New HMM-based methods for Ultra-large Alignment and Phylogeny Estimation

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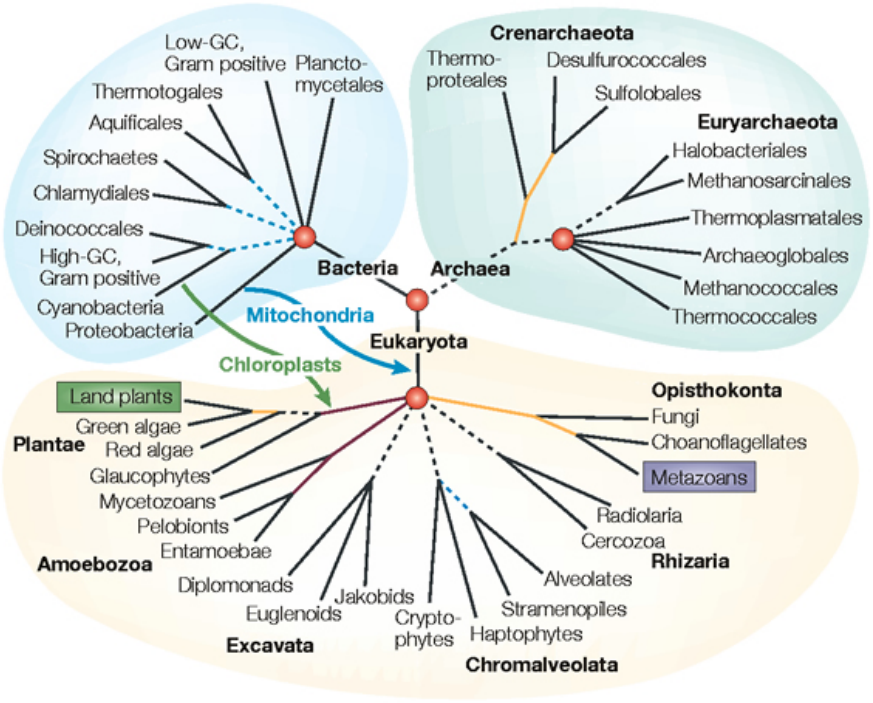
Phylogenies and Applications



Nature Reviews | Genetics

Basic Biology:

How did life evolve?

Applications of phylogenies to:

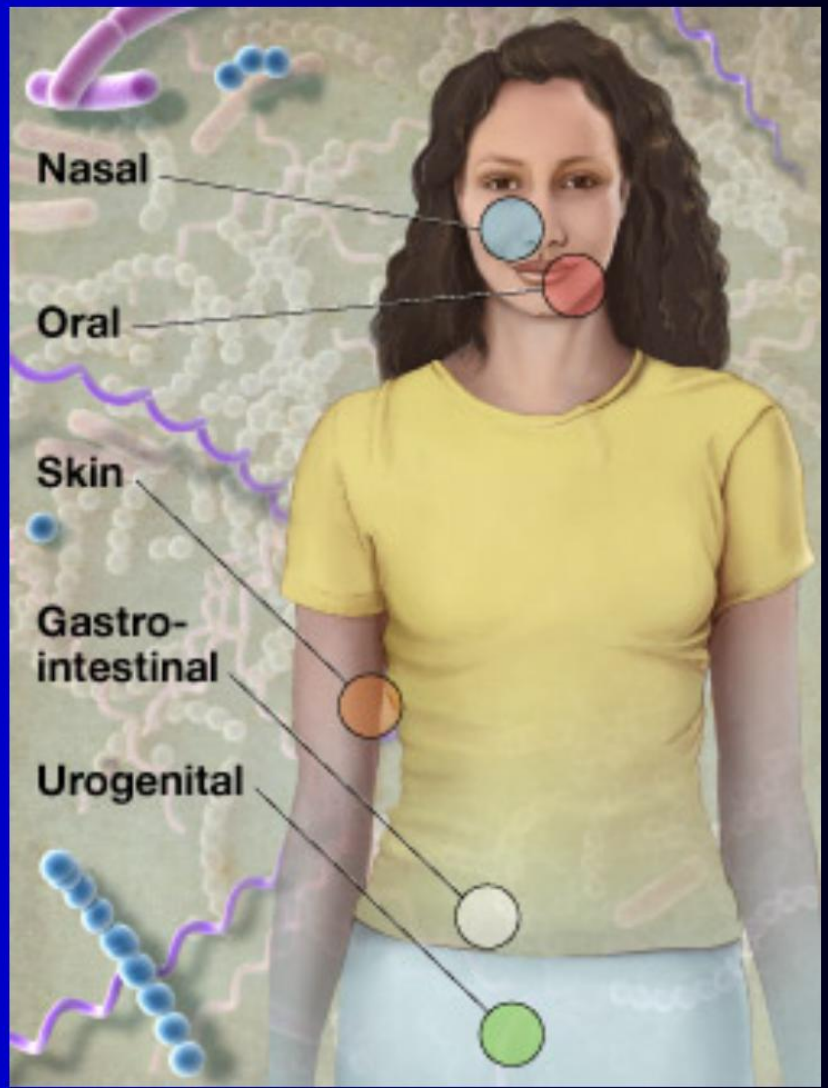
protein structure and function

population genetics

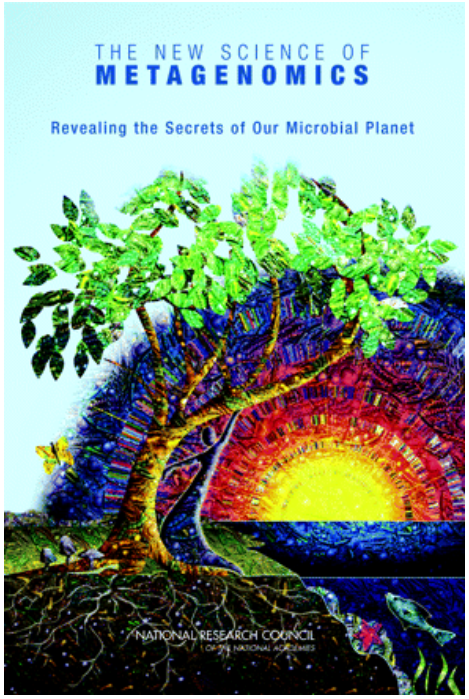
human migrations

The NIH Human Microbiome Project

25,000 human genes,
1,000,000 bacterial genes

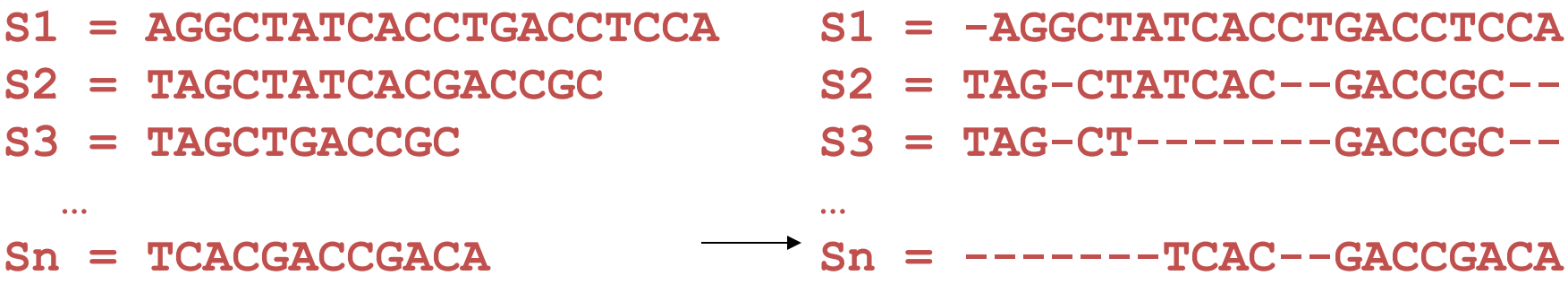


Computational Phylogenetics and Metagenomics



Courtesy of the Tree of Life project

Multiple Sequence Alignment (MSA): *another grand challenge*[1]



Novel techniques needed for scalability and accuracy

NP-hard problems and large datasets

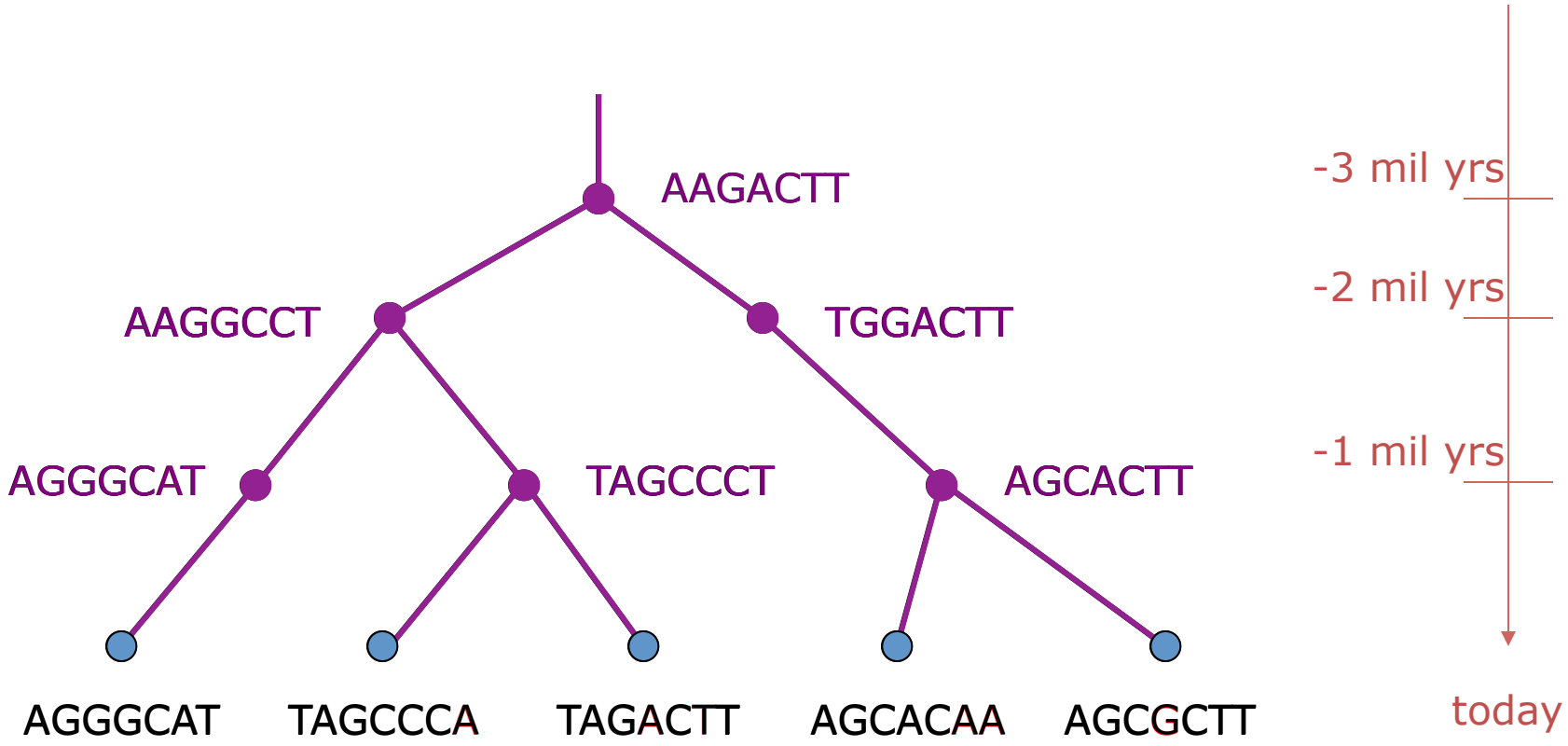
Current methods do not provide good accuracy

Few methods can analyze even moderately large datasets

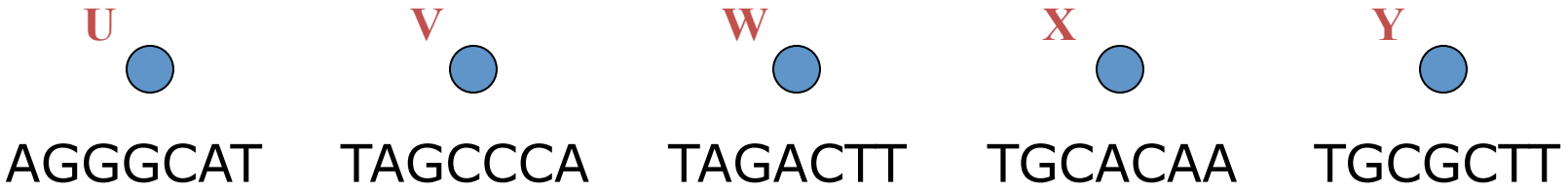
Many important applications besides phylogenetic estimation

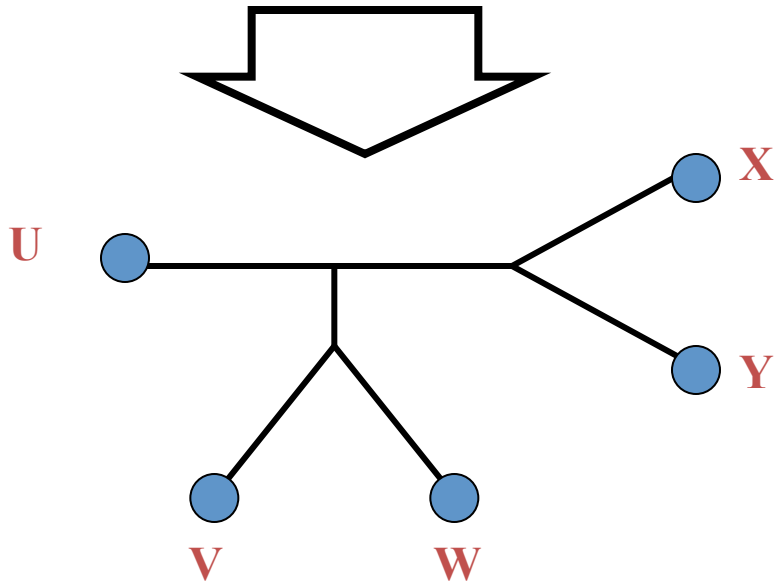
[1] Frontiers in Massive Data Analysis, National Academies Press, 2013

DNA Sequence Evolution

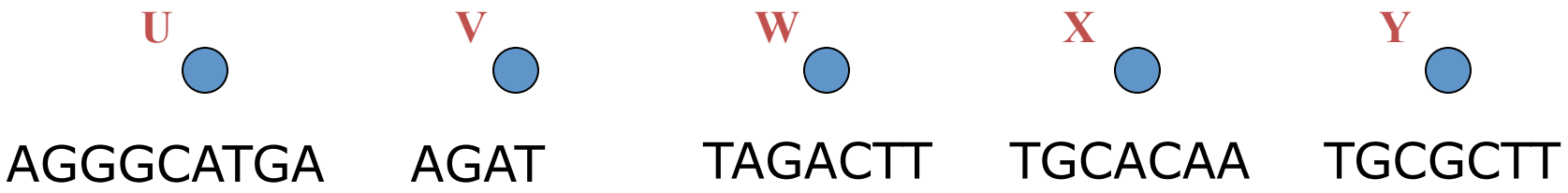


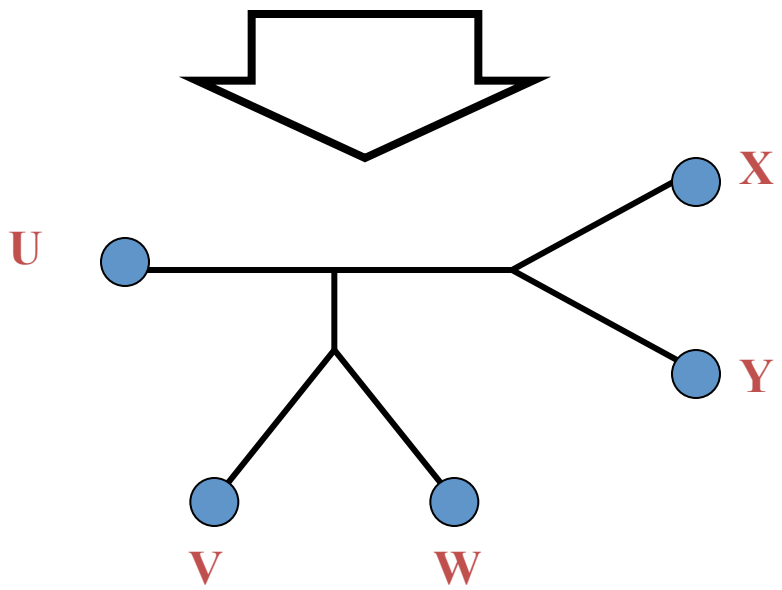
Phylogeny Problem



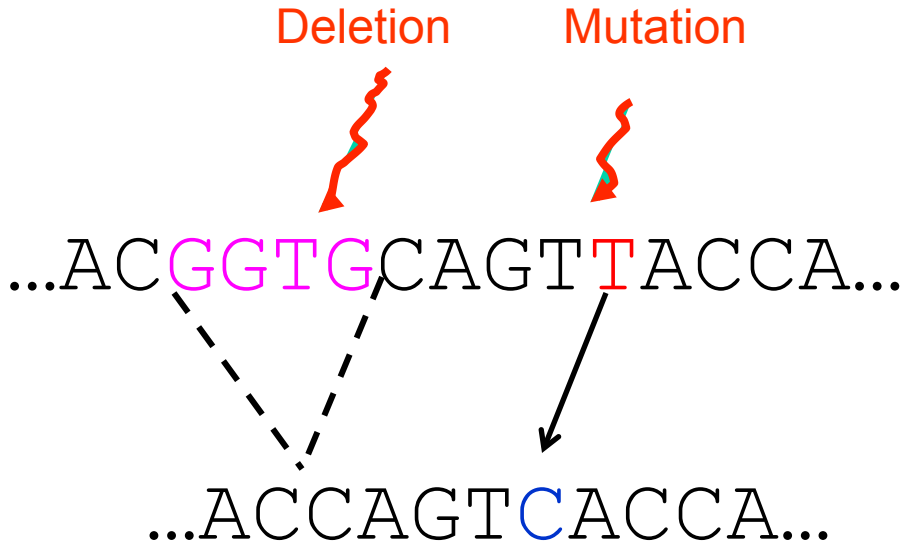


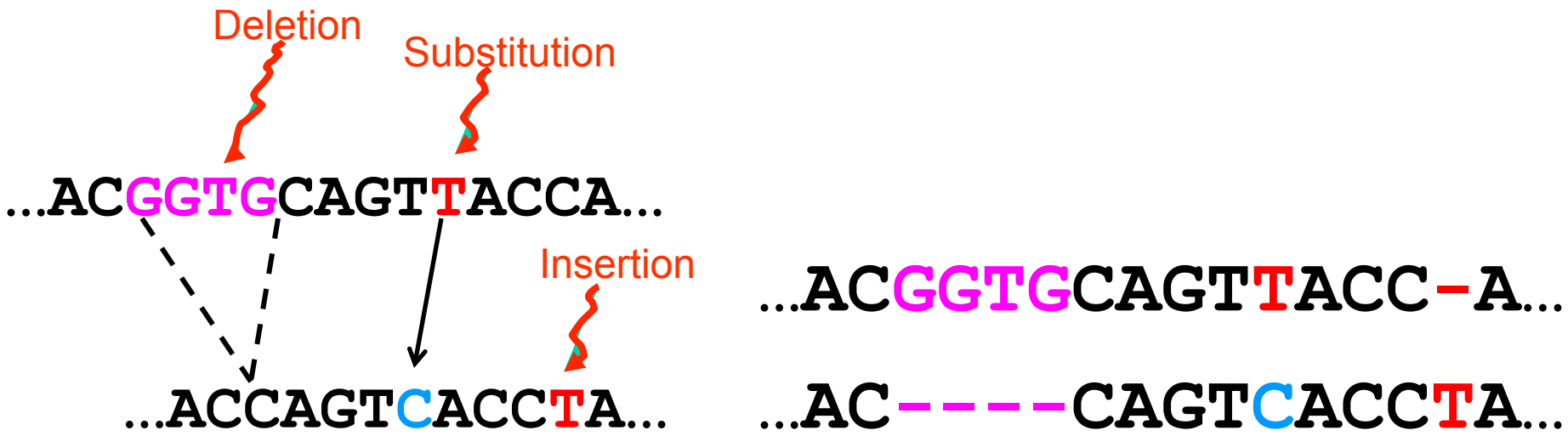
The “real” problem





Indels (insertions and deletions)





The true multiple alignment

- **Reflects historical substitution, insertion, and deletion events**
- **Defined using transitive closure of pairwise alignments computed on edges of the true tree**

