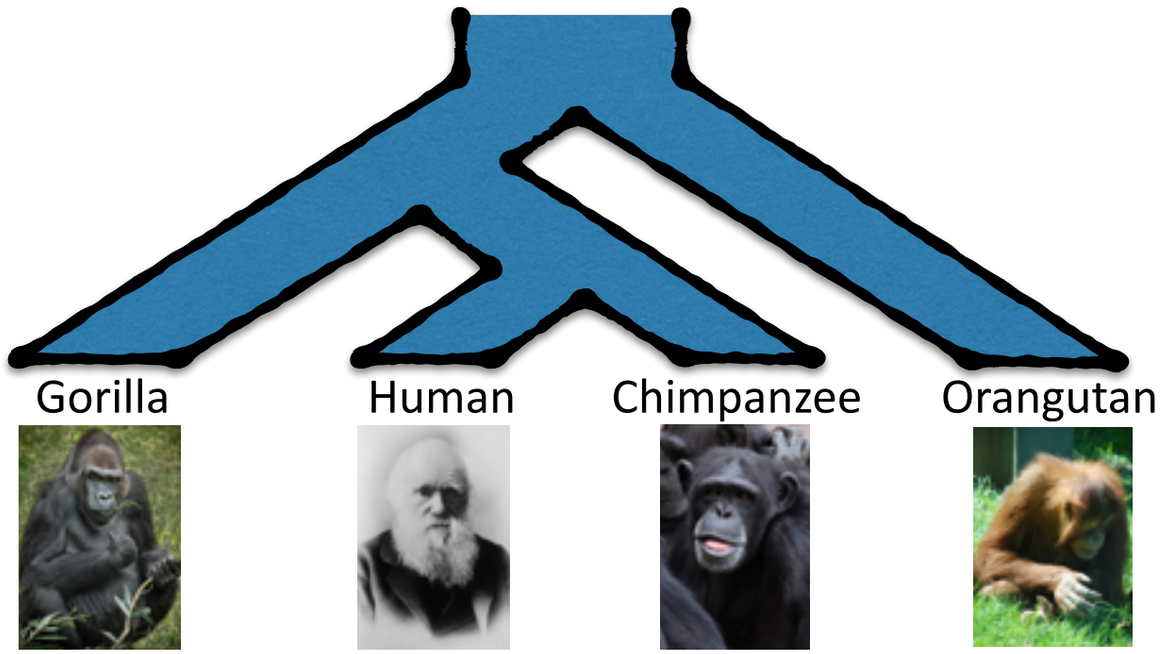
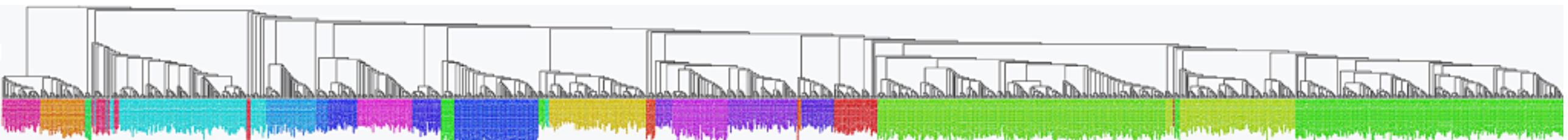
Reconstruction of species histories using genomic data

Siavash Mirarab
University of California San Diego





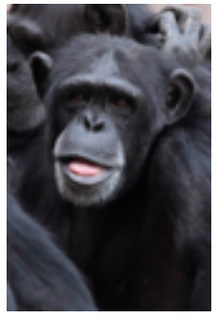
Statistical inference of phylogenies

Gorilla

ACTGCACACCG

Human

ACTGCCCCCG



Chimpanzee

AATGCCCCCG

Orangutan

CTGCACACGG

D

Gorilla ACTGCACACCG

Human ACTGC-CCCCG

Chimpanzee AATGC-CCCCG

Orangutan -CTGCACACGG

$P(D|T)$

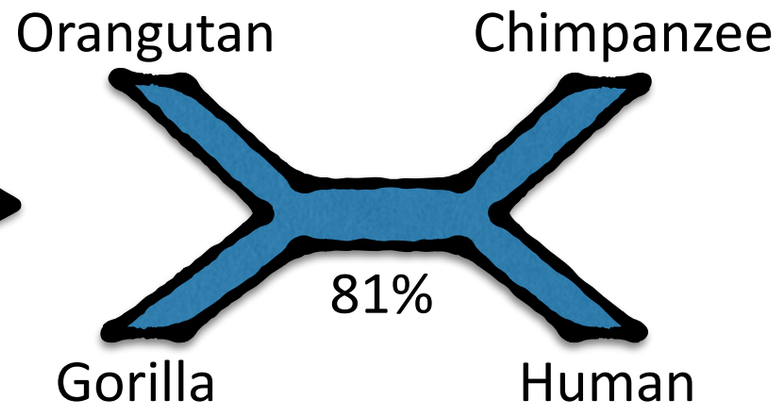
Maximum likelihood

Bayesian

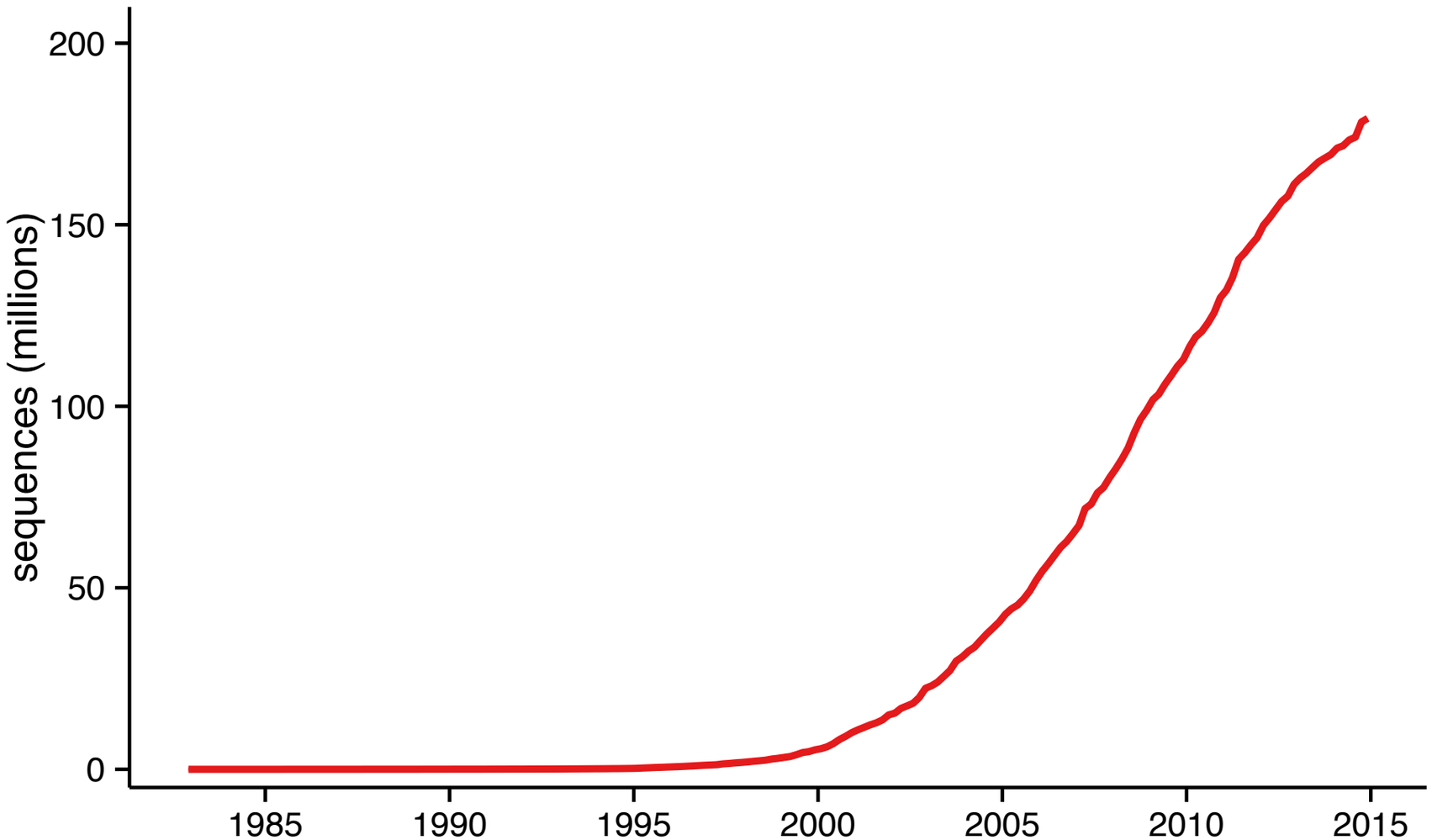
Distance-based

Parsimony

T

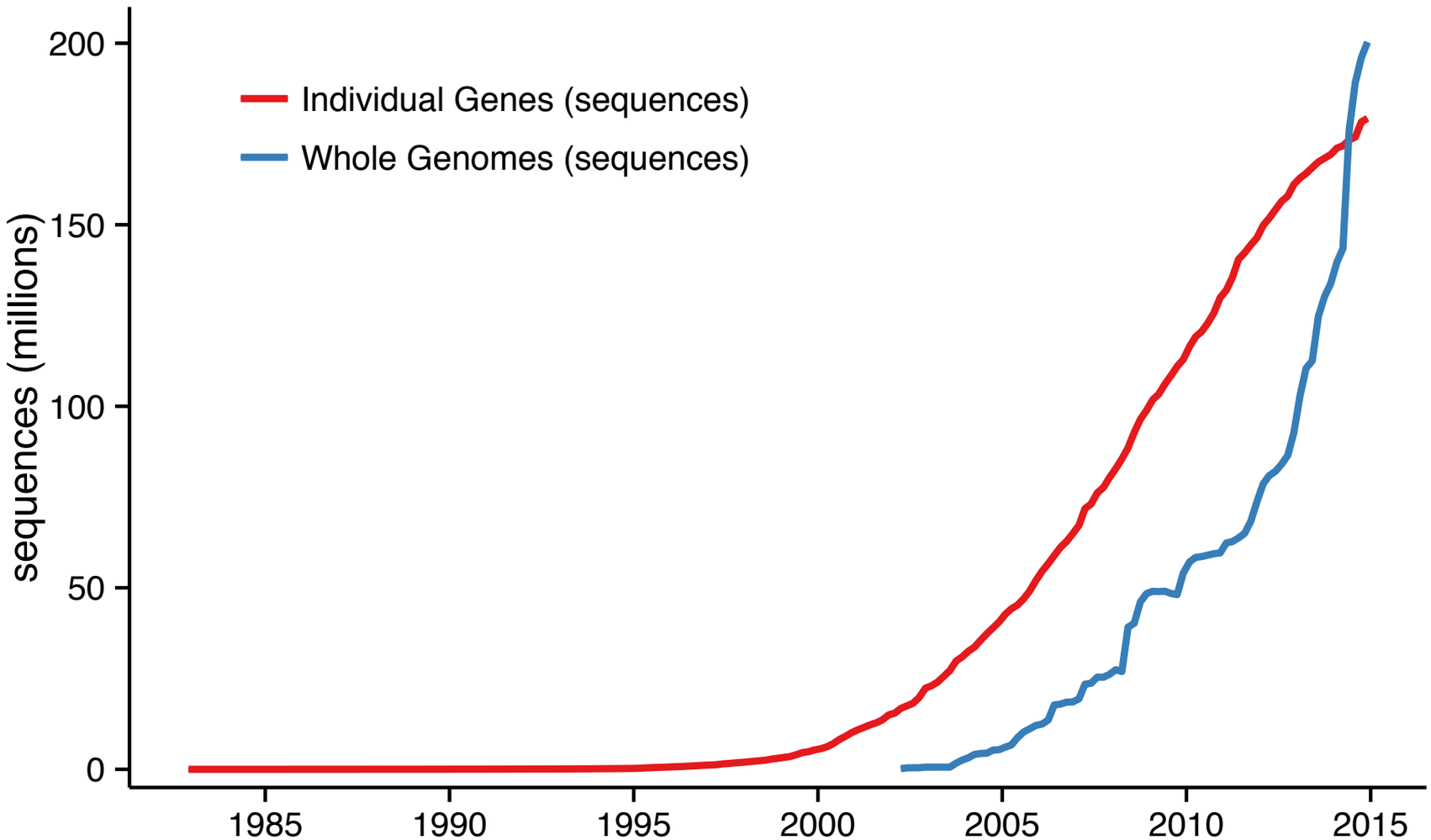


Sequence data growth



Growth in Genebank sequence data
data source: NCBI (http://www.ncbi.nlm.nih.gov/genbank/statistics)

Sequence data growth



Growth in Genebank sequence data
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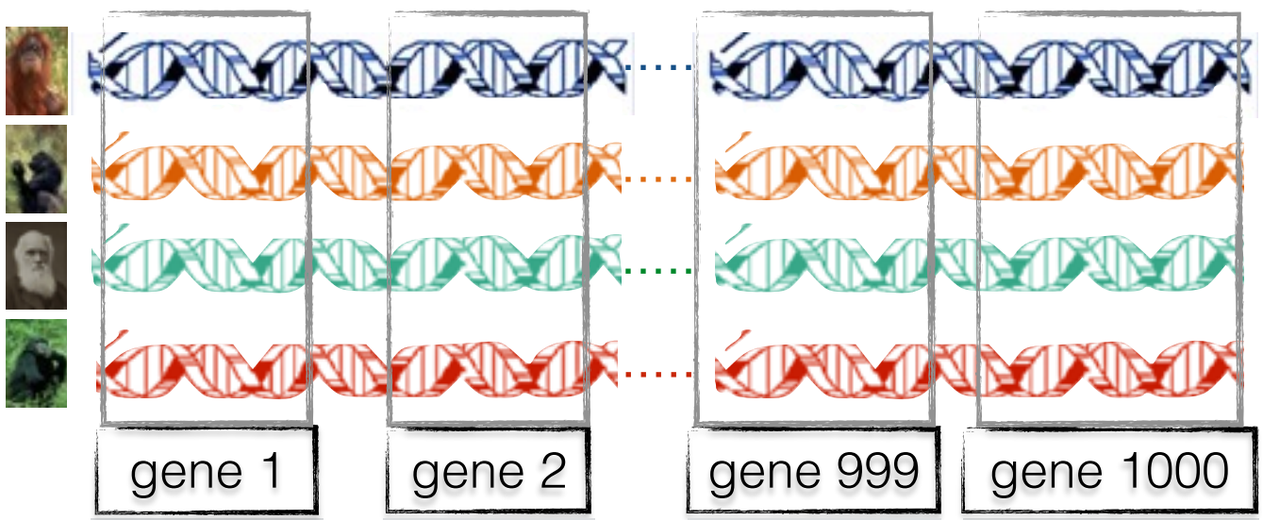
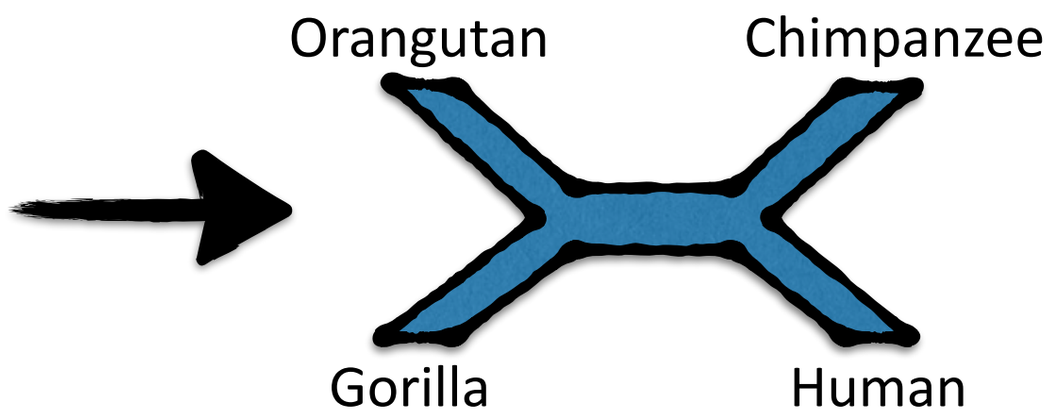
Phylogenomics

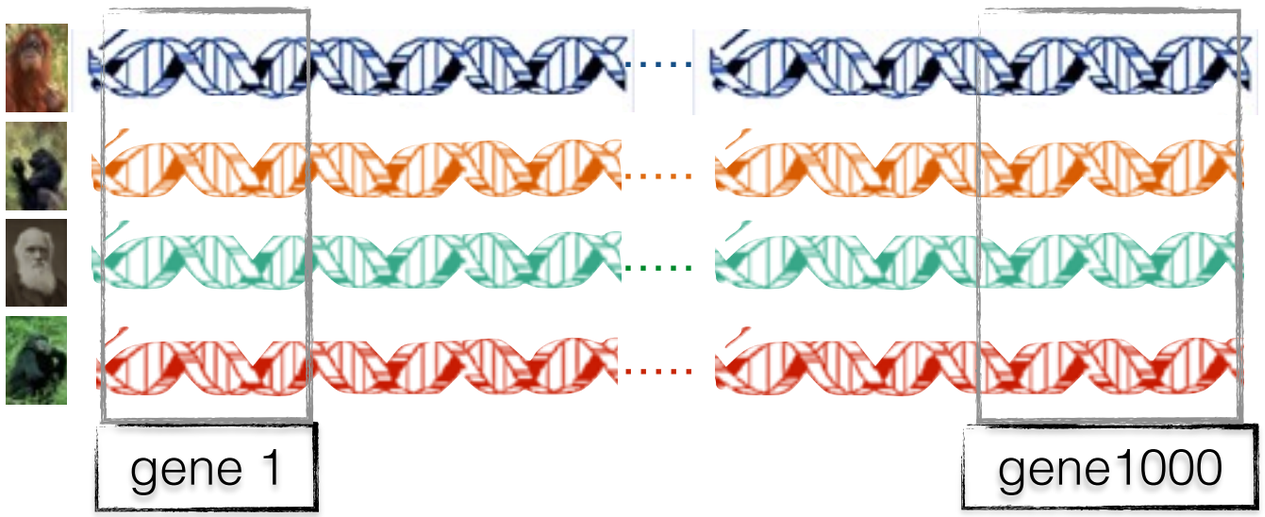




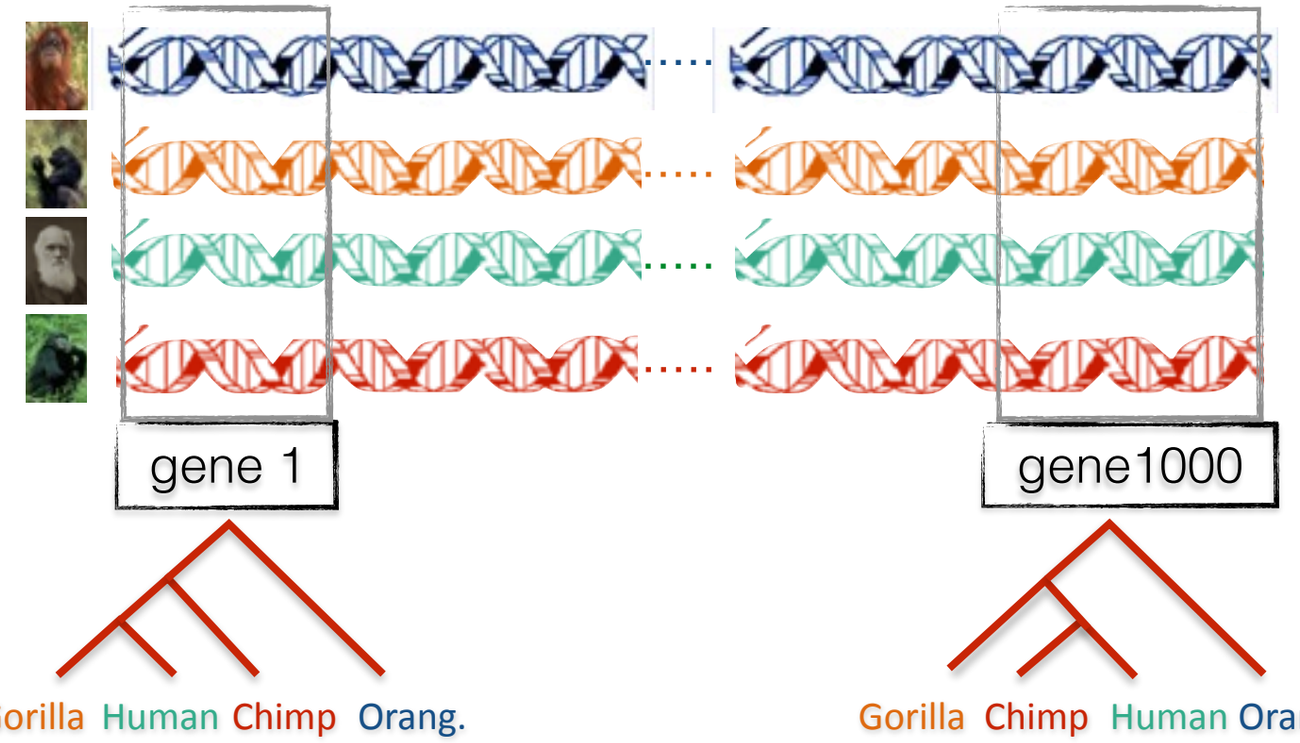

```
ACTGCACACCG   CTGAGCATCG     AGCAGCATCGTG CAGGCACGCACGAA
ACTGC-CCCCG   CTGAGC-TCG ... AGCAGC-TCGTG AGC-CACGC-CATA
AATGC-CCCCG   ATGAGC-TC-     AGCAGC-TC-TG ATGGCACGC-C-TA
-CTGCACACGG   CTGA-CAC-G     C-TA-CACGGTG AGCTAC-CACGGAT
```

