# CS 394C
## Algorithms for Computational Biology

Tandy Warnow

Spring 2012

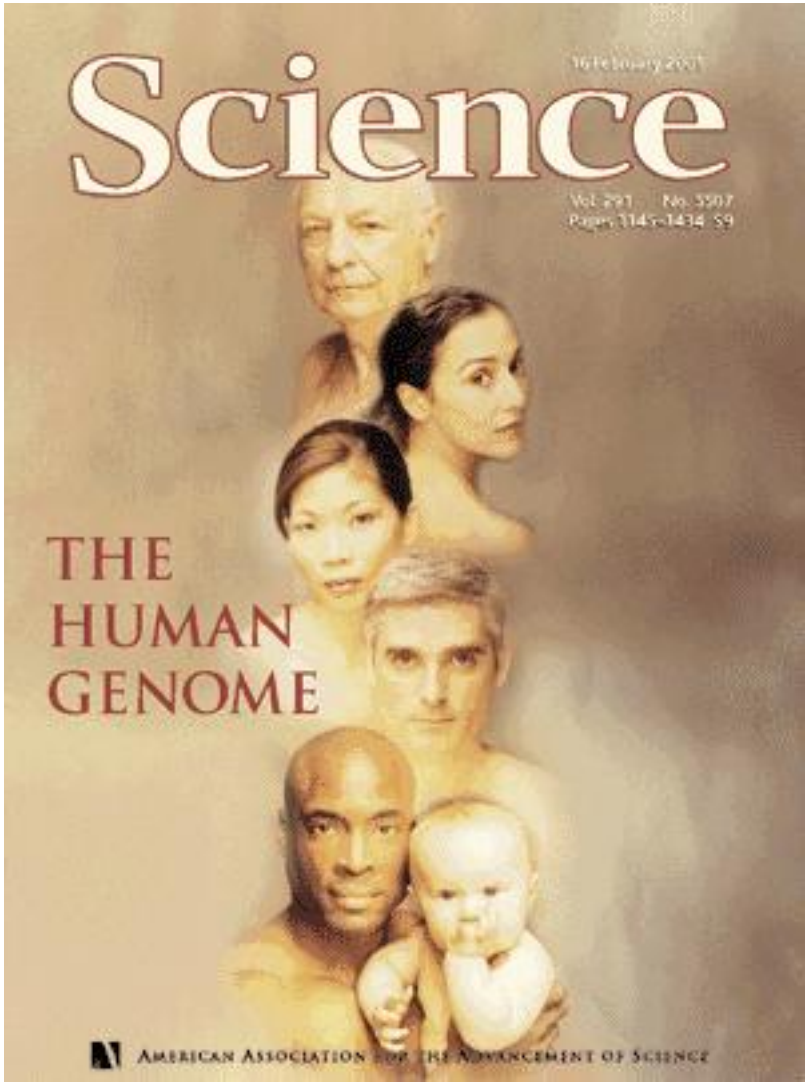
# Biology: 21st Century Science!

"When the human genome was sequenced seven years ago, scientists knew that most of the major scientific discoveries of the 21st century would be in biology."

January 1, 2008, guardian.co.uk

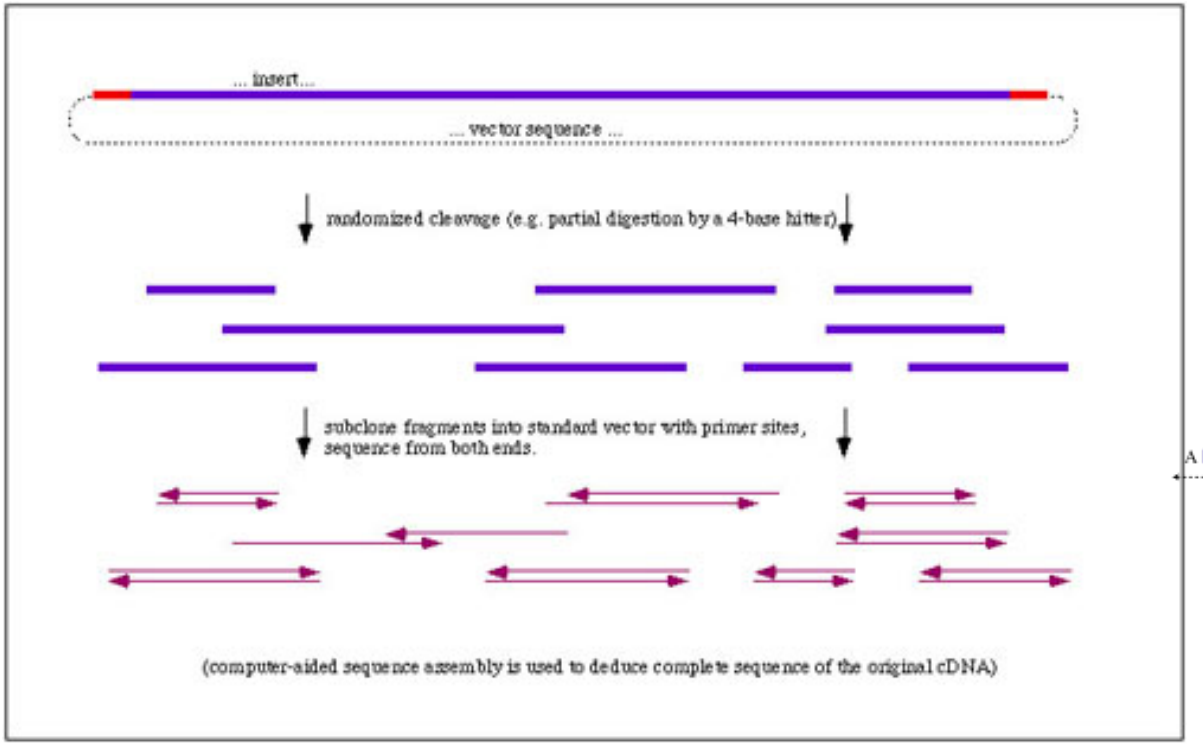
Genome Sequencing Projects:

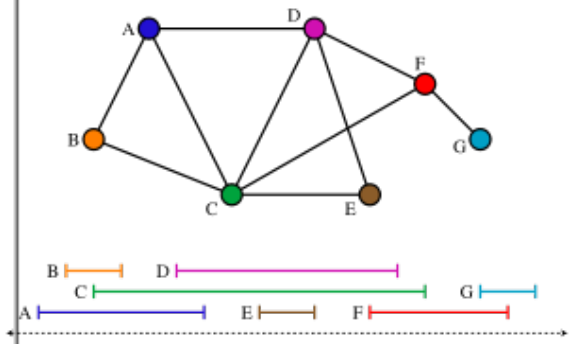
Started with the Human Genome Project



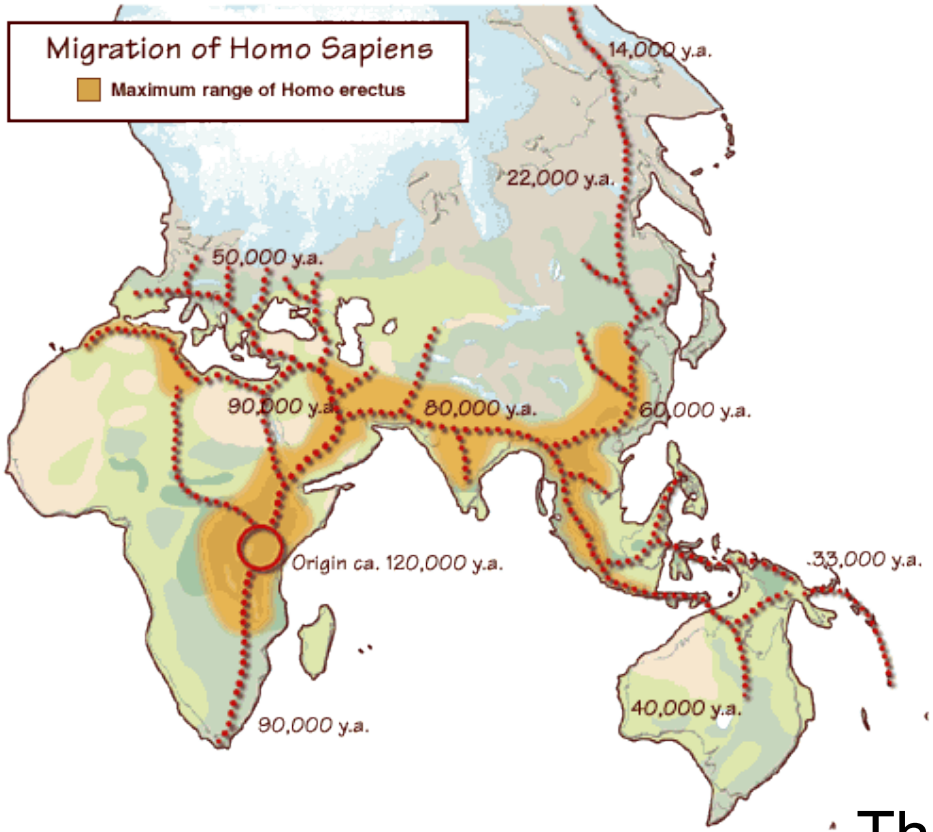
# Whole Genome Shotgun Sequencing:

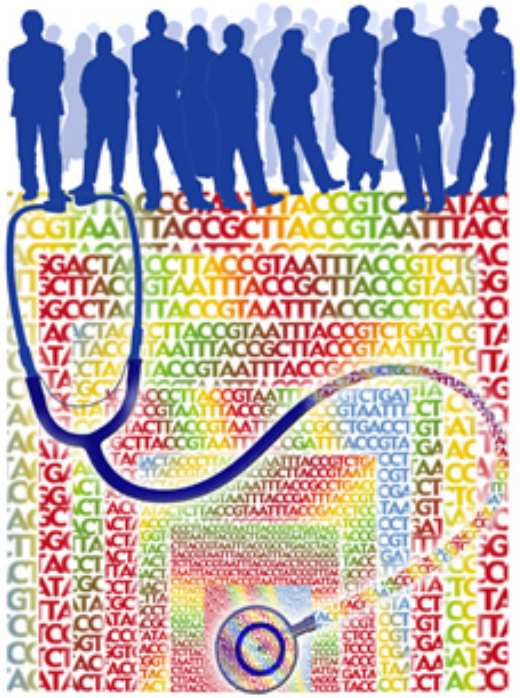
## *Graph Algorithms and Combinatorial Optimization!*



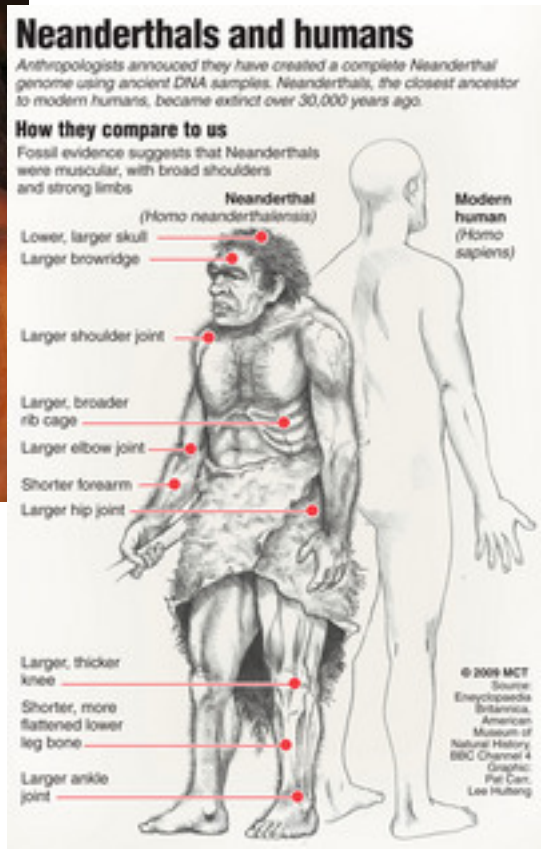
Where did humans come from, and how did they move throughout the globe?