Input: unaligned sequences

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

Phase 1: 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
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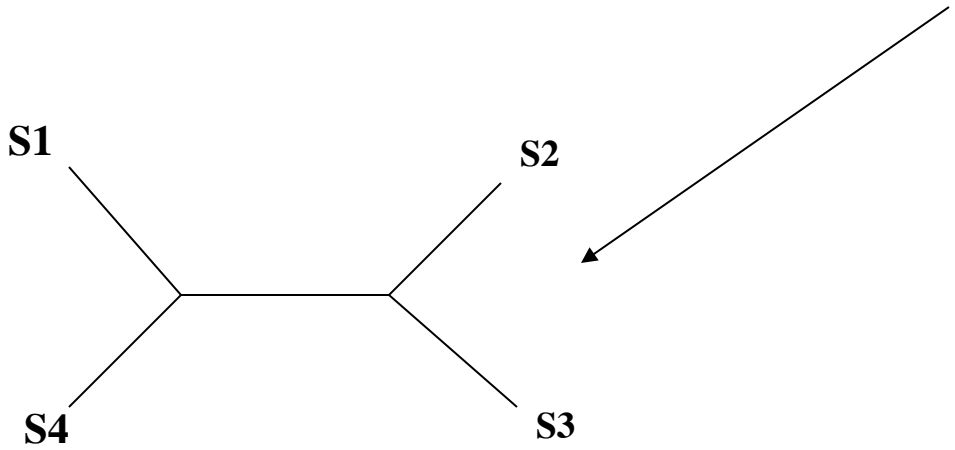
```



Phylogenomic pipeline

- Select taxon set and markers
- Gather and screen sequence data, possibly identify orthologs
- Compute multiple sequence alignments for each locus
- Compute species tree or network:
  - Compute gene trees on the alignments and combine the estimated gene trees, OR
  - Estimate a tree from a concatenation of the multiple sequence alignments
- Get statistical support on each branch (e.g., bootstrapping)
- Estimate dates on the nodes of the phylogeny
- Use species tree with branch support and dates to understand biology

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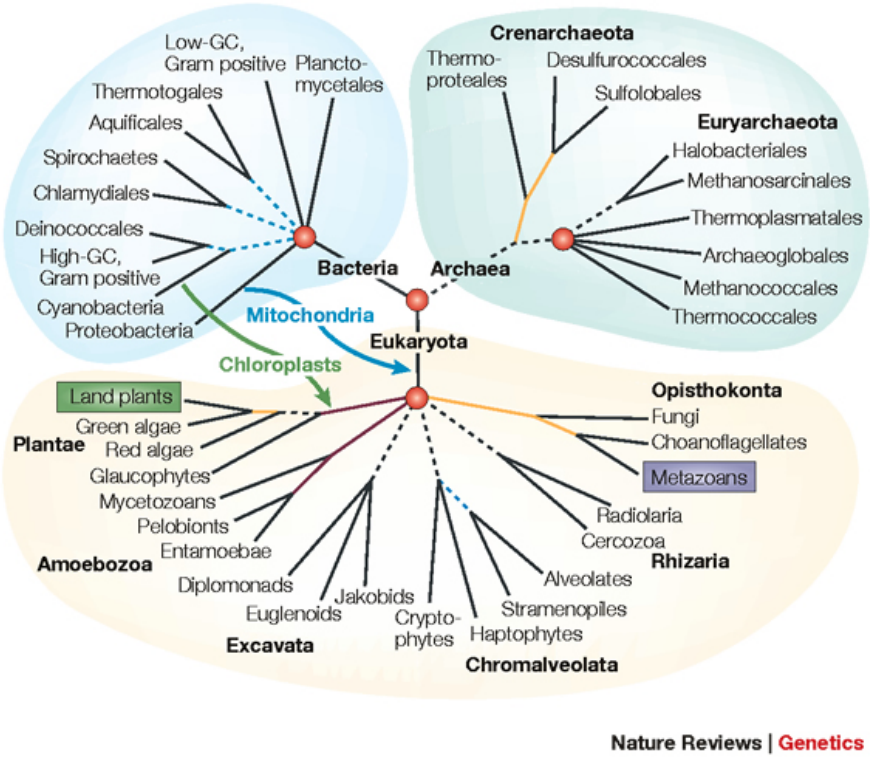
Large-scale Alignment Estimation

- Many genes are considered unalignable due to high rates of evolution
- Only a few methods can analyze large datasets
- iPlant (NSF Plant Biology Collaborative) and other projects planning to construct phylogenies with 500,000 taxa

Hard Computational Problems



NP-hard problems

Large datasets

- 100,000+ sequences
- thousands of genes

"Big data" complexity:

- model misspecification
- fragmentary sequences
- errors in input data
- streaming data

1kp: Thousand Transcriptome Project

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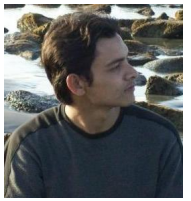


Plus many many other people…

- Plant Tree of Life based on transcriptomes of ~1200 species
- More than 13,000 gene families (most not single copy)

Challenges:

Species tree estimation from conflicting gene trees

Alignment of datasets with > 100,000 sequences

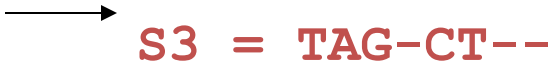
This talk

- “Big data” multiple sequence alignment
- SATé (2009, 2012) and PASTA (2014), methods for co-estimation of alignments and trees
- The HMM Family technique, and applications to
  - phylogenetic placement (SEPP, PSB 2012),
  - multiple sequence alignment (UPP, submitted), and
  - metagenomic taxon identification (TIPP, submitted).

Multiple Sequence Alignment

First Align, then Compute the Tree

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



