Tree-of-life reconstruction using ASTRAL: complexity, support, and parallelism

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in collaboration with

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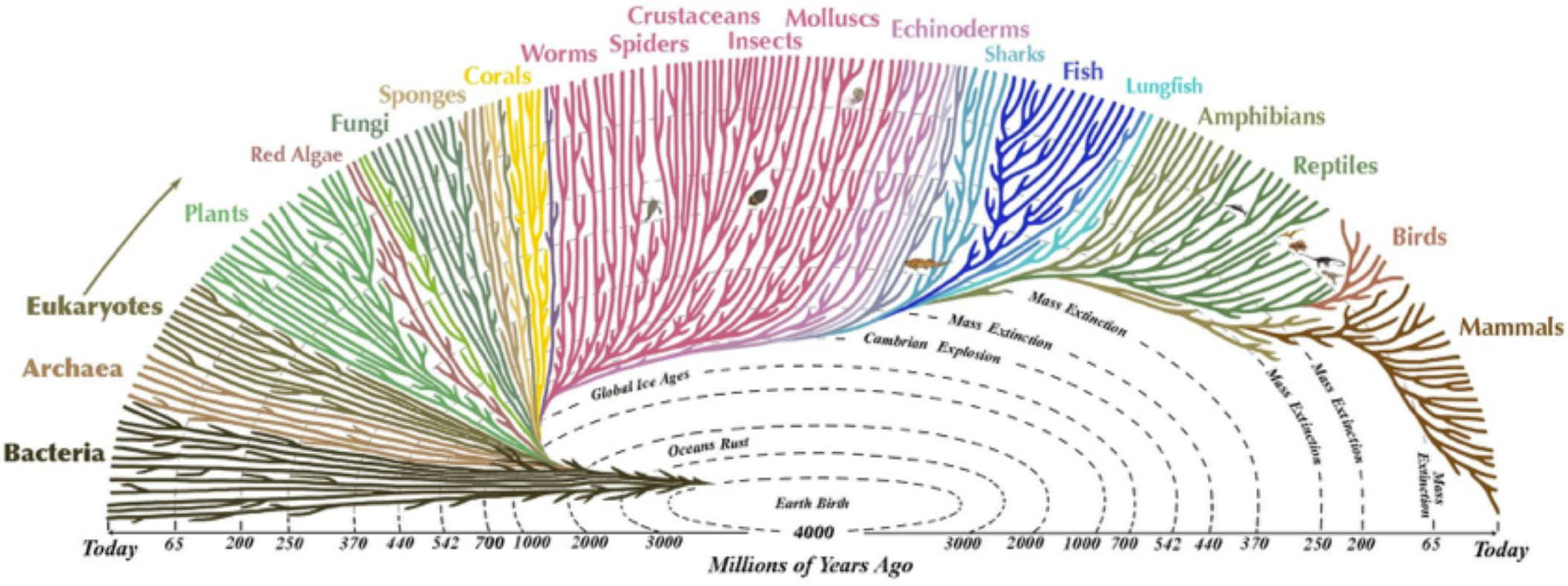
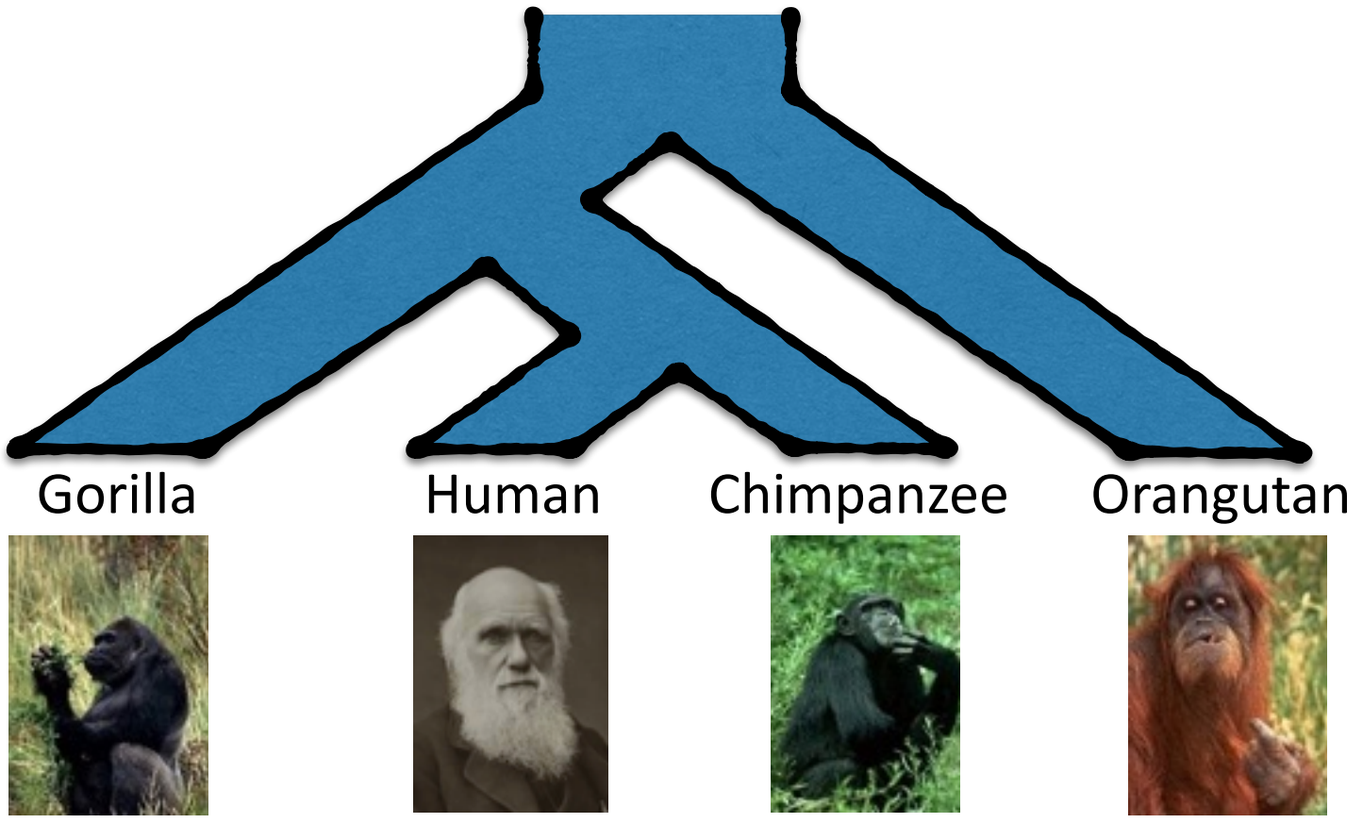


source: http://www.evogeneao.com/

Phylogeny

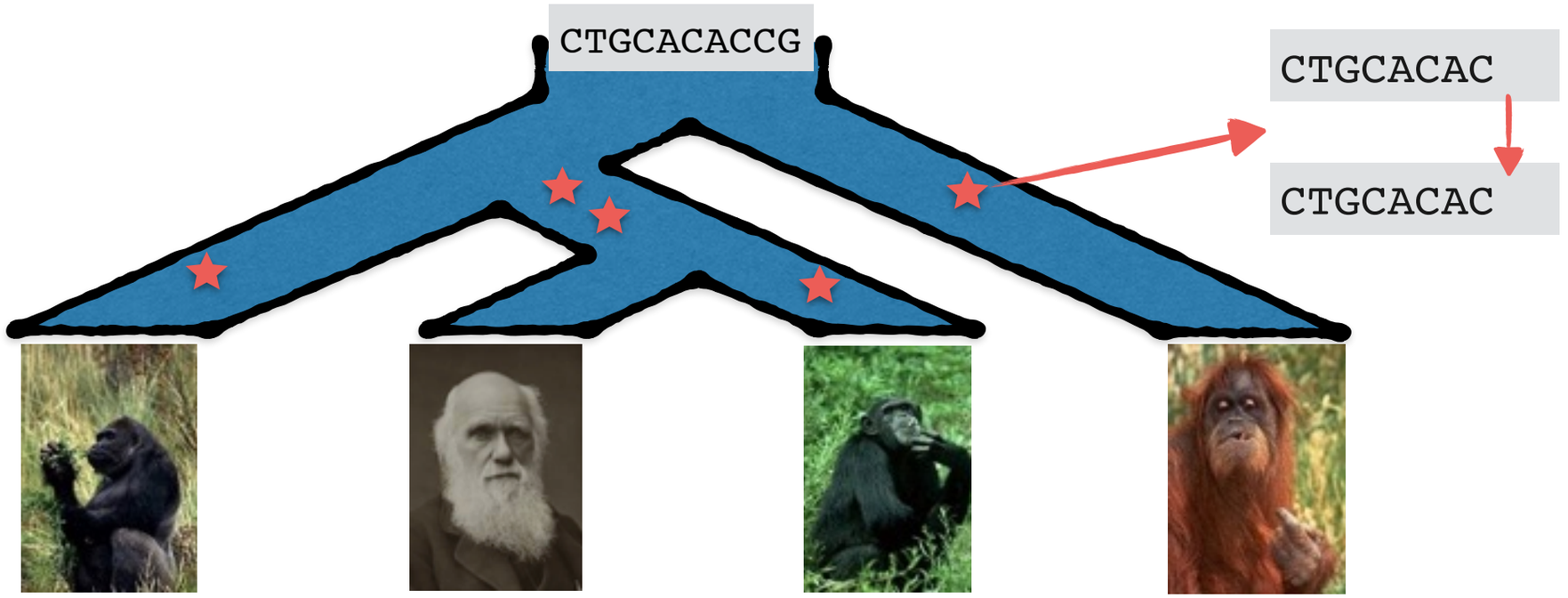
Leaves are Species (a.k.a. **taxa**)



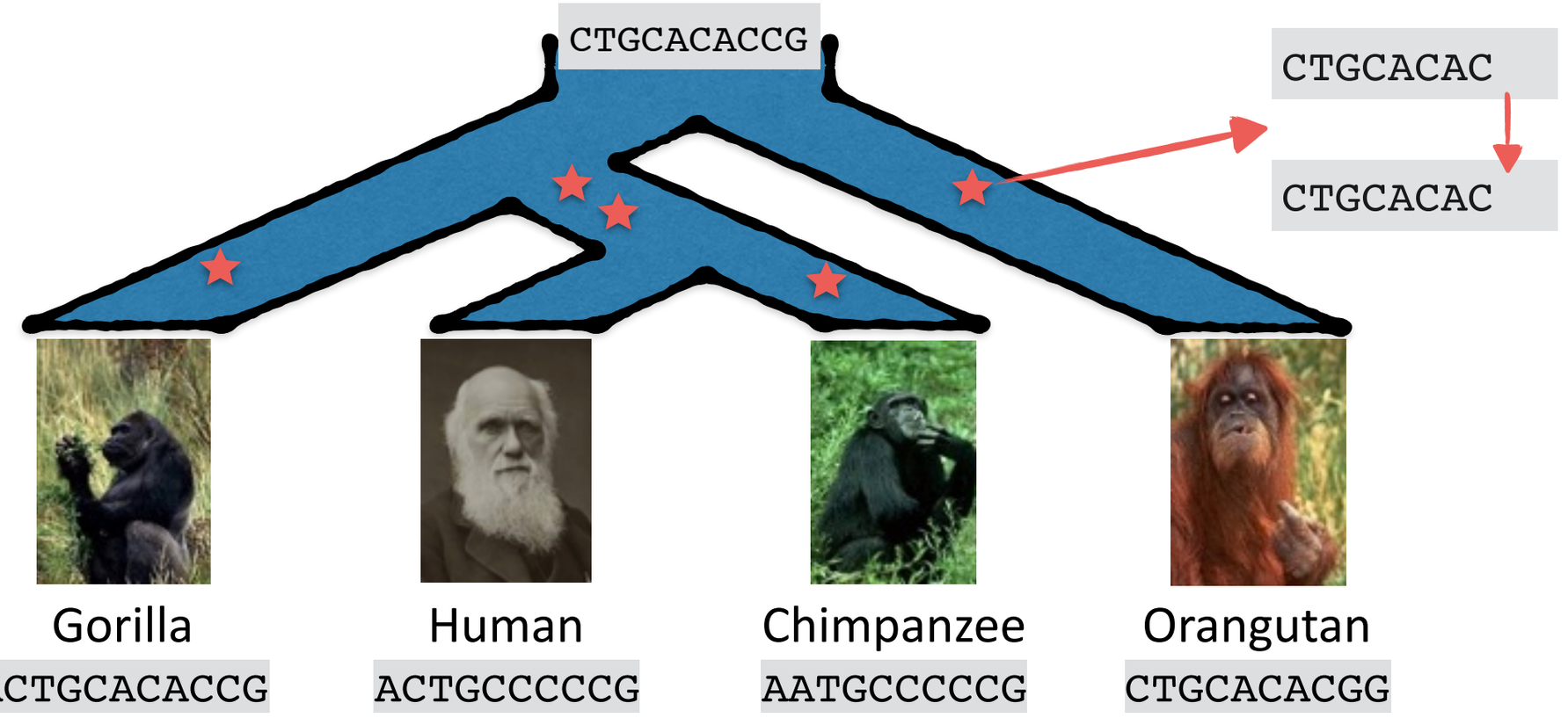
Tree topology: The branching structure, showing evolutionary relationships

Branch length and width: can be related to time between speciation events and the size of the populations, but we will draw them arbitrarily

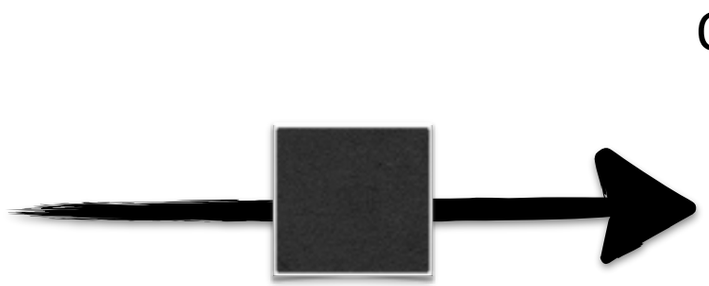
Statistical inference of phylogenies

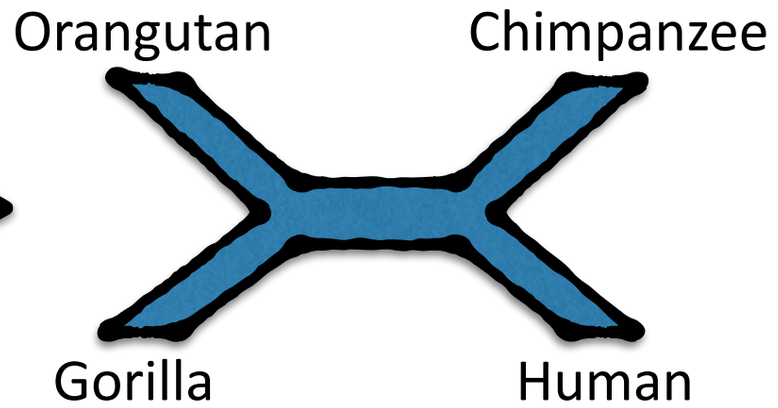


Statistical inference of phylogenies



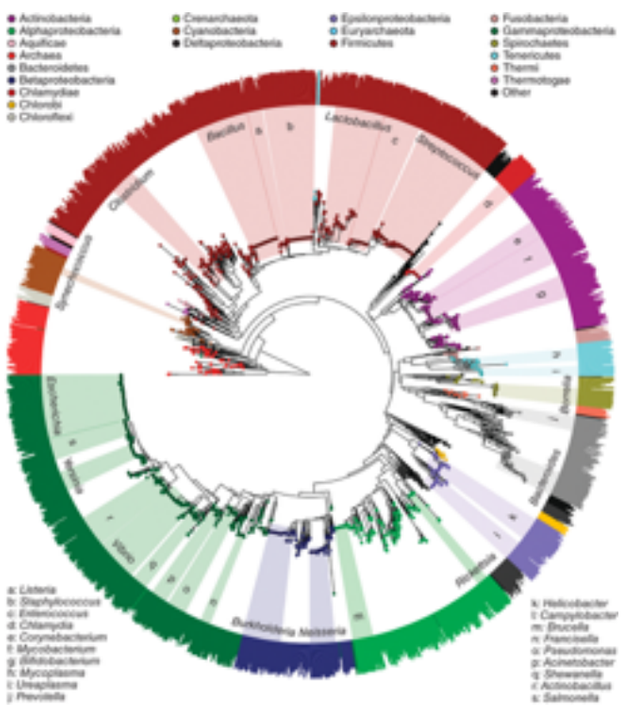
Gorilla ACTGCACACCG
Human ACTGC-CCCCG
Chimpanzee AATGC-CCCCG
Orangutan -CTGCACACGG





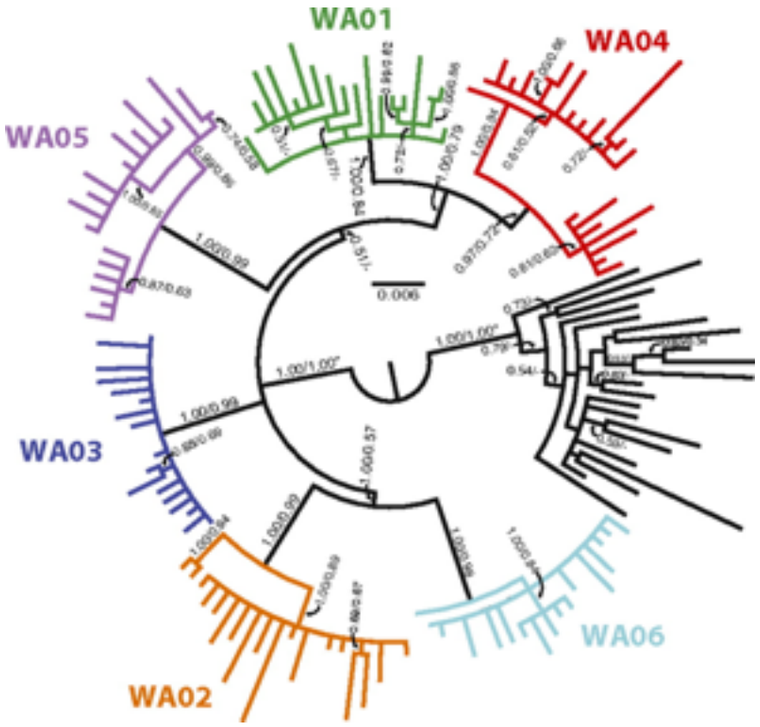
D $P(D|T)$ T

Applications



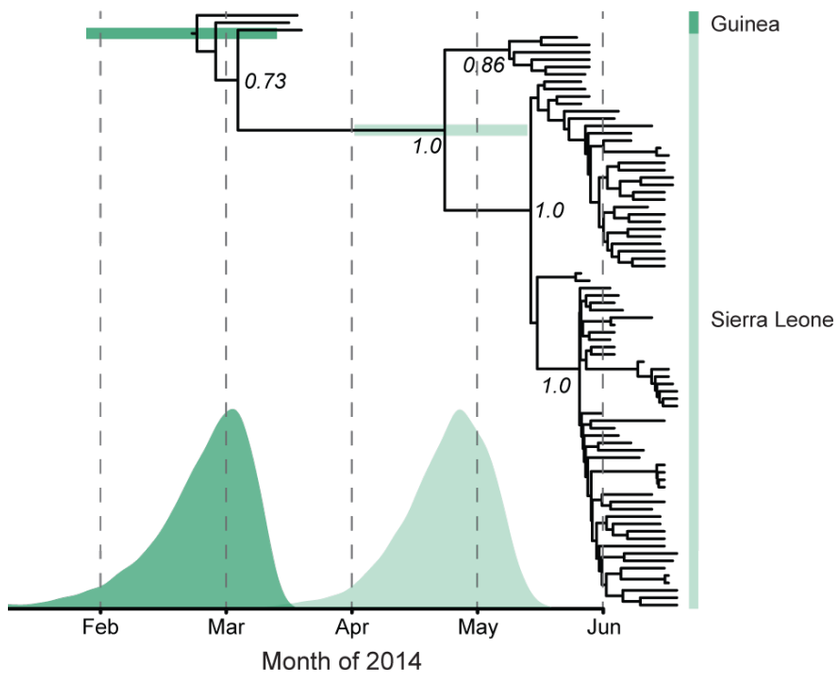
source: Langille et al., Nature, 2013

Microbiome



source: Scaduto et al., PNAS, 2010

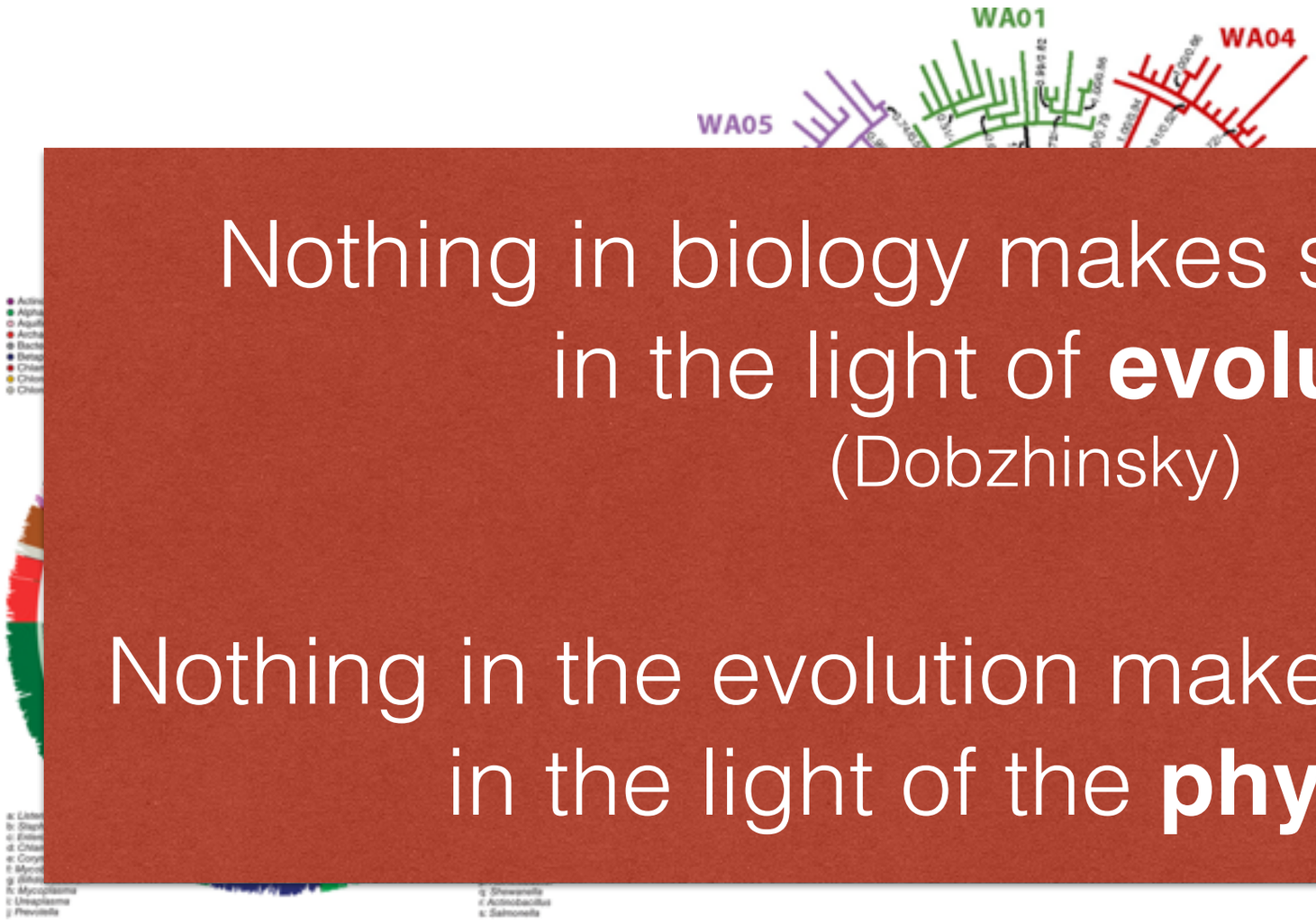
HIV forensic



source: Gire et al., Science, 2014

Ebola

Applications



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Microbiome

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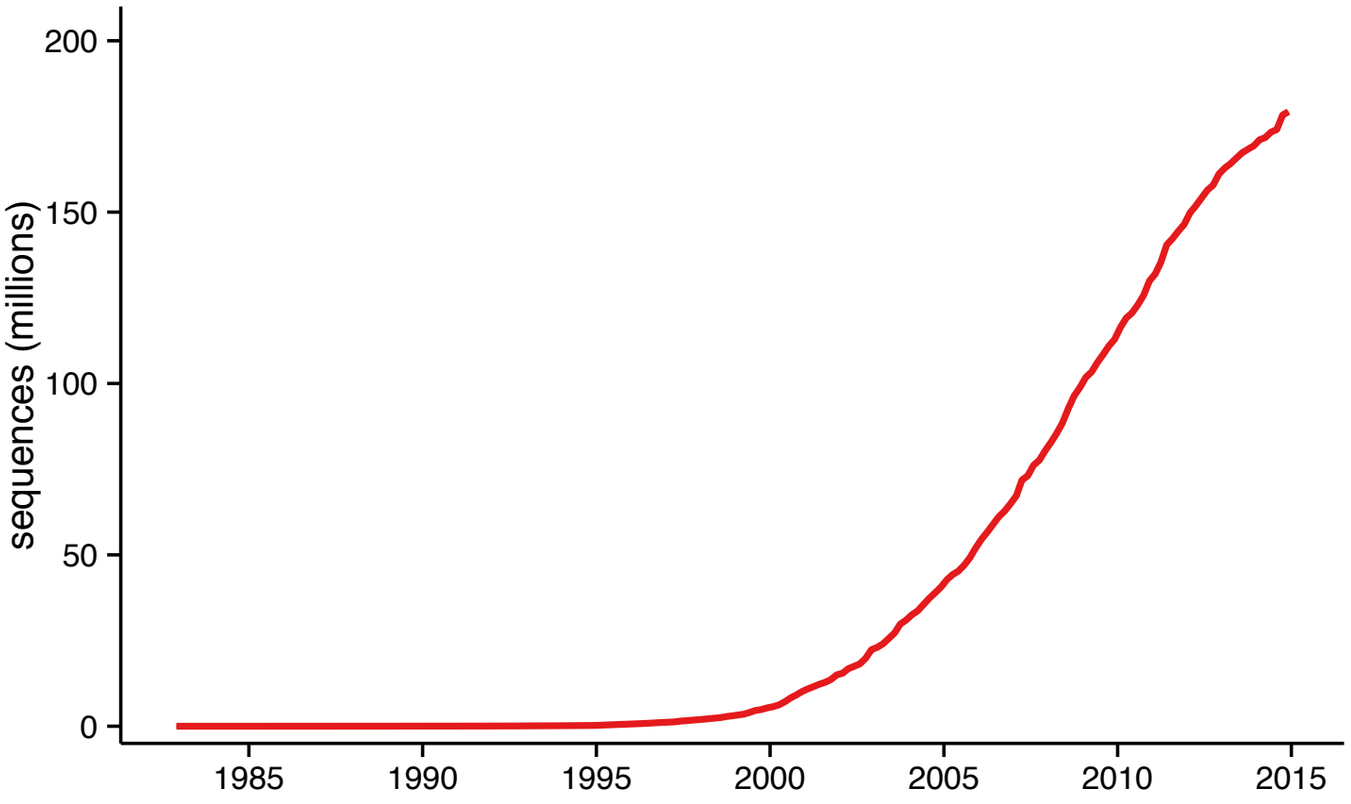
Ebola

