Phylogenetic analysis

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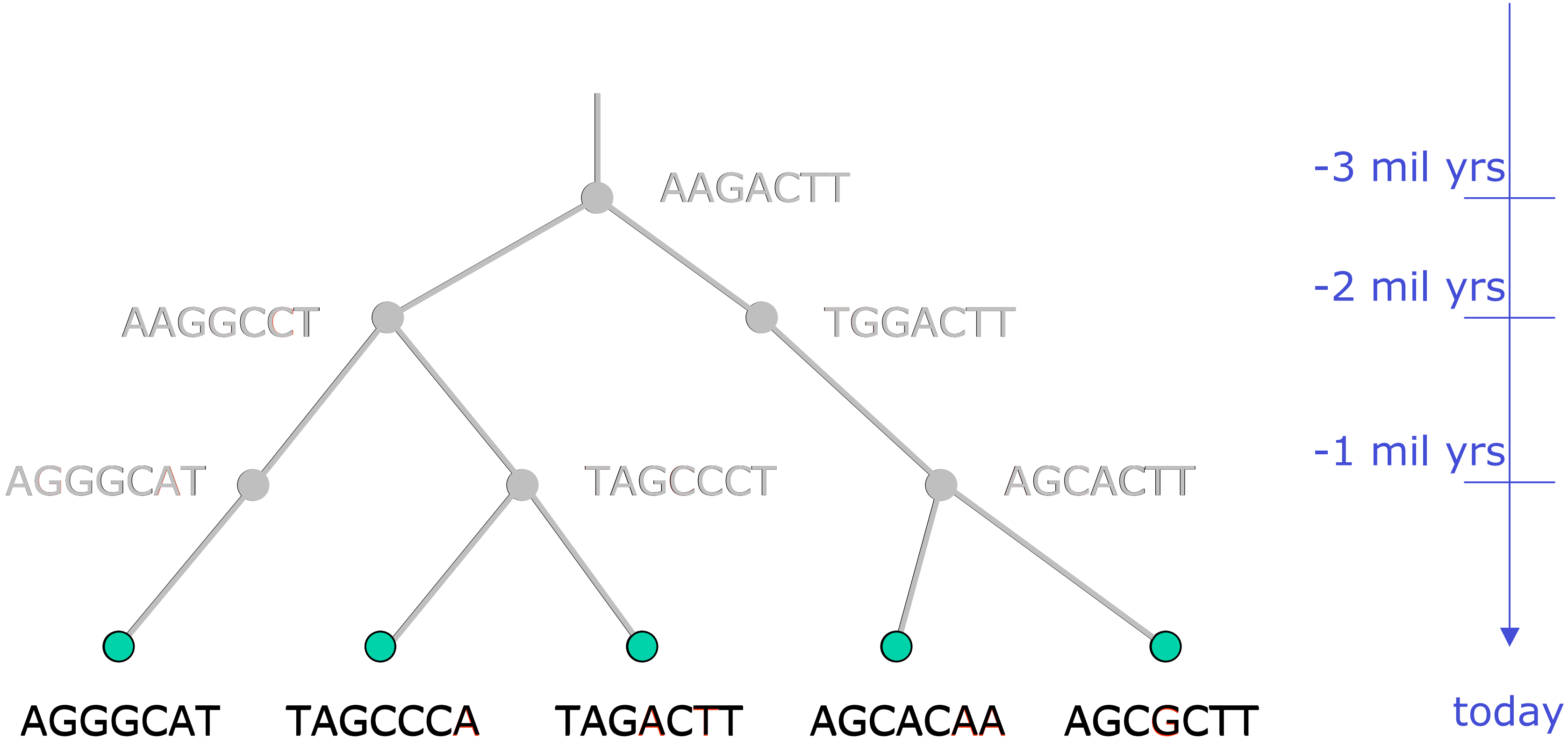
Jan. 13, 2007