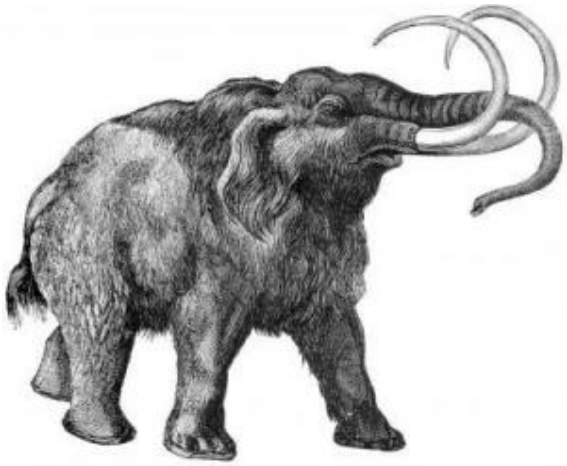


- The 1000 Genome Project: using human genetic variation to better treat diseases

# Other Genome Projects! (Neandertals, Wooly Mammoths, and more ordinary creatures…)

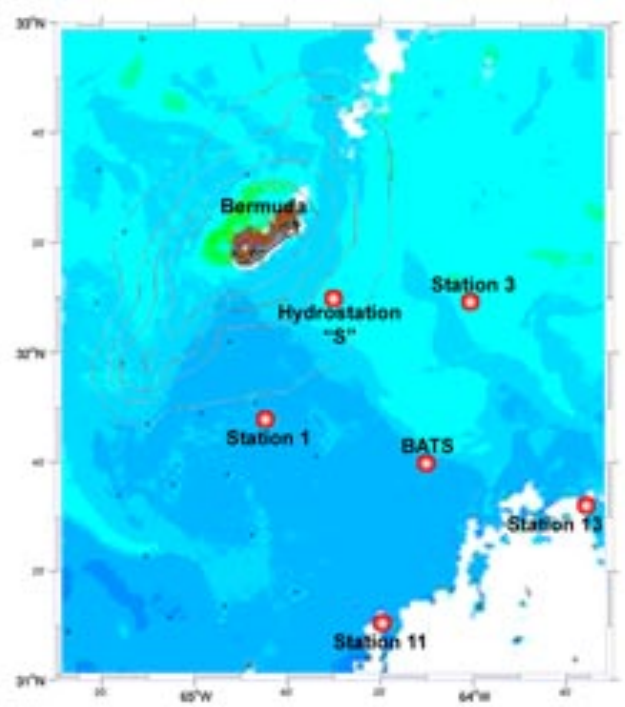


**Metagenomics:**

**C. Ventner et al., Exploring the Sargasso Sea:**

## Scientists Discover One Million New Genes in Ocean Microbes




# How did life evolve on earth?

Courtesy of the Tree of Life project

Current methods often use months to estimate trees on 1000 DNA sequences

Our objective:

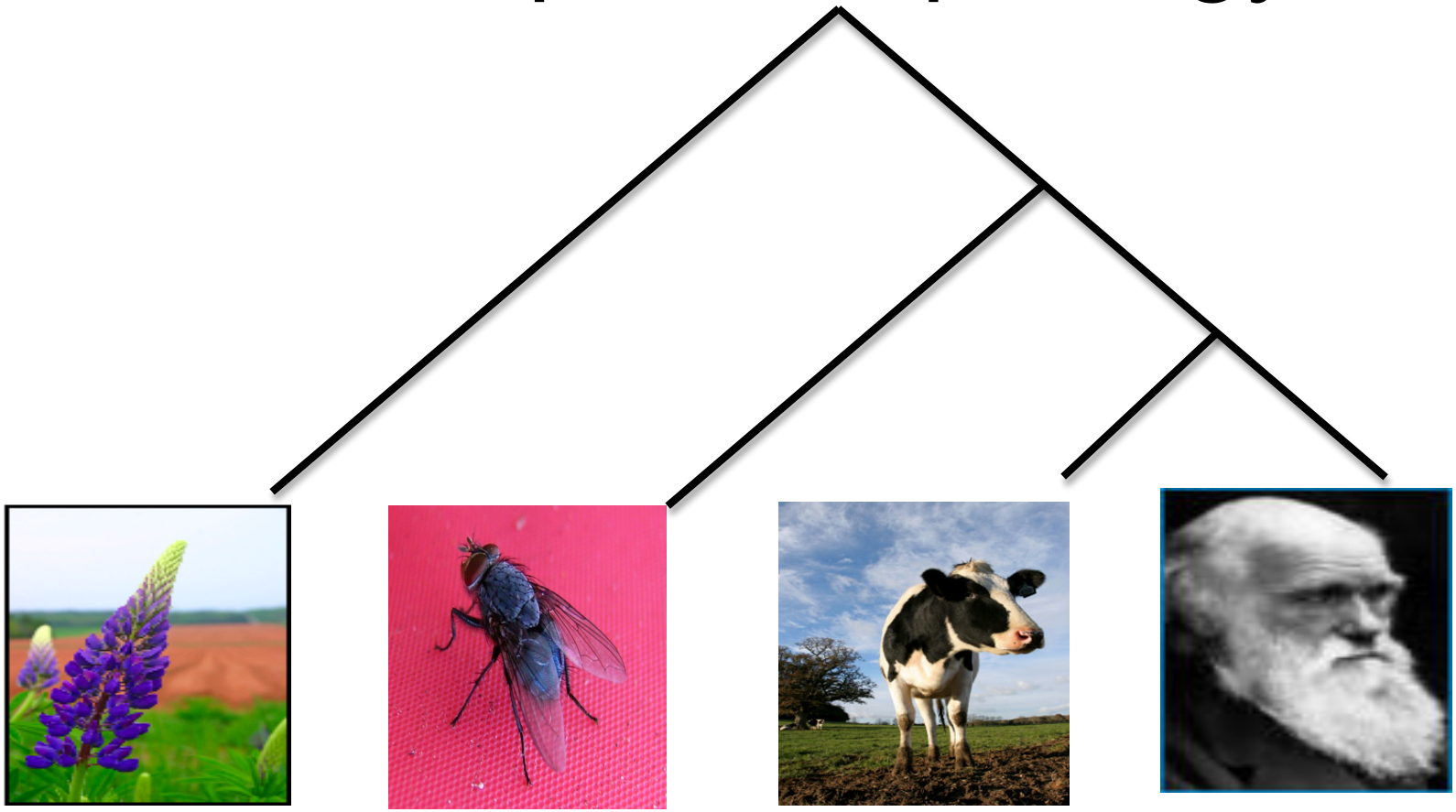
More accurate trees and alignments on 500,000 sequences in under a week

We prove theorems using graph theory and probability theory, and our algorithms are studied on real and simulated data.

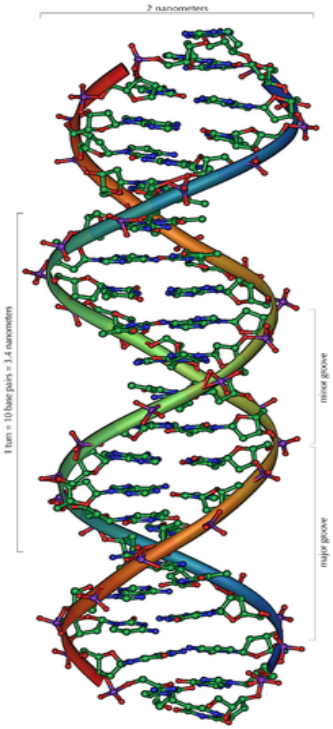
# This course

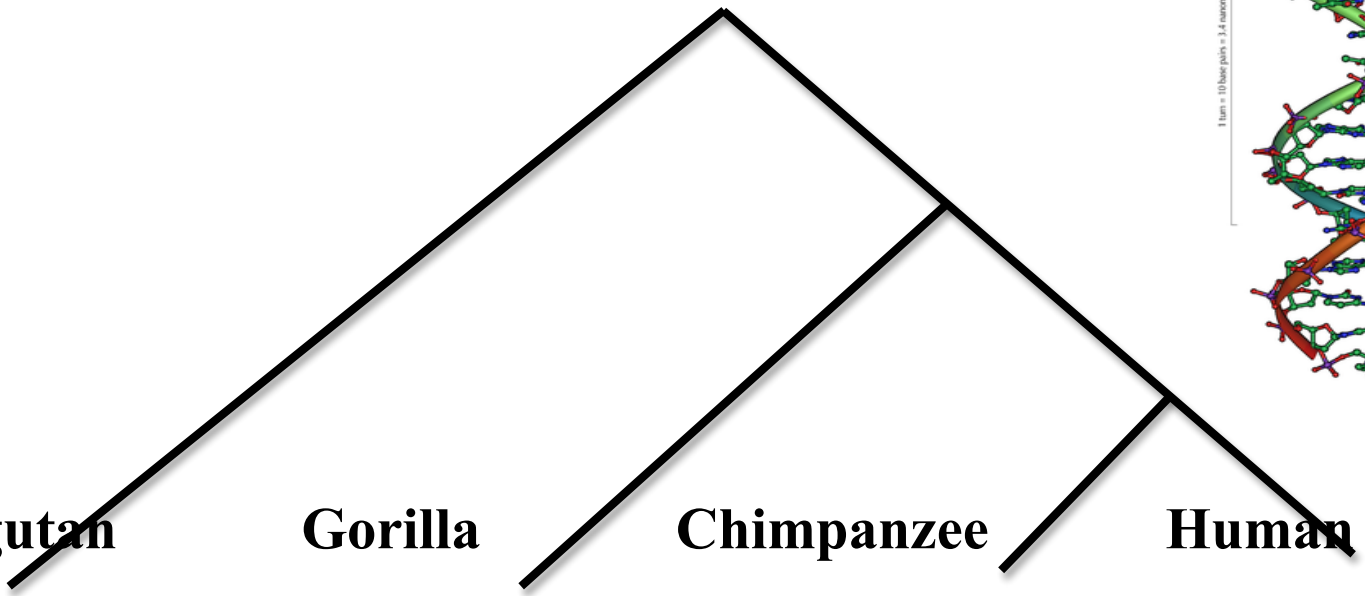
- Fundamental mathematics of phylogeny and alignment estimation
- Applied research problems:
  - Metagenomics
  - Simultaneous estimation of alignments and trees
  - Ultra-large alignment and tree estimation
  - Phylogenomics
  - De novo genome assembly
  - Historical linguistics

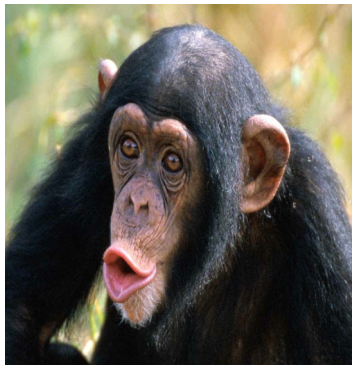
# Phylogenetic trees can be based upon morphology