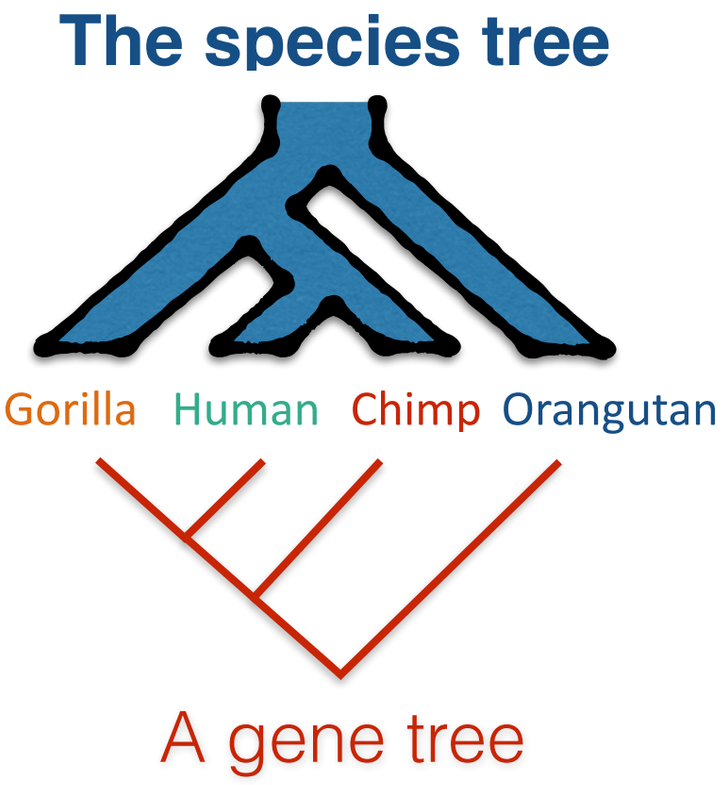
I'll use the term "gene" to refer to "c-genes":
recombination-free orthologous stretches of the genome

Gene tree discordance

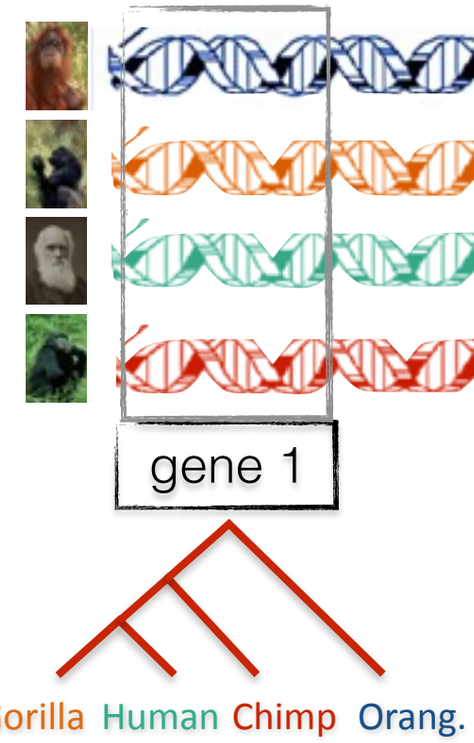


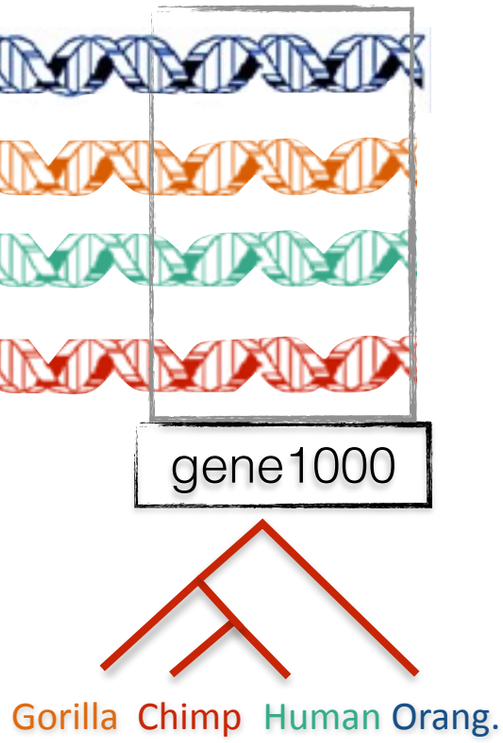
Gene tree discordance

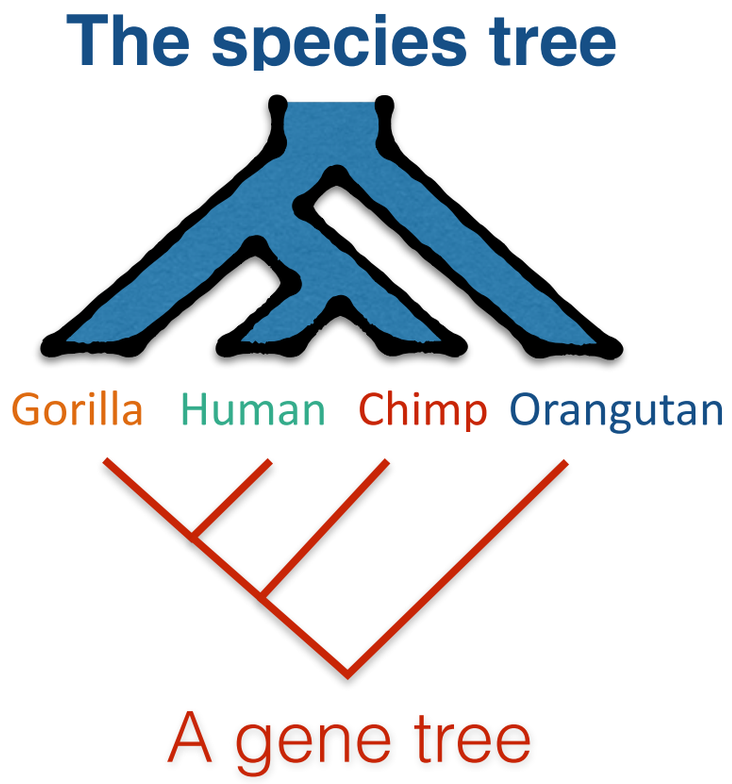




Gene tree discordance





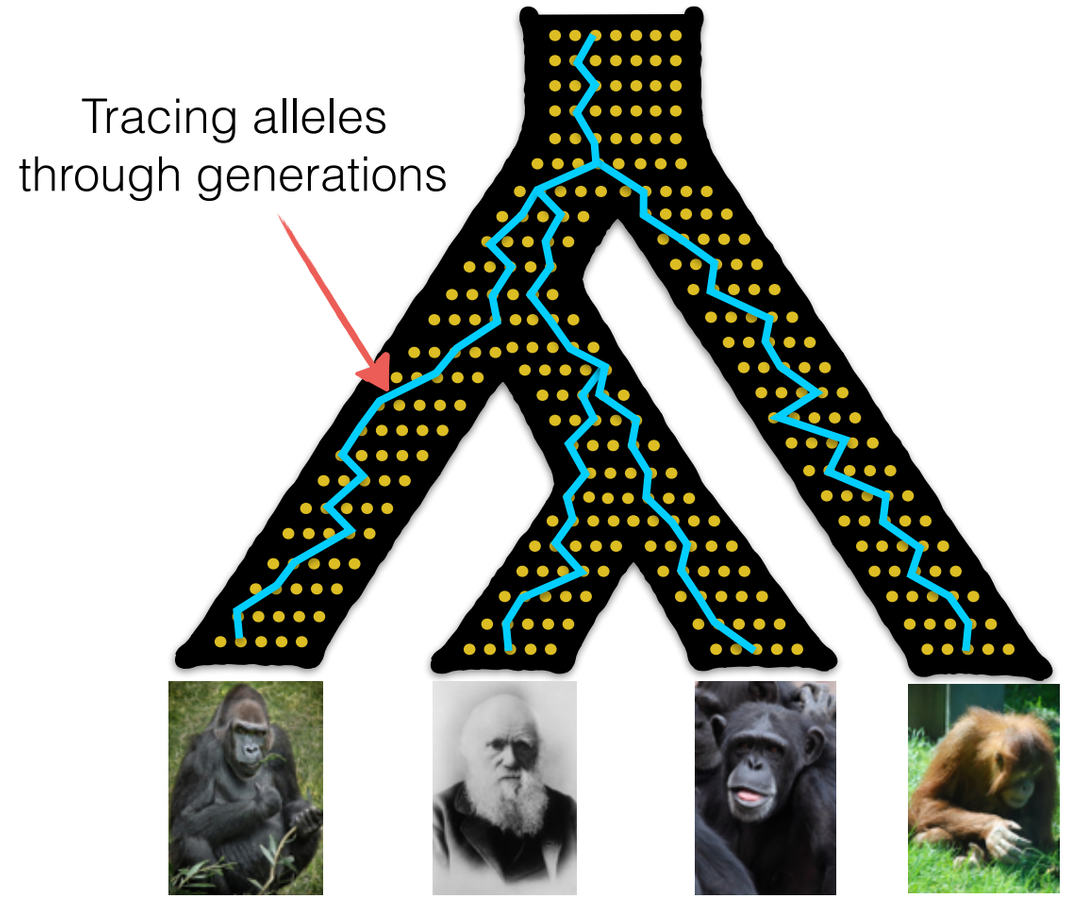


Causes of gene tree discordance include:

- Incomplete Lineage Sorting (ILS)
- Duplication and loss
- Horizontal Gene Transfer (HGT)

Incomplete Lineage Sorting (ILS)

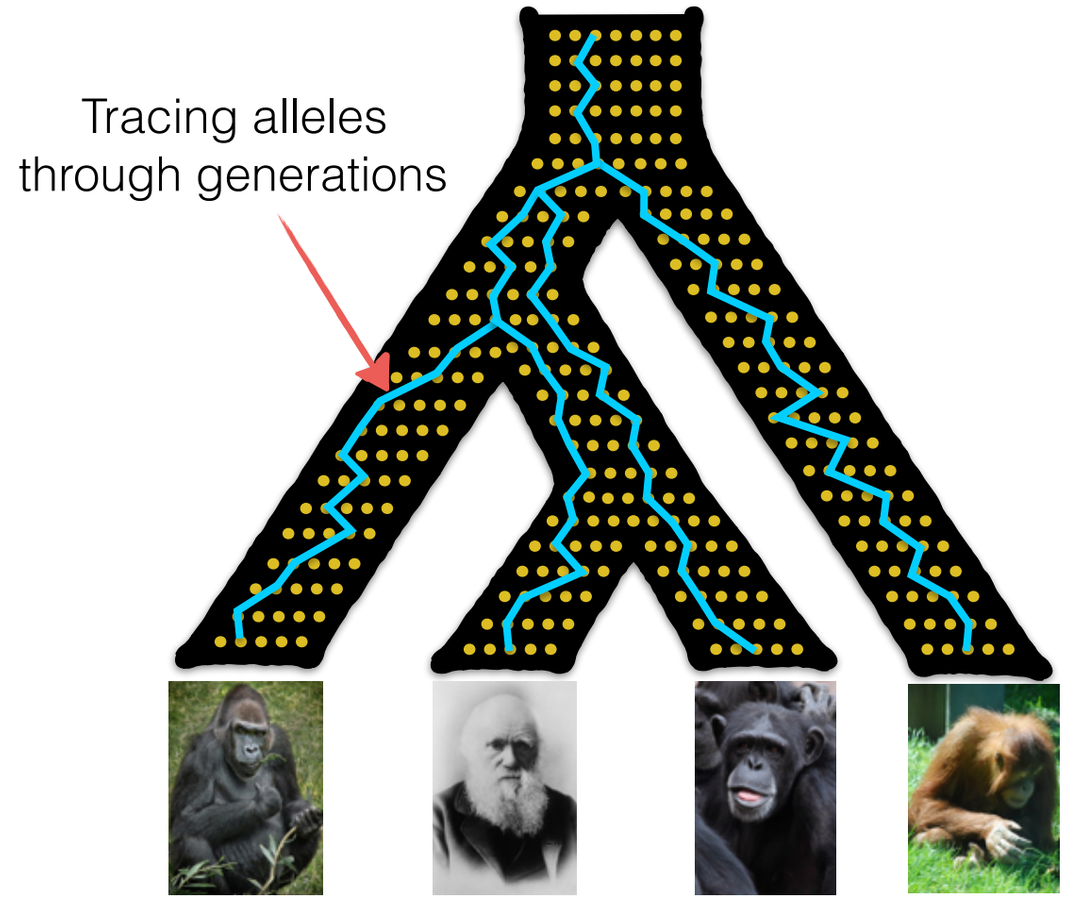
- A random process related to having multiple versions of each gene in a population



Incomplete Lineage Sorting (ILS)

- A random process related to having multiple versions of each gene in a population

- Omnipresent; most likely for short branches and large population size



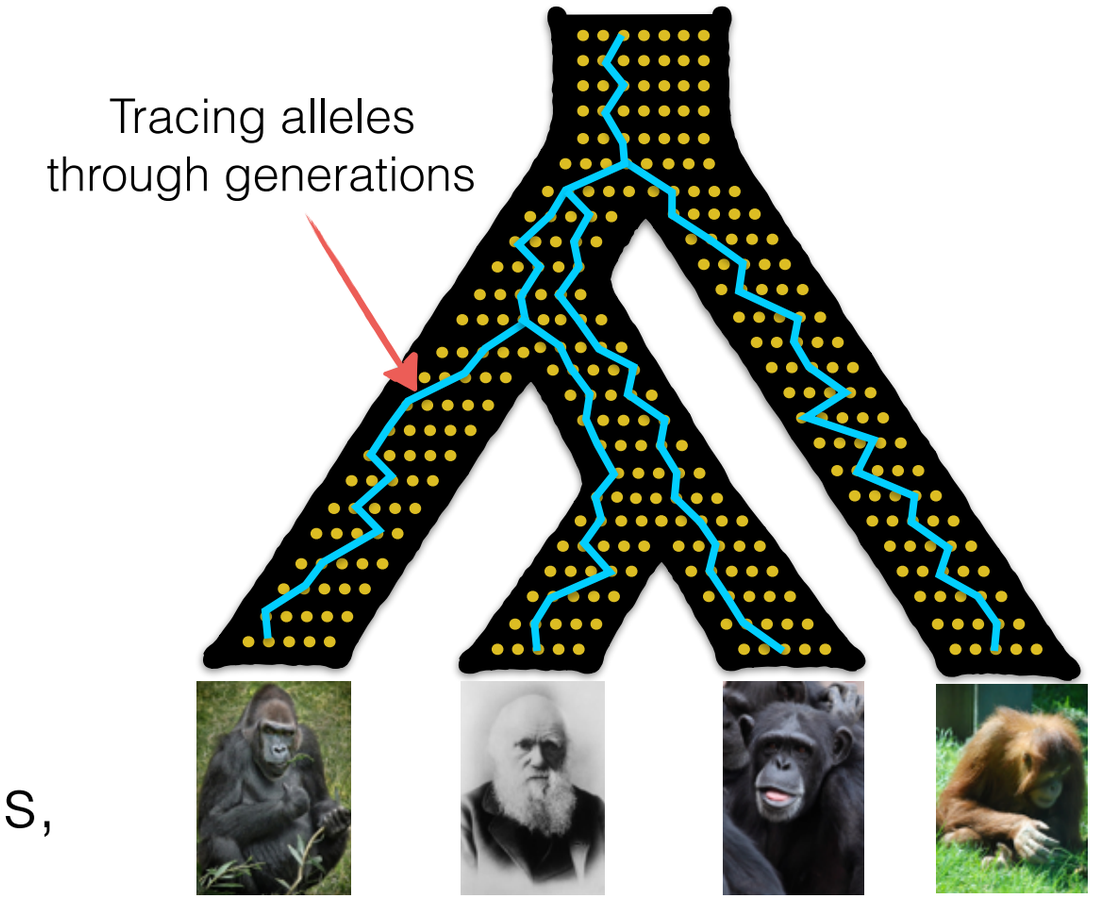
Incomplete Lineage Sorting (ILS)

- A random process related to having multiple versions of each gene in a population

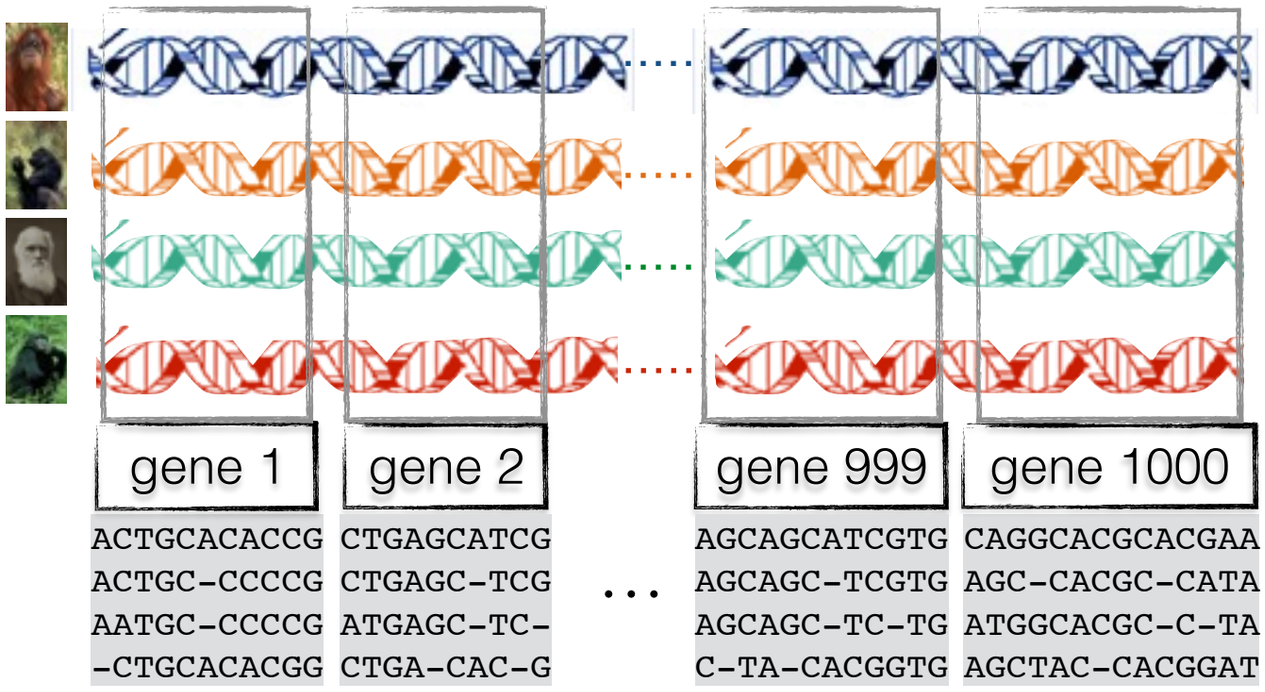
- Omnipresent; most likely for short branches and large population size

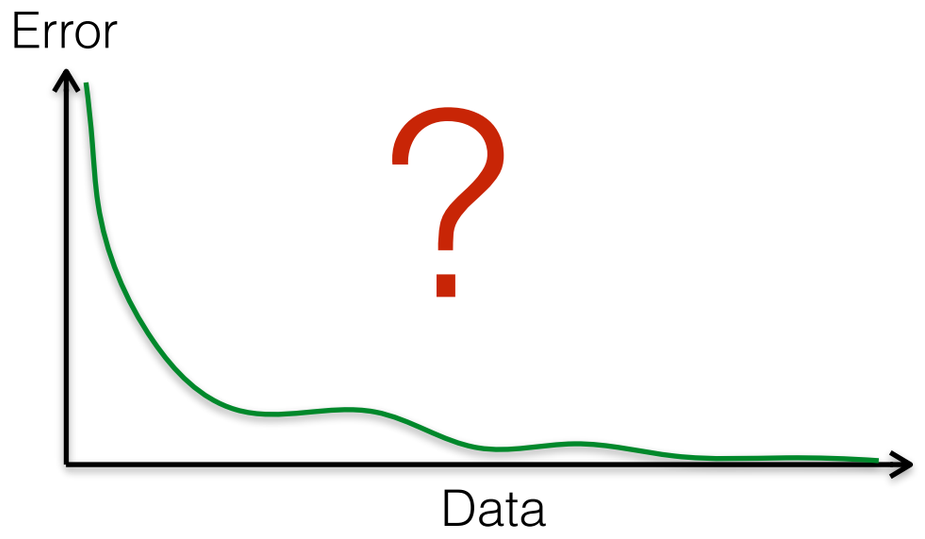
- We have statistical models of ILS (multi-species coalescent)

  - The species tree defines the probability distribution on gene trees, and is identifiable from the distribution on gene trees
    [Degnan and Salter, Int. J. Org. Evolution, 2005]



Increased data —> accuracy?

