Distance-based methods for the construction of phylogenetic trees

Lecture 14

Problem 1

- How to measure distance between 2 DNA molecules so it reflects the time since they have separated from a common ancestor?

The relative distance between genomes can be based on the number of mutational events

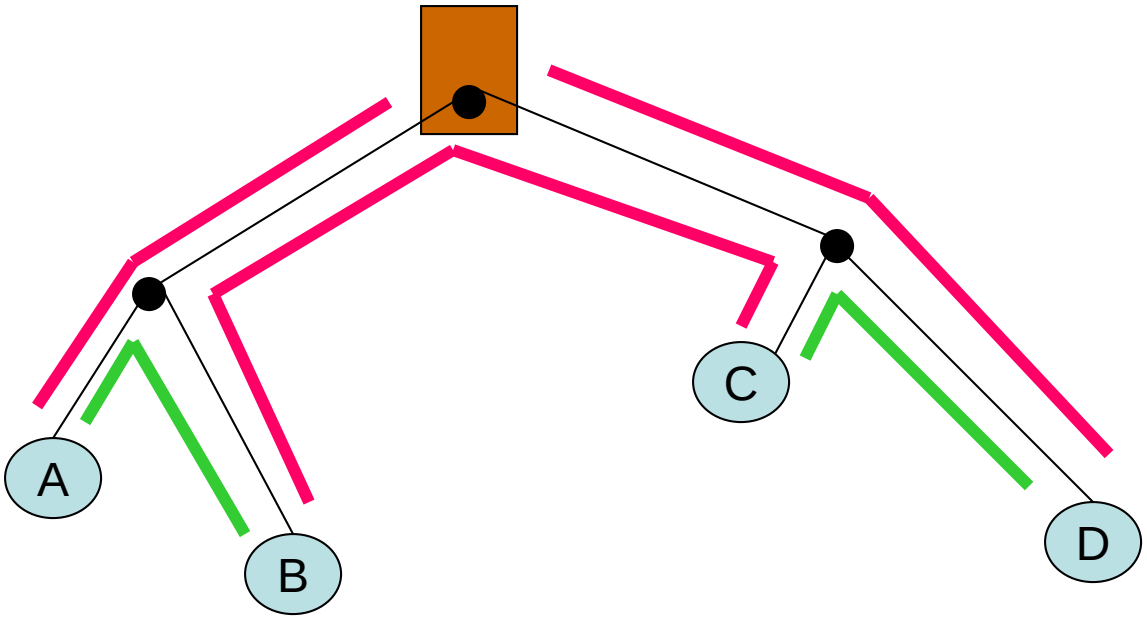
- Non computational: the melting temperature of DNA hybrids
- Computational
  - Based on DNA or protein sequences
    - Edit distance – based on point mutations
  - Gene-sequence based
    - Alignment traces – align chromosomes from the different species, connect homologous genes by an edge. The number of crosses can be used as an evolutionary distance
- Better to combine different events

Problem 2

- Given a set of pairwise distances, find the best tree for a given data

Additive distances

- Distances that fit onto some tree are called *additive*. To determine if the distances are additive use *the four point criterion:*

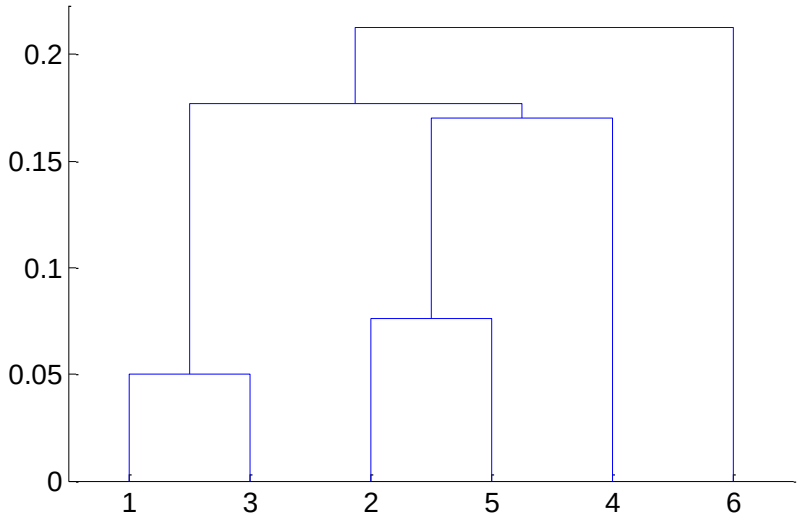


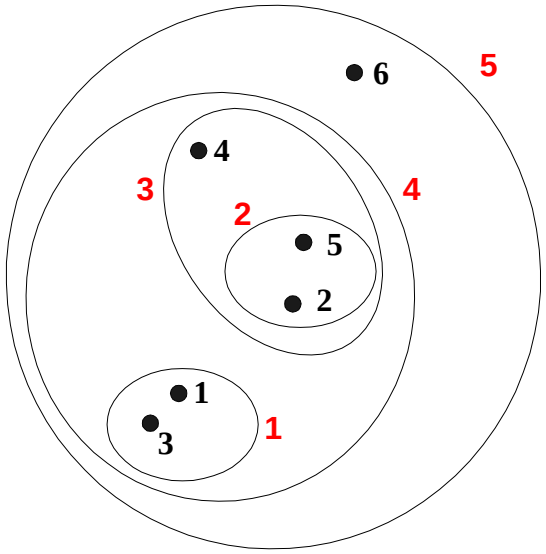
1. The sums of pairwise distances that traverse the trunk are equal
2. The sum of distances that traverse the trunk is >= the sum of remaining distances

$$d_{AD}+d_{BC}=d_{BD}+d_{AC}>=d_{AB}+d_{CD}$$

Hierarchical Clustering

- Produces a set of nested clusters organized as a hierarchical tree
- Can be visualized as a dendrogram
  - A tree-like diagram that records the sequences of merges or splits





Hierarchical Clustering

- Start with the points as individual clusters
- At each step, merge the closest pair of clusters until only one cluster left.

Algorithm

Let each data point be a cluster

Compute the distance matrix

Repeat

Merge the two closest clusters

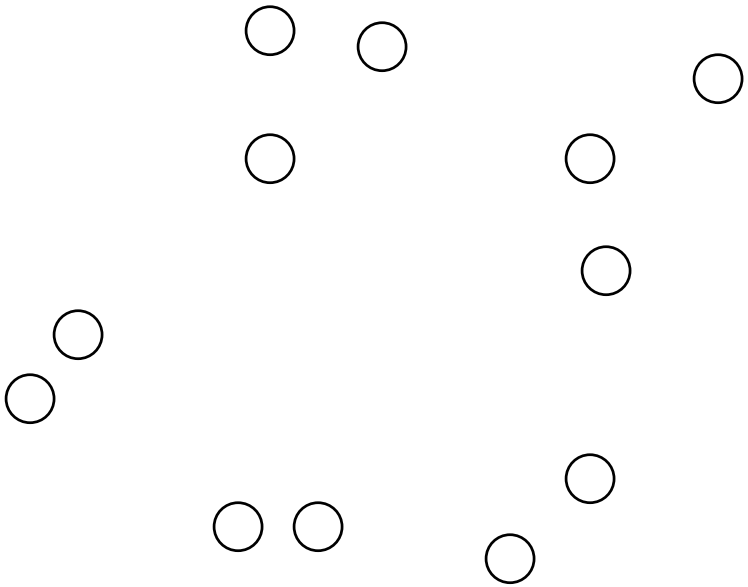
Update the distance matrix

Until only a single cluster remains

- Key operation is *the computation of the distance between two clusters.*

Starting Situation

- Start with clusters of individual points and a distance matrix

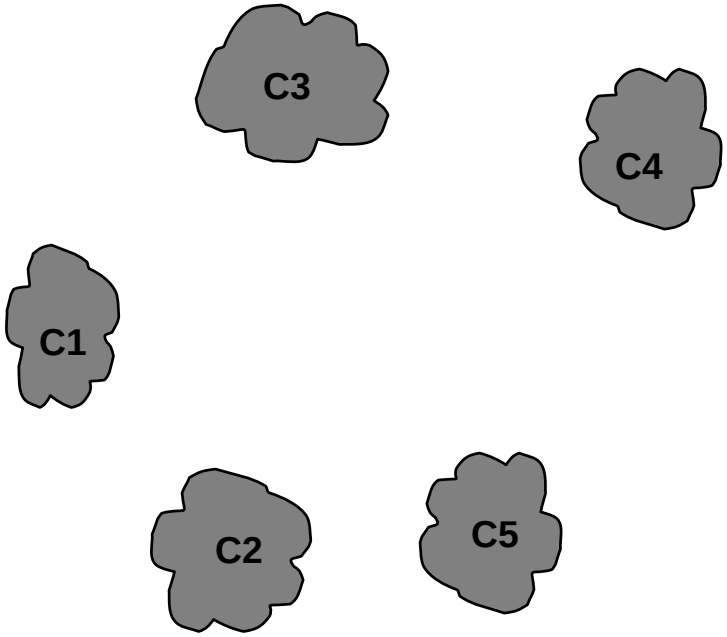


	p1	p2	p3	p4	p5	. . .
p1						
p2						
p3						
p4						
p5						
.						
.						
.						

