Phylogenetics — some terminology

operational taxonomic unit (OTU)
- — OTUs are the things being classified (e.g. species, genes)

homologous
- — having a common ancestor, and therefore inherited similarity

analogous
- — similar, but not due to a common ancestry

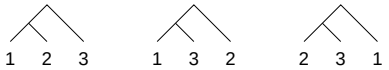
clade
- — a grouping that includes a common ancestor and all descendents

phenotype
- — an organism's obervable characteristics

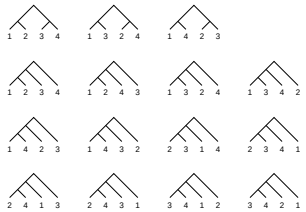
genotype
- — an organism's genetic consitution

Rooted trees

3 nodes

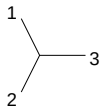


4 nodes

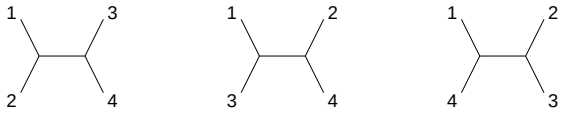


Unrooted trees

3 nodes

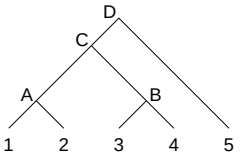


4 nodes



Phylogenetic tree

A branching diagram that shows inferred evolutionary relationships



- Internal nodes represent "inferred ancestors".
- Terminal nodes represent genes or organisms or species (OTUs).
- Newick format: (((1,2),(3,4)),5)

UPGMA

Unweighted-pair-group method with arithmetic mean

Oldest (early 1960s) and simplest method for tree reconstruction.

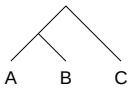
Species	A	B	C	D
B	9			
C	8	11		
D	12	15	10	
E	15	18	13	5

Species	B	AC
AC	10	
DE	16.5	12.5

Species	A	B	C
B	9		
C	8	11	
DE	13.5	16.5	11.5

Estimating branch length (1)

Assuming rate of evolution to be constant in all lineages.

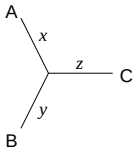


	A	B
B	2	
C	5	4

	AB
C	4.5

Estimating branch length (2)

Not assuming constant rate of evolution.



	A	B
B	2	
C	5	4

$$x = (d_{AB} + d_{AC} - d_{BC})/2$$

$$y = (d_{AB} + d_{BC} - d_{AC})/2$$

$$z = (d_{AC} + d_{BC} - d_{AB})/2$$

Neighbour-joining

a) Start with a star network.

b) A score matrix is computed in which scores are based on the distance between nodes i and j, and the distances between i and j and all other nodes.
   (n - 2) times the distance between i and j
   minus the sum of distances between i and all nodes
   minus the sum of distances between j and all nodes

c) Find a pair with the lowest score, and join that pair with a new node.

d) Compute distance from each node in the pair to the new node.

e) Compute distance from all other OTUs to the new node.

f) Repeat from step b, with the pair of joined nodes replaced by the new node.

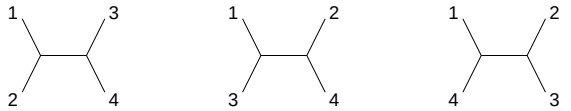
Neighbour-joining — advantages

- Fast. Practical for 100s or 1000s of OTUs.
- If input distances are correct, then output tree will be correct.
- Doesn't assume same rate of evolution in all lineages.

Informative and uninformative sites

To be informative, a position in a multiple alignment must have at least two different characters, each of which occurs at least twice.

Invariant sites are uninformative.



Parsimony

- The quality of being careful with money or resources.
- In science, prefer the simplest explanation that fits the evidence.
- In phylogenetics, prefer the tree that represents the fewest mutational events.
- Inferred ancestral sequences can be obtained as a by-product of the parsimony approach.

Unweighted parsimony

- Consider every possible tree for every informative site in a multiple alignment.
- For each possible tree, add up the minimum number of mutations at each site.
- Tree with the fewest mutations is the most likely tree.

Weighted parsimony

- e.g. transitions vs. transversions

Sum of pairs score for a multiple sequence alignment

- could imagine generalising substitution matrix to N-dimensions, but is there good data to determine reliable scores?
- one alternative approach is to use the sum of pairs

Compute the sum of column scores, where each column score is:

$$\sum_{i<j} s(a_{i,} a_j)$$

where a_i and a_j are the residues in that column from sequences i and j, and $s(x, y)$ is a score taken from a substitution matrix (e,g, from the BLOSUM or PAM families).

This score is simple to compute, but a drawback is that it assumes that all sequences in the set are separated by the same evolutionary distance.

Progressive alignment

```
Sequence 1: MGLPKSFVSM
Sequence 2: MGVPKTFVSM
Sequence 3: MGVPKTFVASM
Sequence 4: MGGLPKSYAVSM

1: MGLPKSFVSM       1: MGLPKSFV-SM      1: M-GLPKS-FVSM
   || || |||| (2)      || || || || (3)     | |||||  ||| (3)
2: MGVPKTFVSM       3: MGVPKTFVASM      4: MGGLPKSYAVSM

                    2: MGVPKTFV-SM      2: M-GVPK-TFVSM
                       |||||||| || (1)     | | ||   ||| (5)
                    3: MGVPKTFVASM      4: MGGLPKSYAVSM

                                        3: M-GVPKTFVASM
                                           | | ||    || (5)
                                        4: MGGLPKSYAVSM
Sequence 1: M-GLPKSFV-SM
Sequence 2: M-GVPKTFV-SM
Sequence 3: M-GVPKTFVASM
Sequence 4: MGGLPKSYAVSM
```


Multiple sequence alignment

Dynamic programming

- in principle this could be done, using the sum of pairs approach for scoring matches/mismatches
- possible for a few short sequences
- not practical for many long sequences

Progressive alignment

- perform pairwise alignment between all pairs of sequences
- construct a guide tree based on distances between each pair
- add sequences into the multiple alignment in the order given by the guide tree
- “once a gap, always a gap”