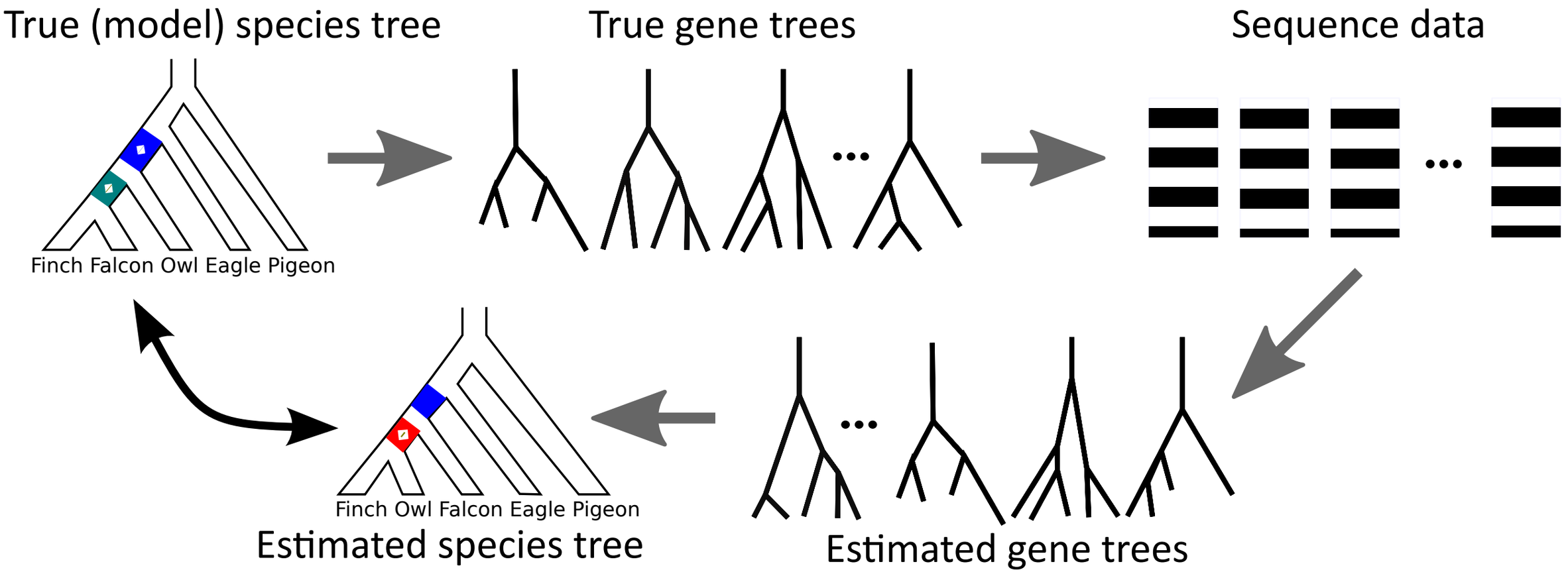




A. **Theoretical statistical guarantees:** assuming data are generated under the multi-species coalescent model, we aspire to statistical consistency

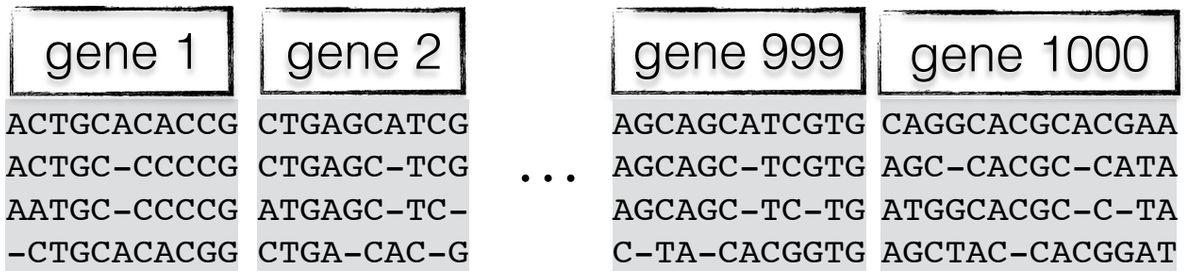
B. **Simulation studies**, generating synthetic data according to the multi-species coalescent model and models of sequence evolution

Simulation studies



Error metric: percentage of branches in true tree that are missing from the estimated tree

Species tree estimation from phylogenomic data (Approach 1: concatenation)



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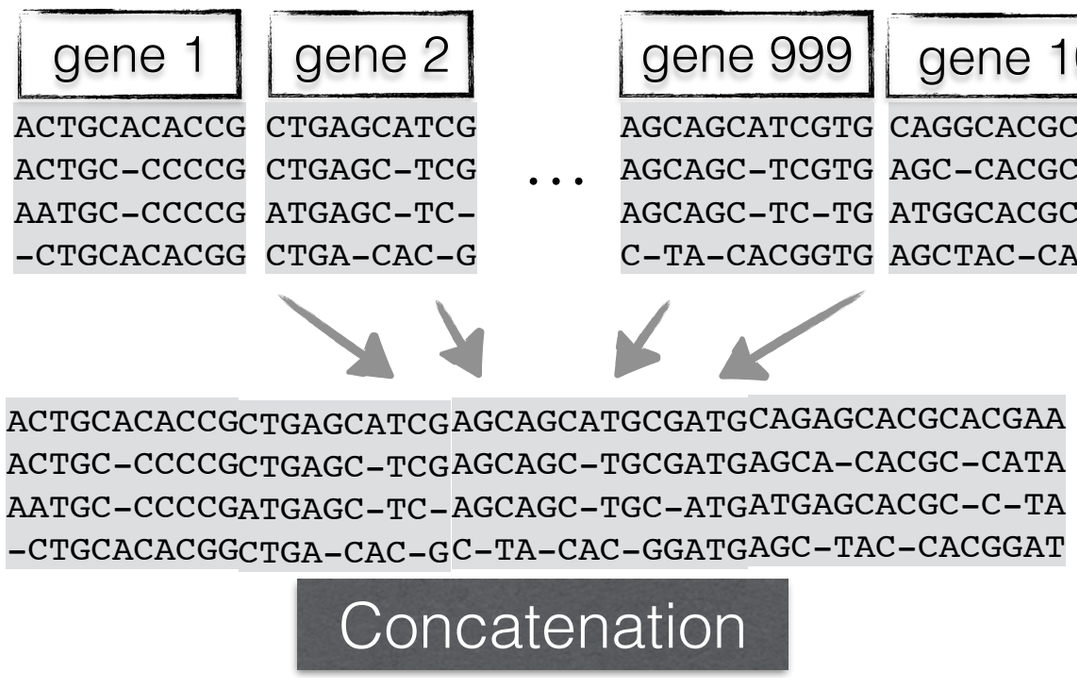

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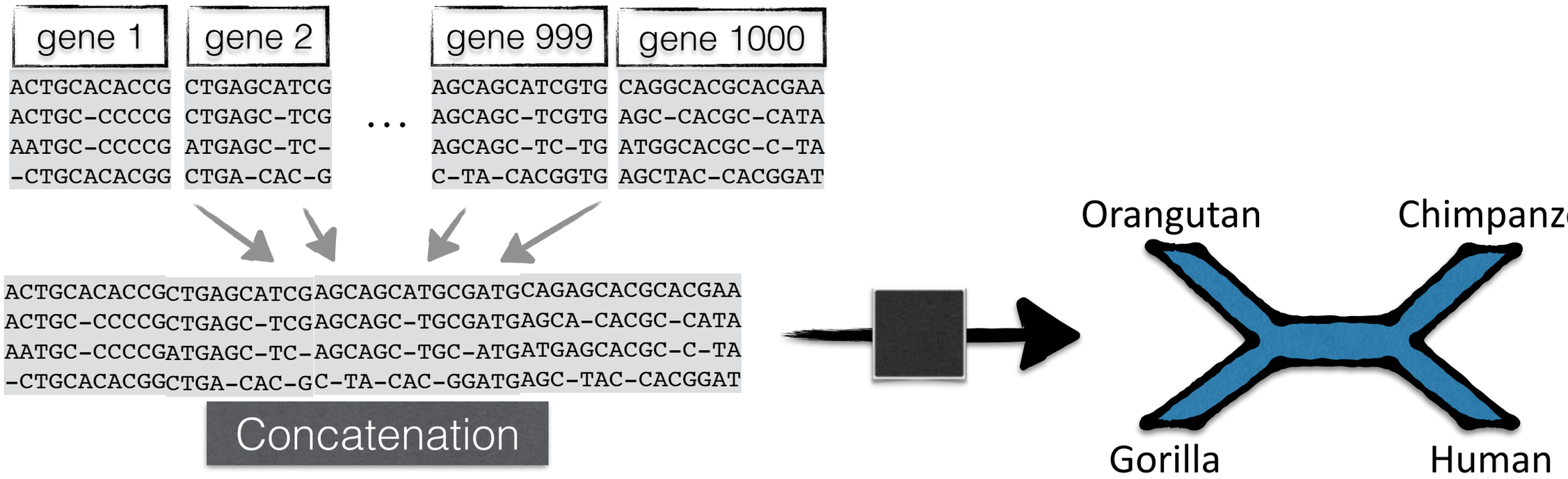

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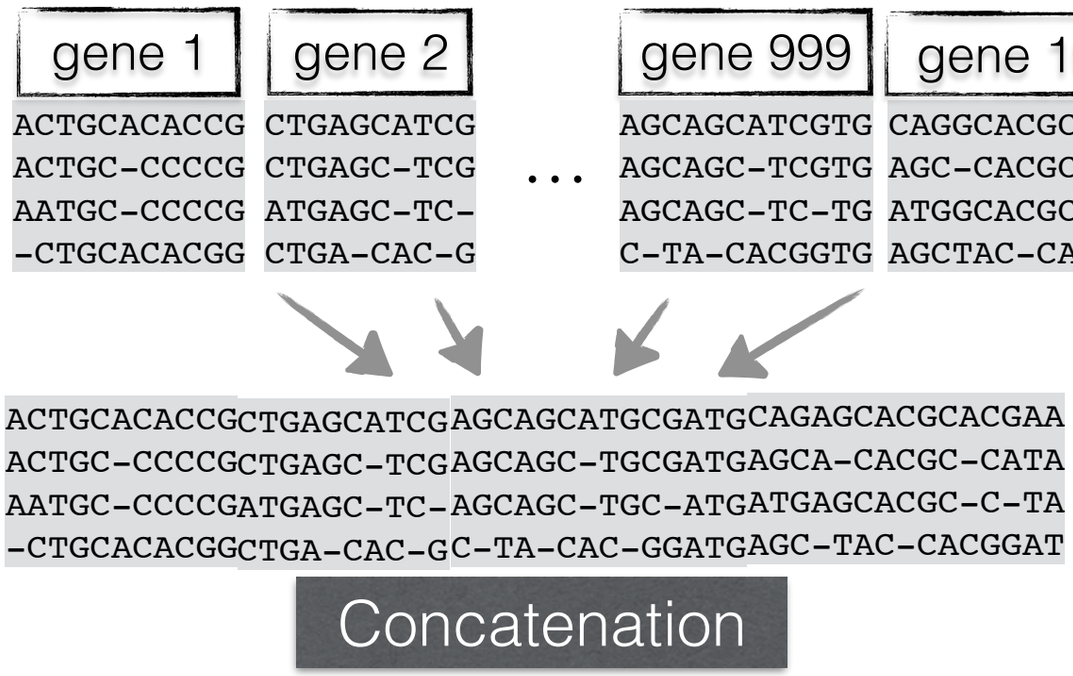
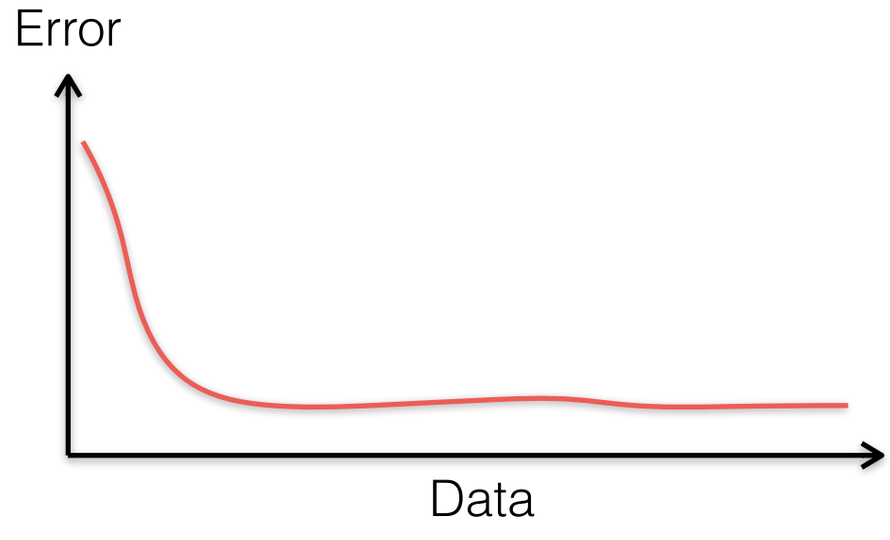


Statistically <u>inconsistent</u> & positively misleading
(proof for unpartitioned maximum likelihood)

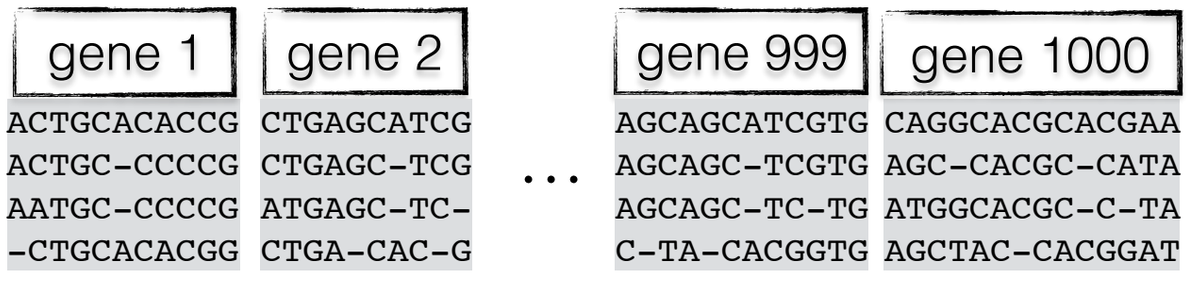
[Roch and Steel, Theo. Pop. Gen., 2014]

Mixed accuracy in simulations

[Kubatko and Degnan, Systematic Biology, 2007]
[Mirarab, et al., Systematic Biology, 2014]



Species tree estimation from phylogenomic data (Approach 2: summary methods)



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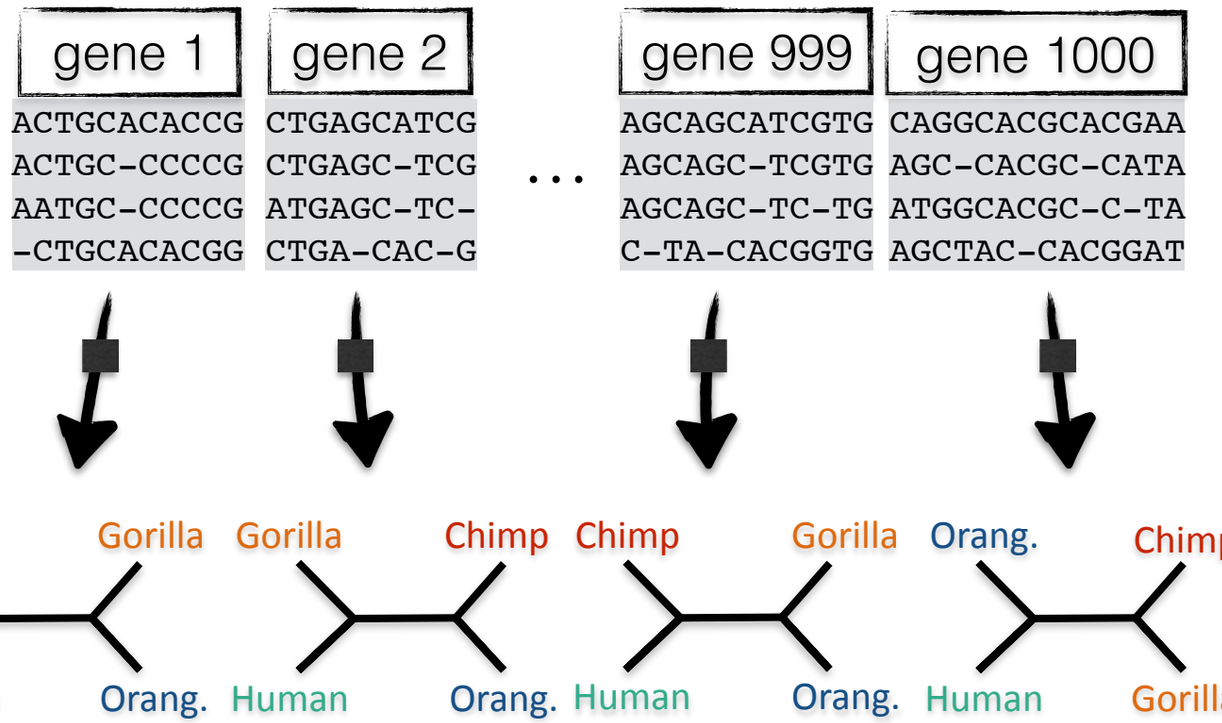

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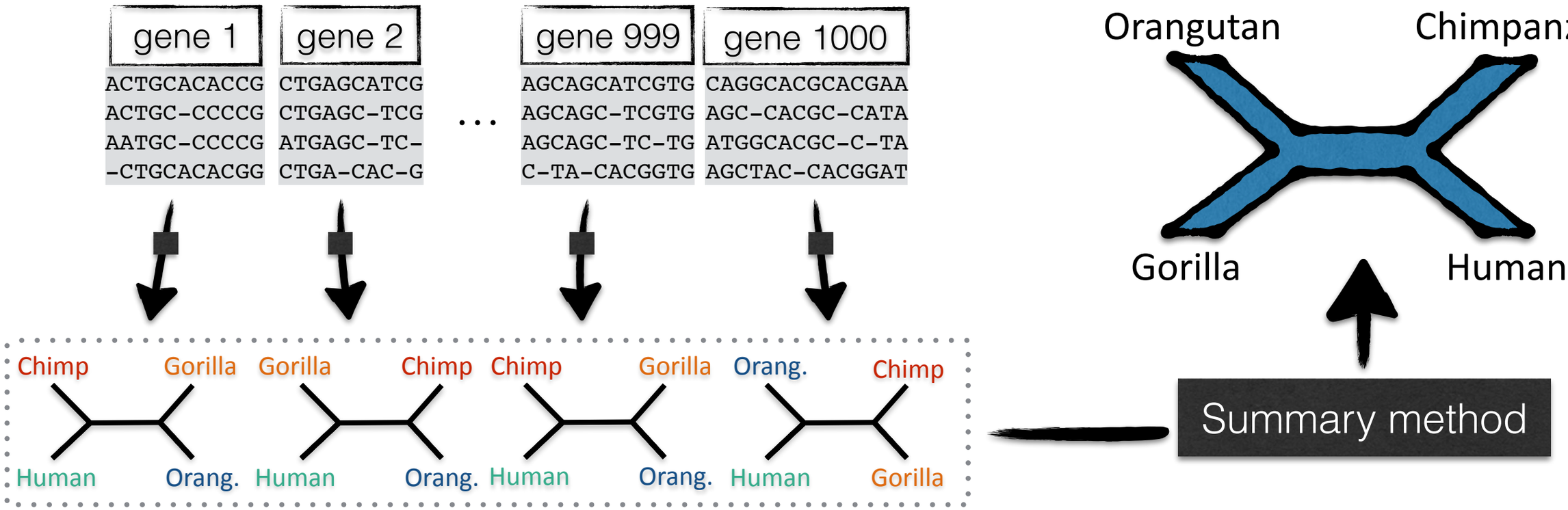