Nothing in biology makes sense except in the light of **evolution**
(Dobzhinsky)

Nothing in the evolution makes sense except in the light of the **phylogeny**

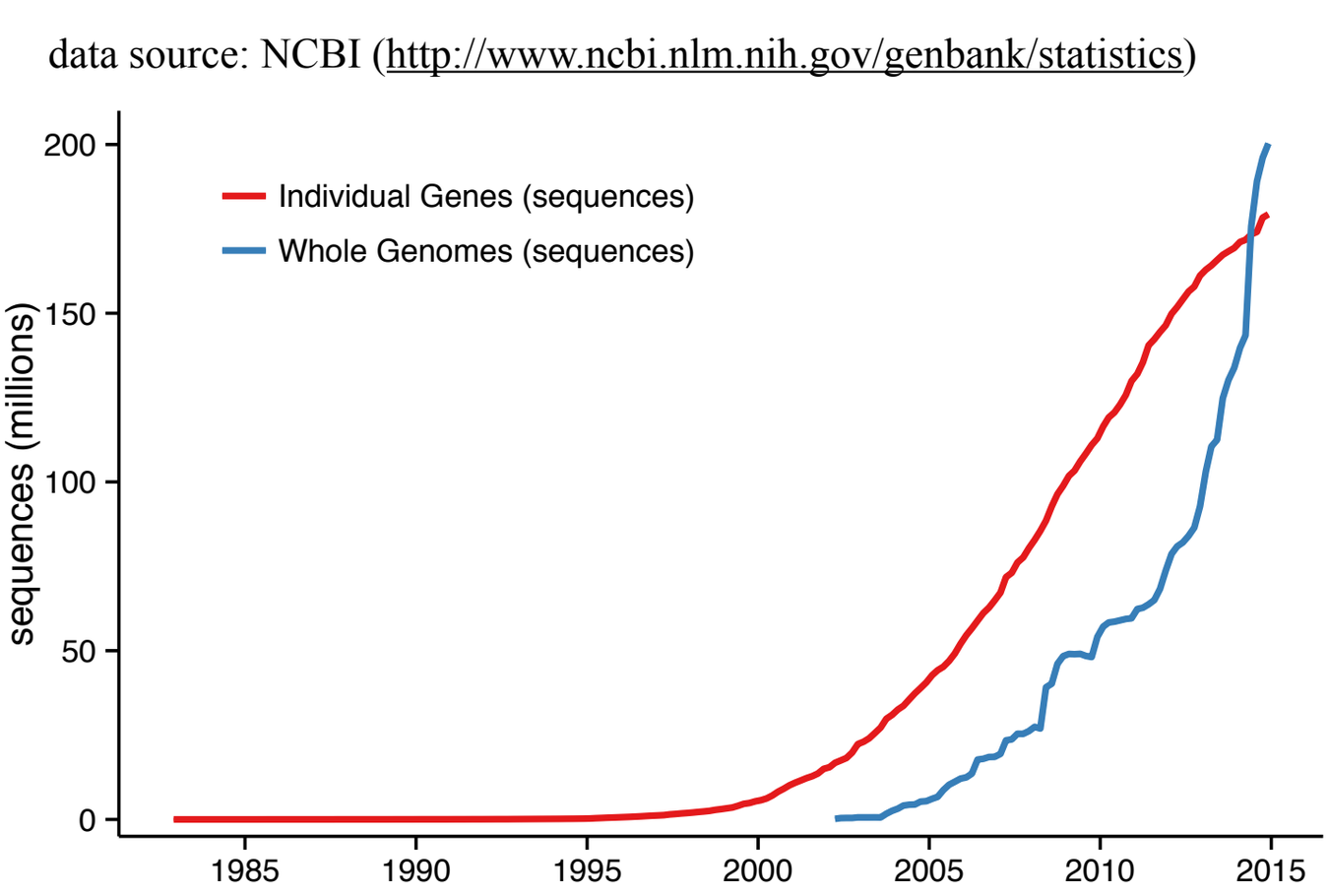
Sequence data growth

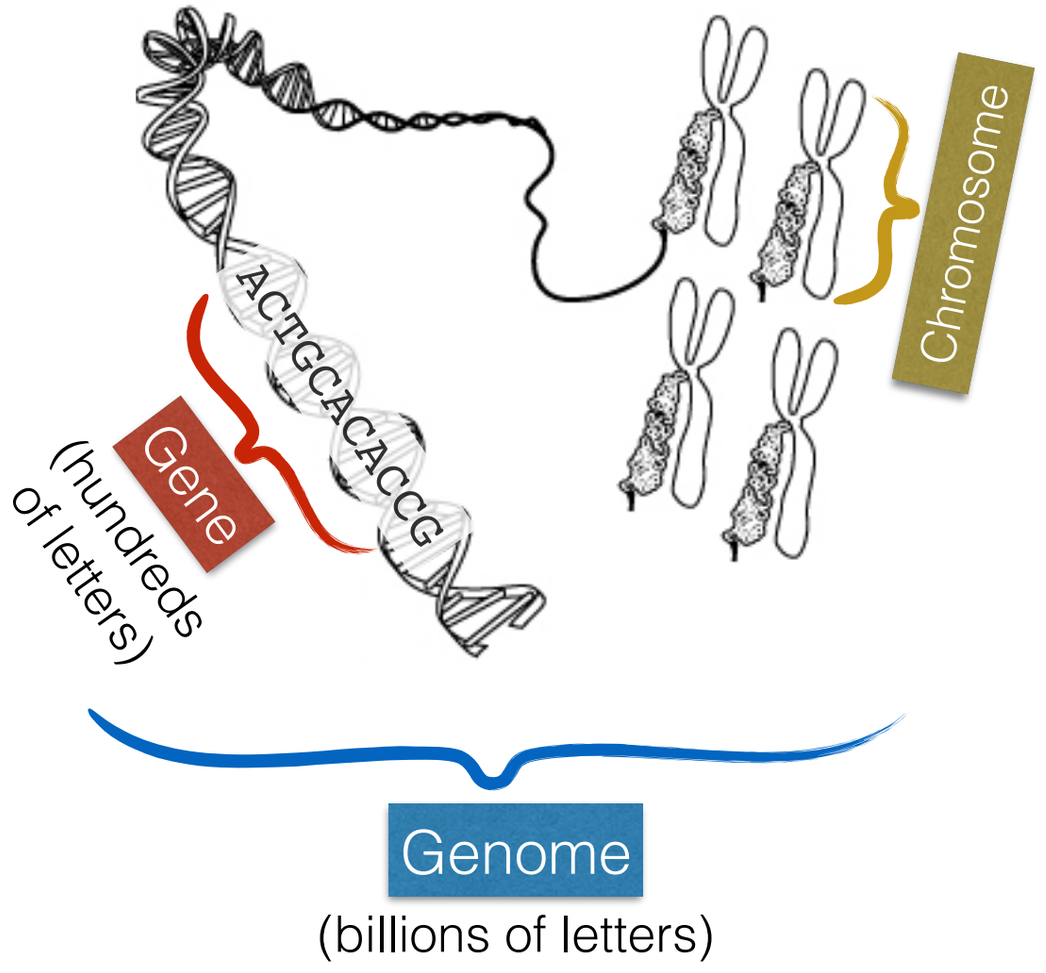
data source: NCBI (http://www.ncbi.nlm.nih.gov/genbank/statistics)



- Rapid growth in the number of sequences

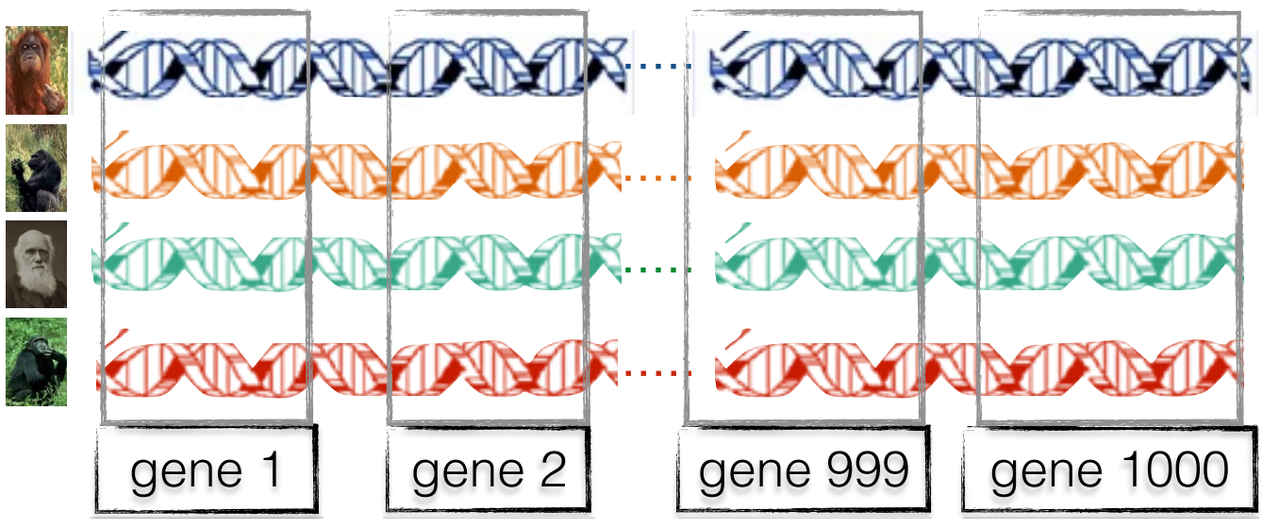
Sequence data growth



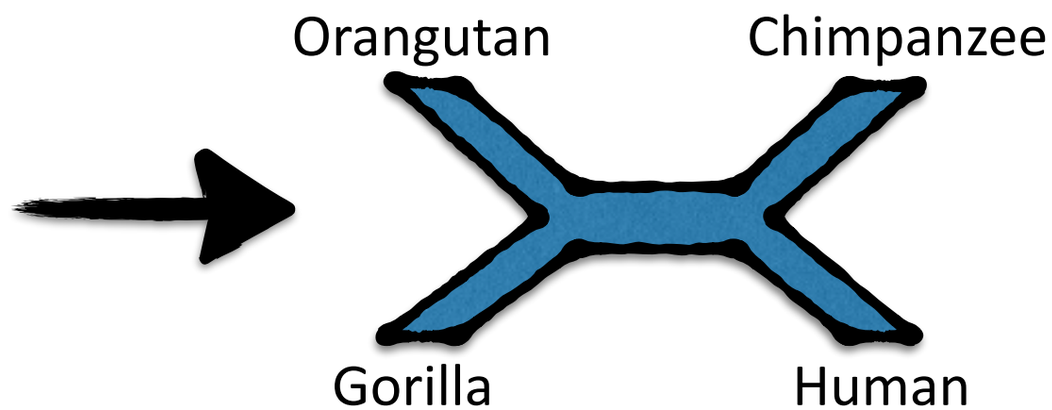


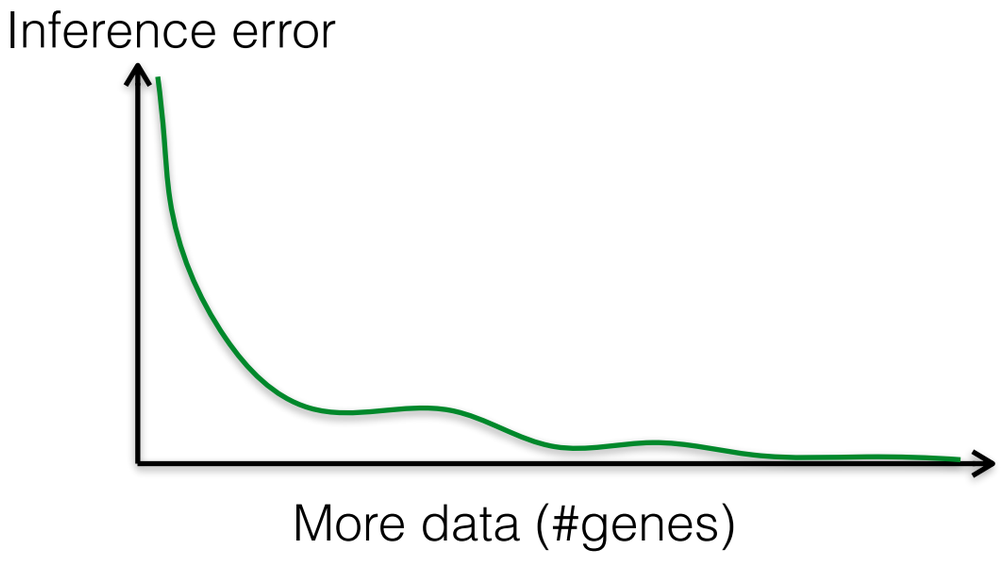
- Rapid growth in the number of sequences
- Our focus has shifted to “whole genomes”

Phylogenomics

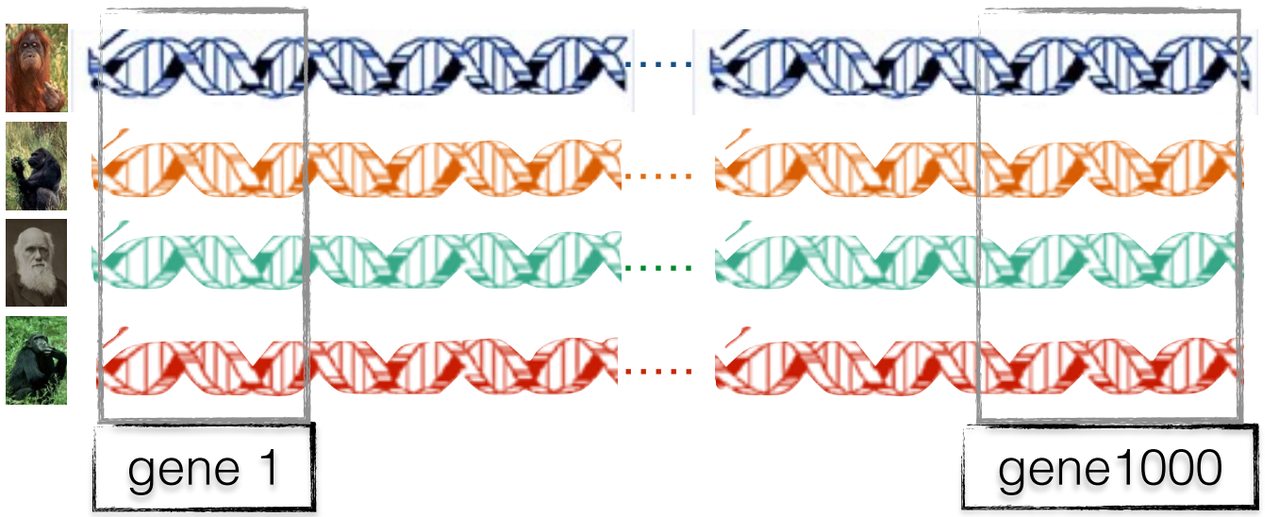


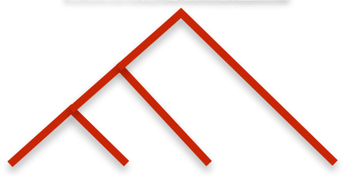

```
ACTGCACACCG   CTGAGCATCG     AGCAGCATCGTG  CAGGCACGCACGAA
ACTGC-CCCCG   CTGAGC-TCG ... AGCAGC-TCGTG  AGC-CACGC-CATA
AATGC-CCCCG   ATGAGC-TC-     AGCAGC-TC-TG  ATGGCACGC-C-TA
-CTGCACACGG   CTGA-CAC-G     C-TA-CACGGTG  AGCTAC-CACGGAT
```

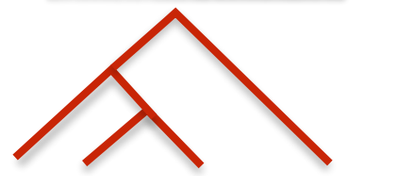




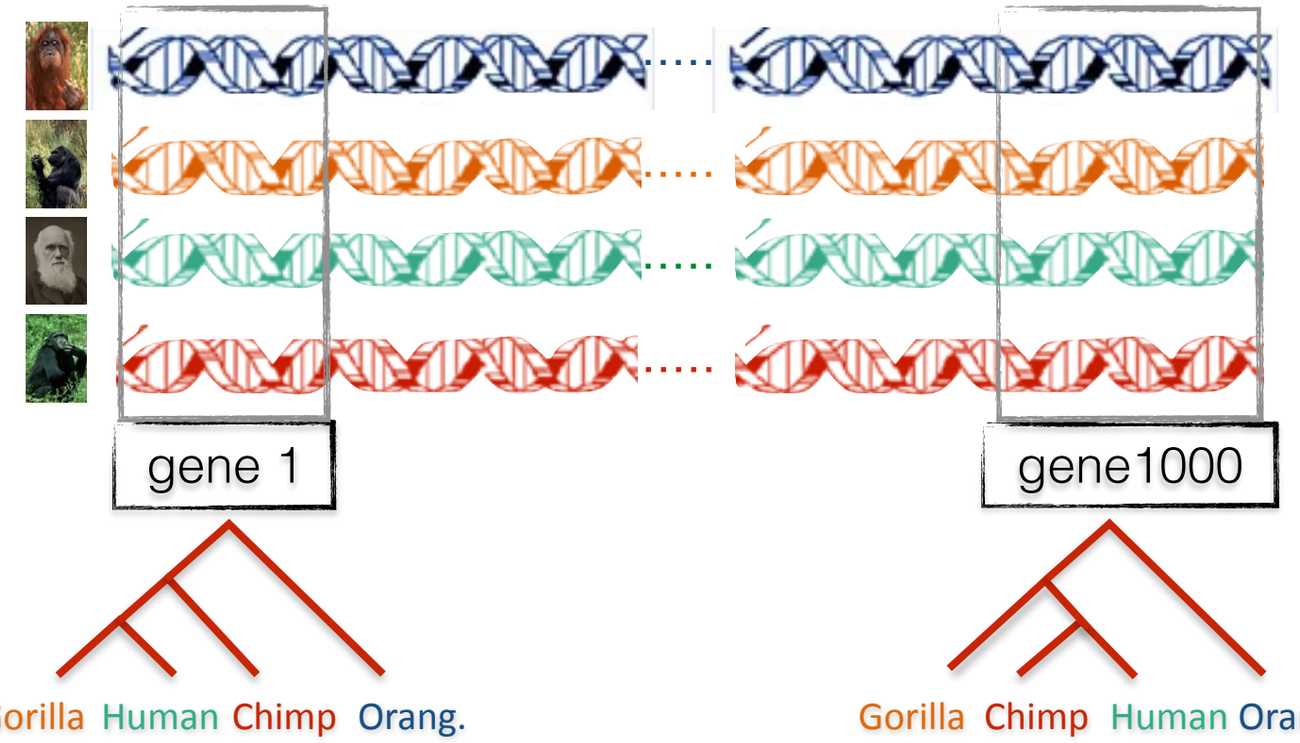
Gene tree discordance

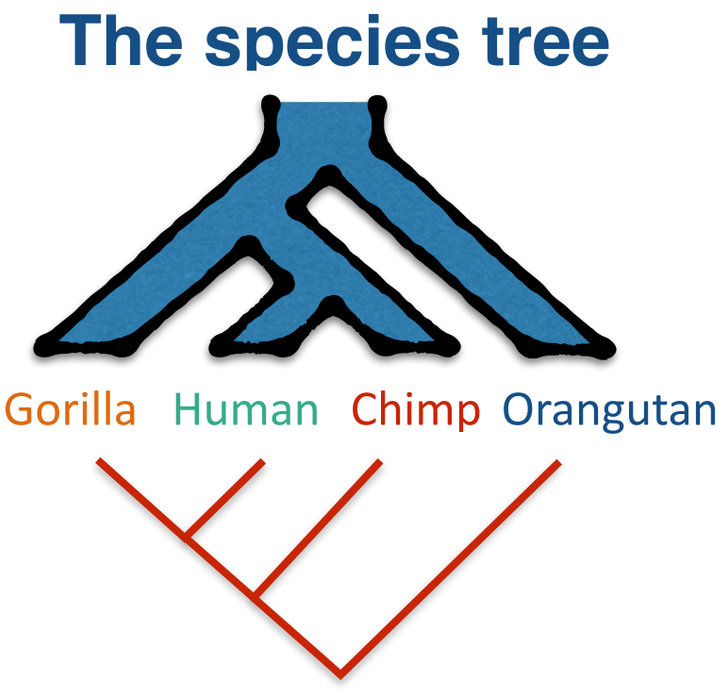






Gene tree discordance





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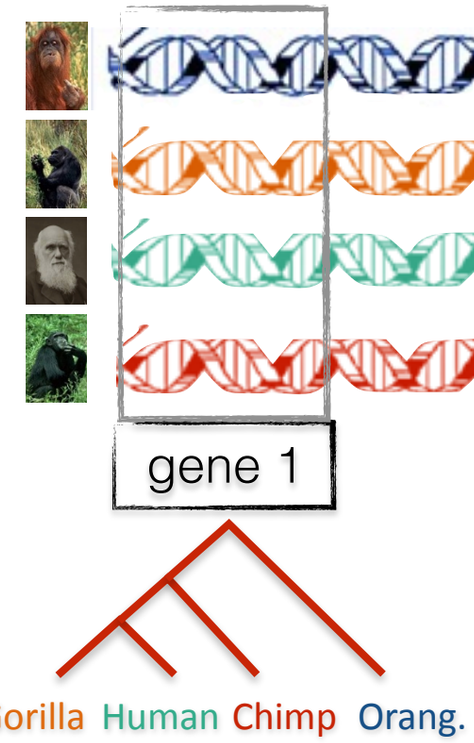
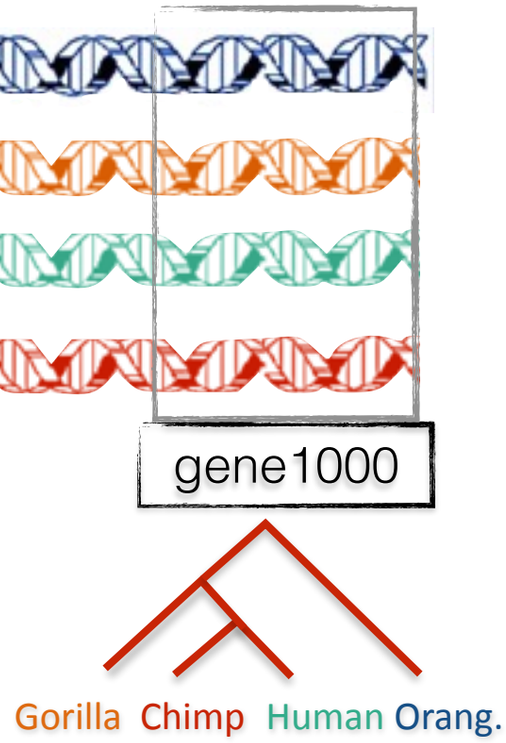
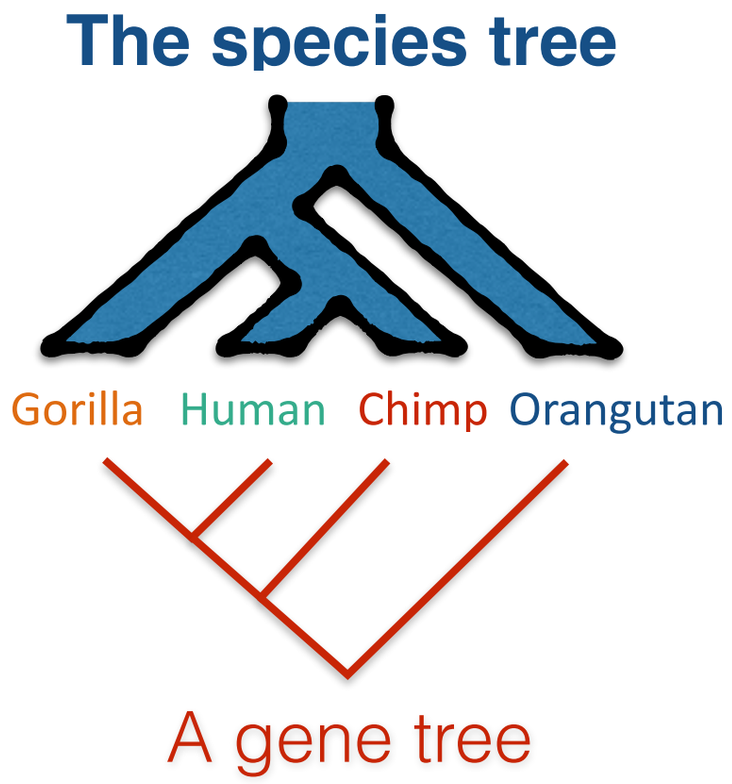




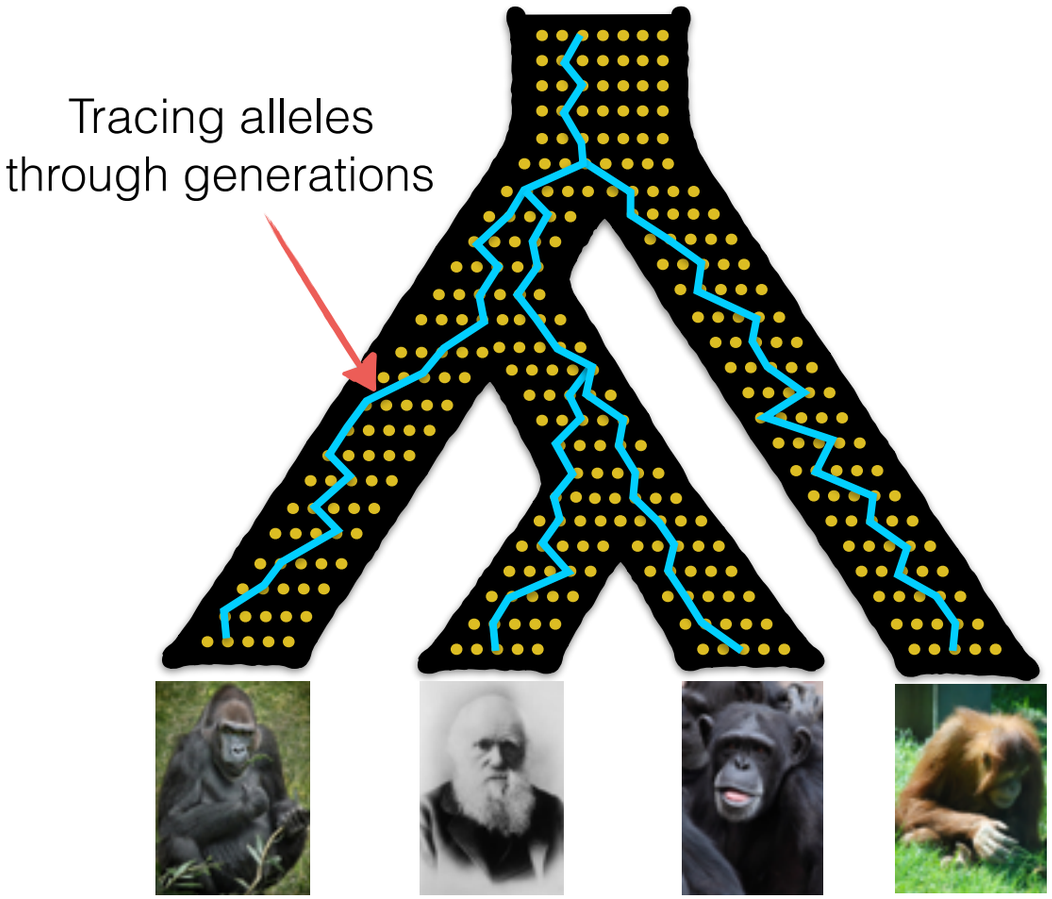


Causes of gene tree discordance include:

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

Incomplete Lineage Sorting (ILS)

- A random process related to the coalescence of alleles across various populations



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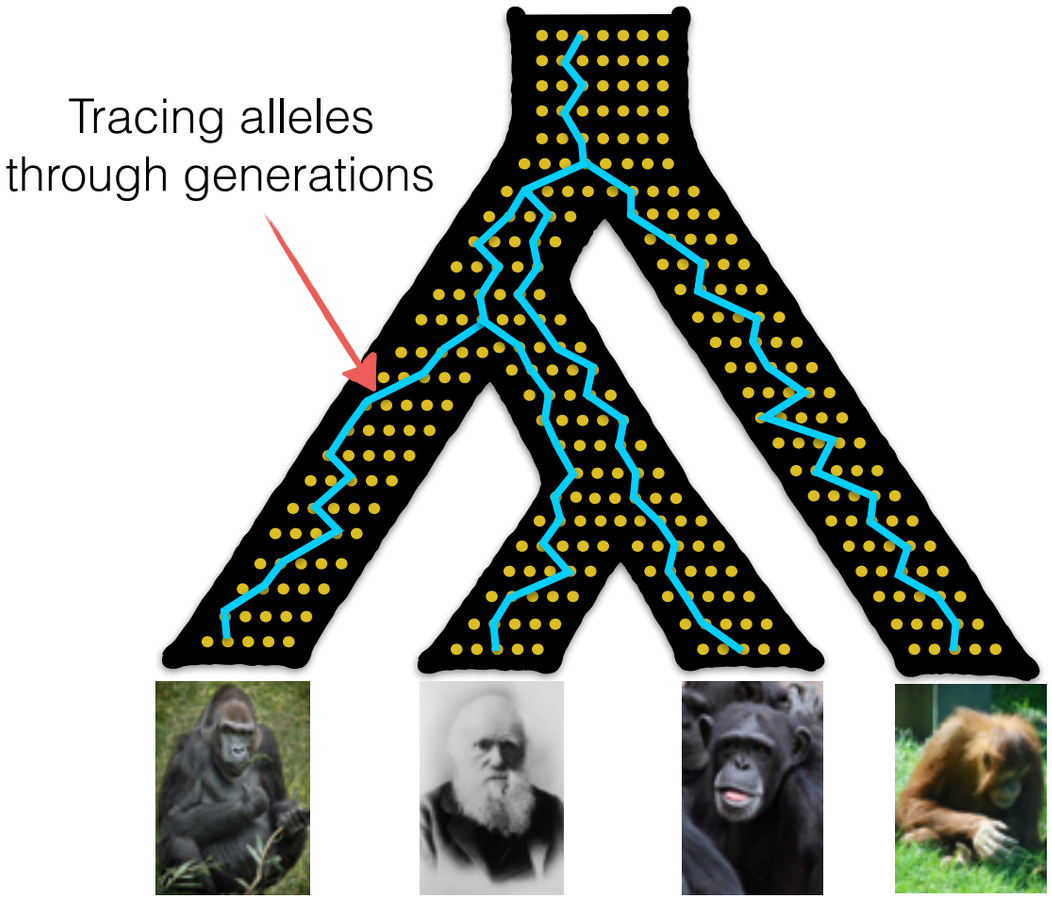
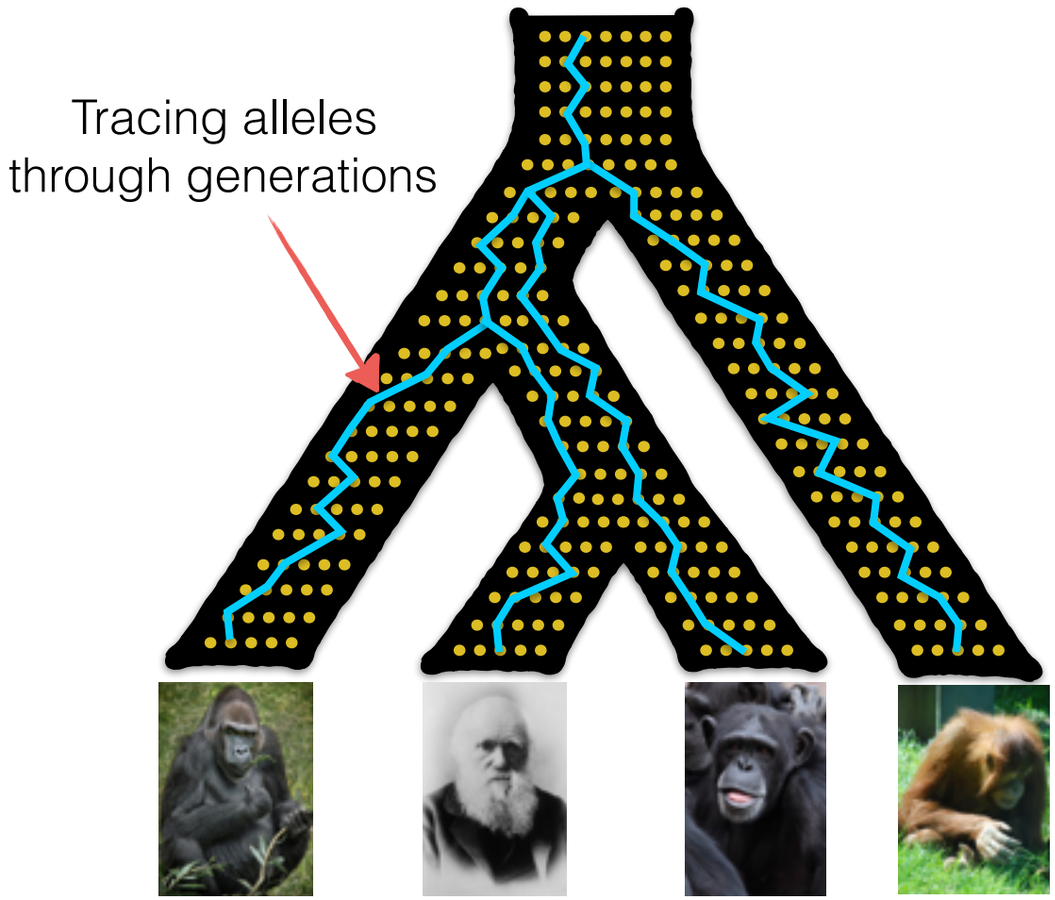


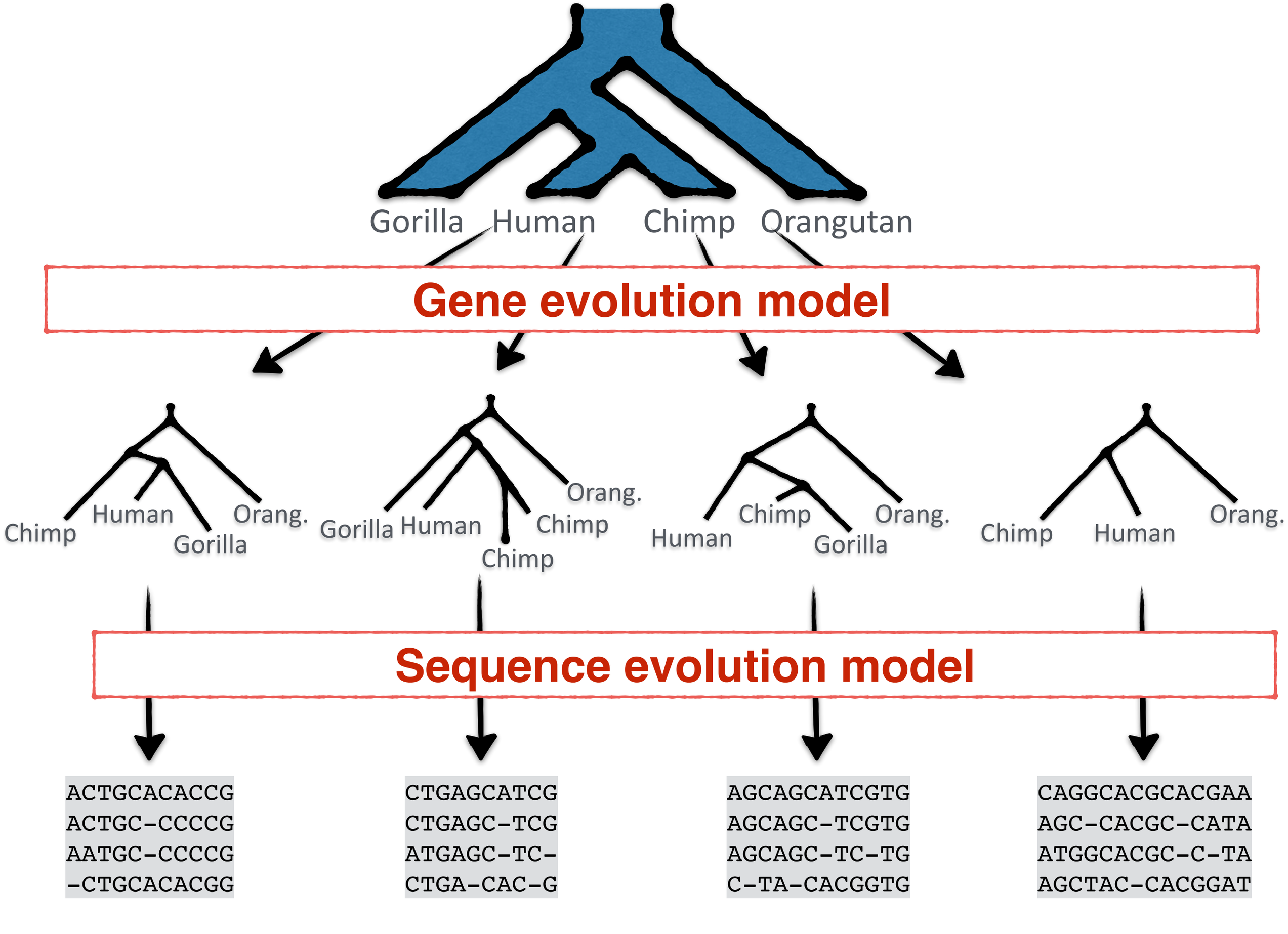
Incomplete Lineage Sorting (ILS)

- A random process related to the coalescence of alleles across various populations

- Omnipresent: possible for every tree

    - Likely for short branches or large population sizes




Gorilla
Human
Chimp
Orangutan
Gene evolution model
Chimp
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Orang.
Gorilla
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AGCAGC-TC-TG
C-TA-CACGGTG
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MSC and Identifiability

- A statistical model called multi-species coalescent (MSC) can generate ILS.

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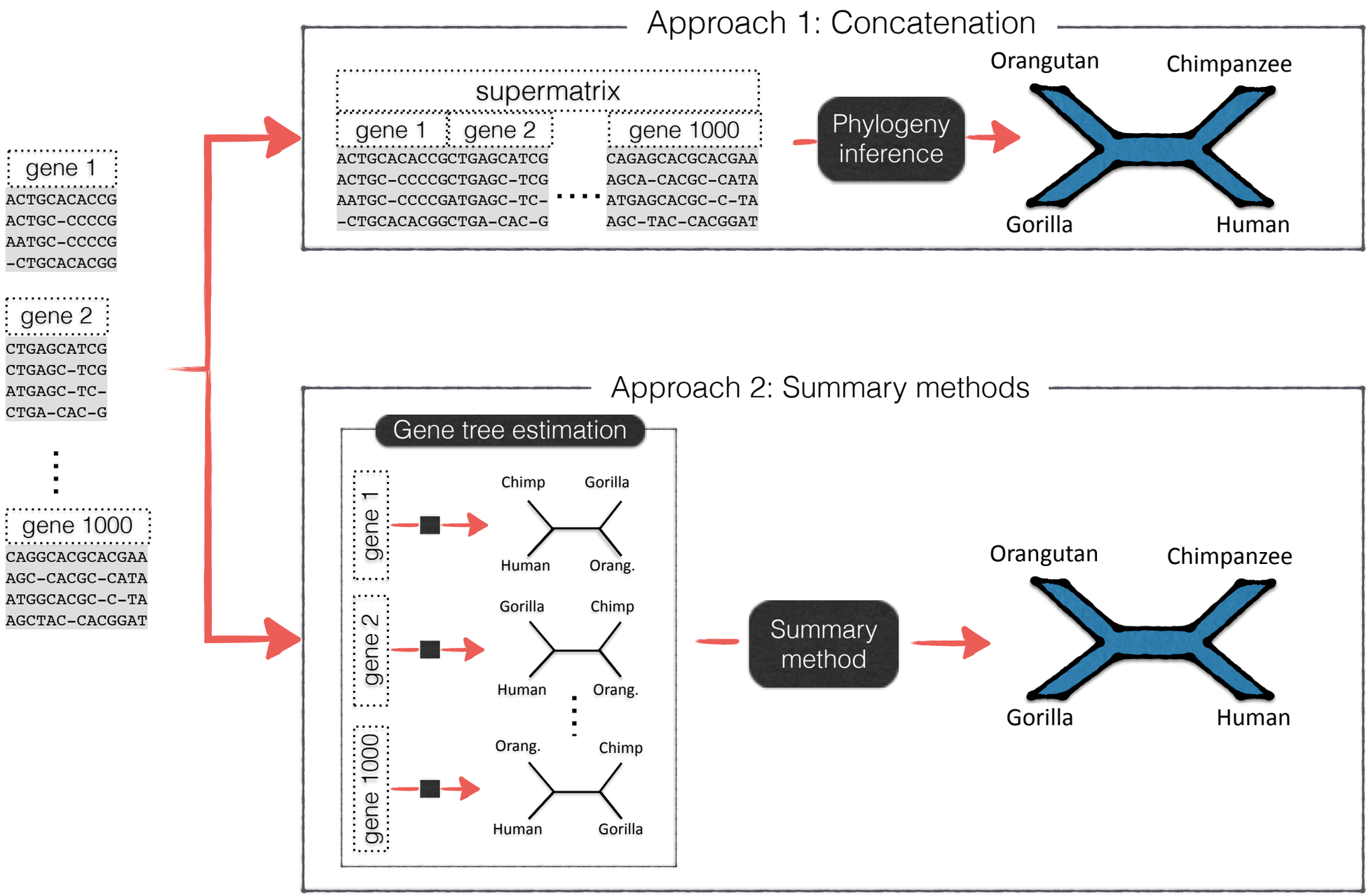
- A statistical model called multi-species coalescent (MSC) can generate ILS.

- Any species tree defines a unique distribution on the set of all possible gene trees

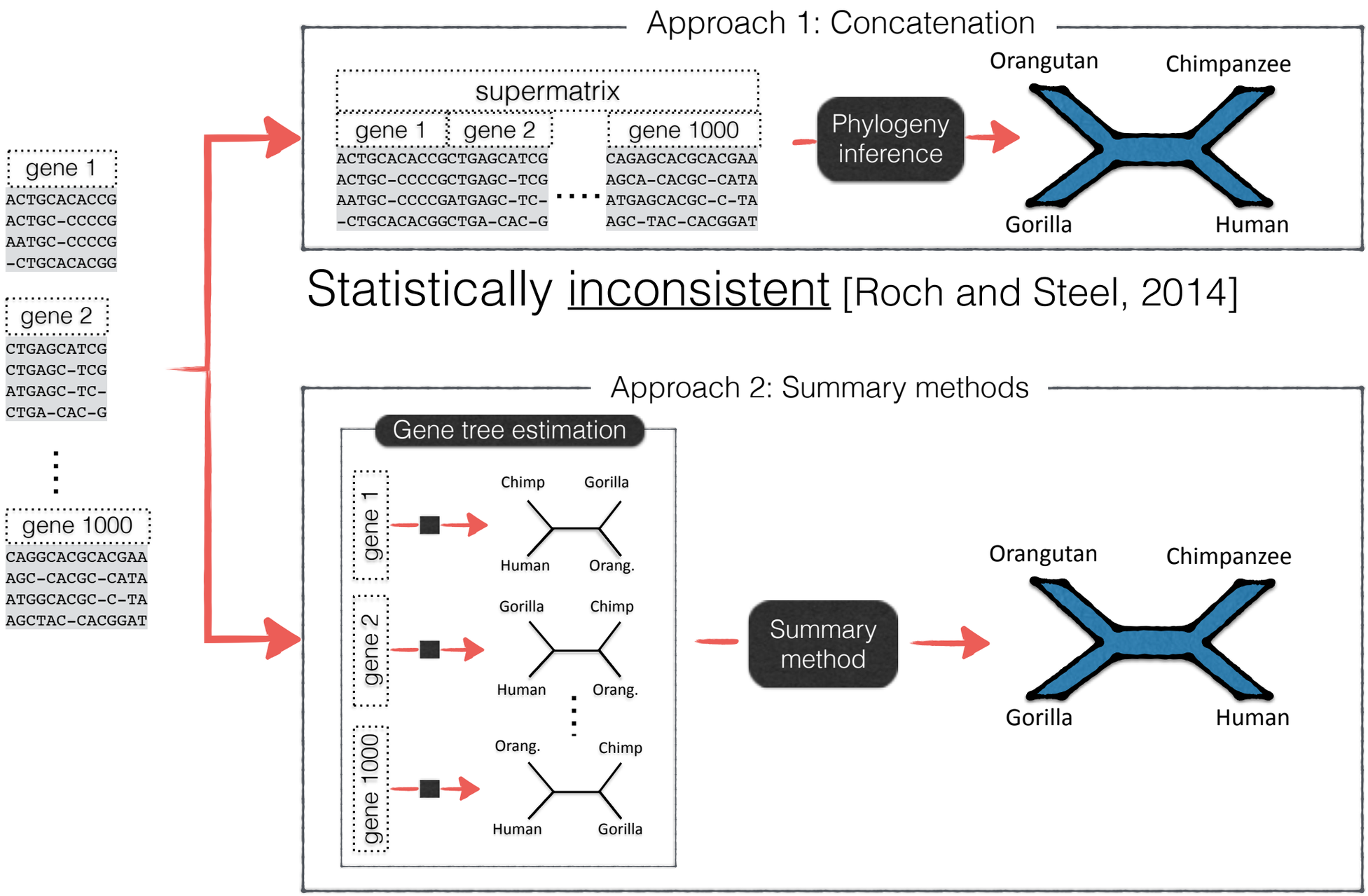
- In principle, the species tree can be identified despite high discordance from the gene tree distribution

Multi-gene tree estimation pipelines



There are also other approaches:
co-estimation (e.g., *BEAST), site-based (SVDQuartets)

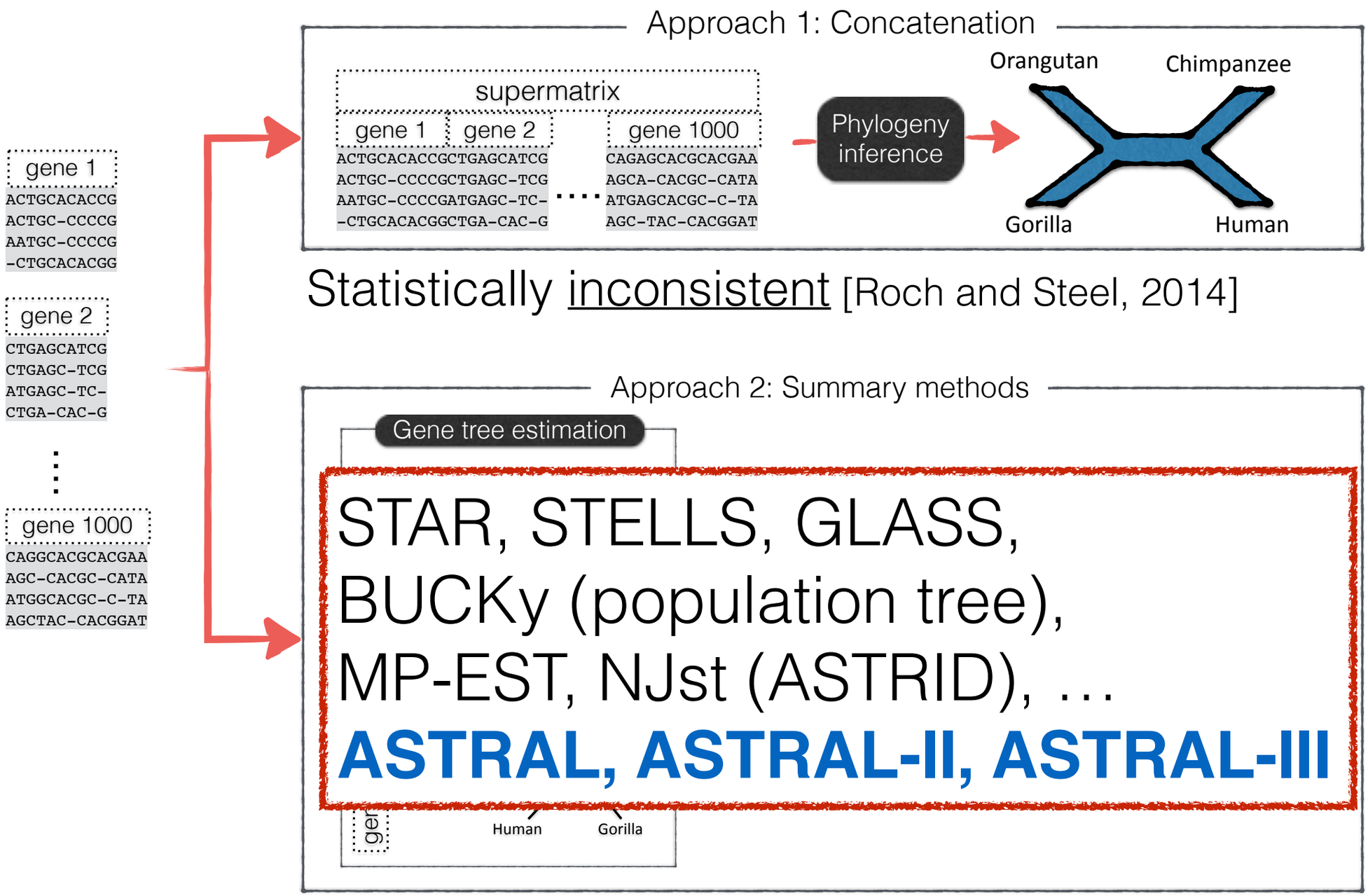
Multi-gene tree estimation pipelines



Statistically <u>inconsistent</u> [Roch and Steel, 2014]

Can be statistically consistent given <u>true gene trees</u>

Multi-gene tree estimation pipelines



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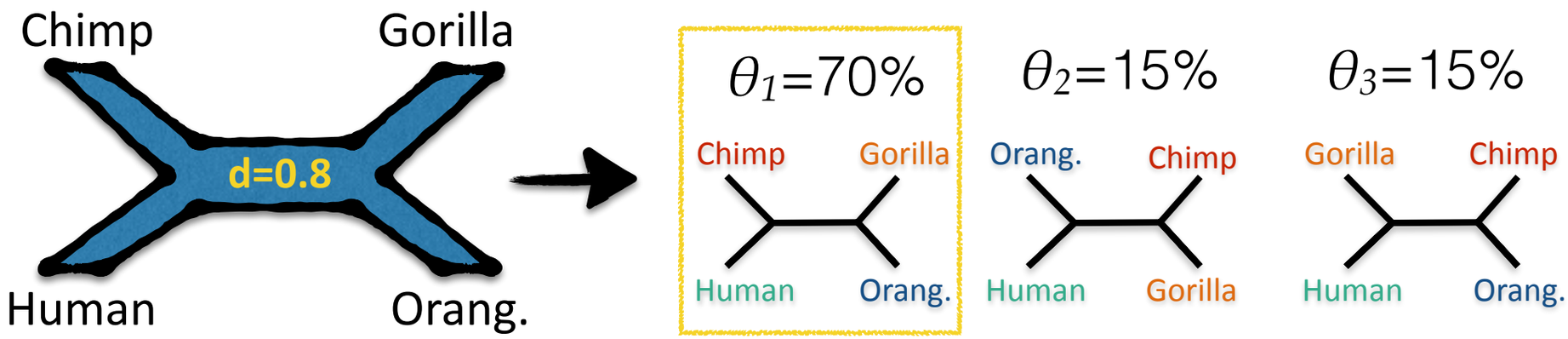
This talk: ASTRAL

- Optimization problem
- Dynamic programming solution
- Accuracy in simulation studies
    - With strong model violations
- Sample complexity
- Time complexity
- Handling of non-standard input

Unrooted quartets under MSC model

For a quartet (4 species), the unrooted species tree topology has at least 1/3 probability in gene trees (Allman, et al. 2010)



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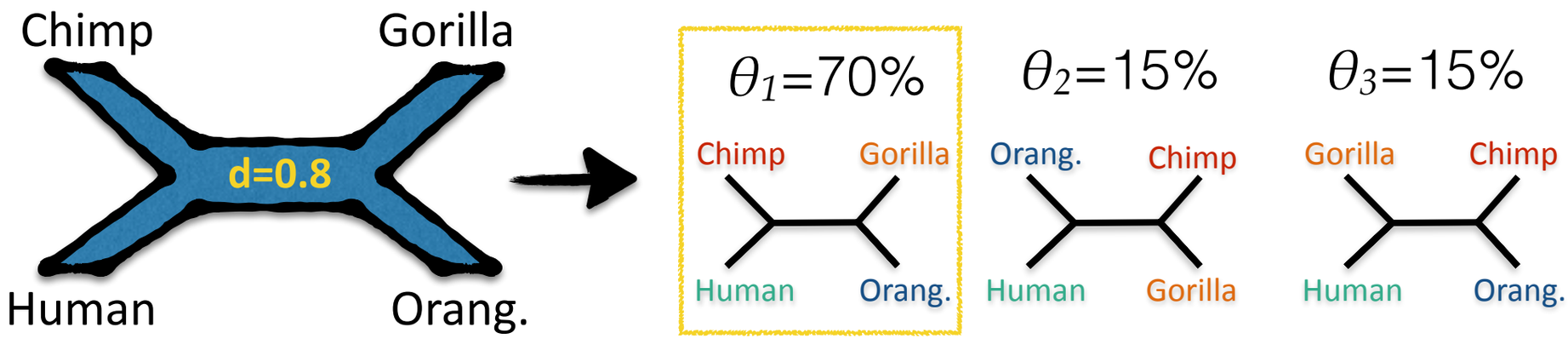

The most frequent gene tree
=
The most likely species tree

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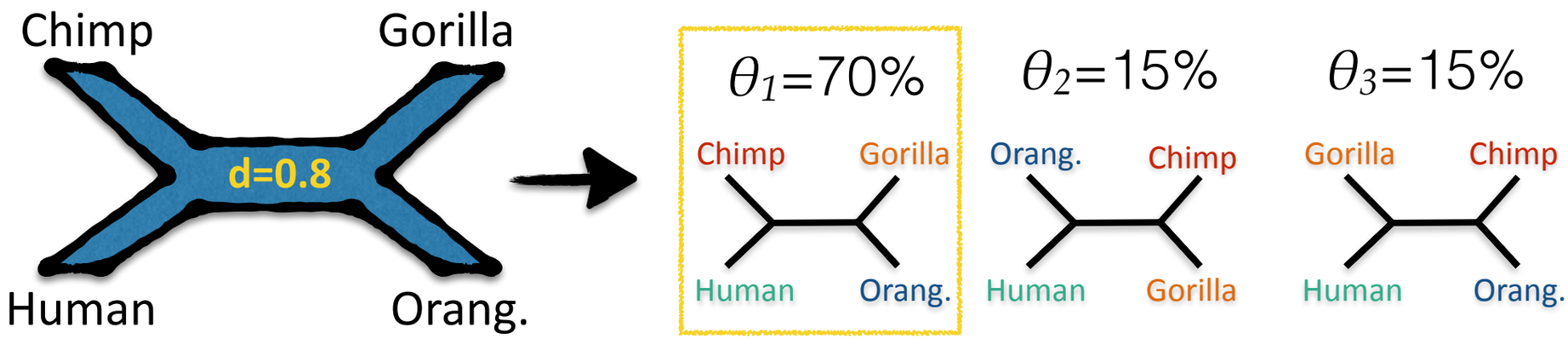