Tree of the life

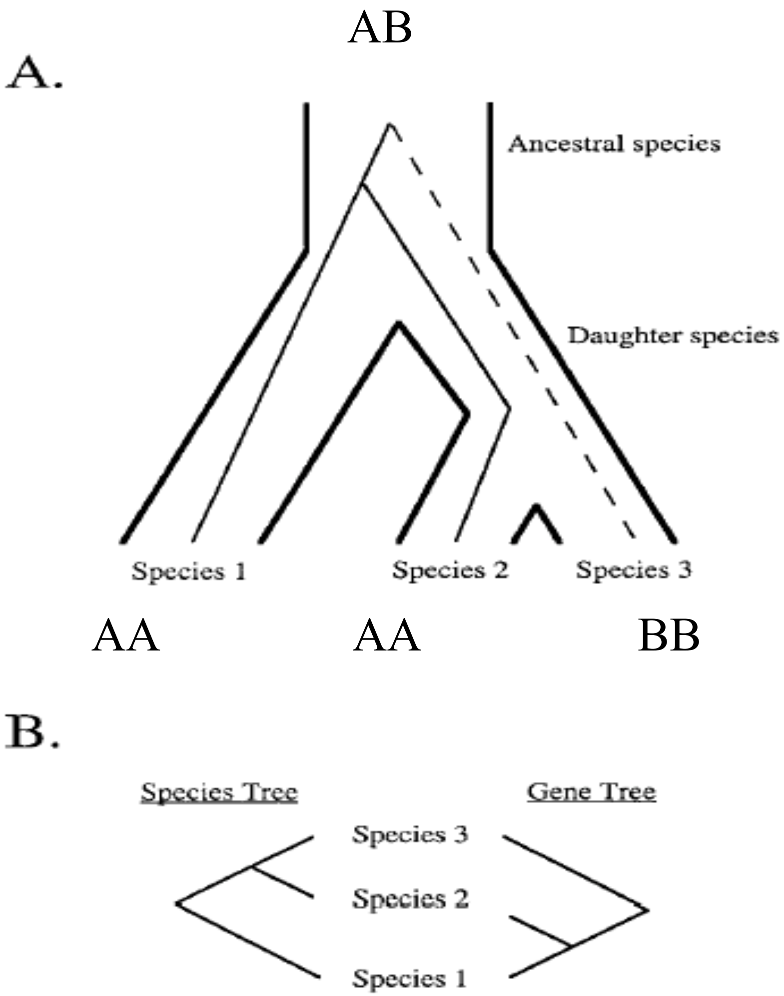
- From http://tolweb.org/tree/

DNA Sequence Evolution



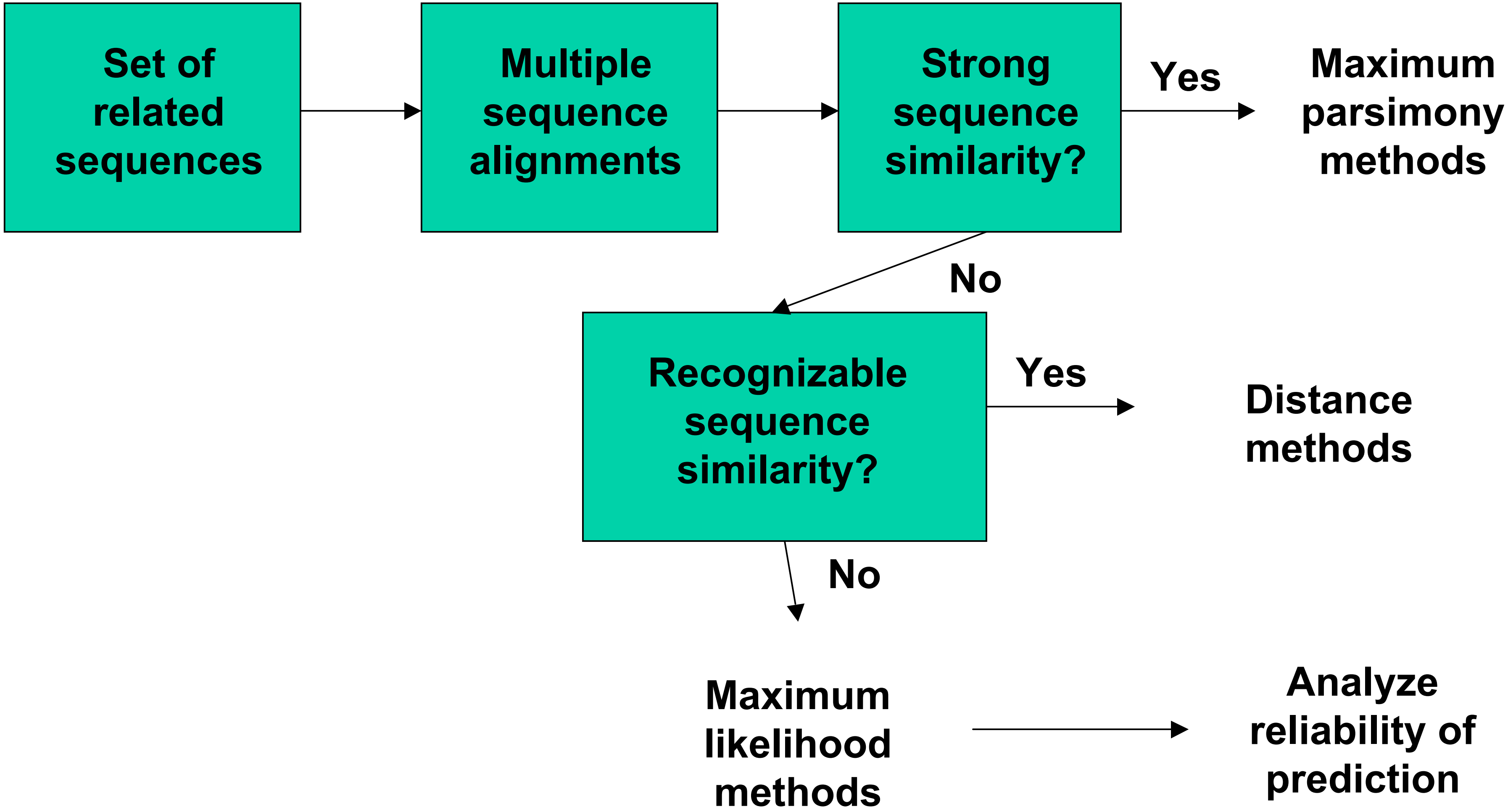
- From Tandy Warnow 2004

Gene Trees and Species Trees



From Doyle and Gaut; Plant Molecular Biology 42:1-23, 2000

Methods for phylogenetic trees construction.



Set of related sequences

Multiple sequence alignments

Strong sequence similarity?

Yes

Maximum parsimony methods

No

Recognizable sequence similarity?

