582670 Algorithms for Bioinformatics

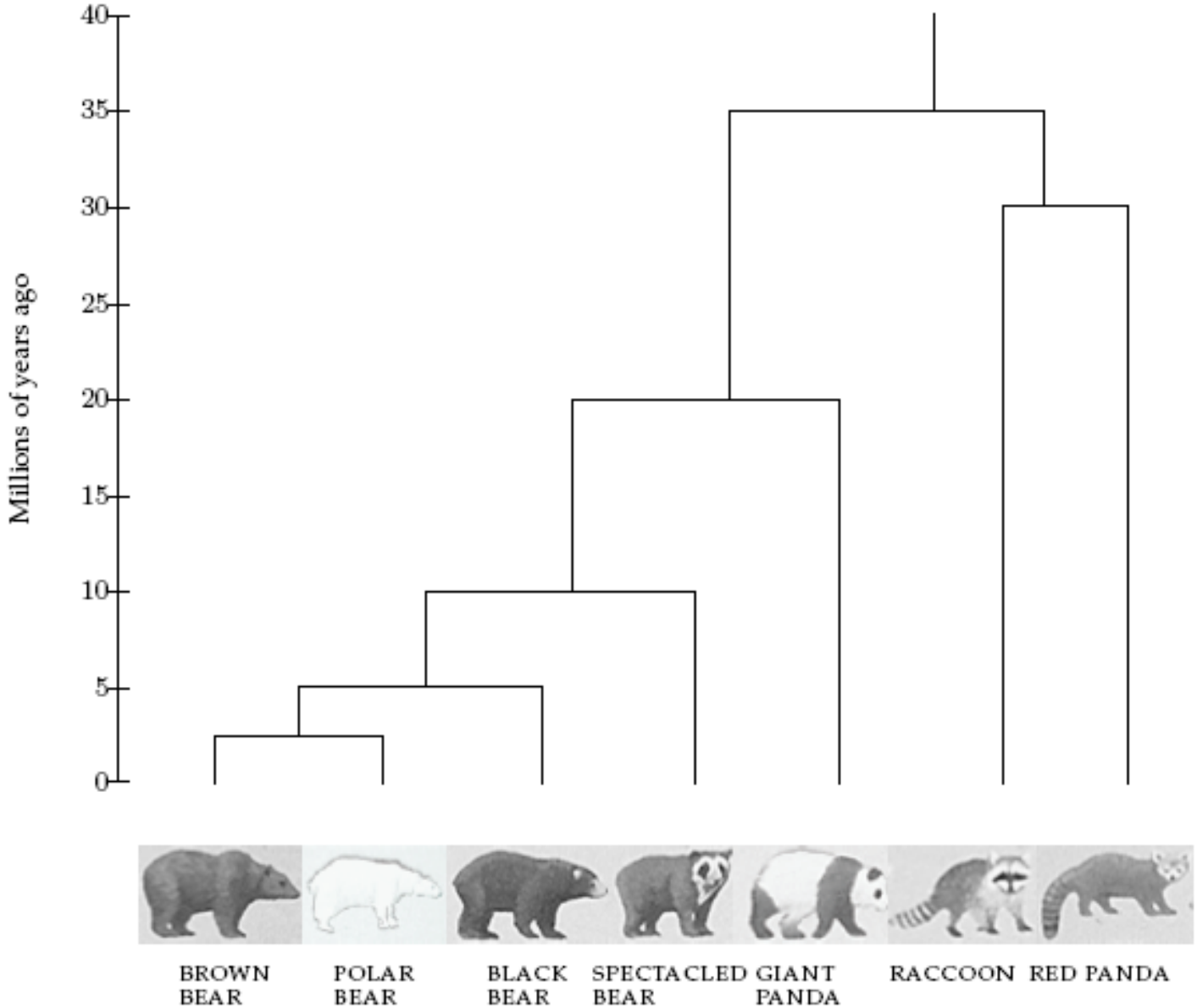
Lecture 6: Distance based clustering and phylogeny