Distance Matrix

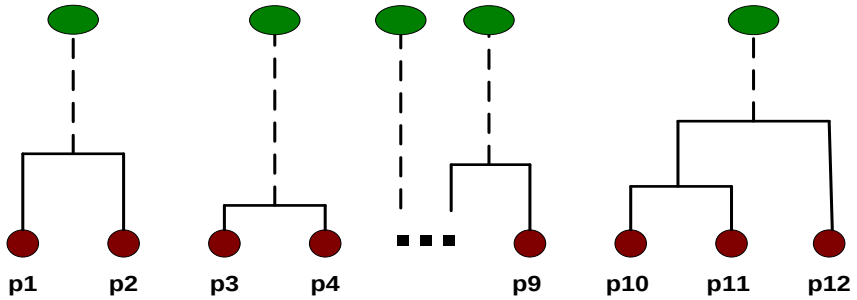
Intermediate Situation

- After some merging steps, we have some clusters



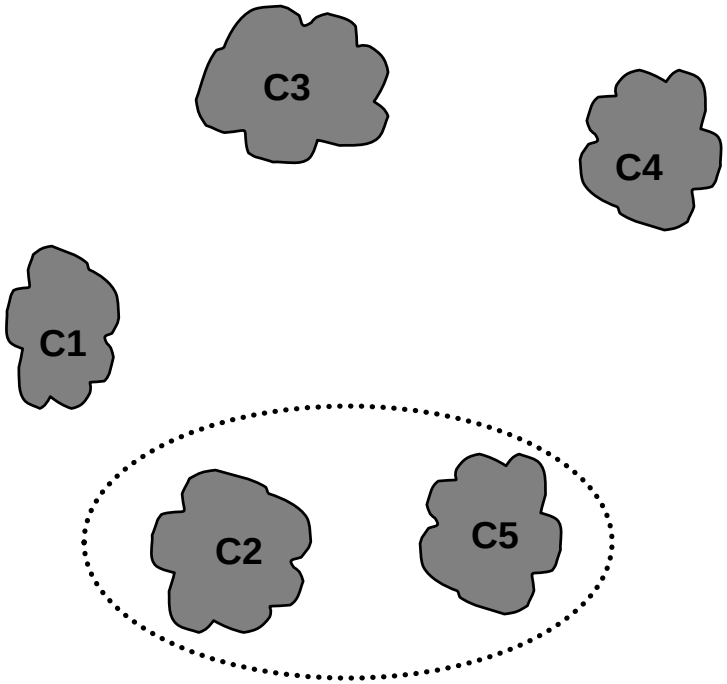
	C1	C2	C3	C4	C5
C1					
C2					
C3					
C4					
C5					

Distance Matrix



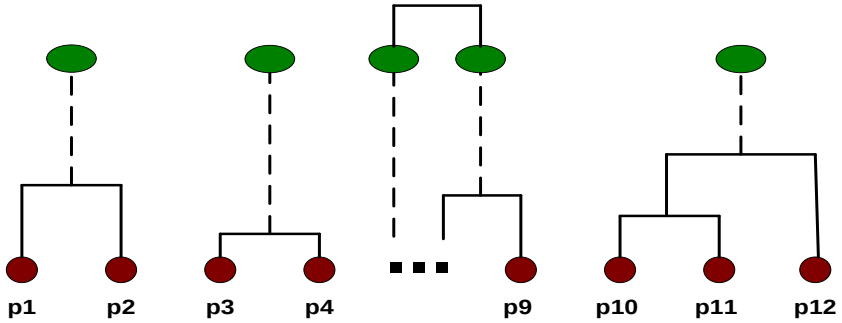
Intermediate Situation

- We want to merge the two closest clusters (C2 and C5) and update the distance matrix.



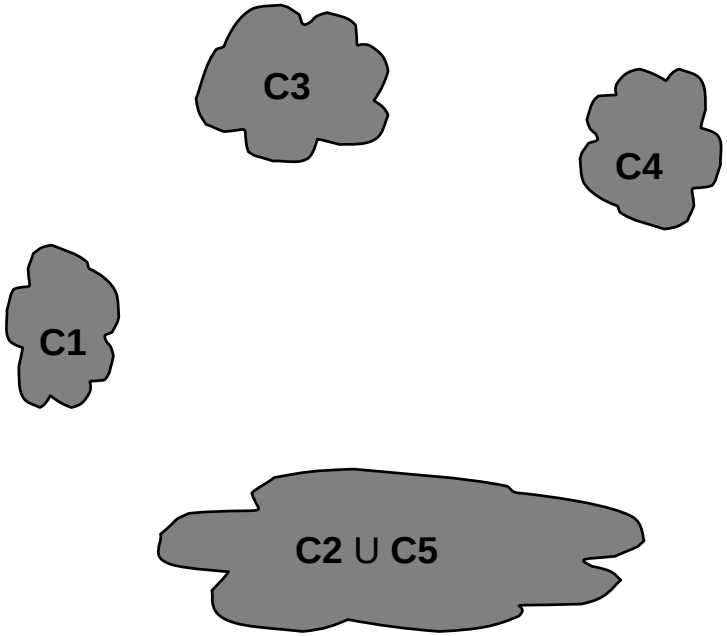
	C1	C2	C3	C4	C5
C1					
C2					
C3					
C4					
C5					

Distance Matrix



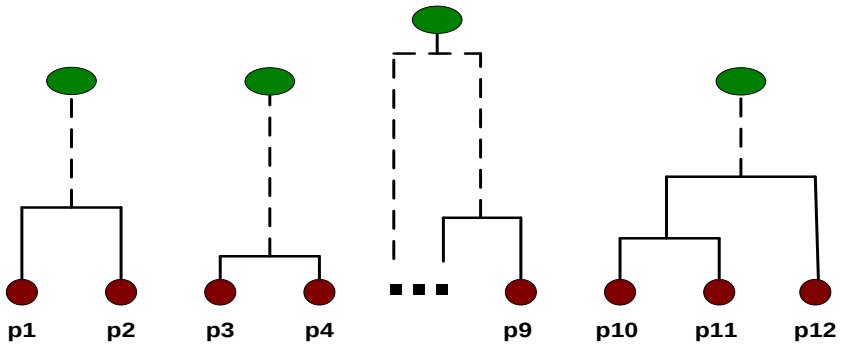
After Merging

- The question is "How do we update the distance matrix for clusters?"

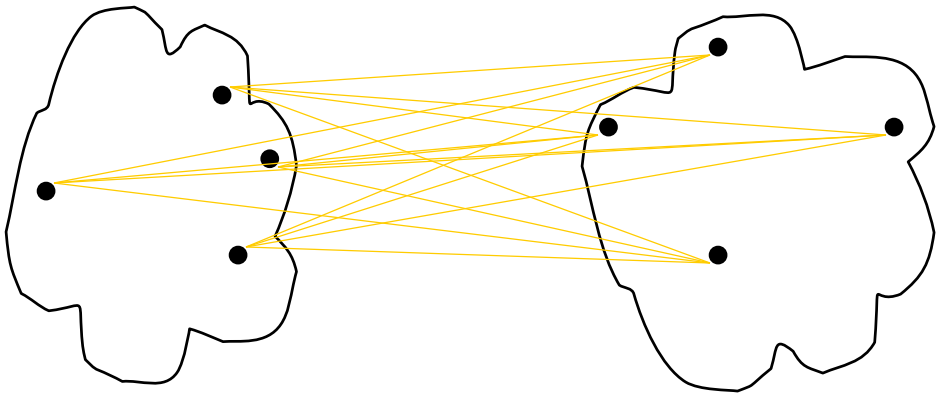


	C1	C2 U C5	C3	C4
C1		?		
C2 U C5	?	?	?	?
C3		?		
C4		?		

