# *The Disk-Covering Method for Tree Reconstruction*

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*Bonn, 1998*

# *Report on joint work with:*

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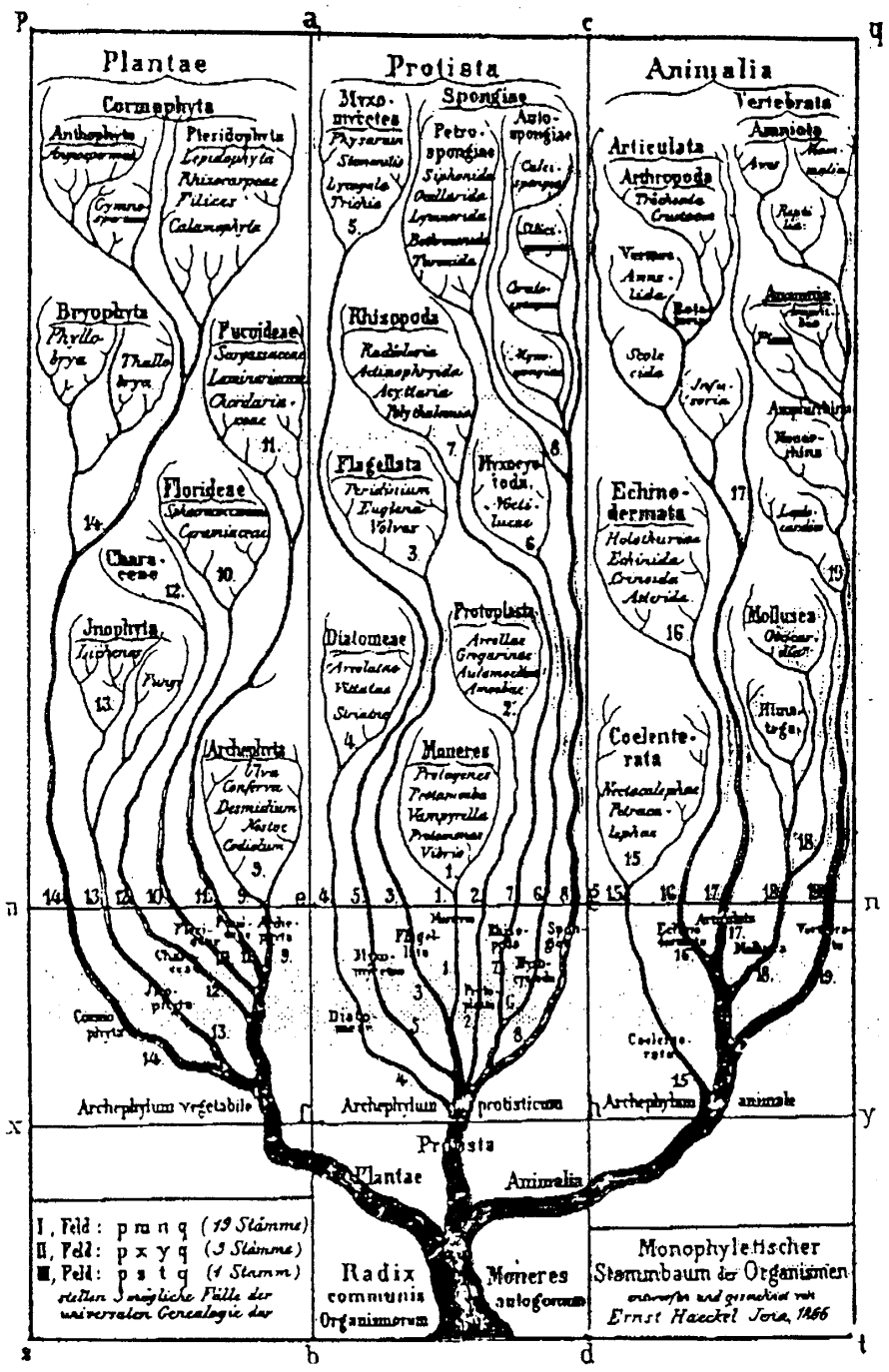
# *References*

- D.H. Huson, S. Nettles, L. Parida, T.J. Warnow and S. Yooseph. The Disk-Covering Method for Tree Reconstruction. In: R. Battiti and A.A. Bertossi eds., Proceedings of *Algorithms and Experiments* (ALEX'98) (Trento, Italy, Feb. 9–11, 1998), 62-75, 1998.

- D.H. Huson and K. Rice and S. Nettles and T.J. Warnow and S. Yooseph. Hybrid Tree Construction Methods. Submitted to: *Workshop on Algorithms Engineering* (WAE'98).

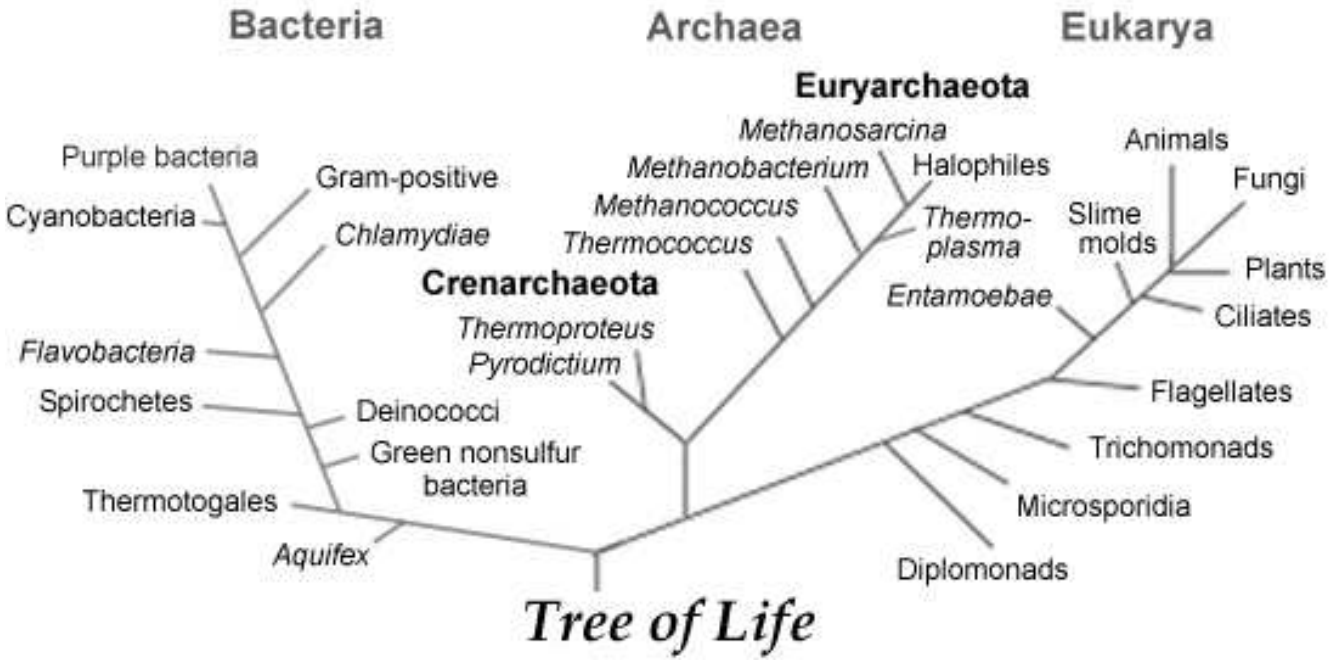
- D.H. Huson, S. Nettles and T.J. Warnow. Obtaining highly accurate topology and evolutionary estimates of evolutionary trees from very short sequences. Submitted to: *Recomb'99*.

