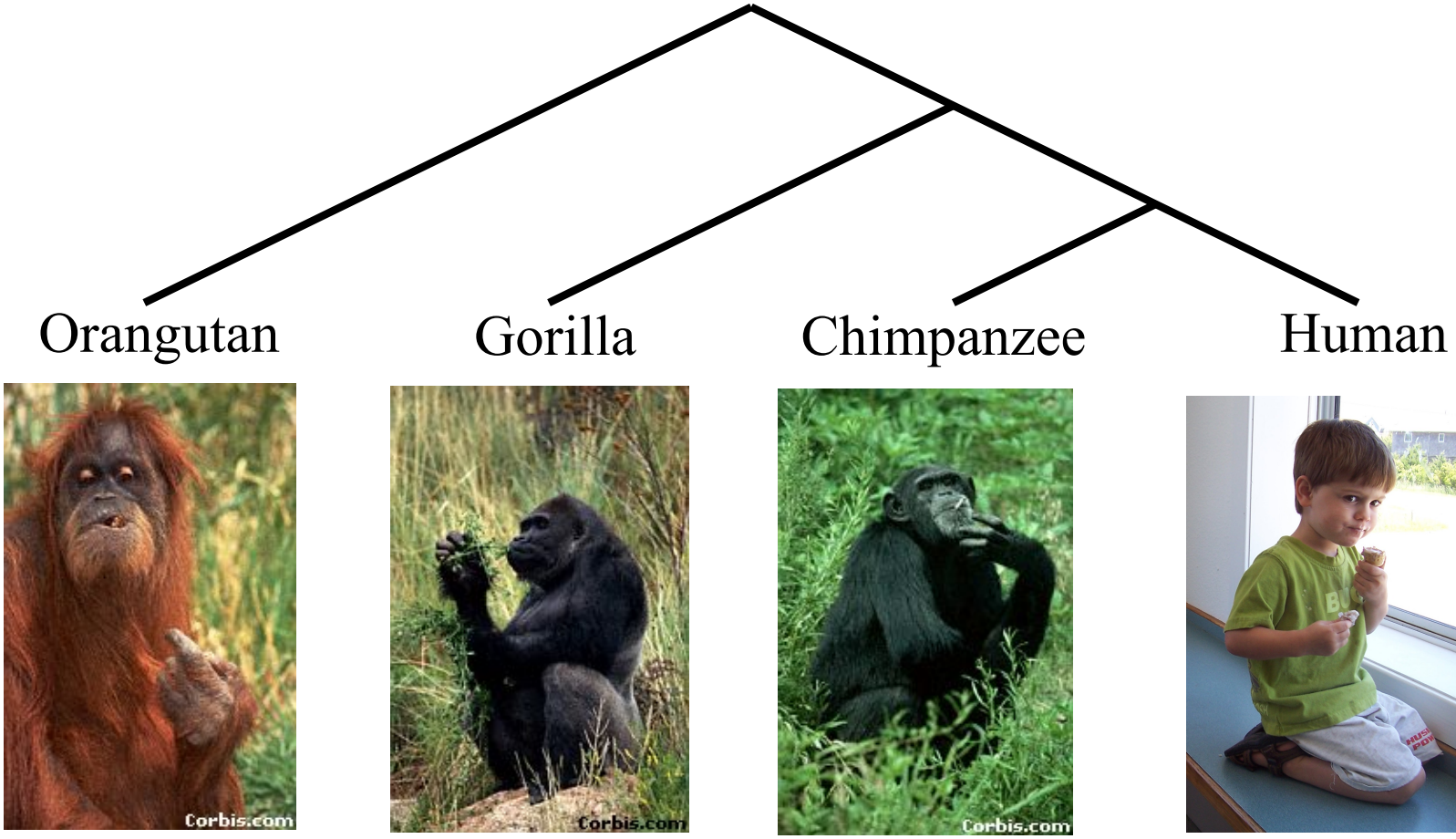
Mathematical and Computational Challenges in Reconstructing Evolution

Tandy Warnow

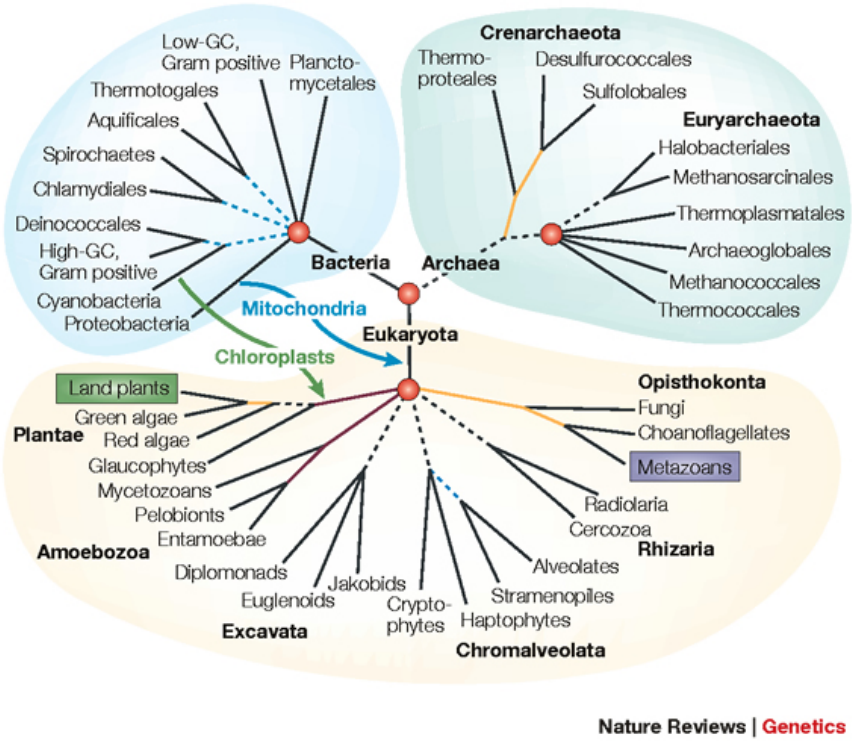
The University of Illinois

Phylogeny
(evolutionary tree)



From the Tree of the Life Website,
University of Arizona

Phylogenomics



Nature Reviews | Genetics

Phylogeny + genomics = genome-scale phylogeny estimation

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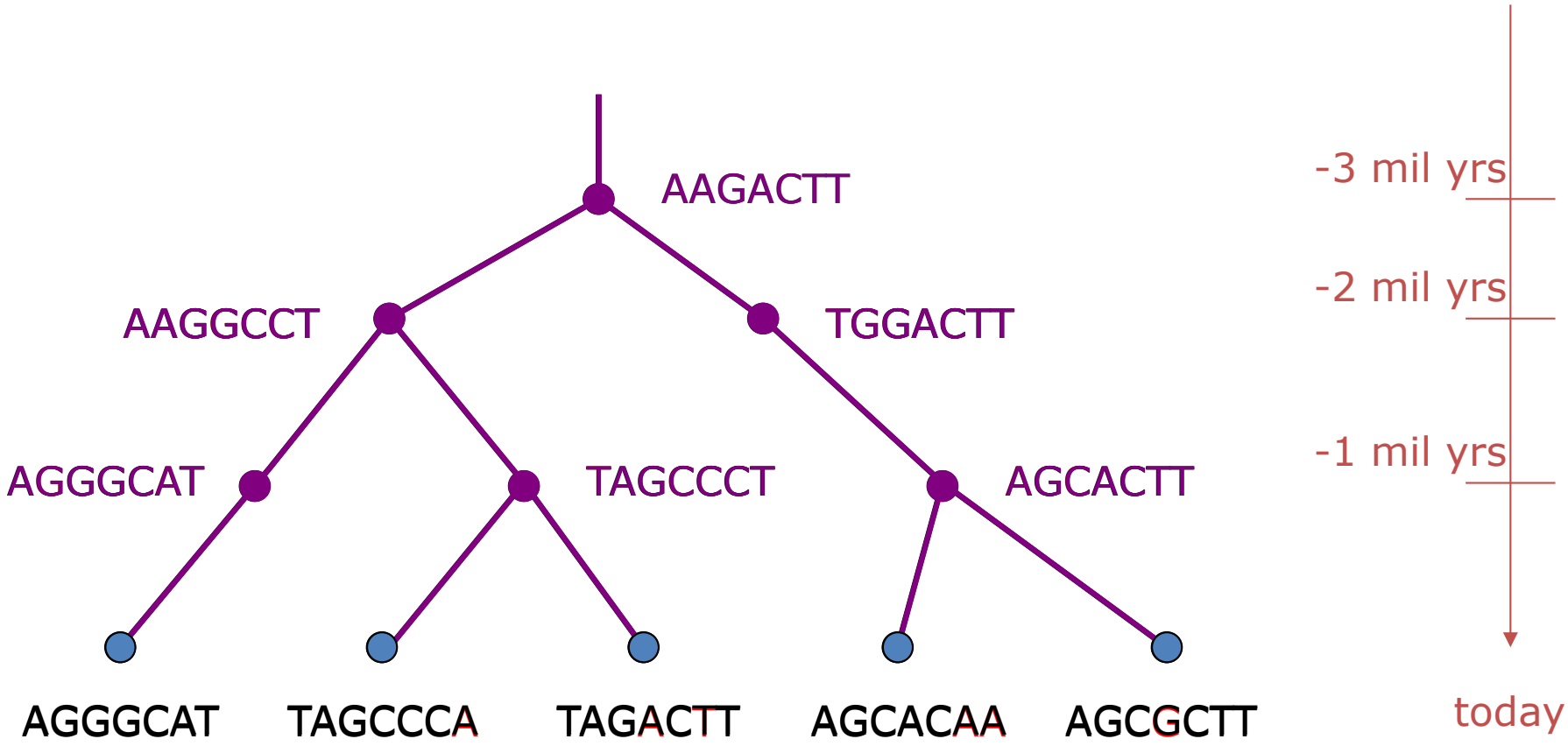
- "Nothing in biology makes sense except in the light of evolution"
  - Theodosius Dobzhansky, 1973 essay in the American Biology Teacher, vol. 35, pp 125-129

- *"…… nothing in evolution makes sense except in the light of phylogeny …"*
  - *Society of Systematic Biologists, http://systbio.org/teachevolution.html*

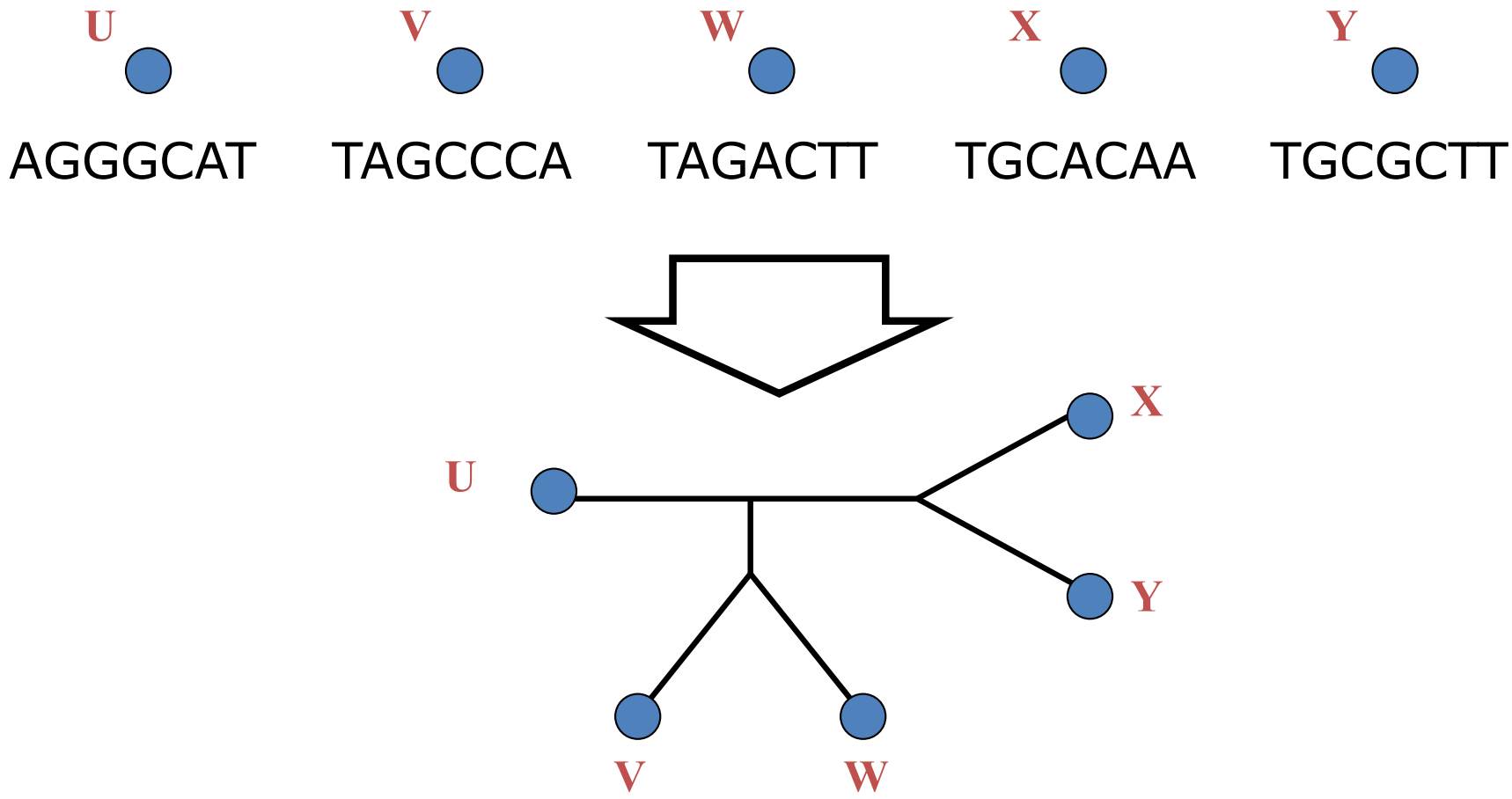
This Talk

- Models of evolution, identifiability, statistical consistency
- Genome-scale phylogeny:
  - Incomplete lineage sorting and species tree estimation under the Multi-Species Coalescent model (MSC)
  - ASTRAL: non-parametric accurate and statistically consistent species tree estimation under the MSC
  - NJMerge: scaling species tree methods to large datasets
  - Statistical consistency when number of sites per locus is bounded
- Open questions
- Future directions

DNA Sequence Evolution (Idealized)



Phylogeny Problem



Markov Models of Sequence Evolution

The different sites are assumed to evolve ***i.i.d***. down the model tree (with rates that are drawn from a gamma distribution).