02.10.2014

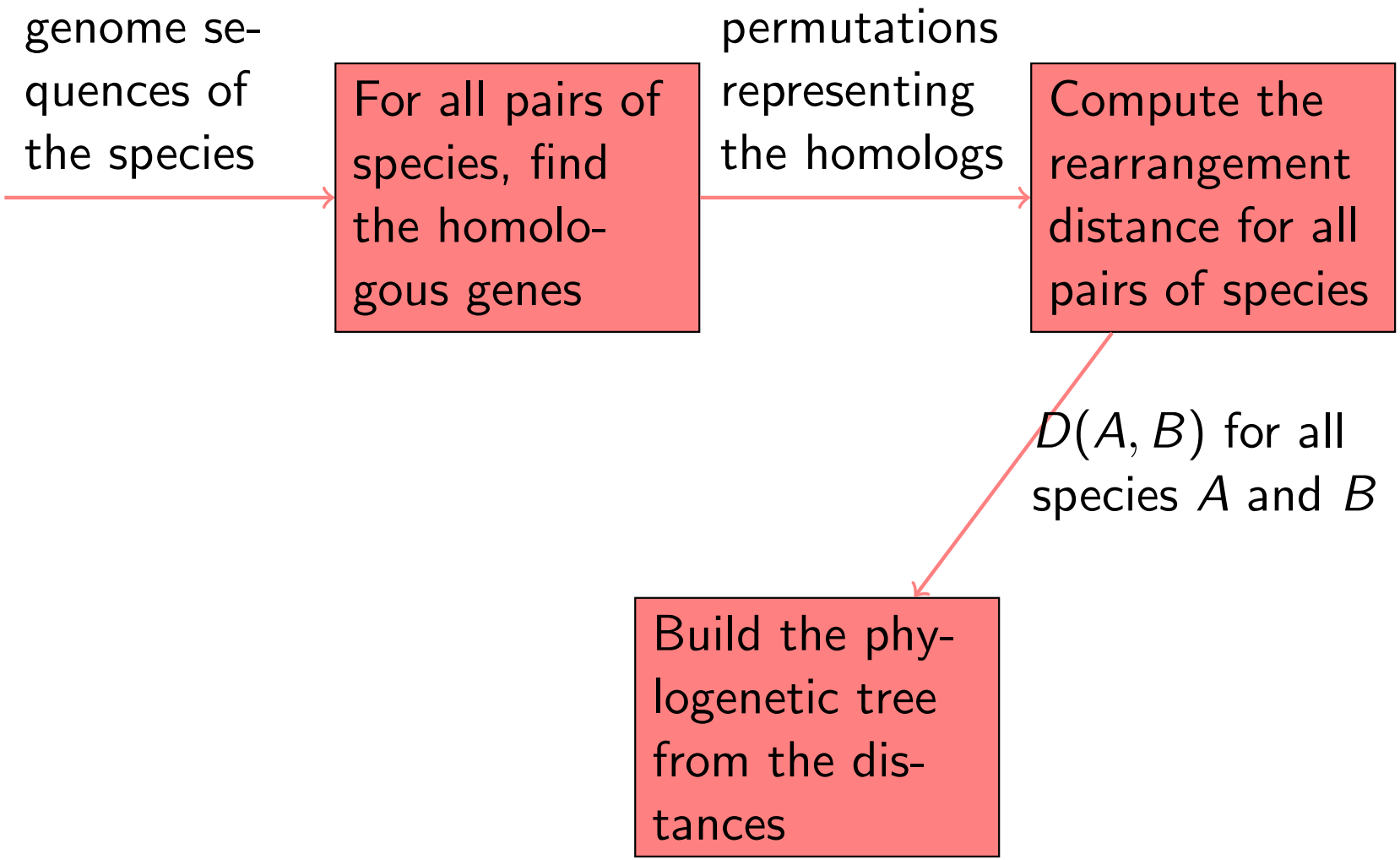
Adapted from slides by Alexandru Tomescu, Leena Salmena and Veli Mäkinen, which are partly from `http://bix.ucsd.edu/bioalgorithms/slides.php`