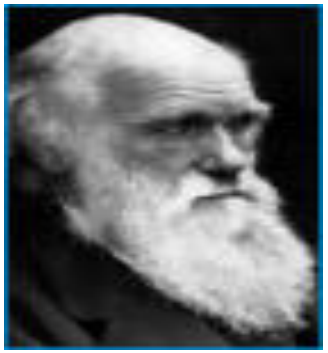


# But some estimations need DNA!

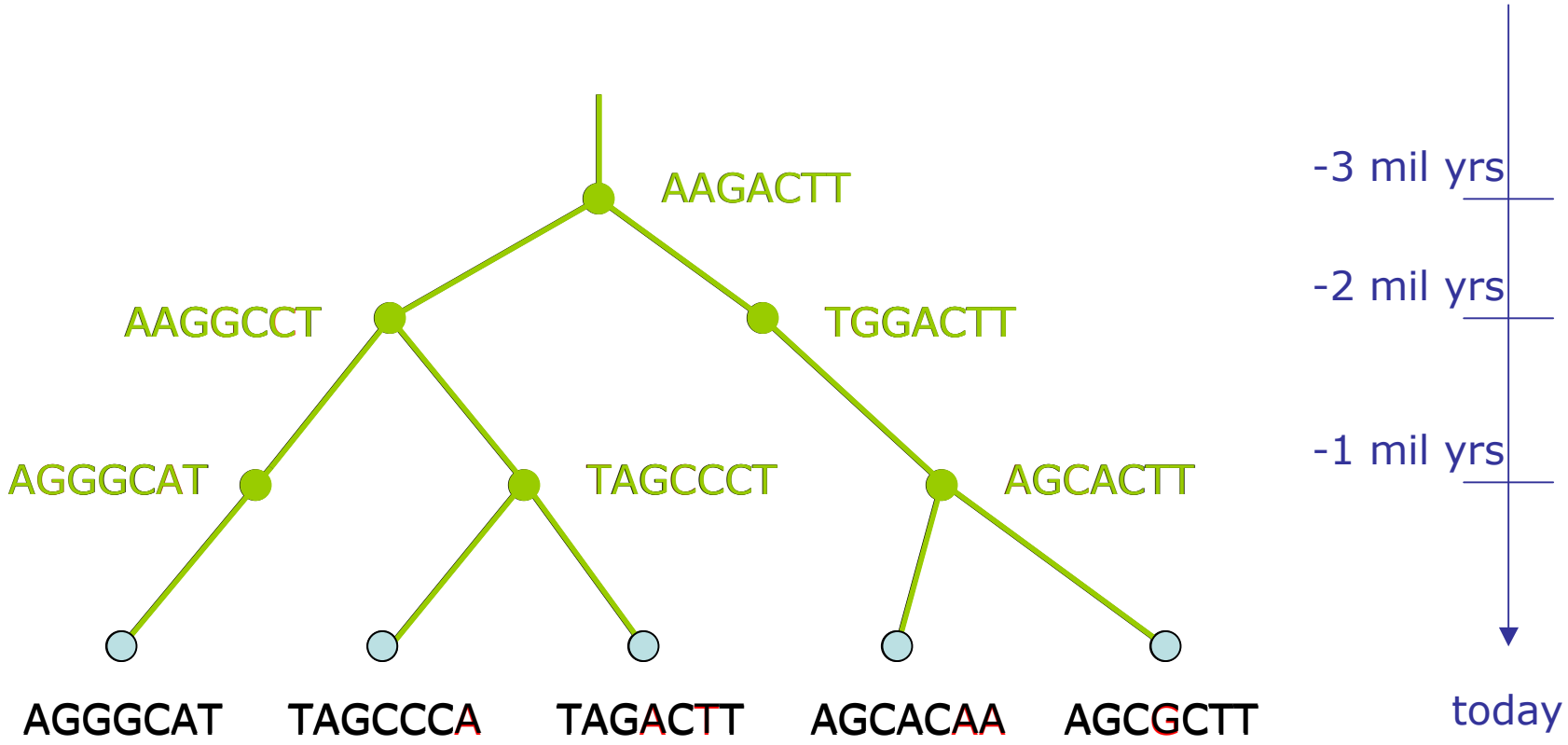






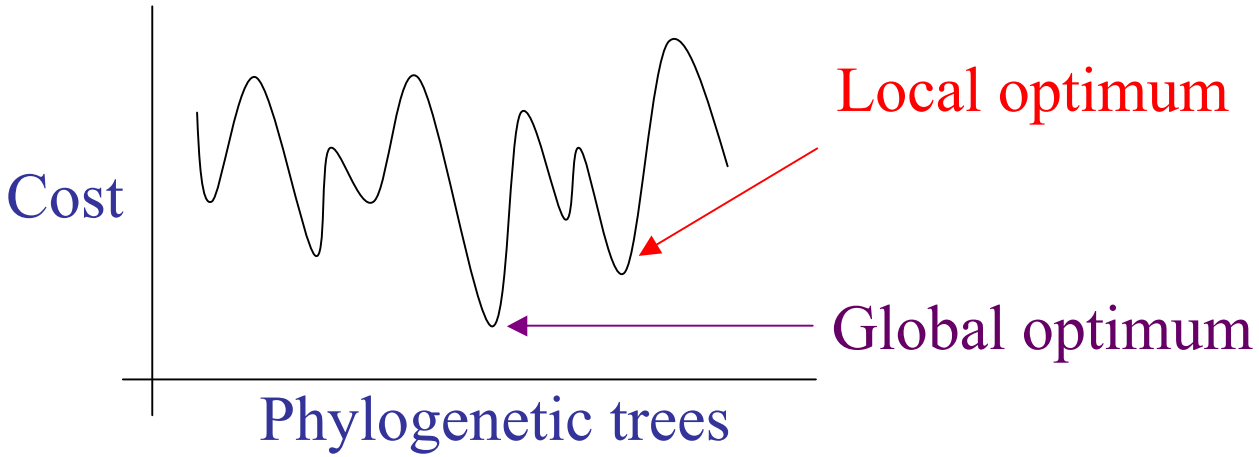
# DNA Sequence Evolution



# Phylogenetic reconstruction methods

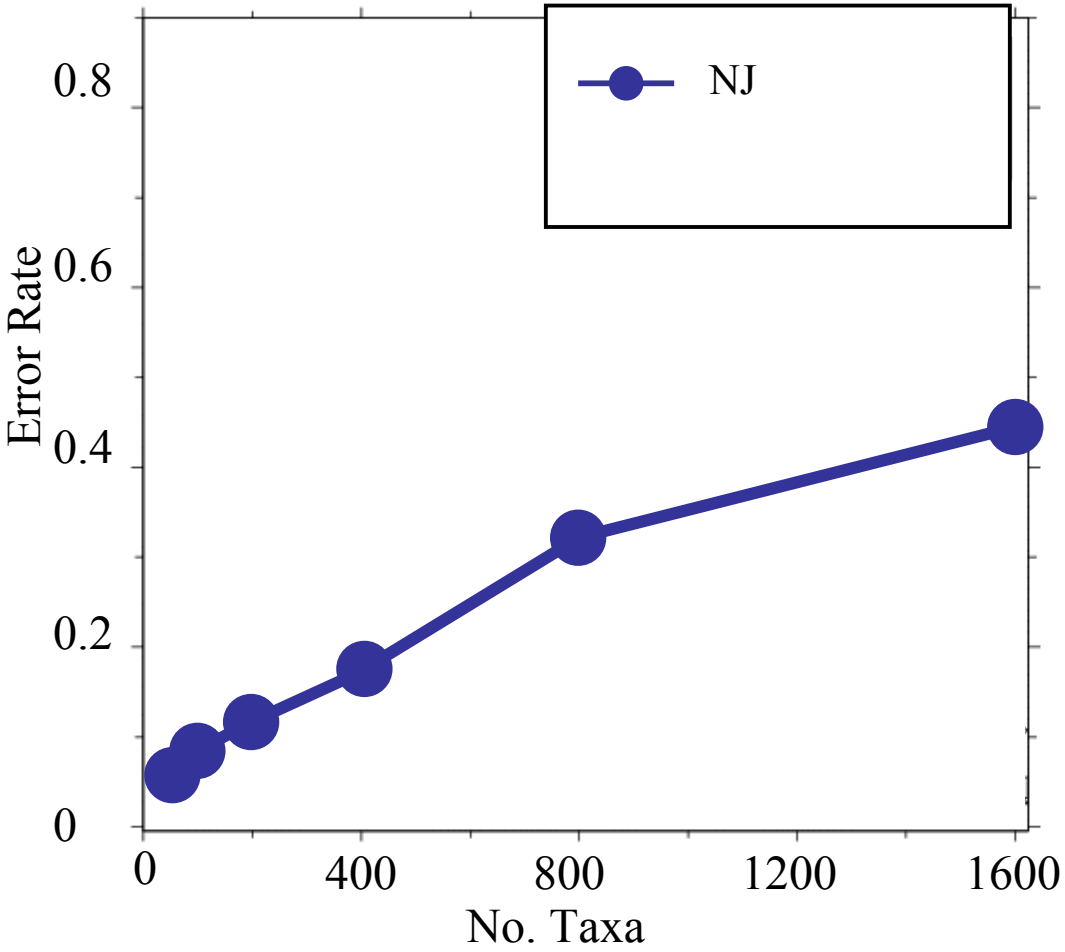
1. **Polynomial time distance-based methods (e.g., Neighbor-Joining)**

2. **Hill-climbing heuristics for NP-hard optimization criteria (Maximum Parsimony and Maximum Likelihood)**




3. **Bayesian methods**

# The neighbor joining method has high error rates on large trees




Simulation study based upon fixed edge lengths, K2P model of evolution, sequence lengths fixed to 1000 nucleotides.

Error rates reflect proportion of incorrect edges in inferred trees.

***[Nakhleh et al. ISMB 2001]***

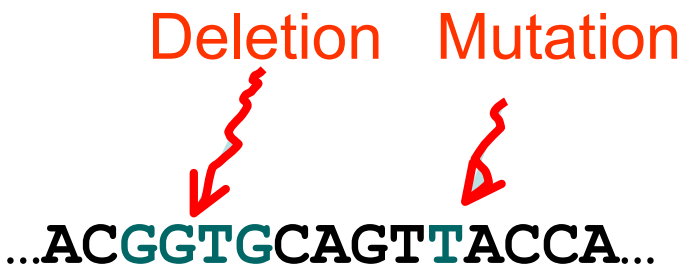
# And solving NP-hard optimization problems in phylogenetics is … *unlikely*

| # of Taxa | # of Unrooted Trees |
|---|---|
| 4 | 3 |
| 5 | 15 |
| 6 | 105 |
| 7 | 945 |
| 8 | 10395 |
| 9 | 135135 |
| 10 | 2027025 |
| 20 | $2.2 \times 10^{20}$ |
| 100 | $4.5 \times 10^{190}$ |
| 1000 | $2.7 \times 10^{2900}$ |

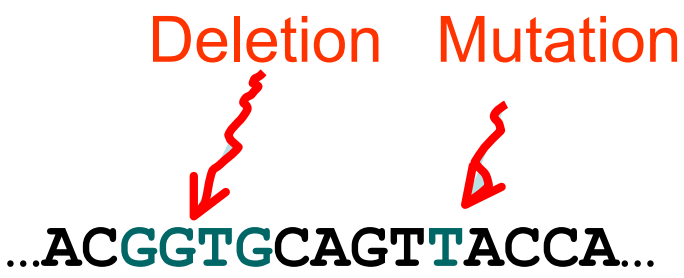
# Indels and substitutions at the DNA level

...**ACGGTGCAGTTACCA**...

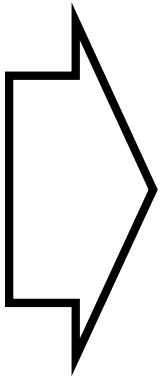
# Indels and substitutions at the DNA level

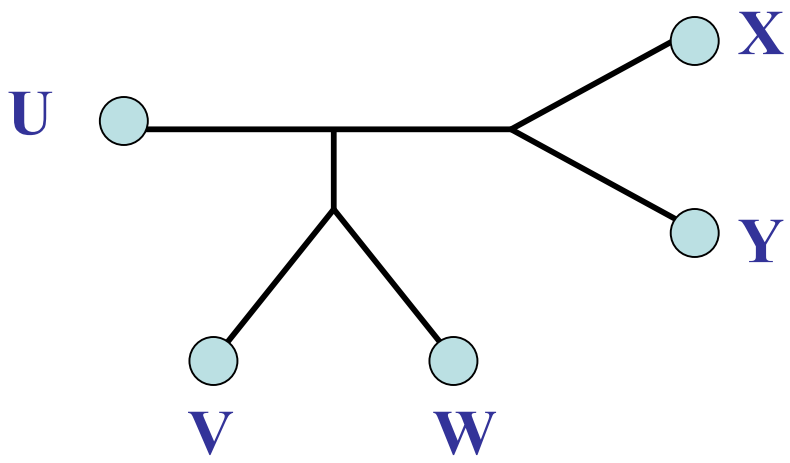


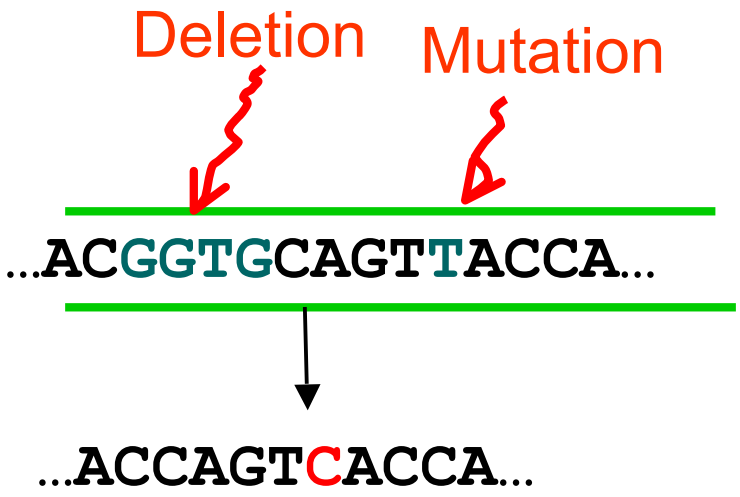
# Indels and substitutions at the DNA level



| | |
|---|---|
| **U** | AGTGGAT |
| **V** | TATGCCCA |
| **W** | TATGACTT |
| **X** | AGCCCTA |
| **Y** | AGCCCGCTT |








The true pairwise alignment is:

...ACGGTGCAGTTACCA...

...AC----CAGTCACCA...

The **true multiple alignment** on a set of homologous sequences is obtained by tracing their evolutionary history, and extending the pairwise alignments on the edges to a multiple alignment on the leaf sequences.

