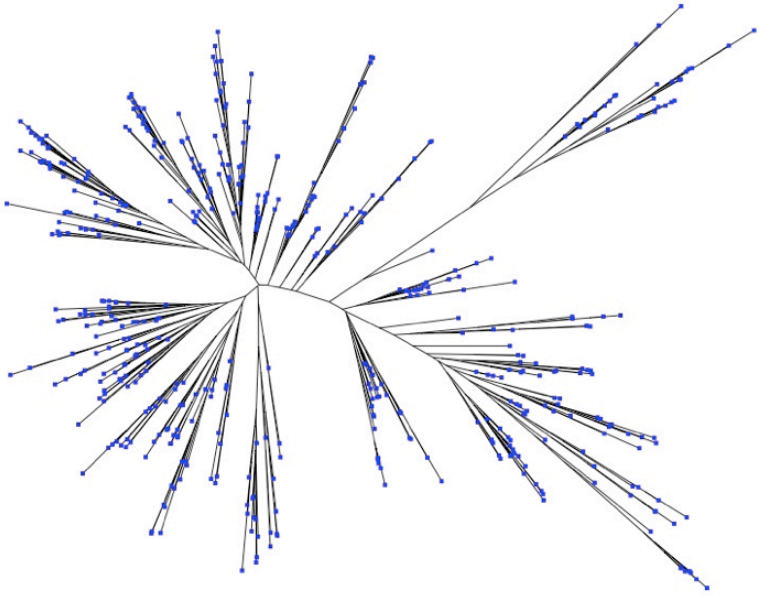
DIMACS Tutorial on Phylogenetic Trees and Rapidly Evolving Pathogens



Thanks to the DIMACS Staff

- Linda Casals
- Walter Morris
- Nicole Clark

Tutorial Outline

- Day 1: Introduction to Phylogenetic Reconstruction
- Day 2: Applications to Rapidly Evolving Pathogens

Tutorial Outline

- Day 1: Introduction to Phylogenetic Reconstruction
  - Overview: Katherine St. John, CUNY
  - Parsimony Reconstruction of Phylogenetic Trees: Trevor Bruen, McGill University
  - Using Maximum Likelihood for Phylogenetic Tree Reconstruction: Rachel Bevan, McGill University
  - Hands-on Session: Constructing Trees Katherine St. John
- Day 2: Applications to Rapidly Evolving Pathogens

Tutorial Outline

- Day 1: Intro to Phylogenetic Reconstruction
- Day 2: Applications to Rapidly Evolving Pathogens
  - Statistical Overview: Alexei Drummond, University of Auckland
  - Tricks for trees: Having reconstructed trees, what can we do with them? Mike Steel, University of Canterbury
  - Hands-on Session: Katherine St. John

Overview Outline

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- Constructing Trees

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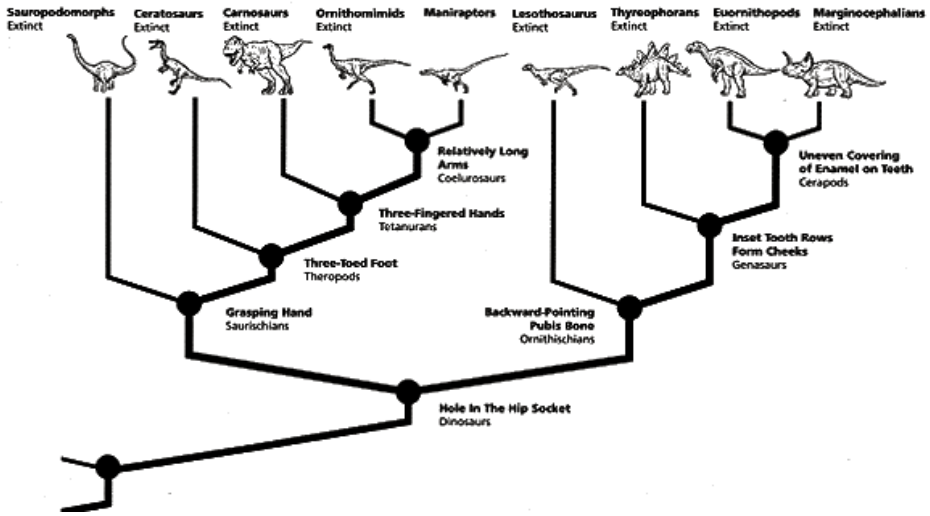
Goal: Reconstruct the Evolutionary History



(www.amnh.org/education/teacherguides/dinosaurs)

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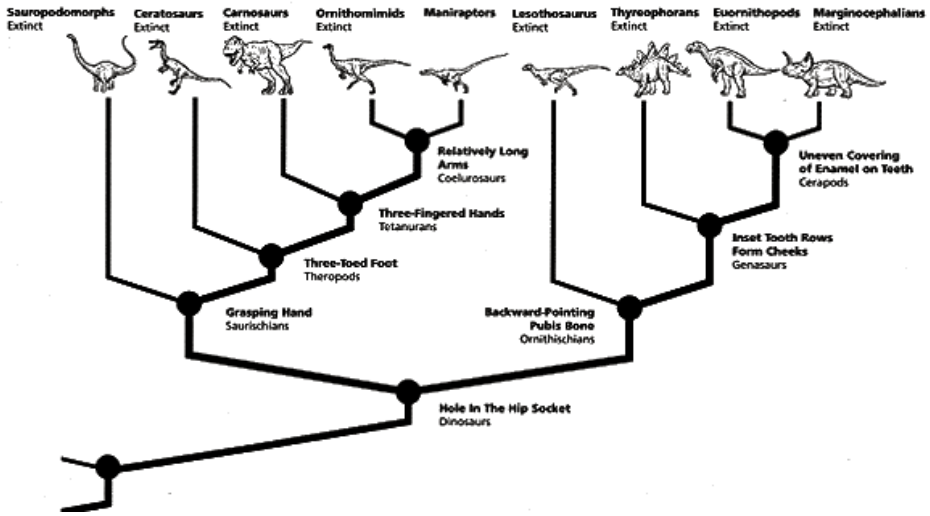

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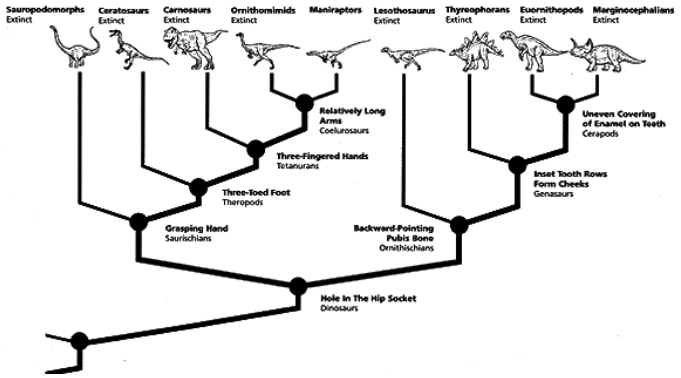
The evolutionary process not only determines relationships among taxa, but allows prediction of structural, physiological, and biochemical properties.

