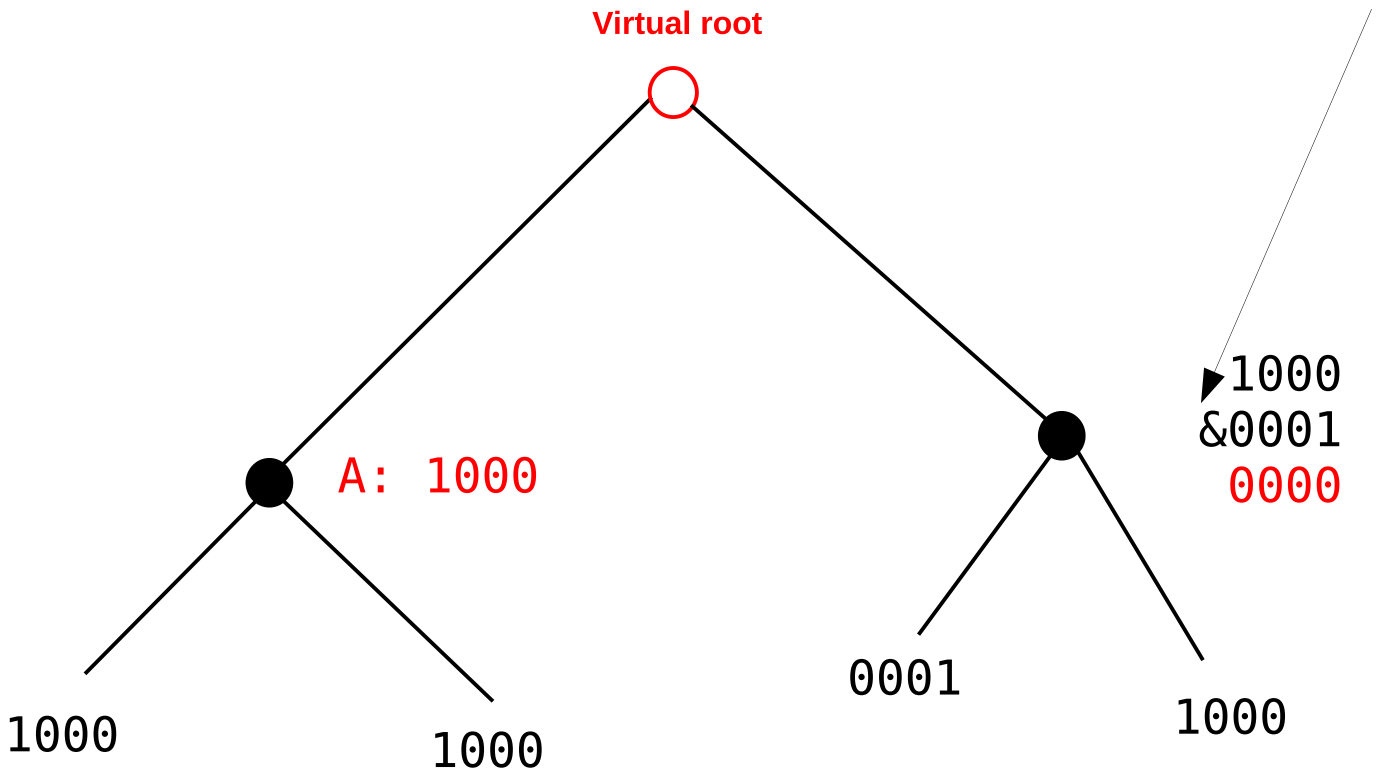


Intersection empty
→ count one mutation

Parsimony

+1

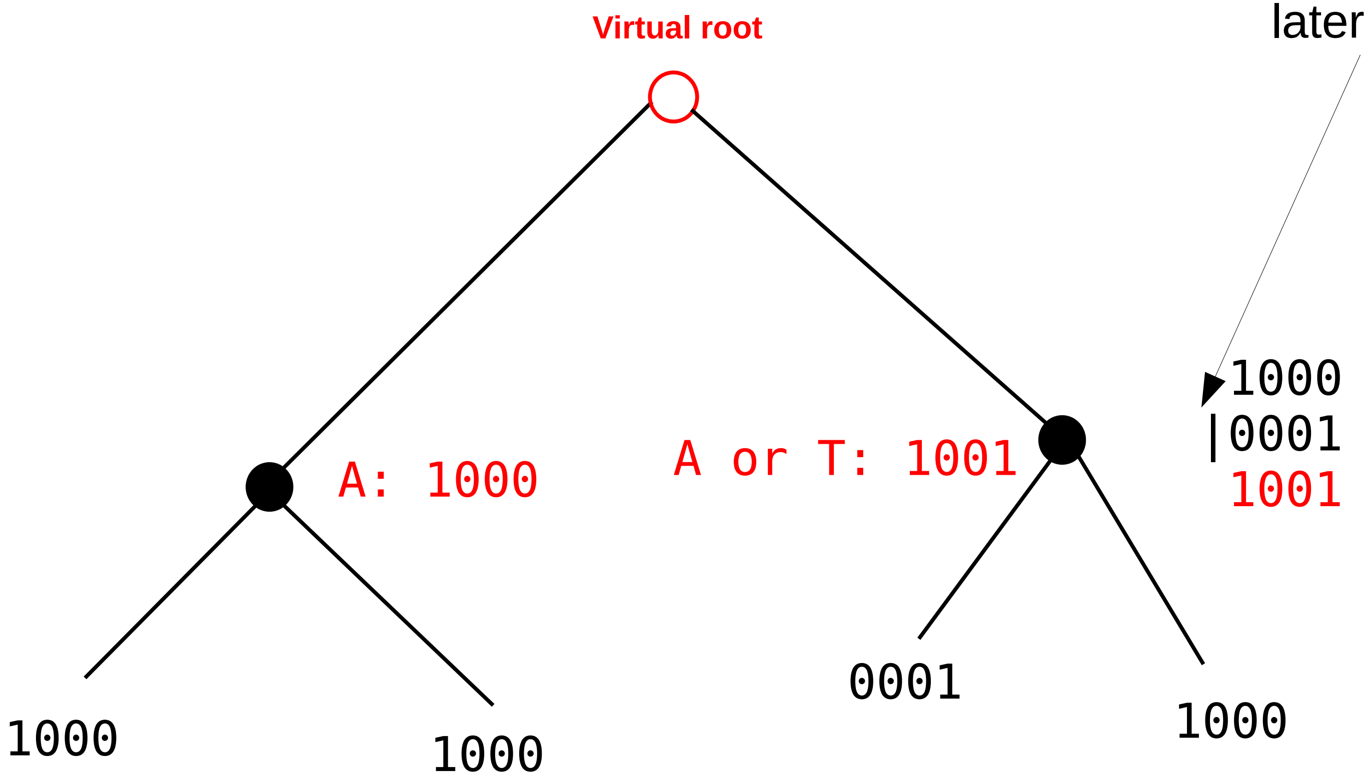
Intersection empty
→ count one mutation



Parsimony

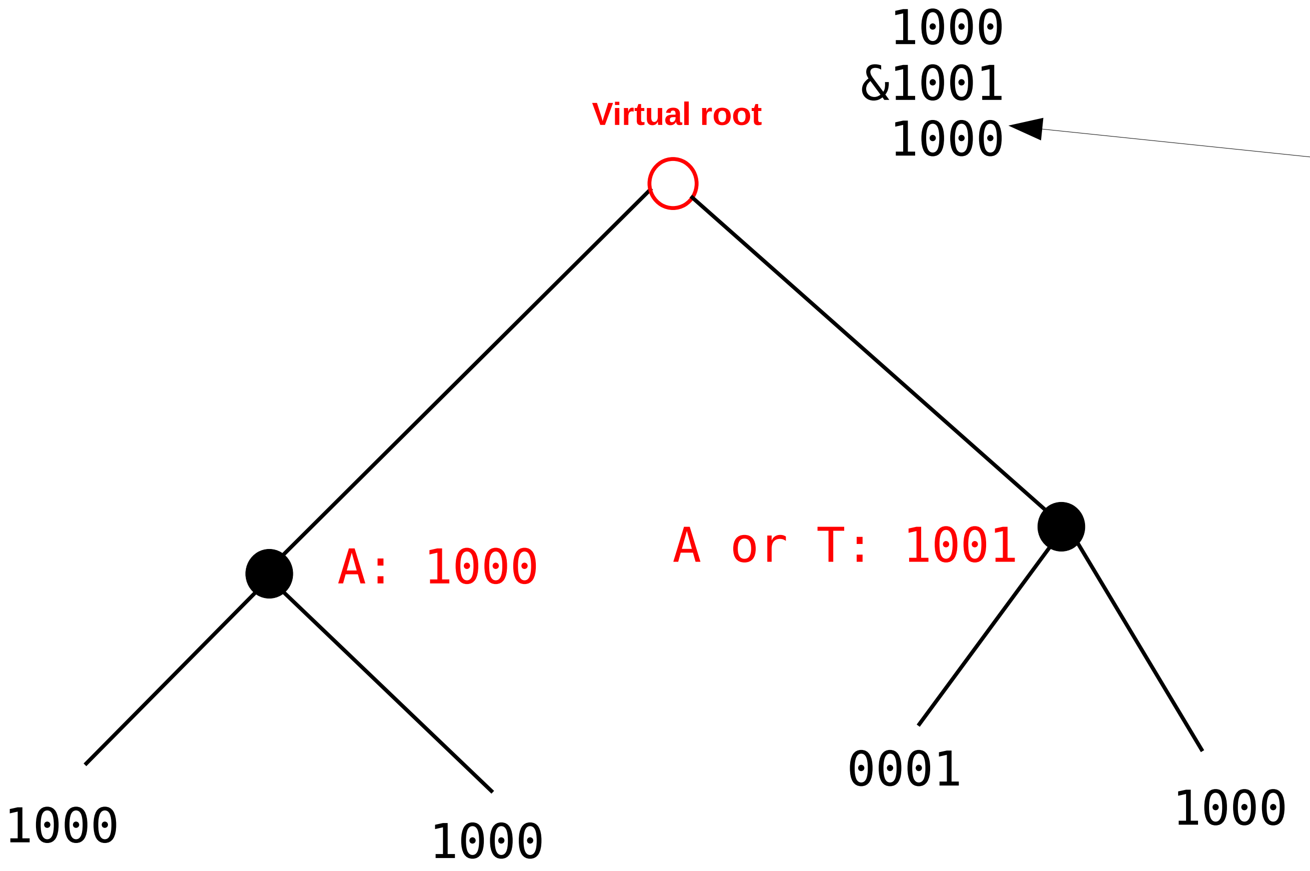
1

Ancestral state: **union!**
→ key trick, defer decision
Whether this is a T or A to a
later point!