# Input: unaligned sequences

```
S1 = AGGCTATCACCTGACCTCCA
S2 = TAGCTATCACGACCGC
S3 = TAGCTGACCGC
S4 = TCACGACCGACA
```

# Phase 1: Multiple Sequence Alignment

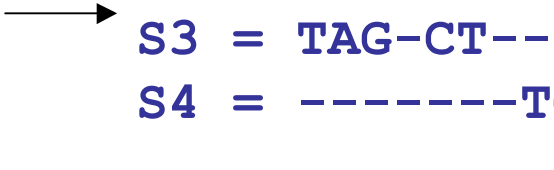
```
S1 = AGGCTATCACCTGACCTCCA
S2 = TAGCTATCACGACCGC
S3 = TAGCTGACCGC
S4 = TCACGACCGACA
```



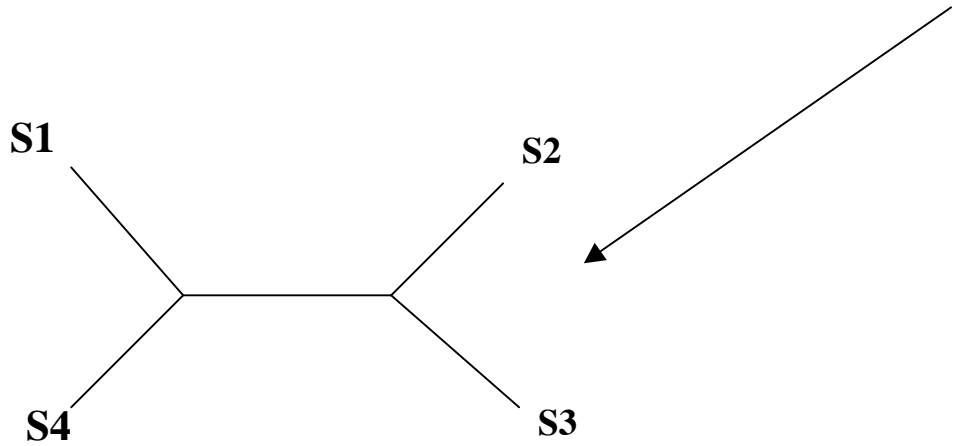
```
S1 = -AGGCTATCACCTGACCTCCA
S2 = TAG-CTATCAC--GACCGC--
S3 = TAG-CT-------GACCGC--
S4 = -------TCAC--GACCGACA
```

# Phase 2: Construct tree

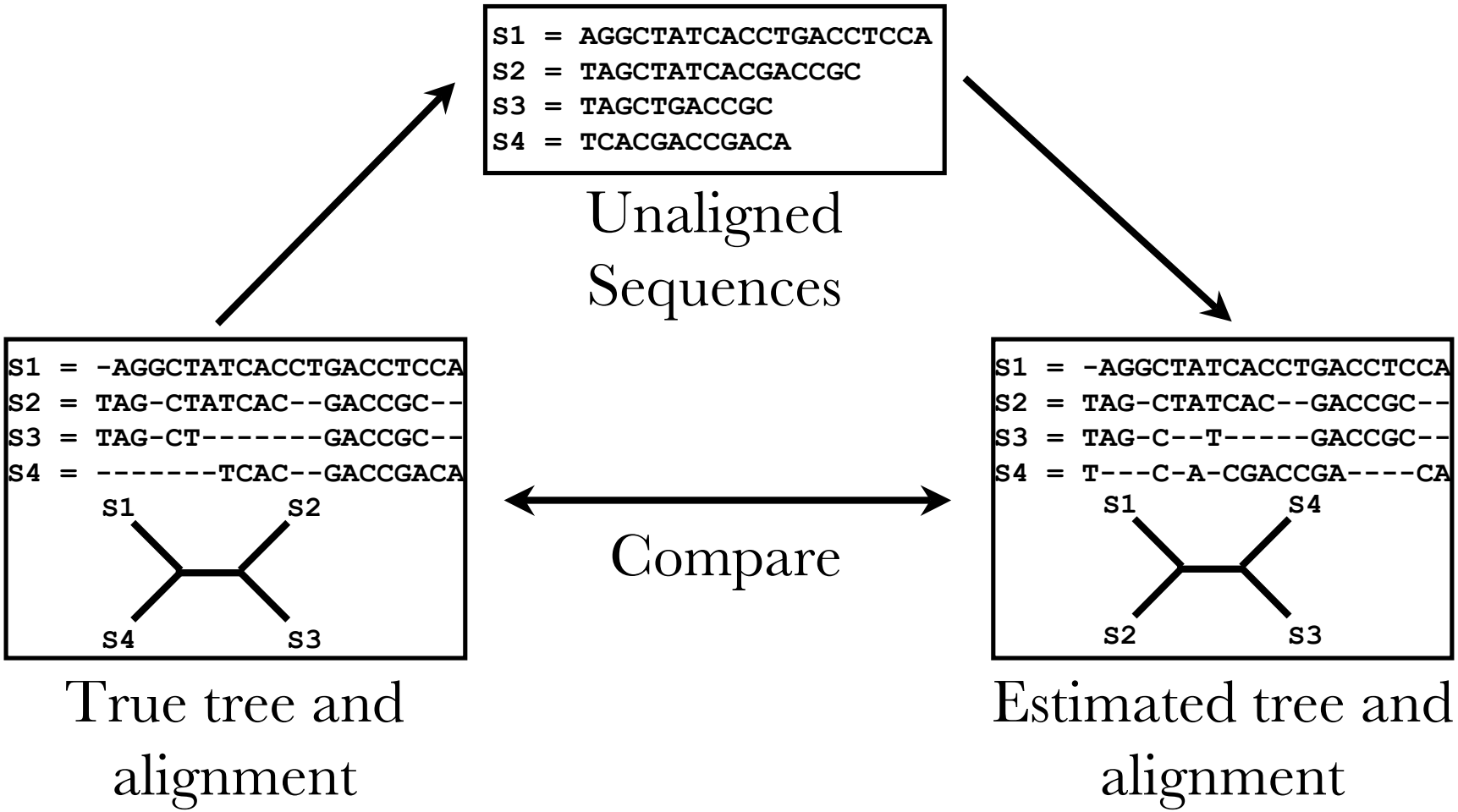
```
S1 = AGGCTATCACCTGACCTCCA
S2 = TAGCTATCACGACCGC
S3 = TAGCTGACCGC
S4 = TCACGACCGACA
```

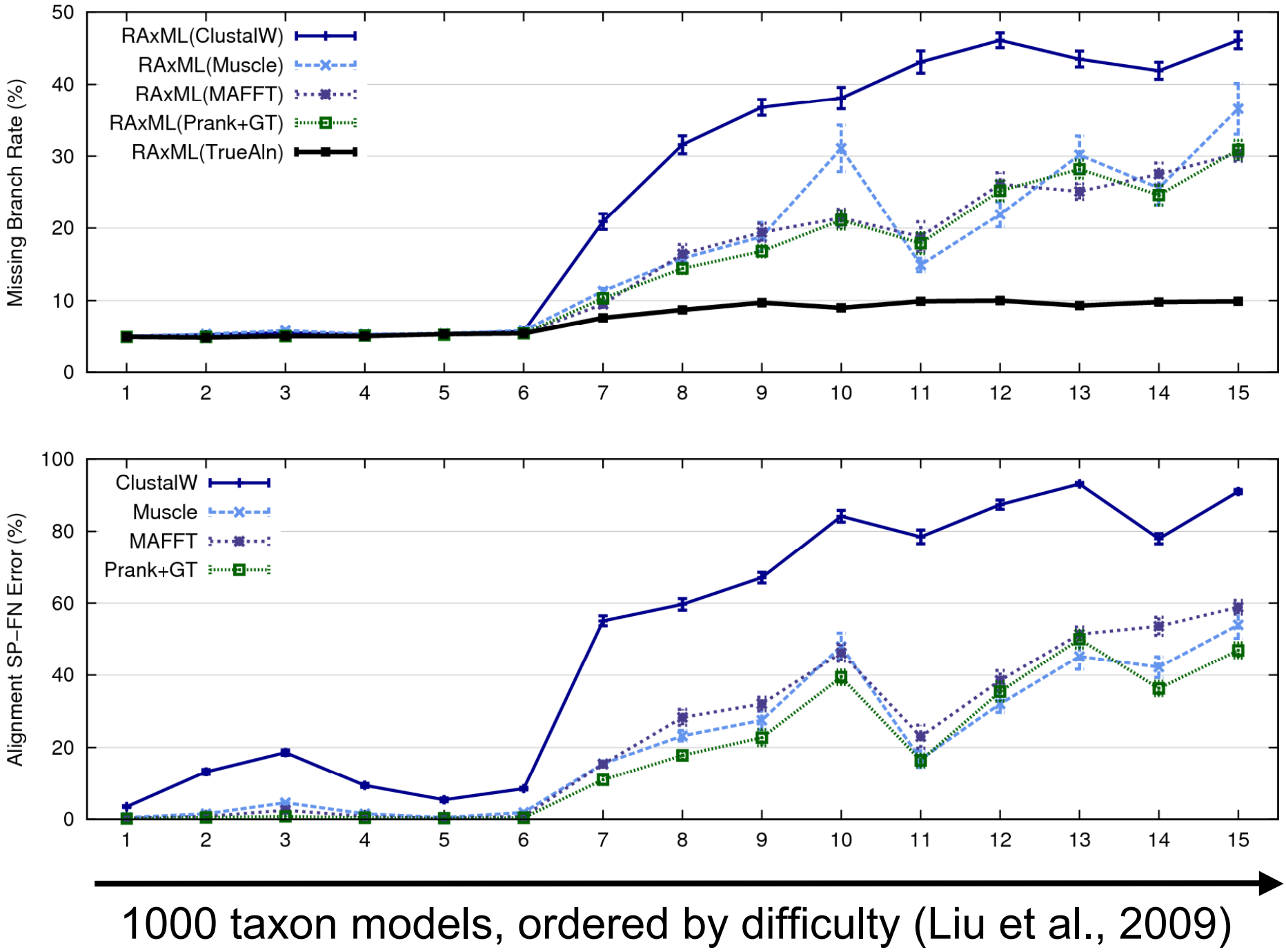


```
S1 = -AGGCTATCACCTGACCTCCA
S2 = TAG-CTATCAC--GACCGC--
S3 = TAG-CT-------GACCGC--
S4 = -------TCAC--GACCGACA
```



# Simulation Studies




Missing Branch Rate (%)
RAxML(ClustalW)
RAxML(Muscle)
RAxML(MAFFT)
RAxML(Prank+GT)
RAxML(TrueAln)
Alignment SP–FN Error (%)
ClustalW
Muscle
MAFFT
Prank+GT
1000 taxon models, ordered by difficulty (Liu et al., 2009)

# Problems

- Large datasets with high rates of evolution are hard to align accurately, and phylogeny estimation methods produce poor trees when alignments are poor.
- Many phylogeny estimation methods have poor accuracy on large datasets (even if given correct alignments)
- *Potentially useful genes are often discarded* if they are difficult to align.

These issues seriously impact large-scale phylogeny estimation (and Tree of Life projects)

# Major Challenges

- Current phylogenetic datasets contain hundreds to thousands of taxa, with multiple genes.
- Future datasets will be substantially larger (e.g., iPlant plans to construct a tree on 500,000 plant species)
- *Current methods have poor accuracy or cannot run on large datasets.*

# The Tree of Life

**Theoretical Challenges:**

- NP-hard problems
- Model violations

**Empirical Challenges:**

- Alignment estimation
- Data insufficient OR too much data
- Heuristics insufficient

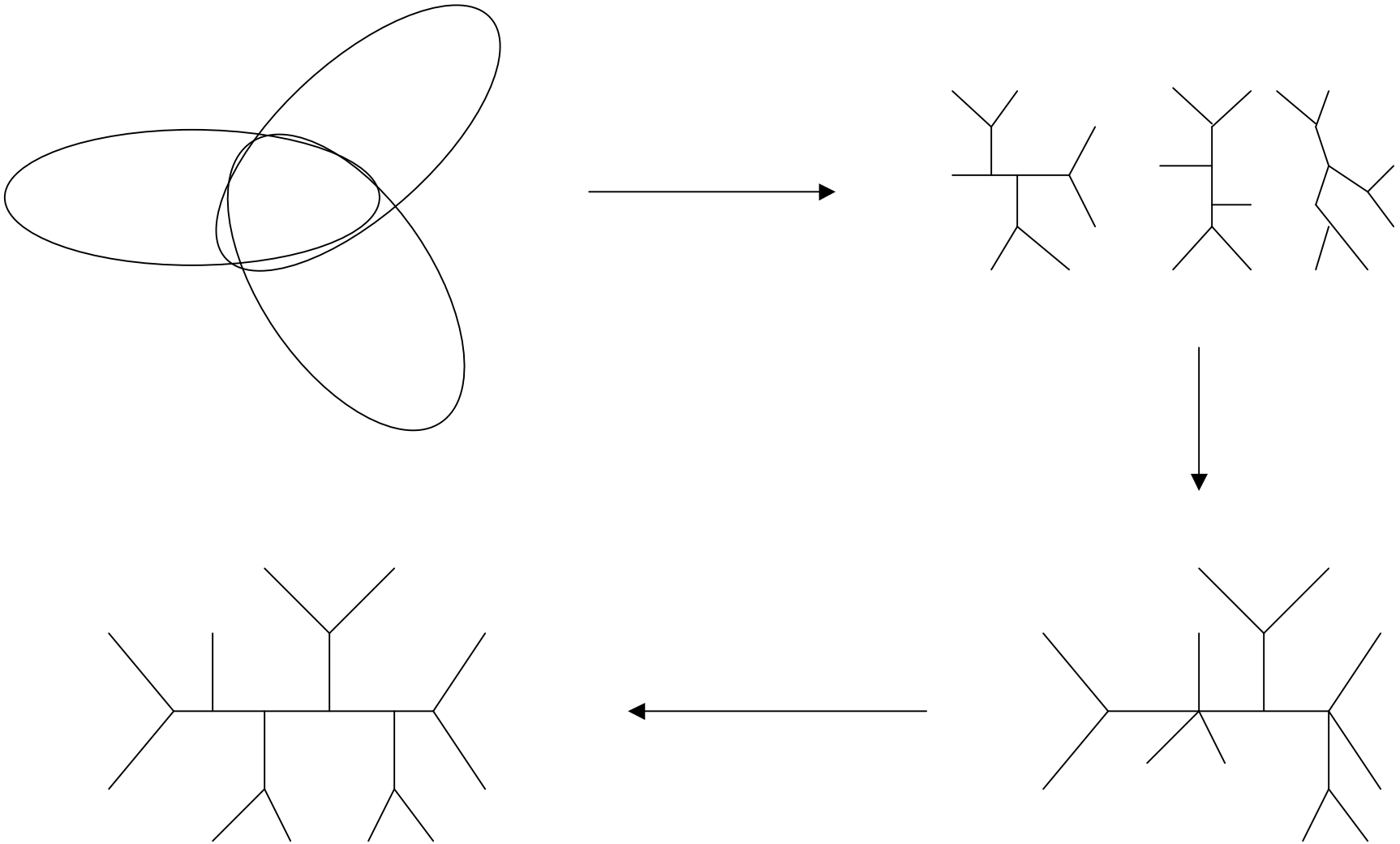
# Phylogenetic “boosters” (meta-methods)