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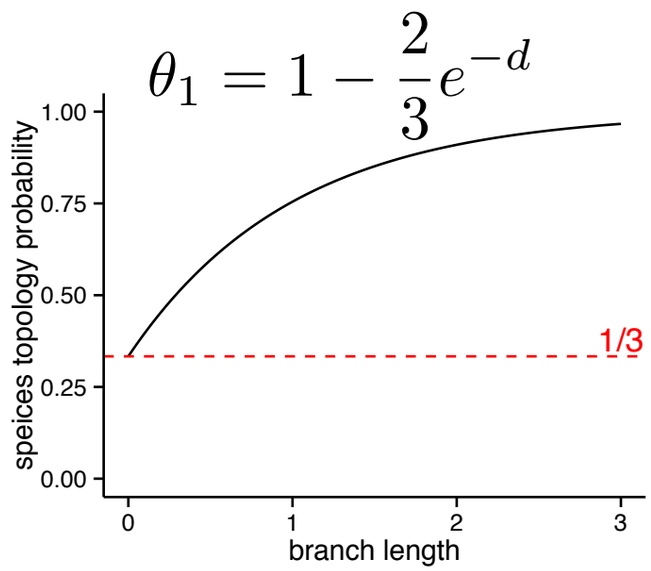

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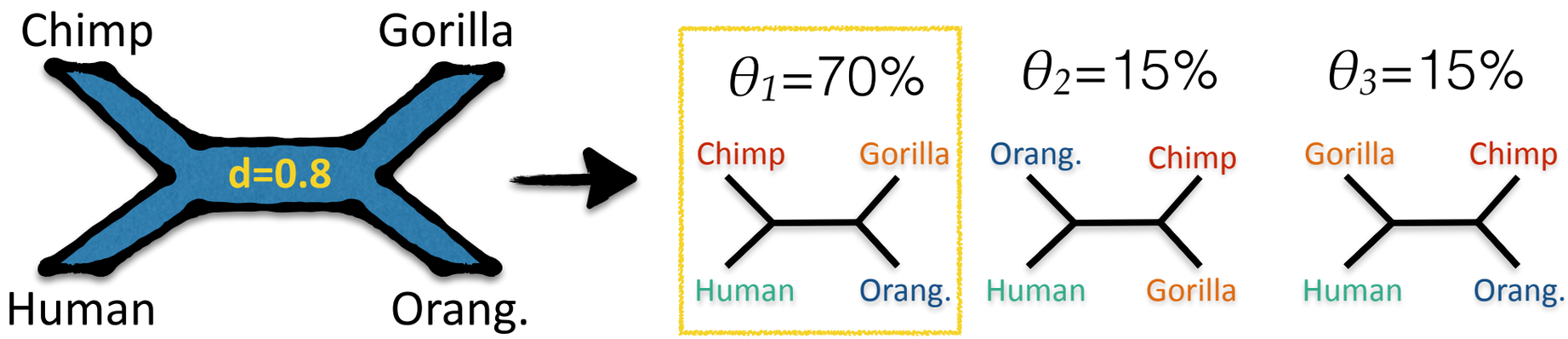

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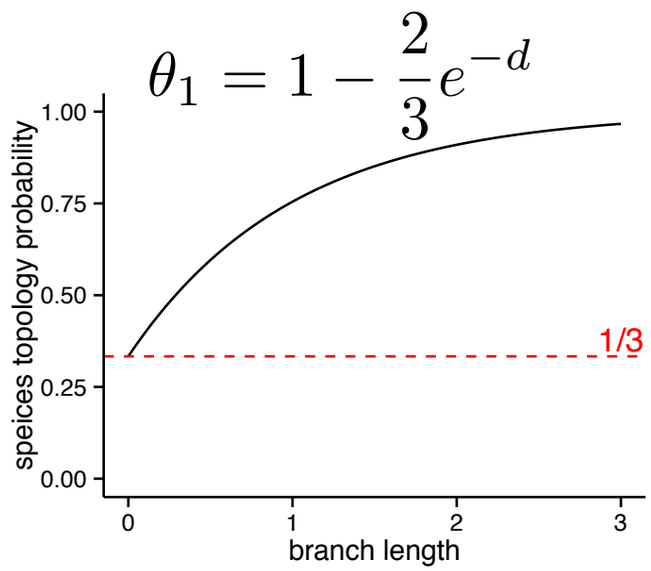


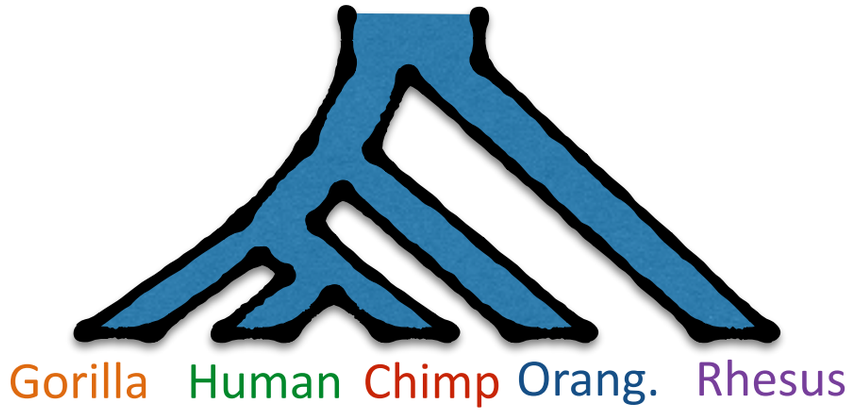
shorter branches ⇒

more discordance ⇒

a harder species tree reconstruction problem

More than 4 species

For >4 species, the species tree topology can be different from the most like gene tree (called anomaly zone) (Degnan, 2013)



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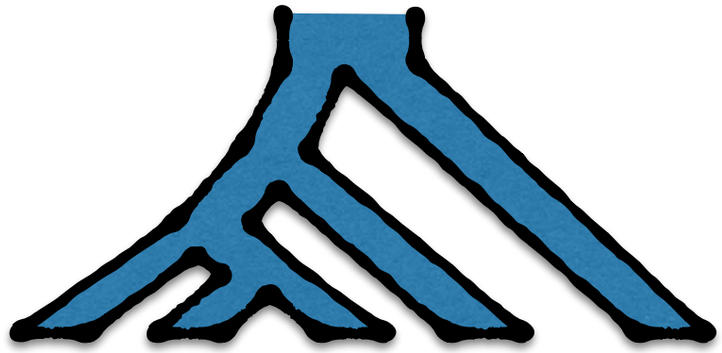
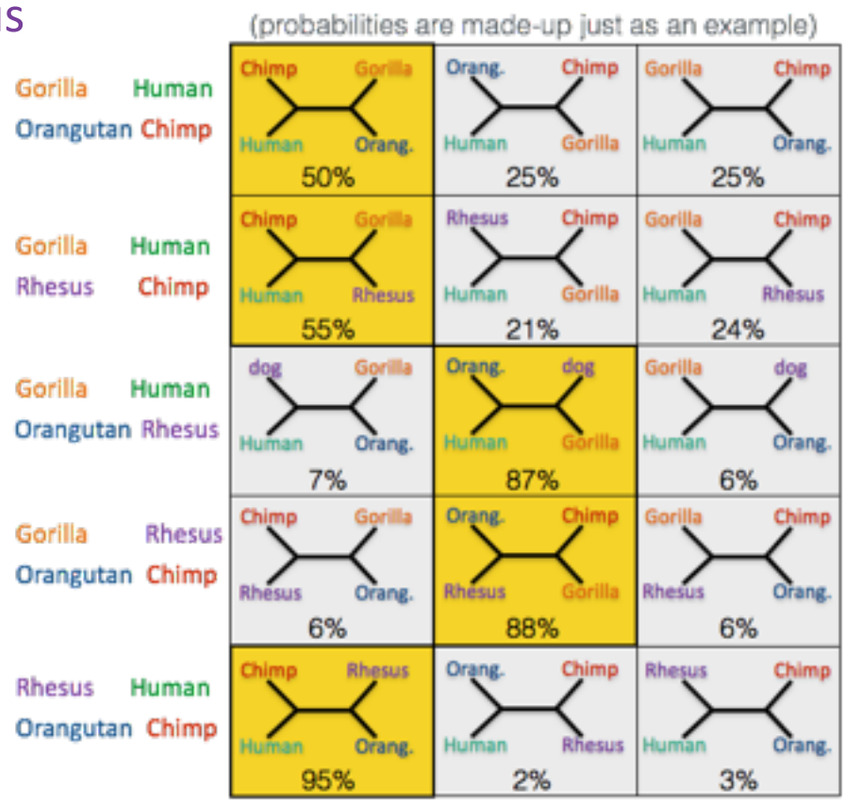


1. Break gene trees into $\binom{n}{4}$ quartets of species
2. Find the dominant tree for all quartets of taxa
3. Combine quartet trees

   Some tools (e.g.. BUCKy-p [Larget, et al., 2010])



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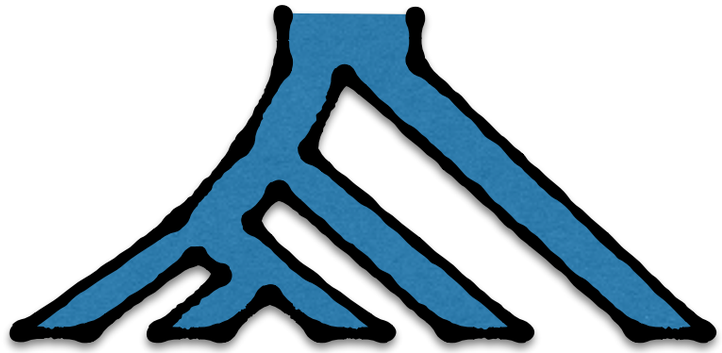


Gorilla Human Chimp Orang. Rhesus

1

2

3

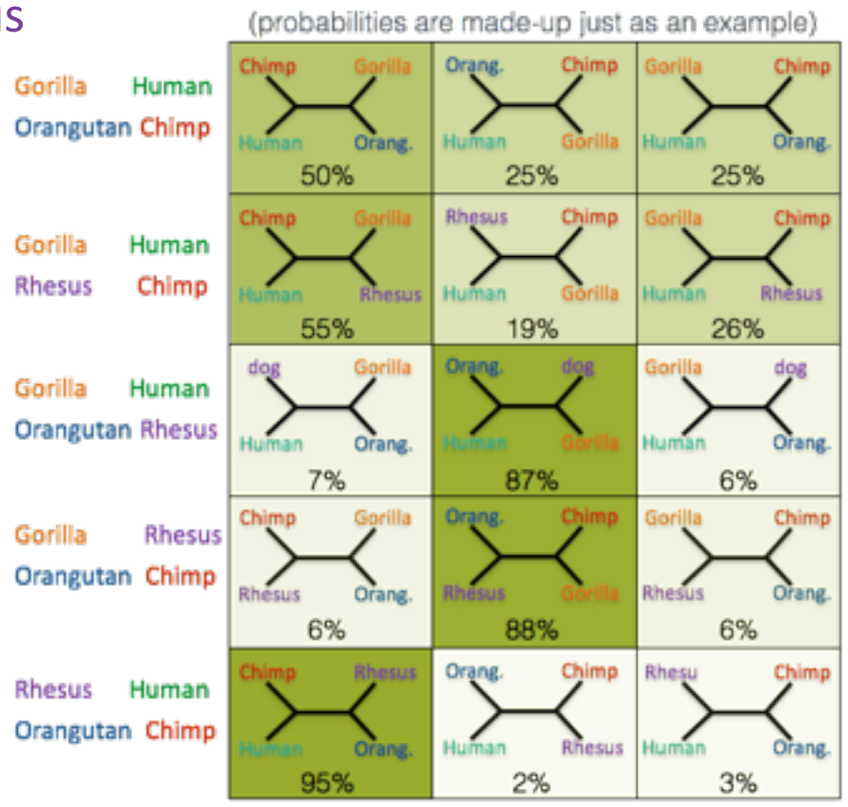
s

Alternative:

weight all $3\binom{n}{4}$ quartet topologies

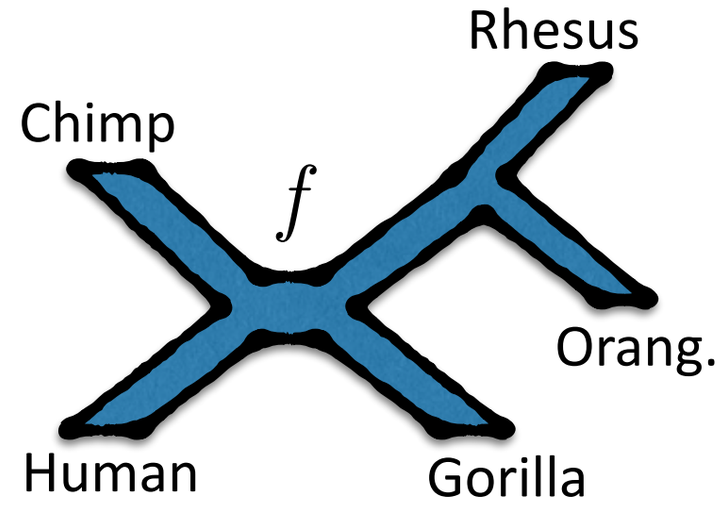
by their frequency

and find the optimal tree

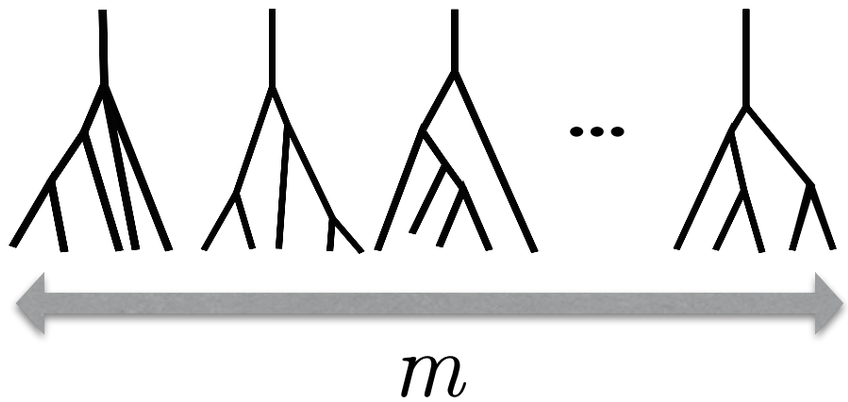


Notations

- n = the number of species
- m = the number of gene trees
- f = the length of the shortest branch



$n=5$



Maximum Quartet Support Species Tree

- Optimization problem:

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

$$Score(T) = \sum_{1}^{m} |Q(T) \cap Q(t_i)|$$

the set of quartet trees induced by T

a gene tree

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- Optimization problem: NP-Hard [Lafond & Scornavaccaori, 2016]

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ASTRAL-I

[Mirarab, et al., Bioinformatics, 2014]

- ASTRAL solves the problem exactly using **dynamic programming**
  - Exponential running time (feasible for $n<18$)

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- ASTRAL solves the problem exactly using **dynamic programming**
  - Exponential running time (feasible for $n<18$)
- Introduced a **constrained version** of the problem
  - Draws the set of branches in the species tree from a given set $\mathcal{X}$ = {all bipartitions in all gene trees}
  - Species tree branches tend to be in at least one gene tree
  - **Theorem**: the constrained version is statistically consistent
  - Running time: $O(n^2 m|\mathcal{X}|^2)$

ASTRAL-II

[Mirarab and Warnow, Bioinformatics, 2015]

1. Faster calculation of the score function inside DP

   - $O(nm|\mathcal{X}|^2)$ instead of $O(n^2m|\mathcal{X}|^2)$

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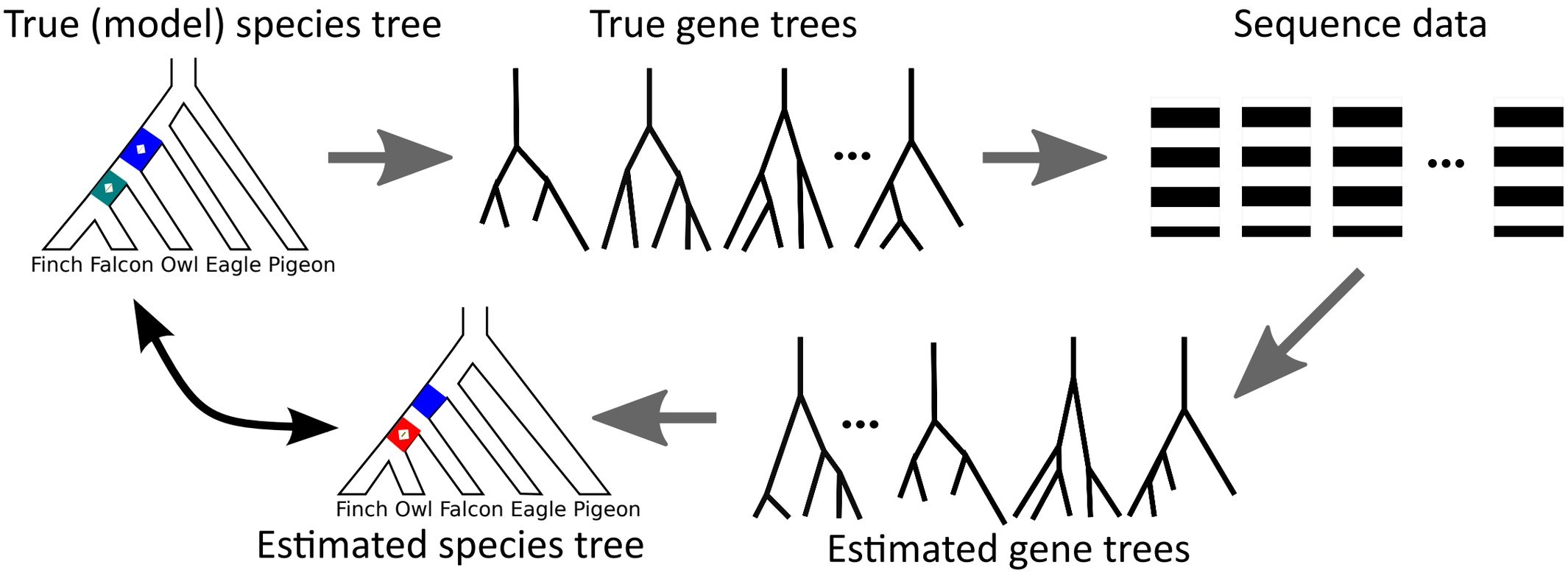
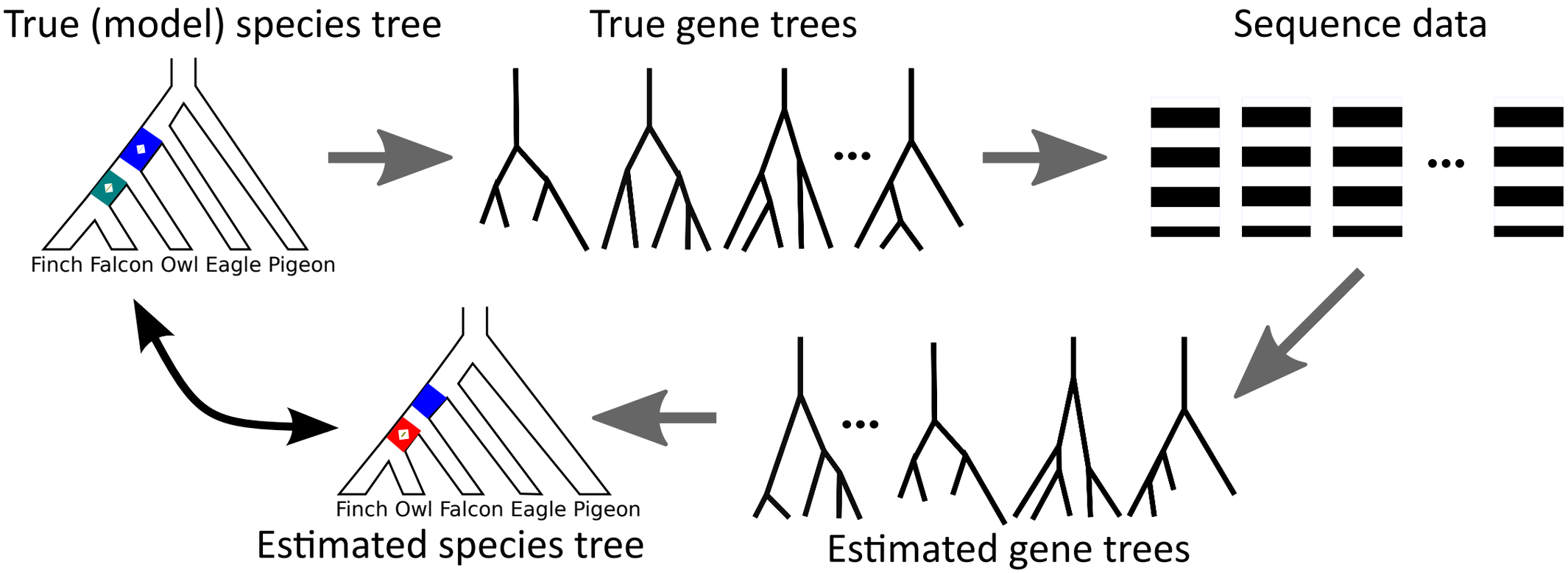
   - Complete incomplete gene trees
3. Ability to take as input gene trees with polytomies

Simulation study



- Vary parameters: the number of species, the number of genes, and the amount of ILS.

Simulation study



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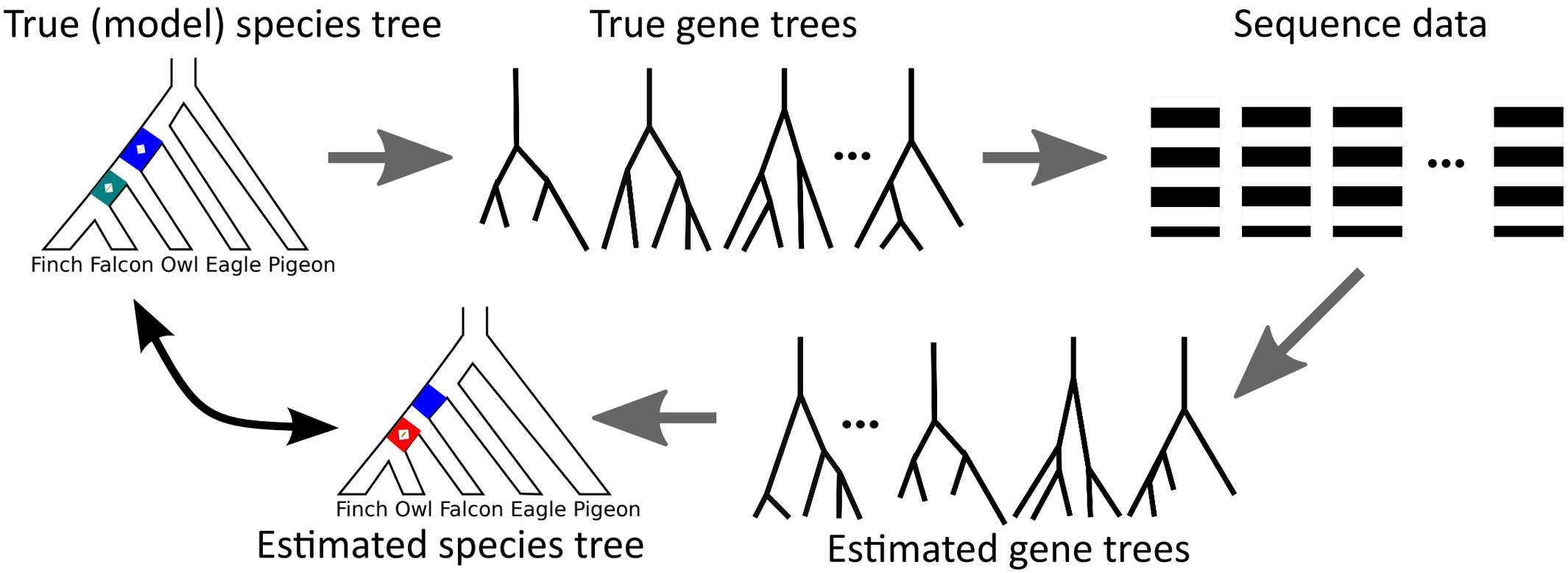
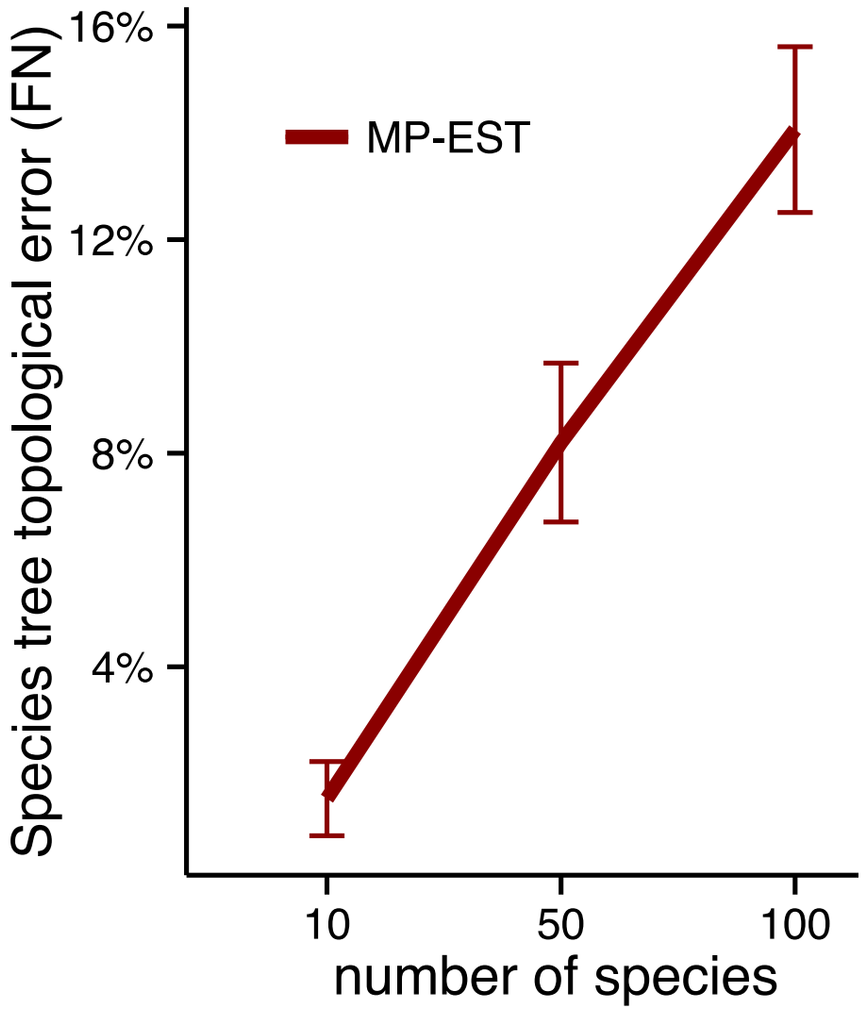


- Vary parameters: the number of species, the number of genes, and the amount of ILS.
- Compare to other strong methods (NJst, MP-EST, concatenation)