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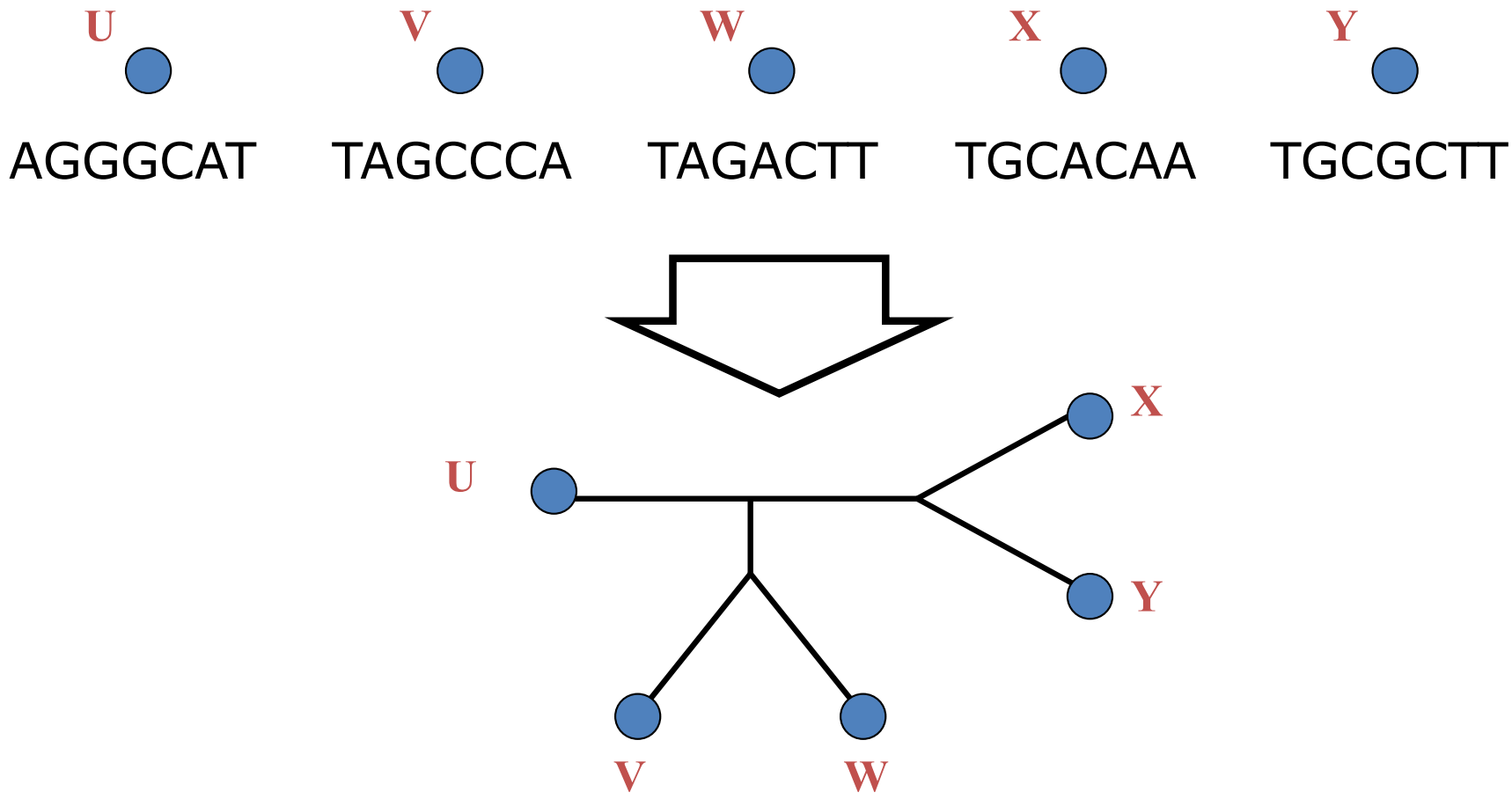
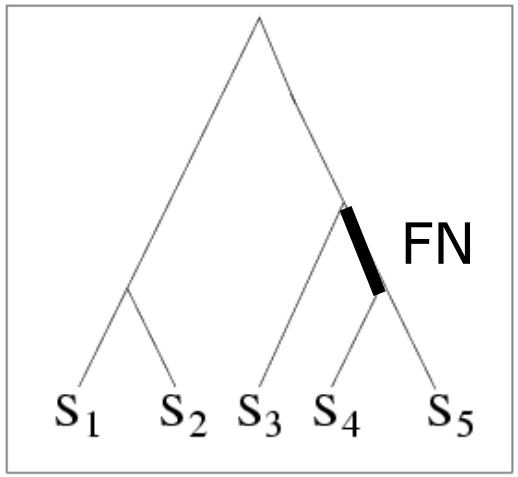
Simplest site evolution model (Jukes-Cantor, 1969):

- The model tree T is binary and has substitution probabilities p(e) on each edge e, with $0<p(e)<3/4$.
- The state at the root is randomly drawn from {A,C,T,G} (nucleotides)
- If a site (position) changes on an edge, it changes with equal probability to each of the remaining states.
- The evolutionary process is Markovian.

More complex models (such as the General Markov model) are also considered, often with little change to the theory.

Phylogeny Problem



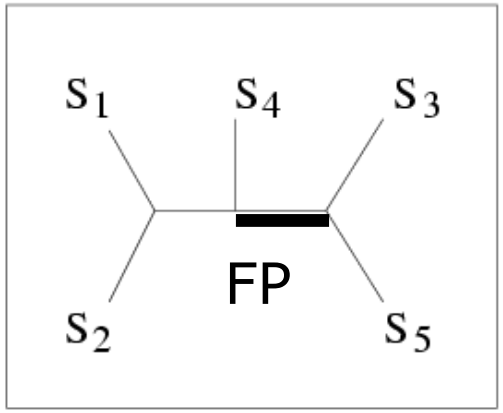


TRUE TREE

S_1	ACAATTAGAAC
S_2	ACCCTTAGAAC
S_3	ACCATTCCAAC
S_4	ACCAGACCAAC
S_5	ACCAGACCGGA

DNA SEQUENCES

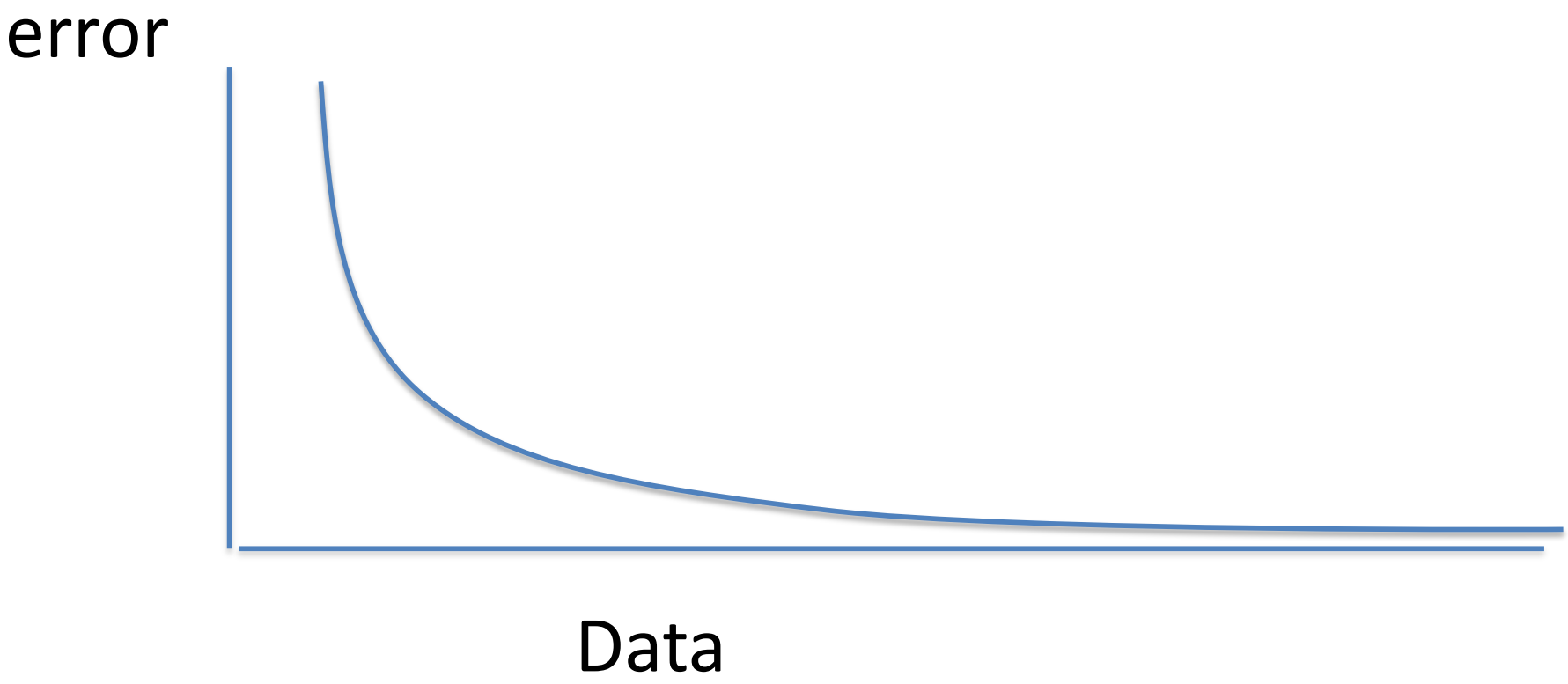
FN: false negative
(missing edge)
FP: false positive
(incorrect edge)



INFERRED TREE

50% error rate

Statistical Consistency



Questions

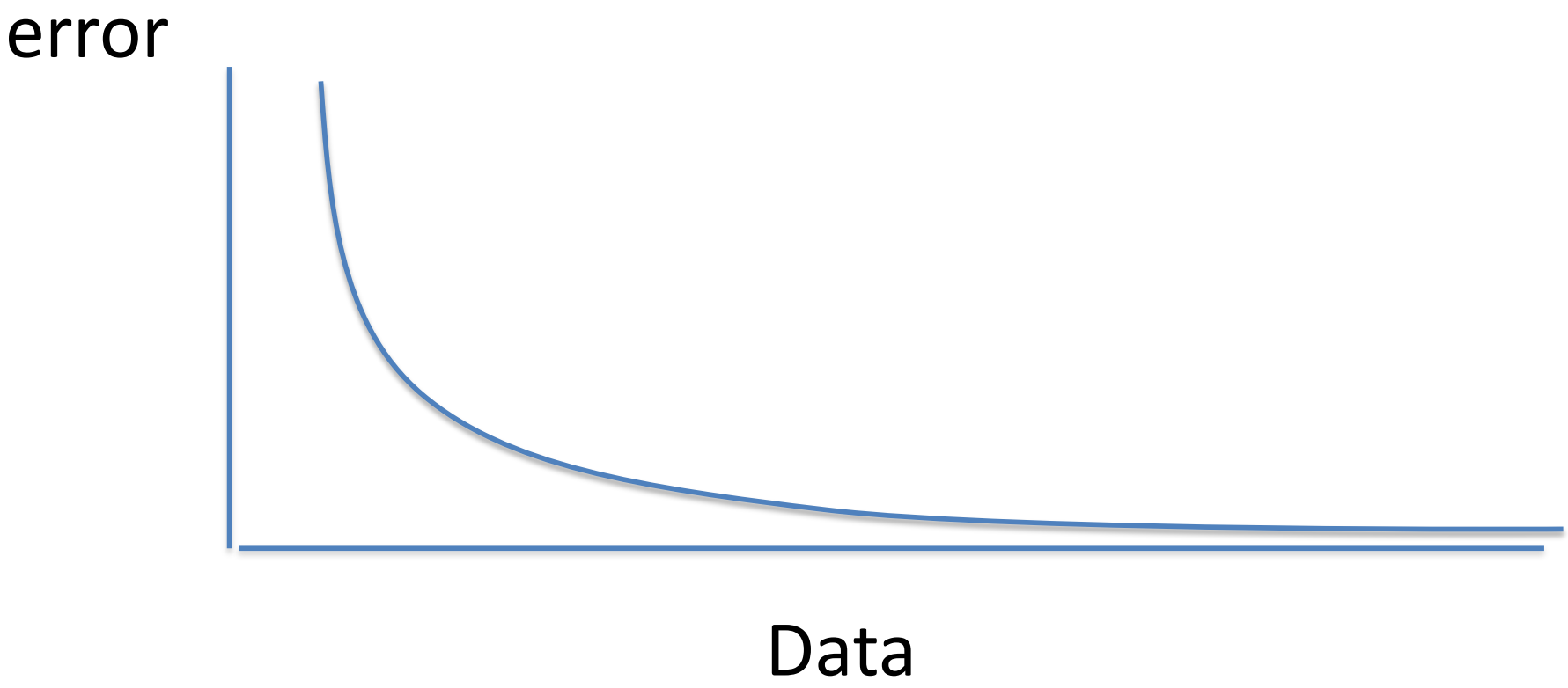
- Is the model tree identifiable?
- Which estimation methods are statistically consistent under this model?
- How much data does the method need to estimate the model tree correctly (with high probability)?