Goal: improve accuracy, speed, robustness, or theoretical guarantees of base methods

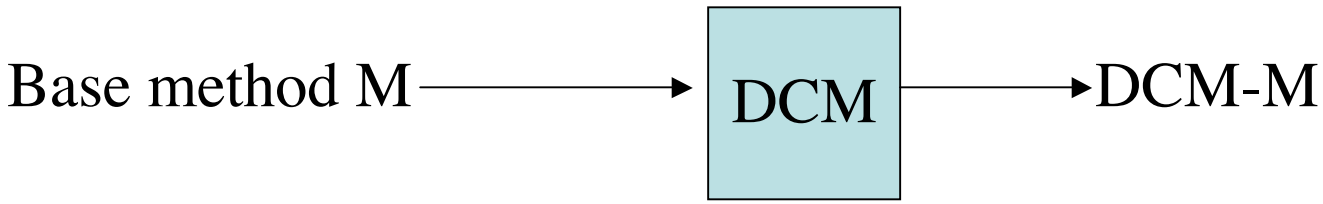
Examples:

- DCM-boosting for distance-based methods (1999)
- DCM-boosting for heuristics for NP-hard problems (1999)
- SATé-boosting for alignment methods (2009)
- SuperFine-boosting for supertree methods (2011)
- DACTAL-boosting for all phylogeny estimation methods (2011)
- SEPP-boosting for metagenomic analyses (2011)

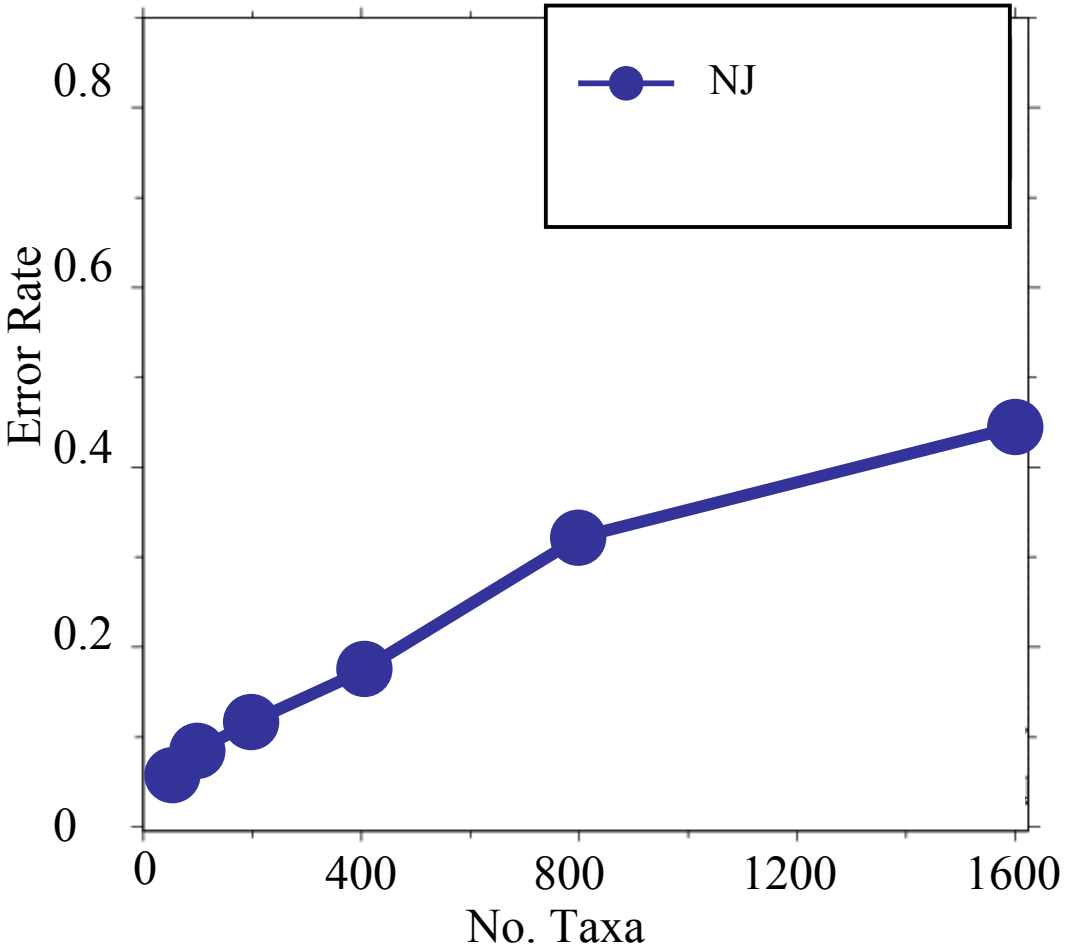
# Disk-Covering Methods (DCMs) (starting in 1998)



- DCMs “boost” the performance of phylogeny reconstruction methods.



# The neighbor joining method has high error rates on large trees



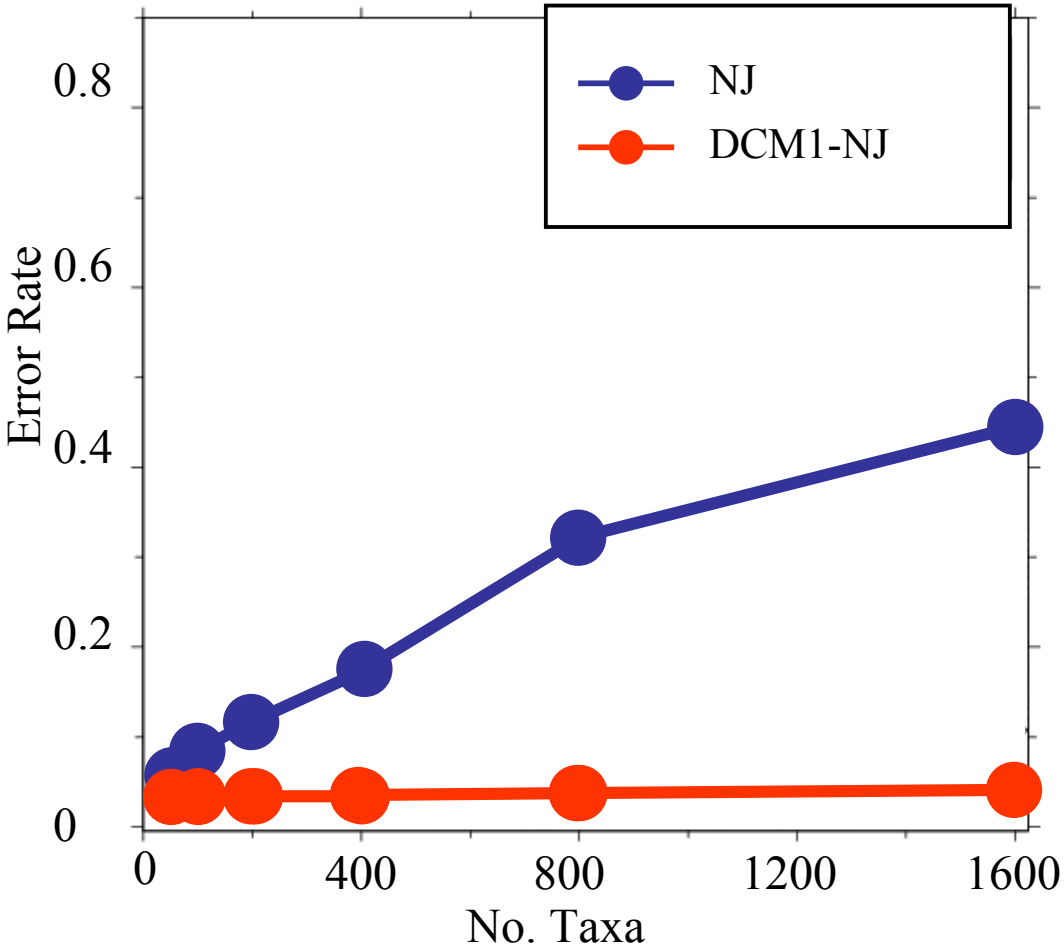

Simulation study based upon fixed edge lengths, K2P model of evolution, sequence lengths fixed to 1000 nucleotides.

Error rates reflect proportion of incorrect edges in inferred trees.