Outline

Phylogenetic tree: Bears



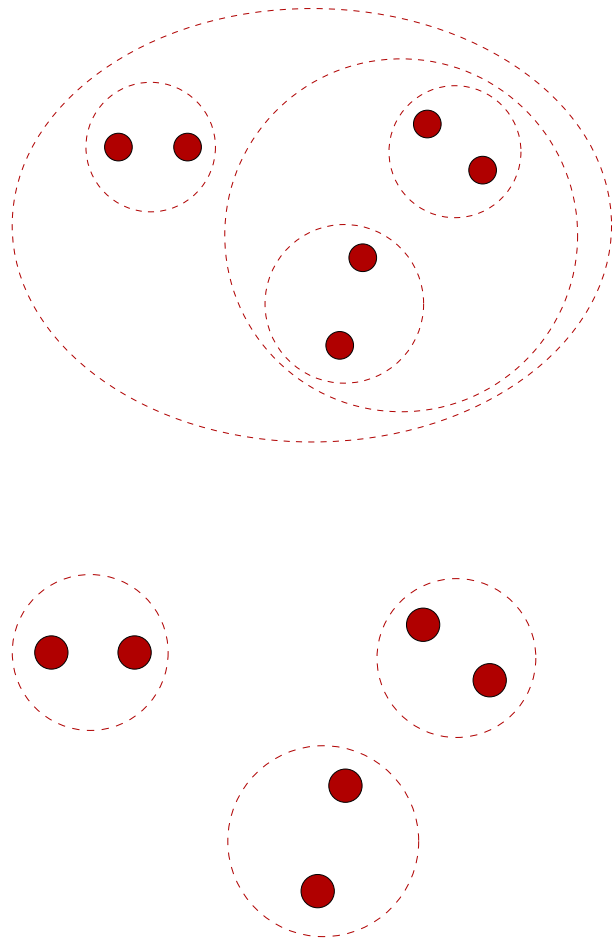
Phylogeny by distance method pipeline



Clustering

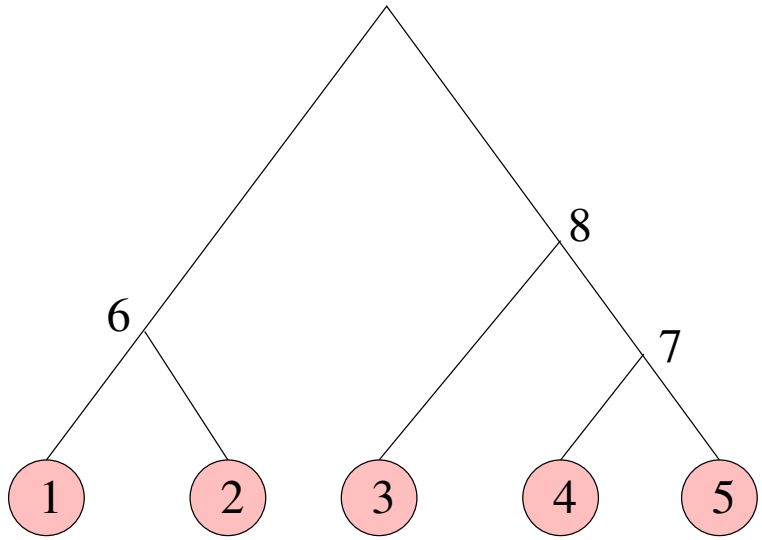
- *Clustering* can be loosely stated as the problem of grouping objects into sets called clusters, where the members of the cluster are similar in some sense.

- *Hierarchical clustering*:
  - Iteratively join two closest clusters forming a tree hierarchy (agglomerative... also divisive version exists)
  - Distance between clusters can be e.g. max pair-wise distance (complete linkage), min (single linkage), UPGMA (average linkage), neighbor joining
- *Partitional clustering:*
  - k-means



Distances in a phylogenetic tree

- Distance matrix $D = (d_{ij})$ gives pairwise distances for *leaves* of the phylogenetic tree
- In addition, the phylogenetic tree will now specify distances between internal nodes
  - Internal nodes represent commmon ancestor species
  - Denote these with d_{ij} as well



Distance d_{ij} states how far apart species i and j are evolutionary.

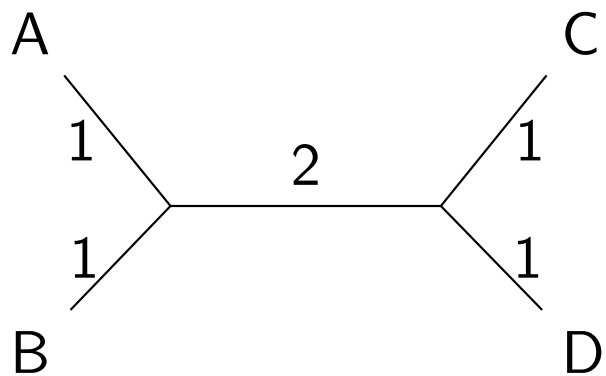
Distances in evolutionary context

- Distance d_{ij} in evolutionary context satisfy the following conditions:
  - Positivity: $d_{ij} \geq 0$
  - Identity: $d_{ij} = 0$ if and only if $i = j$
  - Symmetry: $d_{ij} = d_{ji}$ for each i, j
  - Triangle inequality: $d_{ij} \leq d_{ik} + d_{kj}$ for each i, j, k
- Distance satisfying these conditions is called *metric*
- In addition, evolutionary mechanisms may impose additional constraints on the distances
  - *additive* and *ultrametric* distances

Additive trees

- Suppose that every edge in a tree is labeled with a distance d_{ij}
- A tree is called *additive* if for every pair of leaves the distance between the leaves is the sum of the edge distances on the path between the leaves.
- Example:

	A	B	C	D
A	0	2	4	4
B	2	0	4	4
C	4	4	0	2
D	4	4	2	0

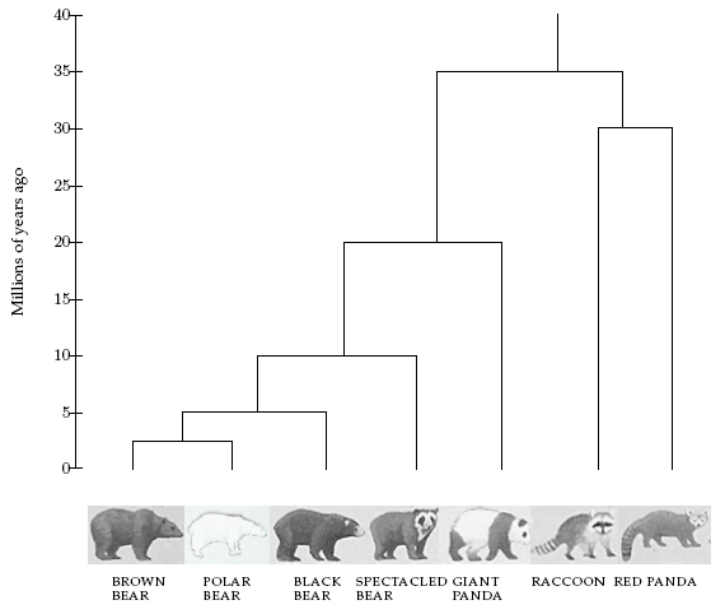


Ultrametric trees

- A rooted additive tree is called an *ultrametric tree* if the distances between any two leaves i and j and their common ancestor k are equal