Yes

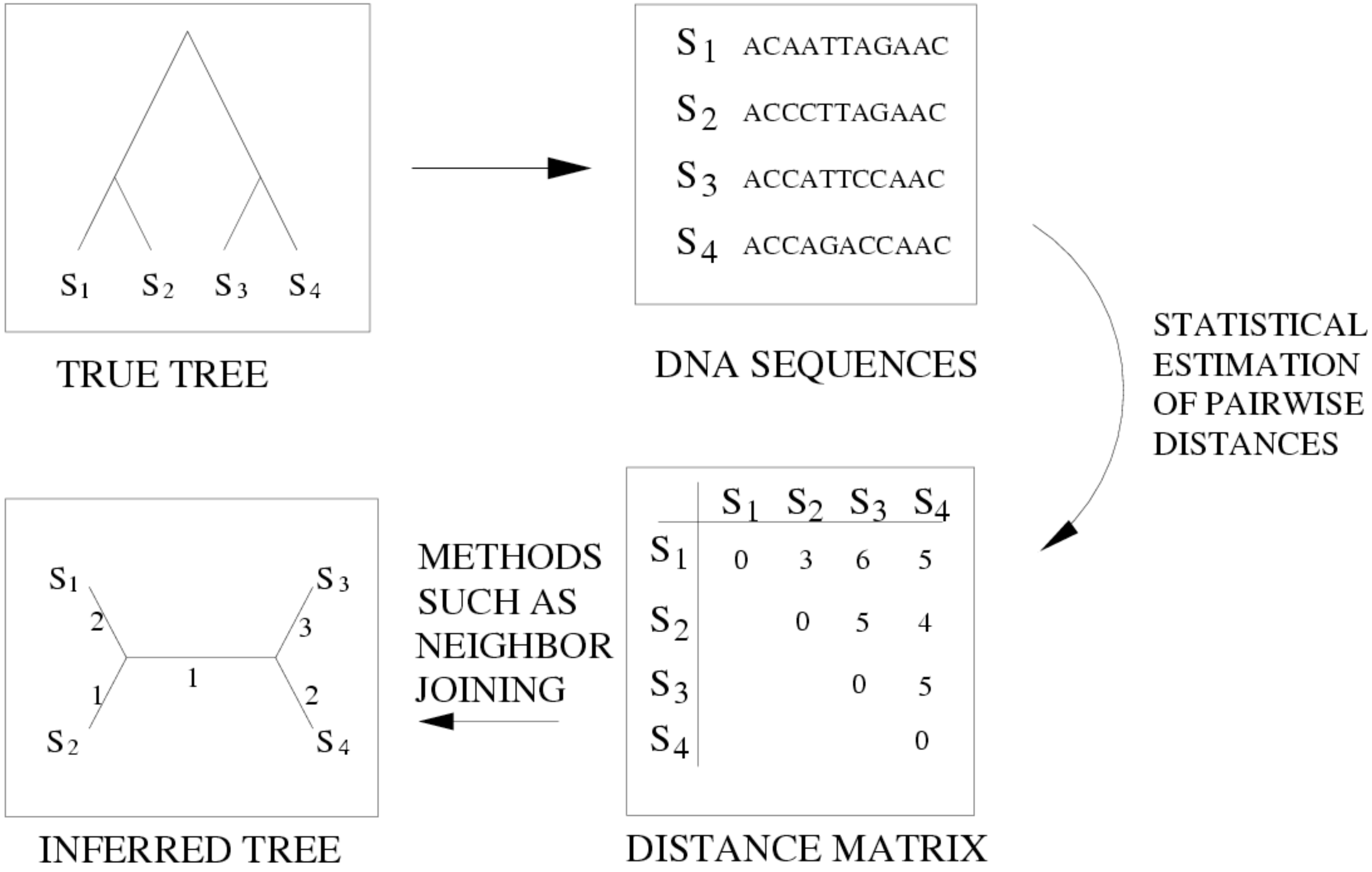
Distance methods

No

Maximum likelihood methods

Analyze reliability of prediction

Distance Based Methods



TRUE TREE

S_1 ACAATTAGAAC
S_2 ACCCTTAGAAC
S_3 ACCATTCCAAC
S_4 ACCAGACCAAC

DNA SEQUENCES

STATISTICAL ESTIMATION OF PAIRWISE DISTANCES

	S_1	S_2	S_3	S_4
S_1	0	3	6	5
S_2		0	5	4
S_3			0	5
S_4				0

DISTANCE MATRIX

METHODS SUCH AS NEIGHBOR JOINING

INFERRED TREE

•From Tandy Warnow 2004

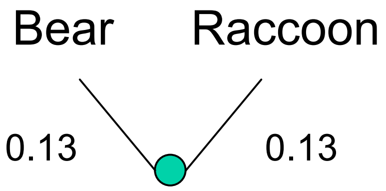
Distance Based Methods

- UPGMA algorithm
  (Michener & Sokal 1957)
- ME algorithm
  (Rzhetsky & Nei 1993)
- NJ algorithm
  (Saitou & Nei 1987)

UPGMA algorithm

1. AGGCCATGAATTAAGAATAA
2. AGCCCATGGATAAAGAGTAA
3. AGGACATGAATTAAGAATAA
4. AAGCCAAGAATTACGAATAA

D_{ij}	Bear	Raccoon	Weasel	Seal
Bear	-	**0.26**	0.34	0.29
Raccoon		-	0.42	0.44
Weasel			-	0.44
Seal				-



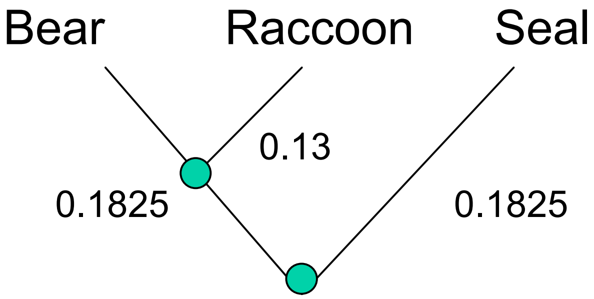
1. Pick smallest entry D_{ij}
2. Join the two intersecting species and assign branch lengths $D_{ij}/2$ to each of the nodes
3. Compute new distances to the other species using arithmetic means