# *The Tree of Life*




The first phylogenetic tree of life, Ernst Haeckel (1866)

# *The Tree of Life*




A modern view of the tree of life

# *Tree Reconstruction Methods*

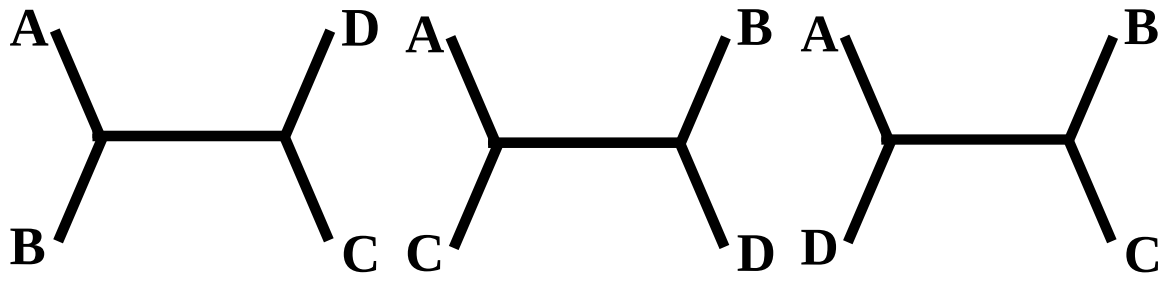
- Maximum Parsimony
  - Popular sequence method
  - NP-hard Hamming distance Steiner tree problem, *most parsimonious tree*
  - Use heuristics
- Neighbor-Joining
  - Popular distance method
  - Successively "join" close pairs of *taxa*
- Buneman Tree
  - Distance-based method with nice mathematical properties, but low resolution
- 3-Approximation methods
  - Agarwala et al. SODA'96

# *Maximum Parsimony*

Find tree that explains data using a minimal number of *mutations*.

```
A: 0 1 0 1 1
B: 0 0 0 1 0
C: 0 1 0 1 1
D: 1 0 0 1 0
```

Determine tree topology and labeling of internal nodes:



# *New Variants of Neighbor-Joining*

- Bio-NJ
  - Improved version of the NJ algorithm based on a simple model of sequence data
  - Oliver Gascuel, 1997.
- Weighbor
  - Weighted Neighbor-Joining
  - W. Bruno, A. Halpern & N. D. Socci, 1998

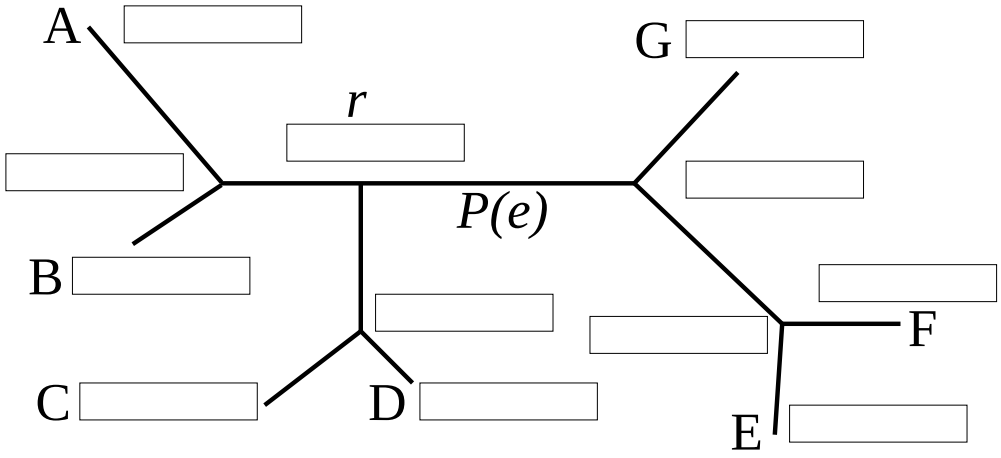
# *Experimental Simulation Studies*

- Choose model tree $T$ (e.g. inspired by biology)
- Choose model of evolution (e.g. Jukes-Cantor model)
- Evolve sequences along the model tree
- Apply tree reconstruction method $M$ to evolved sequences $S$
- Compare estimation $M(S)$ with model tree $T$ for topological accuracy

Software: ecat, seqgen, PAUP, Phylip. Our programs in C++, LEDA.

# *Jukes-Cantor Model of Evolution*

- Given a *model tree* $T$, with edge weights $P(e)$




- Interpret $P(e)$ as the probability of change at *any* given position in a sequence along the edge $e$

- 4-state characters, all transitions have equal probabilities, i.i.d.

- Fix a sequence length $k$. Choose a root $r$ and a random start sequence $S$ at $r$

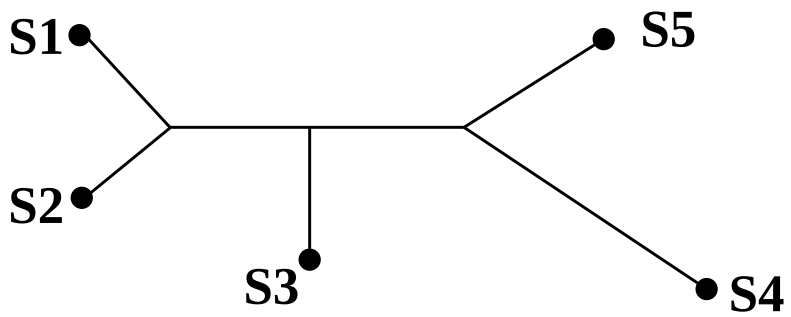
- Evolve sequences along the tree $T$, *Markov tree*.