Answers?

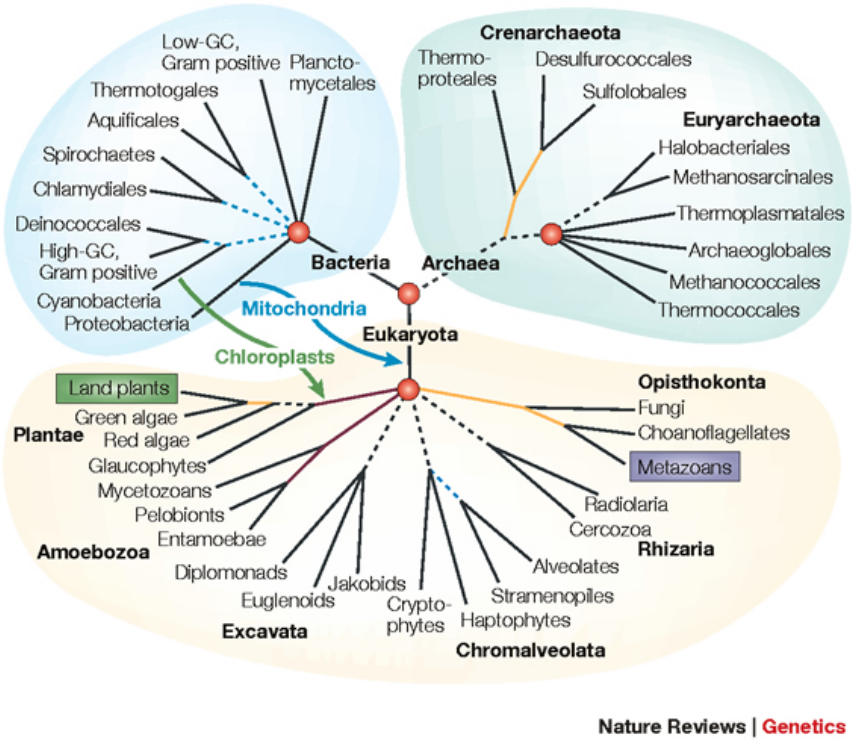
- We know a lot about which site evolution models are identifiable, and which methods are statistically consistent.
- We know a little bit about the sequence length requirements for standard methods.

Take home message: need to limit (or not allow) heterogeneity to get identifiability!

Genome-scale data?



Phylogenomics



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Phylogeny + genomics = genome-scale phylogeny estimation

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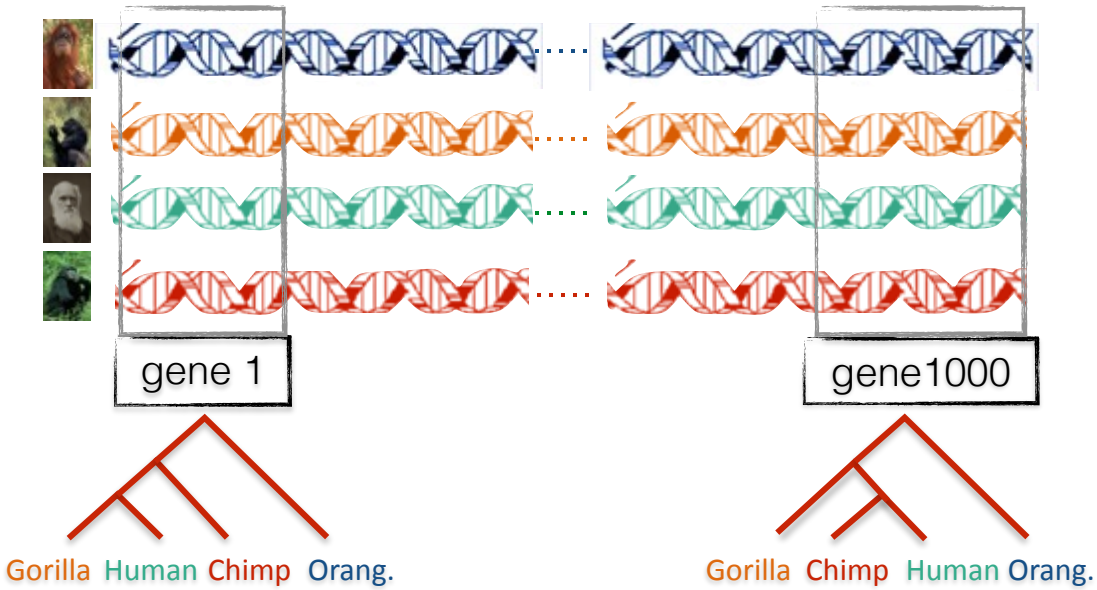
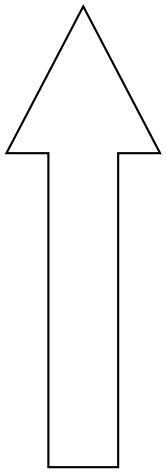
Gene tree discordance



Incomplete Lineage Sorting (ILS) is a dominant cause of gene tree heterogeneity

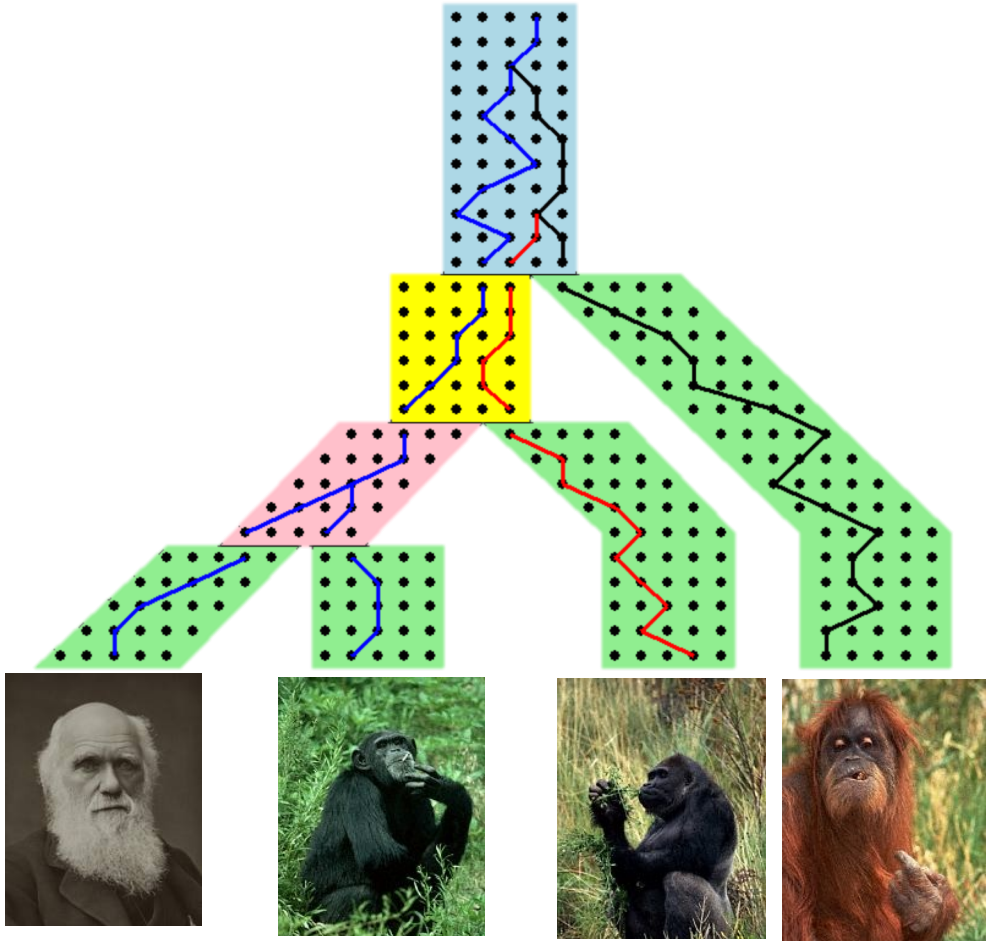
Gene trees inside the species tree (Coalescent Process)

Past



Present

Courtesy James Degnan



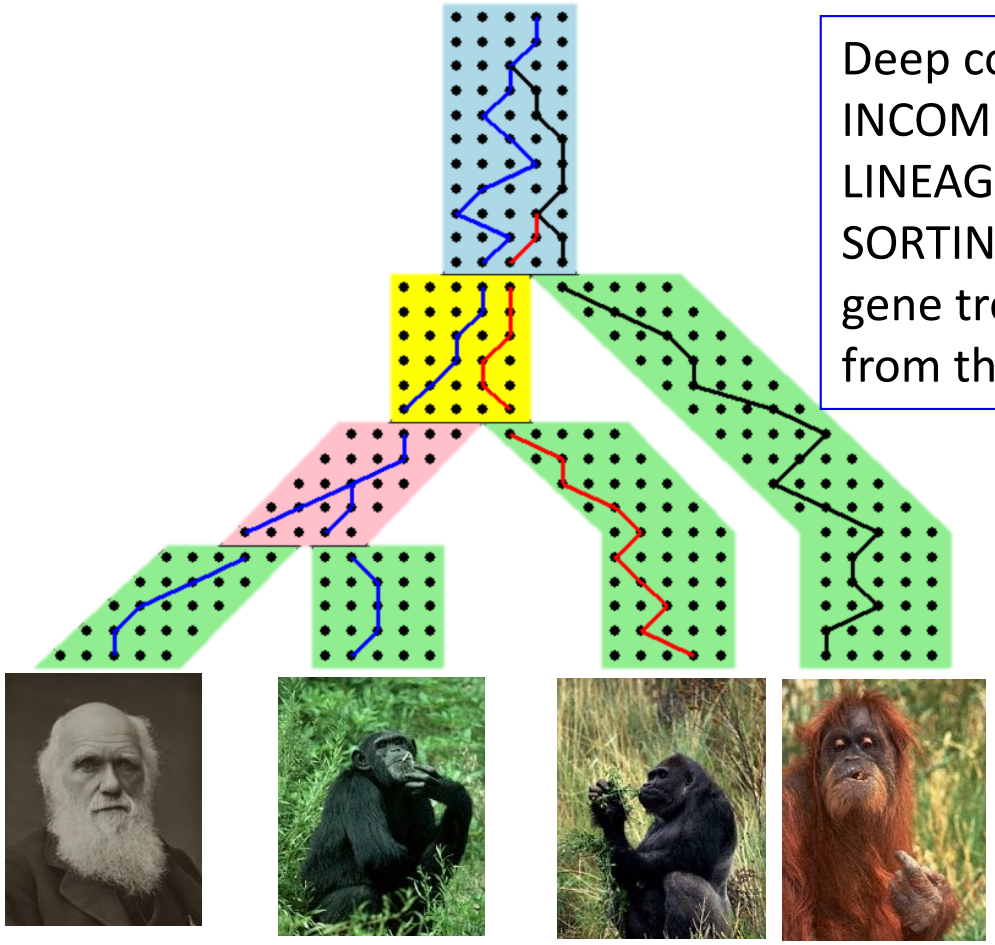
Gorilla and Orangutan are not siblings in the species tree, but they are in the gene tree.

Gene trees inside the species tree (Coalescent Process)

Past

Present

Courtesy James Degnan



Deep coalescence = INCOMPLETE LINEAGE SORTING (ILS): gene tree can be different from the species tree

Gorilla and Orangutan are not siblings in the species tree, but they are in the gene tree.