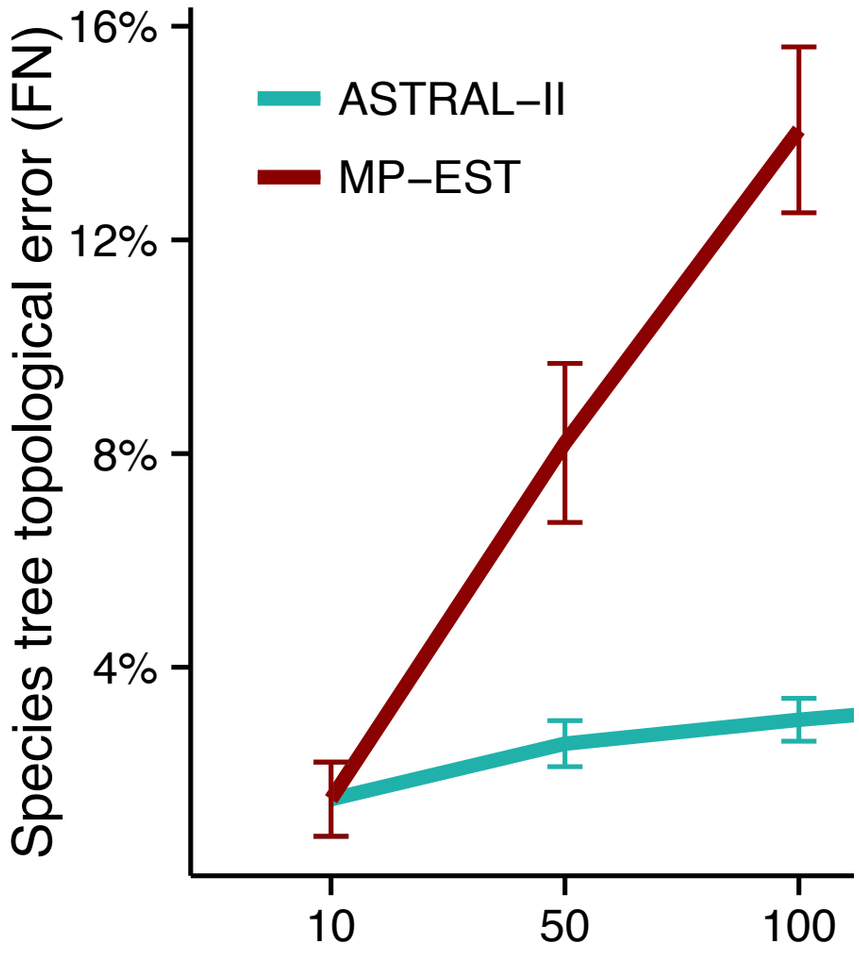
- Evaluate using the **FN rate**: the percentage of branches (bipartitions) in the true tree that are missing from the estimated tree

Number of species impacts estimation error in the species tree



1000 genes, “medium” levels of ILS, simulated species trees
[S. Mirarab, T. Warnow, 2015]

ASTRAL: accurate and scalable



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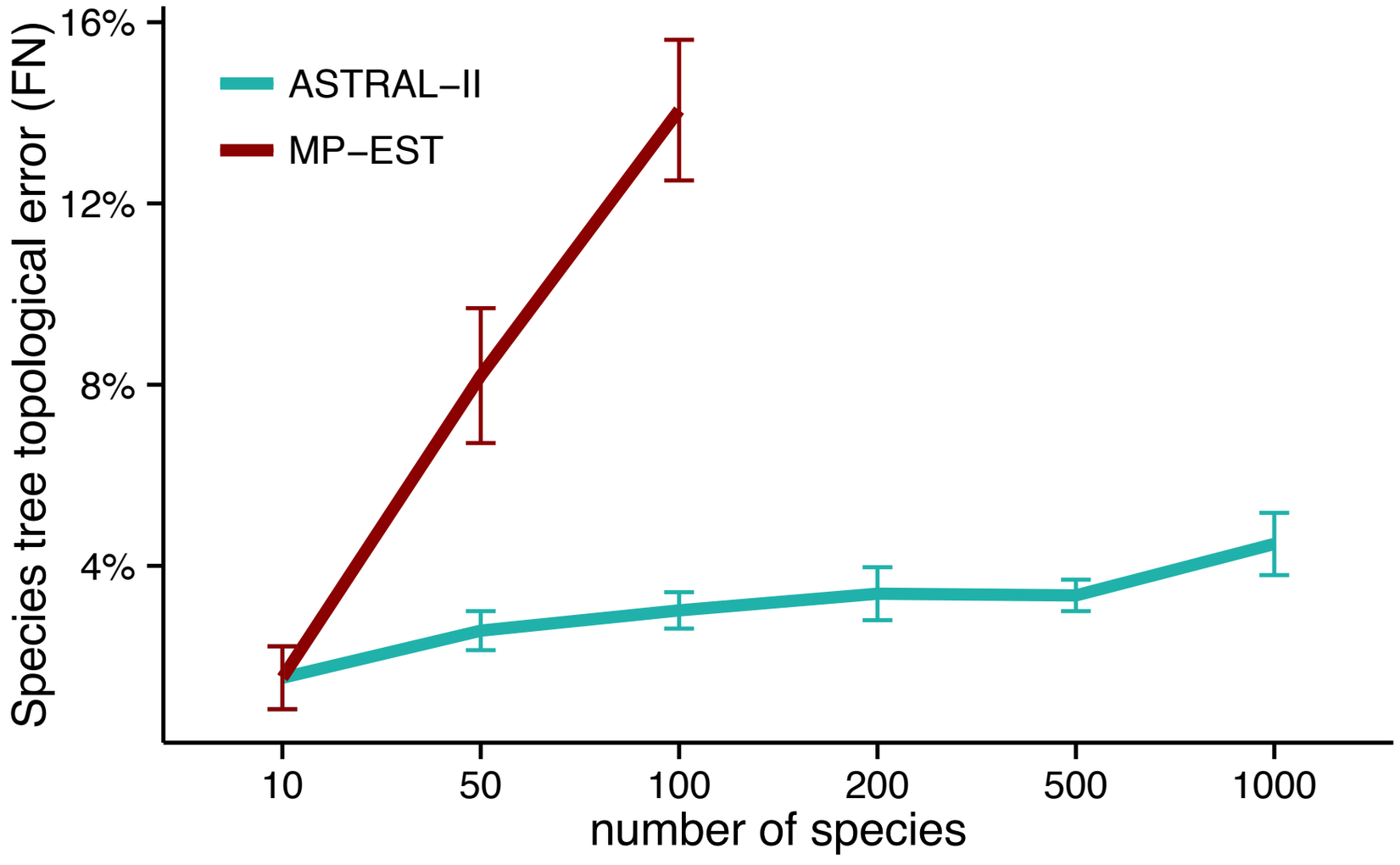
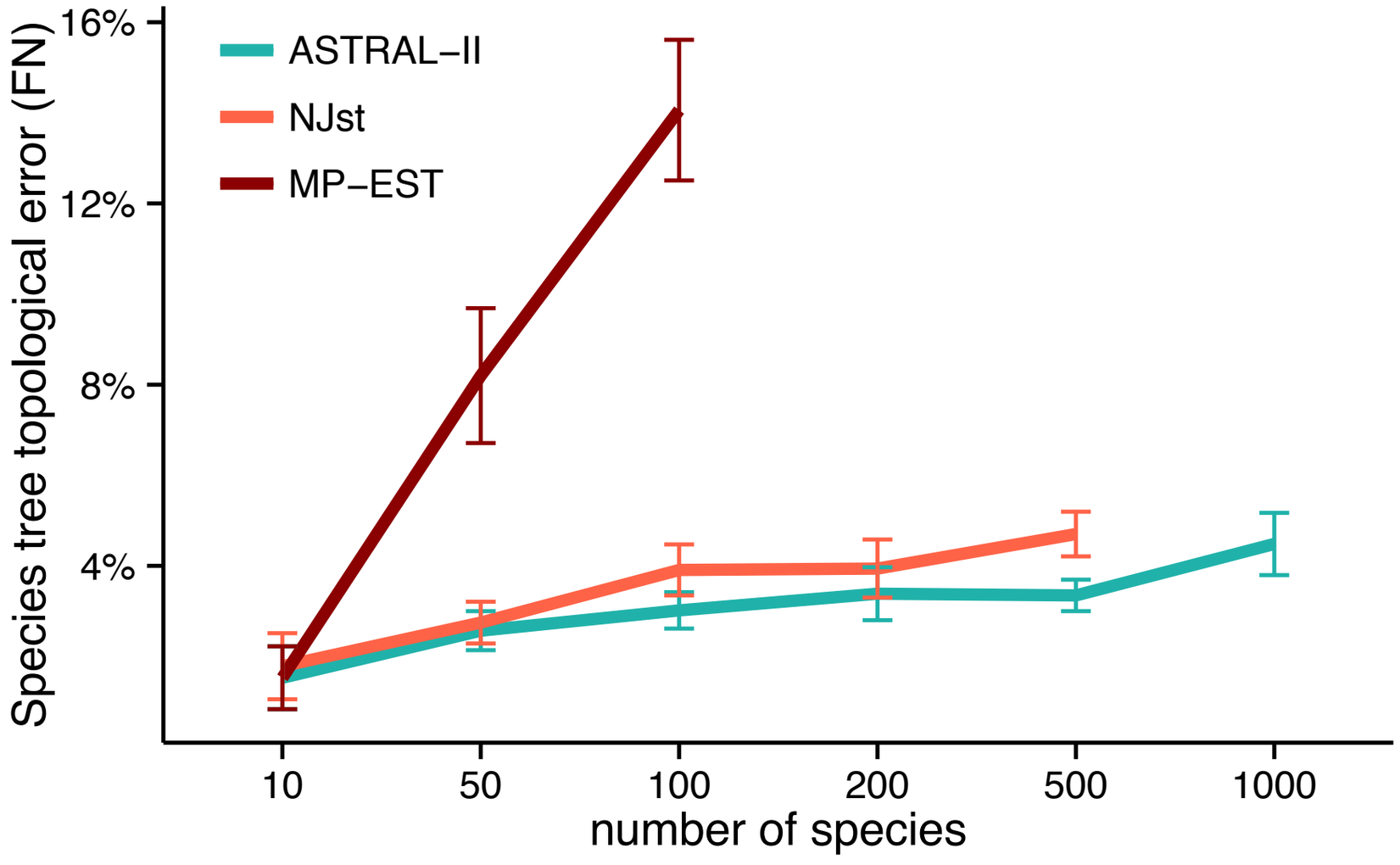


1000 genes, “medium” levels of ILS, simulated species trees
[S. Mirarab, T. Warnow, 2015]

Tree error as a function of # species



1000 genes, “medium” levels of ILS, simulated species trees
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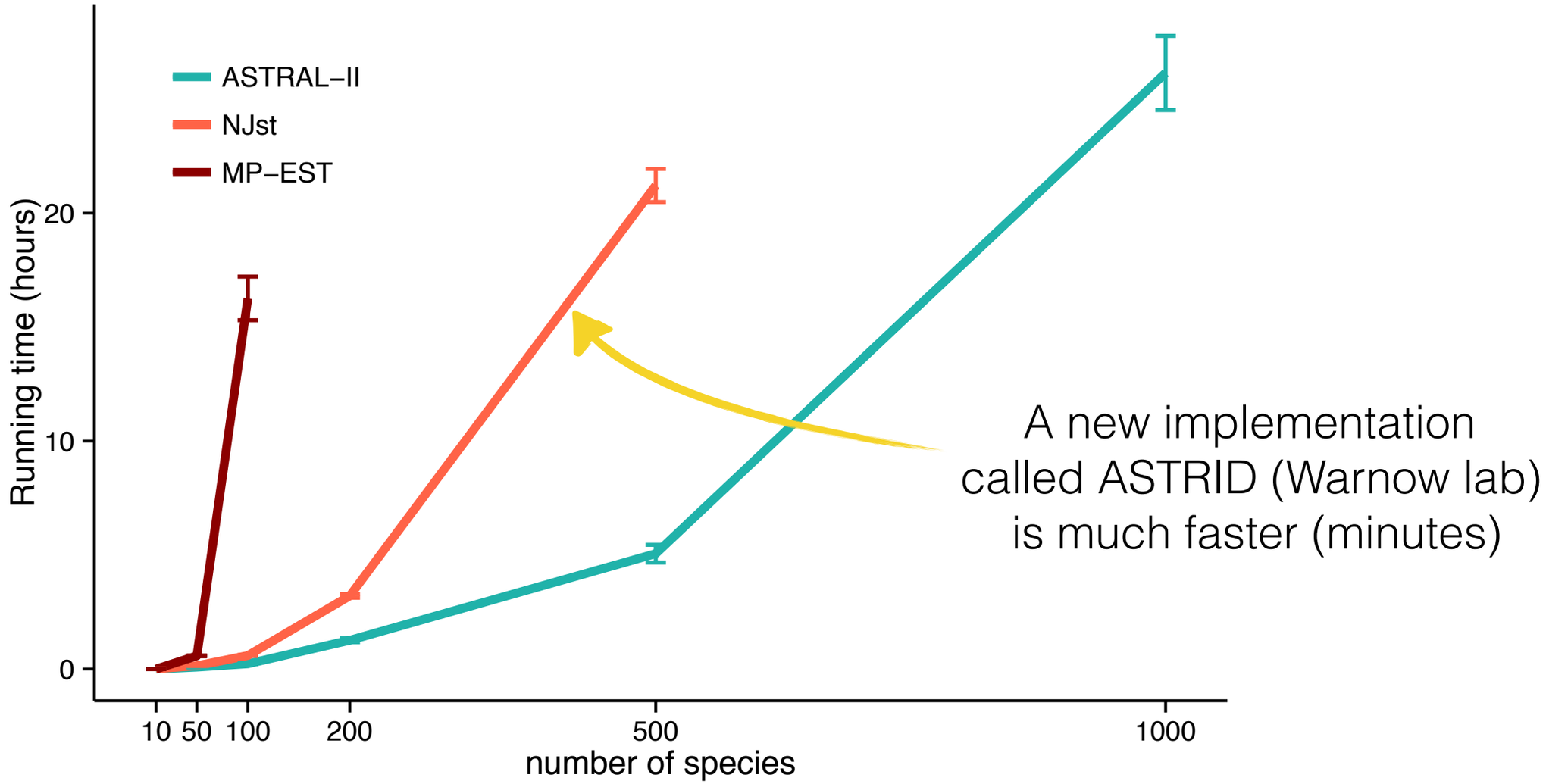
Running time as function of # species



1000 genes, “medium” levels of ILS, simulated species trees
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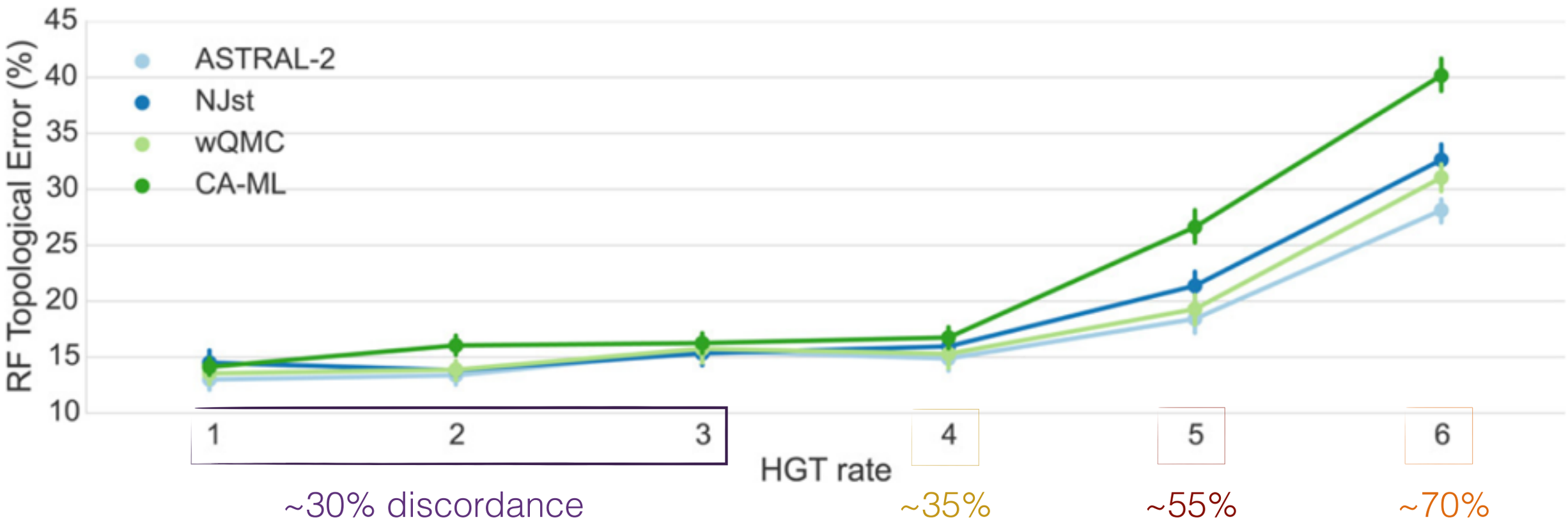
Horizontal Gene Transfer (HGT)

[R. Davidson et al., BMC Genomics. 16 (2015)]

Model violation: the simulated discordance is due to both ILS and randomly distributed HGT

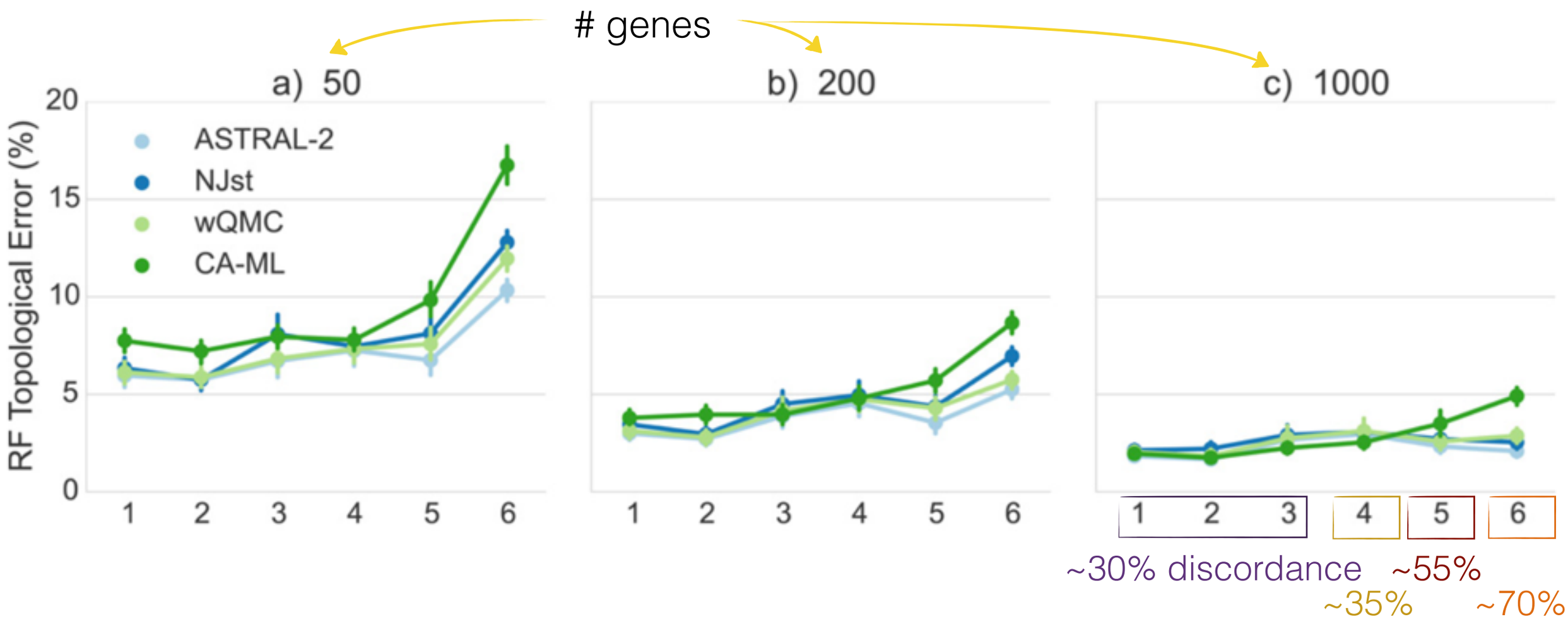


50 species, 10 genes

Horizontal Gene Transfer (HGT)

[R. Davidson et al., BMC Genomics. 16 (2015)]

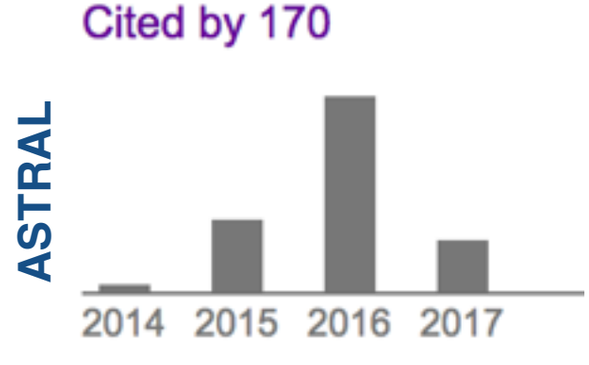
Randomly distributed HGT is tolerated with enough genes

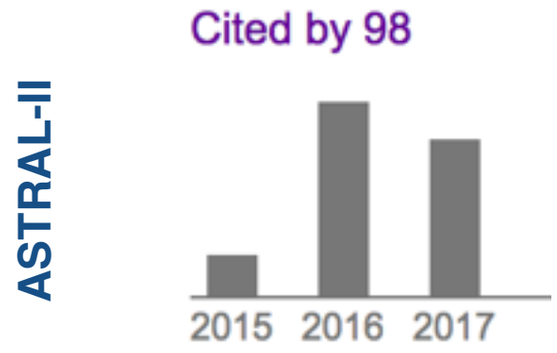


50 species, varying # genes

Used by the biologists

- Plants: Wickett, et al., 2014, PNAS
- Birds: Prum, et al., 2015, Nature
- Xenoturbella, Cannon et al., 2016, Nature
- Xenoturbella, Rouse et al., 2016, Nature
- Flatworms: Laumer, et al., 2015, eLife
- Shrews: Giarla, et al., 2015, Syst. Bio.
- Frogs: Yuan et al., 2016, Syst. Bio.
- Tomatoes: Pease, et al., 2016, PLoS Bio.
- Angiosperms: Huang et al., 2016, MBE
- Worms: Andrade, et al., 2015, MBE



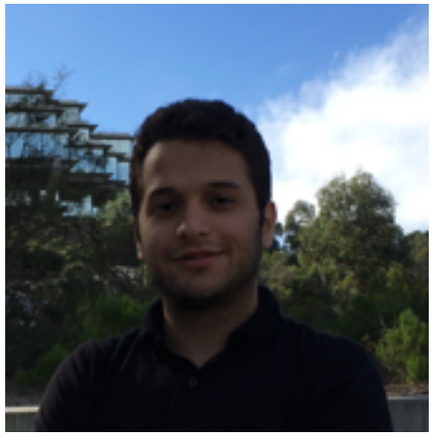


UCSD Work

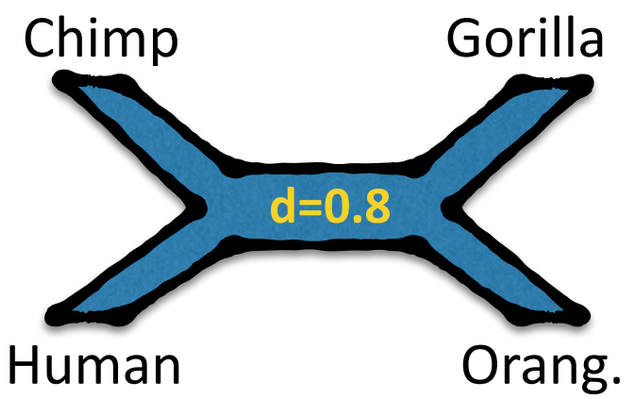
1. Statistical support
2. Sample complexity
3. Running time complexity
4. Parallelism and new data types

Going beyond the topology

[Sayyari and Mirarab, MBE, 2016]

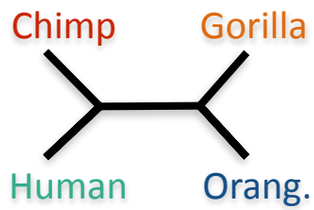


- **Branch length**:
  simply a function of the level of discordance

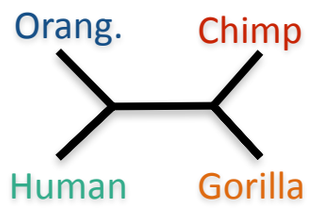


$$\theta_1 = 1 - \frac{2}{3}e^{-d}$$

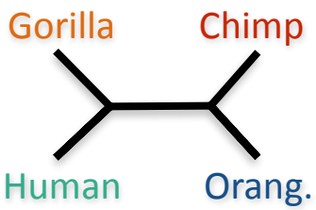
θ_1=70%



θ_2=15%



θ_3=15%



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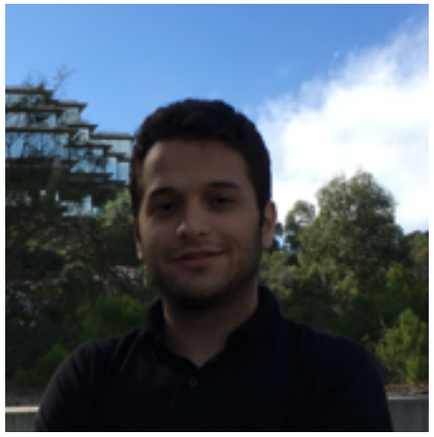
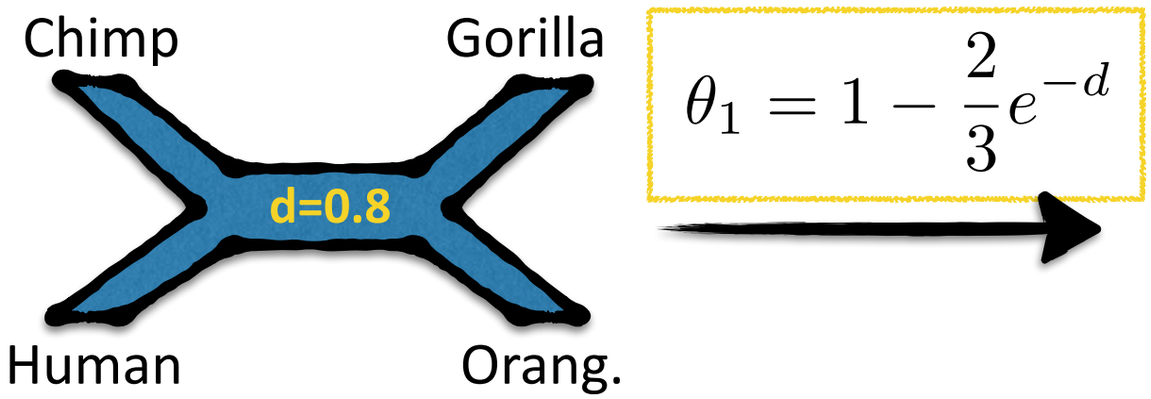


- **Branch length**:
  simply a function of the level of discordance
- A single quartet ($n=4$)
  - Easy: just reverse the discordance formula
  - gives the ML estimate



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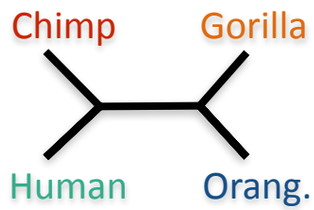

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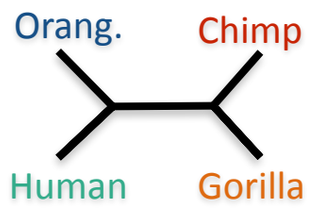