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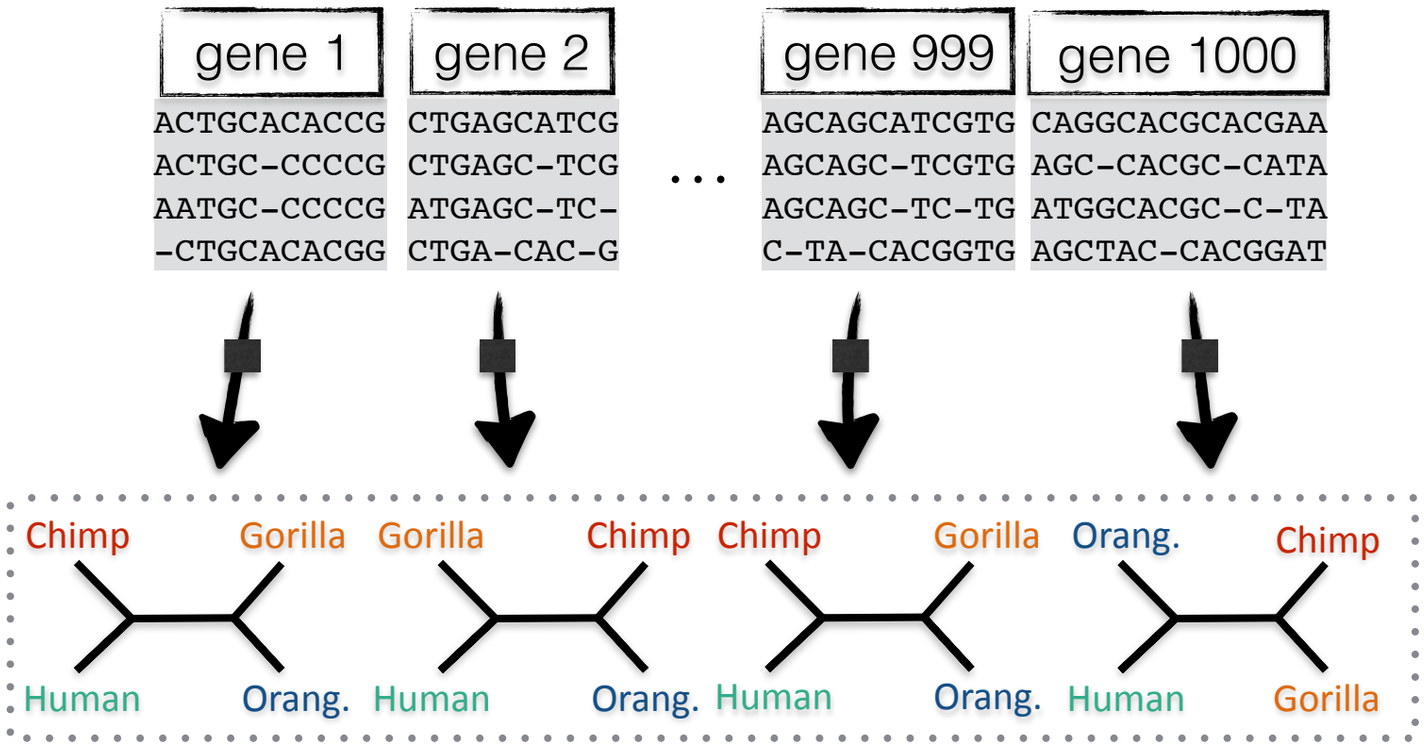
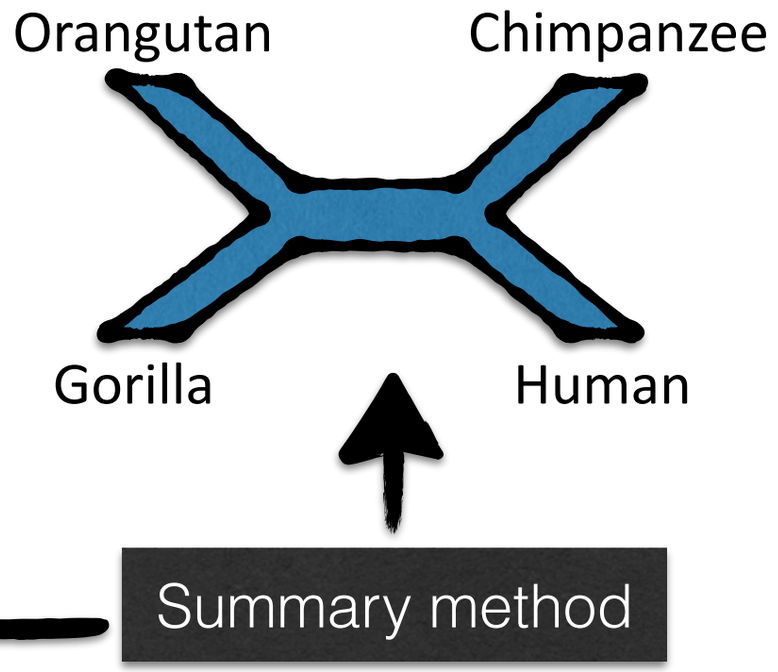
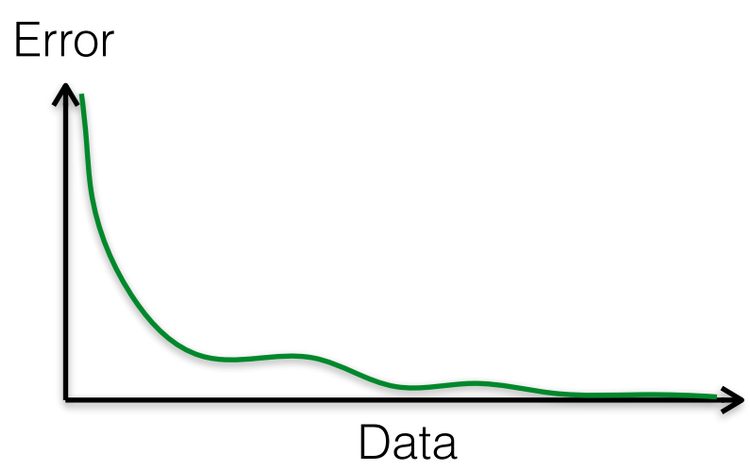




Can be statistically consistent

- **MP-EST** (maximum pseudo-likelihood)
  [Liu, Yu, Edwards, BMC Evol. Bio., 2010]
- NJst, STAR, STELLS, … BUCKy-population



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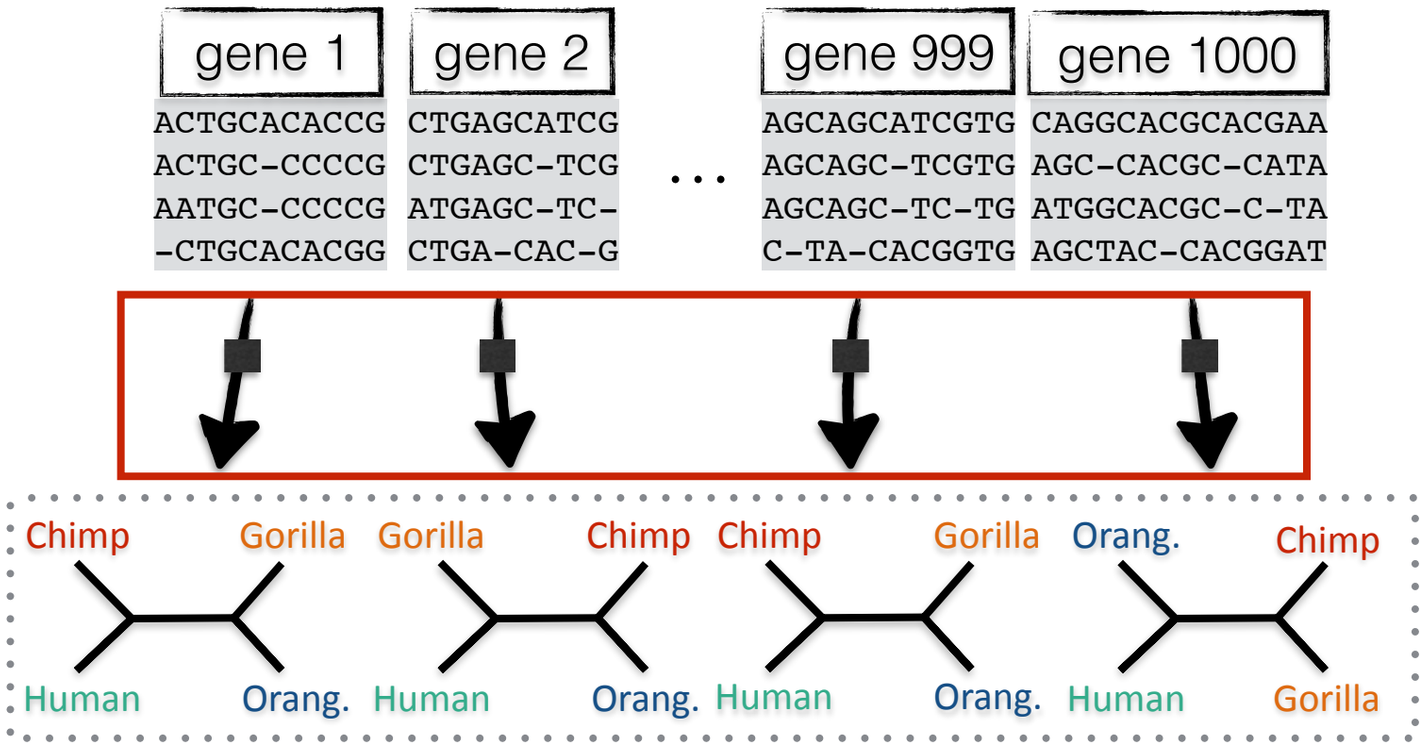

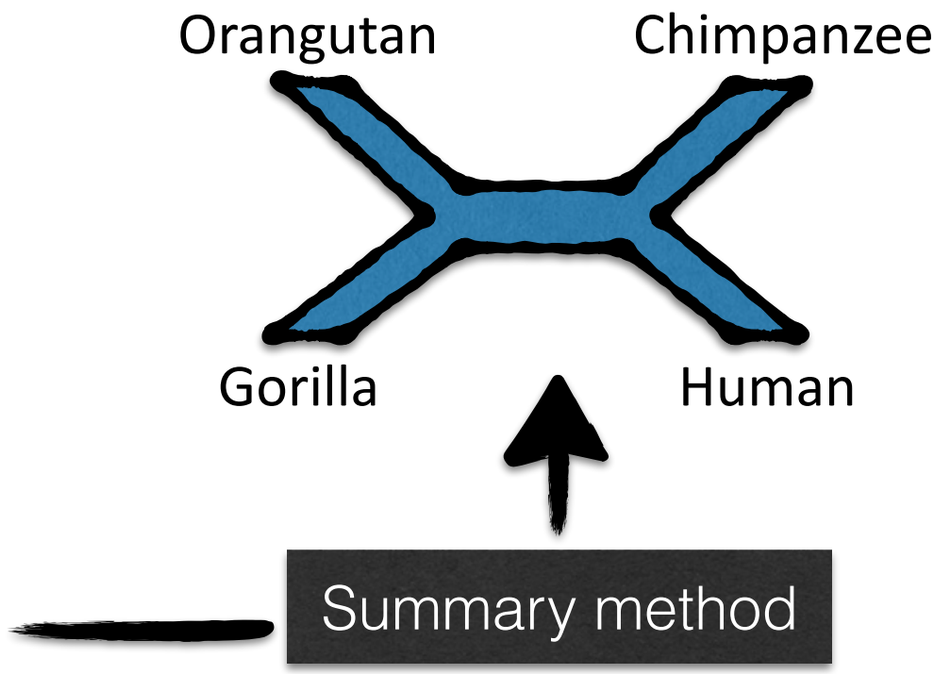

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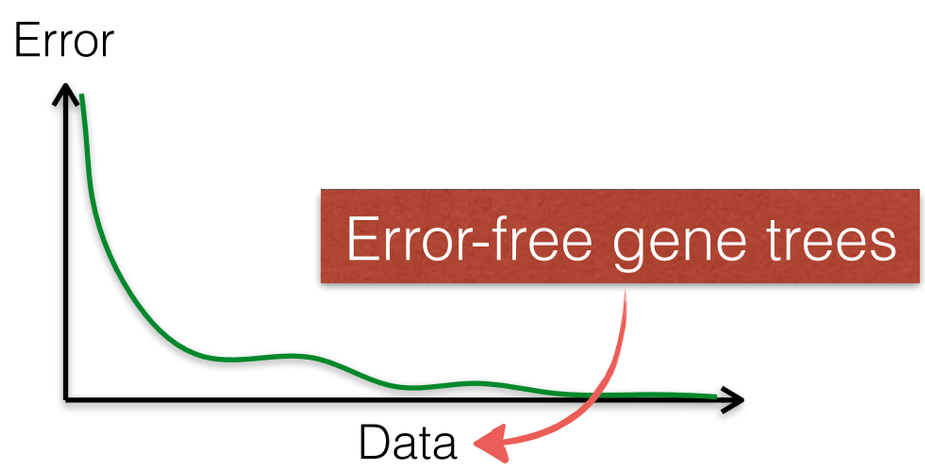


New methods

- Statistical Binning — improves estimation of gene tree distribution (input to summary methods)
  [Mirarab et al., Science, 2014] [Bayzid et al., PLoS ONE, 2015]

- ASTRAL — a summary method with improved accuracy and scalability compared to other summary methods
  [Mirarab et al., Bioinformatics, 2014 and 2015]

Recent large-scale phylogenomic projects

Avian phylogenomics [Jarvis, Mirarab, et al., Science, 2014]

Whole-genome analyses resolve early branches in the tree of life of modern birds

Erich D. Jarvis,[1*†] Siavash Mirarab,[2*] Andre J. Aberer,[3] Bo Li,[4,5,6] Peter Houde,[7] Cai Li,[4,6] Simon Y. W. Ho,[8] Brant C. Faircloth,[9,10] Benoit Nabholz,[11] Jason T. Howard,[1] Alexander Suh,[12] Claudia C. Weber,[12] Rute R. da Fonseca,[6] Jianwen Li,[4] Fang Zhang,[4] Hui Li,[4] Long Zhou,[4] Nitish Narula,[7,13] Liang Liu,[14] Ganesh Ganapathy,[1] Bastien Boussau,[15] Md. Shamsuzzoha Bayzid,[2] Volodymyr Zavidovych,[1] Sankar Subramanian,[16] Toni Gabaldón,[17,18,19] Salvador Capella-Gutiérrez,[17,18] Jaime Huerta-Cepas,[17,18] Bhanu Rekepalli,[20] Kasper Munch,[21] Mikkel Schierup,[21] Bent Lindow,[6] Wesley C. Warren,[22] David Ray,[23,24,25] Richard E. Green,[26] Michael W. Bruford,[27] Xiangjiang Zhan,[27,28] Andrew Dixon,[29] Shengbin Li,[30] Ning Li,[31] Yinhua Huang,[31] Elizabeth P. Derryberry,[32,33] Mads Frost Bertelsen,[34] Frederick H. Sheldon,[33] Robb T. Brumfield,[33] Claudio V. Mello,[35,36] Peter V. Lovell,[35] Morgan Wirthlin,[35] Maria Paula Cruz Schneider,[36,37] Francisco Prosdocimi,[36,38] José Alfredo Samaniego,[6] Amhed Missael Vargas Velazquez,[6] Alonzo Alfaro-Núñez,[6] Paula F. Campos,[6] Bent Petersen,[39] Thomas Sicheritz-Ponten,[39] An Pas,[40] Tom Bailey,[41] Paul Scofield,[42] Michael Bunce,[43] David M. Lambert,[16] Qi Zhou,[44] Polina Perelman,[45,46] Amy C. Driskell,[47] Beth Shapiro,[26] Zijun Xiong,[4] Yongli Zeng,[4] Shiping Liu,[4] Zhenyu Li,[4] Binghang Liu,[4] Kui Wu,[4] Jin Xiao,[4] Xiong Yinqi,[4] Qiuemei Zheng,[4] Yong Zhang,[4] Huanming Yang,[48] Jian Wang,[48] Linnea Smeds,[12] Frank E. Rheindt,[49] Michael Braun,[50] Jon Fjeldsa,[51] Ludovic Orlando,[6] F. Keith Barker,[52] Knud Andreas Jønsson,[51,53,54] Warren Johnson,[55] Klaus-Peter Koepfli,[56] Stephen O'Brien,[57,58] David Haussler,[59] Oliver A. Ryder,[60] Carsten Rahbek,[51,54] Eske Willerslev,[6] Gary R. Graves,[51,61] Travis C. Glenn,[62] John McCormack,[63] Dave Burt,[64] Hans Ellegren,[12] Per Alström,[65,66] Scott V. Edwards,[67] Alexandros Stamatakis,[3,68] David P. Mindell,[69] Joel Cracraft,[70] Edward L. Braun,[71] Tandy Warnow,[2,72]† Wang Jun,[48,73,74,75,76]† M. Thomas P. Gilbert,[6,43]† Guojie Zhang[4,77]†

1K Plants (1KP) [Wickett, Mirarab, et al., PNAS, 2014]

PNAS

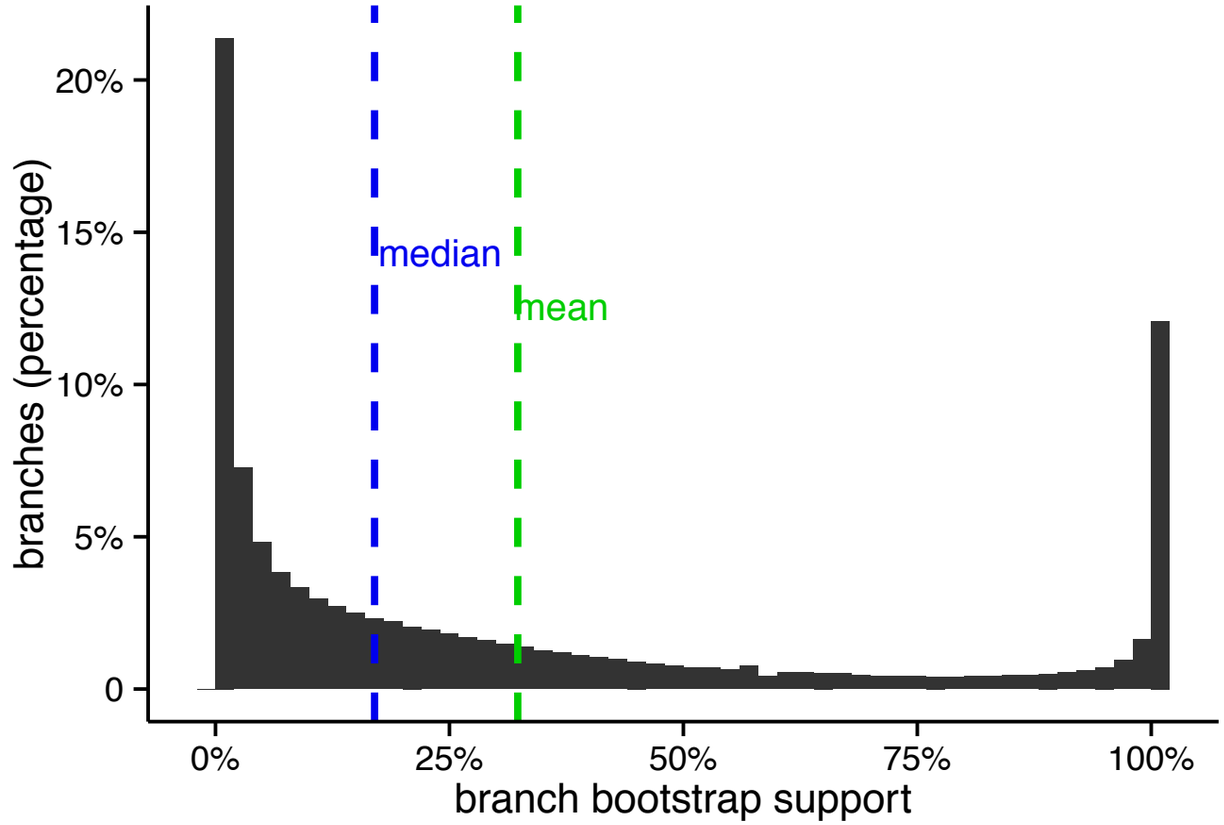
Phylotranscriptomic analysis of the origin and early diversification of land plants