1KP: Thousand Transcriptome Project


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

- 103 plant transcriptomes, 400-800 single copy “genes”
- Next phase will be much bigger
- Wickett, Mirarab et al., *PNAS* 2014

Major Challenge:

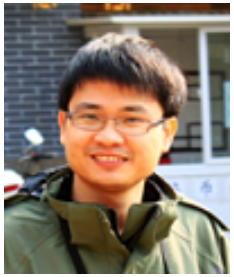
- Massive gene tree heterogeneity consistent with ILS

Avian Phylogenomics Project

Erich Jarvis, HHMI

MTP Gilbert, Copenhagen

Guojie Zhang, BGI



Siavash Mirarab, Texas

Tandy Warnow, Texas and UIUC

- Approx. 50 species, whole genomes
- 14,000 loci
- Multi-national team (100+ investigators)
- 8 papers published in special issue of Science 2014

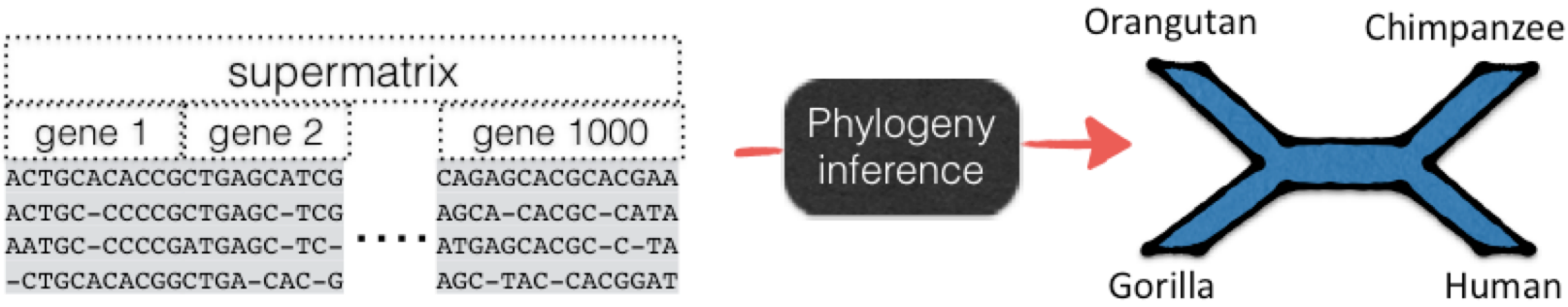
Major challenge:

- Massive gene tree heterogeneity consistent with ILS.

Big picture challenge

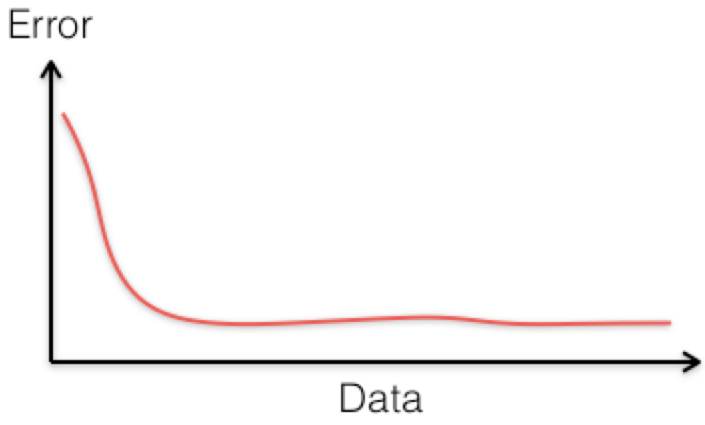
- Multi-locus data, generated by a hierarchical model
  - Species tree generates gene trees
  - Gene trees generate sequences
- How can we estimate the species tree from the sequence data?
- Suppose the number of genes and the sequence data per gene both go to infinity?

Traditional approach: concatenation



- Statistically <u>inconsistent</u> and can even be positively misleading (proved for unpartitioned maximum likelihood)
  [Roch and Steel, Theo. Pop. Gen., 2014]

- Mixed accuracy in simulations
  [Kubatko and Degnan, Systematic Biology, 2007]
  [<u>Mirarab</u>, et al., Systematic Biology, 2014]



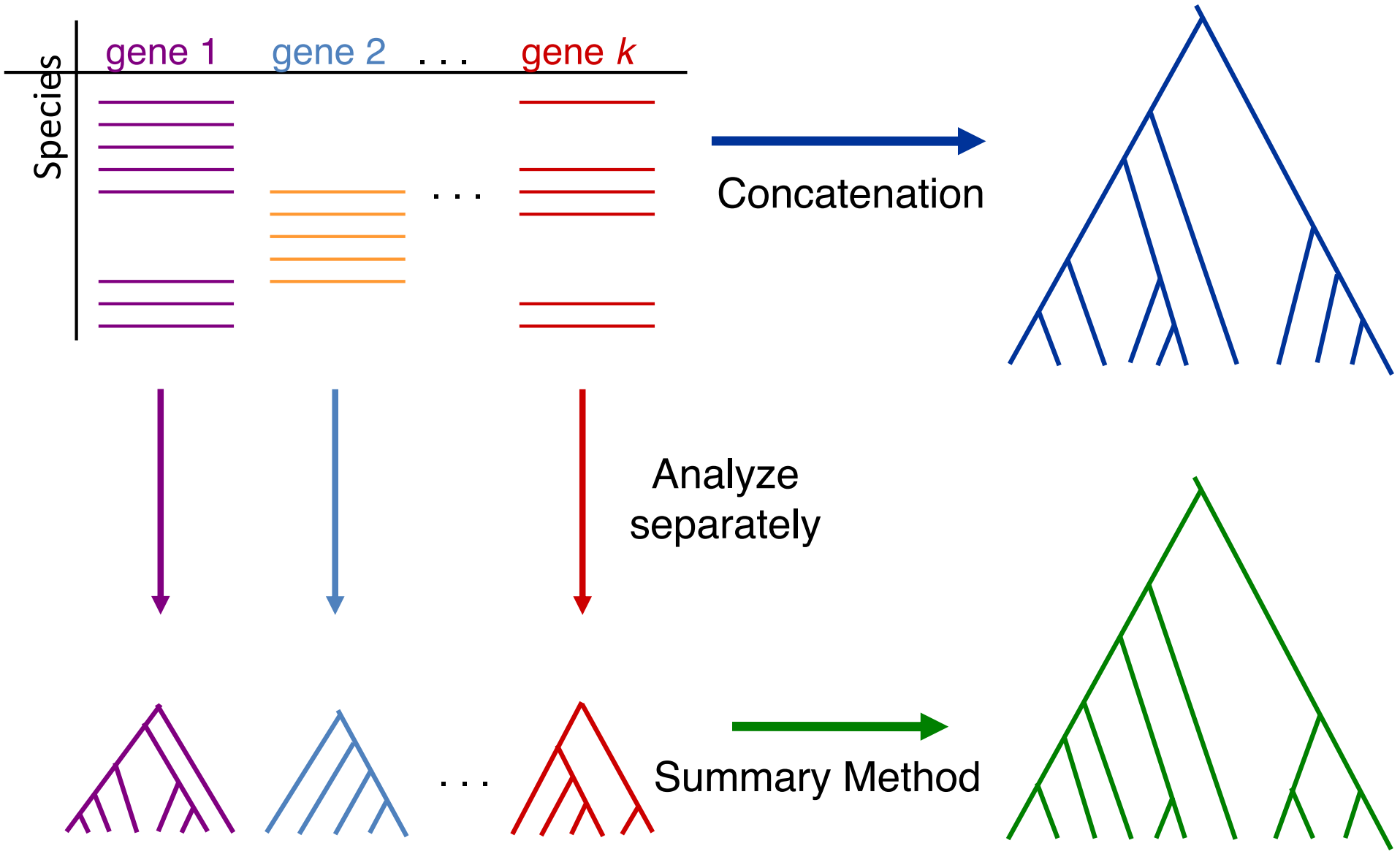
Statistically consistent methods

- **Coalescent-based summary methods:** Estimate gene trees, and then combine together (ASTRAL, ASTRID, MP-EST, NJst, and others)

- **Co-estimation methods**: Co-estimate gene trees and species trees (TOO EXPENSIVE)

- **Site-based methods:** estimate the species tree from the concatenated alignment, and do not estimate gene trees (NOT WELL STUDIED)

Main competing approaches



What about summary methods?

What about summary methods?

Techniques:

- Most frequent gene tree?
- Consensus of gene trees?
- Other?

Species tree estimation from unrooted gene trees

Theorem (Allman et al.): Under the multi-species coalescent model, for any four taxa A, B, C, and D, the most probable unrooted gene tree on {A,B,C,D} is identical to the unrooted species tree induced on {A,B,C,D}.

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Proof: For every four species, select most frequently observed tree as the species tree. Then combine quartet trees!

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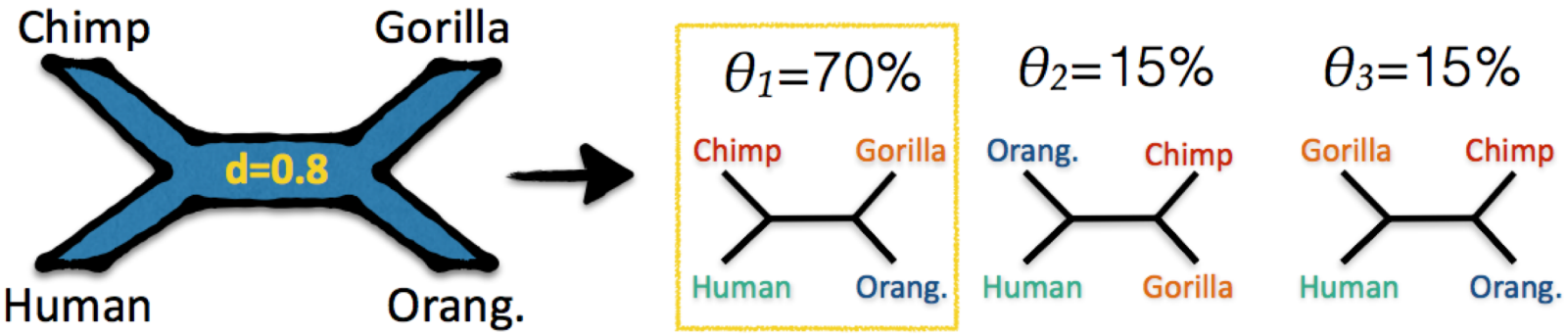
Proof: For every four species, select most frequently observed tree as the species tree. Then combine quartet trees!



ASTRAL

[Mirarab, et al., ECCB/Bioinformatics, 2014]

- Optimization Problem (NP-Hard):

Find the species tree with the maximum number of induced quartet trees shared with the collection of input gene trees

Set of quartet trees induced by T

$$Score(T) = \sum_{t \in \mathcal{T}} |Q(T) \cap Q(t)|$$

a gene tree

all input gene trees

- **Theorem**: Statistically consistent under the multi-species coalescent model when solved exactly

Constrained Maximum Quartet Support Tree

- Input: Set $\mathcal{T} = \{t_1, t_2, \ldots, t_k\}$ of unrooted gene trees, with each tree on set S with n species, and set X of allowed bipartitions
- Output: Unrooted tree T on leafset S, maximizing the total quartet tree similarity to $\mathcal{T}$, subject to T drawing its bipartitions from X.

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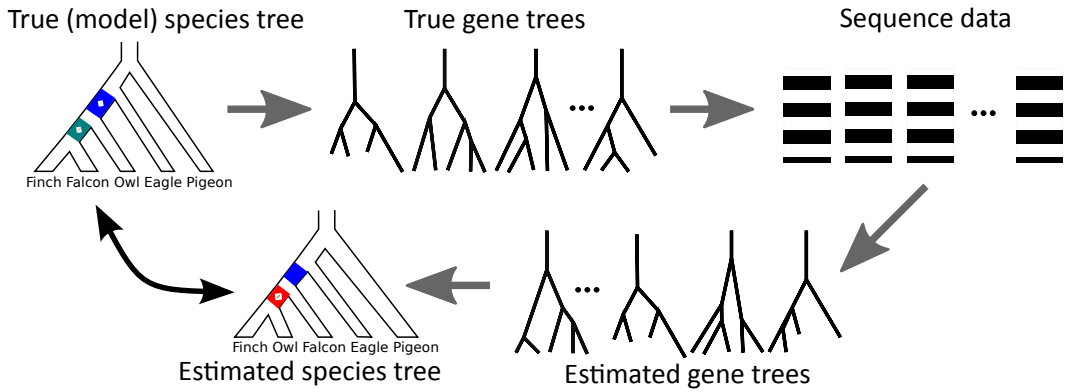
Theorems (Mirarab et al., 2014):

- If X contains the bipartitions from the input gene trees (and perhaps others), then an exact solution to this problem is statistically consistent under the MSC.
- The constrained MQST problem can be solved in $O(|X|^2 nk)$ time. (We use dynamic programming, and build the unrooted tree from the bottom-up, based on "allowed clades" – halves of the allowed bipartitions.)