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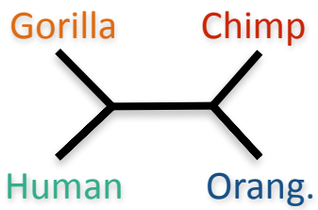
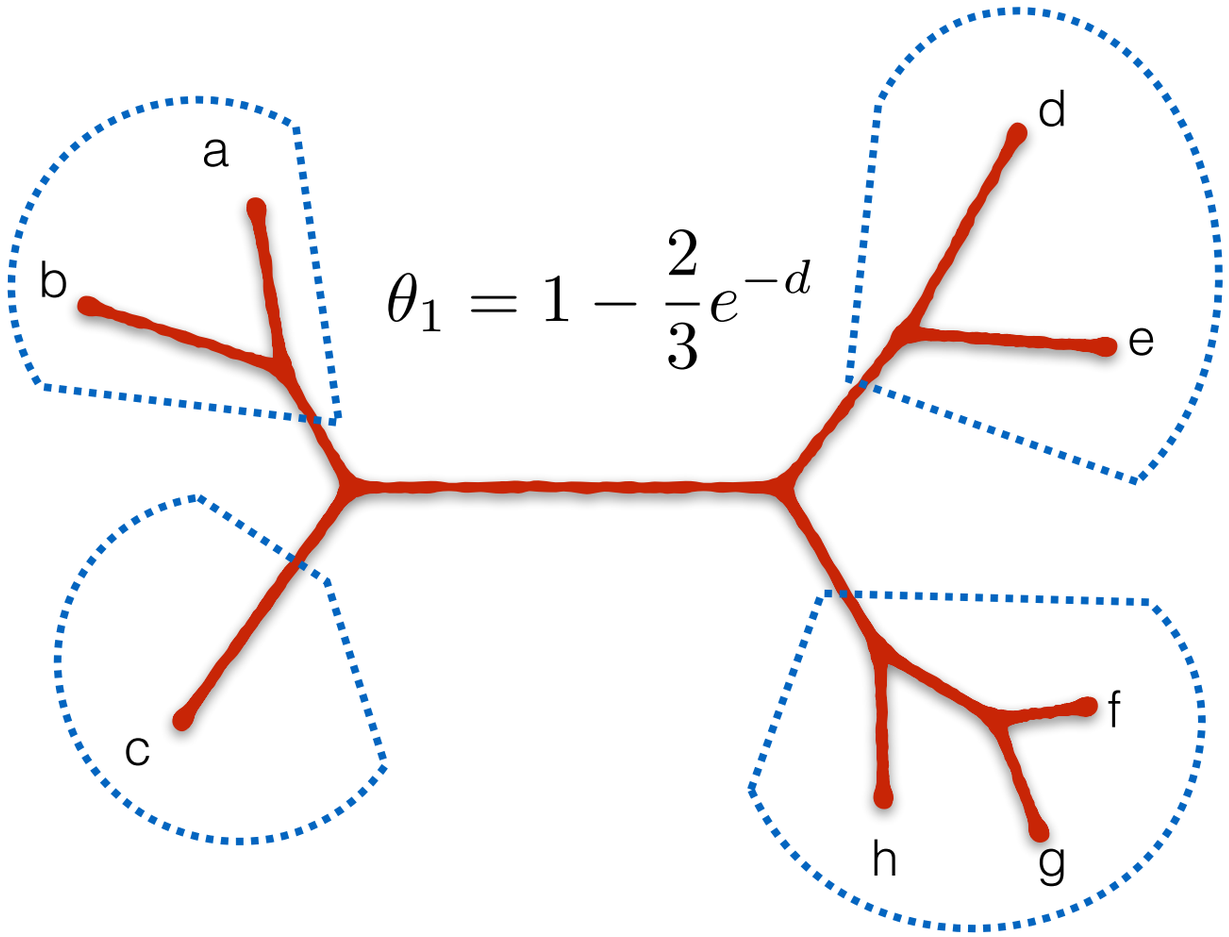


Branch length for $n > 4$

- Simply average all quartet frequencies "around" that branch
  - Justified given some assumptions



Branch length for $n > 4$

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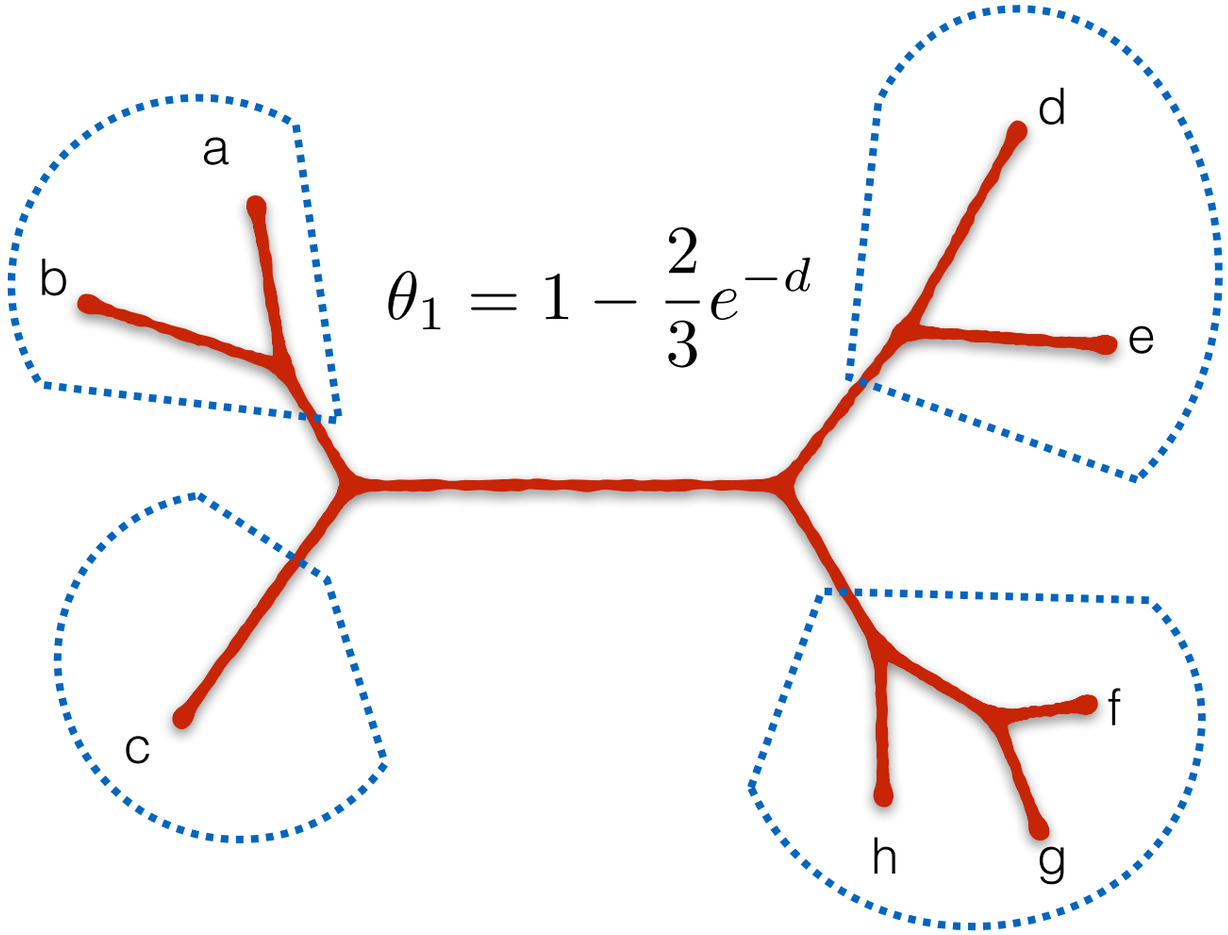
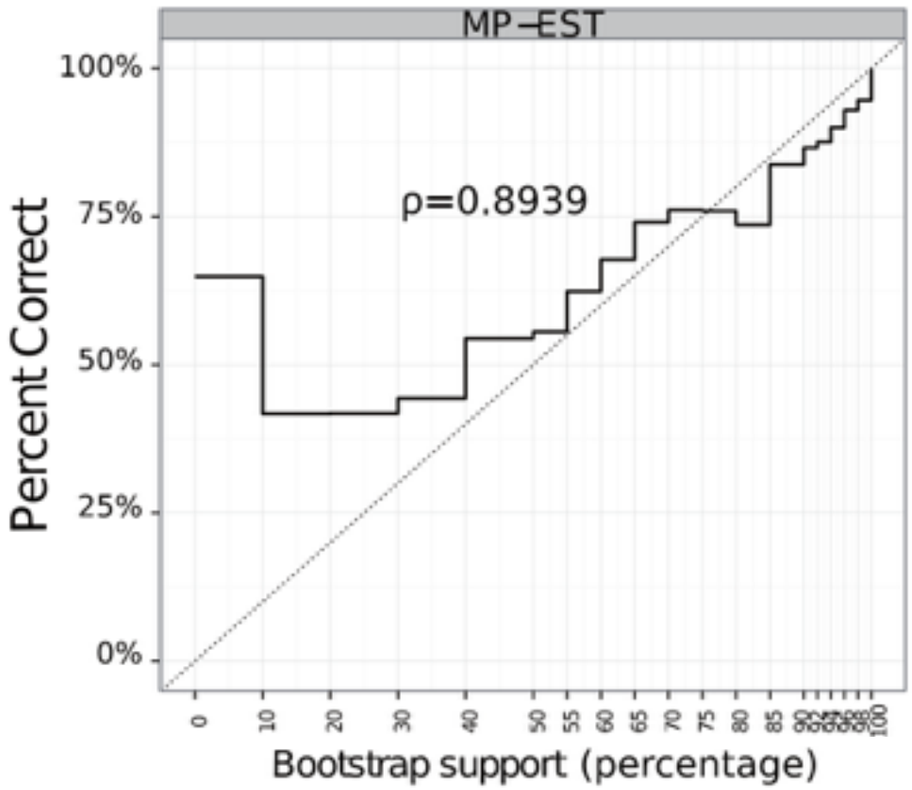
  - Justified given some assumptions
- Can be done efficiently in $\Theta(n^2 m)$ for all branches



Branch support

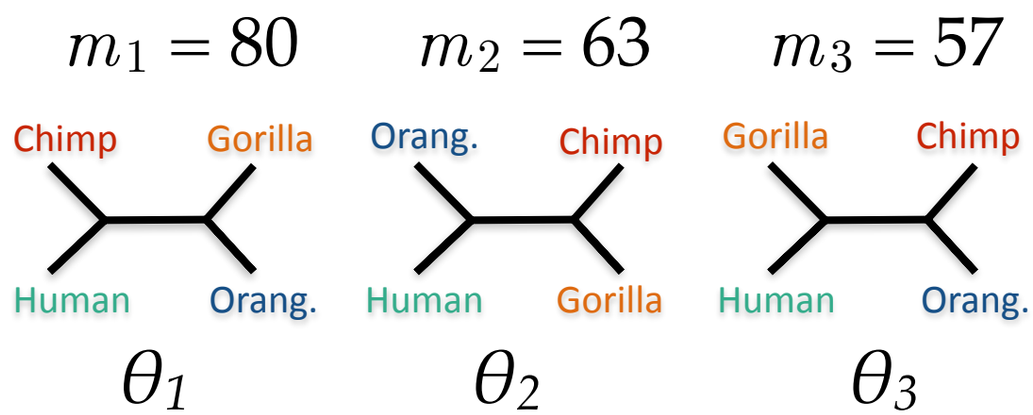
- Traditional approach:
  Multi-locus bootstrapping (MLBS)
  - Slow: requires bootstrapping all genes
    (e.g., 100×m ML tree inferences)
  - Inaccurate and hard to interpret
    [Mirarab et al., Sys bio, 2014;
    Bayzid et al., PLoS One, 2015]
- We can do better!



[Mirarab et al., Sys bio, 2014]

Branch support idea: $n=4$

- Recall quartet frequencies follow a multinomial distribution



- $\boldsymbol{P}$ (topology seen in m_1 / m gene trees is the species tree) =
  $\boldsymbol{P}$ ($\theta_1 > 1/3$) =
  $\boldsymbol{P}$ (a 3-sided coin tossed m times is biased towards
  the side that shows up m_1 times)

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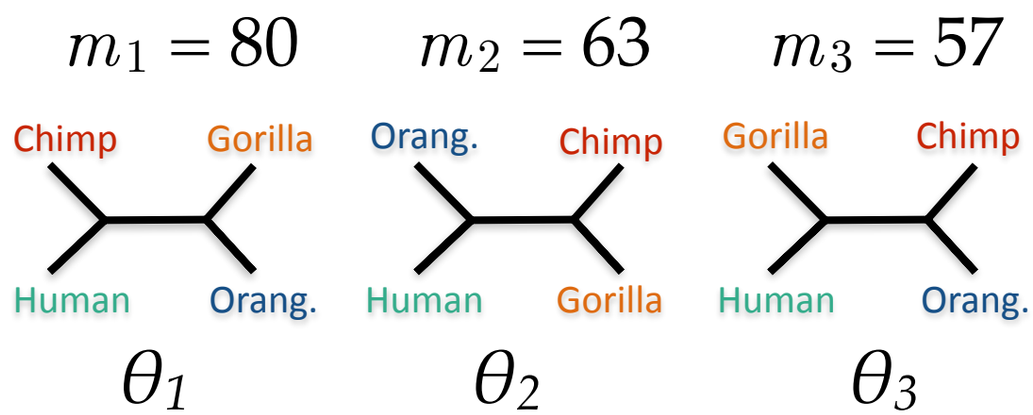

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  $\boldsymbol{P}$ (a 3-sided coin tossed m times is biased towards
  the side that shows up m_1 times)

- Can be analytically solved

Posterior

$$\Gamma t^{z_1}\left(\frac{1-t}{2}\right)^{n-z_1}$$

Prior: Yule process become conjugate

$$P\left(\theta_1 > \frac{1}{3}|\bar{Z}=\bar{z}\right) = \frac{\int_{\frac{1}{3}}^{1} P(\bar{Z}=\bar{z}|\theta_1=t) f_{\theta_1}(t)\mathrm{d}t}{P(\bar{Z}=\bar{z})}$$

$$\sum_{j=1}^{3}\int_{\frac{1}{3}}^{1} P(\bar{Z}=\bar{z}|\theta_j=t) f_{\theta_j}(t)\mathrm{d}t$$

- Fast to calculate
- Depends on the frequency of not just the first topology, but also the frequency of second and third topologies

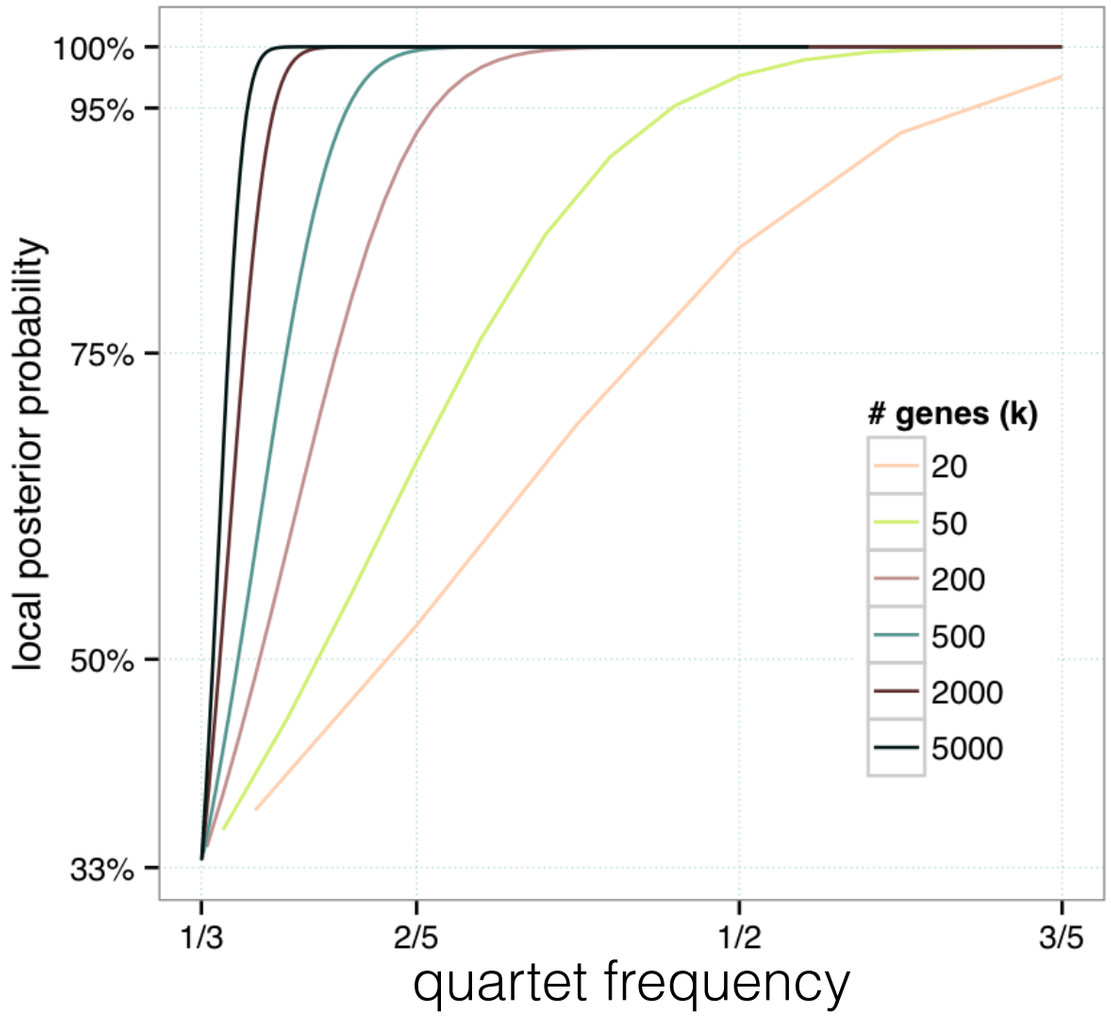
Prior

- All three topologies have equally prior

$$Pr(\theta_1 > \frac{1}{3}) = Pr(\theta_2 > \frac{1}{3}) = Pr(\theta_3 > \frac{1}{3}) = \frac{1}{3}$$

- The species tree generated through a Birth-only (Yule) process with rate λ
  - Turns out to be the conjugate prior
  - (default) λ =0.5 → uniformly distributed branch lengths

Quartet support v.s. posterior

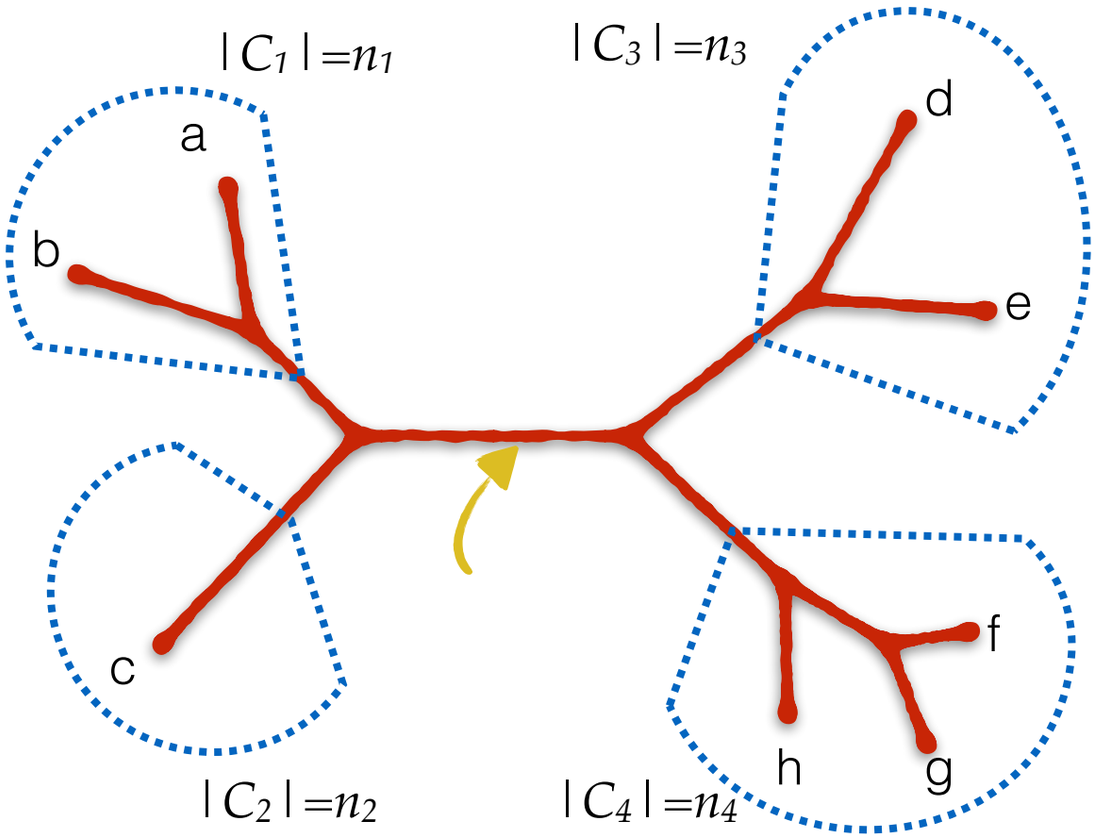


Increased number of genes (m) $\Rightarrow$ increased support

Decreased discordance $\Rightarrow$ increased support

How about $n>4$?

- **Locality Assumption**: All four clusters around a branch are correct
  - Treat branches independently



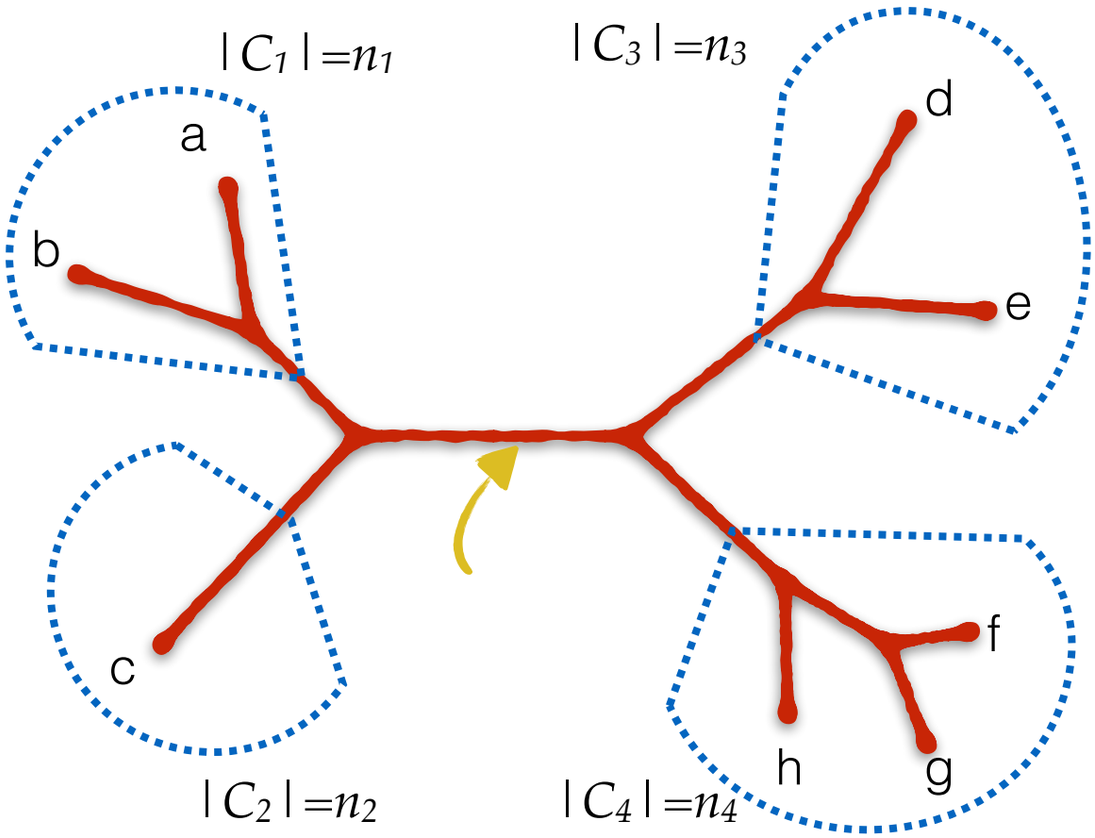
$$k = n_1 \times n_2 \times n_3 \times n_4$$

How about $n>4$?

- **Locality Assumption**: All four clusters around a branch are correct
  - Treat branches independently
- k quartets around a branch?
- Independence assumption would be too liberal ($m \times k$ tosses of the coin)
- Fully dependent assumption:

  — k quartets give noisy estimates of a single hidden true frequency.