$$D_{W(BR)} = \frac{D_{WB} + D_{WR}}{2} = \frac{0.34 + 0.42}{2} = 0.38$$

$$D_{S(BR)} = \frac{D_{SB} + D_{SR}}{2} = \frac{0.29 + 0.44}{2} = 0.365$$

UPGMA algorithm

D_{ij}	BR	Weasel	Seal
BR	-	0.38	0.365
Weasel		-	0.44
Seal			-

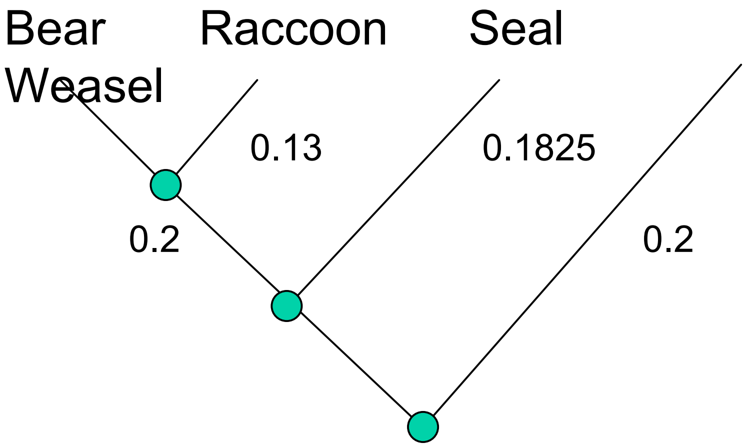


1. Pick smallest entry Dij
2. Join the two intersecting species and assign branch lengths Dij/2 to each of the nodes
3. Compute new distances to the other species using arithmetic means

$$D_{W(BRS)} = \frac{D_{WB} + D_{WR} + D_{WS}}{3} = \frac{0.34 + 0.42 + 0.44}{3} = 0.4$$

UPGMA algorithm

D_{ij}	BRS	Weasel
BRS	-	**0.4**
Weasel		-



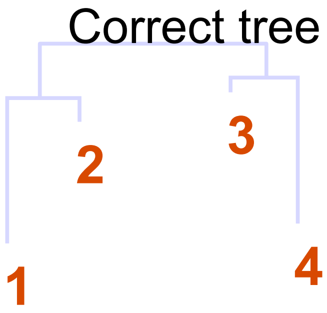
1. Pick smallest entry Dij.

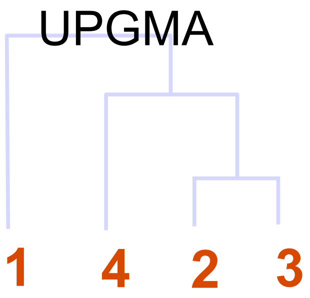
2. Join the two intersecting species and assign branch lengths Dij/2 to each of the nodes.

3. Done!

Neighbor Joining

- Goal
  - Join closest ***neighbors*** (nodes with same parent) in tree
  - Avoids problem with UPGMA when rates of change differ
  - Closest leaves are not neighbors in correct tree but are joined first by UPGMA
- Assumptions
  - Rate of change can differ
  - Branch lengths for tree are ***additive***

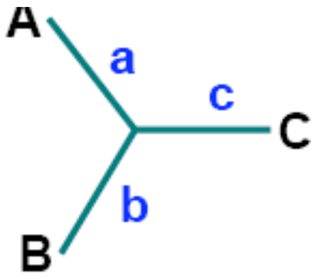




Neighbor Joining

- Calculating branch length after join (additive tree)

	A	B	C
A	—	$d_{A,B}$	$d_{A,C}$
B		—	$d_{B,C}$
C			—



- Simple algebra shows
  - Given
    - $d_{A,B} = a + b$
    - $d_{A,C} = a + c$
    - $d_{B,C} = b + c$
  - We can calculate
    - $a = \frac{1}{2}(d_{A,B} + d_{A,C} - d_{B,C})$
    - $b = \frac{1}{2}(d_{A,B} + d_{B,C} - d_{A,C})$
    - $c = \frac{1}{2}(d_{B,C} + d_{A,C} - d_{A,B})$

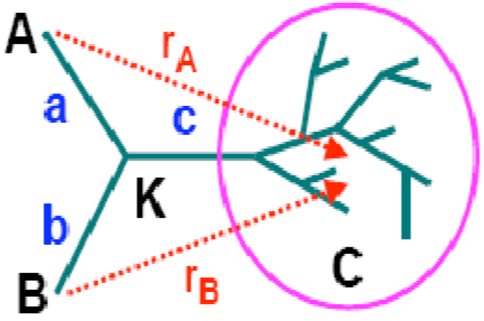
Neighbor Joining

- Basic principle for neighbor joining algorithm
  - Simply treat all other nodes as C, and treat distance to C as r.