# *Objective: Topological Accuracy*

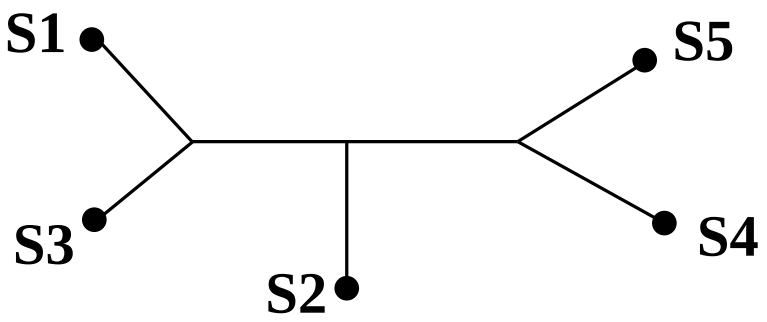
The main goal in biology is to correctly infer the *order* of speciation events, hence the objective is to minimize:

- *False positives*: wrongly inferred edges
- *False negatives*: missing edges

Model tree $T$:




Estimation $M(T)$:



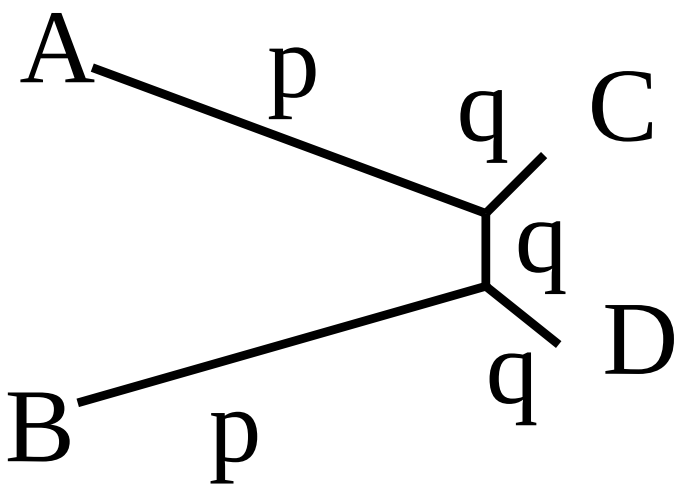

One false positive: $\{S_1, S_3\}$ vs. $\{S_2, S_4, S_5\}$

One false negative: $\{S_1, S_2\}$ vs. $\{S_3, S_4, S_5\}$

## *Statistical Consistency*

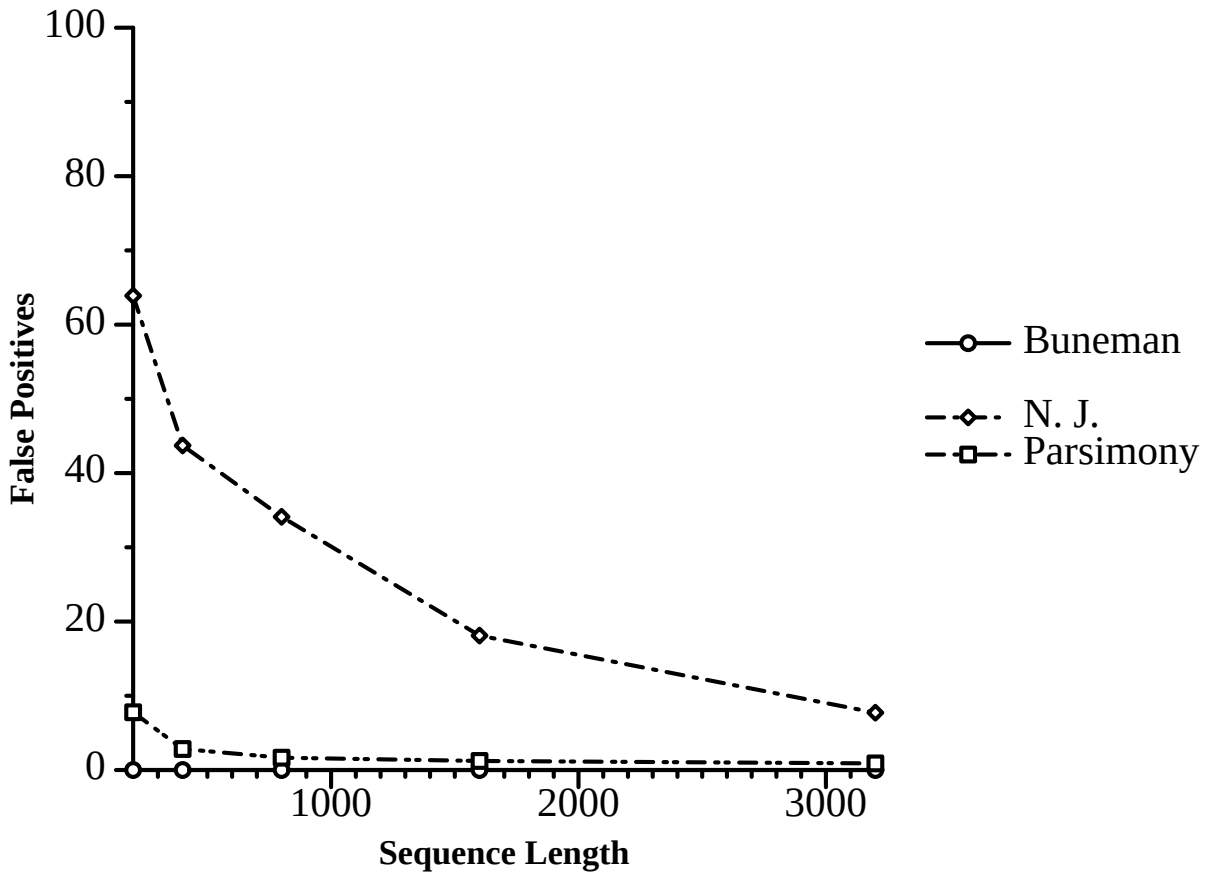
Given longer and longer sequences (i.e. better and better approximations of the tree distances), does the result of the method converge to the correct tree?

- Distance methods: yes
- Maximum Parsimony: not always.