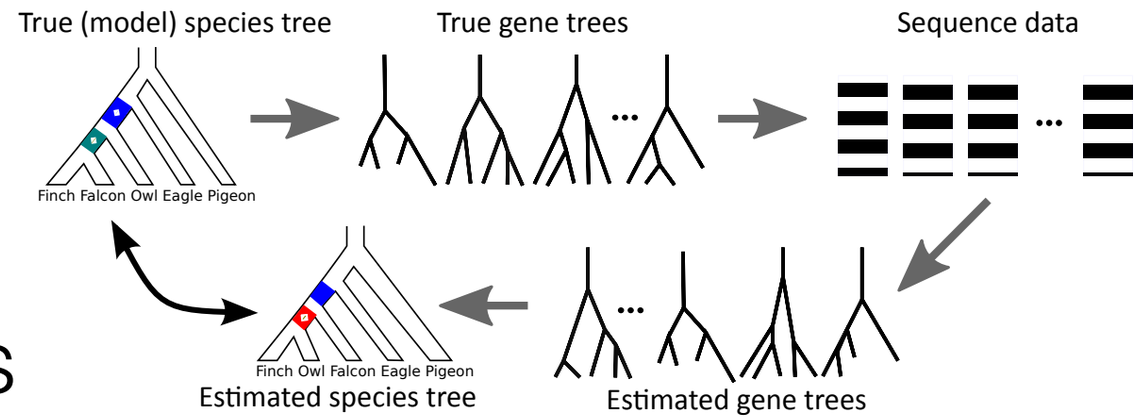
  — Simply average their frequencies
- m tosses, m×k readings



$$k = n_1 \times n_2 \times n_3 \times n_4$$

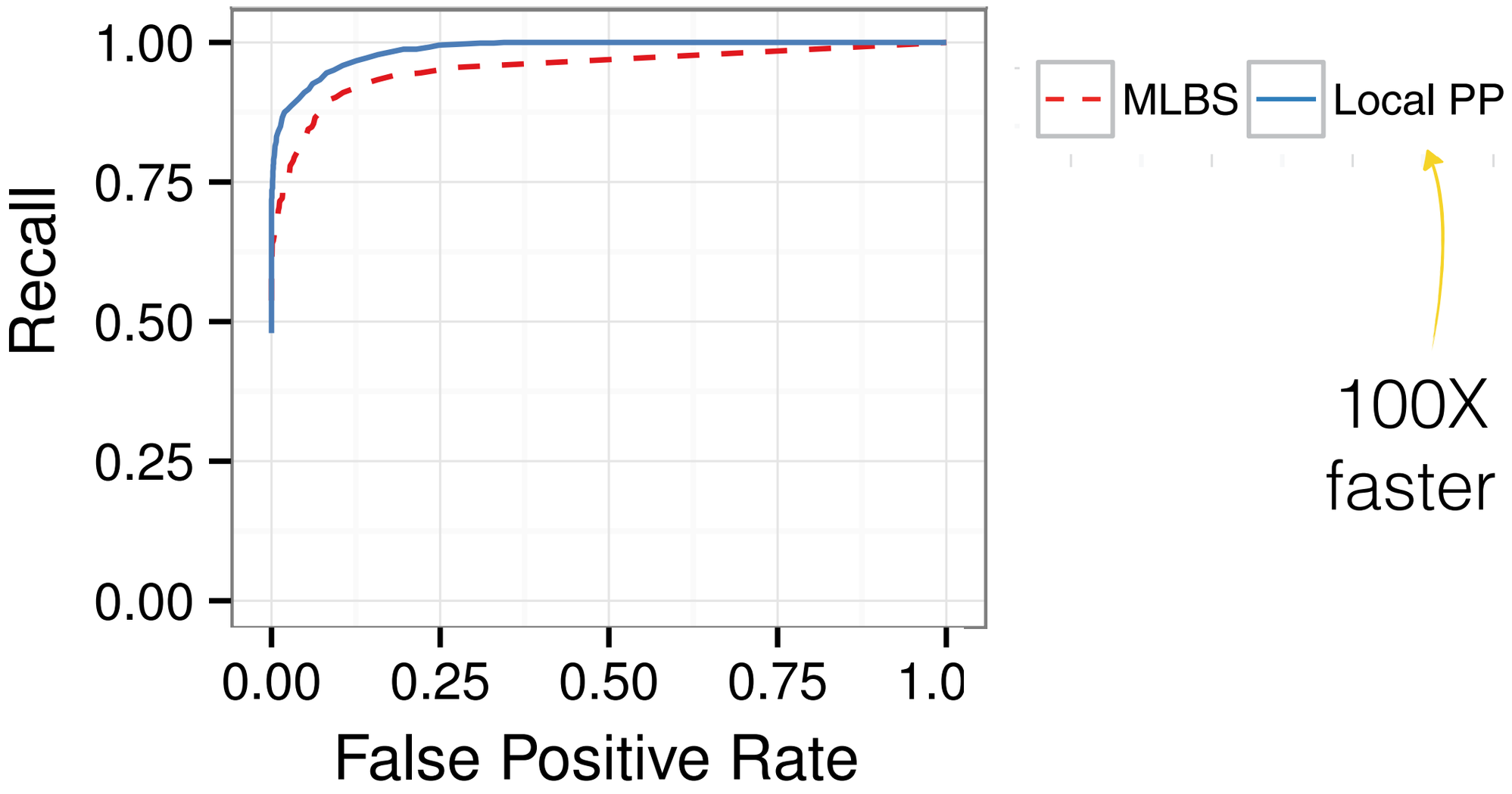
Simulation studies

- Assumption **violations**:
  - Estimated gene trees
    instead of true gene trees
  - Estimated species trees:
    the locality assumption can be violated



- Measuring the support accuracy: ROC curves
  — based on the number of false positive and false negatives above various thresholds of support

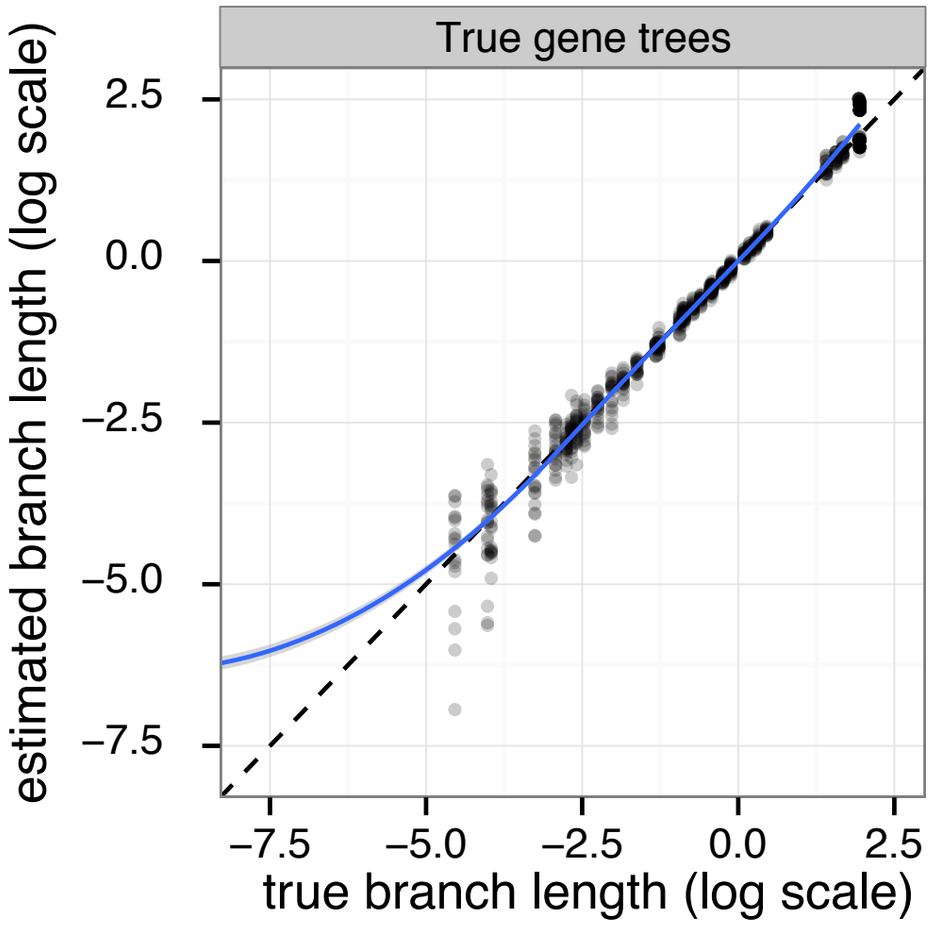
Results (Avian, ROC)



Avian simulated dataset (48 taxa, 1000 genes)

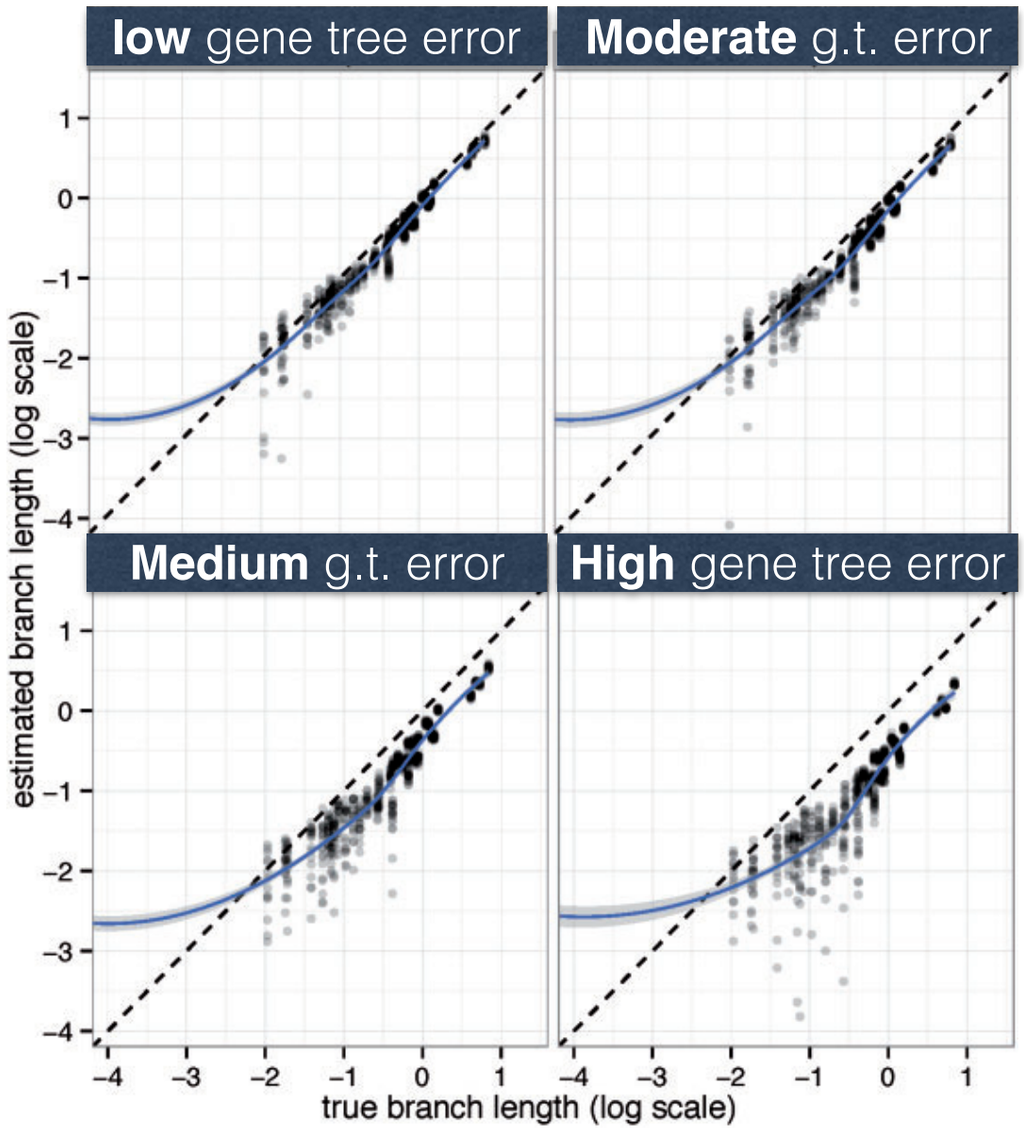
[Sayyari and Mirarab, MBE, 2016]

Branch length accuracy



With true gene trees, ASTRAL correctly estimates BL

Branch length accuracy



With error-prone estimated gene trees, ASTRAL underestimates BL

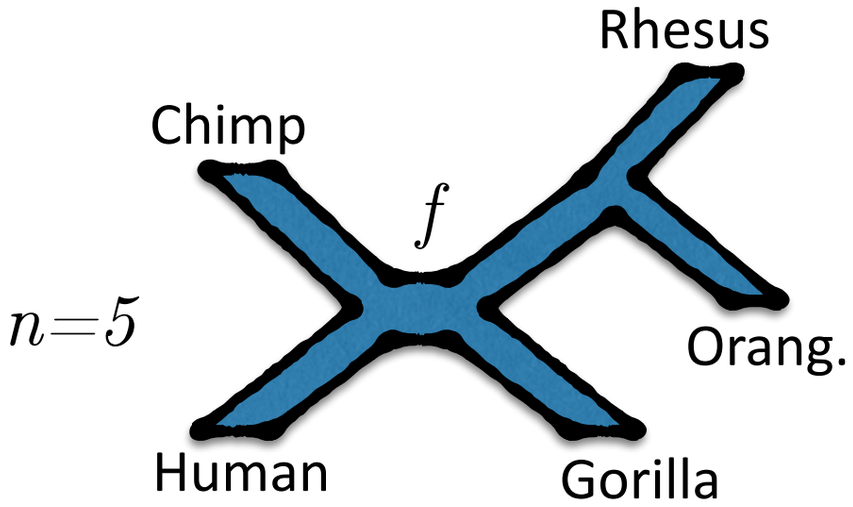
Sample complexity

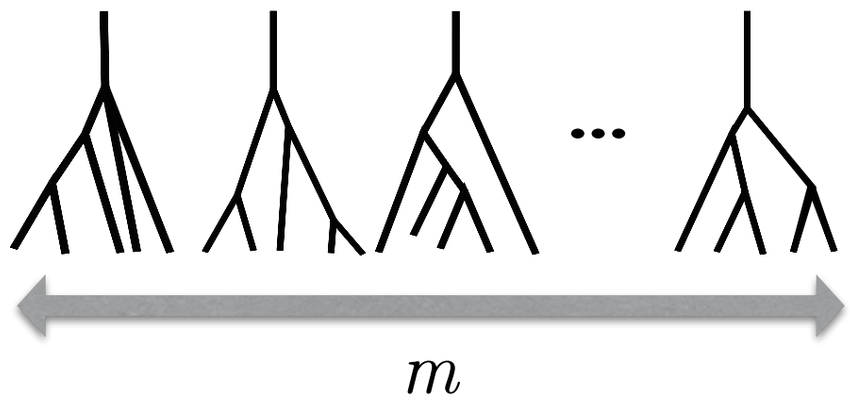
Shubhanshu Shekhar

Sebastien Roch

Sample complexity?

- **How many genes** are needed to guarantee an arbitrarily high probability of finding the true species tree?

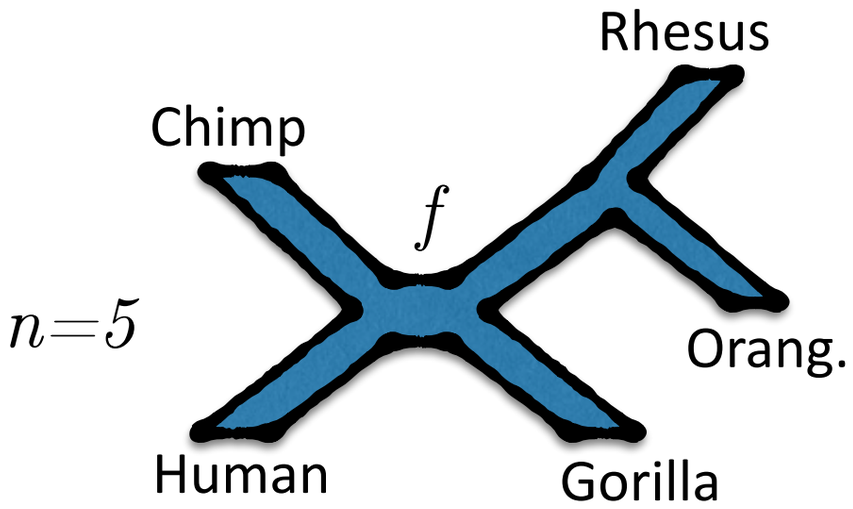


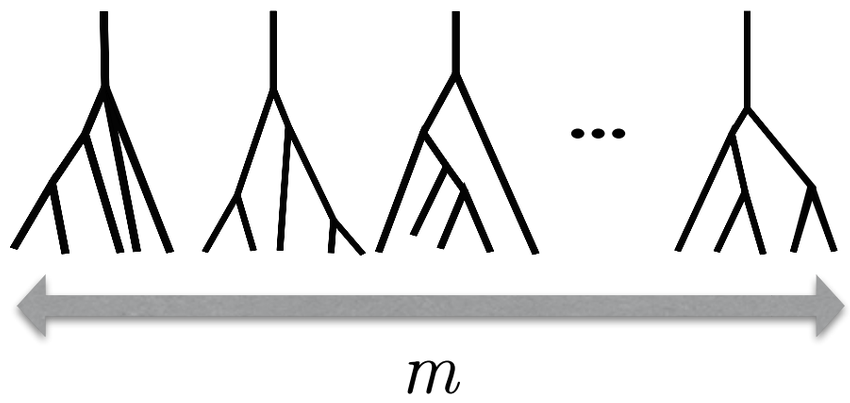


Sample complexity?

- **How many genes** are needed to guarantee an arbitrarily high probability of finding the true species tree?

- … asymptoticly, as the problem gets more difficult.
  - f: the length of the shortest branch (difficulty)
  - Find m, as a function of f and n for probability of error ϵ





Theorem 1

Consider a model species tree with minimum branch length $f < \log(\sqrt{2})$. *Then, for any* $\epsilon > 0$, *ASTRAL (exact) returns the true species tree with probability at least* $1 - \epsilon$ *if the number of input error-free gene trees satisfies*

$$m > \frac{9}{2} \log\left(\frac{4}{\epsilon}\binom{n}{4}\right) \frac{1}{(1 - e^{-f})^2} \tag{1}$$

Theorem 2

For any $\rho \in (0, 1)$ *and* $a \in (0, 1)$, *there exist constants* f_0 *and* n_0 *such that the following holds. For all* $n \geq n_0$ *and* $f \leq f_0$, *there exists a species tree with* n *leaves and shortest branch length* f *such that when ASTRAL (exact) is used with* $m \leq \frac{a \log n}{5f^2}$ *gene trees, the event* E *that ASTRAL (exact) reconstructs the wrong tree has probability*

$$\mathbf{P}(E) \geq 1 - \rho. \tag{3}$$

Theorem 1

Consider a model species tree with minimum branch length $f < \log(\sqrt{2})$. *Then, for any* $\epsilon > 0$, *ASTRAL (exact) returns the true species tree with probability at least* $1 - \epsilon$ *if the number of input error-free gene trees satisfies*

The sample complexity of the ASTRAL optimization problem (exact solution) is

$$O(\log(n) f^{-2})$$

such that when ASTRAL (exact) is used with $m \leq \frac{a \log n}{5f^2}$ *gene trees, the event* E *that ASTRAL (exact) reconstructs the wrong tree has probability*

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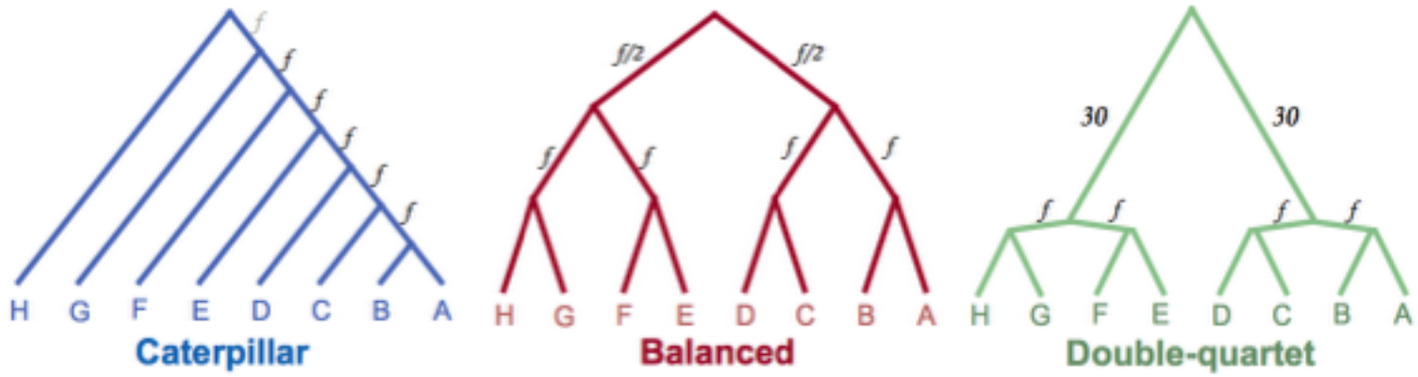
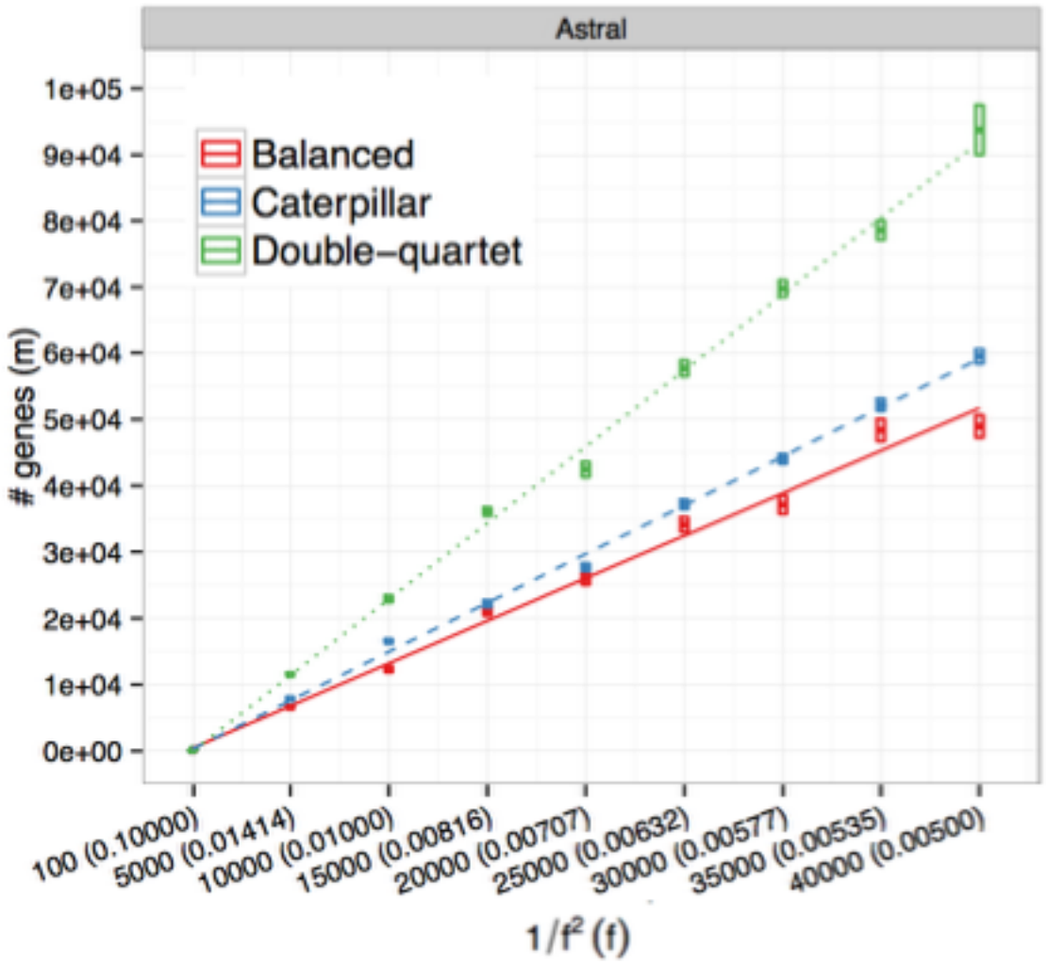
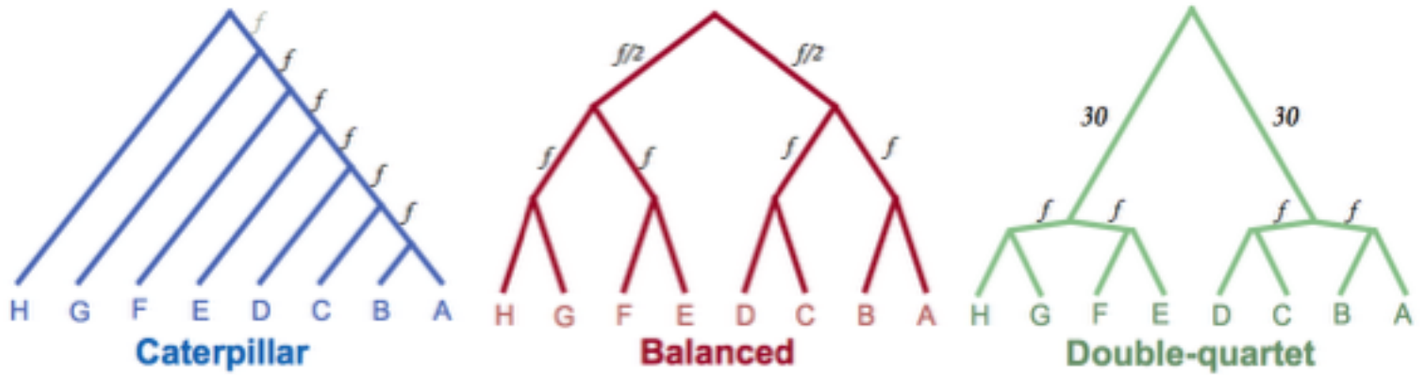
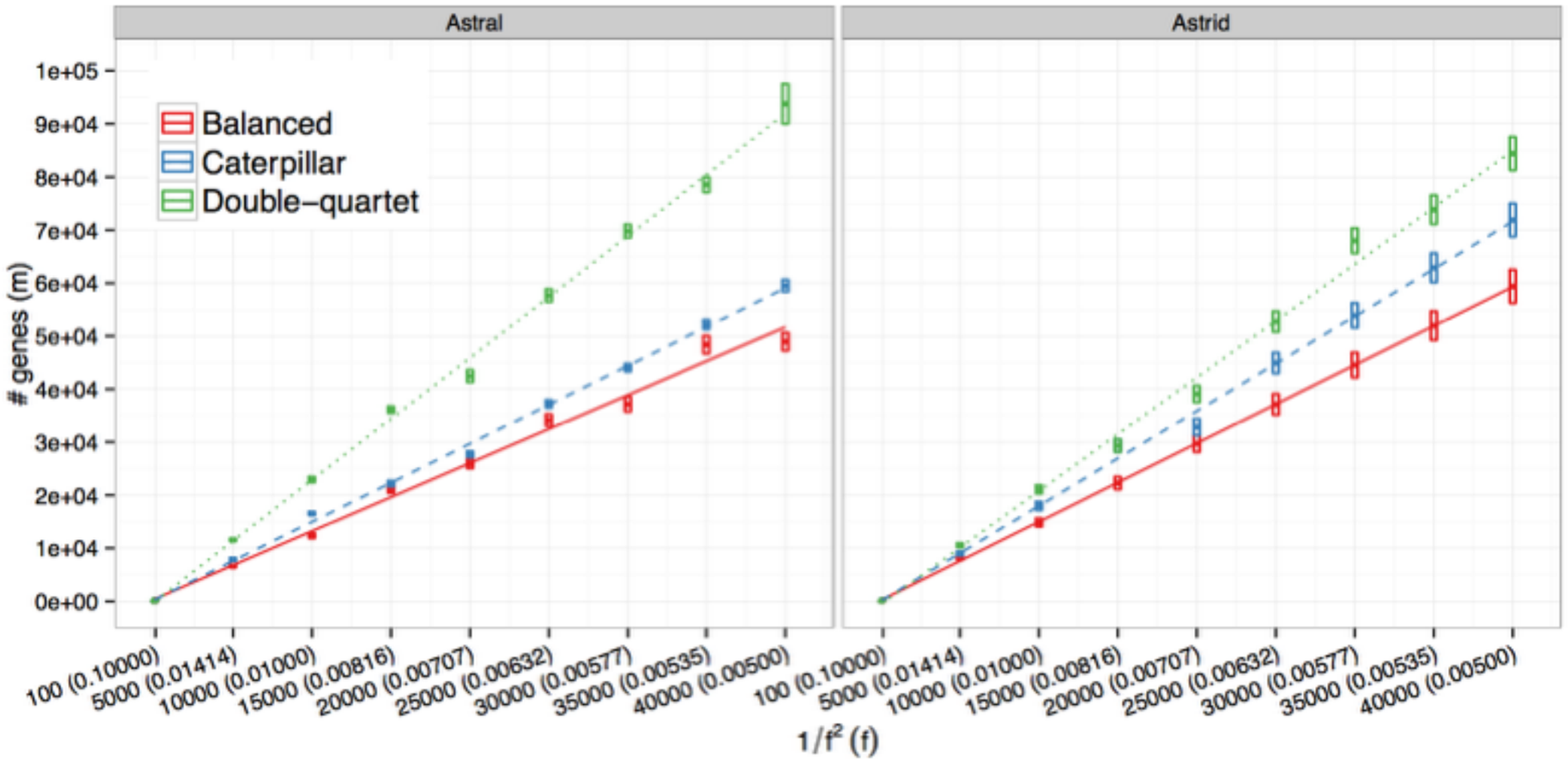
Simulations match theory