Process for Reconstruction: Input Data

Start with information about the taxa. For example:

Morphological
Characters



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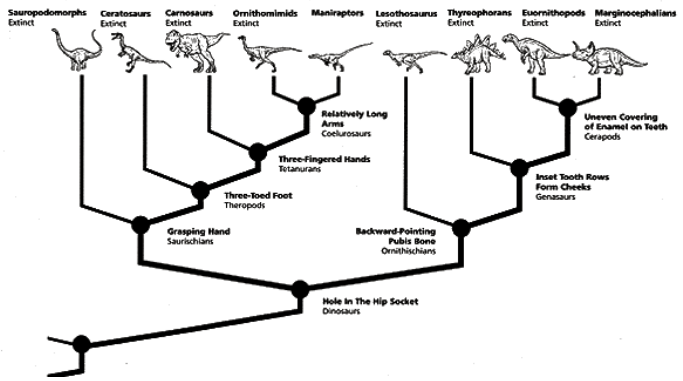


Biomolecular Sequences

A	GTTAGAAGGCGGCCAGCGAC. . .
B	CATTTGTCCTAACTTGACGG. . .
C	CAAGAGGCCACTGCAGAATC. . .
D	CCGACTTCCAACCTCATGCG. . .
E	ATGGGGCACGATGGATATCG. . .
F	TACAAATACGCGCAAGTTCG. . .

(Other: molecular markers (ie SNPs), gene order, etc.)

Process for Reconstruction

Process for Reconstruction

Input

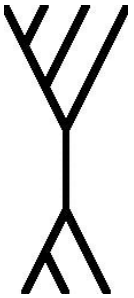
Data

A	GTTAGAAGGC...
B	CATTTGTCCT...
C	CAAGAGGCCA...
D	CCGACTTCCA...
E	ATGGGGCACG...
F	TACAAATACG...

Process for Reconstruction

Input Data			Reconstruction Algorithms
A	GTTAGAAGGC...	$\longrightarrow$	Maximum Parsimony
B	CATTTGTCCT...		Maximum Likelihood
C	CAAGAGGCCA...		Distance Methods: NJ,
D	CCGACTTCCA...		Quartet-Based,
E	ATGGGGCACG...		Fast Convering,
F	TACAAATACG...		⋮

Process for Reconstruction

Input Data		Reconstruction Algorithms	Output Tree
A	GTTAGAAGGC...	Maximum Parsimony	
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- multiple sequence alignment
- origin of virus and bacteria strains

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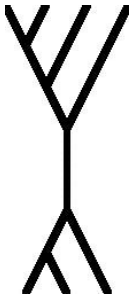
Output Tree



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- More on these later today...

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  - drug design: predicting function via similarity
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  - use as priors or starting points for expensive searches

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    (use clever ways to limit the number of trees checked, while still sampling much of "tree-space")
  - Polynomial-time methods, often based on the distance between taxa

Distance-Based Methods

- These methods calculate the distance between taxa:

	B	D	A	C	F	E
B	0	0.496505	0.496505	0.444519	0.375798	0.268166
D	0.496505	0	0.496505	0.375798	0.275673	0.279728
A	0.496505	0.496505	0	0.362124	0.323812	0.496505
C	0.444519	0.375798	0.362124	0	0.496505	0.496505
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- One way to calculate distance is to take differences divided by the length (the normalized Hamming distance).

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- UPGMA ("Unweighted Pair Group Method with Arithmetic Mean") (Sneath & Snokal '73) similarly clusters close taxa, assuming the rate of evolution is the same across lineages.
- Quartet-based methods that decide the topology for every 4 taxa and then assemble them to form a tree (Berry *et al.* 1999, 2000, 2001).

Other Distance-Based Methods

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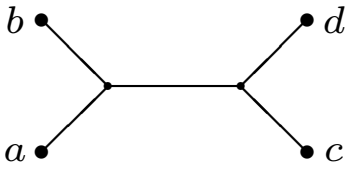
  - Joining the leaves with the minimal distance does not suffice, so subtract the averaged distances to compensate for long edges.
  - Experimental work shows that NJ trees are reasonably accurate, given a rate of evolution is neither too low nor too high.

Quartet Methods

- A *quartet* is an unrooted binary tree on four taxa:



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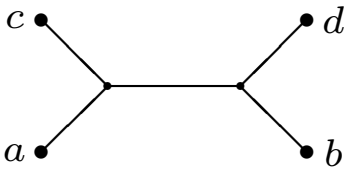

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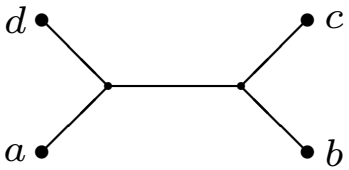

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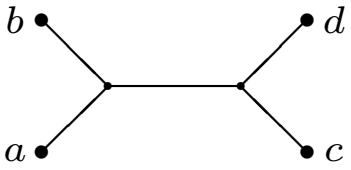

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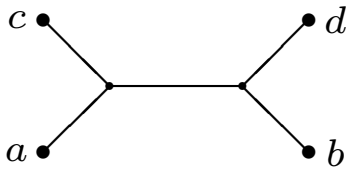

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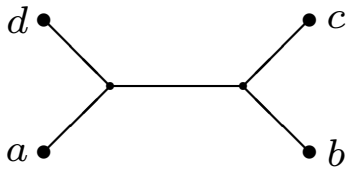

$\{ad|bc\}$

- Let $Q(T) =$ all quartets that agree with T.
  [Erdős *et al.* 1997]: T can be reconstructed from $Q(T)$ in polynomial time.

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  - There are $\Theta(n^4)$ quartets, giving $\Omega(n^4)$ running time.
  - In practice, the input quality is insufficient to ensure that all quartets are accurately inferred.
  - Quartet methods have to handle incorrect quartets.

Popular Quartet Methods

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- Quartet Puzzling [Strimmer & von Haeseler 1996]: "Order taxa randomly, greedily add edges, repeat 1000 times." Output majority tree.

  Most popular with biologists.