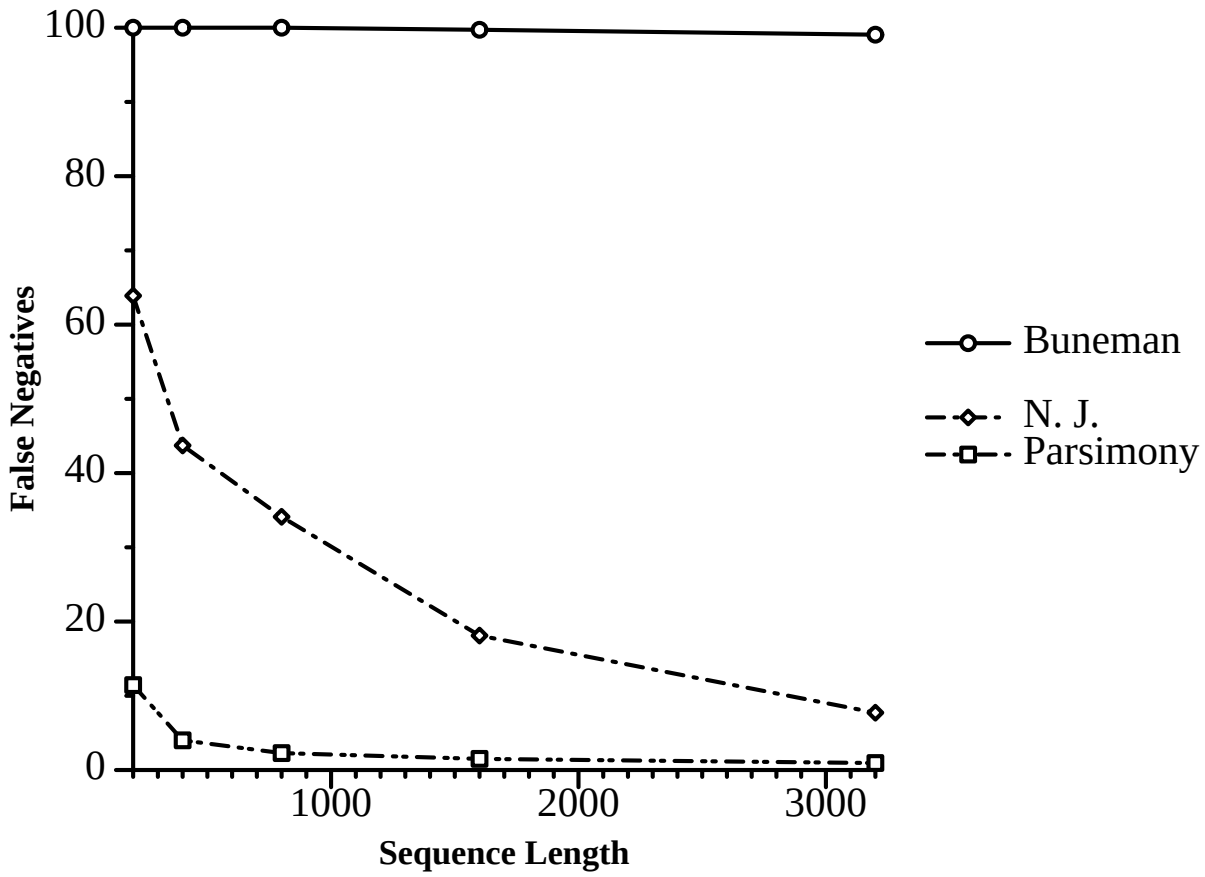

*Felsenstein-zone*

# *Comparison of False Positive Rates*



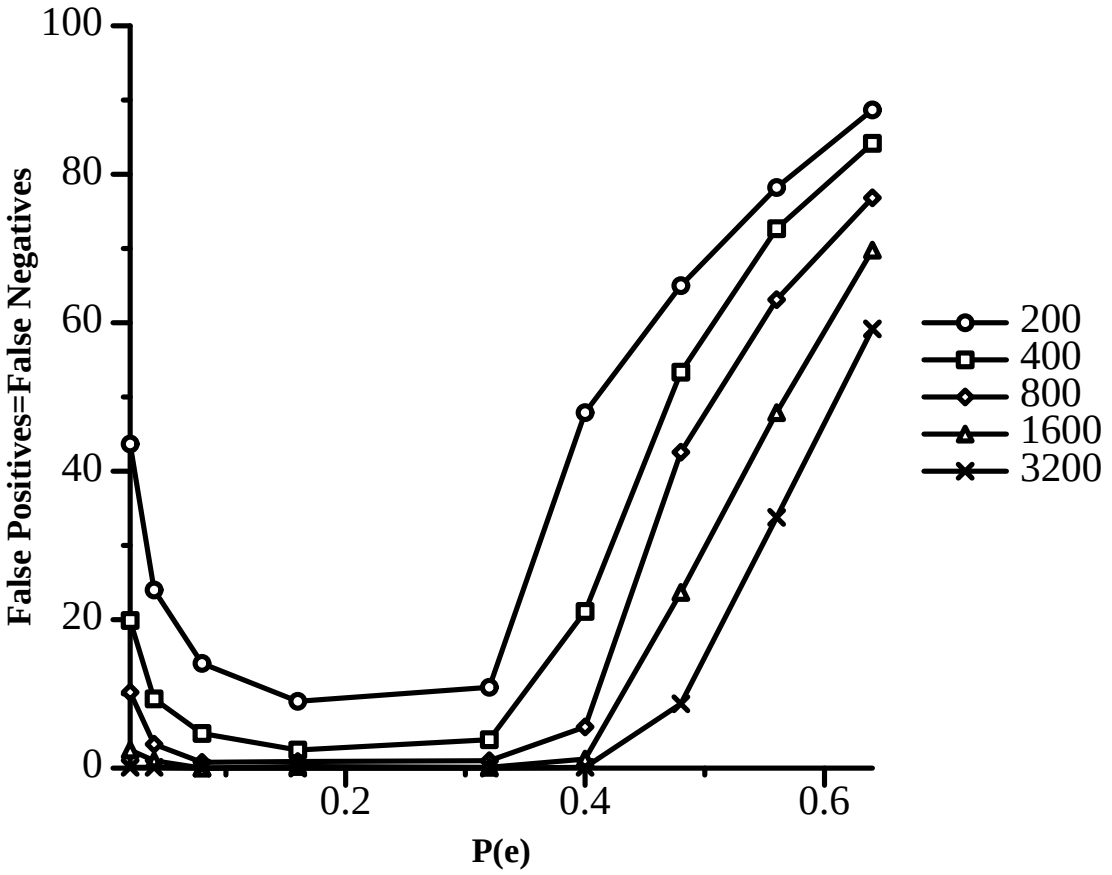

- sequence length vs. false positive rate
- 93 taxon tree (from 500 taxon *rbc*L dataset)
- maximum substitution probability $p(e)$ is 0.48
- 20 experiments per point

# *Comparison of False Negative Rates*




- sequence length vs. false negative rate
- 93 taxon tree (from 500 taxon *rbc*L dataset)
- maximum substitution probability $p(e)$ is 0.48
- 20 experiments per point

# *Performance of Neighbor-Joining*




P(e) vs. FP by Length

- 93 taxon tree (from 500 taxon *rbc*L dataset)
- maximum mutation probability $p(e)$ vs. FP (=FN) rate
- 20 experiments per point

# *Big Trees are Hard to Infer*

- Distance-based methods (e.g. Neighbor-Joining, 3-approximation, Buneman tree, split decomposition) are fast, but **degrade in accuracy** with high evolutionary divergence.

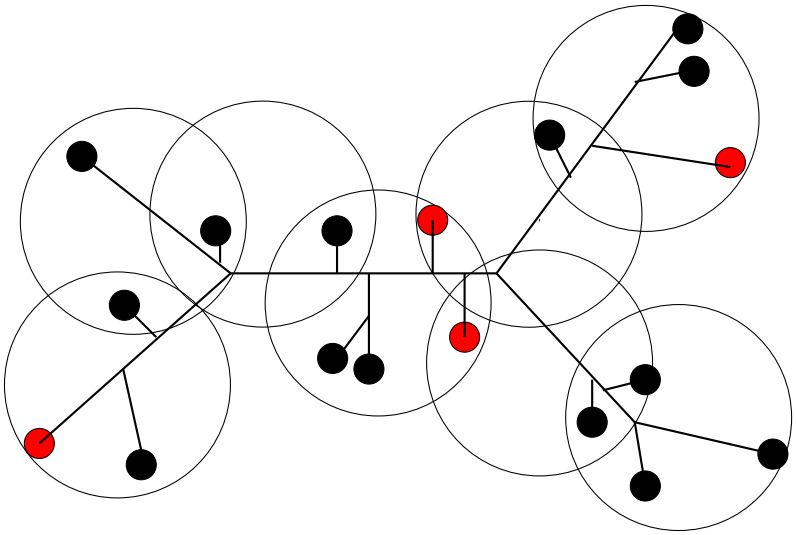
- Sequence-based methods (e.g. maximum Parsimony and maximum likelihood) do not degrade, but are **computationally expensive**.