Parsimony

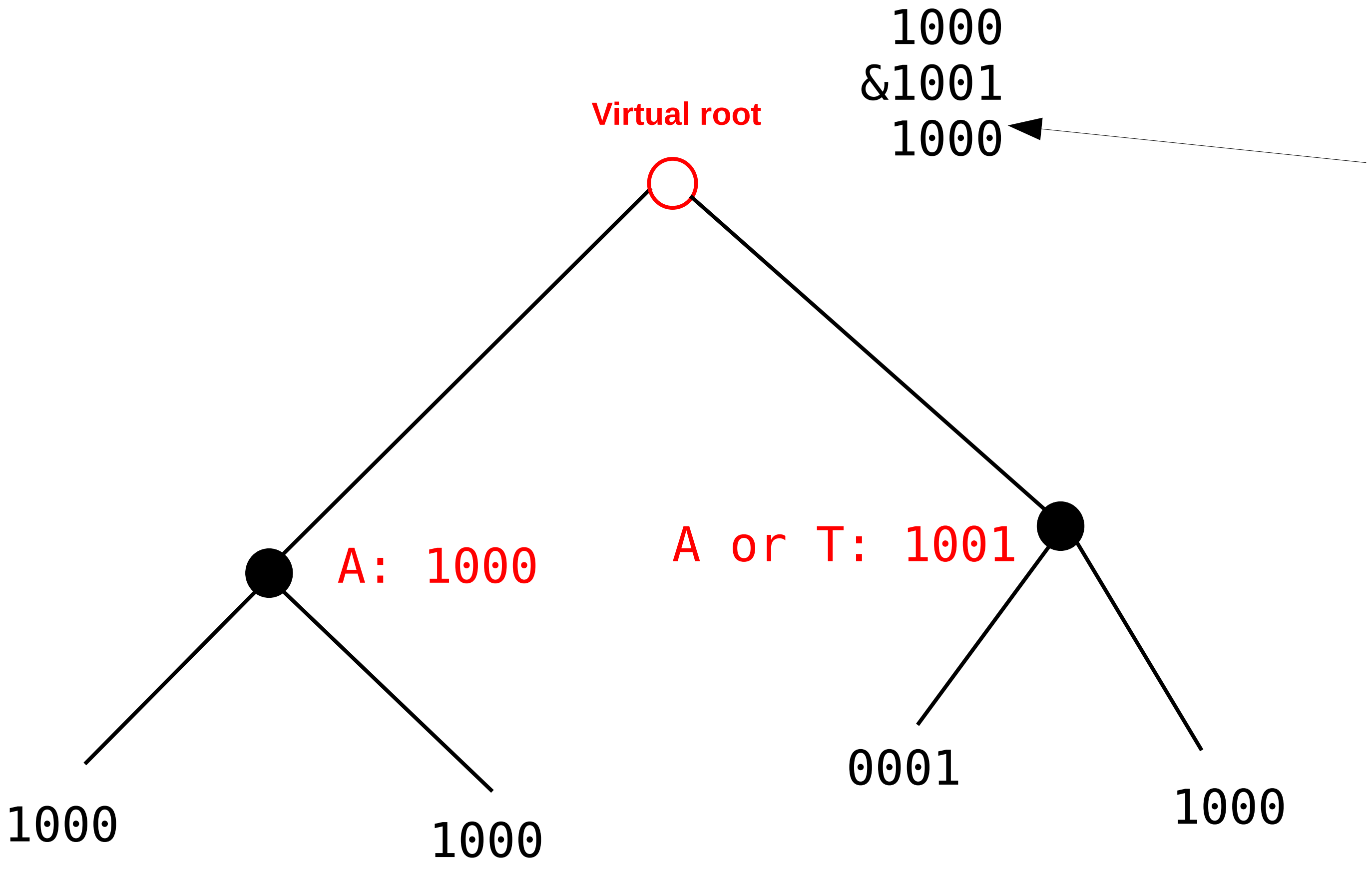
1



Intersection non-empty,
Overall score for this
Site: 1

Parsimony

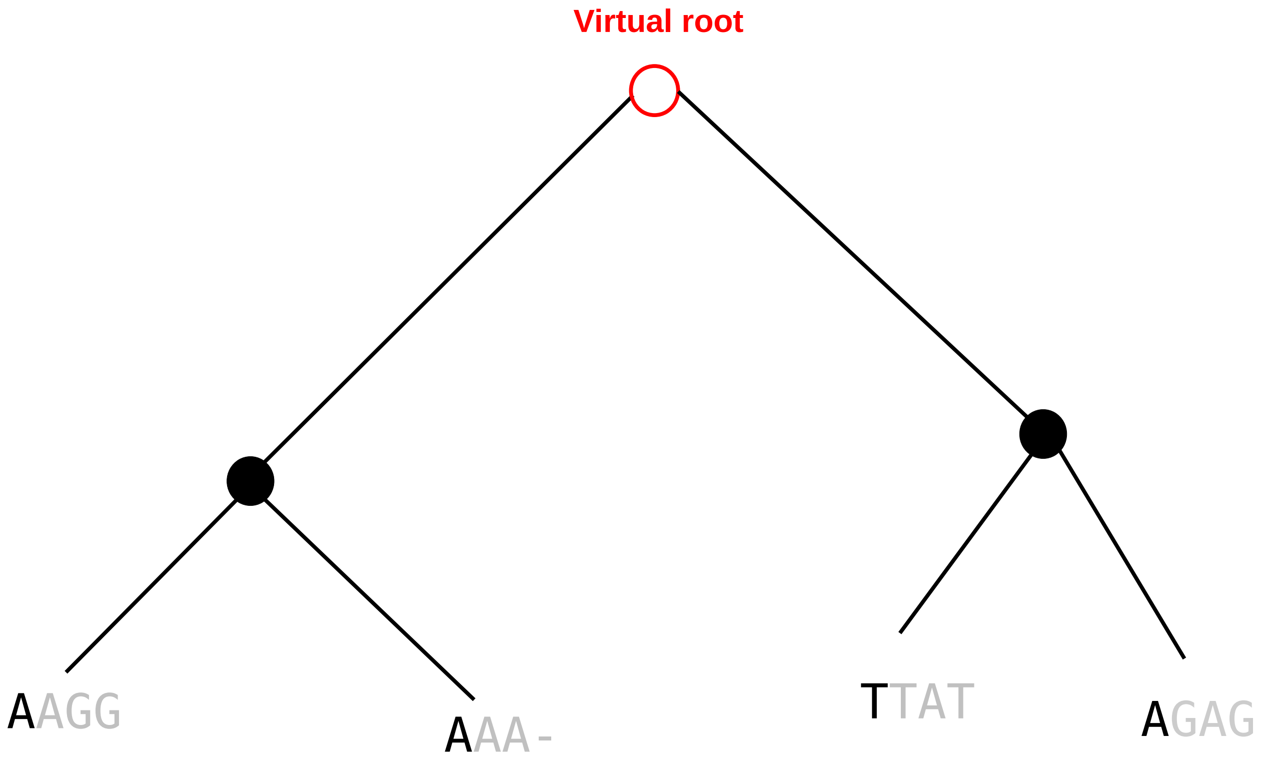
1



Intersection non-empty,
Overall score for this
Site: 1

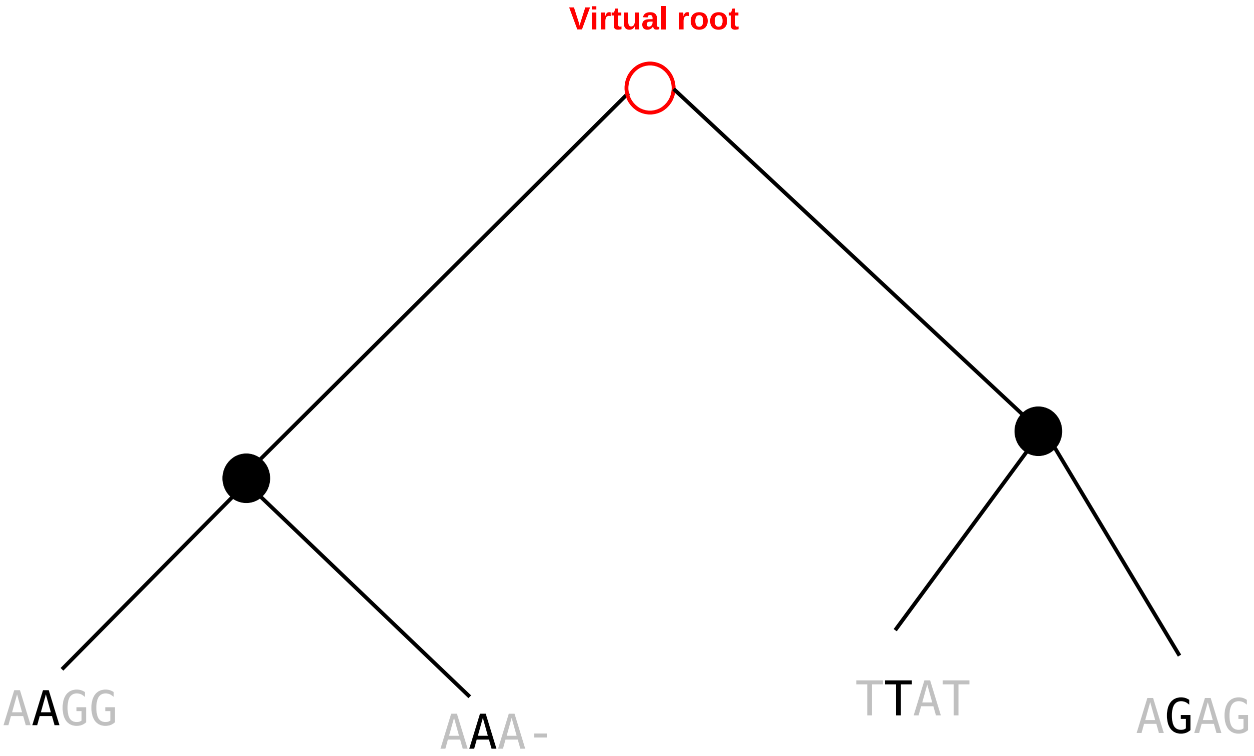
Parsimony

1



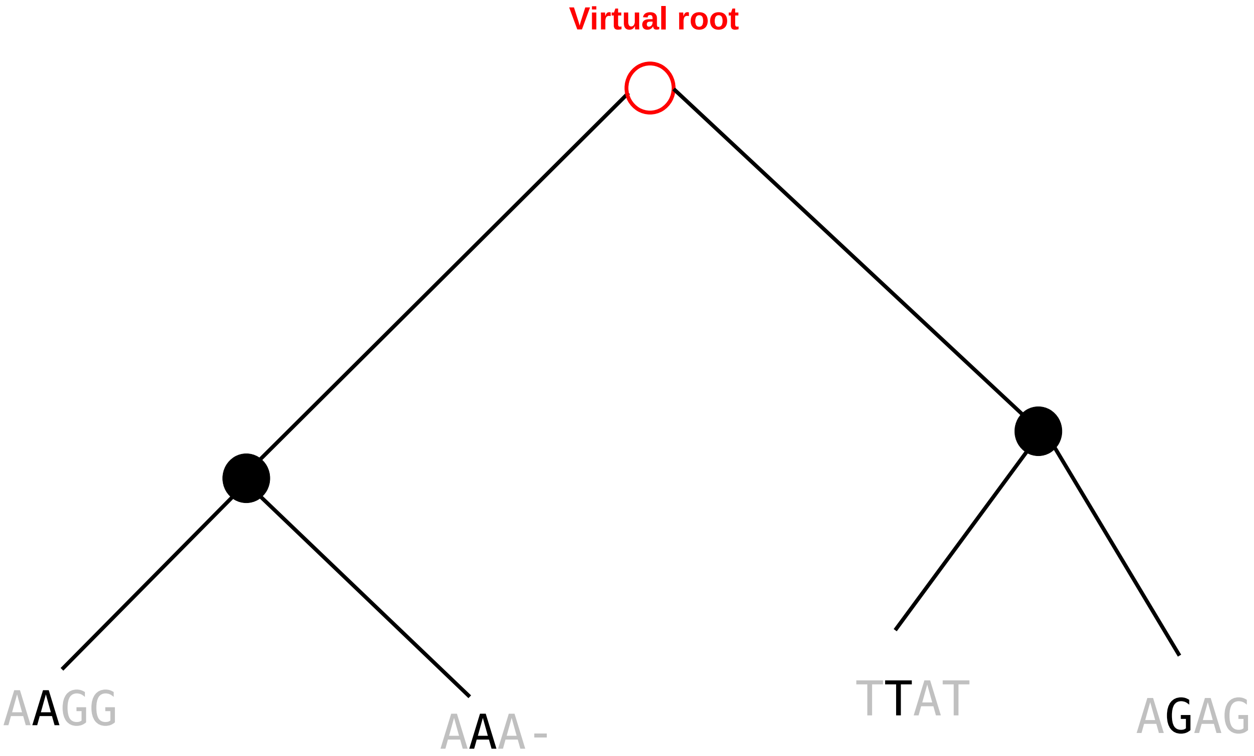
Parsimony

1+?



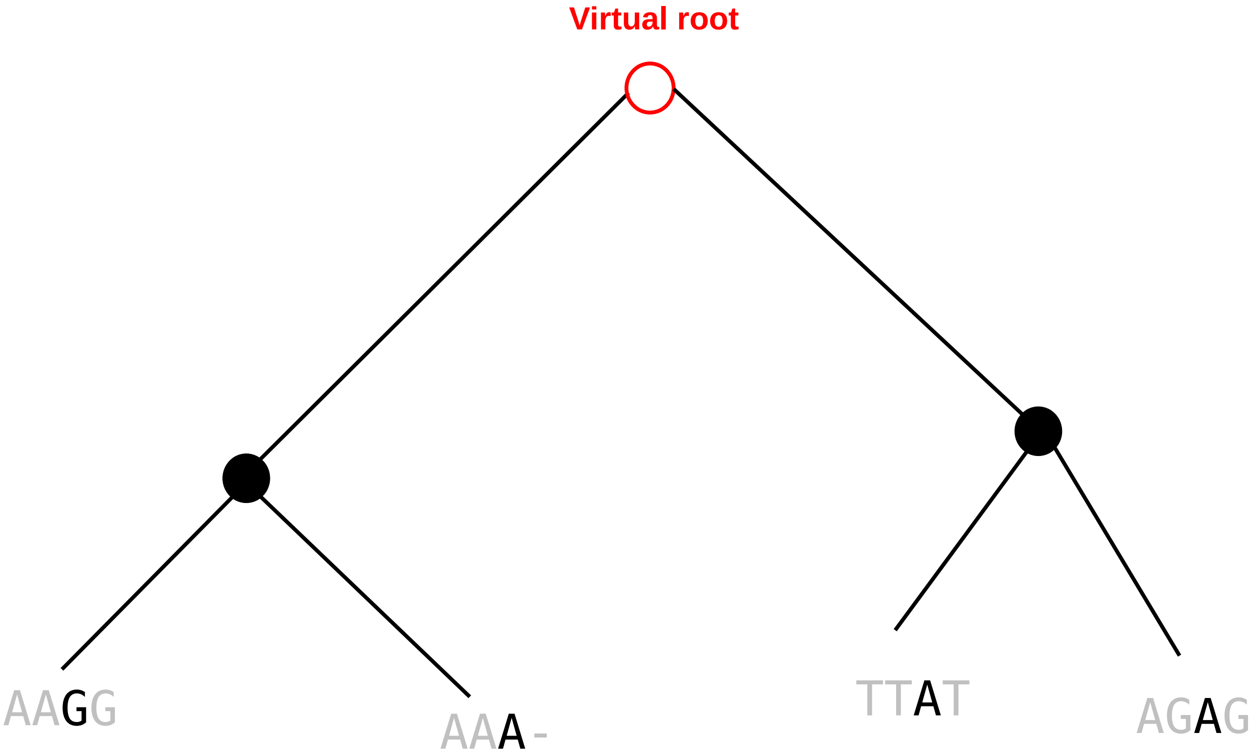
Parsimony

1+2



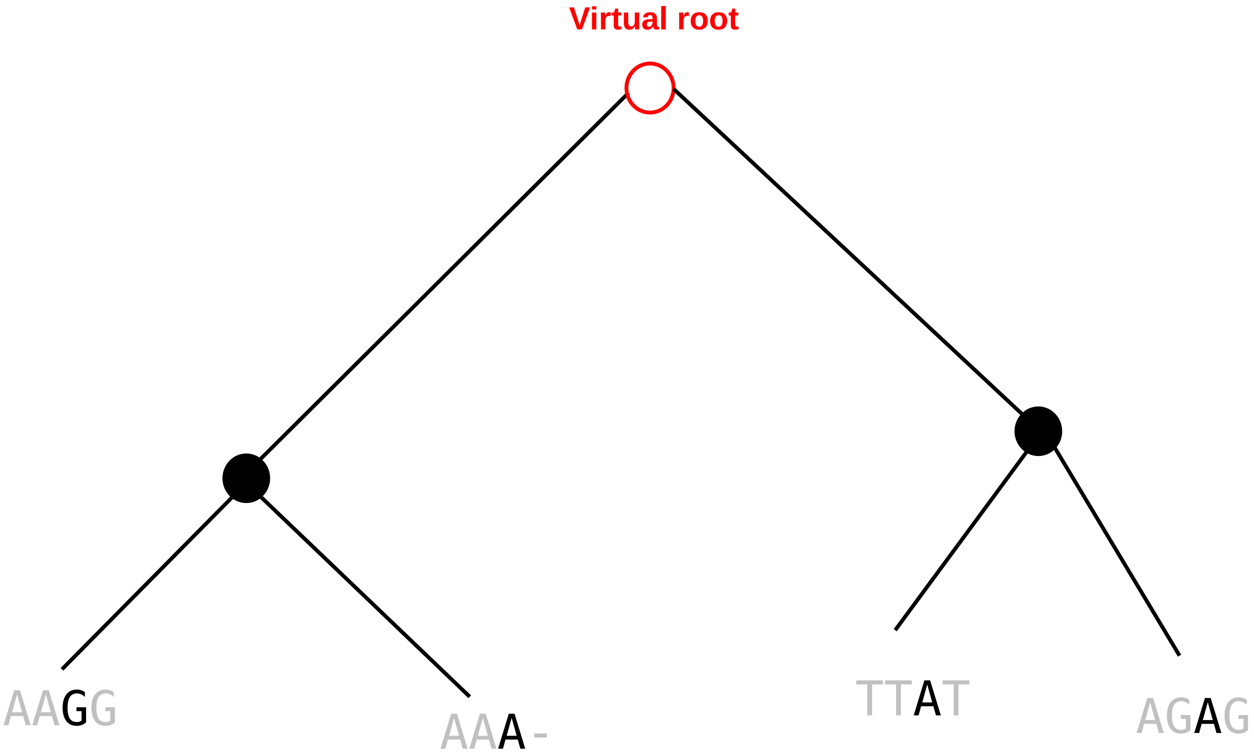
Parsimony

1+2+?



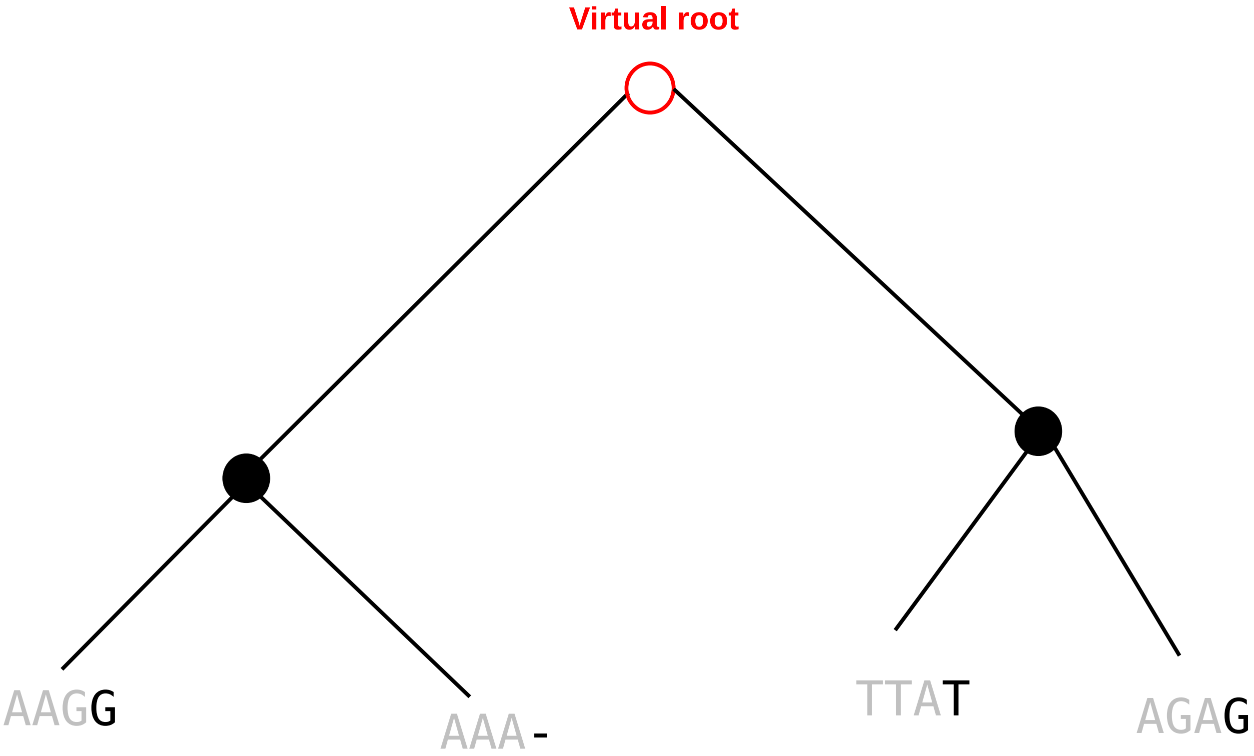
Parsimony

1+2+1



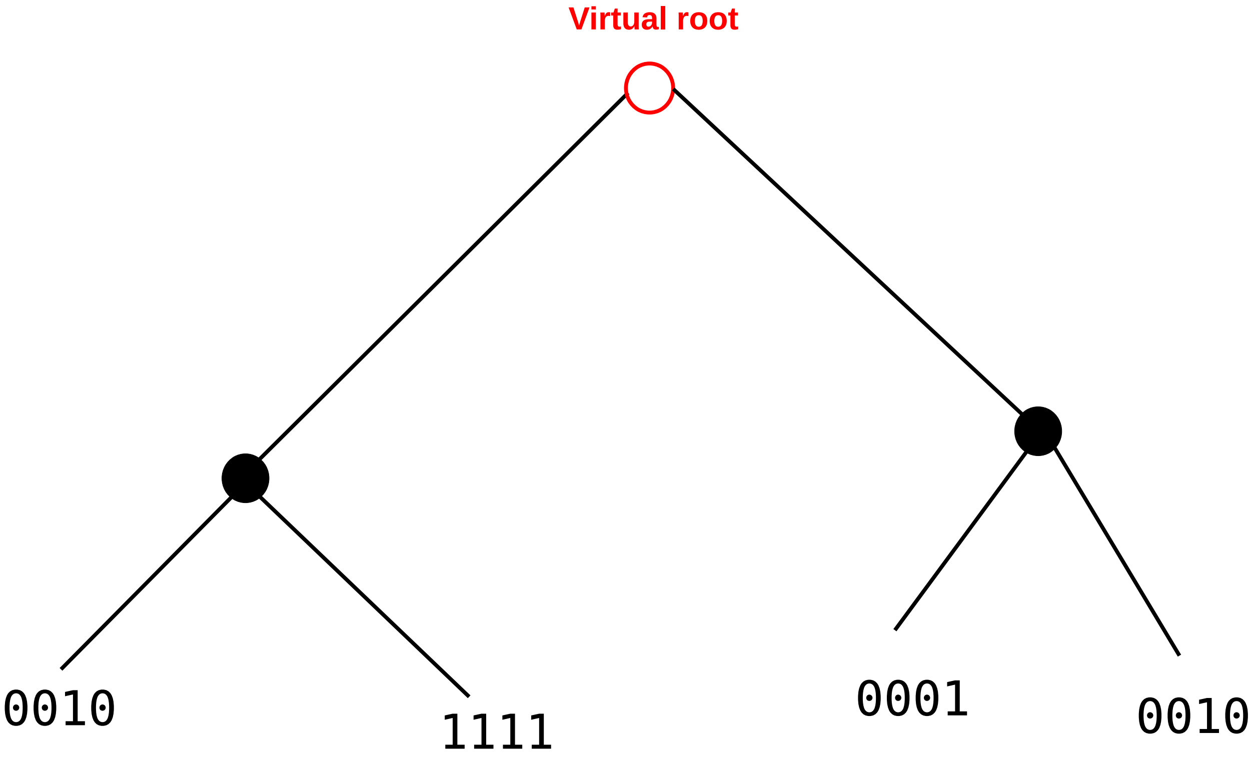
Parsimony

1+2+1



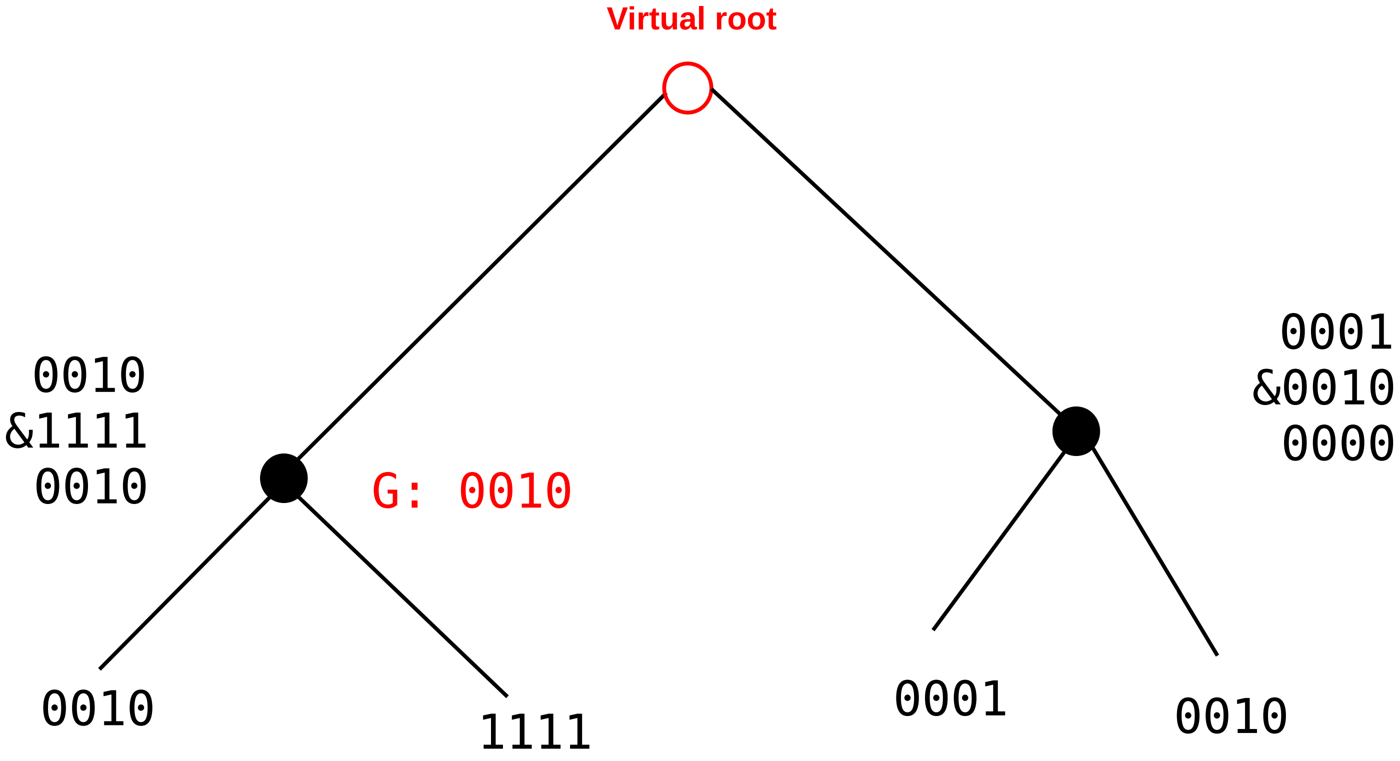
Parsimony

1+2+1



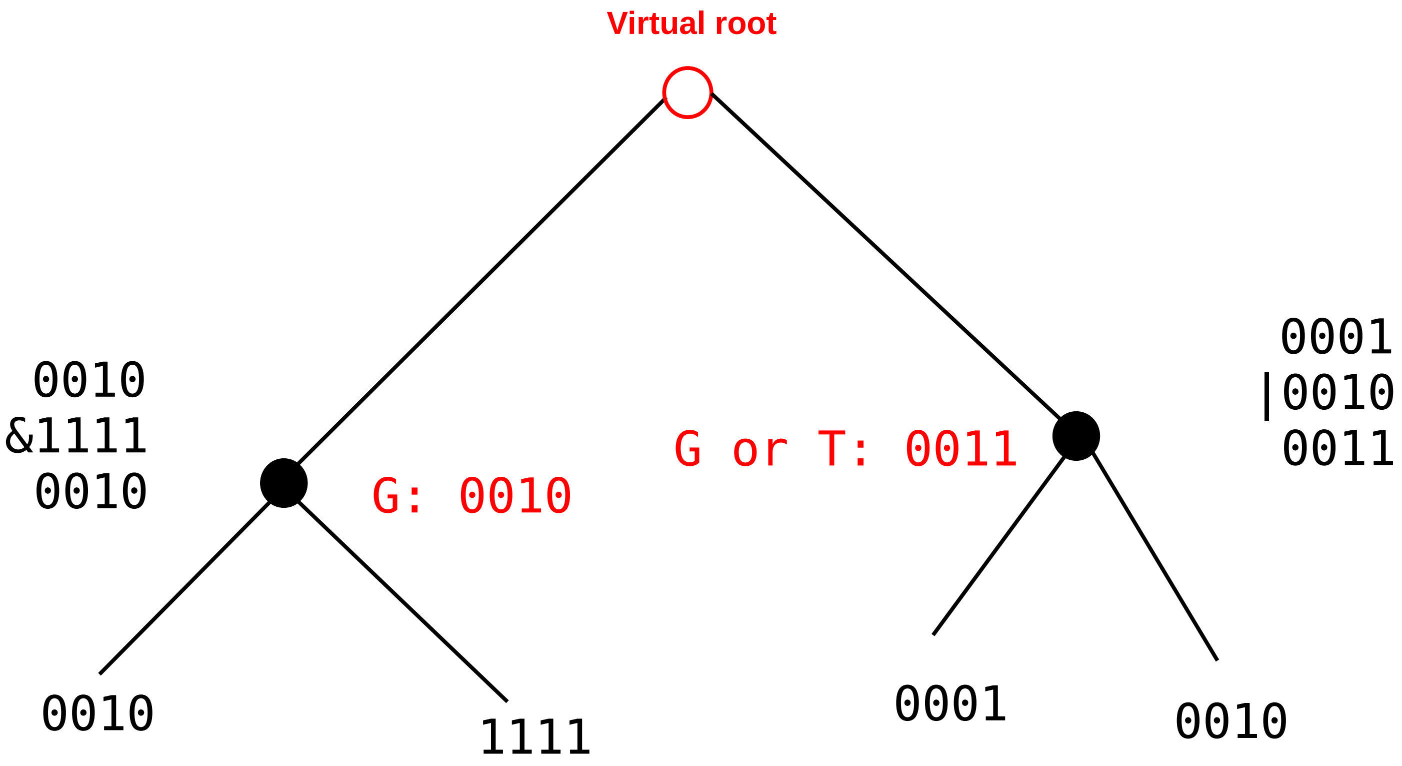
Parsimony

1+2+1



Parsimony

1+2+1+?