Constructing Networks

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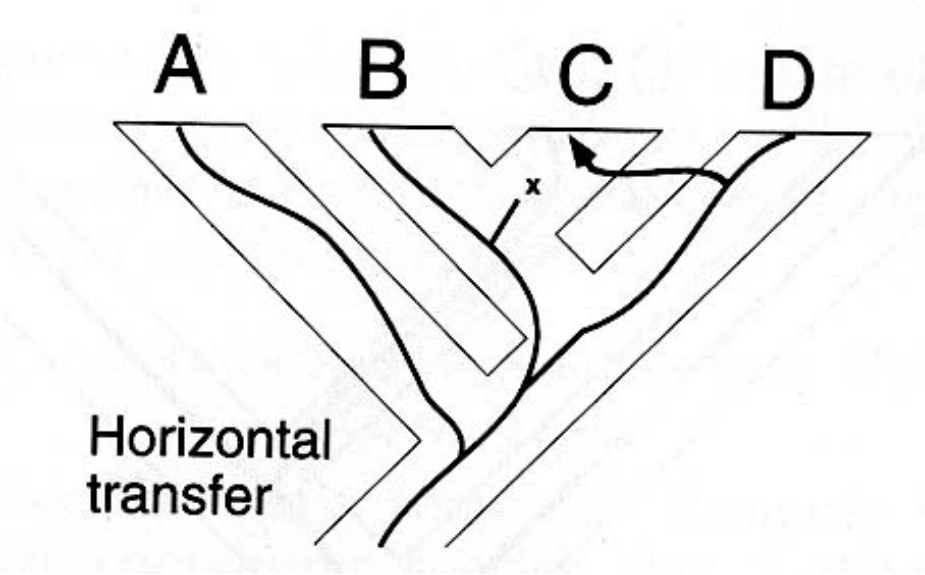

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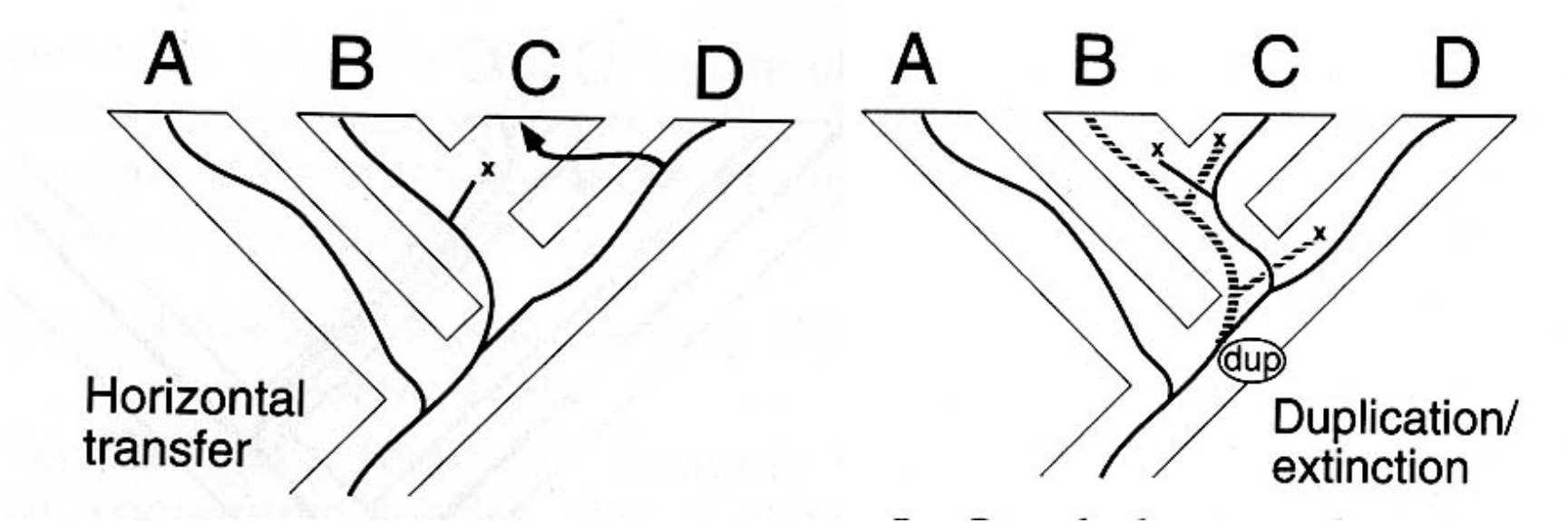

(from W.P. Maddison, *Systematic Biology* '97)

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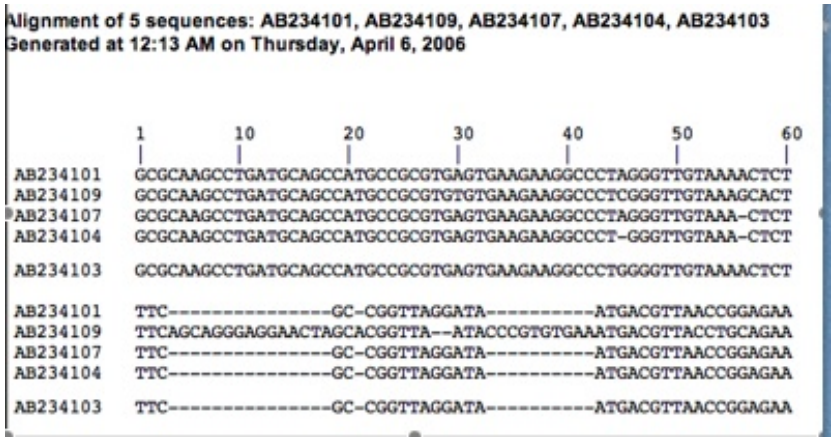
- TCS (Posada & Crandall '01) estimates gene phylogenies based on statistical parsimony method.

Input to Reconstruction Algorithms

- Almost all assume that the data is aligned:



(Alignment of bacterial genes by Geneious (Drummond '06).)

- Many assume corrections have been made for the underlying model of evolution.