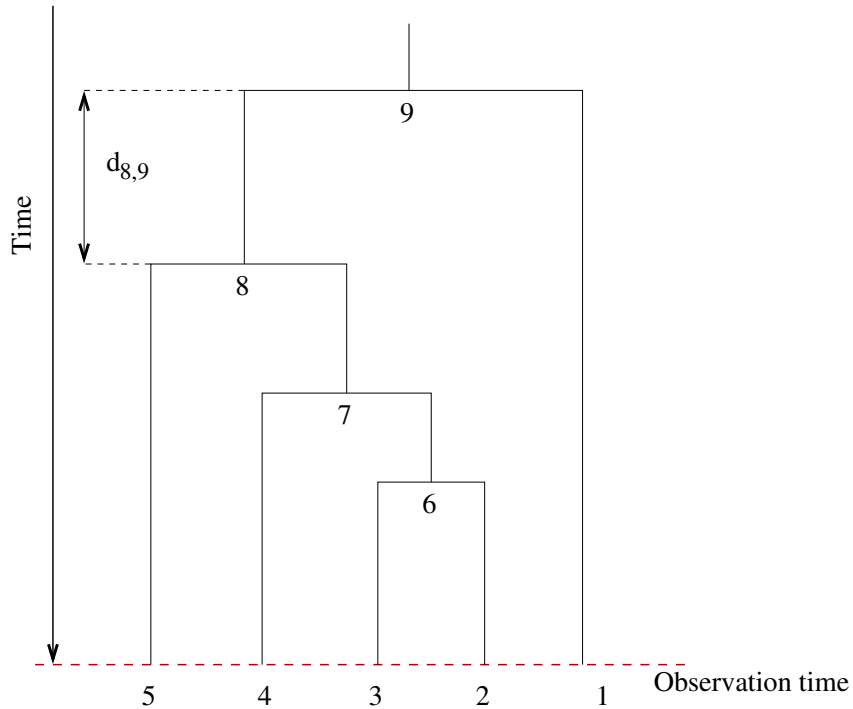
$$d_{ik} = d_{jk}$$

- $d_{ij}/2$ corresponds to the time elapsed since divergence of i and j from the common parent
- In other words, edge lengths are measured by a *molecular clock* with a constant rate



Ultrametric trees

- Only vertical segments of the tree have correspondence to some distance d_{ij}
- Horizontal segments act as connectors
- $d_{ik} = d_{jk}$ for any two leaves i, j and any ancestor k of i and j



Identifying ultrametric data

- Without knowing the underlying tree structure, we can identify distances to be ultrametric by the three-point condition:
  - D corresponds to an ultrametric tree if and only if for any three (current) **species** we can label them i, j, and k such that the distances satisfy:

$$d_{ik} = d_{jk} \geq d_{ij}$$

- If we find out that the data is ultrametric, we can utilise a simple algorithm to find the corresponding tree

UPGMA algorithm

- UPGMA (unweighted pair group method with arithmetic mean) constructs a phylogenetic tree via clustering
- The algorithm works by at the same time
  - Merging two clusters
  - Creating a new node on the tree
- The tree is built from leaves towards the root
- UPGMA produces a ultrametric tree

Cluster distances

- Let distance d_{ij} between clusters C_i and C_j be

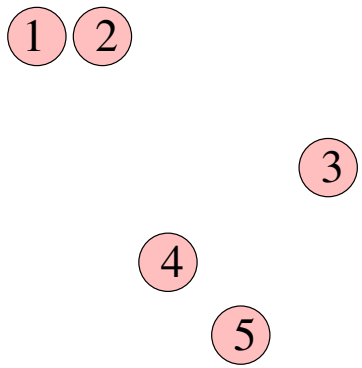
$$d_{ij} = \frac{1}{|C_i||C_j|} \sum_{p \in C_i, q \in C_j} d_{pq},$$

that is, the average distance between points (species) in the cluster.

UPGMA algorithm

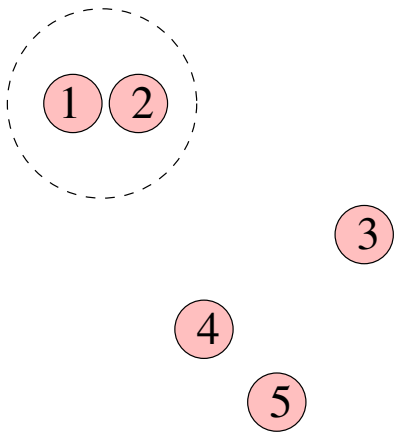
- Initialisation
  - Assign each point i to its own cluster C_i
  - Define one leaf for each point and place it at height zero
- Iteration
  - Find clusters i and j for which d_{ij} is minimal
  - Define new cluster k by $C_k = C_i \cup C_j$ and compute $d_{k\ell}$ for all ℓ
  - Add a node k with children i and j to the tree. Place k at height $d_{ij}/2$
  - Remove clusters i and j
- Termination
  - When only two clusters i and j remain, place root at height $d_{ij}/2$