- Parsimony does best if all branches are short, so that large numbers of taxa may be needed for accurate tree reconstruction using Parsimony.

- Year-long Parsimony analyses (Rice *et al.*) of large divergent datasets are infeasible for most researchers.

# *The Disk-Covering Method (DCM)*

A divide-and-conquer approach based on the idea of covering given sequence data with small overlapping disks



- Each disk contains a small number of taxa.
- Taxa within a disk are very similar.
- Apply given *base-method* to subproblems.
- Use overlap to merge subtrees to obtain final tree.

# *The DCM Algorithm*

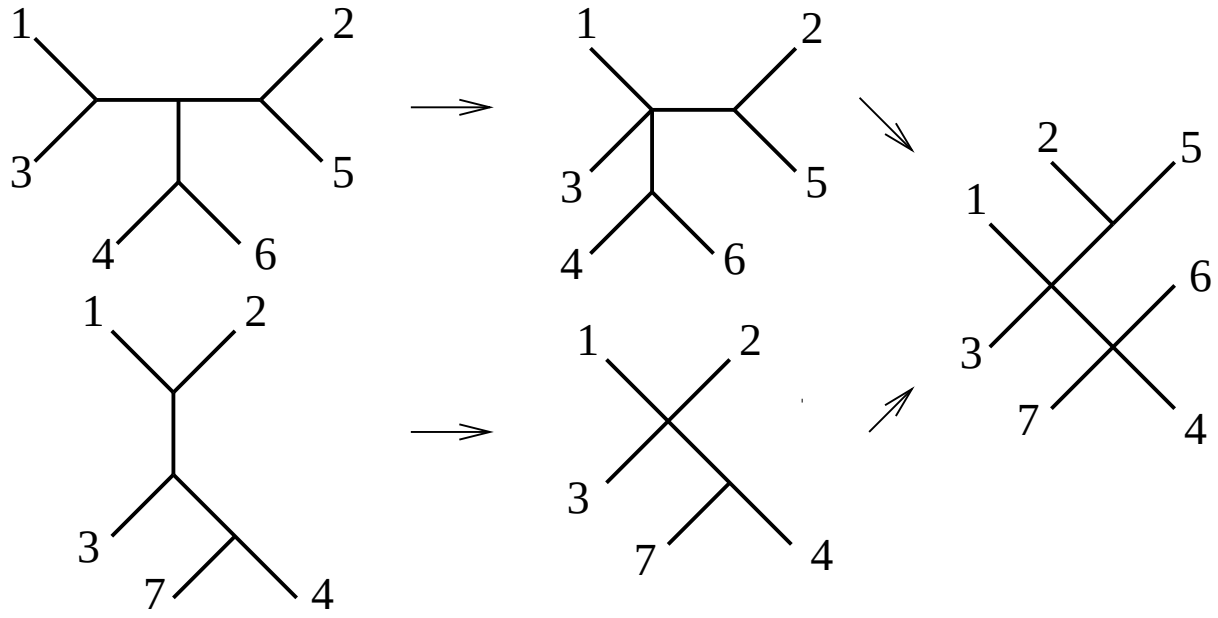
- Input: distances and sequences
- Choose base-method (e.g. Parsimony or NJ)

  - **For a given threshold $w$:**
    - Compute threshold graph $G$
      - Vertices are taxa
      - Join two vertices if their distance $\leq$ threshold
    - Compute triangulation $G^*$ of threshold graph
      - Produce perfect elimination scheme
      - Makes the following step easy:
    - Apply base-method to all maximal cliques in $G^*$
    - Merge trees guided by perfect elimination scheme

- Infer consensus of $\{T_w\}$.

# *Merging Two Trees*

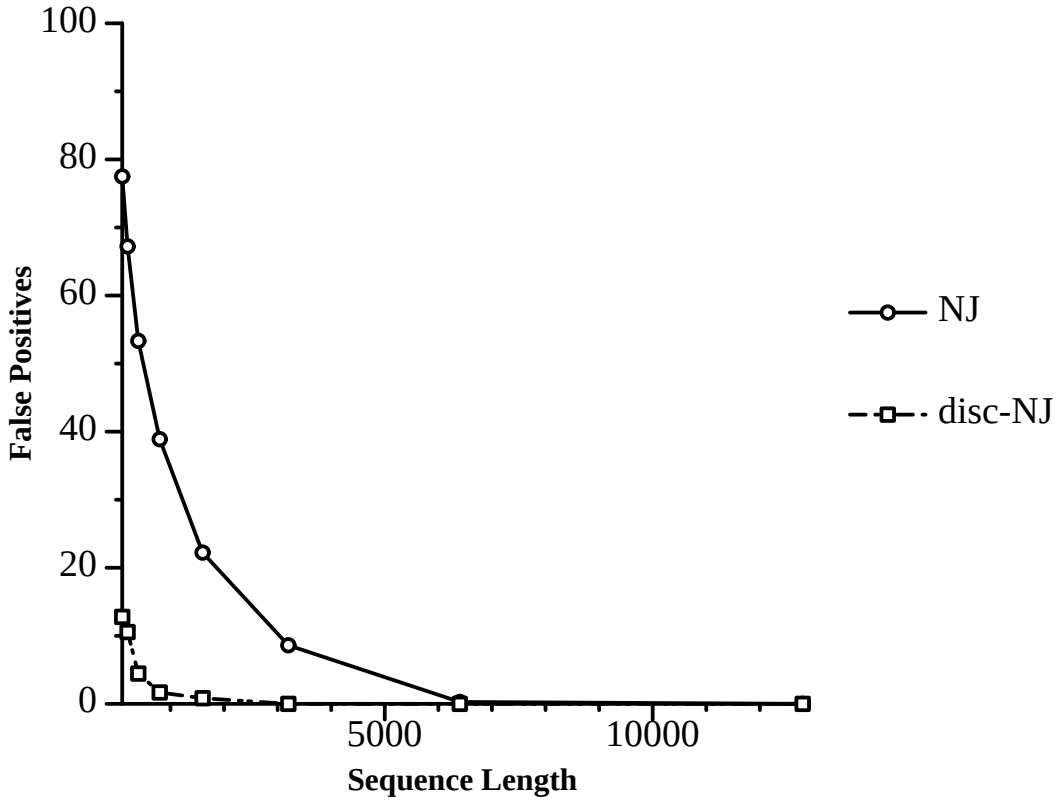
Given trees on two overlapping sets of taxa, e.g. $\{1,2,3,4,5,6\}$ and $\{1,2,3,4,7\}$.