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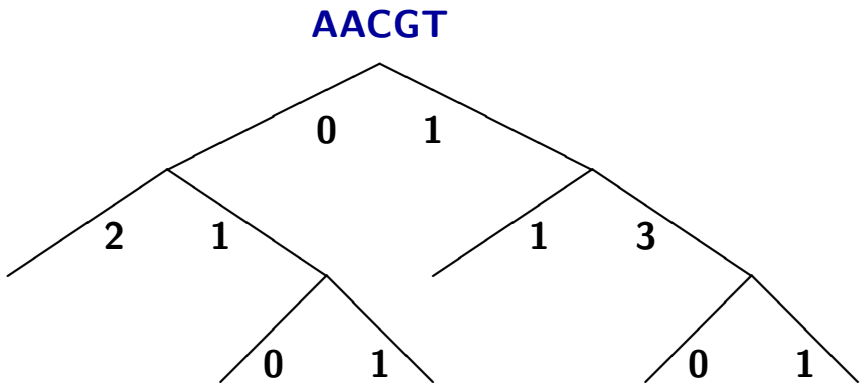

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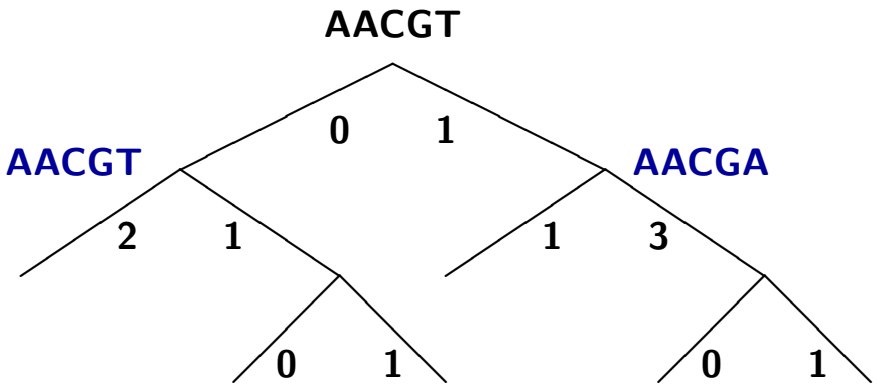

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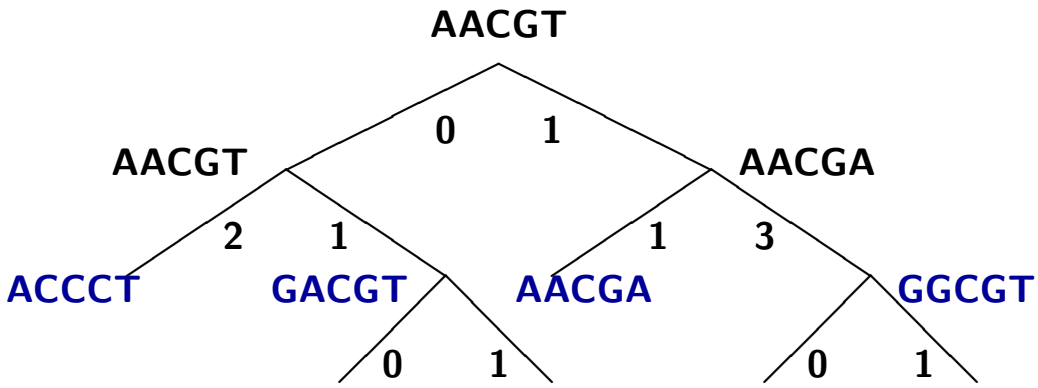

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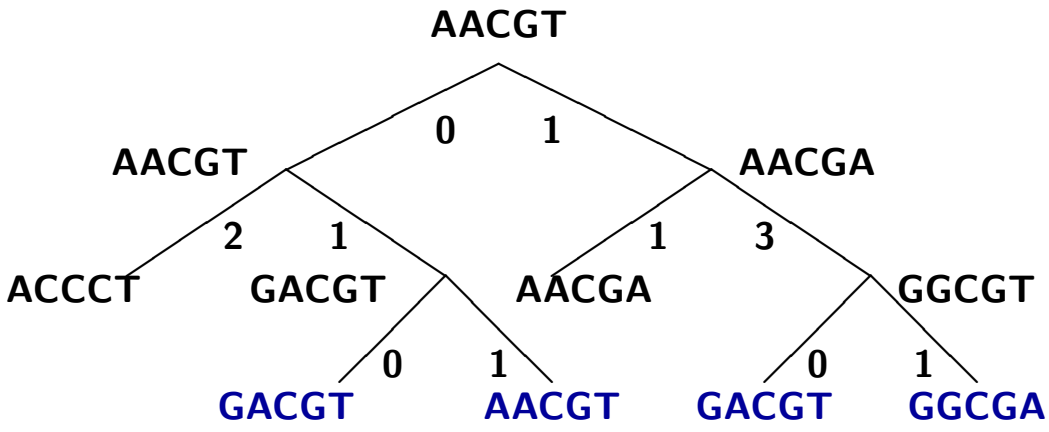

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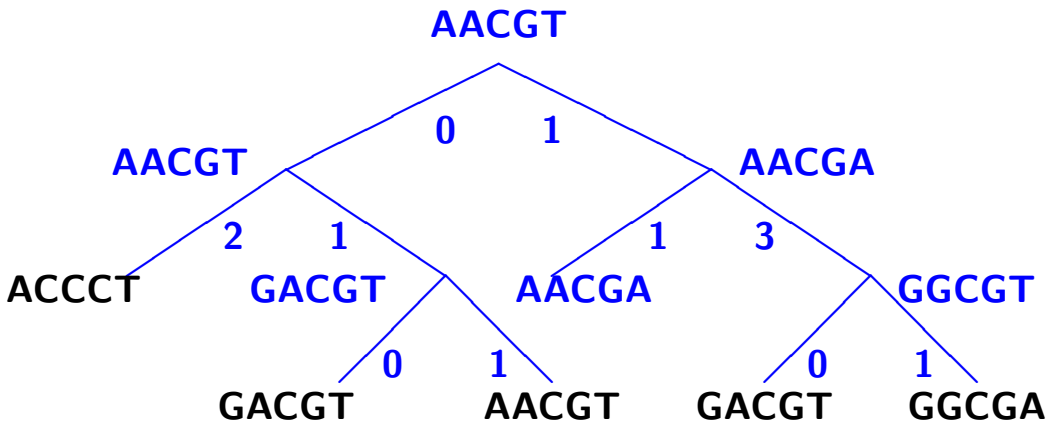

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{ACCCT, GACGT, AACGT, GACGT, GGCGA}

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- A DNA sequence (a string over $\{A, C, T, G\}$) at the root evolves down a rooted binary tree T.
- The assumptions of the model are:
  1. the sites (i.e., the positions within the sequences) evolve independently and identically
  2. if a site changes state it changes with equal probability to each of the remaining states, and
  3. the number of changes of each site on an edge e is a Poisson random variable with expectation $\lambda(e)$ (this is also called the "length" of the edge e).

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- Indirectly, via assumptions on the data or by inputting data that has been corrected under a certain model.

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- Simulation is used instead to evaluate methods, given a model of evolution.