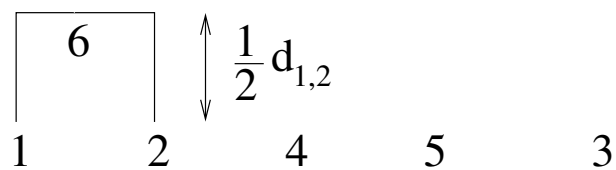
UPGMA example



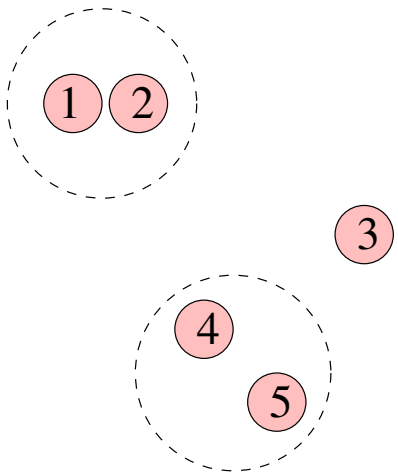
1 2 4 5 3

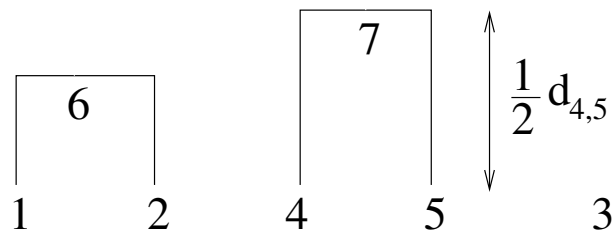
UPGMA example



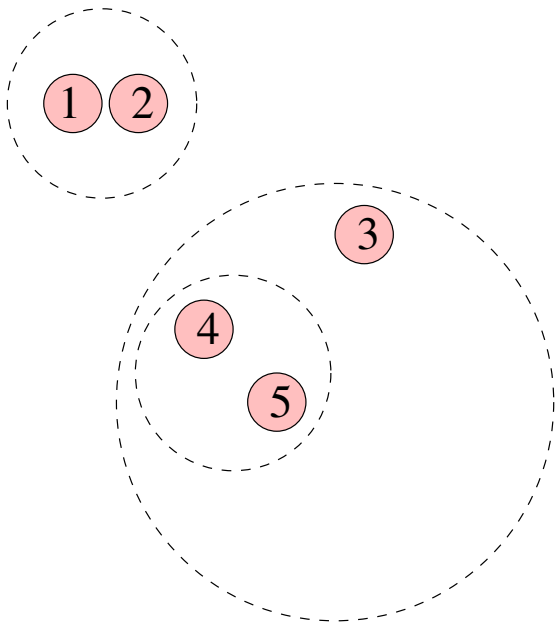


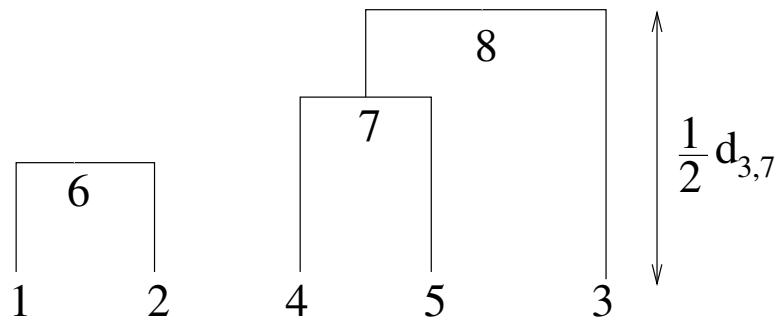
UPGMA example



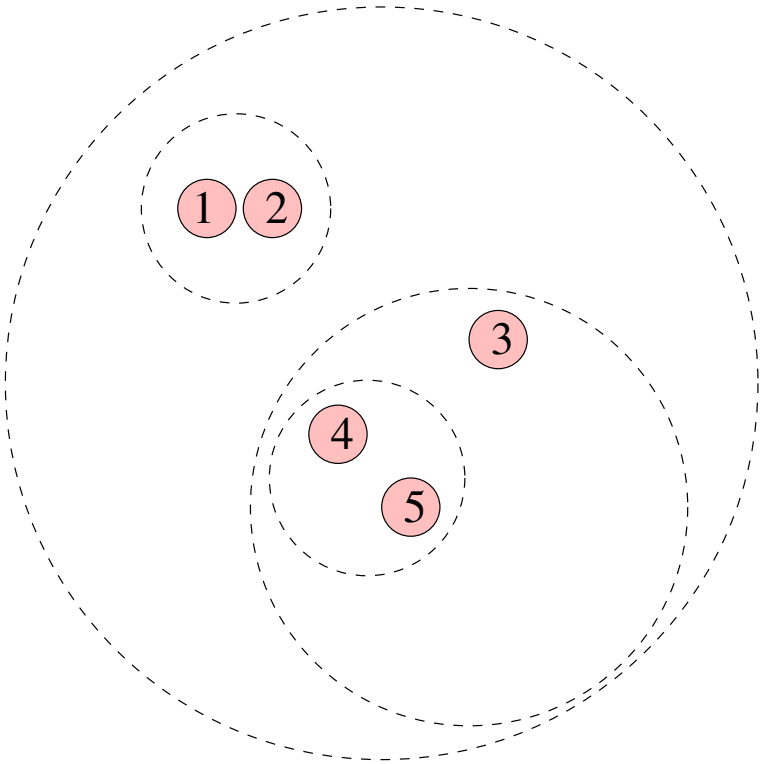


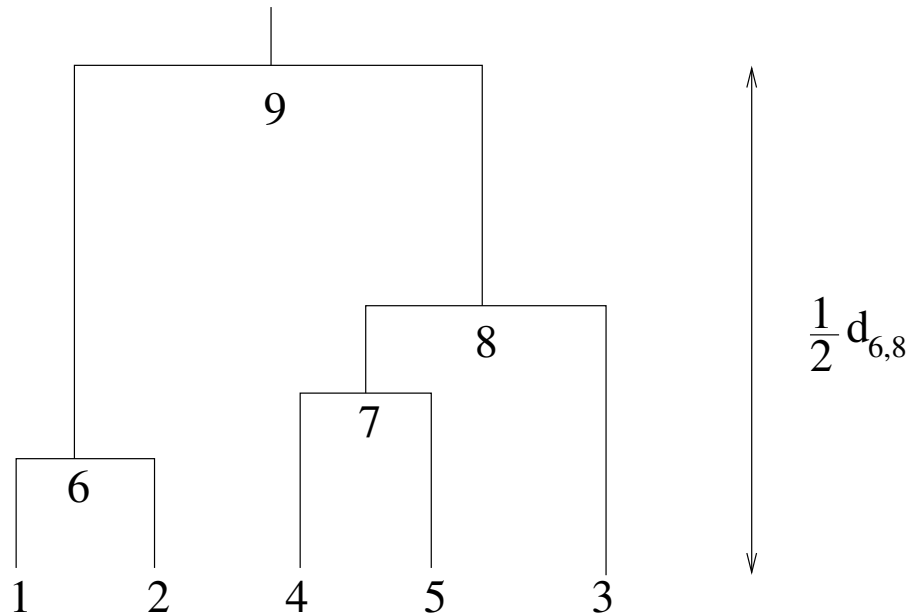
UPGMA example