Norman J. Wickett[a,b,1,2], Siavash Mirarab[c,1], Nam Nguyen[c], Tandy Warnow[c], Eric Carpenter[d], Naim Matasci[e,f], Saravanaraj Ayyampalayam[g], Michael S. Barker[f], J. Gordon Burleigh[h], Matthew A. Gitzendanner[h,i], Brad R. Ruhfel[h,j,k], Eric Wafula[l], Joshua P. Der[l], Sean W. Graham[m], Sarah Mathews[n], Michael Melkonian[o], Douglas E. Soltis[h,i,k], Pamela S. Soltis[h,i,k], Nicholas W. Miles[k], Carl J. Rothfels[p,q], Lisa Pokorny[p,r], A. Jonathan Shaw[p], Lisa DeGironimo[s], Dennis W. Stevenson[s], Barbara Surek[o], Juan Carlos Villarreal[t], Béatrice Roure[u], Hervé Philippe[u,v], Claude W. dePamphilis[l], Tao Chen[w], Michael K. Deyholos[d], Regina S. Baucom[x], Toni M. Kutchan[y], Megan M. Augustin[y], Jun Wang[z], Yong Zhang[v], Zhijian Tian[z], Zhixiang Yan[z], Xiaolei Wu[z], Xiao Sun[z], Gane Ka-Shu Wong[d,z,aa,2], and James Leebens-Mack[g,2]

Challenges of avian phylogenomics

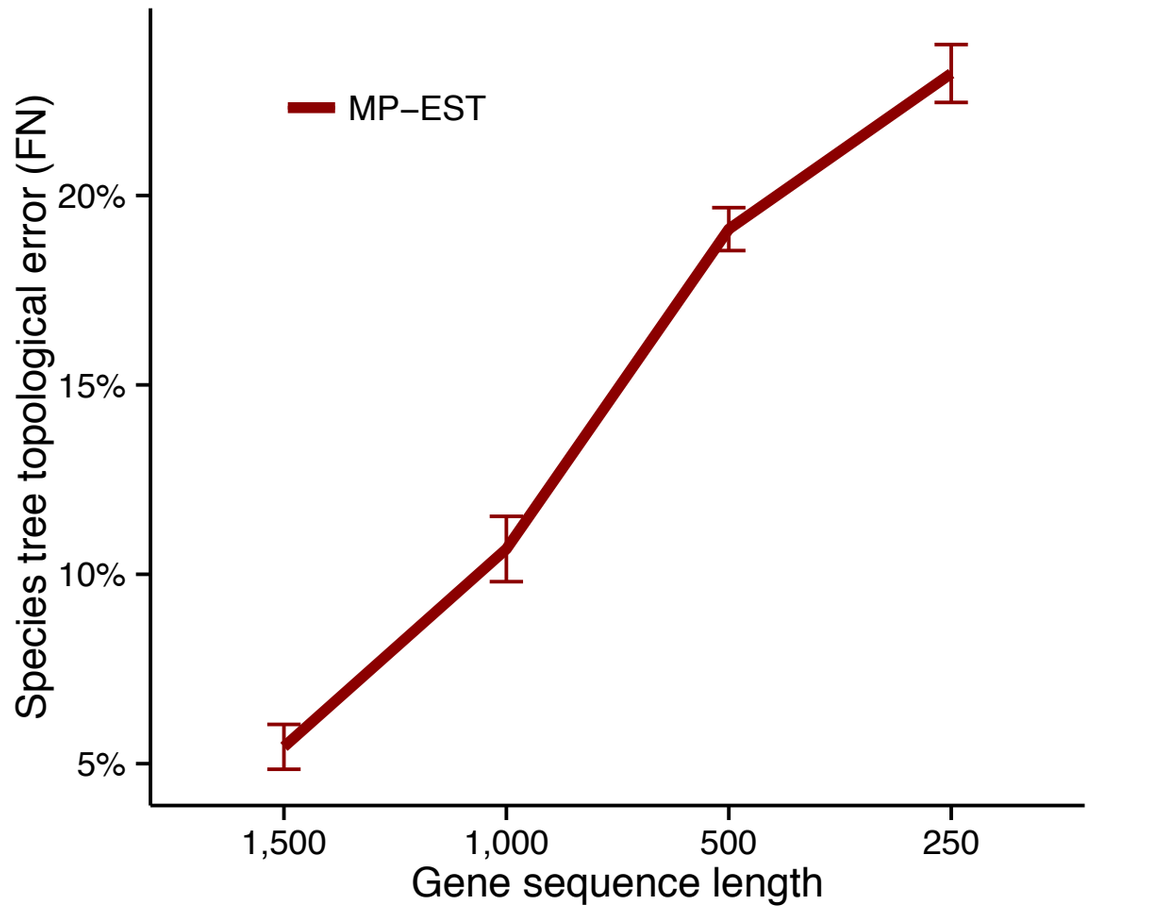
[Jarvis, Mirarab, et al., Science, 2014]

- Whole genomes for 48 bird species (~100m years of evolution)
- Goal: a phylogeny of bird orders
- Extremely challenging due to rampant gene tree incongruence
- 14,000 “noisy” genes (i.e., high gene tree error)



bootstrap support of all branches
in all estimated gene tree

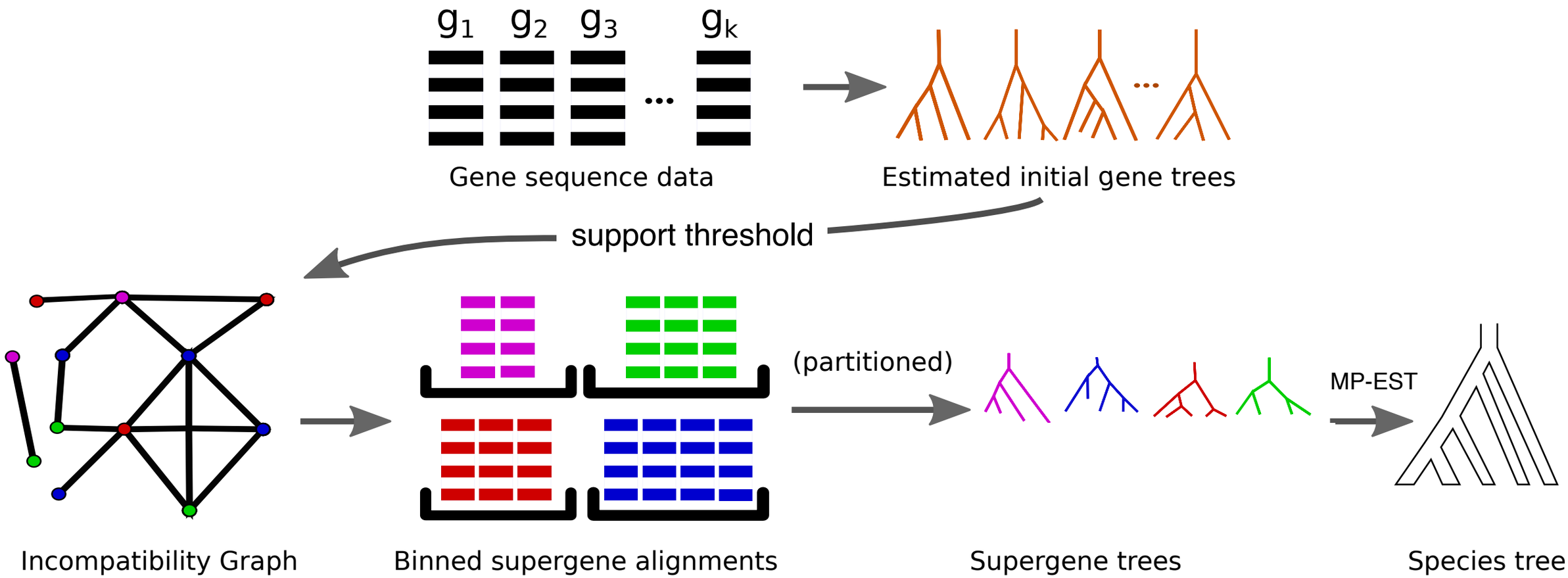
Gene tree estimation error impacts species tree estimation



more gene tree error →

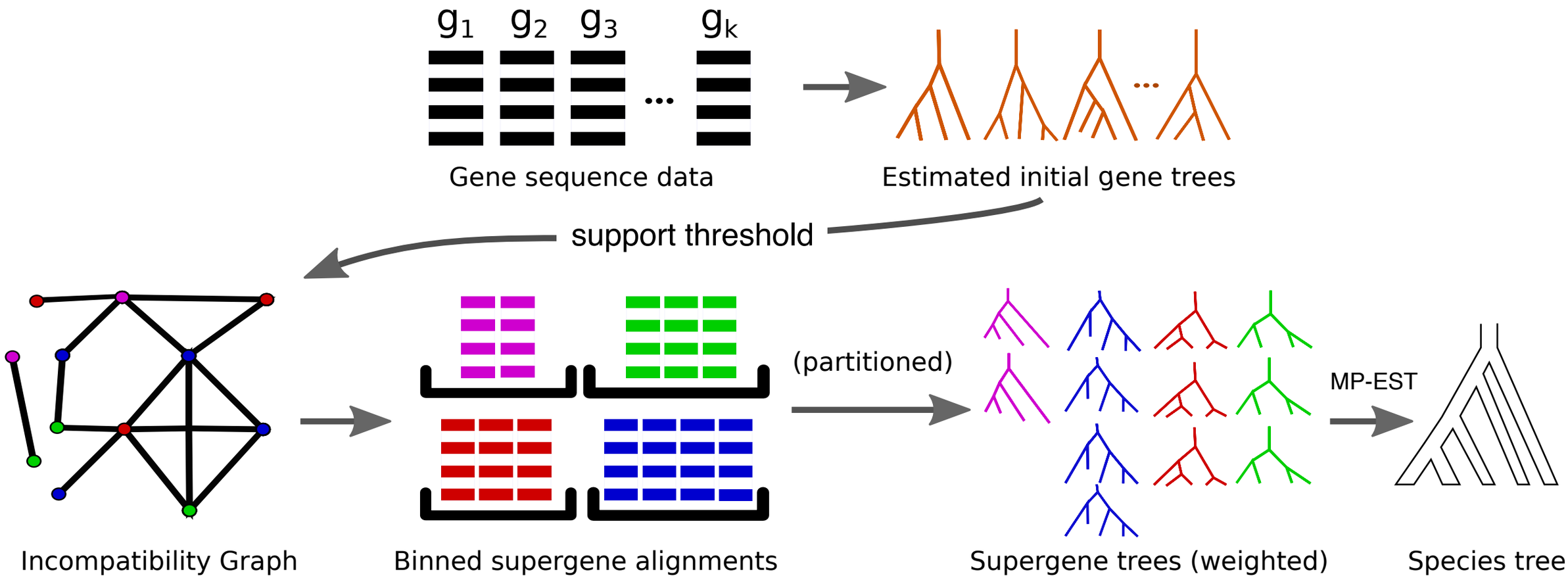
45 avian-like species, 1000 genes
[Mirarab, et al., Science, 2014]

Statistical binning: overview



Original version: unweighted [Mirarab, et al., Science, 2014]

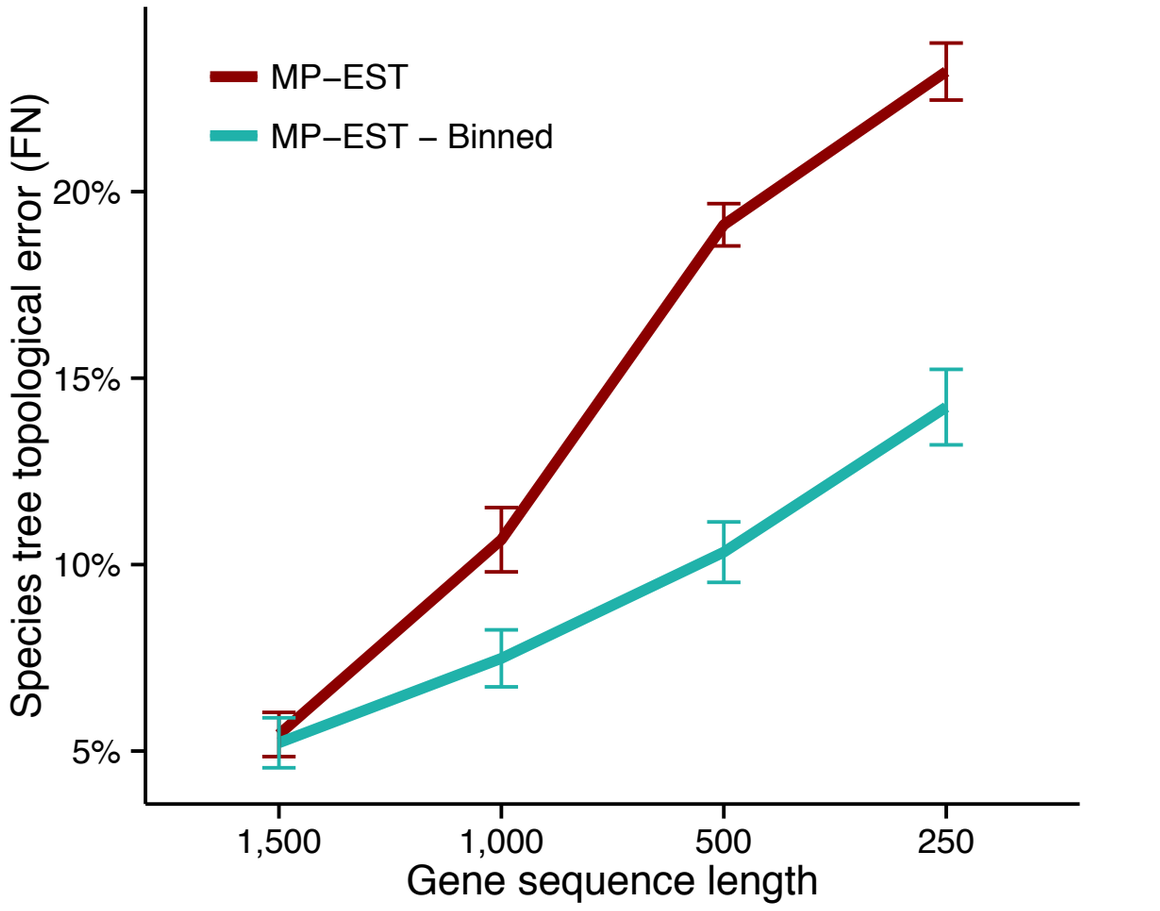
Statistical binning: overview



Original version: unweighted [Mirarab, et al., Science, 2014]

New version: weighted; statistically consistent [Bayzid, Mirarab, Warnow, PloS ONE, 2015]

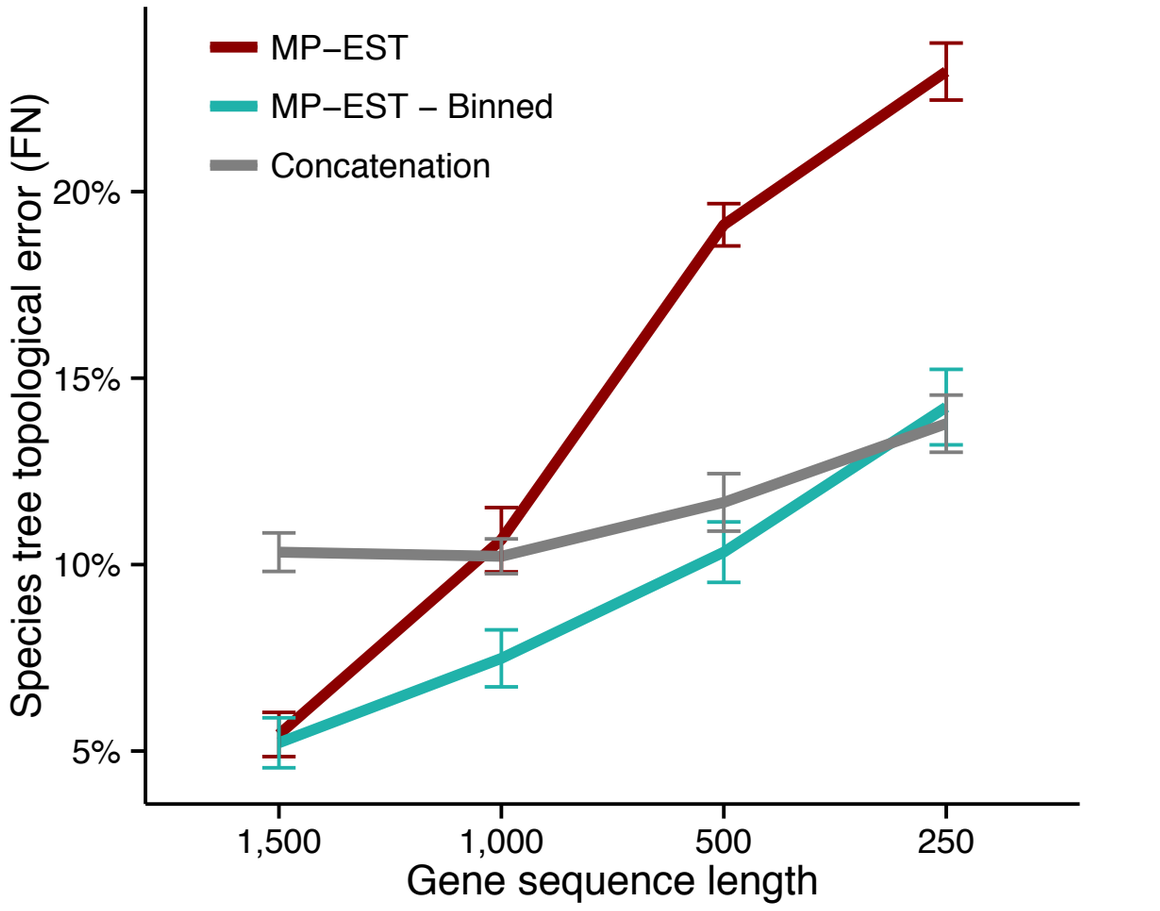
Statistical binning improves species tree estimation



more gene tree error →

45 avian-like species, 1000 genes
[Mirarab, et al., Science, 2014]

Statistical binning improves species tree estimation



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Binning also improves other measures of accuracy

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  - Fewer false positives with high support

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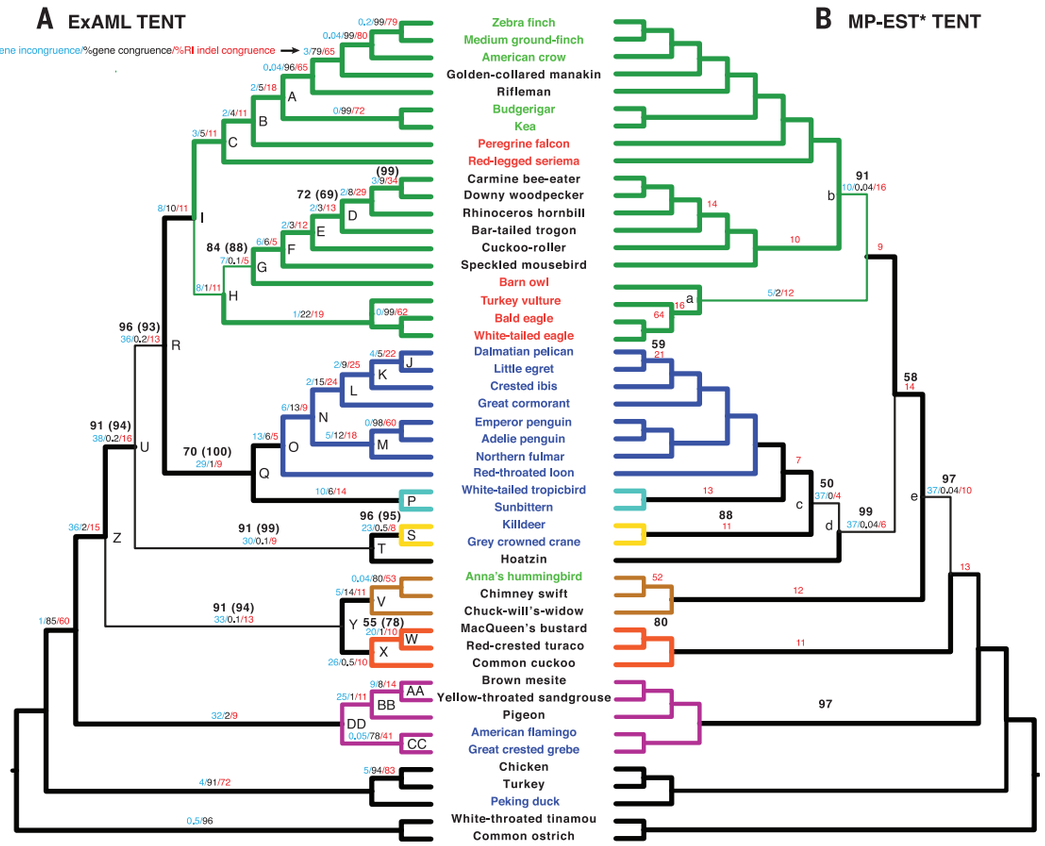
- More accurate gene tree distributions
- Better Species tree bootstrap support
  - Higher support for true positives
  - Fewer false positives with high support
- More accurate species tree branch lengths
  - Hence, estimates of ILS levels

Binning on the Avian dataset

Binned analyses results in a tree that was largely congruent with the concatenation