	A	B	C
A	—	$d_{A,B}$	$d_{A,C}$
B		—	$d_{B,C}$
C			—

r_A

r_B



- Replace distance to C
  - Use normalized divergence r_A, r_B(~avg. distance to nodes)
- $a = ½ (d_{A,B} + d_{A,C} – d_{B,C}) \rightarrow ½ (d_{A,B} + r_A – r_B)$
- $b = ½ (d_{A,B} + d_{B,C} – d_{A,C}) \rightarrow ½ (d_{A,B} + r_B – r_A)$
- $c = ½ (d_{B,C} + d_{A,C} – d_{A,B}) \rightarrow ½ (d_{B,C} + d_{A,C} – d_{A,B})$

Neighbor Joining

- Approach
  - To find closest pair of neighbors

    Reduce branch length for a node by the average distance of the node from all other nodes

    Find smallest distance between nodes after reduction.
- Definitions

  For all pairs of nodes A & B in set of all nodes L, let

  $d_{A,B}$ = distance between A,B

  $R_X = \Sigma\, d_{X,N}$ where $N \in L$ (total distance from X to all N)

  $r_X = R_X / (|L| - 2)$, where $|L|$ = # of nodes

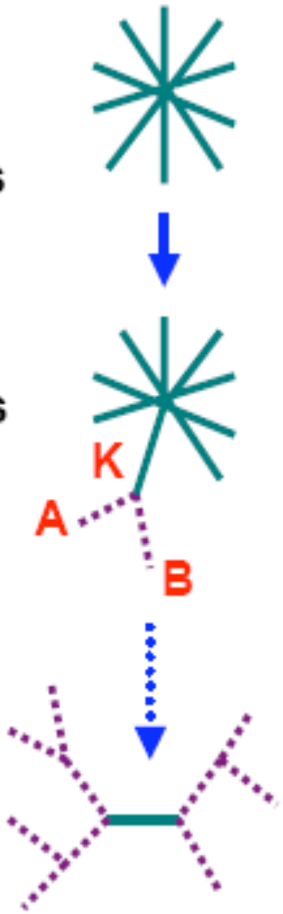
  (normalized divergence from X to all other nodes)

  $D_{A,B} = d_{A,B} - (r_A + r_B)$ (rate-corrected distance)
- Key points- 2 nodes with minimum D are always neighbors

Neighbor Joining

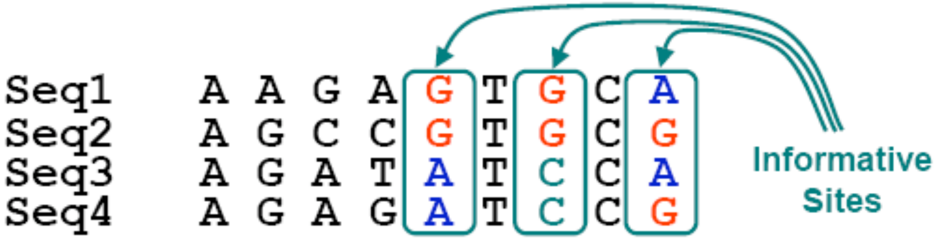
- Algorithm

1. Begin with star tree & all sequences as nodes in L
2. Find pair of nodes A & B ∈ L with minimum $D_{A,B}$
3. Create & insert new join (node K) w/ branch lengths
    - $d_{A,K} = ½ (d_{A,B} + r_A - r_B)$
    - $d_{B,K} = ½ (d_{A,B} + r_B - r_A)$
4. For remaining nodes C ∈ L, update distance to K as
    - $d_{K,C} = ½ (d_{A,C} + d_{B,C} - d_{A,B})$
5. Insert K and remove A, B from L
6. Repeat steps 2–5 until only two nodes left



Maximum parsimony

- Maximum parsimony
  - Minimize number of sequence change in tree
  - Assume fewest changes is most likely
- Informative site
  - Must have more than 2 different bases and each of them at least appears in two sequences.