To merge the two trees together, first transform them (through edge contractions) so that they induce the same subtrees on their shared leaves and then combine them.

# *Neighbor-Joining vs. DCM-NJ*

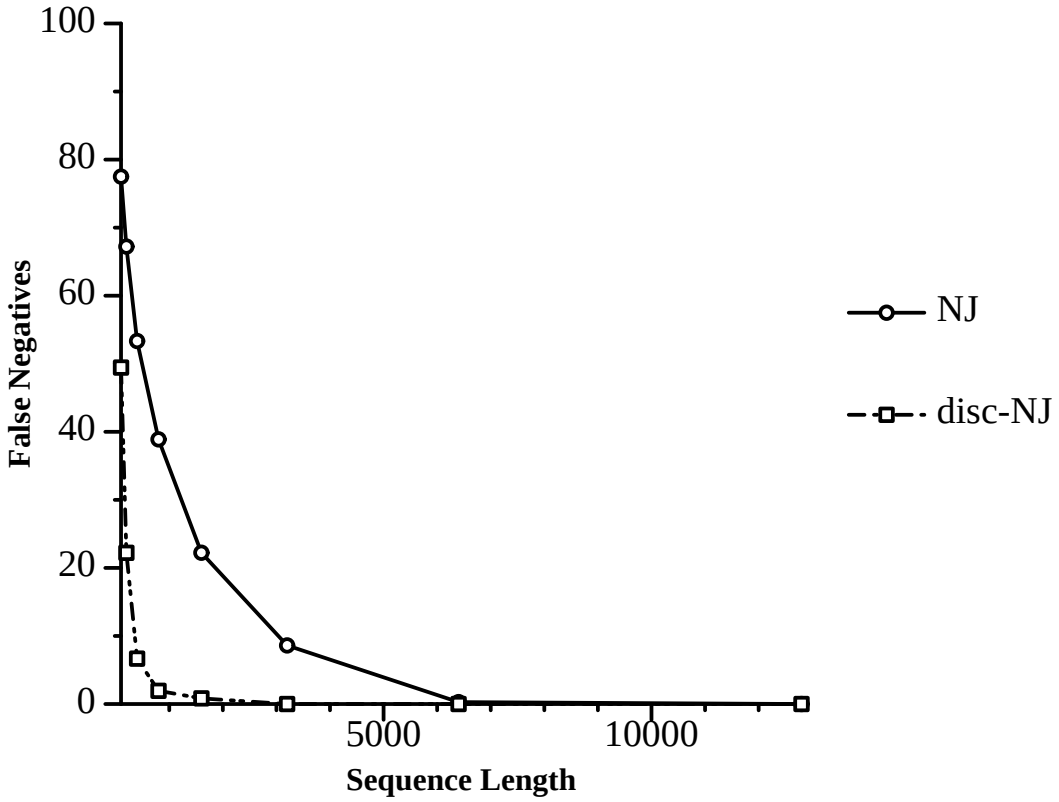
## False Positives




- 93 taxon tree
- maximum mutation probability $p(e) = 0.48$
- 10 experiments per point
- *Greedy asymmetric median tree*, i.e. consensus over all trees $\{T_w\}$.

# *Neighbor-Joining vs. DCM-NJ*

## False Negatives




- 93 taxon tree
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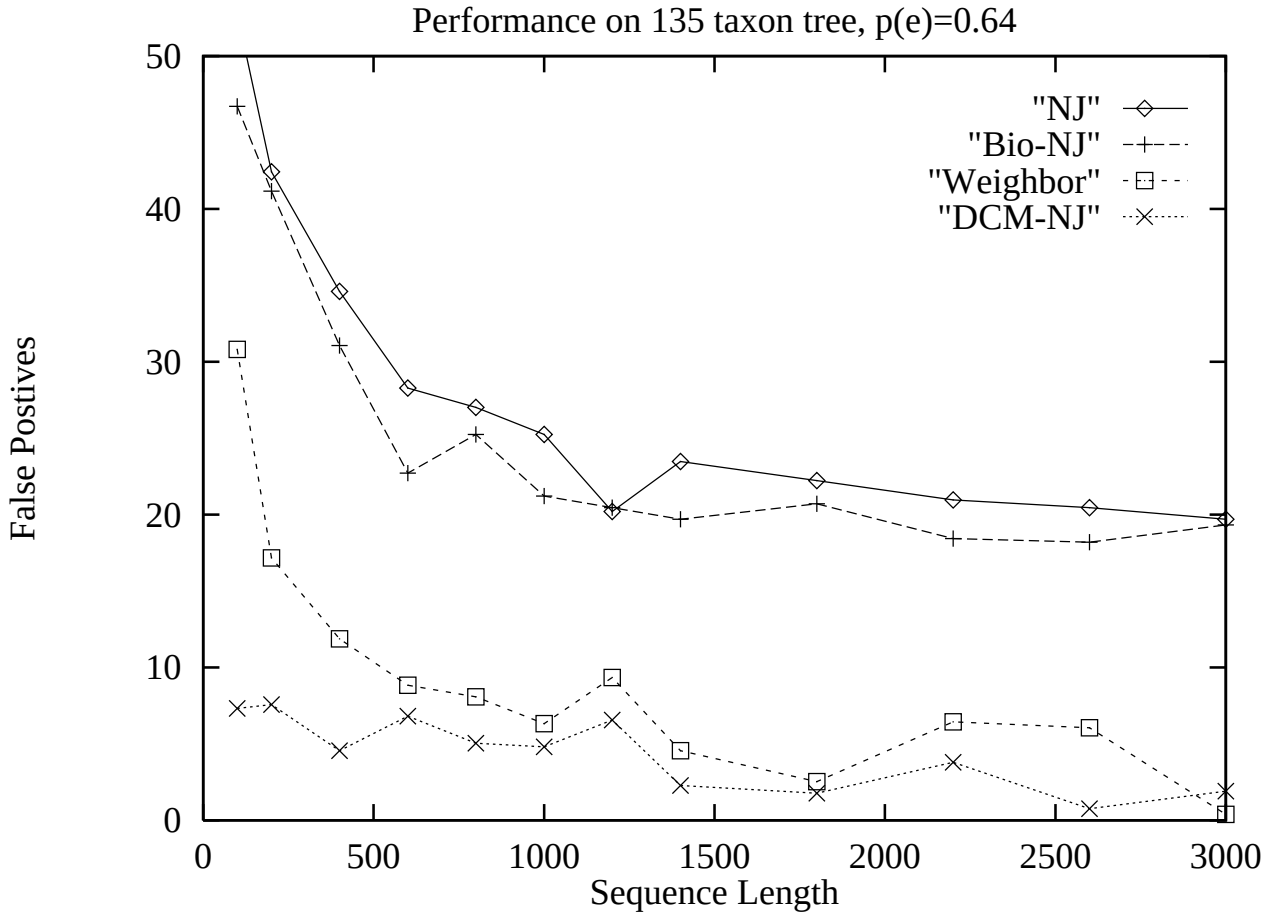
# *NJ, Bio-NJ, Weighbor & DCM-NJ*