```
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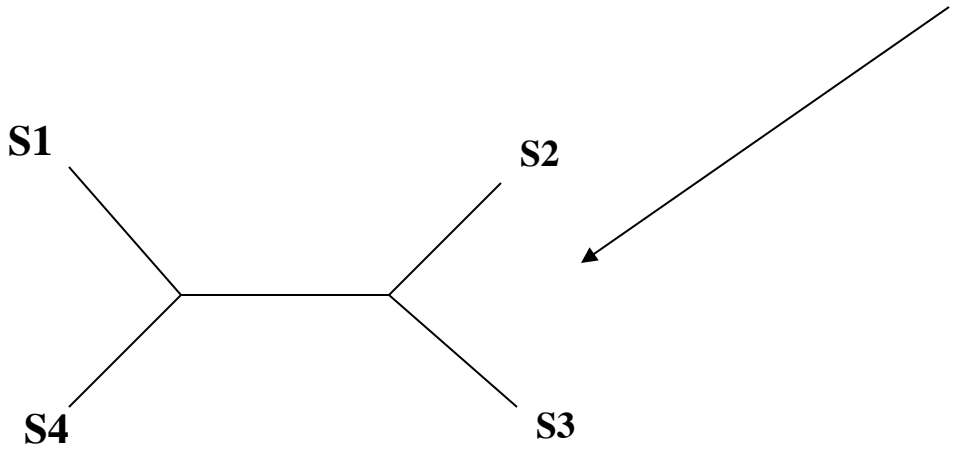
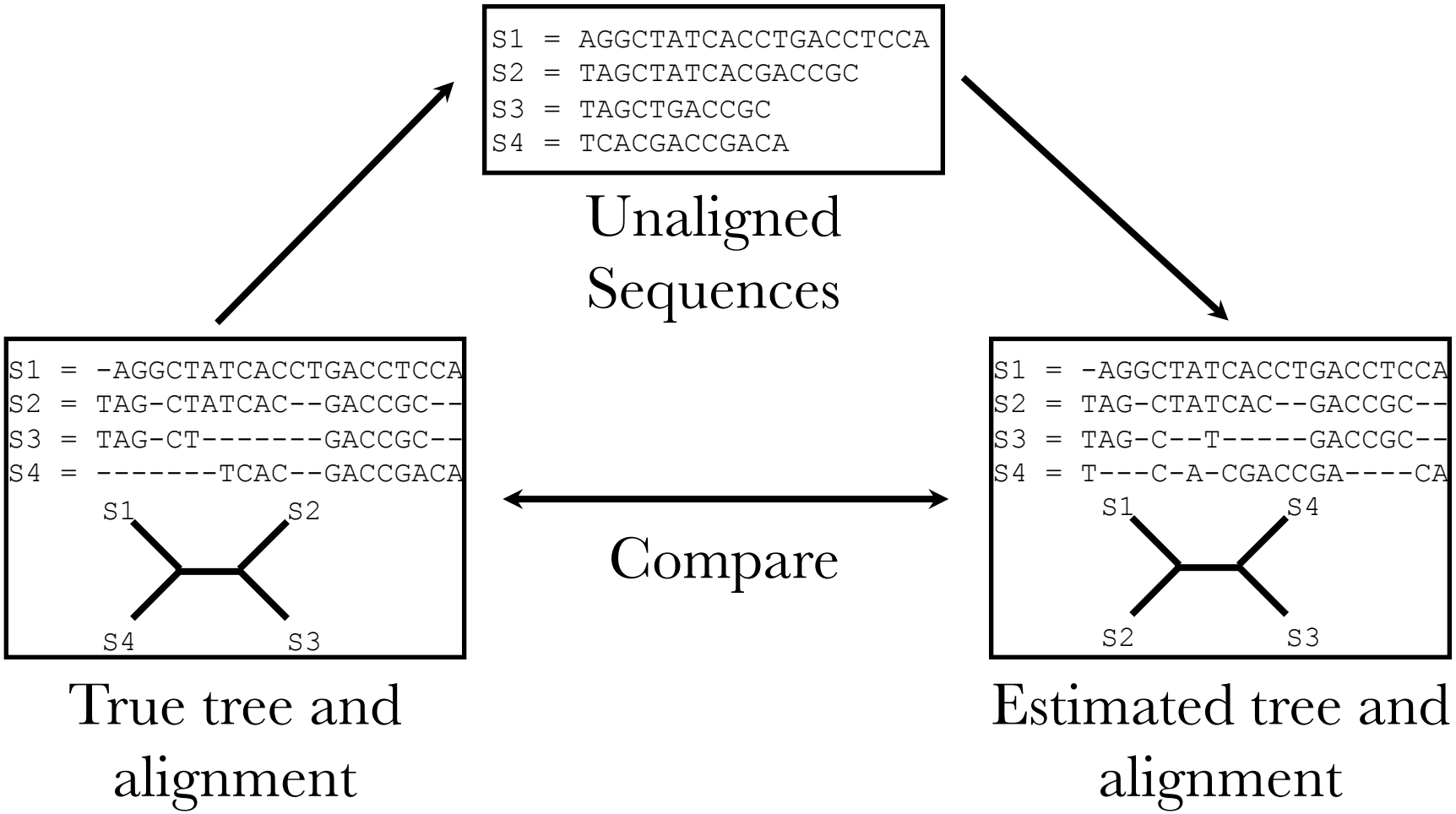
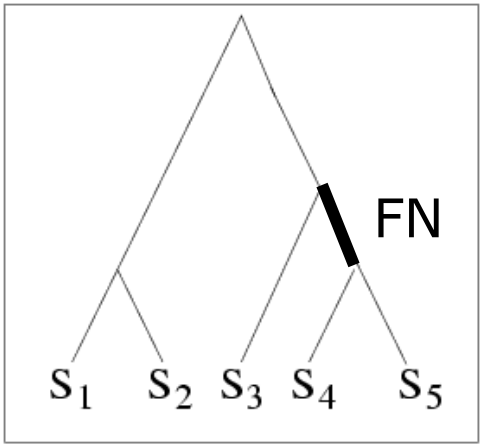
```



Simulation Studies



Quantifying Error



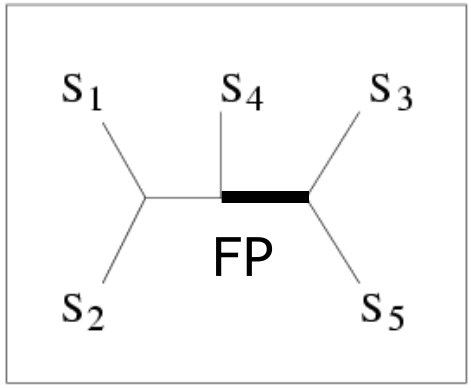
TRUE TREE

S_1	ACAATTAGAAC
S_2	ACCCTTAGAAC
S_3	ACCATTCCAAC
S_4	ACCAGACCAAC
S_5	ACCAGACCGGA

DNA SEQUENCES

FN: false negative
(missing edge)
FP: false positive
(incorrect edge)

50% error rate



INFERRED TREE

Two-phase estimation

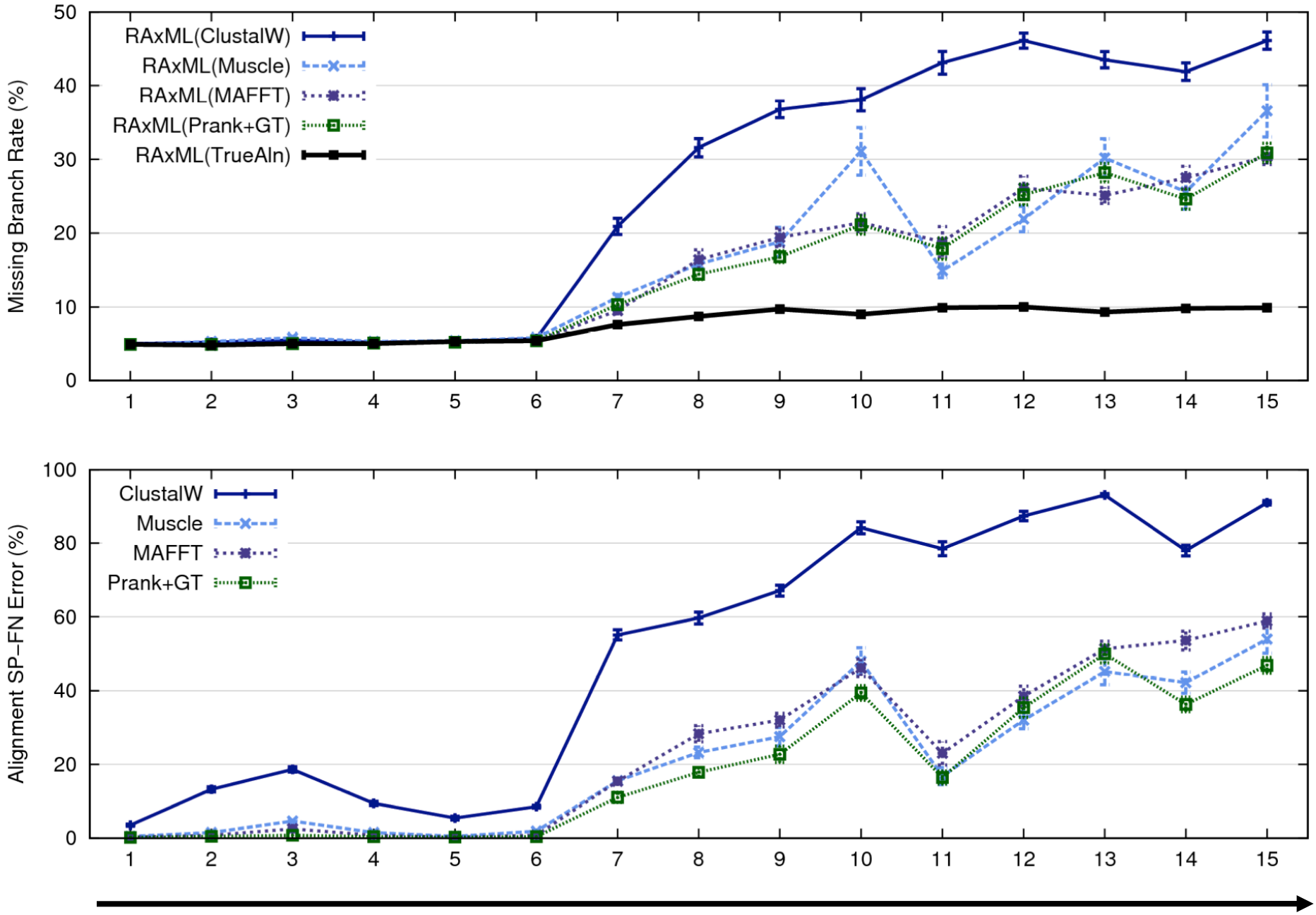
Alignment methods

- Clustal
- POY (and POY*)
- Probcons (and Probtree)
- Probalign
- MAFFT
- Muscle
- Di-align
- T-Coffee
- Prank (PNAS 2005, Science 2008)
- Opal (ISMB and Bioinf. 2007)
- *FSA (PLoS Comp. Bio. 2009)*
- *Infernal (Bioinf. 2009)*
- Etc.

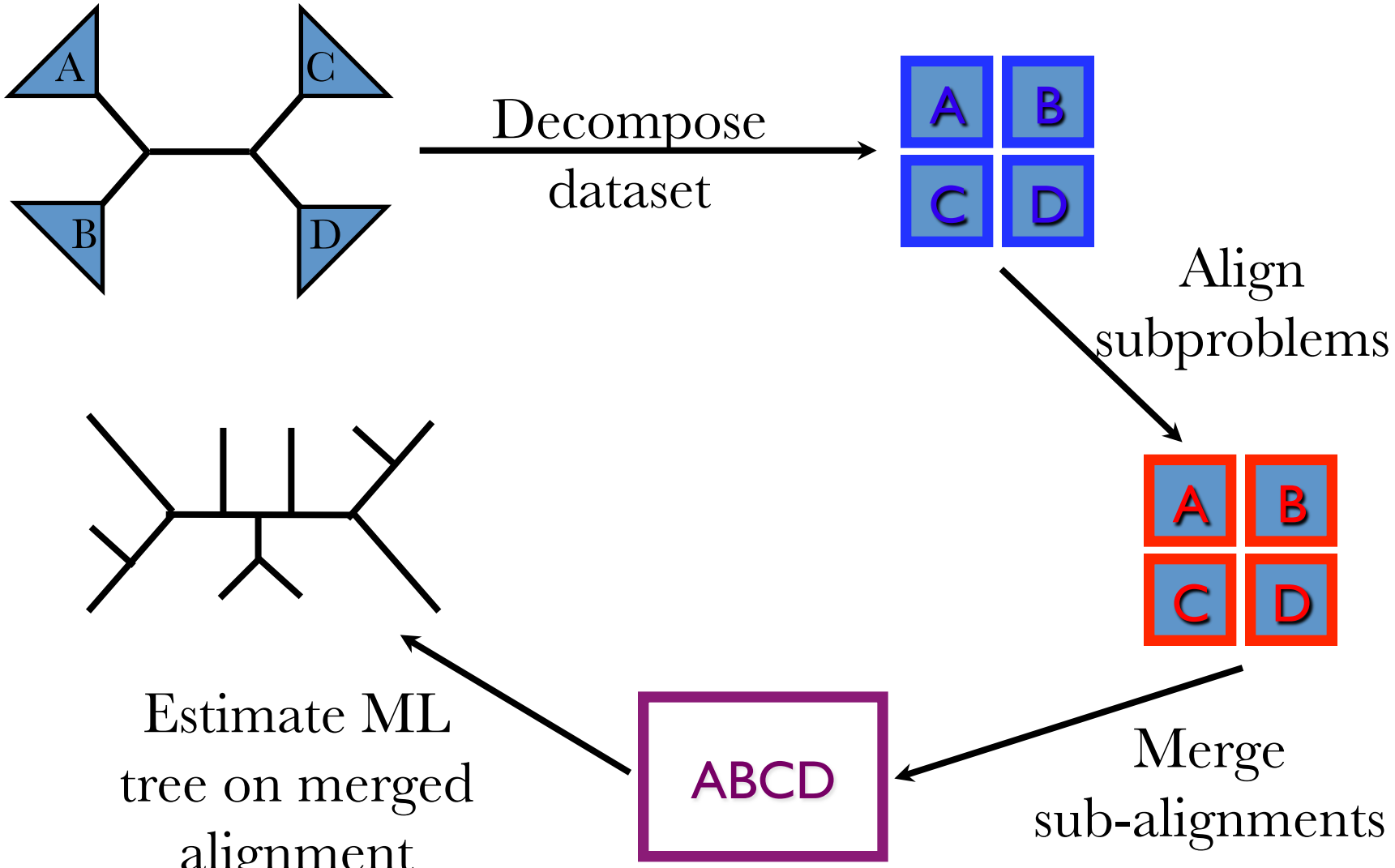
Phylogeny methods

- Bayesian MCMC
- Maximum parsimony
- Maximum likelihood
- Neighbor joining
- FastME
- UPGMA
- Quartet puzzling
- Etc.

***RAxML**: heuristic for large-scale ML optimization*

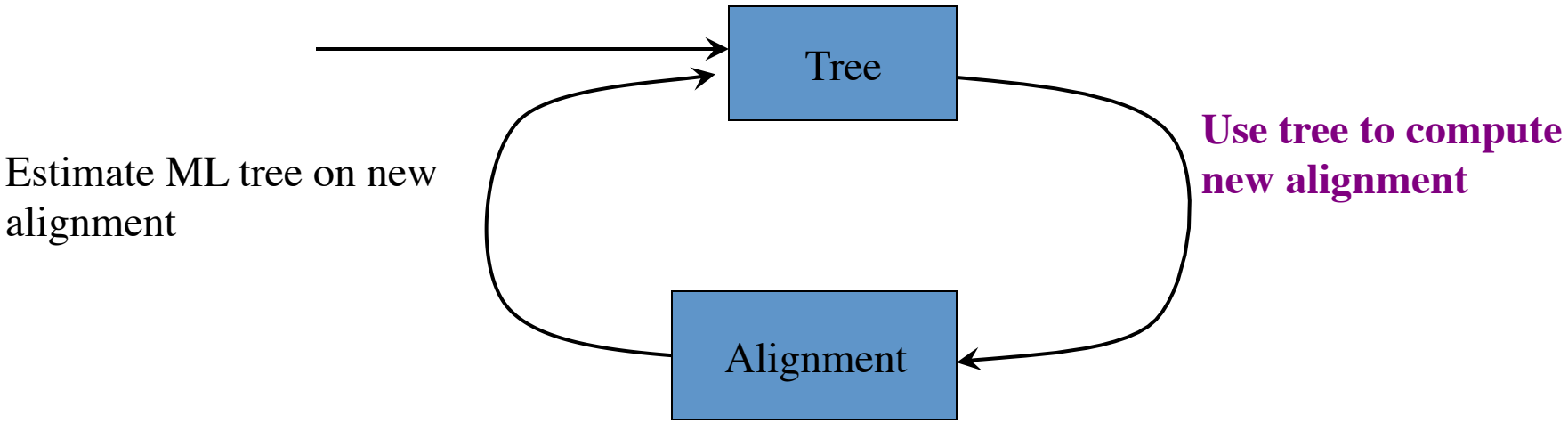

Missing Branch Rate (%)
RAxML(ClustalW)
RAxML(Muscle)
RAxML(MAFFT)
RAxML(Prank+GT)
RAxML(TrueAln)
Alignment SP–FN Error (%)
ClustalW
Muscle
MAFFT
Prank+GT
1000-taxon models, ordered by difficulty (Liu et al., 2009)

Re-aligning on a tree



SATé and PASTA Algorithms

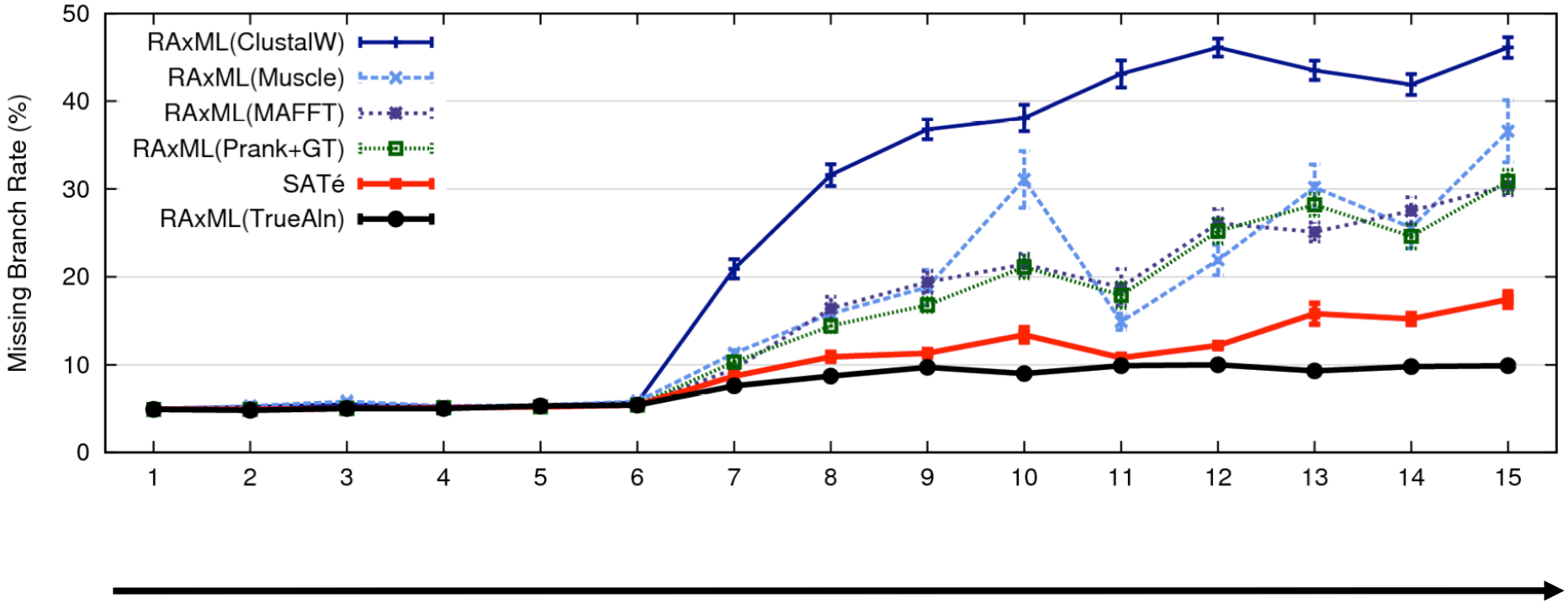
Obtain initial alignment and estimated ML tree



If new alignment/tree pair has worse ML score, realign using a different decomposition

Repeat until termination condition (typically, 24 hours)

SATé-1 (Science 2009) performance



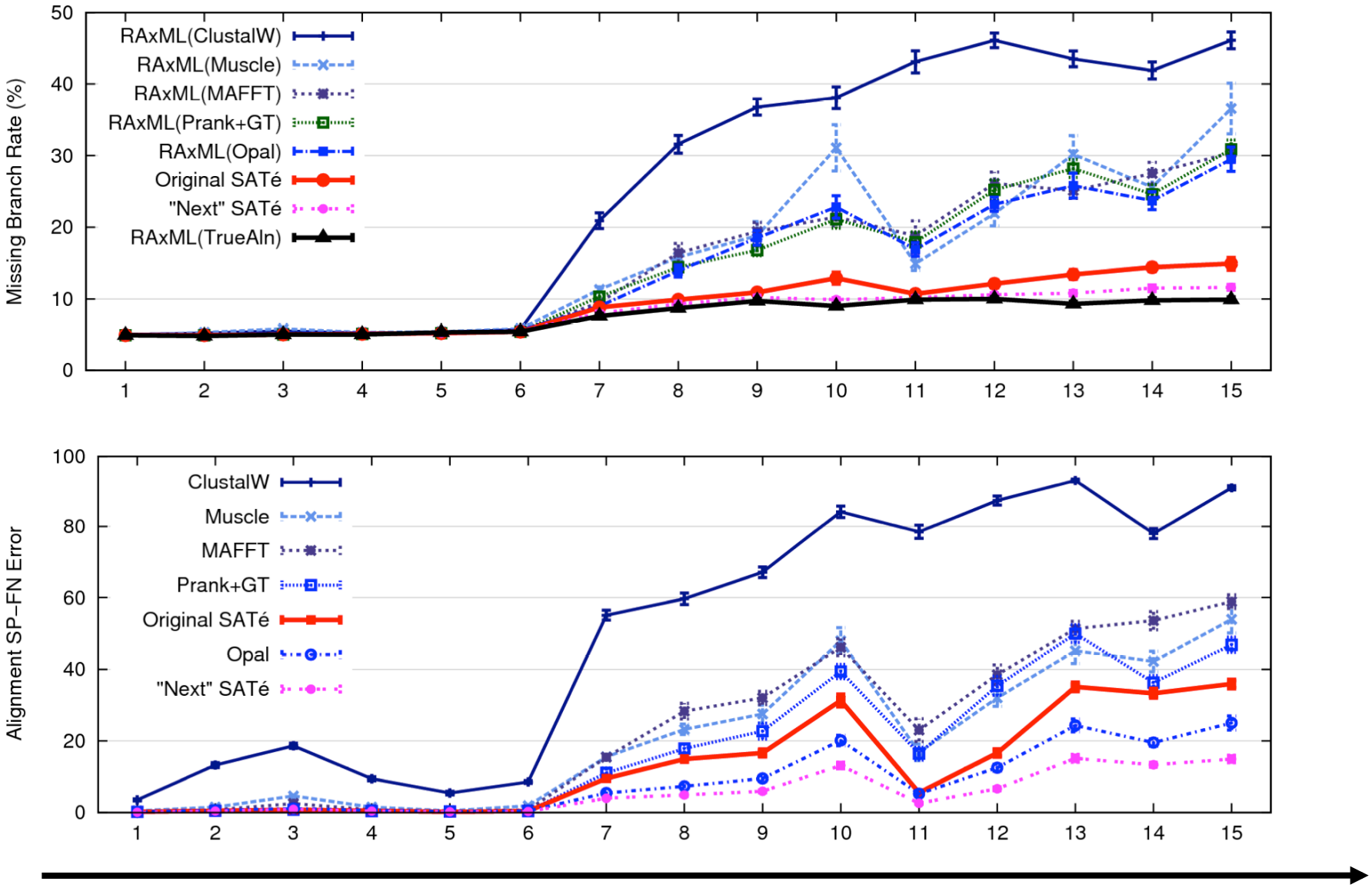
1000 taxon models, ordered by difficulty

SATé-1 24 hour analysis, on desktop machines

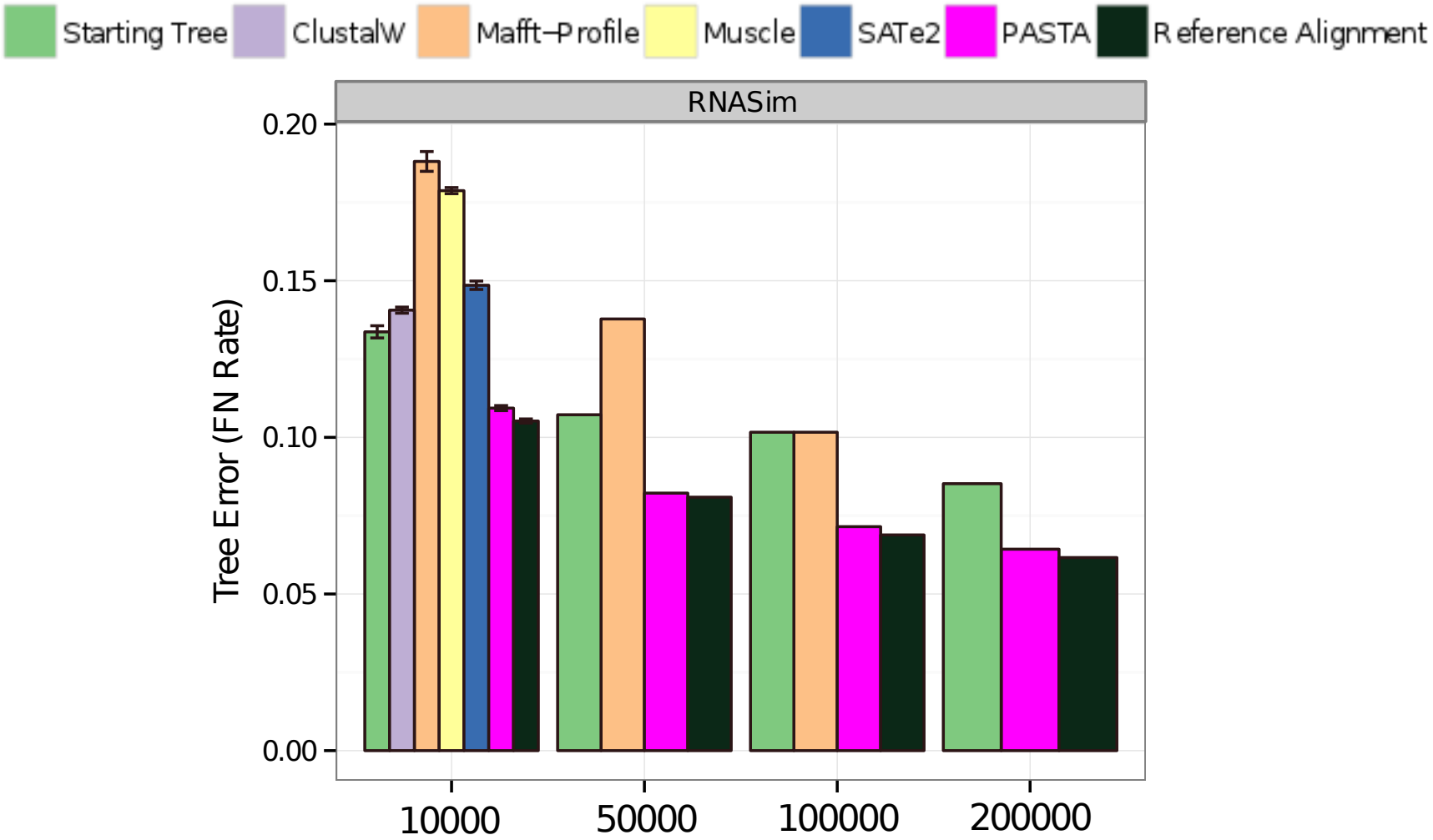
(Similar improvements for biological datasets)

SATé-1 can analyze up to about 30,000 sequences.

SATé-1 and SATé-2 (Systematic Biology, 2012)



PASTA (2014): even better than SATé-2



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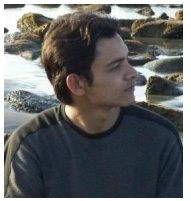
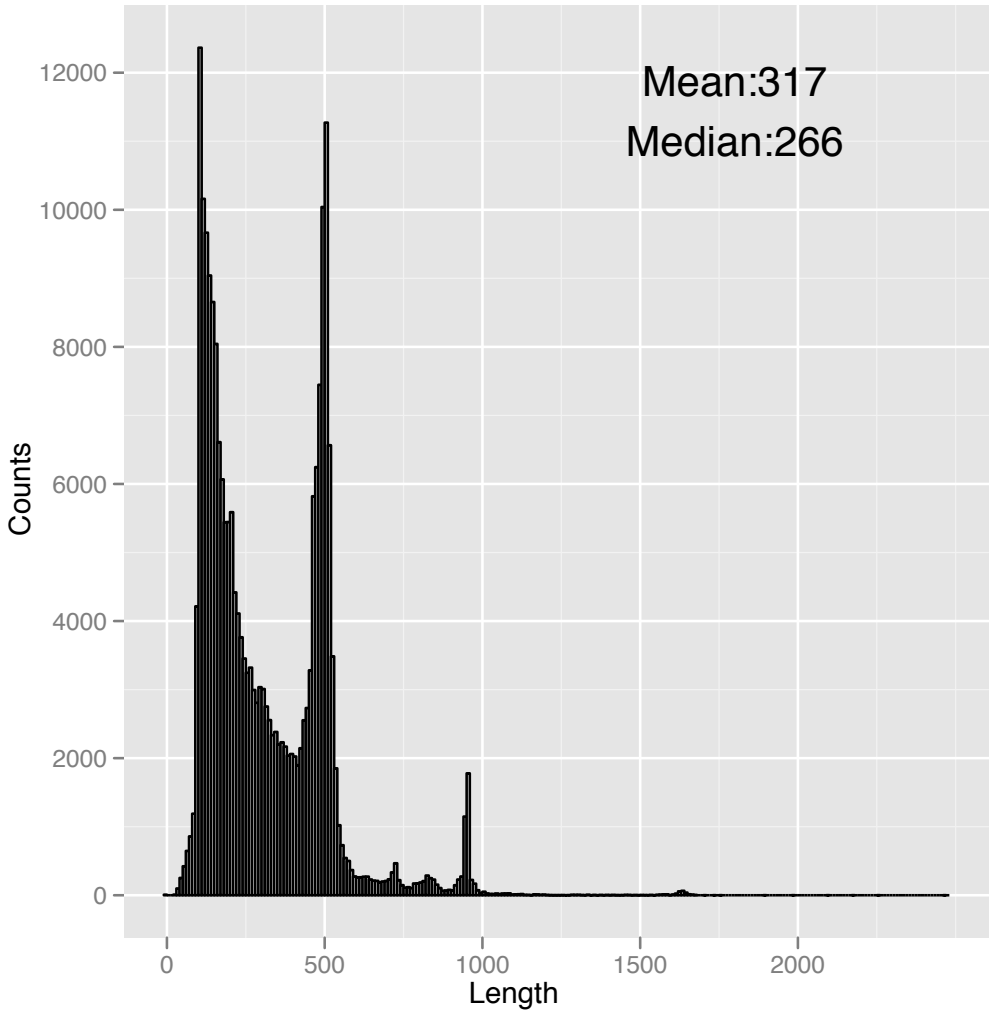


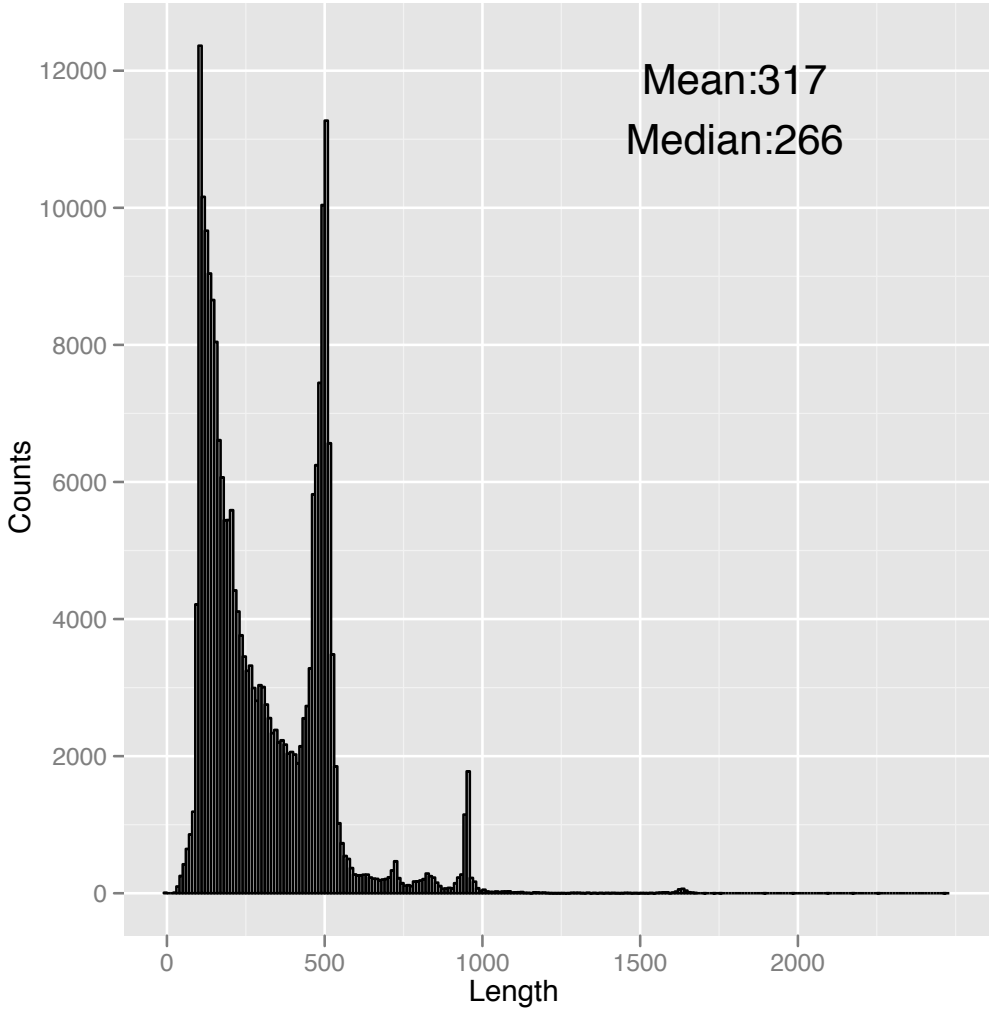
Plus many many other people…

- Plant Tree of Life based on transcriptomes of ~1200 species
- More than 13,000 gene families (most not single copy)

Challenge:
Alignment of datasets with > 100,000 sequences



1KP dataset: more than 100,000 p450 amino-acid sequences, many fragmentary



1KP dataset: more than 100,000 p450 amino-acid sequences, many fragmentary

All standard multiple sequence alignment methods we tested performed poorly on datasets with fragments.

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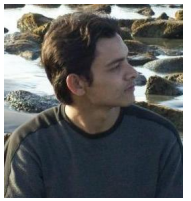

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Challenge:
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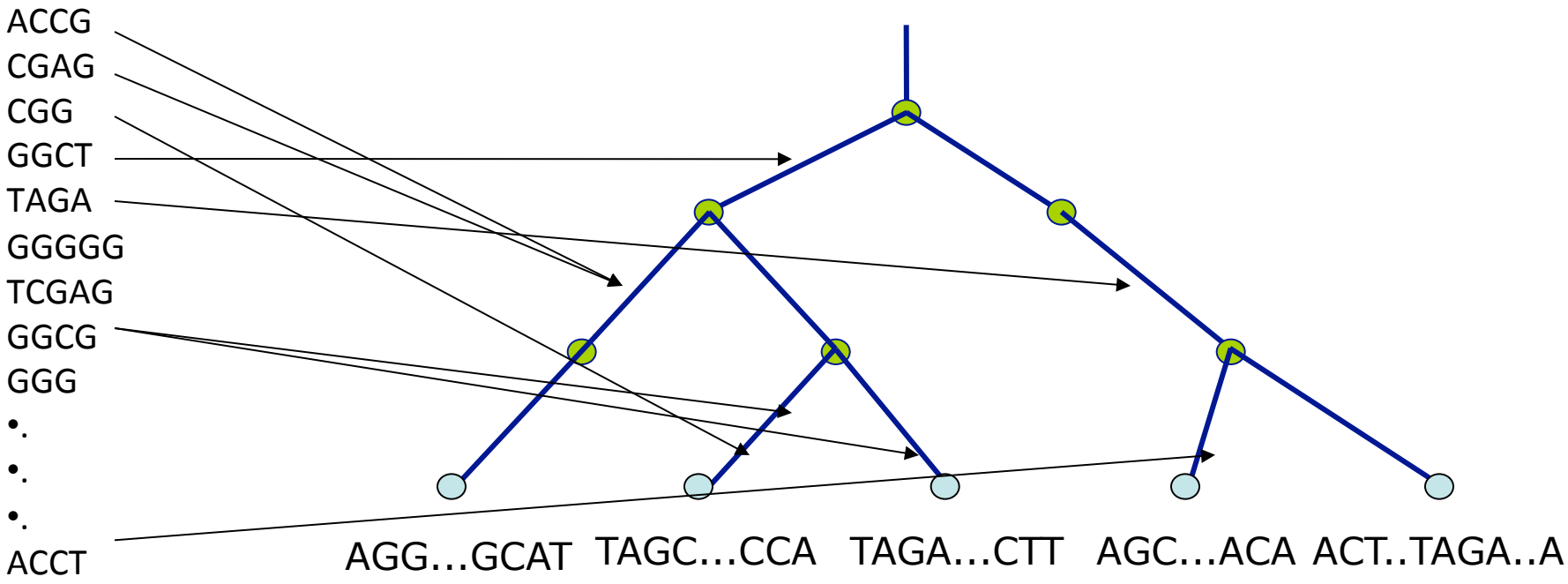
Phylogenetic Placement

Fragmentary sequences from some gene

Full-length sequences for same gene, and an alignment and a tree



SEPP

- **SEPP: SATé-enabled Phylogenetic Placement**, by Mirarab, Nguyen, and Warnow. Pacific Symposium on Biocomputing, 2012, special session on the Human Microbiome

- Objective:
  - phylogenetic analysis of single-gene datasets with fragmentary sequences

- Introduces “HMM Family” technique

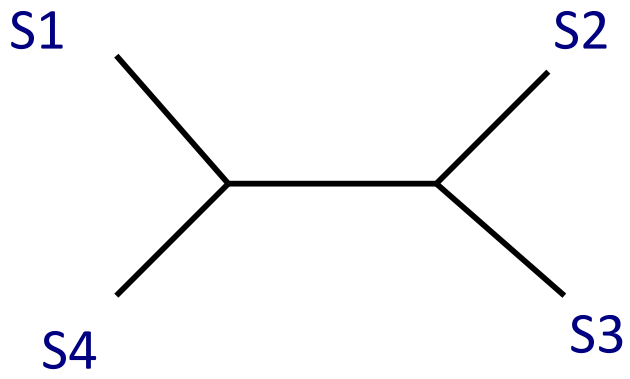
Phylogenetic Placement

Step 1: Align each query sequence to backbone alignment

Step 2: Place each query sequence into backbone tree, using extended alignment

Align Sequence

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



Align Sequence

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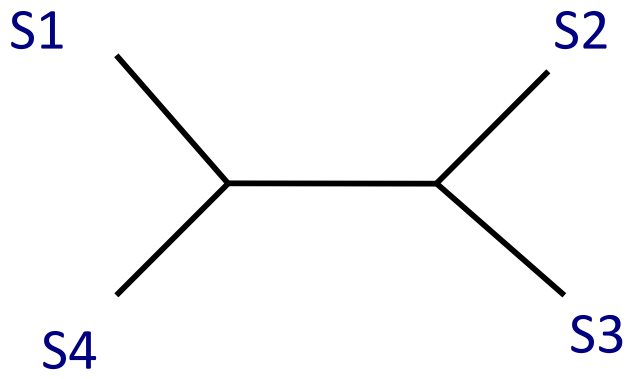
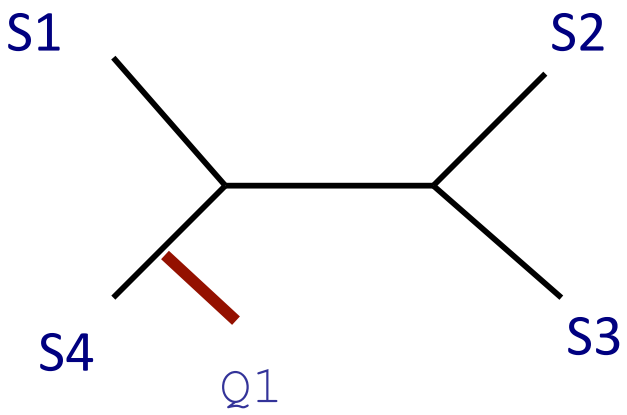
S1   = -AGGCTATCACCTGACCTCCA-AA
S2   = TAG-CTATCAC--GACCGC--GCA
S3   = TAG-CT-------GACCGC--GCT
S4   = TAC----TCAC--GACCGACAGCT
Q1   = -------T-A--AAAC--------
```