Simulation Studies

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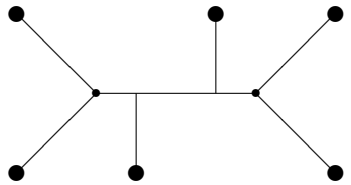

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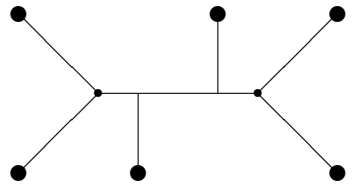

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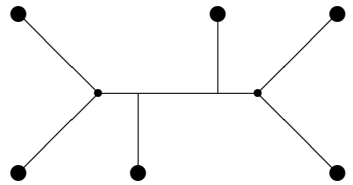

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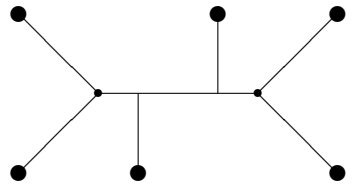

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  - assign weights or branch lengths to the shape.

Simulating Data: Evolving Sequences

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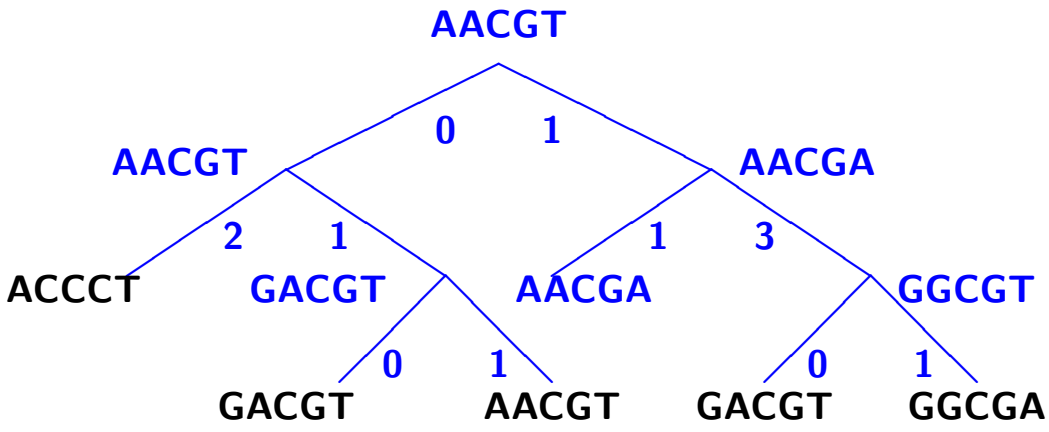
- A DNA sequence (a string over $\{A, C, T, G\}$) at the root evolves down a rooted binary tree T.



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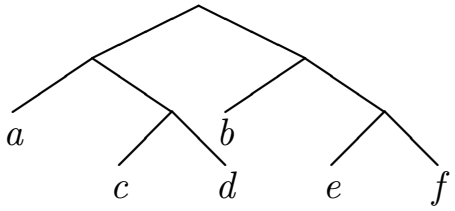
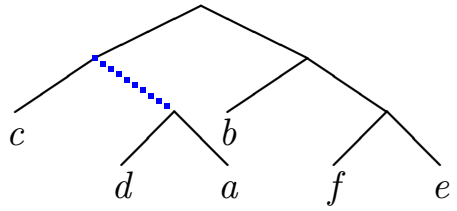
$$\frac{\text{False Positives} + \text{False Negatives}}{\text{total edges}}$$

- 



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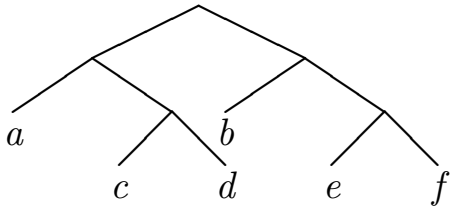
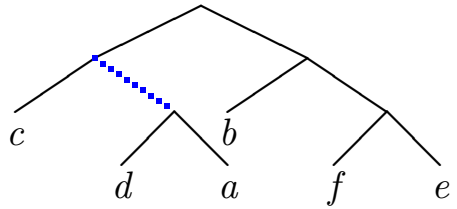
- 



  If there are many possible answers, choose the one with the best *parsimony score*: the sum of the number of site changes acrosss the edges in the tree.

Talk Outline

- Overview
- Constructing Trees
- Constructing Networks
- Comparing Reconstruction Methods
- Evaluating the Results

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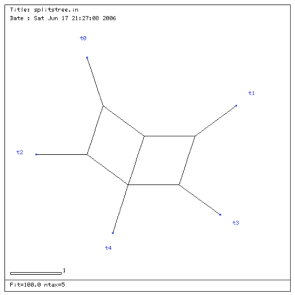
Analyzing & Visualizing Sets of Trees

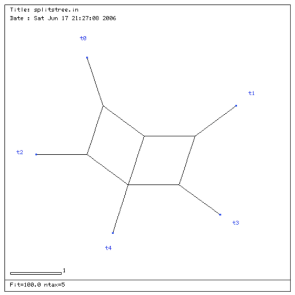
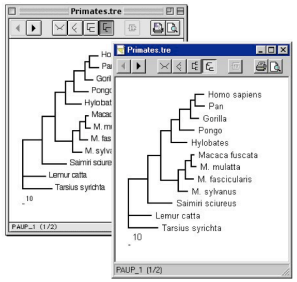
- Visualizing single trees
- Comparing pairs of trees
- Handling Large Sets of Trees

Visualizing Single or Pairs of Trees

- 

SplitsTree (Huson *et al.*)

Visualizing Single or Pairs of Trees

-  SplitsTree (Huson *et al.*)
- 

TreeView (Page *et al.*)

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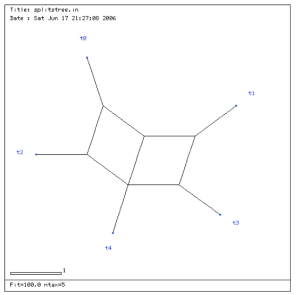
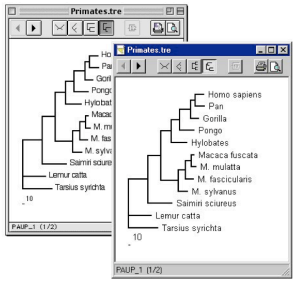
-  SplitsTree (Huson *et al.*)
- 