Simulation study

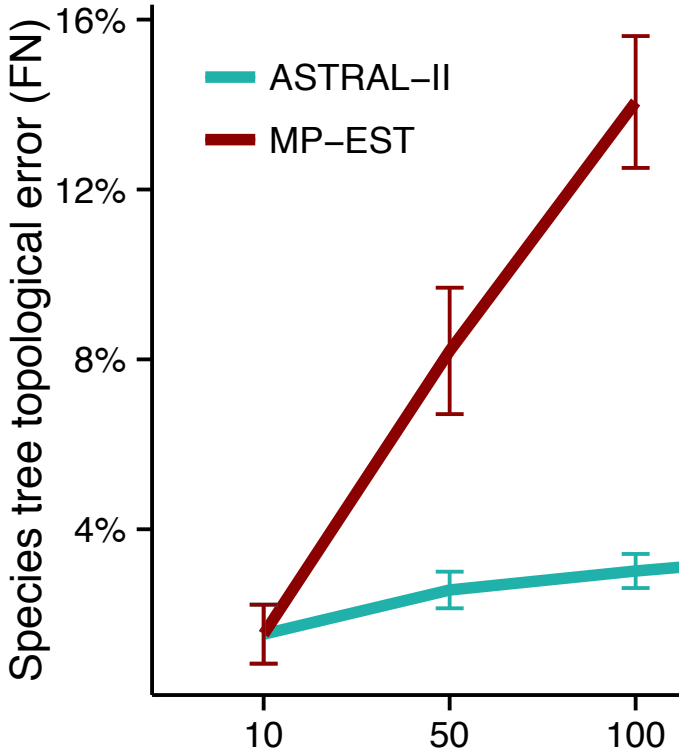
- Variable parameters:
  - Number of species: 10 – 1000
  - Number of genes: 50 – 1000
  - Amount of ILS: low, medium, high
  - Deep versus recent speciation



- 11 model conditions (50 replicas each) with heterogenous gene tree error
- Compare to NJst, MP-EST, concatenation (CA-ML)
- Evaluate accuracy using FN rate: the percentage of branches in the true tree that are missing from the estimated tree

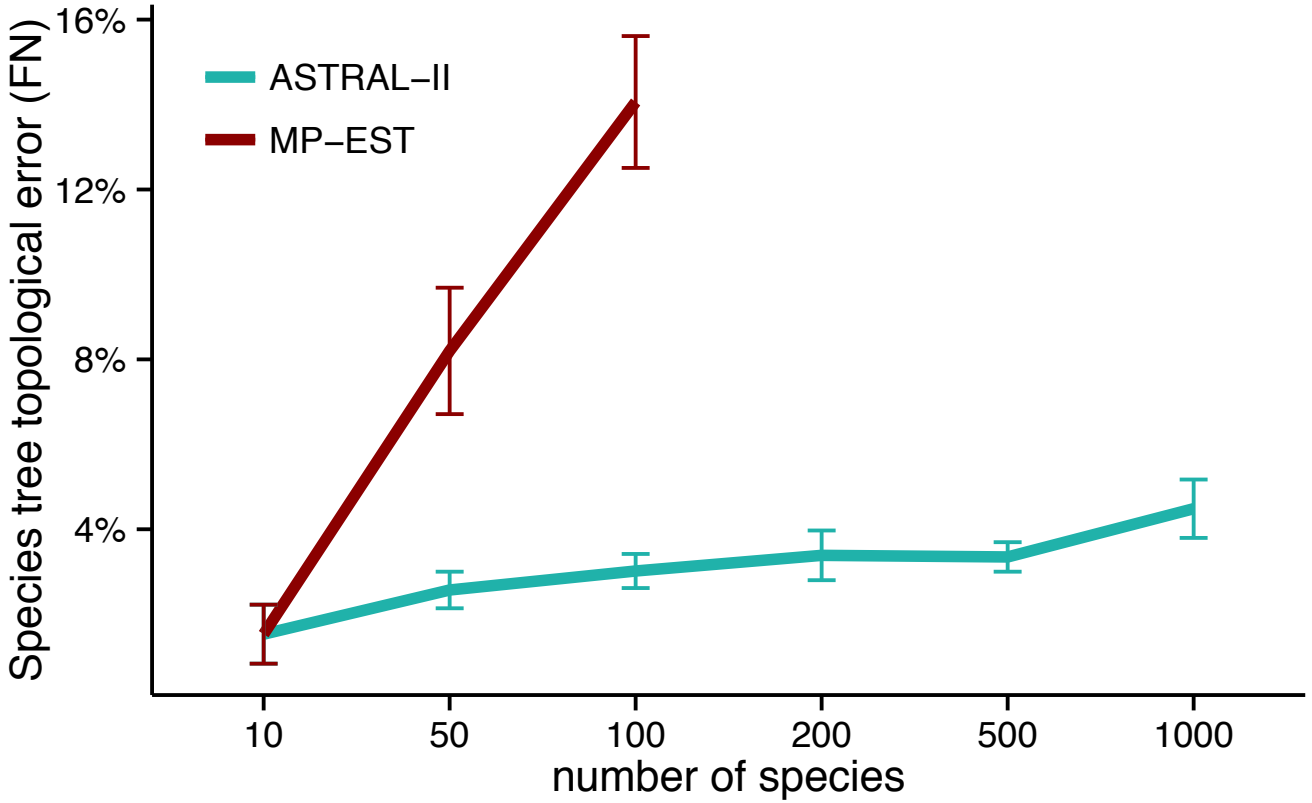
Used SimPhy, Mallo and Posada, 2015

Tree accuracy when varying the number of species



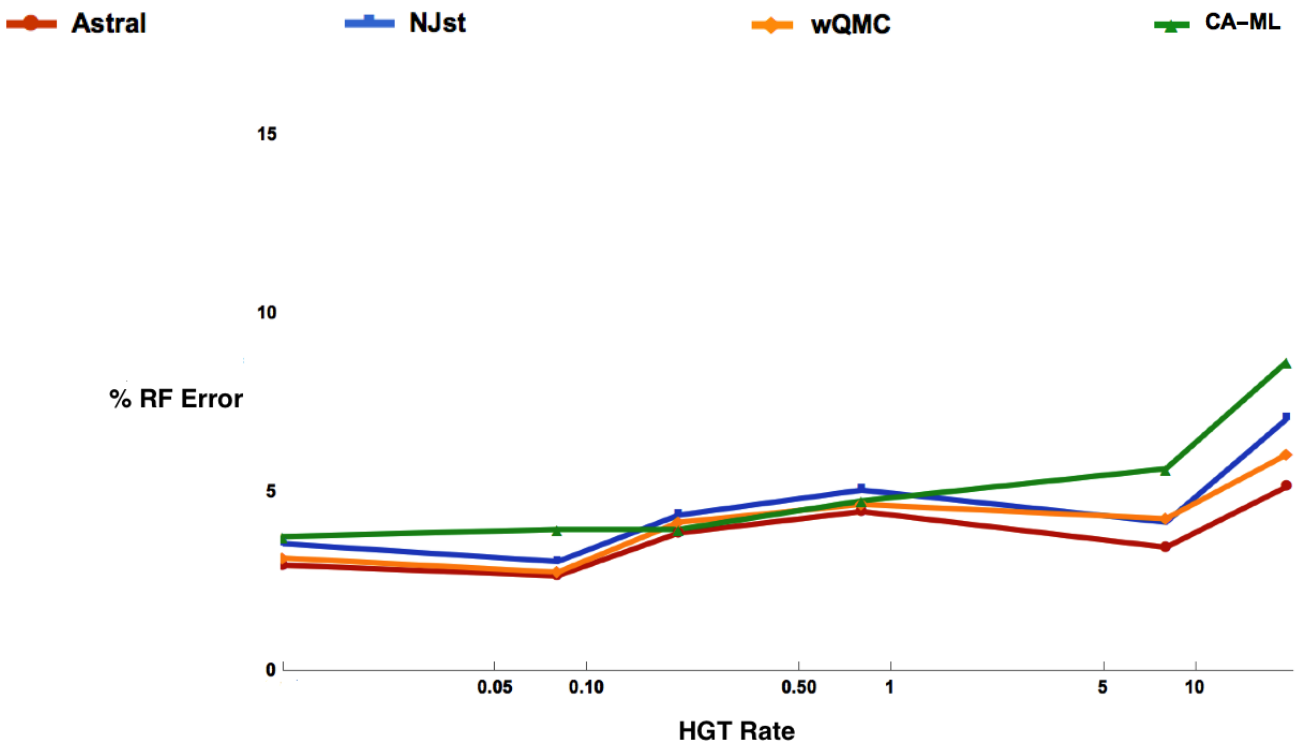
1000 genes, “medium” levels of recent ILS

Tree accuracy when varying the number of species



1000 genes, “medium” levels of recent ILS

Accuracy in the presence of HGT + ILS



Data: Fixed, moderate ILS rate, 50 replicates per HGT rates (1)-(6), 1 model species tree per replicate on 51 taxa, 1000 true gene trees, simulated 1000 bp gene sequences using INDELible [8], 1000 gene trees estimated from GTR simulated sequences using FastTree-2[7]

[7] Price, Dehal, Arkin 2015

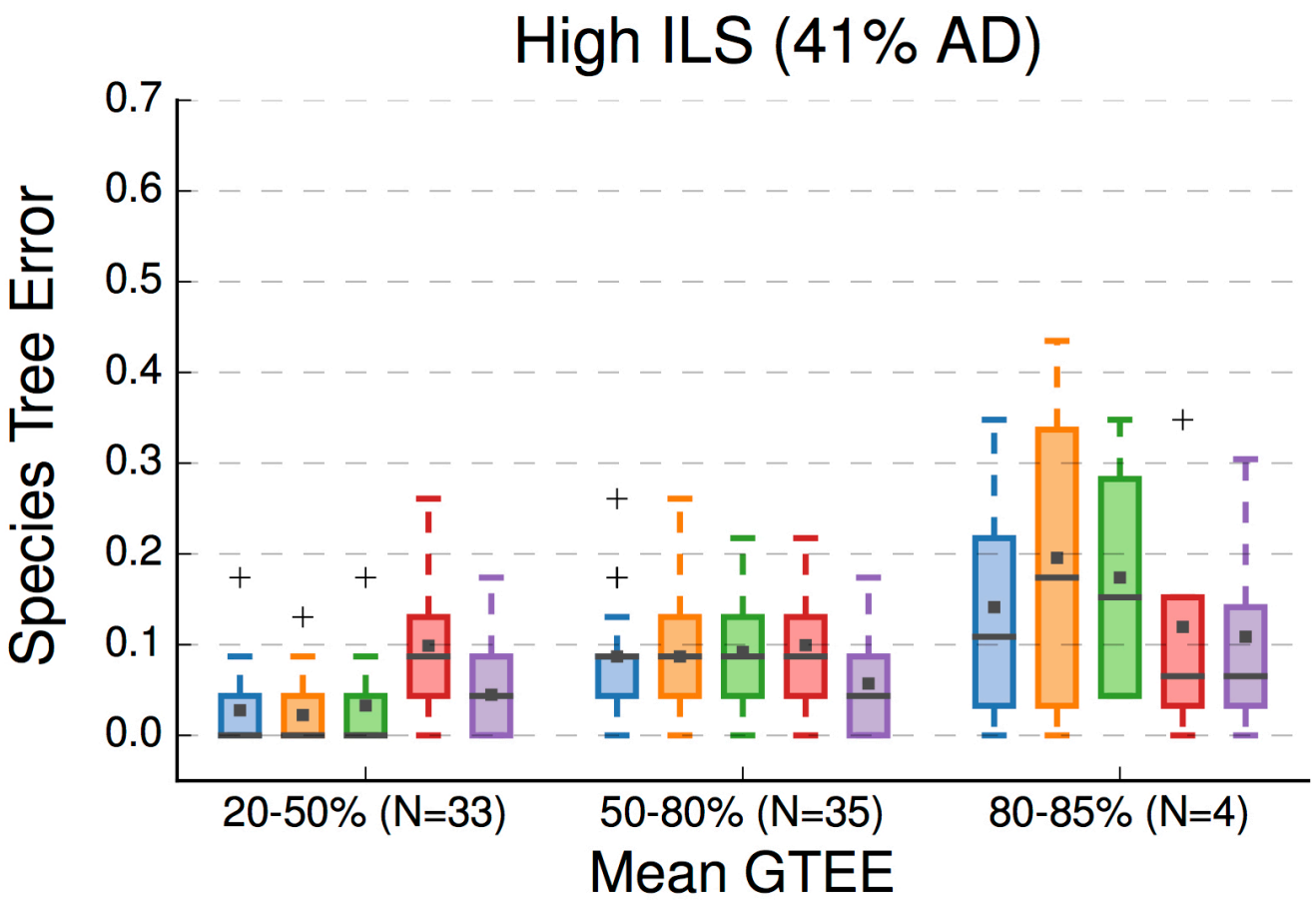
[8] Fletcher, Yang 2009

Davidson et al., RECOMB-CG, BMC Genomics 2015

Impact of Gene Tree Estimation Error

(from Molloy and Warnow 2017)

Error is fraction of bipartitions that are not recovered



ASTRAL ASTRID MP-EST SVDquartets CA-ML

Summary Methods

Site-based Method

Impact of Gene Tree Estimation Error

(from Molloy and Warnow 2017)