Place Sequence

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

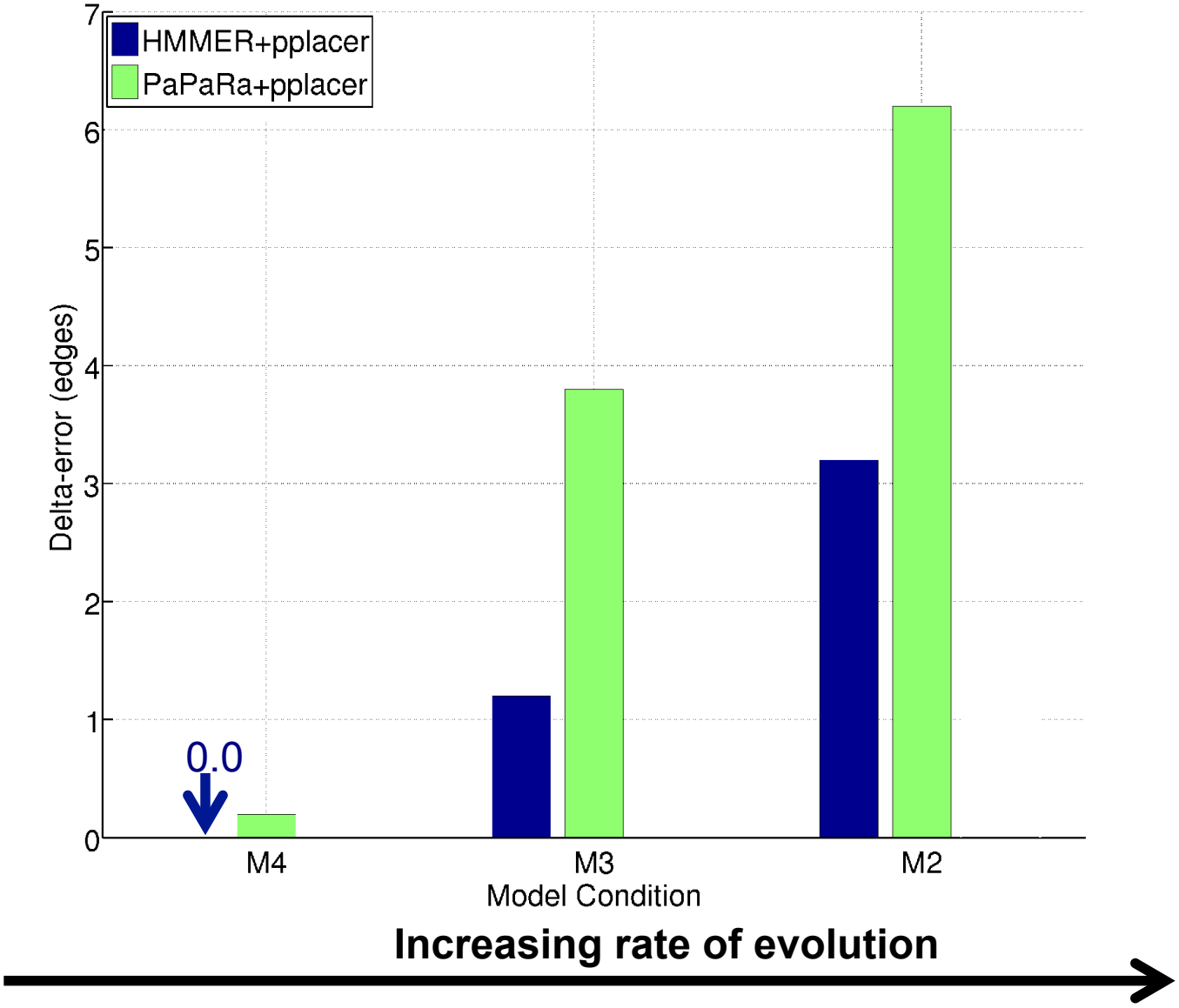


Phylogenetic Placement

- Align each query sequence to backbone alignment
  - HMMALIGN (Eddy, Bioinformatics 1998)
  - PaPaRa (Berger and Stamatakis, Bioinformatics 2011)
- Place each query sequence into backbone tree
  - Pplacer (Matsen et al., BMC Bioinformatics, 2011)
  - EPA (Berger and Stamatakis, Systematic Biology 2011)

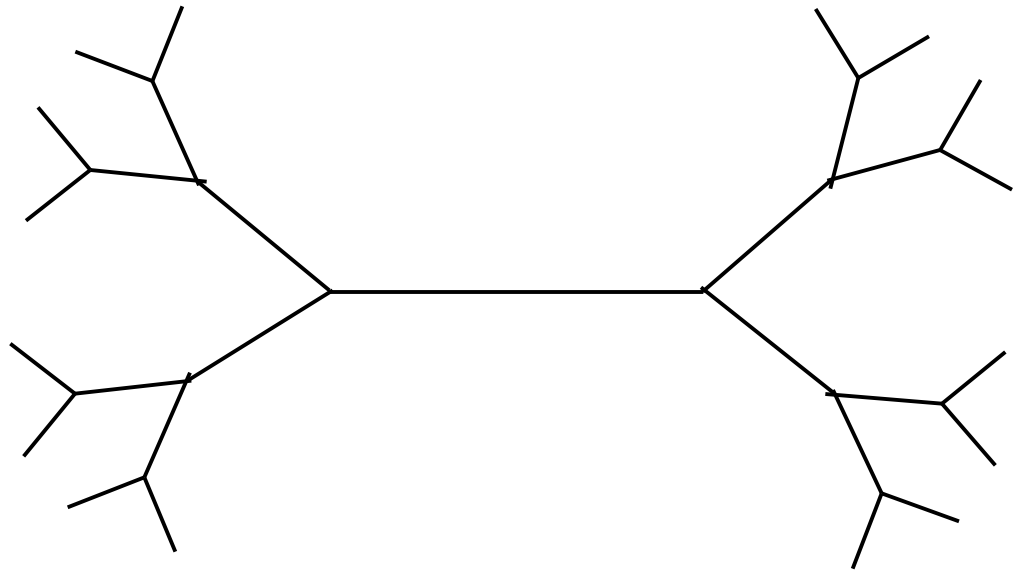
Note: pplacer and EPA use maximum likelihood, and are reported to have the same accuracy.

HMMER vs. PaPaRa

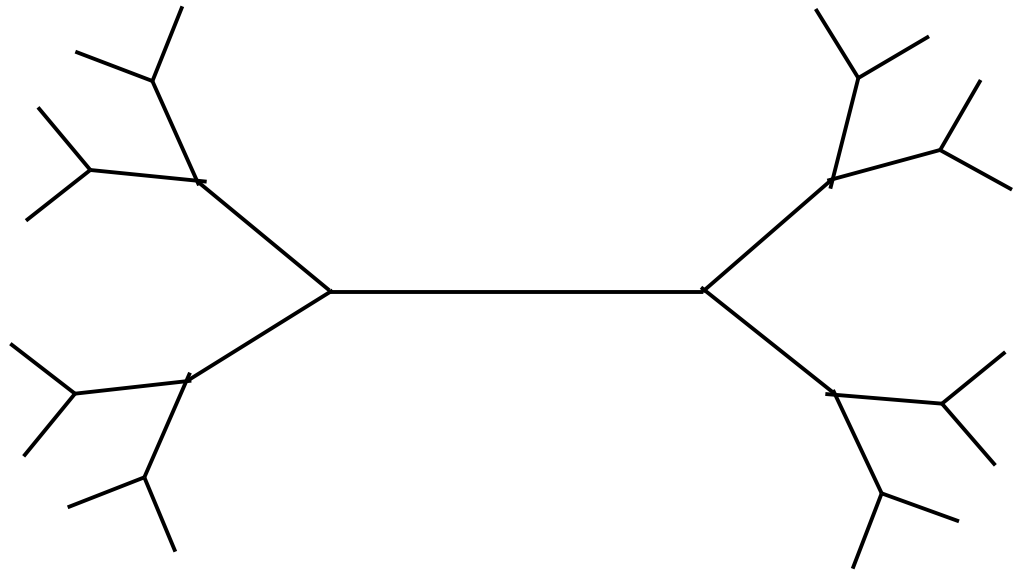


HMMER+pplacer:

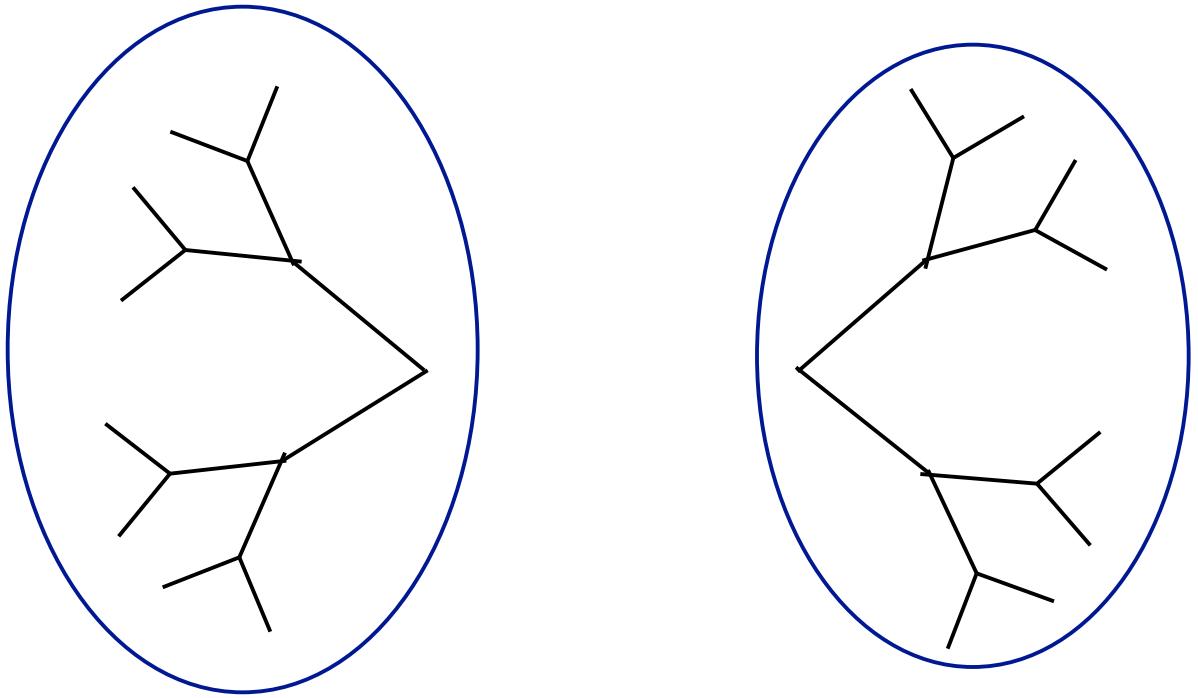
1) build one HMM for the entire alignment
2) Align fragment to the HMM, and insert into alignment
3) Insert fragment into tree to optimize likelihood



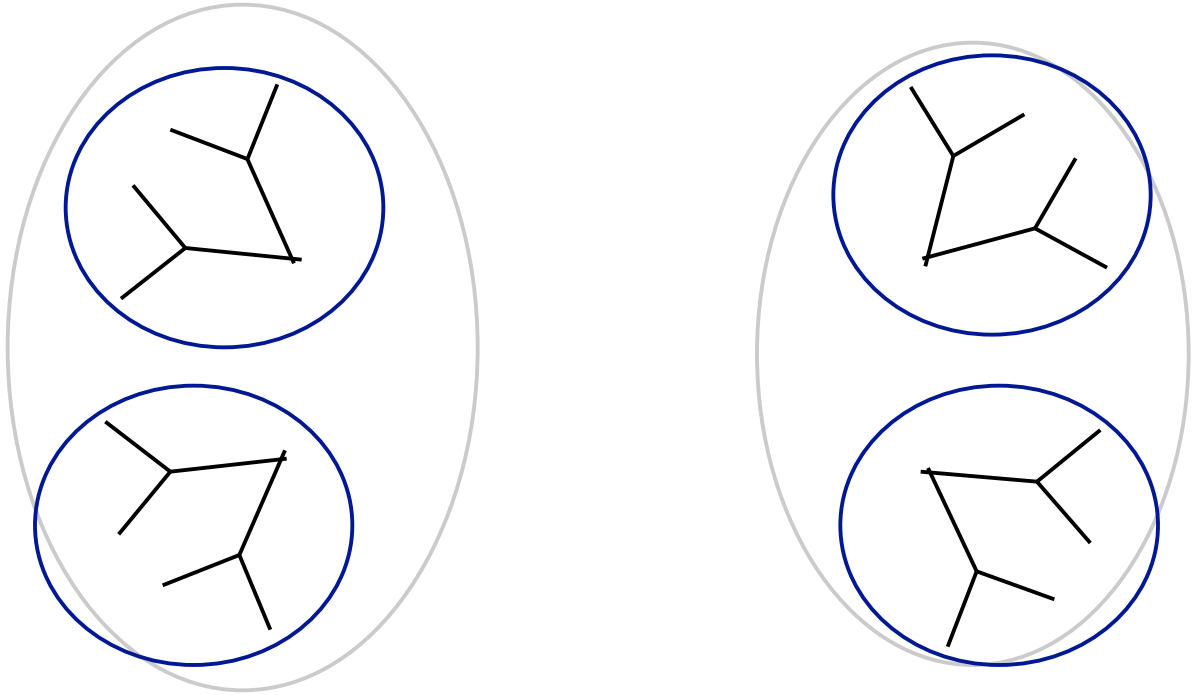
One Hidden Markov Model for the entire alignment?



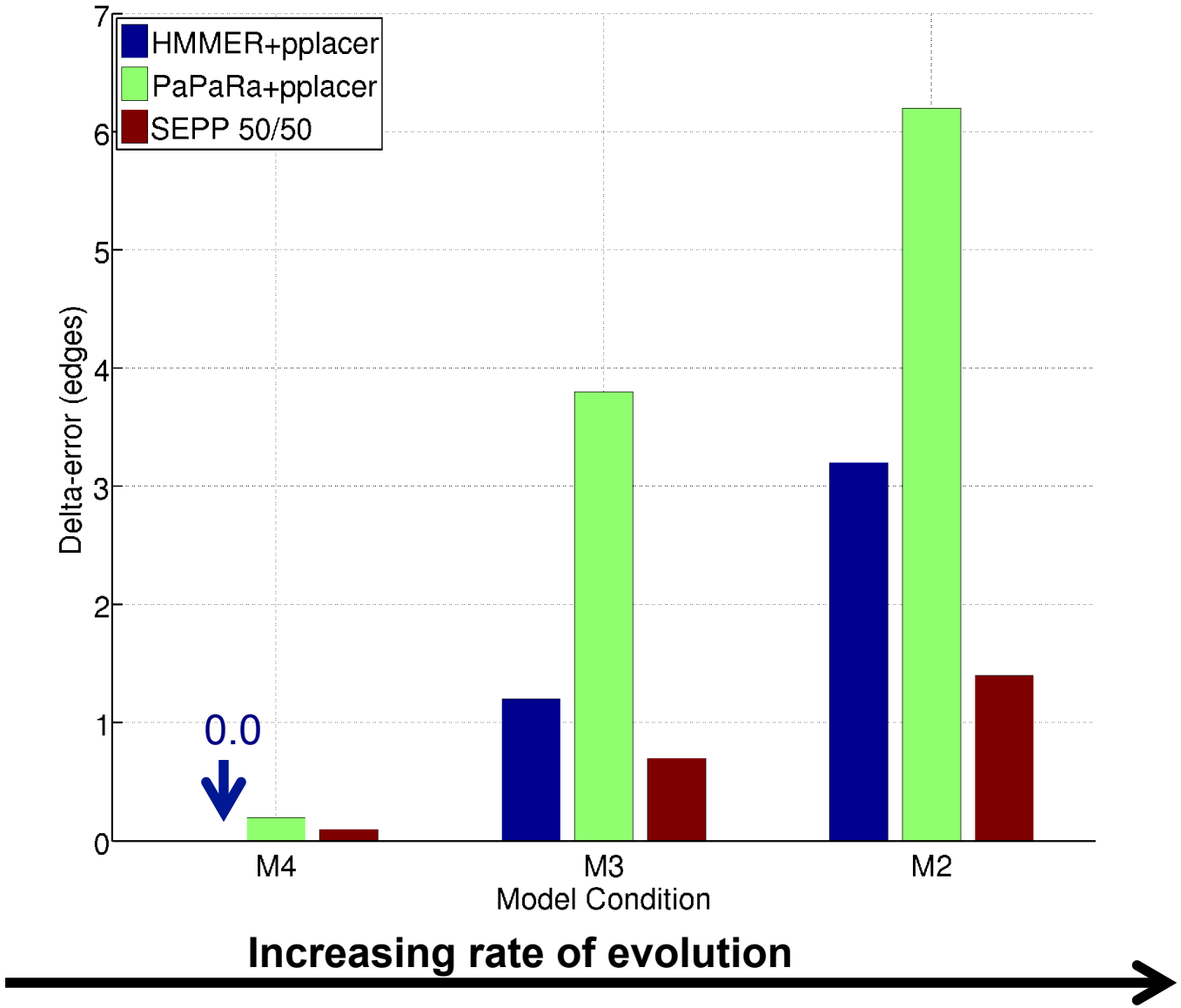
Or 2 HMMs?



Or 4 HMMs?



SEPP(10%), based on ~10 HMMs



SEPP vs. HMMER+pplacer

- SEPP produced more accurate phylogenetic placements than HMMER+pplacer.
- The only difference is the use of a Family of HMMs instead of one HMM.
- The biggest differences are for datasets with high rates of evolution.

UPP: large-scale MSA estimation

UPP = "Ultra-large multiple sequence alignment using Phylogeny-aware Profiles"

Nguyen, Mirarab, and Warnow. In preparation.

Objective: highly accurate large-scale multiple sequence alignments, even in the presence of fragmentary sequences.