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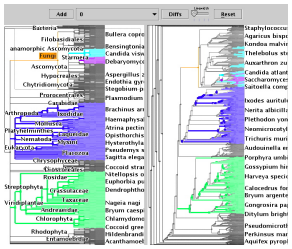
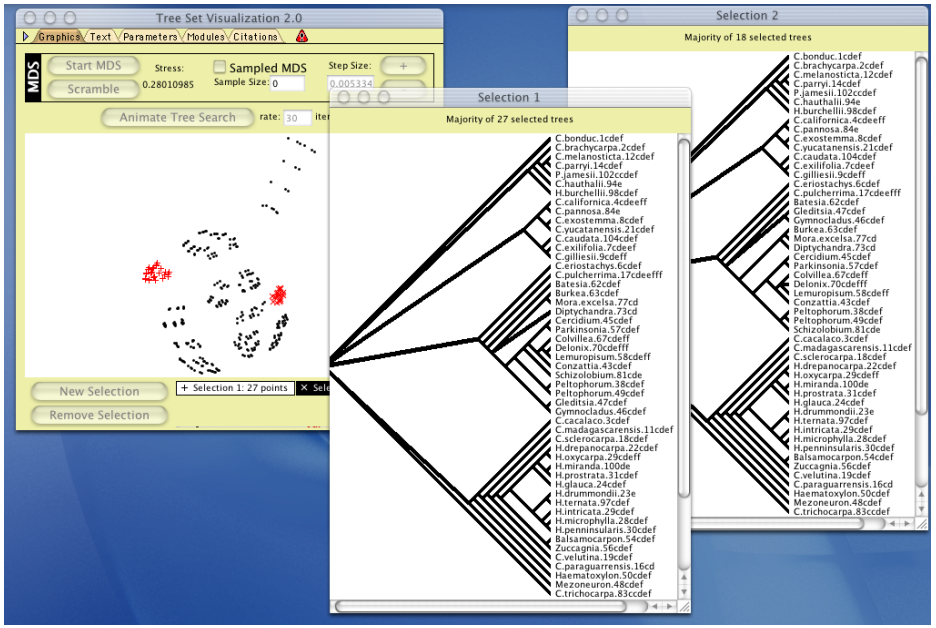
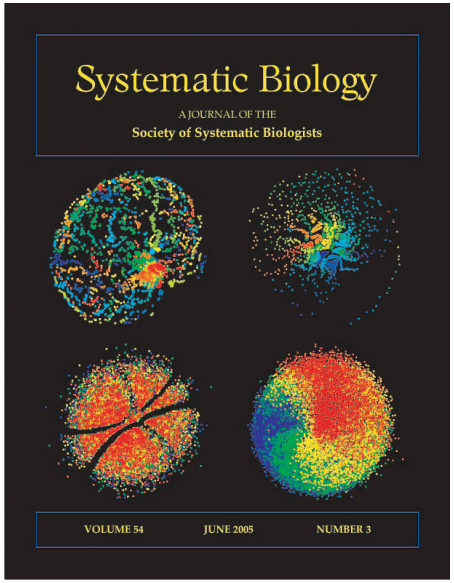
-  TLreeJuxtaposer (Munzner *et al.*)

Analyzing & Visualizing Sets of Trees



Amenta & Klingner, InfoVis '02



Hillis, Heath, &
St. John, Sys. Biol. '05

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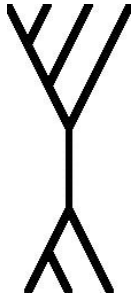
Reconstruction Algorithms

Maximum Parsimony
Maximum Likelihood
Distance Methods: NJ,
Quartet-Based,
Fast Convering,
⋮

→

Output Tree



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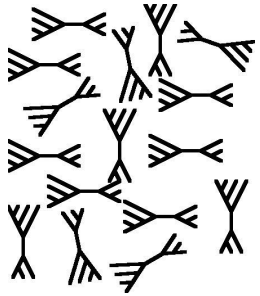
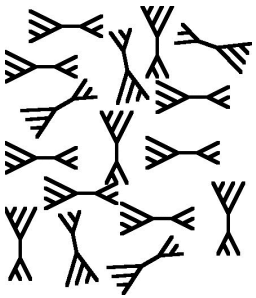


Summarizing Trees

Input Trees



→

Consensus Method

Strict Consensus
Majority-rule

→

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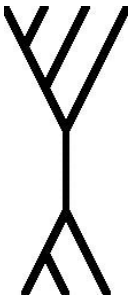
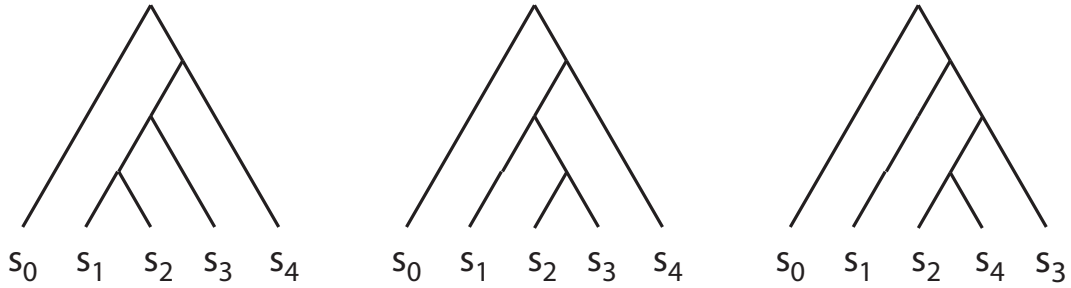


Strict Consensus Tree

Input trees



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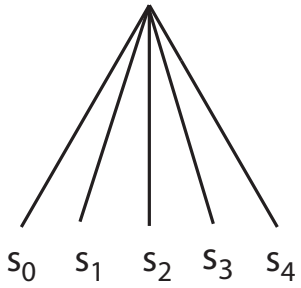