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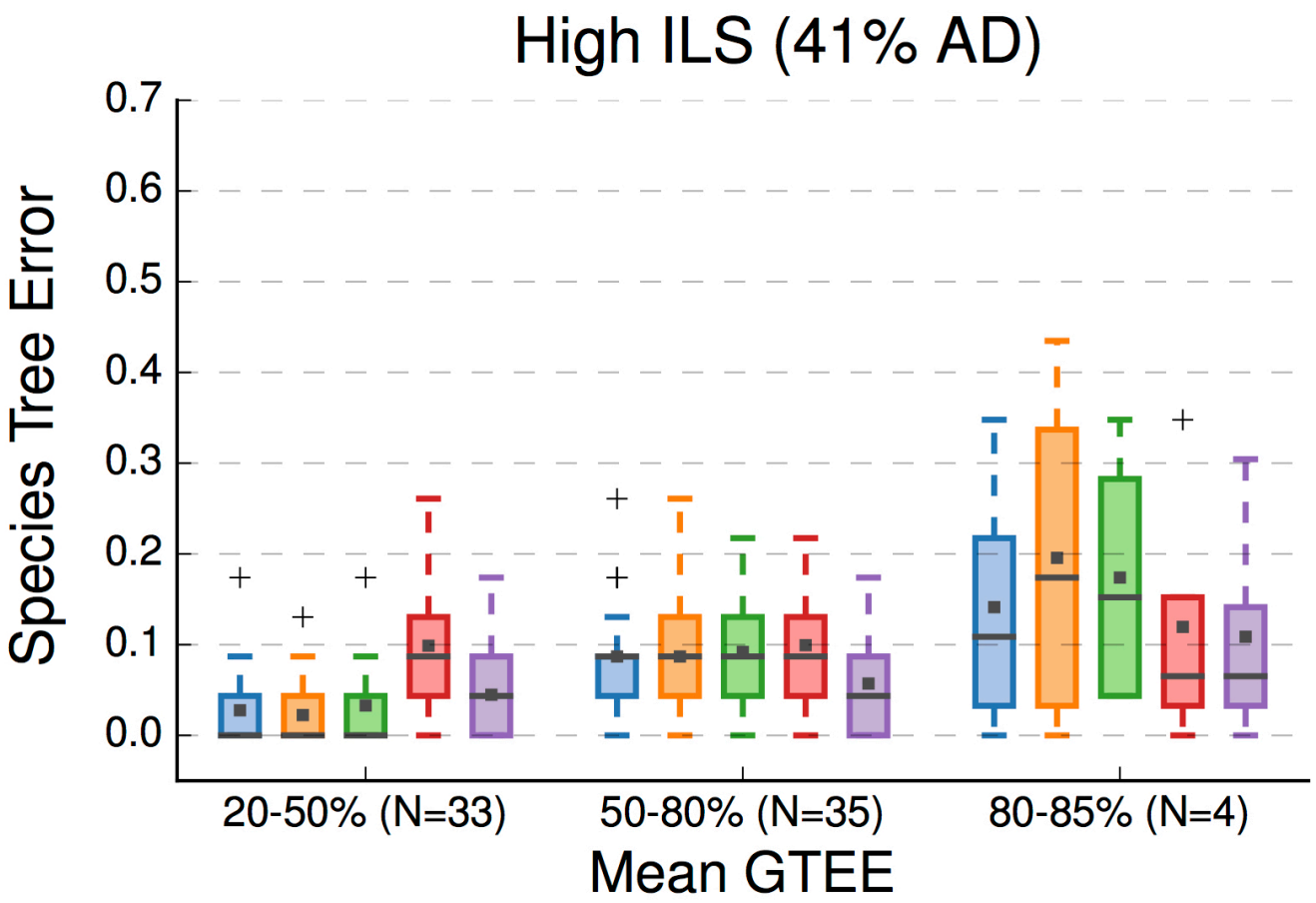


Note: Summary methods better than CA-ML for low GTEE, then worse!

ASTRAL ASTRID MP-EST SVDquartets CA-ML

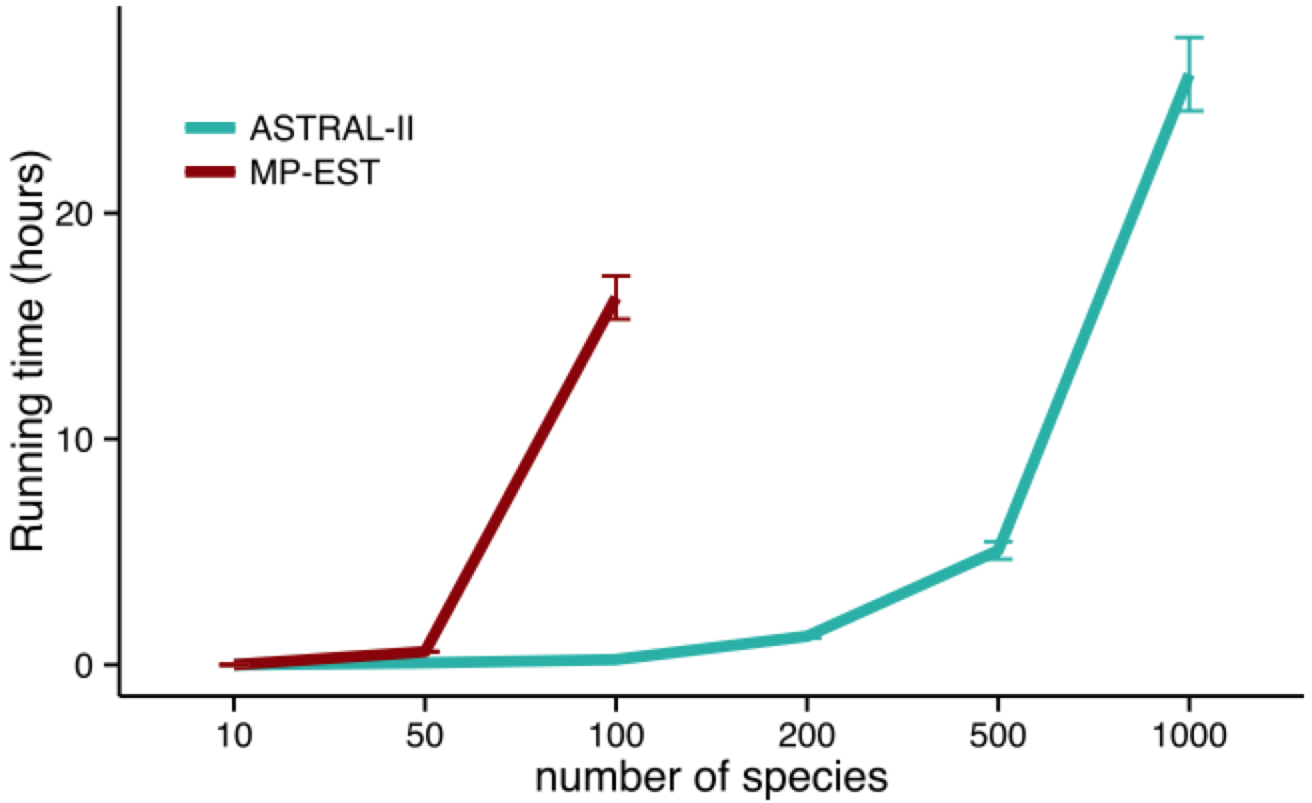
Summary Methods

Site-based Method

Summary (so far)

- ASTRAL has high accuracy, is relatively robust to gene tree estimation error, missing data, and HGT.
- ASTRID is also good, but not generally quite as accurate as ASTRAL.
- Concatenation using ML: unpartitioned CA-ML not statistically consistent under the MSC but can be more accurate than even the best summary methods when ILS is low enough or gene tree estimation error is high enough
- Site-based methods (e.g., SVDquartets): promising but not as good on simulated data as CA-ML, and not as good as summary methods except under very high gene tree estimation error

Running time as function of # species



1000 genes, “medium” levels of ILS, simulated species trees
[Mirarab and Warnow, ISMB, 2015]

X

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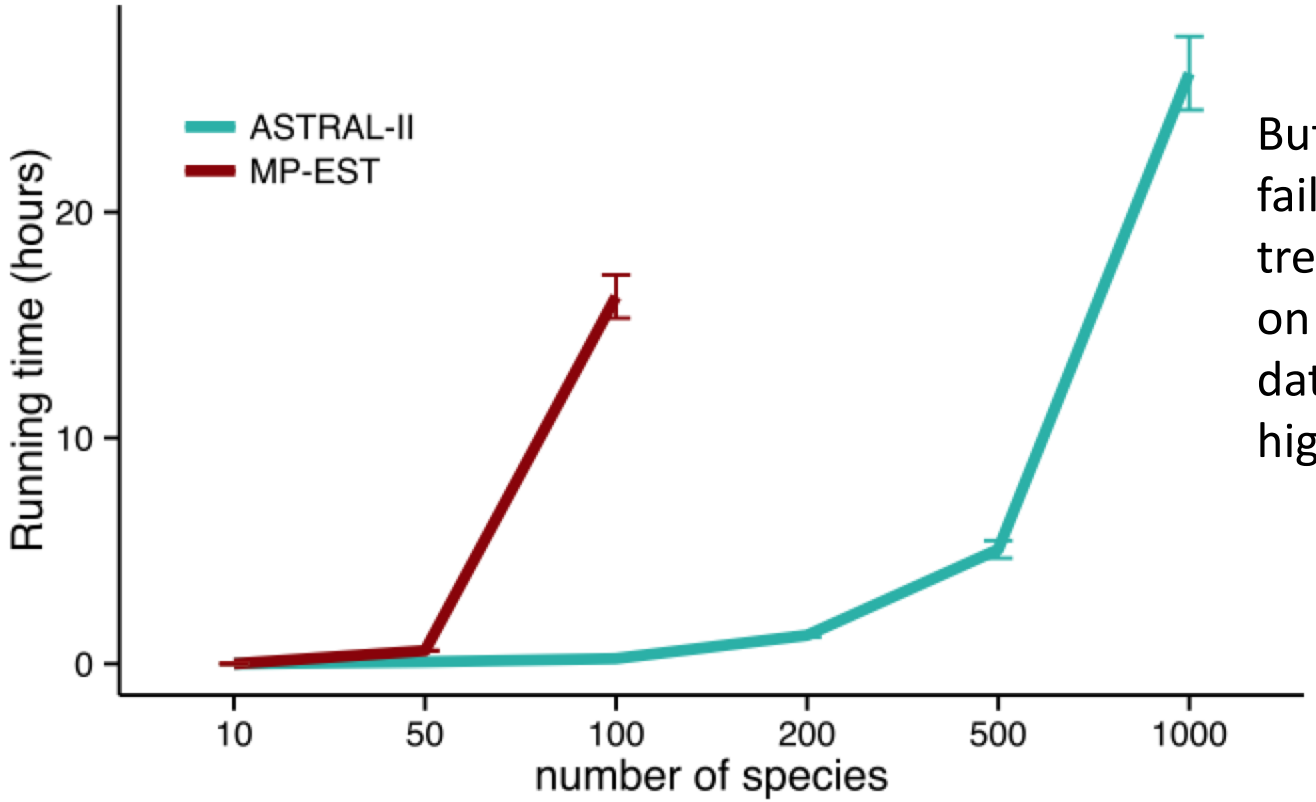


But ASTRAL can fail to return a tree within 24 hrs on some very large datasets with high ILS

1000 genes, "medium" levels of ILS, simulated species trees
[Mirarab and Warnow, ISMB, 2015]