Virtual root

0010
&1111
0010

G: 0010

G or T: 0011

0001
|0010
0011

0010

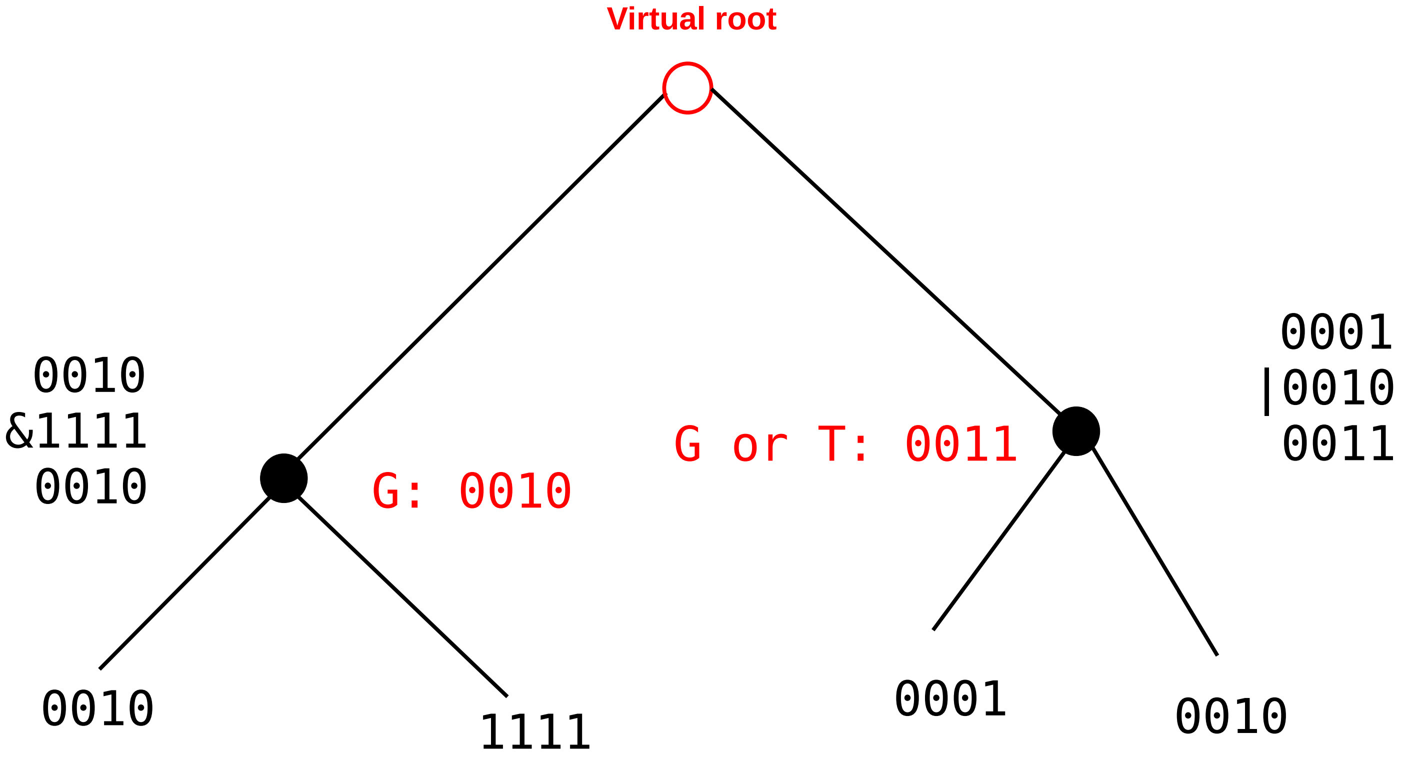
1111

0001

0010

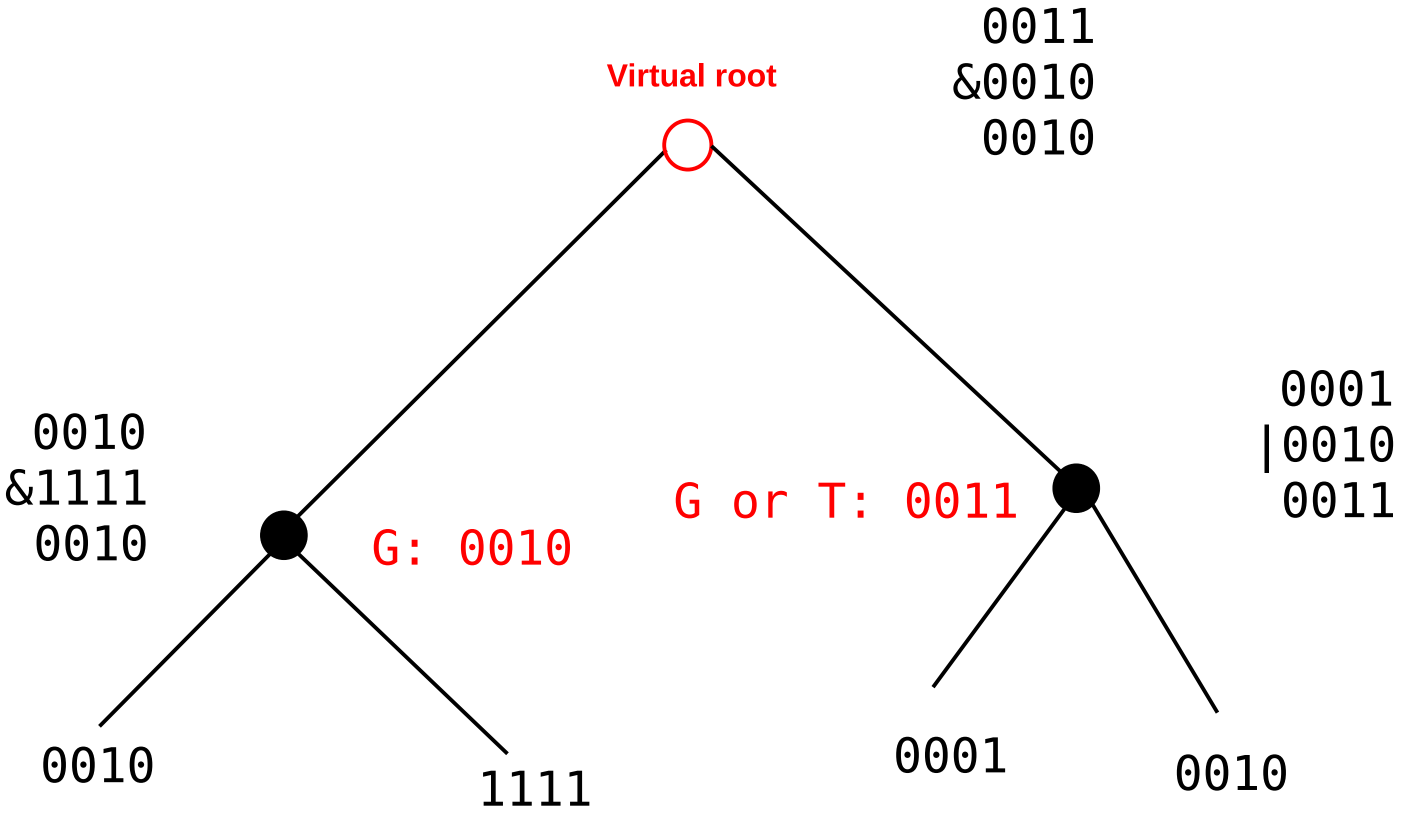
Parsimony

1+2+1+1



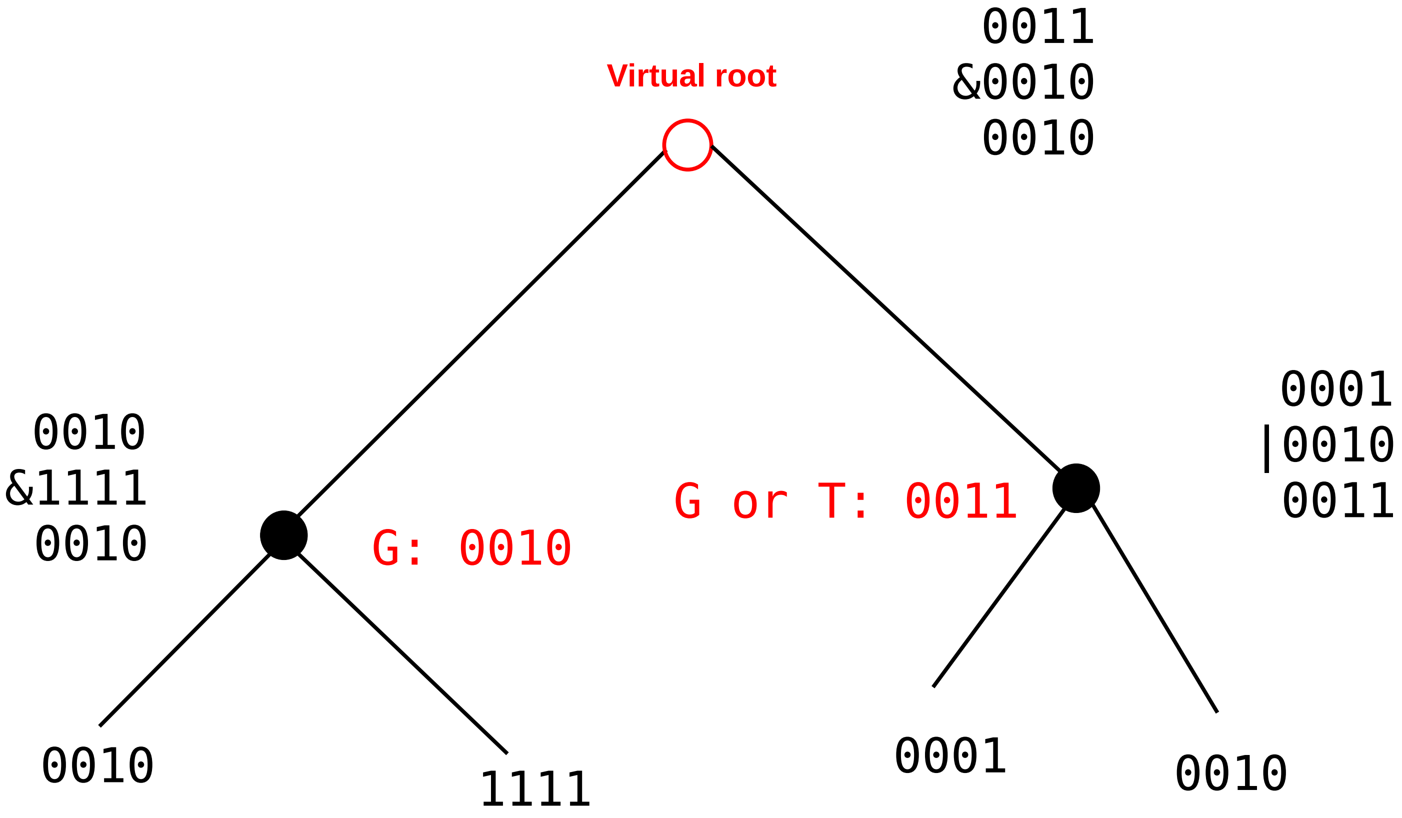
Parsimony

1+2+1+1



Parsimony

1+2+1+1= 5



Virtual root

0011
&0010
0010

0010
&1111
0010

G: 0010

G or T: 0011

0001
|0010
0011

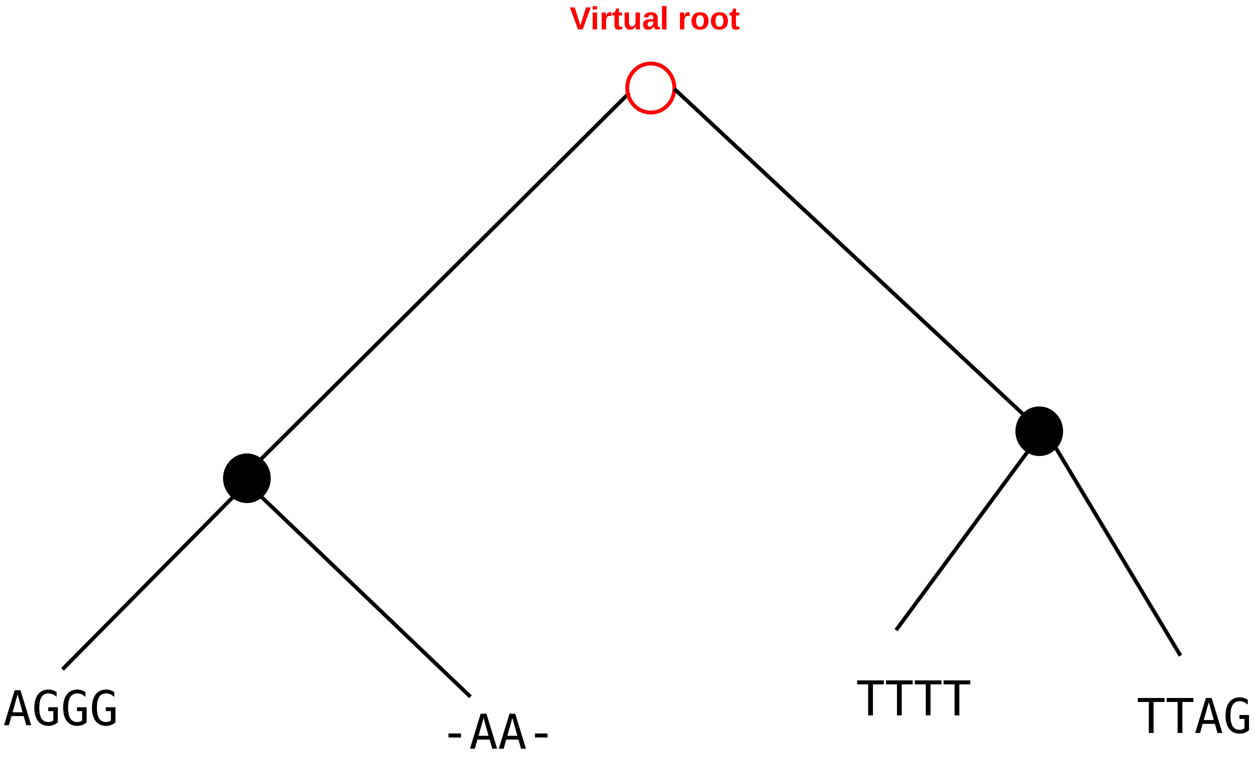
0010

1111

0001

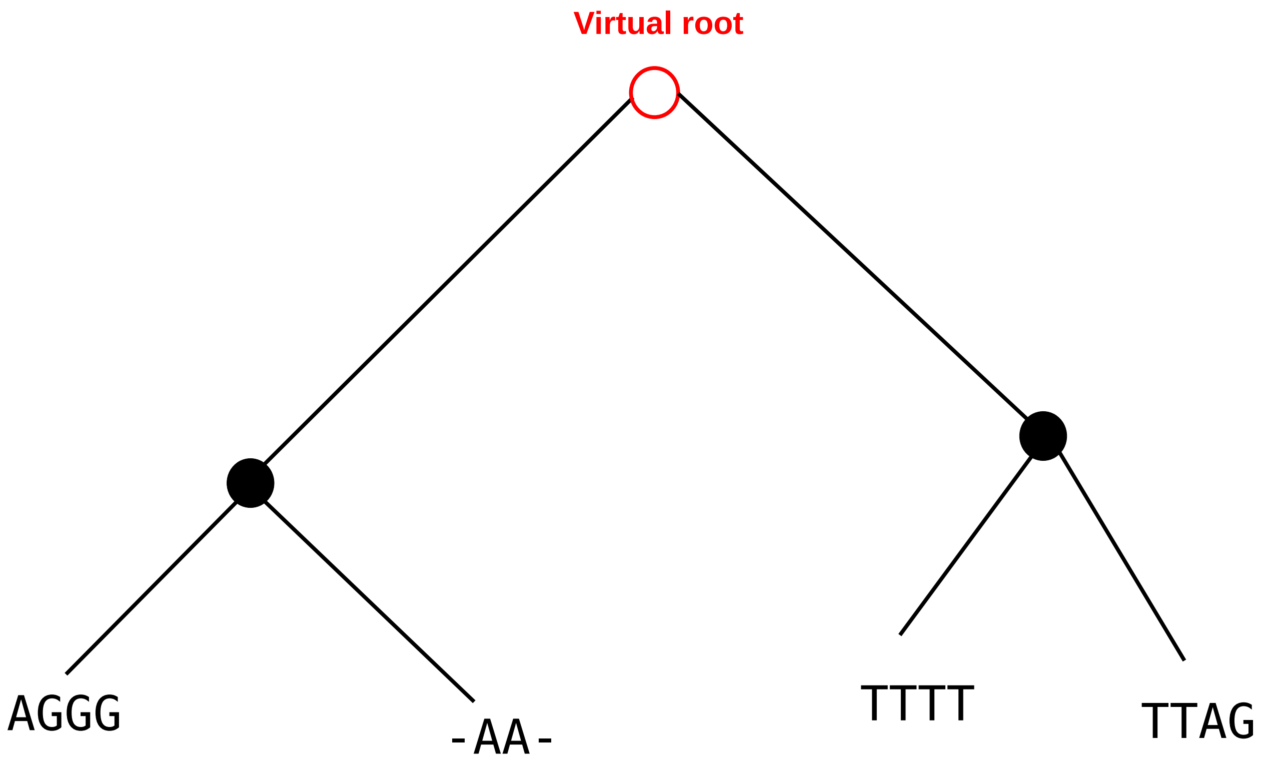
0010

Exercise: What's the parsimony score of this tree?



Exercise: What's the parsimony score of this tree?

1+2+2+1=6



Parsimony

- Time complexity to score one tree

  MSA with *n* taxa and *m* sites

  → *(n-2) * m* calculations; *n-2* is the number of inner nodes of a tree with *n* taxa

  → *O(nm)*, but the constant hidden in *O()* is very small

- Space complexity *DNA* data

  → alignment: *n * m* * 4 bits

  → ancestral nodes: *(n-2) * m* * 4 bits

  → score counter: *(n-2)* * 32 bits

  → space complexity *O(nm)*, but the constant hidden in *O()* is very small

- **Maximum Likelihood**: same time & space complexity, but constants much, much larger!