$s_1 s_2 \mid s_0 s_3 s_4$ $s_2 s_3 \mid s_0 s_1 s_4$ $s_2 s_4 \mid s_0 s_1 s_3$

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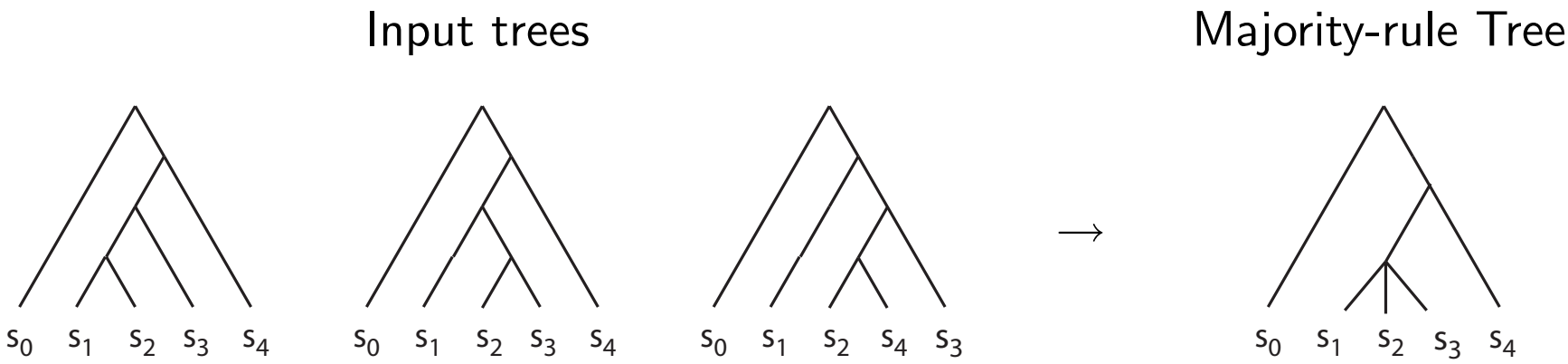
$O(nt)$ running time: Day '85.

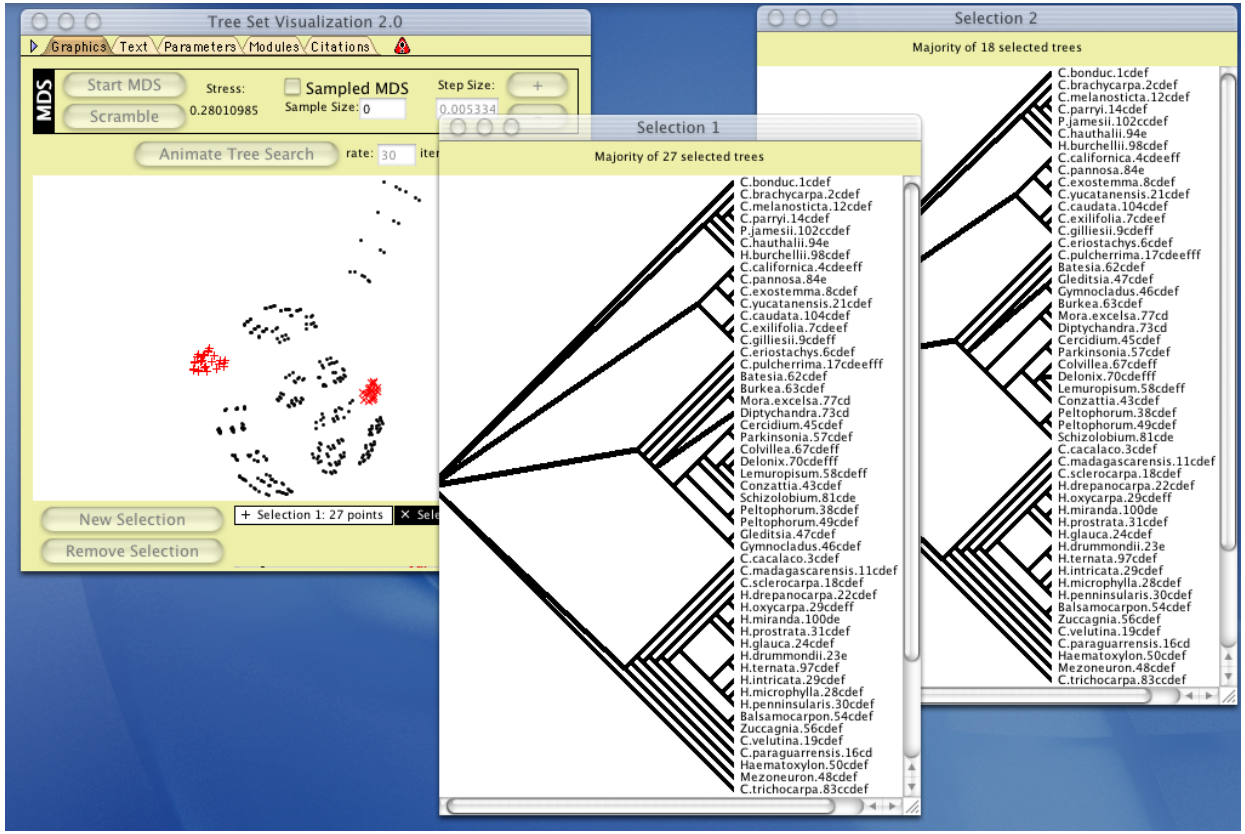
Majority-rule Tree



Includes splits found in a majority of trees
Can be $2/3$ majority, etc.

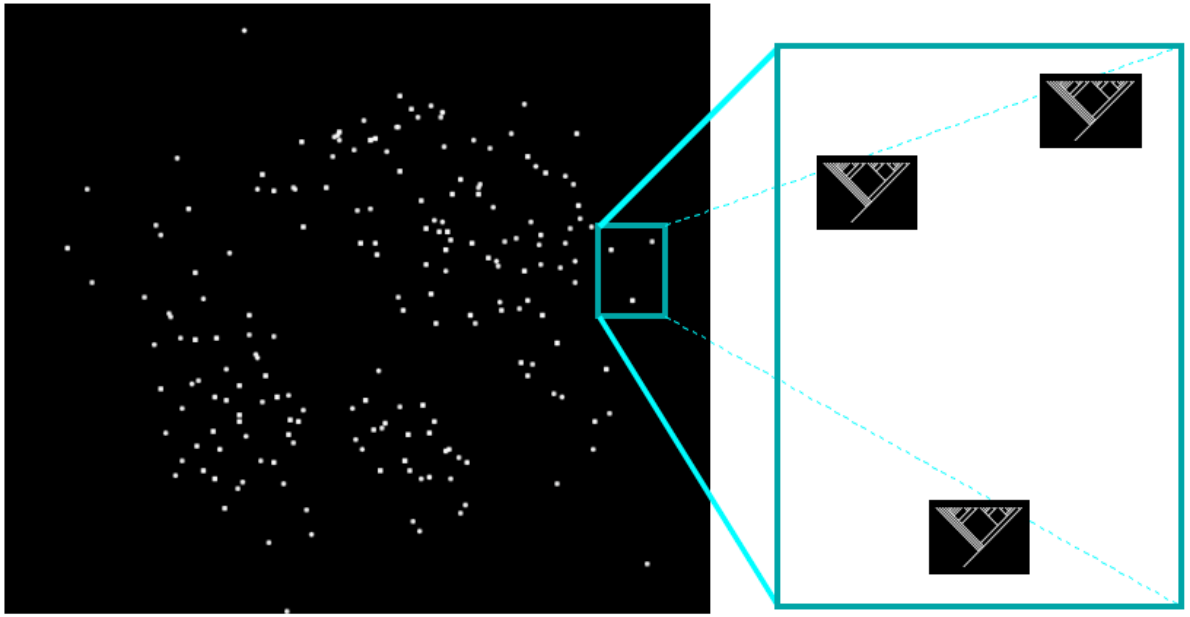
$O(nt)$ randomized running time: Amenta, Clark, & S. '03.