UPGMA example





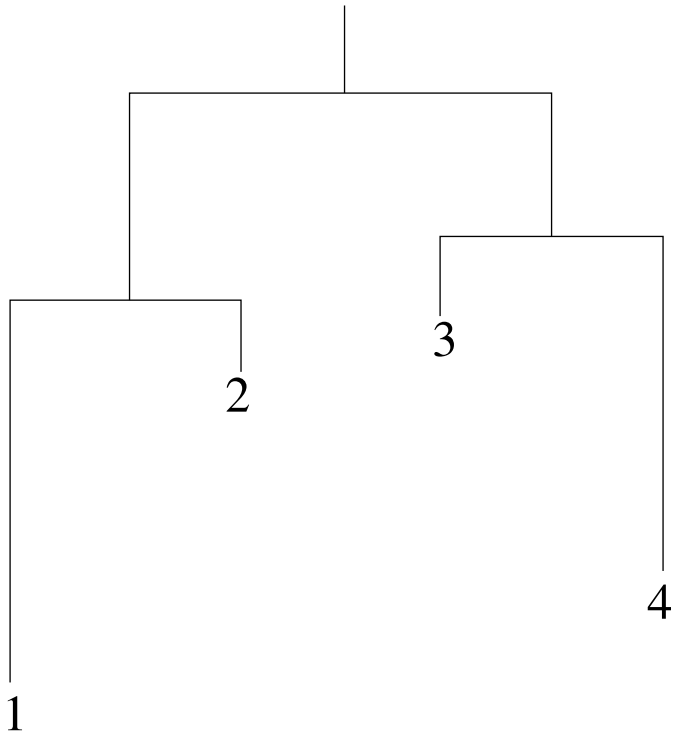
UPGMA implementation

- In naive implementation, each iteration takes $O(n^2)$ time with n initial points $\implies$ algorithm takes $O(n^3)$ time
- The algorithm can be implemented to take only $O(n^2)$ time (see Gronau & Moran, 2006, for a survey)

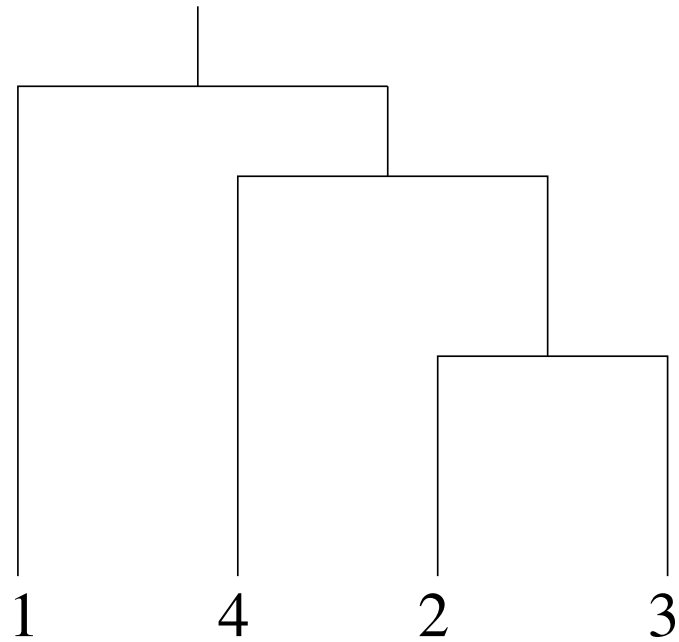
Problem solved?