Uses a variant of the HMM Family technique in SEPP

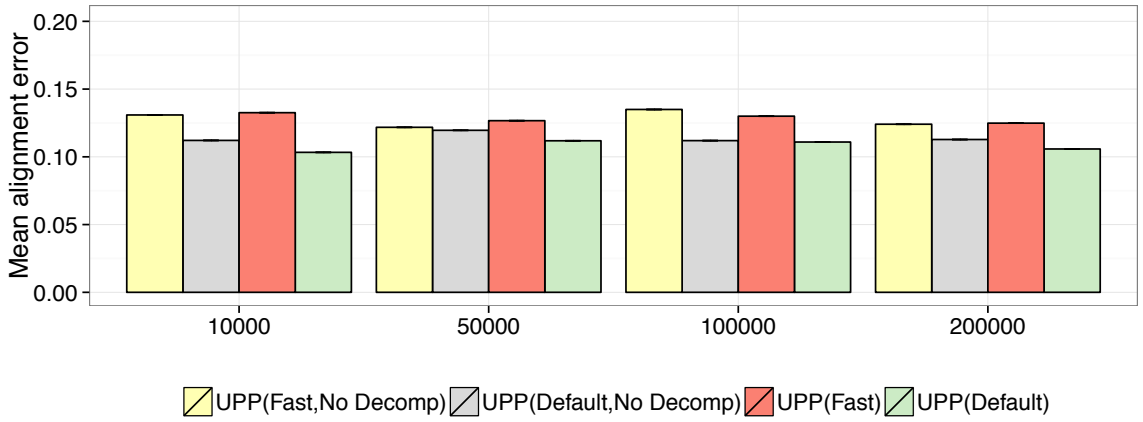
UPP Algorithmic Approach

- Select random subset of sequences, and build "backbone alignment"
- Construct a "Family of Hidden Markov Models" on the backbone alignment (the family has HMMs on many subsets of different sizes, not disjoint)
- Add all remaining sequences to the backbone alignment using the Family of HMMs

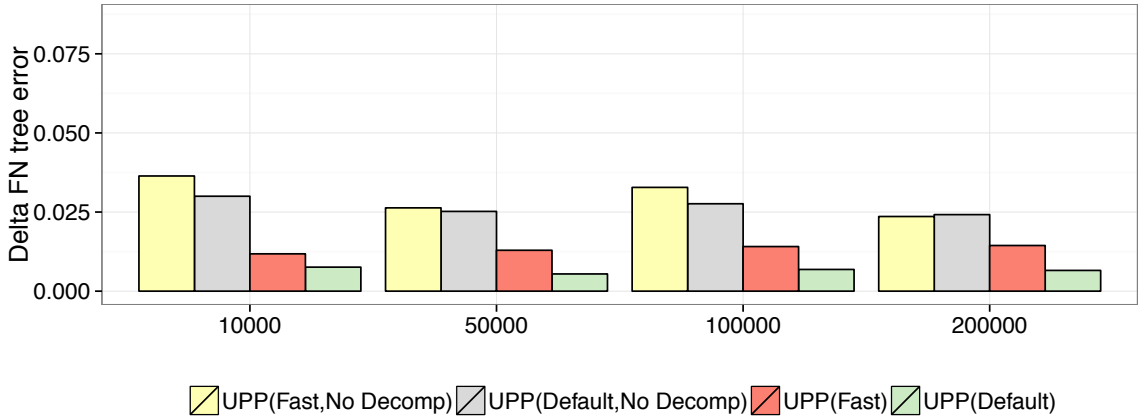
Evaluation

- Simulated datasets (some have fragmentary sequences):
  - 10K to 1,000,000 sequences in RNASim (Guo, Wang, and Kim, arxiv)
  - 1000-sequence nucleotide datasets from SATé papers
  - 5000-sequence AA datasets (from FastTree paper)
  - 10,000-sequence Indelible nucleotide simulation
- Biological datasets:
  - Proteins: largest BaliBASE and HomFam
  - RNA: 3 CRW datasets up to 28,000 sequences

Impact of backbone size and use of HMM Family technique



(a) Average alignment error



(b) Average tree error

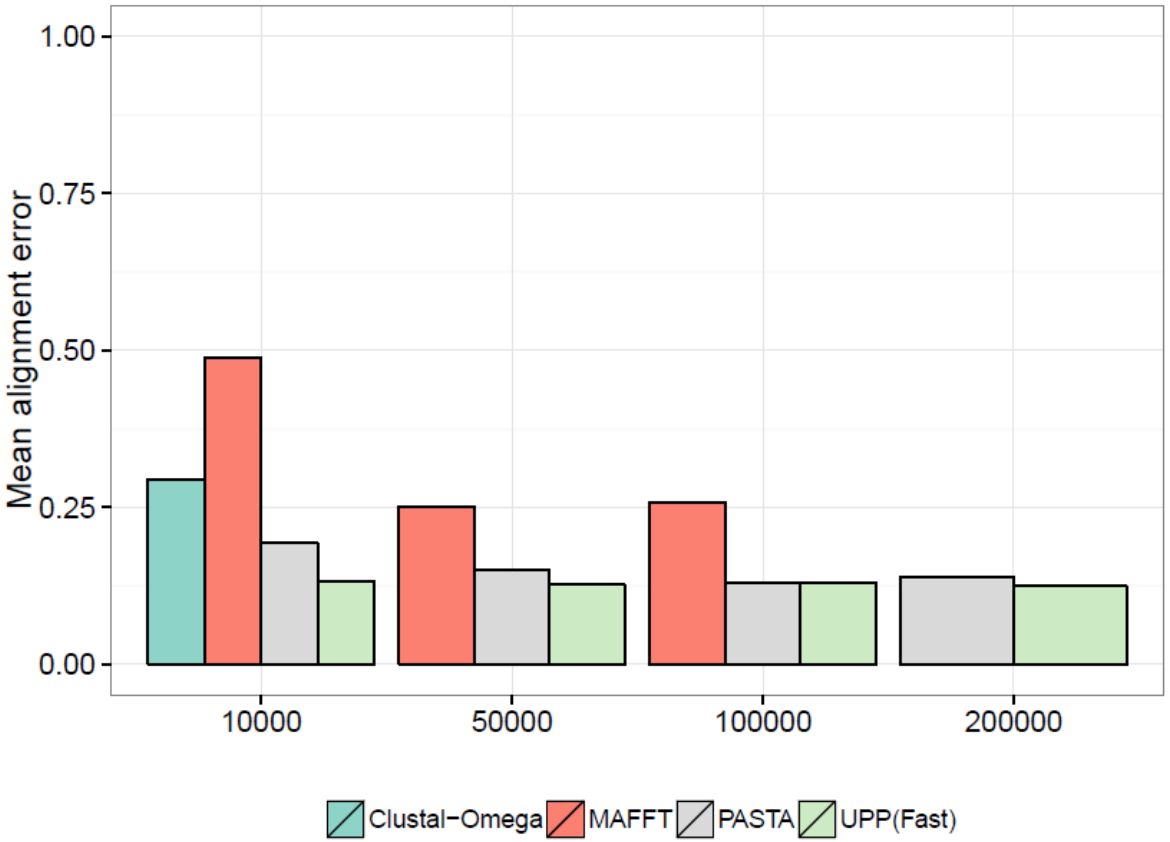
Notes:

Relative performance under standard alignment criteria is not predictive of relative performance for tree estimation.

For alignment estimation, a large backbone is important.

For tree estimation, the use of the HMM Family is most important, but large backbones also help.

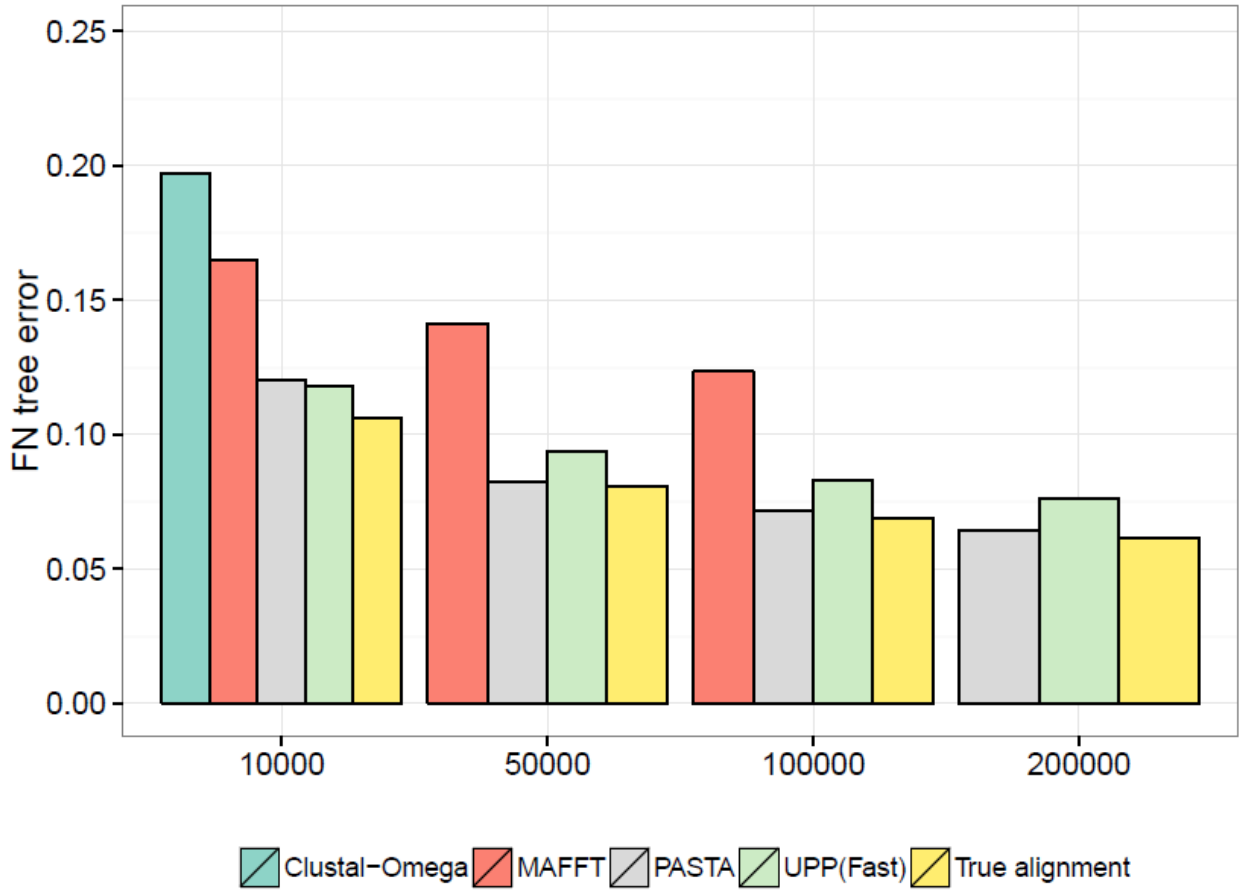
RNASim: alignment error



All methods given 24 hrs on a 12-core machine

Note: Mafft was run under default settings for 10K and 50K sequences and under Parttree for 100K sequences, and fails to complete under any setting For 200K sequences. Clustal-Omega only completes on 10K dataset.

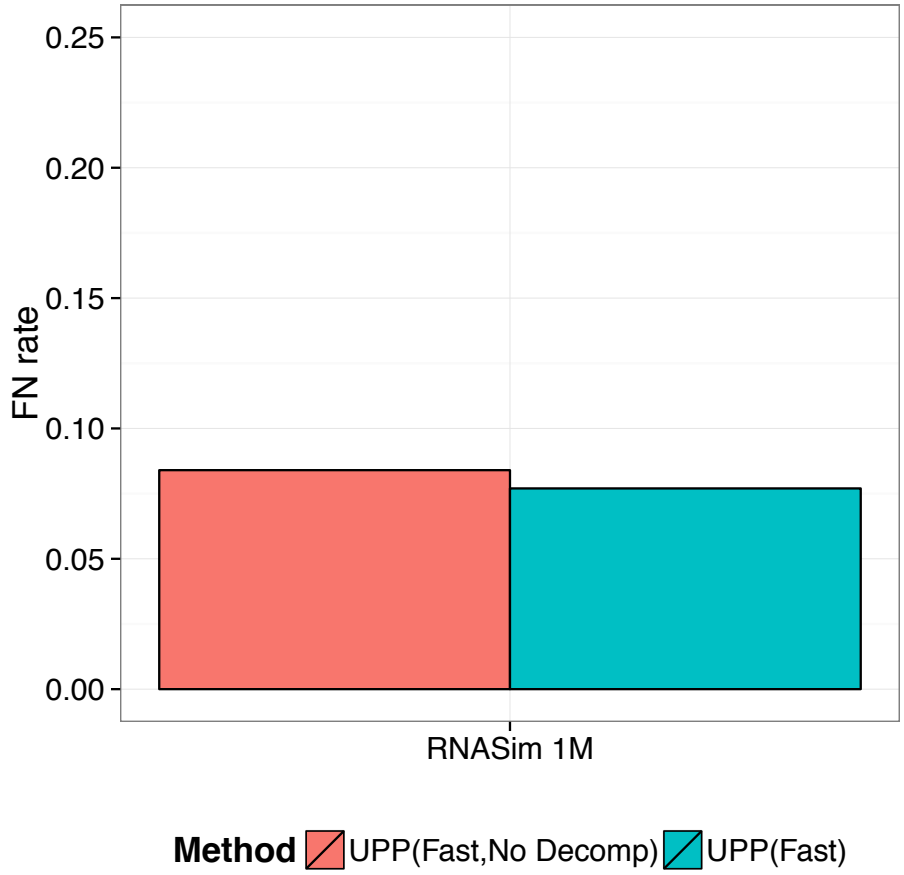
RNASim: tree error



All methods given 24 hrs on a 12-core machine

Note: Mafft was run under default settings for 10K and 50K sequences and under Parttree for 100K sequences, and fails to complete under any setting For 200K sequences. Clustal-Omega only completes on 10K dataset.

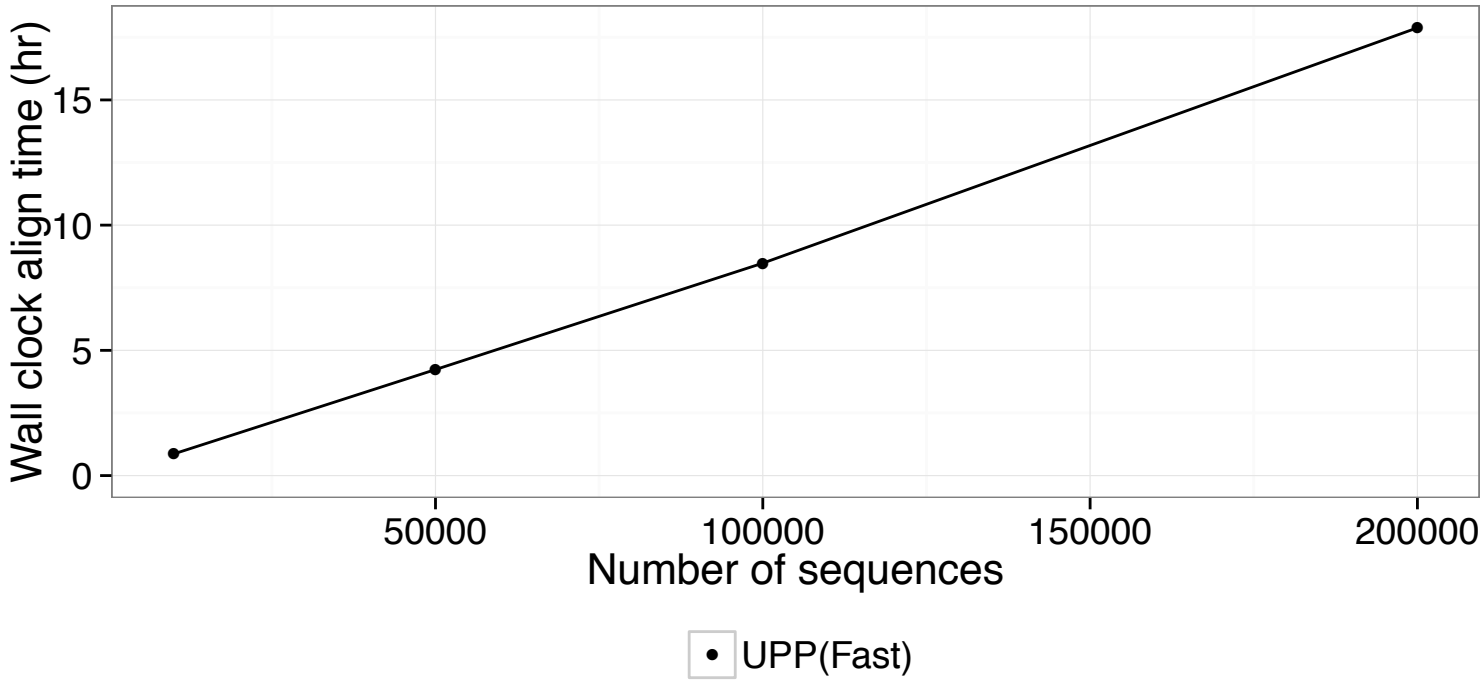
RNASim Million Sequences: tree error



Using 12 processors:

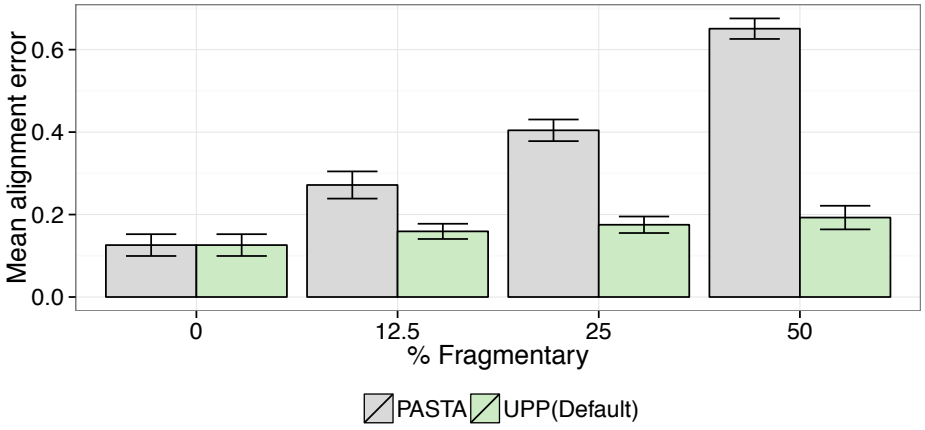
- UPP(Fast,NoDecomp) took 2.2 days.
- UPP(Fast) took 11.9 days.

Running Time

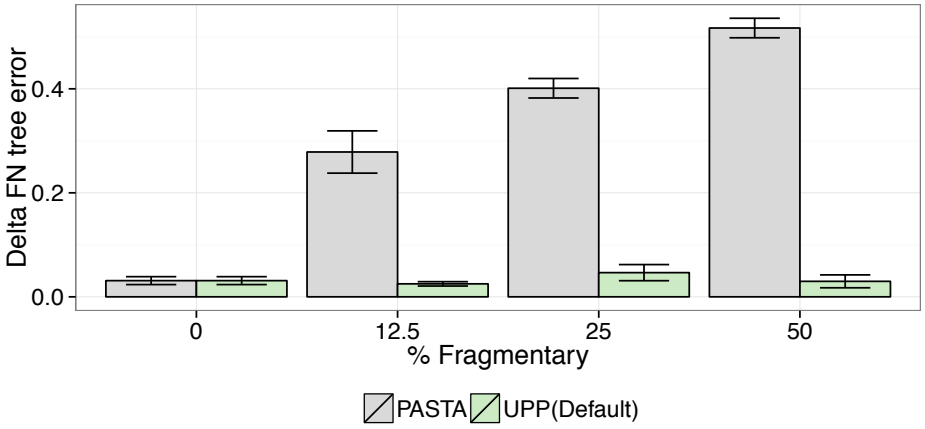


Wall-clock time used (in hours) given 12 processors

UPP vs. PASTA: impact of fragmentation



(a) Average alignment error



(b) Average tree error

Under high rates of evolution, PASTA is badly impacted by fragmentary sequences (the same is true for other methods).

Under low rates of evolution, PASTA can still be highly accurate (data not shown).

UPP continues to have good accuracy even on datasets with many fragments under all rates of evolution.