Distance Matrix



How to Define Inter-Cluster Distance



- MIN
- MAX
- Group Average –UPGMA:
  Unweighted **P**air-**G**roup **M**ethod using an arithmetic **A**verage

	p1	p2	p3	p4	p5	. . .
p1						
p2						
p3						
p4						
p5						
.						

.

.

Distance Matrix

Cluster Distance: Group Average

- Distance between two clusters is the average of all pairwise distances between points in the two clusters.

$$\mathbf{distance}(\mathbf{Cluster}_i, \mathbf{Cluster}_j) = \frac{\sum_{\substack{\mathbf{p}_i \in \mathbf{Cluster}_i \\ \mathbf{p}_j \in \mathbf{Cluster}_j}} \mathbf{distance}(\mathbf{p}_i, \mathbf{p}_j)}{|\mathbf{Cluster}_i| * |\mathbf{Cluster}_j|}$$

Example

	Human	Chimpanzee	Gorilla	Orangutan	Gibbon
Human					
Chimpanzee	1				
Gorilla	4	2			
Orangutan	8	7	5		
Gibbon	10	9	2	9	

The distances are determined based on the melting temperature of the DNA hybrids (mitochondrial DNA)

Distance matrix

Distance matrix

	A	B	C	D	E
A					
B	1				
C	4	3			
D	8	7	2		
E	10	9	4	6	

Are the distances additive?