- We now have a simple algorithm which finds an ultrametric tree
  - If the data is ultrametric, then there is exactly one ultrametric tree corresponding to the data
  - The tree found is then the "correct" solution to the phylogeny problem if the assumptions hold
- Unfortunately, the data is not ultrametric in practice
  - Measurement errors distort distances
  - Basic assumption of a molecular clock does not hold usually very well

Incorrect reconstruction of non-ultrametric data by UPGMA



Tree which corresponds to non-ultrametric distances

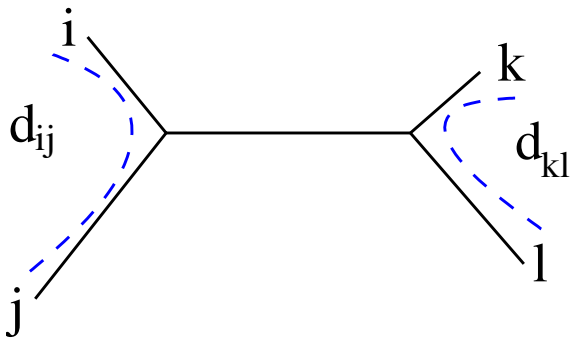


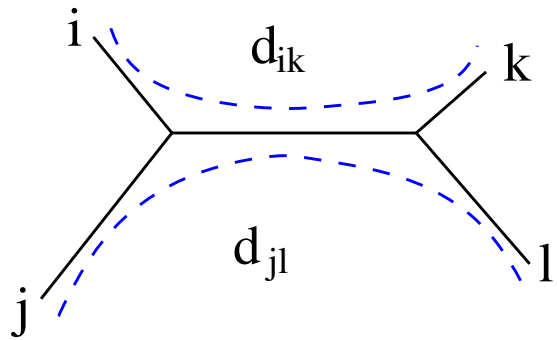
Incorrect ultrametric reconstruction by UPGMA algorithm

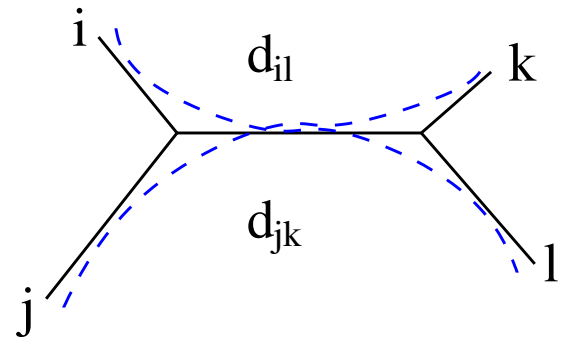
Outline

Checking for additivity

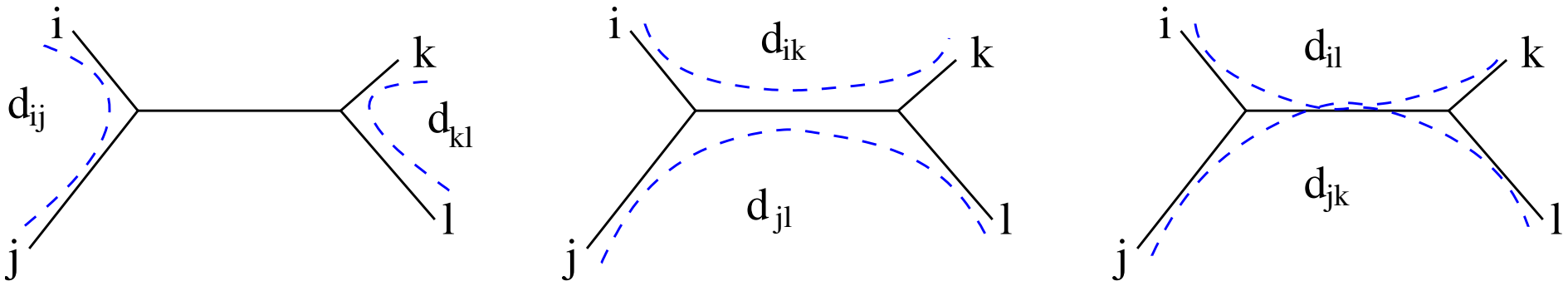
- Recall: a tree is additive if for every pair of leaves the distance between the leaves is the sum of the edge distances on the path between the leaves.
- How can we check that the data is additive?
- Let i, j, k, and ℓ be four **distinct** species
- Compute three sums
  - $d_{ij} + d_{k\ell}$
  - $d_{ik} + d_{j\ell}$
  - $d_{i\ell} + d_{jk}$







Four-point condition



- Sums represented by the middle and right figures cover all edges
- Sum represented by the left figure does not cover all edges
- *Four-point condition*: i, j, k, and ℓ satisfy the four-point condition if two of the sums $d_{ij} + d_{k\ell}$, $d_{ik} + d_{j\ell}$, and $d_{i\ell} + d_{jk}$ are equal and the third one is smaller than these two.
- An $n \times n$ matrix D is additive if and only if the four-point condition holds for every 4 elements $1 \leq i, j, k, \ell \leq n$.