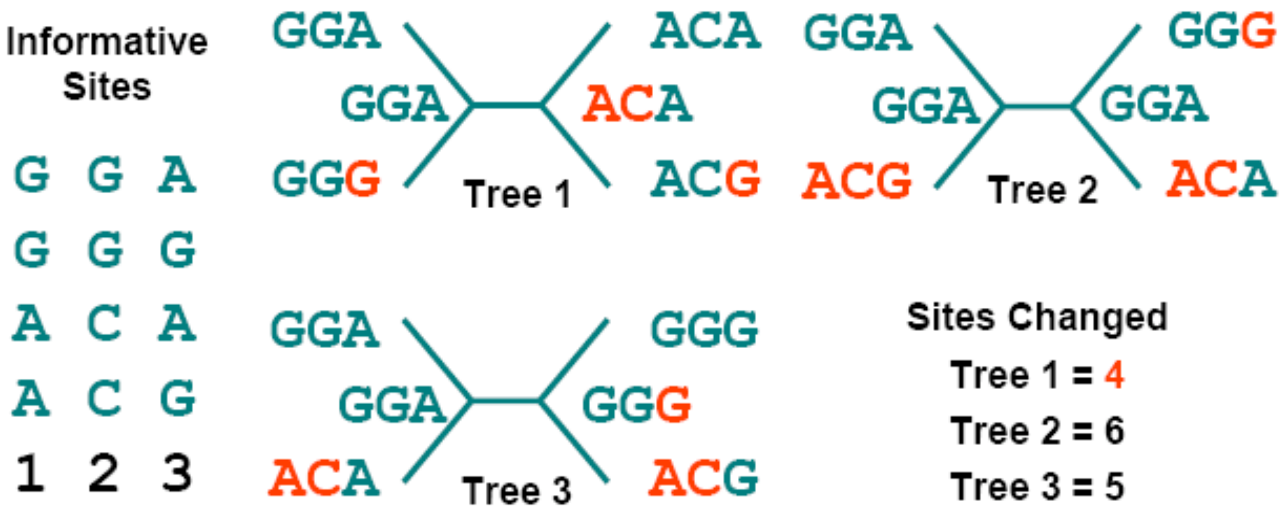


Seq1 A A G A G T G C A
Seq2 A G C C G T G C G
Seq3 A G A T A T C C A
Seq4 A G A G A T C C G

Informative Sites

Maximum parsimony

- Most parsimony tree
  - Tree with fewest total number of changes at informative sites.



Sites Changed
Tree 1 = 4
Tree 2 = 6
Tree 3 = 5

Maximum parsimony

Weakness:

- Misleading if rates of changes vary among branches
- long branch attraction which is random similarity due to long periods of divergence among ***some numbers*** of clades.

Maximum Likelihood

- Goal
  - Given the probability P(x|y,t) for a sequence y to evolve (mutant) to sequence x along an edge of length t (time)
  - Find tree that has highest probability of taking place
- Mutation probabilities
  - Bases: Jukes-Cantor model; Kimura two parameters model
  - Amino acids: PAM; BLOSUM.
- Algorithm
  - Search over all tree topologies & sequences alignments
  - For each topology & assignment, search all branch lengths.
- Characteristics
  - Very computationally expensive

Robustness and reliability

- Bootstrapping is a statistical technique that can use random resampling of data to determine sampling error for tree topologies
- Bootstrapp proportions are not the same as confidence intervals. There is no simple mapping between bootstrap values and confidence intervals.

Computer Software for Phylogenetics

- **PHYLIP** is a free package that includes 30 programs that compute various phylogenetic algorithms on different kinds of data.
- The **GCG** package (available at most research institutions) contains a full set of programs for phylogenetic analysis including simple distance-based clustering and the complex **cladistic** analysis program **PAUP** (**P**hylogenetic **A**nalysis **U**sing **P**arsimony)
- **CLUSTALW** is a multiple alignment program that includes the ability to create tress based on **Neighbor Joining.**
- **MrBayes** is a program for **Bayesian inference** of phylogeny using Markov Chain Monte Carlo methods.
- **MEGA** is an integrated tool for automatic and manual sequence alignment, inferring **phylogenetic** trees, mining web-based databases, estimating rates of molecular evolution, and testing evolutionary hypotheses.

Thanks