ABCD

AC+BD=BC+AD=11>AB+CD=3

ABCE

AC+BE=AE+BC=13>AB+CE=5

ACDE

AD+CE=AE+CD=12>AC+DE=10

BCDE

BD+CE=CD+BE=11>BC+DE=9

	A	B	C	D	E
A					
B	1				
C	4	3			
D	8	7	2		
E	10	9	4	6	

Yes, the distances are additive, we can build the tree

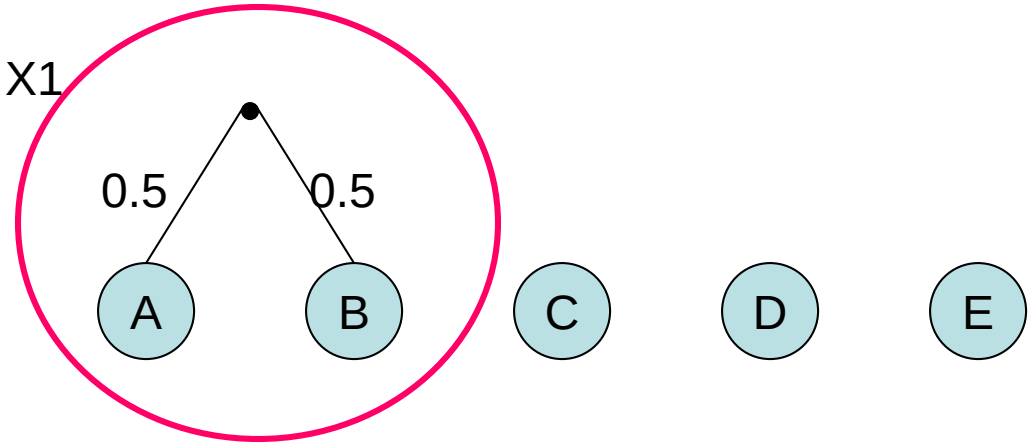
UPGMA – demo 1

	A	B	C	D	E
A					
B	1				
C	4	3			
D	8	7	2		
E	10	9	4	6	

Basic clusters – distance 0 between the elements of each cluster

UPGMA – demo 2

	A	B	C	D	E
A	0				
B	1	0			
C	4	3	0		
D	8	7	2	0	
E	10	9	4	6	0

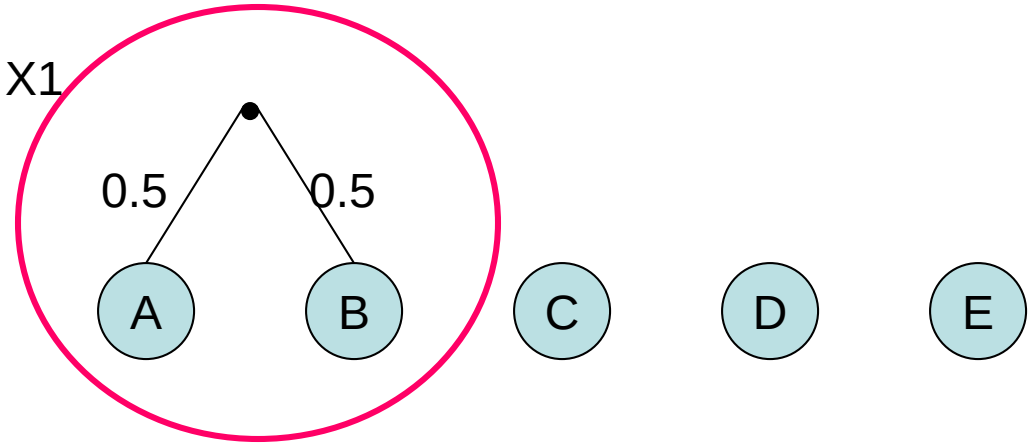


Form cluster X1 with min distance between two points

UPGMA – demo 2

	X1	C	D	E
X1	0			
C	3.5	0		
D	7.5	2	0	
E	9.5	4	6	0

	A	B	C	D	E
A	0				
B	1	0			
C	4	3	0		
D	8	7	2	0	
E	10	9	4	6	0



$dX_1C=(dAC+dBC)/(2)*1=3.5$

$dX_1D=(dAD+dBD)/(2)*1=7.5$

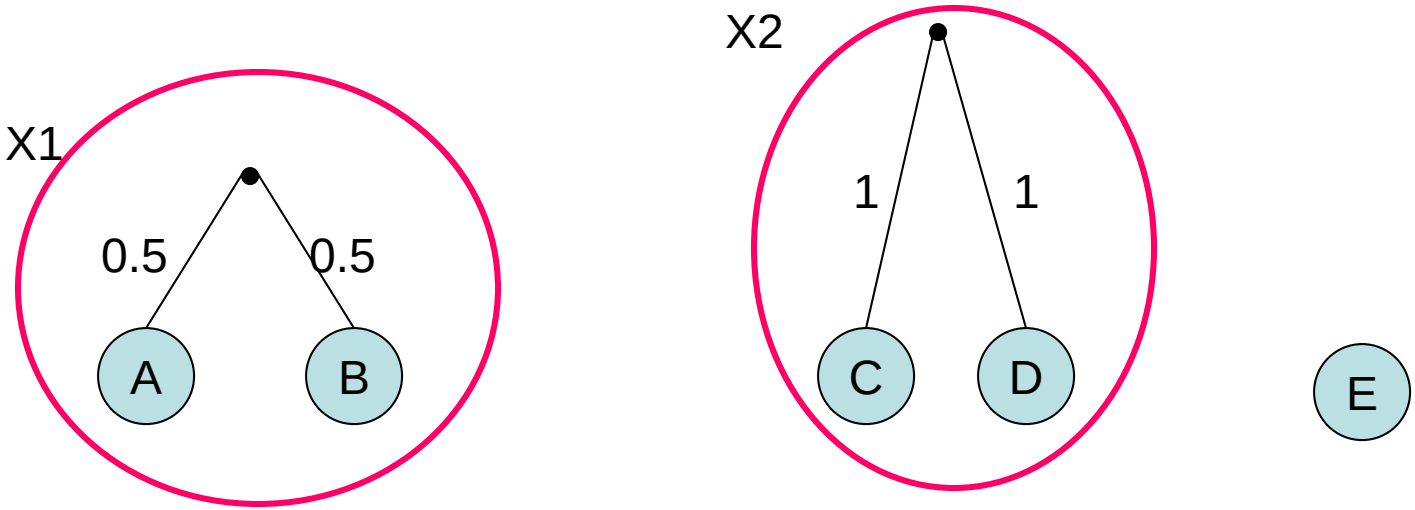
$dX_1E=(dAE+dBE)/(2)*1=9.5$

Update distance matrix

UPGMA – demo 3

	X1	C	D	E
X1	0			
C	3.5	0		
D	7.5	2	0	
E	9.5	4	6	0

	A	B	C	D	E
A	0				
B	1	0			
C	4	3	0		
D	8	7	2	0	
E	10	9	4	6	0



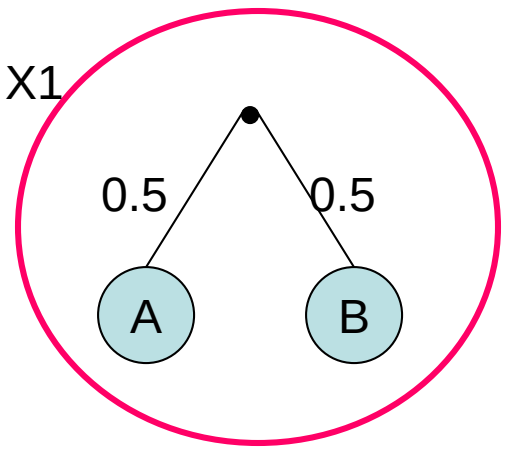
Form cluster X2 with min distance between two points