***[Nakhleh et al. ISMB 2001]***

# DCM1-boosting distance-based methods

*[Nakhleh et al. ISMB 2001]*



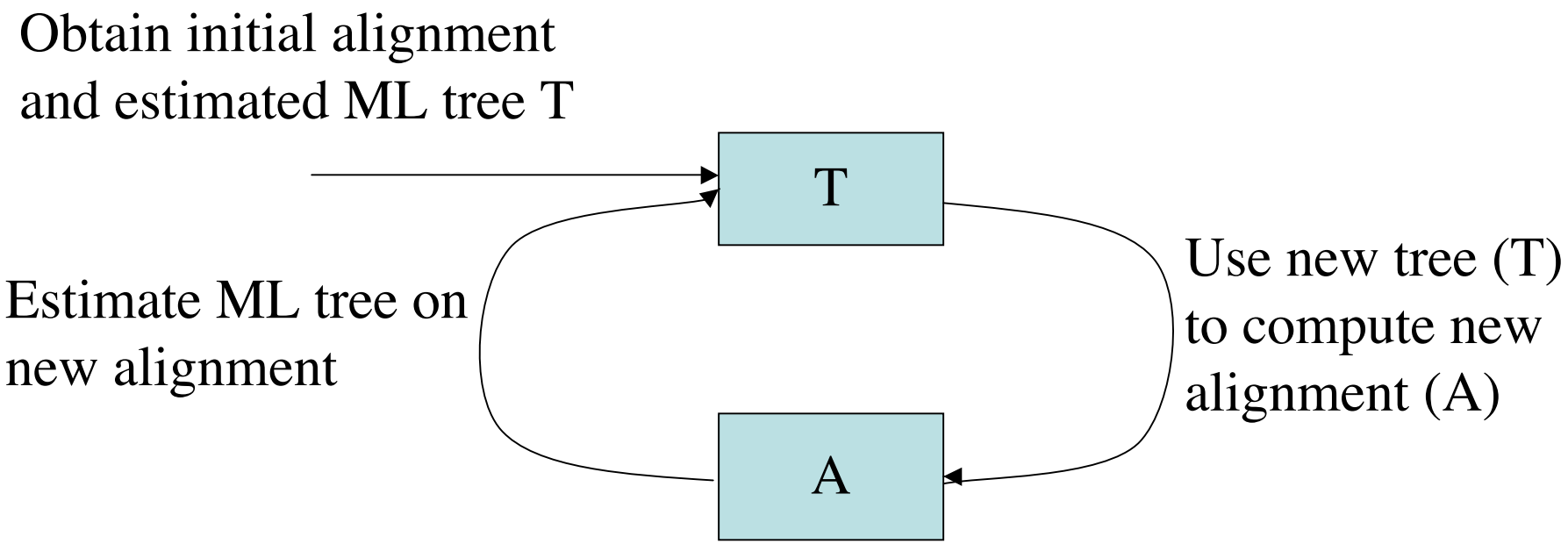

**Theorem:**
DCM1-NJ converges to the true tree from polynomial length sequences

# Other “boosters”

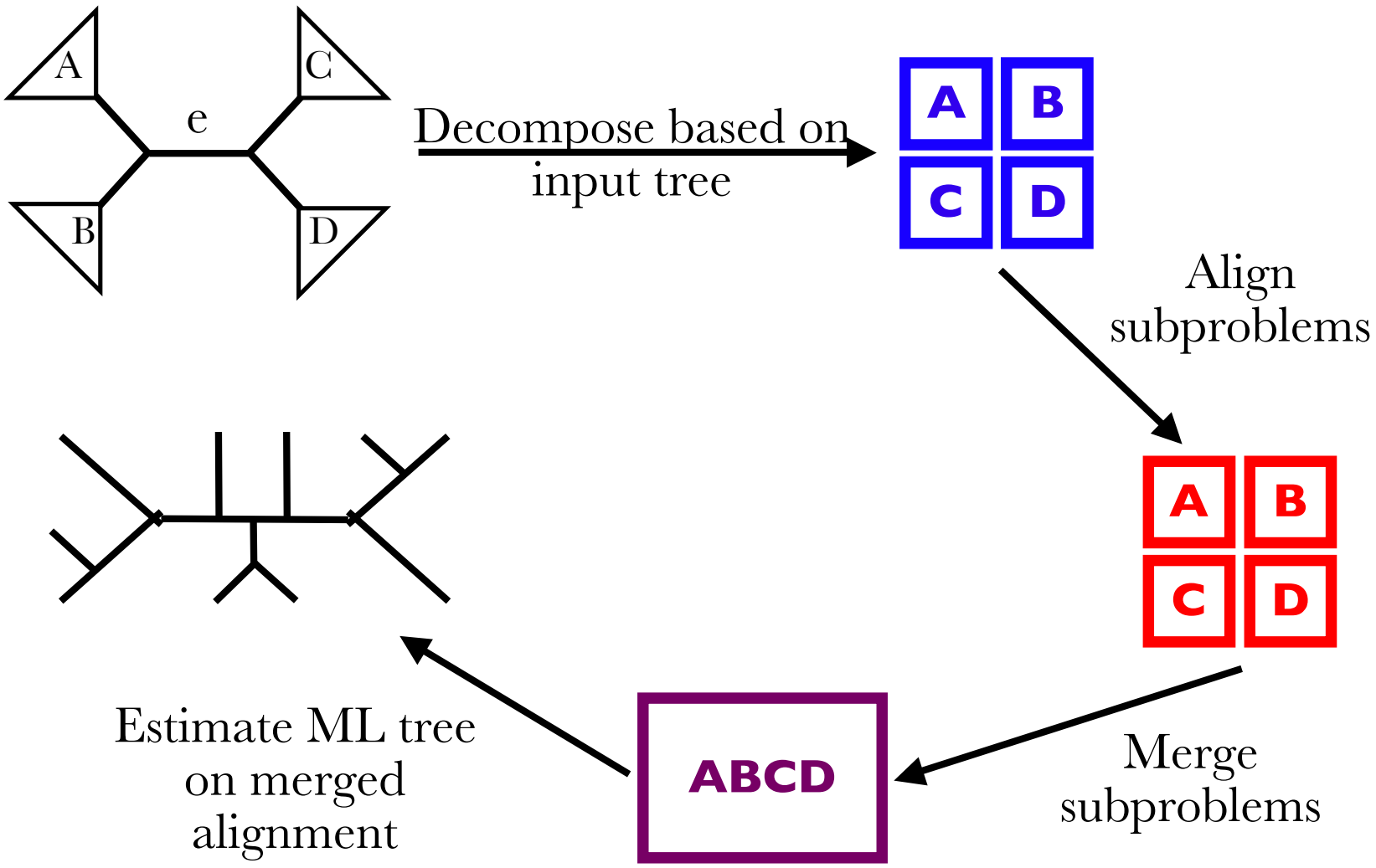
- SATé: Simultaneous Alignment and Tree Estimation (Liu et al., Science 2009, and Liu et al. Systematic Biology, in press)
- DACTAL: Divide-and-Conquer Trees (Almost) without alignments (Nelesen et al., submitted)
- SEPP: SATé-enabled Phylogenetic Placement (Mirarab, Nguyen and Warnow, to appear, PSB 2012)

# SATé Algorithm (Liu et al. Science 2009)

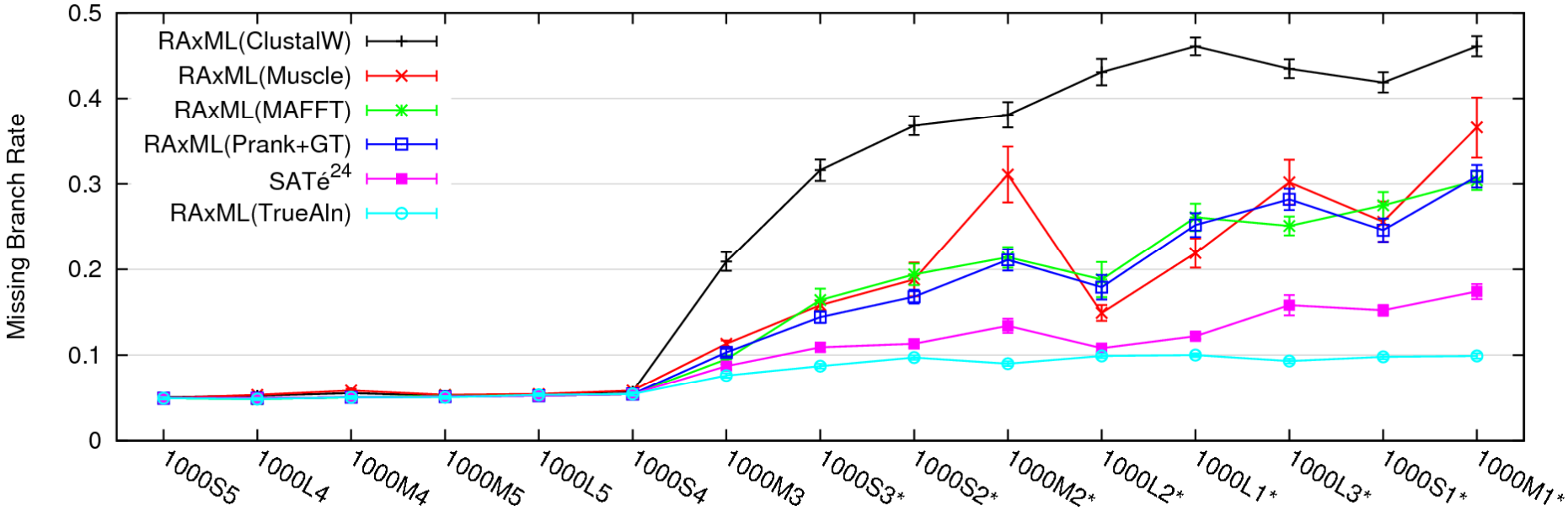
SATé = Simultaneous Alignment and Tree Estimation



# One SATé iteration (really 32 subsets)

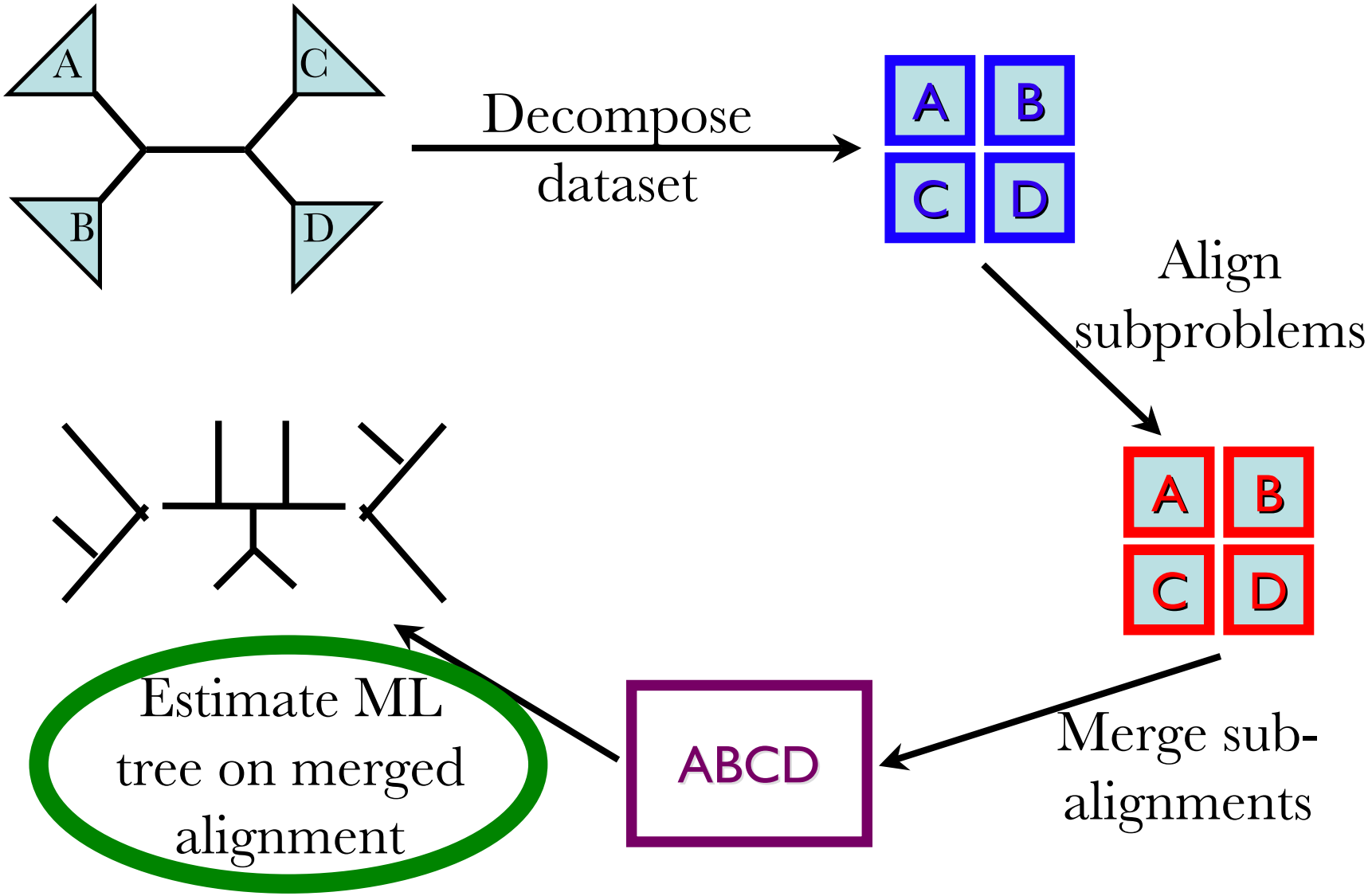


# Results on 1000-taxon datasets




- 24 hour SATé analysis
- Other simultaneous estimation methods cannot run on large datasets

# Limitations of SATé

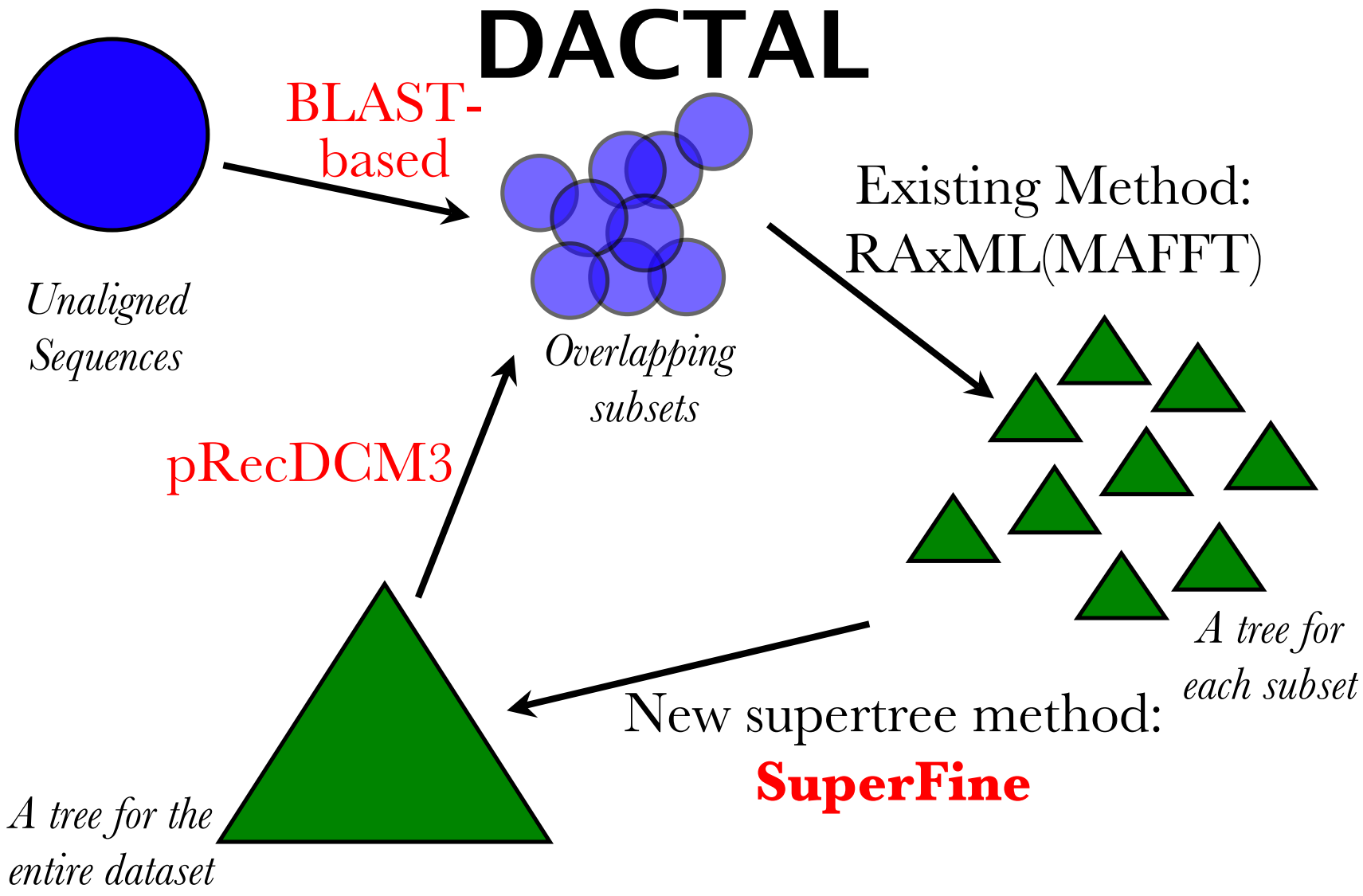


# Part II: DACTAL

## (Divide-And-Conquer Trees (Almost) without alignments)

- Input: set S of unaligned sequences
- Output: tree on S (but no alignment)