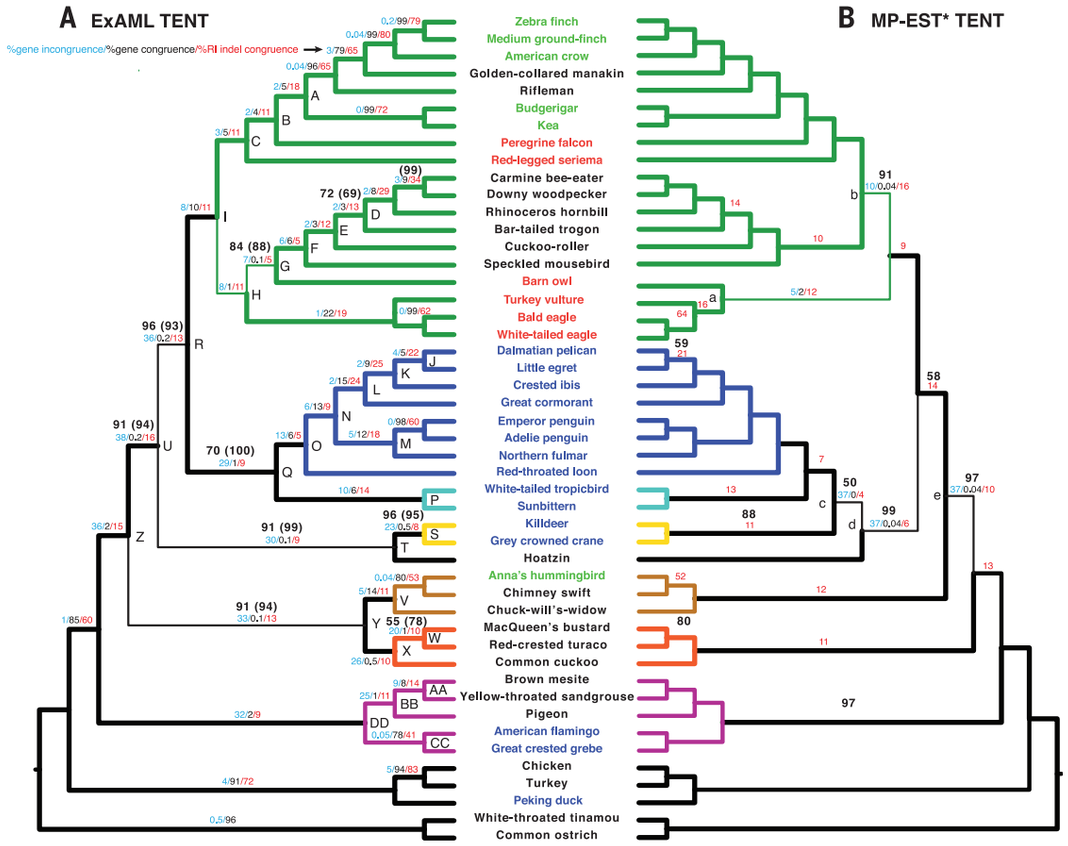


[Jarvis, Mirarab, et al., Science, 2014]

Binning on the Avian dataset

Binned analyses results in a tree that was largely congruent with the concatenation

The binned analyses recovered almost all highly supported gene tree branches



[Jarvis, Mirarab, et al., Science, 2014]

New methods

- Statistical Binning — improves estimation of gene tree distribution (input to summary methods)
[Mirarab et al., Science, 2014] [Bayzid et al., PLoS ONE, 2015]

1KP: Plant whole transcriptomes

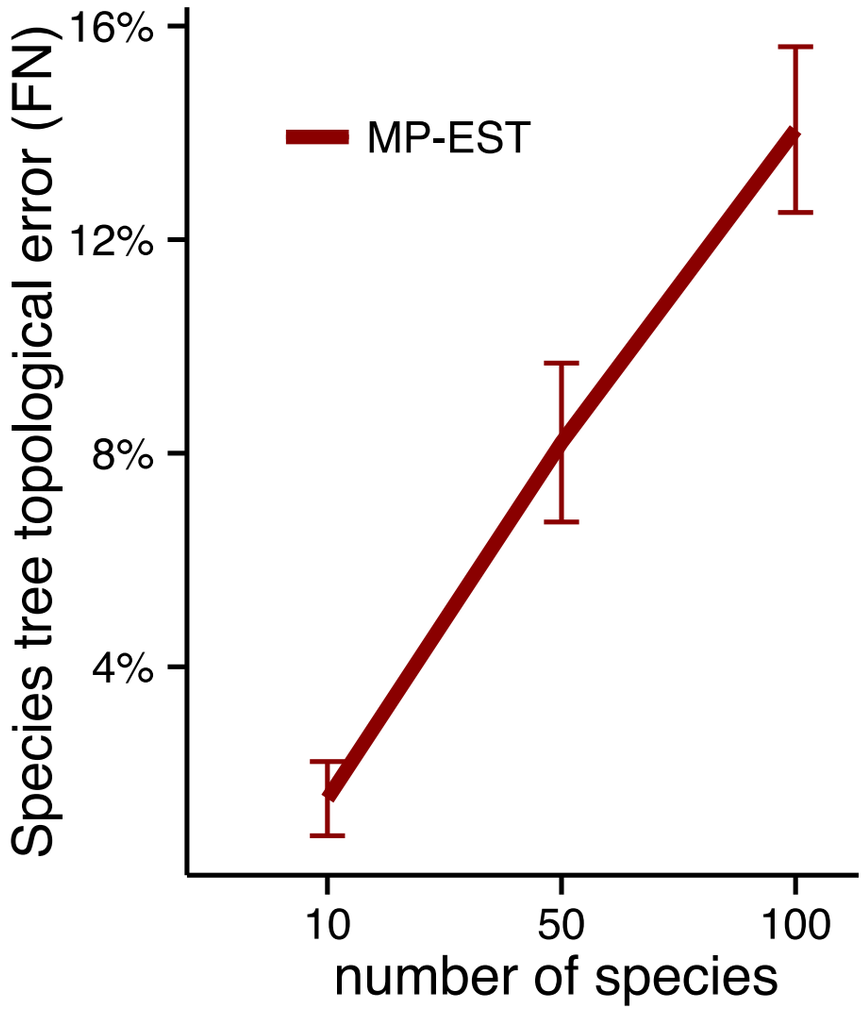
PNAS

Phylotranscriptomic analysis of the origin and early diversification of land plants

Norman J. Wickett[a,b,1,2], Siavash Mirarab[c,1], Nam Nguyen[c], Tandy Warnow[c], Eric Carpenter[d], Naim Matasci[e,f], Saravanaraj Ayyampalayam[g], Michael S. Barker[f], J. Gordon Burleigh[h], Matthew A. Gitzendanner[h,i], Brad R. Ruhfel[h,j,k], Eric Wafula[l], Joshua P. Der[l], Sean W. Graham[m], Sarah Mathews[n], Michael Melkonian[o], Douglas E. Soltis[h,i,k], Pamela S. Soltis[h,i,k], Nicholas W. Miles[k], Carl J. Rothfels[p,q], Lisa Pokorny[p,r], A. Jonathan Shaw[p], Lisa DeGironimo[s], Dennis W. Stevenson[s], Barbara Surek[o], Juan Carlos Villarreal[t], Béatrice Roure[u], Hervé Philippe[u,v], Claude W. dePamphilis[l], Tao Chen[w], Michael K. Deyholos[d], Regina S. Baucom[x], Toni M. Kutchan[y], Megan M. Augustin[y], Jun Wang[z], Yong Zhang[v], Zhijian Tian[z], Zhixiang Yan[z], Xiaolei Wu[z], Xiao Sun[z], Gane Ka-Shu Wong[d,z,aa,2], and James Leebens-Mack[g,2]

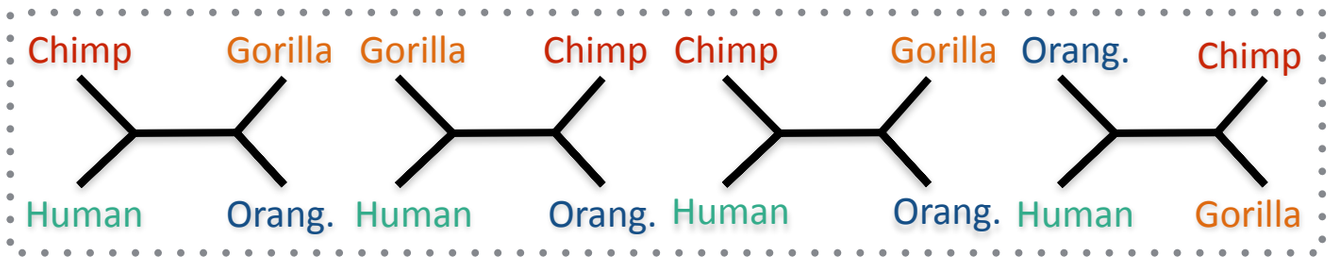
- Whole transcriptomes for <u>103 plant species</u>
  - 1,200 in the next phase
- 400-800 single copy “genes”
- Spans ~1 billion years of evolution
- Many unanswered questions about plant evolution

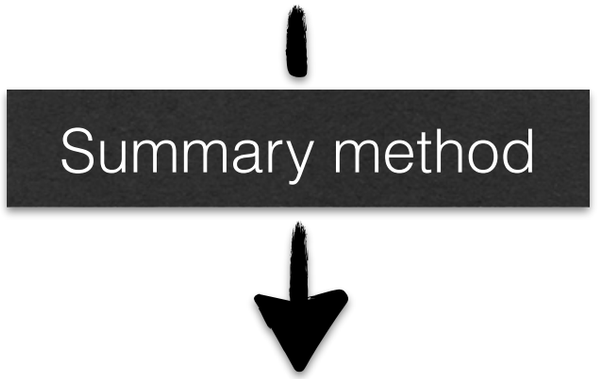
Number of species impacts estimation error in the species tree

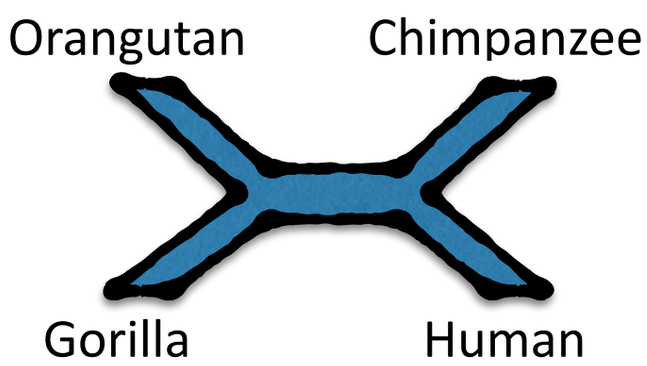


1000 genes, “medium” levels of ILS, simulated species trees
[Mirarab and Warnow, ISMB, 2015]

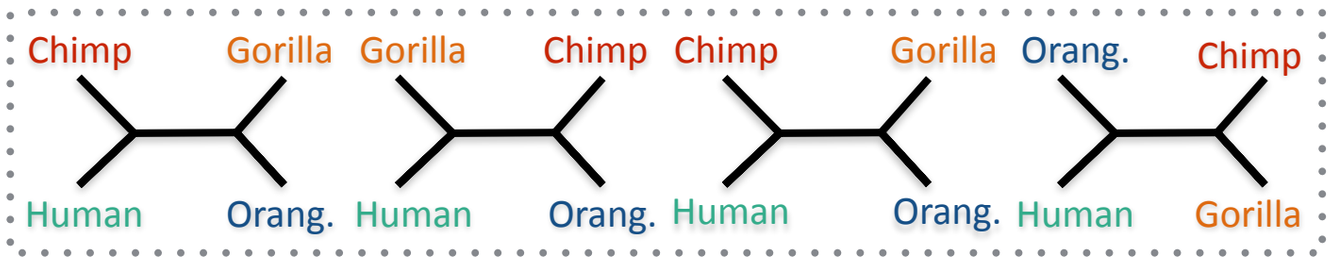
Designing summary methods for quartets of taxa

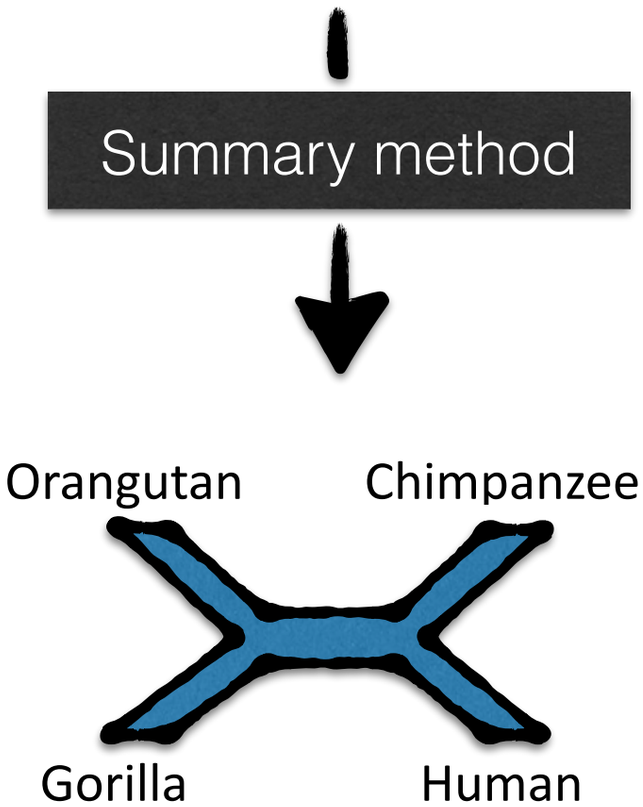




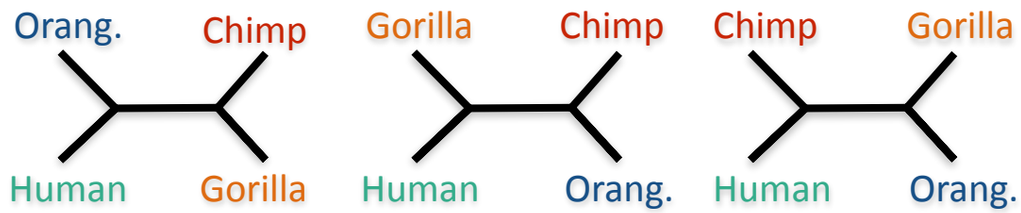


Designing summary methods for quartets of taxa

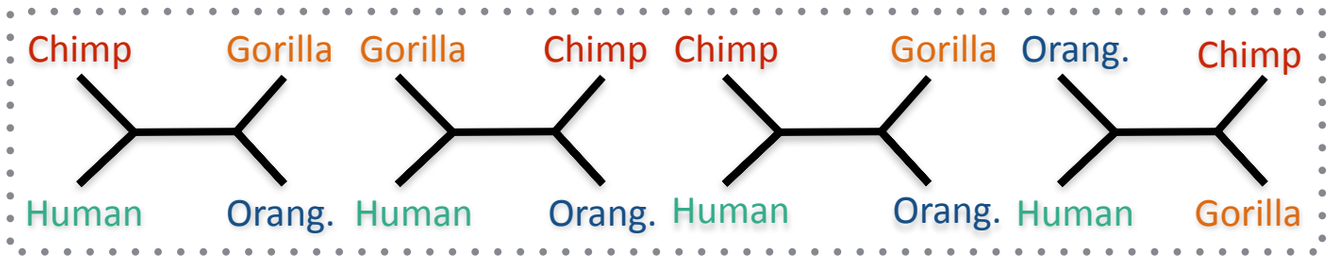


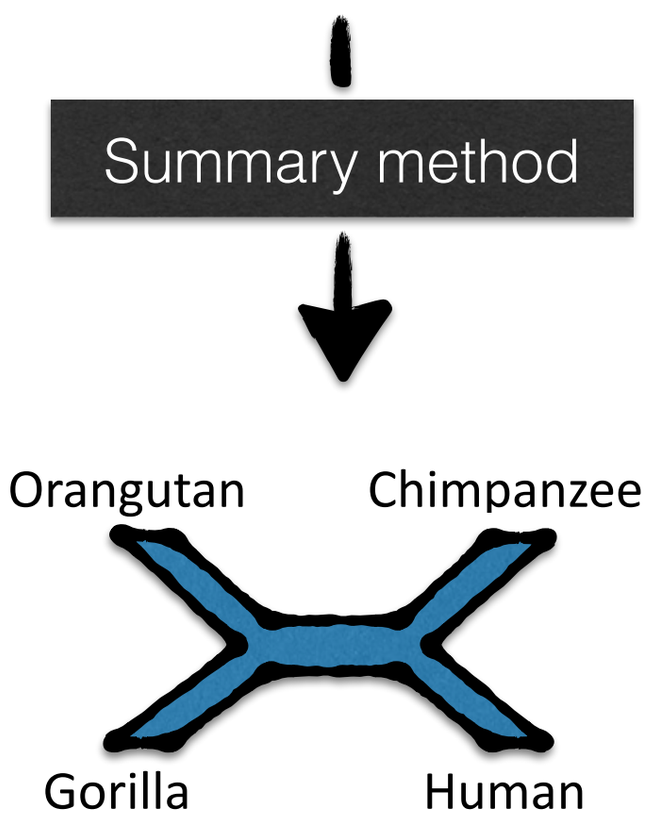


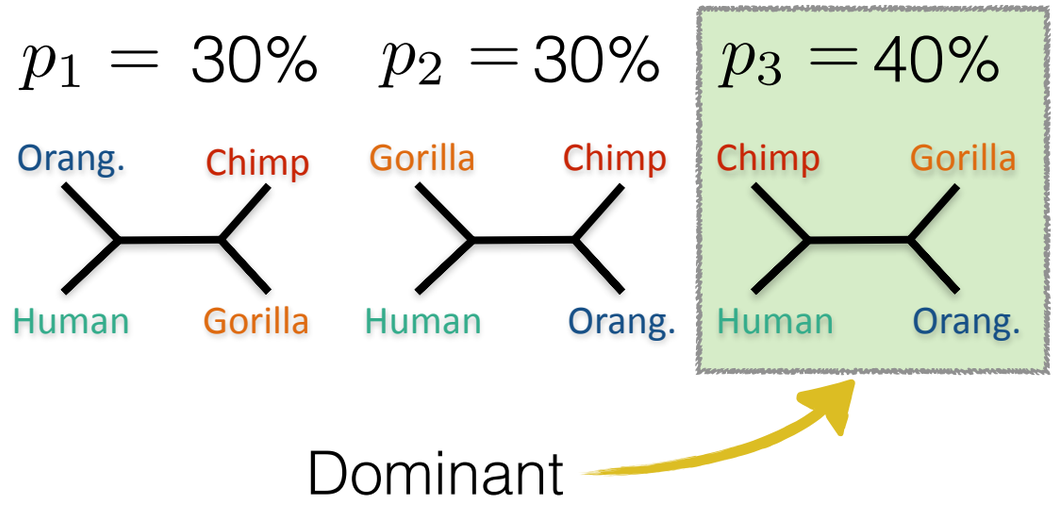
$p_1 = 30\%$ $p_2 = 30\%$ $p_3 = 40\%$



Designing summary methods for quartets of taxa

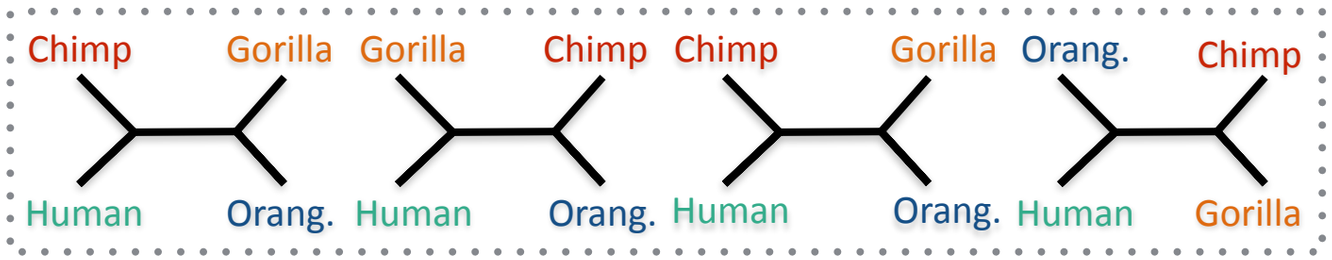


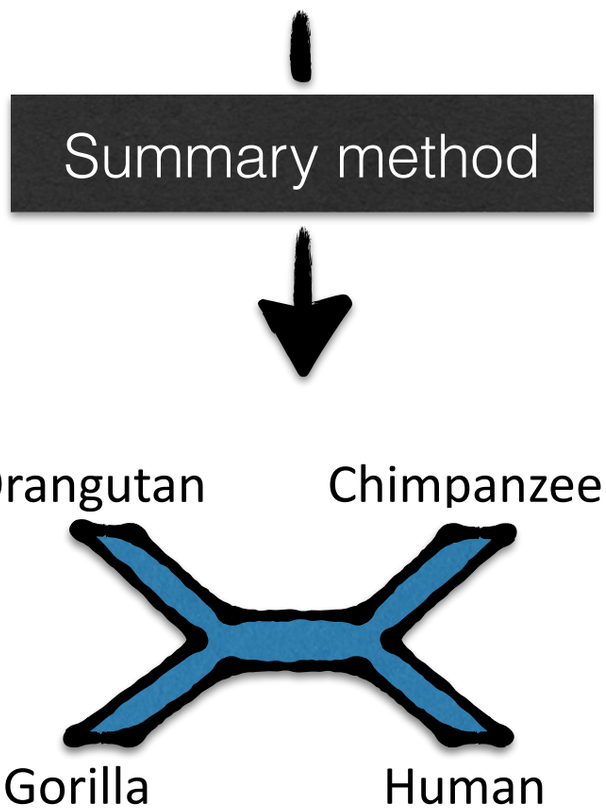


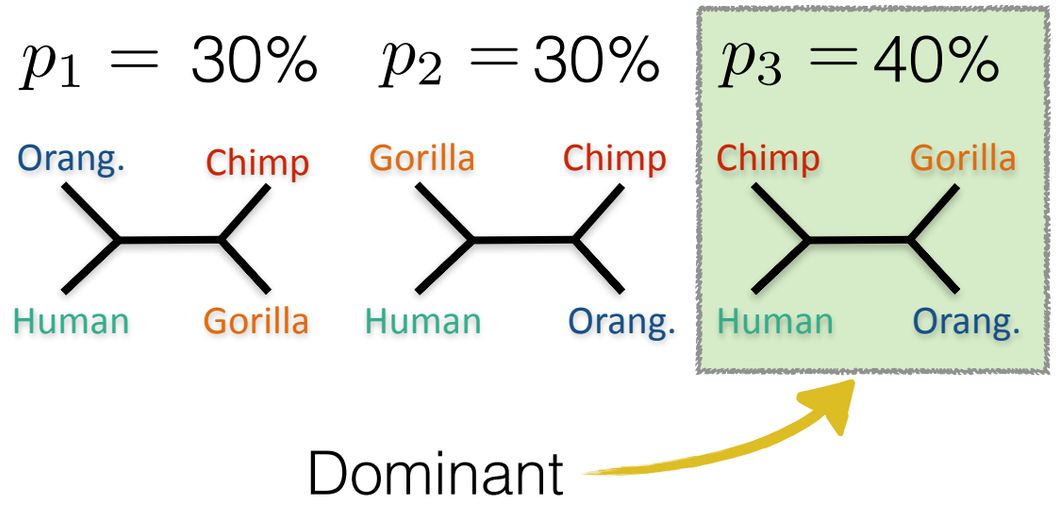


- For 4 species, the dominant quartet topology is the species tree
  [Allman, et al. 2010], [Degnan, 2014]