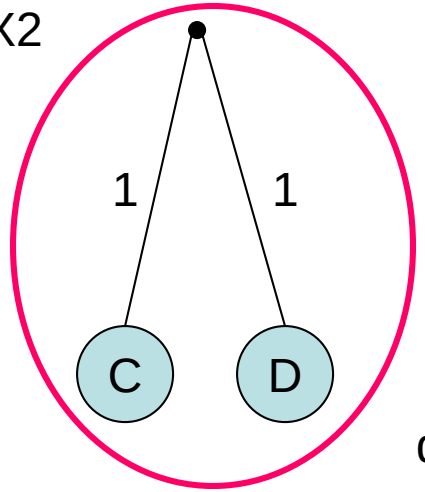
UPGMA – demo 3

	X1	X2	D
X1	0		
X2	5.5	0	
E	7.5	5	0

	X1	C	D	E
X1	0			
C	3.5	0		
D	7.5	2	0	
E	9.5	4	6	0

	A	B	C	D	E
A	0				
B	1	0			
C	4	3	0		
D	8	7	2	0	
E	10	9	4	6	0





$dX_2E=(dCE+dDE)/(2)*1=5$

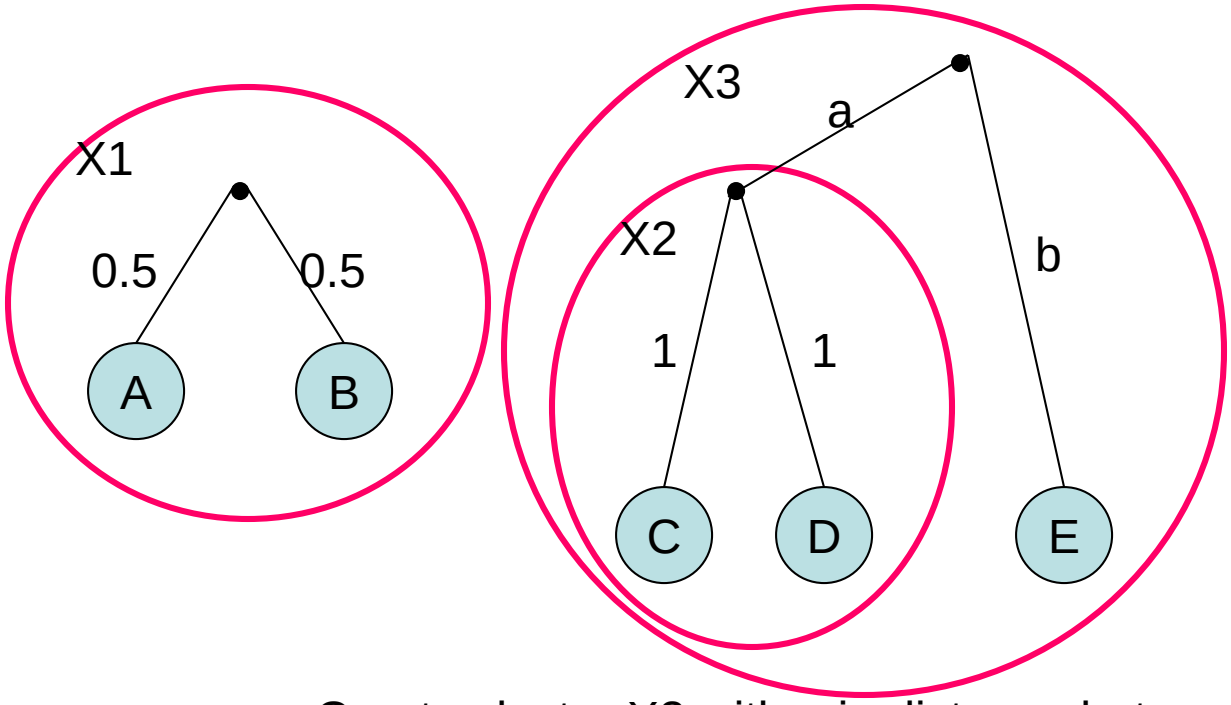
$dX_1X_2=(dAC+dBC+dAD+dBD)/(2*2)=5.5$

Update distance matrix

UPGMA – demo 4

	X1	X2	D
X1	0		
X2	5.5	0	
E	7.5	5	0

	A	B	C	D	E
A	0				
B	1	0			
C	4	3	0		
D	8	7	2	0	
E	10	9	4	6	0



a=1/2*5-1=1.5

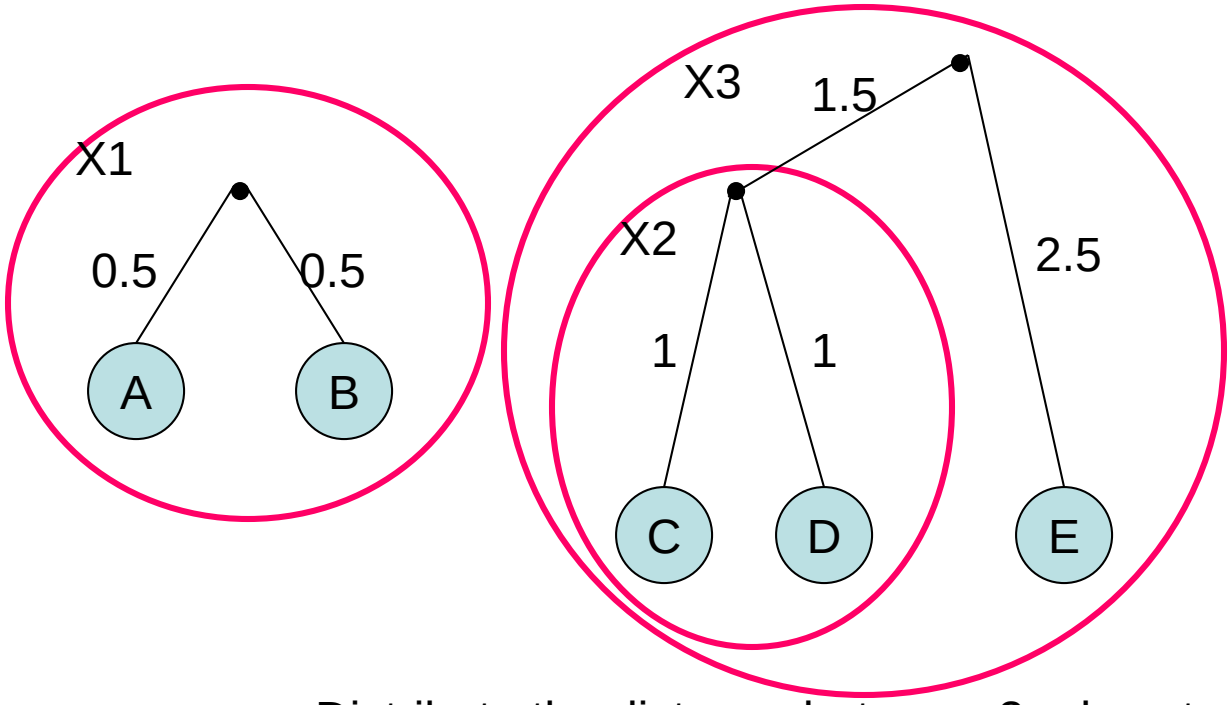
b=1/2*5=2.5

Create cluster X3 with min distance between 2 clusters

UPGMA – demo 4

	X1	X2	D
X1	0		
X2	5.5	0	
E	7.5	5	0

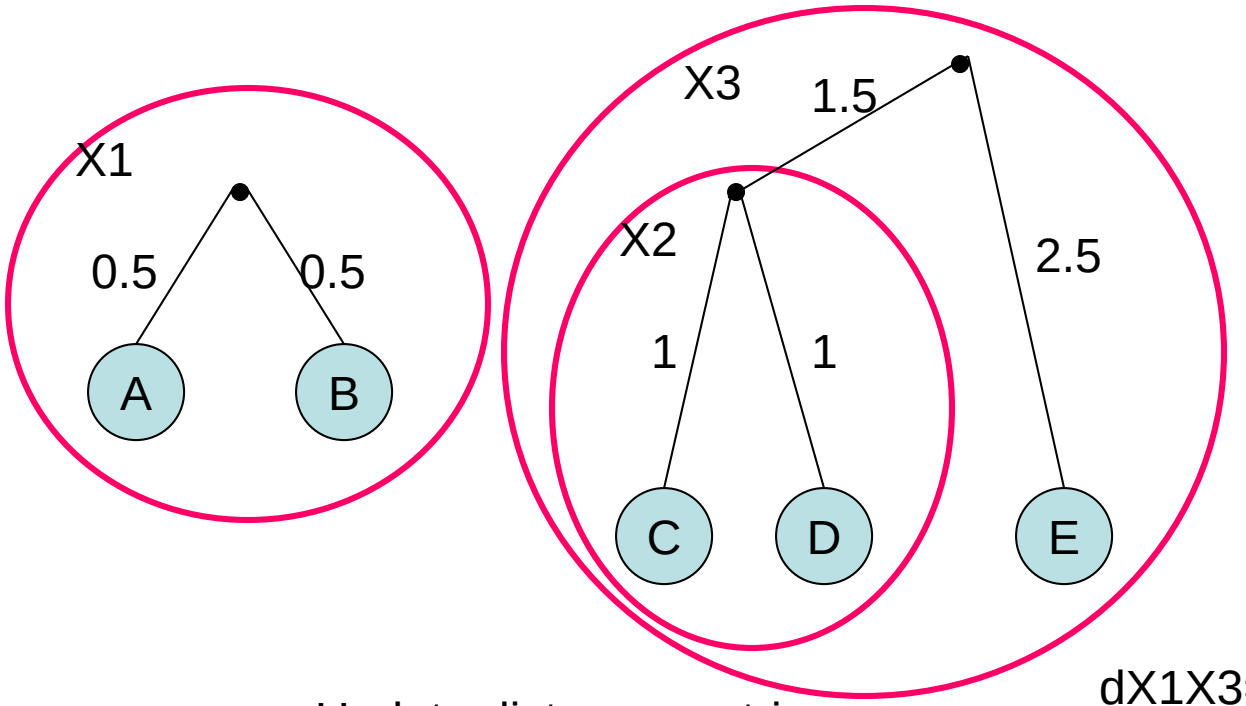
	A	B	C	D	E
A	0				
B	1	0			
C	4	3	0		
D	8	7	2	0	
E	10	9	4	6	0



Distribute the distance between 2 edges to have half of this distance from the root to leaves in both branches