X

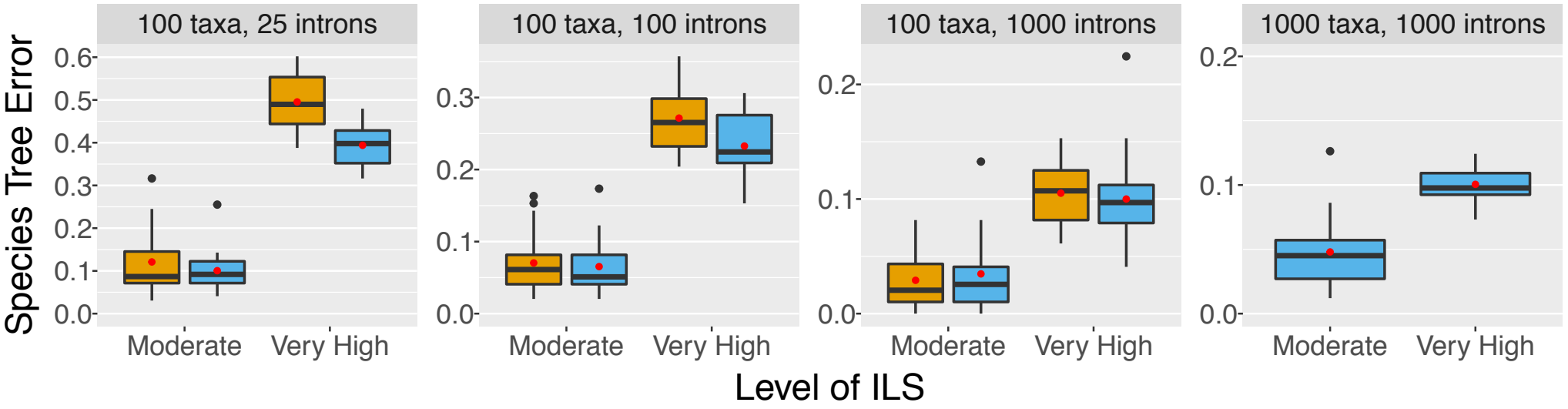
Scalability to large datasets

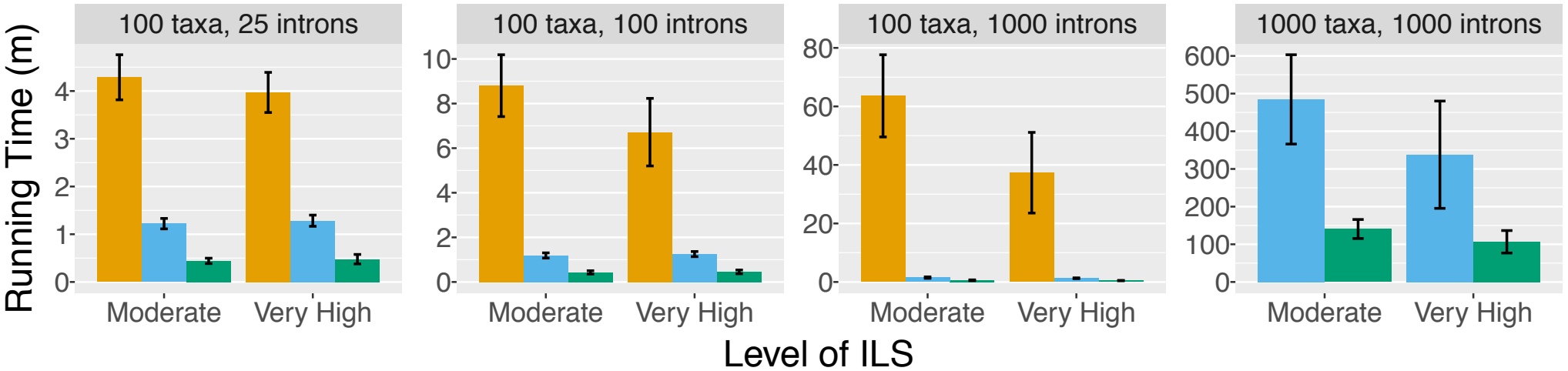
- All the methods described here (except distance-based methods such as ASTRID, NJst) have computational challenges on datasets with large numbers of species:
  - SVDquartets: best accuracy obtained if computing all quartet trees
  - ASTRAL: can fail on some datasets with many species and genes (constraint space too big)
  - CA-ML: no current method scales to large numbers of species and genes

NJMerge

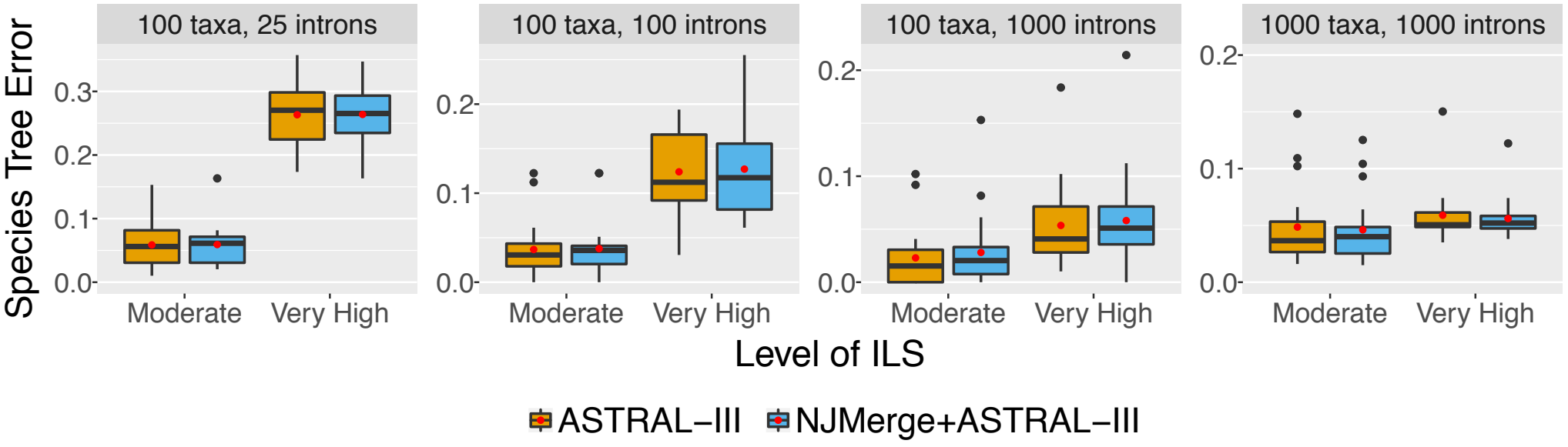
- General technique for scaling phylogeny estimation methods to large numbers of species
- Approach:
  - Divide species set into disjoint subsets
  - Construct species tree (constraint tree) on each subset
  - Merge together using a modification of Neighbor Joining, obeying constraint trees, using pairwise distances between species from the “internode distance matrix” (used in ASTRID and NJst)
  - Note: can sometimes fail to return a tree (0.2% of cases in our experiments)
- Molloy and Warnow, RECOMB-CG 2018 (journal version in preparation)

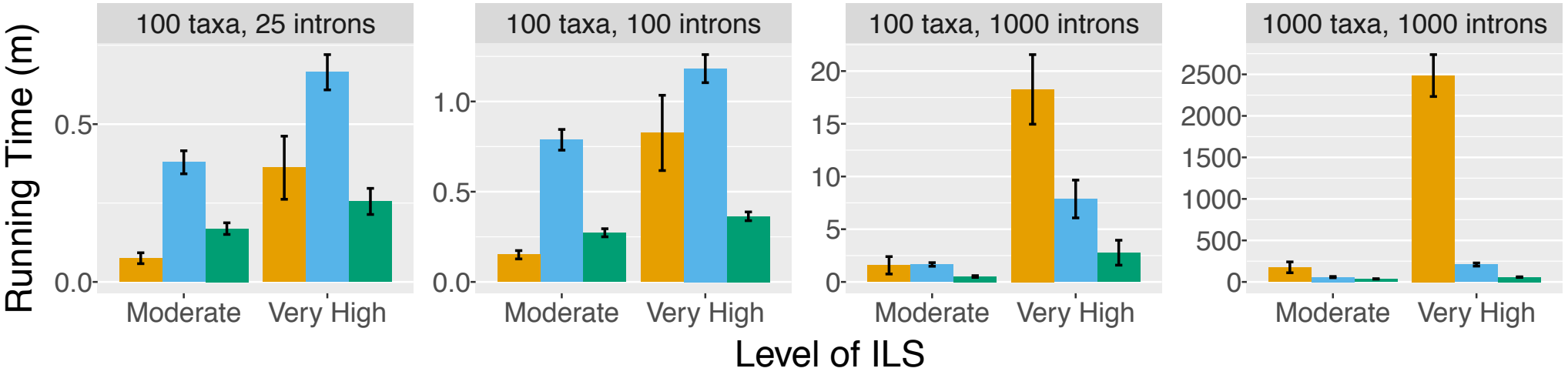
NJMerge + SVDquartets vs. SVDquartets: Better accuracy and can analyze larger datasets!



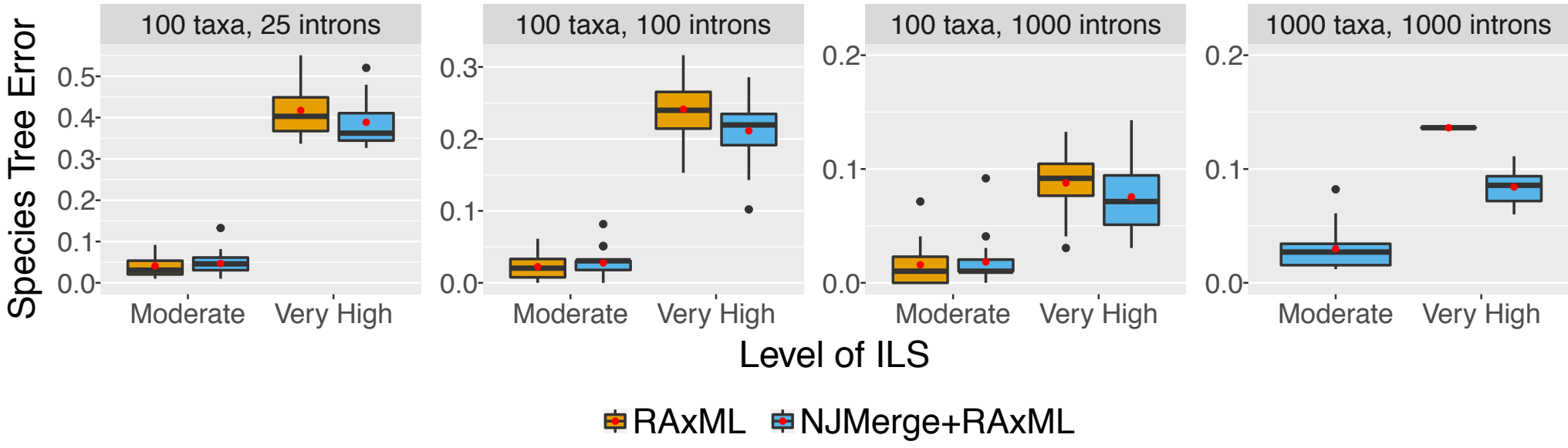


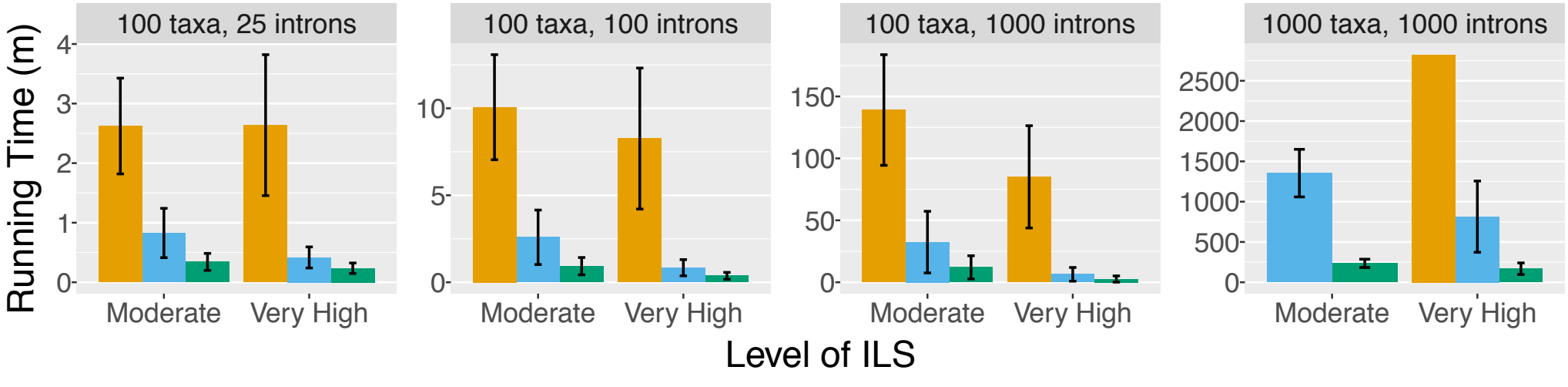
NJMerge + ASTRAL vs. ASTRAL:
Comparable accuracy and can analyze larger datasets





NJMerge + RAxML vs. RAxML: Better accuracy and faster!





NJMerge summary

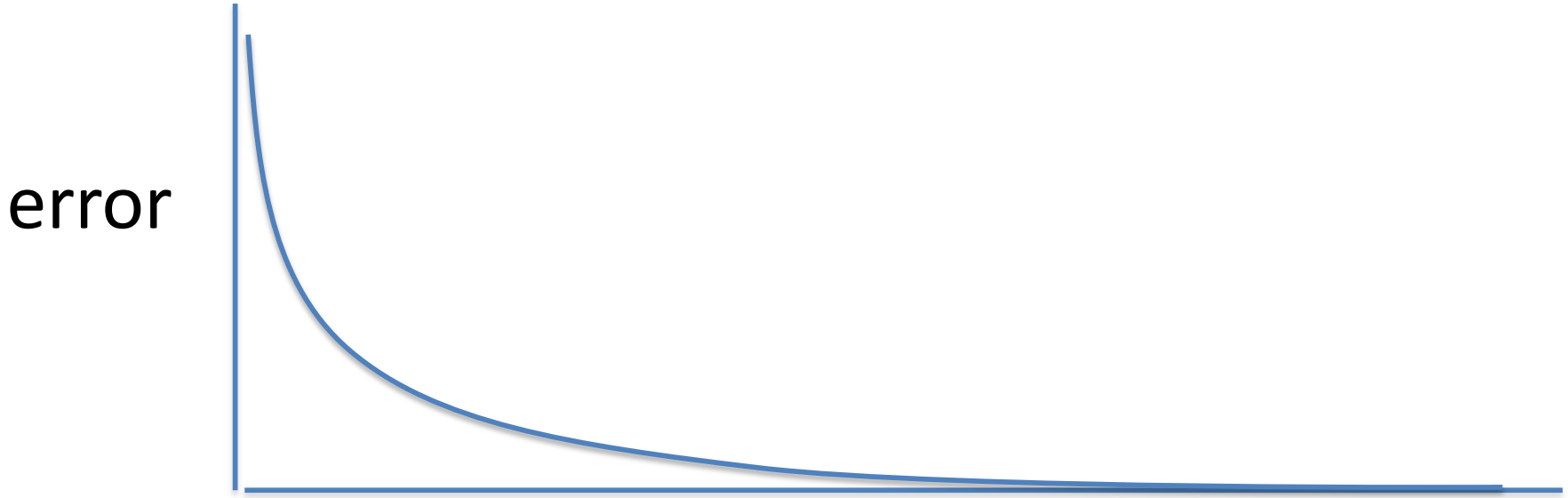
- NJMerge+ASTRAL: generally as accurate and faster on large datasets than ASTRAL
- NJMerge+SVDquartets: more accurate and much faster, greater scalability than SVDquartets
- NJMerge+CA-ML: more accurate and much faster, greater scalability than CA-ML

Only limitation: NJMerge can sometimes fail to return a tree, but this only occurred in 0.2% of the datasets we examined in our experiments. (Other methods also fail to return a tree due to time constraints.)