Designing summary methods for quartets of taxa

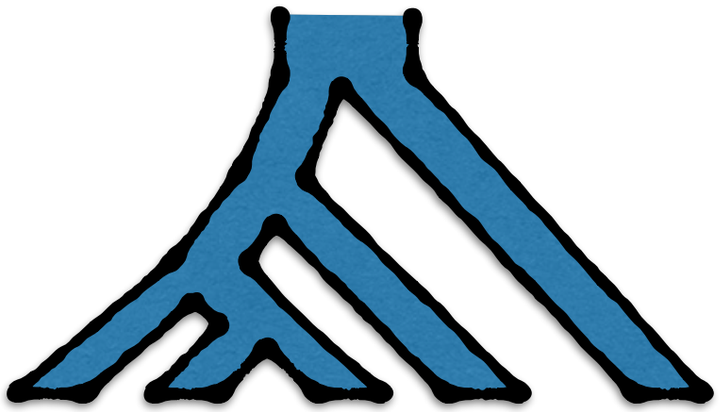






- For 4 species, the dominant quartet topology is the species tree
  [Allman, et al. 2010], [Degnan, 2014]
- For >4 species, the dominant topology may be different from the species tree
  [Degnan and Rosenberg, 2006, 2009]

More than 4 species



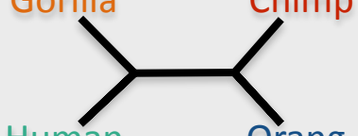
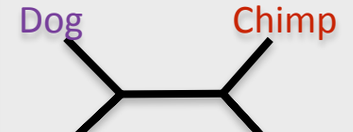
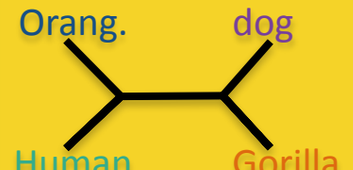
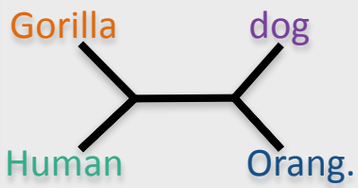
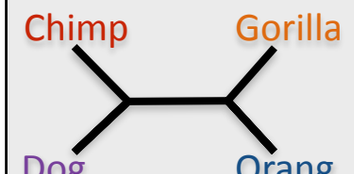
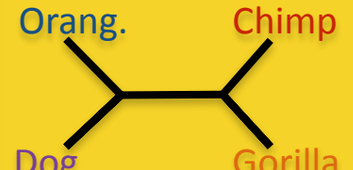
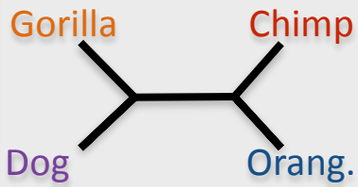
1. Break gene trees into $\binom{n}{4}$ quartets of species

2. Find the dominant tree for all quartets of taxa

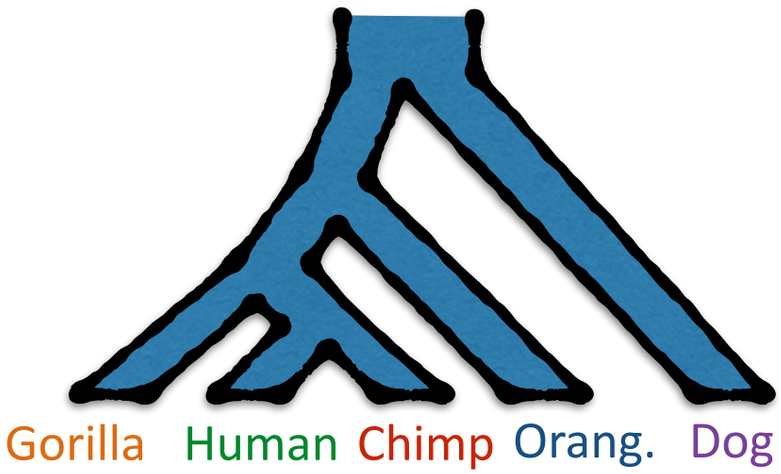
3. Combine quartet trees

Example: BUCKy-pop. [Larget, et al., Bioinformatics, 2010]

(probabilities are made-up just as an example)

Gorilla Human Orangutan Chimp	 50%	 25%	 25%
Gorilla Human Dog Chimp	 55%	 21%	 24%
Gorilla Human Orangutan Dog	 7%	 87%	 6%
Gorilla Dog Orangutan Chimp	 6%	 88%	 6%
Dog Human Orangutan Chimp	 95%	 2%	 3%

ASTRAL: weighting by frequency



1. Break gene trees into $\binom{n}{4}$ quartets of species
2. Find the tree that "satisfies" the maximum number of weighted quartets from gene trees

(probabilities are made-up just as an example)

Gorilla Human / Orangutan Chimp 50%	Orang. Chimp / Human Gorilla 25%	Gorilla Chimp / Human Orang. 25%
Gorilla Human / Dog Chimp 55%	Dog Chimp / Human Gorilla 19%	Gorilla Chimp / Human Dog 26%
Gorilla Human / Orangutan Dog 7%	Orang. dog / Human Gorilla 87%	Gorilla dog / Human Orang. 6%
Gorilla Dog / Orangutan Chimp 6%	Orang. Chimp / Dog Gorilla 88%	Gorilla Chimp / Dog Orang. 6%
Dog Human / Orangutan Chimp 95%	Orang. Chimp / Human Dog 2%	Dog Chimp / Human Orang. 3%

Maximum Quartet Support Species Tree

[Mirarab, et al., ECCB, 2014]

- Optimization Problem (suspected NP-Hard):

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

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

Set of quartet trees induced by T

a gene tree

all input gene trees

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

ASTRAL

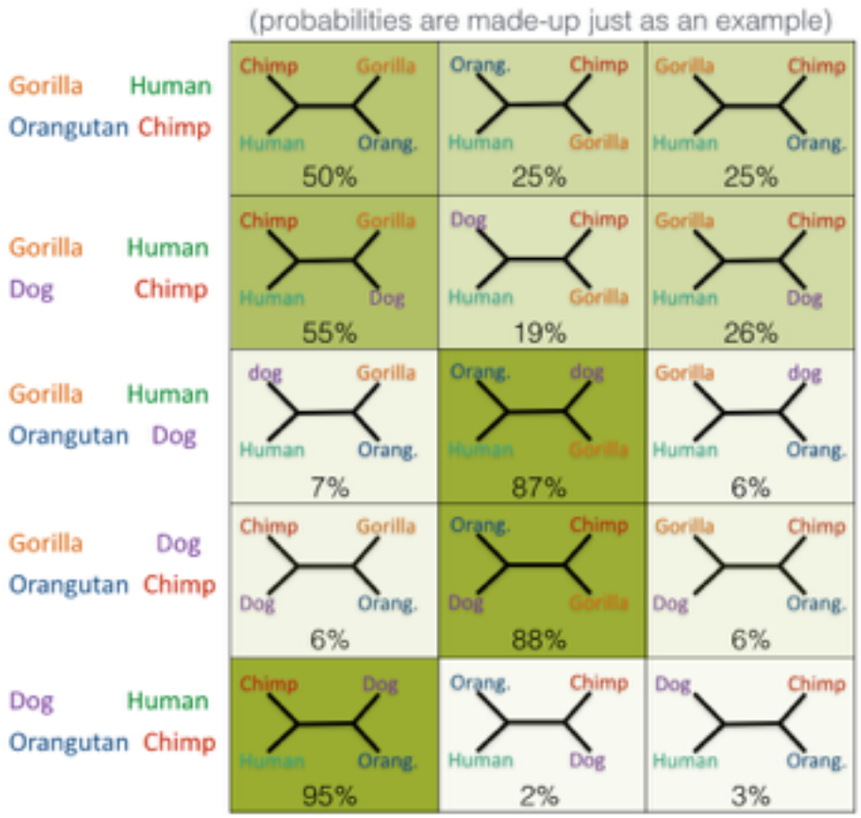
- We developed a dynamic programming algorithm to solve the problem exactly
  - Exponential running time (still feasible for <18 species)
- Developed a constrained version of the problem that can be solved exactly in polynomial time
  - Constraints search to branches that appear in gene trees ($\mathcal{X}$)
  - Runs for 1000 species and 1000 genes in about a day
  - Remains statistically consistent

Asymptotic running time

- $O(nk|\mathcal{X}|^2)$ for *k* genes of *n* species

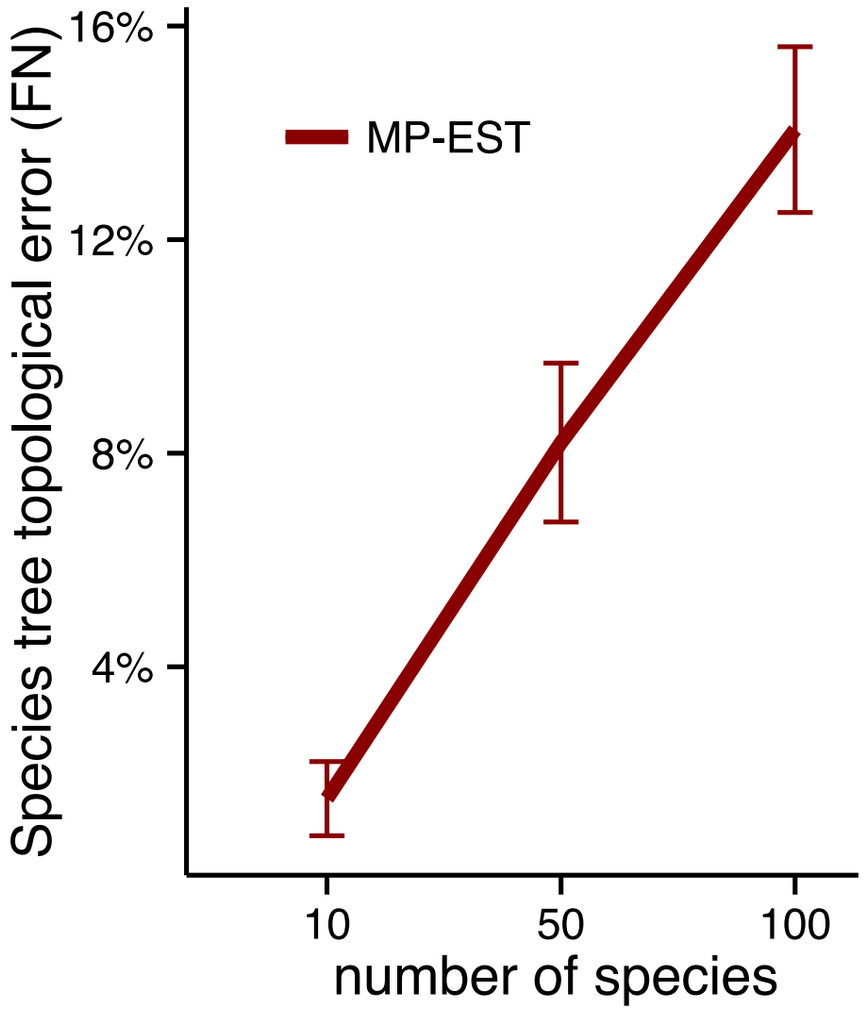
Asymptotic running time

- $O(nk|\mathcal{X}|^2)$ for *k* genes of *n* species



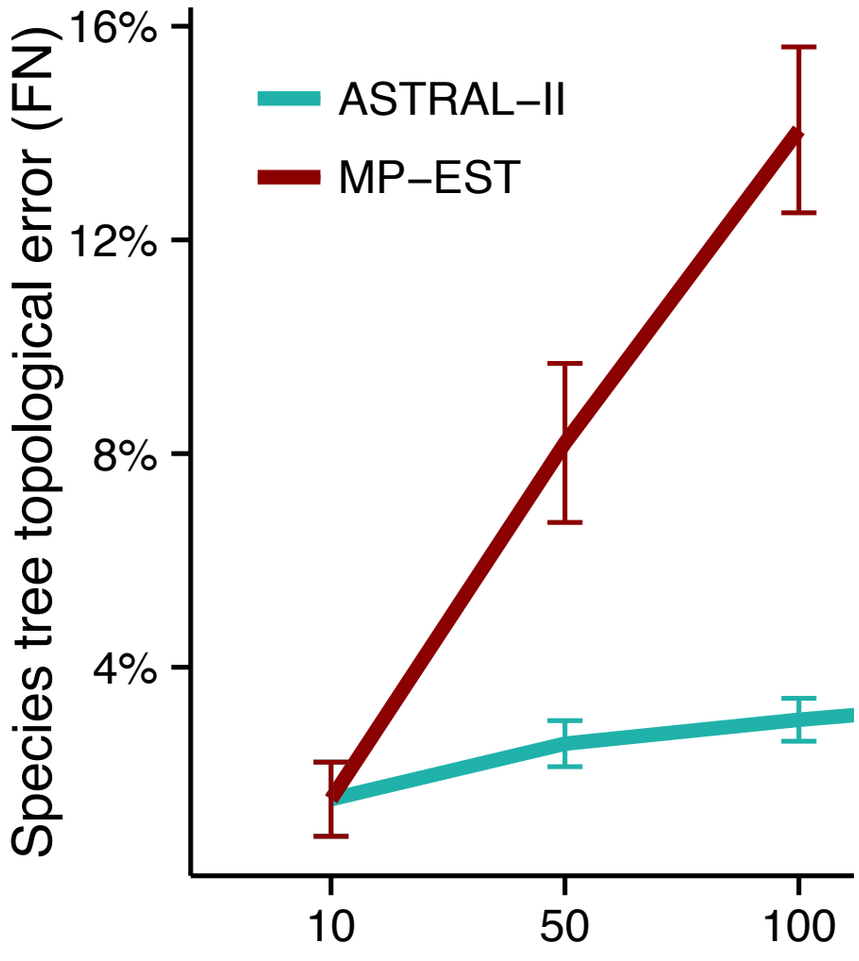
- Surprise: running time is better than $\Theta(n^4)$
- Don't we have to at least list all $\binom{n}{4}$ quartets?
- No! we calculate scores without listing $\binom{n}{4}$ quartets

Number of species impacts estimation error in the species tree



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

ASTRAL: accurate and scalable



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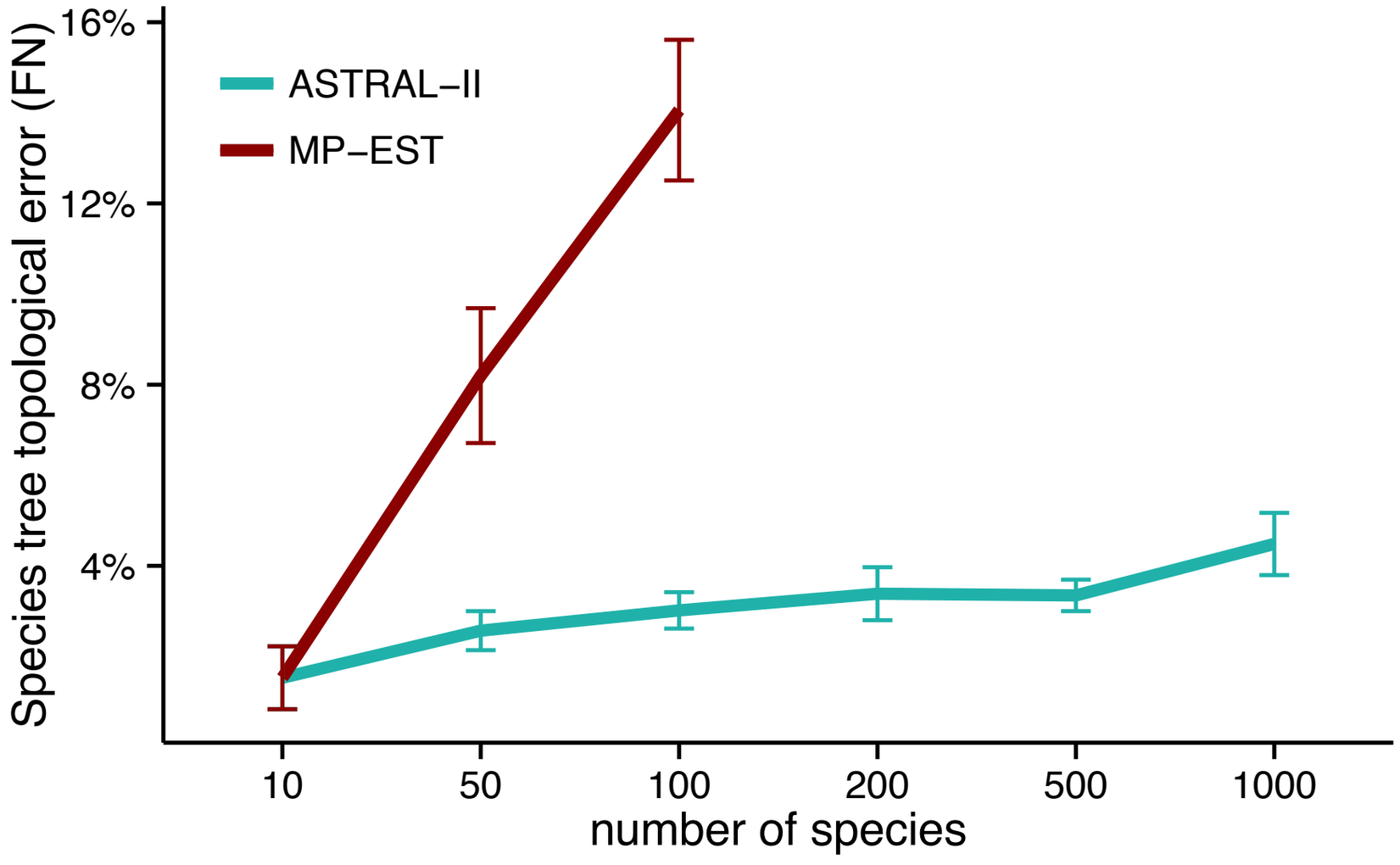