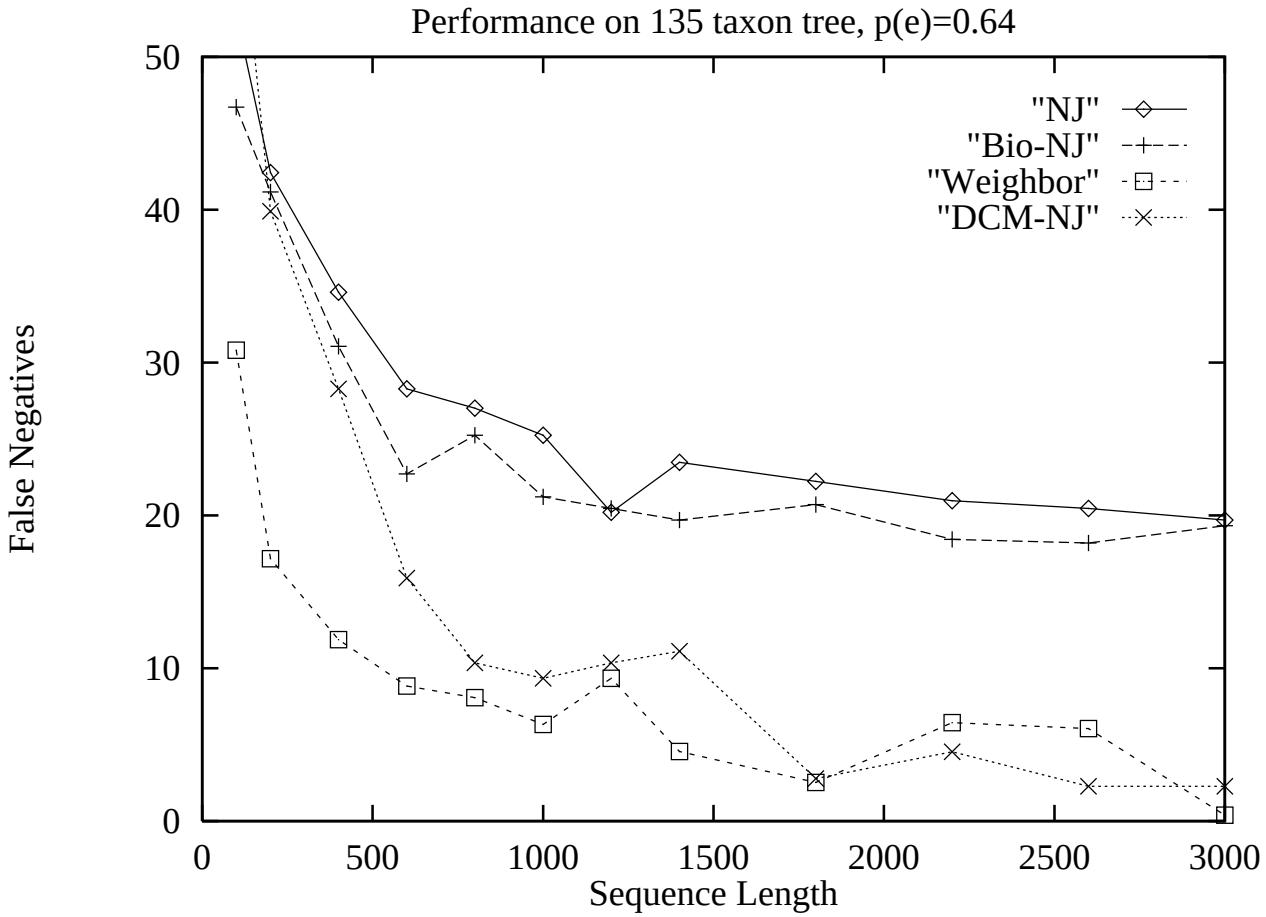
## False Positives




- 135 taxon tree
- maximum mutation probability $p(e) = 0.64$
- 3-5 experiments per point
- *Greedy asymmetric median tree* of a small subset of $\{T_w\}$.
- Work in progress. . .

# *NJ, Bio-NJ, Weighbor & DCM-NJ*

## False Negatives

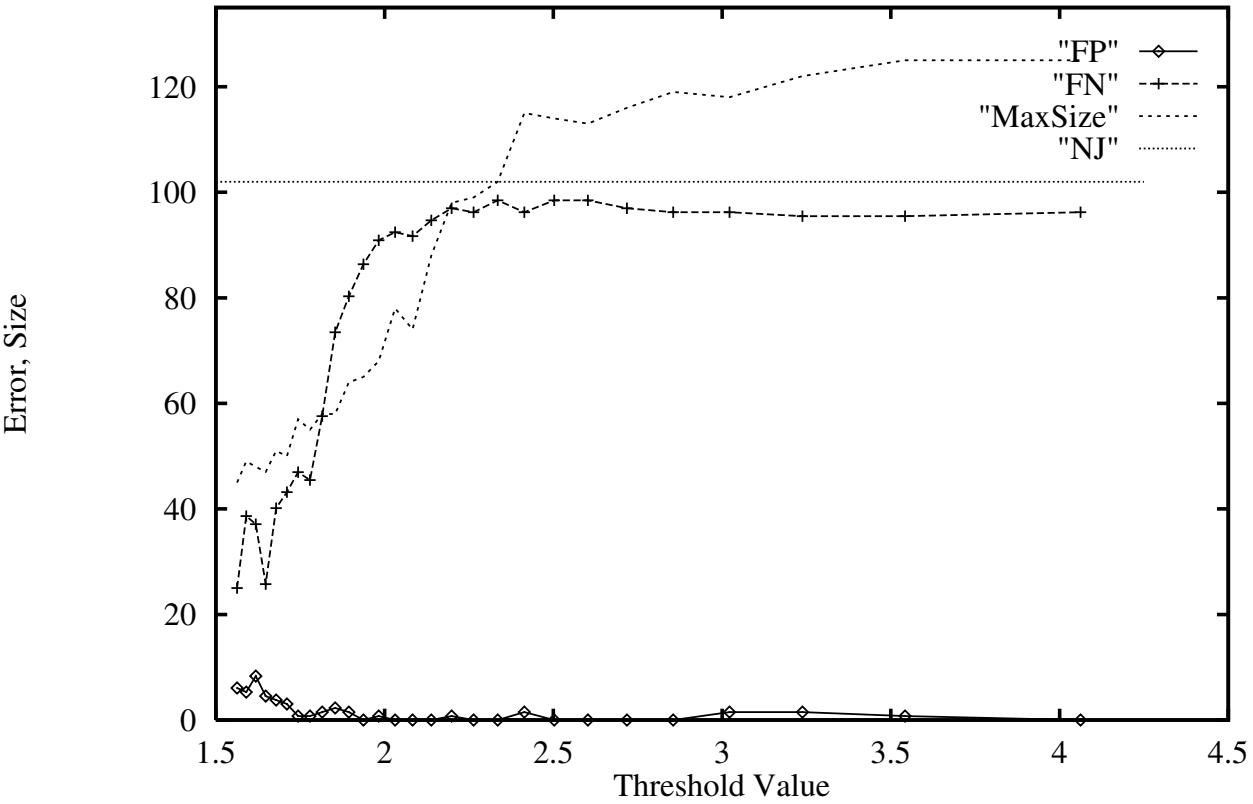



- 135 taxon tree
- maximum mutation probability $p(e) = 0.64$
- 3-5 experiments per point
- *Greedy asymmetric median tree* of a small subset of $\{T_w\}$.
- Work in progress. . .