(Nelesen, Liu, Wang, Linder, and Warnow, submitted)


DACTAL
BLAST-based
Unaligned Sequences
Overlapping subsets
Existing Method: RAxML(MAFFT)
A tree for each subset
New supertree method:
SuperFine
pRecDCM3
A tree for the entire dataset

# Average of 3 Largest CRW Datasets

CRW: Comparative RNA database,

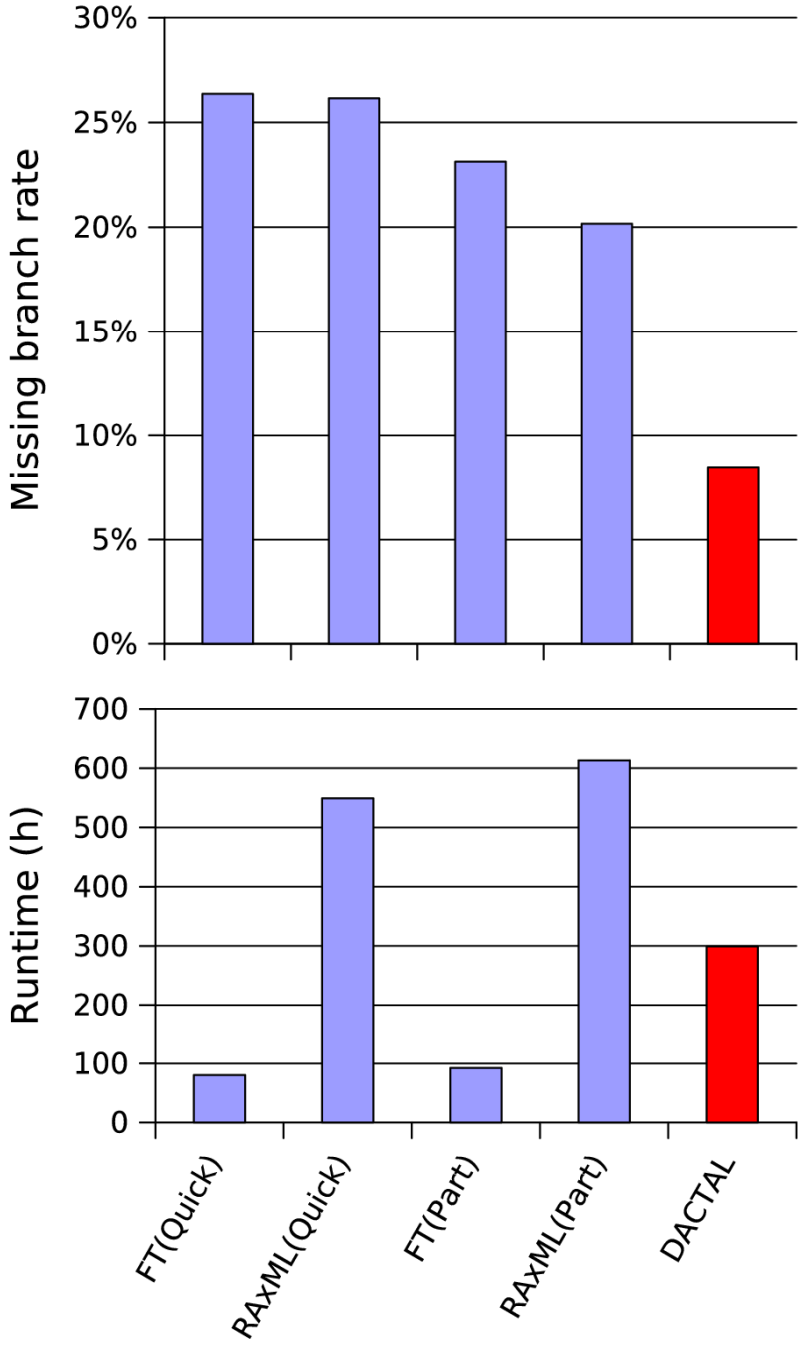
Three 16S datasets with 6,323 to 27,643 sequences

Reference alignments based on secondary structure

Reference trees are 75% RAxML bootstrap trees

DACTAL (shown in red) run for 5 iterations starting from FT(Part)

FastTree (FT) and RAxML are ML methods



# Observations

- DACTAL gives more accurate trees than all other methods on the largest datasets
- DACTAL is much faster than SATé (and can analyze datasets that SATé cannot)
- DACTAL is robust to starting trees and other algorithmic parameters

# Taxon Identification in Metagenomics

- Input: set of shotgun sequences (very short)
- Output: a tree on the set of sequences, indicating the species identification of each sequence

- Issues: the sequences are not globally alignable, they are very short, and there are millions of them

# Phylogenetic Placement

Input: Backbone alignment and tree on full-length sequences, and a set of query sequences (short fragments)

Output: Placement of query sequences on backbone tree

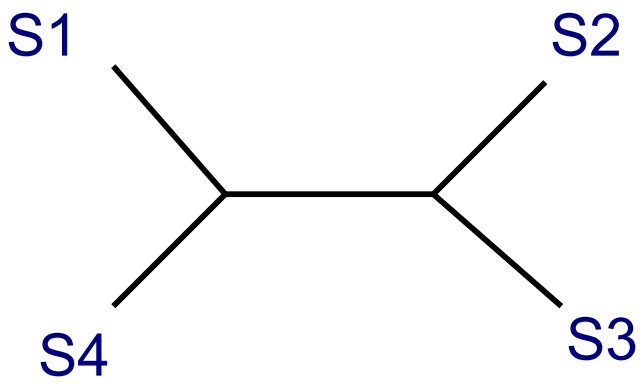
Applications:

taxon identification of metagenomic data,

phylogenetic analyses of NGS data.

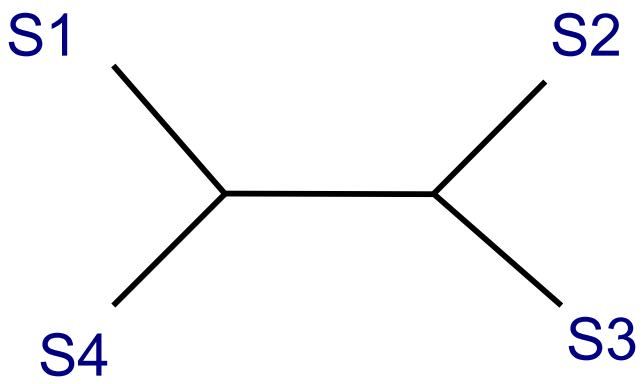
# Align Sequence

```
S1   = -AGGCTATCACCTGACCTCCA-AA
S2   = TAG-CTATCAC--GACCGC--GCA
S3   = TAG-CT-------GACCGC--GCT
S4   = TAC----TCAC--GACCGACAGCT
Q1   = TAAAAC
```



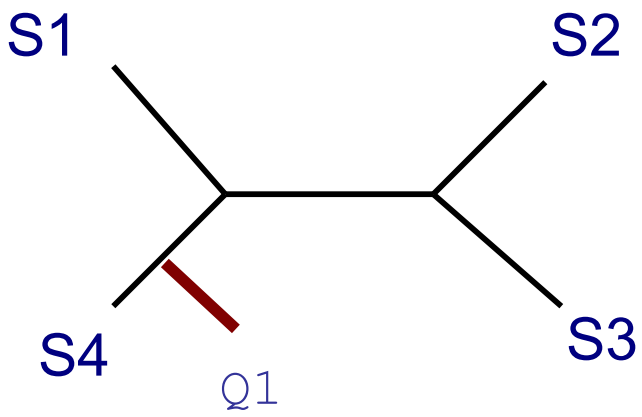
# Align Sequence

```
S1  = -AGGCTATCACCTGACCTCCA-AA
S2  = TAG-CTATCAC--GACCGC--GCA
S3  = TAG-CT-------GACCGC--GCT
S4  = TAC----TCAC--GACCGACAGCT
Q1  = -------T-A--AAAC--------
```

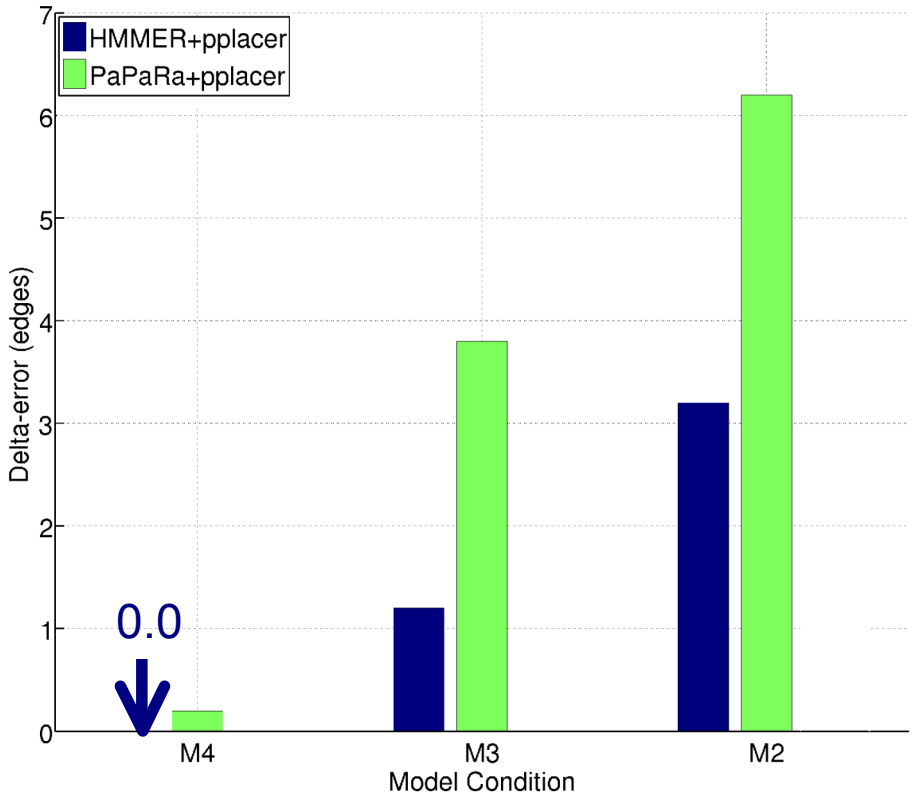


# Place Sequence

```
S1  = -AGGCTATCACCTGACCTCCA-AA
S2  = TAG-CTATCAC--GACCGC--GCA
S3  = TAG-CT-------GACCGC--GCT
S4  = TAC----TCAC--GACCGACAGCT
Q1  = -------T-A--AAAC--------
```