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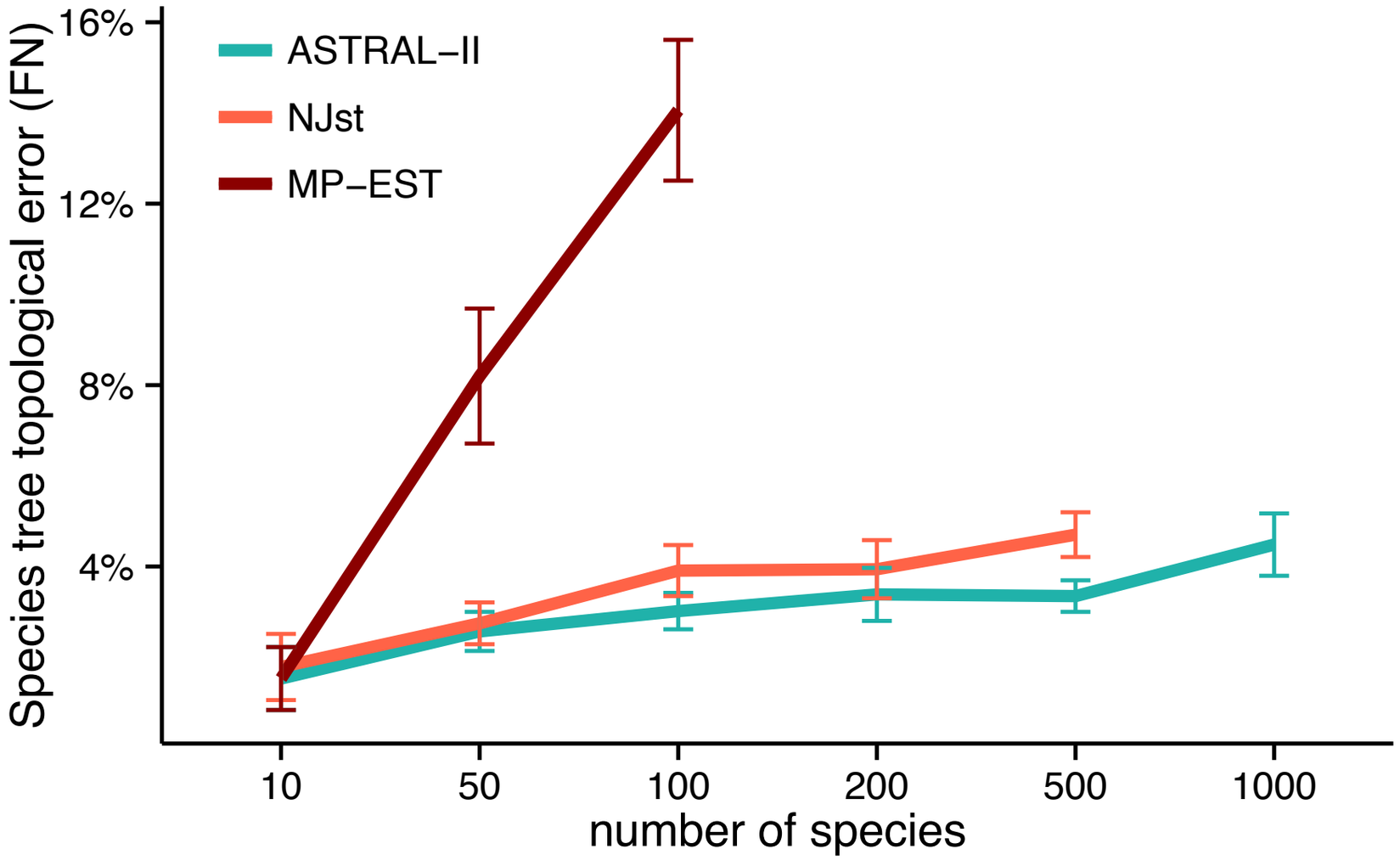
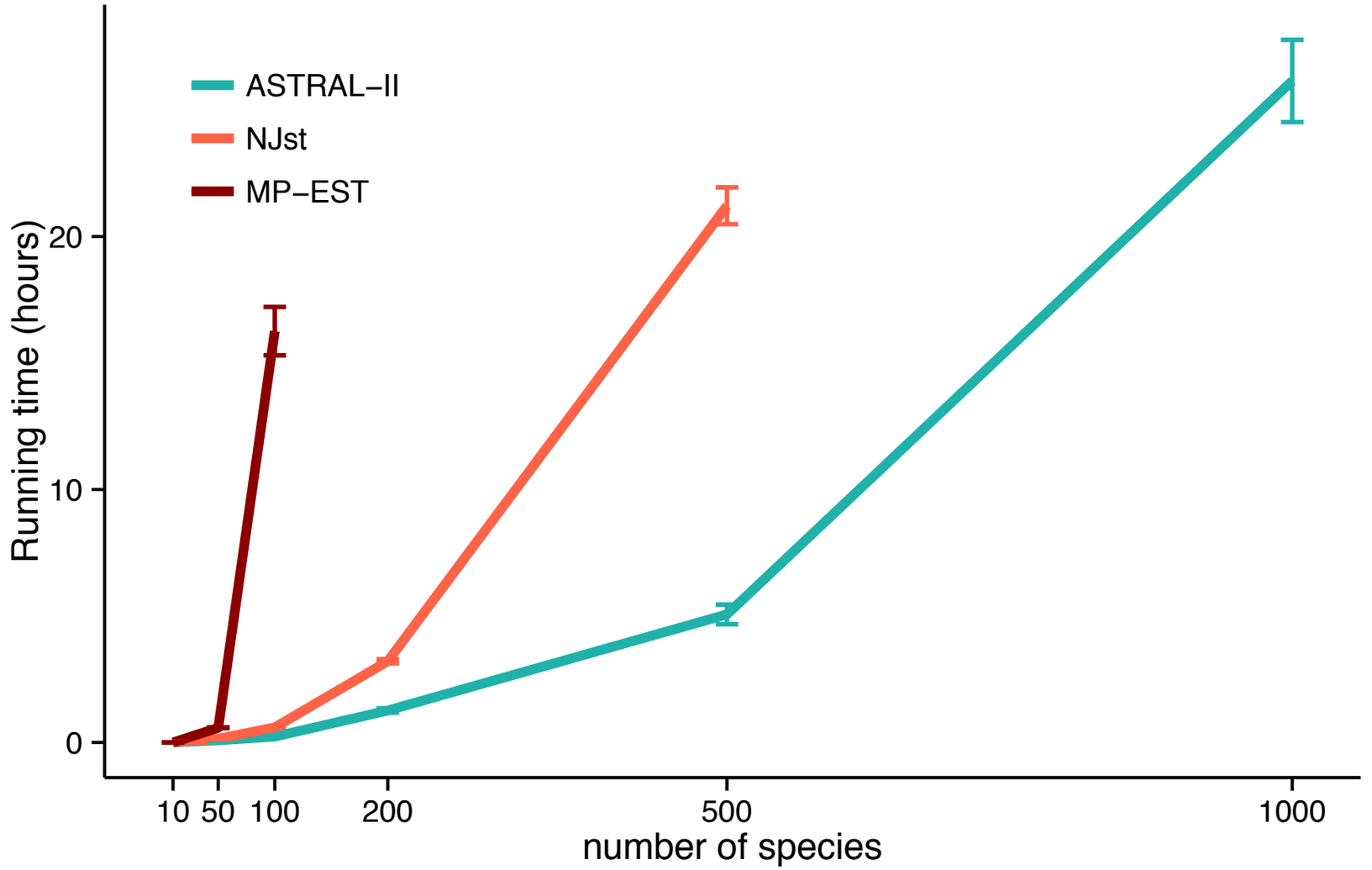


1000 genes, “medium” levels of ILS, simulated species trees
[Mirarab and Warnow, ISMB, 2015]

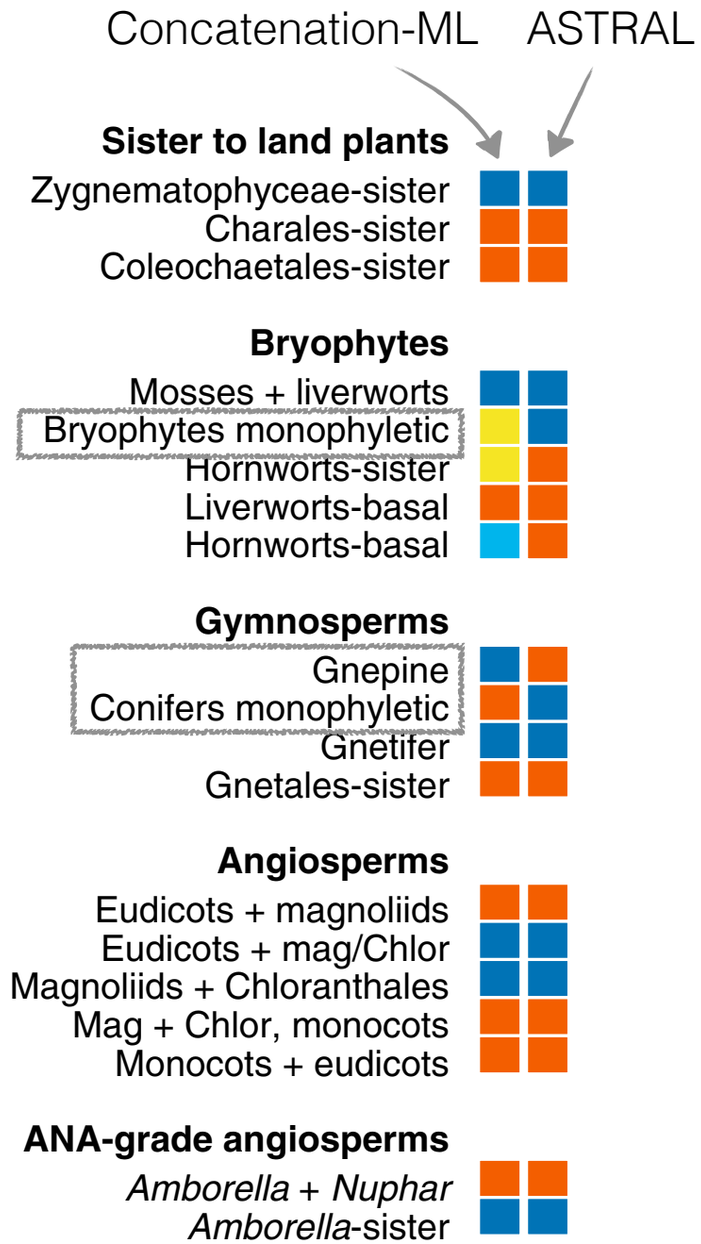
Running time as function of # species



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

ASTRAL on plants dataset

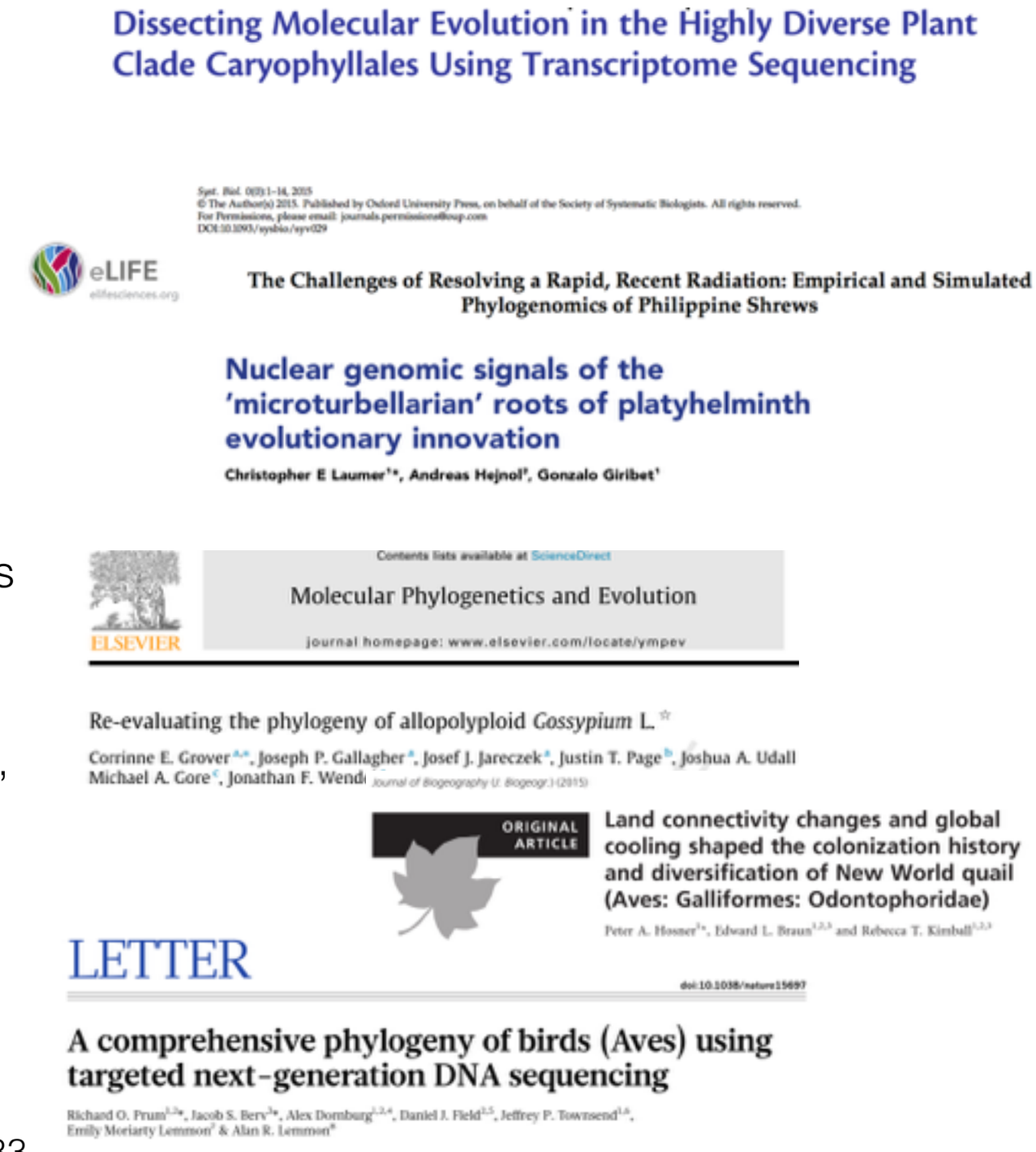
- The ASTRAL tree:
  - High support
  - Similar to concatenation with some interesting differences (e.g., recovered bryophytes)
- ASTRAL took only about 10 minutes (serial running time) on 103 taxa and 400 genes



[Wickett, Mirarab, et al., PNAS, 2014]

ASTRAL on biological datasets

- 1KP: **103** plant species, 400-800 genes
- Yang, et al. **96** Caryophyllales species, 1122 genes
- Dentinger, et al. **39** mushroom species, 208 genes
- Giarla and Esselstyn. **19** Philippine shrew species, 1112 genes
- Laumer, et al. **40** flatworm species, 516 genes
- Grover, et al. **8** cotton species, 52 genes
- Hosner, Braun, and Kimball. **28** quail species, 11 genes
- Simmons and Gatesy. **47** angiosperm species, 310 genes
- Prum et al, **198** avian species, 259 genes



ASTRAL-II on biological datasets (ongoing collaborations)

- 1200 plants with ~ 400 genes (1KP consortium)
- 250 avian species with 2000 genes (with LSU, UF, and Smithsonian)
- 200 avian species with whole genomes (with Genome 10K, international)
- 250 suboscine species (birds) with ~2000 genes (with LSU and Tulane)
- 140 Insects with 1400 genes (with U. Illinois at Urbana-Champaign)
- 50 Hummingbird species with 2000 genes (with U. Copenhagen and Smithsonian)
- 40 raptor species (birds) with 10,000 genes (with U. Copenhagen and Berkeley)
- 38 mammalian species with 10,000 genes (with U. of Bristol, Cambridge, and Nat. Univ. of Ireland)

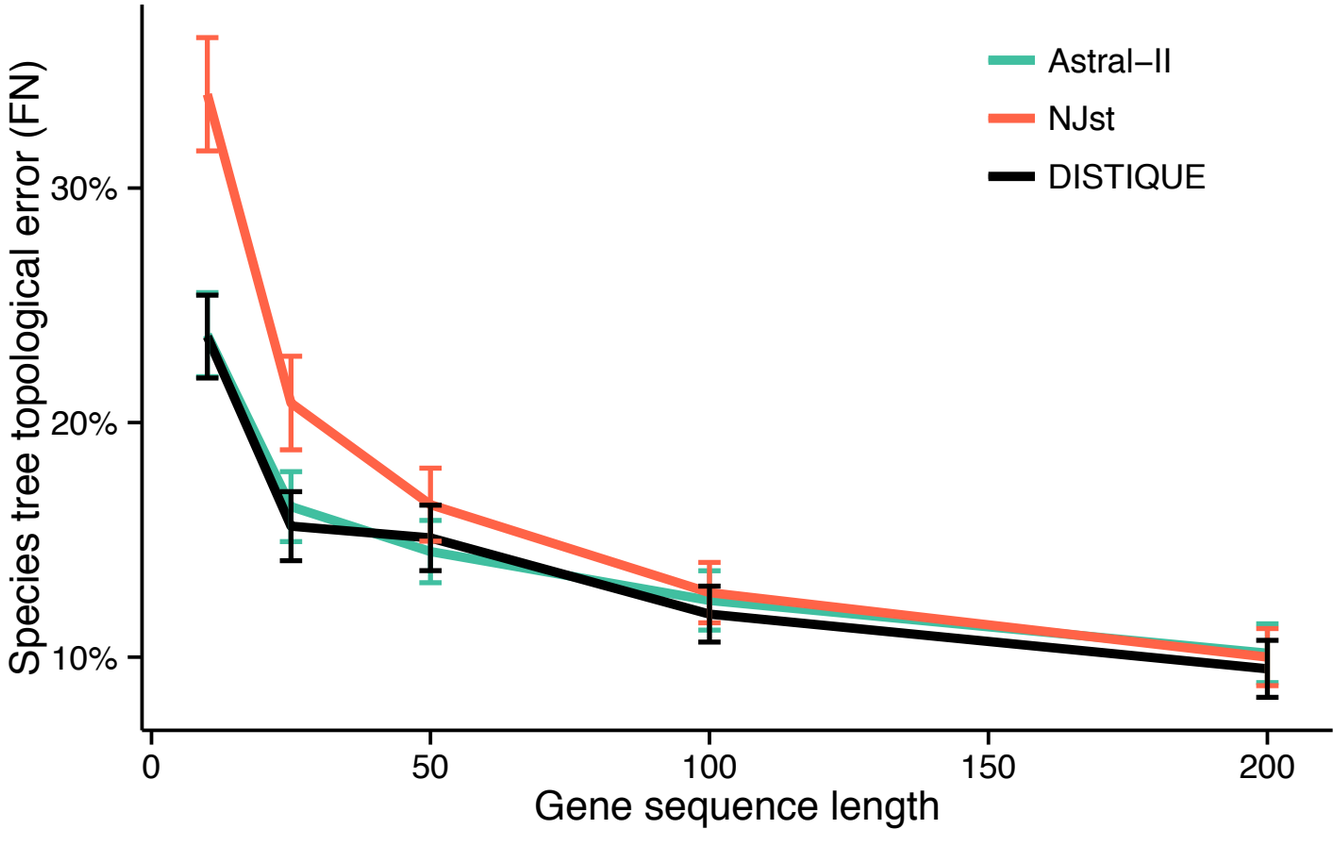
New methods

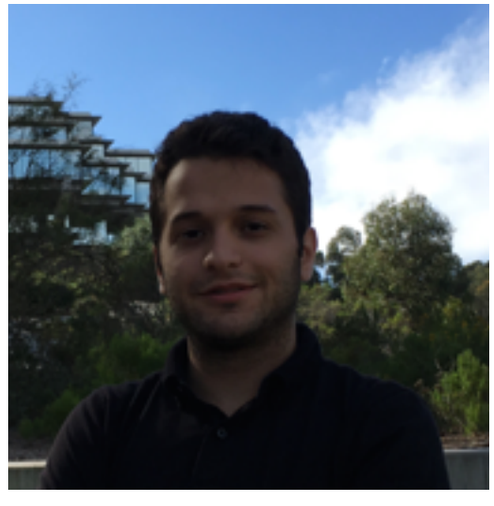
- Statistical Binning — improves estimation of gene tree distribution (input to summary methods)
  [Mirarab et al., Science, 2014] [Bayzid et al., PLoS ONE, 2015]

- ASTRAL — a summary method with improved accuracy and scalability compared to other summary methods
  [Mirarab et al., Bioinformatics, 2014 and 2015]

Ongoing work

DISTIQUE — a family of summary method, some with quadratic running time and interesting theory
[unpublished and unfinished work; with Erfan Sayyari]





Summary

- Genome-scale sequence data provides a wealth of information
- Yet, reconstruction of species phylogenies remains challenging
  - Scalability to many species: ASTRAL
  - Limited data per gene: statistical binning
  - Impact of model violations
  - Recombination
  - Missing data
  - Multiple sources of gene tree discordance
- Many interesting statistical and computational questions and need for method development

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