Parsimony Implementation Notes

- Intersections and Unions can be implemented efficiently at the bit-level
- 4 bits for one DNA character (remember, ambiguous character encoding)
- Plain implementation: 32 bits
- `SSE3` vector intrinsics: 128 bits
- `AVX` vector intrinsics: 256 bits
- `Parsimonator` program (www.exelixis-lab.org/software.html)
  - → uses SSE3 and AVX intrinsics
  - → I will show a demo now
  - → Implements simple search algorithm
  - → probably fastest available open-source parsimony implementation

Parsimony Implementation Notes

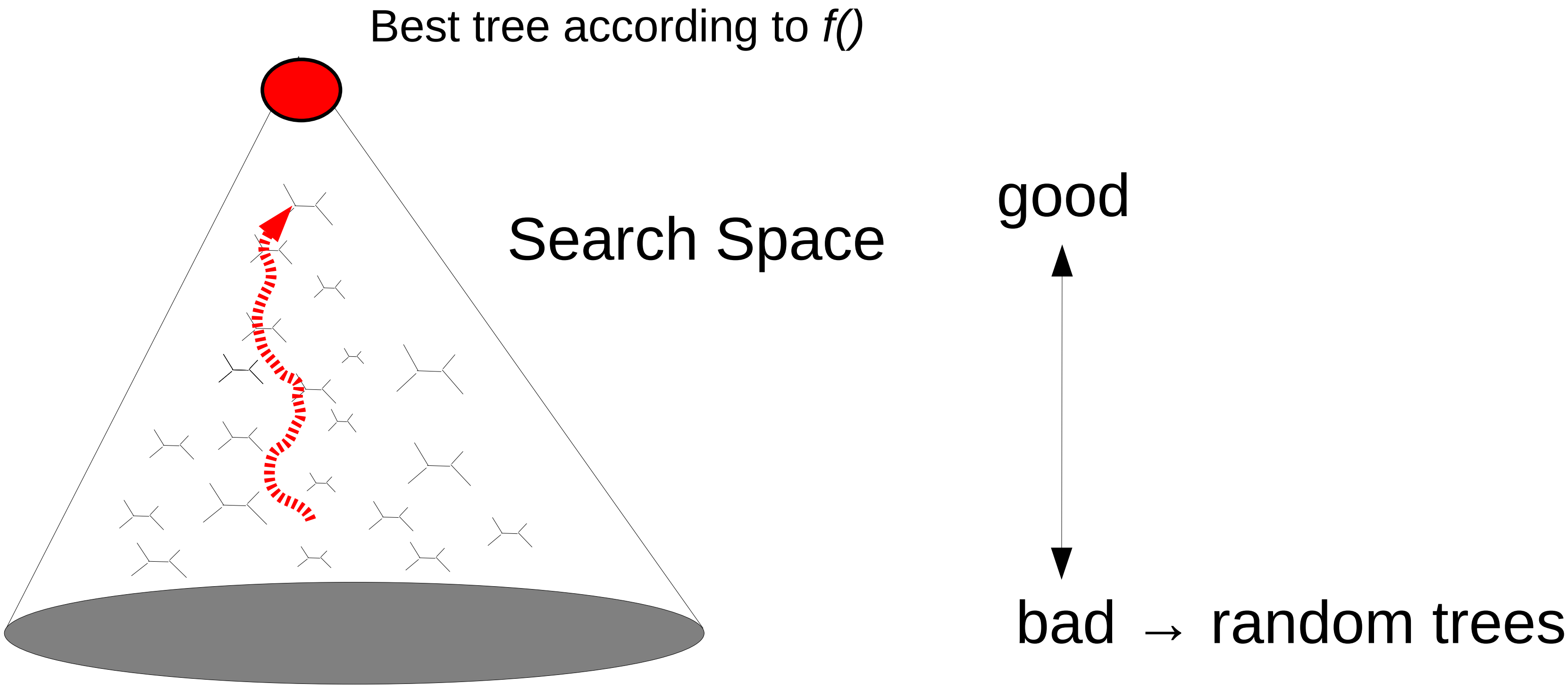
- Without going into the details:
- In the `parsimonator` implementation we need to compute a so-called population count (`popcount`) that computes the number of bits (# mutations) that are set to `1` in a 32-, 128-, or 256-bit word
- `popcount` is a very important operation
- There are various fancy bit-twisting implementations for fast `popcounts`
- In fact, this operation is so important that modern `x86` architectures have a dedicated HW-based `popcount`
- You can use it in C code via `__builtin_popcount(x)`

Parsimony Implementation Notes

- Why did we write `parsimonator`?
- A paper was published that claimed to have achieved a FPGA-based acceleration of the parsimony function of up to factor 10,000
- Remember: the speedup is defined as *T(1)/T(N)*, where *T(1)* is the fastest available sequential implementation/algorithm!
- Compared to Parsimonator (`AVX` version), the corresponding FPGA design achieved a speedup of up to 10, only!
- N. Alachiotis, A. Stamatakis: "FPGA Acceleration of the Phylogenetic Parsimony Kernel**?**", *FPL 2011*.

How do we search for “good” trees under any criterion?

Search Space



Best tree according to *f()*

Search Space

good

bad → random trees

Tree Search Algorithms

- How do we obtain an initial starting tree with *n* taxa → comprehensive tree

  → NJ or UPGMA tree

  → random tree

  → stepwise addition algorithm

- How do we change such a comprehensive tree to improve its score?

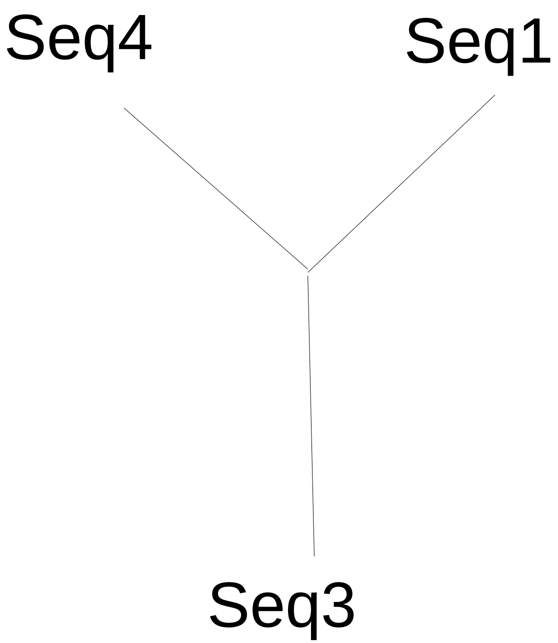
  Scores can be improved with optimality criteria: least squares, minimum evolution, parsimony, maximum likelihood

Building a Random Tree

Seq0
Seq1
Seq2
Seq3
Seq4

Building a Random Tree

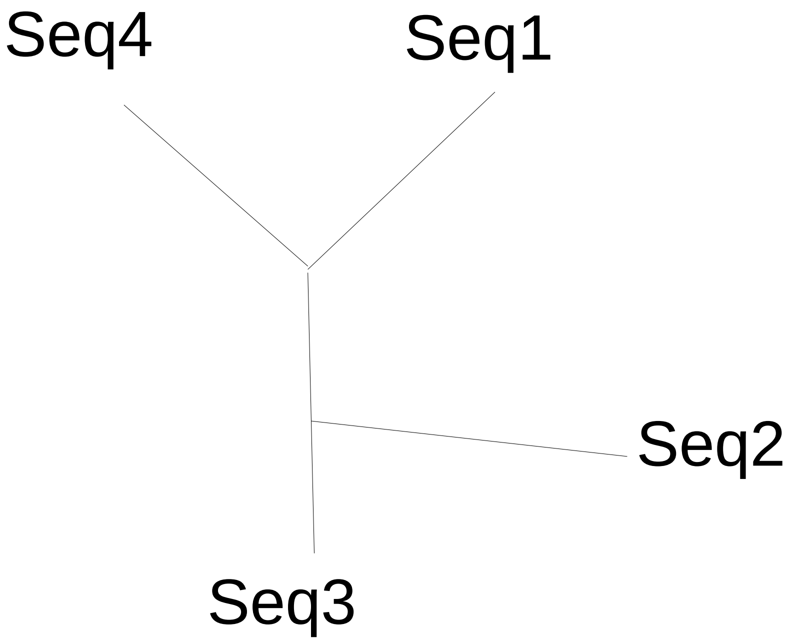
Seq0
~~Seq1~~
Seq2
~~Seq3~~
~~Seq4~~



Seq4
Seq1
Seq3

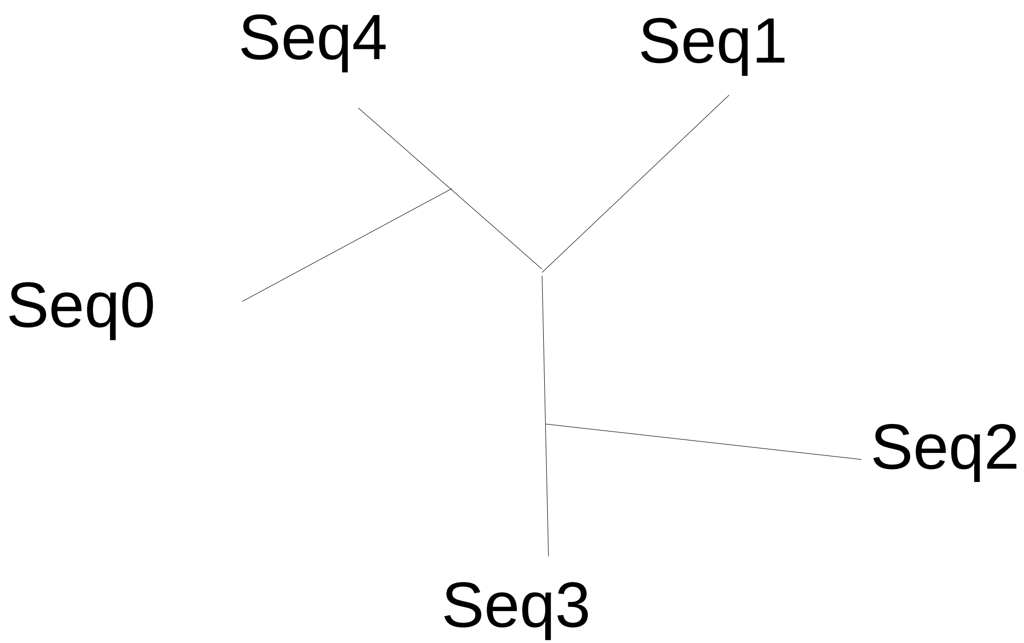
Building a Random Tree

Seq0
~~Seq1~~
~~Seq2~~
~~Seq3~~
~~Seq4~~



Building a Random Tree

~~Seq0~~
~~Seq1~~
~~Seq2~~
~~Seq3~~
~~Seq4~~

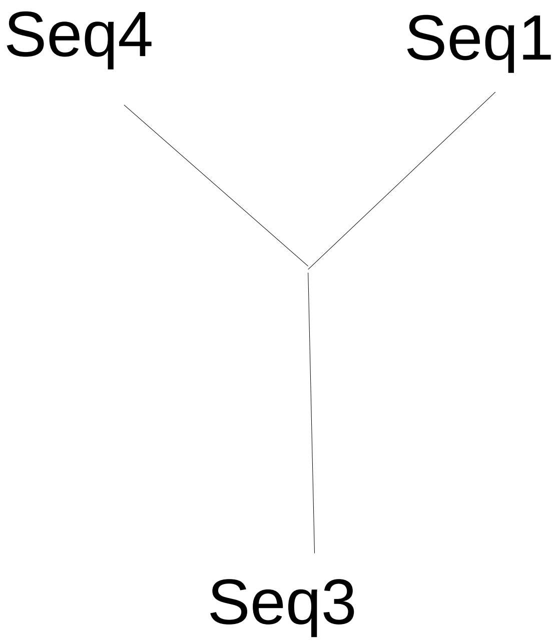


Randomized Stepwise Addition Order Algorithm

Seq0
Seq1
Seq2
Seq3
Seq4

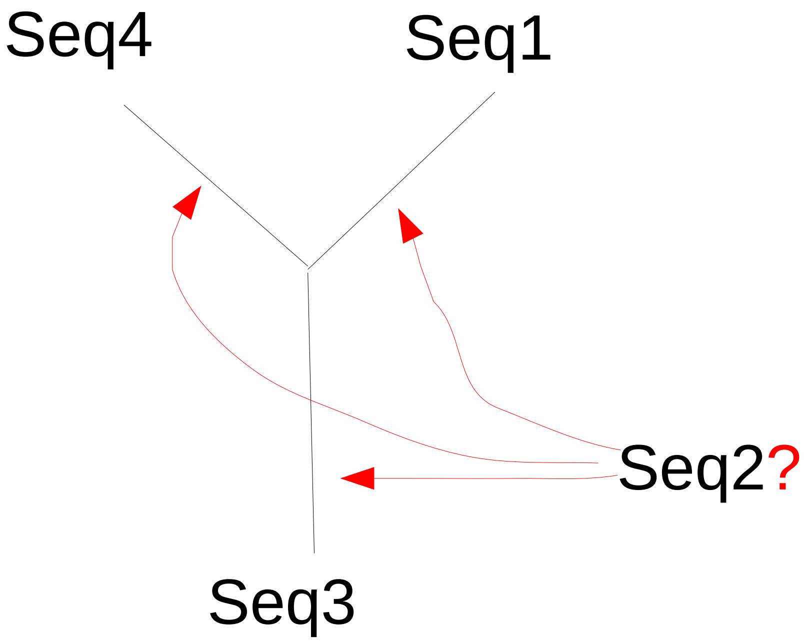
Randmoized Stepwise Addition Order Algorithm

Seq0
~~Seq1~~
Seq2
~~Seq3~~
~~Seq4~~



Randomized Stepwise Addition Order Algorithm

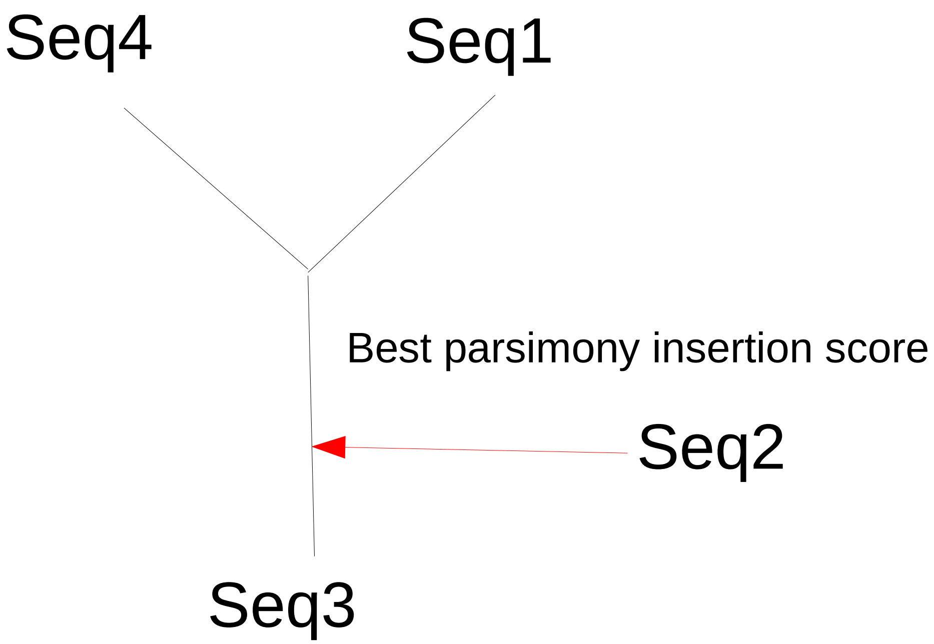
Seq0
~~Seq1~~
~~Seq2~~
~~Seq3~~
~~Seq4~~



Seq4
Seq1
Seq2?
Seq3

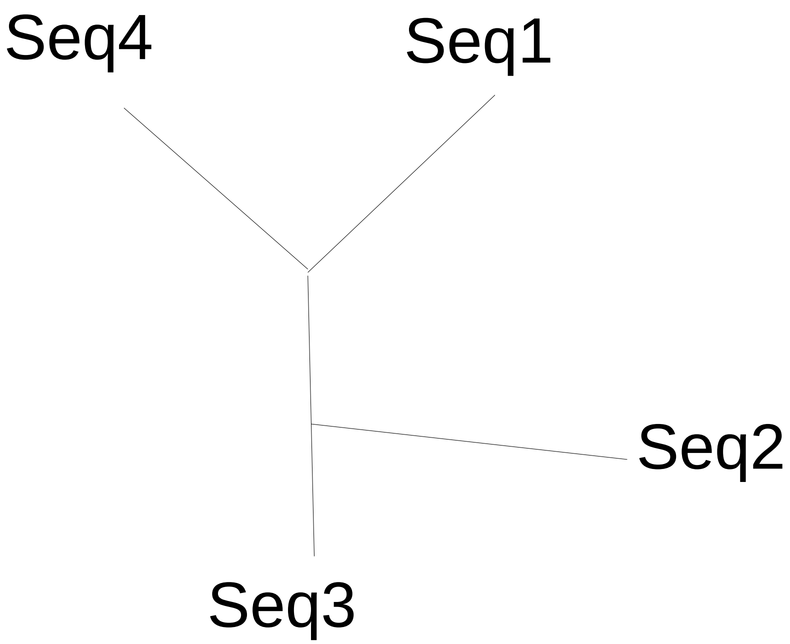
Randomized Stepwise Addition Order Algorithm

Seq0
~~Seq1~~
~~Seq2~~
~~Seq3~~
~~Seq4~~


Seq4
Seq1
Best parsimony insertion score
Seq2
Seq3

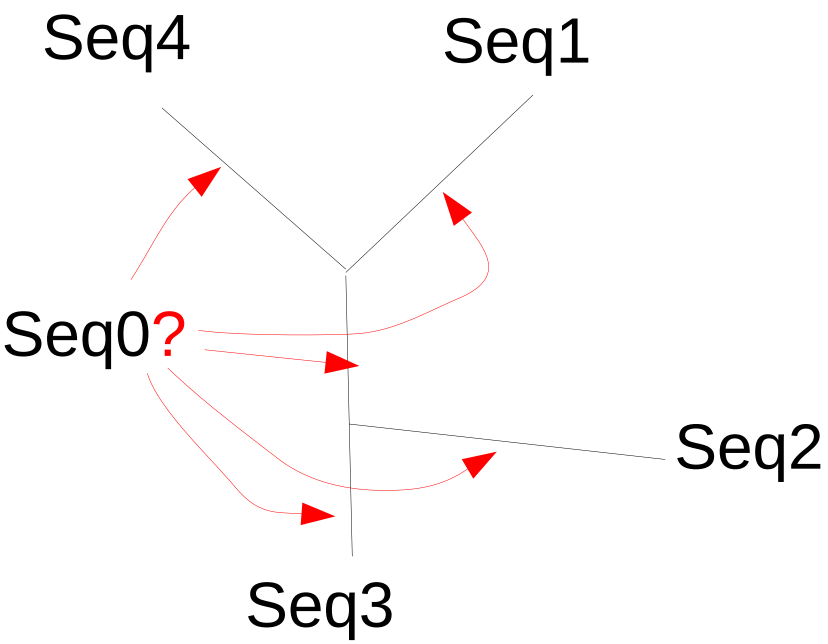
Randomized Stepwise Addition Order Algorithm

Seq0
~~Seq1~~
~~Seq2~~
~~Seq3~~
~~Seq4~~



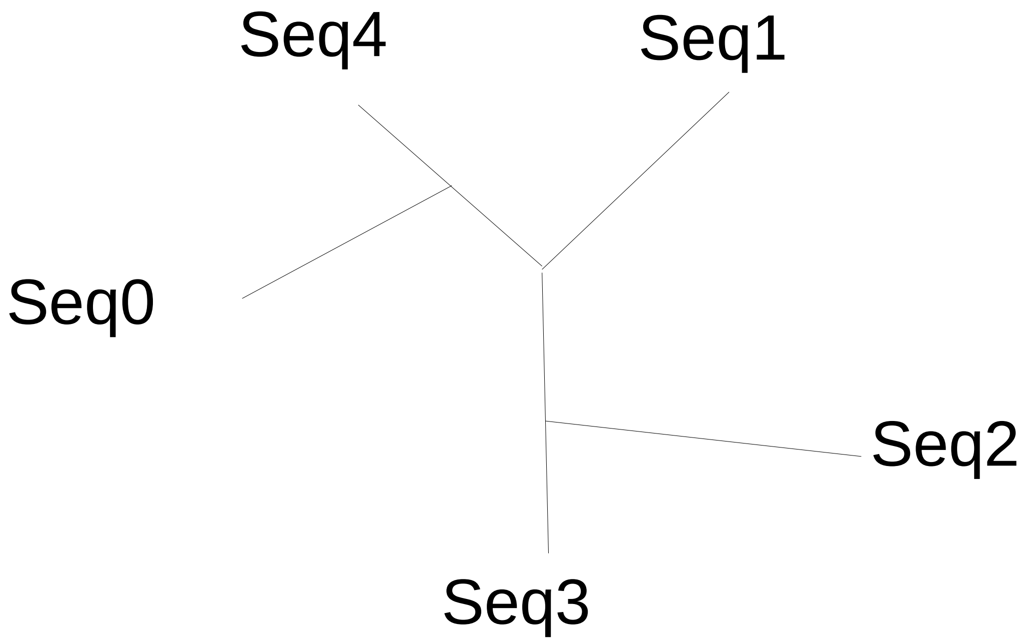
Randomized Stepwise Addition Order Algorithm