UPGMA – demo 4

	A	B	C	D	E
A	0				
B	1	0			
C	4	3	0		
D	8	7	2	0	
E	10	9	4	6	0



	X1
X1	0
X3	6.8

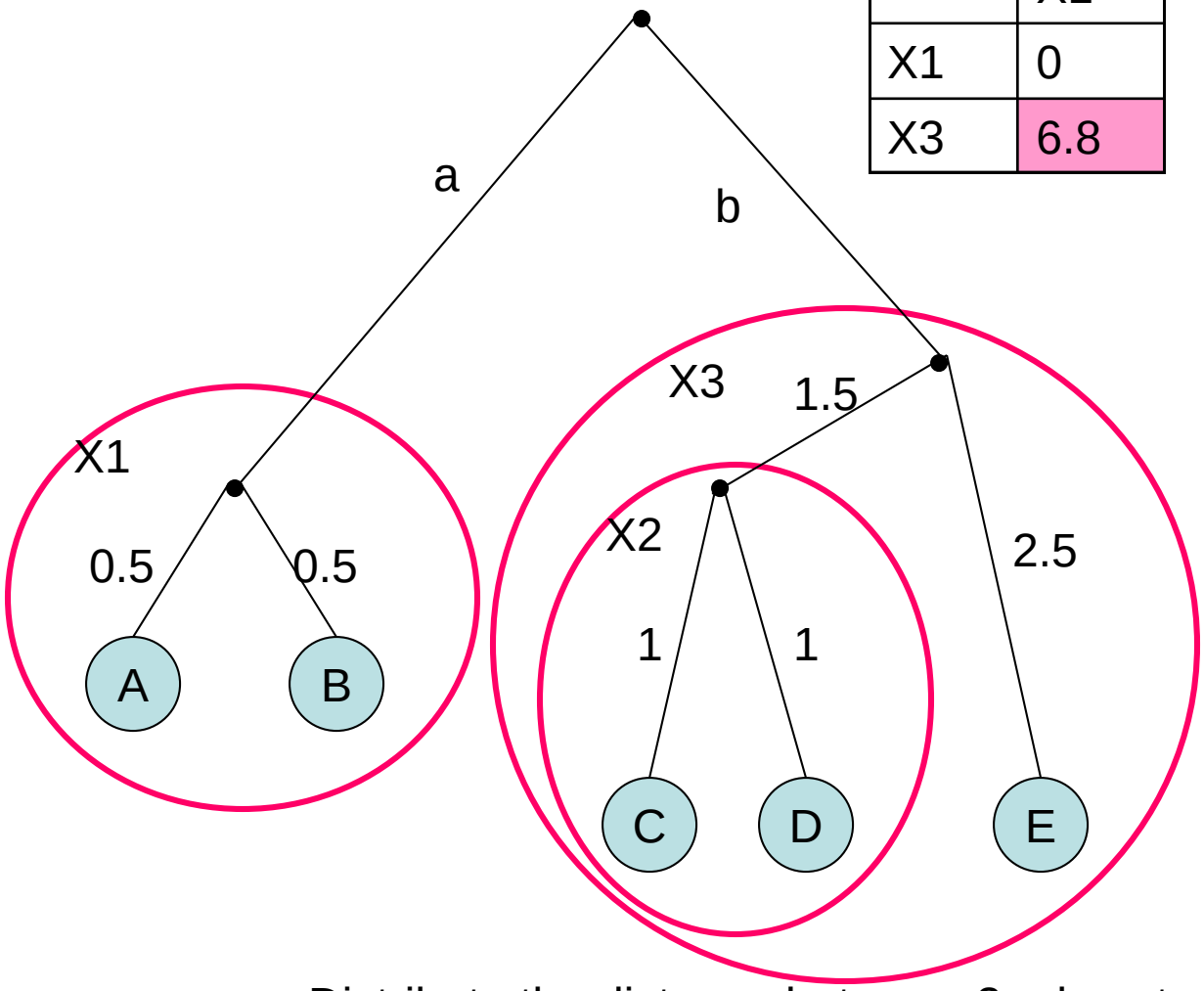
Update distance matrix

dX1X3=(dAC+dAD+dAE+dBC +dBD+dBE)/2*3=(4+8+10+3+7 +9)/6=6.8

UPGMA – demo 4

	X1
X1	0
X3	6.8

	A	B	C	D	E
A	0				
B	1	0			
C	4	3	0		
D	8	7	2	0	
E	10	9	4	6	0

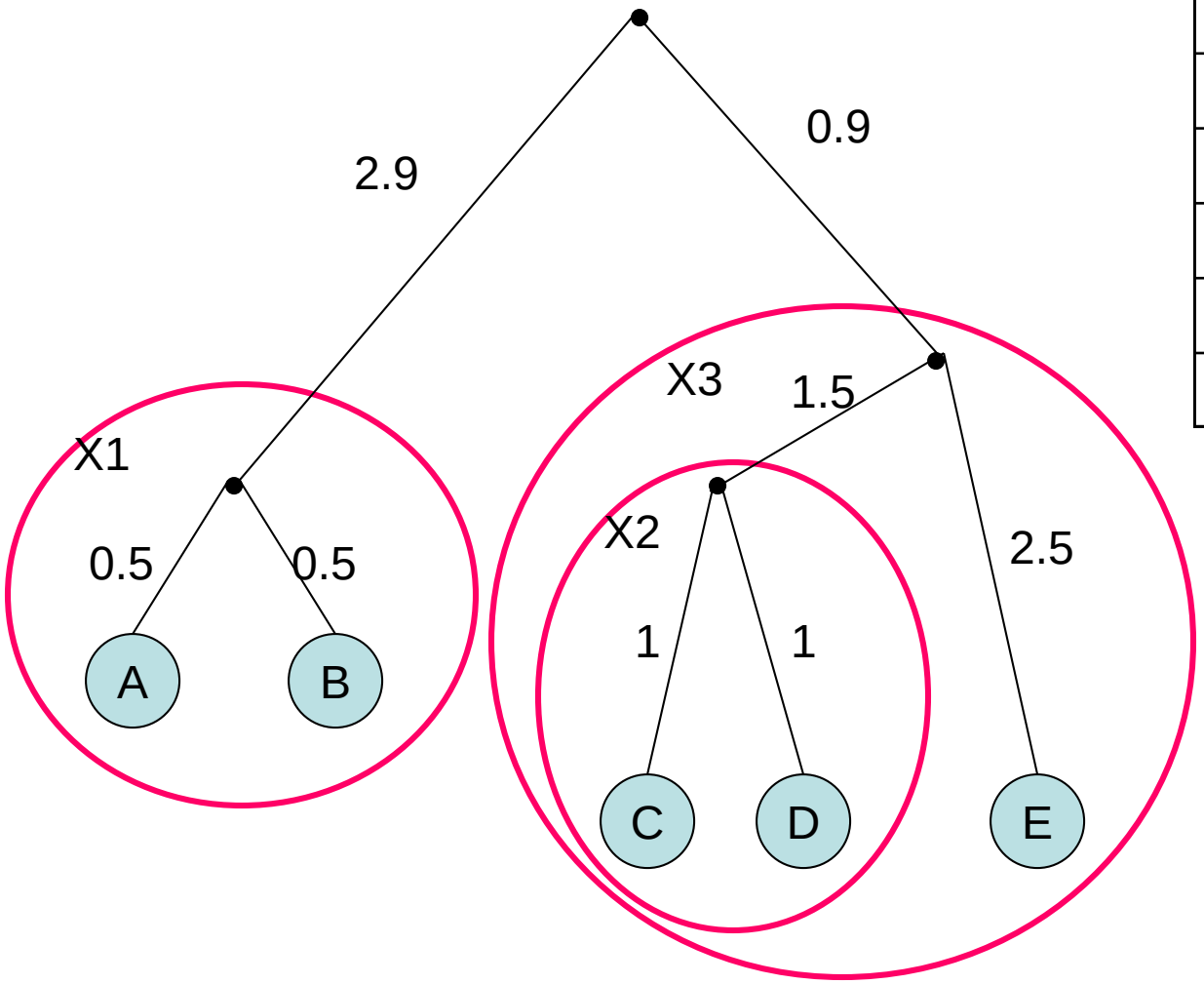


a=6.8/2-0.5=2.9

b=6.8/2-2.5=0.9

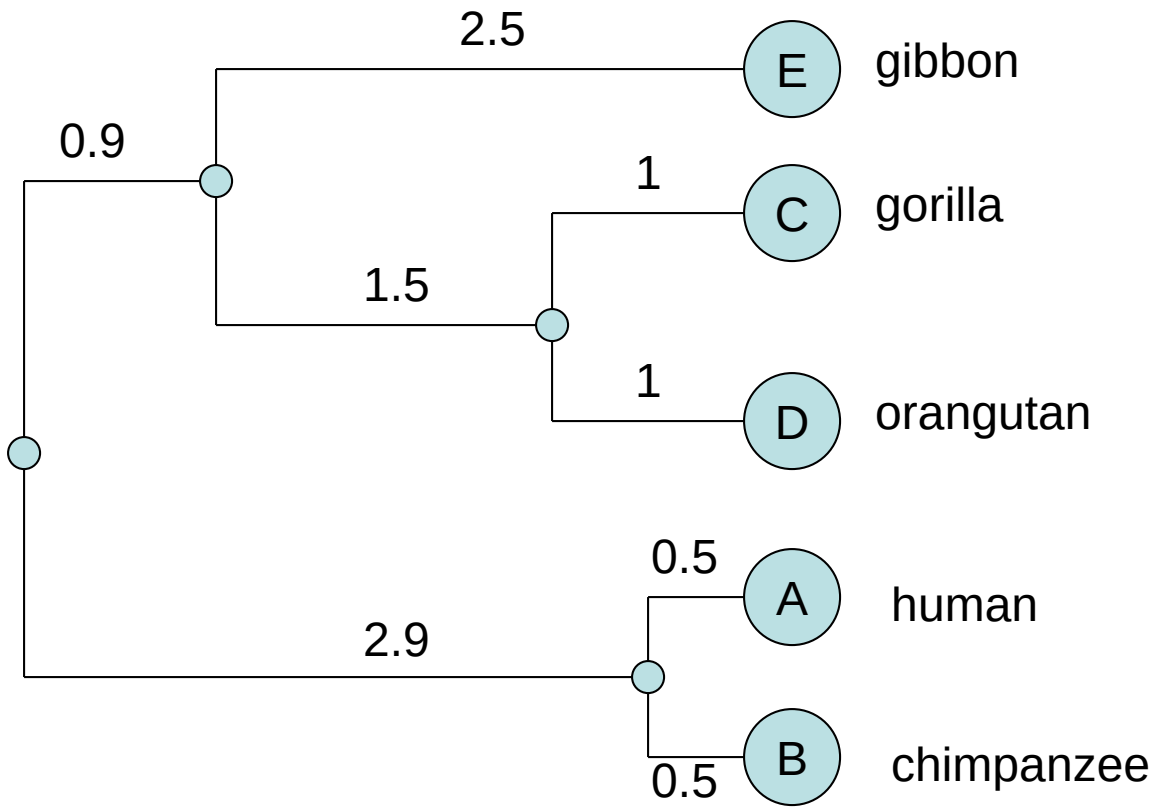
Distribute the distance between 2 edges to have half of this distance from the root to leaves in both branches