Performance on fragmentary datasets of the 1000M2 model condition

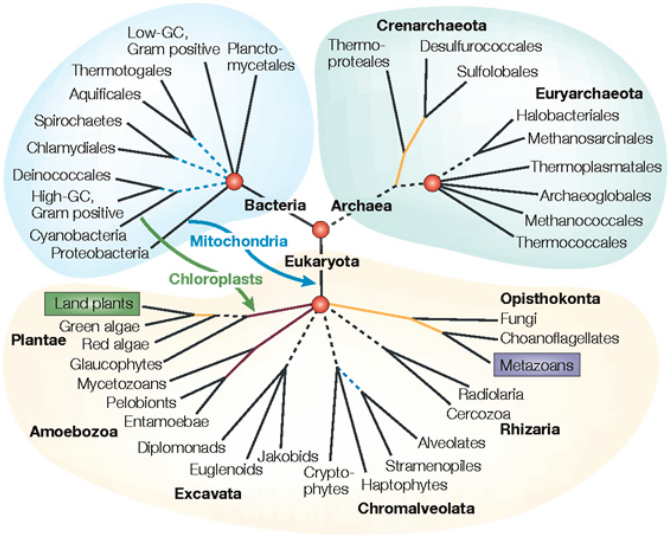
Summary

- SATé-1 (Science 2009), SATé-2 (Systematic Biology 2012), and PASTA (RECOMB 2014): methods for co-estimating gene trees and multiple sequence alignments. PASTA can analyze up to 1,000,000 sequences, and is highly accurate for full-length sequences.
  - *But none of these methods are robust to fragmentary sequences.*
- HMM Family technique: uses an ensemble of HMMs to represent a "backbone alignment". HMM families improve accuracy, especially in the presence of high rates of evolution.
- Applications of HMM Families in:
  - SEPP (phylogenetic placement)
  - UPP (ultra-large multiple sequence alignment) up to 1,000,000 sequences
  - TIPP (metagenomic taxon identification and abundance profiling)

The Tree of Life: *Multiple Challenges*

Scientific challenges:

- Ultra-large multiple-sequence alignment
- Alignment-free phylogeny estimation
- Supertree estimation
- Estimating species trees from many gene trees
- Genome rearrangement phylogeny
- Reticulate evolution
- Visualization of large trees and alignments
- Data mining techniques to explore multiple optima
- Theoretical guarantees under Markov models of evolution



Nature Reviews | Genetics

Techniques:
machine learning, applied probability theory, graph theory, combinatorial optimization, supercomputing, and heuristics

Acknowledgments



PhD students: Siavash Mirarab*and Nam Nguyen**
Undergrad: Keerthana Kumar
Lab Website: http://www.cs.utexas.edu/users/phylo
Personal Website: http://tandy.cs.illinois.edu

Funding: Guggenheim Foundation, NSF, Microsoft Research New England, David Bruton Jr. Centennial Professorship, TACC (Texas Advanced Computing Center), and the University of Alberta (Canada)

TACC and UTCS computational resources

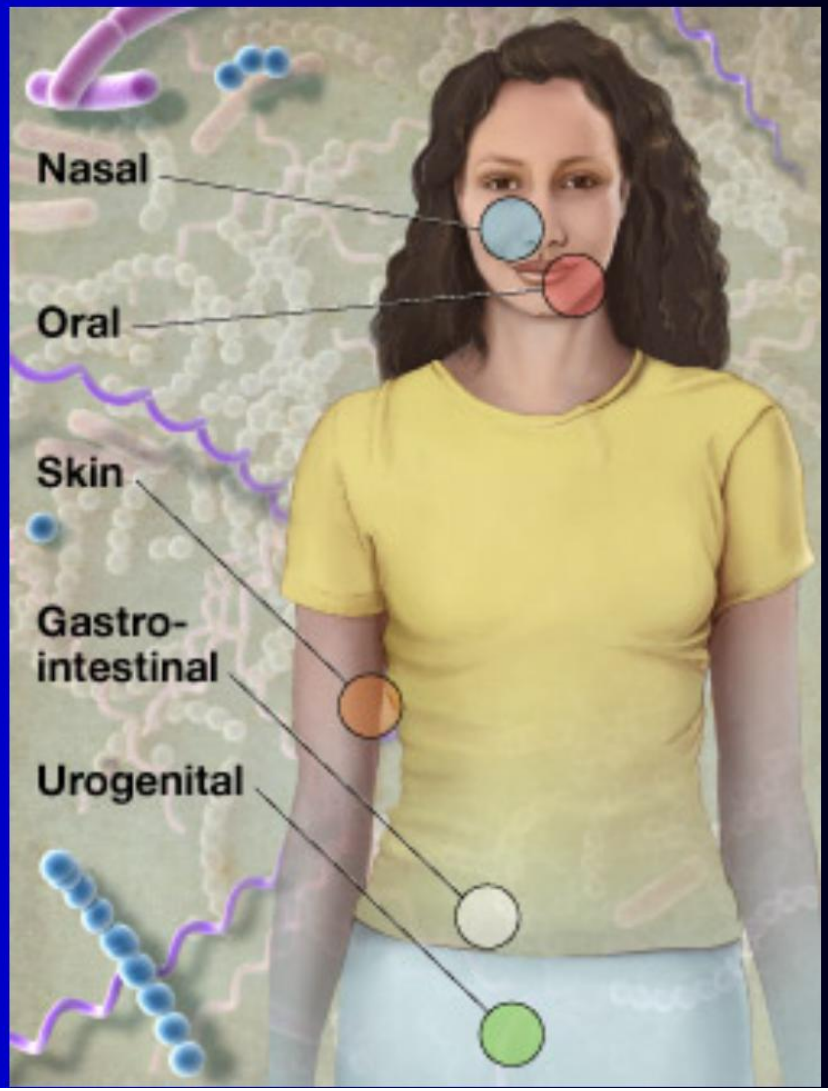
* Supported by HHMI Predoctoral Fellowship
** Now a postdoc at the University of Illinois Urbana-Champaign

Research Projects

- Using iteration within UPP
- Using other MSA models and methods (not just HMMs) within the "Ensemble"
- Using structural alignments (or sophisticated statistical estimations of alignments) for the backbone
- Re-analyzing biological datasets
- Application to protein structure and function
- Other classification problems

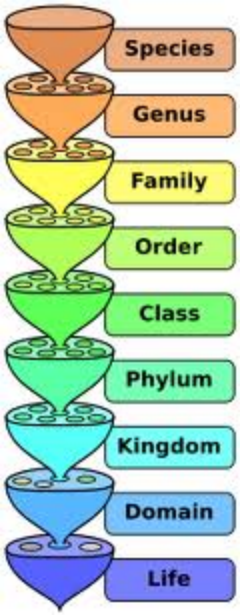
The NIH Human Microbiome Project

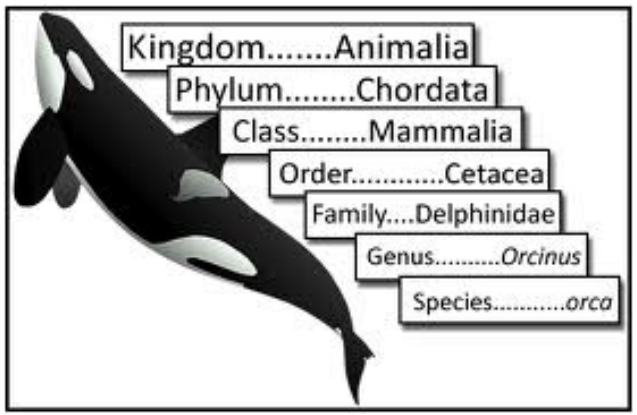
25,000 human genes,
1,000,000 bacterial genes



Metagenomic Taxon Identification

Objective: classify short reads in a metagenomic sample





Basic Questions

1. What is this fragment? (Classify each fragment as well as possible.)

2. What is the taxonomic distribution in the dataset? (Note: helpful to use marker genes.)

3. What are the organisms in this metagenomic sample doing together?

Abundance Profiling

Objective: Distribution of the species (or genera, or families, etc.) within the sample.

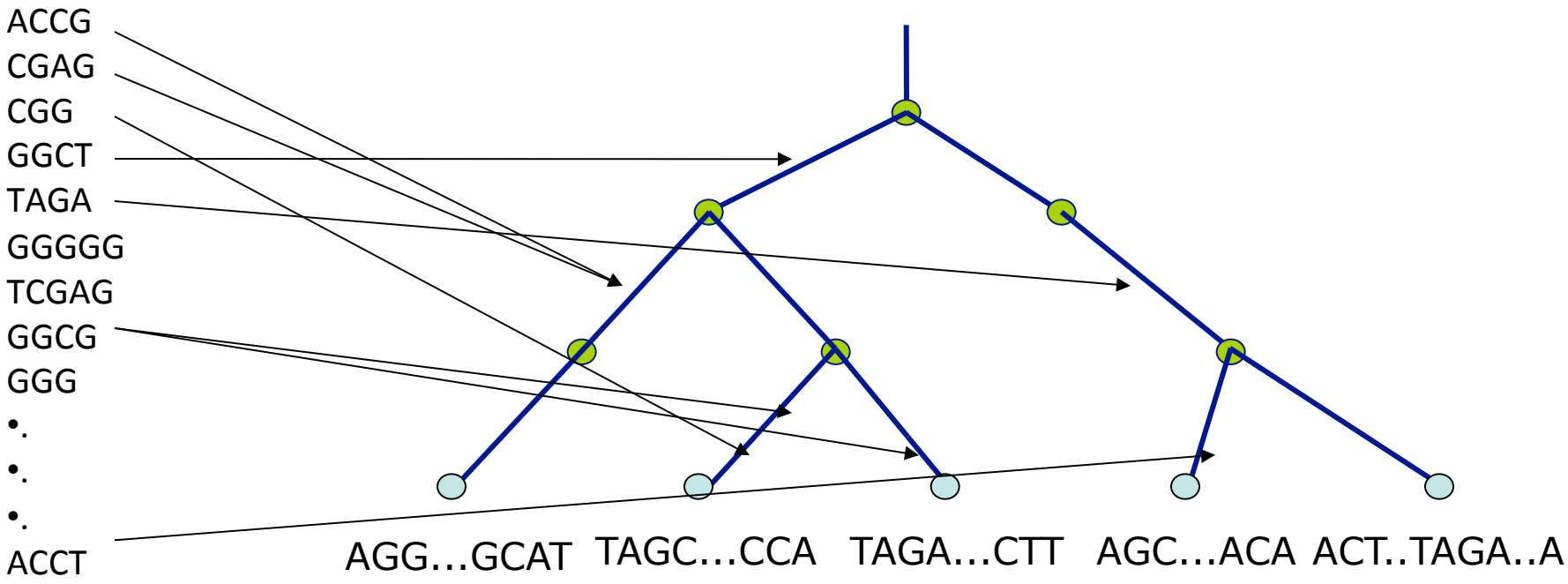
For example: The distribution of the sample at the species-level is:

50%	species A
20%	species B
15%	species C
14%	species D
1%	species E

Phylogenetic Placement

Fragmentary sequences from some gene

Full-length sequences for same gene, and an alignment and a tree



TIPP: SEPP + statistics

SEPP has high recall but low precision (classifies almost everything)

TIPP: dramatically reduces false positive rate with small reduction in true positive rate, by considering uncertainty in alignment (HMMER) and placement (pplacer)

TIPP: Taxon Identification and Phylogenetic Profiling. N. Nguyen, S. Mirarab, and T. Warnow. Under review.

Abundance Profiling

Objective: Distribution of the species (or genera, or families, etc.) within the sample.

Leading techniques:

PhymmBL (Brady & Salzberg, Nature Methods 2009)

NBC (Rosen, Reichenberger, and Rosenfeld, Bioinformatics 2011)

MetaPhyler (Liu et al., BMC Genomics 2011), from the Pop lab at the University of Maryland

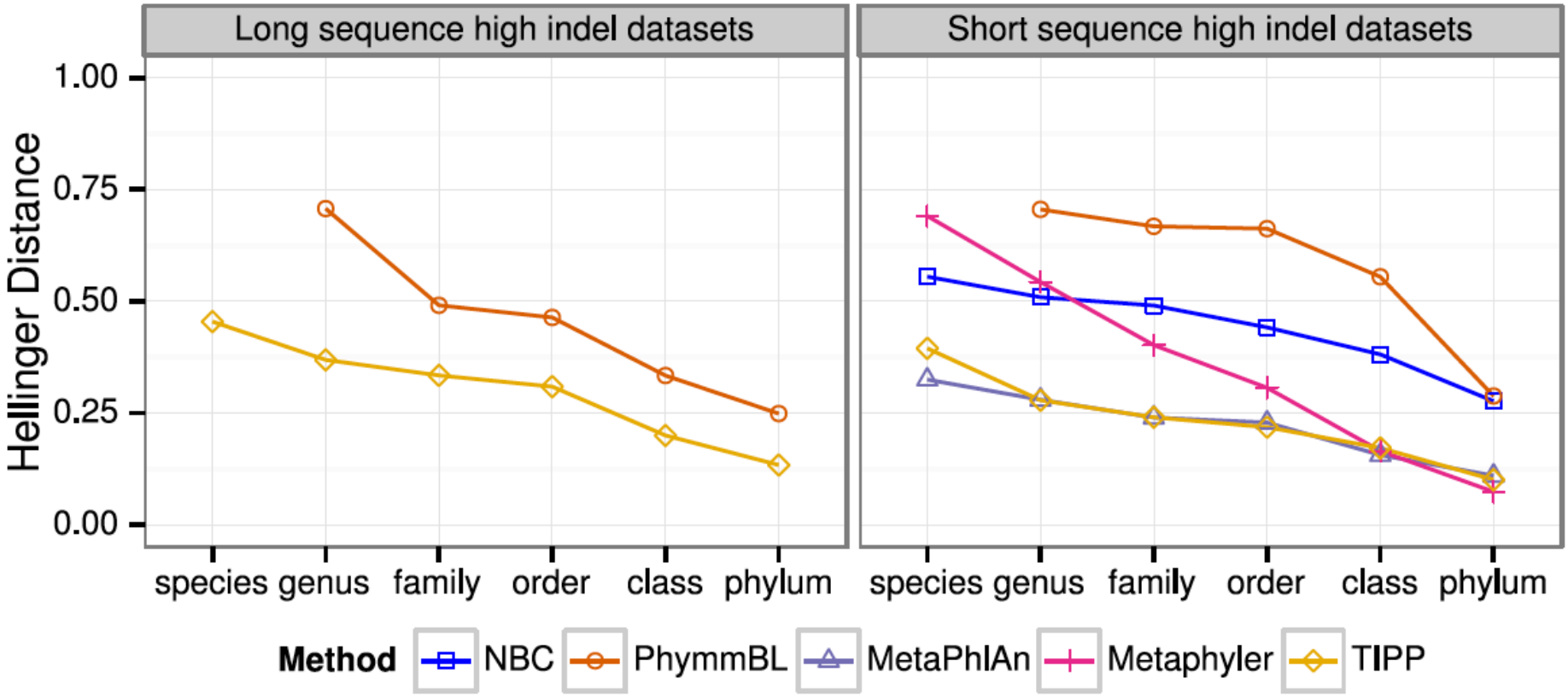
MetaPhlAn (Segata et al., Nature Methods 2012), from the Huttenhower Lab at Harvard

mOTU (Bork et al., Nature Methods 2013)

MetaPhyler, MetaPhlAn, and mOTU are marker-based techniques (but use different marker genes).

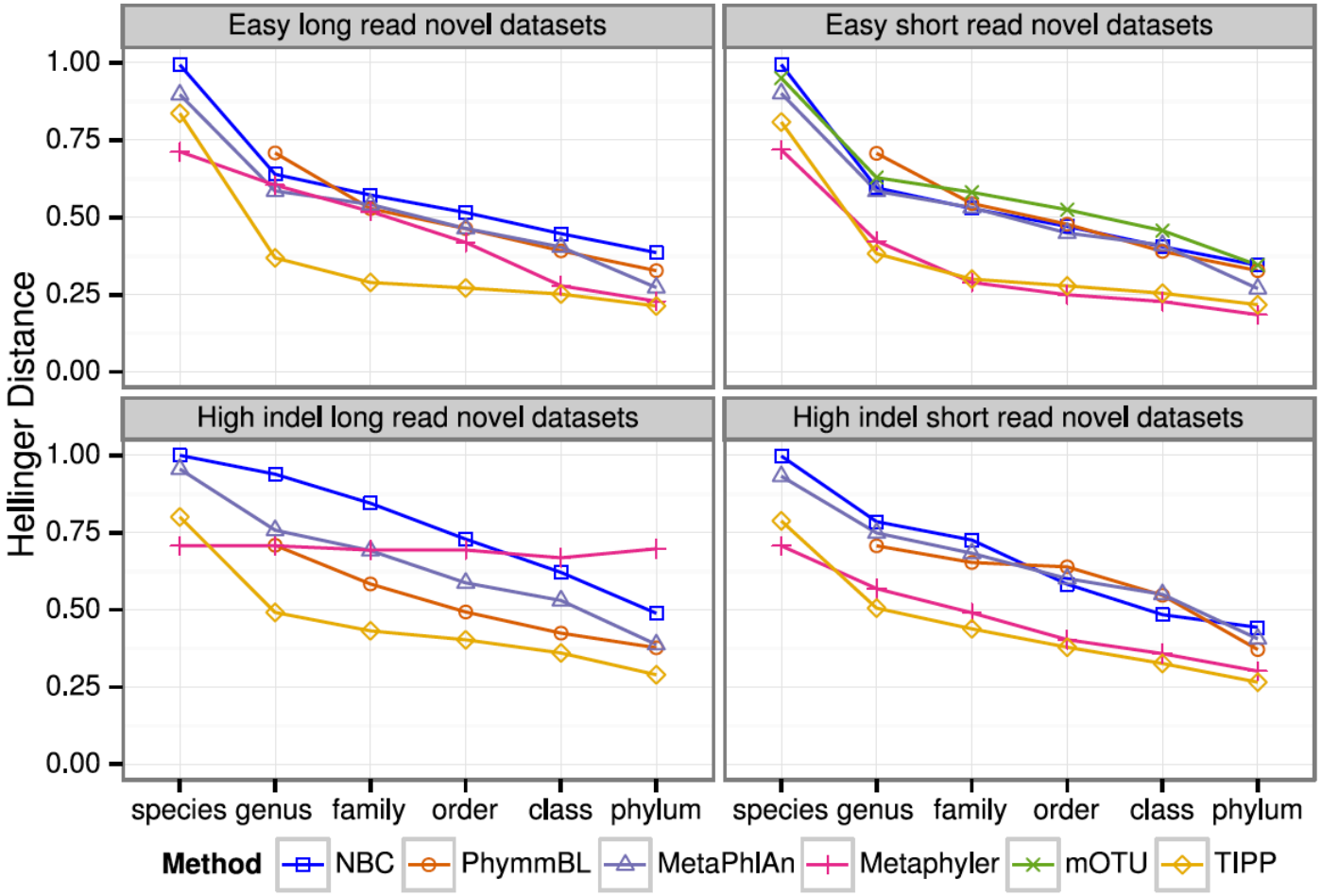
Marker gene are single-copy, universal, and resistant to horizontal transmission.

High indel datasets containing known genomes



Note: NBC, MetaPhlAn, and MetaPhyler cannot classify any sequences from at least one of the high indel long sequence datasets, and mOTU terminates with an error message on all the high indel datasets.

“Novel” genome datasets



Note: mOTU terminates with an error message on the long fragment datasets and high indel datasets.

TIPP vs. other abundance profilers

- TIPP is highly accurate, even in the presence of high indel rates and novel genomes, and for both short and long reads.

- All other methods have some vulnerability (e.g., mOTU is only accurate for short reads and is impacted by high indel rates).

Phylogenetic "boosters"

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

Techniques: divide-and-conquer, iteration, chordal graph algorithms, and "bin-and-conquer"

Examples:

- DCM-boosting for distance-based methods (1999)
- DCM-boosting for heuristics for NP-hard problems (1999)
- SATé- and PASTA-boosting for alignment methods (2009, 2012, and 2014)
- SuperFine-boosting for supertree methods (2012)
- DACTAL: almost alignment-free phylogeny estimation methods (2012)
- SEPP-boosting for phylogenetic placement of short sequences (2012)
- TIPP-boosting for metagenomic taxon identification (submitted)
- UPP-boosting for alignment methods (in preparation)
- Bin-and-conquer for coalescent-based species tree estimation (2013 and 2014)

Algorithmic Strategies

- Divide-and-conquer
- Chordal graph decompositions
- Iteration
- Multiple HMMs
- Bin-and-conquer (technique used for improving species tree estimation from multiple gene trees, Bayzid and Warnow, Bioinformatics 2013)

1kp: 1000 Plant Transcriptomes

G. Ka-Shu Wong
U Alberta

J. Leebens-Mack
U Georgia

N. Wickett
Northwestern

N. Matasci
iPlant

T. Warnow,
UT-Austin

S. Mirarab,
UT-Austin

N. Nguyen,
UT-Austin

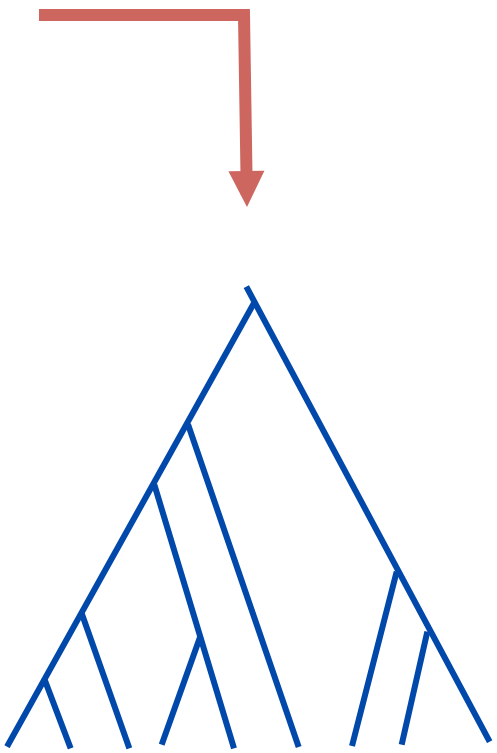
Plus many many other people…

- Whole Transcriptomes of 103 plant species and 850 single copy loci (1200 taxa in next phase)
  - Most accurate summary methods cannot handle this size
- Common ancestor about 1 billion years ago and so gene trees are hard to root
  - Most summary methods need rooted gene trees
- Pre-existing summary methods do not provide reasonable results on this dataset

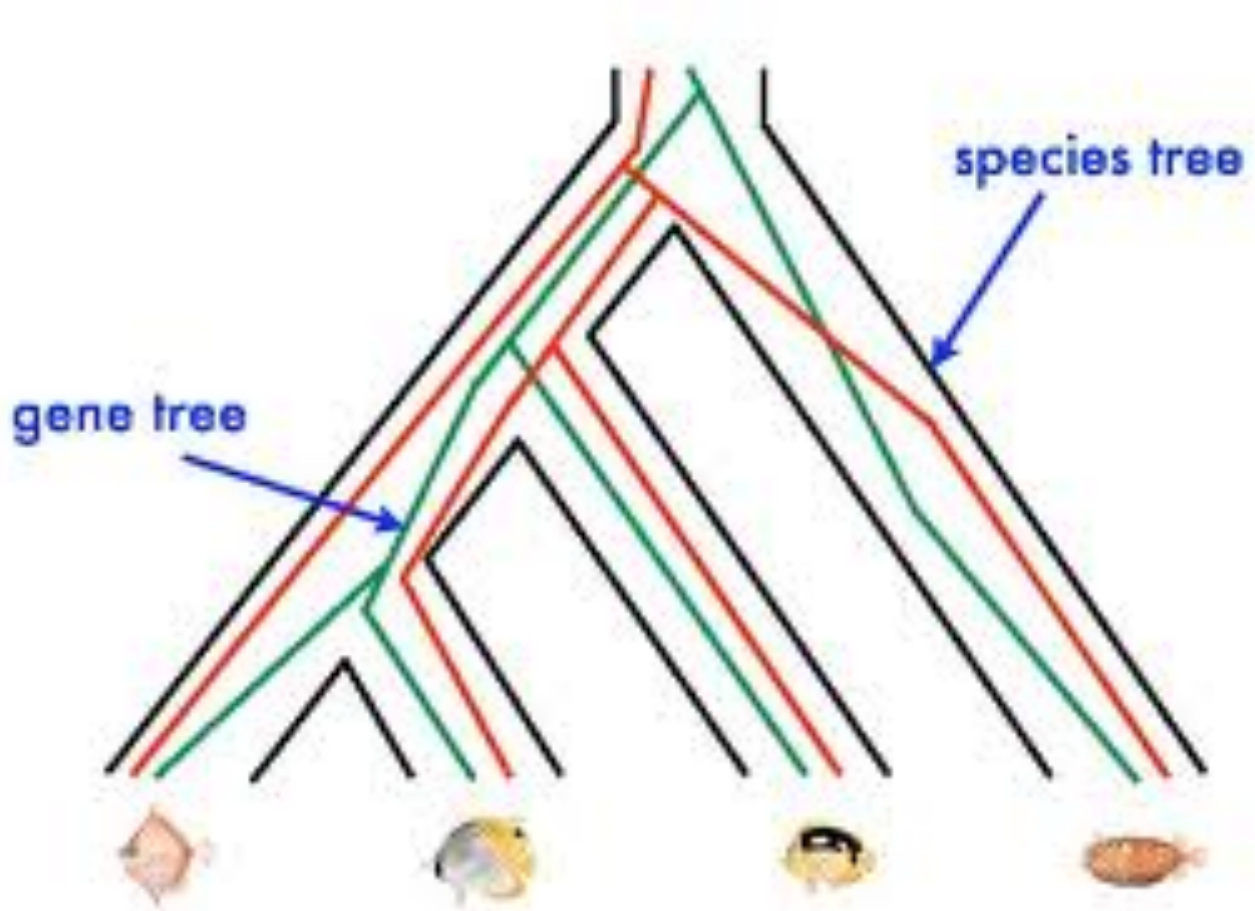
[Wickett et al. (under review), 2014.]