~~Seq0~~
~~Seq1~~
~~Seq2~~
~~Seq3~~
~~Seq4~~



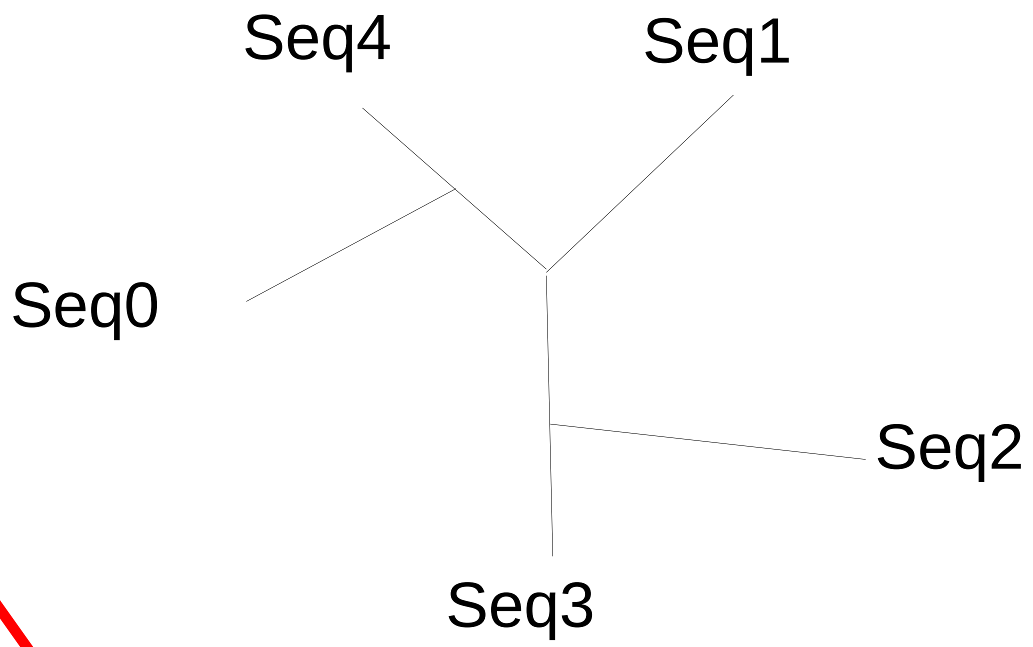
Randomized Stepwise Addition Order Algorithm

~~Seq0~~
~~Seq1~~
~~Seq2~~
~~Seq3~~
~~Seq4~~



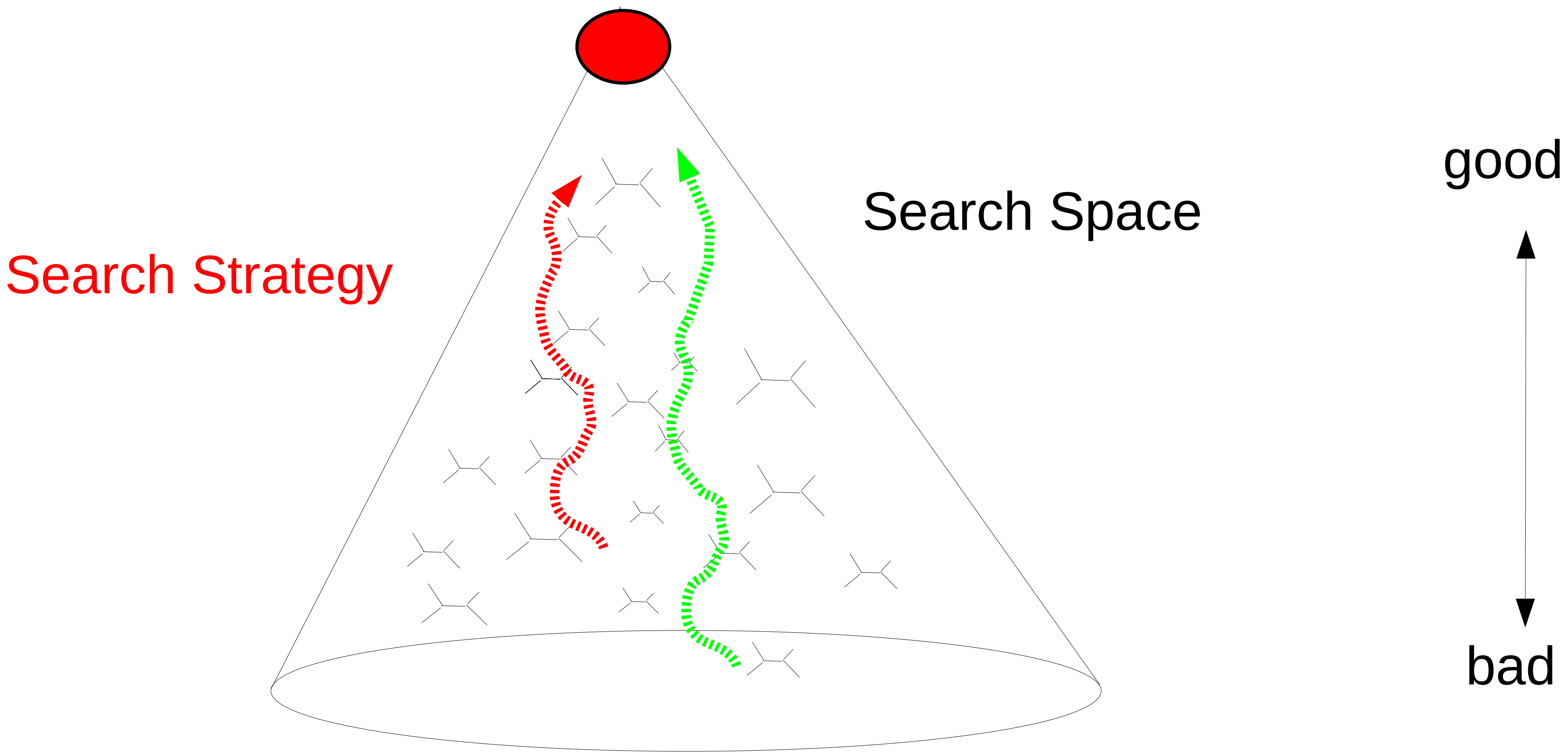
Randomized Stepwise Addition Order Algorithm

~~Seq0~~
~~Seq1~~
~~Seq2~~
~~Seq3~~
~~Seq4~~

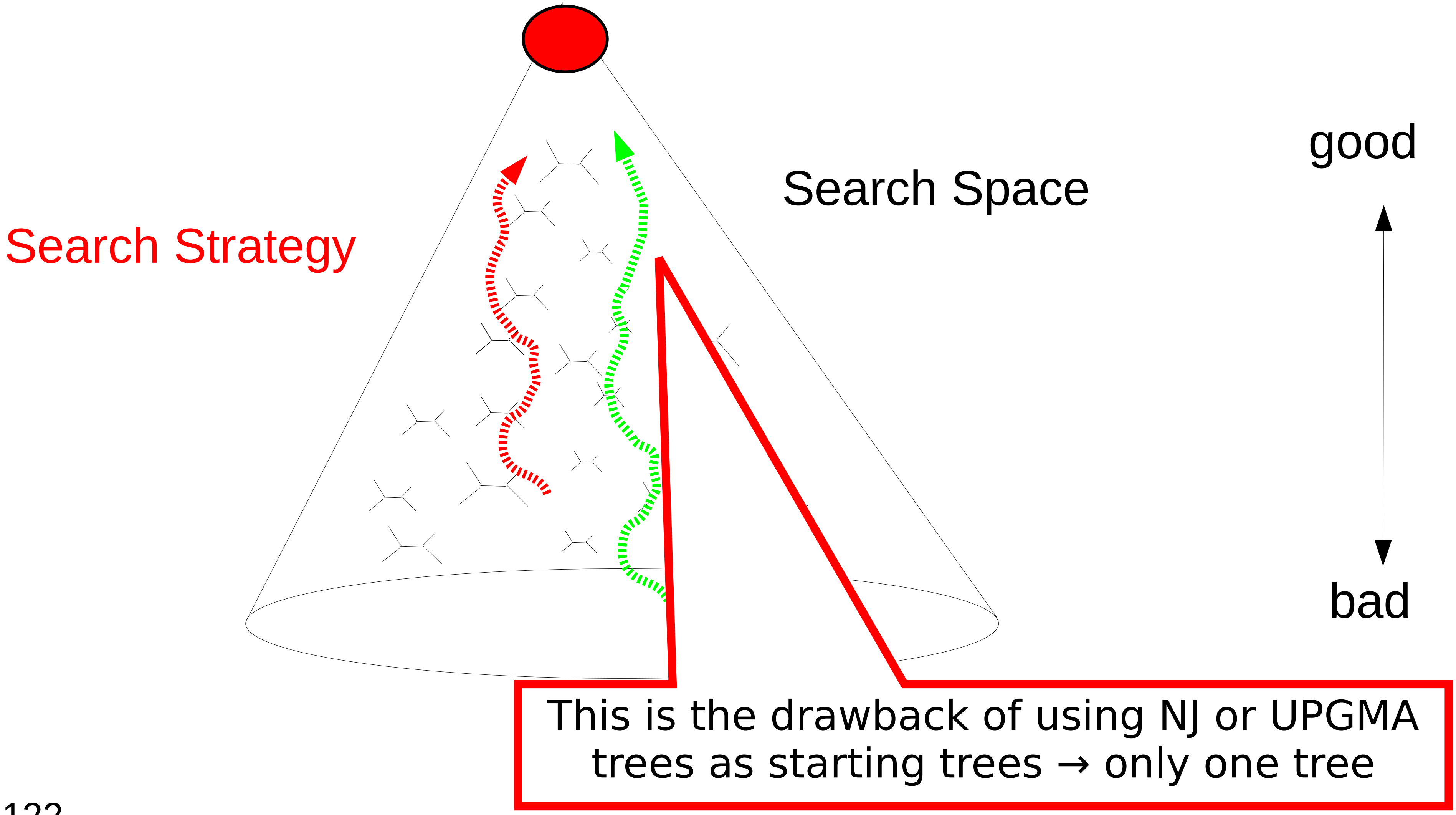


Distinct addition order, e.g.,
Seq0→Seq1→Seq2→Seq3→Seq4
can yield a different tree!

Why are distinct Starting Trees useful?

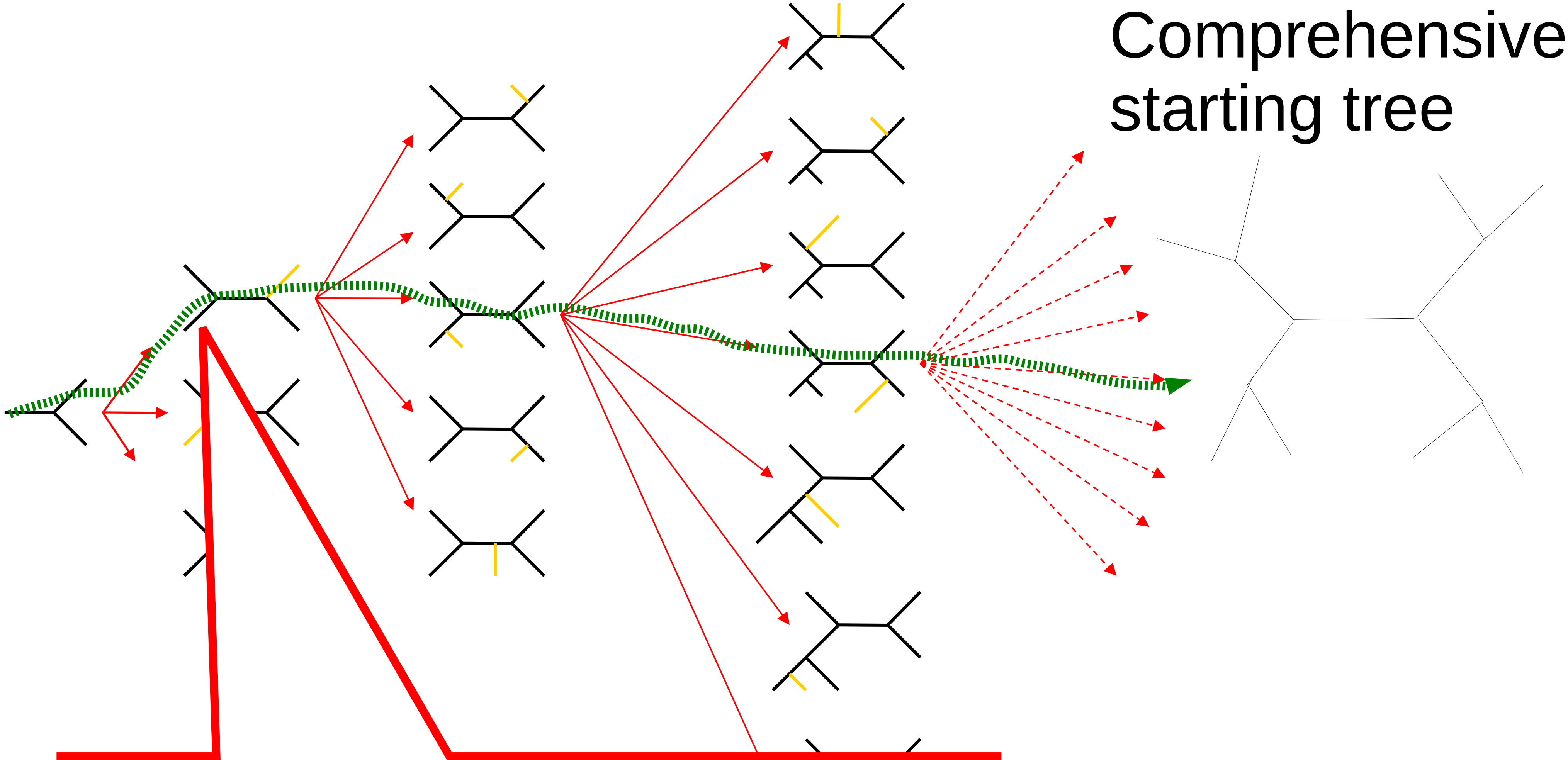


Why are distinct Starting Trees useful?



This is the drawback of using NJ or UPGMA trees as starting trees → only one tree

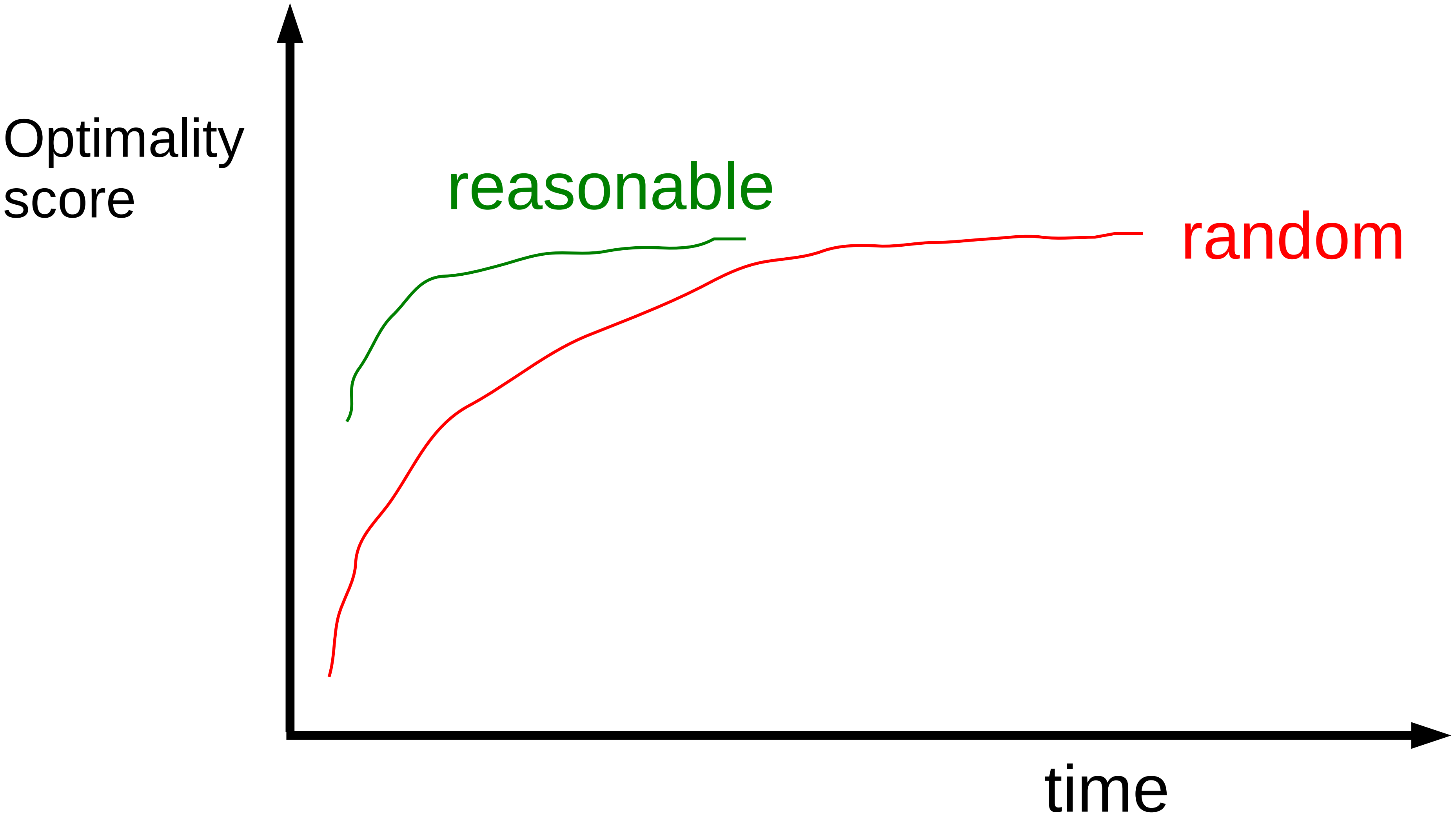
The number of trees



Comprehensive starting tree

Stepwise addition is like following a single path through this!