Visualizing Sets of Trees



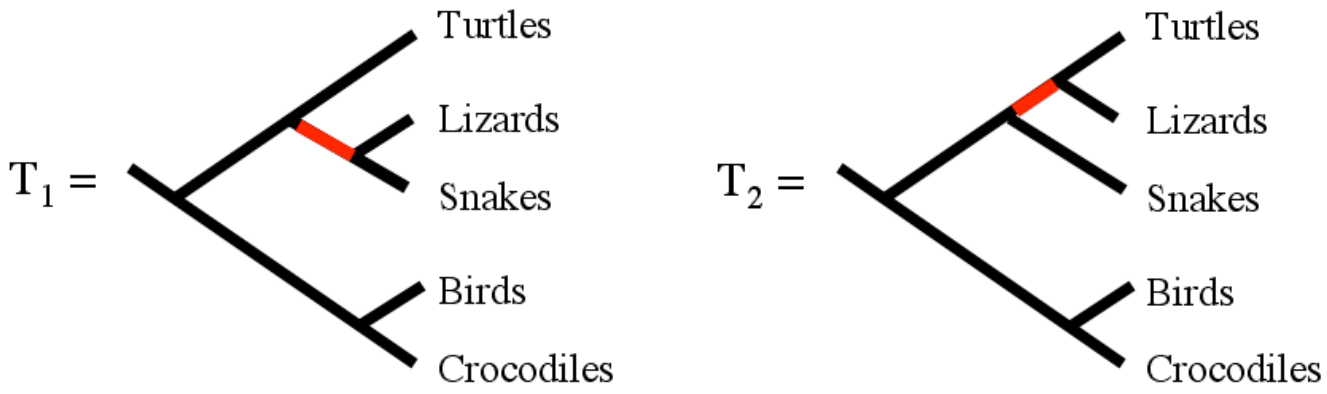
Efficiency is important for real-time visualization.

Multidimensional Scaling (MDS)



- Each point represents a tree.
- Points for similar trees are displayed near one another.

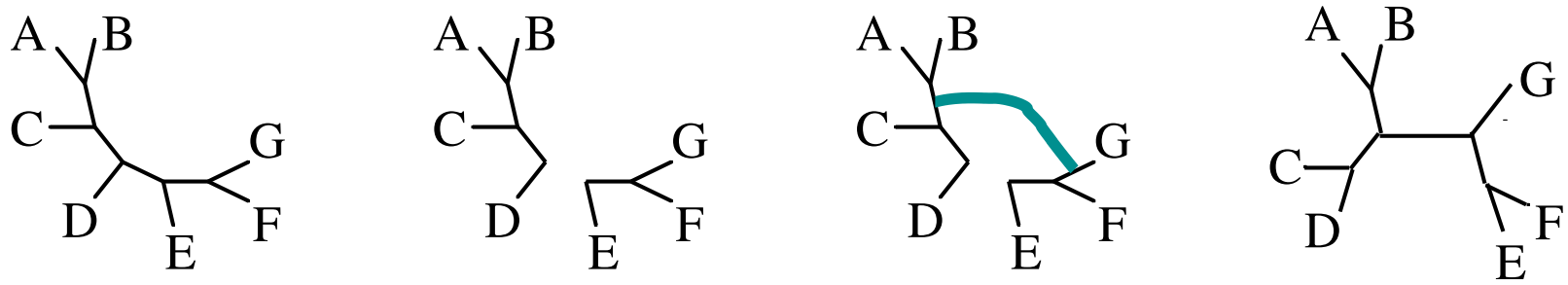
Distances Between Trees



- Robinson-Foulds distance: # of edges that occur in only one tree.
- Calculate in $O(n)$ time using Day's Algorithm (1985).
- Extends naturally to weighted trees.

Other Natural Metrics

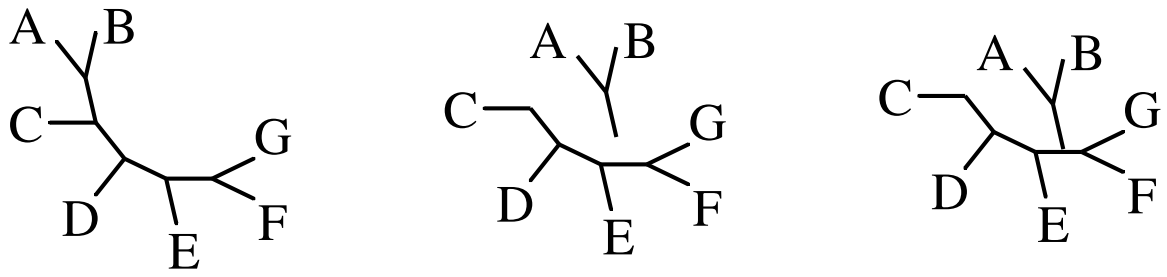
- Tree-bisection-reconnect (TBR):



- TBR is NP-hard. (Allen & Steel '01)
- Many attempts, but no approximations with provable bounds.

Other Natural Metrics

- Subtree-prune-regraft (SPR):



- NP-hard for rooted trees (Bordewich & Semple '05).
- 5-approximation for rooted trees (Bonet, Amenta, Mahindru, & S.).

Summary

- Constructing Trees
- Constructing Networks
- Comparing Reconstruction Methods:
- Evaluating the Results:

Tutorial Outline

- Day 1: Introduction to Phylogenetic Reconstruction
  - Overview: Katherine St. John, CUNY
  - Parsimony Reconstruction of Phylogenetic Trees: Trevor Bruen, McGill University
  - Using Maximum Likelihood for Phylogenetic Tree Reconstruction: Rachel Bevan, McGill University
  - Hands-on Session: Constructing Trees Katherine St. John
- Day 2: Applications to Rapidly Evolving Pathogens

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- Day 2: Applications to Rapidly Evolving Pathogens
  - Statistical Overview: Alexei Drummond, University of Auckland
  - Tricks for trees: Having reconstructed trees, what can we do with them? Mike Steel, University of Canterbury
  - Hands-on Session: Katherine St. John