Checking for additivity: Example

	A	B	C	D
A	0	6	7	5
B		0	11	9
C			0	6
D				0

- $d_{AB} + d_{CD} = 6 + 6 = 12$
- $d_{AC} + d_{BD} = 7 + 9 = 16$
- $d_{AD} + d_{BC} = 5 + 11 = 16$

- Two of the sums are equal and the third is smaller
  $\Longrightarrow$ Four-point condition holds
  $\Longrightarrow$ Matrix is additive

Finding an additive phylogenetic tree

- Additive trees can be found for example by the neighbor joining method (Saitou & Nei, 1987)
- However, in real data, even additivity usually does not hold very well

Neighbor joining algorithm

- Neighbor joining works in a similar fashion to UPGMA
  - Find clusters C_1 and C_2 that minimize a function $f(C_1, C_2)$
  - Join the two clusters C_1 and C_2 into a new cluster C
  - Add a node to the tree corresponding to C
  - Assign distances to new branches
- Differences in
  - The choice of function $f(C_1, C_2)$
  - How to assign the distances

Neighbor joining algorithm: Separation of a cluster

- Let $u(C_i)$ be the *separation* of cluster C_i from other clusters defined as

$$u(C_i) = \frac{1}{n-2} \sum_{C_j} d_{ij}$$

where n is the number of clusters.

Neighbor joining algorithm

- Neighbor joining at the same time
  - Minimizes the distance between clusters C_i and C_j to be joined
  - Maximizes the separation of both C_i and C_j from other clusters
- Recall that UPGMA only minimizes the distance between the clusters C_i and C_j

Neighbor joining algorithm

- Initialization as in UPGMA
- Iteration
  - Find clusters C_i and C_j for which $d_{ij} - u(C_i) - u(C_j)$ is minimum
  - Define a new cluster $C_k = C_i \cup C_j$ and compute $d_{k\ell}$ for all ℓ:

$$d_{k\ell} = \frac{1}{2}(d_{i\ell} + d_{j\ell} - d_{ij})$$

  - Remove clusters C_i and C_j
  - Define a node k with edges to i and j
  - Assign length $\frac{1}{2}(d_{ij} + u(C_i) - u(C_j))$ to the edge $i \to k$
  - Assign length $\frac{1}{2}(d_{ij} + u(C_j) - u(C_i))$ to the edge $j \to k$
- Termination
  - When two clusters i and j remain, add an edge between them with weight d_{ij}.

Neighbor joining algorithm: Example

	A	B	C	D
A	0	6	7	5
B		0	11	9
C			0	6
D				0

i	$u(C_i)$
A	$(6+7+5)/2 = 9$
B	$(6+11+9)/2 = 13$
C	$(7+11+6)/2 = 12$
D	$(5+9+6)/2 = 10$

i,j	$d_{ij} - u(C_i) - u(C_j)$
A,B	$6 - 9 - 13 = -16$
A,C	$7 - 9 - 12 = -14$
A,D	$5 - 9 - 10 = -14$
B,C	$11 - 13 - 12 = -14$
B,D	$9 - 13 - 10 = -14$
C,D	$6 - 12 - 10 = -16$

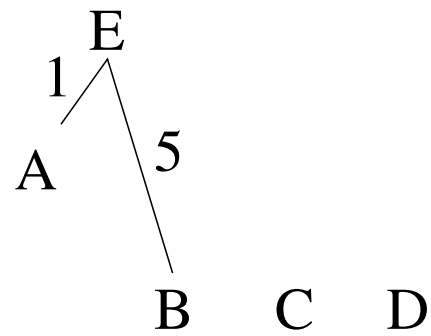
Choose either one of the red pairs to join

Neighbor joining algorithm: Example

	A	B	C	D
A	0	6	7	5
B		0	11	9
C			0	6
D				0

i	$u(C_i)$
A	$(6+7+5)/2 = 9$
B	$(6+11+9)/2 = 13$
C	$(7+11+6)/2 = 12$
D	$(5+9+6)/2 = 10$

i,j	$d_{ij} - u(C_i) - u(C_j)$	
A,B	$6 - 9 - 13$	$= -16$
A,C	$7 - 9 - 12$	$= -14$
A,D	$5 - 9 - 10$	$= -14$
B,C	$11 - 13 - 12$	$= -14$
B,D	$9 - 13 - 10$	$= -14$
C,D	$6 - 12 - 10$	$= -16$



$d_{AE} = \frac{1}{2}(6 + 9 - 13) = 1$
$d_{BE} = \frac{1}{2}(6 + 13 - 9) = 5$

This is only the first step!

Neighbor joining algorithm

- **Theorem:** If D is an additive matrix, neighbor joining algorithm correctly constructs the corresponding additive tree.
- A straightforward implementation runs in $O(n^3)$ time but there are heuristics with roughly $O(n^2)$ time complexity.

Outline

Study Group 1: Random allocation at lecture

(Ask lecturer for your group if you were not present)

- Read pages 368–373 from Jones and Pevzner.
  - Small parsimony problem
  - Dynamic programming for small parsimony
  - Large parsimony problem
- At study group summarize the problems and simulate the algorithm with some example.

Study Group 2: Random allocation at lecture

(Ask lecturer for your group if you were not present)

- Read pages 184–187 from Sung: Algorithms in Bioinformatics, CRC Press, 2010 (Especially Lemma 7.13).
  - Correctness of UPGMA algorithm
- At study group, summarize the proof for the correctness of UPGMA.

Study Group 3: Random allocation at lecture

(Ask lecturer for your group if you were not present)

- Read pages 190–191 from Durbin et al.: Biological Sequence Analysis, Cambridge University Press, 1998.
  - Correctness of neighbor joining.
  - Note that their notation of D_{ij} equals our $d_{ij} - u(C_i) - u(C_j)$.
- At study group, summarize the proof for correctness of neighbor joining.