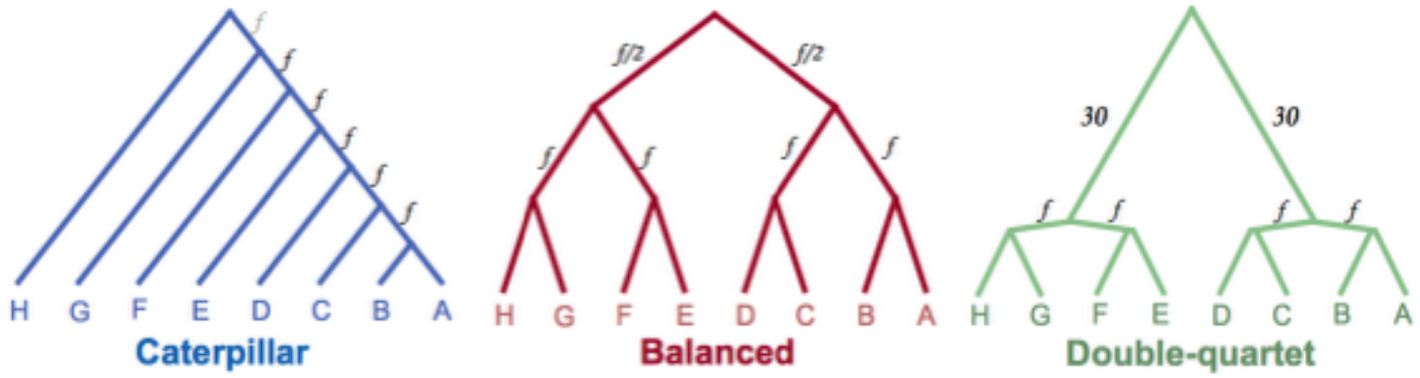


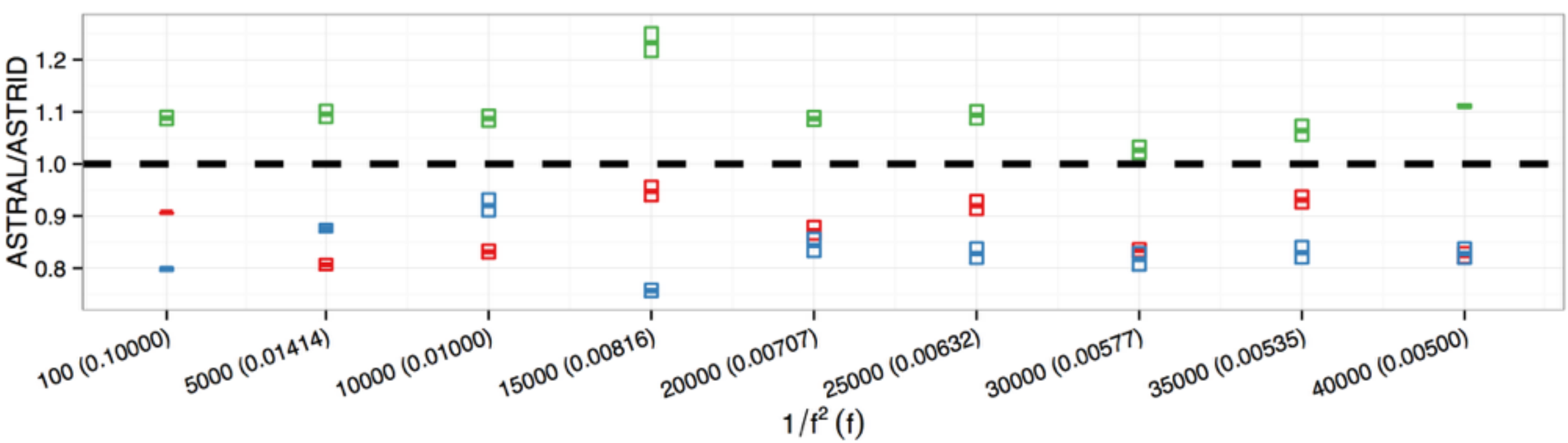
Simulations match theory





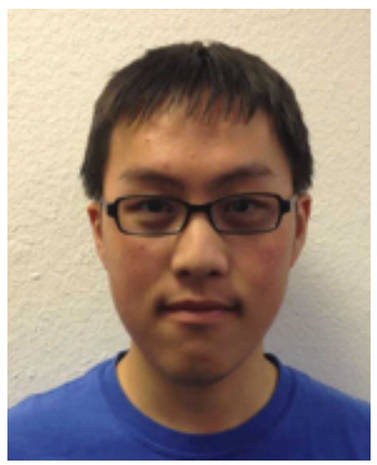
ASTRAL v.s. ASTRID: depends



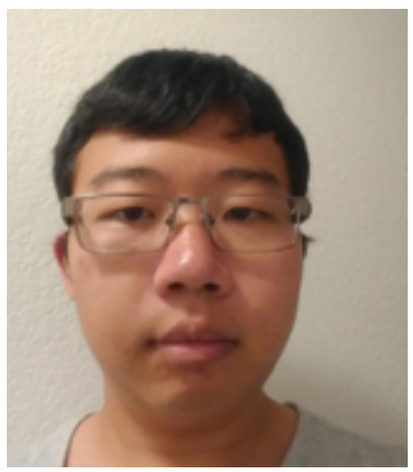


Running time complexity & ASTRAL-III (unpublished work)

Maryam Rabiee Hashemi



John Yin



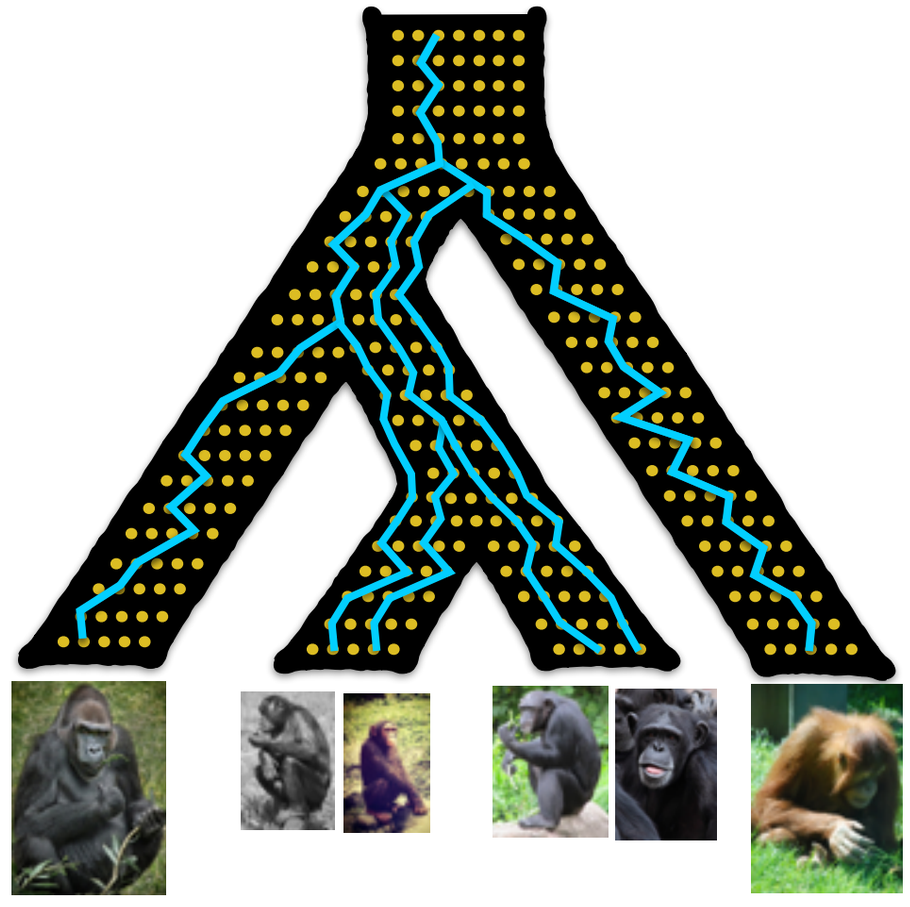
Chao Zhang

ASTRAL-III new features

- Handling new dataset types (multiple individuals)
- Bounded polynomial running time: $O((nm)^{2.73})$
- GPU and CPU parallelism
- Using a polytree to reduce speed to $O(|\mathcal{U}|(nm)^{1.73})$
  - $\mathcal{U}$ = {unique nodes in gene trees}; $|\mathcal{U}|=O(nm)$

Multiple individuals

- What if we sample multiple individuals from each species?



- In recently diverged species individuals *may* have different trees for each gene

- Sampling multiple individuals may provide extra signal

Extending ASTRAL to multiple individuals

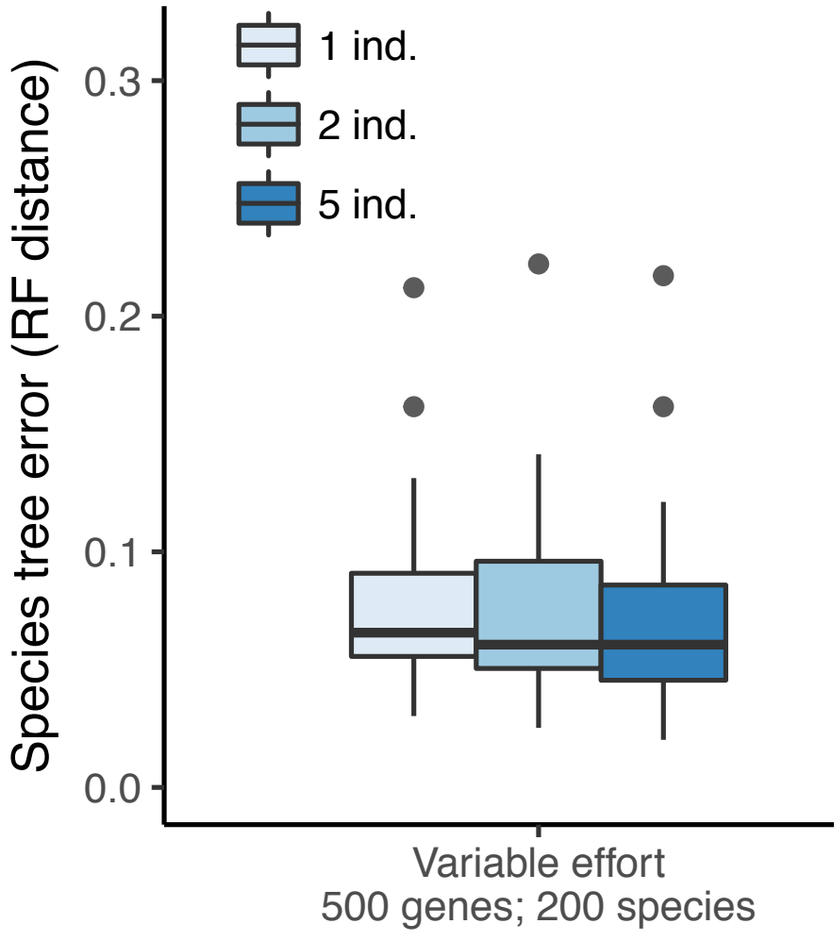
- Optimization problem: quartet-based score easily extends (simply ignore multi-individual quartets)

- Dynamic programming: simply adjust boundary conditions

- **Challenge**: forming constrained search space (set $\mathcal{X}$)

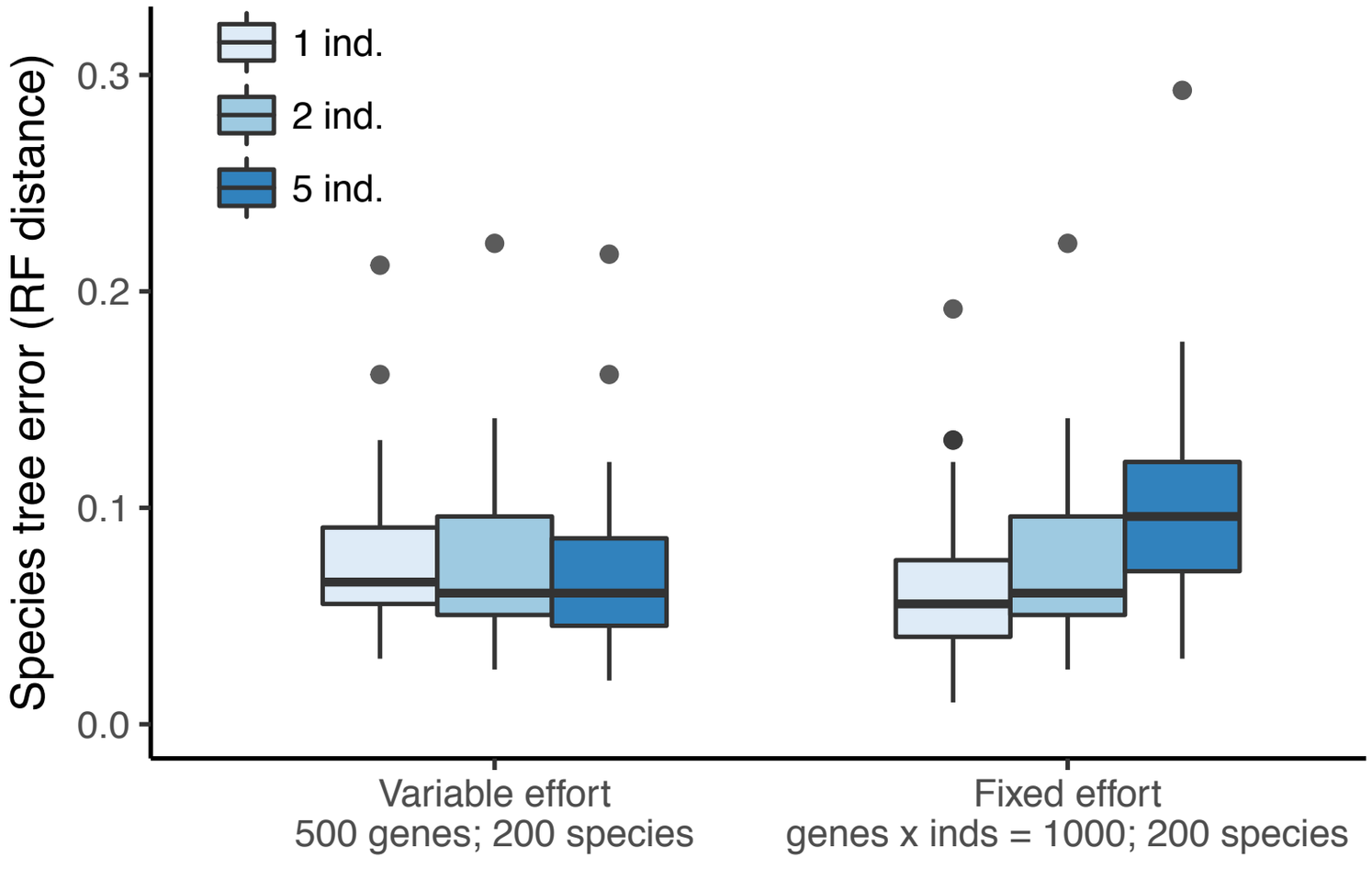
  - New heuristics: repeated subsampling of individuals and taking a consensus among subsamples

Multiple individuals helpful?



Yes, it marginally helps accuracy

Multiple individuals helpful?



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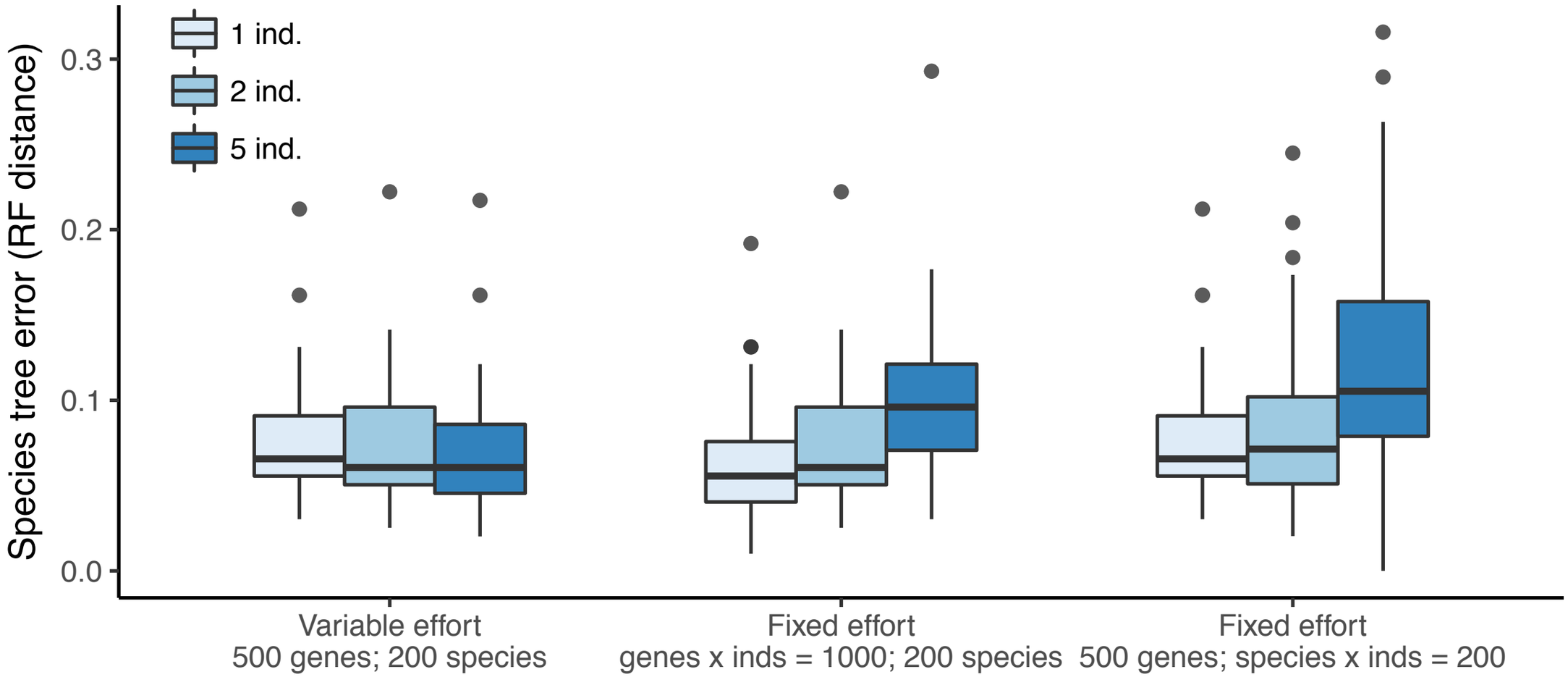
But **not** if sequencing **effort** is kept **fixed**

Multiple individuals helpful?



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But **not** if sequencing **effort** is kept **fixed**

Asymptotic running time?

- Simple discrete math question:

  - $\mathcal{X}$ = a set of subsets of some set $\mathcal{L}$.
    $\mathcal{Y} = \{\ (a,b) \in \mathcal{X} \mid\ a \cap b = \varnothing\ ,\ a \cup b \in \mathcal{X}\ \}$

  - Clearly, $|\mathcal{Y}| < |\mathcal{X}|^2$

  - What's the maximum $|\mathcal{Y}|$ with respect to $|\mathcal{X}|$?

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    - Clearly, $|\mathcal{Y}| < |\mathcal{X}|^2$
    - What's the maximum $|\mathcal{Y}|$ with respect to $|\mathcal{X}|$?
- Turns out to be rather challenging
  - Daniel Kane and Terence Tao proved: $|\mathcal{Y}| = O(|\mathcal{X}|^{1.73})$

Bounding ASTRAL running time

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- What is $|\mathcal{X}|$?
  - ASTRAL-I: edges in gene trees ⇒ $|\mathcal{X}|=O(nm)$
  - ASTRAL-II: ASTRAL-I + uncontrolled heuristics
  - ASTRAL-III: control heuristics to $|\mathcal{X}|=O(nm)$

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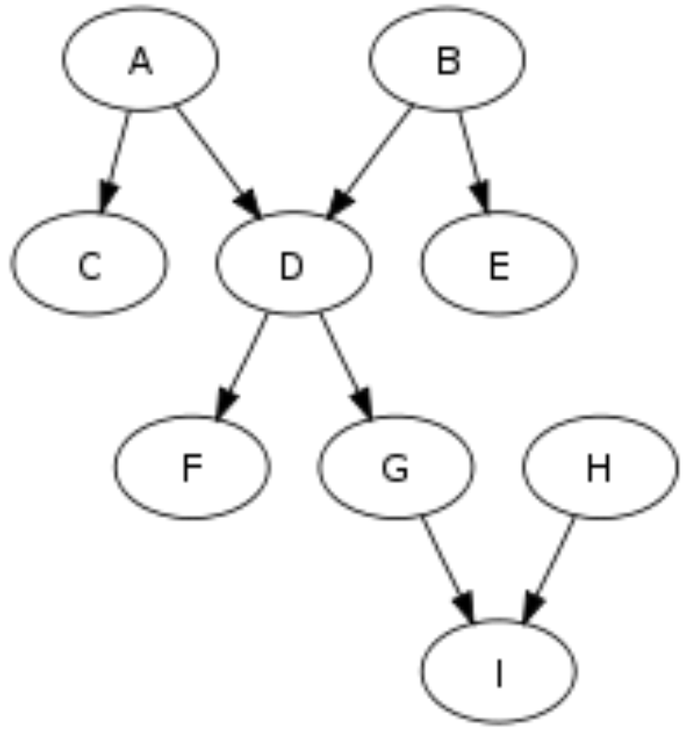
  - ASTRAL-III: control heuristics to $|\mathcal{X}|=O(nm)$
- ASTRAL-III is bounded at $O((nm)^{2.73})$
  - Bounding the running time does not hurt accuracy (simulations)

Further improvements

- Use a polytree to overly all the input gene trees into one data structure



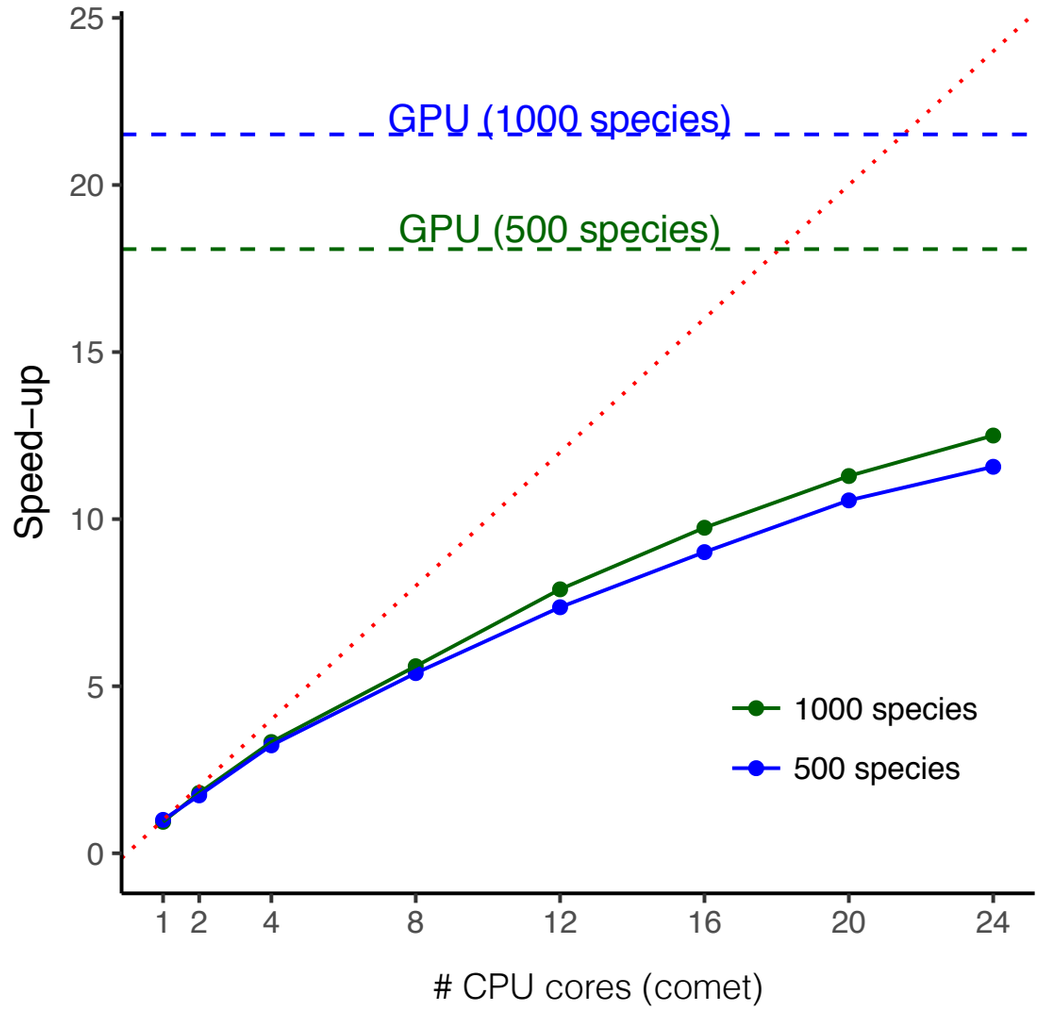
- Allows us to spend time for each unique node in gene trees once
  - $O(|\mathcal{U}|(nm)^{1.73})$

unique nodes in gene trees = $O(nm)$

- 3X running time improvement

Parallelism

- We need $O((nm)^{1.73})$ weights
  - "almost" independent
    - can send each task to a different CPU or GPU core
- Can now infer trees with 10,000 species & 400 genes in less than a day



Moving forward …

- ASTRAL, like all other two-step approaches, is sensitive to errors in the input gene trees
  - Can it be changed to use characters directly?
    possible but slow for binary characters …
  - More broadly, can alternative scalable methods be developed for better gene tree estimation?

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- ASTRAL scales to 10K leaves. We have 90K bacterial genomes.
  - Can we scale further? … divide-and-conquer …
- Theory: can the running time be further improved? Can the sample complexity be established for heuristic ASTRAL?

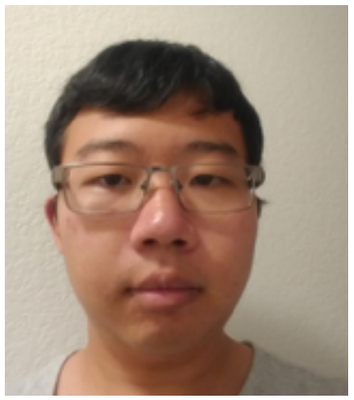
Summary

- ASTRAL is one of the leading methods for species tree reconstruction from gene trees
  - Can handle all types of inputs used in practice (missing data, polytomies, multiple individuals, …)
  - Has high accuracy given good gene trees
  - Seems robust to *some* model violations (but not high gene tree error)
  - Is scalable to very large datasets (10K leaves)
- Combines CS theory+statistics+heuristic techniques +efficient implementation+parallelism+software support

Tandy Warnow

Sebastien Roch

Maryam Rabiee Hashemi



Chao Zhang

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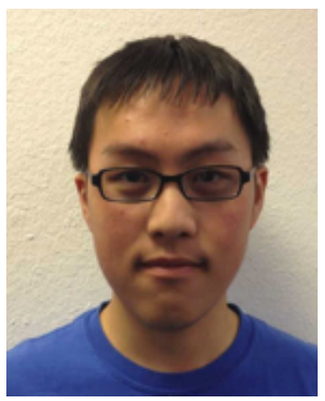

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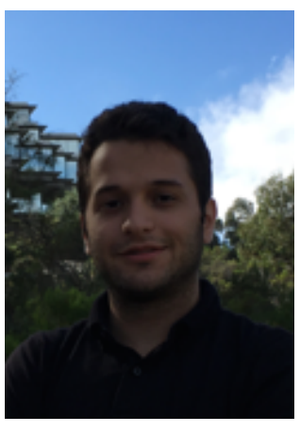

Erfan Sayyari

Shubhanshu Shekhar

Theoretical sample complexity results

How many genes are enough to reconstruct the tree?

$$m \geq \frac{9}{2} \log \left(\frac{4\binom{n}{4}}{\epsilon} \right) \frac{c}{\alpha^2 f^2}$$