UPGMA – the resulting tree

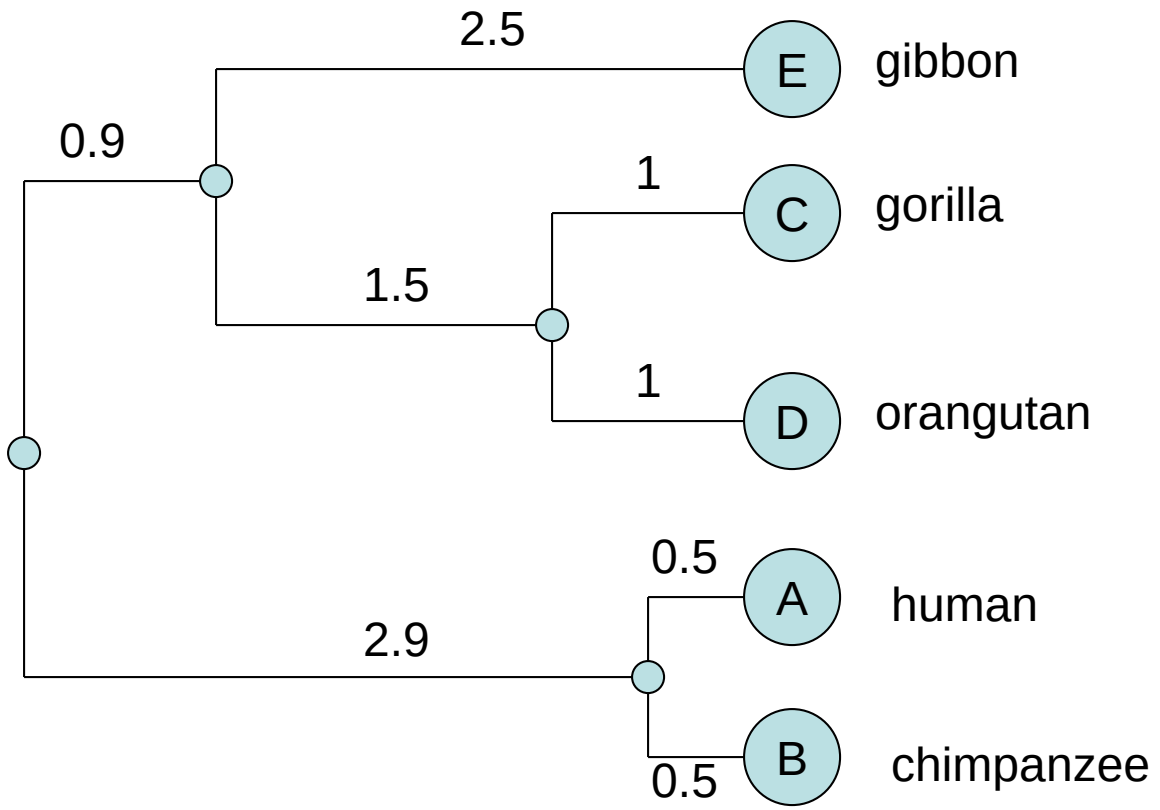


	A	B	C	D	E
A	0				
B	1	0			
C	4	3	0		
D	8	7	2	0	
E	10	9	4	6	0

The resulting tree with distances



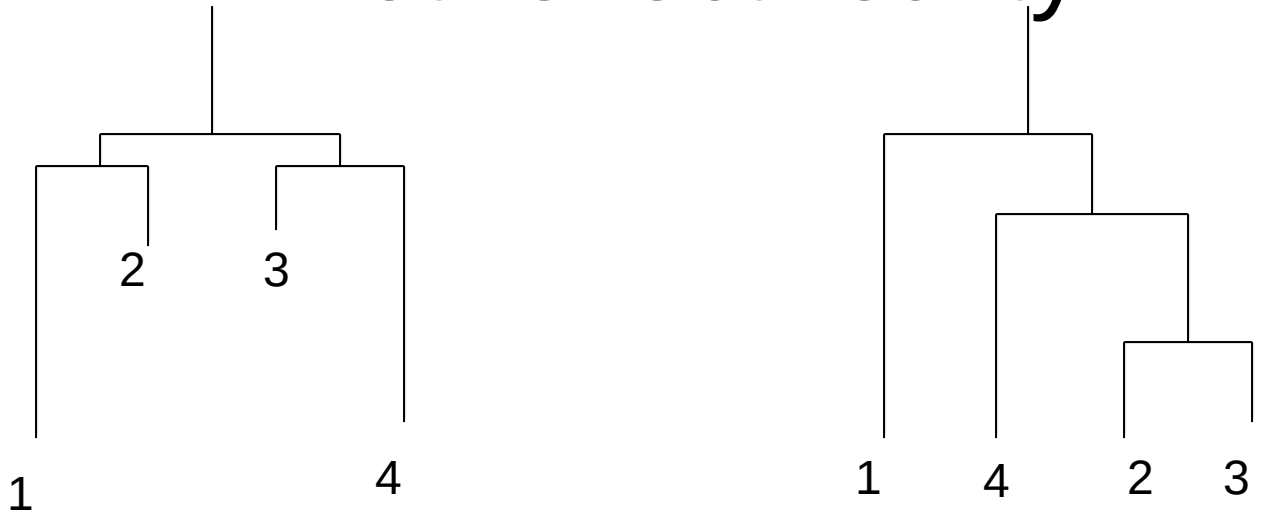
Molecular clock



The edge lengths can be viewed as times measured by *molecular clock* with a constant rate of mutational events.

We assume that divergence occurred at the same time at all branching points, the sum of edge lengths from any node to the leaf is the same for any possible path

When the tree we constructed does not reflect reality



- If the original tree, which we try to reconstruct, had different path lengths to its leaves, it may be reconstructed incorrectly by UPGMA.
- In this case, the closest leaves (2,3) are not siblings and they do not have a common parent, which will be assigned to them by UPGMA

Test for ultrametric condition

- We can predict whether the reconstruction of the real tree is likely to be correct by testing our distances for *ultrametric condition*:

The distance matrix is ultrametric if for any triplet of sequences, Xi, Xj, Xk, the distances dij, dik, djk are either all equal or two are equal and the remaining one is smaller

Thus, if distances were derived from a real tree with a molecular clock, the distance matrix has to be ultrametric

Ultrametric and non-ultrametric distance matrices

	A	B	C	D
A	0			
B	1	0		
C	4	2	0	
D	8	7	5	0

dAB=1, dAC=4, dBC=2

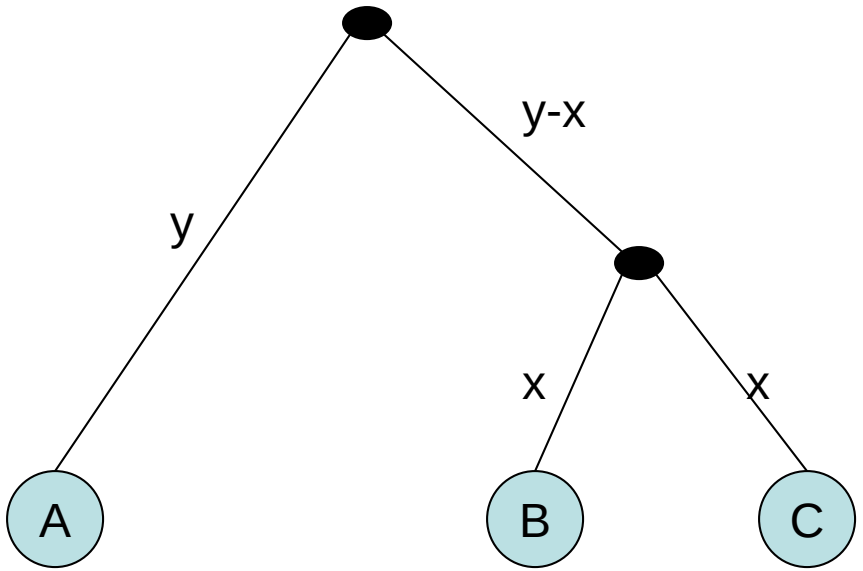
Non-ultrametric matrix

	A	B	C	D
A	0			
B	4	0		
C	2	4	0	
D	8	8	8	0

Ultrametric matrix

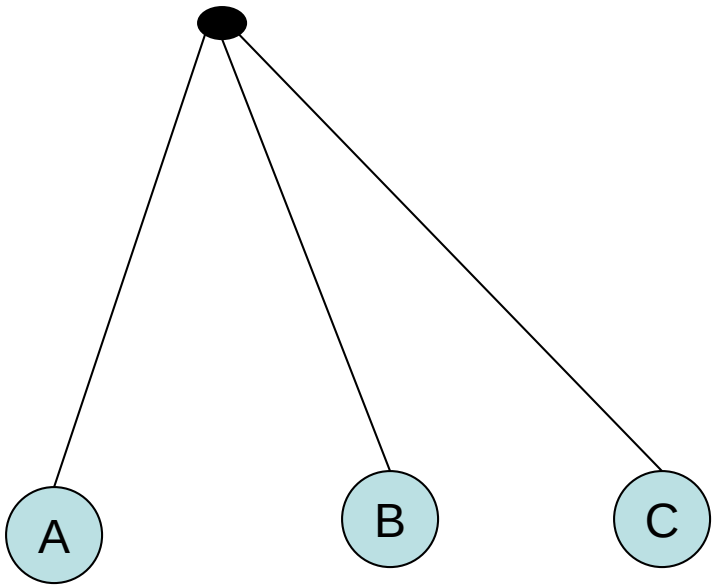
Ultrametric trees

AB=AC>BC



or

AB=AC=BC



AB=y+y-x+x=2y

AC=2y

BC=2x, x<=y, since y-x>=0 (no negative edge lengths)