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

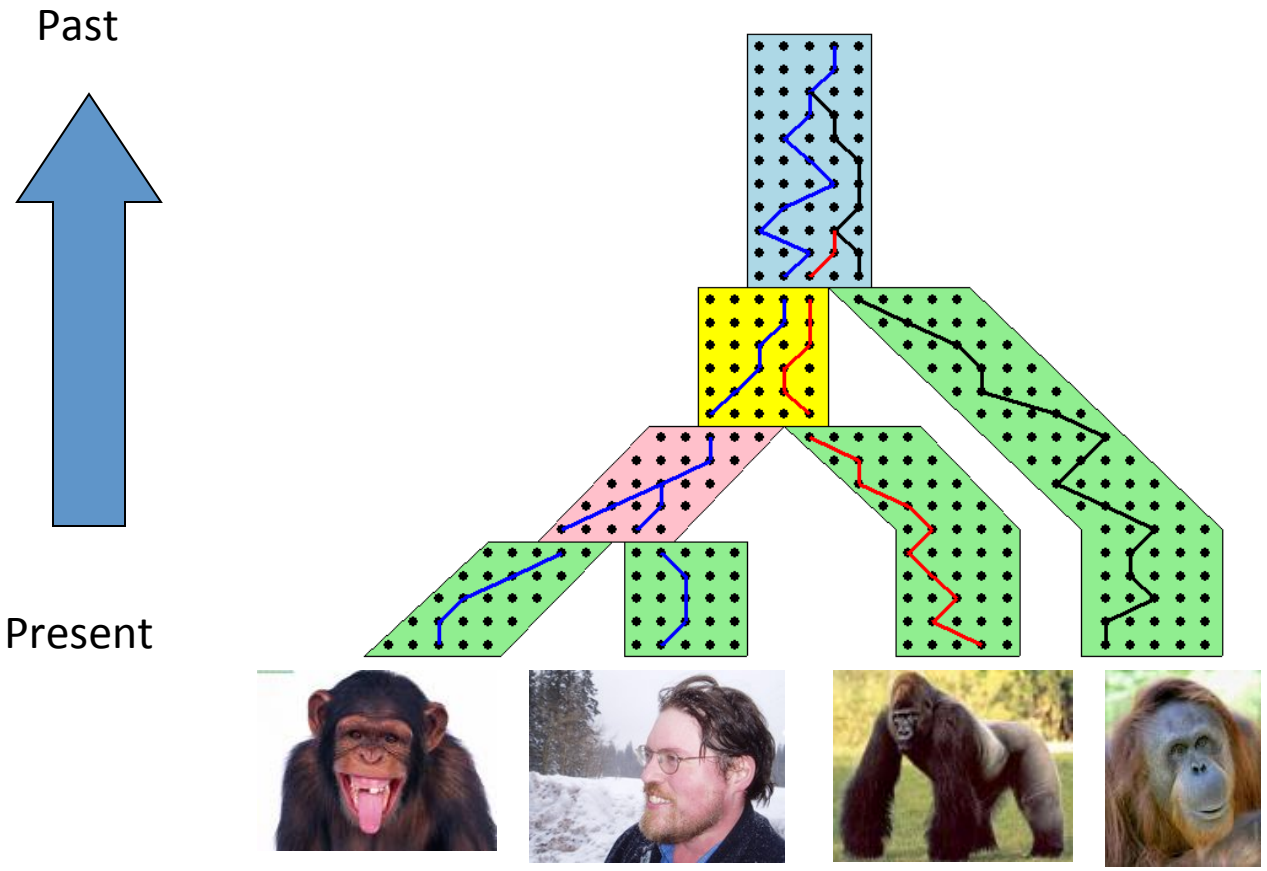


Red gene tree ≠ species tree
(green gene tree okay)



The Coalescent

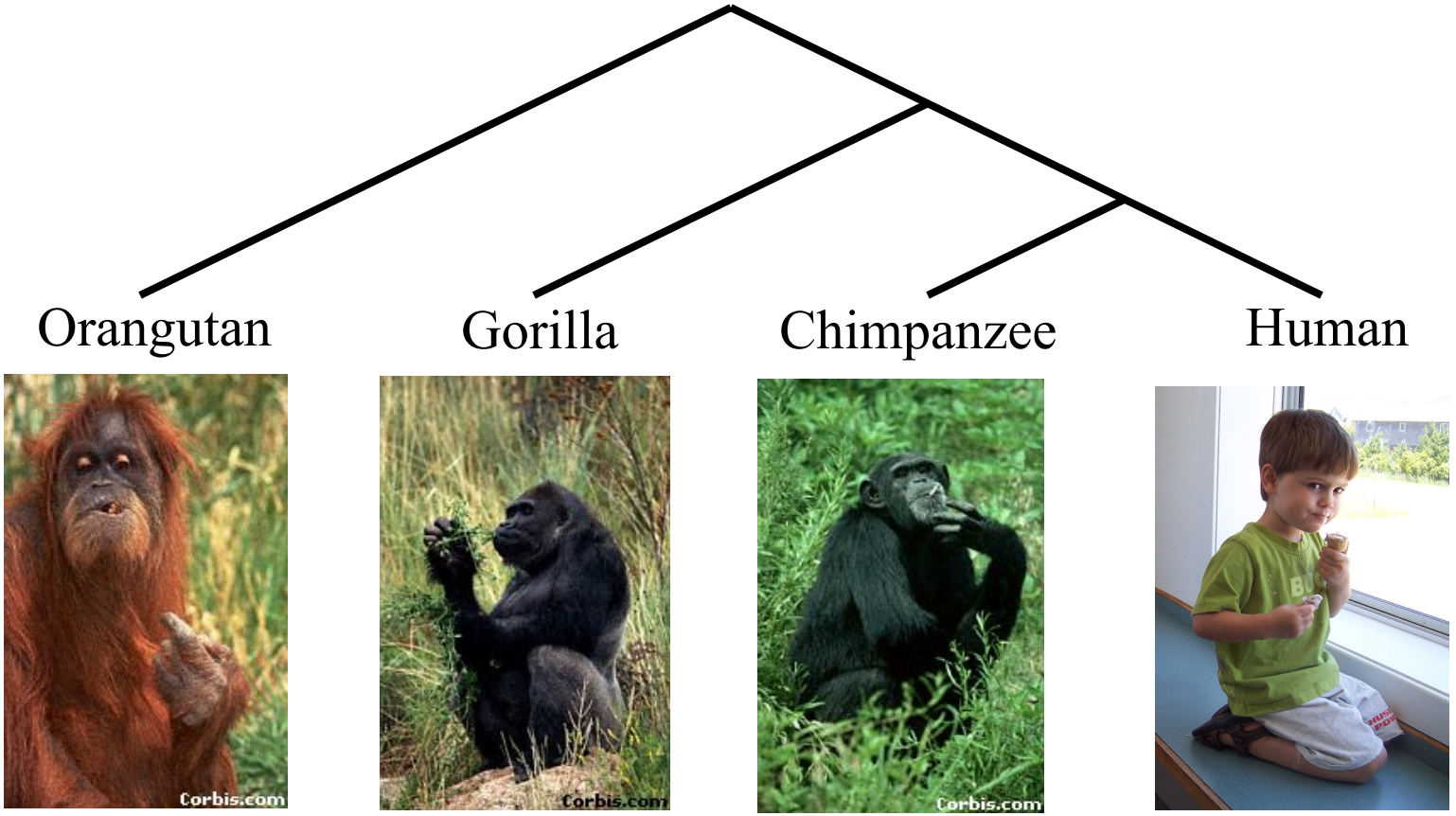
Courtesy James Degnan



Incomplete Lineage Sorting (ILS)

- 1000+ papers in 2013 alone
- Confounds phylogenetic analysis for many groups:
  - Hominids
  - Birds
  - Yeast
  - Animals
  - Toads
  - Fish
  - Fungi
- There is substantial debate about how to analyze phylogenomic datasets in the presence of ILS.

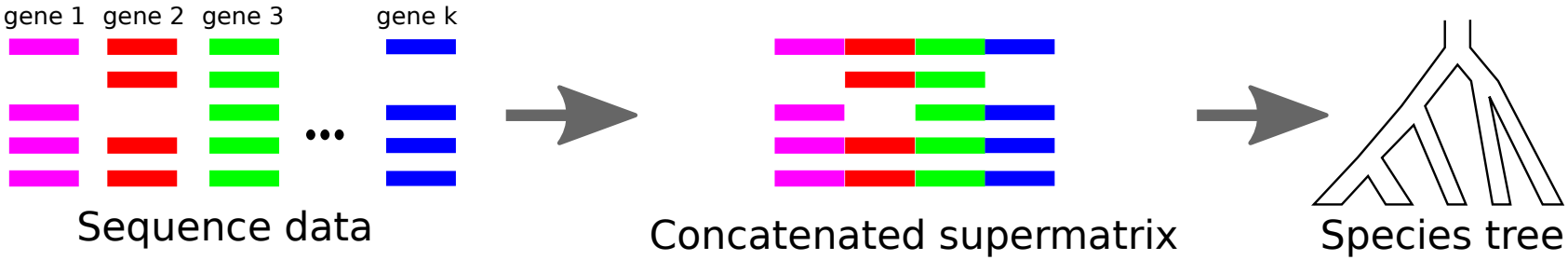
Species tree estimation: difficult, even for small datasets



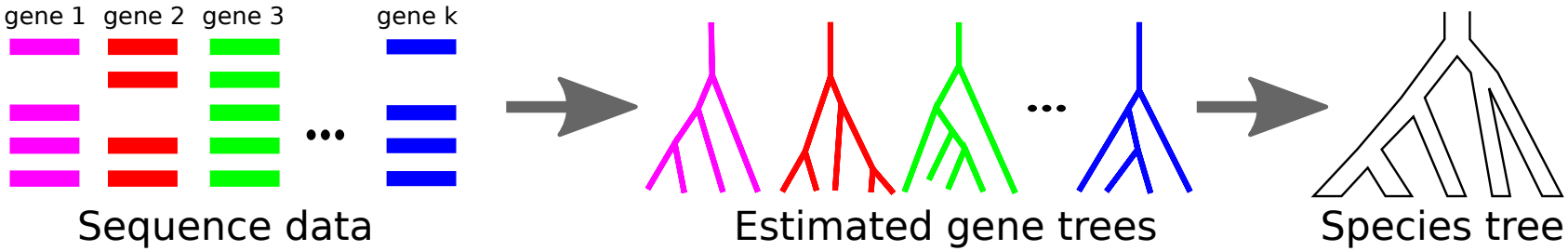
From the Tree of the Life Website, University of Arizona

Species tree estimation

1- Concatenation: statistically inconsistent (Roch & Steel 2014)



2- Summary methods: can be statistically consistent



3- Co-estimation methods: too slow for large datasets

Is Concatenation Evil?

- Joseph Heled:
  - YES
- John Gatesy
  - No

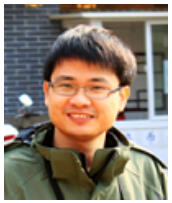
- Data needed to held understand existing methods and their limitations
- Better methods are needed

Avian Phylogenomics Project (100+ people)

Erich Jarvis, HHMI

MTP Gilbert, Copenhagen

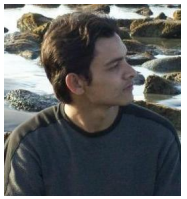
G Zhang, BGI



T. Warnow UT-Austin

S. Mirarab UT-Austin

Md. S. Bayzid UT-Austin



- Approx. 50 species, whole genomes
- 8000+ genes, UCEs
- Gene sequence alignments and trees computed using SATé (Science 2009, Systematic Biology 2012)
- Concatenation analysis (multi-million site) using ExaML (new version of RAxML for very long alignments)
- Massive gene tree incongruence suggestive of incomplete lineage sorting -- coalescent-based species tree estimation computed using "Statistical Binning" (Science, in press)

Our methods

- "Statistical Binning" (accepted): uses a statistical method to determine sets of "combinable" gene sequence alignments, improves coalescent-based species tree estimation accuracy when gene trees have poor resolution (used for Avian Phylogenomics Project).
- ASTRAL (Bioinformatics 2014): polynomial time statistically consistent method, can run on very large datasets of unrooted gene trees.

Mammalian simulations

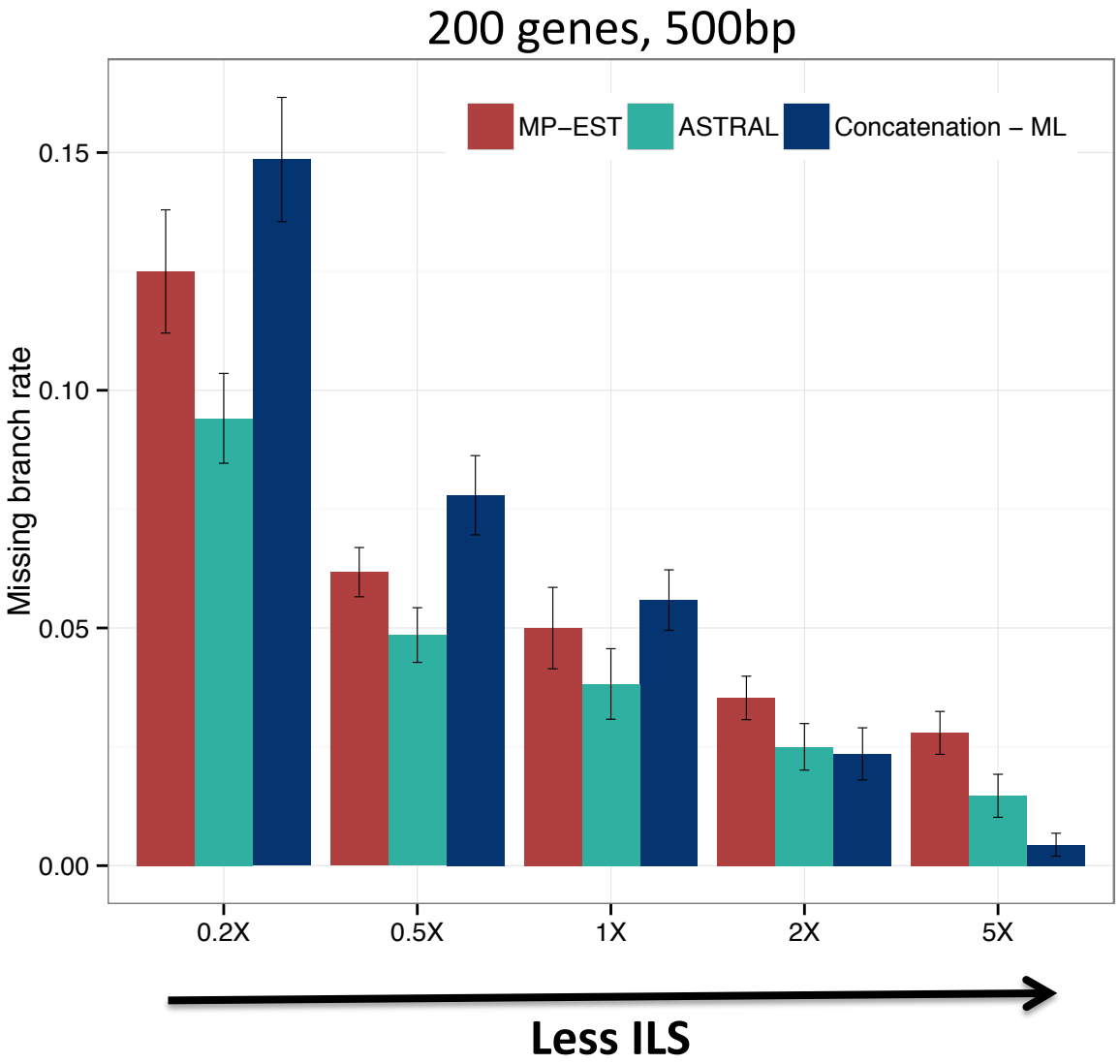
- Based on a biological mammalian dataset of 37 taxa and 442 genes, published by Song et al., PNAS, 2012.

- In simulations, we vary
  - Levels of ILS
  - Number of genes
  - Alignment length to control gene tree estimation error

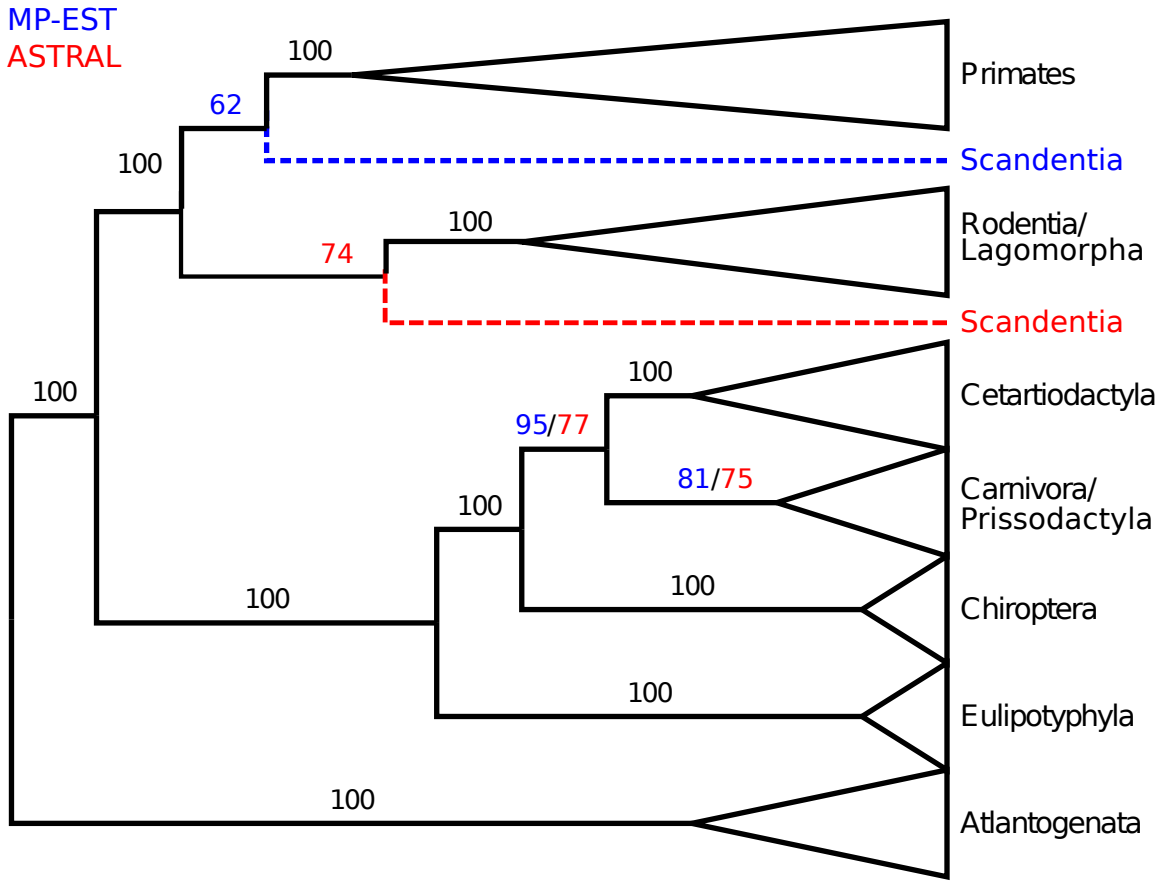
- Compare ASTRAL to
  - MP-EST, BUCKy
  - Concatenation
  - MRP, Greedy