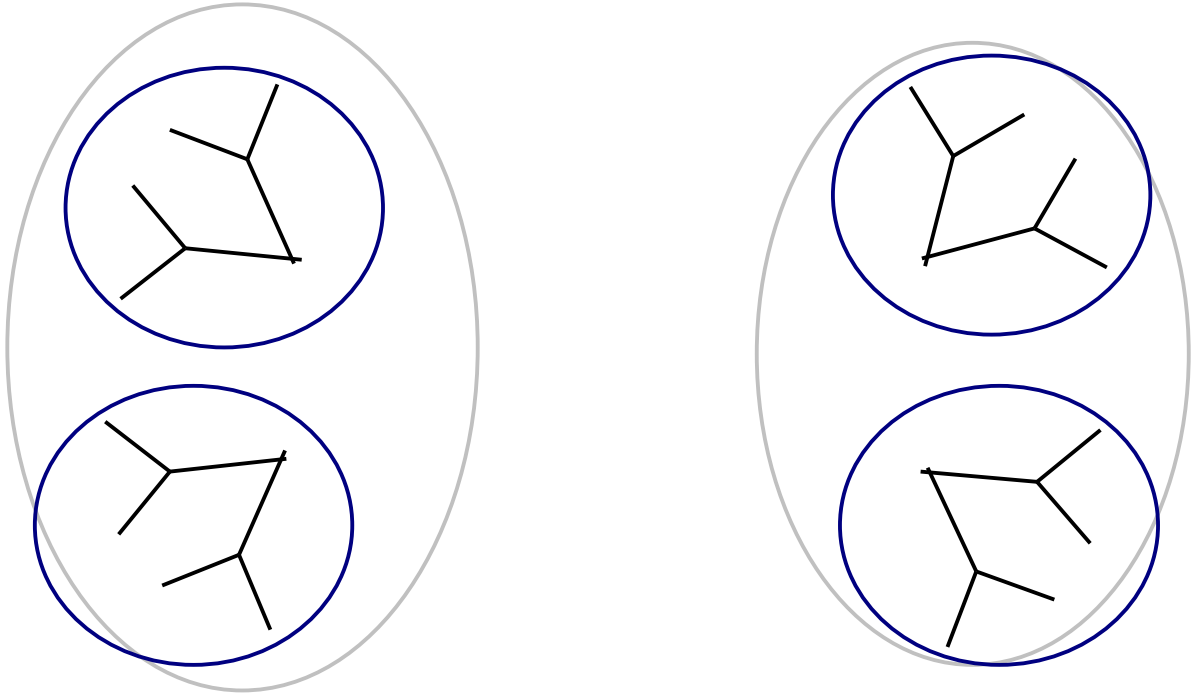


# HMMER vs. PaPaRa

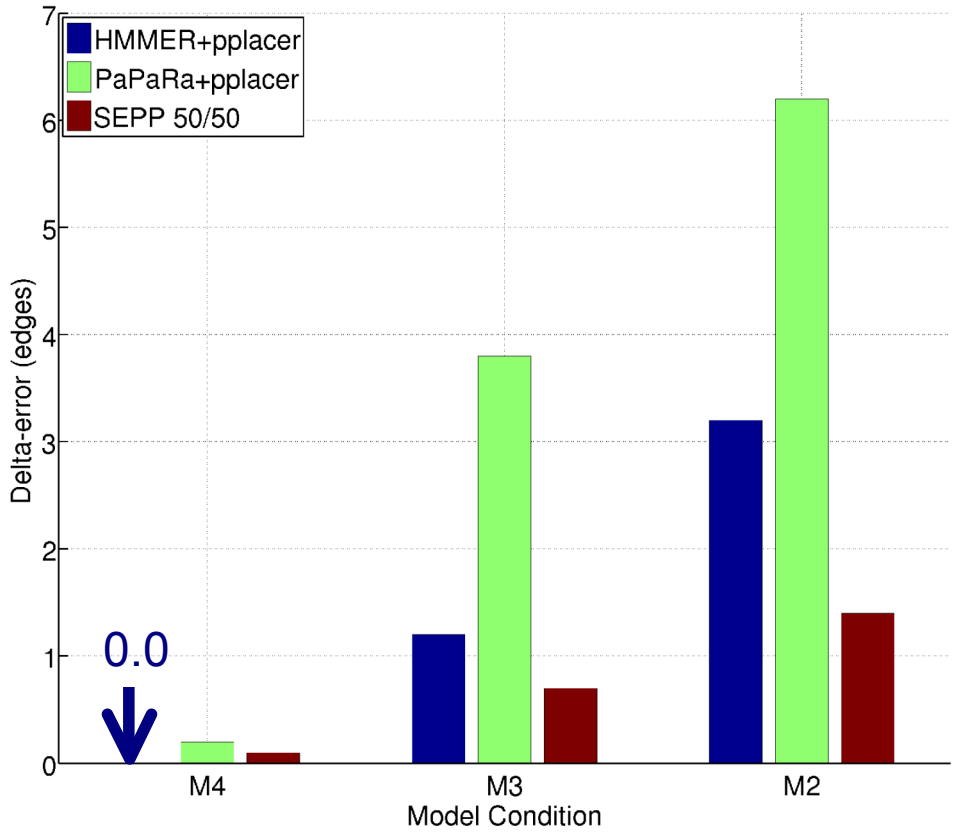



**Increasing rate of evolution**

# Divide-and-conquer with HMMER+pplacer



# SEPP (10%-rule) on simulated data




**Increasing rate of evolution**

# Historical linguistics

- Languages evolve, just like biological species.
- How can we determine how languages evolve?
- How can we use information on language evolution, to determine how human populations moved across the globe?

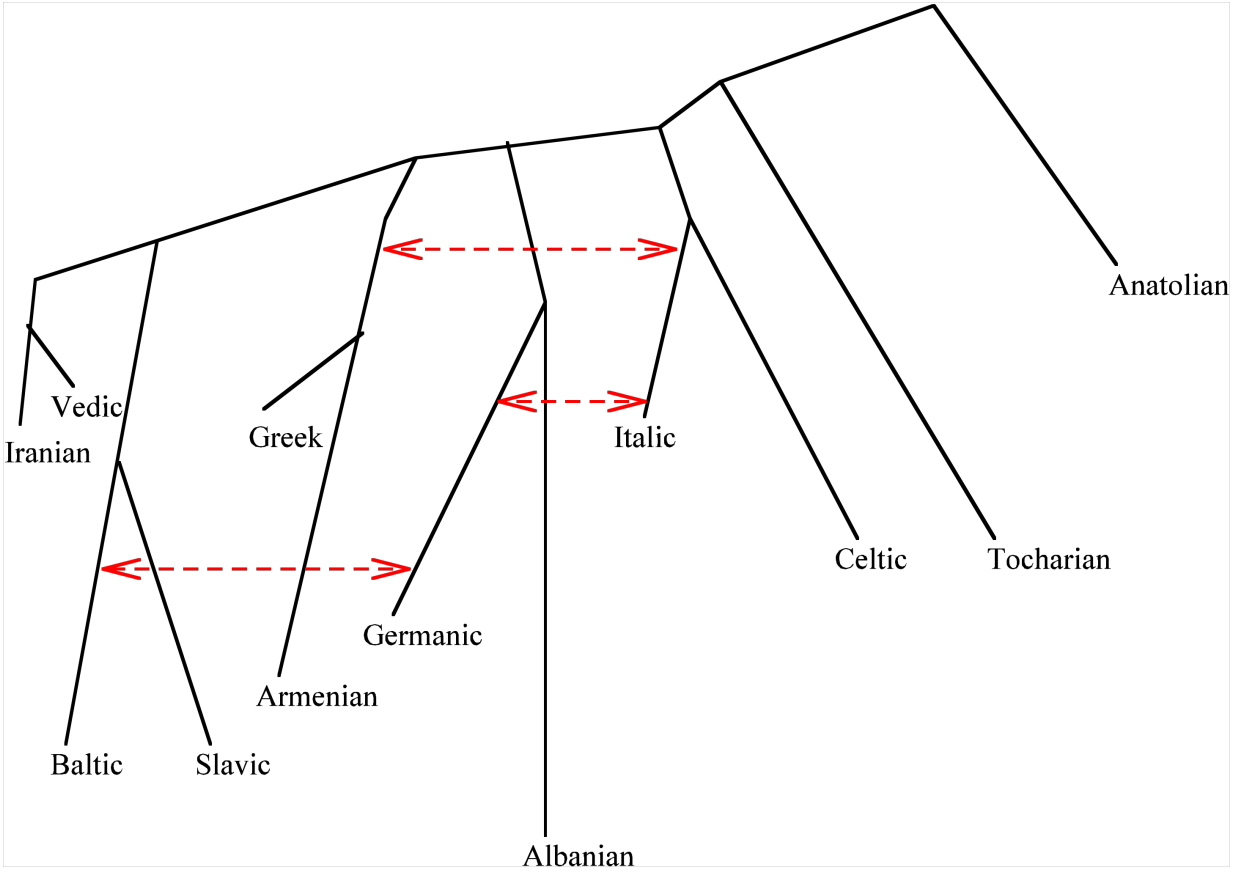
# Questions about Indo-European (IE)

- How did the IE family of languages evolve?
- Where is the IE homeland?
- When did Proto-IE “end”?
- What was life like for the speakers of proto-Indo-European (PIE)?

# Estimating the date and homeland of the proto-Indo-Europeans

- Step 1: Estimate the phylogeny
- Step 2: Reconstruct words for proto-Indo-European (and for intermediate proto-languages)
- Step 3: Use archaeological evidence to constrain dates and geographic locations of the proto-languages

# “Perfect Phylogenetic Network” (Nakhleh et al., Language)



# Reticulate evolution

- Not all evolution is tree-like:
  - Horizontal gene transfer
  - Hybrid speciation
- How can we detect reticulate evolution?

# Course Details

- Phylogeny and multiple sequence alignment are the basis of almost everything in the course
- The first 1/3 of the class will provide the basics of the material
- The next 2/3 will go into depth into selected topics

# Course details

- There is no textbook; I will provide notes.
- Homeworks: basic material and critical review of papers from the scientific literature
- Course project: either a research project (two students per project) or a literature survey (one student per project). The best projects should be submitted for publication in a journal or conference.
- Final exam: comprehensive, take home.

# Grading

- Homework: 20%
- Class participation: 20%
- Final exam: 30%
- Class project: 30%

# Combined Analysis Methods

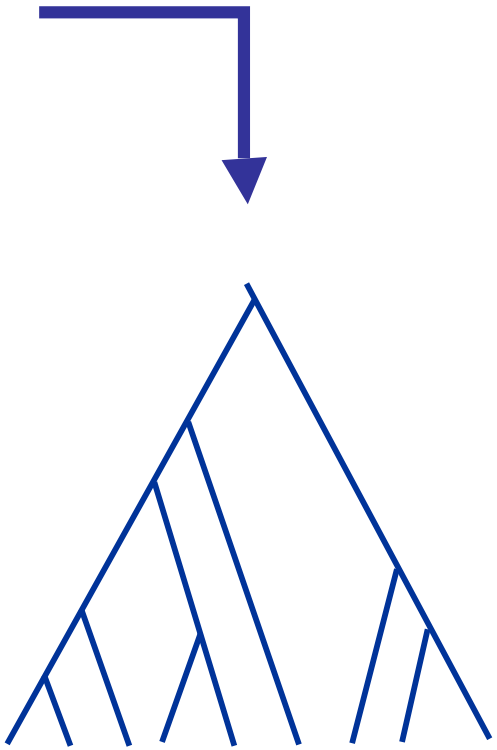
| | gene 1 |
|---|---|
| $S_1$ | TCTAATGGAA |
| $S_2$ | GCTAAGGGAA |
| $S_3$ | TCTAAGGGAA |
| $S_4$ | TCTAACGGAA |
| $S_7$ | TCTAATGGAC |
| $S_8$ | TATAACGGAA |

| | gene 2 |
|---|---|
| $S_4$ | GGTAACCCTC |
| $S_5$ | GCTAAACCTC |
| $S_6$ | GGTGACCATC |
| $S_7$ | GCTAAACCTC |

| | gene 3 |
|---|---|
| $S_1$ | TATTGATACA |
| $S_3$ | TCTTGATACC |
| $S_4$ | TAGTGATGCA |
| $S_7$ | TAGTGATGCA |
| $S_8$ | CATTCATACC |

# Combined Analysis

| | gene 1 | gene 2 | gene 3 |
|---|---|---|---|
| $S_1$ | TCTAATGGAA | ? ? ? ? ? ? ? ? ? ? | TATTGATACA |
| $S_2$ | GCTAAGGGAA | ? ? ? ? ? ? ? ? ? ? | ? ? ? ? ? ? ? ? ? ? |
| $S_3$ | TCTAAGGGAA | ? ? ? ? ? ? ? ? ? ? | TCTTGATACC |
| $S_4$ | TCTAACGGAA | GGTAACCCTC | TAGTGATGCA |
| $S_5$ | ? ? ? ? ? ? ? ? ? ? | GCTAAACCTC | ? ? ? ? ? ? ? ? ? ? |
| $S_6$ | ? ? ? ? ? ? ? ? ? ? | GGTGACCATC | ? ? ? ? ? ? ? ? ? ? |
| $S_7$ | TCTAATGGAC | GCTAAACCTC | TAGTGATGCA |
| $S_8$ | TATAACGGAA | ? ? ? ? ? ? ? ? ? ? | CATTCATACC |



# Two competing approaches