Random versus Reasonable Starting trees

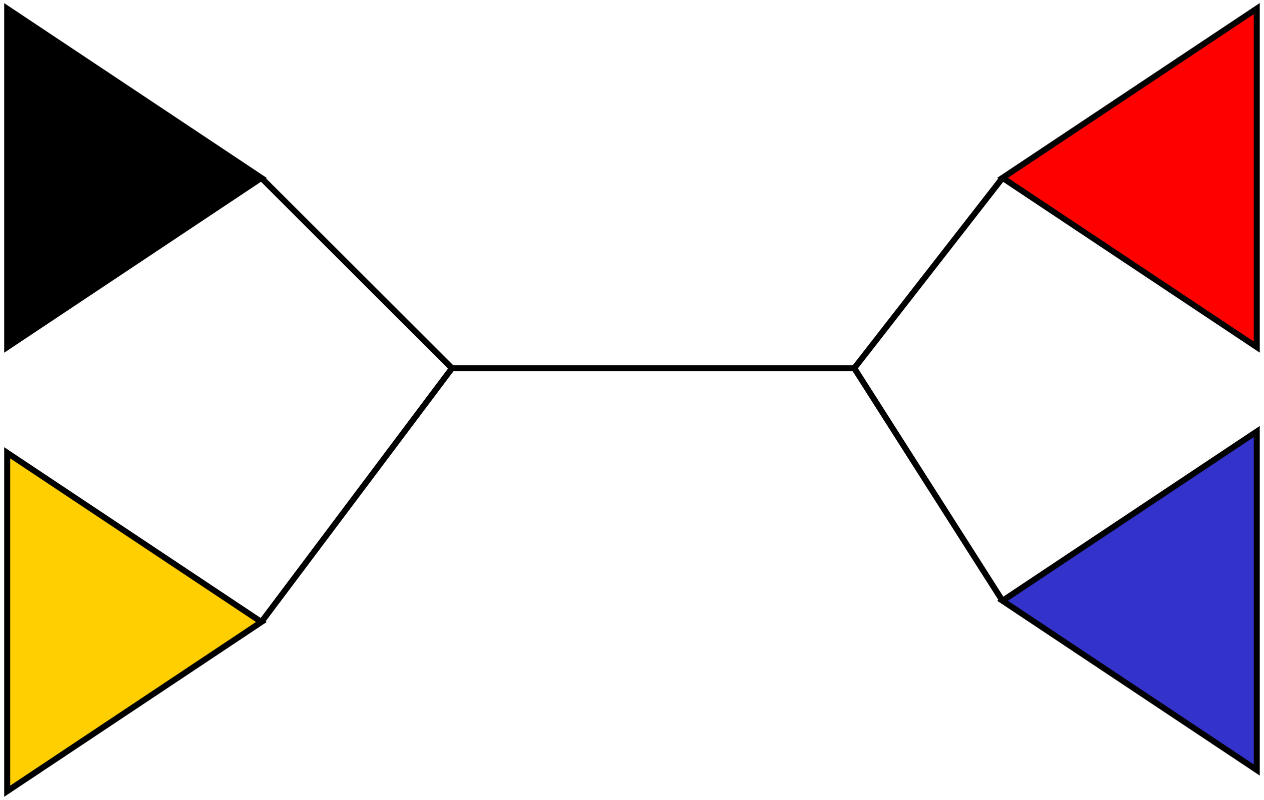


Search Strategies

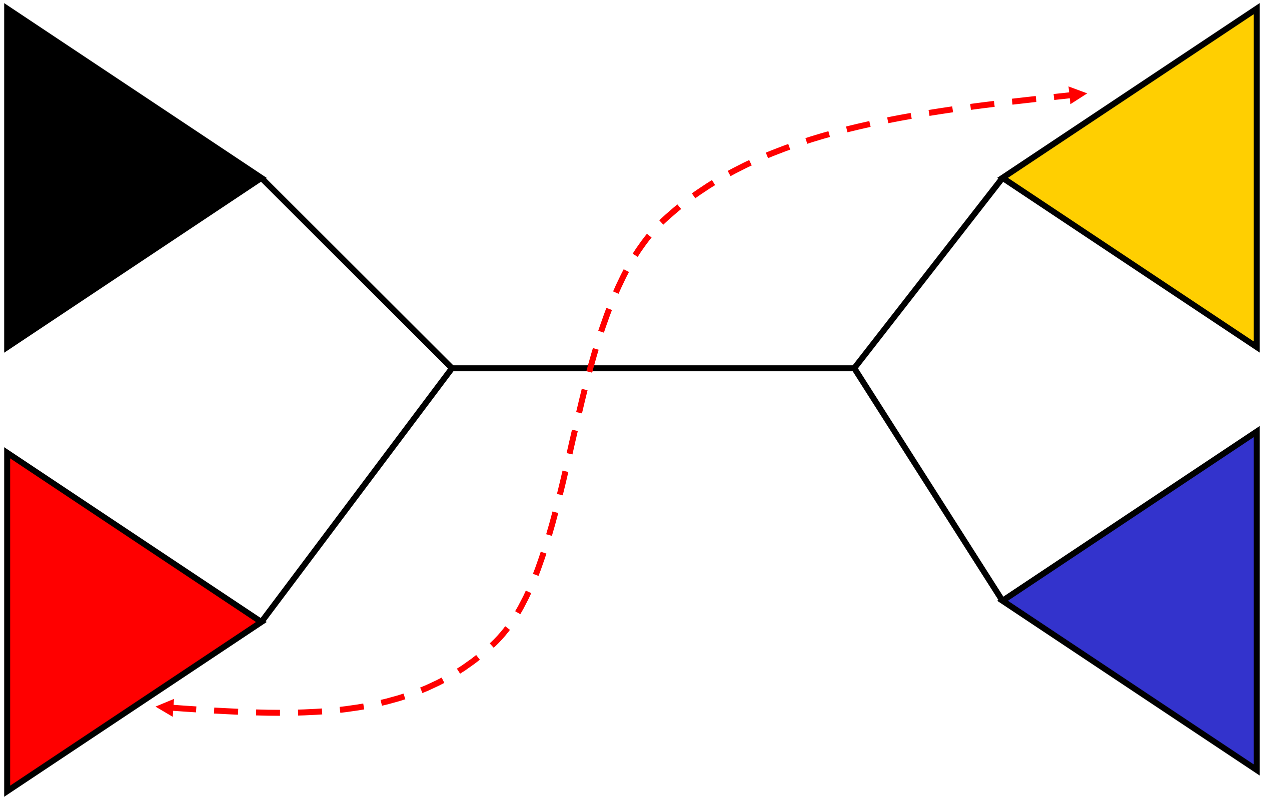
- Given a comprehensive tree
- Apply topological alteration mechanisms in some order to improve the score, for instance, via
  - Hill-climbing
  - Simulated annealing
  - Some other technique

    → design of ad hoc heuristics
- The three basic moves are:
  - **NNI**: Nearest Neighbor Interchange
  - **SPR**: Subtree Pruning and Re-Grafting
  - **TBR**: Tree Bisection and Reconnection