- Measure species tree error compared to the known true tree

ASTRAL vs. Concatenation



Analyses of the Song et al. Mammalian dataset

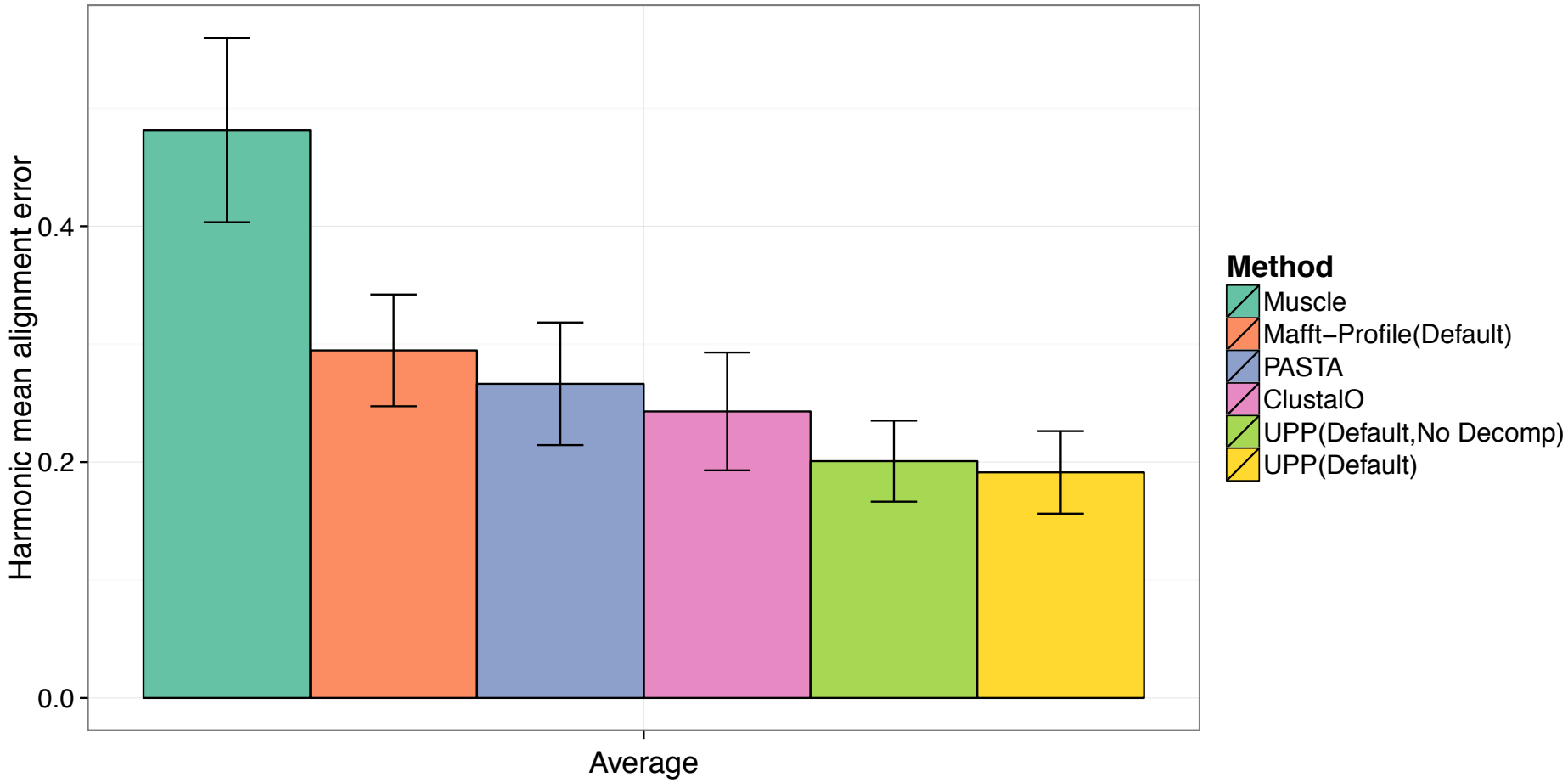


The placement of Scandentia (Tree Shrew) is controversial.
The ASTRAL analysis agrees with maximum likelihood concatenation analysis of this dataset.

Summary

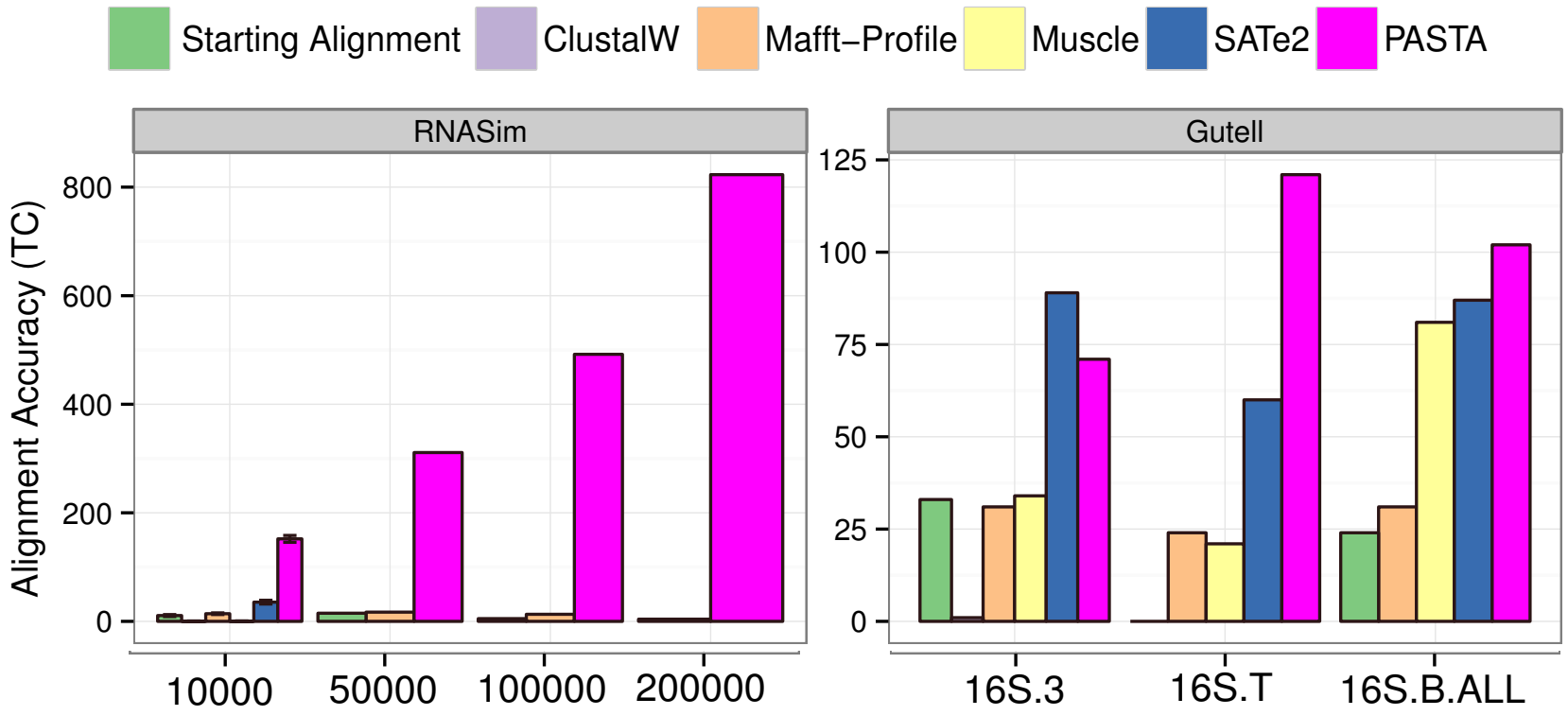
- New multiple sequence alignments with improved accuracy and scalability, as well as high robustness to fragmentary data – SATé used in many studies.
- New coalescent-based species tree estimation methods that have better accuracy than current methods, and can analyze large datasets (used in 1KP and Avian Phylogenomics project analyses)
- New methods for metagenomic taxon identification and abundance profiling with improved accuracy (will be used in analyses here at Illinois)
- Method development inspired by collaboration with biologists, and improves biological analyses.

AA Sequence Alignment Error (13 HomFam datasets)



Homfam: Sievers et al., MSB 2011
10,000 to 46,000 sequences per dataset; 5-14 sequences in each seed alignment
Sequence lengths from 46-364 AA

Alignment Accuracy – Correct columns



Other co-estimation methods

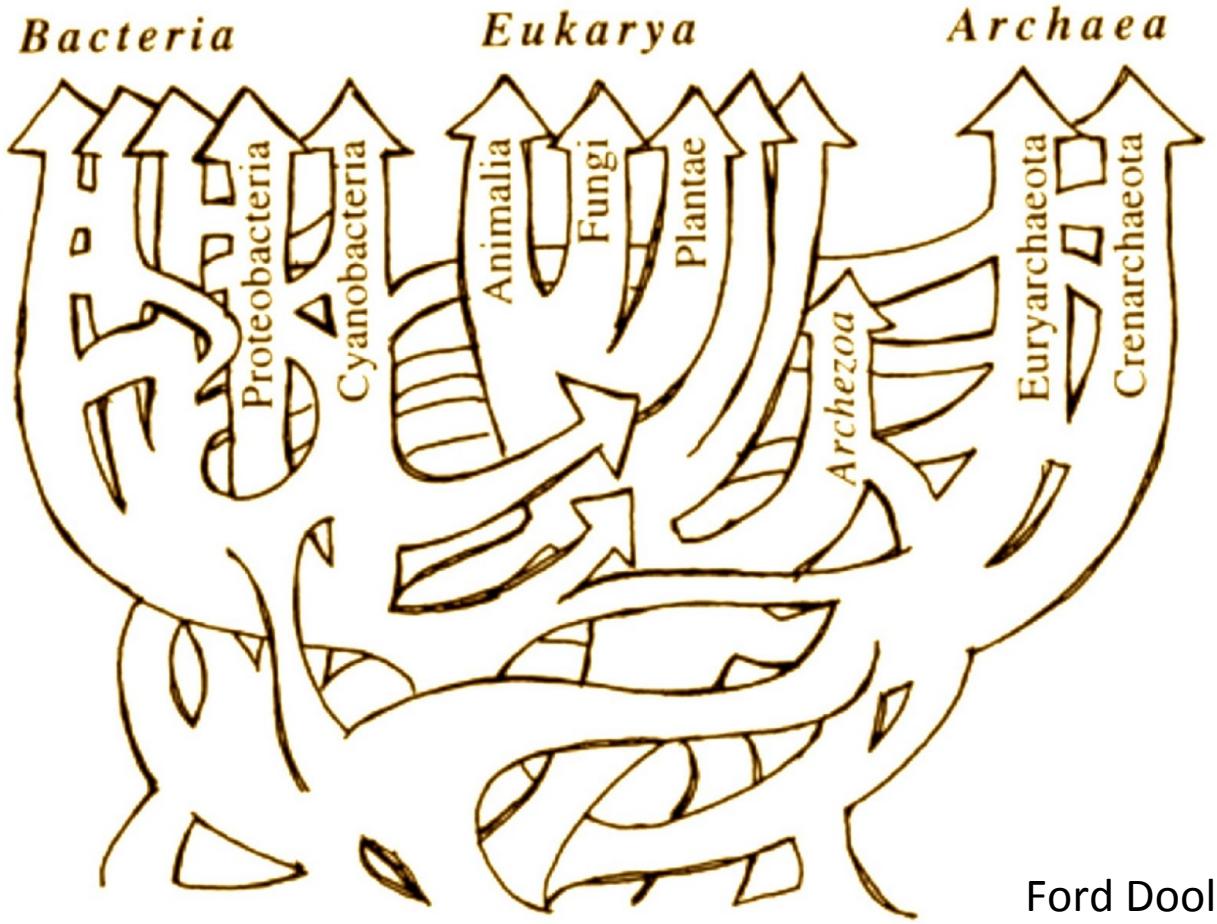
Statistical methods:

- BAli-Phy (Redelings and Suchard): Bayesian software to co-estimate alignments and trees under a statistical model of evolution that includes indels. Can scale to about 100 sequences, but takes a very long time.
  - http://www.bali-phy.org/
- StatAlign: http://statalign.github.io/

Extensions of Parsimony

- POY (most well known software)
  - http://www.amnh.org/our-research/computational-sciences/research/projects/systematic-biology/poy
- BeeTLe (Liu and Warnow, PLoS One 2012)

Horizontal Gene Transfer – Phylogenetic Networks

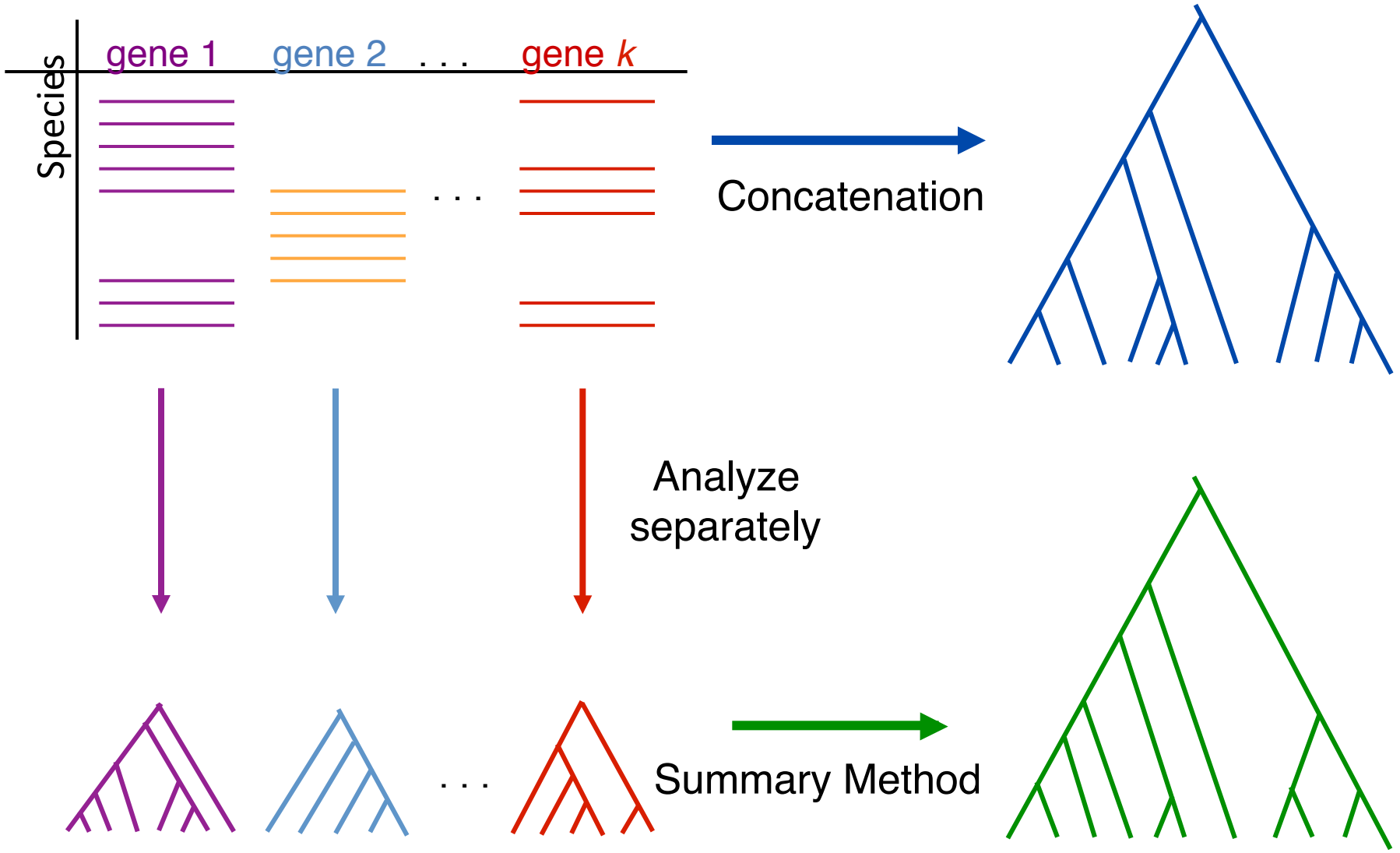


Ford Doolittle

But…

- Gene trees may not be identical to species trees:
  - Incomplete Lineage Sorting (deep coalescence)
  - Gene duplication and loss
  - Horizontal gene transfer
- This makes combined analysis and standard supertree analyses inappropriate

Two competing approaches



How to compute a species tree?

Statistically consistent under ILS?

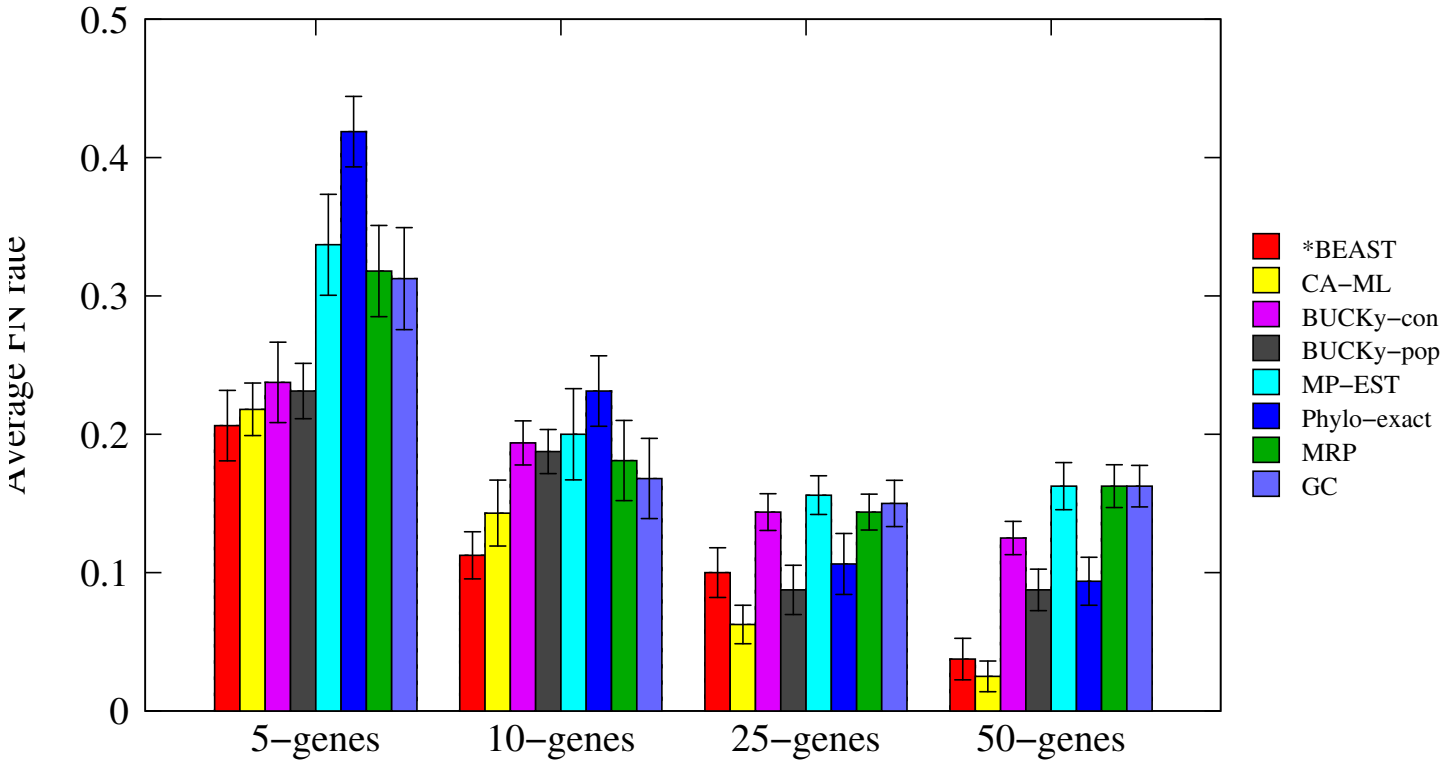
- MP-EST (Liu et al. 2010): maximum likelihood estimation of rooted species tree – YES
- BUCKy-pop (Ané and Larget 2010): quartet-based Bayesian species tree estimation –YES
- MDC – NO
- Greedy – NO
- Concatenation under maximum likelihood – NO
- MRP (supertree method) – open

The Debate: Concatenation vs. Coalescent Estimation

- In favor of coalescent-based estimation
  - Statistical consistency guarantees
  - Addresses gene tree incongruence resulting from ILS
  - Some evidence that concatenation can be positively misleading

- In favor of concatenation
  - Reasonable results on data
  - High bootstrap support
  - Summary methods (that combine gene trees) can have poor support or miss well-established clades entirely
  - Some methods (such as *BEAST) are computationally too intensive to use

Results on 11-taxon datasets with strongILS



***BEAST** more accurate than summary methods (MP-EST, BUCKy, etc)
CA-ML: (concatenated analysis) also very accurate

Datasets from Chung and Ané, 2011
Bayzid & Warnow, Bioinformatics 2013

Species tree/network estimation

- Methods have been developed to estimate species phylogenies (trees or networks!) from gene trees, when gene trees can conflict from each other (e.g., due to ILS, gene duplication and loss, and horizontal gene transfer).
- Phylonet (software suite), has effective methods for many optimization problems – including MDC and maximum likelihood.
- Tutorial on Wednesday.
- Software available at http://bioinfo.cs.rice.edu/phylonet?destination=node/3

Two Basic Questions

1. What is this fragment? (Classify each fragment as well as possible.)

2. What is the taxonomic distribution in the dataset? (Note: helpful to use marker genes.)

SEPP

- **SEPP: SATé-enabled Phylogenetic Placement**, by Mirarab, Nguyen, and Warnow
- Pacific Symposium on Biocomputing, 2012 (special session on the Human Microbiome)
- Tutorial on Thursday.

Other problems

- Genomic MSA estimation:
  - Multiple sequence alignment of very long sequences
  - Multiple sequence alignment of sequences that evolve with rearrangement events
- Phylogeny estimation under more complex models
  - Heterotachy
  - Violation of the rates-across-sites assumption
  - Rearrangements
- Estimating branch support on very large datasets