# *Choosing the Threshold for DCM-NJ*

Choice of threshold is ruled by two factors:

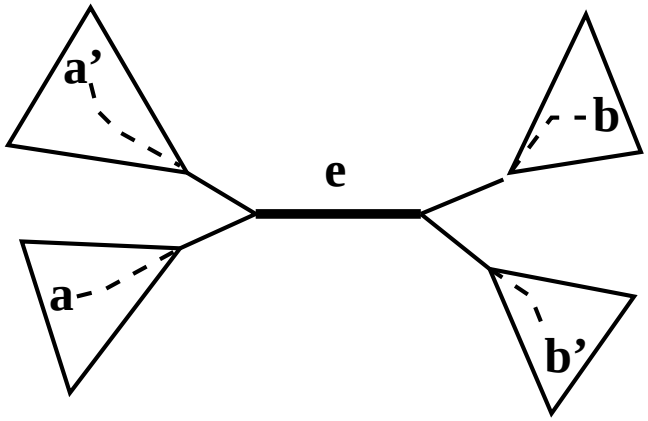
- The accuracy of NJ degrades on subproblems with increasing threshold $w$.
- For small thresholds, the merger of subproblems is not uniquely defined.




- 135 taxon tree, $p(e) = 0.64$, sequence length 300

# *Threshold and Merge Step*

Let $T$ be a model tree and $d$ an estimated distance matrix. A *short quartet* around an internal edge $e$ is a set of four taxa $a, a', b, b'$ that lie in the four subtrees induced by $e$, of minimal width.




**Theorem** If the threshold $w$ is chosen large enough such that every short quartet induces a four-clique in $G^*$, then every merger is unique and a DCM method will recover the model tree $T$, if the base method is accurate on the base problems.

# *Sequence Lengths Required for Accuracy*

The length of biological sequences obtainable for phylogenetic analysis is bounded by a *few thousand* base pairs, so the question how sequence length affects performance is critical.

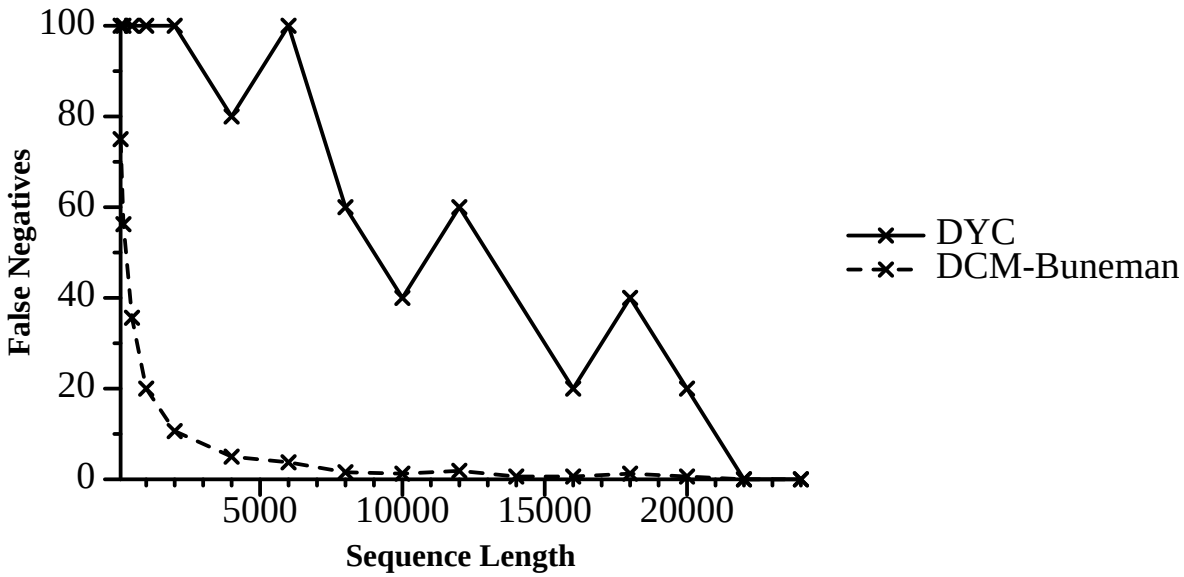
The sequence lengths that suffice for accuracy of distance methods such as Neighbor-Joining or the Buneman Tree grow **exponentially** in the divergence of the model tree.
(Atteson 1997, Erdös et al. 1997)

For DCM-boosted distances methods we can show:

> For almost all trees, **polylogarithmic** length suffices for accuracy with high probability, and **polynomial** length suffices for all trees with high probability.

# *DCM vs. Short Quartet Method*

P. Erdös, M. Steel, L. Székely and T. Warnow (1997) introduced the **Short Quartet Method** (SQM), the first method known to require only **polylogarithmic** length sequences for complete accuracy with high probability. Drawback: SQM returns **nothing**, if complete accuracy is unachievable.




- **Average performance** (5 experiments per point) of the SQM compared with DCM-Buneman, on a 35 taxon tree with maximum $p(e)$ equal to 0.04.

- For each dataset, SQM returns **either 0% or 100%** false negatives.

## *Other Methods with Similar Theoretical Properties*

- M. Cryan, L.A. Goldberg and P.W. Goldberg, Evolutionary Trees can be Learned in Polynomial Time in the Two-State General Markov Model, FOCS'98.

- M. Csürös and M.-Y. Kao, Recovering Evolutionary Trees Through Harmonic Greedy Triplets, Recomb'99.

# *Conclusion and Future Research*

By reduction to small and closely related-datasets, the DCM-method can substantially improve the accuracy and/or time requirements of phylogenetic tree reconstruction methods for large and divergent datasets.

Future research will focus on:

- using non-iid evolutionary models
- Parsimony and MLE
- using model trees that stress the methods explicitly
- exploring the application to multiple sequence alignment
- investigating real data sets and determining and how they are likely to respond to this approach
- Optimal tree refinement: returning binary trees with edge weights
- reporting expected Robinson-Foulds error
- **developing a public version of the software.**