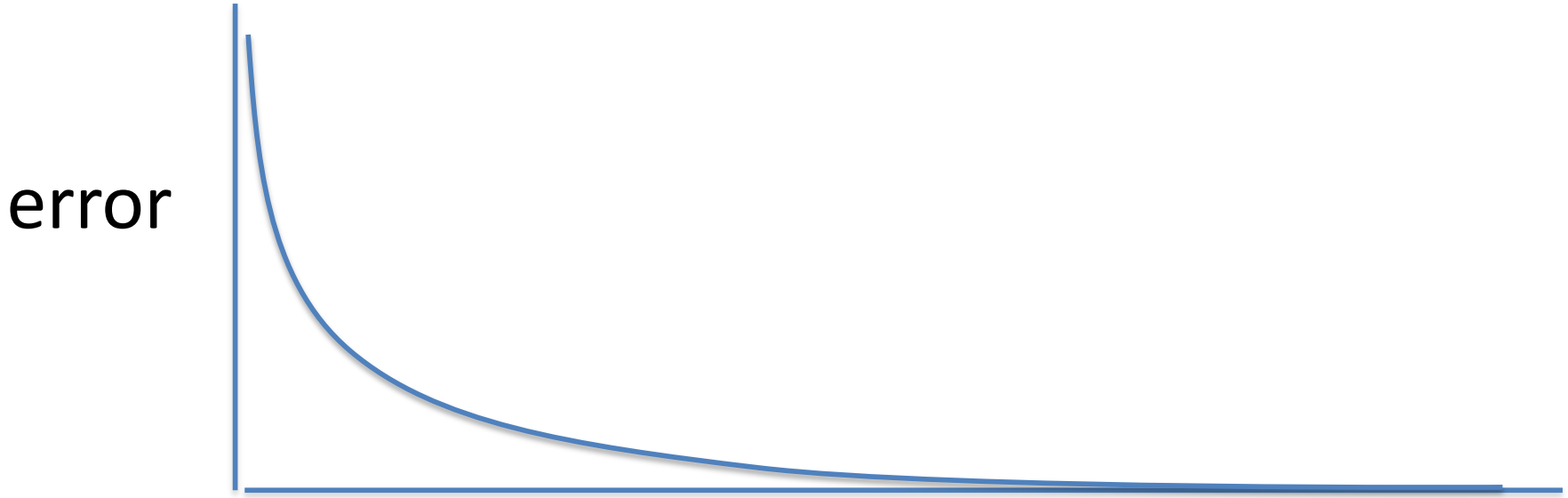
Which type of method is best?

- What is the meaning of “best”?
  - Statistically consistent under the MSC?
  - Good accuracy on simulated data?
  - Good accuracy on biological data?

Genome-scale data?



Statistical consistency for summary methods

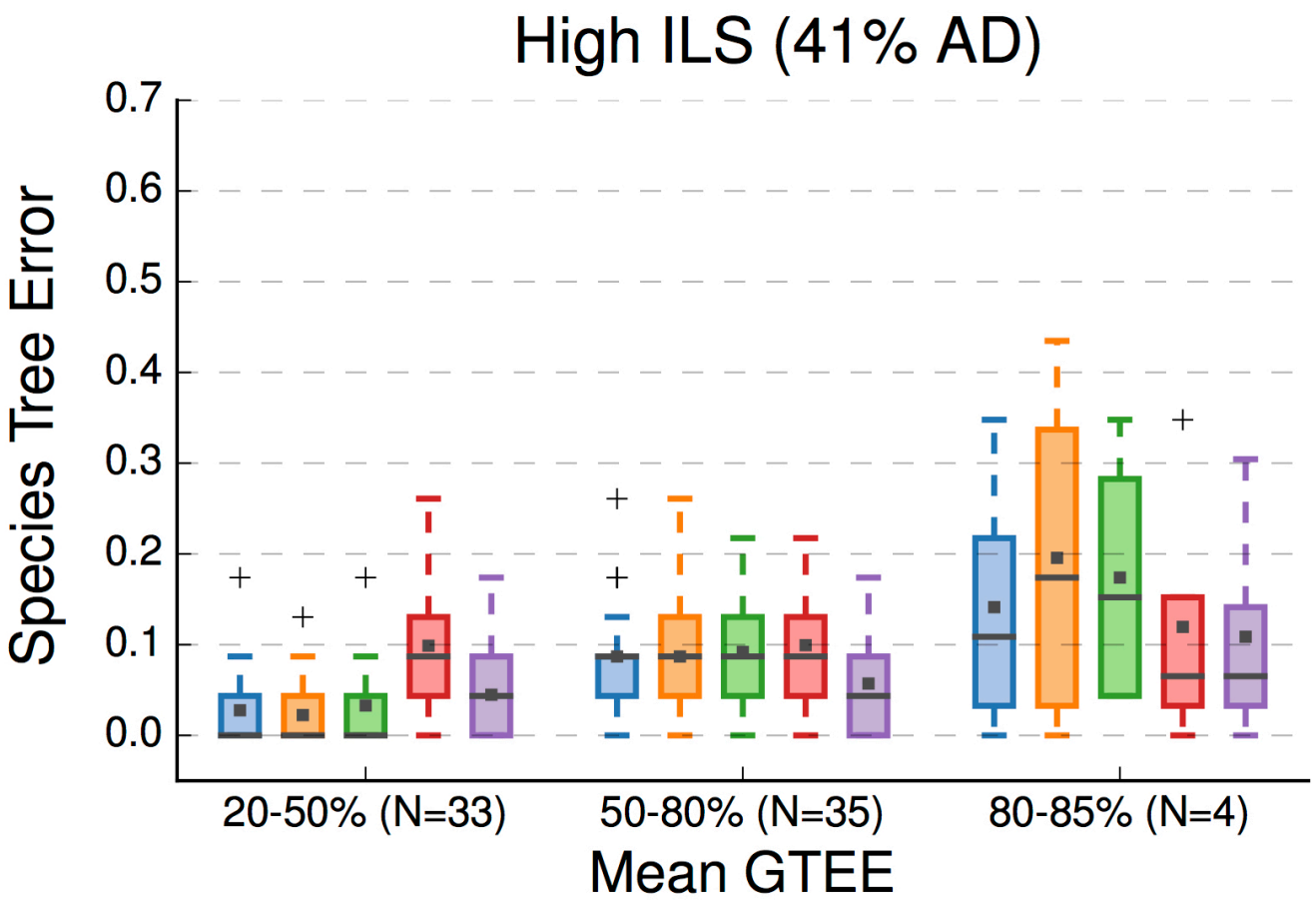


Data = true gene trees!

Impact of Gene Tree Estimation Error

(from Molloy and Warnow 2017)

Error is fraction of bipartitions that are not recovered



Note: Summary methods better than CA-ML for low GTEE, then worse!

ASTRAL ASTRID MP-EST SVDquartets CA-ML

Summary Methods

Site-based Method

Gene tree estimation error: key issue in the debate

- Multiple studies show that *summary methods can be less accurate than concatenation* in the presence of high gene tree estimation error.
- Genome-scale data includes a range of markers, not all of which have substantial signal. Furthermore, removing sites due to model violations reduces signal.
- Some researchers also argue that "gene trees" should be based on very short alignments, to avoid intra-locus recombination.

What about performance on bounded number of sites?

- Question #1: Do any summary methods converge to the species tree as the number of loci increase, but where each locus has only a constant number of sites?
- Answer #1: Roch & Warnow, Syst Biol, March 2015:
  - Strict molecular clock: Yes for some new methods, even for a single site per locus
  - No clock: Unknown for all methods, including MP-EST, ASTRAL, etc.

S. Roch and T. Warnow. "On the robustness to gene tree estimation error (or lack thereof) of coalescent-based species tree methods", Systematic Biology, 64(4):663-676, 2015

What about performance on bounded number of sites?

- Question #1: Do any summary methods converge to the species tree as the number of loci increase, but where each locus has only a constant number of sites?
- Answer #2: Roch, Nute, & Warnow, Syst. Biol. 2018
  - No! Summary methods are not only not consistent, they can be positively misleading! (Felsenstein Zone)

S. Roch, M. Nute, and T. Warnow. "Long-branch attraction in species tree estimation: inconsistency of partitioned likelihood and topology-based summary methods." Systematic Biology 2018

What about performance on bounded number of sites?

- Question #2: What about concatenation using maximum likelihood?
- Answer: Roch, Nute, & Warnow, Syst Biol. 2018
  - Not if fully partitioned! Concatenation using maximum likelihood, if fully partitioned is also not consistent and can be positively misleading (even if there is NO ILS)! (Felsenstein Zone)

S. Roch, M. Nute, and T. Warnow. "Long-branch attraction in species tree estimation: inconsistency of partitioned likelihood and topology-based summary methods." Systematic Biology 2018

Statistically consistent methods

- **Coalescent-based summary methods:** Estimate gene trees, and then combine together (ASTRAL, ASTRID, MP-EST, NJst, and others)

- **Co-estimation methods**: Co-estimate gene trees and species trees (TOO EXPENSIVE)

- **Site-based methods:** estimate the species tree from the concatenated alignment, and do not estimate gene trees (NOT WELL STUDIED)

Statistically consistent methods (??)

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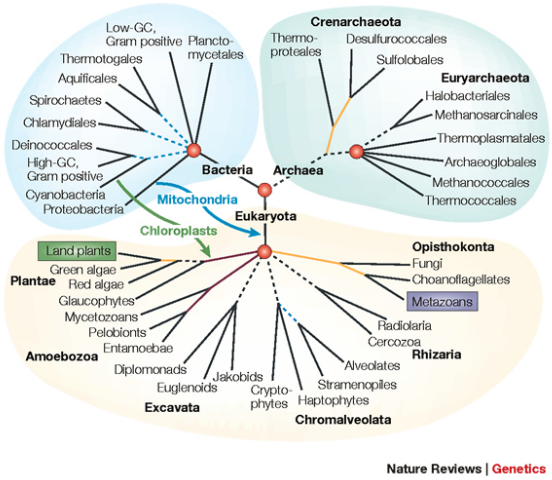
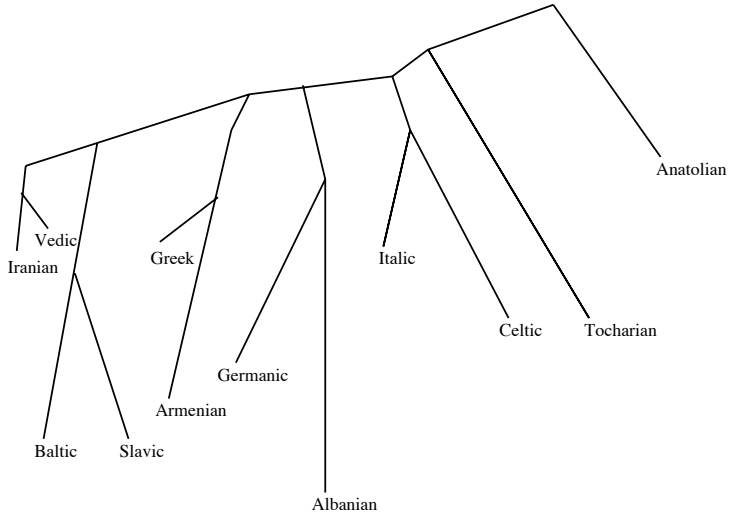
Future Directions

- Theory: Determine which species tree estimation methods are statistically consistent when the number of sites per locus is bounded, and heterogeneity between loci is not constrained
- Practice: Understand why concatenation performs well, and develop better coalescent-based methods

Phylogenetic Inference





- NP-hard optimization problems and large datasets
- Statistical estimation under stochastic models of evolution
- Probabilistic analysis of algorithms
- Graph-theoretic divide-and-conquer
- Chordal graph theory
- Combinatorial optimization

Acknowledgments




Roch and Warnow, Systematic Biology 2014
Mirarab and Warnow, Bioinformatics 2015
Molloy and Warnow, Systematic Biology 2017
Molloy and Warnow, RECOMB-CG 2018
Roch, Nute, and Warnow, Systematic Biology 2018
Papers available at http://tandy.cs.illinois.edu/papers.html

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