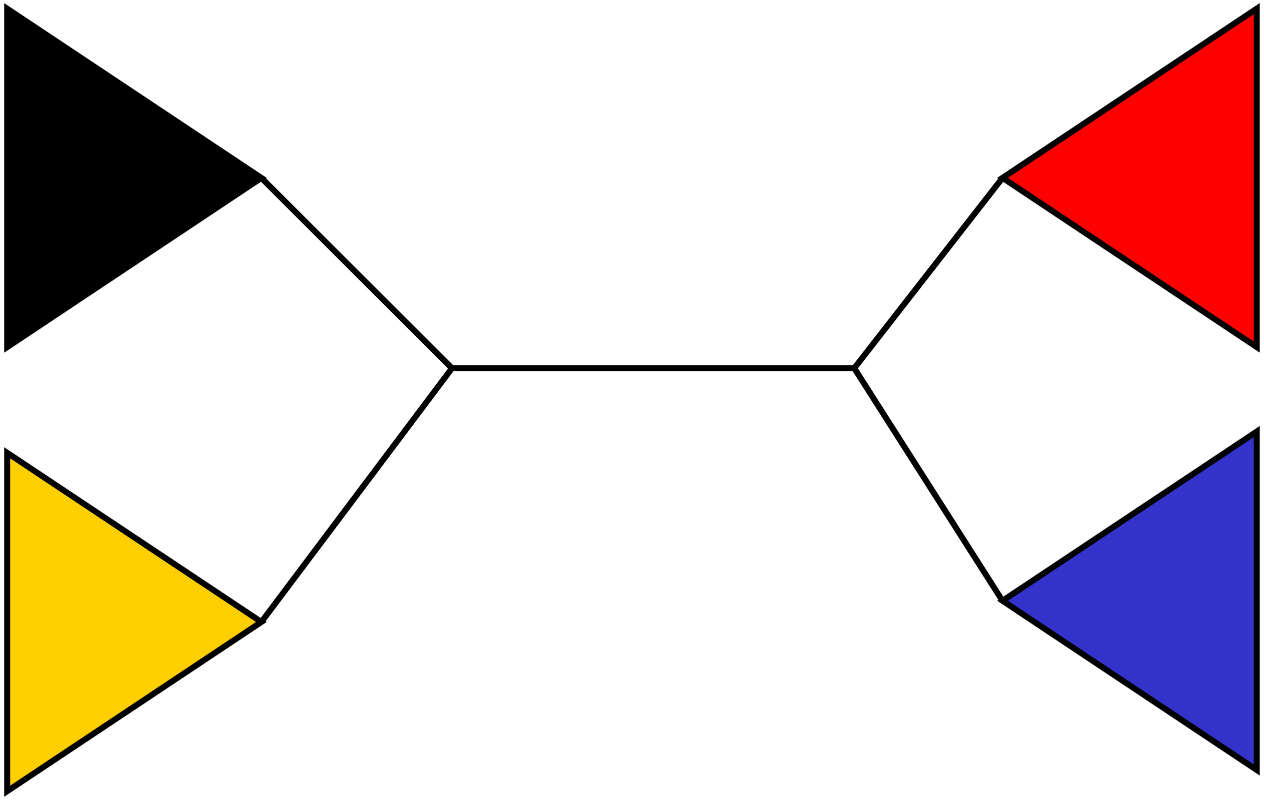
NNI



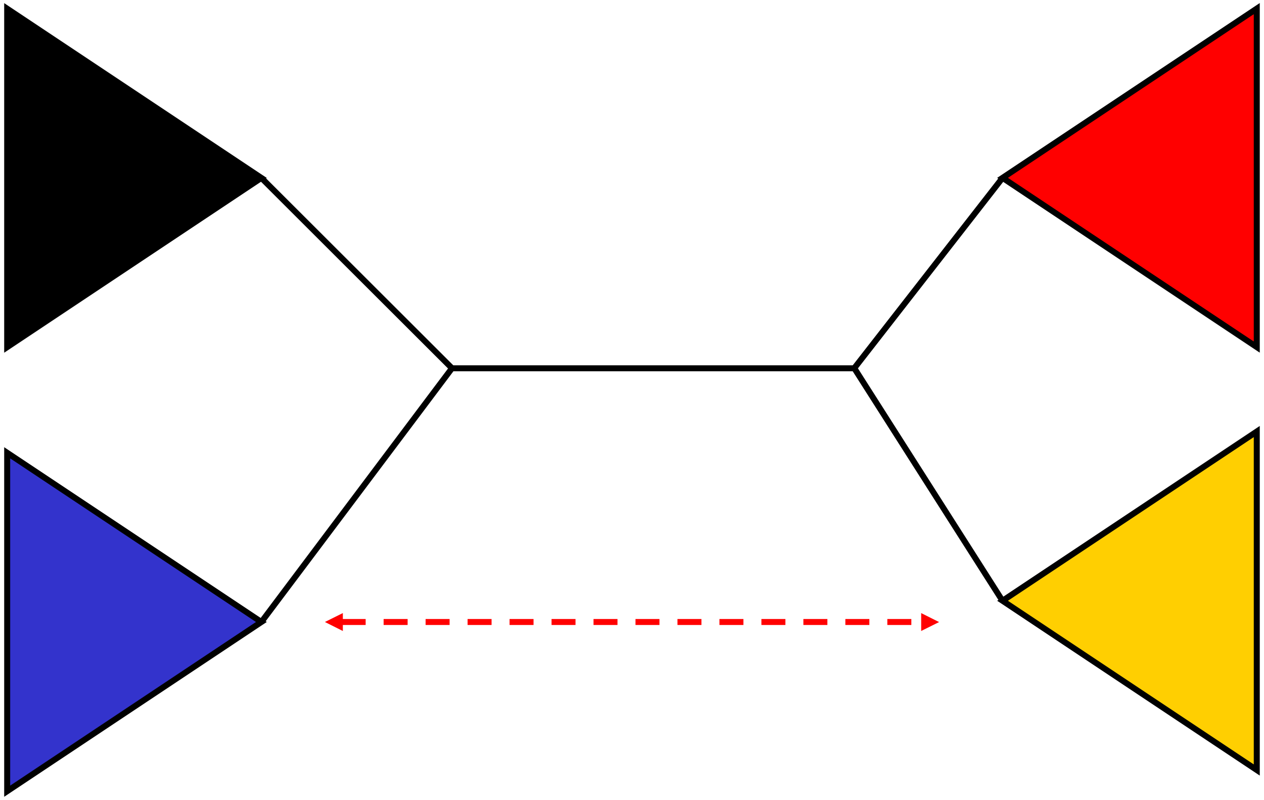
NNI



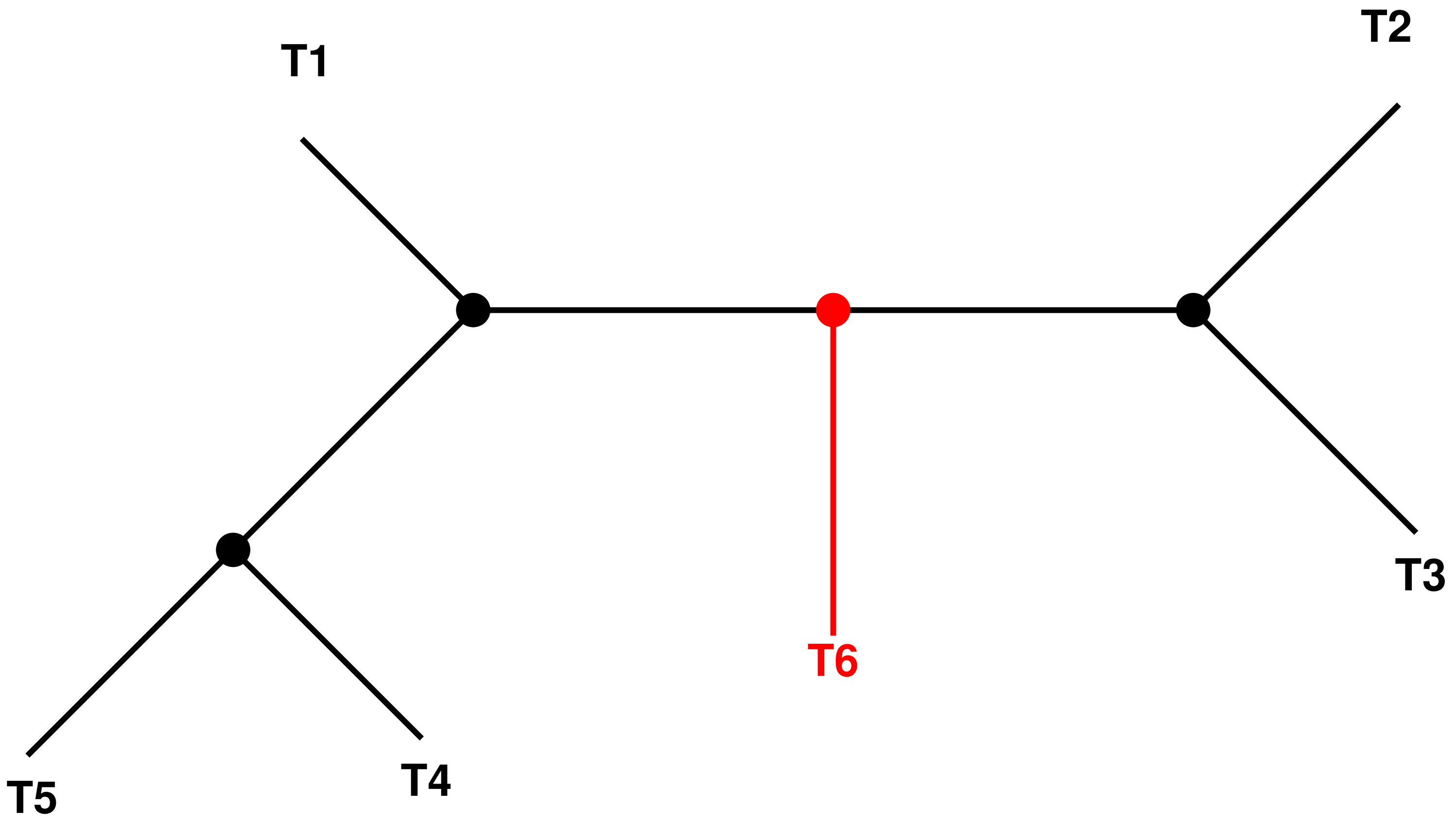
NNI



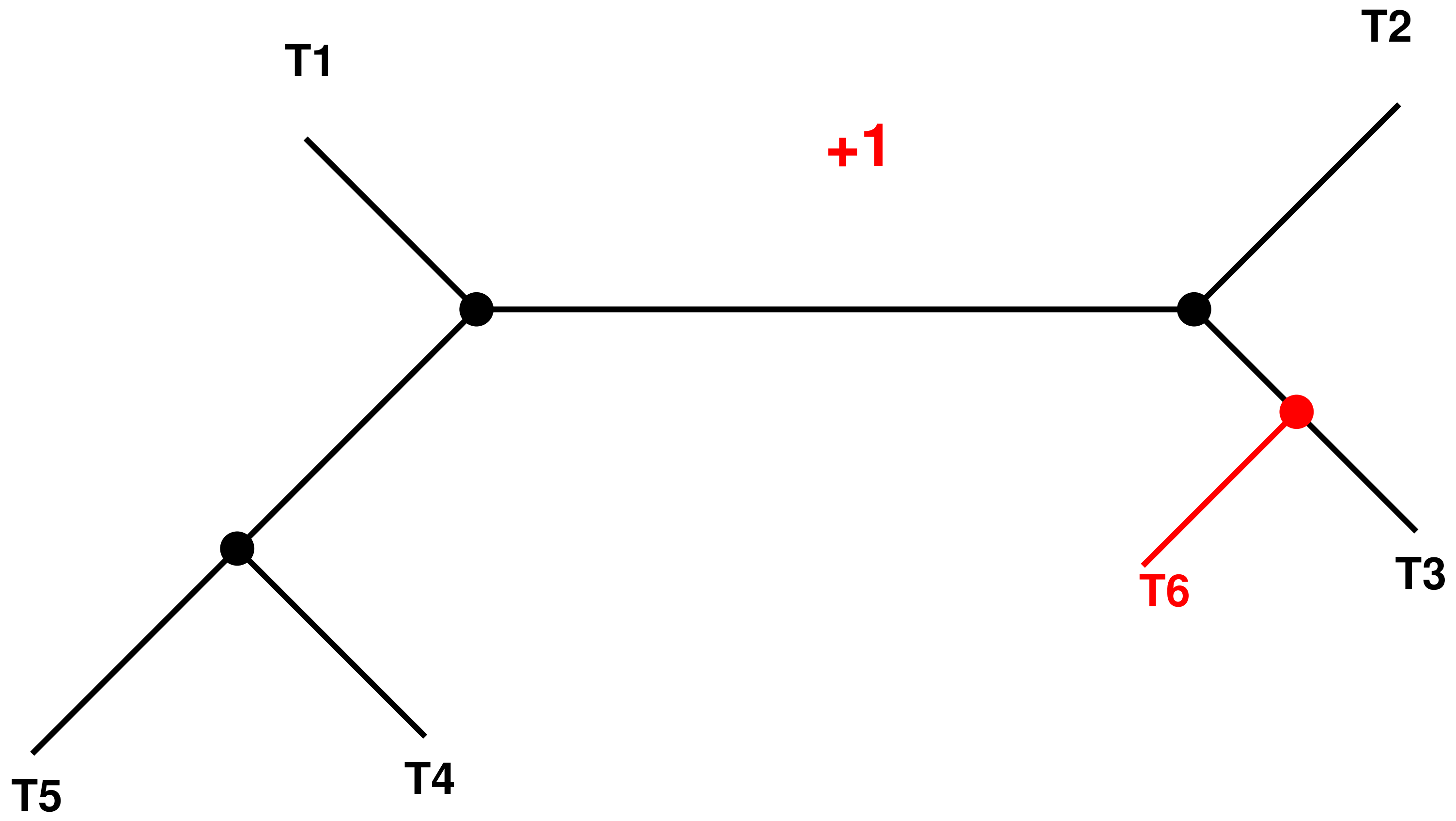
NNI



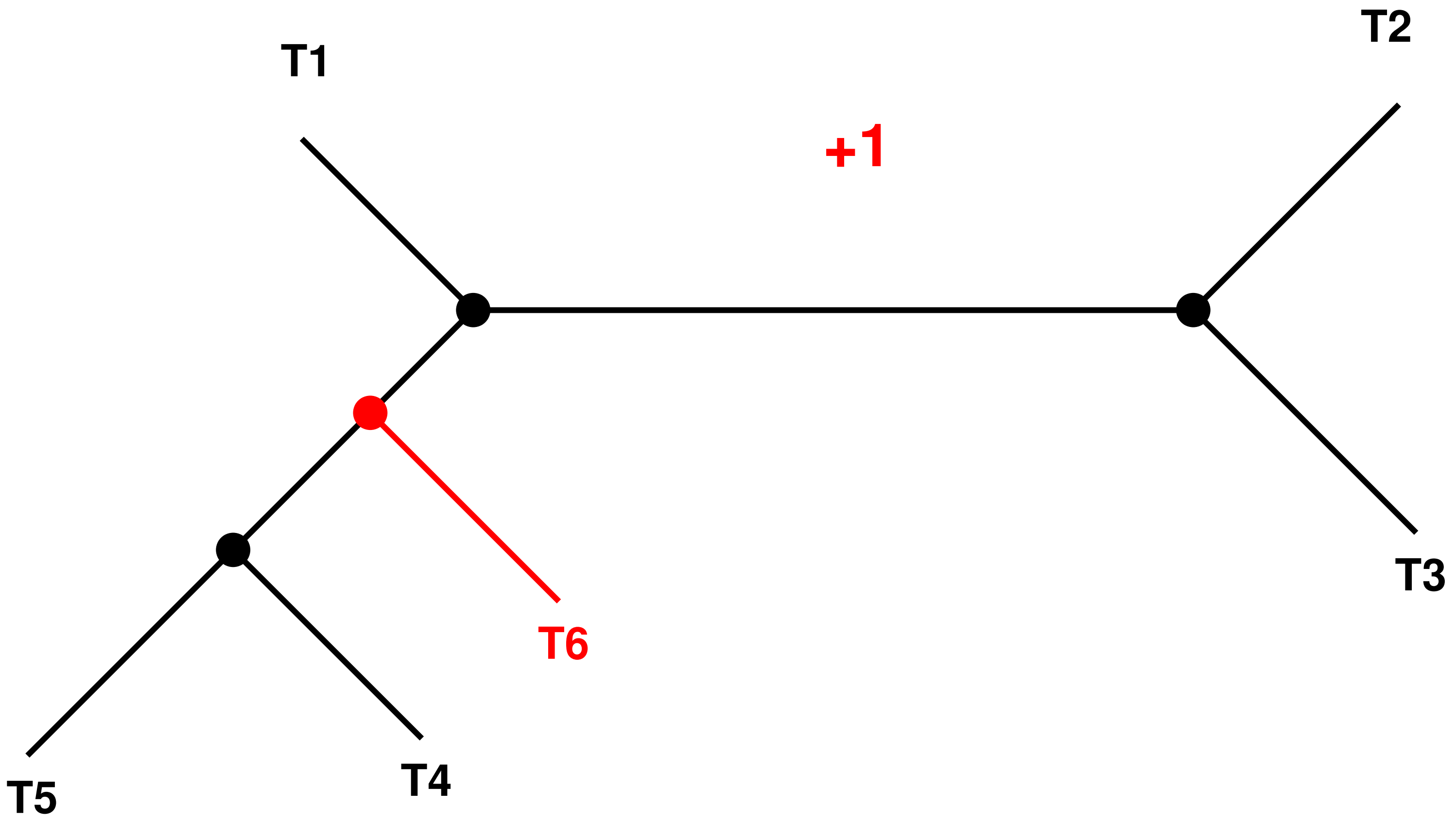
SPR



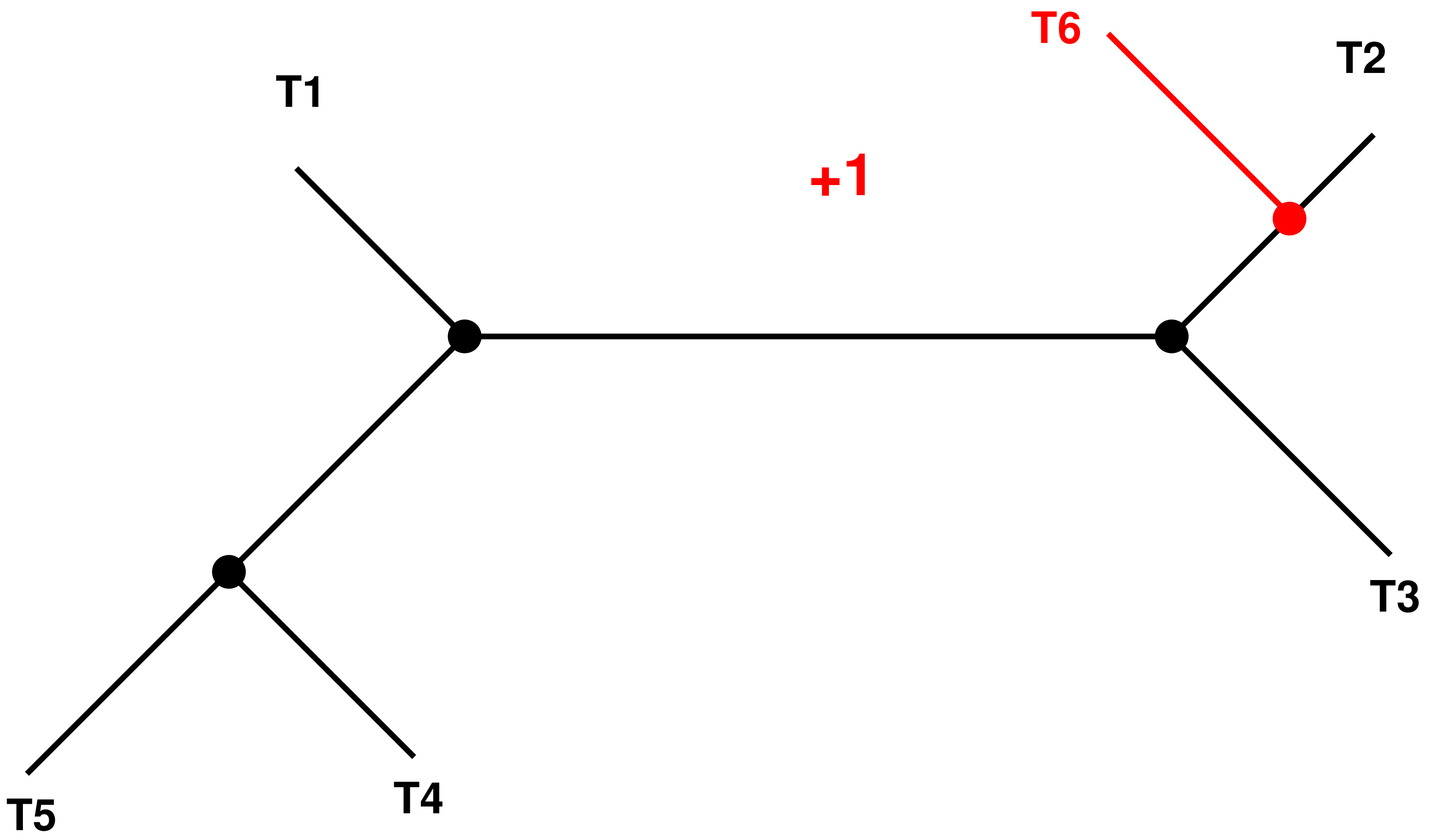
SPR



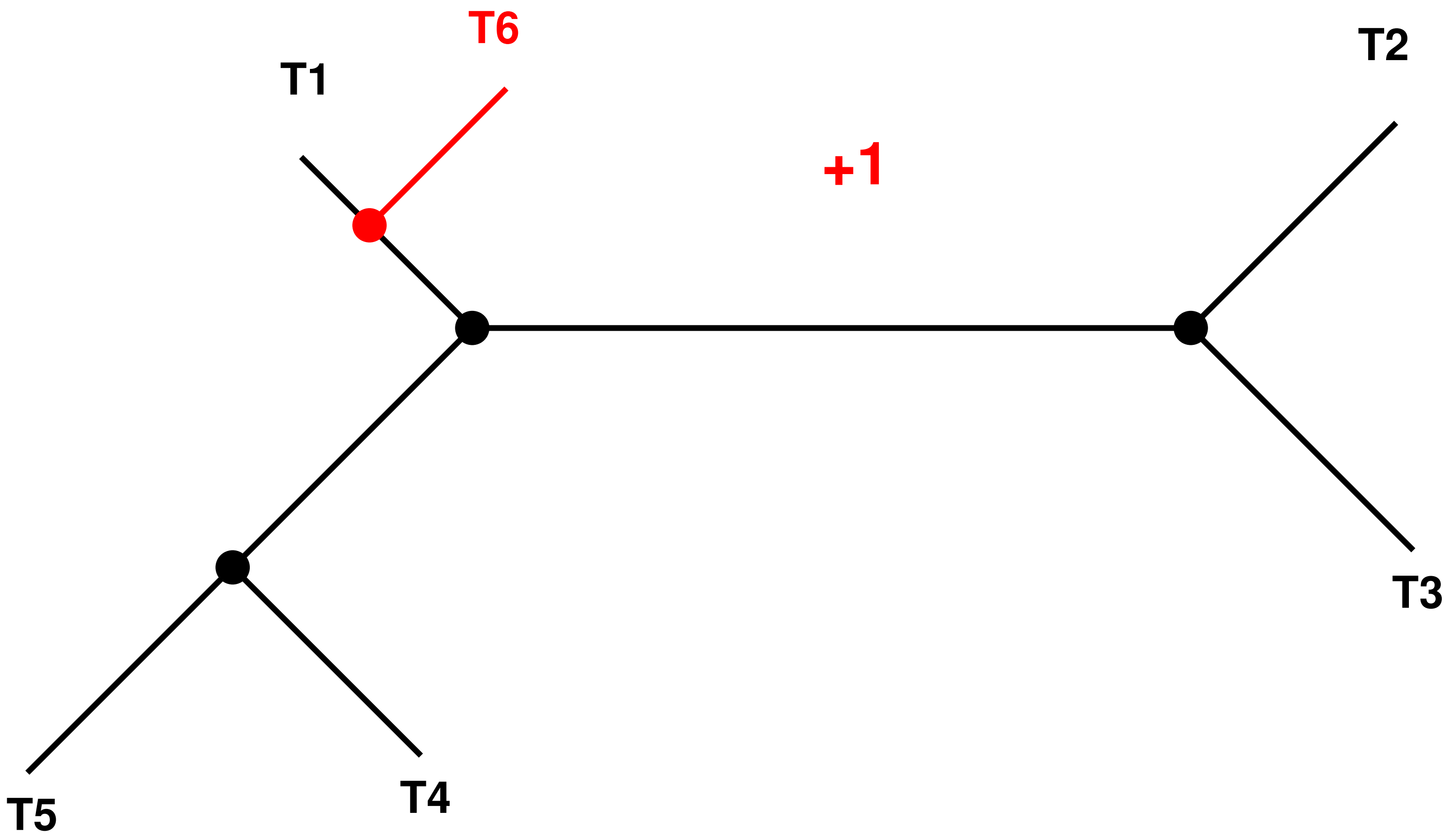
SPR



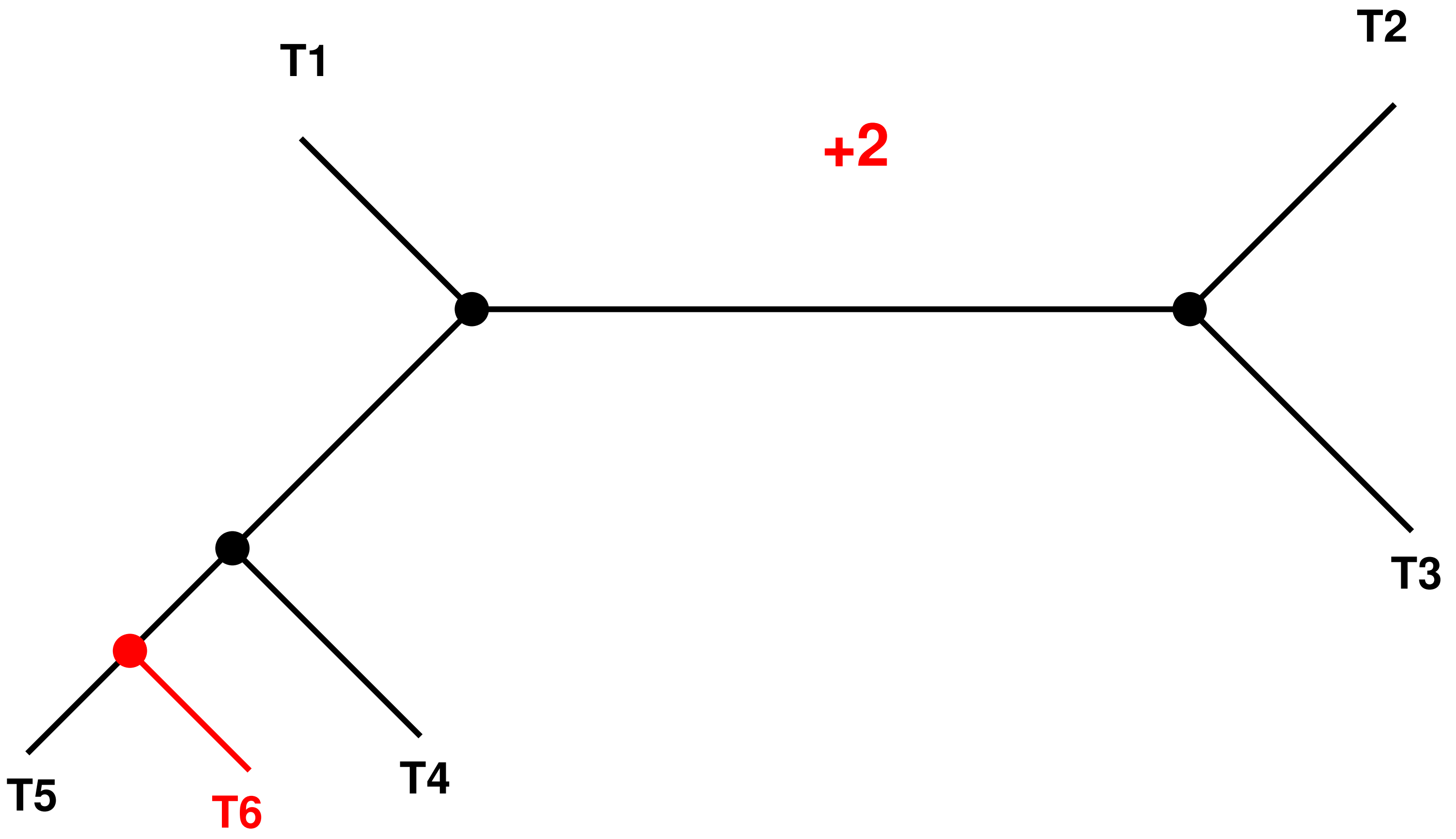
SPR



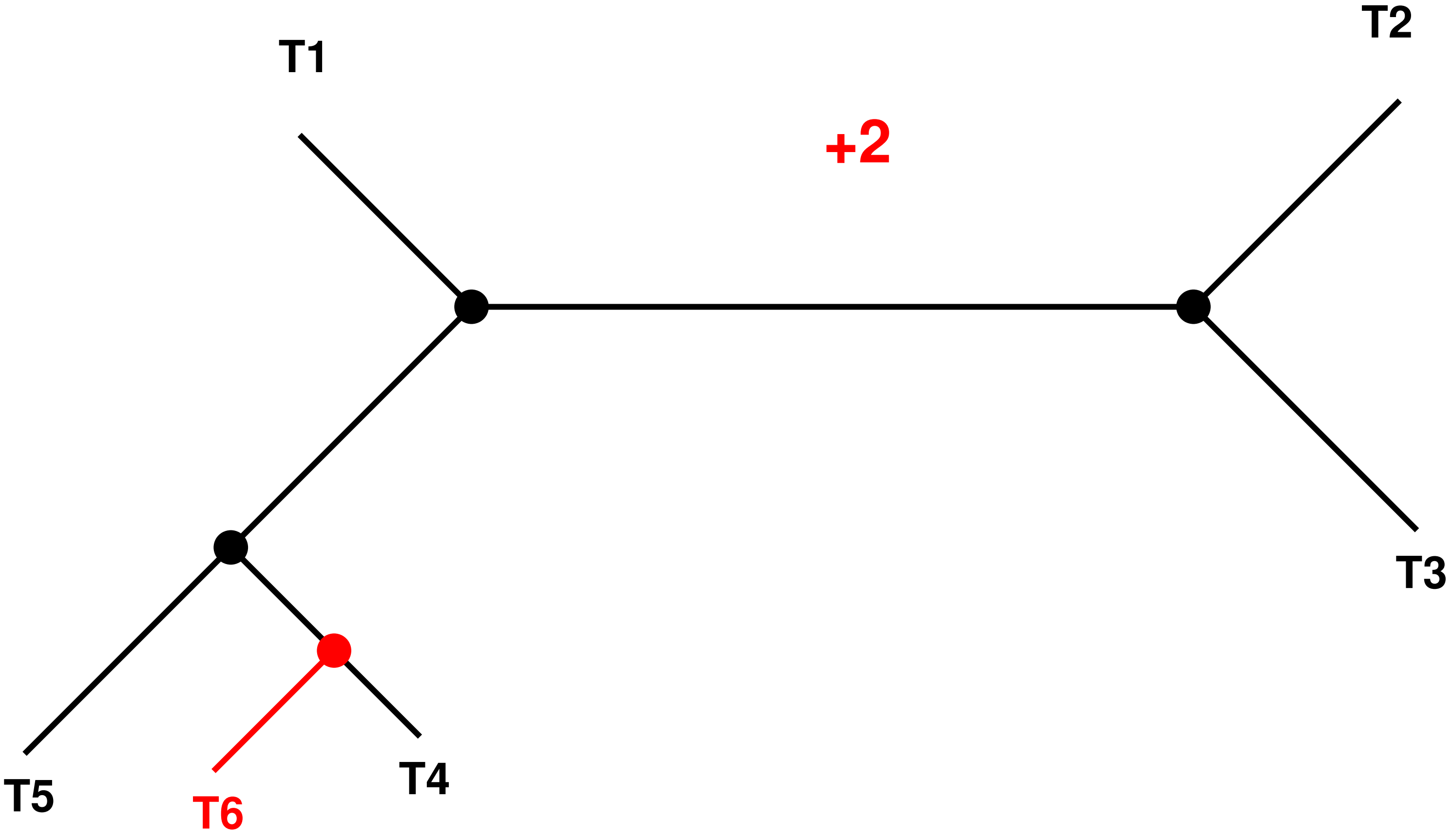
SPR



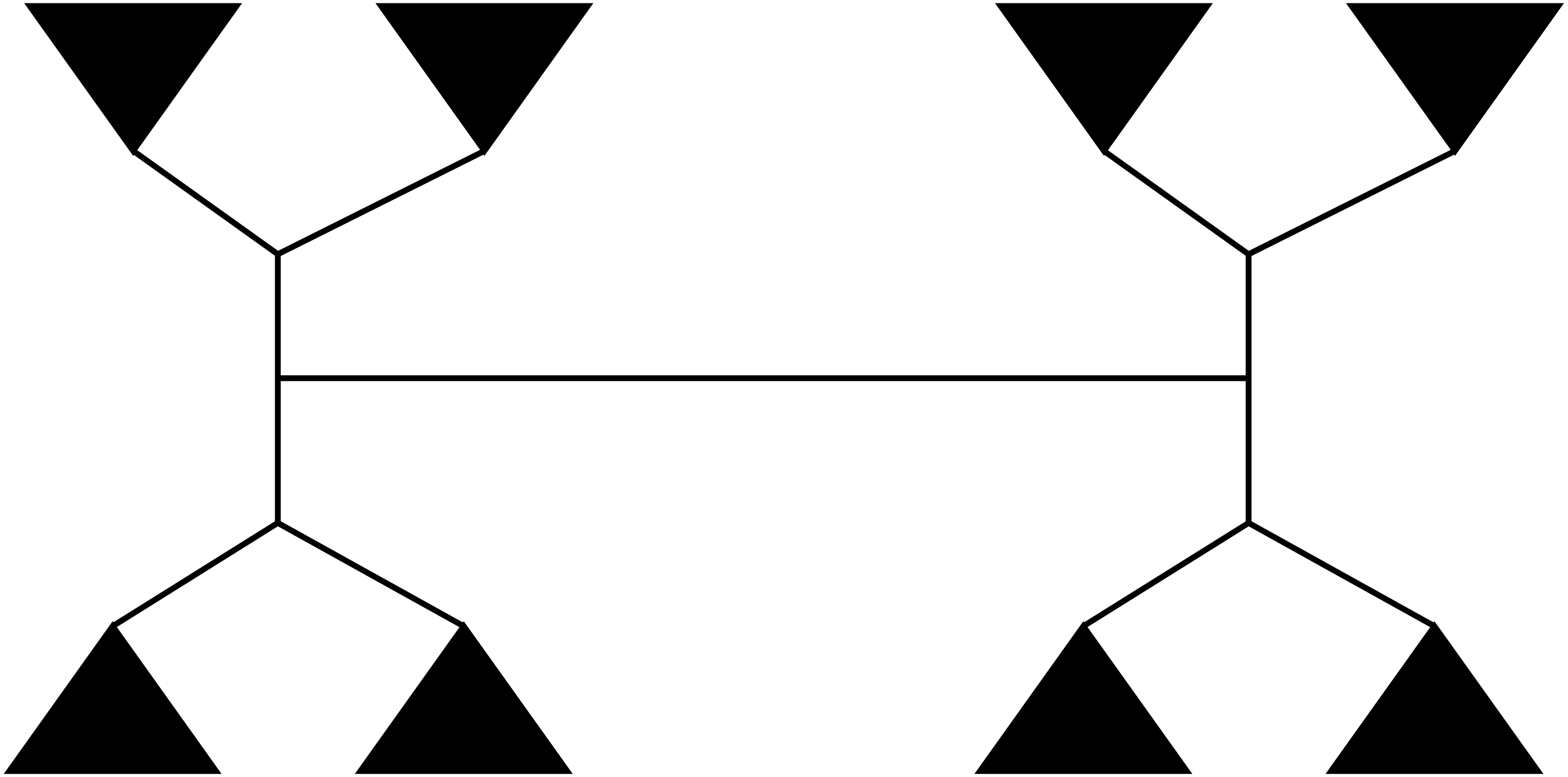
SPR



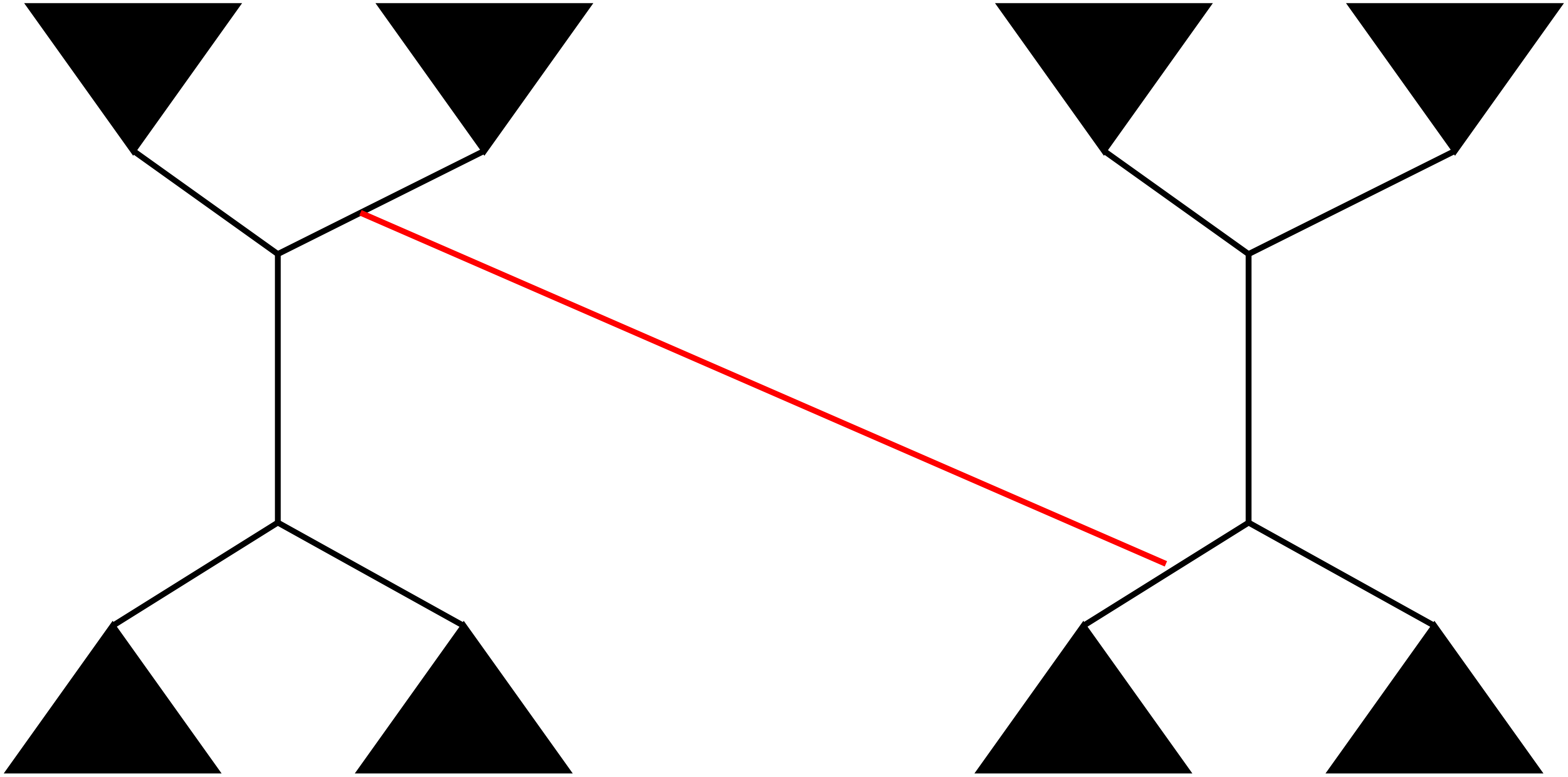
SPR



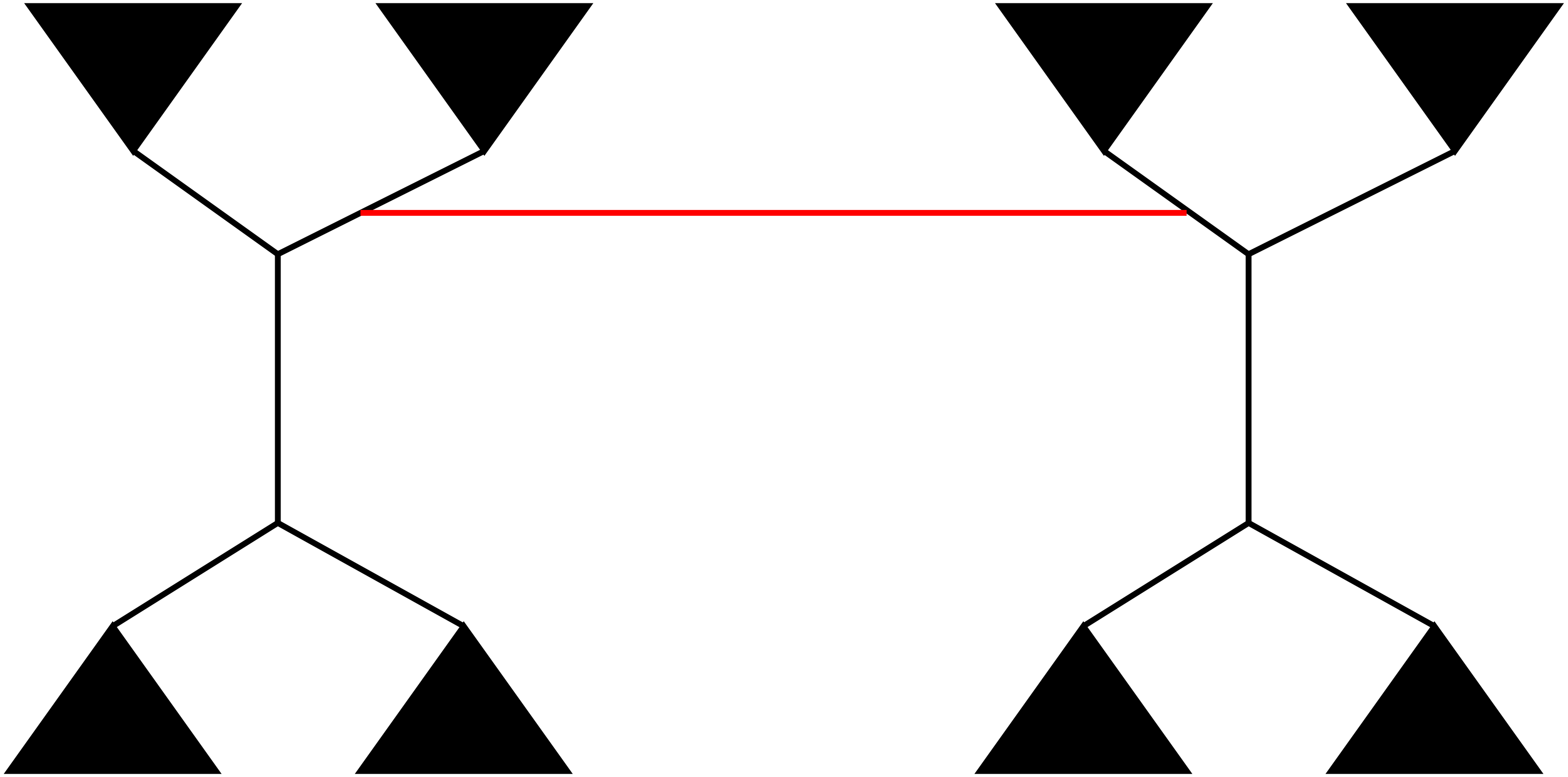
TBR



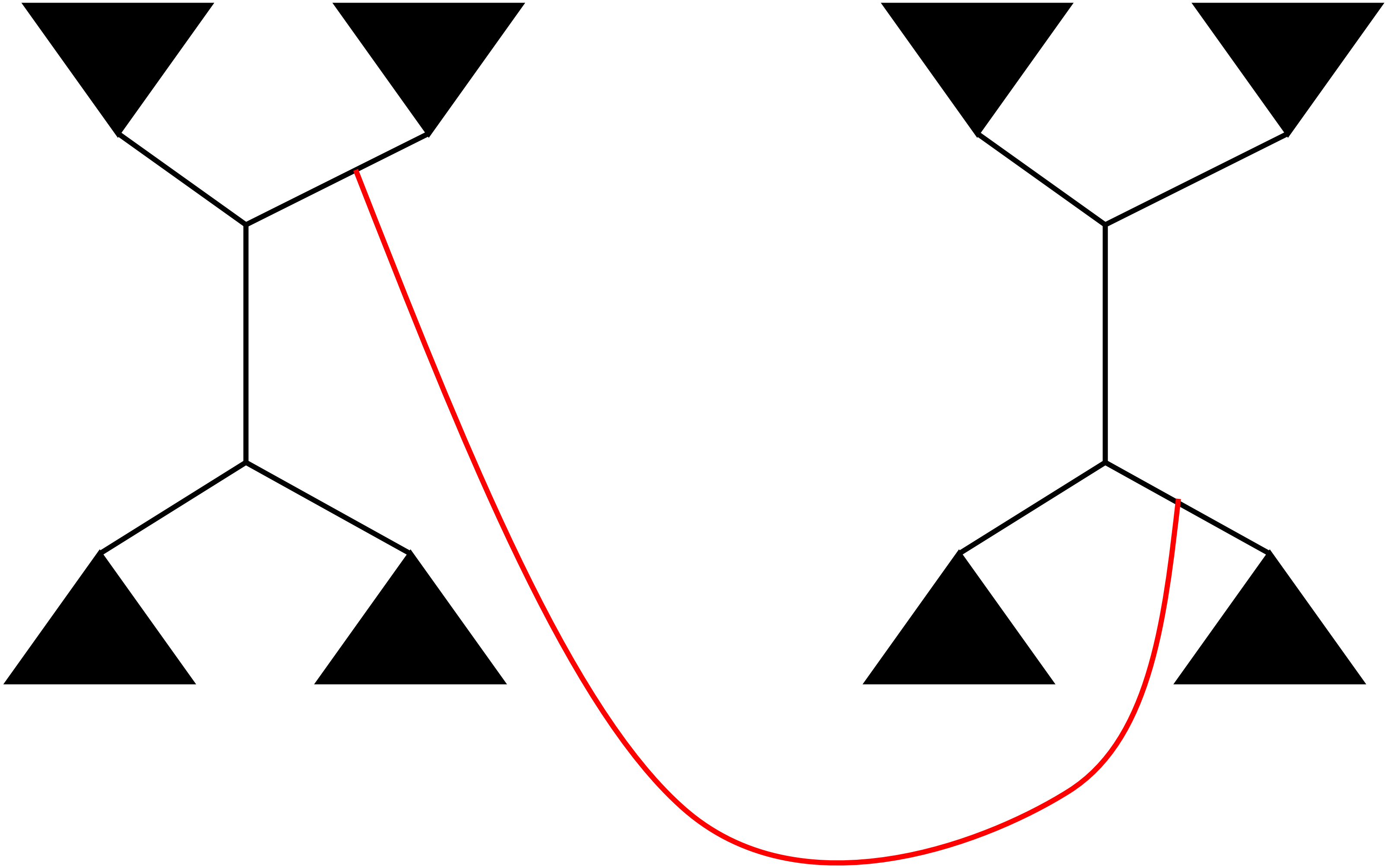
TBR



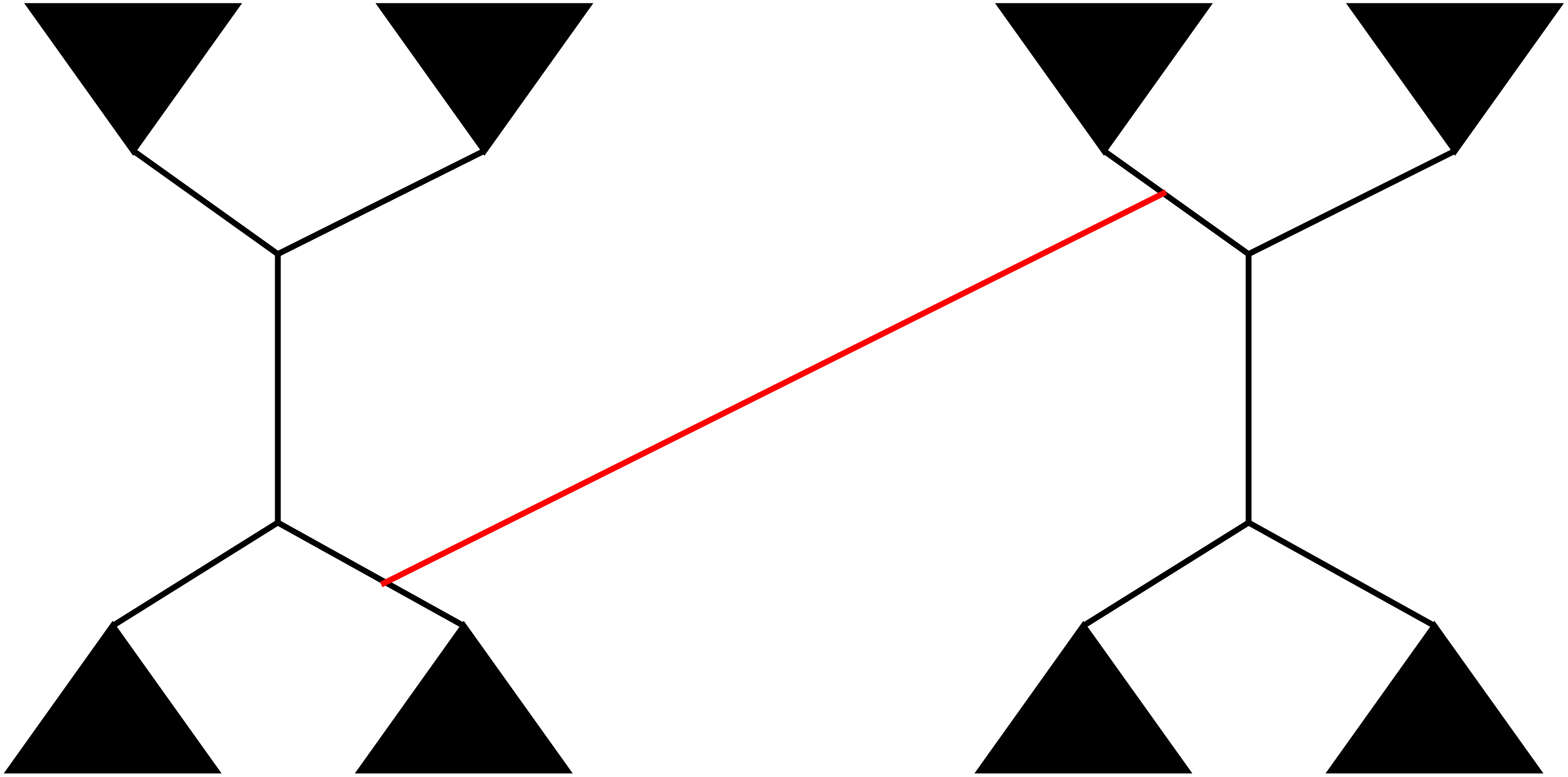
TBR



TBR



TBR



Question

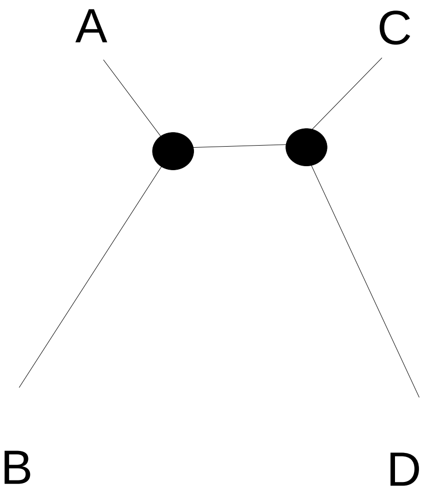
- How could one design a search algorithm for the least squares criterion given a function *f()* and a distance matrix *D* to compute the least squares score on a given tree?

The Parsimonator Algorithm

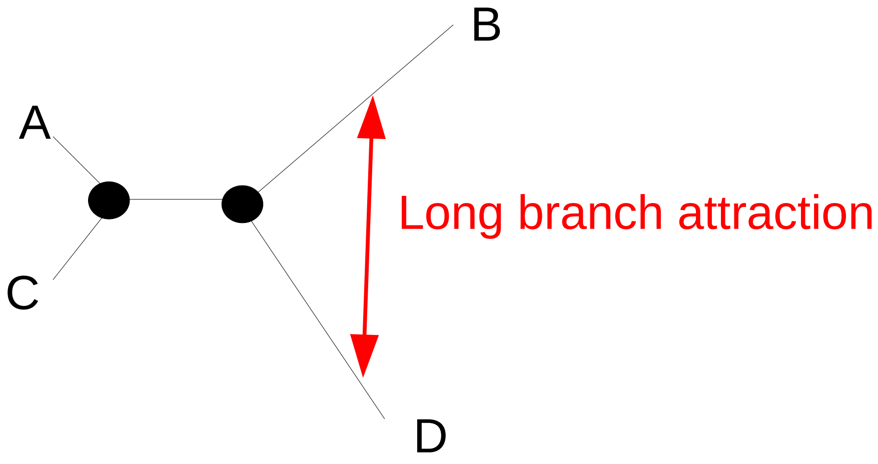
- Build a randomized stepwise addition order parsimony tree
- Apply SPR moves to all subtrees of the current (comprehensive) tree with a rearrangement radius of 20
- If the rearrangement of a subtree yields an improved parsimony score, keep it immediately
  - → this is somewhat greedy as opposed to a steepest ascent hill climbing algorithm
- Continue applying SPR moves with a radius of 20 to all subtrees until no tree with a better parsimony score can be found
- There are much more sophisticated algorithms available
  - → TNT tool by Pablo Goloboff
- Keep in mind that parsimony returns discrete scores, that is, there may be many equally parsimonious trees among which we can not distinguish!

Parsimony & Long Branch Attraction

- Because parsimony tries to minimize the number of mutations it faces some problems on trees with long branches



Correct tree



Wrong tree inferred by parsimony

Parsimony & Long Branch Attraction

- Settings under which parsimony recovers the wrong tree are also called “the Felsenstein Zone” after *Joe Felsenstein* who has made numerous very important contributions to the field, e.g.
  - The Maximum Likelihood model
  - The Bootstrapping procedure
- If you are interested in statistics, there are some on-line courses by Joe at http://evolution.gs.washington.edu/courses.html

On-line Resources

- https://cme.h-its.org/exelixis//web/teaching/slides.html
- At the above page you will find all slides of my regular lecture on “Introduction to Bioinformtics for Computer Scientists” including many more advanced topics in the area of phylogenetic inference
- You will also find links to youtube recordings of these lectures there !