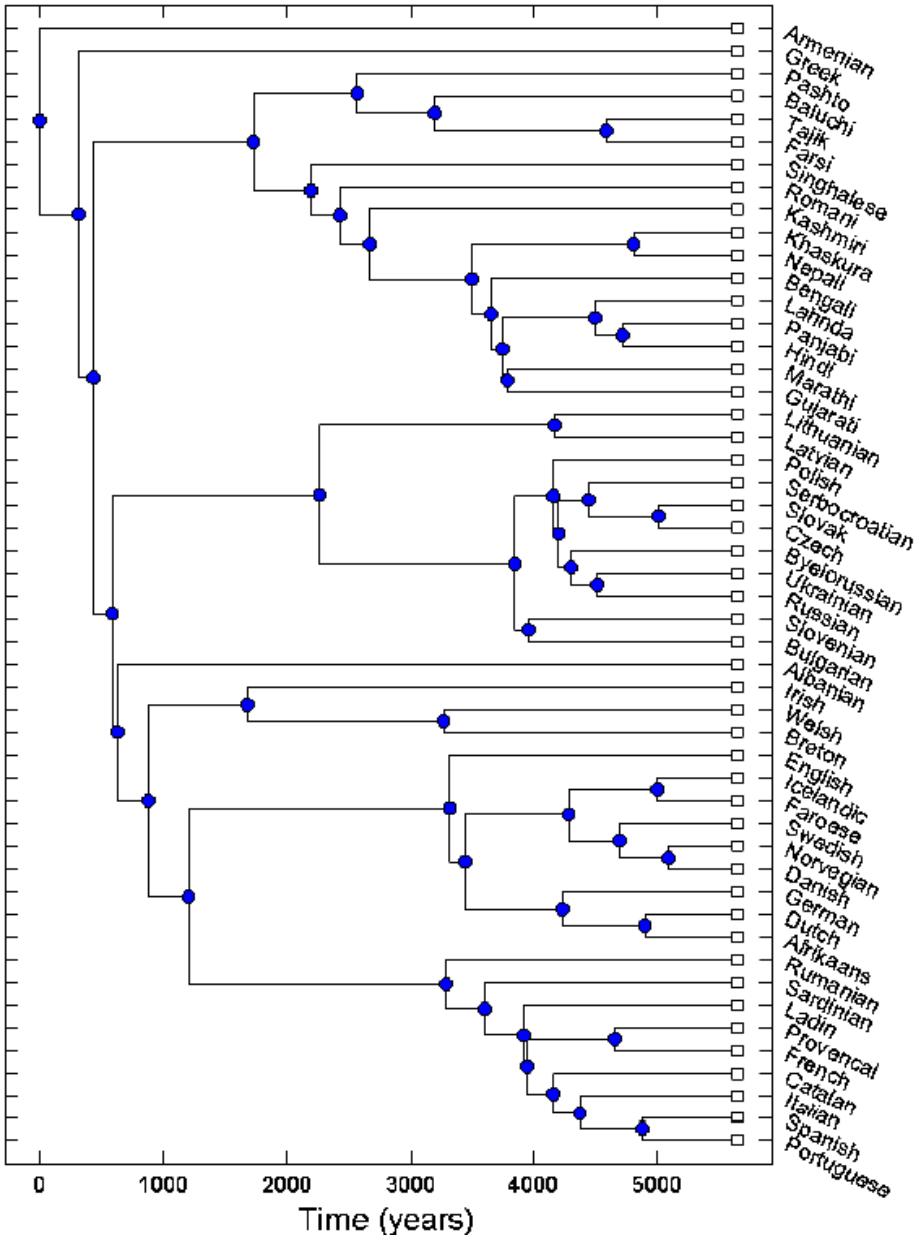
The rule for ultrametric trees:

2 out of 3 distances have a tie, and are >= than the third distance

If the distances are not ultrametric?

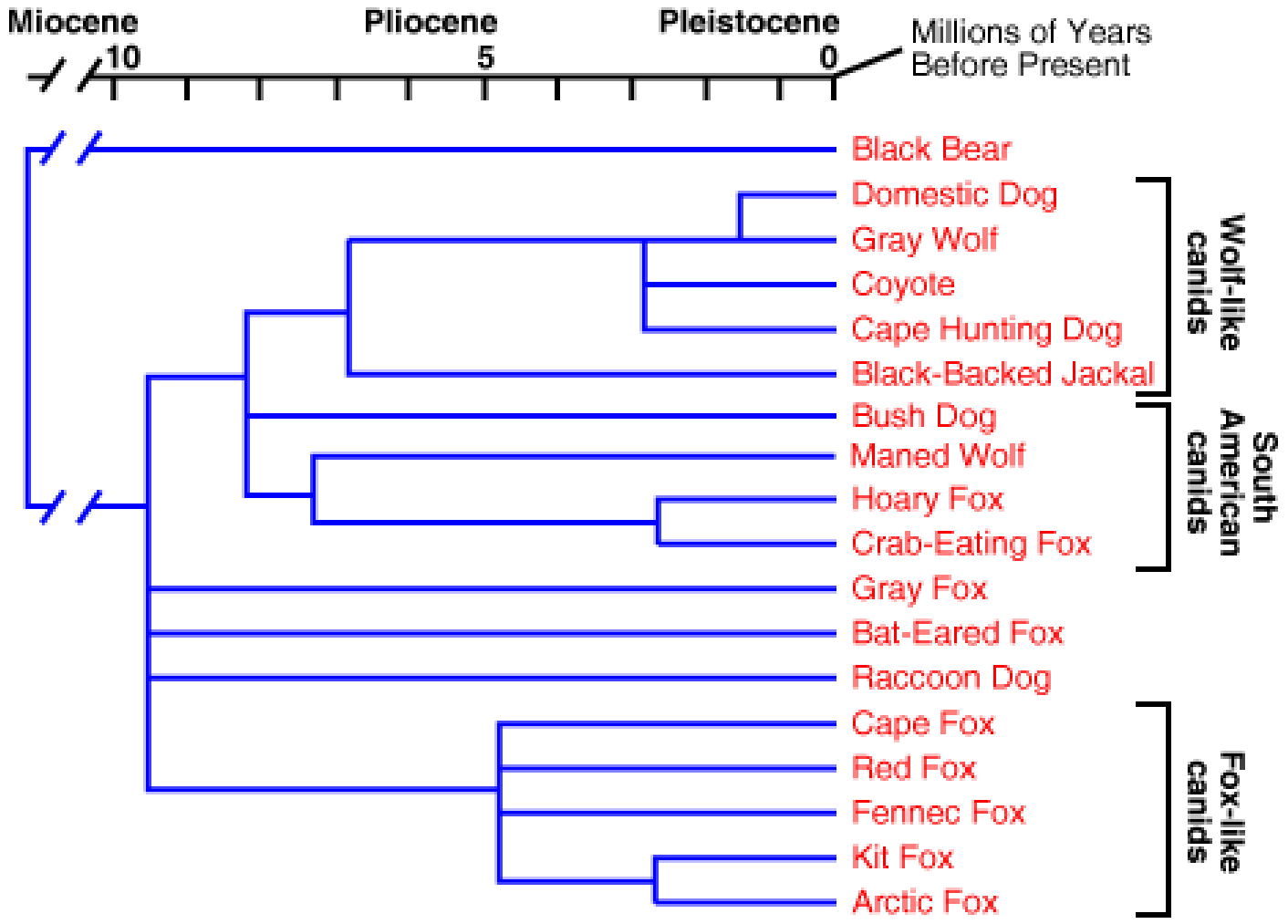
- We can apply UPGMA, but it may produce an incorrect tree.
- **The neighbor-joining algorithm** produces better results for non-ultrametric distances
- The main feature of the neighbor-joining algorithm is that we take into account not only how close are two clusters, but also how far away are they from other clusters
- This algorithm produces unrooted trees

Tree Example 1



From "Indo-European languages tree by Levenshtein distance" by M. Serva1 and F. Petroni

Tree Example 2



Tree Example 3